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Rapid versus standard antibiotic susceptibility testing for treating bloodstream infections (Protocol)

Anton-Vazquez V, Hine P, Krishna S, Richardson M, Planche T

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[Intervention Protocol]

Rapid versus standard antibiotic susceptibility testing for treating bloodstream infections

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects of rapid susceptibility testing versus standard susceptibility testing for bloodstream infections (BSIs).

BACKGROUND

Description of the condition

Bloodstream infections (BSIs) can be defined as the presence of viable bacteria or fungi in the blood that is associated with infection (Laupland 2014). Blood culture is the reference standard for detection of these micro-organisms in blood (Baron 2013). BSIs may be categorized as primary infections, defined as those not secondary to an infection at another body site, and secondary infections, where organisms are seeded from a site-specific infection at another body site, for example a pneumonia. In primary BSIs, organisms may enter the bloodstream through broken skin or mucous membranes, gastrointestinal tract or by the direct introduction of contaminated material to the bloodstream (Reimer 1997).

Positive blood cultures may not always signify BSI, and may represent contamination or the transient presence of bacteria in the blood that do not cause clinical illness. Similarly, BSI may not always lead to sepsis.

Incidence estimates for BSI vary from 166 to 204 episodes per 100,000 person-years in North America and Europe (Goto 2013). BSI is also common in Africa, with a prevalence of 7.4% (4.2% to 16.9%) among all admissions irrespective of fever history, with higher risk in the immunocompromised (Reddy 2010).

BSIs are often associated with and, less frequently, may cause sepsis, defined as life-threatening organ dysfunction due to a dysregulated host response to infection (Rhodes 2017). Given the complex nature of the condition and its diagnosis, it is impossible to give precise estimates for the global burden of disease from sepsis. However, the World Health Organization (WHO) estimates that there are up to 31 million and 24 million global cases of sepsis and

septic shock, respectively, with the clinical conditions resulting in sepsis accounting for up to six million deaths (WHO 2017).

Observational studies indicate that inappropriate empirical antimicrobials and delays in the initiation of appropriate antibiotic therapy are risk factors for mortality in sepsis, with a progressive increase in mortality with increasing delays (Ferrer 2014; Kumar 2006; Kumar 2009; Paul 2010). By necessity, the evidence for the antibiotic treatment of sepsis is observational, as randomized controlled trials (RCTs) would be unethical. Notwithstanding, sepsis guidelines emphasize early broad-spectrum antimicrobial treatment aimed at ensuring adequate therapy to reduce mortality.

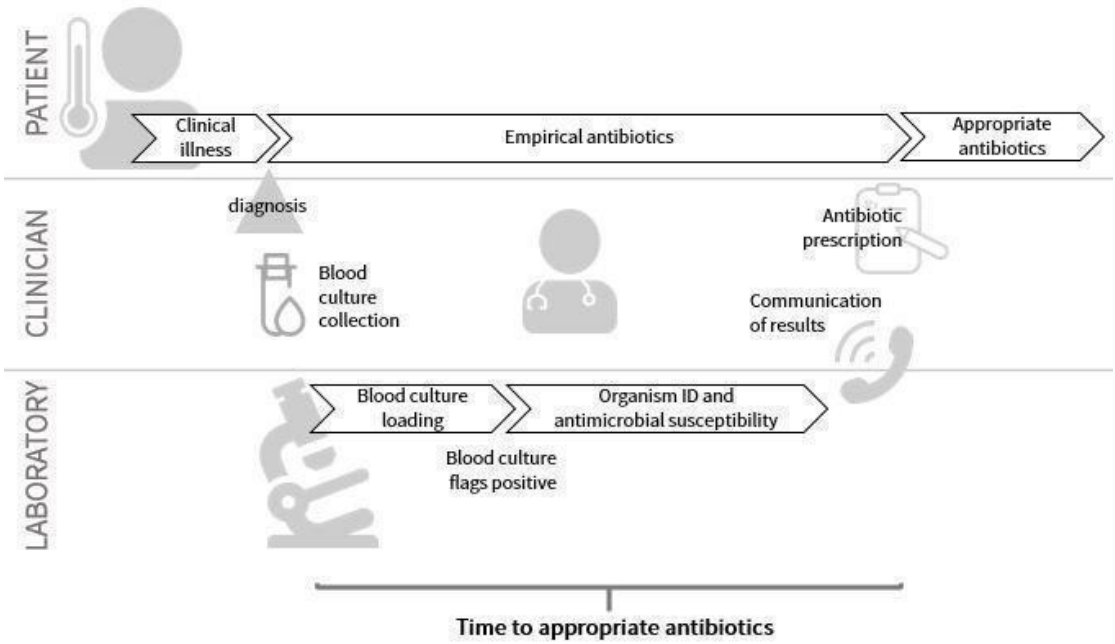
Such use of early broad-spectrum antimicrobials has led to concerns that patients are exposed to overuse of antimicrobials, which may result in antimicrobial resistance (Silva 2013). As such, guidelines recommend that antimicrobial therapy is targeted to a specific pathogen, if this is identified microbiologically (Rhodes 2017). The use of targeted therapy is regarded as an important component of antimicrobial stewardship, defined as a set of actions that promote using antimicrobials responsibly (Dyar 2017).

