Rise in *E. coli* May Challenge Empiric Therapy

BY NEIL OSTERWEIL

FROM THE ANNUAL INTERSCIENCE CONFERENCE ON ANTIMICROBIAL AGENTS AND CHEMOTHERAPY

BOSTON – Infections with dangerous strains of *Escherichia coli* and *Klebsiella pneumoniae* are on the rise in some European hospitals and communities, with potentially serious implications for infection control efforts, warned researchers.

Investigators from the Netherlands mined data from a national laboratory–based surveillance system on changes in the drug susceptibility of *E. coli* and *K. pneumoniae* from 2008 through the first 6 months of 2010.

They found "a strong increase in [extended-spectrum beta-lactamase–producing] *E. coli* in urine outside the hospital, and a strong increase in ESBL-positive *K. pneumoniae* in urine in hospitals," said Dr. Maurine A. Leverstein-van Hall of the University Medical Center Utrecht, the Netherlands.

In a second study, French investigators examining the effect of bacteremias caused by ESBL-producing enterobacteria found there was a significant increase in the prevalence of ESBL *E. coli* infections from 2005 to 2008.

Surprisingly, they did not see an increase in mortality rates associated with the infections, despite inadequate initial antimicrobial therapy in about half of all patients. However, that may have been due to study limitations, said Dr. Blandine Denis of St. Louis Hospital in Paris.

Dr. Leverstein-van Hall and her colleagues looked at the overall proportion of ESBL-positive isolates in the Netherlands from 2008 through 2010 in 19 labs covering one-third of all Dutch hospital beds. They found that during the study period, the proportion of ESBL-positive *E. coli* increased by 1.3%, and ESBL-positive *K. pneumoniae* rose by 1.5%.

Similarly, the proportion of ESBL-positive blood isolates increased by 1.5% and 1.7%, respectively, from 2008 through 2010. The increases in blood isolates were seen in both hospital inpatient and outpatient settings, and the increase in urine isolates were seen in general practices, long-term care facilities, and hospital inpatient and ambulatory settings.

The researchers also looked at the adequacy of empiric therapy for sepsis according to Dutch national guidelines. At least 30% of patients with sepsis received inadequate therapy, the researchers reported at the meeting, which was sponsored by the American Society for Microbiology.

The Dutch guidelines call for second- or third-generation cephalosporins or amoxicillin-clavulanic acid plus an aminoglycoside such as amikacin for sepsis of unknown origin, or an aminoglycoside combined with other agents for sepsis with a probable focus on the urogenital or digestive tracts. However, a substantial number of patients received only cephalosporins – despite the 100% resistance rate of ESBL-positive isolates to second- or third-generation agents in that class.

Empiric therapy for gram-negative sepsis should include beta-lactam/inhibitor combinations or cephalosporins, each in combination with amikacin. A switch to carbapenems could be made if culture results yield an ESBL-positive bacterial strain, Dr. Leverstein-van Hall said.

In the single-center French study, Dr. Denis and her colleagues performed a retrospective case-control analysis comparing patients with ESBL-positive bacteremia in their hospital with ESBL-negative controls matched by date. They found that slightly less than half of all ESBL-positive patients (48%) received adequate antimicrobial therapy based on the susceptibility of their respective isolates.

In an adjusted analysis of risk factors for ESBL-positive bacteremia, the French investigators found that the only statistically significant factor was previous ESBL colonization.

They also found that there were no significant differences in hospital length of stay or in 21-day mortality rates between cases and controls, although their failure to find an effect of ESBL positivity may be related to the relatively small sample size (45 cases from 2005 to 2008) and to the retrospective design, Dr. Denis acknowledged.

The Netherlands National Institute for Public Health and the Environment funded Dr. Leverstein-van Hall's study. Dr. Denis' study was internally funded. Neither physician had conflicts of interest to disclose. ■

Shortage of New Antibiotics May Help Superbugs Flourish

BY MICHELE G. SULLIVAN

FROM THE AMERICAN ACADEMY OF DERMATOLOGY'S ACADEMY 2010 MEETING

CHICAGO – By all measures, methicillin-resistant *Staphylococcus aureus* cases and related deaths are steadily increasing around the globe, according to Dr. Theodore Rosen.

But MRSA isn't the only bug that's ramping up its antibiotic smarts these days.

