Chapter 3
Resistance

The Basics

Bacteria resistant to antibiotics existed long before antibiotics were even a twinkle in the eye of the pharmaceutical industry. Most of the antibiotics on the market today, including penicillin, erythromycin, tetracycline and all their relatives started as byproducts of the metabolism of microorganisms in soil, on plants or in our oceans. Antibiotics are part of the never-ending competition among species for survival or dominance within an ecological niche.

To start with, if you are a fungus producing a toxic metabolite, say penicillin, you better be able to resist your own toxin. Microorganisms have evolved an entire bag of tricks to evade the toxic effects of their own antibiotics and those of other competitor organisms. Each toxin produced has some particular target. For example, penicillin targets the enzymes that make the cell wall of bacteria. Fungi, including the mold that produces penicillin, *Penicillium*, do not have the same type of cell wall and therefore do not even have the enzymes targeted by penicillin. Other tricks to avoid these poisons include pumps which literally pump the toxin back out of the bacterial cell faster than it diffuses in; or enzymes that either degrade the antibiotic or modify it in a way that it can no longer work; or even to have an alternative pathway for making your cell wall such that your pathway cannot be blocked by antibiotics that target enzymes in the normal pathway. Some organisms modify the target of the antibiotic such that the antibiotic can no longer bind. It is important to understand that all of these bacterial tools to deal with antibiotics were present for eons before man started using antibiotics to cure disease.

Enter the age of antibiotics. You are a bacterium. You can divide and reproduce every 20–30 min. You can easily exchange genetic material with other bacteria. You are invincible! This principle is the basis for my belief in the "you use it you lose it" theory of antibiotics. If you introduce a new antibiotic into use in people or animals or for crops or any combination of these, you immediately apply pressure on the bacterial populations. All living things live in some kind of relationship with bacteria. Humans (and animals and plants) have enormous populations of bacteria living on their surface and in their guts. These bacteria serve a useful purpose – they crowd out the bad actors, they help digest some foods, etc. As soon as you add

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large quantities of an antibiotic to the mix, everything is turned upside down. We kill the bad guys (we hope) but we also kill a lot of the good guys. And everybody is trying to survive. If, in that population of bacteria, there are just a tiny number that are resistant to the antibiotic in question (and there frequently are), when you apply the antibiotic those few will survive. With time, they will multiply and may come to dominate the niche during antibiotic therapy and even afterwards in some cases. These resistant bacteria may be able to share the mutation or the gene causing resistance with other bacteria. They may have acquired some gene coding for resistance to the antibiotic in question eons ago, but this may be the first time it has actually been needed for a major assault. This foreign gene may also be capable of transfer to other bacteria. How fast all this happens and how quickly it spreads is very variable. So some antibiotics were on the market for decades before we discovered significant resistance to them while resistance plagued others before they were ever manufactured in large scale.

The other point I am making is that resistance may be more likely to arise out of collateral damage to the friendly bacteria we live with all the time rather than through our efforts to knock off the particular organism causing the infection we are treating. The friendlies can mix with the pathogens on our skin or in our gut and transfer their resistance genes. An interesting possible example of this is *Staphylococcus sciuri*, a species of staph that is essentially not pathogenic (rarely causes disease) and is found more often colonizing the skin of animals. It seems to be the origin of the gene that is responsible for methicillin resistance in *Staphylococcus aureus* (MRSA). *S. sciuri* with this gene might have been selected when penicillin began to be used in veterinary medicine back in the late 1940s. This is now coming back to haunt us with a vengeance with the highly resistant and virulent MRSA strains we currently face in our hospitals and communities.

Antibiotics for Animals and Crops Lead to Resistance for People

And speaking of collateral damage, at least half of all the antibiotic use in the United States is for animals and crops. This has been a controversial topic for over 30 years. A 1998 report from the prestigious Institute of Medicine of the National Academy of Sciences noted that about 4 million pounds of antibiotics were used to treat sick farm animals and another 16 million pounds were used as growth promotants (low doses of antibiotics usually included in animal feed) for animals every year. Nobody knows to this day why low doses of antibiotics make animals grow faster, but its true. They grow about 4–8% faster than animals not fed on low dose antibiotics. Of course, you then have to add the additional 300,000 pounds of antibiotic pesticides, mostly tetracycline and streptomycin, which are used every year on crops. This total is roughly equal to the total antibiotic use for the treatment of people each year.

