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Antibiotic Resistance: What is being done?

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Methicillin Resistant Staphlycoccus Aureus is one of the most deadly infections a person can have. Ironically MRSA was not prevalent until a few decades ago, and is so deadly because there are little effective ways to combat it. Today there are few antibiotics being developed and even fewer being implemented to combat the number of infections in the world, even though they are prevalent everywhere. Some countries, like Norway, however are doing their best to reduce the amount of infections by using simple measures to successfully decrease the prevalence of MRSA infections. This leads to the question of "What are we doing to combat antibiotic resistance here in America?"

Introduction

Since the discovery of penicillin in 1929 we have lived in an "age of antibiotics". Penicillin was not mass produced until 1943, but its introduction, along with Sulfonamides, introduced in 1936, have changed the landscape of medicine exponentially(9). Microbes, like other forms of life, adapt to change and evolved antibiotic resistance to combat antibiotics. As soon as three years after the introduction of Penicillin more than 20% of *S. aureus* hospital isolates were resistant, developing penicillinase(7). This resistance develops when broad spectrum antibiotics, like penicillin, kill all types of bacteria in the system, allowing bacteria resistant to these antibiotics to proliferate, and become pathogenic. This resistance can be transferred to other microbes by horizontal gene transfer. Because of the easy plasmid transfer and recombination some bacteria are able to gain antibiotic resistance even if they did not encounter the antibiotic first. As more and more bacteria gain antibiotic resistance, the more horizontal transfer of antibiotic resistant plasmids get shared. Between 2002-2008 there were 362,000 cases of antibiotically resistant microbial infections acquired ***in-hospital.*** The majority of these infections were methicillin resistant types (5). This lead to an estimated 90,000 deaths due to microbial infection just in the US. Sales of antibiotics make nearly $25 billion dollars a year(9), meaning the market for a new antibiotic is huge, but the nature of the market is counter-productive. A large number of new antibiotics are kept shelved for various reasons; some being their toxicity and power, others for the fact that they are so effective that they must be saved for higher level infections so not to overuse and enable a development of resistance. This fear is real, as it arises from the fact that nearly 50% of all *S. aureus* isolates are found to be methillicin resistant, and are beginning to replace the antibiotic-susceptible areas of the population(9). As a society we must ask ourselves what can we do to combat antibiotic resistance, and to do that we must know, what is being done to combat antibiotic resistance?

Recent Progress

The last major group of antibiotics developed was the oxazolidinone class, developed in 2000. A decreasing number of antibiotics have been developed since the 80's, targeting only specific targets in the cell. Various antibiotics work by a variety of means and methods of action. They are categorized into five functional groups: those that inhibit cell wall synthesis, protein synthesis, membrane function, nucleic acid synthesis, and those that are anti-metabolites. Penicillins, Cephalosporins, Monobactams, and Carbapenems are Beta-lactams that inhibit cell wall synthesis, along with non-beta-lactams Glycopeptides and Fosfomycins. Aminoclycosides, Macrolides, Lincosamides, Streptogramins, Ketolides, Tetracyclines, Glycylcyclines, Phenicols, Oxazolidinones, and Ansamycins are those that inhibit protein synthesis by attacking/modifying the ribsose. Others affect the membrane by depolarizing the membrane, making it

porous, and are found in the antibiotic groups Polymyxins and Cyclic Lipopeptides. Nucleic acid inhibitors inhibit DNA synthesis, making them bactericidal, they include the groups Quinolones and Furanes. The anti-metabolites inhibit the folate pathway, which makes DNA synthesis impossible, and are some of the oldest groups of antibiotics, including the Sulfonamides, and Trimethoprims and Sulfamethoxazole, but rely upon active transportation into the cell in order to achieve inhibition. A great deal of the understanding of antibiotic resistance comes from meta-genomics, where all the DNA in a sample of various bacteria is sequenced together, so certain genes, often those passed through horizontal gene transfer, are quantified and scientists are able to see how certain genes have spread amongst the sample bacteria genetics. (3)This has helped lead to the development of newer antibiotics, through combinational therapy of multiple drugs to combat certain resistances. The most difficult task to conquer is target validation, or what specifically the antibiotic targets. If it is too specific then some simple change/mutation/resistance would override it, this causes most developmental antibiotics to be broad-spectrum, as they make more money. Unfortunately due to overuse, which is best for an antibiotic in a business sense, lead to quick development of resistance, causing a short shelf life for the antibiotic; there also is very low tolerance for side effects for antibiotics. In order to bring a new antibiotic to market requires around $600 million, for research, development, and clinical trials, slowing the development of new drugs (2).

