

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 Analytical Approach (for protocol) Bayesian hierarchical meta-regression Weakly informative priors informed by microbiological plausibility Heterogeneity assessed via τ^2 and prediction intervals

A shorter time to positivity (TTP) of blood cultures is a strong and independent predictor of antibiotic failure, manifested as persistent bacteremia and increased mortality, although its predictive strength is moderated by the specific pathogen and clinical context.

Abstract

A substantial body of evidence indicates that a shorter time to positivity (TTP) of blood cultures is an independent predictor of adverse outcomes in adults with bloodstream infections. For both Gram-positive organisms like *Staphylococcus aureus* and Gram-negative organisms such as *Escherichia coli* and *Pseudomonas aeruginosa*, a shorter TTP is consistently associated with a higher risk of persistent bacteremia and increased in-hospital or 30-day mortality. Effect sizes vary, but multivariable analyses frequently confirm TTP's prognostic value after adjusting for patient severity and comorbidities. Some studies have successfully incorporated TTP into clinical prediction models with good discrimination for mortality.

However, significant heterogeneity exists across the literature, limiting the universal application of specific TTP cutoffs. The definition of a "short" TTP is inconsistent, ranging from <7 to ≤18 hours depending on the pathogen. Furthermore, a few studies report non-linear or conflicting associations, such as a U-shaped mortality risk for *S. aureus* bacteremia where both very short and very long TTPs are detrimental. In some critically ill populations, TTP was not found to be a significant predictor of mortality. The evidence linking TTP directly to relapse or recurrence is less developed. Overall, while shorter TTP is a strong indicator of a higher bacterial load and poorer prognosis, its precise clinical utility is moderated by pathogen type, infection source, and patient acuity.

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: "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

Analytical Approach (for protocol)

Bayesian hierarchical meta-regression Weakly informative priors informed by microbiological plausibility Heterogeneity assessed via τ^2 and prediction intervals"

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:** Does the study include adults (≥ 18 years) with documented bloodstream infection?
- **Blood Culture and TTP Data:** Does the study confirm bacteremia by positive blood culture AND report time-to-positivity (TTP) data (either quantitative measurements or clear dichotomized TTP categories)?
- **Relevant Outcomes:** Does the study report at least one of the following outcomes: persistent bacteremia, relapse/recurrence, microbiological clearance, or mortality?
- **Antibiotic Treatment Definition:** Does the study provide a clear definition of antibiotic appropriateness or treatment protocols?
- **True Bloodstream Infection:** Does the study focus on clinically significant bloodstream infections (rather than contaminated blood cultures or skin commensals without clinical significance)?
- **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)?
- **Bacterial Infection Focus:** Does the study focus on bacterial (gram-positive and/or gram-negative) bloodstream infections rather than exclusively fungal infections?
- **Data Extractability:** Can TTP data be extracted or calculated from the study AND is antibiotic treatment status clearly documented?

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.

- **TTP Measurement:**

Extract all details about how time to positivity (TTP) was measured and categorized for predicting antibiotic failure, including:

- Exact TTP measurement method and timing
- Cutoff values used (e.g., <12h, ≤7h, >27h)
- Whether analyzed as continuous (hours) or categorical variable
- Blood culture system/methodology used
- Number of culture sets and timing of collection
- Any sequential TTP measurements or ratios

- **Antibiotic Failure Outcomes:**

Extract specific definitions and measurements of antibiotic failure outcomes relevant to TTP prediction, including:

- Persistent bacteremia (timing of follow-up cultures, definition of persistence)
- Relapse/recurrence (timeframe, definition, detection method)
- Microbiological clearance (timing, definition of clearance)
- Treatment failure (clinical or microbiological criteria)
- Mortality (timeframe: in-hospital, 30-day, 90-day)
- How each outcome was measured and at what time points
- Whether outcomes were primary or secondary endpoints

- **Study Population:**

Extract characteristics of patients with bloodstream infections relevant to TTP-antibiotic failure prediction, including:

- Organism type (Gram-positive, Gram-negative, specific species like *S. aureus*, *E. coli*)
- Infection source and whether source control was achieved
- Patient demographics and comorbidities affecting outcomes
- Severity of illness indicators (e.g., septic shock, ICU admission)
- Hospital vs. community-acquired infection
- Sample size and inclusion/exclusion criteria
- Any subgroup analyses performed

- **Predictive Association:**

Extract the statistical relationship between TTP and antibiotic failure outcomes for prediction assessment, including:

- Effect sizes (odds ratios, hazard ratios, risk ratios) with 95% confidence intervals
- Statistical significance (p-values) for TTP as predictor
- Direction of association (shorter vs. longer TTP risk)
- Predictive accuracy metrics if reported (sensitivity, specificity, AUC, positive/negative predictive values)
- Whether TTP was an independent predictor in multivariable analysis

- Comparison of different TTP cutoffs for prediction

- **Antibiotic Treatment:**

Extract antibiotic treatment details that affect interpretation of TTP-failure relationships, including:

- Definition of 'appropriate therapy' used in the study
- Timing of antibiotic initiation relative to blood culture
- Specific antibiotics used and dosing adequacy
- Duration of treatment
- Whether treatment was guided by susceptibility results
- Any treatment modifications based on TTP or clinical response
- Source control procedures and timing

- **Analysis Method:**

Extract analytical approach used to assess TTP as predictor of antibiotic failure, including:

- Type of analysis (logistic regression, Cox proportional hazards, survival analysis)
- Variables included in multivariable models
- How confounding was addressed
- Sample size calculations or power analysis
- Handling of missing data
- Subgroup or sensitivity analyses performed
- Whether prediction models were developed or validated

- **Study Design:**

Extract study design features relevant to assessing TTP as prognostic factor, including:

- Study type (prospective cohort, retrospective cohort, case-control)
- Study setting (single-center, multi-center, population-based)
- Time period and duration of study
- Follow-up duration and completeness
- Blinding of outcome assessors to TTP
- Whether TTP was measured in real-time or retrospectively
- Risk of bias considerations specific to prognostic studies

Study Characteristics and Design Quality

The included studies examining time to positivity (TTP) as a predictor of antibiotic failure in bloodstream infections consist predominantly of retrospective cohort designs, with a smaller number of prospective cohort studies. Settings were varied, including single-center, multi-center, and population-based cohorts. Study durations ranged from a few months to over a decade. Sample sizes varied widely, from under 100 patients to large population-based studies with tens of thousands of participants. Follow-up durations were most commonly 30 days, although periods such as 28 days, 90 days, and in-hospital mortality were also used. No studies explicitly mentioned blinding of outcome assessors to TTP values, except for one which specified blinding of outcome assessors and data analysts. Methodological quality is subject to the inherent limitations of observational research, primarily confounding by indication and selection bias, although some studies attempted to mitigate this through multivariable adjustment and propensity score methods.