E. coli is a common bacteria colonizing our intestinal tract, but also causing urinary tract infections. It can cause severe sepsis and meningitis (inflammation of

the membrane surrounding the brain and spinal cord) in newborns, especially the premature infants. It also is a common cause of diarrhea, especially that disease of travelers we call *la tourista*. More rarely, certain strains cause a very severe diarrhea sometimes associated with kidney failure – the famous *E. coli* OH157 of undercooked burger fame. It tends to remain rather susceptible to antibiotics globally. But, about 60% of isolates causing infections in patients in the US are resistant to tetracycline. Of course, tetracycline is still used in humans as well as animals and for crops. But surprisingly, around 20% of strains were also resistant to streptomycin even though this drug is hardly ever used for treatment of people anymore. There is good reason to believe that part of this is due to streptomycin use for crops.

A more dramatic example comes from an organism called *Enterococcus*. Starting in 1989, US hospitals have experienced an outbreak of *Enterococcus* resistant to what was our last line antibiotic at the time, vancomycin (they were frequently already resistant to everything else). About 50% of US hospital strains are now resistant to all but our latest two last line antibiotics, daptomycin and linezolid. During the late 1980s and early 1990s, there was no daptomycin and no linezolid for infected patients. There was nothing that worked. It turns out that the resistance seems to have been derived from animals in Europe where they were fed low concentrations of an antibiotic called avoparcin to promote growth. Avoparcin is closely related to vancomycin and the vancomycin-resistance genes found in enterococci infecting people are essentially identical to those found in animals fed avoparcin. Although this is one dramatic and threatening example of the transmission of antibiotic resistance from animals to humans, there are lots of others.

Salmonella is a type of bacteria that causes diarrheal disease in humans. It is frequently carried by animals but can cause diarrheal disease in them as well. Many of the recent food-borne outbreaks in the US that resulted in large recalls (peanut butter for example) were caused by *Salmonella*. *Salmonella typhimurium* DT104 was first isolated from a human stool specimen in England in 1984 and was resistant to the antibiotics commonly used to treat such infections including bactrim and tetracycline. It remained relatively rare until around 1990. In 1993 the strain became epidemic in Europe and in the US. It rapidly acquired resistance to other antibiotics including the quinolones and the modern cephalosporin antibiotics (related to the penicillins). It is clear that this strain can be transmitted back and forth between humans and animals. Animals treated with antibiotics are more likely to harbor the strain. The headline from a local Colorado newspaper below (Fig. 3.1) refers to King Soopers of Denver (a subsidiary of Kroger Foods) who recalled over 466,000 pounds of ground beef (about 1000 cows' worth of meat) for DT104 contamination causing illness in several states. DT104 is now found throughout the world. In one recent outbreak, almost 50% of infected patients were hospitalized and 10% died of their infection. The strongest risk factor for infection with this strain in humans is the recent use of any of the antibiotics to which the strain is resistant. For these multiply resistant strains of *Salmonella*, we have a single, reliable class of antibiotics left in our armamentarium, the carbapenems that includes

Contaminated beef recalled from King Soopers, City Market (reprinted with permission)

Friday, July 24, 2009

About a half-million pounds of King Soopers ground beef is being recalled by King Soopers of Denver for possible Salmonella contamination Colorado Department of Public Health and Environment officials announced Thursday. The ground beef was sold statewide at King Soopers and City Market retail grocery stores. Identified as Salmonella typhimurium DT104, it is a strain resistant to many antibiotics prescribed for treatment which can increase risk of hospitalization, or possible treatment failure in infected individuals. Although the product may be no longer available in stores, state health officials urge consumers who may have purchased the product between May 23 and June 23, at local King Soopers and City Market stores, to check their freezers for any product and discard it or return it to the place of purchase.

Fig. 3.1 Headline article from a local Colorado Newspaper with permission

imipenem (from Chapter 1) among others. You will see that this will be a repeated theme in this chapter.

An underappreciated use of antibiotics occurs in fish farming. Here, it is exceedingly difficult to quantify the antibiotics used, but the quantities, and potentially the human health consequences might be no less important than antibiotic use in

other animals and in crops. A recent publication from Scandinavian scientists highlighted the problem. They noted that one study of ready to eat shrimp (13 brands in four different countries) showed that 42% of the bacteria recovered from the shrimp were antibiotic resistant and that 81% of the bacteria isolated were human pathogens including *E. coli* and staph. Clearly, antibiotic-resistant organisms from farmed fish pose a risk of worldwide spread of antibiotic resistant organisms and their resistance genes.

