

Antibiotics, the host microbiome and superbugs

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With the elucidation of the germ theory in the late 19th century by Louis Pasteur and Robert Koch, there followed the concept of a unique bacterium causing a specific disease. Organisms were either pathogens or non-pathogens. Koch's postulates, in fact, specified that the implicated microbe would be found in all cases of the infection in pure culture and cause illness whenever introduced to

lin, sulfonamide and streptomycin, respectively, would each receive the Nobel prize in medicine or physiology: Alexander Fleming in 1945; Gerhard Domagk in 1939 (but because of the war, he was not recognized until 1947); and Selman Waksman in 1952. The impact of antibiotics was stunning. Before penicillin, 82 percent of patients with *Staphylococcus aureus* bloodstream infection died, but mortality fell dramatically with the drug to 31 percent. These data

percent of all causes), followed by pneumonia, influenza, diarrhea and enteritis. Infections of all stripes were equal opportunity pathogens and unchecked microbial terrorists. Today, pneumonia and influenza rank as the 6th leading cause of death — constituting fewer than 5 percent of deaths — and represent the only infections in the top 10.

Anticipating antibiotic resistance

In his Nobel address in 1945, Fleming described the spectrum of *in vitro* activity of penicillin — effective against many Gram positive organisms including: Staph; Strep, including the pneumococcus, *C. diphtheria*; *B. anthracis*; and the Gram negative diplococcus, *N. gonorrhoea*. In that final year of World War II, these microbes caused the vast majority of infections. In his closing comments, Fleming showed remarkable prescience when he speculated: "The time may come when penicillin can be bought by anyone in the shops. There is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant." He went on to suggest transmission of the resistance

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a person. This model of pathogenesis was reinforced with the linkage in some species to virulence markers such as toxins or bacterial capsules. With that perspective, the hunt began for substances that would inhibit the activity of pathogenic bacteria.

The miracle of antibiotics would wait another 50 years, and the three scientists who discovered penicil-

alone suggest an approximately 50 percentage point absolute reduction in mortality, so long as the bacterium was susceptible.

The emotional impact of antibiotics was also remarkable. On a day-to-day basis in the pre-antibiotic era, infections were uniformly feared. Recall that in 1908, tuberculosis was the leading cause of death (some 25

from the careless patient to another in the family, illustrating not only the concept of selection for antibiotic resistance, but framing the transmission of resistant pathogens in ethical terms. Only a few years before, in 1941, Edward P. Abraham and Ernst B. Chain reported their laboratory discovery of a beta-lactamase elaborated by *E. coli* destroying the activity of penicillin. In the subsequent five years, the emergence of penicillin resistance, mediated by a beta lactamase elaborated by *S. aureus*, would quickly reach a prevalence of 50 percent.

In the last 75 years there have been discoveries of several new classes of antibiotics with specific bacterial targets as well as many minor variations within each class. Most importantly, with every discovery, the microbes have sooner or later developed resistance to every antibiotic to which they were exposed (see timeline).

New concept — what is a host?

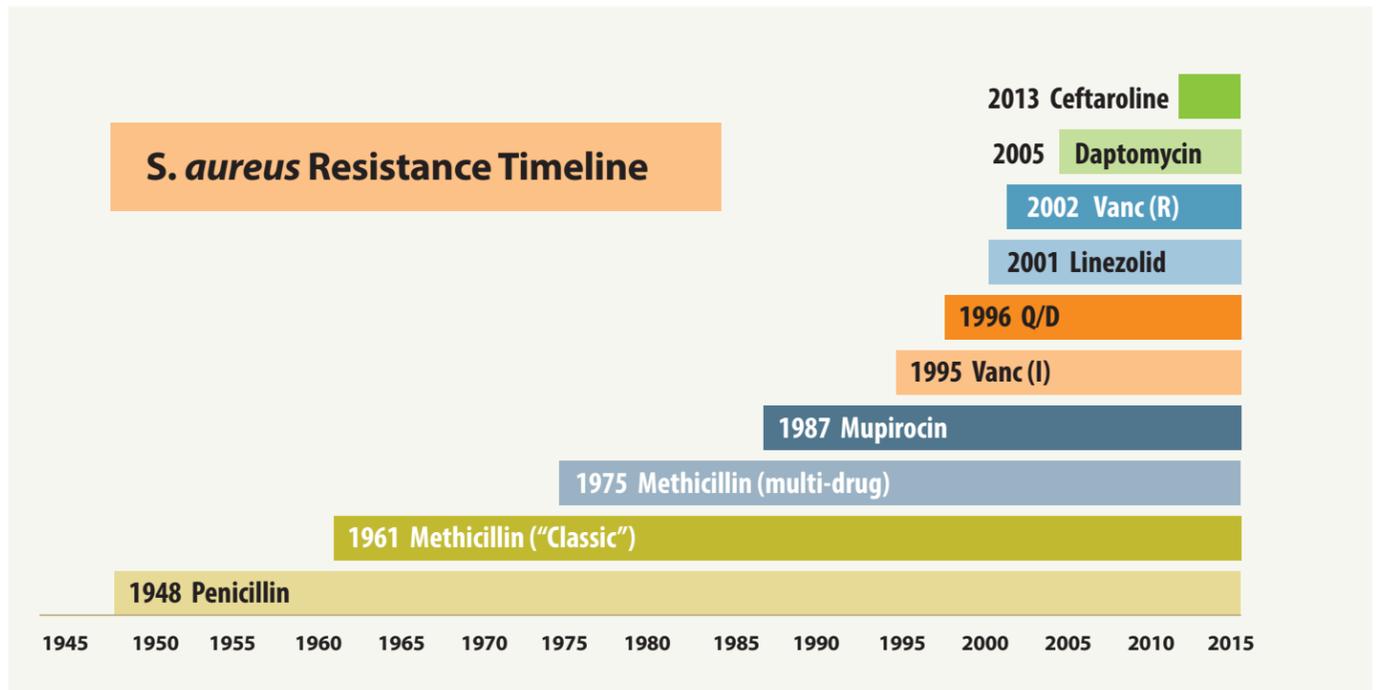
With the expansion of the use of antibiotics in the 1940s and 1950s, a key challenge to the concept of a pathogen arose. Researchers noted that patients receiving antibiotics de-

