Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.
eAppendix 1. Systematic review protocol.

Project Title: Association of follow-up blood cultures with mortality in patients with gram-negative bloodstream infections

Investigators: Joshua T. Thaden, MD, PhD; Felicia Ruffin, PhD; Stacey A. Maskarinec, MD, PhD; Stacy Goins, BA; Matthew Sinclair, MD; Joshua Parsons, MD, PhD; Yazhong Tao, PhD; Emily Eichenberger, MD, Michael Dagher, MD; Vance G. Fowler, Jr., MD, MHS

Search Librarian: Sarah Cantrell, MLIS, AHIP

I. Background

Bloodstream infection (BSI) with gram-negative bacteria is a common medical problem that is associated with high morbidity and mortality. However, there are ongoing controversies on how patients with gram-negative BSI should be best managed. For example, data from published studies has not clearly established whether follow-up blood cultures to document clearance of BSI are necessary in patients with gram-negative BSI. Some studies have shown that getting follow-up blood cultures to document clearance of the BSI is associated with decreased mortality,¹⁻³ while other studies have not shown an association between follow-up blood cultures and mortality.⁴⁻⁶

The purpose of this project is to conduct a systematic review of randomized controlled trials and observational studies assessing the association between obtaining follow-up blood cultures and mortality in patients with gram-negative BSI. This evidence synthesis will be used to inform the decision about whether to obtain such cultures.

Project Timeline
Kickoff call: February 1, 2022
Project Start: February 14, 2022
Anticipated draft manuscript due: April 1, 2022
Anticipated manuscript submission: May 1, 2022

II. Key question

The key research questions for this systematic review were developed after a topic refinement process that included a preliminary review of published, peer-reviewed literature; consultation with internal partners and investigators; and consultation with content experts.

The key questions (KQ) for this systematic review are:

**KQ 1:** For patients with gram-negative bloodstream infections, is obtaining follow-up blood cultures after the initial positive blood culture(s) associated with decreased patient mortality?

**KQ 2:** For patients with gram-negative bloodstream infection and follow-up blood cultures, are positive follow-up blood cultures associated with increased mortality relative to negative follow-up blood cultures?

A. Population

The population will be hospitalized adults (age 18 years and older) with gram-negative BSI. Studies that include patients with both gram-negative and gram-positive BSI will be included so long as the gram-negative cohort is analyzed separately.

B. Intervention

KQ1: The intervention is obtaining a follow-up blood culture after the index blood culture that is positive with the gram-negative bacteria. We will not specify the time range in which the follow-up blood culture must be drawn, though in general studies define follow-up blood cultures as those drawn 1-7 days after the index positive culture.

KQ2: Not necessarily an intervention per se, but the experimental group is patients with gram-negative BSI who had a positive follow-up blood culture.

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C. Comparators

KQ1: The comparator group will be patients with gram-negative BSI and no follow-up blood cultures.

KQ2: The comparator group will be patients with gram-negative BSI who had negative follow-up blood cultures.

D. Outcomes

The outcome will be mortality.

E. Timing

In-hospital mortality or mortality up to 30 days.

F. Settings

Patients will be admitted to the hospital.

III. Analytical Framework

IV. Methods

A. Criteria for inclusion and exclusion of studies in this systematic review

Inclusion criteria
- Study design: Randomized controlled trials or observational studies with N>10. The sample size requirement is designed to exclude case reports. This size requirement does permit smaller pilot studies that are typically underpowered and have more methodological problems than larger studies. In order to account for differences in methodology between the studies, we will perform analyses with two sets of studies: 1) the entire set of papers identified through this systematic review, and 2) the subset of studies identified

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through this systematic review that meet a baseline level of methodological rigor. The methodological requirements for inclusion in this second group are defined below in section IV.E.

- **Age:** Adults aged 18 years or older with gram-negative BSI
- **Setting:** Inpatients
- **Studies** must stratify patients by whether follow-up blood cultures obtained (KQ1) or by whether follow-up blood cultures were positive or negative (KQ2)
- **Study** must report effects of follow-up blood cultures on at least one of the following relevant outcomes:
  - In-hospital mortality
  - Mortality up to 30 days (e.g., 28-day mortality, 30-day mortality)

- **Article** is a full publication, research letter, or meeting abstract published in a peer-reviewed journal.
- **Article** is an English language publication

**Exclusion criteria**

- Not an English language publication
- Outpatient setting
- Polymicrobial BSI

**B. Literature search strategies**

We will conduct a primary search of MEDLINE (via Ovid), the Cochrane Central Register of Controlled Trials (via Wiley), Embase (via Elsevier), and Web of Science – Science Citation Index and Social Sciences Citation Index (via Clarivate). We will further evaluate the bibliographies of any systematic or nonsystematic reviews for relevant studies. We will manually review titles and abstracts from the journal *Antimicrobial Stewardship and Healthcare Epidemiology* as it is a new journal that is not indexed in the above databases at the time of this search. In an effort to be fully comprehensive, we will manually review abstracts from the most recent IDWeek conference to identify emerging research that has not yet been published. We anticipate using a combination of database-specific controlled vocabulary and selected free-text terms to search titles and abstracts. To ensure completeness, search strategies will be developed and executed by a medical librarian, with input on terms from the research team. We will also search ClinicalTrials.gov to identify completed but unpublished studies meeting our eligibility criteria in an effort to reduce publication bias.

Using pre-specified inclusion/exclusion criteria, titles and abstracts of articles included in the existing reviews and identified through our primary search will be reviewed independently by two reviewers for potential relevance to the KQs. Articles included by any two reviewers will undergo full-text screening. Conflicts at this stage will be resolved by a third person. At the full-text screening stage, articles will be reviewed independently by two reviewers. The screeners must agree on a final inclusion/exclusion decision. Conflicts at this stage will be resolved by a third person. Articles meeting eligibility criteria will be included for data abstraction. All results will be tracked in Covidence, a web-based data synthesis software program, and, for manuscript preparation, EndNote X20 reference management software (Thomson Reuters).

**C. Data abstraction and data management**

Data from published reports will be abstracted into a customized Covidence data extraction form by one reviewer and over-read by a second reviewer. Disagreements will be resolved by consensus or by obtaining a third reviewer’s opinion when consensus cannot be reached. Data elements include descriptors to assess applicability, quality elements, intervention/exposure details, and outcomes.

Key characteristics abstracted will include patient descriptors (including age, gender, race, level of acute illness, source of BSI), setting, definitions of the intervention, and outcomes as described previously. We will capture any subgroup analyses of particular interest, including differential intervention effects by level of acute illness. When critical data are missing or are unclear in published reports, we plan to request supplemental data from the study authors. Key features relevant to applicability include the match between the sample and target populations and statistical adjustment for patient comorbidities.
D. Assessment of methodological quality of individual studies

Quality assessment will be performed by the researcher abstracting or evaluating the included article; this initial assessment will then be overread by a second, highly experienced reviewer. Disagreements will be resolved between the two reviewers or when needed by arbitration from a third reviewer.

We will use the key quality criteria described in the Agency for Healthcare Research and Quality’s (AHRQ’s) “Methods Guide for Effectiveness and Comparative Effectiveness Reviews” adapted to this specific topic. We will assign a summary quality score (good, fair, or poor) to individual studies.

E. Data synthesis

We will summarize the primary literature by abstracting the relevant data. We will develop a summary table describing the key outcomes and the types of study designs used to evaluate the association of follow-up blood cultures and mortality in patients with gram-negative BSI (KQ1) and the association between positive follow-up blood cultures and mortality in patients with gram-negative BSI (KQ2). We will then determine the feasibility of completing a quantitative synthesis (i.e., meta-analysis) to estimate summary effects for each KQ. Feasibility depends on the volume of relevant literature, conceptual homogeneity of the studies, and completeness of results reporting. We will aggregate outcomes when there are at least three studies with the same outcome, based on the rationale that one or two studies do not provide adequate evidence for summary effects. If meta-analyses are feasible, we will explore the possibility of subgroup analyses to explore the consistency of effects across conditions (e.g., different levels of acute illness). If such subgroup analyses are possible, we will stratify analyses to determine how follow-up blood cultures impact mortality in the individual subgroups (e.g., high level of acute illness versus lower level of acute illness). We recognize that subgroup analyses involve indirect comparisons (across studies) and are subject to confounding.

Studies included in this systematic review will report the dichotomous outcome of mortality. If quantitative synthesis is possible, mortality will be reported using risk ratio or odds ratio. We will evaluate for statistical heterogeneity using visual inspection and Cochrane’s Q and I² statistics. Publication bias will be assessed using findings from the ClinicalTrials.gov search (described previously) and using funnel plots (when there are >10 studies in an analysis).

If a quantitative synthesis is not feasible, we will analyze the data qualitatively. We will give more weight to the evidence from higher quality studies with more precise estimates of effect. A qualitative synthesis would focus on documenting and identifying patterns in efficacy and safety of the intervention. We will analyze potential reasons for inconsistency in treatment effects across studies by evaluating differences in the study population, intervention, comparator, and outcome definitions.

In order to account for methodological differences between studies, we will perform analyses with two sets of studies: 1) the entire set of papers identified through this systematic review that meet the inclusion/exclusion criteria outlined above, and 2) the subset of studies identified through this systematic review that have more than 100 patients and meet a baseline level of methodological rigor. We have defined methodological rigor as studies that are either randomized controlled trials or observational studies that employ statistical approaches to adjust for differences in level of acute illness between patients in the intervention and control groups. We believe that statistical adjustment for acute level of illness is critical since patients that get follow-up blood cultures are often much different (e.g., much sicker) than patients that do not get follow-up blood cultures. Multiple methods for statistical adjustment are permissible, including propensity score-based approaches, exact matching techniques, or multivariable logistic regression. Statistical adjustment should be made, at minimum, for level of acute illness. Acute illness can be determined through validated scoring approaches (e.g., Pitt bacteremia score, APACHE-II score, SOFA score) or through individual clinical characteristics (e.g., ICU admission, need for vasopressor support, need for ventilatory support, etc.).

