Effect of Direct-from-blood Bacterial Testing on Antibiotic Administration and Clinical Outcomes

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Effect of direct-from-blood bacterial testing on antibiotic administration and clinical outcomes: A learning healthcare pragmatic randomized trial

Version 1.5

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Study Protocol- v1.5
Full Study Title: Effect of direct-from-blood bacterial testing on antibiotic administration and clinical outcomes: A learning healthcare pragmatic randomized trial
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1.0 Study Summary

Title	Effect of direct-from-blood bacterial testing on antibiotic administration and clinical outcomes: A learning healthcare pragmatic randomized trial
Coordinating Center	Center for Learning Healthcare, Vanderbilt Institute for Clinical and Translational Research (VICTR), Vanderbilt University Medical Center (VUMC)
Sponsor	T2 Biosystems
Background	Bacterial blood stream infections are common and life-threatening. Bloodstream infections have historically been identified using blood cultures, which often take 24-72 hours to result and are imperfectly sensitive. Diagnostic tests that can rapidly detect bacteria directly from whole blood samples without relying on growth in culture are increasingly used in clinical care. Use of direct-from-blood bacterial testing has been hypothesized to decrease exposure to unnecessary antibiotics and shorten the time to appropriate antibiotic therapy. More evidence is needed to fully understand the effects of use of direct-from-blood bacterial testing, compared to blood cultures alone, on antibiotic administration and clinical outcomes.
Aims	Primary Aim: Evaluate the effect of using direct-from-blood testing, compared to blood cultures alone, on the time to last dose of intravenous vancomycin among adult patients presenting to the emergency department with suspected infection and empiric initiation of vancomycin. Secondary Aim: Evaluate the effect of using direct-from-blood testing, compared to blood cultures alone, on time to systemic anti-pseudomonal beta-lactam antibiotic among adult patients presenting to the emergency department with suspected infection and empiric initiation of vancomycin.
Primary Hypothesis	We hypothesize that using direct-from-blood testing, compared with blood cultures alone, will decrease the time to the time to last dose of intravenous vancomycin.
Study Design	Single-center, parallel-group, non-blinded, pragmatic, randomized clinical trial
Inclusion Criteria	• Patient is located in the Emergency Department at Vanderbilt University Hospital • ≤ 12 hours from patient presentation to the Emergency Department at Vanderbilt University Hospital • Age ≥ 18 years • Clinician has ordered blood cultures

	• Clinician has ordered intravenous vancomycin
Exclusion Criteria	• Patient is known to be a prisoner • Patient is known to be pregnant • Patient is known to have received 2 or more doses of vancomycin since presentation to the Vanderbilt ED • Patient is known to have a positive bacterial culture in the previous 7 days • Patient is known to have an infection for which at least 7 days of intravenous vancomycin would routinely be administered regardless of bacterial testing results (e.g., skin and soft tissue infection)
Randomization	For patients who meet eligibility criteria, a computerized randomization within the electronic health record will assign patients in a 1:1 ratio to the direct-from-blood testing group or the blood culture group.
Interventions	Direct-from-blood testing Group. In addition to blood cultures, patients will receive direct-from-blood testing using the T2Bacteria® Panel. Blood culture Group. Patients will receive blood cultures and will not receive direct-from-blood testing.
Primary Outcome	Time to last dose of intravenous vancomycin
Secondary Outcome	Time to last dose of systemic anti-pseudomonal beta-lactam antibiotic
Analysis	The primary analysis will be an intention-to-treat comparison of patients randomized to the direct-from-blood testing group versus patients randomized to the blood culture group with regard to the primary outcome of time to last dose of intravenous vancomycin using a Cox proportional hazards model.
Sample Size	The trial will include 500 patients (250 patients per group).
Expected Duration	12 months of enrollment

2.0 Background

2.1 Blood cultures versus direct-from-blood tests for identifying bacterial pathogens

Bacterial infections of the bloodstream are a major cause of morbidity and mortality and are recognized as a major public health problem worldwide.[1] Bacteria in the bloodstream have historically been identified using blood cultures. Blood cultures, however, are limited by prolonged time to full identification - often 24-72 hours for bacteria[2–5]- and imperfect sensitivity that depends on the volume of the sample and a patient's prior exposure to antibiotics.[6] Because of these limitations, there has been increasing interest in using rapid diagnostic tests that identify bacteria directly from whole blood

samples without relying on growth in culture, referred to as "direct-from-blood" tests, in addition to standard blood cultures, to guide early therapeutic management of patients with suspected bloodstream infections .[7–9]

One such direct-from-blood test is the T2Bacteria® Panel. This panel's accuracy and performance as a direct-from-blood test for bacterial pathogens has been described in previous studies.[10–13] For this test, whole blood in a standard EDTA tube is used to amplify microbial cell-associated DNA for detection on a dedicated instrument platform in a clinical laboratory. This panel detects five bacterial pathogens: *Staphylococcus aureus*, *Enterococcus faecium*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Escherichia coli*. These five bacterial pathogens account for approximately 50% of organisms from positive blood cultures, are known for their antibiotic resistance mechanisms and nosocomial spread, and are leading causes of sepsis.[14–17] In a recent prospective, multicenter study, this direct-from-blood test demonstrated a sensitivity and specificity of 90% for these 5 organisms. The negative predictive value was 99.7%. Results were available within 4 to 8 hours.[10] Additionally, a recent meta-analysis of largely observational studies reported a faster transition to targeted microbial therapy and de-escalation of empirical microbial therapy, as well as a shorter duration of intensive care unit stay and hospital stay for patients who received this direct-from-blood test.[17]