Description of the intervention

The parallel global drives to improve both the treatment of severe infections associated with BSI and to avoid antimicrobial resistance have catalyzed new strategies to reduce the turn-around time between the collection of blood culture samples from patients and the reporting of antimicrobial susceptibility results. Proported benefits of reduced turn-around times include reduced morbidity and mortality, improved patient care, reduced healthcare costs, and reduced antimicrobial resistance (PHE 2014).

Figure 1 depicts an overview of the laboratory diagnosis and clinical management of BSI. A clinician collects a blood culture from a patient with possible BSI, and may commence empirical antibiotics. The clinician sends this to the microbiology laboratory. Upon receipt, the laboratory staff load the blood cultures into an incubation machine. Different blood culture systems then use a variety of methods to detect micro-organisms, and the culture bottles will 'flag positive' if detected. The term 'time to positivity' is the time between which the clinician collects the culture, and the time at which the culture 'flags positive'. Time to positivity is typically 12 to 24 hours.

Figure 1. Time to appropriate antibiotics: time to first appropriate antibiotic (from collection time of positive blood culture to start of an antibiotic which has in vitro activity versus the identified organism)



After the blood culture 'flags positive', laboratory staff remove the blood culture from the machine, and perform a Gram stain and microscopy. Laboratory staff then perform subcultures to isolate one or more organisms, and use either conventional culture methods or rapid testing to report organism identification and antimicrobial susceptibility. Using conventional methods, this period is typically a further 36 hours (Maurer 2017). The clinician is then required to act upon this report, and change or continue antibiotics appropriately. The term 'time to appropriate antibiotic' is the time between which the clinician collects the culture, and the time at which targeted antibiotics are prescribed according to the susceptibility result.

The advent of mass spectrometry over the past decade has allowed great reductions in the time to identification (Doern 2018). However, a reduction in time from a blood culture flagging positive and antimicrobial susceptibility results being available, is a more elusive target.

In recent years, novel rapid antimicrobial susceptibility tests are emerging. These can be grouped into the following two main categories (Maurer 2017).

- Genotypic or molecular antimicrobial susceptibility testing: this form of testing identifies the presence or absence of a resistance gene or its product. It can indicate which antimicrobials the organism is unlikely to be susceptible to.
- Rapid phenotypic antimicrobial susceptibility testing: this describes detection of growth in the presence of an antibiotic.

For the purpose of this review, the term 'rapid' includes those that produce susceptibility results in $\leq$ 8 hours from the time the blood culture flags positive. This definition relates to the laboratory work day, in which batch testing is performed one or more times per 8-hour working shift (Buehler 2015).

How the intervention might work

Rapid antimicrobial susceptibility tests are expected to reduce the time to clinically important results of a blood culture. This might allow clinicians to better target therapy to patients' needs, and thereby both improve patient outcomes (mortality, morbidity, length of hospital stay), and reduce unnecessary prescribing of broad-spectrum antibiotics and so reduce antimicrobial resistance rates.

