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Antibiotic and antiseptic resistance: impact on public health

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Antibiotic resistance was recognized soon after the discovery of antibiotics. During the past 50 years the rise in the frequency of resistance, particularly to multiple drugs, has thwarted treatment of patients in the hospital and the community.[1] Bacteria have continued to respond to human attempts to keep them in check. Methicillin was developed and introduced in the 1960s to circumvent inactivation by the common beta-lactamases that caused penicillin resistance. But methicillin-resistant *Staphylococcus aureus* (MRSA) emerged soon after to combat the beta-lactamase-resistant penicillin analog. More recently vancomycin, the antibiotic of choice for treating multidrug-resistant MRSA, has confronted resistant strains in Japan, the United States and Europe.[2] In England MRSA with heterogeneous resistance to vancomycin has been implicated in the treatment failure of 12 out of 14 patients who underwent orthopedic procedures.[3] Heterogeneous resistance to vancomycin implies that only one in a million progeny of the isolates taken from the patients showed intermediate resistance to vancomycin. Some hospital-acquired vancomycin-resistant enterococcal infections are resistant to all current antibiotics.[4] Other problem strains in the hospital include *Klebsiella* and *Enterobacter* and the opportunistic pathogens *Pseudomonas aeruginosa* and *Acinetobacter baumanii*.

In the community a number of different bacteria that cause relatively common diseases have acquired multidrug resistance. These include strains of *Streptococcus pneumoniae*, which cause otitis media, pneumonia and meningitis. This finding is at least partially linked to misuse and overuse of antibiotics for viral-caused ear infections and upper respiratory symptoms. Although two-thirds of all ear infections are bacterial,[5] 85% will resolve with no antibiotic treatment, yet antibiotics are prescribed for almost every child in the United States.[5] Because of widespread resistance, penicillin can no longer be relied on for treating meningitis caused by *S. pneumoniae*. A combination of drugs, i.e. vancomycin plus a cephalosporin, is recommended for the treatment of this community-acquired infection.[6]

Neisseria gonorrhoeae, previously easily treated with a single penicillin injection, has become so frequently resistant to this antibiotic that alternative drugs have been required. Today resistance to tetracyclines and fluoroquinolones has developed in *N. gonorrhoeae* as well, making a third generation cephalosporin the preferred antibiotic therapy. There are no other single dose drug therapy options remaining to treat this community-acquired disease when cephalosporin resistance emerges. The history of *Neisseria* treatment illustrates an important phenomenon of drug resistance. With time there is often an accumulation of resistance to many drugs in the same organism.[1]

Another example is *Streptococcus pyogenes*, the "flesh-eating bacteria" and the cause of strep throat. Historically this organism remained susceptible to all drugs. Its present day resistance to erythromycin and tetracycline reveals that with continued antibiotic use over time, resistance, even multidrug resistance, will emerge.[7] Likewise *Escherichia coli* and other enteric organisms such as *Salmonella* have also acquired multidrug resistance. Some *Salmonella* strains, like *Salmonella typhimurium* DT104, are resistant to five different antibiotics; therefore fluoroquinolones have become the only remaining effective treatment. When quinolones were first introduced, it was thought that bacteria resistant to quinolones would not become a problem because of the high susceptibility of the bacterium and the seemingly low frequency of resistance. This hope has been dispelled. Resistance to fluoroquinolones has appeared and patients are failing treatment.[8] This resistance requires at least two chromosomal mutations to be clinically relevant. Today in certain parts of Asia, 50 to 60% of *E. coli* may be fluoroquinolone-resistant.

Simplistically antibiotic resistance is a natural expression of evolution and bacterial genetics. The more a particular antibiotic is used, the greater is the chance of developing a resistance problem. Over time multidrug resistance can be acquired through stepwise accumulation of mutations or by acquisition of resistance genes from other bacteria.[9] DNA plasmids containing drug resistance genes can be exchanged among bacteria by a process of cell-to-cell association called conju-

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gation. In this way, multidrug resistance can be spread among different bacterial types. Transposons, which are smaller pieces of DNA, can transpose (move) between chromosomes and plasmids in a cell. Through a process called transformation or through bacterial viruses called bacteriophages, bacteria can pick up foreign DNA bearing new genes, including resistance genes. These genetic exchanges constantly occur among bacteria and are usually harmless, but the exchange of resistance genes, aided by antibiotic selection, has fostered widespread resistance among bacteria of vastly different genera.[1]