2.2 Empiric, broad-spectrum antibiotics for suspected bacterial infections of the bloodstream

Early administration of antimicrobial therapy is a fundamental component of the management of adults presenting to the hospital with a suspected bloodstream infection or sepsis.[18] However, a major predictor of length of stay and mortality in these patients is administration of appropriate and targeted antimicrobial therapy.[18] Because blood cultures frequently take 24-72 hours to result, patients are typically treated with empiric, broad-spectrum antibiotics.[19] Thus, patients are commonly exposed to unnecessary antibiotics without evidence of infection or with evidence of infection requiring narrow antibiotic selection. In a meta-analysis of sepsis studies, empirical antibiotic therapy was inappropriate for the organism that ultimately grew in culture in almost half of patients.[18]

2.3 Empiric vancomycin for MRSA bacteremia

Current guidelines recommend the use of empiric intravenous vancomycin as coverage for methicillin-resistant *S. aureus* (MRSA) bacteremia.[20] In a multicenter, prospective surveillance study of adults hospitalized with community-acquired pneumonia, approximately one third of patients received empiric anti-MRSA antibiotics (vancomycin or linezolid), despite only 2.7% of ICU patients and 0.7% of patients overall growing MRSA in culture.[21] At Vanderbilt, vancomycin is the most commonly used antimicrobial and, as a result, the antimicrobial that generates the most cost for the health system. Vancomycin requires careful monitoring due to its narrow therapeutic range and high risk of toxicity.[22] Up to two-thirds of patients receiving high dose vancomycin develop acute kidney injury.[23,24] Vancomycin can also cause bone marrow suppression, linear IgA bullous dermatosis, anaphylaxis, and life-threatening hypersensitivity reactions.[25–28] Administration of vancomycin to patients who do not have MRSA can lead to avoidable adverse drug events and costs, as well as drive antimicrobial resistance.

2.4 Overview of trial

We will conduct a pragmatic, randomized clinical trial examining the effect of using direct-from-blood testing for bacterial pathogens, compared to using blood cultures alone, on antimicrobial receipt and clinical outcomes for adults presenting to the hospital with suspected infection who have been initiated on empiric therapy with intravenous vancomycin.

2.5 Rationale for trial

The accuracy and performance characteristics of direct-from-blood testing for bacterial pathogens are well-described.[7,10–12,17] Direct-from-blood testing has been adopted into clinical care at health systems across the United States. Several studies have also suggested the importance of pairing rapid diagnostic testing with active antimicrobial stewardship efforts to achieve antibiotic de-escalation.[7–9,29] However, the effect of using direct-from-blood testing as a part of clinical care on antibiotic administration and clinical outcomes remains unclear. A rigorous, real-world, randomized trial is required to compare the effects of direct-from-blood testing to blood cultures alone on the de-escalation of empirical antibiotic therapy, transition to targeted antimicrobial therapy, antimicrobial stewardship efforts, and clinical outcomes.[7,8,11,17,30,31] Before considering implementation of direct-from-blood testing across the health system, Vanderbilt seeks to better understand how the use of direct-from-blood testing for bacterial pathogens impacts use of antimicrobials, antimicrobial stewardship, health system resources, and costs. Therefore, this pragmatic, randomized clinical trial is designed to compare the use of direct-from-blood testing for bacterial pathogens to the use of blood cultures alone within clinical care.

3.0 Aims and Hypotheses

Study Aims

Primary Aim: Evaluate the effect of using direct-from-blood testing, compared to blood cultures alone, on the time to last dose of intravenous vancomycin among adult patients presenting to the emergency department with suspected infection initiated on empiric vancomycin.

Secondary Aim: Evaluate the effect of using direct-from-blood testing, compared to blood cultures alone, on time to last dose of systemic anti-pseudomonal beta-lactam antibiotic among adult patients presenting to the emergency department with suspected infection initiated on empiric vancomycin.

Study Hypotheses

We hypothesize that using direct-from-blood testing, compared to using blood cultures alone, will decrease the time from randomization to time to last dose of intravenous vancomycin among adult patients presenting to the emergency department with suspected infection initiated on empiric vancomycin.

4.0 Study Description

To address these aims, we will perform a single center, parallel-group, non-blinded, randomized clinical trial comparing the use of direct-from-blood testing for bacterial pathogens to blood cultures alone. The

study population will be 500 adult patients presenting to the Emergency Department at Vanderbilt University Medical Center with suspected infection for whom collection of blood cultures and empiric initiation of intravenous vancomycin are ordered within 12 hours of presentation to the Emergency Department. Patients in the direct-from-blood testing group will receive both blood cultures and direct-from-blood testing for bacterial pathogens. Patients in the blood cultures group will receive blood cultures and will not receive direct-from-blood testing for bacterial pathogens. The primary outcome will be the time to last dose of intravenous vancomycin. The secondary outcome will be the time to definitive antibacterial therapy. We will also report exploratory antimicrobial stewardship outcomes, safety outcomes, and clinical outcomes.