F. Grading the evidence of the key question

The strength of evidence for the key question will be assessed using the approach described in AHRQ’s “Methods Guide.” In brief, this approach requires assessment of four domains: risk of bias, consistency, directness, and precision. Additional domains are to be used when appropriate: coherence, impact of plausible residual confounders, strength of association (magnitude of effect), and publication bias. These domains will be
considered qualitatively, and a summary rating will be assigned after discussion by two providers as high, moderate, or low strength of evidence. In some cases, high, moderate, or low ratings will be impossible or imprudent to make. In these situations, a grade of insufficient will be assigned.
**Appendix 2. Search Strategies.** Below are the search strategies and study results for searching the MEDLINE, Embase, Web of Science, and Cochrane Central Register of Controlled Trials databases. The initial searches were conducted on 2/11/2022. Repeat searches were performed on 3/11/2022 to identify any studies published while the systematic review was being conducted. In addition to the searches below, we manually searched the new journal *Antimicrobial Stewardship and Healthcare Epidemiology* as it was not indexed in the above databases at the time of this review (n=69) and IDWeek 2021 abstracts (*Open Forum Infectious Diseases*, Volume 8, Issue Supplement_1, 2021; n=1656). Librarian searcher: Sarah Cantrell, MLIS; Duke University Medical Center Library & Archives, Duke University School of Medicine. Peer-review conducted by: Brandi Tuttle, MSLS; Duke University Medical Center Library & Archives, Duke University School of Medicine.

**Database: MEDLINE (via Ovid)**

Original search date: 2/11/2022

*Note: Ovid MEDLINE(R) ALL 1946 to February 10, 2022*

| Search Set | Search Strategy | Results |
|------------|-----------------|---------|
| #1 Gram-negative bacteria terms | exp Gram-Negative Bacteria/ OR exp Gram-Negative Bacterial Infections/ OR ("gram negative" OR gram-negative OR GNB OR GNBs OR enterobacteriaceae OR enterobacter OR "bacillary dysentery" OR escherichia OR "E.coli" OR "E. coli." OR "E coli" OR "granuloma inguinale" OR klebsiella OR rhinoscleroma OR proteus OR salmonella OR "typhoid fever" OR "paratyphoid fever" OR serratia OR yersinia OR citrobacter OR morganella OR providencia OR stenotrophomonas OR moraxellaceae OR acinetobacter OR mycoplasmatas OR mycoplasma OR ureaplasm OR "contagious pleuropneumonia" OR neisseriae OR gonorrhea OR meningococcal OR meningitis OR meningococcemia OR "neisseria meningitidis" OR "ophthalmia neonatorum" OR pasteurellaceae OR actinobacillus OR actinobacillosis OR haemophilus OR chancroid OR "haemophilus meningitis" OR pasteurella OR "hemorrhagic septicemia" OR "hemorrhagic septicaemia" OR "haemorrhagic septicemia" OR "pneumonic pasteurellosis" OR pseudomonas).ti,ab,kw,kf. | 1227804 |
| #2 Bacteremia terms | Bacteremia/ OR (bacteremia OR bacteraemia OR bacteremic OR bacteraemic OR "bloodstream infection" OR "blood stream infection" OR "bloodstream infections" OR "bloodstream infections" OR "blood infection" OR "blood infections" OR pyemia OR pyemias OR pyaemia).ti,ab,kw,kf. | 54,611 |
| #3 blood culture terms | exp Blood culture/ OR (culture or cultures or cultured).ti,ab,kw,kf. | 1103054 |
| #4 Follow-up terms | (follow-up OR "follow up" OR "following up" OR "follow ups" OR follow-ups OR followup OR followups OR "followed up" OR "followed-up" OR repeat OR repeated OR repeating OR repeats OR repetitive OR repetitively OR "next day" OR "following day" OR serial OR serially OR surveillance OR surveil OR surveils OR surveilled OR surveilling OR FUBC OR FUBCs).ti,ab,kw,kf. | 2040370 |
| #5 | 3 and 4 | 51805 |
| #6 Add'l blood culture follow-up terms | ((culture OR cultures OR cultured) ADJ3 (frequent or frequently or daily)).ti,ab,kw,kf. | 1804 |
| #7 | 5 or 6 | 53415 |
| #8 | 1 and 2 and 7 | 1034 |
| #9 Remove animal studies | 8 not (exp animals/ not exp humans/) | 997 |
| #10 Remove certain study designs | 9 not (case reports OR editorial OR congress).pt. | 831 |
**Search Update:**

**Database: MEDLINE (via Ovid)**

Search date: 3/11/2022

*Note: Ovid MEDLINE(R) ALL 1946 to March 10, 2022*

| Search Set       | Search Strategy                                                                 | Results   |
|------------------|---------------------------------------------------------------------------------|-----------|
| #1 Gram-negative bacteria terms    | exp Gram-Negative Bacteria/ OR exp Gram-Negative Bacterial Infections/ OR  | 1231002   |
|                  | ("gram negative" OR gram-negative OR GNB OR GNBs OR enterobacteriaceae OR  |           |
|                  | enterobacter OR "bacillary dysentery" OR escherichia OR "E.coli" OR "E. coli." OR  |           |
|                  | "E coli" OR "granuloma inguinale" OR klebsiella OR rhinoscleroma OR proteus OR  |           |
|                  | salmonella OR "typhoid fever" OR "paratyphoid fever" OR serratia OR yersinia OR  |           |
|                  | citrobacter OR morganella OR providencia OR stenotrophomonas OR moraxellaceae OR  |           |
|                  | acinetobacter OR mycoplastamates OR mycoplasma OR ureaplasma OR "contagious pleuropneumonia" OR neisseriaeae OR gonorrhea OR meningococcal OR meningitis OR meningococcemia OR "neisseria meningitidis" OR "ophthalmia neonatorum" OR pasteurellaceae OR actinobacillus OR actinobacillosis OR haemophilus OR chancroid OR "haemophilus meningitis" OR pasteurella OR "hemorrhagic septicemia" OR "hemorrhagic septicemia" OR "haemorrhagic septicaemia" OR "fimbrial pasteurellosis" OR pseudomonas).ti,ab,kw,kf. |           |
| #2 Bacteremia terms    | Bacteremia/ OR (bacteremia OR bacteraemia OR bacteremic OR bacteraeemic OR "bloodstream infection" OR "blood infection" OR "blood infections" OR "bloodstream infections" OR "bloodstream infections") OR pyemia OR pyemias OR pyemia OR pyemias OR pyemias OR pyemia).ti,ab,kw,kf. | 54814     |
| #3 blood culture terms | exp Blood culture/ OR (culture or cultures or cultured).ti,ab,kw,kf.          | 1105862   |
| #4 Follow-up terms     | (follow-up OR "follow up" OR "following up" OR "follow ups" OR follow-ups OR  | 2049338   |
|                  | followup OR followups OR "followed up" OR "followed-up" OR repeat OR repeated OR  |           |
|                  | repeating OR repeats OR repetitive OR repetitively OR "next day" OR  |           |
|                  | "following day" OR serial OR serially OR surveillance OR surveil OR surveils OR  |           |
|                  | surveilled OR surveilling OR FUBC OR FUBCs).ti,ab,kw,kf.                     |           |
| #5               | 3 and 4                                                                         | 52039     |
| #6 Add'l blood culture follow-up terms | ((culture OR cultures OR cultured) ADJ3 (frequent or frequently or daily)).ti,ab,kw,kf. | 1812      |
| #7               | 5 or 6                                                                          | 53658     |
| #8               | 1 and 2 and 7                                                                   | 1042      |
| #9 Remove animal studies     | 8 not (exp animals/ not exp humans/)                                           | 1005      |
| #10 Remove certain study designs     | 9 not (case reports OR editorial OR congress).pt.                              | 838       |
| #11              | Limit 10 to da=20220211-20220311                                                | 10        |
### Search Set | Search Strategy | Results
--- | --- | ---
#1 Gram-negative bacteria terms | "Gram negative bacterium'/exp OR 'Gram negative infection'/exp OR ("gram negative" OR gram-negative OR GNB OR GNBs OR enterobacteriaceae OR enterobacter OR "bacillary dysentery" OR escherichia OR "E.coli" OR "E. coli." OR "E coli" OR "granuloma inguinale" OR klebsiella OR rhinoscleroma OR proteus OR salmonella OR "typhoid fever" OR "paratyphoid fever" OR serratia OR yersinia OR acinetobacter OR morganella OR providencia OR stenotrophomonas OR moraxellaceae OR citrobacter OR acinetobacter OR mycoplasmatales OR mycoplasma OR ureaplasma OR "contagious pleuropneumonia" OR neisseriaceae OR gonorrhea OR meningococcal OR meningitis OR meningococcemia OR "neisseria meningitidis" OR "opthalmia neonatorum" OR pasteurellaceae OR actinobacillus OR actinobacillosis OR haemophilus OR chancroid OR "haemophilus meningitis" OR pasteurella OR "hemorrhagic septicemia" OR "hemorrhagic septicaemia" OR "haemorrhagic septicaemia" OR "pneumonic pasteurellosis" OR pseudomonas):ti,ab,kw | 1267935
#2 Bacteremia terms | 'bacteremia'/exp OR (bacteremia OR bacteraemia OR bacteremic OR bacteraemic OR 'bloodstream infection' OR 'blood stream infection' OR 'bloodstream infections' OR 'blood stream infections' OR 'blood infection' OR 'blood infections' OR pyemia OR pyemias OR pyohemia OR pyohemias OR pyaemia):ti,ab,kw | 87601
#3 blood culture terms | 'blood culture'/exp OR (culture OR cultures OR cultured):ti,ab,kw | 1452437
#4 Follow-up terms | (follow-up OR 'follow up' OR 'following up' OR 'follow ups' OR follow-ups OR followup OR followups OR 'followed up' OR 'followed-up' OR repeat OR repeated OR repeating OR repeats OR repetitive OR repetitively OR 'next day' OR 'following day' OR serial OR serially OR surveillance OR surveil OR surveils OR surveilled OR surveilling OR FUBC OR FUBCs):ti,ab,kw | 3090369
#5 combining | #3 AND #4 | 84227
#6 Add'l blood culture follow-up terms | ((culture OR cultures OR cultured) NEAR/3 (frequent or frequently or daily)):ti,ab,kw | 2623
#7 combining | #5 OR #6 | 86530
#8 combining | #1 AND #2 AND #7 | 2203
#9 Remove animal studies | #8 AND [humans]/lim | 1976
#10 Remove certain study designs | #9 NOT ('case report'/exp OR 'editorial'/exp OR [editorial]/lim OR [conference abstract]/lim OR 'conference abstract'/exp OR 'conference abstract'/it) | 978
Search update:
**Database: Embase (via Elsevier)**
Search date: 3/11/2022
*Note: Search from the results page*