Antibiotic resistance in bacteria is often carried on segments of DNA that can jump from one organism to another. One recent report documented that these DNA segments carrying multiple antibiotic-resistance genes were identical in *E. coli* from humans and animals and in *Salmonella* from humans and animals.

Our environment in general is becoming polluted with antibiotics. Runoff from farms and from our own sewers (yes, antibiotics are excreted in urine and in feces) exposes more and more of the worlds bacteria to low concentrations of antibiotics. The world, in the words of Julian Davies, one of the original and most important researchers in antibiotic resistance, is a dilute solution of antibiotics. This will continue to select for antibiotic resistance among environmental organisms. A *Pseudomonas* with a new gene causing resistance to our last line antibiotics for these bacteria and associated with multiple other antibiotic resistance genes was recently fished out of the Seine River in Paris. In a recent study of *E. coli* from recreational beaches and private drinking water in Canada, of a total of about 15,000 isolates, 142 were highly resistant to multiple antibiotics. This represents a small percentage but shows the risk we are taking.

Europe has already banned the use of any antibiotic related to those used in human health for non-therapeutic use in animals. In the US, congress is once again considering a similar ban (HR 1549). Given that this discussion has been ongoing for over 30 years, one wonders what everyone has been thinking. Of course the bill is strongly opposed by the beef and poultry industry.

The issue of antibiotic use animals as treatment or prevention of infection is also controversial. For example, one of the antibiotics used in this way is a fluoroquinolone closely related to antibiotics used in people. It is clear that resistance to the human antibiotics like ciprofloxacin can be selected by therapy in animals and that these resistant strains or their resistance genes can be transmitted to people. The FDA has continued to allow therapeutic use of these antibiotics in animals, and has been doing so for almost 15 years while monitoring data. As a first step, the World Health Organization has recently ranked antibiotics according to their importance in human health. Their top priorities are the fluoroquinolones, the macrolides (like erythromycin and azithromycin) and the modern cephalosporins. The idea would be to identify antibiotics that could be used in animals that would be so unrealated to those used in human health that resistance to human antibiotics would not be selected by the veterinary antibiotics. This may be an unrealizable pipe dream given the difficulty we have in discovering new human antibiotics.

In Our Hospitals, Things Are Getting Critical

The chart from the Centers for Disease Control (Fig. 3.2) shows the increase in multiply resistant staph (MRSA), enterococci (VRE) and *Pseudomonas aeruginosa* (FQRP) over the last 30 years in US hospital intensive care units. The ICU is the last place we want to see very resistant pathogens, and yet this is where they seem to be the most frequent.

Table 3.1 below shows the latest data from the Centers for Disease Control on frequency of resistance of these and other pathogens to key antibiotics. The data specifically represent ICU infections that were associated with devices such as intravenous catheters, breathing tubes and urinary catheters.

In Europe, the situation is not much different. The chart below (Fig. 3.3) shows the state of resistance in key pathogens isolated from bloodstream infections in Europe. The rates of MRSA infection are not very different from those in the US – hovering around 30%. About 20% of European bloodstream isolates of *Pseudomonas aeruginosa* are resistant to our last line antibiotic class, the carbapenems.

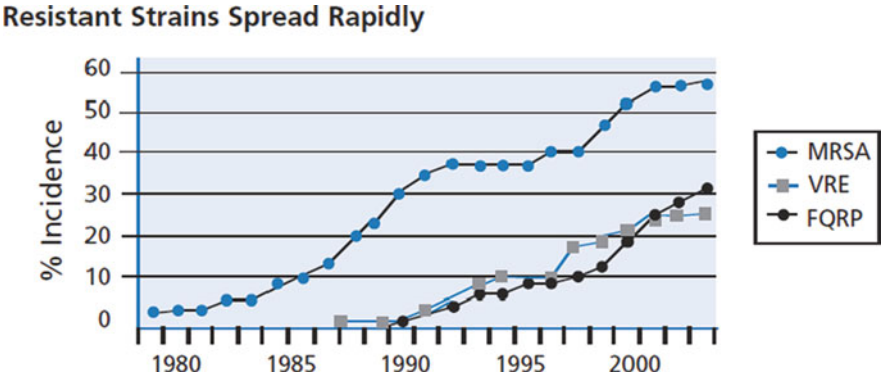

Fig. 3.2 Resistance rates in US intensive care units over time. MRSA – methicillin-resistant *Staphylococcus aureus*. VRE – Vanomycin-resistant enterococcus. FQRP – Fluoroquinolone (ciprofloxacin) resistant *Pseudomonas aeruginosa*. From the CDC and the Infectious Diseases Society of America with permission

