SMGroup

SM Preventive Medicine and Public Health

Perspective

Epidemiological Consideration: The Epidemic of AMR; A Global Crisis *A Final Call to Action*

Nicholas A Kerna[1,2]*

[1]*College of Medicine, University of Science, Arts and Technology, Montserrat, BWI*
[2]*Department of Biostatistics and Epidemiology, Suriwongse Medical Center, Thailand*

Article Information

Received date: May 10, 2018
Accepted date: May 31, 2018
Published date: Jun 07, 2018

***Corresponding author**

Nicholas A Kerna, College of Medicine, University of Science, Arts and Technology, USA, Email: nicholas.kerna@usat.edu

Article DOI 10.36876/smpmph.1017

Preface

According to Penders et al.:

Antimicrobial resistance (AMR) is, worldwide, one of the most critical public health threats that humanity currently faces. AMR reduces clinical efficacy and increases treatment costs. Furthermore, AMR jeopardizes the achievements of modern medicine; the success of interventions such as organ transplantation, cancer chemotherapy, and major surgery depends on effective antimicrobial agents for the prevention and treatment of (nosocomial) infections. With a lack of novel antibiotics in the pharmaceutical pipeline, the conservation of existing antibiotics is crucial [1].

Introduction

A Review of Antimicrobial Resistance Pathways

The human intestinal microbiota is a densely populated ecosystem. While the microbiome performs many vital functions and exerts numerous health benefits, the extreme density of microorganisms within this ecosystems facilitates the transfer of antimicrobial resistance genes to potentially pathogenic bacteria [2].

Antibiotics exert selective pressure on bacterial populations, killing susceptible bacteria while allowing strains with resistance to certain antibiotics to survive and multiply. Traits for such resistance are passed "vertically" to offspring cells. The resultant resistant bacteria can spread, and become additional sources of resistance genes for other bacterial strains. Therefore, resistance to a variety of antibiotics may accumulate over time. This accretion can lead to strains of multiple drug resistant bacteria that are more difficult to destroy due to reduced treatment options [3].

Discussion

Bacterial organisms exploit various strategies to resist antimicrobial agents. Two distinct pathways of antimicrobial resistance (AMR) are the "intrinsic pathway" and "acquired pathway".

The Intrinsic Resistance Pathway

The first pathway of AMR to describe is "intrinsic resistance" or "vertical resistance". Vertical resistance is passed directly from parent cell to offspring cell. Intrinsic resistance is naturally coded and expressed by all (or almost all) strains of a particular bacterial species. In this regard, intrinsic resistance could be considered inherent resistance [3]. Furthermore, intrinsic resistance is the innate ability of a bacterial species to resist the action of a particular antimicrobial agent through its inherent structural or functional characteristics. This innate ability results in "tolerance" of a particular drug or antimicrobial class. Intrinsic resistance is also termed "insensitivity" since it occurs in organisms that have never been susceptible to a particular drug. Such natural insensitivity can occur due to any of the following mechanisms:

- lack of affinity of the drug for the bacterial target,
- inaccessibility of the drug into the bacterial cell,
- extrusion of the drug by chromosome-encoded active exporters
- or native production of enzymes that inactivate the drug.

An example of intrinsic resistance is the natural resistance of anaerobes to aminoglycosides and Gram-negative bacteria against vancomycin.

OPEN ACCESS
ISSN: 2576-4004

The Acquired Resistance Pathway

The second pathway of AMR to describe is "acquired resistance". Acquired resistance develops via mutation or "horizontal" resistance acquired through the microbe's environment, e.g., resistant gene segments and other resources.

Changes in the bacterial genome through mutation or horizontal gene acquisition may, consequentially, lead to a change in the nature of proteins expressed by the organism. Such change may may cause an alteration in the structural and functional features of the bacteria involved that may result in resistance against a particular antibiotic. This pathway is limited to selected isolates of a particular bacterial species or group of microorganisms [5].

There are two subpathways of acquired resistance: mutation and horizontal gene transfer.

Mutation: Acquired AMR Resistance Subpathway I

A mutation is a spontaneous change in a DNA sequence within a gene that may cause a change in the trait that the gene expresses. Any change in a single base pair may result in a corresponding change in one or more of the amino acids for which that gene codes altering the enzyme or cell structure that consequently disrupts the affinity or practical activity of the antimicrobials. In prokaryotic genomes, mutations frequently occur due to base changes caused by exogenous agents, DNA polymerase errors, deletions, insertions, and duplications. In prokaryotes, there is a constant rate of spontaneous mutation of approximately 0.0033 mutations per DNA replication, which is relatively uniform for a diverse spectrum of organisms. The mutation rate for individual genes varies widely among and within genes [8]. The following are examples of AMR via mutation.

