Supplementary Material for the 2024 Clinical Practice Guideline Update by the Infectious Diseases Society of America on Complicated Intra-abdominal Infections: Utility of Blood Cultures in Adults, Children, and Pregnant People

Table of Contents

METHODS

Panel formation and conflicts of interest

The chair of the guideline panel was selected by the leadership of IDSA. Fifteen additional panelists comprised the full panel. The panel included clinicians with expertise in infectious diseases, pediatric infectious diseases, surgery, emergency medicine, microbiology, and pharmacology. Panelists were diverse in gender, geographic distribution, and years of clinical experience. Guideline methodologists oversaw all methodological aspects of the guideline development and identified and summarized the scientific evidence for each clinical question. IDSA staff oversaw all administrative and logistic issues related to the guideline panel.

All members of the expert panel complied with the IDSA policy on conflict of interest (COI), which requires disclosure of any financial, intellectual, or other interest that might be construed as constituting an actual, potential, or apparent conflict. Evaluation of such relationships as potential conflicts of interest was determined by a review process which included assessment by the Standards and Practice Guideline Committee (SPGC) Chair, the SPGC liaison to the Guideline panel and the Board of Directors liaison to the SPGC, and if necessary, the Conflicts of Interests Task Force of the Board. This assessment

of disclosed relationships for possible COI was based on the relative weight of the financial relationship (i.e., monetary amount) and the relevance of the relationship (i.e., the degree to which an independent observer might reasonably interpret an association as related to the topic or recommendation of consideration). The reader of these guidelines should be mindful of this when the list of disclosures is reviewed. See the Notes section at the end of this guideline for the disclosures reported to IDSA.

Practice recommendations

Clinical Practice Guidelines are statements that include recommendations intended to optimize patient care by assisting practitioners and patients in making shared decisions about appropriate health care for specific clinical circumstances. These are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options [IOM 2011]. The "IDSA Handbook on Clinical Practice Guideline Development" provides more detailed information on the processes followed throughout the development of this guideline [IDSA CPG Handbook].

Review and approval process

Feedback was obtained from five external individual peer expert reviewers as well as the endorsing organizations. The IDSA Standards and Practice Guidelines Subcommittee (SPGS) and Board of Directors reviewed and approved the guideline prior to publication.

Process for updating

IDSA guidelines are regularly reviewed for currency. The need for updates to the guideline is determined by a scan of current literature and the likelihood that any new data would impact the recommendations. Any changes to the guideline will be submitted for review and approval to the appropriate Committees and Board of IDSA.

Clinical questions

Each clinical question was formatted according to the PICO style: Patient/Population (P), Intervention/Indicator (I), Comparator/Control (C), Outcome (O). For each PICO question, outcomes of interest were identified a priori and rated for their relative importance for decision-making.

Literature search

A medical librarian designed the literature searches and MeSH terms for Ovid Medline, Embase, and Cochrane Library. Searches were limited to studies published in English. The initial formal literature searches were performed in July to November 2018, and updated literature searches were conducted in March 2021 and October 2022. To supplement the electronic searches, reference lists of related articles and guidelines were reviewed for relevance.

MEDLINE

#1 exp Intraabdominal Infections/

#2 ((intraabdom?n* or abdom?n* or appendix or appendectom* or appendic* or peritonitis* or typhlitis* or diverticul* or subdiaphragmat* or subphren* or sub-diaphragmat* or sub-phren* or peritoneal* or pericolon* or peri-colon* or periappendic* or phlegmon*) adj2 (complicated or infect* or candidias* or bacteremia* or abscess* or abcess* or sepsis or septic or shock*)).tw,kf.

#3 1 or 2

#4 Blood Culture/

#5 (blood* adj5 culture*).tw,kf.

#6 (culture* adj5 (spike* or fever* or febrile* or timing* or technique*)).tw,kf.

#7 Blood/mi

#8 Fever/mi

#9 or/4-8

#10 3 and 9

#11 *Body Fluids/mi and (blood* adj5 culture*).tw,kf.

#12 (blood adj5 culture* adj10 (intraabdom?n* or abdom?n* or appendix or appendectom* or appendic* or peritonitis* or typhlitis* or diverticul* or subdiaphragmat* or subphren* or sub-diaphragmat* or sub-phren* or peritoneal* or pericolon* or peri-colon* or periappendic* or phlegmon*)).tw,kf.

