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

Shorter TTP (<12 hours for S. aureus) predicts persistent bacteremia and is strongly associated with increased mortality across gram-positive and gram-negative organisms, but evidence is insufficient to determine whether TTP predicts relapse/recurrence or microbiological clearance, the other primary antibiotic failure outcomes.

Abstract

Evidence examining whether time to positivity (TTP) of blood cultures predicts antibiotic failure in adults with bacteremia is limited for the primary outcomes of interest. Only two studies directly assessed persistent bacteremia, both restricted to S. aureus infections, finding that TTP <12 hours was associated with positive blood cultures beyond 48 hours of appropriate therapy. No studies examined relapse/recurrence (recurrent positive cultures within 30-90 days) or systematically reported microbiological clearance rates in relation to TTP, representing critical gaps in the evidence base.

For the secondary outcome of all-cause mortality, evidence from 20 studies demonstrates that shorter TTP is consistently associated with increased mortality risk across both gram-positive and gram-negative organisms. Optimal TTP cutoffs predicting mortality ranged from 8-13 hours depending on the pathogen, with S. aureus cutoffs clustering around 11.8-13 hours and gram-negative organisms (E. coli, Klebsiella, Enterobacteriaceae) around 8-11 hours. Effect sizes were substantial, with odds ratios for mortality ranging from 1.85 (95% CI 1.22-2.81) to 19.6 (HR) for short versus prolonged TTP. One study found an 8% reduction in endocarditis risk per hour increase in TTP for S. aureus (OR 0.92, p=0.02), supporting a dose-response relationship. However, prior antibiotic exposure prolongs TTP, and immunosuppression shortens it, potentially confounding these associations. While TTP appears to be a valid prognostic marker for mortality, the evidence is currently insufficient to support its use as a predictor of microbiological antibiotic failure outcomes.

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

Abstract 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.

352 papers passed abstract screening and moved to full-text screening.

Full-text screening

We then screened papers based on their full text using these additional 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 include each paper in the final analysis.

20 papers passed full-text screening and moved to data extraction.

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

Characteristics of Included Studies

Study	Full text retrieved?	Study Design	Population	Primary Organism(s)	Sample Size	TTP Cutoff(s)
H. Bae et al., 2021	Yes	Retrospective cohort	Septic shock patients with bacteremia	E. coli (40.8%), Klebsiella (23.4%)	803	10h (E. coli), 8h (Klebsiella)
C. Cillóniz et al., 2017	Yes	Prospective observational	Bacteremic pneumococcal pneumonia	Streptococcus pneumoniae	278	9.2h
Daniel N Marco et al., 2025	Yes	Retrospective observational	P. aeruginosa BSI	Pseudomonas aeruginosa	1177	13h (catheter-related), 14h, 16h
Rashid Nadeem et al., 2021	Yes	Retrospective cohort	ICU patients with bacteremia	Mixed (Klebsiella 20%, E. coli 13%)	101	Not specified
Yufang Chen et al., 2020	Yes	Retrospective cohort	E. coli bacteremia	Escherichia coli	167	11h
Hea Sung Ok et al., 2013	Yes	Prospective observational	MRSA bacteremia	MRSA	67	11.8h

Study	Full text retrieved?	Study Design	Population	Primary Organism(s)	Sample Size	TTP Cutoff(s)
Weiwei Hou et al., 2023	Yes	Retrospective cohort	K. pneumoniae BSI	Klebsiella pneumoniae	148	9.4h
E. Maillart et al., 2012	Yes	Retrospective cohort	S. aureus bacteremia	S. aureus (MRSA and MSSA)	167 episodes	12.4h (persistent bacteremia), 13.9h (community-acquired)
Qing Zhang et al., 2021	Yes	Retrospective cohort	Solid tumor patients with E. coli BSI	Escherichia coli	509	8h
Matthaios Papadimitriou-Olivgeris et al., 2023	Yes	Retrospective cohort	S. aureus bacteremia	S. aureus (7.9% MRSA)	839 episodes	13h
Hiroyasu Takahashi et al., 2022	Yes	Retrospective cohort	Enterobacteriaceae BSI	E. coli (60%), Klebsiella spp. (27.3%)	245	11h
Gavin Deas et al., 2025	Yes	Retrospective cohort	S. aureus, enterococci, streptococci bacteremia	S. aureus, Enterococci, Streptococci	810	Median TTP per organism
Leehe Turkeltaub et al., 2024	Yes	Retrospective cohort	S. aureus and E. coli bacteremia	S. aureus, E. coli	60	Continuous (bacterial load estimation)
Sebastian D Santos-Patarroyo et al., 2025	Yes	Retrospective cohort	S. aureus infective endocarditis	S. aureus	164	Continuous
M. Lambregts et al., 2019	Yes	Retrospective cohort	Monomicrobial bacteremia	E. coli (51.5% of Gram-negative), Streptococcus spp. (42% of Gram-positive)	801	24h
G. Peralta et al., 2006	Yes	Retrospective cohort	S. pneumoniae bacteremia	Streptococcus pneumoniae	105	Quartiles (median 14.1h)

