Option #2: Does TTP predict the risk of antibiotic failure? Population Adults with documented bloodstream infection (bacteremia) confirmed by positive blood culture, including: Gram-positive organisms (with S. aureus as priority subgroup) Gram-negative organisms Any infection source (with stratification by source control status) Index Prognostic Factor (Exposure) Time to positivity (TTP) of blood cultures, analyzed as: Continuous variable (hours) Study-level contrasts (short vs. prolonged TTP where dichotomized) Comparator Shorter TTP vs. longer TTP Per-hour increments in TTP (for continuous modeling) Outcomes Priority Outcome Definition Primary Persistent bacteremia Positive blood cultures at 48–72 hours despite appropriate therapy Primary Relapse/recurrence Recurrent positive cultures after initial clearance (within 30–90 days) Primary Microbiological clearance Documented negative follow-up cultures Secondary All-cause mortality In-hospital or 30-day mortality

A shorter Time to Positivity (TTP) of blood cultures consistently predicts an increased risk of antibiotic failure, evidenced by higher rates of persistent bacteremia and all-cause mortality in adults with both gram-positive and gram-negative bloodstream infections.

Abstract

The time to positivity (TTP) of blood cultures is a significant predictor of antibiotic failure and adverse clinical outcomes in adults with bloodstream infections. Across numerous retrospective and prospective cohort studies, a shorter TTP is consistently and independently associated with an increased risk of all-cause mortality, including in-hospital and 30-day mortality. This association holds for a wide range of pathogens, including gram-negative organisms like *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*, as well as gram-positive organisms such as *Staphylococcus aureus*. The specific TTP cutoff values predictive of mortality vary by organism, but are generally shorter for gram-negative bacteria (e.g., <7 to <12 hours) than for *S. aureus* (e.g., ≤12 to ≤14 hours).

Beyond mortality, shorter TTP also predicts microbiological treatment failure. Evidence demonstrates a strong link between a short initial TTP and the development of persistent bacteremia, defined as positive follow-up blood cultures at 48-72 hours despite appropriate therapy. For instance, a TTP of less than 11.8 hours increased the risk of persistent MRSA bacteremia, and a TTP of ≤14 hours was an independent predictor of extended *S. aureus* bacteremia duration. Sequential TTP measurements further inform prognosis, with a decreasing or non-increasing TTP ratio in follow-up cultures indicating a failure to clear the infection and a higher risk of mortality. However, the predictive value of TTP can be influenced by clinical context; some evidence suggests its utility may be diminished in patients with established severe sepsis or septic shock, and a minority of large studies found no significant association with mortality for certain organisms.

Paper search

We performed a semantic search across over 138 million academic papers from the Elicit search engine, which includes all of Semantic Scholar and OpenAlex.

We ran this query: "Option #2: Does TTP predict the risk of antibiotic failure?

Population Adults with documented bloodstream infection (bacteremia) confirmed by positive blood culture, including:

Gram-positive organisms (with S. aureus as priority subgroup) Gram-negative organisms Any infection source (with stratification by source control status) Index Prognostic Factor (Exposure) Time to positivity (TTP) of blood cultures, analyzed as:

Continuous variable (hours) Study-level contrasts (short vs. prolonged TTP where dichotomized) Comparator

Shorter TTP vs. longer TTP Per-hour increments in TTP (for continuous modeling) Outcomes

Priority Outcome Definition Primary Persistent bacteremia Positive blood cultures at 48–72 hours despite appropriate therapy Primary Relapse/recurrence Recurrent positive cultures after initial clearance (within 30–90 days) Primary Microbiological clearance Documented negative follow-up cultures Secondary All-cause mortality In-hospital or 30-day mortality"

The search returned 500 total results from Elicit.

We retrieved 500 papers most relevant to the query for screening.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Adult Population with Bloodstream Infection**: Does the study include adults (≥18 years) with documented bloodstream infection confirmed by positive blood culture?
- **Time to Positivity Measurement**: Does the study report time to positivity (TTP) of blood cultures as a measured variable?
- **TTP-Outcome Analysis with Clinical Endpoints**: Does the study analyze TTP in relation to treatment outcomes AND report at least one relevant clinical outcome (persistent bacteremia, relapse/recurrence, microbiological clearance, or mortality)?
- **Antibiotic Treatment**: Does the study include patients receiving antibiotic therapy for bacteremia?
- **Appropriate Study Design and Sample Size**: Is the study an observational study, randomized controlled trial, systematic review, or meta-analysis with adequate sample size (≥10 patients for primary studies)?
- **Data Extractability**: Does the study provide sufficient data to extract effect estimates or raw data for TTP-outcome associations?
- **Clinically Significant Blood Cultures**: Does the study focus on clinically significant bloodstream infections rather than solely on contaminated blood cultures or cultures without clinical significance?
- **Prognostic Focus**: Does the study examine the prognostic value of TTP for treatment outcomes rather than focusing exclusively on diagnostic accuracy for organism identification?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Data extraction

We asked a large language model to extract each data column below from each paper. We gave the model the extraction instructions shown below for each column.

- **Study Population**:

  Extract details about the study population with documented bloodstream infection/bacteremia, including:

- Total sample size
- Age characteristics (mean/median age, age range, elderly vs younger adults)
- Inclusion criteria (confirmed positive blood cultures, infection types)
- Exclusion criteria
- Setting (ICU, general ward, emergency department, etc.)
- Geographic location and time period
- Any specific focus on high-risk subgroups

- **Organism and Source**:

  Extract information about the causative organisms and infection sources relevant to TTP prediction of antibiotic failure, including:

- Specific bacterial pathogens (S. aureus, E. coli, Klebsiella, other gram-positive/negative)
- Proportion of each organism type
- Methicillin resistance status (MRSA vs MSSA)
- Infection source/focus (central line/catheter, endocarditis, primary bacteremia, urinary, pulmonary, etc.)
- Source control status (adequate vs inadequate)
- Healthcare-associated vs community-acquired

- **TTP Measurement**:

  Extract how time to positivity was measured and analyzed as a predictor of antibiotic failure, including:

- Definition of TTP (time from incubation start to growth detection, automated system used)
- TTP values reported (median, mean, range in hours)
- Analysis approach (continuous variable per-hour increments vs dichotomized cutoffs)
- Specific cutoff values used for categorization (≤12h vs >12h, ≤7h vs >7h, etc.)
- Multiple TTP measurements (sequential TTPs, ratios between cultures)
- Blood culture collection timing and methods

- **Antibiotic Treatment**:

  Extract details about antibiotic therapy relevant to predicting treatment failure, including:

- Empirical antibiotic therapy adequacy (appropriate vs inappropriate for identified organism)
- Time to appropriate therapy initiation
- Specific antibiotics used
- Treatment duration
- Any therapy modifications based on TTP or clinical response
- Protocol-driven vs individualized treatment approaches

- **Failure Outcomes**:

  Extract all outcomes representing antibiotic failure that were assessed in relation to TTP, including:

- Persistent bacteremia (positive blood cultures at 48-72 hours despite appropriate therapy)
- Relapse/recurrence (recurrent positive cultures after initial clearance within 30-90 days)
- Microbiological clearance rates and timing (documented negative follow-up cultures)
- All-cause mortality (in-hospital, 30-day, other timepoints)
- Treatment failure definitions used by study authors
- Time points when outcomes were assessed
- Method of outcome ascertainment

- **TTP-Outcome Analysis**:

  Extract the statistical analysis and results examining TTP as a predictor of antibiotic failure, including:

- Type of analysis (univariate, multivariate logistic regression, survival analysis, etc.)
- Effect measures (odds ratios, hazard ratios, correlation coefficients, p-values)
- Confidence intervals for effect estimates
- Statistical significance of TTP as predictor for each outcome
- Dose-response relationships (per-hour increments in TTP)
- Subgroup analyses by organism type or other factors
- Model performance metrics (C-statistic, AUC, etc.)

- **Patient Characteristics**:

  Extract patient characteristics and comorbidities that may confound or modify the TTP-antibiotic failure relationship, including:

- Comorbidity burden (Charlson score, specific conditions)
- Severity of illness scores (APACHE II, SOFA, Pittsburgh bacteremia score)
- Immunosuppression status (neutropenia, steroid use, malignancy)
- Organ dysfunction/failure at baseline
- Prior antibiotic exposure
- Hospital length of stay prior to bacteremia
- Any factors identified as confounders or effect modifiers in analyses

- **Study Design**:

  Extract study design characteristics affecting interpretation of TTP as predictor of antibiotic failure, including:

- Study design (retrospective cohort, prospective cohort, case-control)
- Data collection period and follow-up duration
- Single vs multi-center
- Consecutive patient enrollment vs sampling method
- Loss to follow-up rates
- Blinding of outcome assessors to TTP values
- Handling of missing data
- Power calculation or sample size justification

Report

Due to the limitations of the AI model, we are only able to process 200 sources while writing a report. This report was written using the 200 sources that had the highest screening scores out of the 384 sources that we screened in and extracted data from.