#13 Bacteremia/mi and (*Blood Culture/ or *Community-Acquired Infections/mi or exp *Cross Infection/mi or *Fever/mi)

#14 ((bacteremi* or bacteraemia*) adj5 (blood* adj5 culture*)).tw,kf.

#15 ((nosocomial* or HAI or ((communit* or healthcare* or health-care* or hospital*) adj2 (acquire* or onset* or transmit*))) adj10 ((blood* or bactec*) adj5 culture*)).tw,kf.

#16 (blood adj5 culture*).ti,kf. and (bacteremia* or bacteraemia*).tw,kf.

#17 or/10-16

#18 Animals/ not (Animals/ and Humans/)

#19 ((animal or animals or canine* or cat or cats or dog or dogs or feline or hamster* or mice or monkey or monkeys or mouse or murine or pig or pigs or piglet* or porcine or primate* or rabbit* or rats or rat or rodent* or sheep*) not (human* or patient*)).tw,kf.

#20 17 not (18 or 19)

#21 limit 20 to (comment or editorial or letter or case reports or congress or clinical conference or consensus development conference or consensus development conference, nih)

#22 20 not 21

#23 limit 20 to review

#24 22 or 23

#25 limit 24 to english

EMBASE

#1 exp abdominal infection/

#2 ((intraabdom?n* or abdom?n* or appendix or appendectom* or appendic* or peritonitis* or typhlitis* or diverticul* or subdiaphragmat* or subphren* or sub-diaphragmat* or sub-phren* or peritoneal* or pericolon* or peri-colon* or periappendic* or phlegmon*) adj2 (complicated or infect* or candidias* or bacteremia* or abscess* or abcess* or sepsis or septic or shock*)).tw,kw,kf.

#3 1 or 2

#4 blood culture/

#5 (blood* adj5 culture*).tw,kw,kf.

#6 (culture* adj5 (spike* or fever* or febrile* or timing* or technique*)).tw,kw,kf.

#7 or/4-6

#8 3 and 7

#9 blood/

#10 fever/

#11 9 or 10

#12 exp microbiology/

#13 11 and 12

#14 3 and 13

#15 8 or 14

#16 (body fluid/ or *bacterium culture/) and (blood* adj5 culture*).tw,kw,kf.

#17 (blood adj5 culture* adj10 (intraabdom?n* or abdom?n* or appendix or appendectom* or appendic* or peritonitis* or typhlitis* or diverticul* or subdiaphragmat* or subphren* or sub-diaphragmat* or sub-phren* or peritoneal* or pericolon* or peri-colon* or periappendic* or phlegmon*)).tw,kw,kf.

#18 ((bacteremi* or bacteraemia*) adj5 (blood* adj5 culture*)).tw,kw,kf.

#19 ((nosocomial* or HAI or ((communit* or healthcare* or health-care* or hospital*) adj2 (acquire* or onset* or transmit*))) adj10 ((blood* or bactec*) adj5 culture*)).tw,kw,kf.

#20 (blood adj5 culture*).ti,kw. and (bacteremia* or bacteraemia*).tw,kw,kf.

#21 or/15-20

#22 (exp animal/ or exp juvenile animal/ or adult animal/ or animal cell/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not human/

#23 ((animal or animals or canine* or cat or cats or dog or dogs or feline or hamster* or mice or monkey or monkeys or mouse or murine or pig or pigs or piglet* or porcine or primate* or rabbit* or rats or rat or rodent* or sheep*) not (human* or patient*)).tw,kw,kf.

#24 21 not (22 or 23)

#25 case report/

#26 24 not 25

#27 limit 26 to (books or "book review" or chapter or conference abstract or conference paper or "conference review" or editorial or letter or note)

#28 26 not 27

#29 limit 28 to english

#30 remove duplicates from 29

COCHRANE

#1 ((intraabdom?n* or abdom?n* or appendix or appendectom* or appendic* or peritonitis* or typhlitis* or diverticul* or subdiaphragmat* or subphren* or sub-diaphragmat* or sub-phren* or peritoneal* or pericolon* or peri-colon* or periappendic* or phlegmon*) NEAR/2 (complicated or infect* or candidias* or bacteremia* or abscess* or abcess* or sepsis or septic or shock*)):ti,ab,kw

#2 (blood* NEAR/5 culture*):ti,ab,kw

#3 (culture* NEAR/5 (spike* or fever* or febrile* or timing* or technique*)):ti,ab,kw