Why it is important to do this review

Rapid susceptibility testing offers a theoretical benefit to patient outcomes, with reduced time to targeted antibiotic therapy and, as such, potential reduced morbidity and mortality. It also offers theoretical benefit to improve antimicrobial stewardship and, as such, reduce antimicrobial resistance, which is a key concern globally. Notwithstanding the theoretical benefits, there is limited certainty in the evidence. This Cochrane Review may help improve certainty regarding potential benefits of this emerging technology to patient outcomes and stewardship outcomes. As such, the review may guide clinicians and laboratories in the effective implementation of rapid susceptibility testing, and appropriate resource allocation to the technology.

OBJECTIVES

To assess the effects of rapid susceptibility testing versus standard susceptibility testing for bloodstream infections (BSIs).

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs).

Types of participants

People of any age with a BSI caused by any bacteria, as identified by a positive blood culture and clinical signs of infection.

Types of interventions

Experimental intervention

Rapid antimicrobial susceptibility testing, defined as an in vitro laboratory test to determine if an antimicrobial agent will be active in inhibiting the growth of an organism, performed directly from a positive blood culture bottle, with a time-to-result of $\leq$ 8 hours from the blood culture flagging positive. These may include molecular antimicrobial susceptibility tests or phenotypic antimicrobial susceptibility tests, using the definitions given above, and may include other methods not incorporated by these definitions, if they are identified by our search. Appendix 1 lists interventions that may meet these criteria.

Comparator

Conventional routine standard antimicrobial susceptibility techniques (automated systems, broth microdilution, manual susceptibilities, disc diffusion or E-tests).

Types of outcome measures

Primary outcomes

- Mortality (all-cause 30-day mortality, after date of positive blood culture)
- Time to discharge from hospital after positive blood culture in days

Secondary outcomes

Time from empirical antibiotic prescription to targeted or definitive therapy; to include the following.

- Time to patient receipt of an antibiotic with in vitro activity versus the identified organism
- Time to de-escalation: switching from a broad- to a narrow-spectrum antibiotic or discontinuation of one or more antibiotics
- Time to escalation: switching from a narrow- to a broad-spectrum antibiotic or initiation of one or more antibiotics

Search methods for identification of studies

We will attempt to identify all relevant studies regardless of language or publication status (published, unpublished, in press, ongoing).

Electronic searches

We will search the following databases using the search terms and strategy described in Appendix 2: Cochrane Infectious Diseases Group Specialized Register; Central Register of Controlled Trials (CENTRAL), published in the Cochrane Library; MEDLINE (PubMed); and LILACS. We will also search the WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp), and ClinicalTrials.gov (clinicaltrials.gov), for trials in progress, using "bloodstream infection*" and "antimicrobial susceptibility tests" as search terms.

Searching other resources

Reference lists

We will also check the reference lists of all studies identified by the above methods and of previously published reviews, and we will use the "similar articles" function in PubMed to identify related data.

Researchers and organizations

In addition to the electronic searches described above, we will contact researchers in the field to identify additional published and unpublished studies.

Data collection and analysis

Selection of studies

Two review authors (VA and PH) will independently screen references by title and abstract according to our inclusion criteria. We will exclude studies that do not report on our primary or secondary outcomes. We will include studies that assess a single resistance trait. We will resolve any disagreement through discussion; if unable to reach agreement we will discuss with a third review author (TP or SK). We will obtain and assess the full-text of potentially eligible articles. We will list studies we exclude after full-text screening and their reasons for exclusion in a 'Characteristics of excluded studies' table. We will present a PRISMA flow diagram (Moher 2009).