| Study | Full text retrieved? | Study Type | Setting | Time Period | Sample Size | Follow-up Duration |
|-----------------------------------|----------------------|---|------------------|----------------|------------------|----------------------------|
| A. Bläckberg et al. (2022) | Yes | Retrospective observational cohort study | Population-based | 2015-2018 | 286 | At least 30 days |
| A. Bläckberg et al. (2023) | Yes | Retrospective cohort | Population-based | 2015-2018 | 287 | 30 days |
| A. Marra et al. (2006) | Yes | Retrospective cohort study | Not specified | Not specified | 91 | Not specified |
| A. Nelson et al. (2017) | Yes | Retrospective cohort | Single-center | 2010-2013 | 411 | Not mentioned |
| A. Peri et al. (2023) | Yes | Prospective observational study | Multicenter | Not specified | 102 | 4 days |
| A. Sastry et al. (2024) | Yes | Retrospective cohort | Single-center | 4-year period | 38,606 samples | Not mentioned |
| A. T. Aslan et al. (2024) | Yes | Prospective cohort | Multi-center | 2021-2022 | 378 | Not mentioned |
| A. Turjeman et al. (2022) | Yes | Individual participant data meta-analysis of RCTs | Multi-center | Up to May 2022 | 1186 | At least 90 days |
| Achim J. Kaasch et al. (2013) | Yes | Prospective observational study | Multi-center | Not specified | 256 | 3 months |
| Arianna Di Marcello et al. (2025) | Yes | Prospective, pre-post interventional study | Single-center | 2022-2023 | 446 BSI episodes | Not mentioned |
| C. Cillóniz et al. (2017) | Yes | Prospective observational study | Single-center | 2003-2015 | 278 | 30-40 days after discharge |
| C. Fang et al. (2006) | Yes | Retrospective cohort | Single-center | 1997-2001 | 162 | Up to 3 years |
| C. Forstner et al. (2013) | Yes | Retrospective cohort study | Single-center | 2000-2011 | 124 | At least 28 days |
| C. Kang et al. (2004) | Yes | Retrospective cohort | Not mentioned | Not mentioned | 286 | 30-day mortality |
| C. Liao et al. (2009) | Yes | Prospective cohort study | Single-center | 2007 | 231 | At least 30 days |
| Chih-Cheng Lai et al. (2011) | Yes | Retrospective cohort | Single-center | 2015 | 80 | Not mentioned |
| Chih-Chi Lee et al. (2017) | Yes | Retrospective cohort study | Single-center | 2008-2013 | 2349 | 28 days |

| Study | Full text retrieved? | Study Type | Setting | Time Period | Sample Size | Follow-up Duration |
|---------------------------------|----------------------|---|---------------|---------------|-------------|--------------------------|
| Chih-Chi Lee et al. (2019) | Yes | Retrospective cohort study | Multi-center | 2010-2015 | 1247 | Not mentioned |
| Chih-Chi Lee et al. (2021) | Yes | Cohort study | Multicenter | 4 years | 2357 | At least 30 days |
| Chih-Ping Chen et al. (2023) | Yes | Retrospective observational, case-control study | Single-center | 2016-2021 | 101 | At least 30 days |
| Ching-Chi Lee et al. (2021) | Yes | Cohort study | Multicenter | 4 years | 2357 | At least 30 days |
| Christelle Kassis et al. (2009) | Yes | Retrospective cohort | Single-center | 2005-2008 | 272 | Not mentioned |
| Daniel Gao et al. (2023) | Yes | Case-control | Single-center | 2014-2018 | 598 | Not specified |
| Daniel N Marco et al. (2025) | Yes | Retrospective cohort study | Single-center | 1991-2019 | 1177 | 30 days |
| David Zhang et al. (2015) | Yes | Retrospective cohort | Single-center | 2008-2012 | 1058 | Not mentioned |
| E. Maillart et al. (2012) | Yes | Retrospective cohort study | Single-center | 2007-2010 | 167 | Not detailed |
| E. Minejima et al. (2015) | Yes | Prospective observational study | Multi-center | 2012-2014 | 196 | At least 30 days |
| E. Minejima et al. (2019) | Yes | Prospective observational cohort | Multi-center | 2012-2017 | 884 | At least 30 days |
| E. von Dach et al. (2020) | Yes | Prospective cohort, randomized clinical trial | Multi-center | 2017-2019 | 504 | 90 days |
| E. Zasowski et al. (2016) | Yes | Retrospective cohort study | Single-center | 2010-2014 | 190 | 30 days |
| Emily Fox et al. (2022) | Yes | Retrospective case-control study | Single-center | 2016-2020 | 108 | Not explicitly mentioned |
| Evan J Zasowski et al. (2020) | Yes | Systematic review | Multi-study | Post-2007 | 145 studies | Not mentioned |
| F. Hamilton et al. (2021) | Yes | Prospective cohort | Multi-center | Not mentioned | 3462 | Not mentioned |

| Study | Full text retrieved? | Study Type | Setting | Time Period | Sample Size | Follow-up Duration |
|-----------------------------------|----------------------|----------------------------|--------------------------------------|---------------|------------------|-----------------------------------|
| Felicity Edwards et al. (2025) | Yes | Retrospective cohort | Population-based | 2000-2019 | 84,341 | Not mentioned |
| G. Martín-Gutiérrez et al. (2017) | Yes | Retrospective cohort study | Not specified | Not specified | 361 BSI episodes | Not specified |
| G. Peralta et al. (2006) | Yes | Retrospective cohort | Single-center | 1995-2004 | 105 | Limited by hospital records |
| G. Peralta et al. (2007) | Yes | Retrospective cohort | Single-center | 1997-2005 | 459 | Not mentioned |
| Gavin Deas et al. (2025) | Yes | Retrospective cohort study | Multi-center | 2017-2024 | 810 | Not mentioned |
| H. Bae et al. (2021) | Yes | Retrospective cohort study | Single-center | 2014-2018 | 2499 | 28 days |
| H. Le et al. (2014) | Yes | Retrospective cohort | Single-center | 2008-2012 | 174 | Not mentioned |
| H. Mitaka et al. (2022) | Yes | Retrospective cohort study | Multi-center | 2017-2018 | 376 | Not specified |
| H. Palmer et al. (2013) | Yes | Prospective cohort | Single-center | Not specified | 100 | Until hospital discharge or death |
| Hang-Cheng Chen et al. (2013) | Yes | Prospective cohort | Single-center | 2008-2009 | 937 | At least 30 days |
| Hea Sung Ok et al. (2013) | Yes | Prospective cohort | Single-center | 2009-2010 | 79 | Until clearance |
| Heather Savage et al. (2019) | Yes | Retrospective cohort | Single-center | 2016-2017 | 164 | Not mentioned |
| Hiroyasu Takahashi et al. (2022) | Yes | Retrospective cohort study | Single-center | 1-year period | 245 | 14 days |
| Hiroyoshi Iwata et al. (2025) | Yes | Retrospective cohort study | Multi-center | 2018-2022 | 1084 | Not mentioned |
| I. Comba et al. (2022) | Yes | Retrospective cohort | Single healthcare system, multi-site | 2019 | 186 | At least 90 days |
| I. Comba et al. (2024) | Yes | Observational study | Not specified | Not mentioned | 186 | Not mentioned |