#4 #2 OR #3

#5 #1 AND #4

#6 (blood NEAR/5 culture* NEAR/10 (intraabdom?n* or abdom?n* or appendix or appendectom* or appendic* or peritonitis* or typhlitis* or diverticul* or subdiaphragmat* or subphren* or sub-diaphragmat* or sub-phren* or peritoneal* or pericolon* or peri-colon* or periappendic* or phlegmon*)):ti,ab,kw

#7 ((bacteremi* or bacteraemia*) NEAR/5 (blood* NEAR/5 culture*)):ti,ab,kw

#8 ((nosocomial* or HAI or ((communit* or healthcare* or health-care* or hospital*) NEAR/2 (acquire* or onset* or transmit*))) NEAR/10 ((blood* or bactec*) NEAR/5 culture*))

#9 (blood NEAR/5 culture*):ti,kw and (bacteremia* or bacteraemia*):ti,ab,kw

#10 #5 OR #6 OR #7 OR #8 OR #9

Study selection

Titles and abstracts were screened in duplicate for all identified citations using Rayyan [Ouzzani 2016]. All potentially relevant citations were subjected to a full-text review, using predefined inclusion and exclusion criteria tailored to meet the specific population, intervention, and comparator of each clinical question. The steps of the literature selection process were supervised and reviewed by a guideline methodologist for the final selection of the relevant articles.

The following eligibility criteria were used:

Inclusion criteria:

- *Patient population*- Adults, children, or pregnant people admitted to the hospital/emergency department and receiving a blood culture for any reason
- *Intervention*- Blood culture
- *Comparator*- N/A
- *Outcomes*- Change in antimicrobial therapy or clinical management, mortality, true positivity and contamination rates (secondary)
- *Study design*- Randomized controlled trials (RCTs) with no date limit, observational studies published 2005-present, no minimum number of study participants

Exclusion criteria:

- *Patient population*- Patients with spontaneous bacterial peritonitis or cirrhosis
- *Intervention*- N/A
- *Comparator*- N/A
- *Study design*- Observational studies published prior to 2005 (cutoff decided on in 2020 for the question on antimicrobials and associated questions, to capture 15 years of data), abstracts and conference proceedings, letters to the editor, editorials, and review articles

Data extraction and analysis

A guideline methodologist in conjunction with panelists extracted the data for each pre-determined patient-important outcome. If a relevant publication was missing raw data for an outcome prioritized by the panel, an attempt was made to contact the author(s) for the missing data. Where applicable, data were pooled using random-effects model (fixed effects model for pooling of rates) using RevMan

[RevMan]. Modeling was undertaken using positivity rates for blood cultures and prevalence rates of likely contaminants reported in the studies to estimate proportion of patients with a change in antimicrobial therapy or mortality.