| Search Set | Search Strategy | Results |
|------------|-----------------|---------|
| #1 Gram-negative bacteria terms | 'Gram negative bacterium'/exp OR 'Gram negative infection'/exp OR ('gram negative" OR gram-negative OR GNB OR GNBS OR enterobacteriaceae OR enterobacter OR "bacillary dysentery" OR escherichia OR "E.coli" OR "E. coli." OR "E coli" OR "granuloma inguinale" OR klebsiella OR rhinoscleroma OR proteus OR salmonella OR "typhoid fever" OR "paratyphoid fever" OR serratia OR yersinia OR citrobacter OR morganella OR providencia OR stenotrophomonas OR moraxellaceae OR acinetobacter OR mycoplasmatales OR mycoplasma OR ureaplasma OR "contagious pleuropneumonia" OR neisseriaceae OR gonorrhea OR meningococcal OR meningitis OR meningococcemia OR "neisseria meningitidis" OR "ophthalmia neonatorum" OR pasteurellaceae OR actinobacillus OR actinobacillosis OR haemophilus OR chancroid OR "haemophilus meningitis" OR pasteurella OR "hemorrhagic septicemia" OR "hemorrhagic septicaemia" OR "haemorrhagic septicaemia" OR "pneumonic pasteurellosis" OR pseudomonas):ti,ab,kw | 1272600 |
| #2 Bacteremia terms | 'bacteremia'/exp OR (bacteremia OR bacteraemia OR bacteremic OR bacteremic OR 'bloodstream infection' OR 'blood stream infection' OR 'bloodstream infections' OR 'blood stream infections' OR 'blood infection' OR 'blood infections' OR pyemia OR pyemias OR pyohemia OR pyohemias OR pyaemia):ti,ab,kw | 88113 |
| #3 blood culture terms | 'blood culture'/exp OR (culture OR cultures OR cultured):ti,ab,kw | 1456773 |
| #4 Follow-up terms | (follow-up OR 'follow up' OR 'following up' OR 'follow ups' OR follow-ups OR followup OR followed OR followups OR 'followed up' OR 'followed-up' OR repeat OR repeated OR repeating OR repeats OR repetitive OR repetitively OR 'next day' OR 'following day' OR serial OR serially OR surveillance OR surveil OR surveils OR surveilled OR surveilling OR FUBC OR FUBCs):ti,ab,kw | 3105757 |
| #5 combining | #3 AND #4 | 84633 |
| #6 Add'l blood culture follow-up terms | ((culture OR cultures OR cultured) NEAR/3 (frequent or frequently or daily)):ti,ab,kw | 2633 |
| #7 | #5 OR #6 | 86946 |
| #8 combining | #1 AND #2 AND #7 | 2228 |
| #9 Remove animal studies | #8 AND [humans]/lim | 2000 |
| #10 Remove certain study designs | #9 NOT ('case report'/exp OR 'editorial'/exp OR [editorial]/lim OR [conference abstract]/lim OR 'conference abstract'/exp OR 'conference abstract'/it) | 985 |
| #11 | #10 AND [11-02-2022]/sd | 15 |
Database: Web of Science – Science Citation Index Expanded (1900 – present) and Social Science Citation Index (1900-present) (via Clarivate)

Search date: 2/11/2022

Note: select indices from homepage, under Editions; search from the Advanced page

| Search Set | Search Strategy | Results |
|------------|-----------------|---------|
| #1 Gram-negative bacteria terms | TS=("gram negative" OR gram-negative OR GNB OR GNBs OR enterobacteriaceae OR enterobacter OR "bacillary dysentery" OR escherichia OR "E.coli" OR "E. coli." OR "E coli" OR "granuloma inguinale" OR klebsiella OR rhinoscleroma OR proteus OR salmonella OR "typhoid fever" OR "paratyphoid fever" OR serratia OR yersinia OR citrobacter OR morganella OR providencia OR stenotrophomonas OR moraxellaceae OR acinetobacter OR mycoplasmatales OR mycoplasma OR ureaplasma OR "contagious pleuropneumonia" OR neisseriaceae OR gonorrhea OR meningococcal OR meningitis OR meningococcemia OR "neisseria meningitidis" OR "ophthalmia neonatorum" OR pasteurellaceae OR actinobacillus OR actinobacilosis OR haemophilus OR chancroid OR "haemophilus meningitis" OR pasteurella OR "hemorrhagic septicemia" OR "hemorrhagic septicaemia" OR "haemorrhagic septicemia" OR "pneumonic pasteurellosis" OR pseudomonas) | 933674 |
| #2 Bacteremia terms | TS=(bacteremia OR bacteraemia OR bacteremic OR bacteraemic OR "bloodstream infection" OR "blood stream infection" OR "bloodstream infections" OR "blood stream infections" OR "blood infection" OR "blood infections" OR pyemia OR pyemias OR pyohemia OR pyohemias OR pyaemia) | 57205 |
| #3 blood culture terms | TS=(culture or cultures or cultured) | 1358832 |
| #4 Follow-up terms | TS=(follow-up OR "follow up" OR "following up" OR "follow ups" OR follow-ups OR followup OR followups OR "followed up" OR "followed-up" OR repeat OR repeated OR repeating OR repeats OR repetitive OR repetitively OR "next day" OR "following day" OR serial OR serially OR surveillance OR surveil OR surveils OR surveilled OR surveilling OR FUBC OR FUBCs) | 2123891 |
| #5 #3 AND #4 | | 52215 |
| #6 Add'l blood culture follow-up terms | TS=((culture OR cultures OR cultured) NEAR/3 (frequent or frequently or daily)) | 2244 |
| #7 #5 OR #6 | | 54221 |
| #8 #1 AND #2 AND #7 | | 1091 |
| #9 #8 NOT Document Types: Book Chapters or Editorial Materials | | 1087 |
Search update:

**Database:** Web of Science – Science Citation Index Expanded (1900 – present) and Social Science Citation Index (1900-present) (via Clarivate)

Search date: 3/11/2022

*Note: select indices from homepage, under Editions; search from the Advanced page*

| Search Set | Search Strategy | Results |
|------------|-----------------|---------|
| #1 Gram-negative bacteria terms | TS=("gram negative" OR gram-negative OR GNB OR GNBs OR enterobacteriaceae OR enterobacter OR "bacillary dysentery" OR escherichia OR "E.coli" OR "E. coli." OR "E coli" OR "granuloma inguinale" OR klebsiella OR rhinoscleroma OR proteus OR salmonella OR "typhoid fever" OR "paratyphoid fever" OR serratia OR yersinia OR citrobacter OR morganella OR providencia OR stenotrophomonas OR moraxellaceae OR acinetobacter OR mycoplasmatales OR mycoplasma OR ureaplasma OR "contagious pleuropneumonia" OR neisseriaceae OR gonorrhea OR meningococcal OR meningitis OR meningococcemia OR "neisseria meningitidis" OR "optalhia neonatorum" OR pasteurellaceae OR actinobacillus OR actinobacillosis OR haemophilus OR chancroid OR "haemophilus meningitis" OR pasteurella OR "hemorrhagic septicaemia" OR "hemorrhagic septicaemia" OR "haemorrhagic septicaemia" OR "pneumonic pasteurellosis" OR pseudomonas) | 936455 |
| #2 Bacteremia terms | TS=(bacteremia OR bacteraemia OR bacteremic OR bacteraemic OR "bloodstream infection" OR "blood stream infection" OR "bloodstream infections" OR "bloodstream infections" OR "blood infection" OR "blood infections" OR pyemia OR pyemias OR pyohemia OR pyohemias OR pyaemia) | 57456 |
| #3 blood culture terms | TS=(culture or cultures or cultured) | 1362573 |
| #4 Follow-up terms | TS=(follow-up OR "follow up" OR "following up" OR "follow ups" OR follow-ups OR followup OR followups OR "followed-up" OR repeated OR repeating OR repeats OR repetitive OR repetitively OR "next day" OR "following day" OR serial OR serially OR surveillance OR surveil OR surveils OR surveilled OR surveilling OR FUBC OR FUBCs) | 2134139 |
| #5 | #3 AND #4 | 52414 |
| #6 Add'l blood culture follow-up terms | TS=(culture OR cultures OR cultured) NEAR/3 (frequent or frequently or daily)) | 2251 |
| #7 | #5 OR #6 | 54426 |
| #8 | #1 AND #2 AND #7 | 1094 |
| #9 | #8 NOT Document Types: Book Chapters or Editorial Materials | 1090 |
| #10 | Refine – Publication Year: 2022 | 10 |

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| Search Set | Search Strategy | Results |
|------------|----------------|---------|
| #1 Gram-negative bacteria terms | [mh "Gram-Negative Bacteria"] OR [mh "Gram-Negative Bacterial Infections"] OR ("gram negative":ti,ab OR gram-negative:ti,ab OR GNB:ti,ab OR GNBs:ti,ab OR enterobacteriaceae:ti,ab OR enterobacter:ti,ab OR "bacillary dysentery":ti,ab OR escherichia:ti,ab OR E.coli:ti,ab OR "E. coli":ti,ab OR "E coli":ti,ab OR "granuloma inguinale":ti,ab OR klebsiella:ti,ab OR rhinoscleromacti,ab OR proteus:ti,ab OR salmonella:ti,ab OR "typhoid fever":ti,ab OR "paratyphoid fever":ti,ab OR serratia:ti,ab OR yersinia:ti,ab OR citrobacter:ti,ab OR morganella:ti,ab OR providencia:ti,ab OR stenotrophomonas:ti,ab OR moraxellaceae:ti,ab OR acinetobacter:ti,ab OR mycoplasmatales:ti,ab OR mycoplasma:ti,ab OR ureaplasma:ti,ab OR "contagious pleuropneumonia":ti,ab OR neisseriae:ti,ab OR gonorheae:ti,ab OR meningococcal:ti,ab OR meningitis:ti,ab OR meningococcemia:ti,ab OR "neisseria meningitidis":ti,ab OR "opthalmia neonatorum":ti,ab OR pasteurellaceae:ti,ab OR actinobacillus:ti,ab OR actinobacillosis:ti,ab OR haemophilus:ti,ab OR haemophilus meningitis:ti,ab OR pasteurella:ti,ab OR "hemorrhagic septicemia":ti,ab OR "hemorrhagic septicaemia":ti,ab OR "haemorrhagic septicaemia":ti,ab OR "pneumonic pasteurellosis":ti,ab OR pseudomonas:ti,ab) | 19373 |
| #2 Bacteremia terms | [mh "Bacteremia"] OR (bacteremia:ti,ab OR bacteremia:ti,ab OR bacteremic:ti,ab OR bacteremiac:ti,ab OR "bloodstream infection":ti,ab OR "blood stream infection":ti,ab OR "bloodstream infections":ti,ab OR "blood stream infections":ti,ab OR "blood infection":ti,ab OR "blood infections":ti,ab OR pyemia:ti,ab OR pyemias:ti,ab OR pyemia:ti,ab OR pyemia:ti,ab) | 3351 |
| #3 blood culture terms | [mh "Blood culture"] OR (culture:ti,ab OR cultures:ti,ab OR cultured:ti,ab) | 19359 |
| #4 Follow-up terms | (follow-up:ti,ab OR "follow up":ti,ab OR "following up":ti,ab OR "follow ups":ti,ab OR follow-ups:ti,ab OR followup:ti,ab OR followups:ti,ab OR "followed up":ti,ab OR followed-up:ti,ab OR repeat:ti,ab OR repeated:ti,ab OR repeating:ti,ab OR repeats:ti,ab OR repetitively:ti,ab OR "next day":ti,ab OR "following day":ti,ab OR serial:ti,ab OR serially:ti,ab OR surveillance:ti,ab OR surveil:ti,ab OR surveils:ti,ab OR surveilled:ti,ab OR surveilling:ti,ab OR FUBC:ti,ab OR FUBCs:ti,ab) | 312131 |
| #5 #3 AND #4 | | 4075 |
| #6 Add'l blood culture follow-up terms | ((culture:ti,ab OR cultures:ti,ab OR cultured:ti,ab) NEAR/3 (frequent:ti,ab OR frequently:ti,ab OR daily:ti,ab)) | 108 |
| #7 #5 OR #6 | | 4159 |
| #8 #1 AND #2 AND #7 | | 57 |
| #9 From Results Page: Limit 8 to Trials | | 57 |
Search update:
Database: Cochrane Central Register of Controlled Trials (via Wiley)
Search date: 3/11/2022
Note: Go to Advanced Search > Search Manager

