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Examining the effect of direct-from-blood bacterial testing on antibiotic administration and clinical outcomes: a protocol and statistical analysis plan for a pragmatic randomised trial

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ABSTRACT

Introduction Patients with suspected bacterial infection frequently receive empiric, broad-spectrum antibiotics prior to pathogen identification due to the time required for bacteria to grow in culture. Direct-from-blood diagnostics identifying the presence or absence of bacteria and/or resistance genes from whole blood samples within hours of collection could enable earlier antibiotic optimisation for patients suspected to have bacterial infections. However, few randomised trials have evaluated the effect of using direct-from-blood bacterial testing on antibiotic administration and clinical outcomes. This manuscript describes the protocol and statistical analysis plan for a randomised trial designed to evaluate the effect of blood cultures plus direct-from-blood bacterial testing results compared with blood culture results alone on antibiotic administration and clinical outcomes.

Methods and analysis We are conducting a prospective, single-centre, parallel-group, non-blinded, pragmatic, randomised trial. The trial will enrol 500 adult patients presenting to the emergency department at Vanderbilt University Medical Center with suspected bacterial infection who have been initiated on empiric intravenous vancomycin. Eligible patients are randomised 1:1 to receive Food and Drug Administration-approved direct-from-blood bacterial testing in addition to blood cultures or blood cultures alone. The primary outcome is the time to the last dose of intravenous vancomycin within 14 days of randomisation. The secondary outcome is the time to the last dose of systemic antipseudomonal beta-lactam antibiotics within 14 days of randomisation. Additional outcomes include highest stage of acute kidney injury, lowest platelet count and receipt of kidney replacement therapy within 14 days of randomisation, as well as hospital-free days, intensive care unit-free-days and all-cause, in-hospital mortality within 28 days of randomisation. Enrolment began on 13 December 2023.

Ethics and dissemination The trial involves human participants and was approved by the Vanderbilt University Medical Center institutional review board with a waiver of informed consent (IRB#231229). Results will be submitted in a peer-reviewed journal and presented at scientific conferences.

Trial registration number NCT06069206.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Randomised trial design minimises potential bias.
⇒ Broad eligibility criteria can provide more representative findings.
⇒ Real-world evaluation of effectiveness promotes uptake of findings into practice.
⇒ Clinicians and investigators are unblinded to study group assignment, which can affect the validity of results.
⇒ Study conduct at a single centre, limiting potential generalisability of the findings.

INTRODUCTION

Early empiric antibiotics are fundamental in the treatment of adults presenting to the hospital with a suspected bacterial infection[1] or sepsis.[2] Guidelines recommend antibiotics empirically covering for methicillin-resistant *Staphylococcus aureus* (MRSA), such as vancomycin, in patients with sepsis and other high-risk features.[2 3] More than half of patients with suspected infection are administered antibiotics with MRSA coverage;[4] however, MRSA only accounts for 2%–10% of infections among critically ill adults.[5] Administration of vancomycin to patients who do not have MRSA can lead to avoidable adverse drug events, higher costs and antibiotic resistance.[6–12] Guidelines recommend de-escalation of vancomycin when it is known that MRSA is not the cause of infection.[2]

While bacterial pathogens in the blood are currently identified using blood cultures, blood cultures often require 24–72 hours to result[13–16] and have variable sensitivity,[17] leading to delays in de-escalation or discontinuation of antibiotic therapy.

Molecular diagnostics identifying pathogens directly from blood could improve antibiotic stewardship by providing faster results. Presently, the only FDA-certified in vitro diagnostic direct-from-blood test is the T2Bacteria panel. A recent meta-analysis reported a faster transition to targeted antibiotic therapy and de-escalation of empiric antibiotic therapy for patients who received this direct-from-blood test.[18] Several studies have suggested the importance of pairing rapid diagnostic testing with active antibiotic stewardship efforts for more rapid antibiotic de-escalation.[19–22] However, the effect of using direct-from-blood testing with stewardship interventions on antibiotic administration and clinical outcomes remains unclear.[18 23 24] To address this knowledge gap, we designed a pragmatic, randomised clinical trial to compare the use of direct-from-blood testing for bacterial pathogens to the use of blood cultures alone on antibiotic receipt and clinical outcomes for adults presenting to the emergency department (ED) initiated on empiric intravenous vancomycin.