Table 3.1 Pathogens causing device-associated infections in US hospital ICUs January 2007 to October 2007

Pathogen	%
MRSA	56
Vancomycin resistant *E. faecalis*	7
Vancomycin resistant *E. faecium*	80
Carbapenem-resistant *Pseudomonas aeruginosa*	25
Klebsiella pneumoniae resistant to new cephalosporins	25
Carbapenem-resistant *Acinetobacter baumanii*	35

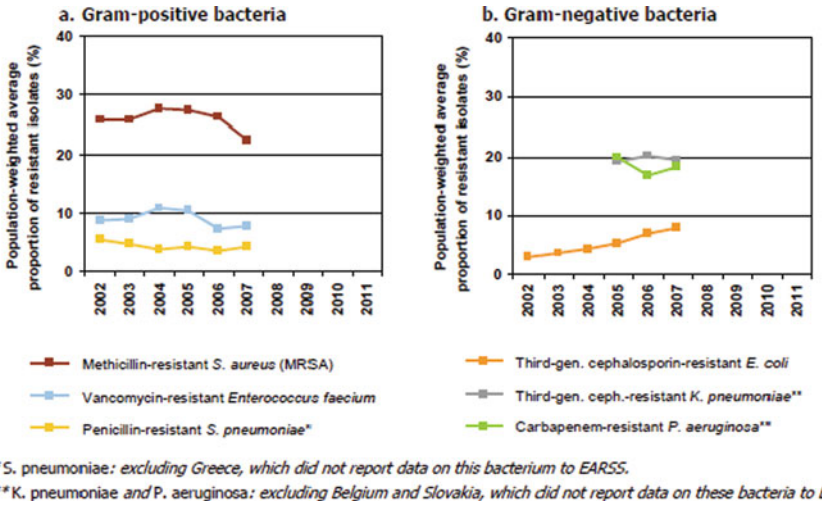

Fig. 3.3 Population-weighted, average proportion of resistant isolates among blood isolates of bacteria frequently responsible for bloodstream infections, EU Member States, Iceland and Norway, 2002–2007. Taken from The Bacterial Challenge, a Time to React, published by the European Centre for Disease Prevention and Control and the European Medicines Agency

For the MRSA and the vancomycin-resistant enterococci, we now have two antibiotics that will work. One is only available intravenously, not orally, and does not have regulatory approval specifically for treatment of enterococcal infections. Resistance to both has been reported.

The situation in Gram negative bacteria is becoming even more alarming. In years past, we had a wide choice of antibiotics active against these bacteria. The sulfa drugs and tetracycline worked. Ampicillin or the combination of amoxicillin (similar to ampicillin) plus an inhibitor of the enzyme that destroys ampicillin, B-lactamase, worked (Augmentin). Most of the cephalosporins (similar to ampicillin but with activity against a wider array of bacteria) were also effective. Hospitals had the luxury of deciding which of the many effective drugs they would put on their formularies. In many parts of the world, including the US, those days are long gone.

In many hospitals and chronic care facilities today, resistance has gotten to the point where only one (essentially) class of antibiotics is left for physicians and patients, the carbapenems. For many physicians and patients, our antibiotic of last resort has become our drug of first choice. Given the "you use it you lose it" rule of antibiotics, you can guess what is happening now. These Gram negative pathogens, especially *Klebsiella* have acquired a gene for a new enzyme (B-lactamase) that can destroy the carbapenems. Its called KPC for *Klebsiella pneumoniae* carbapenemase. The first one of these was isolated from a patient in North Carolina in 1996. The new enzyme destroys the penicillins like ampicillin, even our most modern cephalosporins, and our last line drugs, the carbapenems. KPC is not inhbited by

currently marketed B-lactamase inhibitors – so those combinations like Augmentin and others are not effective. In addition, these bacteria are frequently resistant to multiple other antibiotics, even the quinolones like ciprofloxacin or levofloxacin. To treat infections by these pan-resistant strains, physicians are going back to our old friend (not), colisitin.