| Study | Full text retrieved? | Study Type | Setting | Time Period | Sample Size | Follow-up Duration |
|-------------------------------------|----------------------|--|--------------------------|---------------|---------------------|---------------------|
| Ioannis Baltas et al. (2020) | Yes | Retrospective cohort study | Single-center | 2017-2019 | 789 | 30 days |
| J. Martinez et al. (2006) | Yes | Prospective cohort | Single-center | 1 year | 185 | Not mentioned |
| J. Martínez et al. (2007) | Yes | Retrospective cohort | Single-center | 2 years | 1872 | Not mentioned |
| Jasanjeet Jawanda et al. (2023) | Yes | Before-and-after observational study | Single-center | 2021 | 154 | At least 30 days |
| Jasper Van Heuverswyn et al. (2022) | Yes | Retrospective cohort study | Single-center | 2012-2019 | 10,628 BSI episodes | Up to 30 days |
| Javier López et al. (2013) | Yes | Retrospective cohort | Not explicitly mentioned | 1996-2011 | 407 | Not mentioned |
| Joe Pardo et al. (2014) | Yes | Retrospective cohort | Single-center | 2011 | 626 | Not mentioned |
| Joseph Kim et al. (2010) | Yes | Retrospective cohort | Population-based | 2006-2008 | 684 | At least 30 days |
| Jun Shinohara et al. (2022) | Yes | Systematic review and meta-analysis of retrospective studies | Not mentioned | Not mentioned | 7778 | Not mentioned |
| K. Buell et al. (2020) | Yes | Retrospective cohort | Multi-center | Not mentioned | 15,802 | Not mentioned |
| K. Buell et al. (2020a) | Yes | Retrospective cohort | Multi-center | Not mentioned | 15,802 | Not mentioned |
| K. Ishikawa et al. (2025) | Yes | Retrospective cohort | Single-center | Not mentioned | 317 | Not mentioned |
| K. Ishikawa et al. (2025a) | Yes | Retrospective cohort | Single-center | 2015-2023 | 317 | Not mentioned |
| K. Paquette et al. (2021) | Yes | Prospective cohort | Multicenter | Not specified | 325 | 90 days |
| K. Seidl et al. (2010) | Yes | Prospective cohort | Multi-center | Not mentioned | 36 MRSA isolates | Not mentioned |
| Karl Oldberg et al. (2021) | Yes | Retrospective cohort study | Population-based | 2015-2018 | 367 episodes | Minimum of 180 days |
| Katharina Michelson et al. (2021) | Yes | Retrospective cohort | Single-center | 2014-2016 | 244 | Not mentioned |

| Study | Full text retrieved? | Study Type | Setting | Time Period | Sample Size | Follow-up Duration |
|---------------------------------|----------------------|---|-----------------------------|---------------|-----------------|---------------------------------------|
| Kelly A. Cairns et al. (2016) | Yes | Prospective randomized controlled trial | Multi-center | Not mentioned | 160 | Not mentioned |
| Kevin B. Laupland et al. (2024) | Yes | Retrospective cohort | Population-based | 2000-2019 | 88,314 | At least 30 days |
| L. Zornitzki et al. (2023) | Yes | Prospective cohort | Single-center | 2019-2023 | 155 | Not explicitly mentioned |
| Lauren Cooper et al. (2024) | Yes | Retrospective cohort | Multi-center | Not mentioned | 29,570 | Not mentioned |
| Lena Gajdos et al. (2025) | Yes | Prospective cohort | Multi-center, international | Not mentioned | 2600 | Up to 28 days |
| M. Cheng et al. (2019) | Yes | Prospective cohort | Multi-center | 2013-2018 | 325 | Not explicitly mentioned |
| M. Falcone et al. (2020) | Yes | Retrospective cohort study | Multi-center | 2015-2018 | 102 | 30 days |
| M. Fida et al. (2021) | Yes | Prospective cohort | Multi-center | Not specified | Not mentioned | Not detailed |
| M. Giannella et al. (2020) | Yes | Retrospective cohort | Single-center | 2013-2016 | 1576 | At least 30 days |
| M. Holubar et al. (2021) | Yes | Prospective observational study | Multicenter | Not mentioned | 884 | Not mentioned |
| M. Lambregts et al. (2019) | Yes | Retrospective cohort study | Single-center | 2013-2015 | 801 | Electronic medical records 30 days |
| M. Rolo et al. (2022) | Yes | Retrospective cohort | Single-center | 2013-2020 | 328 | |
| M. Spaziante et al. (2020) | Yes | Retrospective cohort | Hospital-based | 1 year | 307 | Not explicitly mentioned |
| Martin Strömdahl et al. (2024) | Yes | Retrospective cohort study | Single-center | 2011-2021 | 1703 episodes | Not mentioned |
| Matthias Willmann et al. (2013) | Yes | Retrospective cohort study | Multi-center | 2006-2012 | 74 | Not mentioned |
| Meng-Shiuan Hsu et al. (2014) | Yes | Retrospective cohort | Single-center | 5 years | 87 | Not mentioned |
| N. Deguchi et al. (2023) | Yes | Retrospective cohort | Single-center | Not mentioned | 221 (S. aureus) | Not mentioned |

| Study | Full text retrieved? | Study Type | Setting | Time Period | Sample Size | Follow-up Duration |
|---------------------------------|----------------------|------------------------------------|------------------|---------------|-----------------|-----------------------------------|
| Nicole R. Hume et al. (2022) | Yes | Retrospective cohort study | Single-center | 2014-2020 | 178 | Excluded if discharged within 48h |
| O. Lesens et al. (2004) | Yes | Prospective cohort | Multi-center | Not mentioned | 104 | Not mentioned |
| Oskar Ljungquist et al. (2025) | Yes | Retrospective cohort | Population-based | 2021-2023 | 12,585 episodes | 30 days |
| P. Krisanapan et al. (2019) | Yes | Retrospective cohort study | Single-center | 2014 | 181 | Not mentioned |
| P. Moise et al. (2010) | Yes | Prospective cohort | Multi-center | 1998-2002 | 29 | Daily until clearance |
| P. Puerta-Alcalde et al. (2019) | Yes | Prospective cohort | Multi-center | 2003-2017 | 850 episodes | Not mentioned |
| P. Simos et al. (2022) | Yes | Retrospective cohort | Single-center | Not mentioned | 106 | Not mentioned |
| P. Tsai et al. (2025) | Yes | Retrospective cohort | Not mentioned | Not mentioned | 1015 | 30-day mortality |
| Paige A. Melling et al. (2020) | Yes | Prospective cohort ancillary study | Single-center | 2015-2017 | 263 | Not mentioned |
| Qing Zhang et al. (2016) | Yes | Retrospective cohort | Single-center | 19 months | 386 episodes | Not mentioned |
| Qing Zhang et al. (2020) | Yes | Retrospective cohort study | Single-center | 2013-2018 | 509 | Not mentioned |
| Qing Zhang et al. (2021) | Yes | Retrospective cohort study | Single-center | 2013-2018 | 509 | Not mentioned |
| R. Álvarez et al. (2012) | Yes | Retrospective observational study | Single-center | Not mentioned | 226 | Not mentioned |
| R. García Fenoll et al. (2022) | Yes | Retrospective cohort study | Single-center | 2020-2021 | 95 | At least 30 days |
| R. Khatib et al. (2005) | Yes | Prospective cohort | Single-center | 2002-2003 | 357 | Not mentioned |
| R. Khatib et al. (2006) | Yes | Retrospective cohort | Not mentioned | 2002-2003 | 342 | Not mentioned |
| R. Khatib et al. (2006a) | Yes | Prospective cohort | Single-center | 2002 | 245 BSI cases | Not specified |
| R. Rosa et al. (2016) | Yes | Retrospective cohort | Single-center | 2012-2013 | 250 episodes | Not mentioned |

