Antibiotic Resistance: How Serious Is the Problem, and What Can Be Done?

Bob Barrett: This is the podcast from *Clinical Chemistry*. I am Bob Barrett.

Antibiotic resistance and the resulting risk for ineffective treatment of infections are serious and growing problems. These concerns have mobilized governments and non-governmental organizations to address these issues.

In the August 2012 issue of *Clinical Chemistry*, a question and answer feature examined how serious the problem of antibiotic resistance is and what can be done. Dr. Alexander McAdam, an Associate Professor of Pathology at Harvard Medical School and the Medical Director of the Infectious Diseases Diagnostic Laboratory, was moderator of this Q&A. He's our guest in this podcast.

Dr. McAdam, can you give us an idea of the scope of the problem of antibiotic resistance?

Dr. Alexander McAdam: This is a very broad question because of the great diversity of bacteria that cause infections and the many drugs that are used to treat infections. That said, there's a general consensus the antibiotic resistance is a common, serious, and growing problem. Let me give you a couple of specific examples to illustrate the problem.

Staphylococcus aureus or Staph aureus is a bacterium that is a common cause of many types of infections including infections in the bloodstream, joints, bones, and lungs. Without antibiotic treatments, many invasive Staph aureus infections would certainly be fatal. When penicillin was introduced for clinical use in 1942, most isolated Staph aureus were killed by the drug and penicillin treatment was usually effective for these infections. But by the 1960s, over 80% of Staph aureus isolates were resistant to penicillin. And now, over 90% are resistant.

In 1961, methicillin was introduced for clinical use. Methicillin is an antibiotic that's useful for treating penicillin-resistant Staph aureus infections, isolates of Staph aureus that are killed by Methicillin are also killed by several other related drugs, including the first generation cephalosporins. Such drugs became the mainstay of treatment for infections with Staph aureus. Unfortunately, methicillin-resistant Staph aureus, or MRSA, has become common as many people know from reading the newspaper or watching the news on television.

In the U.S., many studies have found that from 1 to 2/3 of clinical isolates of Staph aureus are resistant to methicillin and related drugs. Because of this, many physicians no longer use these drugs for empiric treatment of infections caused by Staph aureus. There's recent evidence that the frequency of invasive infections with MRSA in the U.S. is actually declining a bit, which is certainly good news.

For many years, vancomycin was considered to be effective against all isolates of Staph aureus including MRSA. While vancomycin remains very effective for nearly all Staph aureus, there were a small number of reports of infections caused by vancomycin-resistant Staph aureus. Fortunately, these highly resistant bacteria have not spread from one person to another person.

In addition to vancomycin, there are other antibiotics both new and old that are effective against most isolates of MRSA so these infections can still be treated. But the treatment has become complex and can require expensive drugs or drugs that cannot be given orally and must be given intravenously.

A second example that illustrates the problem of antibiotic resistance is the bacterium Neisseria gonorrhoeae. As the name suggests, this organism is the cause of the sexually transmitted infection, gonorrhea. During the 1990s, fluoroquinolone antibiotics could be conveniently given in a single oral dose to effectively treat gonorrhea. But in 1999, fluoroquinolone-resistant Neisseria gonorrhoeae were first detected in the US, specifically in Hawaii. The frequency of fluoroquinolone-resistant Neisseria gonorrhoeae subsequently increased and the resistant bacteria became widespread in the U.S. As a result, in 2007, the CDC said the fluoroquinolones should no longer be used to treat gonorrhea. After that, only one class of drugs, third generation cephalosporins was recommended by the CDC for treatment of gonorrhea.

Until recently, either oral or injected cephalosporins were recommended by the CDC for treatment of gonorrhea. Unfortunately, resistance to the oral cephalosporin has become common in many parts of the U.S. This August, the CDC issued a recommendation that the injected cephalosporins should be used for treating gonorrhea rather than the oral form. Injected treatment is obviously painful and less convenient for patients.

I could provide more examples but I think that these two illustrate that bacteria rapidly develop resistance to antibiotics under the selective pressure of exposure to these drugs and also demonstrate some of the challenges this presents for patient care.

Bob Barrett: Well doctor, in general terms, what are the mechanisms of antibiotic resistance in bacteria?

Dr. Alexander McAdam: To understand how bacteria become resistant to antibiotics, we have to first understand how antibiotics work. Each antibiotic interacts with a specific target molecule produced by bacteria. That bacterial target molecule performs a function that is essential for the growth or survival of the bacterium. The antibiotic specifically inhibits the target molecule from performing that essential function and so the bacteria can't grow, or they die.

To inhibit the target's function, an antibiotic must do three things. First, the antibiotic has to reach the site of its molecular target. Second, the antibiotic has to persist at the site of the target long enough to have its effect. Third, the antibiotic has to bind to and inhibit the target molecule's function. Bacteria become resistant to an antibiotic by preventing one or more of these three steps.

So first, a bacterium can prevent an antibiotic from reaching the target either by blocking the antibiotic from entering the site of the target or by rapidly pumping the antibiotic away from the site of the target. Most targets of antibiotics are found inside the bacterial cell and so gain or loss of a pore or pump molecule in the bacterial membrane can change whether an antibiotic will reach its target. Second, antibiotic can make enzymes that modify the antibiotic in such a way that the antibiotic is no longer active. And third, bacteria can change the target such that the antibiotic can't inhibit the target. Bacteria can do this by having a different or altered form of the target or less commonly, by expressing greatly increased levels of the target to escape from inhibition by the antibiotics.

Bob Barrett: Where did this all began? Where did antibiotic resistance originate?