KPC *Klebsiella* are now spread throughout the world. We don't have good survey data for many geographic locales. (I can't understand why this is so). In New York City, about 30% of hospital *Klebseilla* carry KPC. The strains are also widespread in urban hospitals of Pennsylvania and New Jersey. Israel, Greece and China also have suffered significant epidemics of infection with these strains.

As I noted above, our antibiotic class of last resort, the carbapenems, has now become our antibiotic of first choice for many Gram negative infections. This is not a good sign. Unfortunately, about 25% of US ICU isolates of *Pseudomonas* and 35% of *Acinetobacter* are also resistant to carbapenems. In many of these cases, we are again back to colistin that I remember from my days of training in the 1970s (see Chapter 1). Because colisitin was developed and marketed so long ago, we think it may work, but we don't know how well and we know it is toxic but we don't know how toxic.

Acinetobacter has become a big problem in the military. Our soldiers wounded in Iraq and Afghanistan are being transferred back to the military hospital at Landstuhl in Germany or Walter Reed here in the US with multi-resistant *Acinetobacter* infections. One outbreak of *Acinetobacter* infection involved 70 soldiers and six medical evacuation centers and military hospitals. Ten percent of the strains were resistant to carbapenems, our last line of defense against these organisms. A separate study of *Acinetobacter* from returning soldiers showed a 36% resistance rate to the carbapenems. For most of these strains, the therapeutic choice is very limited if one exists at all. Crude mortality rates from *Acinetobacter* infections vary from 16 to 43% overall and they tend to increase when the *Acinetobacter* are resistant to multiple antibiotics.

The Infectious Diseases Society of America, an organization of physicians specializing in the treatment of infectious diseases, has developed a priority list of bacteria for which we desperately need new antibiotics and often, where we also need more information on the antibiotics we already have. Their acronym for these bacteria is ESKAPE. The list below is taken almost directly from the Society's latest publication on this topic.

E: *E. faecium* (VRE) has consistently identified as the third most frequent cause of nosocomial bloodstream infection in the United States. Vancomycin resistance likewise continues to increase, with a rate of ~60% among *E. faecium* isolates.

S: *S. aureus* (MRSA). Despite the addition of several new agents to treat MRSA infection, clinicians are routinely faced with treatment challenges involving patients with invasive disease. Although criteria for treating skin and skin-structure infection due to community associated MRSA are evolving, the need is great for oral agents for step-down therapy for the group of patients who require initial parenteral therapy. Novel classes are clearly needed for MRSA, because current drug classes exhibit treatment-limiting toxicities and emerging resistance.

K: ESBL-producing *E. coli* and *Klebsiella* species. ESBL producing strains are those that produce enzymes that inactivate most penicillin and cephalosporin antibiotics before they can kill the bacteria. Infection due to ESBL-producing *E. coli* and *Klebsiella* species continue to increase in frequency and severity. Despite this growing, serious problem, the molecules in late stage development represent only incremental advances over existing carbapenems.

More K: *K. pneumoniae* Carbapenem-Hydrolyzing Enzymes. Carbapenem-resistant Enterobacteriaceae are increasingly recognized as the cause of sporadic and outbreak infections in the United States and Europe. These organisms cause severe infections among residents of long-term-care facilities and are not easily detected in the clinical microbiology laboratory. Little is known with regard to optimal antimicrobial therapy, and few drugs demonstrate activity. Tigecycline (a relative of tetracycline active against many resistant bacteria) and the polymyxins, including colistin have been used in individual cases with variable success. There are currently no antibacterials in advanced development for these resistant pathogens.

A: *A. baumannii.* The incidence of infection due to multiply resistant Acinetobacter species continues to increase globally. Unfortunately, as in 2006, we cannot identify candidate compounds in late stage development for treatment of resistant Acinetobacter infection; this pathogen is emblematic of the mismatch between unmet medical needs and the current antimicrobial research and development pipeline.

P: *P. aeruginosa.* Rates of infection due to resistant *P. aeruginosa* continue to increase in the United States and globally, as does resistance to both the quinolones and carbapenems. Recent reports also document resistance to the polymyxins like colistin. To date, no drugs in clinical development address the issue of carbapenem resistance or offer a less toxic alternative to the polymyxins.