| Study | Full text retrieved? | Study Type | Setting | Time Period | Sample Size | Follow-up Duration |
|-------------------------------------|----------------------|---|----------------------------------|-----------------|---------------|--------------------|
| Rachel Perry et al. (2022) | Yes | Quasi-experimental study | Single-center | 2014-2021 | 296 | Not mentioned |
| Rashid Nadeem et al. (2021) | Yes | Retrospective cohort study | Single-center | 2017-2018 | 101 | Not mentioned |
| Riley Karpen et al. (2023) | Yes | Retrospective cohort | Single-center | 2018-2020 | Not specified | Not mentioned |
| Ritu Banerjee et al. (2023) | Yes | Secondary analysis of a randomized controlled clinical trial | Not mentioned | Not mentioned | 386 | Not mentioned |
| S. Choi et al. (2012) | Yes | Not mentioned | Not specified | Not specified | Not mentioned | Not specified |
| S. Siméon et al. (2019) | Yes | Prospective cohort | Multi-center | 2009-2011 | 587 | At least 30 days |
| S. Tong et al. (2020) | Yes | Prospective cohort | Multi-center or population-based | Not mentioned | 987 | Not mentioned |
| S. W. Ong et al. (2024) | Yes | Retrospective cohort | Population-based | 2017-2021 | 8807 | 2-5 days for FUBC |
| S. de la Villa et al. (2023) | Yes | Retrospective times-series study | Single-center | 2014-2021 | 109 episodes | 30 days |
| Sandra Tingsgård et al. (2023) | Yes | Emulated trial using real-world data | Multi-center | 2018-2021 | 1040 | 90 days |
| Sandhya Bhat K et al. (2022) | Yes | Cross-sectional study | Single-center | 2018 | 75 | Not mentioned |
| Santiago Grillo Perez et al. (2024) | Yes | Systematic review and meta-analysis of non-randomized studies | Not specified | Up to June 2023 | 1700 | Not specified |
| Sarah Cain et al. (2014) | Yes | Retrospective cohort | Single-center | 2011-2012 | 390 | At least 28 days |
| Sarah Cain et al. (2015) | Yes | Retrospective cohort | Single-center | 2010-2013 | 830 | Not mentioned |

| Study | Full text retrieved? | Study Type | Setting | Time Period | Sample Size | Follow-up Duration |
|---------------------------------|----------------------|---|---------------|-----------------|----------------------|--------------------|
| Shang-Yu Chen et al. (2018) | Yes | Retrospective cohort | Not mentioned | 30-month period | 206 | Not mentioned |
| Shi-ning Bo et al. (2010) | Yes | Retrospective cohort | Single-center | 2007-2009 | 112 | Not mentioned |
| Shi-ning Bo et al. (2011) | Yes | Retrospective cohort | Multi-center | 2007-2009 | 353 episodes | Not mentioned |
| Siddharth Swamy et al. (2014) | Yes | Retrospective cohort | Single-center | 2006-2013 | 178 | Not mentioned |
| Siddharth Swamy et al. (2016) | Yes | Retrospective cohort | Single-center | 2006-2013 | 178 | Not mentioned |
| Suellen Gavronski et al. (2020) | Yes | Retrospective cohort | Single-center | 2013-2018 | 5,425 blood cultures | Not mentioned |
| Susannah Jerwood et al. (2012) | Yes | Prospective cohort | Single-center | Not mentioned | 48 | Not mentioned |
| T. Bias et al. (2017) | Yes | Retrospective cohort | Single-center | 2011-2012 | 111 | Not mentioned |
| T. Dinh et al. (2015) | Yes | Retrospective cohort | Single-center | Not mentioned | 793 blood samples | Not mentioned |
| Tae-Hoon No et al. (2025) | Yes | Retrospective cohort study | Multi-center | 2018-2023 | 220 | Up to 30 days |
| V. Fowler et al. (2004) | Yes | Prospective cohort | Single-center | Not mentioned | 39 | Not mentioned |
| Weiwei Hou et al. (2023) | Yes | Retrospective cohort study | Single-center | 2016-2020 | 148 | Not mentioned |
| Y. Chong et al. (2013) | Yes | Prospective cohort with nested case-control study | Single-center | 2008-2010 | 483 | At least 12 weeks |
| Ya-Chu Hsieh et al. (2022) | Yes | Systematic review and meta-analysis | Multi-study | Up to Aug 2021 | 24 studies | Not applicable |
| Yong-Ye Yang et al. (2024) | Yes | Retrospective cohort | Single-center | 2016-2021 | 196 | Not mentioned |
| Yong-zhong Ning et al. (2016) | Yes | Retrospective cohort | Single-center | 2011-2013 | 886 isolates | Not mentioned |
| Yufang Chen et al. (2020) | Yes | Retrospective cohort study | Single-center | 2014-2016 | 167 | Not mentioned |

| Study | Full text retrieved? | Study Type | Setting | Time Period | Sample Size | Follow-up Duration |
|----------------------------|----------------------|----------------------------|------------------|---------------|-------------|--------------------|
| Yufang Chen et al. (2020a) | Yes | Retrospective cohort study | Single-center | 2014-2016 | 167 | Not specified |
| Yunwei Zheng et al. (2025) | Yes | Retrospective cohort | Population-based | 2020-2023 | 610 | At least 30 days |
| Zhanni Weber et al. (2016) | Yes | Not specified | Not specified | Not specified | 71 | Not specified |

Patient Populations and Bloodstream Infection Characteristics

The patient populations across studies were diverse, spanning adults with monomicrobial bloodstream infections from various pathogens. A significant portion of the research focused on specific organisms, including *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and various streptococcal species. Both Gram-positive and Gram-negative organisms were extensively represented.

Common sources of infection included catheter-related infections, urinary tract, intra-abdominal sites, and endovascular sources like infective endocarditis. Source control was noted as an important variable in several studies, with delayed source control being associated with worse outcomes, especially in *S. aureus* bacteremia. Patient populations were frequently elderly, and common comorbidities included malignancy, diabetes, and renal disease. Severity of illness was frequently high, with many patients experiencing septic shock or requiring ICU admission. Studies included both hospital-acquired and community-acquired infections.

| Study | Sample Size | Organism Distribution | Infection Source | Source Control | Severity Indicators |
|-------------------------------|-------------|-----------------------|--|----------------|--|
| Meng-Shiuan Hsu et al. (2014) | 87 | <i>S. aureus</i> | Catheter-related (31%), Infective Endocarditis (18%) | Not mentioned | Pittsburgh score 2.7 |
| H. Palmer et al. (2013) | 100 | Gram-negative bacilli | Not mentioned | Not mentioned | ICU admission |
| Yufang Chen et al. (2020) | 167 | <i>E. coli</i> | Not mentioned | Not mentioned | Septic shock (15.6%), ICU admission |
| Qing Zhang et al. (2020) | 509 | <i>E. coli</i> | Not mentioned | Not mentioned | Fever $\geq 39^{\circ}\text{C}$, ARDS |
| A. Marra et al. (2006) | 91 | <i>S. aureus</i> | Central venous catheter | Not mentioned | Septic shock |
| P. Tsai et al. (2025) | 1015 | Monomicrobial BSIs | Not mentioned | Not mentioned | Not mentioned |

| Study | Sample Size | Organism Distribution | Infection Source | Source Control | Severity Indicators |
|---------------------------------|---------------|-----------------------|---|------------------------------------|---|
| Martin Strömdahl et al. (2024) | 1703 episodes | <i>S. aureus</i> | Not mentioned | Not mentioned | 30-day mortality (24%), Endocarditis (9%) |
| Matthias Willmann et al. (2013) | 74 | <i>P. aeruginosa</i> | Not mentioned | Not mentioned | SAPS II score |
| M. Rolo et al. (2022) | 328 | <i>P. aeruginosa</i> | Respiratory source | Not mentioned | Septic shock |
| R. Khatib et al. (2005) | 357 patients | <i>S. aureus</i> | Endovascular source | Not mentioned | Metastatic infection (8.0%) |
| Chih-Ping Chen et al. (2023) | 101 | <i>K. pneumoniae</i> | Intra-abdominal | Not mentioned | Not mentioned |
| G. Peralta et al. (2007) | 459 | <i>E. coli</i> | Non-urinary tract or unknown | Not mentioned | Severe sepsis or shock |
| Daniel N Marco et al. (2025) | 1177 | <i>P. aeruginosa</i> | Catheter-related | Catheter removal mentioned | Not mentioned |
| Hea Sung Ok et al. (2013) | 79 | MRSA | Catheter-related, metastatic infections | Delayed catheter removal mentioned | Pitt bacteremia scores, ICU stay |

TTP Measurement Methods and Categorization

The measurement of TTP was generally defined as the time from the start of blood culture incubation to an automated alert signal. Automated blood culture systems such as BACTEC (BD) and BacT/ALERT (bioMérieux) were commonly used. Most studies required at least two sets of blood cultures.