METHODS AND ANALYSIS

This manuscript was written in accordance with Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (figure 1, online supplemental file 1).[25] The Vanderbilt Center for Learning Healthcare supports the conduct of this pragmatic, randomised clinical trial embedded within clinical care.[26]

Study design

We are conducting a pragmatic, single-centre, unblinded, parallel-group, randomised trial comparing the effect of direct-from-blood bacterial testing in addition to blood cultures (intervention group) to blood cultures alone (control group) on antibiotic receipt and clinical outcomes for adults presenting to the emergency department (ED) who have been initiated on empiric intravenous vancomycin therapy. The primary outcome is time to last dose of intravenous vancomycin within 14 days. We hypothesise that patients in the intervention group will have a shorter time from enrolment to the last dose of vancomycin as compared with patients in the control group. The trial protocol was approved by the institutional review board at Vanderbilt University Medical Center and registered prior to initiation of enrolment (NCT06069206).

Study population

Inclusion criteria

1. Patient is located in the ED at Vanderbilt University Hospital
2. ≤12 hours from patient presentation to the ED at Vanderbilt University Hospital
3. Age≥18 years
4. Clinician has ordered blood cultures
5. Clinician has ordered intravenous vancomycin

Exclusion criteria

1. Patient is known to be a prisoner
2. Patient is known to be pregnant
3. Patient is known to have received two or more doses of vancomycin since presentation to the Vanderbilt ED
4. Patient is known to have a positive bacterial culture in the previous 7 days
5. 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 (eg, skin and soft tissue infection).

In exclusion criterion number 5, 'bacterial testing results' refers to results obtained from blood cultures or direct-from-blood bacterial testing and 'an infection for which at least 7 days of intravenous vancomycin would routinely be administered' was determined by the clinician at the time of eligibility assessment, with examples including skin and soft tissue infection, catheter infections, endocarditis or osteomyelitis.

Screening and enrolment

At the time that a treating clinician places the orders for a patient who meets all inclusion criteria, a clinical decision support (CDS) tool within the electronic health record (EHR) informs the provider of the study and queries the provider regarding the presence of any exclusion criteria (figure 1). If the treating clinician confirms that no exclusion criteria are present, the patient is enrolled and randomised. The CDS tool tracks the reasons for exclusion for patients determined to be ineligible.

Randomisation and treatment allocation

Eligible patients are randomised in a 1:1 ratio using simple, computerised randomisation embedded in the EHR. Study group assignment remains concealed until the patient has been enrolled.

Study interventions

Figure 2 provides a schematic of study procedures for the intervention group and the control group.

Direct-from-blood test group (intervention group)

For patients assigned to the direct-from-blood test group, direct-from-blood testing for bacterial pathogens is performed using the T2Bacteria panel in addition to standard blood cultures. Standard blood cultures allow detection of pathogens not included on the T2Bacteria panel. Institutional methods for blood culture and pathogen identification that apply to patients enrolled in both the intervention and control groups are described in the 'Blood culture alone group (control group)' section below.

	STUDY PERIOD				
	Eligibility Screen	**Randomization & Allocation**	**Post-allocation**		**Final Outcome Assessment**
TIMEPOINT	*Order entry for BC and Vanc*	EHR enrollment advisor	*Within 1 hour*	*14 days after enrollment*	*Discharge or 28 days after enrollment*
ENROLLMENT:		X			
EHR-based inclusion criteria screening	X				
Manual screening for exclusion criteria by treating clinicians	X				
Allocation		X			
INTERVENTIONS:					
Direct-from-blood testing + BC			X		
BC alone			X		
ASSESSMENTS:					
Baseline variables		X			
Adverse events		X	X	X	X
Primary and secondary outcome				X	X
Exploratory outcomes				X	X

Figure 1 Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist. Enrolment, interventions and assessments. BC, blood cultures; EHR, electronic health record; Vanc, intravenous vancomycin.

Clinical personnel collect 4 mL of blood in an EDTA tube for T2Bacteria panel testing (online supplemental file 3). This test's accuracy and performance have been described in previous studies.[23 27–29] The T2Dx instrument utilises magnetic resonance to detect PCR amplicons bound to targeted magnetic particles. The T2Bacteria panel detects five bacterial pathogens: *S. 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 high rates of antibiotic resistance and are leading causes of sepsis.[30–32] The average time to result is approximately 6 hours.[23 28 29] T2Bacteria panel test results are reported in several ways:

1. The result and interpretation for all five pathogens queried by the panel are reported in the EHR (table 1). All medical decisions are deferred to the ordering provider.
2. The results and interpretation for all five pathogens are also sent to the treating clinicians via a text page, with an accompanying full interpretation provided in the EHR (table 1). If multiple pathogens are detected, providers receive a page for each pathogen.
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 alert (box 1) reminds the treating clinician of the result and prompts the clinician to select a reason for continuing vancomycin.