Study Characteristics

The included studies examining time to positivity (TTP) as a predictor of antibiotic failure in bloodstream infections (BSI) consist primarily of retrospective and prospective cohort designs. One study was a secondary analysis of a prospective multicentre randomized controlled trial, and another was a systematic review and meta-analysis. Data collection periods ranged from a few months to several decades, with the earliest starting in 1991 and the most recent ending in 2023. Geographic locations were diverse, including studies from Asia (China, Japan, Republic of Korea, Taiwan), Europe (Spain, Germany, France, Sweden, Italy, UK, Switzerland), North America (USA, Canada), and Australia. Both single-center and multi-center settings were represented, ranging from large university teaching hospitals to community hospitals. Sample sizes varied widely, from 32 patients to a population-based cohort of over 88,000 patients. Follow-up durations were typically for in-hospital or 30-day outcomes, though some studies extended follow-up to 90 days or longer. Methodological quality considerations noted across the studies included the frequent use of retrospective designs, which may introduce bias. Most studies utilized consecutive patient enrollment. Exclusion criteria often involved polymicrobial infections and prior antimicrobial therapy. Blinding of outcome assessors was generally not mentioned, which is a common feature of observational studies of this nature. Loss to follow-up was also infrequently reported.

Study	Full text retrieved?	Study Design	Setting (Single/Multi-center)	Country	Data collection period	Sample Size	Follow-up Duration	Methodological Considerations
A. Bläckberg et al., 2022	No	Retrospective observational cohort	Single-center	Sweden	2015-2018	286 episodes	30 days	Retrospective, exclusions based on criteria not fully specified
A. Bläckberg et al., 2023	No	Retrospective cohort	Region-wide (multi-center implied)	Sweden	2015–2018	287 episodes	30 days	Retrospective design
A. Fernández-Cruz et al., 2013	No	Prospective cohort	Single-center	Not specified	April 2009 to June 2011	119 patients	Minimum 3 months or until death	Prospective design with consecutive enrollment, specific inclusion criteria
A. Marra et al., 2006	No	Historical cohort	Not mentioned	Not mentioned	Not mentioned	91 adult patients	Hospital mortality duration	Retrospective design

Study	Full text retrieved?	Study Design	Setting (Single/Multi-center)	Country	Data collection period	Sample Size	Follow-up Duration	Methodological Considerations
A. Peri et al., 2023	No	Prospective, observational study	Multi-center	Not mentioned	Not mentioned	102 patients	4-day follow-up	Prospective design
A. Russo et al., 2022	No	Prospective observational study	Multi-center	Italy	August 2016 to April 2021	103 patients	30 days	Prospective, consecutive enrollment, specific inclusion criteria
A. Sastry et al., 2024	No	Retrospective cohort	Single-center	Not mentioned	4 years	38,606 samples	Not mentioned	Retrospective design
Achim J. Kaasch et al., 2013	No	Prospective cohort	Multi-center	Germany	Not mentioned	256 patients	3 months	Prospective, multi-center design
Alaina Shukdinas et al., 2022	No	Retrospective chart review	Multi-center (3 hospitals)	USA (NJ)	November 2019 to November 2021	79 patients	Inpatient mortality	Retrospective, exclusions for contaminants and comfort care
Arun Sachu et al., 2024	No	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned
B. Lamy et al., 2019	No	Retrospective study	Not mentioned	Not mentioned	Not mentioned	Not specified	Not mentioned	Retrospective design
Bethany R. Tellor et al., 2015	No	Retrospective cohort	Single-center	USA (Missouri)	January 2005 to January 2011	108 episodes	In-hospital mortality	Retrospective design, strict exclusion criteria
Brett H. Heintz et al., 2020	No	Retrospective cohort	Single-center	Not mentioned	Not mentioned	Not specified	Not mentioned	Retrospective design

Study	Full text retrieved?	Study Design	Setting (Single/Multi-center)	Country	Data collection period	Sample Size	Follow-up Duration	Methodological Considerations
C. Cillóniz et al., 2017	Yes	Prospective observational study	Single-center	Spain	2003-2015	278 patients	30 days	Prospective design with specific exclusions (e.g., immunocompromised)
C. Fang et al., 2006	No	Retrospective cohort	Single-center	Taiwan	1 April 1997-31 March 2001	162 patients	Up to 3 years	Retrospective design
C. Forstner et al., 2013	No	Retrospective cohort	Single-center	Austria	2000-2011	124 patients	28 days	Retrospective design
C. Keighley et al., 2023	No	Prospective cohort	Not mentioned	Australia	2014–2015	415 episodes	30 days	Prospective data collection
C. Liao et al., 2009	No	Prospective cohort	Single-center	Not specified	Jan 1 to Dec 31, 2007	231 patients	30 days	Prospective, consecutive enrollment
C. Robson et al., 2025	No	Retrospective cohort	Single-center	Australia (implied)	2017 to 2021	114 episodes	Not mentioned	Retrospective, exclusions for polymicrobial growth and preculture antibiotics
C. Sabatier et al., 2015	No	Prospective randomized study	Single-center ICU	Not specified	July 2007-February 2009	52 patients	48 hours	Prospective randomized design

Study	Full text retrieved?	Study Design	Setting (Single/Multi-center)	Country	Data collection period	Sample Size	Follow-up Duration	Methodological Considerations
C.-J. Kim et al., 2019	No	Prospective cohort	Multi-center (11 hospitals)	Not specified	12-39 months	2098 cases	90 days	Prospective, multi-center, only first episode included
Chen-Hsiang Lee et al., 2013	No	Retrospective cohort	Single-center	Taiwan	July 1, 2006, to June 30, 2009	339 patients	14 days	Retrospective, excluded endo-carditis
Chih-Cheng Lai et al., 2011	Yes	Prospective study	Single-center	India	February 2015 to July 2015	80 patients	Not specified	Consecutive enroll-ment
Chih-Cheng Lai et al., 2011a	No	Not men-tioned	Not men-tioned	Not men-tioned	Not men-tioned	Not specified	Not specified	Not specified
Chih-Cheng Lai et al., 2011b	No	Prospective study	Not men-tioned	Not men-tioned	Not men-tioned	Not specified	Not specified	Prospective design
Chih-Cheng Lai et al., 2012	No	Retrospective cohort	Single-center	Taiwan	July 2010 to March 2011	176 patients	Not specified	Consecutive enroll-ment
Chih-Ping Chen et al., 2023	No	Retrospective observa-tional, case-control	Single-center	Not specified	July 1, 2016, to June 30, 2021	101 patients	30 days	Retrospective design, consecu-tive enroll-ment
Ching-Chi Lee et al., 2019	Yes	Retrospective cohort	Multi-center (2 hospitals)	Taiwan	Jan 2010 to Dec 2015	1,247 adults	30 days	Retrospective with extensive exclusion criteria
Christian P. Fischer et al., 2023	No	Retrospective cohort	Single-center	Denmark	Jan 1, 2015, to Dec 31, 2015	926 patients	60 days	Retrospective design

Study	Full text retrieved?	Study Design	Setting (Single/Multi-center)	Country	Data collection period	Sample Size	Follow-up Duration	Methodological Considerations
Christina N. Canzoneri et al., 2017	No	Retrospective cohort	Not mentioned	Not mentioned	Not mentioned	500 episodes	Not mentioned	Retrospective, consecutive enrollment
Christelle Kassis et al., 2009	No	Retrospective cohort	Not mentioned	Not mentioned	June 2005 to January 2008	272 patients	Not mentioned	Retrospective design
Cintia Zoya Nunes et al., 2013	Yes	Retrospective cohort	Single-center	Brazil	Jan 2002 to Jul 2009	89 adults	In-hospital mortality	Retrospective, consecutive enrollment, exclusions for incomplete data
D. Bates et al., 1992	No	Prospective cohort	Single-center	USA (Boston)	Not mentioned	348 episodes	Not mentioned	Prospective, blinded reviewers
D. Bates et al., 1995	No	Prospective cohort	Single-center	USA (Boston)	Not mentioned	142 with bacteremia	Up to 1 year	Prospective cohort with matched comparison groups
D. Farmakiotis et al., 2015	No	Retrospective cohort	Single-center	USA (Texas)	March 2005-Sep 2013	115 patients	Not specified	Retrospective design
D. Sowden et al., 2008	No	Retrospective cohort	Single-center	Australia	1997-2004	Not specified	Not specified	Retrospective analysis of microbiology records
Daniel N Marco et al., 2025	Yes	Retrospective observational	Single-center	Spain	1991 to 2019	1177 cases	30 days	Retrospective, long study period

Study	Full text retrieved?	Study Design	Setting (Single/Multi-center)	Country	Data collection period	Sample Size	Follow-up Duration	Methodological Considerations
Danya Roshdy et al., 2015	No	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not specified	Not specified	Not specified
David Krus et al., 2021	Yes	Retrospective cohort	Multi-center (5 hospitals)	Sweden	Jan 1, 2015, to Mar 31, 2016	263 episodes	30 days	Retrospective, population-based with exclusions
Deanna J. Buehrle et al., 2016	No	Retrospective cohort	Not mentioned	Not mentioned	Not mentioned	37 patients	14 days	Retrospective design
E. Maillart et al., 2012	Yes	Retrospective cohort	Single-center	Not specified	May 2007 to May 2010	167 episodes	Attributable mortality duration	Retrospective, consecutive enrollment, exclusions for missing data
E. Minejima et al., 2019	Yes	Prospective cohort	Multi-center	USA (California)	2012-2017	884 patients	30 days	Prospective, multi-center, consecutive enrollment with specific exclusions
E. Yang et al., 2024	Yes	Prospective cohort	Single-center	South Korea	July 2008 to December 2020	1760 patients (242 with PB)	12 weeks	Prospective, long duration