| Search Set       | Search Strategy                                                                                           | Results |
|------------------|-----------------------------------------------------------------------------------------------------------|---------|
| #1               | [mh "Gram-Negative Bacteria"] OR [mh "Gram-Negative Bacterial Infections"] OR                           | 19804   |
| Gram-negative    | ("gram negative":ti,ab OR gram-negative:ti,ab OR GNB:ti,ab OR GNBs:ti,ab OR enterobacteriaceae:ti,ab OR enterobacter:ti,ab OR "bacillary dysentery":ti,ab OR escherichia:ti,ab OR E.coli:ti,ab OR "E. coli":ti,ab OR "E coli":ti,ab OR "granuloma inguinale":ti,ab OR klebsiella:ti,ab OR rhinoscleroma:ti,ab OR proteus:ti,ab OR salmonella:ti,ab OR "typhoid fever":ti,ab OR "paratyphoid fever":ti,ab OR serratia:ti,ab OR yersinia:ti,ab OR citrobacter:ti,ab OR morganella:ti,ab OR providencia:ti,ab OR stenotrophomonas:ti,ab OR moraxellaceae:ti,ab OR acinetobacter:ti,ab OR mycoplasmatales:ti,ab OR mycoplasma:ti,ab OR ureaplasma:ti,ab OR "contagious pleuropneumonia":ti,ab OR neissieracea:ti,ab OR gonorrhoea:ti,ab OR meningococcal:ti,ab OR meningitis:ti,ab OR meningococcalia:ti,ab OR "neisseria meningitidis":ti,ab OR "opthalmia neonatorum":ti,ab OR pasteurellacea:ti,ab OR actinobacillus:ti,ab OR actinobacillosis:ti,ab OR haemophilus:ti,ab OR chancroid:ti,ab OR "haemophilus meningitis":ti,ab OR pasteurella:ti,ab OR "hemorrhagic septicaemia":ti,ab OR "haemorrhagic septicaemia":ti,ab OR "pneumonic pasteurellosis":ti,ab OR pseudomonas:ti,ab) |         |
| negative bacteria|                                                                                                          |         |
| terms            |                                                                                                          |         |
| #2               | [mh ^Bacteremia] OR (bacteremia:ti,ab OR bacteraemia:ti,ab OR bacteremic:ti,ab OR OR bacteraemic:ti,ab OR bloodstream infection":ti,ab OR "blood stream infection":ti,ab OR "bloodstream infections":ti,ab OR "blood stream infections":ti,ab OR "blood infection":ti,ab OR "blood infections":ti,ab OR pyemia:ti,ab OR pyemias:ti,ab OR pyohemia:ti,ab OR pyohemias:ti,ab OR pyaemia:ti,ab) | 3370    |
| Bacteremia terms |                                                                                                          |         |
| #3               | [mh "Blood culture"] OR (culture:ti,ab OR cultures:ti,ab OR cultured:ti,ab)                            | 19447   |
| blood culture    |                                                                                                          |         |
| terms            |                                                                                                          |         |
| #4               | (follow-up:ti,ab OR "follow up":ti,ab OR "following up":ti,ab OR "follow ups":ti,ab OR followed-up:ti,ab OR followed:ti,ab OR followed-up:ti,ab OR followups:ti,ab OR "followed up":ti,ab OR followed-up:ti,ab OR repeat:ti,ab OR repeated:ti,ab OR repeating:ti,ab OR repeats:ti,ab OR repetitively:ti,ab OR repetitively:ti,ab OR "next day":ti,ab OR "following day":ti,ab OR serial:ti,ab OR serially:ti,ab OR surveillance:ti,ab OR surveil:ti,ab OR surveils:ti,ab OR surveilled:ti,ab OR surveilling:ti,ab OR FUBC:ti,ab OR FUBCs:ti,ab) | 314425  |
| Follow-up terms  |                                                                                                          |         |
| #5               | #3 AND #4                                                                                                | 4085    |
| #6               | ((culture:ti,ab OR cultures:ti,ab OR cultured:ti,ab) NEAR/3 (frequent:ti,ab OR frequently:ti,ab OR daily:ti,ab)) | 108     |
| Add'l blood culture follow-up terms |                                                                                                          |         |
| #7               | #5 OR #6                                                                                                | 4169    |
| #8               | #1 AND #2 AND #7                                                                                         | 59      |
| #9               | From Results Page: Limit 8 to Trials                                                                   | 59      |
| #10              | Limit to Year 2022                                                                                       | 2       |
eAppendix 3. Criteria for inclusion and exclusion of studies in this systematic review.

**Inclusion criteria**
1. Study design: Randomized controlled trials or observational studies with N>10. The sample size requirement is designed to exclude case reports. This size requirement does permit smaller pilot studies that are typically underpowered and have more methodological problems than larger studies.
2. For observational studies, matching or statistical adjustment for differences in (at minimum) level of acute illness between patients in the intervention (e.g., FUBCs obtained) and control groups (e.g., FUBCs not obtained) must be performed. Only observational studies meeting this criteria were included in the primary analyses for KQ1 and KQ2. However, observational studies not meeting this criteria were included in exploratory analyses of KQ1 and KQ2.
3. Age: Adults aged 18 years or older with gram-negative bloodstream infection
4. Setting: Inpatients
5. Studies must stratify patients by whether follow-up blood cultures obtained (KQ1) or by whether follow-up blood cultures were positive or negative (KQ2)
6. Study must report effects of follow-up blood cultures on at least one of the following relevant outcomes:
   - In-hospital mortality
   - Mortality up to 30 days (e.g., 28-day mortality, 30-day mortality)
7. Article is a full publication, research letter, or meeting abstract published in a peer-reviewed journal.
8. Article is an English language publication

**Exclusion criteria**
1. Outpatient setting
2. Polymicrobial bloodstream infection
eAppendix 4. Studies excluded at full text review.

1. Alsfeld LC, Rockey DC. Utility of Routine Blood Cultures for Inpatient Hematology/Oncology Patients Receiving Antimicrobials. American Journal of the Medical Sciences 2019; 358: 175-81. Reason for exclusion: Wrong outcome.

2. Canzoneri CN, Akhavan BJ, Andrade PEA et al. Prospective Trials Are Required to Alter Practice for Follow-up Blood Cultures for Gram-Negative Bacilli Bacteremia Reply. Clinical Infectious Diseases 2018; 67: 316-. Reason for exclusion: Commentary without data.

3. Canzoneri CN, Akhavan BJ, Tosur Z et al. Follow-up Blood Cultures in Gram-Negative Bacteremia: Are They Needed? Clinical Infectious Diseases 2017; 65: 1776-9. Reason for exclusion: Data not stratified by gram-negative bacteria.

4. Canzoneri CN, Akhavan BJ, Tosur Z et al. Follow-up Blood Cultures: A 2.0 Diagnostic Tool in Patients With Gram-Negative Bacteremia and Septic Thrombophlebitis Reply. Clinical Infectious Diseases 2018; 66: 1155-6. Reason for exclusion: Commentary without data.

5. Ceccarelli G, Giuliano S, Falcone M et al. Follow-up Blood Cultures: A 2.0 Diagnostic Tool in Patients With Gram-Negative Bacteremia and Septic Thrombophlebitis. Clinical Infectious Diseases 2018; 66: 1154-5. Reason for exclusion: Case report.

6. Chan JD, Bryson-Cahn C, Kassamali-Escobar Z et al. The Changing Landscape of Uncomplicated Gram-Negative Bacteremia: A Narrative Review to Guide Inpatient Management. Journal of Hospital Medicine (Online) 2020; 15: 746-53. Reason for exclusion: Review article.

7. Cogliati Dezza F, Curtolo A, Volpicelli L et al. Are Follow-Up Blood Cultures Useful in the Antimicrobial Management of Gram Negative Bacteremia? A Reappraisal of Their Role Based on Current Knowledge. Antibiotics 2020; 9: 11. Reason for exclusion: Review article.

8. Deal EN, Micek ST, Reichley RM et al. Effects of an alternative cefepime dosing strategy in pulmonary and bloodstream infections caused by Enterobacter spp, Citrobacter freundii, and Pseudomonas aeruginosa: a single-center, open-label, prospective, observational study. Clinical Therapeutics 2009; 31: 299-310. Reason for exclusion: Wrong intervention.

9. Fabre V, Sharara SL, Salinas AB et al. Does this patient need blood cultures? A scoping review of indications for blood cultures in adult nonneutropenic inpatients. Clinical Infectious Diseases 2020; 71: 1339-47. Reason for exclusion: Review article.

10. Funada H, Machi T, Matsuda T. [Pseudomonas aeruginosa bacteremia associated with hematologic disorders [II]. Blood culture isolates and surveillance cultures]. Kansenshogaku Zasshi - Journal of the Japanese Association for Infectious Diseases 1989; 63: 874-9. Reason for exclusion: Article not in English.

11. Giannella M, Malosso P, Scudeller L et al. Quality of care indicators in the MANageMent of BIOOdstream infections caused by Enterobacteriaceae (MAMBOO-E study): state of the art and research agenda. International journal of antimicrobial agents 2021; 57: 106320. Reason for exclusion: Review article.

12. Gubbels S, Nielsen J, Voldstedlund M et al. Utilization of blood cultures in Danish hospitals: a population-based descriptive analysis. Clinical Microbiology and Infection 2015; 21. Reason for exclusion: Wrong patient population.