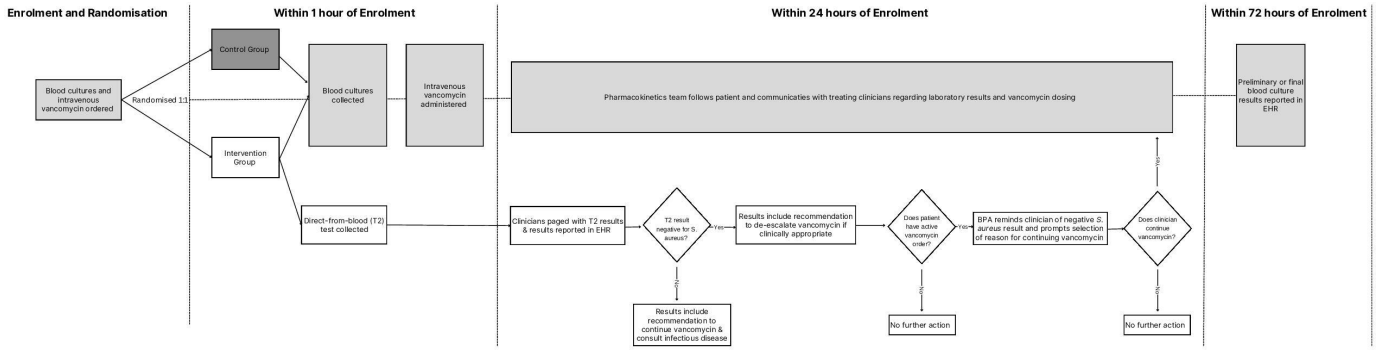

Figure 2 Schematic of study procedures for the intervention group and the control group, from time of enrolment and randomisation to 72 hours following enrolment.

4. All patients receiving multiple doses of intravenous vancomycin at our institution are followed by the pharmacokinetics service. This service incorporates the results of the direct-from-blood testing into their recommendations and communication with the treating clinicians.

Blood culture alone group (control group)

For patients assigned to the blood culture alone group, the blood cultures ordered at the time of eligibility assessment are collected, performed and reported as in routine clinical care. At the study hospital, positive blood culture Gram-stain results are updated within an hour of positivity. Following a gram stain for a positive blood culture the ePlex (Roche, Indianapolis, IN) test, a nucleic acid amplification test for 95% of the most common bacterial pathogens recovered in blood cultures, is performed on the blood culture broth.[33] Gram-stain results are reported in the EHR and sent via electronic alert to the ordering provider, whereas the results of the ePlex are only reported in the EHR. Identification of selected organisms (*S. aureus*, *Staphylococcus lugdunensis*, *Enterococcus* spp., *Candida* spp.) is also alerted to the Infectious Disease fellow on call. Negative blood cultures are reported without growth until finalised after 5 days.

Table 1 T2Bacteria panel result and accompanying text page to primary clinical team and full interpretation in the EHR