Evidence to decision

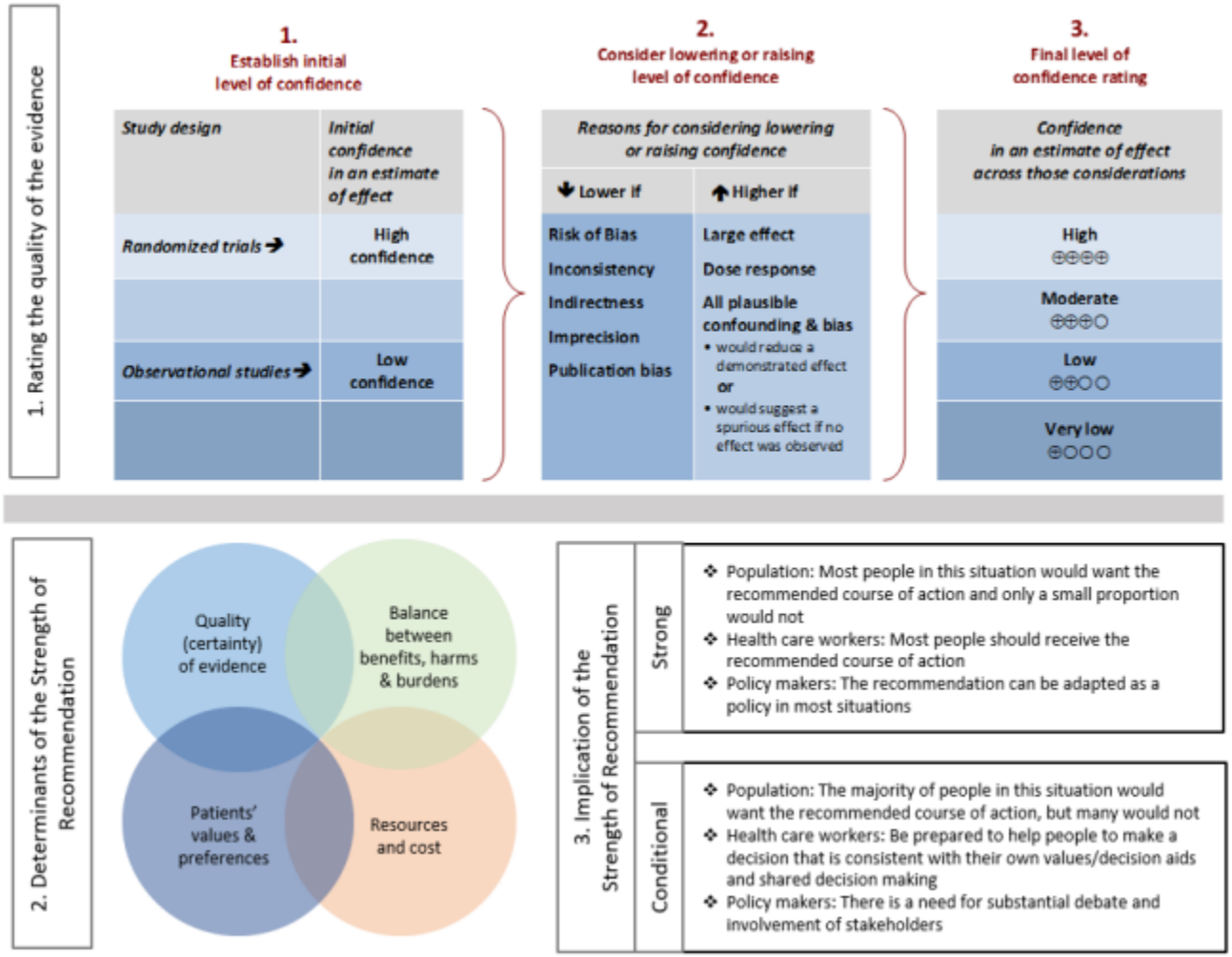
Guideline methodologists prepared the evidence summaries for each question and assessed the risk of bias and the certainty of evidence. Risk of bias was assessed by using the QUIPS tool for studies addressing risk/prognostic factors [Hayden 2013] and the QUADAS-2 tool for diagnostic test accuracy studies [Whiting 2011]. The certainty of evidence was determined first for each critical and important outcome and then for each recommendation using the GRADE approach for rating the confidence in the evidence [Guyatt 2008, GRADE Handbook]. Evidence profiles were developed using the GRADEpro Guideline Development Tool [Guyatt 2008] and reviewed by panel members responsible for each PICO.

The Evidence to Decision framework [GRADEpro] was used to translate the evidence summaries into practice recommendations. All recommendations were labeled as either “strong” or “conditional” according to the GRADE approach [IDSA CPG Handbook]. The words “we recommend” indicate strong recommendations and “we suggest” indicate conditional recommendations. Supplementary Figure 1 provides the suggested interpretation of strong and conditional recommendations for patients, clinicians, and healthcare policymakers. For recommendations where the comparator treatment or tests are not formally stated, the comparison of interest is implicitly referred to as “not using the intervention” (either not using a specific treatment or a diagnostic test).

All members of the panel participated in the preparation of the draft guideline and approved the recommendations.

TABLES AND FIGURES

Supplementary Figure 1. Approach and implications to rating the quality of evidence and strength of recommendations using GRADE methodology (unrestricted use of figure granted by the U.S. GRADE Network)



Supplementary Table 1. Characteristics of included studies for blood cultures in adults