Data extraction and management

Two review authors (VA and PH) will independently extract data using a piloted, tailored data extraction form. We will resolve any disagreement by discussion or through a third review author (TP). For dichotomous outcomes (mortality), we will extract the number of events in each arm of the included RCTs. For all other outcomes, which are time-to-event outcomes, we will extract the log hazard ratio and its standard error from Cox proportional hazards models. If trial authors do not report standard errors, we will extract the hazard ratio with its confidence interval (CI) or P value, or both, and use these to obtain estimates of standard error. If trials analyse time-to-event data with models other than a Cox proportional hazards model, we will collect the relevant data for methods of meta-analysis of time-to-event outcomes as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Assessment of risk of bias in included studies

Two review authors (VA and PH) will independently assess risk of bias using the Cochrane 'Risk of bias' tool (Higgins 2011), and where necessary, contacting trial authors for further information. We will resolve any disagreement via discussion. In the event that a disagreement cannot be resolved, a third review author (TP) will make the final decision. We will record the rationale used to determine the risk of bias in each of the six domains for each included study. The six domains include: selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias. We will make a final decision on each study's level of bias based on this.

Measures of treatment effect

For mortality, a dichotomous outcome, we will present risk ratio (RR), comparing rapid susceptibility testing to conventional methods with respective 95% CIs.

For all other outcomes, which are time-to-event outcomes (time to discharge from hospital, time to first appropriate escalation/de-escalation, time to first appropriate antibiotic), we will present hazard ratios (HRs) with respective 95% CIs.

Unit of analysis issues

When a trial with more than two arms contributes multiple comparisons to a particular meta-analysis, we will combine treatment groups or split the 'shared' group to avoid double-counting.

If we encounter cluster-RCTs that did not adjust results for cluster design, we will adjust the sample sizes using an estimate of the intracluster correlation coefficient (ICC) before including data from these studies in our meta-analysis. If the ICC is not available, we will use an ICC from another, similar study.

Dealing with missing data

We will assess missing data to ascertain whether it may be related to the outcomes. If missing data restricts the use of the study in quantitative synthesis, we will contact trial authors for clarification or to provide further information. If data are missing at random, we will analyse only available cases. If the amount of incomplete outcome data is such that the trial is thought to be at a high risk of bias, we may use imputation and perform sensitivity analyses to investigate the impact of this missing data.

Assessment of heterogeneity

We will visually inspect the forest plots for overlapping CIs as an indicator of heterogeneity. We will also assess the Chi^2 and I^2 tests of heterogeneity. For the purposes of this review, an I^2 statistic value > 75% will indicate considerable heterogeneity. However we will not consider this as a simple 'threshold', but instead interpret this in the context of the size and direction of events, the Chi^2 P value, and possible causes. Where heterogeneity remains considerable, we will not perform meta-analysis.

Assessment of reporting biases

We will create funnel plots to assess reporting bias if more than 10 studies contribute to an outcome in meta-analysis, and examine this for asymmetry.

Data synthesis

We will meta-analyse data using Review Manager 5 (Review Manager 2014). We anticipate that we will find heterogenous populations and interventions, so we therefore plan to use a random-effects model for meta-analysis for both dichotomous and time-to-event data.

In addition to quantitative synthesis using meta-analysis, we will perform planned qualitative (narrative) synthesis based on formal guidance. If we are unable to meta-analyse due to heterogeneity in outcome measures, to develop a preliminary synthesis we will use textual descriptions of studies, groupings and clusters, and tabulation (Popay 2006).

We will also perform qualitative synthesis to explore the relationships between data by examining moderating variables that may explain findings at study level, developing conceptual models, and giving qualitative case descriptions where rapid susceptibility testing has been particularly effective or ineffective.

Subgroup analysis and investigation of heterogeneity

We will perform subgroup analysis of instances where rapid susceptibility testing is introduced alone, and where it is introduced as a multicomponent intervention, for example, including other elements of antimicrobial stewardship. If our search indicates that rapid susceptibility testing is being introduced within different settings, we may investigate the effect of this. We recognise that there may be heterogeneity in our antimicrobial stewardship outcomes, as the concept of 'targeting' antibiotics, and of escalation or de-escalation, are by nature subjective. If we encounter different methods of defining these outcomes, we will explore this using subgroup analysis.