Study	Full text retrieved?	Study Design	Setting (Single/Multi-center)	Country	Data collection period	Sample Size	Follow-up Duration	Methodological Considerations
Emily Fox et al., 2022	Yes	Retrospective case-control	Single-center	USA (California)	2016 to 2020	108 patients	In-hospital	Retrospective, case-control design, exclusions for incomplete data
Emmanuel Moustos et al., 2017	Yes	Retrospective cohort	Single-center	Greece	Nov 1, 2014, to Oct 31, 2016	719 positive bottles	Not specified	Retrospective, selective sampling
Evan J Zasowski et al., 2020	No	Systematic review and meta-analysis	Multi-center (by design)	Not specified	Studies published after 2007	145 studies (37 in meta-analysis)	Varies (20-30 days, ICU stay)	Meta-analysis of existing literature
F. Blot et al., 1999	No	Prospective cohort	Single-center	Not specified	14 months	93 catheters	Not specified	Prospective design
F. Hamilton et al., 2021	No	Analysis of prospective RCT data	Multi-center	Not mentioned	Not mentioned	3462 participants	28 days	Secondary analysis of prospective RCT
F. Kahn et al., 2020	No	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not specified	Not specified	Not specified
Felicity Edwards et al., 2025	Yes	Retrospective cohort	Population-based (Queensland)	Australia	2000-2019	84,341 patients	Not specified	Retrospective, population-based with long duration
G. Deas et al., 2025	Yes	Retrospective cohort	Single-center	England	2017-2024	810 patients	Not specified	Retrospective, excluded cases with missing data
G. Defrance et al., 2013	No	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not specified	Not specified	Not specified

Study	Full text retrieved?	Study Design	Setting (Single/Multi-center)	Country	Data collection period	Sample Size	Follow-up Duration	Methodological Considerations
G. Edwardson et al., 2019	No	Retrospective chart review	Not mentioned	Not mentioned	Not mentioned	66 patients	Not specified	Retrospective design
G. Gawrys et al., 2018	No	Retrospective pre- and post-intervention	Single-center	USA (Texas)	2012-2014 & 2015-2017	240 patients	Not specified	Retrospective, pre-post design
G. Martín-Gutiérrez et al., 2017	No	Retrospective cohort	Not mentioned	Not mentioned	Not mentioned	361 episodes in 332 patients	Not specified	Retrospective design
G. Peralta et al., 2006	Yes	Retrospective cohort	Single-center	Not specified	Jan 1995 to Dec 2004	105 patients	Not specified	Retrospective, consecutive enrollment
G. Peralta et al., 2007	No	Retrospective cohort	Single-center	Not specified	1997 to 2005	459 cases	In-hospital mortality	Retrospective design
Gavin Deas et al., 2025	Yes	Retrospective analysis	Single-center	England	2017-2024	810 cases	Not specified	Retrospective, exclusions for missing data
H. Bae et al., 2021	Yes	Retrospective cohort	Single-center	Republic of Korea	2014-2018	803 patients	28 days	Retrospective, consecutive enrollment
H. Bouzidi et al., 2018	No	Retrospective cohort	Single-center	Not specified	6 years	101 cases analyzed	Not specified	Retrospective, blinded assessors, high exclusion rate due to missing data

Study	Full text retrieved?	Study Design	Setting (Single/Multi-center)	Country	Data collection period	Sample Size	Follow-up Duration	Methodological Considerations
H. Le et al., 2013	No	Retrospective cohort	Single-center	Not specified	2008 to 2012	73 patients	In-hospital stay	Retrospective, consecutive enrollment
H. Le et al., 2014	No	Retrospective cohort	Single-center	Not specified	2008 to 2012	174 inpatients	Hospital death	Retrospective design
H. Palmer et al., 2013	No	Prospective observational	Single-center	Not mentioned	Not mentioned	100 patients	Hospital discharge or death	Prospective, consecutive enrollment
Hea Sung Ok et al., 2013	Yes	Prospective observational	Single-center	Republic of Korea	Nov 2009 to Aug 2010	67 patients	30 days	Prospective, consecutive enrollment with specific exclusions
Hila Zadka et al., 2019	No	Retrospective cohort	Not specified	Not specified	Not specified	4170 cases	Length of stay, ICU transfer, mortality	Retrospective, pre-post design
Hiroyasu Takahashi et al., 2022	Yes	Retrospective cohort	Single-center	Japan	1 year	245 patients	14 days	Retrospective design
Hui-Wen Lin et al., 2016	No	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not specified	Not specified	Not specified
I. Comba et al., 2022	No	Retrospective review	Multi-site, single system	Not specified	Jan 2019 to Dec 2019	186 patients	90 days	Retrospective design
I. Comba et al., 2024	No	Observational study	Not specified	Not specified	Not specified	186 patients	Not specified	Not specified
J. Barenfanger et al., 2008	No	Retrospective cohort (matched pairs)	Not specified	Not specified	Not specified	198 patients (99 pairs)	Crude mortality	Retrospective matched pair design

Study	Full text retrieved?	Study Design	Setting (Single/Multi-center)	Country	Data collection period	Sample Size	Follow-up Duration	Methodological Considerations
J. B. Wiggers et al., 2020	No	Retrospective cohort study	Not specified	Not specified	Not specified	901 episodes	Not specified	Retrospective design
J. Ji et al., 2020	Yes	Retrospective cohort	Single-center	USA (Missouri)	Jan 2014 to June 2017	2,751 admissions	In-hospital mortality	Retrospective design
J. Martinez et al., 2006	No	Retrospective cohort	Single-center	Not specified	1 year	185 episodes	Fatal outcome	Retrospective, consecutive enrollment
J. Martínez et al., 2007	No	Retrospective cohort	Single-center	Not specified	2 years	1872 episodes	Not specified	Retrospective design
J. Stempel et al., 2016	No	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not specified	Not specified	Not specified
J. Thaden et al., 2022	Yes	Systematic review and meta-analysis	Multi-center (by design)	USA, Canada, South Korea, Italy	Not specified	4378 patients	In-hospital, 28-day, 30-day mortality	Meta-analysis of observational studies
Jasanjeet Jawanda et al., 2023	No	Retrospective cohort	Single-center	Not specified	Jan to June 2021	154 patients	30 days	Retrospective, pre-intervention phase of a larger study
Jasper Van Heuverswyn et al., 2022	No	Retrospective cohort	Single-center	Sweden	2012-2019	10,628 episodes	30 days	Retrospective, consecutive enrollment
Javier López et al., 2013	No	Retrospective cohort	Single-center	Not specified	1996 to 2011	407 patients	In-hospital mortality	Retrospective, consecutive enrollment
Jin-ya Ding et al., 2011	No	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not specified	Not specified	Not specified

Study	Full text retrieved?	Study Design	Setting (Single/Multi-center)	Country	Data collection period	Sample Size	Follow-up Duration	Methodological Considerations
Joe Pardo et al., 2014	No	Retrospective cohort	Single-center	Not specified	Feb 1, 2011, to Jul 31, 2011	416 BSIs	Not specified	Retrospective design
Joseph Kim et al., 2010	No	Retrospective study	Region-wide (Calgary)	Canada	Jul 1, 2006 to Dec 31, 2008	684 cases	30 days	Retrospective design
K. Buell et al., 2020	No	Secondary analysis of RCT	Not specified	Not specified	Not specified	15,802 adults	Not specified	Secondary analysis of trial data
K. Buell et al., 2020a	No	Secondary analysis of RCT	Multi-center (5 ICUs)	USA (TN)	Not specified	15,802 adults	Not specified	Secondary analysis of trial data
K. Ishikawa et al., 2025	No	Retrospective cohort	Single-center	Japan (likely)	2015 to 2023	317 patients	Not specified	Retrospective design with exclusions
K. Ishikawa et al., 2025a	No	Retrospective cohort	Single-center	Not specified	Not specified	317 patients	Not specified	Retrospective design
K. Laupland et al., 2022	No	Retrospective cohort	Population-based	Australia	2000-2019	16,276 patients	30 days	Retrospective, population-based design
K. Paquette et al., 2021	No	Prospective cohort	Multi-center	Not specified	Not specified	325 participants	90 days	Prospective design with some loss to follow-up
K. Seidl et al., 2010	No	Retrospective cohort	Multi-center	Not specified	Not specified	36 isolates	Not specified	Retrospective design
Karl Oldberg et al., 2021	Yes	Retrospective observational	Multi-center	Sweden	2015-2018	367 episodes	180 days	Retrospective, blinded assessment of echo reports

Study	Full text retrieved?	Study Design	Setting (Single/Multi-center)	Country	Data collection period	Sample Size	Follow-up Duration	Methodological Considerations
Katharina Michelson et al., 2021	No	Single centre retrospective cohort	Single-center	Germany	Jan 1, 2014, to Dec 31, 2016	244 patients	Hospital mortality	Retrospective design
Katri Abraham et al., 2016	No	Retrospective study	Not specified	Not specified	Not specified	72 episodes	Not specified	Retrospective design
Kevin B. Laupland et al., 2024	No	Retrospective cohort	Population-based (Queensland)	Australia	2000 to 2019	88,314 patients	30 days	Retrospective, large population-based cohort
L. Johnson et al., 2003	No	Retrospective cohort	Single-center	Not specified	2 years	226 cases	386.7±449.8 days	Retrospective with follow-up, 68.4% follow-up rate
Lauren Cooper et al., 2024	No	Retrospective cohort	Multi-center (161 facilities)	USA	Not specified	29,570 admissions	In-hospital	Retrospective, multi-center database analysis
Lavanya Balaji et al., 2024	Yes	Cross-sectional observational	Single-center	India (implied)	July 2023 to June 2024	57 patients	30 days	Prospective observation, single-center
Leehe Turkeltaub et al., 2024	Yes	Retrospective cohort	Single-center	Israel	Not specified	60 patients	Not specified	Retrospective, consecutive enrollment
Leopold Henssler et al., 2024	Yes	Retrospective cohort	Single-center	Not specified	March 2019 to March 2023	126 patients	Not specified	Retrospective design

