

# New Drugs Against MRSA, Other Superbugs Still Lacking

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Posted on: 12/01/2008

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Infectious disease experts warn that new drugs are urgently needed to treat six drug-resistant bacteria that cause most hospital infections and increasingly escape the effects of antibiotics.

The ESKAPE pathogens -- as these six bad bugs have been dubbed -- are still on the loose more than four years after the Infectious Diseases Society of America (IDSA) first drew attention to the growing shortage of effective antibiotics. As the crisis of antibiotic resistance continues to grow, the latest IDSA "Bad Bugs, No Drugs" report examines the trickle of new antibiotics in the research and development (R&D) pipeline and proposes steps to tackle the shortage.

"The six bad bugs we call the ESKAPE bacteria -- *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella* species, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species -- are among the biggest threats infectious diseases physicians face today," said Helen Boucher, MD, of Tufts Medical Center in Boston, lead author of the new report, published in the Jan. 1 issue of *Clinical Infectious Diseases* and now available online. "We desperately need new drugs to fight them. But we also need cooperation among industry, academia, and government to create a sustainable R&D infrastructure that will fill the pipeline to meet today's needs and keep it filled with drugs that tackle tomorrow's infectious diseases threats."

Amid the continuing downward trend in new antibiotics, the new report shows a few signs of hope. The Food and Drug Administration (FDA) has approved a small number of new antibiotics in the last several years, most of them active against methicillin-resistant *Staphylococcus aureus* (MRSA). However, just one can be taken orally (the rest are intravenous); they are too toxic for some patients to handle; and resistance to them is already beginning to emerge.

But the medicine cabinet is particularly bare when it comes to *Acinetobacter*, *Klebsiella*, and *Pseudomonas*. Called "Gram-negative" for the way they react to a common staining test used to identify bacteria in a microscope, they attack some of the most vulnerable patients, including those in intensive care units and long-term care facilities, burn victims, and those with cystic fibrosis. These especially bad bugs are becoming more and more resistant to antibiotics. Physicians are now facing some strains that are resistant to every antibiotic in the arsenal. Only one new drug was approved for gram-negative infections last year, and resistance already exists to other drugs in its class.

In its 2004 report, "Bad Bugs, No Drugs: As Antibiotic Development Stagnates...A Public Health Crisis Brews," IDSA detailed the complex mix of factors driving drug makers out of the antibiotics market. One factor is the high cost of drug development coupled with the low rate of return on investment antibiotics provide compared with drugs for chronic conditions such as heart disease, diabetes, or cancer. Furthermore, regulations for new drug approvals have been murky, and drug manufacturers have been reluctant to gamble.

In the new report, IDSA outlines steps Congress should take to make antibiotics a more attractive business proposition. The report applauds FDA for taking steps toward clarifying regulations for drug approvals, and urges more movement in this direction. IDSA also urges Congress to pass the Strategies To Address Antimicrobial Resistance (STAAR) Act, a bill designed to improve research, surveillance, and prevention of antimicrobial-resistant germs.

"More than four years after our first report, the bad bugs are getting worse, and we still don't have the drugs we need," Boucher said. "We need new tools to fight the ESKAPE bugs now. But there will always be bad bugs. We need industry, academia, and government working together so we are never again left with no

drugs for bad bugs."

#### The ESKAPE Bacteria

According to the latest data from the Centers for Disease Control and Prevention (CDC), the six ESKAPE bacteria are responsible for two-thirds of all healthcare-associated infections (HAIs). They are:

-- **Enterococcus species:** Enterococci were responsible for one out of eight HAIs in 2006-2007. A 2004 study found about two thirds of *E. faecium* bloodstream infections were resistant to vancomycin, one of the most commonly used antibiotics to treat enterococcal infections. Some physicians are treating vancomycin-resistant *E. faecium* with the new antibiotics linezolid, daptomycin, and tigecycline, but these drugs have not been studied extensively for use against these infections. Furthermore, many patients cannot tolerate them.

-- **Staphylococcus aureus:** The only household name among the ESKAPE bugs, methicillin-resistant *Staphylococcus aureus* (MRSA) outbreaks have been reported among otherwise-healthy athletes, military recruits, school children, and others. MRSA caused an estimated 94,000 invasive infections—more than 19,000 of them fatal—in 2005, according to a recent study by CDC. MRSA is a serious and growing threat in hospitals and other health care facilities, but this study found 14 percent of patients had no obvious exposure to a health care facility. MRSA has drawn more attention from the pharmaceutical industry than any of the other ESKAPE bugs. Several new drugs are effective against these infections. However, all but one are given intravenously and are primarily to be used in hospitals. Many patients cannot tolerate these potent drugs. Also, only one drug in the pipeline works using a mechanism different from the ones to which some bad bugs have already developed resistance.

-- **Klebsiella species:** These gram-negative bacteria cause infections in the urinary, biliary, and gastrointestinal tracts, and in trauma wounds. *Klebsiella* species and their gram-negative cousin *E. coli* together accounted for 18 percent of all HAIs in 2006-2007, and a growing proportion of these two bad bugs carry resistance to a remarkable spectrum of antibiotics. Of the very few drugs in late-stage development, none works by a novel mechanism.

-- **Acinetobacter baumannii:** Drug resistance is a major problem in *Acinetobacter* infections, which are responsible for about 3 percent of all HAIs,. Soldiers are returning from Iraq and Afghanistan with cases of highly resistant *Acinetobacter* wound infections. Strains have emerged that are resistant to all but the most toxic drugs. Physicians have been forced to resort to an old drug that is known to cause organ damage, and resistance is even developing to this drug. Yet there is nothing in development against *Acinetobacter*.

-- **Pseudomonas aeruginosa:** *Pseudomonas* is a particular problem for patients on respirators and those with cystic fibrosis. Eight percent of all HAIs are caused by *P. aeruginosa*, and one quarter of these are resistant to carbapenems, a class of antibiotics commonly used for these infections. There are no new drugs in development for these highly resistant infections.

-- **Enterobacter species:** One in 20 HAIs is caused by this group of bacteria. Like *Klebsiella*, *E. coli*, and the other gram-negatives, *Enterobacter* species have developed broad-spectrum resistance to multiple classes of antibiotics. One drug, tigecycline, might work against these infections. There is nothing else in the pipeline.

Source: IDSA