TTP was analyzed both as a continuous variable (per-hour) and as a categorical variable based on various cutoff values. The specific cutoff values varied considerably across studies and by organism. For *E. coli*, cutoffs of $\leq 7\text{h}$, $\leq 8\text{h}$, $\leq 11\text{h}$, and 10h were used. For *S. aureus*, common cutoffs included $<12\text{h}$, $\leq 11.8\text{h}$, $\leq 12\text{h}$, $<13\text{h}$, $\leq 13.7\text{h}$, and $\leq 14\text{h}$. For *P. aeruginosa*, studies used cutoffs of $\leq 18\text{h}$ and $\leq 16\text{h}$. A few studies investigated sequential TTP measurements, using a ratio of the second TTP to the first TTP, with a ratio of <1.5 indicating a poor prognosis. The rationale for selecting cutoffs was often based on receiver-operating characteristic (ROC) curve analysis to optimize sensitivity and specificity for predicting outcomes like septic shock or mortality.

| Study | Blood Culture System | Number of Culture Sets | TTP Analyzed As | Cutoff Values Used | Rationale for Cutoffs |
|---------------------------------|------------------------|--------------------------------|----------------------------------|-----------------------------------|---|
| Meng-Shiuan Hsu et al. (2014) | Not mentioned | Not mentioned | Categorical (ratio) | Second TTP/first TTP ratio <1.5 | Not mentioned |
| Yufang Chen et al. (2020) | BACTEC 9120 | At least two sets | Continuous & Categorical | ≤11 h | ROC analysis for predicting septic shock |
| Qing Zhang et al. (2020) | Not mentioned | Not mentioned | Categorical | ≤ 8h | Not mentioned |
| A. Marra et al. (2006) | Automated system | Not mentioned | Categorical | ≤12 h | Not mentioned |
| Martin Strömdahl et al. (2024) | Not mentioned | Not mentioned | Continuous & Categorical | <13 h | Median TTP value |
| Matthias Willmann et al. (2013) | Not mentioned | Not mentioned | Categorical | ≤ 18 h | Not mentioned |
| M. Rolo et al. (2022) | Automatically recorded | Not mentioned | Continuous & Categorical | ≤16 h | ROC analysis for predicting mortality |
| R. Khatib et al. (2005) | Not mentioned | Not mentioned | Continuous & Categorical | ≤14 h | Best sensitivity and specificity for prediction |
| Daniel N Marco et al. (2025) | BACTEC systems | 8-10 mL per vial | Continuous & Categorical | <13h, <14h, <16h | Not mentioned |
| Hea Sung Ok et al. (2013) | BacT ALERT 3D | Every 2-3 days until clearance | Continuous & Categorical | <11.8 h | Not mentioned |
| Qing Zhang et al. (2021) | BACTEC FX400 | Not mentioned | Categorical | ≤ 8 h | Not mentioned |
| C. Cillóniz et al. (2017) | BACTEC 9240 | Not specified | Continuous & Categorical | 9.2 h | ROC analysis to differentiate risk groups |
| I. Comba et al. (2024) | Not specified | Not specified | Continuous & Categorical (ratio) | TTP ratio ≤1.5; initial TTP <12 h | Not mentioned |

Antibiotic Treatment Context

The definition of “appropriate therapy” across studies was consistently based on in vitro susceptibility of the isolated pathogen to the administered antibiotic regimen. The timing of initiation was a key variable, with “appropriate” often requiring commencement within a specific timeframe, such as 24 hours, after blood culture collection. Delays in appropriate therapy were associated with worse outcomes, though the critical time window varied. For instance, one study on KPC-producing *K. pneumoniae* bacteremia found that receiving active therapy within 24 hours was associated with lower 30-day mortality. Another study on community-onset bacteremia found the optimal timing

for non-critically ill patients was within 48 hours, but shifted to within 1 hour for critically ill patients.

Specific antibiotic regimens were mentioned, including glycopeptides like vancomycin for MRSA infections, and broad-spectrum beta-lactams or carbapenems for Gram-negative infections. Dosing adequacy was sometimes addressed, particularly for vancomycin, where maintaining target trough levels (e.g., ≥ 15 mg/L) was noted as a factor in preventing persistent bacteremia. The duration of treatment was a focus of several studies comparing shorter courses (e.g., 7-10 days) with longer courses (e.g., 14 days or more) for uncomplicated Gram-negative bacteremia, with mixed findings on efficacy.

Source control procedures, such as removal of infected catheters or drainage of abscesses, were identified as critical components of management. Delays in source control were linked to persistent bacteremia and poorer outcomes. Some studies noted that treatment modifications, such as antibiotic de-escalation, could be guided by negative culture results after 48-72 hours, although the risk of delayed growth of resistant organisms was also highlighted.

| Study | Definition of Appropriate Therapy | Median Time to Appropriate Antibiotics | Common Antibiotic Regimens | Source Control Timing |
|------------------------------|---|---|--|--|
| Yufang Chen et al. (2020) | In vitro susceptibility and initiation within 24h | within 24 hours | Not mentioned | Not mentioned |
| Daniel N Marco et al. (2025) | Active agent within 24h before susceptibility results | within 24 hours | Not mentioned | Catheter removal mentioned, timing not specified |
| Hea Sung Ok et al. (2013) | Not explicitly defined | Not mentioned | Vancomycin, teicoplanin | Catheter removal within 24h considered early |
| Qing Zhang et al. (2021) | Effective against causative microorganism | Not specified | Not mentioned | Not mentioned |
| M. Lambregts et al. (2019) | Based on local sepsis guidelines | Not specified | 2nd-gen cephalosporin + aminoglycoside | Not mentioned |
| C. Cillóniz et al. (2017) | According to IDSA/ATS guidelines for CAP | Not mentioned | β -lactam + macrolide, fluoroquinolone monotherapy | Not mentioned |
| C. Kang et al. (2004) | Susceptible agent within 24h of blood culture | within 24 hours | Not mentioned | Not mentioned |
| M. Falcone et al. (2020) | In vitro susceptibility by EUCAST breakpoints | 8.5h (survivors) vs 48h (non-survivors) | Ceftazidime-avibactam, colistin, meropenem | Within 24 hours |
| E. Zasowski et al. (2016) | Susceptible to enterococci and any copathogen | Median 31.6 hours | Linezolid, daptomycin, ampicillin | Documented but timing not detailed |

| Study | Definition of Appropriate Therapy | Median Time to Appropriate Antibiotics | Common Antibiotic Regimens | Source Control Timing |
|-----------------------------|---|--|-------------------------------|-----------------------|
| Ching-Chi Lee et al. (2017) | Based on Sanford Guide and CLSI breakpoints | Mean 2.0 hours | Various broad-spectrum agents | Not detailed |

Outcome Definitions and Measurement

Studies predominantly defined and measured outcomes related to microbiological persistence and mortality. Persistent bacteremia was a primary outcome, commonly defined as positive follow-up blood cultures (FUBCs) despite appropriate antibiotic therapy. The timeframe for defining persistence varied, with common windows being ≥ 48 hours, ≥ 72 hours, ≥ 4 days, and ≥ 7 days.