13. Harris PNA, Peri AM, Pelecanos AM et al. Risk factors for relapse or persistence of bacteraemia caused by Enterobacter spp.: a case-control study. Antimicrobial Resistance & Infection Control 2017; 6: 14. Reason for exclusion: Wrong outcomes.

14. Jafri F, Knoll BM. Low diagnostic yield of repeat blood cultures in adult haematologic malignancy patients with persistent neutropenic fever. Journal of internal medicine 2021; 289: 584-7. Reason for exclusion: Wrong intervention.

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15. Jones RB, Paruchuri A, Shah SS. Prospective Trials Are Required to Alter Practice for Follow-up Blood Cultures for Gram-Negative Bacilli Bacteremia. Clinical Infectious Diseases 2018; 67: 315-6. Reason for exclusion: Commentary without data.

16. Kimura SI, Gomyo A, Hayakawa J et al. Clinical significance of repeat blood cultures during febrile neutropenia in adult acute myeloid leukaemia patients undergoing intensive chemotherapy. Infectious Diseases 2017; 49: 748-57. Reason for exclusion: Wrong patient population.

17. Lee CC, Yang CY, Hsieh CC et al. Timing of follow-up blood cultures for community-onset bacteremia. Scientific reports 2019; 9. Reason for exclusion: Data not stratified by gram-negative bacteria.

18. Limmathurotsakul D, Wuthiekanun V, Wongsuphan G et al. Short report: Repeat blood culture positive for B. pseudomallei indicates an increased risk of death from melioidosis. American Journal of Tropical Medicine and Hygiene 2011; 84: 858-61. Reason for exclusion: Wrong patient population.

19. McKinnell JA, Connolly LE, Pushkin R et al. Improved outcomes with plazomicin (PLZ) compared with colistin (CST) in patients with bloodstream infections (BSI) caused by carbapenem-resistant enterobacteriaceae (CRE): results from the care study. Open forum infectious diseases 2017; 4: S531-.
Reason for exclusion: Wrong intervention.

20. Pastewski AA, Caruso P, Parris AR et al. Parenteral polymyxin B use in patients with multidrug-resistant gram-negative bacteremia and urinary tract infections: a retrospective case series. Annals of Pharmacotherapy 2008; 42: 1177-87. Reason for exclusion: Wrong outcomes.

21. Paterson DL, Kinoshita M, Baba T et al. Outcomes with Cefiderocol Treatment in Patients with Bacteraemia Enrolled into Prospective Phase 2 and Phase 3 Randomised Clinical Studies. Infectious Diseases and Therapy. Reason for exclusion: Wrong study design.

22. Shi HJ, Kang CI, Cho SY et al. Follow-up blood cultures add little value in the management of bacteremic urinary tract infections. European Journal of Clinical Microbiology and Infectious Diseases 2019; 38: 695-702. Reason for exclusion: Data not stratified by gram-negative bacteria.

23. Shi HJ, Lee JS, Cho YK et al. Predictors of Mortality in Patients with Carbapenem-Resistant Gram-Negative Bacilli or Vancomycin-Resistant Enterococci Bacteremia. Infection & Drug Resistance 2020; 13: 3535-42. Reason for exclusion: Data not stratified by gram-negative bacteria.

24. Spaziante M, Giuliani S, Ceccarelli G et al. Gram-negative septic thrombosis in critically ill patients: A retrospective case-control study. International Journal of Infectious Diseases 2020; 94: 110-5. Reason for exclusion: Wrong intervention.

25. Sutton JD, Sayood S, Spivak ES. Top questions in uncomplicated, non-staphylococcus aureus Bacteremia. Open forum infectious diseases 2018; 5. Reason for exclusion: Review article.

26. Trachtenberg BH, Cordero-Reyes AM, Aldeiri M et al. Persistent blood stream infection in patients supported with a continuous-flow left ventricular assist device is associated with an increased risk of cerebrovascular accidents. Journal of Cardiac Failure 2015; 21: 119-25. Reason for exclusion: Data not stratified by gram-negative bacteria.

27. Wang YL, Scipione MR, Dubrovskaya Y. Monotherapy with Fluoroquinolone or Trimethoprim-Sulfamethoxazole for Treatment of Stenotrophomonas maltophilia Infections. Antimicrobial agents and chemotherapy 2014; 58: 176-82. Reason for exclusion: Wrong outcomes.

28. Wiggers JB, Daneman N. The culture of follow-up blood cultures. Clinical Microbiology & Infection 2020; 26: 811-3. Reason for exclusion: Review article.

29. Zmora N, Shrestha S, Neuberger A et al. Open label comparative trial of mono versus dual antibiotic therapy for Typhoid Fever in adults. PLoS Neglected Tropical Diseases [electronic resource] 2018; 12: e0006380. Reason for exclusion: Wrong comparator.

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eAppendix 5. Newcastle-Ottawa Quality Assessment Scale for assessing risk of bias in cohort (A) and case-control (B) studies. The detailed criteria used to assess these study types, as well as the thresholds for converting the Newcastle-Ottawa scale to AHRQ standards (good, fair, and poor), are shown below.

A. Cohort studies

Selection

1. Representativeness of the exposed cohort
   a. Truly representative of the average person with gram-negative bloodstream infection in the community (*)
   b. Somewhat representative of the average person with gram-negative bloodstream infection in the community (*)
   c. Selected group of patients
   d. No description of the derivation of the cohort

2. Selection of the non-exposed cohort
   a. Drawn from the same community as the exposed cohort (*)
   b. Drawn from a different source
   c. No description of the derivation of the non-exposed cohort

3. Ascertainment of exposure
   a. Secure record (e.g. medical records) (*)
   b. Structured interview (*)
   c. Written self report
   d. No description

4. Demonstration that outcome of interest was not present at start of study
   a. Yes (*)
   b. No

Comparability of cohorts on basis of design or analysis

1. Study controls for level of acute illness.
   a. Yes (*)
   b. No

2. Study controls for any additional factor.
   a. Yes (*)
   b. No

Outcome

1. Assessment of outcome
   a. Independent blind assessment (*)
   b. Record linkage (*)
   c. Self report
   d. No description

2. Was follow-up long enough for outcomes to occur
   a. Yes (In-hospital mortality or mortality ≤30 days) (*)
   b. No

3. Adequacy of follow up of cohorts
   a. Complete follow up (all subjects accounted for) (*)
b. Subjects lost to follow up unlikely to introduce bias (≤10% lost to follow-up, or description provided of those lost) (*)
c. Follow up rate < 90% and no description of those lost
d. No statement

Thresholds used to convert the Newcastle-Ottawa scale to AHRQ standards (good, fair, and poor):

**Good quality/low risk of bias:** 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

**Fair quality/medium risk of bias:** 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain.

**Poor quality/high risk of bias:** 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

**B. Case-control studies**

**Selection**

1. Is the case definition adequate?
   a. Yes, with independent validation (*)
   b. Yes, with record linkage or based on self-reports
   c. No description

2. Representativeness of the cases
   a. Consecutive or obviously representative series of cases (*)
   b. Potential for selection biases or not stated

3. Selection of Controls
   a. Community controls (*)
   b. Hospital controls
   c. No description

4. Definition of Controls
   a. No history of disease (endpoint) (*)
   b. No description of source

**Comparability of cases and controls on the basis of the design or analysis**

1. Study controls for level of acute illness.
   a. Yes (*)
   b. No

2. Study controls for any additional factor.
   a. Yes (*)
   b. No

**Exposure**

1.Ascertainment of exposure
   a. Secure record (e.g. medical records) (*)
   b. Structured interview where blind to case/control status (*)
   c. Interview not blinded to case/control status
   d. Written self-report or medical record only
   e. No description

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2. Same method of ascertainment for cases and controls
   a. Yes (*)
   b. No

3. Non-Response rate
   a. Same rate for both groups (*)
   b. Non respondents described
   c. Rate different and no designation

Thresholds used to convert the Newcastle-Ottawa scale to AHRQ standards (good, fair, and poor):

**Good quality/low risk of bias:** 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

**Fair quality/medium risk of bias:** 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain.

**Poor quality/high risk of bias:** 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain
### Detailed description of studies that address KQ1 and KQ2.

#### Detailed characteristics of studies that addressed KQ1.

| Study | Design | Patient Population | Micro | Country | # Sites | Number With FUBCs | Number Without FUBCs | Patient Characteristics With FUBCs | Patient Characteristics Without FUBCs | Outcome |
|-------|--------|---------------------|-------|---------|---------|-------------------|----------------------|-----------------------------------|----------------------------------------|---------|
| Amipara 2021<sup>1</sup> | Cohort | Adult inpatients with community-acquired BSI | GN bacilli | USA | 2 | 168<sup>a</sup> | 438<sup>a</sup> | Age (Median [IQR]) 65 (52-75) Female 56% Pitt bacteremia score: Median (IQR) 2 (1-3) | Age: Median (IQR) 68 (56-79) Female 58% Pitt bacteremia score: Median (IQR) 1 (1-3) | 28-day mortality |
| Chan 2021<sup>2</sup> | Cohort | All adult inpatients | *E. coli* and *Klebsiella* | USA | 1 | 299 | 36 | Age (Median [IQR]) 60 (48-71) Female 42% | Age (Median [IQR]) 64 (53-72) Female 67% | 30-day mortality |
| Clemmons 2021<sup>3</sup> | Cohort | Non-critically ill adults in oncology units | All GN | USA | 3 | 35 | 17 | Age: Mean (SD) 59 (14) Female 49% | Age: Mean (SD) 71 (17) Female 53% | In-hospital mortality |
| Giannella 2020<sup>4</sup> | Cohort | All adult inpatients | All GN | Italy | 1 | 278 | 1298 | Age: Mean (SD) 62 (16) Female 49% SOFA: Mean (SD) 3 (1-5) Septic shock 14% | Age: Mean (SD) 70 (16) Female 46% SOFA: Mean (SD) 3 (1-5) Septic shock 8% | 30-day mortality |
| Green 2021<sup>5</sup> | Cohort | All adult inpatients | *P. aeruginosa* | USA | 1 | 127 | 32 | Age: Mean (SD) 57 (17) Female 40% Pitt bacteremia score: Median (IQR) 2 (0-4) | Age: Mean (SD) 59 (15) Female 44% Pitt bacteremia score: Median (IQR) 3 (0.5-5.5) | 30-day mortality |
| Groft 2021<sup>6</sup> | Cohort | Immuno-compromised adults | All GN | USA | 1 | 117 | 22 | ICU 41% Neutropenic 32% | ICU 41% Neutropenic 50% | In-hospital mortality |
| Jung 2020<sup>7</sup> | Cohort | All adult inpatients | All GN | South Korea | 1 | 1276 | 205 | Age: Mean (SD) 69 (14) Female 51% | Age: Mean (SD) 69 (14) Female 43% | In-hospital mortality |
| Maskarinec 2020<sup>8</sup> | Cohort | All adult inpatients | All GN | USA | 2 | 1164 | 538 | Age: Mean (SD) 60 (16) Female 43% APACHE-II: Mean (SD) 7 (6) | Age: Mean (SD) 62 (16) Female 46% APACHE-II: Mean (SD) 7 (5) | In-hospital mortality |
| Mitaka 2021<sup>9</sup> | Cohort | All adult inpatients | All GN | USA | 4 | 276 | 105 | Age: Median (IQR) 69 (59-82) Female 55% | Age: Median (IQR) 73 (64-83) Female 51% | In-hospital mortality |
| Robinson 2021<sup>10</sup> | Cohort | All adult inpatients | All GN | USA | 1 | 338 | 176 | Age: Median (IQR) 63 (52-72) | Age: Median (IQR) 67 (57-76) | In-hospital mortality |
| Wiggers 2016<sup>11</sup> | Cohort | All adult inpatients | All GN | Canada | 1 | 247 | 654 | Not reported | Not reported | 30-day mortality |