Author, year of publication	Location, years of data collection	Study design	Number of patients and age	Population included	Intervention	Outcome
Boerman 2022	Netherlands Sept 2018-June 2020	Retrospective cohort	4885 visits Median + IQR: 66 years (52-76)	Adult patients presenting to the ED who received at least one blood culture	Blood culture Positivity rate: 12.24%	30-day mortality
Brown 2017	Australia Jan 2012-Dec 2012	Retrospective case-control	301 patients Median + IQR: Cases: 71 years (53-81) Controls: 63 (42-80)	Cases: Patients with positive blood culture collected in ED Controls : Negative blood cultures collected in ED chosen at random	Blood culture	Change in therapy[1]
Ehrenstein 2005	Germany October 2002-October 2003	Prospective cohort	428 visits (390 patients) Mean + SD: 53.2 years (± 19.1)	Adult patients presenting to the ED who received at least one blood culture and who stayed at least 3 days in hospital	Blood culture Positivity rate: 13.3%	Change in therapy[2]
Jessen 2016	Denmark Jan 2011- Dec 2011	Retrospective matched cohort	420 patients Mean + SD: Cases: 71.2 years (± 17) Controls: 62.5 (± 20)	Adult patients presenting to the ED who received at least one blood culture	Blood culture Positivity rate: 6.9%	Prediction of bacteremia
Mountain 2006	Australia 2 months	Retrospective chart review	218 cultures Mean + Range: Cases: 68.14 years (40-89) Controls: 56.5 (13-96)	All patients receiving blood culture during the study period	Blood culture Positivity rate: 6.4%	Change in therapy[3]
Nakamura 2006	Japan Aug 1999- Dec 2002	Retrospective cohort	739 cultures Mean + SD: 66years (± 16.7)	Patients ≥18 receiving blood culture	Blood culture Positivity rate: 19.49%	In-hospital mortality
Nishiyama 2022	Japan Jan 2016-Dec 2016	Retrospective cohort	627 cultures (597 patients) Not reported	Not reported	Blood culture	Change in therapy[4]
Otani 2022	Japan Jan 2019- Dec 2020	Retrospective cohort	310 cultures Median + IQR: 66 years (52-76)	Patients ≥15 years with acute cholangitis who visited the emergency department and received blood cultures	Blood culture Positivity rate: 48%	In-hospital mortality
Thompson 2017	Canada Jan 2007-Dec 2008	Retrospective chart review	288 cultures taken (1027 controls w/out culture)	Children age 2-17 presenting to ED who were subsequently investigated for suspected appendicitis	Blood culture	Change in therapy[5]

			Cases: 10.3 years (± 4.6) Controls: 12.2 (± 3.7)			

1. Changes in therapy for Brown 2017 included narrowing, broadening, optimizing (changing), or increasing duration of antimicrobial therapy. Recall to hospital for appropriate diagnosis was also included.
2. Ehrenstein 2005 reported prolonging, narrowing, and broadening antimicrobial therapy.
3. Mountain 2006 defined change in therapy as "change in clinical management".
4. Nishiyama 2022 reported changes in therapy as new administration of antimicrobial therapy or change to appropriate administration of antimicrobial therapy.
5. Only one true positive culture was obtained in Thompson 2017. There was no change in antimicrobial therapy reported (patient was treated surgically).

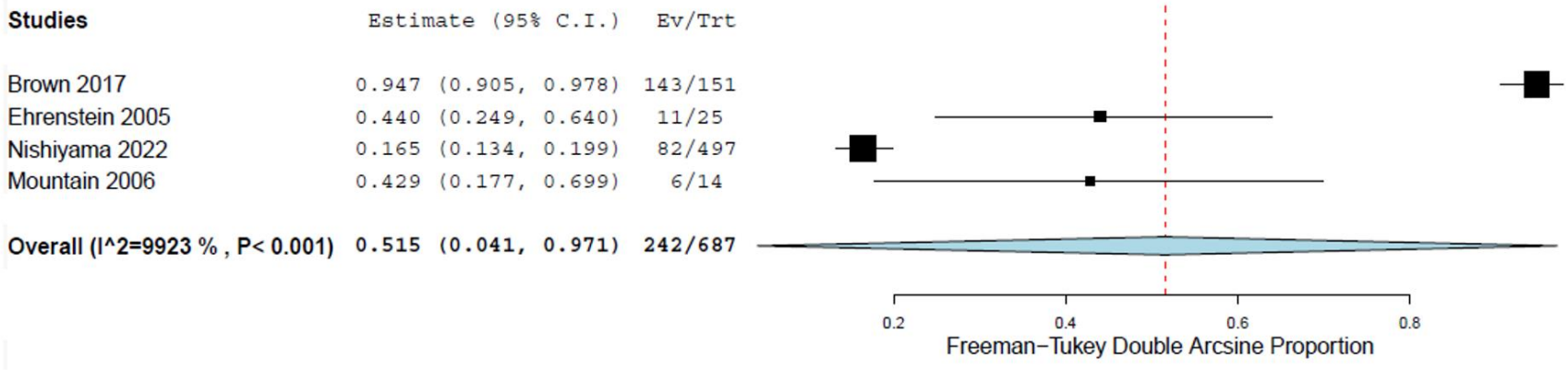
Supplementary Table 2. GRADE evidence profiles for adults and children