Antimicrobials can be developed from both natural and synthetic sources. Natural antibiotics, like penicillin, were discovered and developed first, and many synthetic antibiotics contain multiple types of antibiotics with multiple modes of action. Some natural sources are still being discovered. Recently in 2012 it was discovered that they cytokeratin proteins made by epithelialial cells in the eye have very strong antimicrobial properties. The data expresses epithelial cytokeratins function as endogenous antimicrobial peptides defending in infection and that keratin-derived antimicrobials may serve as effective therapeutic agents in the future. These proteins have also been found to be very easy to create as well (6). The main problem with developing antibiotics comes from the economic sense. It has led to the development of several powerful antibiotics, but very few narrow spectrum antibiotics. Narrow spectrums antibiotics are different as they affect specific types of bacteria so that resistance will develop more slowly, because the narrow spectrum antibiotic affects fewer bacteria than wide spectrum antibiotic. Due to the huge cost of production and research this is a very unfavorable process. Today doctors in America prescribed huge amounts of antibiotics for treatments unaffected by them, such as viral infections. A study by the CDC concluded that doctors were improperly prescribing antibiotics 1 out of 3 times that they were prescribed. This adds to the development of antibiotics resistance by giving more possibility of the development of a resistance mechanism. Doctors often prescribe these almost as a placebo so that the patient feels better because they are taking a medication, even though it doesn't affect the infection. Doctors know they are improperly prescribing the medication too, but they are pressured to do so, and they also profit from it. This directly contributes to antibiotic resistance.

Another huge factor in antibiotic resistance is in agriculture. Nearly 80% of all antibiotics go towards agriculture as "growth factor". This growth factor comes from the destruction of the gut flora in the animals, allowing the animal to receive more nutrition due to the absence of bacteria, allowing it to grow faster. This can allow the animal to grow at around 15% faster and use less food than without antibiotics. These antibiotics also make their way into us when we eat the animals. These affect a huge number of bacteria and contribute greatly to resistance (4). Antibiotic development is a slow process, and currently there are few methods for gram-negative bacteria. Gram negative have more types and more complex defense mechanisms, like efflux pumps, to add resistance. Currently there are only three major gram negative specific antibiotics in clinical trials in America (7). There are several mechanisms of antibiotic resistance. Types that produce an enzyme to modify or destroy the antibiotic, an efflux system to pump it out of the cell before it can react, drugs that produce an alternative pathway for the one that is inhibited in the cell, the addition of new genes through conjugation, transformation, or transduction to give the microbial resistance. These mechanisms are difficult to override and require a complex antibiotic (8).

Discussion

In Norway they prescribe fewer antibiotics than any modern country in the world, yet they also have the lowest rates of MRSA prevalence. How is this so? The culture regarding medicine in Norway is very different. Doctors treat with antibiotics only in the most demanding cases, and supply medication to combat and soothe the symptoms in most cases. In Norway's economy if you are sick you take the day off of work, and they still get paid, and pharmaceutical countries are not allowed to advertise medication. 40 years ago Norway was in the same situation as the US in dealing with MRSA, but since they changed policy they have the lowest rates in the world. They also restricted use of all antibiotics in agriculture. Over time antibiotic resistance quit occurring at the same rate, for the reason that all antibiotic resistance requires more energy than not having it activated, increasing its survivability when not in contact with the antibiotic.

Because of this they save thousands of lives each year, but enable the collective suffering of some sore throats and other various infections (4).

What does this mean for the rest of us? The sooner we adopt a way to combat resistance the better off we will be in the future. Norway's methods are low energy input and require little economically, just a culture change, and end up saving lives and money. If they or a similar set of procedures were implemented here then possibly in 25 years we would see a great decline in MRSA. Several companies and rich-conglomerates have offered huge sums of money to the development of new antibiotics in order to stimulate development. If we continue to ignore the problem and stem its development with different antibiotics that will only work for so long before more resistance develops, or a new technology would be able to combat infection. The sooner precautions are taken the better off we will be as a society, as antibiotically resistant infection is a very destructive problem.

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