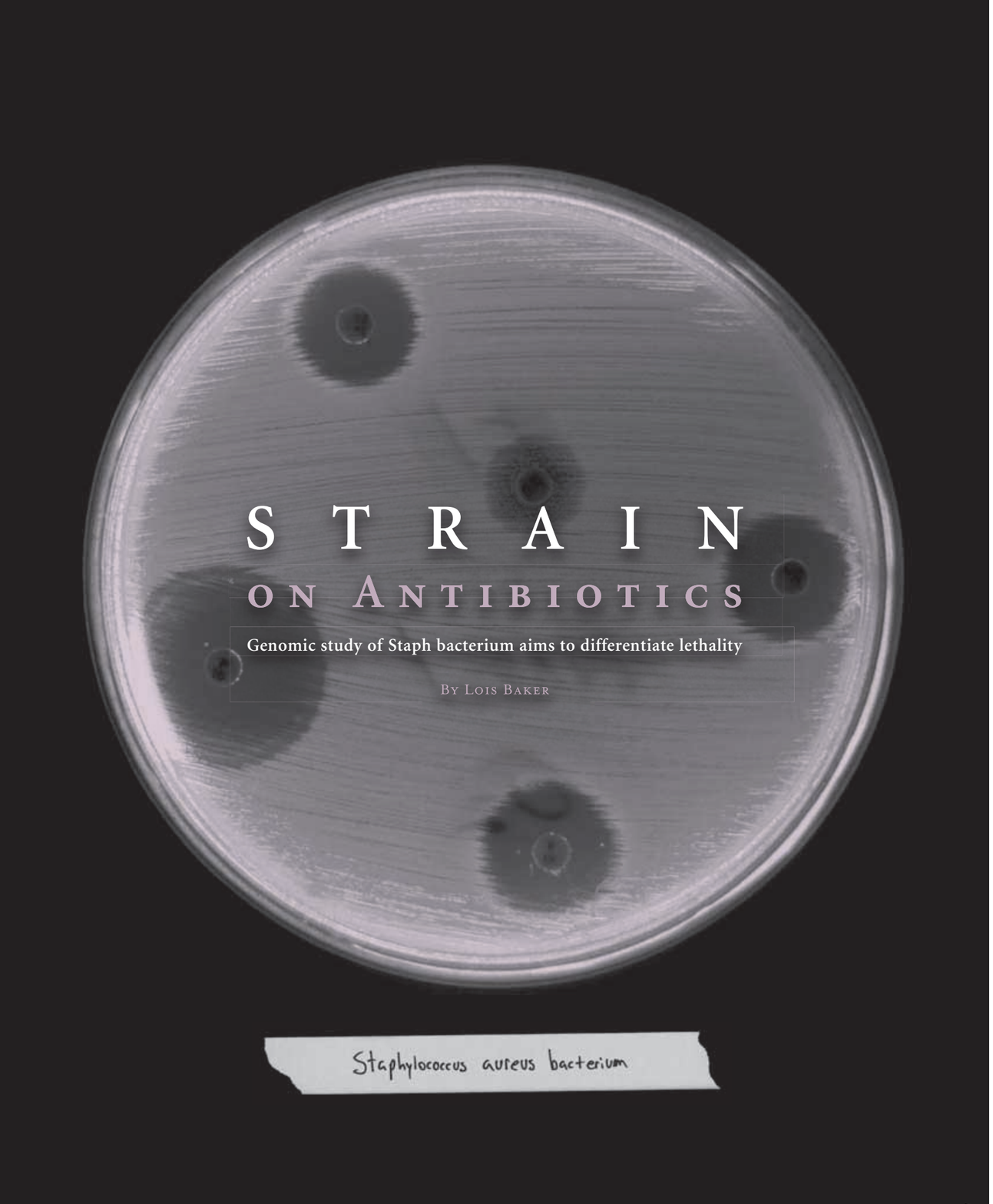
STRAIN ON ANTIBIOTICS

Genomic study of Staph bacterium aims to differentiate lethality

By Lois Baker



Staphylococcus aureus bacterium

PHIL.CDC.GOV

The *Staphylococcus aureus* bacterium is one of the most common and most important disease-causing organisms in humans.

S. aureus frequently invades the bloodstream, causing *S. aureus* bacteremia, or SAB, an infection that attacks the heart valves and other organs with potentially deadly consequences. Even with the best care and antibiotic therapy, the mortality rate of patients with SAB is 20 to 30 percent, a rate that hasn't changed in 30 years.

Because there currently is no way to rule out the presence of *S. aureus* endocarditis, or heart-valve infection, with 100 percent accuracy, even with an echocardiogram, most patients infected with the bacteria automatically receive 4 to 6 weeks of antibiotic therapy.

Prolonged use of antibiotics, however, contributes to the development of antibiotic resistance and increases the overall cost of medical care. Patients also may suffer the consequences of unnecessary antibiotic administration, ranging from allergy to a potentially lethal form of infectious diarrhea.

"One of the principles of infectious disease is that you aren't treating just the patient in front of you, you are treating everyone who comes afterward, because you are introducing antibiotics into the microbial ecology," states Alan J. Lesse, MD, associate professor of medicine, pharmacology and toxicology, and microbiology and immunology in the School of Medicine and Biomedical Sciences, who is based in the Buffalo VA Medical Center.

"We need to find ways to limit excess antibiotic use while giving patients the medicine they need to get well," he adds.

