

**Life Sciences: Biotech**

## New front developing in war on killer bugs

Drug tested against toughest bacteria

By **Diedra Henderson**

GLOBE STAFF

A Lexington company has successfully completed the first clinical trial for a drug to combat a bacterium that ranks high on an infectious disease group's "hit list" of killer bugs.

The bad bugs list compiled by the Infectious Diseases Society of America includes six harmful microbes that are becoming more prevalent at a time when there are a shrinking number of drugs to treat them effectively.

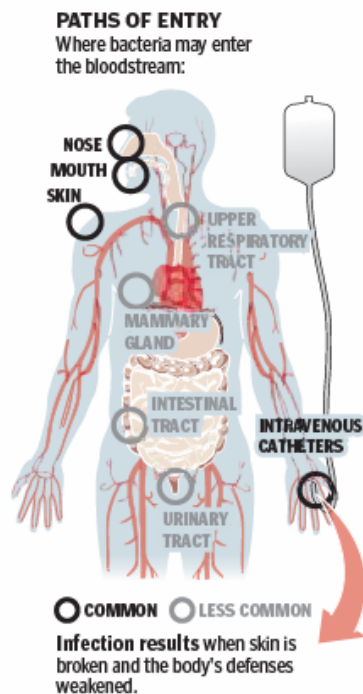
Cubist Pharmaceuticals says that its drug Cubicin, already used by doctors to treat complicated skin infections, can be effective at combating *Staphylococcus aureus* in the bloodstream. According to the Food and Drug Administration, *S. aureus* is the second-most-common bacteria identified in hospitalized patients whose blood becomes infected with bacteria. American hospitals spend \$9.7 billion per year treating the resulting infections.

"The Cubist drug was tested in perhaps the toughest of all infections," said Dr. John G. Bartlett, chief of infectious disease at Johns Hopkins. "The stakes do not get any higher, not in infectious disease."

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## When bacteria become deadly

Common bacteria can become harmful if they enter the bloodstream and infect the heart. Cubist Pharmaceuticals Inc. has developed a drug to combat *Staphylococcus aureus* bacteria in the blood.

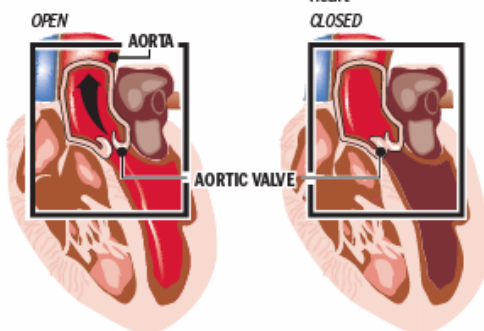


SOURCES: National Institutes of Health; Merck Manual; Cubist Pharmaceuticals Inc.

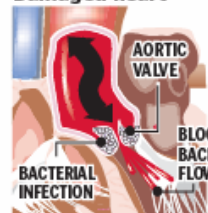
### WHEN BACTERIA KILLS

#### Normal heart

The aortic valve opens as the heart contracts...



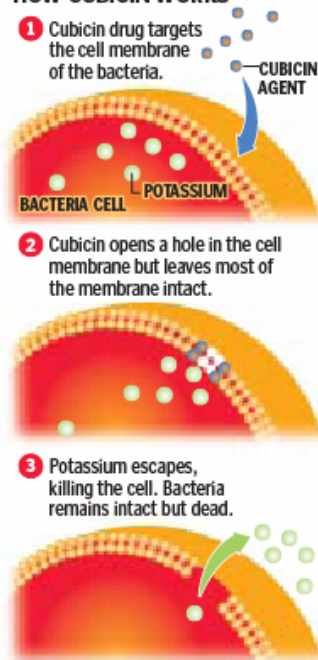
#### Damaged heart



#### Infective endocarditis

Bacteria nestle on the irregular surfaces of heart valves allowing blood to flow back into the heart. Bacterial infection can be fatal when it compromises the heart's ability to pump blood efficiently.

### HOW CUBICIN WORKS



JOAN McLAUGHLIN/GLOBE STAFF

# Lexington firm opens new front in battle against killer infections

## ► BACTERIA

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To show Cubicin's effectiveness, the company had to pull off the unprecedented feat of testing the drug against the *S. aureus* bacteria while it was coursing through patients' bloodstreams.

The logistics of the trial were complicated: Potential trial participants had bacterial infections that could — but not always — lead to the heart complications the company also wanted to study. Cubist screened 5,000 patients in 76 potential study sites in six countries. Older drugs now used to treat bacteria-induced heart in-

## A new generation of superbugs

A "hit list" of drug-resistant microbes, released this month by the Infectious Diseases Society of America:

- Methicillin-resistant *Staphylococcus aureus*, or MRSA: causes the majority of healthcare associated infections.
- *Escherichia coli* and *Klebsiella*: cause many urinary tract, gastrointestinal tract, and wound infections.
- *Acinetobacter baumannii*: increasingly cause of hospital-acquired pneumonia with death rates up to 50%.