Outcome	# studies; # cases	Risk of Bias	Indirectness	Imprecision	Inconsistency	GRADE certainty of the evidence
Change in therapy due to culture results (adults)	4 observational studies; 13,650 cases	Moderate	Very serious[a]	Not serious	Not serious	⨁◯◯◯ VERY LOW
In-hospital mortality following positive blood culture (adults)	3 observational studies; 1,237 cases	Moderate	Very serious[a]	Not serious	Serious[b]	⨁◯◯◯ VERY LOW
Change in therapy due to culture results (children)	1 observational study; 288 cases	Moderate	Not serious	Serious[c]	Not serious	⨁⨁◯◯ LOW

a. Patients presenting to ED, inpatients, and ICU patients.
b. Pre-test probability varied widely across studies.
c. Rated down due to wide confidence interval.

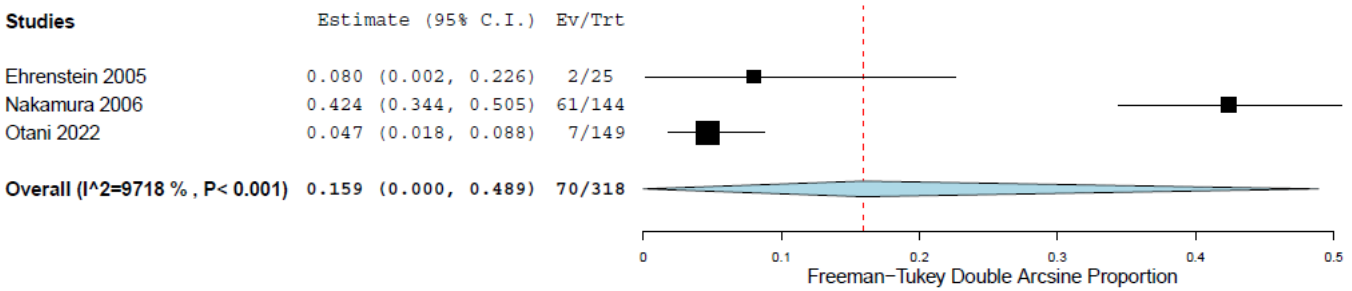
Results of modeling:

Supplementary Figure 2. Proportion of cases with a change in therapy due to culture results



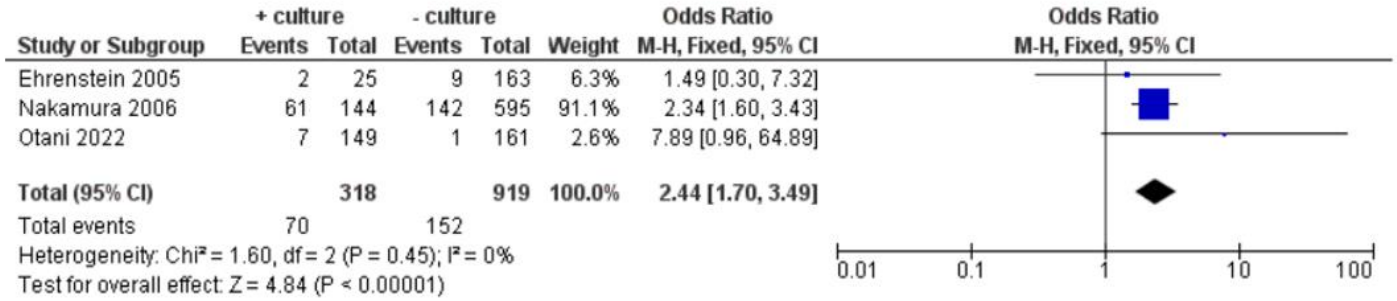
Modeling: Start with 100 patients… ~9-25 return positive cultures… of those, ~2-17 are contaminated or false positives, leaving ~7-8 true bacteremia patients… of those (range of 16.5 -94.3% or weighted mean ~51.5%) result in a change in therapy, resulting in ~4 changes in antimicrobial management.