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### Detailed characteristics of studies that addressed KQ1 (continued).

| Study              | Mortality With FUBCs n (%) | Mortality Without FUBCs n (%) | Timing of FUBC from index culture | Matching/adjustment | Covariates Matched/Adjusted (selected) | Adjusted Estimate of Mortality with FUBCs (95% CI) | Method(s) to Address Survival Bias | Study Funding | Conflict Of Interest | Risk of bias |
|--------------------|---------------------------|-------------------------------|-----------------------------------|---------------------|----------------------------------------|-------------------------------------------------|--------------------------------|----------------|----------------------|--------------|
| Amipara 2021<sup>3</sup> | 12 (7.1)                  | 57 (13.0)                     | 24-96h                            | IPTW                | Age, Charlson comorbidity score, Pitt bacteremia score, antibiotic therapy, FUBC | HR 0.47 (0.23-0.87) | Excluded patients that died or were discharged <72h from index culture | None            | None                | Low          |
| Chan 2021<sup>3</sup>   | 27 (9.0)                  | 5 (13.9)                      | 24h-7d                            | None                | None                                   | None                                            | Excluded patients that died <48h or discharged <24h after index culture | None            | None                | High         |
| Clemmons 2021<sup>6</sup> | 3 (8.6)                   | 1 (5.9)                       | 4-72h                             | None                | None                                   | None                                            | None reported                      | None            | None                | High         |
| Giannella 2020<sup>2</sup> | 38 (13.7)                 | 126 (9.7)                     | 24h-7d                            | Logistic regression and matching on SOFA score (separately performed) | Charlson comorbidity score, SOFA score, septic shock, urinary tract source, source control, antibiotic therapy, FUBC | Logistic regression: HR 0.48 (0.27-0.83) Matching: HR 0.45 (0.22-0.92) | FUBCs treated as time-dependent covariate; patients with and without FUBCs matched by SOFA score, and those without FUBCs survived at least as long as it took for matched patient to get FUBCs; Excluded patients that died <72h from index culture | None            | None                | Low          |
| Green 2021<sup>7</sup>   | 24 (18.9)                 | 16 (50.0)                     | 24h-7d                            | Cox regression      | Age, Elixhauser comorbidity index, Pitt bacteremia score, immunosuppression | HR 0.43 (0.17-1.08) | FUBCs treated as time-dependent variable in Cox model | IDSA/SHEA | None                | Low          |
| Groft 2021<sup>8</sup>   | 7 (6.0)                   | 1 (4.5)                       | 24h-7d                            | None                | None                                   | None                                            | None reported                      | None            | None                | High         |
| Jung 2020<sup>4</sup>    | 87 (7)                    | 18 (9)                        | 2-7d                              | None                | None                                   | None                                            | Excluded patients that died <2 days from index culture | None            | None                | High         |
| Study          | Mortality With FUBCs n (%) | Mortality Without FUBCs n (%) | Timing of FUBC from index culture | Matching/adjustment | Covariates Matched/Adjusted (selected) | Adjusted Estimate of Mortality with FUBCs (95% CI) | Method(s) to Address Survival Bias | Study Funding | Conflict Of Interest | Risk of bias |
|---------------|---------------------------|-------------------------------|-----------------------------------|---------------------|----------------------------------------|---------------------------------------------------|-----------------------------------|---------------|----------------------|-------------|
| Maskarinec 2020<sup>a</sup> | 176 (15)                  | 108 (20)                      | 24h-7d                            | IPTW                | Age, APACHE-II acute physiology score, diabetes mellitus, transplant, hemodialysis, source of BSI, antibiotic therapy | HR 0.63 (0.51-0.72) | FUBCs treated as time-dependent variable in Cox model; Excluded patients that died <24h from index culture (sensitivity analysis with patients that died <48h from index culture performed and no change in findings) | None          | None                 | Low          |
| Mitaka 2021<sup>b</sup>   | 4 (4.6)<sup>c</sup>       | 10 (11.5)<sup>c</sup>        | ≥24h                              | Propensity score matching | Not reported<sup>b</sup> | OR 0.36 (0.12-1.14) | Excluded patients that received hospice care or died within 3 days of index culture | None          | None                 | Low          |
| Robinson 2021<sup>c</sup> | 338 (6.5)                 | 176 (5.7)                     | 24h-7d                            | None                | None                                   | None                                                                             | None          | None                 | Low          |
| Wiggers 2016<sup>d</sup>  | 35 (14.2)<sup>d</sup>     | 96 (14.7)<sup>d</sup>        | 2-7d                              | None                | None                                   | None                                                                             | Excluded patients that died <2 days from index culture | Canadian Institutes of Health Research | None          | High                 |             |

<sup>a</sup>Censored patients (n=51 in FUBCs group; n=109 in No FUBCs group) were removed to generate these numbers.

<sup>b</sup>Specific covariates not described in the conference abstract, though two intervention/control arms matched with respect to acute illness parameters (e.g., vasopressor support, ventilatory support, ICU level of care)

<sup>c</sup>Mortality figures only provided for propensity score-matched cohort

<sup>d</sup>Mortality data from this study was further stratified by gram-negative bacteria in other reports<sup>12,13</sup>

**Abbreviations:** CI, confidence interval; FUBCs, follow-up blood cultures; GN, gram-negative; HR, hazard ratio; IPTW, inverse probability of treatment weighting; IQR, interquartile range; OR, odds ratio; SD, standard deviation
Detailed characteristics of studies that addressed KQ2.

| Study     | Design    | Patient Population          | Micro       | Country   | # Sites | Number With Positive FUBCs | Number With Negative FUBCs | Patient Characteristics With Positive FUBCs                                                                 | Patient Characteristics With Negative FUBCs                                                                 | Outcome            |
|-----------|-----------|----------------------------|-------------|-----------|---------|-----------------------------|----------------------------|-----------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|
| Amipara   | Cohort    | Adult inpatients with community-acquired BSI | GN bacilli  | USA       | 2       | 13\(^a\)                     | 155\(^a\)                  | Not reported                                                                                                                                  | Not reported                                                                                                                                  | 28-day mortality |
| Chan 2021  | Cohort    | All adult inpatients       | E. coli and Klebsiella | USA       | 1       | 37                           | 262                        | Age: Median (IQR) 54 (44-67) Female 46%                                                                                                  | Age: Median (IQR) 60 (48-71) Female 41%                                                                                                  | 30-day mortality |
| Groft 2021  | Cohort    | Immuno-compromised adults  | All GN      | USA       | 1       | 3                            | 114                        | Not reported                                                                                                                                  | Not reported                                                                                                                                  | In-hospital mortality |
| Kang 2013  | Case control | All adult inpatients            | K. pneumoniae | South Korea | 2       | 62                           | 186                        | Age: Mean (SD) 64 (15) Female 27% APACHE-II score: Mean (SD) 19 (9) Pitt bacteremia score: Mean (SD) 3 (3) | Age: Mean (SD) 64 (14) Female 27% APACHE-II score: Mean (SD) 17 (8) Pitt bacteremia score: Mean (SD) 2 (2) | In-hospital mortality |
| Kim 2022   | Cohort    | All adult inpatients       | All GN      | South Korea | 1       | 89                           | 556                        | Age: Median (IQR) 60 (49-67) Female 41% Septic shock 47%                                                                                   | Age: Median (IQR) 64 (55-73) Female 27% Septic shock 30%                                                                                  | 30-day mortality |
| Maskarinec 2020 | Cohort | All adult inpatients          | All GN      | USA       | 2       | 228                          | 885                        | Age: Mean (SD) 59 (15) Female 46% APACHE-II score: Mean (SD) 8 (5)                                                                 | Age: Mean (SD) 60 (16) Female 45% APACHE-II score: Mean (SD) 7 (5)                                                                        | In-hospital |
| Mitaka 2020  | Cohort    | All adult inpatients       | All GN      | USA       | 4       | 28                           | 278                        | Age: Median (IQR) 66 (57-77) Female 43% Septic shock 29%                                                                                  | Age: Median (IQR) 70 (59-83) Female 46% Septic shock 23%                                                                                  | In-hospital |
| Spaziante 2020  | Cohort    | Critically ill adult inpatients | All GN      | Italy      | 1       | 23                           | 26                         | Age: Mean (SD) 55 (41-66) Female 30% SOFA score: Median (IQR) 7 (5-10)                                                                  | Age: Mean (SD) 61 (44-73) Female 19% SOFA score: Median (IQR) 9 (7-10)                                                                      | 30-day mortality |
| Wiggers 2016  | Cohort    | All adult inpatients       | All GN      | Canada     | 1       | 27                           | 220                        | Not reported                                                                                                                                  | Not reported                                                                                                                                  | 30-day mortality |
Detailed characteristics of studies that addressed KQ2 (continued).