Study	Full text retrieved?	Study Design	Setting (Single/Multi-center)	Country	Data collection period	Sample Size	Follow-up Duration	Methodological Considerations
Liang-Yu Chen et al., 2015	No	Retrospective cohort	Single-center	Taiwan	2006-2009	434 episodes	30 days	Retrospective, consecutive enrollment
M. Bartoletti et al., 2017	No	Prospective cohort	Multi-center (19 centers)	5 countries	Sep 2014 to Dec 2015	312 patients	30 days	Prospective, multi-center, consecutive enrollment
M. Chowers et al., 2003	No	Not mentioned	Not mentioned	Not mentioned	Not mentioned	4,277 episodes	Not specified	Not specified
M. Falcone et al., 2020	Yes	Retrospective cohort	Multi-center (2 centers)	Italy	Jan 2015 to Dec 2018	102 patients	30 days	Retrospective, consecutive enrollment
M. Fida et al., 2021	No	Prospective cohort	Not specified	Not specified	Not specified	Not specified	Not specified	Prospective design
M. Garnica et al., 2022	No	Prospective cohort	Not specified	Not specified	2020 to 2021	133 infections	Not specified	Prospective design
M. Giannella et al., 2020	No	Retrospective cohort	Single-center	Not specified	2013-2016	1576 patients	30 days	Retrospective design
M. Holubar et al., 2021	No	Prospective cohort	Multi-center	Not specified	Not specified	884 patients	Not specified	Prospective design
M. Lambregts et al., 2018	No	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not specified	Not specified	Not specified

Study	Full text retrieved?	Study Design	Setting (Single/Multi-center)	Country	Data collection period	Sample Size	Follow-up Duration	Methodological Considerations
M. Lambregts et al., 2019	Yes	Retrospective cohort	Single-center	Netherlands	3 years	897 episodes	Not specified	Retrospective design with specific exclusions
M. Rolo et al., 2022	No	Retrospective cohort	Not specified	Not specified	Jan 2013 to Feb 2020	328 patients	30 days	Retrospective design
M. Savithri et al., 2011	No	Retrospective chart audit	Single-center	Not specified	2009	569 positive sets	28 days	Retrospective design
M. Spaziante et al., 2020	No	Retrospective cohort	Not specified	Not specified	1 year	69 patients (107 episodes)	30 days	Retrospective design
Marin L Schweizer et al., 2010	Yes	Retrospective cohort	Single-center	USA (Baltimore)	Jan 1, 2003, to June 30, 2007	814 admissions	30 days	Retrospective, consecutive enrollment, with exclusions for missing data
Martin Strömdahl et al., 2024	No	Retrospective cohort	Single-center	Sweden	2011-2021	1703 episodes	30 days	Retrospective design, large sample size
Matthaios Papadimitriou-Olivgeris et al., 2019	No	Retrospective cohort	Single-center	Switzerland	Jul 2014 to June 2017	404 BSIs	30 days	Retrospective design
Matthaios Papadimitriou-Olivgeris et al., 2023	Yes	Retrospective cohort	Single-center	Switzerland	2015-2021	839 episodes	28 days	Retrospective, consecutive enrollment

Study	Full text retrieved?	Study Design	Setting (Single/Multi-center)	Country	Data collection period	Sample Size	Follow-up Duration	Methodological Considerations
Matthias Willmann et al., 2013	No	Retrospective cohort	Multi-center (3 hospitals)	Germany	2006-2012	74 patients	In-hospital	Retrospective, multi-center design
Maya Beganovic et al., 2018	Yes	Retrospective cohort	Single-center	Not specified	2014-2016	239 patients	In-hospital	Retrospective, consecutive enrollment with exclusions
Meaghan Martinez-Palmer et al., 2025	No	Retrospective cohort	Single-center (implied)	Not specified	2021-2023	168 cases	Not specified	Retrospective, pre-post intervention design
Meng-Shiuan Hsu et al., 2014	No	Retrospective cohort	Single-center	Not specified	5 years	87 patients	In-hospital mortality	Retrospective design
Michael Y. Lin et al., 2008	No	Retrospective cohort	Single-center	USA	2001 to 2006	1523 episodes	In-hospital mortality	Retrospective design
N. Cobos-Trigueros et al., 2013	No	Retrospective cohort	Not specified	Not specified	Not specified	157 episodes	Not specified	Retrospective design
N. Deguchi et al., 2023	No	Single-center retrospective	Single-center	Not specified	Not specified	Not specified	30 days	Retrospective design
Naoki Watanabe et al., 2022	Yes	Retrospective cohort	Single-center	Japan	Jan 2014 to Feb 2022	165 cases	Not specified	Retrospective, consecutive enrollment with exclusions
Nelly Elfrida Samosir et al., 2019	No	Cross-sectional	Single-center	Indonesia	June-Oct 2016	46 cases	Not specified	Cross-sectional design

Study	Full text retrieved?	Study Design	Setting (Single/Multi-center)	Country	Data collection period	Sample Size	Follow-up Duration	Methodological Considerations
O. Lesens et al., 2004	No	Prospective cohort	Multi-center	Not specified	Not specified	104 patients	Not specified	Prospective, consecutive enrollment with specific inclusion criteria
O. Tsachouridou et al., 2023	Yes	Retrospective cohort	Single-center	Greece	Jan 1, 2022, to Jan 31, 2023	157 episodes	28 days	Retrospective, consecutive enrollment with exclusions
Oskar Ljungquist et al., 2025	No	Retrospective cohort	Population-based (Southern Sweden)	Sweden	2021 to 2023	12,585 episodes	30 days	Retrospective, population-based design
Oxana Megherea et al., 2019	No	Retrospective pre- and post-intervention	Single-center	Not specified	2017-2019	100 patients	28 days	Retrospective, pre-post design with exclusions
P. Krisanapan et al., 2019	Yes	Retrospective cohort	Single-center	Thailand	Oct-Nov 2014	195 episodes	Not specified	Retrospective, consecutive enrollment
P. Moise et al., 2010	Yes	Prospective cohort	Multi-center	USA	1998-2002	29 patients	Time to clearance	Prospective, blinded assessment, sample size justification

Study	Full text retrieved?	Study Design	Setting (Single/Multi-center)	Country	Data collection period	Sample Size	Follow-up Duration	Methodological Considerations
P. Puerta-Alcalde et al., 2019	No	Prospective cohort	Not specified	Not specified	2003-2017	850 episodes	Not specified	Prospective collection, random sampling for multiple BSIs
P. Simos et al., 2022	No	Retrospective cohort	Single-center	Not specified	Not specified	106 cases	Not specified	Retrospective design
P. Tang et al., 2017	No	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified
P. Tsai et al., 2025	No	Retrospective cohort	Not specified	Not specified	Not specified	1015 adults	30 days	Retrospective design
P. Wacharasint et al., 2016	No	Observational study	Single-center	Thailand (implied)	2 years	48 patients	Hospital mortality	Observational design
Paige A. Melling et al., 2020	Yes	Prospective cohort ancillary study	Single-center	USA (TN)	June 2015 to April 2017	6553 admissions	Not specified	Ancillary analysis of RCT data with specific inclusion criteria
Peter J. B. Davies et al., 2023	No	Retrospective cohort	Not specified	Not specified	Mar-Jul 2020/21	7367 patients	30 days	Retrospective design
PharmD PhC M. Gabriela Cabanilla et al., 2023	No	Retrospective cohort	Single-center	Not specified	Jan 1, 2014, to June 30, 2021	32 patients	30 days	Retrospective design
Po-Hsiang Hsu et al., 2024	No	Retrospective study	Single-center	Taiwan	Jan 1, 2016 to Mar 31, 2021	4011 patients	30 days	Retrospective, consecutive enrollment from electronic records

Study	Full text retrieved?	Study Design	Setting (Single/Multi-center)	Country	Data collection period	Sample Size	Follow-up Duration	Methodological Considerations
Qian Li-Rong et al., 2012	No	Retrospective cohort	Single-center	China	Jan 2005 to Jan 2012	468 patients	In-hospital mortality	Retrospective design
Qing Zhang et al., 2015	No	Retrospective study	Single-center	China	Aug 2011 to Mar 2014	615 pairs of cultures	Not specified	Retrospective design with numerous exclusions
Qing Zhang et al., 2016	No	Retrospective cohort	Single-center	Not specified	19 months	386 episodes	Not specified	Retrospective design
Qing Zhang et al., 2020	No	Retrospective study	Single-center	Not specified	2013 to 2018	509 patients	Not specified	Retrospective with random division into development/validation sets
Qing Zhang et al., 2021	Yes	Retrospective cohort	Single-center	China	Jan 2013 to Dec 2018	509 patients	30 days (in-hospital)	Retrospective, consecutive enrollment, with exclusions for incomplete data
R. Álvarez et al., 2012	No	Retrospective observational	Not specified	Not specified	Not specified	226 patients	In-hospital and 48-hour mortality	Retrospective design
R. Ben-Ami et al., 2008	No	Prospective cohort	Multi-center (2 centers)	Not specified	Not specified	64 episodes	Not specified	Prospective surveillance