- *Aspergillus*: Especially of concern for people with weakened immune systems, such as cancer patients, organ transplant recipients, people with HIV.
- Vancomycin-resistant *Enterococcus faecium*, or VRE: a major cause of bloodstream infections, heart infections, meningitis, and intra-abdominal infections.
- *Pseudomonas aeruginosa*: causes severe infection that can be life-threatening.

flammation were studied in just a few patients.

Cubist's ensuing trial cost the company an estimated \$100,000 per patient for the 246 patients enrolled in the international trial, said Bartlett at Johns Hopkins, who did not participate in the trial but has studied it closely.

Mike Bonney, Cubist's chief executive, said the company's "bold decision" gives it a nearly four-year lead over its rivals.

"We persevered and got it done," Bonney said. "I'm not convinced others will do it."

Cubists' upcoming reward: the FDA's first-ever approval of a drug to treat *Staphylococcus aureus* bacteria in the bloodstream, which can lead to infective endocarditis, an ailment that inflames and imperils hearts.

Late Friday, the company reported the FDA's conditional approval of expanded use of its drug. Today, the company and the agency will continue finalizing the wording of the drug's label, complicated negotiations that delayed full FDA approval of the product.

While Cubist estimates a market opportunity of up to \$1 billion per year, infectious disease experts say they really need three or four more Cubicins as reserves to offer patients when it and other drugs stop working against *S. aureus*.

Doctors say they lack effective treatments for many tenacious germs they see daily in hospitals, drug-resistant microbes that can spread in the time it takes drug firms to develop a new therapy.

"These bugs are small bugs. They become big bugs in five years. And it takes eight years to develop a new drug," said Bartlett, chairman of the Infectious Diseases Society of America task force that's pushing for more and better antimicrobial drugs.

At the top of their list: *S. aureus*, which has become resistant to the antibiotic methicillin. That bacteria — a common cause of a

wound infection after surgery — is creeping into community settings, such as locker rooms. The experts' wish list also includes additional remedies for *Acinetobacter baumannii*, a bug that infects the wounds of soldiers returning from Iraq.

"We're worried about that because that is becoming more of a problem," Bartlett said. Plus, doctors don't know how it gets into soldiers' wounds. It could happen after they're airlifted out of Iraq for medical care.

The bacteria commonly live on the body's surfaces and normally are kept in check by the immune system, said Dr. Alice M. Mascette of the National Heart, Lung and Blood Institute. Dispatched into the bloodstream through such means as dental work and intravenous catheters, researchers believe the bacteria's sticky surfaces help them latch onto opportune places. Think Velcro.

A minuscule abnormality in the heart valve may give the organism an ideal place to "stick and grow," said Mascette, director of the clinical and molecular medicine program within the division of heart and vascular disease. Once embedded, they're difficult to flush out. "Vegetations" — clusters of organisms — act like a blood clot and can trigger a stroke.

In the heart, the bacteria hone in on valves and can compromise the body's blood-pumping system. Endocarditis, an inflammation of the lining of the heart and valves caused by the bacteria, can strike the heart's right or left side. "Left-sided" endocarditis compromises the part of the heart that provides blood to feed the entire body, she said.

"Endocarditis is what many of us feel is the mother of all infections," said Bartlett. "Without treatment, it's 100 percent fatal. Everybody dies."

Cubists' \$1 billion sales esti-

mate is based on the 120,000 Americans who suffer from *S. aureus* bacteremia annually.

For hospitals, an effective treatment for *S. aureus* in the blood could result in substantial cost savings.

Patients who develop *S. aureus* bacteremia stay in the hospital 14.3 days on average, compared with 4.5 days for patients who don't develop it. And their care costs \$48,000 versus \$14,000 for a hospital stay uncomplicated by the bacterial infection. The Staph infection increases hospital mortality rates to 11.2 percent, compared with 2.3 percent without it, Bartlett said.

Federal advisers whose votes guide FDA decisions unanimously agreed on March 6, 9-0, that the drug is safe and effective for use against *S. aureus* bacteremia. The approval margin narrowed to 5-4 in deciding whether Cubicin is safe and effective for treating infective endocarditis.

Dr. Gregory Townsend, a University of Virginia infectious disease expert, voted no. He is unconvinced by data from the small number of patients in the Cubicin trial who had infective endocarditis. Townsend is also alarmed that when Cubicin failed to tamp down bacterial infection, some patients showed signs of developing resistance to the drug.

"The Cubicin issue is, in some ways, a microcosm of what we're seeing in the world of infectious diseases," said Townsend, an associate professor in the division of infectious diseases and international health.

"If Cubicin gets used more than it needs to, then we're going to see increasing resistance to Cubicin," he said. "It's now one of the last lines of defense. Where do we go to from there?"

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