| Study         | Mortality With Positive FUBCs n (%) | Mortality With Negative FUBCs n (%) | Timing of FUBC from index culture | Matching/adjustment | Covariates Matched/Adjusted (selected) | Adjusted Estimate of Mortality with Positive FUBCs (95% CI) | Study Funding | Conflict Of Interest | Risk of bias |
|---------------|------------------------------------|------------------------------------|----------------------------------|---------------------|----------------------------------------|-------------------------------------------------------------|---------------|----------------------|--------------|
| Amipara 2021  | 2 (15.4)                           | 10 (6.5)                           | 24-96h                           | None                | None                                   | None                                                        | None          | None                 | Low          |
| Chan 2021     | 6 (16.2)                           | 21 (8.0)                           | 24h-7d                           | None                | None                                   | None                                                        | None          | None                 | High         |
| Groft 2021    | 1 (33.3)                           | 6 (5.3)                            | 24h-7d                           | None                | None                                   | None                                                        | None          | None                 | High         |
| Kang 2013     | 19 (30.6)                          | 34 (18.3)                          | Not reported                     | None                | Logistic regression                     | OR 2.01 (1.07-3.76)                                         | None          | None                 | Low          |
| Kim 2022      | 31 (34.8)                          | 55 (9.9)                           | 48-72h                           | Logistic regression | Age, need for HD dependence, positive FUBC, stem cell transplant, need for vasopressor, antibiotic therapy | OR 2.01 (1.07-3.76)                                         | Asan Institute for Life Sciences                          | None          | Low                  |
| Maskarinec 2020 | 49 (21.5)                         | 110 (12.4)                        | 24h-7d                           | IPTW                | Age, APACHE-II acute physiology score, diabetes mellitus, transplant, hemodialysis, source of BSI, antibiotic therapy | HR 1.56 (1.13-2.16)                                         | None          | None                 | Low          |
| Mitaka 2020   | 3 (10.7)                           | 25 (9.0)                           | ≥24h                             | None                | None                                   | None                                                        | None          | None                 | High         |
| Spaziante 2020 | 8 (40.0)                          | 12 (46.1)                          | <48h after antibiotics started   | None                | None                                   | None                                                        | None          | None                 | High         |
| Wiggers 2016  | 7 (25.9)                           | 28 (12.7)                          | 2-7d                             | None                | None                                   | None                                                        | None          | None                 | High         |

*Censored patients with positive FUBCs (n=2 with positive FUBCs and n=49 with negative FUBCs) were removed to generate these numbers. The number of censored patients were provided by authors.

*Mortality data from this study was further stratified by gram-negative bacteria in other reports.12,13

**Abbreviations:** BSI, bloodstream infection; CI, confidence interval; GN, gram-negative; HR, hazard ratio; IPTW, inverse probability of treatment weighting; IQR, interquartile range; OR, odds ratio; SD, standard deviation
Appendix 6. Risk of bias (quality) assessment of included cohort (A) and case-control (B) studies using the Newcastle-Ottawa Quality Assessment Scale. The Newcastle-Ottawa Quality Assessment Scale determines a study’s risk of bias through nine questions (detailed in eAppendix 6). For each study, the grades for the nine questions are shown below. Grades that receive a star are highlighted in green, while those that do not are highlighted in red. Based on the grades from each question in the Newcastle-Ottawa Scale, an overall risk of bias (high, medium, low) can be assigned (detailed in eAppendix 6).

A. Cohort studies

| Study            | Selection: Representativeness of the exposed cohort | Selection: Non-exposed cohort | Ascertainment of exposure | Outcome not present at start of study | Comparability: Controls for level of acute illness | Controls for any additional factor | Outcome: Was follow-up long enough | Outcome: Adequacy of follow-up | Risk of bias |
|------------------|----------------------------------------------------|-------------------------------|---------------------------|--------------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------|---------------|
| Amipara 2021     | B A A A A A A B A C                               |                               |                           |                                      |                                 |                                 |                                 |                           | Low           |
| Chan 2021        | C A A A B B B A A                                |                               |                           |                                      |                                 |                                 |                                 |                           | High          |
| Clemmons 2021    | C A A A B B B A A                               |                               |                           |                                      |                                 |                                 |                                 |                           | High          |
| Giannella 2020   | B A A A A A B A A                               |                               |                           |                                      |                                 |                                 |                                 |                           | Low           |
| Green 2021       | C A A A A A B A B                               |                               |                           |                                      |                                 |                                 |                                 |                           | Low           |
| Groft 2021       | C A A A B B B A A                               |                               |                           |                                      |                                 |                                 |                                 |                           | High          |
| Jung 2020        | B A A A B B B A A                               |                               |                           |                                      |                                 |                                 |                                 |                           | High          |
| Kim 2022         | B A A A A A B A A                               |                               |                           |                                      |                                 |                                 |                                 |                           | Low           |
| Maskarinec 2020  | B A A A A A A B A A                             |                               |                           |                                      |                                 |                                 |                                 |                           | Low           |
| Mitaka 2020      | B A A A B B B A A                               |                               |                           |                                      |                                 |                                 |                                 |                           | High          |
| Mitaka 2021      | B A A A A A A B A A                             |                               |                           |                                      |                                 |                                 |                                 |                           | Low           |
| Robinson 2021    | B A A A B B B A A                               |                               |                           |                                      |                                 |                                 |                                 |                           | High          |
| Spaziante 2020   | C A A A B B B A A                               |                               |                           |                                      |                                 |                                 |                                 |                           | High          |
| Wiggers 2016     | B A A A B B B A A                               |                               |                           |                                      |                                 |                                 |                                 |                           | High          |
| Study                           |
|--------------------------------|
| **Selection:** Is case definition adequate? |
| **Selection:** Representativeness of the cases |
| **Selection:** Selection of controls |
| **Selection:** Definition of controls |
| **Comparability:** Controls for level of acute illness |
| **Comparability:** Controls for any additional factor |
| **Exposure:** Ascertainment of exposure |
| **Exposure:** Same method for ascertainment of cases and controls |
| **Exposure:** Non-response rate |

Risk of bias: Low
eFigure 1. Funnel plot for Key Question (KQ) 1. A funnel plot with studies that address KQ1 did not reveal evidence of publication bias (Egger’s test p-value = 0.59). There were less than 10 studies that addressed KQ2, so a funnel plot was not generated.
eFigure 2. Robustness of KQ1 primary analysis. (A) Studies included in the KQ1 primary analysis (n=5) were stratified by whether full study results were published in a peer-reviewed manuscript (n=4) or whether data obtained from a conference abstract (n=1). A meta-analysis of the four studies with full results in a peer-reviewed manuscript is shown. The mortality hazard ratio is listed, with hazard ratio less than 1 indicating decreased mortality with obtaining follow-up blood cultures [FUBCs]. (B) Giannella et al. performed two adjusted KQ1 analyses. In the first, patients with and without FUBCs were matched 1:1 based on sequential Organ Failure Assessment [SOFA] scores, and patients without FUBCs survived at least to the time when FUBCs were obtained in the matched patient. The data from this analysis was incorporated into the meta-analysis shown in Figure 2. In the second analysis, the influence of FUBCs on mortality was addressed with a multivariable Cox regression model. The data from this second analysis was incorporated into the meta-analysis in this figure. There were no major differences in the results from the two meta-analyses. (C) An influence analysis showed that the overall result (i.e., decreased mortality with FUBCs) did not change with omission of any single study. All five studies in the KQ1 primary analysis had good quality (i.e., low risk of bias) and so no further stratification by study quality was necessary. Abbreviations: CI, confidence interval; HR, hazard ratio.

A

| Source                  | HR (95% CI)  | Favors FUBC | Favors No FUBC |
|-------------------------|--------------|-------------|----------------|
| Amipara et al,3 (2021)  | 0.47 [0.24; 0.91] | ![FUBC](image) | ![No FUBC](image) |
| Giannella et al,2 (2020)| 0.45 [0.22; 0.92] | ![FUBC](image) | ![No FUBC](image) |
| Maskarinec et al,1 (2020)| 0.63 [0.53; 0.75] | ![FUBC](image) | ![No FUBC](image) |
| Green et al,7 (2021)    | 0.43 [0.17; 1.08] | ![FUBC](image) | ![No FUBC](image) |
| Total                   | 0.58 [0.45; 0.75]  | ![FUBC](image) | ![No FUBC](image) |

Heterogeneity: $\chi^2 = 1.92$ ($P = .59$), $I^2 = 0\%$

B

| Source                  | HR (95% CI)  | Favors FUBC | Favors No FUBC |
|-------------------------|--------------|-------------|----------------|
| Amipara et al,3 (2021)  | 0.47 [0.24; 0.91] | ![FUBC](image) | ![No FUBC](image) |
| Maskarinec et al,1 (2020)| 0.63 [0.53; 0.75] | ![FUBC](image) | ![No FUBC](image) |
| Green et al,7 (2021)    | 0.43 [0.17; 1.08] | ![FUBC](image) | ![No FUBC](image) |
| Mitaka et al,9 (2021)   | 0.37 [0.12; 1.19] | ![FUBC](image) | ![No FUBC](image) |
| Giannella et al,2 (2020)| 0.48 [0.27; 0.84] | ![FUBC](image) | ![No FUBC](image) |
| Total                   | 0.57 [0.46; 0.71]  | ![FUBC](image) | ![No FUBC](image) |

Heterogeneity: $\chi^2 = 2.55$ ($P = .64$), $I^2 = 0\%$

C

|                | HR  | 95% CI   | p-value | tau^2 | tau | I^2 |
|----------------|-----|----------|---------|-------|-----|-----|
| Omitting Amipara 2021 | 0.5778 | 0.4277; 0.7806 | 0.0102 | 0.0125 | 0.1118 | 0.0% |
| Omitting Giannella 2020 | 0.6062 | 0.4985; 0.7386 | 0.0040 | 0.0000 | 0.0000 | 0.0% |
| Omitting Maskarinec 2020 | 0.4597 | 0.3796; 0.5568 | 0.0010 | 0.0000 | 0.0000 | 0.0% |
| Omitting Green 2021 | 0.6037 | 0.4926; 0.7398 | 0.0042 | 0.0001 | 0.0104 | 0.0% |
| Omitting Mitaka 2021 | 0.6034 | 0.4978; 0.7314 | 0.0036 | 0.0000 | 0.0000 | 0.0% |
| Pooled estimate | 0.5820 | 0.4757; 0.7121 | 0.0017 | 0.0060 | 0.0775 | 0.0% |

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eFigure 3. Exploratory analysis of KQ1 with unadjusted mortality data. (A) Meta-analysis of mortality odds ratios (OR) using unadjusted mortality data from all studies included in KQ1 (n=11). (B) Meta-analysis of mortality OR using unadjusted mortality data from all studies included in KQ1 except Giannella et al. (C) Influence analysis showed that omission of Giannella et al. substantially reduced the observed heterogeneity in the meta-analysis.