5.0 Inclusion and Exclusion Criteria

5.1 Inclusion Criteria

- Patient is located in the Emergency Department at Vanderbilt University Hospital
- ≤ 12 hours from patient presentation to the Emergency Department at Vanderbilt University Hospital
- Age ≥ 18 years
- Clinician has ordered blood cultures
- Clinician has ordered intravenous vancomycin

5.2 Exclusion Criteria

- Patient is known to be a prisoner
- Patient is known to be pregnant
- Patient is known to have received 2 or more doses of vancomycin since presentation to the Vanderbilt ED Patient is known to have a positive bacterial culture in the previous 7 days
- Patient is known to have an infection for which at least 7 days of intravenous vancomycin would routinely be administered regardless of bacterial testing results (e.g., skin and soft tissue infection, etc.)

6.0 Enrollment and Randomization

6.1 Study Site

Vanderbilt University Adult Hospital at Vanderbilt University Medical Center; Nashville, Tennessee, USA

6.3 Enrollment

At the time that a treating clinician in the Emergency Department at Vanderbilt University Adult Hospital initiates orders for blood cultures and intravenous vancomycin for a patient who meets all inclusion criteria, an advisor within the electronic health record (details in section 7) will prompt treating clinicians to record whether the patient meets any exclusion criteria. If the treating clinician confirms that the patient does not meet any exclusion criteria, the patient will be enrolled and randomized. Enrollment times will be flexible to accommodate clinical staff. For patients who are determined to be

ineligible, the advisor will track the number and reasons for exclusion. The time of randomization will be defined as "time zero" on "study day 0."

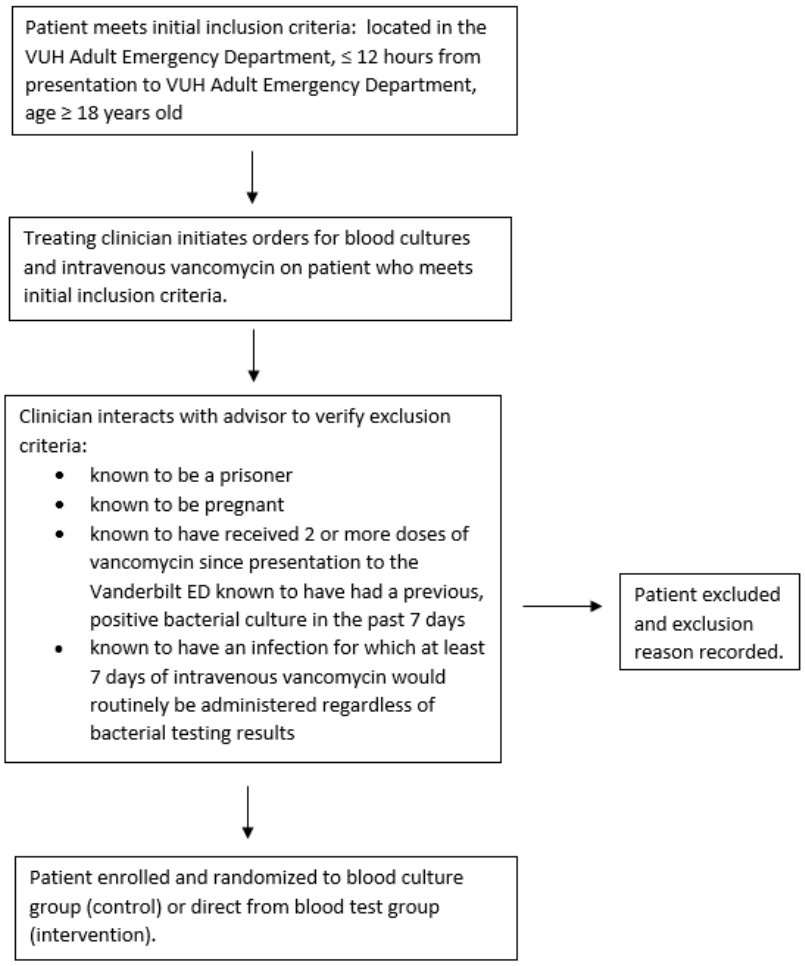

Figure 1: Enrollment Schema

6.4 Consent

Because this study involves minimal incremental risk, the study would not adversely affect the welfare or privacy rights of the participant, and obtaining informed consent would be impracticable, we will request a waiver of informed consent. Numerous previous randomized trials comparing two clinically available approaches to diagnosis of acute infection have been completed with a waiver of informed consent.[29,32–34]