veloped an overgrowth of *Candida* in their oral cavity. Until then, *Candida* and Gram negative rods were considered non-pathogens. No one imagined their ability to harm. So the concept arose that some people receiving broad spectrum antibiotics must have had their mouth flora altered. Subsequently, with the emergence of HIV infections in the 1980s, the term “opportunistic pathogens” gained wider use to describe disease caused

by “non-pathogens” occurring in a person with altered immunity. In 2017, it is broadly recognized that the same genus and species can cause disease in some people but only colonize others without creating illness.

So a basic question has arisen: What is a host? Can it be defined by immunity and genetics alone? Are there environmental exposure

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factors? A few years ago, two microbiologists suggested we abandon the term “pathogen” and instead focus on the reaction that occurs when a microbe interacts with a person. That interaction, described by Arturo Casadevall and Liiseanne Pirofsky, yields one of three possibilities:

- Infection–damage occurs
- Colonization–indifference
- Commensal–benefit occurs

More recently the authors include that person’s microbiome into their model. The implication is that variations in the microbiome itself can influence the host response to a microbial challenge. A person and her microbiome are inseparable.

The microbiome’s role

The microbiome is the community of all microbes — bacteria, fungi, viruses and even mites — that reside on our skin or within us on mucous membranes. It is critical to maintaining health and defending against external threats from microbes. Just look at the numbers: There are about 1013 human cells and some 1014

bacteria defining our microbiome. Thus, *Homo sapiens* are 10 parts bacteria to 1 part human! Furthermore, there are a thousandfold more microbial genes in our microbiome than human genes. On this basis alone, we should humbly seek to respect our microbiome and work to maintain its integrity.

Antibiotics drastically reduce the numbers of the normal microbiome and severely alter its composition. The consequences of a severe reduction in microbiome quantity and altered diversity can be life-threatening. One of the common examples is *Clostridium difficile* colitis after use of broad spectrum antibiotics. Remarkably, restoring the gut microbiome with a fecal transplant can cure the disorder in 70-80 percent of all cases. More recently a biotech company has tested the efficacy of the oral ingestion of 50 species of the normal gut microbiome and found that it cured *C. difficile* colitis in 87 percent of recipients.

Insight into the role of antibiotics in ICU patients came from studies of the intestinal microbiome of patients with *C. difficile* colitis. These ill patients harbor 10 to 30 multiple antibiotic resistant genes in their gut

microbiome compared to three such genes in donors of fecal transplants. So patients with *C. difficile* colitis not only have a severe colitis from a disordered microbiome, they are virtual storehouses of antibiotic resistant genes. A question arises: If the colitis can be cured with restoration of normal gut microbiome, will there also be a reduction of the number of antibiotic-resistant genes?

A recent study of 20 patients with *C. difficile* colitis treated with a fecal transplant showed that the number of antibiotic-resistant genes fell from as high as 30 down to 10-12 soon after transplant, and then to five resistant genes within weeks afterward — not much higher than in controls. Maintaining a normal microbiome then becomes a key component in the control of highly antibiotic-resistant microbes.

‘Superbugs’

In September 2016, the Centers for Disease Control and Prevention (CDC) reported the isolation of an *E. coli* strain harboring a gene resistant to a last-resort antibiotic, the family of polymyxins including polymixin and colistin. The CDC said it was the fourth detection of

the “untreatable” bacteria harboring a gene — *mcr-1* — that resides on a transmissible plasmid. Individual isolations of bacteria containing *mcr-1* have occurred in Pennsylvania, New York, New Jersey and, by the end of 2016, Connecticut. A prototype victim of infection with the superbug is an ICU patient with prior exposure to many classes of antibiotics and now ill with a serious infection due to *Pseudomonas* or *Acinetobacter*. The current challenges have often been labeled in fearful terms such as the “antibiotic crisis” or the “end of the antibiotic era.”

Recently, an emerging candida species, *C. auris*, has earned superbug status, preying on the sickest patients in hospitals. In a November 2015 report, the CDC said it had detected 13 cases since May 2013. In an earlier outbreak the crude mortality was 58 percent of all infected and 68 percent for those with *Candida* bloodstream infections. Diabetes, recent surgery and central venous catheters are most commonly noted risk associations. The yeast is uniformly resistant to fluconazole. One-third of species tested were also resistant to voriconazole, and resistance has also been described for amphotericin B and caspofungin.

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