E: Enterobacter Species. Enterobacter species cause an increasing number of health care–associated infections and are increasingly resistant to multiple antibacterials. Other than colistin and perhaps tigecycline, few antibacterials are active against these resistant organisms, and we found no drug in late stage development for these pathogens.

Drs. Elemam, Rahimian, and Mandell of St. Vincent's Hospital in New York recently expressed their frustration in describing two cases of infection caused by *Klebsiella* resistant to all known antibiotics. They said, "It is a rarity for a physician in the developed world to have a patient die of an overwhelming infection for which there are no therapeutic options. These cases were the first instance in our clinical experience in which we had no effective treatment to offer. Trends in urban hospitals are often the harbinger of the future. We share these cases to highlight some troubling issues that soon may be relevant to increasing numbers of physicians and patients across the United States." For the ESKAPE organisms, we are going back to a pre-antibiotic era.

Antibiotic Resistance Plus Toxin Production Equals Death

The US is now experiencing a major epidemic of infections caused by a gastrointestinal pathogen called *Clostridium difficile*. This organism produces toxins that cause inflammation and fluid secretion in the lower GI tract. The disease produced ranges from mild diarrhea to severe life threatening disease. The older you are, the

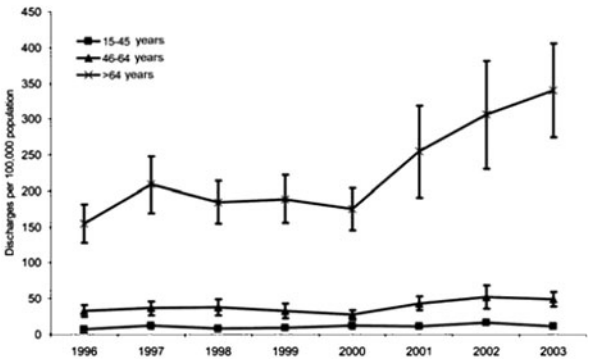

Fig. 3.4 Rates of US short-stay hospital discharges with *Clostridium difficile* listed as any diagnosis, by age. Isobars represent 95% confidence intervals. From McDonald et al., EID 2006. 12: 409

more likely you are to have severe disease. *C. diff*, as the pathogen is known in the jargon of infectious diseases specialists, is normally inhibited from growing by the normal gut flora. It most frequently causes disease when the normal gut flora is perturbed by antibiotic use. It survives because it is resistant to most antibiotics.

These data (Fig. 3.4) from the CDC show that the rates of *C. diff* diarrhea have increased about 100% between 1996 and 2003 and that virtually all of this increase occurred in patients older than 64 years of age. We find the same picture when we look at deaths from *C. diff*. The death rate has climbed tremendously over the same time period and it is mainly coming from the older population. In 1993, *C. diff* was associated with an 8% chance of death while in 2003, the death rate was between 9.5 and 10%. Most of this mortality was among those over 64 years of age where the death rate in recent years ranges from 30 to 50%. It is estimated that the cost for *C. diff* alone in the US is over $1 billion per year and climbing rapidly.

Of course, the CDC is giving us only a picture of what is happening in acute care hospitals. There is also disease occurring in long-term care facilities and in our communities.

Why have we had this sudden increase in cases and in severity of *C. diff* disease? Part of the explanation is that much of this increase is related to one or two strains now spreading worldwide that seem to be better able to disseminate and are more virulent. This seems also to be a disease of antibiotic resistance coupled with the other normal effect of antibiotics – a perturbation in the normal flora of the gut.

All of these problems are interrelated. For example, the treatment of choice for serious *C. diff* disease is vancomycin administered orally. Vancomycin is not absorbed from the gut – so its concentrations there are very high. These high vancomycin concentrations may tend to select for enterococci, a normal gut inhabitant, resistant to vancomycin. Such strains are often multiply antibiotic resistant and can also cause infection.

Some believe that with good hygiene, handwashing, meticulous cleaning, somehow all these infections in hospitals will disappear or at least those caused by resistant pathogens will somehow diminish. While we might be able to reduce the incidence of these infections in hospitals, we will never be entirely rid of them. For example, even in the best hospitals under the best of circumstances, the highest rates of handwashing between patients are only around 70–80% with most hospitals averaging around 30–50%. For many reasons, perfection is unlikely to be achieved. Also, there is no real evidence that many of the infections that occur in hospitals are actually preventable either by good hygiene or by improved environmental cleaning procedures. Therefore, although it is easy to blame hospitals and their staffs for infections that are acquired there, no matter how good our infection control procedures become in the hospital, we will always need to have new antibiotics active against resistant strains. The corollary to this is that punishing hospitals for hospital-acquired infection financially, as currently proposed for medicare, will have little impact on true infection rates. All it may do is encourage hospitals to hide the truth.

