Bacteria race ahead of drugs

Falling behind: Deadly infections increasingly able to beat antibiotics

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At a busy microbiology lab in San Francisco, bad bugs are brewing inside vials of human blood, or sprouting inside petri dishes, all in preparation for a battery of tests.

These tests will tell doctors at UCSF Medical Center which kinds of bacteria are infecting their patients, and which antibiotics have the best chance to knock those infections down.

With disturbing regularity, the list of available options is short, and it is getting shorter.

Dr. Jeff Brooks has been director of the UCSF lab for 29 years, and has watched with a mixture of fascination and dread how bacteria once tamed by antibiotics evolve rapidly into forms that practically no drug can treat.

"These organisms are very small," he said, "but they are still smarter than we are."

Among the most alarming of these is MRSA, or methicillin-resistant Staphylococcus aureus, a bug that used to be confined to vulnerable hospital patients, but now is infecting otherwise healthy people in schools, gymnasiums and the home.

As MRSA continues its natural evolution, even more drug-resistant strains are emerging. The most aggressive of these is one called USA300.

Last week, doctors at San Francisco General Hospital reported that a variant of that strain, resistant to six important antibiotics normally used to treat staph, may be transmitted by sexual contact and is spreading among gay men in San Francisco, Boston, New York and Los Angeles.

Yet the problem goes far beyond one bug and a handful of drugs. Entire classes of mainstay antibiotics are being threatened with obsolescence, and bugs far more dangerous than staph are evolving in ominous ways.

"We are on the verge of losing control of the situation, particularly in the hospitals," said Dr. Chip Chambers, chief of infectious disease at San Francisco General Hospital.

The reasons for increasing drug resistance are well known:

- Overuse of antibiotics, which speeds the natural evolution of bacteria, promoting new mutant strains resistant to those drugs.
- Careless prescribing of antibiotics that aren't effective for the malady in question, such as a viral infection.
- Patient demand for antibiotics when they aren't needed.

Heavy use of antibiotics in poultry and livestock feed, which can breed resistance to similar drugs for people.

Germ strains that interbreed at hospitals, where infection controls as simple as hand-washing are lax.

All this is happening while the supply of new antibiotics from drug company laboratories is running dry.

Since commercial production of penicillin began in the 1940s, antibiotics have been the miracle drugs of modern medicine, suppressing infectious diseases that have afflicted human beings for thousands of years. But today, as a generation of Baby Boomers begins to enter a phase of life marked by the ailments of aging, we are running out of miracles.

Top infectious disease doctors are saying that lawmakers and the public at large do not realize the grave implications of

this trend.

"Within just a few years, we could be seeing that most of our microorganisms are resistant to most of our antibiotics," said Dr. Jack Edwards, chief of infectious diseases at Harbor-UCLA Medical Center.

At Brooks' microbiology laboratory, the evolutionary struggle of bacteria versus antibiotics is on display every day. He grabbed a clear plastic dish that grew golden-hued MRSA germs taken from a patient a few days earlier. Inside were seven paper dots, each impregnated with a different drug. If the antibiotic worked, the dot had a clear ring around it - a zone where no germs could grow. No ring meant the drug had failed. This test was typical. Three drugs worked, four had failed.

The strategy for nearly 70 years has been to stay a step ahead of resistance by developing new antibiotics. In the past decade, however, major drugmakers have been dropping out of the field. The number of new antibiotics in development has plummeted. During the five-year period ended in 1987, the FDA licensed 16 novel antibiotics. In the most recent five-year period, only five were approved.

For drugmakers, the economics are simple: An antibiotic can cure an infection in a matter of days. There is much more money in finding drugs that must be taken for a lifetime.

Toll of antibiotic resistance

With antibiotic research lagging, the bugs are catching up, and infections are taking a terrible toll. The federal Centers for Disease Control and Prevention estimates that each year 99,000 Americans die of various bacterial infections that they pick up while hospitalized - more than double the number killed every year in automobile accidents.

Of the 1.7 million hospital-acquired infections that occur each year, studies show, 70 percent are resistant to at least one antibiotic.

Drug-resistant staph is rapidly becoming a major public health menace. Last fall, the CDC estimated that MRSA alone has killed 19,000 Americans. Most of these patients picked up the bug in the hospital, but it is now spreading in urban and suburban neighborhoods across the nation.

"MRSA is killing people. It almost killed me," said Peg McQueary, whose life was upended when she nicked her leg with a razor three years ago.

Within days, her leg was grotesquely swollen, red from foot to knee. Her husband wheeled her into a Kaiser medical office, where her doctor took one look and rushed her to an isolation room.

She was placed on intravenous vancomycin, a drug reserved for the most serious cases of MRSA. Since that frightening week, the 42-year-old Roseville woman has spent much of her life in and out of hospitals, and she's learned just how difficult these infections can be to treat. McQueary has burned through drug after drug, but the staph keeps coming back.