**Abbreviation:** CI, confidence interval; FUBC, follow-up blood culture.

### A

| Source                  | OR (95% CI)   | Favor FUBC | Favor No FUBC |
|-------------------------|---------------|------------|---------------|
| Amipara et al. (2021)   | 0.51 [0.27; 0.98] |            |               |
| Giannella et al. (2020) | 1.47 [1.00; 2.17] |            |               |
| Maskarinec et al. (2020)| 0.71 [0.54; 0.92] |            |               |
| Green et al. (2021)     | 0.23 [0.10; 0.53] |            |               |
| Mitaka et al. (2021)    | 0.37 [0.11; 1.23] |            |               |
| Chan et al. (2021)      | 0.62 [0.22; 1.71] |            |               |
| Clemmens et al. (2021)  | 1.50 [0.14; 15.59] |            |               |
| Jung et al. (2020)      | 0.76 [0.45; 1.29] |            |               |
| Wiggers et al. (2016)   | 0.96 [0.63; 1.46] |            |               |
| Robinson et al. (2021)  | 1.16 [0.53; 2.50] |            |               |
| Groft et al. (2021)     | 1.34 [0.16; 11.43] |            |               |
| **Total**               | 0.75 [0.54; 1.04] |            |               |

Heterogeneity: $\chi^2 = 24.63 (P = .008)$, $I^2 = 59\%$

### B

| Source                  | OR (95% CI)   | Favor FUBC | Favor No FUBC |
|-------------------------|---------------|------------|---------------|
| Amipara et al. (2021)   | 0.51 [0.27; 0.98] |            |               |
| Maskarinec et al. (2020)| 0.71 [0.54; 0.92] |            |               |
| Green et al. (2021)     | 0.23 [0.10; 0.53] |            |               |
| Mitaka et al. (2021)    | 0.37 [0.11; 1.23] |            |               |
| Chan et al. (2021)      | 0.62 [0.22; 1.71] |            |               |
| Clemmens et al. (2021)  | 1.50 [0.14; 15.59] |            |               |
| Jung et al. (2020)      | 0.76 [0.45; 1.29] |            |               |
| Wiggers et al. (2016)   | 0.96 [0.63; 1.46] |            |               |
| Robinson et al. (2021)  | 1.16 [0.53; 2.50] |            |               |
| Groft et al. (2021)     | 1.34 [0.16; 11.43] |            |               |
| **Total**               | 0.68 [0.52; 0.90] |            |               |

Heterogeneity: $\chi^2 = 13.50 (P = .14)$, $I^2 = 33\%$

### C

| Source                  | OR       | 95% CI         | p-value | tau^2 | tau | I^2 (%) |
|-------------------------|----------|----------------|---------|-------|-----|--------|
| Omitting Amipara 2021   | 0.7802   | 0.5459; 1.1151 | 0.1732  | 0.1713 | 0.4138 | 60.2 |
| Omitting Giannella 2020 | 0.6845   | 0.5214; 0.8987 | 0.006   | 0.0587 | 0.2423 | 33.3 |
| Omitting Maskarinec 2020| 0.7472   | 0.5039; 1.0787 | 0.1470  | 0.2133 | 0.4619 | 61.1 |
| Omitting Green 2021     | 0.8458   | 0.6449; 1.1093 | 0.2262  | 0.0713 | 0.2670 | 41.9 |
| Omitting Mitaka 2021    | 0.7785   | 0.5551; 1.0919 | 0.1469  | 0.1581 | 0.3976 | 60.8 |
| Omitting Chan 2021      | 0.7556   | 0.5289; 1.0794 | 0.1236  | 0.1816 | 0.4262 | 63.0 |
| Omitting Clemmens 2021  | 0.7375   | 0.5257; 1.0345 | 0.0778  | 0.1675 | 0.4093 | 63.0 |
| Omitting Jung 2020      | 0.7399   | 0.5048; 1.0845 | 0.1226  | 0.2052 | 0.4529 | 63.4 |
| Omitting Wiggers 2016   | 0.7143   | 0.4883; 1.0448 | 0.0829  | 0.1971 | 0.4439 | 62.3 |
| Omitting Robinson 2021  | 0.7132   | 0.4979; 1.0218 | 0.0654  | 0.1789 | 0.4230 | 62.1 |
| Omitting Groft 2021     | 0.7375   | 0.5250; 1.0359 | 0.0790  | 0.1609 | 0.4107 | 63.1 |
| **Pooled estimate**     | **0.7482** | **0.5373; 1.0417** | **0.0858** | **0.1609** | **0.4012** | **59.4** |

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**eFigure 4. Robustness of KQ2 exploratory analysis.** (A) Meta-analysis of mortality odds ratios (OR) using unadjusted mortality data from all studies with cohort design (n=8). A single study with case-control design was excluded from this analysis. (B) Meta-analysis of mortality odds ratios using unadjusted mortality data from all studies that address KQ2 and have low risk of bias. (C) Influence analysis showed that general findings of the meta-analysis (i.e., increased odds of mortality with positive blood cultures relative to negative blood cultures) did not change with omission of any single study. **Abbreviation:** CI, confidence interval.

**A Meta-analysis with cohort studies**

| Source | OR (95% CI) | Decreased mortality | Increased mortality |
|--------|-------------|---------------------|---------------------|
| Amipara et al. (2021) | 2.64 [0.51; 13.55] | 0.0001 | 0.1491 | 0.3861 | 51.6 |
| Maskarinec et al. (2020) | 1.93 [1.33; 2.80] | 0.0004 | 0.1829 | 0.4277 | 45.0 |
| Chan et al. (2021) | 2.22 [0.83; 5.93] | 0.0002 | 0.1672 | 0.4089 | 51.6 |
| Wiggers et al. (2016) | 2.40 [0.93; 6.19] | 0.0003 | 0.1694 | 0.4116 | 51.6 |
| Groft et al. (2021) | 9.00 [0.71; 113.81] | <0.0001 | 0.1013 | 0.3183 | 36.3 |
| Spaziante et al. (2020) | 0.78 [0.24; 2.53] | 0.0003 | 0.1774 | 0.4212 | 50.6 |
| Mitaka et al. (2020) | 1.21 [0.34; 4.31] | 0.0002 | 0.1356 | 0.3682 | 47.8 |
| Kim et al. (2022) | 4.87 [2.90; 8.17] | <0.0001 | 0.1013 | 0.3183 | 36.3 |
| Total | 2.31 [1.47; 3.63] | <0.0001 | 0.1332 | 0.3650 | 44.7 |

Heterogeneity: $\chi^2 = 14.18 (P = .05)$, $I^2 = 51\%$

**B Meta-analysis with studies rated as having low risk of bias**

| Source | OR (95% CI) | Decreased mortality | Increased mortality |
|--------|-------------|---------------------|---------------------|
| Amipara et al. (2021) | 2.64 [0.51; 13.55] | 0.0001 | 0.1491 | 0.3861 | 51.6 |
| Maskarinec et al. (2020) | 1.93 [1.33; 2.80] | 0.0004 | 0.1829 | 0.4277 | 45.0 |
| Kim et al. (2022) | 4.87 [2.90; 8.17] | <0.0001 | 0.1376 | 0.3709 | 47.7 |
| Kang et al. (2013) | 1.98 [1.03; 3.81] | <0.0001 | 0.1376 | 0.3709 | 47.7 |
| Total | 2.64 [1.55; 4.50] | <0.0001 | 0.1376 | 0.3709 | 47.7 |

Heterogeneity: $\chi^2 = 8.72 (P = .03)$, $I^2 = 66\%$

**C Influence analysis**

| | OR  | 95% CI | p-value | tau^2 | tau | I^2 (%) |
|---|-----|--------|---------|-------|-----|---------|
| Omitting Amipara 2021 | 2.2434 | 1.4931; 3.3708 | <0.0001 | 0.1491 | 0.3861 | 51.6 |
| Omitting Maskarinec 2020 | 2.3422 | 1.4607; 3.7559 | <0.0001 | 0.1829 | 0.4277 | 45.0 |
| Omitting Chan 2021 | 2.2581 | 1.4648; 3.4810 | <0.0001 | 0.1672 | 0.4089 | 51.6 |
| Omitting Wiggers 2016 | 2.2361 | 1.4466; 3.4563 | <0.0001 | 0.1694 | 0.4116 | 51.6 |
| Omitting Groft 2021 | 2.1975 | 1.4831; 3.2561 | <0.0001 | 0.1376 | 0.3709 | 47.7 |
| Omitting Spaziante 2020 | 2.4860 | 1.7092; 3.6158 | <0.0001 | 0.1013 | 0.3183 | 36.3 |
| Omitting Mitaka 2020 | 2.3769 | 1.5902; 3.5528 | <0.0001 | 0.1356 | 0.3682 | 47.8 |
| Omitting Kim 2022 | 1.9090 | 1.4542; 2.5061 | <0.0001 | 0.0000 | 0.0000 | 0.0 |
| Omitting Kang 2013 | 2.3056 | 1.4655; 3.6274 | <0.0001 | 0.1774 | 0.4212 | 50.6 |
| Pooled estimate | 2.2678 | 1.5421; 3.3351 | <0.0001 | 0.1332 | 0.3650 | 44.7 |

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eTable 2. Evidence profile for association of obtaining follow-up blood cultures with mortality in patients with gram-negative bloodstream infections.

| Patient population                  | Gram-negative bloodstream infections |
|-------------------------------------|--------------------------------------|
| Setting                             | Hospital                             |
| Intervention                        | Follow-up blood cultures             |
| Comparison                          | No follow-up blood cultures          |
| Outcome                             | Mortality (In-hospital or up to 30 days) |
| Studies (Participants)              | 5 (4584)                             |
| Risk of bias                        | Low                                  |
| Consistency                         | Consistent                           |
| Precision                           | Precise                              |
| Directness                          | Direct                               |
| Other limitations                   | No randomized controlled trials       |
| Overall strength of evidence        | Moderate                              |
| Conclusions                         | Follow-up blood cultures associated with decreased mortality Hazard ratio 0.56 (95% Confidence interval 0.45 to 0.71) |
eMethods. Approach for grading the overall strength of evidence.

We used the Evidence-based Practice Center (EPC) model from the U.S. Agency for Healthcare Research and Quality (AHRQ) to grade the overall strength of evidence. The EPC approach evaluates the following domains: study limitations/risk of bias, consistency, directness, precision, and reporting bias. In brief, the EPC classification system applies an overall strength of evidence grade rating to an estimate effect from a body of evidence: high (we are very confident that the estimate of effect lies close to the true effect for this outcome), moderate (we are moderately confident that the estimate of effect lies close to the true effect for this outcome), low (we have limited confidence that the estimate of effect lies close to the true effect for this outcome), or insufficient (we have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome). The initial strength of evidence grade was moderate given that the included observational studies in the primary analysis reduced bias from confounding through matching or statistical adjustment. This baseline category could be rated down if the included studies demonstrated high risk of bias, imprecision, inconsistency, indirectness, or reporting bias.
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