The Infectious Diseases Society is worried. They have even formed a Task Force to deal with the conundrum of rapidly growing antibiotic resistance and the lack of new products available to treat these infections. We will discuss this in more detail in a later chapter.

Our Communities are Not Spared

We all agree that hospitals are to be avoided if possible. Are we safe from antibiotic resistance in the community? Most of the antibiotics that we use every year for human health are used in our communities. The principle of "you use it, you lose it" therefore would predict that our communities would not be spared either.

Let's look at a common cause of urinary tract infection (UTI) in our communities, *E. coli*. This is a normal inhabitant of our intestinal tract that occasionally gets somewhere it shouldn't be. If it's equipped with the right stuff (virulence factors), it can cause disease. Antibiotics that have been commonly used to treat UTI include ampicillin, bactrim, and ciprofloxacin. Table 3.2 below shows resistance rates to those antibiotics.

The isolates from the US tended to be more resistant than those from Canada. The resistance to ciprofloxacin, a quinolone, is increasing with time, especially among

Table 3.2 Antibiotic Resistance in outpatient urinary isolates

North American UTI Collaborative Alliance 2005	
E. coli	% Resistant
Ampicillin	38
Bactrim	21
Cipro	5.5

urinary tract isolates. Most clinicians believe that these resistance rates would preclude routine therapy with ampicillin and bactrim. While ciprofloxacin remains a viable option for therapy in the US, resistance is increasing and there are occasional isolates where even ciprofloxacin would not work.

Essentially all the antibiotics used for UTI in communities are under threat with the possible exception of nitrofurantoin. Nitrofurantoin is an old antibiotic and we still do not have a good understanding of how it works. Resistance remains rare. The problem with nitrofurantoin is that, although it works well against *E. coli*, it does not work reliably against many of the other bacteria that cause UTI. Nitrofurantoin may also be more toxic than the other drugs. For these reasons, its use diminished with the availability of ampicillin, bactrim and the quinolones. Now that *E. coli* is becoming resistant to these drugs, we still have nitrofurantoin in our back pocket. Unfortunately, using this drug would require physicians to obtain a sample of urine for culture to be sure that the bacterial cause is in fact *E. coli* or another susceptible organism. Physicians don't often do that anymore.

These data are all consistent with our hypothesis – antibiotic use begets resistance. Animal use of fluoroquinolones probably does not help.

Strains of staph resistant to our most powerful antibiotics have now also invaded our communities. *Staphylococcus aureus* has an interesting history. In the pre-antibiotic era, severe infections with staph like pneumonia and bloodstream infections were almost invariably fatal. When the sulfonamides and later penicillin came along, we were suddenly able to cure most of even the most severe infections. In the case of penicillin in particular, though, resistance was recognized even before the antibiotic was introduced for military use. As I mentioned in a previous chapter, penicillin-resistant staph started out causing infections in hospitals. With the pressure of widespread penicillin use and the easy transmission of staph from hospital patients and employees to family and friends in the community, penicillin resistance quickly spread. By the 1970s, most strains of staph were penicillin resistant whether or not they were causing infections in the hospital or in our communities. Luckily, right about this time, several antibiotics appeared on the market that worked against the penicillin resistant strains. They included a new penicillin derivative called methicillin, the cephalosporins which are related to the penicillins and a drug called vancomycin. Shortly after the introduction of methicillin, the first strains of methicillin resistant staphylococci, called MRSA for methicillin-resistant *Staphylococcus aureus*, were described in Great Britain. One of the problems with MRSA is that they are frequently resistant to most antibiotics used to treat staph infections including the cephalosporins, tetracyclines, etc. They remain susceptible to vancomycin. Vancomycin is an antibiotic that can only be administered intravenously.

In the 1980s, the US began to experience an epidemic of MRSA infections in hospitals. Figure 3.2 shows that in the early 1980s, only about 10% of ICU isolates of staph were MRSA. Today, that number is over 50% and the MRSA is not just limited to the ICU. MRSA is found in all areas of our hospitals. Vancomycin has become the drug of choice for the treatment of MRSA infections. Linezolid was introduced to the market in 2000 and in 2003 daptomycin was marketed. Both are also active against MRSA but only linezolid can be given as a pill.