Supplementary Figure 3. Proportion of adults who died in-hospital after positive blood culture (Ehrenstein 2005, Nakamura 2006, Otani 2022)

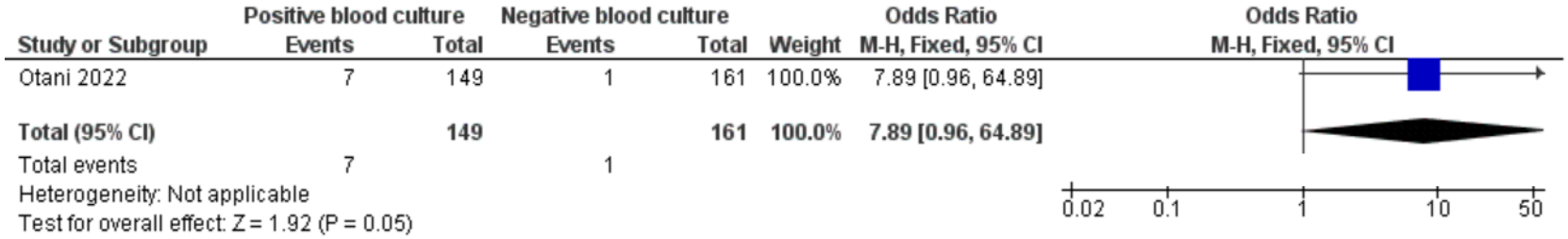


Modeling: Start with 100 patients…~31 return positive cultures…of those, ~7-8 are contaminated or false positives…leaving ~23-24 true bacteremia patients…of those (range 4.7-42.4% or weighted mean ~16%) resulted in death, or ~3-4 patients.

Supplementary Figure 4. Blood culture as a predictor of in-hospital mortality (Ehrenstein 2005, Nakamura 2006, Otani 2022)



Supplementary Figure 5. Blood culture as a predictor of in-hospital mortality (in acute cholangitis) (Otani 2022)



Supplementary Table 3. Prevalence rates for outcomes among patients presenting to the ED*

Study	Culture TP prevalence	Change in tx	Mortality	Shapiro validation	Notes	Definition
Nishiyama 2022	79.3% TP; 20.7% contaminants (calculated) vs. 2.3% contaminants (author reported)	16.5% (n=82) of TP had a change in therapy; - 36 change after first lab report; 25 new administration after lab report; 21 new administration after ICT-intervention;	Reported an 18.1% mortality rate but could not determine % that were TP vs. Contaminants or those who had appropriate change in abx vs. those who did not	N/A	Unclear whether intra-abdominal infection (IAI) patients were in sample; no patient demographic info given (age, gender, other co-morbidities, or infection source)	**Change in therapy:** The impact of the first laboratory report on a physician's use of appropriate antimicrobials was assessed using 5 categories: (1) New antibiotic administration after the first laboratory report; (2) Change to appropriate antimicrobials after the first laboratory report; (3) New antibiotic administration or change to appropriate antimicrobials after guidance by ICT (ICT-intervention); (4) No change to antimicrobials already being administered; and (5) No administration.
Boerman 2022	12.24% TP; 5.2% FP (contaminant)	N/A	TP: 69/598 = 11.5% Cx (-): 287/4287 = 6.7% OR: 12.02 (8.526 - 16.950)	N/A	Suspected contamination classified as negative culture	Bacteremia was defined as at least one positive BC with a pathogenic microorganism collected during the ED visit.
Brown 2017	3.8% TP; 5.64% FP (contaminant)	94.3% bacteremic pts had change in tx; 51% broadened, 38.5% narrowed, 51% increased duration	N/A	SN: 98.8 (97.8-99.8) SP: 48.7 (40.7-56.7) PPV: 7.2% NPV: 99.9%	78.8% (n=119) of bacteremia pts met Shapiro criteria prior to culture result and 21% (n=32) of non-bacteremia pts met criteria; 2 pts with positive BC would have been missed if only those pts meeting criteria for BC had it drawn	**Meaningful change in therapy**: The effect of a positive culture on antibiotic choice and clinical care was judged against predetermined criteria after chart review by the investigator. These criteria were 'narrowed' – antimicrobial treatment was de-escalated to a narrower spectrum, "broadened' – antimicrobial treatment was broadened to cover a previously untreated pathogen, 'optimised' – antibiotics were changed to a significantly more effective regimen in a suboptimally treated isolate (e.g. ceftriaxone changed to flucloxacillin for methicillin-sensitive Staphylococcus aureus [MSSA]), 'increased duration' – antimicrobial therapy was prolonged, 'recalled' – the patient was recalled to hospital for assessment or 'assisted diagnosis' – the correct diagnosis was considered or investigated on the basis of the isolate. Doctors within the hospital are encouraged to use the 'Therapeutic Guidelines: Antibiotic' for empiric antibiotic prescribing.