6.4.1 Minimal risk

This study compares two standard-of-care laboratory methods for detecting bacterial pathogens in blood samples. The technology used in both laboratory methods is approved by the U.S. Food and Drug Administration, available for use in routine clinical care, and used in current clinical care in health systems across the U.S. In current clinical care, the technology a health system uses to detect bacterial pathogens in the blood is based primarily on the preferences of health system leaders and laboratory administrators because no large, randomized trials or evidence-based guidelines support the use of one method over the other and clinicians, patients, and families generally do not determine which laboratory methods a health system uses to identify bacterial pathogens in blood samples. As such, determining which laboratory method for detecting bacterial pathogens in blood samples a patient receives (blood cultures alone vs blood cultures plus direct-from-blood testing) as part of this research study poses minimal incremental risk compared to clinical care outside of the study. The total volume of blood drawn is approximately 4 mL greater with the use of direct-from-blood testing and blood cultures, compared to blood cultures alone. This volume of blood is similar to that normally drawn during a routine medical examination. Because a patient not participating in this study could experience any potential risks and benefits of use of direct-from-blood testing or use of blood cultures alone if presenting for care to a health system that primarily uses direct-from-blood testing or a health system that primarily uses blood cultures alone, a primary risk of the research that would not be present in clinical care is the potential for loss of confidentiality from the use of protected health information for research. All data that will be used for the study are collected in the electronic health record as part of routine clinical care. The extensive procedures the study takes to prevent loss of confidentiality are detailed in Section 13.

6.4.2 Practicability of obtaining written, informed consent

Obtaining written informed consent prior to enrollment in this study would be impracticable. Patients presenting to an emergency department with a suspected blood stream infection are experiencing a medical emergency. Blood for cultures or direct-from-blood testing must be obtained prior to administration of antibiotics and each hour of delay in the initiation of antibiotics increases mortality by 7%.[35] The average time between initiation of an order for an intravenous antibiotic and its administration is 28 minutes in the Emergency Department at Vanderbilt. Obtaining prospective written informed consent during this interval is impracticable and risks delaying antibiotic administration. Moreover, patients presenting to the Emergency Department with suspected infection requiring empiric intravenous antibiotics are frequently unconscious or delirious, and a legally authorized representative (LAR) is frequently not present. Because the trial determines the laboratory method for detecting bacterial pathogens in the initial blood sample drawn before antibiotic administration in the Emergency Department but defers all subsequent aspects of treatment to clinicians (e.g., choice of antibiotics, timing of discontinuation of antibiotics), the primary study procedure will be completed within 1 hour of meeting eligibility criteria. While additional attempts to collect the sample for direct-from-blood testing may be made for up to 12 hours following randomization if an adequate sample is not initially drawn for patients in the intervention arm, consent would still not be feasible or practicable in this instance as 1)

consent would not be obtained for patients in usual care and thus 2) the study could be biased if patients differentially consented to participate in the study across study arms.

6.5 Randomization

Eligible patients will be randomized in a 1:1 ratio to the direct-from-blood test group or the blood culture alone group. A series of study group assignments will be generated by computerized randomization using EPIC functionality. Simple randomization without stratification, permuted blocks, or minimization will be used.

7.0 Study Procedures

7.1 Blood Culture Group

For patients assigned to the blood culture group, the blood cultures ordered at the time of eligibility assessment will be collected, performed, and reported as in routine clinical care. The blood culture testing will be performed in the clinical laboratory at Vanderbilt. At Vanderbilt, blood culture results are updated intermittently as results become available. Negative blood cultures, similar to other tests without a critical result, are uploaded in the electronic health record for review by the clinician. Following a gram stain for a positive blood culture, the ePlex/Roche test is used. This tests for 95% of the most common bacterial pathogens recovered in blood cultures.[36] The results of the ePlex/Roche test on the blood culture are reported in the electronic health record along with an electronic notification (alert) to the clinical team. Identification of selected organisms (e.g., *S. aureus*, *Enterococcus* and *S. lugdunensis*) are also alerted to the Infectious Disease fellows. Blood containing bacteria is plated onto culture media to definitively identify organisms and characterize antibiotic susceptibility, if indicated. These results are also communicated to the clinical team in the electronic health record. Patients will have access to these results in their MyHealth at Vanderbilt portal.

7.2 Direct from Blood Test Group (Intervention Group)

For patients assigned to the direct-from-blood test group, in addition to having blood cultures collected, performed, and reported in the process described above, direct-from-blood testing for bacterial pathogens will be performed. The order for blood cultures will be accompanied by an order for direct-from-blood testing for bacterial pathogens. As the blood is being collected for blood cultures, clinical personnel will collect an additional 4 mL for direct-from-blood testing for bacterial pathogens as possible. If an adequate direct-from-blood test sample is not drawn (e.g. incorrect tube or insufficient sample volume, missed or cancelled lab order, etc.) additional attempts to collect the sample for direct-from-blood testing may be made for up to 12 hours following randomization. Direct-from-blood testing for bacterial pathogens will be performed in the clinical laboratory. Direct-from-blood testing will use the T2Bacteria® Panel. Results of direct-from-blood testing for bacterial pathogens will be reported in the following ways:

1. The results will be reported in the electronic health record in the same section on microbiology in which blood culture results are reported. The report will contain a description of the

performance characteristics of the direct-from-blood testing and an interpretation of the findings. Patients will have access to these results in their MyHealth at Vanderbilt portal.