T2Bacteria panel result	Interpretation
No pathogens are detected	**Text page:** *S. aureus* not detected by T2, consider vancomycin de-escalation if clinically indicated. **In EHR:** *S. aureus* was not detected, strongly suggesting the absence of this organism in the bloodstream. Consider discontinuing vancomycin if clinically indicated. Information on this test is available from the Vanderbilt Antibiotic Stewardship Programme.
S. aureus is detected	**Text page:** *S. aureus* detected by T2. **In EHR:** *S. aureus* was detected. Vancomycin is preferred initial therapy unless medically contraindicated. Correlate with blood culture for susceptibility. ID consult is required. Information on this test is available from the Vanderbilt Antibiotic Stewardship Programme.
E. coli is detected	**Text page:** *E. coli* detected by T2; *S. aureus* not detected by T2, consider vancomycin de-escalation if clinically indicated. **In EHR:** *E. coli* was detected. Ceftriaxone or meropenem (if ESBL history) is preferred initial therapy unless medically contraindicated. Correlate with blood culture for susceptibility. Information on this test is available from the Vanderbilt Antibiotic Stewardship Programme.
E. coli is indeterminant	The provider does not receive a text page. **In EHR:** An indeterminate result for *E. coli* means that the test was valid but could not definitively detect or exclude the presence of *E. coli*. An indeterminate result for *E. coli* cannot be considered positive or negative, and no antimicrobial therapy decisions should be based on this result.
K. pneumoniae is detected	**Text page:** *K. pneumoniae* detected by T2; *S. aureus* not detected by T2, consider vancomycin de-escalation if clinically indicated. **In EHR:** *K. pneumoniae* was detected. Empiric beta-lactam antibiotic or meropenem (if ESBL history) is preferred initial therapy unless medically contraindicated. Correlate with blood culture for susceptibility. Information on this test is available from the Vanderbilt Antibiotic Stewardship Programme.
P. aeruginosa is detected	**Text page:** *P. aeruginosa* detected by T2; *S. aureus* not detected by T2, consider vancomycin de-escalation if clinically indicated. **In EHR:** *P. aeruginosa* was detected. Cefepime or piperacillin-tazobactam is preferred initial therapy unless medically contraindicated. Correlate with blood culture for susceptibility. Information on this test is available from the Vanderbilt Antibiotic Stewardship Programme.
E. faecium is detected	**Text page:** *E. faecium* detected by T2; *S. aureus* not detected by T2, consider vancomycin de-escalation if clinically indicated. **In EHR:** *E. faecium* was detected. Daptomycin is preferred initial therapy unless medically contraindicated. Correlate with blood culture for susceptibility. ID consult is required. Information on this test is available from the Vanderbilt Antibiotic Stewardship Programme.

E. coli, *Escherichia coli*; *E. faecium*, *Enterococcus faecium*; EHR, electronic health record; ESBL, extended-spectrum beta-lactamases; ID, infectious disease; *K. pneumoniae*, *Klebsiella pneumoniae*; *P. aeruginosa*, *Pseudomonas aeruginosa*; *S. aureus*, *Staphylococcus aureus*.

Box 1 Best practice alert displayed to clinicians when a T2Bacteria panel test returns negative for *S. aureus*

Text presented to clinician

Staphylococcus aureus was not detected for this patient on the T2Bacteria panel (direct-from-blood test). This strongly suggests the absence of this organism in the bloodstream. Consider discontinuing vancomycin if clinically indicated.

Acknowledgement response options

⇒ I will discontinue vancomycin.
⇒ Known or suspected infection with a pathogen for which vancomycin is standard of care.
⇒ Severe or serious allergy to alternative antimicrobials.
⇒ Surgical prophylaxis.
⇒ Other.

Cointerventions

For patients in both trial groups, clinical care, including selection of antibiotics, is managed by treating clinicians in the hospital. Antimicrobial Stewardship Programme pharmacists may intervene on patients as part of routine prospective review of patients.

The pharmacokinetics service orders intravenous vancomycin doses and laboratories for monitoring to optimise safety and therapeutic efficacy. Blood culture and direct-from-blood test results are incorporated into their recommendations and communication with the treating clinicians.

Data collection

Baseline data

We will collect demographic and acute and chronic medical conditions including age, sex, race, ethnicity, body mass index, presence of sepsis according to Sepsis-3 criteria,[34] Sequential Organ Failure Assessment score (SOFA score), suspected source of infection (lung, intra-abdominal, genitourinary, other and unknown), presence of chronic kidney disease, presence of end-stage kidney disease on kidney replacement therapy, presence of acute kidney injury at enrolment, baseline vital signs (eg, temperature and heart rate), baseline laboratory values (eg, white cell count), comorbidities (eg, Charlson comorbidity index) and time from ED presentation to enrolment.

Data from enrolment to hospital discharge

We collect data on the diagnostic tests and antibiotic treatments patients receive and their clinical condition from enrolment to hospital discharge, including results of cultures, results of direct-from-blood testing for bacterial pathogens, receipt of antibiotics, dose of antibiotics, vital signs (eg, temperature and heart rate), laboratory values (eg, white cell count), organ function (eg, SOFA score) and treatment locations (eg, ED, hospital ward and intensive care unit).