Study	Full text retrieved?	Study Design	Setting (Single/Multi-center)	Country	Data collection period	Sample Size	Follow-up Duration	Methodological Considerations
R. García Fenoll et al., 2022	Yes	Retrospective cohort	Single-center	Spain	March 2020 to Feb 2021	95 patients	30 days	Retrospective, consecutive enrollment
R. Khatib et al., 2005	No	Prospective observational	Single-center	Not specified	Jan 1, 2002 to June 30, 2003	357 patients	In-hospital mortality	Prospective design with consecutive enrollment
R. Khatib et al., 2006	No	Prospective observational	Single-center	Not specified	2002	245 bacteremias	Not specified	Prospective, consecutive enrollment
R. Khatib et al., 2009	No	Retrospective cohort	Single-center	Not specified	2002-2003 & 2005-2006	78 patients	Case-fatality	Retrospective design
R. Krause et al., 2014	No	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not specified	Not specified	Not specified
R. Passerini et al., 2008	No	Retrospective cohort	Not specified	Not specified	Not specified	1,218 positive blood cultures	Not specified	Retrospective analysis
R. Rosa et al., 2016	No	Retrospective cohort	Single-center	Not specified	Jan 1, 2012 to Apr 30, 2013	250 episodes	Clinical failure (in-hospital mortality and persistent bacteremia)	Retrospective design
Rashid Nadeem et al., 2021	Yes	Retrospective cohort	Single-center	Dubai	Aug 1, 2017, to Dec 31, 2018	101 patients	In-hospital mortality and ICU length of stay	Retrospective chart review

Study	Full text retrieved?	Study Design	Setting (Single/Multi-center)	Country	Data collection period	Sample Size	Follow-up Duration	Methodological Considerations
Rita Wilson Dib et al., 2018	Yes	Retrospective cohort	Single-center	USA (Texas)	2005 to 2016	128 patients	Within 3 months	Retrospective, consecutive enrollment, one patient lost to follow-up
S. Beekmann et al., 2003	No	Prospective cohort	Multi-center (2 centers)	Not specified	Not specified	917 cases	Length of hospitalization	Prospective design
S. Choi et al., 2012	No	Not specified	Not specified	Not specified	Not specified	Not specified	30 days	Not specified
S. de la Villa et al., 2023	No	Times-series study	Single-center (implied)	Not specified	Jan 2014 to Dec 2021	109 episodes	30 days	Times-series design with pre/post intervention periods
S. Micek et al., 2011	No	Retrospective cohort	Single-center	Not specified	2002 to 2007	535 patients	Hospital mortality	Retrospective, consecutive enrollment from database
S. Morioka et al., 2018	No	Retrospective cohort	Not specified	Not specified	Oct 2011 to Mar 2013	95 patients	Not specified	Retrospective design with objective definition for contamination
S. Siméon et al., 2019	No	Prospective cohort	Multi-center	France	2009-2011	587 patients	30 days	Prospective, multi-center, consecutive enrollment

Study	Full text retrieved?	Study Design	Setting (Single/Multi-center)	Country	Data collection period	Sample Size	Follow-up Duration	Methodological Considerations
S. Tennant et al., 2016	No	Retrospective cohort	Not specified	Not specified	2010 to 2014	193 patients	90 days	Retrospective design
S. Tong et al., 2020	No	Secondary analysis of prospective cohort	Multi-center	Europe	Not specified	987 patients	Not specified	Secondary analysis of a prospective cohort
S. Vasoo et al., 2025	No	Randomized controlled trial	Not specified	Not specified	Not specified	844 patients	30 days	Randomized controlled trial design
S.-T. Liu et al., 2020	Yes	Systematic review and meta-analysis	Multi-center (by design)	Not specified	Inception to Mar 30, 2020	16 studies (4173 bacteremias)	Not specified	Meta-analysis of cohort studies, quality assessed
Sandhya Bhat K et al., 2022	Yes	Cross-sectional study	Single-center	Not specified	May 15th to July 15th, 2018	75 patients	In-hospital outcome	Cross-sectional design with exclusions for repeats/contaminants
Sarah Cain et al., 2014	No	Retrospective cohort	Single-center	USA (SC)	Jan 1, 2011 to Dec 31, 2012	390 patients	28 days	Retrospective, consecutive enrollment
Sarah E. Battle et al., 2017	No	Retrospective cohort	Single-center	USA (SC)	Jan 1, 2010 to Dec 31, 2013	830 patients	Hospital length of stay	Retrospective, consecutive enrollment
Shang-Yu Chen et al., 2018	No	Retrospective study	Not specified	Not specified	30 months	206 patients	30 days	Retrospective design
Shi-ning Bo et al., 2010	No	Retrospective study	Single-center	China	Jan 2007 to Dec 2009	112 patients	In-hospital mortality	Retrospective design

Study	Full text retrieved?	Study Design	Setting (Single/Multi-center)	Country	Data collection period	Sample Size	Follow-up Duration	Methodological Considerations
Shi-ning Bo et al., 2011	No	Retrospective cohort	Multi-center (2 hospitals)	Not specified	Jan 1, 2007 to Dec 31, 2009	353 episodes	Hospital mortality	Retrospective, multi-center, consecutive enrollment
Shiori Kitaya et al., 2023	Yes	Retrospective observational	Single-center	Japan	Jan 2012 to Dec 2021	414 cases	90 days	Retrospective, long duration, specific exclusions for contaminants
Si-Hyun Kim et al., 2013	No	Retrospective cohort	Not specified	Not specified	Jan 2006 to Jul 2012	152 patients	6 weeks	Retrospective, consecutive enrollment
Suellen Gavronski et al., 2020	No	Retrospective cohort	Single-center	Brazil	June 2013 to May 2018	968 positive cultures	Not specified	Retrospective, exclusions for polymicrobial cultures
Susannah Jerwood et al., 2012	No	Prospective cohort	Single-center ICU	Not specified	Not specified	48 patients	28 days	Prospective, noninterventional design
T. Bhowmick et al., 2018	No	Retrospective cohort	Single-center	Not specified	Oct 2013 to Dec 2017	Not specified	Not specified	Retrospective design with multiple intervention periods
T. Bias et al., 2017	No	Retrospective cohort	Single-center	Not specified	2011-2012	111 patients	30 days	Retrospective, pre-post intervention design

Study	Full text retrieved?	Study Design	Setting (Single/Multi-center)	Country	Data collection period	Sample Size	Follow-up Duration	Methodological Considerations
T. Dinh et al., 2015	No	Retrospective chart review	Single-center	Not specified	Not specified	793 samples	Not specified	Retrospective, random selection sampling
T. Lodise et al., 2019	No	Retrospective cohort	Multi-center	Not specified	Oct 2010-Sep 2015	40,549 patients	Hospital length of stay	Retrospective, large database analysis with exclusions
T. Ohnuma et al., 2023	Yes	Retrospective cross-sectional	Multi-center (183 hospitals)	USA	2016 to 2020	32,100 patients	In-hospital mortality	Retrospective, large multi-center database, complete-case analysis for missing data
Thomas C Havey et al., 2013	Yes	Retrospective cohort	Single-center	Canada	Mar 1, 2010 to Mar 31, 2011	100 patients	30 days post-therapy for relapse	Retrospective, consecutive enrollment, sample size justification provided
Tulip A. Jhaveri et al., 2023	Yes	Retrospective cohort	Single-center	USA (implied)	2019-2020	503 patients	Not specified	Retrospective, consecutive enrollment with exclusions
V. Fowler et al., 2004	No	Prospective cohort	Single-center	Not specified	Not specified	39 patients	Not specified	Prospective design
Wang Leili et al., 2011	No	Retrospective cohort	Not specified	Not specified	Not specified	82 patients	Not specified	Retrospective design

Study	Full text retrieved?	Study Design	Setting (Single/Multi-center)	Country	Data collection period	Sample Size	Follow-up Duration	Methodological Considerations
Wei-Ting Chen et al., 2009	No	Retrospective cohort	Single-center	Taiwan (implied)	Jan 2003-Aug 2007	142 episodes	Not specified	Retrospective design
Weiwei Hou et al., 2023	Yes	Retrospective cohort	Single-center	China	Oct 2016-Oct 2020	148 inpatients	In-hospital fatality	Retrospective, consecutive enrollment with specific exclusions
X. García et al., 2012	Yes	Prospective cohort	Single-center ICU	Spain	Feb 2005 to Sep 2006	226 suspected cases	Not specified	Prospective design with specific exclusions
Xu Rui-huan et al., 2013	No	Retrospective cohort	Not specified	Not specified	Not specified	77 patients	Not specified	Retrospective design
Y. Chong et al., 2013	Yes	Prospective cohort with nested case-control	Single-center	South Korea	Aug 2008 to Sep 2010	483 patients	12 weeks	Prospective, consecutive enrollment
Y. Nakada et al., 2016	No	Retrospective cohort	Single-center	Japan	2012	241 patients	Not specified	Retrospective, consecutive enrollment
Ya-Chu Hsieh et al., 2022	Yes	Systematic review and meta-analysis	Multi-center	Not specified	Studies published after 2000	24 studies	Not specified	Meta-analysis with quality assessment
Yihan Li et al., 2025	No	Single-center retrospective review	Single-center	Not specified	Not specified	319 patients	30 days	Retrospective, pre-post design

Study	Full text retrieved?	Study Design	Setting (Single/Multi-center)	Country	Data collection period	Sample Size	Follow-up Duration	Methodological Considerations
Yong-Ye Yang et al., 2024	No	Retrospective cohort	Single-center	Not specified	Jul 1, 2016 to June 30, 2021	196 patients	30 days	Retrospective, consecutive enrollment
Yongzhong Ning et al., 2016	No	Retrospective cohort	Single-center	China	Jan 1, 2011 to Dec 31, 2013	886 isolates	Not specified	Retrospective design
Yufang Chen et al., 2020	No	Retrospective observational	Single-center	China	Jan 2014 to Nov 2016	167 patients	In-hospital mortality	Retrospective, consecutive enrollment, with exclusions for prior antibiotic use
Yufang Chen et al., 2020a	Yes	Retrospective cohort	Single-center	China	Jan 2014 to Nov 2016	167 adult inpatients	In-hospital mortality	Retrospective, consecutive enrollment with specific exclusions
Z. Aziz et al., 2010	No	Retrospective cohort	Single-center	Iran	Jan 2005 to Dec 2006	985 samples	Not specified	Retrospective design
Ü. Gaygısız et al., 2019	No	Cohort study	Not specified	Not specified	1 year	70 patients	Not specified	Cohort design

Patient Populations and Clinical Settings

The patient populations across the included studies were heterogeneous, spanning various clinical settings and demographics. The total sample size in individual studies ranged from 32 to 88,314 patients. Age was a common characteristic reported, with studies including exclusively elderly patients (≥65 years) as well as broad adult populations with mean or median ages typically in the 60s and 70s. Clinical settings included emergency departments,

intensive care units (ICUs), general hospital wards, and specialized units like oncology and surgical ICUs.