"We are being bombarded every year by increasingly resistant bacteria," Dr. Rosen said in an interview. "Some of these are relatively trivial, some are really bad – like MRSA – and some are wreaking havoc. I'm talking about *Klebsiella* causing horrendous, frequently fatal drug-resistant pneumonia; multidrug resistant forms of the plague (the same plague that wiped out a third of Europe); and drug-resistant tuberculosis, a disease we thought we'd cornered years ago."

The surge in resistance is a predictable evolutionary response to the widespread use – and overuse – of antibiotics, said Dr. Rosen, professor of dermatology at Baylor College of Medicine, Houston. Unfortunately, science, industry, and federal administrators are not adapting to the new environment nearly as quickly as their microscopic enemies.

"The number of new antibiotics approved over the past few years has been steadily decreasing, and in the last 2 or 3 years, only one new antibiotic has been approved," despite promising data, said Dr. Rosen.

Stung by recent problems with already approved drugs, the Food and Drug Administration has become increasingly stringent about the approval of new medications, including antibiotics, he noted.

Pharmaceutical companies also play a role. "You stand to make a lot more money developing a drug for a chronic disease than one only given for 14 days, like an antibiotic," said Dr. Rosen.

He discussed several antibiotics that showed promise but never found their way to the federal finish line. Two – oritavancin and dalbavancin – are molecularly related to telavancin, which was approved in 2009. "Oritavancin was rejected [by the FDA] because it did not show noninferiority to vancomycin," he said.

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DR. ROSEN

Dalbavancin did well in phase III trials for uncomplicated skin and soft tissue infections. "You can give it once a week, and it's incredibly potent, doing better by far in vitro than anything else available," Dr. Rosen said. The drug received an FDA approvable letter, but never went further. According to the FDA "the studies were not well done and questioned some of the methodology, so Pfizer sold the rights to the drug, fearing it would not be the blockbuster they had hoped," he said. The drug is now in developmental limbo.

Iclaprim, a trimethoprim-related drug, is also languishing. "It's a good drug, with a 99.9% kill rate in vitro. It works in trimethoprim resistance and can be given orally or intravenously. It looked great in its phase II and III trials," said Dr. Rosen.

However, the FDA rejected the drug. Iclaprim met its initial requirement of no more than a 12.5% efficacy difference with its comparator, linezolid. The FDA upped the ante to no more than a 10% difference, at which time Roche sold the drug to another company, which merged with another and sold iclaprim again. "No one knows this drug's future," Dr. Rosen said.

Several linezolid-like drugs have completed phase II trials "and look good," Dr. Rosen said.

"They have greater potency, can be taken orally once daily, and have solved some of the problems associated with linezolid – no hypertension, better gastrointestinal absorption, and less risk of myelosuppression."

Monoclonal antibodies that bind to the staphylococcal clumping factor are also in the works. "This is a very clever way of treating staph bacteria, by keeping them from grabbing hold of fibrinogen so they can't get into tissue," Dr. Rosen said. Early studies have shown that patients who received the antibody plus an antibiotic did better than those who only received the antibiotic, and that the combination was able to clear MRSA carriage.

"Unfortunately, the company developing this ran out of money, so this antibody is sitting on the shelf somewhere until the company finds a new financial partner," he added.

The FDA's insistence on noninferiority trials for antibiotics hinders approval, Dr. Rosen opined.

"It's difficult to figure out how noninferior the new drug has to be. Several have shown noninferiority – there were failures, but the failure rate was relatively low. The FDA, however, has said the rate must be lower, because otherwise, a certain number of patients would have done better on the comparator drug, even though each drug has its own positive and negative attributes."

Placebo-controlled studies "are unconscionable" in patients with infection, and the only other method to determine effectiveness is a superiority study, "which is not really feasible with antibiotics, because so many work so well," Dr. Rosen said.

Both paths to approval have flaws. "The FDA has had conference after conference with infectious disease experts. We have made little progress in negotiation and have no new antibiotics at a time when resistance is rising, and it's critical that we develop more," he said.

Time may be running out. Before the advent of penicillin in 1928, infection was the leading cause of death worldwide; in 2000, it was still the fourth-leading cause of death.

"If our antibiotics stop working, we will rapidly go back to those pre-World War II days when all we had to treat infections were arsenic and sulfa. Yes, that's a doomsday scenario, but it's not inconceivable that we could once again live in a time when infections reign supreme," he concluded.

Dr. Rosen reported having no relevant financial disclosures. ■