The first signs of antibiotic resistance

There has probably been a gene pool in nature for resistance to antibiotic as long as there has been for antibiotic production, for most microbes that are antibiotic producers are resistant to their own antibiotic. In retrospect, it is not surprising that resistance to penicillin in some strains of staphylococci was recognized almost immediately after introduction of the drug in 1946. Likewise, very soon after their introduction in the late 1940s, resistance to streptomycin, chloramphenicol and tetracycline was noted. By 1953, during a *Shigella* outbreak in Japan, a strain of the dysentery bacillus (*Shigella dysenteriae*) was isolated which was multiple drug resistant, exhibiting resistance to chloramphenicol, tetracycline, streptomycin and the sulfonamides. Over the years, and continuing into the present almost every known bacterial pathogen has developed resistance to one or more antibiotics in clinical use.

Evidence also began to accumulate that bacteria could pass genes for drug resistance between strains and even between species. For example, antibiotic-resistance genes of staphylococci are carried on plasmids that can be exchanged with *Bacillus, Streptococcus* and *Enterococcus* providing the means for acquiring additional genes and gene combinations. Some are carried on transposons, segments of DNA that can exist either in the chromosome or in plasmids. In any case, it is clear that genes for antibiotic resistance can be exchanged between strains and species of bacteria by means of the processes of horizontal gene transmission (HGT).

Multiple drug resistant organisms

Multiple drug resistant organisms are resistant to treatment with several, often unrelated, antimicrobial agents as described above in *Shigella*. Some of the most important types of multiple drug resistant organisms that have been encountered include:

- MRSA - methicillin/oxacillin-resistant *Staphylococcus aureus*
- VRE - vancomycin-resistant enterococci
- ESBLs - extended-spectrum beta-lactamases (which are resistant to cephalosporins and monobactams)
- PRSP - penicillin-resistant *Streptococcus pneumoniae*

MRSA and VRE are the most commonly encountered multiple drug resistant organisms in patients residing in non-hospital healthcare facilities, such as nursing homes and other long-term care facilities. PRSP are more common in patients seeking care in outpatient settings such as physicians' offices and clinics, especially in pediatric settings. ESBLs are most often encountered in the hospital (intensive care) setting, but MRSA and VRE also have a significant nosocomial ecology.

**Methicillin-Resistant Staph Aureus.** MRSA refers to "methicillin-resistant *Staphylococcus aureus*," which are strains of the bacterium that are resistant to the action of methicillin, and related beta-lactam antibiotics (e.g. penicillin and cephalosporin). MRSA have evolved resistance not only to beta-lactam antibiotics,
but to several classes of antibiotics. Some MRSA are resistant to all but one or two antibiotics, notably vancomycin-resistant. But there have been several reports of VRSA (Vancomycin-Resistant Staph Aureus) that are troublesome in the ongoing battle against staph infections.

MRSA are often sub-categorized as Hospital-Associated MRSA (HA-MRSA) or Community-Associated MRSA (CA-MRSA), depending upon the circumstances of acquiring disease. Based on current data, these are distinct strains of the bacterial species.

HA-MRSA occurs most frequently among patients who undergo invasive medical procedures or who have weakened immune systems and are being treated in hospitals and healthcare facilities such as nursing homes and dialysis centers. MRSA in healthcare settings commonly causes serious and potentially life threatening infections, such as bloodstream infections, surgical site infections or pneumonia.

In the case of HA-MRSA, patients who already have an MRSA infection or who carry the bacteria on their bodies but do not have symptoms (colonized) are the most common sources of transmission. The main mode of transmission to other patients is through human hands, especially healthcare workers' hands. Hands may become contaminated with MRSA bacteria by contact with infected or colonized patients. If appropriate hand hygiene such as washing with soap and water or using an alcohol-based hand sanitizer is not performed, the bacteria can be spread when the healthcare worker touches other patients.

MRSA infections that occur in otherwise healthy people who have not been recently (within the past year) hospitalized or had a medical procedure (such as dialysis, surgery, catheters) are categorized as community-associated (CA-MRSA) infections. These infections are usually skin infections, such as abscesses, boils, and other pus-filled lesions.

About 75 percent of CA-MRSA infections are localized to skin and soft tissue and usually can be treated effectively. However, CA-MRSA strains display enhanced virulence, spread more rapidly and cause more severe illness than traditional HA-MRSA infections, and can affect vital organs leading to widespread infection (sepsis), toxic shock syndrome and pneumonia. It is not known why some healthy people develop CA-MRSA skin infections that are treatable whereas others infected with the same strain develop severe, fatal infections.