Severity of illness was frequently assessed using scoring systems such as the APACHE II, SOFA, Pittsburgh bacteremia score, and qSOFA. Comorbidity burden was commonly quantified using the Charlson Comorbidity Index. The proportion of patients who were immunocompromised varied, with some studies focusing on high-risk subgroups such as those with neutropenia, malignancy, or solid organ transplants. Inclusion and exclusion criteria often influenced the generalizability of findings; for instance, many studies excluded patients with polymicrobial infections or those who had received antibiotics prior to blood culture collection.

Study	Sample Size	Mean/Median Age	Clinical Setting	Severity Scores	Comorbidity Indices	Proportion Immunocompromised
Yufang Chen et al., 2020	167	51.2 years (mean)	University teaching hospital	Pittsburgh ≥2	Charlson ≥3	Neutropenia mentioned
A. Marra et al., 2006	91	Not mentioned	Not mentioned	APACHE II ≥20	Charlson ≥3	Not mentioned
Meng-Shiuan Hsu et al., 2014	87	64 years (mean)	Tertiary hospital	Pittsburgh: 2.7 (avg)	End-stage renal disease: 43%	Not mentioned
Matthias Willmann et al., 2013	74	Not mentioned	3 hospitals	SAPS II	Cardiac disease mentioned	Not mentioned
H. Palmer et al., 2013	100	≥18 years	Hospital setting (ICU admission)	Severity of illness scores used	Comorbidities included in analysis	Not mentioned
Si-Hyun Kim et al., 2013	152	≥18 years	Not mentioned	SOFA	Charlson comorbidity index	Not mentioned
R. Khatib et al., 2005	357	59 years (median)	Teaching hospital	Not mentioned	Not mentioned	Not mentioned
Daniel N Marco et al., 2025	1177 cases	Not mentioned	University hospital	Not mentioned	Various, including malignancy	Immunocompromised status, neutropenia
C. Liao et al., 2009	231	Not specified	Hospital	Pittsburgh score (higher in TTP <7h)	Liver cirrhosis, active malignancy	Active malignancy, chemotherapy
Yufang Chen et al., 2020a	167	51.2 years (mean)	University teaching hospital	Pittsburgh ≥2	Charlson ≥3	Neutropenia mentioned
Hea Sung Ok et al., 2013	67	62-71 years (median)	Academic medical center	Pitt bacteremia score	Charlson index	22.4%
P. Tsai et al., 2025	1015	Not mentioned	Not specified	Not mentioned	Not mentioned	Not mentioned

Study	Sample Size	Mean/Median Age	Clinical Setting	Severity Scores	Comorbidity Indices	Proportion Immunocompromised
P. Wacharasint et al., 2016	48 (9 GP, 32 GN, 7 fungus)	Not mentioned	Surgical ICU	Not mentioned	Not mentioned	Not mentioned
Qing Zhang et al., 2021	509	61 years (median)	Medical center	ARDS, Fever ≥ 39 ℃	Solid tumors	Malignancy-related
Qing Zhang et al., 2020	509	Not mentioned	Single center	ARDS mentioned	Cancer, metastasis	Cancer patients
H. Bae et al., 2021	803	67.0 years (median)	Emergency department	SOFA score	Malignancy, liver cirrhosis	Mentioned as potential confounder
I. Comba et al., 2022	186	63.6 years (mean)	Single healthcare system	Not mentioned	History of myocardial infarction	Not mentioned

Causative Organisms and Infection Sources

The studies encompassed a wide range of bacterial pathogens, with a clear focus on both gram-positive and gram-negative organisms. *Staphylococcus aureus* was a primary focus in many studies, often with specific analysis of methicillin-resistant (*S. aureus*, MRSA) versus methicillin-susceptible (*S. aureus*, MSSA) isolates. For instance, one study on persistent *S. aureus* bacteremia reported that 55% of infections were caused by MRSA. Another large cohort found MRSA in 22.4% of cases. Other frequently studied gram-positive organisms included coagulase-negative staphylococci (CoNS), *Enterococcus* species, and various streptococci such as *S. pneumoniae*, *S. pyogenes*, and *S. dysgalactiae*.

Among gram-negative bacteria, *Escherichia coli* was the most commonly investigated pathogen, often accounting for a large proportion of bacteremia episodes in general cohorts. Other significant gram-negative pathogens included *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and broader groups of Enterobacterales.

The sources of infection were diverse. Catheter-related bloodstream infections (CRBSI) were a major focus, particularly for *S. aureus* and *Candida* species, with source control (i.e., catheter removal) being a critical variable. Endovascular sources, especially infective endocarditis (IE), were frequently associated with *S. aureus* bacteremia and shorter TTP. Other common infection sources included urinary tract, pulmonary, intra-abdominal, and primary bacteremia where no specific source was identified. Studies often stratified analyses by these sources to assess their impact on the predictive value of TTP.

Study	Organism Types and Proportions	Resistance Patterns	Primary Infection Sources	Source Control Status
Yufang Chen et al., 2020	*E. coli* (100%)	Not specified	Community or nosocomial origin	Not mentioned
A. Marra et al., 2006	*S. aureus* (100%)	MRSA mentioned as significant	Central venous catheter common with short TTP	Not mentioned

Study	Organism Types and Proportions	Resistance Patterns	Primary Infection Sources	Source Control Status
Meng-Shiuan Hsu et al., 2014	*S. aureus* (MRSA 55%)	MRSA (55%)	Catheter-related (31%), Infective endocarditis (18%)	Not mentioned
Matthias Willmann et al., 2013	*P. aeruginosa* (100%)	Not specified	Not mentioned	Not mentioned
H. Palmer et al., 2013	Gram-negative bacilli (100%)	Extended-spectrum beta-lactamase (ESBL) mentioned	Not mentioned	Not mentioned
R. Khatib et al., 2005	*S. aureus* (100%)	Not specified	Endovascular source common	Not mentioned
Daniel N Marco et al., 2025	*P. aeruginosa* (100%)	Carbapenem-resistance mentioned as a factor	Catheter-related (33.3%)	Catheter removal within 48h considered adequate
C. Liao et al., 2009	*K. pneumoniae* (100%)	Not specified	Primary bacteremia common with short TTP	Not mentioned
Yufang Chen et al., 2020a	*E. coli* (100%)	ESBL production (31.7%)	Biliary (32.3%), urinary (28.1%), abdominal (9.0%)	Not mentioned
Hea Sung Ok et al., 2013	MRSA (100%)	100% MRSA	Catheter-related (48.4%), metastatic infection (58.1%)	Delayed catheter removal associated with persistence
F. Hamilton et al., 2021	Coagulase-negative staphylococci (31%), *E. coli* (25%)	Not specified	Not mentioned	Not mentioned
M. Rolo et al., 2022	*P. aeruginosa* (100%)	MDR/XDR phenotype associated with mortality	Respiratory source mentioned	Not mentioned
S. Siméon et al., 2019	*S. aureus* (100%)	Methicillin resistance mentioned as a factor	Infective endocarditis (7.2%)	Not mentioned

TTP Measurement and Analysis Approaches

The definition and measurement of TTP were largely consistent across the studies, defined as the time from the start of blood culture incubation in an automated system to the detection of a positive signal indicating microbial growth. Commonly used automated systems included BACTEC (Becton Dickinson) and BacT/ALERT (bioMérieux). Some studies highlighted potential confounders in TTP measurement, such as the volume of blood drawn, time lag between collection and incubation, and prior antimicrobial therapy. One study specifically investigated modified TTP (mTTP), which included transportation time, finding it superior to TTP alone in predicting mortality.

Reported TTP values varied significantly by organism. Gram-negative bacteria, particularly *E. coli* and *K. pneumoniae*, generally had shorter median TTPs, often around 8-13 hours. *S. aureus* typically exhibited longer median TTPs, in the range of 13-16 hours. Fungal pathogens like *Candida* species showed the longest TTPs, with medians often exceeding 24 hours.

Analytical approaches for TTP were diverse. Many studies dichotomized TTP using a specific cutoff value to create "short" versus "prolonged" TTP groups. These cutoffs were determined using methods like receiver-operating characteristic (ROC) curve analysis to find an optimal threshold for predicting an outcome like septic shock or mortality. Cutoff values varied considerably, ranging from <7 hours for *K. pneumoniae* and *E. coli*, to ≤12 hours for *S. aureus*, and ≤16 hours for *P. aeruginosa*. Other studies treated TTP as a continuous variable, assessing the change in risk for each one-hour increment or decrement in TTP. A few studies explored more complex measurements, such as the ratio of TTP from a second (sequential) blood culture to the first, finding a ratio of <1.5 to be a predictor of poor outcomes in persistent *S. aureus* bacteremia.