Outcome data

Data collected for primary and secondary outcomes include timing and dose of antibiotic therapy, identification and antibiotic susceptibility results of organisms identified, allergic reactions to antibiotics, receipt of organ support (eg, kidney replacement therapy, mechanical ventilation and vasopressor medications), duration of intensive care unit admission, duration of hospital admission and death.

Monitoring for adverse events

Study personnel evaluate the occurrence of adverse events by manual review of the EHR during data collection. Study personnel also communicate regularly with the treating clinicians in the study environments to solicit information about any potential adverse events, including their relatedness to the trial intervention.

Data auditing and storage

Additional information regarding data auditing and storage can be found in online supplemental files 4 and 5, respectively.

Primary outcome

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

Secondary outcomes

The secondary outcome is time to last dose of systemic antipseudomonal beta-lactam antibiotic, defined as the time between randomisation and start time of the last dose of systemic antipseudomonal beta-lactam antibiotic received by the patient within 14 days of randomisation. Guidelines recommend the use of broad-spectrum antibiotics, including antipseudomonal beta-lactam antibiotics, in patients with sepsis and other high-risk features.[2 3] These antibiotics can have adverse effects when used unnecessarily.[35] Overuse also contributes to the emergence of resistance.[36] Accordingly, this outcome derives from antibiotic stewardship initiatives promoting best-use of these antibiotics.

Exploratory outcomes

Exploratory antibiotic stewardship outcomes

1. Total number of doses of intravenous vancomycin received between randomisation and 14 days after randomisation.
2. Total number of days that gram-positive antibiotic therapy was received between randomisation and 14 days after randomisation.
3. Total number of days that gram-negative antibiotic therapy was received between randomisation and 14 days after randomisation.
4. Time to receipt of antibiotic therapy with effective coverage (ie, bacteria is susceptible per antimicrobial susceptibility testing) for blood stream infections iden-

tified by final blood culture results collected prior to or at the same time as randomisation, assessed at 14 days after randomisation.
5. Proportion of patients who experienced *Clostridioides difficile* infection between randomisation and hospital discharge or 28 days after randomisation, whichever occurs first.

Exploratory safety outcomes

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

Exploratory clinical outcomes

1. Highest stage of acute kidney injury by Kidney Disease Improving Global Guidelines (KDIGO) criteria[37] between randomisation and 14 days after randomisation.
2. Receipt of kidney replacement therapy between randomisation and 14 days after randomisation.
3. Lowest platelet count between randomisation and 14 days after randomisation.
4. Hospital-free days to day 28.*
5. Intensive care unit (ICU)-free days to day 28.*
6. All-cause, in-hospital mortality to day 28.

*Defined as the number of calendar days alive and free of the hospital/ICU between randomisation and 28 days after randomisation with outcome assessment censored at hospital discharge

Process measures

Exploratory antibiotic stewardship process measures

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

Sample size estimation

The planned sample size for this trial is 500 patients (250 patients per group). The planned follow-up duration for each patient for the primary outcome is 14 days. Prior data indicate that the median time to the primary outcome in the control group will be approximately 48 hours.[35] If the true median times to the primary outcome in the control and intervention groups are 48 and 36 hours, respectively, we will be able to reject the null hypothesis that the experimental and control survival curves are equal with probability (power) 0.895. The type I error probability associated with this test of this null hypothesis is 0.05.

Statistical analysis principles

Analyses will be conducted following reproducible research principles using R (R Foundation for Statistical Computing, Vienna, Austria). Categorical variables will be presented as number and percentage. Continuous variables will be presented as mean±SD or median and IQR. A two-sided p value of <0.05 will define a statistically significant between-group difference in the primary outcome. With a single-primary outcome, no adjustment for multiplicity will be made. For secondary, safety and exploratory analyses, emphasis will be placed on the magnitude of differences between groups with 95% CIs rather than statistical significance.

To characterise the study sample, baseline demographic and clinical data will be described overall and by group. Missingness will be reported for each variable. Graphical summaries using box plots, violin plots and/or histograms may be used to describe the data graphically. We will describe the primary outcome, secondary outcomes, exploratory outcomes, exploratory safety outcomes and exploratory clinical outcomes overall and grouped by study arm. Summary statistics and graphical representations may be displayed, and missingness will be reported for each variable. No statistical comparisons between groups will be done for this descriptive analysis.

