Case Report

Antimicrobial Resistance: Urban Myths

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Antimicrobial resistance is a popular topic for infection experts, health care workers, and the general public. Over the past few decades, several urban myths surrounding antibiotic resistance have sprung up and have gained credence. In some cases, the experts themselves have not been helpful in dispelling such myths.

Listed below are the more important and common urban myths surrounding antibiotic resistance. As can be found with other urban myths, there is often an element of truth contained within the statement. However, as the text will demonstrate, there may also be a masking of the true concepts that underlie the pronouncements.

Antibiotics Were Invented in the 1930s

In terms of the natural history of our planet, bacteria have been around for billions of years. It is almost certain that antimicrobial substances have been around for a similar period. It is therefore important to clarify what we mean by discovery of antibiotics. The vast majority of antibiotics in commercial use today are naturally occurring or semi-synthetic antimicrobial com-

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pounds that have been produced by environmental organisms, such as bacteria and fungi. These antimicrobial compounds have evolved over billions of years to give the microbes that produce them a competitive survival advantage over other environmental organisms. In order to survive these assaults, bacteria have had to develop resistance mechanisms to these antimicrobial compounds.

This fact at least partially explains why bacteria, and in particular environmental bacteria, are often resistant to several different antibiotics. In the 1930s and 1940s we "discovered antibiotics." Essentially, what this meant is that we developed the ability to purify environmental compounds that have antimicrobial activity and to give them directly to humans in a concentrated form. As the human bacterial flora in general probably had relatively little previous exposure to these antimicrobial compounds, they were susceptible on the whole. Over the past 80 years, the human flora has had to adapt. Table 1 lists some common antimicrobial substances and the microorganisms from which they originated.

Table 1. Examples of common antibiotics and the microorganisms from which they originated

Antimicrobial substance	Microorganism of origin
Penicillins	*Penicillium* spp.
Cephalosporins	*Acremonium* spp.
Gentamicin	*Micromonospora* spp.
Clavulanic acid (beta-lactamase inhibitor)	*Streptomyces clavuligerus*
Erythromycin	*Streptomyces erythreus*
Imipenem	*Streptomyces cattleya*
Vancomycin	*Streptomyces orientalis*

Antibiotic Resistance Developed Soon After the Invention of Antibiotics

Abraham and Chain (1), who were involved in the isolation and purification of penicillin from the *Penicillium* mold, described the presence of a penicillinase in *Escherichia coli*, even before penicillin went into commercial use. However, as described above, it is extremely likely that such beta-lactamases have been around for a long time — long before penicillin came into production as an antibiotic for human use. The main reason that resistance to new commercial antibiotics often develops quickly is that, in the vast majority of cases, the microbial resistance mechanisms already exist in small communities of microorganisms in the environment and as part of the normal flora of humans. The following are some examples.

Methicillin-resistant *Stayphylococcus aureus* (MRSA)

The *mecA* gene encoding methicillin (and flucloxacillin) resistance comes from *Staphylococcus sciuri*, a bacterium found widely on many animal species and generally of low pathogenicity. When methicillin, a semi-synthetic antibiotic, was first introduced commercially, it did not take long before *S. aureus* strains resistant to methicillin appeared. The resistance was a result of the production of a penicillin-binding protein, PBP2a, which is encoded by the *mecA* gene. Human pathogens, such as *S. aureus*, challenged with large amounts of methicillin, needed this *mecA* gene to ensure their survival and quickly acquired it. This demonstrates that even a semi-synthetic antibiotic can be counteracted by genes that encode resistance, which existed long before the so-called semi-synthetic antibiotic was produced. Clearly, bacteria are even smarter than we first thought.

ESBL-producing *Enterobacteriaceae*

At present, the most common extended-spectrum beta-lactamase (ESBL) enzymes are of the sub-type CTX-M, most of which are thought to have been derived from *Kluyvera* species. *Kluyvera* bacteria are widely distributed in nature and generally of low pathogenicity. Commercial introduction of third-generation cephalosporins created a clear requirement for human pathogens, such as *E. coli* and *Klebsiella pneumoniae*, to acquire this resistance mechanism.

Carbapenemases

These resistance enzymes are from multiple environmental sources, including *Bacillus* species. Although we think of carbapenemases as being the "newest" resistance mechanisms of which we are aware, in reality, these naturally occurring carbapenemases, like carbapenems, have most likely been around for millions of years. Once again, introduction of carbapenems into the antibacterial formulary created a need for pathogenic bacteria in humans to acquire this resistance mechanism in order to survive.

As we can see from the above examples, when environmental antimicrobial compounds are purified and given to humans, the human bacterial flora must find ways to resist this antimicrobial assault in order to survive. Horizontal transfer of genetic material by mechanisms such as transformation and conjugation has allowed the human microbial flora to acquire resistance mechanisms, usually from environmental bacteria.

The Antibiotic Era Is Coming to an End

Following the commercial introduction of an antibiotic, there may be a delay before resistance appears while the bacteria acquire the necessary resistance mechanisms. This occurs by horizontal gene transfer, as mentioned above, or occasionally by mutation, particularly in the case of semi-synthetic antibiotics. Eventually, and assuming other factors remain stable, an equilibrium is achieved between the proportions of a bacterium susceptible and resistant to a particular antibiotic. *S. aureus* resistance to penicillin is an example in which 10% of *S. aureus* isolates have remained susceptible to penicillin for the past 50 years. Why equilibrium is achieved is unclear at present, but it is probably due, in principle, to the fact that the human bacterial ecosystem is not a closed system. However, what is apparent is that a better understanding of these equilibriums may allow us to more accurately model the emergence of antimicrobial resistance in the future.

Factors that disturb the bacterial-antibacterial equilibrium include the use of antibiotics, which is probably the main factor, but also the ease of bacterial transmission from host to host.