2. The results will be sent to the treating clinicians on the patient's primary team via a text page at the time the results populate into the patient's electronic health record. The text page will include the results for all five pathogens identified by the panel. Treating clinicians will also be directed to information regarding interpreting the direct-from-blood testing results.
3. For patients with direct-from-blood testing that is negative for *S. aureus* who continue to have an active order for intravenous vancomycin, an interruptive best practice alert (BPA) will remind treating clinicians of the result of the direct-from-blood testing and prompt the clinician to select a reason for continuing vancomycin if continued (e.g., known or suspected infection with a pathogen for which vancomycin is standard of care; severe or serious allergy to alternative antimicrobials; surgical prophylaxis; other). This BPA does not result in any automatic action and does not limit the autonomy of the care provider in the clinical decision-making process. All aspects of the patient's treatment remain at the clinician's discretion.
4. For patients receiving intravenous vancomycin for whom the pharmacokinetics services is consulting, the pharmacokinetics service will incorporate the results of the direct-from-blood testing into their recommendations and communications with the treating clinicians (as they would standard blood culture results as well).

Clinicians and patients may use these results, in addition to information about the patient's demographics, chronic conditions, acute conditions, vital signs, other laboratory results, and concurrent treatments to help inform decisions. Neither the blood cultures nor the direct-from-blood test will serve as the sole basis for diagnosis, treatment, or other management decisions.

7.3 Co-interventions: Management of Vancomycin by Pharmacokinetics Service

For patients in both trial groups of the current study, management of intravenous vancomycin by the pharmacokinetics service will occur as it does in routine clinical care. At Vanderbilt, adult patients with an active order for intravenous vancomycin are followed by the pharmacokinetics service to determine the dosing regimen of vancomycin to maximize safety and therapeutic efficacy. The typical workflow consists of:

- Assessing patient information necessary to dose and monitor the antibiotic.
- Entering order for serum creatinine if one has not been obtained.
- Entering order for dosage regimen based on pharmacokinetic principles.
- Entering order for peak, trough, and/or random levels, as applicable.
- Performing follow-up monitoring and/or dose adjustments, as needed.
- Documenting a consult note in the electronic medical record upon initial consultation and daily until the protocol is discontinued.
- Notifying the provider for further instructions if:
    - Adverse reactions or evidence of hypersensitivity.

- Systemic concentration of specified medication that is two times above the upper limit or if the concentration is significantly below the lower limit of the therapeutic range as defined by VUMC.
- Increases in serum creatinine two times the patient's baseline serum creatinine value.

7.4 Blinding

This will be an unblinded study. Given that this study evaluates the use of diagnostic testing to provide guidance to clinicians, it is not feasible to blind clinicians in this study. As patients will receive the results of the diagnostic tests through communication with their clinicians and directly through access to their electronic health record, it is not feasible to blind patients in this study.

8.0 Data Collection and Outcome Measures

8.1 In-Hospital Outcomes

Primary Outcome

The primary outcome is time to last dose of intravenous vancomycin, defined as the time between randomization and the start time for the last dose of intravenous vancomycin received by the patient within 14 days of randomization.

Secondary Outcome

The secondary outcome is time to last dose of systemic anti-pseudomonal beta-lactam antibiotic, defined as the time between randomization and start time of the last dose of systemic anti-pseudomonal beta-lactam antibiotic received by the patient within 14 days of randomization.

Exploratory Outcomes

<u>Exploratory Antimicrobial Stewardship Outcomes:</u>

1. Total number of doses of intravenous vancomycin received between randomization and 14 days after randomization.
2. Total number of days on which gram-positive antibacterial therapy was received between randomization and 14 days after randomization.
3. Total number of days on which gram-negative antibacterial therapy was received between randomization and 14 days after randomization.
4. Time to receipt of antibacterial therapy with effective coverage for blood stream infections identified by final blood culture results collected prior to or at the same time as randomization, assessed at 14 days after randomization.
5. Proportion of patients who experienced *Clostridioides difficile* infection between randomization and hospital discharge or 28 days after randomization, whichever occurs first.

Exploratory Safety Outcomes:

1. Proportion of patients who experienced an allergic reaction to antimicrobial therapy between randomization and 14 days after randomization
2. Proportion of patients for whom vancomycin was discontinued between randomization and 72 hours for whom any culture from the 24 hours prior to or 24 hours after randomization grew methicillin resistant *S. aureus.*
3. Proportion of patients for whom all anti-staphylococcal therapy was discontinued between randomization and 72 hours for whom any culture from the 24 hours prior to or 24 hours after randomization grew *S. aureus.*
4. Proportion of patients for whom all anti-pseudomonal therapy was discontinued between randomization and 72 hours for whom any culture from the 24 hours prior to or 24 hours after randomization grew *P. aeruginosa*

Exploratory Clinical Outcomes:

1. Highest stage of acute kidney injury by KDGIO creatinine criteria between randomization and 14 days after randomization
2. Receipt of renal replacement therapy between randomization and 14 days after randomization
3. Lowest platelet count between randomization and 14 days after randomization
4. Hospital-free days to day 28, defined as the number of calendar days alive and free of hospitalization between randomization and 28 days after randomization with outcome assessment censored at hospital discharge
5. ICU-free days to day 28, defined as the number of calendar days alive and free of intensive care unit admission between randomization and 28 days after randomization with outcome assessment censored at hospital discharge
6. All-cause, in-hospital mortality to day 28

Process Measures

Antimicrobial Stewardship Process Measures:

1. Time from randomization to a positive test for bacteria in the blood (either direct-from-blood test or bacterial culture)
2. Time from randomization to direct-from-blood test result (in direct-from-blood test group)
3. Time from randomization to blood culture results (in blood culture group)
4. Concordance between direct-from-blood result and blood culture result (in direct-from-blood test group)
5. Receipt of non-vancomycin antimicrobial therapy for MRSA bacteremia in the 14 days following randomization
6. Number of consultations to Infectious Disease in the 14 days following randomization
7. Number of supratherapeutic vancomycin levels in the 14 days following randomization
8. Number of patients followed by the Pharmacokinetics team.

8.2 Baseline Data

We will collect demographic characteristics of the patients and details of their acute and chronic clinical conditions to describe the trial population at baseline. Data collected will include: age, sex, race, ethnicity, body mass index, sepsis, sequential organ failure assessment score, suspected source of infection, presence of chronic kidney disease, presence of end-stage renal disease on renal replacement therapy, presence of acute kidney injury at enrollment, baseline vital signs (e.g., temperature, heart rate), baseline laboratory values (e.g., white blood cell count), comorbidities (e.g., Charlson comorbidity index), and time from presentation to the ED to enrollment.

8.3 Data from enrollment to hospital discharge

We will collect data on the diagnostic tests and treatments patients receive and their clinical condition from enrollment to hospital discharge. Data collected will include: collection and results of cultures, collection and results of direct-from-blood testing for bacterial pathogens, receipt of antimicrobial medications, dose of antimicrobial medications, vital signs (e.g., temperature, heart rate), laboratory values (e.g., white blood cell count), organ function (e.g., sequential organ failure assessment score), location (e.g., emergency department, hospital ward, intensive care unit).

8.4 Outcome Data

We will collect data on the trial outcomes. Data collected will include: timing and dose of antimicrobial therapy, antimicrobial sensitivities of organisms identified, allergic reactions to antimicrobials, receipt of organ support (e.g., kidney replacement therapy, mechanical ventilation), duration of intensive care unit admission, duration of hospital admission, and death.

9.0 Risks and Benefits

At this time, there is no reason to believe that participation in this study comparing two laboratory methods for identifying bacterial pathogens in blood samples would expose patients to greater medical risks or benefits than those experienced by acutely ill patients receiving blood tests for bacterial pathogens as a part of routine care. This study has the potential to provide a direct benefit to patients by decreasing the time to treatment with effective antimicrobial therapy and decreasing patients' exposure to unnecessary antimicrobial therapy and associated side effects. However, whether such benefits exist is currently unknown.

A potential risk to patients participating in this study involves the collection of protected health information (PHI). To limit the associated risks of inadvertent disclosure of PHI, the minimum amount of PHI necessary for study conduct will be collected. After collection, the data will be stored in a secure online database only accessible by the investigators and relevant key study personnel (KSP). Once the data collection period is complete, a de-identified research database will be created for data analysis.

10.0 Safety Monitoring and Adverse Events

10.1 Adverse Event Definitions

Adverse Event – An adverse event will be defined as any untoward or unfavorable medical occurrence in a human subject temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. Any adverse event occurring during the research will be classified according to the following characteristics:

- **Seriousness** – An adverse event will be considered "serious" if it:
    - Results in death
    - Is life-threatening (defined as placing the patient at immediate risk of death)
    - Results in inpatient hospitalization or prolongation of existing hospitalization
    - Results in a persistent or significant disability or incapacity
    - Results in a congenital anomaly or birth defect or
    - Based upon appropriate medical judgment, may jeopardize the patient's health, and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

- **Unexpectedness** – An adverse event will be considered "unexpected" if the nature, severity, or frequency is neither consistent with:
    - The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in the protocol-related documents, such as the IRB-approved research protocol; nor
    - The expected natural progression of any underlying disease, disorder, or condition of the subject experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

- **Relatedness** – The strength of the relationship of an adverse event to a study intervention or study procedure will be defined as follows:
    - Definitely Related: The adverse event follows (1) a reasonable, temporal sequence from a study procedure AND (2) cannot be explained by the known characteristics of the patient's clinical state or other therapies AND (3) evaluation of the patient's clinical state indicates to the investigator that the experience is definitely related to study procedures.
    - Probably or Possibly Related: The adverse event meets some but not all of the above criteria for "Definitely Related".
    - Probably Not Related: The adverse event occurred while the patient was on the study but can reasonably be explained by the known characteristics of the patient's clinical state or other therapies.
    - Definitely Not Related: The adverse event is definitely produced by the patient's clinical state or by other modes of therapy administered to the patient.
    - Uncertain Relationship: The adverse event does not fit in any of the above categories.