ANTIBIOTIC RESISTANCE AND ANTIBACTERIAL USE

The number of days a patient spends in the hospital has dropped significantly in the past decade, from perhaps 7 to 10 days to 2 to 4 days. Doctors send their patients home to save on costs, and removal from the hospital environment also protects patients from nosocomial infections. Many patients go home while still receiving antibiotics. In the past our homes were largely free of antibacterial-containing products. Today, however, antibacterial chemicals are found widely in homes, in soaps, disinfectants, clothes and plastic products. Many contain the compound triclosan that has traditionally been used in clinics and hospitals for 30 years. It has been regarded as a nonspecific biocide. However, recently in our laboratory, triclosan-resistant *E. coli* were isolated spontaneously at a rate of 1 in a million to 10 million progeny.[10] Strains emerged with low, medium and high level resistance. All the mutants were mutated in one gene (*fabI*), which codes for an important enzyme in fatty acid biosynthesis. Thus triclosan was shown to inhibit fatty acid biosynthesis[10] by inhibiting the enzyme enoyl reductase. The *fabI* mutation also produces resistance to other, structurally unrelated antimicrobials with the same target, such as diazoborine and isoniazid. We found that triclosan-resistant mutants of *Mycobacterium smegmatis* (a species closely related to *Mycobacterium tuberculosis*) were resistant to isoniazid as well.[11]

Multiple antibiotic resistant mutants can arise through the overproduction of drug efflux pumps, which are controlled by regulatory loci such as the chromosomal *mar* locus among the Enterobacteriaceae.[12] The *mar* regulatory locus affects the expression of many other chromosomal genes and confers resistance to antibiotics and stress responses. Overexpression of the *mar* locus leads to increased expression of the AcrAB efflux pump, which mediates resistance to antibiotics. The efflux apparatus consists of an intermembrane component linked by an accessory protein in the periplasm with an outer cell membrane protein. Mutations that up-regulate the pump cause antibiotics to be pumped out efficiently, so that they do not regain entry into the bacterial cell. Many of these multidrug resistance efflux pumps are relatively nonspecific, allowing the bacterium to recognize and pump out many different antibiotics and other toxic substances, including antibacterial compounds.[13]

Among a group of 15 "normally susceptible" clinical *E. coli* isolates, we found one that was resistant to triclosan.[14] Examination of this isolate demonstrated that the bacteria had a mutation in the *mar* locus. Twenty-nine antibiotic-resistant *E. coli* isolates were then analyzed. Three of these were resistant to triclosan, of which two were *mar* mutants. Thus, *mar*-mediated overexpression of the AcrAB efflux pump produced cross-resistance to antibiotics and antibacterials.[14] Triclosan could have selected for antibiotic resistance, or antibiotics could have selected for triclosan resistance. Thus there is an interaction between antibiotic and surface antibacterial resistance via a target gene mutation or increased expression of a multidrug efflux pump.

Widespread surface antimicrobial use may help to explain the unexpected appearance of a different kind of MRSA in the community. MRSA resistant not only to methicillin but also to many other drugs is usually associated with hospital infections but has also been found in drug abusers and in contacts of patients returning to the community. However, four children (in separate geographic locations) whose resistance was limited to the beta-lactam antibiotics[15] died with MRSA. Unlike the hospital MRSA these strains were still susceptible to many different antibiotics.

How did MRSA become established in the community? Little if any methicillin is being used there. One possibility may be that the overzealous use of "antibacterial"-containing substances in the home, to keep our environment "super clean" provides a selective advantage for less dominant organisms, such as MRSA. As the environmental flora changes under antibacterial use, small numbers of other bacteria, e.g. MRSA, may increase, making them more dominant members of the microbial ecology. Recently published *in vitro* laboratory studies bear on this point. The investigators showed that selecting MRSA with decreased susceptibility to the antimicrobial quaternary ammonium compounds led to cross-resistance of a wide variety of beta-lactam antibiotics but not to other antibiotics.[16] This finding strikingly mirrors the phenotype of MRSA now emerging in the community.[15]

The inadvertent selection of mutants resistant to surface antibacterials used in the home can potentially propagate strains resistant also to antibiotics. There is a link between antibiotic and antibacterial resistance. Overuse or improper usage of antibacterials in the home can potentially enhance the selection process for resistance to these products and to antibiotics.

SUMMARY

More and more we are moving patients from hospitals to homes for continued treatment. Vancomycin and triclosan were used for 30 years before any resistance emerged, because their applications were strictly limited. Today, after greatly increased use, resistance to both antibiotics and antibacterials has appeared. Of importance there are genetic links between resistance to antibiotics and to antibacterials. Health professionals and the public need to be educated about the rational use of drugs that affect the microbial world. The Alliance for the Prudent Use of Antibiotics, an international organization established in 1981 with members in more than 100 countries, has adopted education as its prime mission. Via its web site (www.apua.org) and linked information on reservoirs of antibiotic resistance (ROAR) among nonpathogenic bacteria, it reaches both providers and consumers. The message is simple: bacteria are needed for our survival. The vast majority of bacteria perform important functions that are crucial for our lives. Prudent use of both antibiotics and antibacterials must be championed to achieve and maintain the balanced microbial environment in which we have entered and evolved.

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