Analysis population

The main analysis of the trial will use an intention-to-treat approach to address the effectiveness question posed. All eligible patients will be evaluated in the treatment group to which they were randomised, regardless of what interventions they received.

Main analysis of the primary outcome

The primary outcome is time to last dose of intravenous vancomycin, defined as the time between randomisation and the start time for the last dose of intravenous vancomycin received by the patient within 14 days of randomisation. The main analysis will be an unadjusted, intention-to-treat comparison of the primary outcome between patients randomised to the direct-from-blood

testing group versus the usual care group. Patients who are discharged on or prior to 14 days after randomisation will be assumed to not receive vancomycin after discharge. Estimation and inferences of the intervention effect will be made using an unadjusted Cox proportional hazards model with the dependent variable of time to last dose of intravenous vancomycin and the independent variable of trial group assignment. The model results will be presented as a hazard ratio (HR) with 95% CI.

Additional analyses of the primary outcome

Sensitivity analyses—we will perform the following sensitivity analyses:

1. We will repeat the primary analysis but will assign patients who died on or prior to day 14 after randomisation a value of 15, higher than the worst possible value for the outcome among patients who did not die. The aim of this sensitivity analysis is to assess whether any observed difference between groups in the time to last dose of intravenous vancomycin is not a result of a difference between groups in the incidence of death, after which additional doses of vancomycin cannot be received.
2. We will compare the primary outcome of time to last dose of intravenous vancomycin between the trial groups using the Fine-Gray subdistribution hazard model that models both the risk of the primary outcome and the competing risk of death. Patients who survive for at least 48 hours after the final dose of vancomycin will be considered to have had vancomycin discontinued, while alive and patients who died within 48 hours after the final dose of vancomycin will be considered to have died without having had vancomycin discontinued.
3. We will compare the primary outcome of time to last dose of intravenous vancomycin between trial groups using a proportional odds model. Each patient will receive a value between 1 day (last dose of vancomycin on the day of enrolment) and 14 days (last dose of vancomycin on day 14). Patients who died within 14 days of enrolment will receive a value of 15 (worse than the longest possible duration of vancomycin therapy).
4. We will repeat the main analysis of the primary outcome in two subsets of the overall trial population defined by receipt of key cointerventions:
   a. Among only patients for whom blood cultures were successfully drawn in the 12 hours prior to or 12 hours after randomisation.
   b. Among only patients who received one or more doses of vancomycin in the 12 hours prior to or 12 hours after randomisation.

Modified intention to treat

We will repeat the primary analysis among all patients for whom blood cultures resulted and, within the intervention group, for whom the direct-from-blood test resulted.

Analyses of effect modification

We will examine whether prespecified baseline variables modify the effect of study group assignment (direct-from-blood testing group vs control group) on the primary outcome using a test of statistical interaction in a Cox proportional hazards model with the primary outcome as the dependent variable and fixed effects of trial group, the prespecified proposed effect modifier and the interaction between the two. For categorical variables, we will present the HR and 95% CIs within each prespecified subgroup. Continuous variables will not be dichotomised for analysis of effect modification, but may be dichotomised for data presentation. All continuous variables will be modelled assuming a non-linear relationship to the outcome using restricted cubic splines with between 3 and 5 knots.

In accordance with the Instrument for Assessing the Credibility of Effect Modification Analyses (ICEMAN) recommendations,[38] we have prespecified the following baseline variables as potential effect modifiers. We hypothesise that the variable will not modify the effect of study group assignment on the primary outcome unless otherwise stated:

1. Presence of End Stage Kidney Disease on Kidney Replacement Therapy (yes/no).[39]
2. Sepsis according to Sepsis-3 criteria[34] (yes/no).[2 40]
3. Severity of illness (SOFA score).[4142]
4. Suspected source of infection (lung, intra-abdominal, genitourinary, other and unknown). We hypothesise that the suspected source of infection will modify the effect of study group assignment on the primary outcome, with a greater difference between trial groups in the time to final dose of vancomycin among patients with non-pulmonary sources of infection compared with among patients with a pulmonary source of infection.[43]
5. Solid organ or stem-cell transplant recipient (yes/no).[44]
6. Neutropenia with absolute neutrophil count less than 1500 cells/mcL (yes/no). We hypothesise that the presence of neutropenia will modify the effect of study group assignment on the primary outcome, with a greater difference between trial groups in the time to final dose of vancomycin among patients without neutropenia than among patients with neutropenia.[45]

Analysis of the secondary outcome

The secondary outcome is time to last dose of systemic antipseudomonal beta-lactam antibiotic, defined as the time between randomisation and start time of the last dose of systemic, antipseudomonal, beta-lactam antibiotic received by the patient within 14 days of randomisation. The analysis of the secondary outcome will use the same approach as described above for the primary outcome.