10.2 Monitoring for Adverse Events

The time interval during which patients will be monitored for the occurrence of adverse events begins at randomization and ends at the first of hospital discharge or 14 days. Adverse events occurring before randomization or after hospital discharge or 14 days will not be collected. The principal investigator (PI) will have primary responsibility for overseeing the monitoring, assessment, and reporting of adverse events. Site study personnel will evaluate for the occurrence of adverse events by review of the electronic health record and by communication with treating clinicians. Site study personnel will evaluate for the occurrence of adverse events by manual review of the electronic health record during initial data collection and during final data collection. Study personnel will also communicate regularly with the treating clinicians in the study environments to solicit information about any potential adverse events. If study personnel at a site identify a potential adverse event, the PI will be immediately notified. The PI will assess the seriousness, unexpectedness, and relatedness of the potential adverse event. The PI at the site will determine whether the event qualifies for recording and reporting.

10.3 Recording and Reporting Adverse Events

The following types of adverse events will be recorded and reported:

- Adverse events that are Serious and Definitely Related, Probably or Possibly Related, or of Uncertain Relationship.
- Adverse events that are Unexpected and Definitely Related, Probably or Possibly Related, or of Uncertain Relationship.

Adverse events that do not meet the above criteria will not be recorded or reported. Adverse events that the PI at a site assesses to meet the above criteria for recording and reporting will be entered into the adverse event electronic case report form in the trial database. The PI at the site will record an assessment of each characteristic for the adverse event, including seriousness, unexpectedness, and relatedness.

For any adverse event that is **serious AND unexpected**, and definitely related, probably or possibly related, or of uncertain relationship, the PI will report the adverse event to the coordinating center **within 24 hours** of becoming aware of the adverse event. For any other adverse event requiring recording and reporting, the PI will report the adverse event to the coordinating center **within 72 hours** of becoming aware of the adverse event. The coordinating center will coordinate with the PI to obtain information about the adverse event regarding each characteristic for the adverse event, including seriousness, expectedness, and relatedness. The PI will be responsible for making final determinations regarding seriousness and unexpectedness. Upon formal reporting, the IRB will be responsible for making final determinations regarding relatedness.

For adverse events that meet the above criteria for recording and reporting, the PI will notify the IRB and the sponsor in accordance with the following reporting plan:

Characteristics of the Adverse Event	**Reporting Period**

Fatal or life-threatening (and therefore serious), unexpected, and definitely related, probably or possibility related, or of uncertain relationship.	Report to the IRB and sponsor within 7 days after notification of the event.
Serious but non-fatal and non-life-threatening, unexpected, and definitely related, probably or possibly related, or of uncertain relationship.	Report to IRB and sponsor within 15 days of notification of the event.

10.4 Clinical Outcomes that may be Exempt from Adverse Event Recording and Reporting

In this study of hospitalized patients with advanced illness at high risk for death and other adverse outcomes due to their underlying advanced illness, clinical outcomes, including death, will be systematically collected and analyzed for all patients. The primary, secondary, and exploratory outcomes will be recorded and reported as clinical outcomes and not as adverse events unless treating clinicians or site investigators believe the event is Definitely Related or Probably or Possibly Related to the study intervention or study procedures. This approach – considering death and other outcomes as clinical outcomes rather than adverse events and systemically collecting these clinical outcomes for analysis – is common in trials among patients with advanced illness. This approach ensures comprehensive data on death and other outcomes for all patients, rather than relying on sporadic adverse event reporting to identify these important events. The following events are examples of study-specific clinical outcomes that would not be recorded and reported as adverse events unless treating clinicians or site investigators believe the event was Definitely Related or Probably or Possibly Related to the study intervention or study procedures:

- Death (all deaths occurring prior to hospital discharge or 28 days will be recorded)
- Duration of ICU admission
- Duration of hospitalization

10.5 Unanticipated Problems involving Risks to Subjects or Others

Investigators must also report to the coordinating center Unanticipated Problems Involving Risks to Subjects or Others ("Unanticipated Problems"), regardless of severity, associated with study procedures **within 24 hours** of the site investigator becoming aware of the Unanticipated Problem. An Unanticipated Problem is defined as any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol; and (b) the characteristics of the subject population being studied; AND
- Definitely Related or Probably or Possibly Related to participation in the research (as defined above in the section on characteristics of adverse events); AND
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

If any study personnel become aware of an event that may represent an Unanticipated Problem, they will immediately contact the PI. The PI will assess whether the event represents an Unanticipated Problem by applying the criteria described above. If the PI determines that the event represents an

Unanticipated Problem, the PI will record the Unanticipated Problem in the Unanticipated Problem electronic case report form in the trial database. The PI will obtain information about the Unanticipated Problem and report the Unanticipated Problem to the IRB and sponsor within 15 days of becoming aware of the Unanticipated Problem.