						Concordance of coverage with both the empiric prescribed antibiotic regime and that recommended by the Therapeutic Guidelines was calculated.
Ehrenstein 2005	13.3% TP; 12.2% FP (contaminant)	TP: 11/25 changes to tx (44%); (including empiric tx prolonged in 1, abx spectrum narrowed in 3 and broadened in 7) FP: 5/21 changes to tx; (abx spectrum broadened in 2, and duration of empiric therapy prolonged in 3)	TP: 2/25 = 8% Cx (-): 9/163 = 5.5% OR: 1.49 (0.3 - 7.3)	N/A	Mortality associated with + BC (NS)	For patients admitted and hospitalized for at least 3 days, with completed ED questionnaire and five BC bottles drawn, a second multiple-choice questionnaire was given to their treating (ward) physicians. The physicians were asked what changes in the antibiotic management, if any, resulted from BC drawn in the ED. In addition, the physicians were asked to rate ("necessary," "helpful," "unnecessary") the importance of those BC results for determining infection etiology and for decisions regarding antibiotic management.
Jessen 2016	6.88% TP; 3.27% FP (contaminant)	N/A	N/A	SN: 94 (88-98) SP: 48 (42-53) PPV: 11.8% NPV: 99.1%	6 bacteremic pts would have been missed by the prediction rule alone	No change in therapy (not an outcome measured)
Mountain 2006	6.42% TP; 7.34% FP (contaminant)	6/14 (42.9%) bacteremic pts had change in clinical mgmt. (specific change not stated)	N/A	N/A	IAI not mentioned in text; patients presented to ED	We reviewed the medical records of those patients returning significant growth BCs to determine whether their treatment had been significantly altered by the positive BC. We defined a significant alteration as occurring when the organism found was unexpected and required either further investigation or change in therapy, management or diagnosis.
Nakamura 2006	19.49% TP;	N/A	TP:	N/A	Mortality was extremely high in this	No change in therapy in this study, instead: Our clinical prediction rules are thus expected to be used for clinical decision regarding the

	13.4% FP (contaminants)		61/144 = 42.4% Cx (-): 142/595 = 23.9% OR: 2.35 (1.60-3.43)		population, but pre-test probability also higher than other studies because inpatients and ICU included	use of antibiotics and other management before the results of blood culture become available. For examples, if the likelihood of true bacteremia is very low, antibiotics can be withheld until the results become available. On the other hand, positivity of gram-negative rods is highly likely, antibiotics covering gram-negative rods can be started immediately after blood withdrawal for culture. By using the estimated mortality at the time of blood culture, a doctor can inform the patient and his family about the prognosis more rationally. Prediction rules such as these are also useful in educating doctors, residents, and medical students to make proper clinical decisions in an explicit way.
Otani 2022	48% TP; contaminated samples excluded from study entirely	N/A	TP: 7/149 = 4.7% Cx (-): 1/161 = 0.006% OR: 7.89 (0.959 - 64.892)	N/A	All patients had suspected acute cholangitis. High TP rate of 48%.	Several outcomes were compared between BC+ and BC- groups, one of which was in-hospital mortality.
Thompson 2017	0.35% TP; 3.47% FP;	0/1 (0%) bacteremic pts had change in clinical mgmt. (This child had a perforated appendix)	N/A	N/A	Culture performed in 288/1315 kids presenting to ED with RLQ pain; kids with cultures had higher pre-test probability (younger, higher acuity CTAS 1-3, and fever documented). This positive result did not change the management or outcome of the child, suggesting that the utility of routine performance of blood cultures in children presenting with suspected appendicitis is negligible.	Positive blood culture was selected [as the primary study outcome] as it was felt that often management is based on or changed due to initial culture results.

*In Brown, Ehrenstein, Jessen, Nakamura, <20% sample were IAI pts (unclear complicated vs uncomplicated since inclusion was pts presenting to ED), all subsequently rated down for indirectness.
Nakamura 2006 mixed patient settings which markedly increased pre-test probability and subsequent likelihood of a TP culture and mortality.

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