The \textit{Staphylococcus aureus} bacterium is one of the most common and most important disease-causing organisms in humans.

\textit{S. aureus} frequently invades the bloodstream, causing \textit{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 \textit{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.
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 any evidence of endocarditis or deep infection after 24 to 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 from the strains in the study can then 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.”

Save the Date

The Medical Student Research Forum poster presentation took place on January 31, 2008, in the atrium of the Biomedical Education Building, with students displaying the results of research projects they conducted at UB and other institutions. Each participant worked closely with a research mentor to complete his or her project, and a variety of funding agencies supported the students with stipends.

“The forum provides students with the opportunity to showcase their research and communicate and interpret their results to other students, as well as to faculty,” says Debra L. Stamm, assistant dean for student services in the Office of Medical Education. “We recognize the importance of research training in providing the best medical care to patients and in providing future physicians with a well-integrated educational experience.”

From left: Lisa Steketee-Weaver, Puneet Belani, Elizabeth Gruber and Justin Mazzillo

First Place

Lisa Steketee-Weaver, Class of 2009, “Comparison of Sedation Techniques for Screening Colonoscopy”

Second Place

Puneet Belani, Class of 2010, “White Coat Hypertension and End Organ Damage in Children”

Third Place (corecipients)

Justin Mazzillo, Class of 2010, “Degranulation of Eosinophils in the Bronchial Lumen of Asthmatic Patients”

Elizabeth Gruber, Class of 2010, “GX15-070 and Bortezomib Induce Up-Regulation of Bcl-2 Single Domain Pro-Apoptotic Proteins Puma and Noxa and are Associated with Sporadic Anti-Tumor Activity in Rituximab-Resistant Cell Lines (RSCL and RRCL), and Primary Lymphoma Patient Specimens”