Sensitivity analysis

We will perform a worst-case scenario analysis by imputing the missing data as poor outcomes in the rapid susceptibility group and good outcomes in the control group, and by comparing this to our available case analysis to explore the effect of missing data on our primary outcomes.

If we identify high risk of bias for some trials, we will perform sensitivity analysis by assessing results after excluding these trials.

Where we are required to estimate ICCs or borrow ICCs from other studies for cluster-RCTs, we will conduct sensitivity analyses to investigate the impact of these assumptions.

Certainty of the evidence

We will summarize our findings in a 'Summary of findings' table. We will present the following primary and secondary outcomes: all-cause 30-day mortality after date of positive blood culture, time to discharge from hospital after positive blood culture, time to patient receipt of an antibiotic with in vitro activity versus the identified organism, time to de-escalation: switching from a broad- to a narrow-spectrum antibiotic or discontinuation of one or more antibiotics, time to escalation: switching from a narrow- to a broad-spectrum antibiotic or initiation of one or more antibiotics, as outlined in the Types of outcome measures section. We will describe the study settings, number of participants, and number of studies addressing each outcome.

We will assess the certainty of evidence using the GRADE approach (Guyatt 2011; GRADE 2014), and GRADEpro GDT software (GRADEpro GDT 2015). We will rate each important outcome as described by Balshem 2011.

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect.
- Low: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

RCTs start as high certainty of evidence but can be downgraded if there are valid reasons within the following five categories: risk of bias, imprecision, inconsistency, indirectness, and publication bias (Balshem 2011).

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Included interventions

Molecular: matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MS) based resistance test (MALDI-TOF MS); fluorescence in situ hybridization with peptide nucleic acid (PNA-FISH); multiplex polymerase chain reaction (PCR); FilmArray; GenoType blood culture; GeneXpert MRSA Cepheid; Verigene Nanosphere; BD Gene Ohm StaphSR Becton Dickinson; BDMax Staph; Eazyplex; AID; LightMix; Check-Direct CPE; MyCycler; Sepsis FlowChip; CheckPoints; Prove-it Sepsis; B-lacta test.

Phenotypic: Accelerate Pheno; Alfred 60/AST; forward laser light scatter; qMAC-sRAST; ViteK2.

Appendix 2. MEDLINE (PubMed) search strategy

Search	Query
#1	Search "bloodstream infection*" or "blood-stream infection*" Field: Title/Abstract
#2	Search "Bacteremia"[Mesh]
#3	Search bacteremia or bacteraemia Field: Title/Abstract
#4	Search "blood culture*" Field: Title/Abstract
#5	Search sepsis Field: Title/Abstract
#6	Search Sepsis [Mesh]
#7	Search ((#6) or (#5) OR (#4) OR #3) or #2) or #1)
#8	Search (Streptococci or "Streptococcus pneumoniae" or "Streptococcus agalactiae" or "Streptococcus pyogenes" or "Streptococcus viridans" or Staphylococci or "Staphylococcus aureus" or MSSA or MRSA or "Staphylococcus epidermidis" or "Staphylococcus saprophyticus" or "Coagulase negative Staphylococci" or Enterococci or "Enterococcus faecium" or "Enterococcus faecalis" or Listeria or "Listeria monocytogenes"or Clostridium or Fusobacterium or Peptostreptococcus or Bacillus or Haemophilus or "Haemophilus influenzae" or Brucella or Enterobacteriaceae or "Escherichia coli" or Klebsiella or Proteus or Enterobacter or Salmonella or Citrobacter or Pseudomonas or "Pseudomona aeruginosa" or Serratia or Acinetobacter or Stenotrophomonas or Legionella or Helicobacter or Moraxella or Neisseria or "Neisseria meningitidis"or "Neisseria gonorrhoeae" or "Gram-negative" or "Gram-positive") AND blood* Field: Title/Abstract
#9	Search (#7) OR #8)
#10	Search "antimicrobial susceptibility test" or "antimicrobial susceptibility testing" or "antibiotic susceptibility testing" or "susceptibility testing" Field: Title/Abstract
#11	Search "rapid" Field: Title/Abstract
#12	Search "maldi tof" OR "PNA-FISH" Field: Title/Abstract
#13	Search PCR Field: Title/Abstract OR "Polymerase Chain Reaction"[Mesh]