Analyses of exploratory outcomes

For each exploratory outcome, we will perform intention-to-treat analyses comparing patients randomised to each

of the two trial groups. For categorical outcomes, we will use the χ^2 test for unadjusted comparisons and a binary or multinomial logistic regression model for adjusted comparisons. For continuous or ordinal outcomes, we will use the Wilcoxon rank sum test for unadjusted comparisons or a proportional odds logistic regression model for adjusted comparisons. For time-to-event analyses, we will use a Cox proportional hazards model. All model results will be summarised with point estimates and 95% CIs, which will be emphasised over p values when reporting the results for exploratory outcomes. No adjustments for multiplicity will be made.

Handling of missing data

We anticipate that no patients will be lost to follow-up before assessment of the primary outcome because outcome ascertainment occurs only during the index hospitalisation. Missing data will not be imputed for any outcomes. In adjusted analyses, missing data for baseline covariates will be imputed using singular imputation.

Data Safety Monitoring Board

This single-centre trial comparing two approved laboratory methods for identifying bacterial pathogens in blood samples was determined to represent minimal risk and did not meet criteria for monitoring by a Data Safety Monitoring Board per US Food and Drug Administration recommended guidance.[46] Site study personnel conduct manual review of the EHR during initial and final data collection and communicate regularly with the treating clinicians in the study environment to solicit information about any potential patient safety concerns, for which the principal investigator is immediately notified. Detailed collection of safety outcomes and a structured process for adverse event reporting are summarised above.

Trial status

This trial started enrolment on 13 December 2023, and is enrolling at the time of manuscript submission.

Patient and public involvement

The trial was presented to the Meharry-Vanderbilt Community Engaged Research Core Community Advisory Council during trial development who provided feedback on the trial design. Patients and the public will not be involved in the conduct of the trial, but patients will be engaged in lay reporting and dissemination of the trial findings.

ETHICS AND DISSEMINATION

Waiver of informed consent

This study compares two standard-of-care laboratory methods for detecting bacterial pathogens in blood samples—blood culture plus direct-from-blood pathogen testing and blood culture alone. The technology used in both laboratory methods is cleared by the US Food and Drug Administration for human in vitro diagnostic use, is available for use in routine clinical care and is used in current clinical care in health systems across the USA. 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, randomised trials or evidence-based guidelines support the use of one method over another. Clinicians, patients and families 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 as part of this research study poses minimal incremental risk compared with clinical care outside of the study.

In addition to the minimal incremental risk posed by participation in the research compared with clinical care outside of the research, obtaining written informed consent prior to enrolment in this study was deemed to be impracticable. Whole blood for cultures is ideally obtained prior to the administration of antibiotics, and current guidelines recommend administering antibiotics immediately for all patients with sepsis or septic shock due to the increased risk for mortality associated with delays in antibiotic administration.[2] Patients presenting to the ED with suspected infection treated with empiric intravenous antibiotics are also frequently unconscious or delirious, and a legally authorised representative is frequently not present. Because the trial defers all subsequent aspects of treatment to clinicians (eg, choice of antibiotics and timing of discontinuation of antibiotics), the primary study procedure is intended to be completed within 1 hour of the patient meeting eligibility criteria.

Because participation in the study posed minimal incremental risk compared with clinical care outside of the study and obtaining informed consent prior to enrolment is impracticable, a waiver of informed consent was requested and granted from the Vanderbilt University Medical Center IRB.

Protocol changes

Protocol changes will be approved by the local IRB, reflected in the protocol maintained on site as an amendment, and updated on ClinicalTrials.gov as per SPIRIT guidelines (online supplemental files 1 and 6).

Dissemination plan

Trial results will be submitted to a peer-reviewed journal for consideration of publication and will be submitted for presentation at scientific conferences. Trial results will be made available to key stakeholders in emergency and critical care, pharmacy, infectious disease and antimicrobial stewardship. A lay summary will be developed to share with patient stakeholders and the public. Data will be made available following publication (online supplemental file 7).

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