Mortality was a key secondary or primary outcome in most studies, with specified timeframes including in-hospital, 28-day, 30-day, and 90-day mortality. Relapse or recurrence of bacteremia was less frequently assessed but was defined as recurrent positive cultures after a period of initial clearance, typically within a 30 to 90-day window. Microbiological clearance was documented via negative follow-up cultures but was not always a formal endpoint. Some studies used composite endpoints, such as clinical failure, which could include persistent bacteremia, mortality, or the need to escalate therapy.

| Study | Persistent Bacteremia Definition | Relapse Definition and Timeframe | Clearance Definition | Mortality Timeframe |
|-------------------------------|----------------------------------|----------------------------------|--------------------------------|---------------------|
| Meng-Shiuan Hsu et al. (2014) | >48 h positive cultures | Not mentioned | Not mentioned | In-hospital |
| Hea Sung Ok et al. (2013) | ≥ 7 days | Not mentioned | Negative FUBCs | 30-day |
| P. Moise et al. (2010) | Not mentioned | Not mentioned | Time to first negative culture | Not mentioned |
| V. Fowler et al. (2004) | ≥ 7 days of therapy | Not mentioned | Not mentioned | Not mentioned |
| E. Minejima et al. (2019) | ≥ 3 days positive cultures | Not explicitly defined | Not explicitly defined | 30-day |
| Y. Chong et al. (2013) | ≥ 7 days despite therapy | Recurrence within 12 weeks | Implied by FUBCs | 12-week & 30-day |
| E. Minejima et al. (2015) | ≥ 4 days positive cultures | Recurrence within 30 days | Not mentioned | 30-day |
| Emily Fox et al. (2022) | ≥ 4 days positive cultures | Recurrence within 14 days | Clearance within 4 days | In-hospital |
| Javier López et al. (2013) | 48-72h positive cultures | Not mentioned | Not mentioned | In-hospital |
| O. Lesens et al. (2004) | >24 h positive cultures | Not mentioned | Not mentioned | Not specified |

| Study | Persistent Bacteremia Definition | Relapse Definition and Timeframe | Clearance Definition | Mortality Timeframe |
|----------------------------|--|----------------------------------|--|---------------------|
| R. Khatib et al. (2006a) | ≥3 days positive cultures | Not mentioned | Not mentioned | Not mentioned |
| C. Forstner et al. (2013) | ≥7 days | Not mentioned | Failure of microbiological eradication mentioned | 28-day |
| M. Giannella et al. (2020) | 24h-7 days positive FUBCs | Not mentioned | Not mentioned | 30-day |
| S. W. Ong et al. (2024) | 2-5 days positive FUBCs | Not mentioned | Not mentioned | 30-day, 90-day |
| K. Paquette et al. (2021) | Persistent bacteremia mentioned, not defined | Not mentioned | Not mentioned | 90-day |

TTP and Persistent Bacteremia/Microbiological Failure

A shorter TTP was frequently associated with persistent bacteremia or microbiological failure. In studies of *S. aureus* bacteremia (SAB), a TTP of <11.8 hours was associated with an increased risk of persistence. Similarly, another study found that a TTP ≤12.4 hours was significantly associated with persistent SAB. The concept of sequential TTP was also explored, where a ratio of the second TTP to the first of <1.5 was identified as an independent risk factor for poor outcomes in persistent SAB, including mortality. Furthermore, a decrease in TTP in follow-up blood cultures after primary therapeutic intervention was associated with a significantly higher frequency of 30-day mortality or secondary infections in patients with persistent SAB.

For Gram-negative bacteremia, the evidence is less extensive but points in a similar direction. One study found that for patients with *P. aeruginosa* BSI, a TTP <13 hours was independently associated with catheter-related infections, a common cause of persistence. Other studies defined persistence based on positive follow-up cultures at various time points (e.g., ≥48-72 hours, ≥3-4 days, or ≥7 days) but did not always directly link this to initial TTP values. The duration of bacteremia itself was found to be a critical predictor, with each additional day of positive blood cultures incrementally increasing the risk of metastatic complications and mortality in SAB.

| Study | Outcome Definition | TTP Exposure (Cutoff or Continuous) | Effect Size Type | Effect Estimate (95% CI) | p-value | Adjustment Variables | | --- | --- | --- | --- | --- | | Hea Sung Ok et al. (2013) | Persistent MRSA bacteremia | < 11.8 hours | Not specified | Not specified | 0.029 | Univariate analysis | | E. Maillart et al. (2012) | Persistent SAB | ≤12.4 hours | Not specified | Not specified | 0.010 | Not specified | | Daniel N Marco et al. (2025) | Catheter-related PAE-BSI | < 13 hours | OR | 3.7 (1.7-8.2) | Not specified | Multivariable analysis | | Meng-Shiuan Hsu et al. (2014) | Poor outcome in persistent SAB | Second TTP/first TTP ratio <1.5 | OR | 0.2 (0.07-0.6) | 0.004 | Higher Pittsburgh scores | | S. Choi et al. (2012) | 30-day mortality or secondary foci | Decrease in TTP of FUPBC | Not specified | Not specified | 0.005 | Not specified | | E. Minejima et al. (2019) | 30-day mortality | Per day of bacteremia | RR | 1.16 (1.10-1.22) | <0.0001 | Not specified | | E. Minejima et al. (2019) | 30-day mortality | 3+ days of bacteremia | aOR | 1.17 (1.06-1.29) | 0.002 | Age, gender, Pitt score, source risk, source control | | R. Khatib et al. (2005) | Extended bacteremia (≥3 days) | ≤14 hours | Not specified | Not specified | <0.0005 | Independent predictor in logistic regression | | R. Khatib et al.

(2005) | Metastatic infection | ≤14 hours | Not specified | Not specified | <0.0005 | Independent predictor in logistic regression |

TTP and Relapse/Recurrence

The association between TTP and the relapse or recurrence of bacteremia is not as extensively documented as other outcomes. One study defined relapse in *S. aureus* bacteremia as an episode occurring more than 8 days after the end of a previous episode, but did not directly link it to TTP. Another investigation of persistent SAB noted a higher rate of relapse within 12 weeks among patients with bacteremia lasting ≥7 days compared to those with resolving bacteremia, though a direct TTP association was not specified. In a study of vancomycin-resistant enterococcal bacteremia, recurrent bacteremia within 14 days was a secondary outcome, but no statistically significant difference was found between patients with persistent and non-persistent initial bacteremia. Overall, while persistent bacteremia (which is correlated with shorter TTP) is linked to higher relapse rates, a direct, independent predictive role of initial TTP for relapse or recurrence has not been firmly established across the included literature.

TTP and Mortality Outcomes

A substantial body of evidence indicates an association between shorter TTP and increased mortality in patients with bloodstream infections. This relationship has been observed for various pathogens and across different mortality timeframes. For Gram-negative bacteremia, a shorter TTP has been identified as an independent predictor of in-hospital or 30-day mortality for infections caused by *E. coli*, *K. pneumoniae*, and *P. aeruginosa*. For instance, studies on *E. coli* bacteremia reported adjusted odds ratios for mortality ranging from 3.80 to 4.89 for patients with TTP below cutoffs of 11 or 7 hours. A large population-based study found that a TTP in the first quartile (≤10 hours) was associated with a significantly increased risk of 30-day mortality across a wide range of both Gram-negative and Gram-positive organisms, with an adjusted odds ratio of 1.43.

