Germ Warfare: Drug-Resistant Bacteria a Growing Threat

By Barbara Ruben

For decades doctors reveled in the knowledge that they had a growing pharmaceutical arsenal that could conquer a plethora of bacteria. Vancomycin vanquished enterococci, an intestinal bug. Penicillin could halt pneumonia. And methicillin stopped the spread of staphylococci in its tracks. But over the years, these and other bacteria built up their own defenses against the drugs designed to kill them. In a dramatic illustration of Darwin's survival of the fittest theory, while these drugs killed vulnerable strains of germs, the toughest survived and flourished.

Bacteria have evolved a variety of ways to evade antibiotics. Organisms can produce an enzyme that destroys the drug. They can alter their permeability to antibiotics, thus blocking a drug from entering the cell to kill it. Some bacteria even pump antibiotics out of cells as fast the drugs enter. In other cases, bacteria can alter the receptor to which an antibiotic would normally bind on a cell's surface.

Around the world, resistance to a number of drugs has sent physicians and microbiologists scrambling to monitor the problem, which can vary greatly from country to country and even hospital to hospital.

"There are different proportions of the problem, but essentially there is drug resistance everywhere," said Thomas F. O'Brien, director of WHO's Collaborating Center for Surveillance of Antimicrobial Drug Resistance, located at Brigham and Women's Hospital in Boston, Massachusetts. "All [nations] have resistance to methicillin, but not all are seeing vancomycin resistance, for example. The variations occur because there have been different levels of abuse of antimicrobials and different levels of hygiene. This is why it is essential to monitor and manage resistance locally."

For example, a 1989 survey in Hungary indicated that as many as 58 percent of adults and 70 percent of children were infected with penicillin-resistant pneumococci, the highest rate in Europe. In Spain, the level was 44 percent. But other European countries showed much lower levels. The Czech Republic's resistance rate is 4 percent, for instance.

Methicillin-resistant Staphylococcus aureus (MRSA) has also invaded hospitals at a widely varying rate. The organism is responsible for a range of infections, from impetigo to osteomyelitis. In the US, roughly 15 percent of the strains are methicillin resistant. The rate in Russia is 14 percent. In the Netherlands the rate is a low 0.3 percent and 0.5 percent in the United Kingdom.But in Croatia, MRSA spiked at 80 percent during the war, primarily due to over crowding, according to Smilja Kalenic, MD, PhD, professor of microbiology at the Medical School University of Zagreb. The resistance rate has now fallen to an average of about 42 percent. But in Zagreb alone the rate varies from 58 percent in Dubrava Hospital to 10 percent at Children's Hospital.

Some of the marked differences in resistance rates can be explained by the availability of antibiotics. In many NIS nations, antibiotics are available without a prescription, and patients can select them without benefit of advice on dose or how long the drug should be taken.

Anatoliy Shapiro, chief of scientific research for the Institute of Microbiology of Infectious Diseases in Kiev, said that he has not seen as large an increase in drug resistance over the last decade as many countries have primarily because there has been limited access to antibiotics until the last few years.

Shapiro admits that "Antibiotics are widely available without a prescription." But he maintains "This is not a problem because the drugs are very expensive, and many people cannot afford them."

His biggest concerns involve hospital-acquired infections in particularly vulnerable patients. "Small numbers of these opportunistic bacteria may not cause disease, but if a patient's immune system is already suppressed by radiation, such as from Chernobyl, or by environmental pollution or HIV, such bacteria can cause serious infections and even death."

The Czech Republic also had limited access to antibiotics under Communist rule. But it also has had more stringent restrictions on their use. Not only are prescriptions required for all antibiotics, but hospitals keep close tabs on emerging resistance and issue lists of antibiotics they recommend that their doctors and ones outside the hospital prescribe to keep new resistance from developing.

That system has led to a low antibiotic resistance rate in the nation, although it is higher near the border regions in northern Moravia and Bohemia, said Jiri Schindler, MD, PhD, director of the World Antibiotic Resistance Network (WARN) and professor of microbiology at Charles University in Prague. WARN maintains a Web site **(http://www.warn.cas.cz**) with information on emerging resistance around the world.

As the Czech Republic makes the transition to a market economy several factors have influenced drug resistance.

"Now companies are lobbying hospitals to reclassify their antibiotic lists to ensure the company's drugs are included. Companies also pressure family physicians to use certain antibiotics. This is a very bad practice," Schindler said.

But countering this pressure to move away from lists of restricted drugs are economic constraints. Since 1990, the price of antibiotics has risen 500 percent in the Czech Republic, and the nation's public health care system will only reimburse for certain drugs. Thus, said Schindler, economics is lending a hand to keep drug resistance low.

The Central Russia Insitute of Epidemiology in Moscow began a division to study antibiotic resistance in 1986. Hospitals specializing in burns, septic diseases and obstetrics and surgery in eight cities of the former Soviet Union--from Tbilisi to Samarkand--send information on nosocomial infections to the Moscow lab. The information is sent in what Institute Director Nina Semina has dubbed a "strain passport," including the patients sex, age, diagnosis and drug resistance.

From that information, Semina's lab has pieced together a portrait of growing resistance across the NIS: All but 15 percent of E. coli strains are resistant to tetracycline and 80 percent are resistant to ampicillin, while only five percent cannot be killed by amikacin. Ninety-four percent of S. aureus strains are resistant to at least one drug.

Despite these sobering numbers, so far, drug development has keep pace with drug resistance around the world. And in August, researchers at Yale University in New Haven, Connecticut announced they had found a way to make a bacteria's own enzyme to block the genes that provide drug resistance.

Although that finding may eventually provide the key to stopping a wide variety of drug resistance, extrapolating that research to actual practice in hospitals may take a while. In the meantime, doctors worry about the worsening resistance problem. O'Brien and Schindler say they are particularly concerned about meningitis, as well as Staphylococcus aureus strains that are becoming resistant to vancomycin, the next line of defense after staph became resistant to methicillin.

"So far we're okay, but there are a lot of bacterial pathogens with which we're one or two steps away from trouble, where we may not have something that will work," O'Brien said.