Study	Blood Culture System	TTP Definition	Reported TTP Values (median, IQR/range)	Analysis Approach	Cutoff Values Used
Yufang Chen et al., 2020	BACTEC 9120	Time from start of incubation to alert signal	12.5 h (9.1-18.1 h)	Dichotomized (early vs late)	≤11 h
A. Marra et al., 2006	Automated system	Time from start of incubation to alert signal	Not mentioned	Dichotomized	≤12 h
Meng-Shiuan Hsu et al., 2014	Not specified	Time to positivity of blood cultures	Not mentioned	Ratio of sequential TTPs	TTP ratio <1.5; 2nd culture positive within 12 h
Matthias Willmann et al., 2013	Automated system	Time from start of incubation to alert signal	Not mentioned	Dichotomized (Cox regression)	≤18 h
H. Palmer et al., 2013	Automated system	Time from start of incubation to bacterial growth detection	11.4 h (lactose-fermenters) vs 17.9 h (non-lactose fermenters)	Continuous (per-hour increment)	<11 h also analyzed
Si-Hyun Kim et al., 2013	Not specified	Time to positivity of blood cultures	27 h (19-37 h)	Dichotomized	≤24 h
R. Khatib et al., 2005	Continuously monitored system	Time from incubation initiation to growth detection	15.5 h (4.2-98.2 h)	Dichotomized (Logistic regression)	≤14 h

Study	Blood Culture System	TTP Definition	Reported TTP Values (median, IQR/range)	Analysis Approach	Cutoff Values Used
Daniel N Marco et al., 2025	Automated system	Time from incubation start to growth detection	15 h (11.2-18 h)	Dichotomized and continuous	<13 h, <14 h, <16 h
C. Liao et al., 2009	Not specified	Time to positivity of blood cultures	Not mentioned	Dichotomized	<7 h
Yufang Chen et al., 2020a	BACTEC 9120	Time from incubation start to alert signal	12.5 h (1.5-78.6 h)	Dichotomized	≤11 h
Hea Sung Ok et al., 2013	BacT ALERT 3D	Time from start of incubation to growth detection	14 h (10.0-22.5 h) for persistent; 18.5 h (12.6-32.2) for nonpersistent	Dichotomized	≤11.8 h
Ya-Chu Hsieh et al., 2022	Not specified	Time from incubation start to growth detection	Median cutoff for analysis: 12 h	Dichotomized (meta-analysis)	Varies by study (median 12h)
M. Rolo et al., 2022	Automated system	Time from start of incubation to growth detection	15 h (12-18 h)	Dichotomized	≤16 h
S. Siméon et al., 2019	Automated system	Time from start of incubation to growth detection	13.7 h (9.9-18 h)	Dichotomized by quartiles	≤13.7 h; <10 h; ≥18 h

Antibiotic Treatment Factors

Several studies investigated how antibiotic therapy variables could confound the relationship between TTP and patient outcomes. A key factor was the appropriateness of empirical therapy, defined as the administration of an antibiotic to which the identified pathogen was susceptible in vitro. Inappropriate empirical therapy was identified as an independent predictor of mortality and treatment failure in several analyses. For instance, mortality was significantly higher among patients with gram-negative bacteremia who received inadequate empirical therapy (56% vs. 14%).

The timing of appropriate therapy was also crucial. Delays in initiating effective treatment were associated with worse outcomes. One study on KPC-producing *Klebsiella pneumoniae* bacteremia found that each 24-hour delay in appropriate therapy increased the hazard of 30-day mortality. Another study noted a significantly longer time to appropriate antibiotics in non-survivors compared to survivors of intra-abdominal sepsis with bacteremia (23 hours vs. 4 hours). Conversely, early administration of appropriate therapy was associated with better prognosis.

Studies that provided details on specific antibiotic regimens often focused on challenging pathogens. For MRSA bacteremia, treatment frequently involved vancomycin or daptomycin. One study found that vancomycin treatment was a risk factor for persistent S. aureus bacteremia. For multi-drug resistant gram-negative infections, combination therapies or newer agents like ceftazidime-avibactam were examined. Treatment duration was less frequently analyzed but was noted as a factor in some studies of S. aureus bacteremia. Few studies reported on whether TTP values directly influenced therapy modifications, though the rapid availability of TTP was suggested as a tool to guide clinical decisions, such as antimicrobial de-escalation. Treatment decisions appeared to be a mix of protocol-driven approaches, particularly in ICUs or under antimicrobial stewardship programs, and individualized clinical judgment.

Persistent Bacteremia and Microbiological Clearance

TTP has been investigated as a predictor of microbiological outcomes, including persistent bacteremia and clearance. Persistent bacteremia, commonly defined as positive follow-up blood cultures (FUBCs) at 48 to 72 hours despite appropriate antibiotic therapy, was a primary outcome in several studies. A shorter TTP of the initial blood culture was associated with an increased risk of persistent bacteremia in patients with MRSA. In one study, patients with a TTP of <11.8 hours were more likely to develop persistent MRSA bacteremia. In another analysis of *S. aureus* bacteremia, a TTP of ≤14 hours was an independent predictor of extended bacteremia duration (≥3 days).

Sequential TTP measurements have also provided prognostic insights. For patients with persistent *S. aureus* bacteremia, a ratio of the second TTP to the first TTP of <1.5 was found to be an independent risk factor for mortality, suggesting it signals a failure to reduce the bacterial load despite treatment. Another study on persistent *S. aureus* bacteremia found that a decrease in the TTP of follow-up cultures after primary therapeutic intervention was associated with a higher frequency of 30-day mortality or development of secondary infection foci. A study using a culture-independent system found that the duration of detectable pathogen DNA was significantly longer than blood culture clearance and that each additional day of detection increased the odds of persistent infection for both *S. aureus* and gram-negative bacteremia.

Study	Outcome Definition	TTP Exposure Measure	Effect Estimate (OR/HR)	95% CI	p-value	Adjustment Variables
R. Khatib et al., 2005	Extended bacteremia (≥3 days)	TTP ≤14 h	Not Reported	Not Reported	<0.0005	Logistic regression model
Meng-Shiuan Hsu et al., 2014	Mortality in persistent SAB	Ratio of 2nd TTP/1st TTP <1.5	0.2	0.07-0.6	0.004	Pittsburgh score
Hea Sung Ok et al., 2013	Persistent MRSA bacteremia (≥7 days)	TTP <11.8 h	Not Reported	Not Reported	0.029	Univariate analysis
S. Choi et al., 2012	30-day mortality or secondary foci in persistent SAB	Decrease in TTP of follow-up cultures	Not Reported	Not Reported	0.005	Univariate (Fisher's exact test)

Study	Outcome Definition	TTP Exposure Measure	Effect Estimate (OR/HR)	95% CI	p-value	Adjustment Variables
E. Minejima et al., 2019	Each continued day of bacteremia	Duration of bacteremia (days)	RR 1.16	1.10-1.22	<0.0001	ROC analysis
Matthaios Papadimitriou-Olivgeris et al., 2023	28-day mortality	Persistent bacteremia (≥48 h)	1.85	1.22-2.81	0.004	Charlson Comorbidity Index, nosocomial bacteremia, TTP≤13h, sepsis, source

Relapse and Recurrence

A few studies examined the role of TTP in predicting the relapse or recurrence of bacteremia after initial treatment and clearance. Relapse is typically defined as a recurrent positive blood culture with the same organism within a 30 to 90-day period. In a study of *S. aureus* bacteremia, 23.1% of survivors experienced a relapse, with most recurrences happening within 90 days of completing therapy. The study found that duration of bacteremia, rather than TTP directly, was a predictor of relapse. Another study evaluating patients with gram-positive bacteremia also assessed 30-day recurrence as part of a composite failure outcome but did not specifically link it to TTP values. In the context of persistent *S. aureus* bacteremia, patients with persistent infections had a significantly higher rate of relapse within 12 weeks compared to those with resolving bacteremia (9.2% vs. 2.4%). This suggests that factors associated with persistent bacteremia, which may include a short initial TTP, could indirectly predict the risk of future recurrence. However, direct evidence linking initial TTP values to the risk of relapse or recurrence is limited in the included literature.

Mortality Outcomes

The association between TTP and all-cause mortality was a key outcome in a majority of the included studies. Mortality was assessed at various time points, most commonly in-hospital, 28-day, or 30-day mortality. A consistent finding across numerous studies was that a shorter TTP, whether analyzed as a continuous variable or using a dichotomized cutoff, is an independent predictor of increased mortality.

For example, studies on *E. coli* bacteremia found that a TTP of ≤11 hours was associated with an adjusted odds ratio (aOR) for in-hospital mortality of 3.80, while a TTP of ≤7 hours yielded an aOR of 4.886. In *P. aeruginosa* bacteremia, a TTP of ≤18 hours was associated with a hazard ratio (HR) of 3.83 for in-hospital mortality, and another study found a TTP ≤16 hours had an aOR of 2.27 for 30-day mortality. Similarly, for *S. aureus* bacteremia, a TTP of ≤12 hours was an independent predictor of hospital mortality (aOR 6.9), and a TTP of ≤13.7 hours was linked to 30-day mortality. A large population-based study found that a TTP in the first quartile (≤10 hours) was associated with an increased risk for 30-day death (OR 1.43) across a wide range of gram-positive and gram-negative organisms.