1. Mycobacterium tuberculosis resistance to rifamycins. (Due to point mutations in the rifampin-binding region of rpoB.)
2. E. coli and Hemophilius influenzae resistance to trimethoprim. (Due to mutations in the chromosomal gene specifying dihydrofolate reductase.)

Horizontal Gene Transfer (HGT): Acquired AMR Subpathway II

Horizontal gene transfer (HGT) is another means by which AMR can develop. HGT is the process of swapping genetic material between coincident bacteria. HGT can occur by three primary mechanisms: transformation, transduction or conjugation. In transformation, a recipient bacterium takes up extracellular donor DNA. In transduction, donor DNA (packaged in a bacteriophage) infects a recipient bacterium. In conjugation, a donor bacterium transfers DNA to a recipient bacterium by mating [9]. Herein, is proposed the abbreviation, hAMR, to represent antimicrobial resistance acquired via horizontal gene transfer (AMR via HGT). The following is an example of hAMR:

Enterococcus faecium and E. faecalis resistance to Vancomycin via the acquisition of one of two related gene clusters, Van A and Van B, that code for enzymes that modify peptidoglycan precursor; thus, reducing affinity to Vancomycin.

Summary of the Mechanisms of AMR

There are two main pathways through which bacteria achieve AMR: intrinsic (resistance) and acquired (resistance).

The Intrinsic Pathway

Bacteria having intrinsic resistance can "resist" certain antimicrobial agents (one or more) due to the bacteria's inherent structure or function. These resistant bacteria may export certain antimicrobial agents that enter them, may neutralize certain antimicrobial agents that breach the bacteria's cell wall or may "ignore" certain antimicrobial agents which, thereby, cannot penetrate the bacteria's cell wall or affect the cell wall structure or function.

The Acquired Pathway

Bacteria can acquire AMR through either of two acquired subpathways: mutation or HGT.

Acquired-Mutation: Mutations in bacteria occur spontaneously through the ongoing process of aberration and natural selection. These mutations can occur in deference to exogenous factors (merely occurring due to rapid mitosis over time), or mutations can ensue due to specific exogenous factors.

Acquired-HGT: HGT occurs by the exchange or swapping of genetic constituents ("debris"). A resistant gene may become attached or spliced into the genome of a nonresistant bacteria making the nonresistant bacteria resistant to certain antimicrobial agents.

Summary of the Pathways of AMR

In summary, vertical: top-down (intrinsic/hereditary); horizontal: laterally from the local environment and neighboring genetic "debris" (acquired).

AMR Resulting from Exposure to Antimicrobial Agents (Antibiotics)

Antibiotic resistance arises as a consequence of exposure to antibiotics. The resistant cells in a population have an advantage over sensitive cells when exposed to antimicrobials. Therefore, the population becomes resistant to antibiotics [2]. How do these resistant microbes develop in hAMR? Integrons are mobile genetic elements that encode integrase and are capable of site-specific recombination; they typically carry antibiotic resistance genes [3]. Resistance genes can be exchanged among bacterial populations [5,6]. Several mechanisms for the acquisition and dissemination of resistance determinants involve DNA exchange. In this way, resistance genes can also spread adroitly among bacterial populations from animals and humans [5,6]. This spread among bacterial populations means that pathologic cells expressing resistance may no longer respond favorably to antibiotic treatment, thereby, rapidly accelerating mortality.

Clinical Epidemiological Considerations of AMR

Currently, AMR prevalence is increasing, and the development of new and effective antimicrobial agents is decreasing. This volatile combination of escalating AMR and lack of innovative antimicrobial treatment is set to manifest as a global crisis as an epidemic of antibiotic resistance. According to researchers Hawkey and Jones (2009):

> Antibiotic resistance is now a linked global problem. Dispersion of successful clones of multi-drug resistant (MDR) bacteria is common, often via the movement of people. Local evolution of MDR bacteria is also important under the pressure of excessive antibiotic use, with horizontal gene transfer providing the means

. . . and the rapid dissemination of novel genes reflects their evolution under the selective pressure of antibiotic usage [1].

Projects in Response to AMR

Considering the short- and long-term implications for the individual patient and the global healthcare system regarding AMR, several key studies and projects have been proposed and enacted to address this crisis.

National Academy of Sciences

The National Academy of Sciences has calculated that increased healthcare costs associated with antibiotic-resistant bacteria exceed $4 billion each year in the United States alone; a figure that reflects the price of pharmaceuticals and extended hospital stays, but does not account for lost workdays, lost productivity or human suffering.