Dr. Alexander McAdam: Most antibiotics in clinical use are derived from natural products produced by bacteria. These naturally occurring antibiotics are made by bacteria found in the environment, presumably, so the antibiotic producing bacteria can inhibit the growth of the neighboring

antibiotic-susceptible bacteria. That gives the antibiotic producers a growth advantage.

Now here's the really interesting thing. Antibiotic resistance occurs in environmental bacteria even in bacteria that are isolated from environments that, as far as we know, contain no antibiotics from man-made processes. This reflects an arms race between different bacteria, with antibiotic resistance emerging in environmental bacteria in response to their antibiotic-producing neighbors. Also, the antibiotic producers must have ways to protect themselves from the inhibitory effects of the antibiotic they make and so this is another potential source for the origin of genes mediating antibiotic resistance.

DNA-carrying genes for antibiotic resistance traits moves between bacteria by several different mechanisms and so antibiotic-resistant bacteria can donate these antibiotic-resistant genes to other bacteria. Eventually, these genes find their way to the pathogenic bacteria that infect humans.

Antibiotic resistance can also be created de novo by exposing antibiotic-susceptible bacteria to an antibiotic. This occurs through point mutations in the DNA of the bacteria, which leads to antibiotic resistance by the general mechanisms we discussed earlier. This can happen whenever bacteria are exposed to antibiotics, whether in the laboratory, the environment, or within a host such as a human or an animal.

Bob Barrett: So, what's driving the increase in antibiotic-resistance in bacteria?

Dr. Alexander McAdam: The increase in antibiotic-resistance is caused by the selective pressure exerted on bacteria by exposure to man-made antibiotics. Of course, antibiotic-resistant bacteria have a growth advantage over antibiotic-susceptible bacteria only when there are antibiotics present.

We usually think about antibiotics being used to treat humans who have infections. There is very strong evidence that the use of antibiotics in humans increases the frequency of antibiotic-resistant bacteria in human infections.

Some people may be surprised to learn that antibiotics are also used in low doses in animal feed to enhance the growth of livestock in the agricultural industry. Estimates are that about 70% to 80% of the antibiotics

used each year in the U.S. are used in food animals. There is contentious debate about whether the use of these antibiotic growth products or AGPs for livestock results in increased resistance to antibiotics in human infections. A number of professional medical organizations, including the American Academy of Pediatrics and the Alliance for the Prudent Use of Antibiotics, have concluded that use of AGPs carries a risk for human health due to an increased risk of infections due to antibiotic-resistant bacteria.

Bob Barrett: Is anything being done to reduce the use of antibiotics in animal feed?

Dr. Alexander McAdam: Several countries have banned the use of antibiotics for growth enhancement of farm animals. Sweden was the first in 1986 and they made this decision following a request from the Federation of Swedish Farmers. Several European nations have followed soon and then the European Union banned all AGPs in 2006.

Progress has been somewhat slower in the U.S. My understanding is that the U.S. Food and Drug Administration, the FDA, has mainly used voluntary measures to discourage the use of AGPs. For example, in April of this year, the FDA asked drug makers to voluntarily change the drug labels on antibiotics to require a prescription from a veterinarian for use in animals. The expectation is that veterinarians will refrain from prescribing antibiotics for use of AGPs.

At times, the FDA has taken stronger measures. This year, the FDA restricted the use of cephalosporin antibiotics in cows, pigs, chickens, and turkeys.

There is some pressure for the FDA to move more decisively. In March of this year, a U.S. magistrate judge ruled that the FDA must act on its long-shelfed plan to limit the use of penicillin and two types of tetracyclines in animal feed. However, the FDA leadership has filed an appeal to overturn this decision and the question is still in the courts.

Bob Barrett: Well, finally doctor, what other steps are being taken to combat the spread of antibiotic resistance?

Dr. Alexander McAdam: It's clear that there are many effective measures we can take to reduce the risk of infections, including infections caused by antibiotic-resistant bacteria. Appropriate use of antibiotics in treating human infections is critical for reducing antibiotic resistance.

That means using antibiotics only when they are truly needed, stopping them as soon as appropriate patient care permits, and selecting antibiotics that will be effective for a patient's specific infection without using broad spectrum or "big gun" antibiotics unnecessarily. Many hospitals now have antibiotics stewardship programs that provide education and guidance to encourage prudent and effective use of antibiotics. Another important step to slow or reduce antibiotic-resistance is to prevent the spread of antibiotic-resistant bacteria from one person to another person. It is really critical that healthcare personnel follow the practices recommended by their infection control group as these practices are known to reduce transmission of pathogens in healthcare settings.

Outside of the healthcare setting, we can all help fight antibiotic-resistance by using antibiotics exactly as prescribed by our physicians and by practicing good hygiene, including frequent hand hygiene.

Bob Barrett: I mean, we're not really getting many new antibiotics, are we? Is that just because you do better by making erectile dysfunction pills or --

Dr. Alexander McAdam: Or baldness cures.

Bob Barrett: Exactly, yeah.

Dr. Alexander McAdam: Yeah, the pipeline does not contain as many new antibiotics as many of us would like, but there have been some new antibiotics in the past few years, and new things will continue to come along.

One of the interesting things is that some old antibiotics like Bactrim, which includes one of the oldest antibiotics known, are still effective against many antibiotic-resistant bacteria.

Bob Barrett: Dr. Alexander McAdam is an Associate Professor of Pathology at Harvard Medical School and the Medical Director of the Infectious Diseases Diagnostic Laboratory. He has been our guest in this podcast from *Clinical Chemistry*. I am Bob Barrett. Thanks for listening.