For *S. aureus* bacteremia, the findings are more complex. Several studies have confirmed that a shorter TTP (e.g., ≤12h or ≤13.7h) is an independent predictor of increased hospital or 30-day mortality. However, other studies have reported a U-shaped or even an inverse relationship. One large study found that a very long TTP (>48h) was also associated with increased 30-day mortality, alongside a short TTP (≤12h). Another reported a U-shaped curve for the risk of infective endocarditis, a complication with high mortality. A meta-analysis concluded that short TTP was significantly associated with mortality (OR 2.98), but some individual studies found no significant association between TTP and mortality, particularly in cohorts of critically ill patients with septic shock or in specific pathogens like *Streptococcus pyogenes*.

| Study | Mortality Timeframe | TTP Exposure Definition | Effect Estimate (95% CI) | Adjustment Variables |
|---------------------------|---------------------|-------------------------|--------------------------|---|
| H. Palmer et al. (2013) | In-hospital | Per hour shorter | OR 1.10 (1.00-1.21) | Severity of illness, ESBL-producing GNB, ICU admission |
| Yufang Chen et al. (2020) | In-hospital | ≤11 h | OR 3.80 (1.04–12.90) | ICU admission, Pittsburgh score, Charlson Comorbidity Index |

| Study | Mortality Timeframe | TTP Exposure Definition | Effect Estimate (95% CI) | Adjustment Variables |
|---------------------------------|-----------------------------|-----------------------------|--|--|
| A. Marra et al. (2006) | In-hospital | ≤12 h | OR 6.9 (1.07-44.66) | Charlson score, MRSA infection |
| Matthias Willmann et al. (2013) | In-hospital | ≤ 18 h | HR 3.83 (Not specified) | SAPS II score, cardiac disease, appropriate treatment |
| M. Rolo et al. (2022) | 30-day | ≤16 h | aOR 2.27 (2.12-4.25) | Neutropenia, septic shock, respiratory source, nosocomial acquisition, MDR/XDR phenotype |
| Chih-Ping Chen et al. (2023) | 30-day | Per hour increase | HR 0.82 (Not specified) | Pittsburg bacteremia score |
| G. Peralta et al. (2007) | In-hospital | Short TTP (lowest quartile) | HR 3.13 (1.28-7.64) | Haematological illness, Charlson score, non-urinary source, severe sepsis/shock |
| J. Martinez et al. (2006) | Fatal outcome (in-hospital) | ≤7 h | OR 4.37 (1.38-13.8) | Immunocompromising condition, peritonitis, pneumonia |
| Kevin B. Laupland et al. (2024) | 30-day | ≤10 h (first quartile) | OR 1.43 (1.35-1.50) | Age, sex, onset, comorbidity, focus of infection |
| Joseph Kim et al. (2010) | 30-day | >48 h and ≤12 h | Not specified | Age, nosocomial acquisition, MRSA, focus of infection, liver disease |
| Shi-ning Bo et al. (2011) | In-hospital | ≤7 h | OR 4.886 (2.572-9.283) | Neutropenia, comedication of steroids/immunosuppressants |
| S. Siméon et al. (2019) | 30-day | ≤13.7 h | Not specified | Age, McCabe score, methicillin resistance, stroke, pneumonia, CRP |
| C. Cillóniz et al. (2017) | In-hospital & 30-day | <9.2 h | OR 5.35 (1.55-18.53) for in-hospital; OR 2.47 (0.85-7.21) for 30-day | Multiple potential confounders |
| C. Liao et al. (2009) | 30-day | <7 h | OR 2.46 (1.20-5.05) | Pittsburg bacteraemia score, active malignancy |

| Study | Mortality Timeframe | TTP Exposure Definition | Effect Estimate (95% CI) | Adjustment Variables |
|----------------------------------|---------------------|--------------------------|--------------------------|---|
| Yong-Ye Yang et al. (2024) | 30-day | Per hour increase | OR 0.79 (Not specified) | Pitt bacteraemia score, source control implementation |
| A. Bläckberg et al. (2023) | 30-day | ≤7.9 h | OR 4.4 (1.6–12.2) | Age |
| A. Bläckberg et al. (2022) | 30-day | Shorter TTP (continuous) | OR 3.7 (1.2–11.3) | Age, Charlson Comorbidity Index, focus of infection |
| Weiwei Hou et al. (2023) | In-hospital | <9.4 h | OR 2.7 (1.0–7.4) | Age, creatinine, WBC, CRP (TTP not independent) |
| Hiroyasu Takahashi et al. (2022) | 14-day | ≤11 h | HR 19.6 (Not specified) | Pitt bacteremia score |

Subgroup Analyses: Organism Type and Source Control

Subgroup analyses consistently highlight the importance of organism type in modifying the predictive value of TTP. The association between shorter TTP and adverse outcomes appears robust for *S. aureus* and common Gram-negative Enterobacterales such as *E. coli* and *K. pneumoniae*. A large population-based study provided specific adjusted odds ratios for 30-day mortality associated with a first-quartile TTP (≤10 hours) for multiple organisms, including *S. aureus* (aOR 1.56), *E. coli* (aOR 1.37), and *Pseudomonas* species (aOR 2.23). Another study found differences in TTP between methicillin-susceptible and methicillin-resistant *S. aureus* (MRSA), and a study on sequential TTP noted that the correlation between initial and subsequent TTP varied by MRSA versus MSSA status. For Enterococcus species, one study found that while shorter TTP was associated with higher mortality rates in univariate analysis for *E. faecalis* and VSEfm, it was not an independent risk factor in survival analysis.

The influence of source control on the TTP-outcome relationship is less clearly defined, though it is recognized as a major prognostic factor in its own right. For *P. aeruginosa* bacteremia, one study found that in catheter-related infections, a TTP <14h exacerbated mortality among patients where the catheter was not removed within 48h (OR 2.9). This suggests that a short TTP may identify a high-risk group where timely source control is particularly critical. In *S. aureus* bacteremia, delayed source control was associated with prolonged bacteremia, which in turn is linked with shorter TTPs and worse outcomes. Another study identified that a short TTP (≤12h) was more common in patients with a central venous catheter source.

| Study | Subgroup Examined | Sample Size | Effect Estimate (95% CI) | Interaction p-value |
|---------------------------------|----------------------------|---------------|--------------------------|---------------------|
| Kevin B. Laupland et al. (2024) | <i>S. aureus</i> | Not specified | aOR 1.56 (1.41-1.73) | Not reported |
| Kevin B. Laupland et al. (2024) | <i>S. pneumoniae</i> | Not specified | aOR 1.91 (1.49-2.46) | Not reported |
| Kevin B. Laupland et al. (2024) | <i>Pseudomonas</i> species | Not specified | aOR 2.23 (1.85-2.69) | Not reported |

| Study | Subgroup Examined | Sample Size | Effect Estimate (95% CI) | Interaction p-value |
|-----------------------------------|---|---------------|---|---------------------|
| Kevin B. Laupland et al. (2024) | <i>E. coli</i> | Not specified | aOR 1.37 (1.23-1.53) | Not reported |
| Kevin B. Laupland et al. (2024) | Enterobacterales | Not specified | aOR 1.38 (1.16-1.63) | Not reported |
| Daniel N Marco et al. (2025) | Catheter-related <i>P. aeruginosa</i> BSI, catheter not removed | Not specified | OR 2.9 (1.04–8) | Not reported |
| Daniel N Marco et al. (2025) | Non-catheter-related <i>P. aeruginosa</i> BSI, inactive empiric therapy | Not specified | OR 3.8 (1.5–10) | Not reported |
| H. Bae et al. (2021) | <i>E. coli</i> bacteremia | 328 | Not specified | Not reported |
| H. Bae et al. (2021) | <i>Klebsiella</i> bacteremia | 188 | Not specified | Not reported |
| Katharina Michelson et al. (2021) | <i>E. faecalis</i> | Not specified | HR 2.73 | p=0.17 |
| Katharina Michelson et al. (2021) | VSEfm | Not specified | HR 1.63 | p=0.15 |
| Katharina Michelson et al. (2021) | VREfm | Not specified | HR 1.24 | p=0.63 |
| Joseph Kim et al. (2010) | MSSA vs MRSA | 684 | Shorter TTP for MSSA (p=0.015) | Not reported |
| I. Comba et al. (2024) | MRSA vs MSSA | 186 | Shorter STTP & lower TTP ratio for MRSA (p<0.001) | Not reported |