She's been hooked up at her home to bags of vancomycin and swallowed doses of linezolid, clindamycin and a half a dozen other antibiotics with barely pronounceable names and limited effect.

One of the newest antibiotics, intravenous daptomycin - approved by the Food and Drug Administration in 2003 - seems to work the best, but it has not prevented recurrences.

"It's just a struggle to do everyday things," she said. "I am ready to scream about it."

Today, she moderates a Web site, MRSA Resources Support Forum, swapping stories with other sufferers. "Giving them a place to vent is some sort of healing for me," she said.

McQueary's travails are becoming an all-too-familiar American experience. As bacteria evolve new ways to sidestep antibiotics, doctors treating infections find themselves with a dwindling list of options. Old-line drugs are losing their punch, while the newer ones are both costly and laden with side effects.

Drugs' weakening grip

Dr. Joseph Guglielmo, chairman of the Department of Clinical Pharmacy at UCSF, closely tracks the effectiveness of dozens of antibiotics against different infectious bacteria. Laminated color-coded cards called antibiograms are printed up for hospital physicians each year. They chart the success rate of each antibiotic against at least 12 major pathogens. These charts show how antibiotics, like tires slowly leaking air, are losing strength year by year.

As head of the hospital pharmacy, Guglielmo oversees a small warehouse at the medical center that stores millions of dollars worth of prescription drugs that are used every day to treat patients there. Strolling down the aisles that houses bins of antibiotics, he reached for a bottle of imipenem, and cradled the little vial in the palm of his hand.

"This one is the last line of defense," he said.

Imipenem was approved by the FDA in 1985. A powerful member of the carbapenem family - the latest in a long line of penicillin-like drugs - it is frequently used in hospitals today because it can still defeat a wide variety of germs that have outwitted the earlier-generation antibiotics.

But at a cost of about $60 a day, and with a safety profile that includes risk of seizure, it is a "Big Gun" drug that must be used carefully. As soon as doctors discover that a lesser antibiotic will work, they will stop prescribing imipenem, like soldiers conserving their last remaining stores of ammunition.

Now, there are signs of trouble.

Imipenem has been the antibiotic of choice for doctors treating Klebsiella, a vigorous microbe that causes pneumonia in hospitalized patients. But in June 2005, New York City doctors reported in the journal Archives of Internal Medicine outbreaks of imipenem-resistant Klebsiella. Fifty-nine such cases were logged at just two hospitals. The death rate among those whose infections entered their bloodstreams was 47 percent.

Last year, Israeli doctors battled an outbreak of carbapenem-resistant Klebsiella that has killed more than 400 patients.

Cipro's dramatic decline

The antibiotic Cipro, approved by the Food and Drug Administration in 1987, is familiar to millions of Americans because it is widely prescribed for pneumonia, urinary tract infections and sexually transmitted diseases. It was the drug used to treat victims of the anthrax mailings that followed the Sept. 11 attacks.

Unlike most antibiotics, which originated from natural toxins produced by bacteria, Cipro came from tinkering with a chemical compound used to fight malaria. The German drug giant Bayer patented Cipro's active ingredient in 1983, and it subsequently became the most widely sold antibiotic in the world.

At hospitals across the country, however, clinicians have witnessed a remarkable drop-off in the utility of Cipro against more commonly encountered germs.

Antibiograms from the UCSF lab highlight the alarming erosion: As recently as 1999, Cipro was effective against 95 percent of specimens of E. coli - bacteria responsible for the most common hospital-acquired infections in the United States. By 2006, Cipro would work against only 60 percent of samples tested.

The bacterial evolution that has so quickly sapped Cipro has also reduced the effectiveness of the entire family of related antibiotics called fluoroquinolones - drugs such as Levaquin, Floxin, and Noroxin. "If there is ever a group of drugs that has taken a beating, it is these," said UCSF pharmacy chief Guglielmo.

Against Acinetobacter - a bug responsible for rising numbers of bloodstream and lung infections in intensive care units, as well as among combat casualties in Iraq - Cipro's effectiveness fell from 80 percent in 1999 to 10 percent just four years later. Cipro has also lost ground against Pseudomonas aeruginosa, a common cause of pneumonia in hospitalized patients. Nearly 80 percent of the bugs tested were susceptible to Cipro in 1999. That fell to 65 percent by 2004.

At UCSF, doctors carefully monitor the trends in drug resistance and modify their prescribing patterns accordingly. As a

result, they have been able to nudge some of these resistance levels down. Cipro's effectiveness against Acinetobacter crept up to 40 percent last year, for example, but the overall trend remains alarming.

Although MRSA infections have been capturing headlines, bugs such as Acinetobacter, Klebsiella and Pseudomonas are keeping doctors awake at night. They come from a class of pathogens called Gram-negative bacteria, which typically have an extra layer of microbial skin to ward off antibiotics, and internal pumps that literally drive out antibiotics that penetrate.