Just as was seen for penicillin resistance in staph, MRSA have now spread to our communities. In a recent CDC study examining staph isolates from emergency rooms across the US, over 60% of strains were MRSA. Most of the isolates in the US actually represent a single strain called USA 300. It is not yet clear what it is about this strain that allows it to carry resistance and cause infection in the community. The story though is again familiar. When penicillin resistance spread to the community, it too was frequently carried by a single strain of staph that seemed well adapted to spread and which was very virulent. That particular strain disappeared after about 10 years for reasons we still don't understand. The penicillin resistance in the community remains, however, probably now carried by multiple different strains. Perhaps we will see the same thing with USA300.

There is one interesting difference between hospital and community MRSA. Although hospital strains of MRSA tend to be resistant to almost all other antibiotics, strains originating in the community tend to remain susceptible to bactrim, tetracycline, clindamycin and certain other antibiotics. None of these antibiotics has been carefully studied for the treatment of staph infections. But because they are inexepensive generics and can be taken orally, physicians often prescribe them for community acquired MRSA infections. There are ongoing trials of these cheaper generic agents in the treatment of MRSA infections, but we don't yet have the results.

Another interesting aspect of the community acquired MRSA is that they are starting to show up in hospitals. Many of the isolates appearing in hospital microbiology laboratories are not the usually multiply resistant variety, but the more susceptible community strains of MRSA. Whether this will allow us to modify the way we treat patients or not remains to be seen.

Resistance – Summing Up

If we can manage to bring new antibiotics to the marketplace, should we anticipate resistance to them as well? The answer is a qualified yes. Although bacteria eventually seem to be able to become resistant to whatever antibiotic we use, the time it takes for this to occur varies but can be very long. For example, resistance to the penicillins was discovered before the drug was ever marketed. Vancomycin, on the other hand, was marketed in 1956 and resistance was not seen until 1986. Another issue is that resistance may arise in one species but not in another. Again, vancomycin resistance is extremely common in *Enterococcus faecium*, but is much less common in its very close cousin *Enterococcus faecalis* even though both organisms live side by side in the gut and can easily exchange genes. We don't know why. In fact, since the discovery of vancomycin resistance in enterococci in 1986, we have all been waiting for its appearance in staph. Scientists have carried out experiments showing that it is easy to transfer the resistance from enterococci to staph in the laboratory, even on the skin of animals. Although there have been a few cases of human infection with vancomycin-resistant staph, these remain exceedingly rare.

Again, we don't know exactly why. When a new antibiotic is marketed, it is often very difficult to predict how long it might take for resistance to appear. If only every antibiotic could last as long as vancomycin!

One of the questions that scientists and economists have struggled with over the years is trying to put a specific price tag on resistance. Most studies show that morbidity like length of hospital stay and mortality are increased with antibiotic resistant infections compared to infections in similar patients with susceptible strains to about 1.5–2-fold. One recent study from South Carolina showed that for the authors' hospital, there was a 30% increase in costs for such patients. Of course, these calculations do not take into account years of life lost or quality years lost, which would add enormously to the overall costs to the US. When you consider that 2 million Americans acquire infections in hospitals every year and that anywhere from 30 to 70% involve resistant bacteria, you can see that the costs could quickly skyrocket. Europe, as noted in a later chapter has also tried to tackle this question and they come up with costs in the billions of dollars.

Antibiotic resistance is a societal problem. It derives from the way we use antibiotics, the way we dispose of our garbage and our sewage and our hygienic practices at home, at work, in schools, in long term care facilities and in hospitals. Resistance costs us lives of loved ones, lost productivity and real dollars in terms of the increased care required for these patients. We can only truly address the problem as a society. Even if we improve our approach to antibiotic use and improve our hygienic practices, it is unlikely that we will be able to solve the problem of the continued selection of antibiotic resistance. We just do not have enough information to know how to halt this natural progression entirely. Therefore, as it stands today, antibiotic resistance also requires that we constantly have new, effective antibiotics coming on line in the marketplace so we can treat patients with resistant bacterial infections. No one ever wants to be in the place of Drs. Elemam, Rahimian, and Mandell or the patients they described. Only we as a society can create conditions where we can have such a pipeline of new antibiotics.