11.0 Study Withdrawal/Discontinuation

Patients can be withdrawn from study participation in the following circumstances:

- The investigator decides that the patient should be withdrawn for safety considerations.
- There is a significant protocol violation in the judgment of the PI such that continuing the study would place the patient at undue risk.

The reason and date of every withdrawal will be recorded in the patient study records. For patients in the direct-from-blood testing group, if they withdraw from the study prior to blood collection for the direct from blood test, the test will not be completed. Once the blood for direct-from-blood testing has been sent to the laboratory, the order will not be discontinued, and the results will not be removed from the medical record. Patients who withdraw from the study will be followed via medical record review to evaluate safety parameters but study personnel will not directly interact with a patient after withdrawal. Follow-up will be performed for all patients who discontinue due to an adverse event or any other safety parameter. If a patient experiences an adverse event meeting criteria reporting criteria above, the patient will be followed until the event has resolved, is deemed chronic and stable, or as long as clinically appropriate. This follow-up will be documented in the patient study record.

12.0 Statistical Considerations

Sample size considerations

The planned sample size for this trial is 500 patients. In a prior study in the same study location among a similar patient population who underwent blood culturing without direct-from-blood bacterial testing, the median time from randomization to discontinuation of intravenous vancomycin was 48 hours (IQR 24 to 96). Assuming a statistical power of 80%, a two-sided alpha of 0.05, and no missing data for the primary outcome, we calculated that detecting a 0.5 day (12 hour) difference in the primary outcome of time to discontinuation of intravenous vancomycin would require enrolling 500 patients (250 patients in each group).

Trial profile:

We will present a Consolidated Standards of Reporting Trials diagram to detail the movement of patients through the study. This diagram will include total number of patients meeting inclusion criteria, number excluded and reason for exclusion, number enrolled and randomized in the study, number followed, and number analyzed.

Baseline Characteristics:

We will summarize in a Table the distribution of baseline variables across the study arms. Categorical variables will be reported as frequencies and percentages and continuous variables as either means with SDs or medians with interquartile ranges.

Primary Analysis of the Primary Outcome:
The primary analysis will be an intention-to-treat comparison of patients randomized to the direct-from-blood testing group versus patients randomized to the blood culture alone group with regard to the primary outcome. The primary outcome will be compared between trial groups using a Cox proportional hazards model.

Secondary Analyses of the Primary Outcome:
We will perform an intention-to-treat comparison of the primary outcome between groups using a multivariable Cox proportional hazard model adjusting for baseline characteristics, which will be prespecified in a statistical analysis plan.

Analyses of Secondary and Exploratory Outcomes
We will perform intention-to-treat comparisons of the secondary and exploratory outcomes between trial groups. Categorical outcomes will be compared with a Chi-square test, continuous or ordinal outcomes will be compared with a Wilcoxan rank sum test, and time-to-event outcomes will be compared between groups using Kaplan-Meier curves or Cox proportional hazards models.

Heterogeneity of Treatment Effect
To evaluate whether pre-specified baseline variables modify the effect of trial group assignment on the primary outcome, we will perform Cox proportional hazards modelling with the primary outcome as the dependent variable and independent variables of the study group, the proposed effect modifier, and the interaction between the two. To account for non-linear relationships, continuous variables will be analyzed using restricted cubic splines with between 3 and 5 knots. Forest plots will be used to graphically display the adjusted analyses, and locally weighted regression or partial effects plots will be used to portray the association between continuous covariates and the outcome. A full list of prespecified variables for evaluating effect modification will be outlined in the detailed Statistical Analysis Plan prior to conclusion of enrollment.

13.0 Privacy and Confidentiality

At no time during the course of this study, its analysis, or its publication will patient identifiers be revealed outside the study team. The minimum necessary data containing patient or provider identities will be collected. As quickly as feasible, all data collected will be uploaded into a password-protected computerized database maintained within a secure, web-based application for building and managing online databases or stored on secure servers with user-level access control. All patients will be assigned a unique study number for use in the computerized database. At the time of publication all identifiers will be removed.

14.0 Follow-up and Record Retention

Patients will be followed for 28 days or until hospital discharge, whichever occurs first. Records will be retained compliant with institutional, federal, and local regulations. PHI will be stored in a secure online database. Only relevant Key Study Personnel will have access to this database containing PHI. Once the data collection period is complete, a de-identified research database will be used for analysis. Additionally, per the VUMC contract with T2 Biosystems, the study team will provide a de-identified data set through a secure, encrypted messaging system at the conclusion of data analysis, as appropriate. Secondary use of the data will be with IRB approval. The dataset may be made available outside of the study team on reasonable request with approval from an authorized Institutional Review Board and concurrence with the study team that the data are fit for purpose.

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16.0 Appendix

16.1 Enrollment Pause

On December 25, 2023, study enrollment was paused (36 patients had been enrolled in the trial). The study team deemed this necessary due to logistical challenges in receiving an adequate direct-from-blood test sample volume for patients in the intervention arm, as well as to evaluate the performance of the instrument that runs the direct-from-blood test samples. All components of trial procedures were evaluated at this time. The trial will resume enrollment upon implementation of procedures to ensure intervention fidelity.