Gram-negative infections have always been difficult to treat, and few new drugs are in development. Some researchers believe that the pipeline for new antibiotics is drying up because it is simply getting more difficult to outwit the bugs. "It may be that we've already found all the good antibiotics," warned Chambers, San Francisco General Hospital's infectious disease chief. "If that is so, then we've really got to be careful how we use the ones we have."

Bacteria's natural evolution

Terry Hazen, senior scientist at Lawrence Berkeley National Laboratory and director of its ecology program, is not at all surprised by the tenacity of our bacterial foes. "We are talking about 3.5 billion years of evolution," he said. "They are the dominant life on Earth."

Bacteria have invaded virtually every ecological niche on the planet. Human explorers of extreme environments such as deep wells and mines are still finding new bacterial species. "As you go deeper into the subsurface, thousands and thousands of feet, you find bacteria that have been isolated for millions of years - and you find multiple antibiotic resistance," Hazen said.

In his view, when bacteria develop resistance to modern antibiotics, they are merely rolling out old tricks they mastered eons ago in their struggle to live in harsh environments in competition with similarly resilient species.

Drug industry economics are also a factor. "It takes a hell of a lot of effort to find the next really good drug," said Steven Projan, vice president of New Jersey pharmaceutical giant Wyeth Inc.

The costs of bringing a new drug to market are hotly debated. A Tufts University study estimated $802 million; the consumer group Public Citizen pegs it at $110 million. Either way, the investment is huge.

By 1990, according to the Infectious Diseases Society of America, half the major drugmakers in Japan and the United States had cut back or halted antibiotic research. Since 2000, some of the biggest names in pharmaceutical development - Roche, Bristol-Myers Squibb, Abbott Laboratories, Eli Lilly, Aventis and Procter & Gamble - had joined the exodus.

By common measures used to gauge the profit potential of new drugs, antibiotics fall way behind, Projan explained. For every $100 million that a new antibiotic might yield, after projected revenue and expenses are tallied, a new cancer drug will generate $300 million. A new drug for arthritis, by this same analysis, brings in $1.1 billion. Investors have been placing their bets accordingly.

In 2002, Wyeth had sharply curtailed its own antibiotic drug discovery programs. "We tried to get out of the field, but one of the reasons we did not get out altogether is we feel we have a public responsibility to fund more research," said Projan.

Wyeth's decision to keep some antibiotic research alive eventually paid off. In June 2005, the FDA licensed Tygacil, an intravenous antibiotic for complicated skin diseases such as drug-resistant staph infection. Only one new antibiotic for oral or intravenous use has won FDA approval since.

Pointing a finger at doctors

The waning of antibiotics in the arsenal of modern medicine has been going on for so long that some doctors fear a kind of complacency has set in. Increasingly, the medical profession is pointing a finger at itself.

"We have behaved very badly," said Dr. Louis Rice, a Harvard-educated, Columbia-trained specialist in infectious diseases. "We have made a lot of stupid choices."

His words brought a nervous silence to thousands of his colleagues, as he delivered a keynote speech in 2006 for the American Society for Microbiology's annual conference in San Francisco.

Rice, a professor at Cleveland's Case Western Reserve University, said doctors and drug companies alike are responsible for breeding resistance by "the indiscriminate dumping of antibiotics into our human patients."

Drug-resistant germs contaminate the bedrails, the catheter lines, the blood pressure cuffs and even the unwashed hands of doctors, nurses and orderlies. The germs keep evolving, swapping drug-resistance traits with other microbes. He likened American intensive-care units - the high-tech enclaves where the most seriously ill patients are treated - to "toxic waste dumps."

Drug companies, he said, have a responsibility to refill the nation's depleted medicine chest. He suggested that a tax - similar to a Superfund tax placed on polluters to clean up toxic waste sites - be imposed on companies that have dropped antibiotic research. It would support drugmakers that are still in the game. "Your products that you've made billions and billions and billions and billions of dollars on have created this problem, and you can't just walk away," he said.

Rice has stressed that the existing arsenal of antibiotics should be used wisely, and that often means sparingly. During a half century of antibiotic use, he said, there is scant research on how short a course of drugs is actually needed to cure a patient. Instead, doctors routinely prescribe a week to 10-day course of drugs recommended by manufacturers. If patients are taking antibiotics after their infections are truly gone, they are creating conditions that breed resistance. Indeed, a Dutch study showed that one kind of pneumonia can be treated just as successfully with three days of amoxicillin as with the traditional eight.

Since drug companies cannot be expected to spend money on research that could trim sales of their products, federally funded agencies such as the National Institutes of Health should do the job, Rice said in a recent interview.

He also took his own specialty to task for failing to protect the most important weapons its arsenal. Infectious disease experts at hospitals must find the "backbone" to stop other doctors from prescribing antibiotics unnecessarily, Rice said. He argued they should assert their authority to control antibiotic usage, just as cancer specialists have a say in which chemotherapy drugs are prescribed by surgeons.

And all health care professionals, he added, "have to wash their hands."