Analytical Approaches and Model Performance

The predominant analytical methods used to assess TTP as a prognostic factor were multivariable logistic regression and Cox proportional hazards models. These models typically included TTP (either as a continuous or dichotomized variable) along with a range of potential confounders. Key covariates frequently adjusted for included severity of illness scores (e.g., Pitt bacteremia score, APACHE II, SOFA score), patient comorbidities (e.g., Charlson Comorbidity Index), demographic factors like age, and infection characteristics such as source, pathogen type, and methicillin resistance.

A few studies reported metrics of predictive accuracy. For predicting septic shock in *E. coli* bacteremia, one study found an Area Under the Curve (AUC) of 0.71, with a sensitivity of 73.1% and specificity of 65.2% for a TTP cutoff of 11 hours. For infective endocarditis in SAB, a negative predictive value of 96% was reported for a TTP >13 hours. Some studies developed and validated formal prediction models incorporating TTP. One such study developed a scoring

model for mortality in cancer patients with *E. coli* bacteremia that included TTP ≤ 8 h as a risk factor, demonstrating excellent discrimination (AUC 0.858 and 0.835 in development and validation cohorts, respectively). Another study developed a prognostic score for *Enterobacteriaceae* BSI combining TTP ≤ 11 h and a Pitt score ≥ 4 points, which stratified patients into different 14-day survival categories.

| Study | Primary Analysis Method | Key Covariates in Multivariable Models | AUC or Other Discrimination Metrics | Model Validation Approach |
|-----------------------------------|----------------------------------|---|---|--|
| Qing Zhang et al. (2020) | Logistic regression | Fever $\geq 39^{\circ}\text{C}$, inappropriate antibiotic therapy, metastasis, ARDS, blood transfusion, TTP ≤ 8 h | AUC: 0.858 (dev), 0.835 (val) | Internal validation group |
| Martin Strömdahl et al. (2024) | Multivariate logistic regression | TTP <13 hours | NPV of TTP >13h: 96% | Not specified |
| M. Rolo et al. (2022) | Multivariate logistic regression | Neutropenia, septic shock, respiratory source, nosocomial acquisition, MDR/XDR phenotype | AUC: 0.62 | Not specified |
| Yufang Chen et al. (2020a) | Multivariate logistic regression | ICU admission, neutropenia, Pittsburgh score, Charlson Index | AUC for septic shock: 0.71 | Not specified |
| C. Cillóniz et al. (2017) | Logistic and linear regression | Age, PSI class, severe CAP, septic shock, renal failure, complications | AUC for in-hospital mortality: 0.91; for 30-day mortality: 0.88 | Internal validation with bootstrapping (implied) |
| Katharina Michelson et al. (2021) | Survival analysis | Not specified | AUC for cardiovascular source: 0.75 | Not specified |
| H. Le et al. (2014) | Logistic regression | Not specified | AUC for severe sepsis/shock: 0.792; for death: 0.708 | Not specified |
| Chih-Ping Chen et al. (2023) | Cox proportional hazards | Pittsburg bacteremia score | AUC for mortality: 0.75 | Not specified |
| Yong-Ye Yang et al. (2024) | Logistic regression | Pitt bacteraemia score, source control | AUC for 30-day mortality: 0.73 | Not specified |
| Weiwei Hou et al. (2023) | Multivariate logistic regression | Age, creatinine, WBC, CRP | AUC for in-hospital mortality: 0.61 | Not specified |
| Hiroyasu Takahashi et al. (2022) | Cox proportional hazards | Pitt bacteremia score | AUC for 14-day mortality: 0.841 | Not specified |

Evidence Synthesis and Meta-Analytic Considerations

The overall body of evidence suggests that a shorter TTP is generally associated with a higher risk of adverse outcomes, including persistent bacteremia and mortality, in patients with bloodstream infections. This association holds across multiple bacterial species, particularly *S. aureus* and various Gram-negative bacilli. A meta-analysis confirmed this trend, reporting a pooled odds ratio of 2.98 for mortality in patients with short TTP. The direction of this association aligns with the microbiological principle that a higher initial bacterial load in the bloodstream would lead to faster growth detection in vitro and reflects a more severe in vivo infection.

However, there is significant clinical and statistical heterogeneity across the studies. The definition of "short" TTP varies widely, with cutoffs ranging from <7 hours to ≤18 hours depending on the pathogen and study population. This lack of a standardized cutoff complicates direct comparisons and meta-analytic efforts. Furthermore, some studies report conflicting or non-linear relationships. For *S. aureus* bacteremia, at least two studies found that a very prolonged TTP (>48 hours or >27 hours) was also associated with increased mortality, suggesting a U-shaped risk curve. Additionally, some large prospective studies and analyses in critically ill populations found no significant association between TTP and mortality, challenging its universal applicability as a prognostic marker.

This heterogeneity indicates that the relationship between TTP and outcome is likely modified by several factors, including the specific pathogen, infection source, severity of illness, and host immune status. A Bayesian hierarchical meta-regression approach would be well-suited to explore these sources of heterogeneity. By incorporating study-level covariates (e.g., proportion of patients with septic shock, specific organism, TTP cutoff used), such a model could estimate the influence of these factors and provide more nuanced, context-specific predictions. The existing data supports the general direction and independence of TTP as a prognostic factor, but its magnitude and clinical utility for decision-making likely depend on a combination of these clinical and microbiological variables.

Limitations and Research Gaps

The current body of evidence on TTP as a prognostic marker has several important limitations. A primary methodological weakness is the predominance of retrospective, single-center study designs, which are susceptible to selection bias, information bias, and limited generalizability. Confounding by indication is a significant concern, as clinicians may have ordered more follow-up cultures or initiated different treatments for patients perceived to be sicker, independent of the TTP value. While many studies used multivariable regression to adjust for confounders, residual confounding likely remains.

Measurement issues also contribute to heterogeneity. There is no standardized TTP cutoff, with values ranging widely across studies, which hinders meta-analysis and the development of universal clinical guidelines. Furthermore, factors that can influence TTP independent of bacterial load—such as blood volume drawn, prior antibiotic exposure, and time delay between blood draw and incubator loading—were not consistently controlled for or reported.

Clinically, several gaps remain. The interaction between TTP and source control is understudied; while delayed source control worsens outcomes, it is unclear if TTP can modify this risk or help identify patients who would benefit most from aggressive early intervention. There is limited data for certain pathogens, including anaerobes and less common Gram-positives and Gram-negatives. Most studies have focused on mortality or persistence, with less attention paid to relapse/recurrence. Finally, very few studies have prospectively evaluated prediction models incorporating TTP or validated them in external cohorts, limiting their clinical applicability. The planned Bayesian meta-regression will be valuable for quantifying the impact of these sources of heterogeneity, but prospective, multicenter studies with standardized protocols for TTP measurement and consistent outcome definitions are needed to

definitively establish the role of TTP in clinical decision-making.

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