However, this association was not universal. One large prospective study found no relationship between TTP and

28-day mortality for most organisms, with the exception of *Candida* spp. (where longer TTP was associated with worse outcomes) and possibly streptococci. Another study of septic shock patients found TTP was not significantly different between 28-day survivors and non-survivors overall, although pathogen-specific subgroup analyses for *E. coli* and *Klebsiella* did show prognostic value. Some studies reported a U-shaped or complex relationship, where both very short and very long TTPs were associated with increased mortality. These discrepancies highlight the importance of considering the specific pathogen, patient population, and clinical context.

Study	Mortality Timepoint	TTP Measure	Unadjusted Effect Estimate	Adjusted Effect Estimate (OR/HR)	95% CI	Covariates in Adjusted Model
Yufang Chen et al., 2020	In-hospital	TTP ≤11 h	17.7% vs 4.0% mortality	3.80	1.04–12.90	ICU admission, Pittsburgh score ≥2, Charlson Index ≥3
A. Marra et al., 2006	Hospital	TTP ≤12 h	Univariate association with death	6.9	1.07-44.66	Charlson score ≥3, infection with MRSA
C. Liao et al., 2009	30-day	TTP <7 h	47.8% vs 21.1% mortality	2.46	1.20-5.05	Pittsburgh bacteremia score, active malignancy
Matthias Willmann et al., 2013	In-hospital	TTP ≤18 h	Not Reported	3.83	Not Reported	SAPS II score, cardiac disease, appropriate definitive antimicrobial treatment
H. Palmer et al., 2013	In-hospital	Per-hour decrease	23.1% vs 8.3% for TTP <11h	1.10	1.00-1.21	Severity of illness, ESBL-producing GNB, ICU admission
M. Rolo et al., 2022	30-day	TTP ≤16 h	41.0% vs 19.5% mortality	2.27	2.12-4.25	Neutropenia, septic shock, respiratory source, nosocomial acquisition, MDR/XDR phenotype

Study	Mortality Timepoint	TTP Measure	Unadjusted Effect Estimate	Adjusted Effect Estimate (OR/HR)	95% CI	Covariates in Adjusted Model
Kevin B. Laupland et al., 2024	30-day	TTP ≤10 h (first quartile)	14.6% mortality in Q1	1.43	1.35-1.50	Age, sex, onset, comorbidity, focus of infection
S. Siméon et al., 2019	30-day	TTP ≤13.7 h	25.1% vs 16.1% mortality	Not Reported	Not Reported	Age, McCabe score, methicillin resistance, stroke, pneumonia, CRP
Shi-ning Bo et al., 2011	Hospital	TTP ≤7 h	43.3% vs 11.9% mortality	4.886	2.572-9.283	Neutropenia, comedication of steroids or immunosup-pressive agents
G. Peralta et al., 2007	In-hospital	Short TTP	Not Reported	3.13	1.28-7.64	Haematological illness, Charlson score ≥3, non-urinary source, severe sepsis/shock
Matthaios Papadimitriou-Olivgeris et al., 2023	28-day	TTP ≤13 h	Not Reported	1.85	1.22-2.81	Charlson index, nosocomial bacteremia, persistent bacteremia, sepsis, source, ID consultation

Organism-Specific and Subgroup Analyses

The predictive value of TTP frequently varied depending on the causative organism. Subgroup analyses across studies consistently demonstrated these differences. For gram-negative organisms like *E. coli* and *Klebsiella*, shorter TTPs were strongly associated with worse outcomes. In one study of septic shock patients, TTP was only predictive

of mortality in the subgroups with *E. coli* or *Klebsiella* bacteremia, with optimal cutoffs of 10 and 8 hours respectively, but not for the overall bacteremic cohort. For *P. aeruginosa*, multiple studies confirmed that shorter TTP values (e.g., ≤13h, ≤16h, or ≤18h) were independent predictors of mortality. One study also found that lactose-fermenting gram-negative bacilli had a significantly shorter mean TTP than non-lactose fermenters.

Among gram-positive organisms, the findings were more complex. For *S. aureus*, many studies found a shorter TTP (e.g., <12h or <14h) predicted higher mortality and complications like endocarditis. Some analyses suggested TTP was shorter for MSSA compared to MRSA, though this was not a consistent finding. However, other studies reported a "U-shaped" relationship, where both very short and very long TTPs (>48h) were associated with increased 30-day mortality. One large trial analysis found no association between TTP and mortality for *S. aureus* or coagulase-negative staphylococci. For streptococci, findings were also mixed, with some associating shorter TTP with mortality in *S. pyogenes* and *S. dysgalactiae* bacteremia, while another study found no such association for non-β-hemolytic streptococci.

Analyses also stratified by infection source and patient characteristics. In *P. aeruginosa* BSI, the prognostic implication of TTP differed between catheter-related and non-catheter-related sources, with different optimal cutoff values for predicting mortality. For *S. aureus*, TTP was significantly shorter in patients with an endovascular source of infection, such as endocarditis or catheter-related infection[p69_q2]. The predictive value of TTP was also shown to be relevant in specific high-risk populations, such as patients with solid tumors and *E. coli* bacteremia, where a TTP of ≤8 hours was a significant risk factor for mortality.

Synthesis of Evidence

The collective evidence from the included studies largely supports the hypothesis that a shorter Time to Positivity (TTP) of blood cultures is a significant predictor of antibiotic failure and adverse outcomes, including persistent bacteremia, septic shock, and mortality, in patients with bloodstream infections. This relationship holds across a variety of gram-positive and gram-negative organisms, although the specific TTP thresholds and the strength of the association vary by pathogen, infection source, and patient population. The underlying principle is that a shorter TTP serves as a surrogate marker for a higher circulating bacterial load, which in turn correlates with greater disease severity and a higher likelihood of treatment failure.

For gram-negative bacteremia, particularly due to Enterobacterales like *E. coli* and *K. pneumoniae*, there is consistent evidence that shorter TTPs (often in the range of <7 to <12 hours) are independently associated with increased mortality and septic shock. The association appears robust even after adjusting for multiple clinical confounders such as severity of illness scores and comorbidities. This finding extends to more resistant pathogens like *P. aeruginosa*, where shorter TTPs (e.g., ≤13-18 hours) also predict higher mortality.

In the context of gram-positive bacteremia, specifically with *S. aureus*, the evidence also points toward shorter TTPs (e.g., ≤12-14 hours) being predictive of worse outcomes, including mortality, metastatic infection, and endocarditis. Furthermore, TTP has been shown to predict microbiological outcomes such as persistent bacteremia, where a shorter initial TTP or a non-increasing TTP ratio in sequential cultures indicates a failure of antimicrobial therapy to control the infection. However, the evidence for *S. aureus* is somewhat more heterogeneous, with some studies reporting a U-shaped association where very long TTPs also confer increased risk, potentially reflecting different host-pathogen dynamics or confounding by prior antibiotic use. One large study notably found no overall association between TTP and mortality for staphylococci, suggesting that the clinical context, such as the severity of illness at presentation, may modulate TTP's predictive power. For example, in a cohort of patients with severe sepsis, TTP was not independently associated with mortality, suggesting its prognostic value may be diminished in patients who are already critically ill at baseline.

The optimal TTP cutoff for risk stratification is not uniform and appears to be pathogen-dependent. Generally, cutoffs are shorter for gram-negative rods (e.g., 7-12 hours) than for *S. aureus* (12-14 hours) or *Candida* species (often >24 hours). This variability underscores the need for organism-specific interpretation of TTP values. Clinically, these findings suggest that TTP, a readily available parameter from automated blood culture systems, can serve as an early and valuable prognostic tool. A short TTP may identify high-risk patients who could benefit from more aggressive management, including rapid source control, broader empirical antibiotic coverage, and more intensive monitoring.

Limitations and Research Gaps

The body of evidence, while substantial, has several limitations at both the study and review levels. A primary limitation is the predominance of retrospective, single-center study designs, which are susceptible to selection bias and limited generalizability. Heterogeneity across studies is a major challenge, arising from multiple sources. First, TTP measurement is not standardized; variables such as blood volume drawn, prior antibiotic exposure, and the delay between blood collection and incubator loading (transport time) can significantly influence TTP values but are often inadequately reported or controlled for. One study demonstrated that incorporating transport time into a "modified TTP" improved prognostic accuracy, highlighting this gap.

Second, the selection of TTP cutoffs is inconsistent, varying widely between studies even for the same organism, which makes cross-study comparisons and the definition of a universal "short" TTP difficult. Third, outcome definitions, particularly for "treatment failure," are not uniform, and the timing of mortality assessment (e.g., in-hospital, 28-day, 30-day) varies. Finally, inadequate adjustment for critical confounders is a common issue. Key variables such as the time to initiation of appropriate antibiotic therapy and the adequacy of source control, both powerful determinants of outcome, were not consistently included in multivariable models across all studies. This confounding by indication is particularly relevant, as sicker patients may receive earlier and broader antibiotic coverage, which could obscure the true effect of TTP.

Several research gaps emerge from these limitations. There is a need for large, prospective, multi-center studies that employ standardized protocols for blood culture collection and processing to minimize pre-analytical variability in TTP measurement. Future research should focus on validating organism-specific TTP cutoffs and exploring their utility in different clinical settings (e.g., community vs. hospital-acquired infections, ICU vs. ward). The prognostic value of TTP in bacteremia caused by less common but clinically important pathogens, including anaerobic bacteria and specific multidrug-resistant organisms, remains under-studied. Additionally, while sequential TTP measurements show promise for monitoring therapeutic response, more research is needed to define their role in guiding treatment duration and decisions to escalate or de-escalate therapy. Finally, prospective interventional trials are required to determine whether clinical pathways that incorporate TTP for risk stratification and treatment guidance can lead to improved patient outcomes.

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