

## Worldwide attention to resistant bacteria

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Infections caused by resistant bacteria can strike anyone, the young and the old, the healthy and the chronically ill. Antibiotic resistance also is a serious problem for patients whose immune systems are compromised, such as people with HIV/AIDS and patients in critical care units. About 2 million people acquire bacterial infections in U.S. hospitals each year, and 90,000 die as a result. About 70 percent of those infections are resistant to at least one drug, according to the Centers for Disease Control and Prevention. The total cost of antimicrobial resistance to U.S. society is nearly \$5 billion annually. Treating resistant pathogens often requires more expensive drugs and extended hospital stays. *Staphylococcus aureus* (staph) is a common cause of hospital infections that can spread to the heart, bones, lungs, and bloodstream with fatal results. In 2002, 57.1 percent (an estimated 102,000 cases) of the staph bacteria found in U.S. hospitals were methicillin-resistant (MRSA), according to CDC. Staph infections (even those that are not drug-resistant) can be deadly and costly (1,2).

A 2000-2001 analysis of U.S. hospitalizations found that staph infections caused 12,000 deaths and \$9.5 billion in hospital costs each year,

according to a study published in the *Archives of Internal Medicine* (3).

Although MRSA used to be limited primarily to hospital patients, it is becoming increasingly common in the broader community. A study of children with community-acquired staph infections at the University of Texas found nearly 70 percent infected with MRSA. In a 2002 outbreak, 235 MRSA infections were reported among military recruits at a training facility in the southeastern United States. In addition, 12,000 cases of community-acquired MRSA were found in three correctional facilities in Georgia, California, and Texas between 2001 and 2003. Since 2000, CDC has reported outbreaks of MRSA among athletes, including college football players (2).

In September 2003, this issue was brought to national attention when MRSA broke out in Florida among the Miami Dolphins, sending two players to the hospital for treatment. Vancomycin-resistant enterococci (VRE) can cause wound infections, infections in blood, the urinary tract and heart, and life-threatening infections for hospital patients. In 2002, 27.5 percent (an estimated 26,000 cases) of tested enterococci samples from ICUs were resistant to vancomycin, according to CDC (1).

The percentage of *Pseudomonas aeruginosa* bacteria resistant to either ciprofloxacin or ofloxacin, two common antibiotics of the fluoroquinolone class (FQRP), has increased dramatically. Recent CDC data show that in 2002,

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nearly 33 percent of tested samples from ICUs were resistant to fluoroquinolones. *P. aeruginosa* causes infections of the urinary tract, lungs, and wounds and other infections commonly found in intensive care units (1).

Rice recently reported these as the “ESKAPE” pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species) to emphasize that they currently cause the majority of hospital infections and effectively “escape” the effects of antibacterial drugs (4). Data published by CDC show rapidly increasing rates of infection due to methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant *E. faecium* (VRE), and fluoroquinolone-resistant *P. aeruginosa* (5). More people now die of MRSA infection in US hospitals than of HIV/AIDS and tuberculosis combined (2,6). Furthermore, panantibiotic-resistant infections now occur. Several highly resistant gram-negative pathogens—namely *Acinetobacter* species, multidrug-resistant (MDR) *P. aeruginosa*, and carbapenem-resistant *Klebsiella* species and *Escherichia coli* are emerging as significant pathogens in all over the world. Our therapeutic options for these pathogens are so extremely limited that clinicians are forced to use older, previously discarded drugs, such as colistin, that are associated with significant toxicity and for which there is a lack of robust data to guide selection of dosage regimen or duration of therapy (5,7). The growing number of elderly patients and patients undergoing surgery, transplantation, and chemotherapy and dramatic increases in population in neonatal intensive care units will produce an even greater number of immunocompromised individuals at risk of these infections.

Although some important molecules are in late-stage development for treatment of infection due to problematic pathogens, such as MRSA, few novel molecules have been advanced for treatment of the other ESKAPE pathogens. Importantly, no drugs have reached advanced stages of development for

infection due to MDR gram-negative bacilli, such as *A. baumannii* and *P. aeruginosa*, and none represents more than an incremental advance over currently available therapies.

New antimicrobials should provide clear advances in treatment of infection, compared with already available therapies. The number of truly novel compounds with a new mechanism of action remains small. Most antibacterial drugs that are currently in the late-stage pipeline do not augur a major advance in our ability to treat infection due to resistant pathogens, and the overall number of compounds in development to treat gram-negative infection is small.

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