Studies have shown that rates of CA-MRSA infection are growing fast. One study of children in south Texas found that cases of CA-MRSA had a 14-fold increase between 1999 and 2001.

CA-MRSA skin infections have been identified among certain populations that share close quarters or experience more skin-to-skin contact. Examples are team athletes, military recruits, and prisoners. However, more and more CA-MRSA infections are being seen in the general community as well, especially in certain geographic regions.

Also, CA-MRSA are infecting much younger people. In a study of Minnesotans published in The Journal of the American Medical Association, the average age of people with MRSA in a hospital or healthcare facility was 68. But the average age of a person with CA-MRSA was only 23.

More people in the U.S. now die from MRSA infection than from AIDS. Methicillin-
resistant Staphylococcus aureus was responsible for an estimated 94,000 life-threatening infections and 18,650 deaths in 2005, as reported by CDC in the Oct. 17, 2007 issue of The Journal of the American Medical Association. The national estimate is more than double the invasive MRSA prevalence reported five years earlier. That same year, roughly 16,000 people in the U.S. died from AIDS, according to CDC. While most invasive MRSA infections could be traced to a hospital stay or some other health care exposure, about 15% of invasive infections occurred in people with no known health care risk. Two-thirds of the 85% of MRSA infections that could be traced to hospital stays or other health care exposures occurred among people who were no longer hospitalized. People over age 65 were four times more likely than the general population to get an MRSA infection. Incidence rates among blacks were twice that of the general population, and rates were lowest among children over the age of 4 and teens.

**Extended-Spectrum beta-lactamase (ESBL) - producing Gram-negative bacteria** Extended-spectrum beta-lactamases (ESBLs) are plasmid-associated beta lactamases that have recently been found in the *Enterobacteriaceae*. ESBLs are capable of hydrolyzing penicillins, many narrow spectrum cephalosporins, many extended-spectrum cephalosporins, oxyimino-cephalosporins (cefotaxime, ceftazidime), and monobactams (aztreonam). Beta-lactamase inhibitors (e.g. clavulanic acid) generally inhibit ESBL producing strains. ESBL producing isolates are most commonly *Klebsiella ssp*, predominantly *Klebsiella pneumoniae*, and *E. coli*, but they have been found throughout the *Enterobacteriaeeae*.

Because ESBL enzymes are plasmid mediated, the genes encoding these enzymes are easily transferable among different bacteria. Most of these plasmids not only contain DNA encoding ESBL enzymes but also carry genes conferring resistance to several non-ß-Lactam antibiotics. Consequently, most ESBL isolates are resistant to many classes of antibiotics. The most frequent coresistances found in ESBL-producing organisms are aminoglycosides, fluoroquinolones, tetracyclines, chloramphenicol, and sulfamethoxazole-trimethoprim. Treatment of these multiple drug-resistant organisms is a therapeutic challenge.

ESBL producing strains have been isolated from abscesses, blood, catheter tips, lung, peritoneal fluid, sputum, and throat cultures. They apparently have a world-wide distribution. Rates of isolation vary greatly worldwide and within geographic areas and are rapidly changing over time. In the United States, between 1990 to 1993, a survey of the intensive care units of 400 hospitals recorded an increase from 3.6% to 14.4% in ESBL producing strains of *Klebsiella*. In 1994, the CDC reported that 8% of *Klebsiella spp* from a few large centers produced ESBLs. In Europe, as of 1995, ESBLs occurred in 20%-25% of *Klebsiella spp* from patients in ICUs, although they were found in patients up to 30%-40% frequency in France.

Known risk factors for colonization and/or infection with organisms harboring ESBLs include admission to an intensive care unit, recent surgery, instrumentation, prolonged hospital stay and antibiotic exposure, especially to extended-spectrum beta-lactam antibiotics. Use of extended-spectrum antibiotics exerts a selective pressure for emergence of ESBL producing strains. The resistance plasmids can then be transferred to other bacteria, not necessarily of the same species, conferring resistance to them.

The lower GI tract of colonized patients is the main reservoir of these organisms. Gastrointestinal carriage can persist for months. In some cities in the United States, nursing homes may be an important reservoir of ESBL producing strains. Nursing home patients are more likely to be treated empirically with antibiotics, and thus on
admission to a hospital to be more likely to possess an ESBL producing strain. Patient to patient transmission of ESBL producing organisms occurs via the hands of hospital staff. It is known that ESBL producing strains can survive in the hospital environment.

Nosocomial infections in patients occur through the administration of extended spectrum beta-lactam antibiotics or via transmission from other patients via health care workers, who become colonized with resistant strains via exposure to patients or other health care workers. Spread of ESBL producing strains can be minimized by good infection control practices, especially by good hand washing technique.