In an effort to develop new guidelines for antibiotic use for SAB, UB researchers headed by Lesse are collecting bacterial isolates and clinical information from SAB-infected patients hospitalized in three area hospitals and following their charted progress.

UB genomic specialists will compare the collected bacteria on a gene-by-gene basis, a process called complete genomic hybridization. Then, in one of the first analyses of its kind, the genomic architecture of the various bacterial strains identified will be compared to the risk factors and outcomes derived from the patients.

The research—which is supported by a three-year, $690,500 grant from the John R. Oishei Foundation of Buffalo—should identify which strains are the most lethal and require long-term antibiotics, and which strains will succumb to short-term treatment.

Joseph Mylotte, MD, professor of medicine, is also a principal researcher on the study, along with Stephen Gill, PhD, associate professor of oral biology in the UB School of Dental Medicine. Gill, who is a member of the Infectious Disease and Genomics Group in UB's New York State Center of Excellence in Bioinformatics and Life Sciences, will conduct the genetic analyses.

"*In this study,* we're mainly concerned with hospital-based staph infections," says Lesse, "but many of the bacteria get into the hospital from the community, and many of those strains have a higher risk of complications.

"Injection drug abusers are a prime example," he adds. "Their situation parallels the hospital situation because they are introducing substances into the bloodstream. Hospital-based staph infections often are associated with intravenous catheters and other invasive procedures, including surgery. These bacteremias are different from community-derived staph, but they still have a very high morbidity and mortality."

From Left: Joseph Mylotte, MD; Alan J. Lesse, MD; and Stephen Gill, PhD.

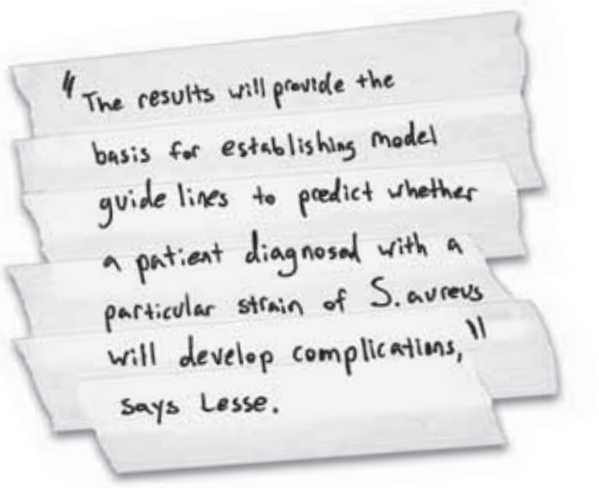
How does a person get bacteremia?

"It's unclear," Lesse acknowledges. "About 40 percent of patients will not have a defined focus and those patients have a very high risk of infection of the heart valves. Unfortunately, just having *S. aureus* in the bloodstream carries a very high mortality risk."

"If there is infection in a heart valve, mortality approaches 40 to 50 percent," he continues. "It's a highly lethal complication. There's significant morbidity associated with it too, because patients with these infections end up with prolonged hospitalizations and prolonged antibiotic administration."

Over the three years of the study, the researchers will collect SAB samples from an anticipated 900 patients, who will be classified as low, moderate or high risk for developing complications based on their clinical status.

Patients classified as low risk will be those who have a removable focus of infection, such as a catheter; a drainable superficial abscess; a superficial, nonremoval focus, such as cellulitis; no evidence of endocarditis or deep infection; no known valvular heart disease; a negative echocardiogram; and clearance of bacteria from the bloodstream within 24 to 72 hours after starting antibiotics.



Patients classified as moderate risk for SAB will have features similar to low-risk patients but without an identifiable focus of the infection.

Patients at high risk of complications will be defined as having a positive blood culture for SAB 24 to 72 hours after starting antibiotics or with persistent signs of infection after 72 hours, whether or not a focus has been identified.

The genomic analysis is the most critical aspect of the research. "While a few recent studies have shown a possible association of *S. aureus* strains with the development of complications," says Lesse, "it is not known whether specific strains of *S. aureus* are more likely to cause complications than others."

Gill will classify the SAB strains into clusters based on the DNA sequence of seven key genes found in all strains, using a technique called multi-locus sequence typing (MLST). UB researchers will be able to compare local isolates with strains from all over the world, based on this electronic database of isolates, according to Lesse.

The second stage of the analysis will use gene arrays, where more than 7,000 genes and intergenic regions known to be present in different strains of *S. aureus* will be "arrayed" or spotted on a tiny chip. The genetic content from the strains in the study can then be applied to the array and a gene-by-gene comparison can be made, creating a genomic map of the infecting bacteria.

A particularly critical hurdle to overcome in genetic research on *S. aureus* is its ability to mutate over time. It is a much different pathogen than it was even in the late 1990s, Lesse notes. The researchers are confident they can avoid this problem by collecting samples from patients in the three hospitals simultaneously and conducting quick but intensive genetic investigations.

"We hope to get a 'snapshot,' so the organisms aren't changing over that period of time," he says.

A statistical comparison of strains known to cause complications and those without complications will identify genes that may be associated with a more serious outcome during infection.

"The results will provide the basis for establishing model guidelines to design studies to predict whether a patient diagnosed with a particular strain of *S. aureus* will develop complications," says Lesse. "This data then can be used in future studies to determine whether the predictions are correct and whether patients at low risk of complications can be treated with shorter versus longer therapy [2 weeks or 4 to 6 weeks].

"Such guidelines will spare patients unnecessary medications, identify patients requiring appropriate longer treatment courses and may help slow the progress of the organism's antibiotic resistance." BP