World Health Organization

Dr. Margaret Chan, former Director-General of the World Health Organization, released a statement on World Health Day 2011 about the bleak future of treating bacterial infections if no steps are taken to slow the development of antibiotic-resistant bacterial strains. She warned: "In the absence of urgent corrective and protective actions, the world is heading toward a post-antibiotic era in which many common infections will no longer have a cure and, once again, kill unabated" [6].

Preservation of Antibiotics for Medical Treatment (PAMTA)

In 2011 (and again in 2013 and 2015), an amendment to the Federal Food, Drug and Cosmetic Act (referred to as Preservation of Antibiotics for Medical Treatment or PAMTA) was introduced in the U.S. House of Representatives. The goal of the amendment was to create legislation that focused on protecting the effectiveness of antibiotics used in treating human and animal diseases. It proposed banning seven classes of antibiotics that are medically significant to humans for use by the food animal industry as well as restricting the use of many other antibiotics in animal feed [7]. According to committee member, Rep. Slaughter: "Right now, we are allowing the greatest medical advancement of the 20th century [antibiotics] to be frittered away, in part because it's cheaper for factory farms to feed these critical drugs to animals rather than clean up the deplorable conditions on the farm" [10] (Figure 1).

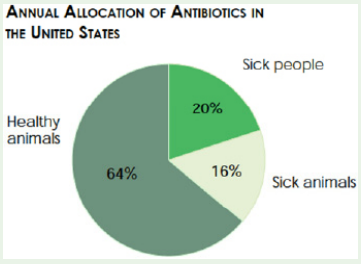

Figure 1: Annual allocation of antibiotics in the united states. The preservation of Antibiotics for Medical treatment act will enhance drug safety standards to reduce the health risks associated with the widespread administration of antibiotics to healthy animals (Adapted from FDA,2009).

Note: The Preservation of Antibiotics for Medical Treatment Act of 2011.

Conclusion

The human gastrointestinal tract is an open system that, everyday, encounters a myriad of bacterial acquisitions from the environment (e.g., from food, water, soil, and other humans or animals) [8]. These incoming bacteria often harbor antibiotic resistance genes that can contribute to hAMR. Some of these encounters are incidental while others are intentional.

Antibiotic resistance is an active and eminent epidemiological threat to human health and survival. With increasing resistance to antimicrobial agents and the lack of new and effective drugs, the progress of previous decades of medical advancement will be compromised or forfeited. AMR jeopardizes the achievements of modern medicine, and may make specific complex procedures that depend on effective medicines too risky to perform. The careless and rampant use of antibiotics in animals and animal feed, and the inappropriate prescription of antibiotics by physicians for humans are contributing to this surging epidemic. More antibiotic prescription restraint, more funding for research for novel antibiotics, and more support for complementary and alternative methods and preventive medicine policies may help put off or reverse this impending catastrophe. The time to act is now, or there may not be a future for most of humankind.

Conflict of Interest Statement

The author declares that this paper was written in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

Supplementary Note

This paper is based on prior unpublished research: Kerna, NA. (2017) Current Practices in the Use of Probiotics During Antibiotic Treatment (unpublished doctoral dissertation). Chapter VIII, pages 124-130. ©2017 Nicholas A Kerna.

References

1. Hawkey P, Jones A. The changing epidemiology of resistance. Oxford Journals. Journal of Antimicrobial Chemotherapy. 2009; 64.
2. Penders J, Stobberingh E, Savelkoul P and Wolfs P. The human microbiome as a reservoir of antimicrobial resistance. Front Microbiol. 2013; 4: 87.
3. Caratolli A. The importance of integrons in the diffusion of resistance. Laboratory of Bacteriology and Medical Mycology. 2016.
4. Stokes HW, Hall R. A novel family of potentially mobile DNA elements encoding site-specific gene-integration functions: integrons. Mol Microbiol. 1989; 12: 1669-1683.
5. CVM Michigan State University. Molecular Basis for Antimicrobial Resistance: Acquired Resistance. 2016.
6. Chan Margeret. Antibiotic Resistance and Public Health. Grace Communication Foundation.
7. Preservation of Antibiotics for Medical Treatment Act of 2011.
8. Baquero F. The multiple roles of antibiotics and antibiotic resistance. 2012; 12-38.
9. Holmes, RK, Jobling, MG. Genetic Information in Microbes. Medical Microbiology. 4th edition. University of Texas Medical Branch at Galveston, Galveston, Texas. 1996.
10. Zuraw L. Rep. Slaughter Reintroduces Preservation of Antibiotics Legislation (2015, March 25) Food and Safety News. 2015.

Citation: Kerna NA. Epidemiological Consideration: The Epidemic of AMR; A Global Crisis *A Final Call to Action*. SM Prev Med Public Health. 2018; 2(2): 1017. https://dx.doi.org/10.36876/smpmph.1017