

**Title:** A Multi-Center, Randomized, Open-Label, Comparative Study to Assess the Safety and Efficacy of a Treatment Algorithm to Reduce the Use of Vancomycin in Adult Patients with Blood Stream Infections due to Staphylococci

**Principal Investigator:** Stephen Heard, M.D.

**Sponsor:** Duke University

**Purpose of Research**

The goal of this research is to decide how long subjects should actually receive antibiotics if they have blood cultures that have grown staphylococcal bacteria. Blood stream infections result in, and sometimes may occur during hospitalization. One of the causes of blood stream infections is intravenous catheters. These infections are caused usually by bacteria called *S. aureus* and CoNS and can often be treated with antibiotics for a short period of time. Severe and life-threatening problems can occur in some cases.

The subject will be assigned to one of two different treatment groups, the planned treatment arm or the standard of care group. The goal of the “planned treatment arm” is to reduce the length of time that the subject will receive antibiotics, when appropriate to the subject’s case.

Vancomycin has been the primary drug used to treat serious infections due to resistant staphylococci for over 30 years. The overuse of vancomycin has made it less powerful in treating staphylococci infections leading to the need to develop new ways to manage and monitor the use of the drug.

**Inclusion Criteria:**

1. If the subject has an intravenous catheter in place then the subject and his/her primary health care provider must agree to have the catheter removed within 48 hours of enrollment with the exception of those subjects who meet criteria for simple CoNS bacteremia as defined in Table 1. The catheter may be retained in those subjects with simple CoNS bacteremia.
2. Has blood stream infection defined as at least two blood culture samples of which at least one is positive for *S. aureus* or CoNS, obtained within 2 calendar days prior to enrollment (Day -2 or Day -1). In most cases, vancomycin (or other study drug alternative) will have been started prior to enrollment. Among patients being evaluated for study enrollment prior to speciation of the bacteria isolated from blood cultures, a Gram stain result of blood culture contents demonstrating Gram positive cocci in clusters will be acceptable. Patients with community-acquired infections may be included unless there is more than one positive blood culture at the time of enrollment. The rationale being that these patients are very likely to have complicated staphylococcal infection.
3. Subject requires intravenous antibiotic therapy in the opinion of his/her physician.
4. Women of child bearing potential must have a negative urine and/or serum pregnancy test.
5. All patients of reproductive potential must be abstinent or agree to use double-barrier contraception while receiving study (algorithm based or Standard of Care) therapy.

**Exclusion Criteria:**

1. Has known or suspected new complicated staphylococcal infection at the time of enrollment.
2. Weighs  $\geq 200$  kg.

3. Has non-removable intravascular foreign material at the time a positive blood culture was drawn (e.g., intracardiac pacemaker or cardioverter/defibrillator wires, hemodialysis access grafts, cardiac prosthetic valve, valvular support ring), which was not removed within 48 hours of enrollment. Exception: patients with epicardial pacemakers, vascular stents and non-hemodialysis grafts in place >90 days are eligible for enrollment. Arthroplasties and other extravascular devices are acceptable as long as there are no signs or symptoms of foreign material-related infection at the time of enrollment.
4. Has a moribund clinical condition such that there is a high likelihood of death or cardiac surgery during the next three days.
5. Has shock or hypotension (supine systolic blood pressure < 80 mmHg) or oliguria (urine output < 20 mL/h) unresponsive to fluids or pressors within four hours.
6. Has received an investigational drug within 30 days of study entry.
7. Has a documented history of significant allergy or intolerance to all protocol-approved antibiotics anticipated to be effective for their infection.
9. Has an infecting pathogen with confirmed reduced susceptibility to vancomycin (Minimum Inhibitory Concentrations (MIC) > 2 µg/mL). Note: If reduced susceptibility to vancomycin is discovered after enrollment, the patient will be treated with daptomycin (if pathogen is susceptible). Patient will remain in study as appropriate and be evaluated in the Intent to Treat (ITT) analysis, but will be excluded from Protocol Population (PP) analyses.
8. Is severely neutropenic (absolute neutrophil count < 0.100x10<sup>3</sup>/mm<sup>3</sup>) or is anticipated to develop severe neutropenia (absolute neutrophil count < 0.100x10<sup>3</sup>/mm<sup>3</sup>) during the study treatment period due to prior or planned chemotherapy.
9. Has previously known Human Immunodeficiency Virus (HIV) infection with a nadir CD4<sup>+</sup> count of 100 cells/mm<sup>3</sup>
10. Is considered unlikely to comply with study procedures or to return for scheduled post-treatment evaluations.
11. Is pregnant or trying to get pregnant, nursing, or lactating.
12. Has known or suspected septic arthritis, osteomyelitis, pneumonia or other metastatic focus of infection.
13. Has polymicrobial blood stream infection including at least one non-staphylococcal species. Note that it is possible that a subject may not have a known polymicrobial bloodstream infection at the time of enrollment, but additional pathogen(s) can subsequently be isolated from the initial blood culture. These patients will be eligible to remain in the trial. Please also note that patients with *S. aureus* plus CoNS will follow the treatment pathway for *S. aureus*.
14. Is hemodialysis dependent or has end stage renal disease (Creatinine Clearance (CrCl) < 30 cc/min).
15. Developed *Staphylococcus aureus* blood stream infection within 72 hours of percutaneous coronary revascularization

16. Received of any of the following antibiotics for 7 or more of the 10 calendar days immediately preceding the calendar day that the initial positive blood culture was drawn:

If methicillin susceptibility of the isolate is unknown at the time of enrollment: vancomycin; daptomycin; telavancin; tigecycline; linezolid (in either oral or intravenous administration); quinupristin/dalfopristin; piperacillin/tazobactam; nafcillin; oxacillin; cloxacillin; cefazolin; ceftriaxone; ceftaroline; levofloxacin or equivalent fluoroquinolone (in either oral or intravenous administration) Note: ciprofloxacin is not an exclusion criteria.

If the staphylococcal isolate is known to be methicillin resistant: vancomycin; daptomycin; telavancin; tigecycline; linezolid (in either oral or intravenous administration), quinupristin/dalfopristin, ceftaroline.

17. Has previously participated in this study.