(*Continued*)

#14	Search FilmArray or Microarray or "molecular test" or "GenoType Blood Culture" or GeneXpert or Cepheid or "Verigene Nanosphere" Field: Title/ Abstract
#15	Search "BD Gene Ohm" or "BDMax Staph" or Eazyplex or LightMixor "Check-Direct CPE" Field: Title/Abstract
#16	Search FlowChip or "Prove-it " or "Betalacta test" Field:Title/Abstract
#17	Search ("Pheno Accelerate" or "Alfred 60 AST" or "Light scattering" or "BacterioScan" or "qMAC-sRAST" or "Vitek2") Field: Title/Abstract
#18	Search "antimicrobial stewardship" or "antimicrobial prescription" Field: Title/Abstract
#19	Search ((((((#18 OR (17) OR #16) OR #15) OR #14) OR #13) OR #12) OR #11) OR #10) OR #9
#20	Search #9 AND #19
#11	Search"Randomized Controlled Trial" [Publication Type] OR "Controlled Clinical Trial" [Publication Type]
#22	Search (random* or placebo or single-blind* or double-blind*) Field:Title/Abstract
#23	Search impact or "clinical impact" or outcomes or clinical or "clinical outcomes" or effect Field: Title/Abstract
#24	Search evaluation or performance AND (impact* or outcome*) Field: Title/Abstract
#25	Search ((#24) OR (#23) OR #22) OR #21
#26	Search #20 AND #25

This is the preliminary search strategy for MEDLINE (PubMed). It will be adapted for other electronic databases. We will report all search strategies in full in the final version of the review.

Appendix 3. Definitions

- Rapid susceptibility technique: an in vitro laboratory test used to determine if an antimicrobial agent will be active in inhibiting the growth of an organism, performed directly from a positive blood culture bottle, producing results in < 8 hours or same working day.
- Phenotypic susceptibility test: the basis of phenotypic method is the minimum inhibitory concentration (MIC). Clinical MIC breakpoints determine whether the organism is categorized as susceptible, intermediate or resistant.
- Molecular or genotypic susceptibility test: a diagnostic test that analyzes the presence or absence of resistant genes in bacteria.
- Appropriate antimicrobial therapy: antimicrobial treatment directed specifically to a micro-organism based on in vitro susceptibility test results.
- Time-to-result: the time that it takes to perform and report a laboratory susceptibility test result from the time that the sample is received in the laboratory.
- Bloodstream infection (BSI) or bacteraemia: positive blood culture result with systemic manifestations of infection.

CONTRIBUTIONS OF AUTHORS

Vanesa Anton (VA) and Paul Hine (PH) wrote the first draft of the protocol. Sanjeev Krishna (SK), Marty Richardson (MR), and Timothy Planche (TP) commented and revised the protocol. All review authors take responsibility for the final version of the protocol.

DECLARATIONS OF INTEREST

VA has no known conflicts of interest.

PH was previously employed full-time by Cochrane Infectious Diseases Group (CIDG), and currently works full-time within the UK National Health Service (NHS). He received a Registration Scholarship to attend the 23rd Annual British HIV Association Conference 2017 from ViiV healthcare. ViiV had no involvement in the selection of recipients of the scholarship. In 2018, he attended a CPD-certified clinical research training programme organized and funded by Gilead Sciences Europe Ltd. To the best of his knowledge, neither financial or non-financial conflicts of interests have influenced the current submitted work.

SK is a scientific advisor and shareholder in QuantuMDx, a company that is developing rapid diagnostic tests for several infections and is a scientific advisor to Foundation for Innovative New Diagnostics (FIND). The opinions in this review are personal opinions and do not represent views of either organization.

MR has no known conflicts of interest.

TP is the clinical? lead of a NHS diagnostic microbiology laboratory at South West London Pathology. He is on advisory boards for Roche, Pfizer, and Singulex for diagnostics.

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