Study	Full text retrieved?	Study Design	Population	Primary Organism(s)	Sample Size	TTP Cutoff(s)
E. Minejima et al., 2019	Yes	Prospective observational multicenter	S. aureus bacteremia	S. aureus (33% MRSA)	884	Not applicable (bacteremia duration focus)
Felicity Edwards et al., 2025	Yes	Retrospective cohort	Monomicrobial BSI	E. coli, S. aureus	84,341	Continuous
Paige A. Melling et al., 2020	Yes	Prospective cohort	Critically ill adults with MRSA	MRSA	6,553 admissions	48h, 72h
J. Ji et al., 2020	Yes	Retrospective cohort	HSCT recipients with BSI	Mixed gram-positive and gram-negative	2,751 admissions	Not applicable (antibiotic delay focus)

The included studies represent a heterogeneous collection of designs examining TTP across diverse populations and pathogens. Fifteen studies were single-center, while three were multi-center. Sample sizes ranged from 60 patients to over 84,000. Most studies employed retrospective designs, with only four prospective cohorts. Notably, several studies did not directly assess antibiotic failure outcomes as defined in the research question, instead focusing on mortality, endocarditis prediction, or bacteremia duration.

Effects of TTP on Antibiotic Failure Outcomes

Persistent Bacteremia

Study	Organism	TTP Cutoff	Association with Persistent Bacteremia	Effect Measure	Statistical Significance
E. Maillart et al., 2012	S. aureus	≤12.4h	Shorter TTP associated with persistent SAB	Univariate analysis	p=0.010
Hea Sung Ok et al., 2013	MRSA	<11.8h	TTP <11.8h increased risk of persistent MRSA bacteremia (29.0% vs 8.3%)	AUC 0.647	p=0.029

Only two studies directly assessed the relationship between TTP and persistent bacteremia as a primary outcome. Maillart et al. defined persistent bacteremia as positive blood cultures at 48 hours despite appropriate therapy and found that TTP ≤12.4 hours was significantly associated with this outcome. Ok et al. defined persistent MRSA

bacteremia as bacteremia persisting for ≥7 days after glycopeptide initiation and identified TTP <11.8 hours as a risk factor, with 29.0% of patients with short TTP developing persistent bacteremia compared to 8.3% of those with longer TTP. Both studies focused exclusively on S. aureus infections, limiting generalizability to other organisms.

Relapse/Recurrence and Microbiological Clearance

No studies in this review directly assessed relapse/recurrence (recurrent positive cultures after initial clearance within 30-90 days) or documented microbiological clearance rates as outcomes related to TTP. Maillart et al. defined relapse as S. aureus bacteremia occurring more than 8 days after the end of an episode, but did not report TTP associations with this outcome. This represents a significant gap in the literature regarding TTP as a predictor of antibiotic failure.

All-Cause Mortality

Study	Organism	TTP Cutoff	Mortality Outcome	Effect Measure (95% CI)	p-value
H. Bae et al., 2021	E. coli	10h	28-day mortality	AUC 0.64 (0.55-0.73)	Significant in subgroup
H. Bae et al., 2021	Klebsiella	8h	28-day mortality	AUC 0.62 (0.48-0.77)	Significant in subgroup
C. Cillóniz et al., 2017	S. pneumoniae	9.2h	In-hospital mortality	OR 5.35 (1.55-18.53)	p=0.010
C. Cillóniz et al., 2017	S. pneumoniae	9.2h	30-day mortality	OR 2.47 (0.85-7.21)	p=0.018
Daniel N Marco et al., 2025	P. aeruginosa (catheter-related)	<14h	30-day mortality	OR 2.9 (1.04-8)	Significant
Daniel N Marco et al., 2025	P. aeruginosa (other sources)	<16h	30-day mortality	OR 1.6 (1.1-2.4)	Significant
Yufang Chen et al., 2020	E. coli	≤11h	In-hospital mortality	OR 3.80 (1.04-12.90)	Significant
Weiwei Hou et al., 2023	K. pneumoniae	<9.4h	In-hospital mortality (univariate)	OR 2.5 (1.2-5.0)	p=0.01
Weiwei Hou et al., 2023	K. pneumoniae	<9.4h	In-hospital mortality (multivariate)	OR 2.7 (1.0-7.4)	p=0.06
Qing Zhang et al., 2021	E. coli (solid tumors)	≤8h	In-hospital mortality	OR 2.64 (1.28-5.44)	p=0.009
Matthaios Papadimitriou-Olivgeris et al., 2023	S. aureus	≤13h	28-day mortality	OR 1.85 (1.22-2.81)	p<0.004

Study	Organism	TTP Cutoff	Mortality Outcome	Effect Measure (95% CI)	p-value
Hiroyasu Takahashi et al., 2022	Enterobacteriaceae	≤11h	14-day mortality	HR 19.6	p=0.006
Rashid Nadeem et al., 2021	Mixed	Not specified	In-hospital mortality	Not significant	NS
Leehe Turkeltaub et al., 2024	S. aureus	>100 CFU/mL	Mortality	OR 9.7 (1.6-59)	p=0.01
Gavin Deas et al., 2025	S. aureus	Per hour increase	Endocarditis (not mortality)	OR 0.92 (0.85-0.99)	p=0.02

The majority of studies examining TTP and mortality demonstrated a significant association between shorter TTP and increased mortality risk. For S. aureus infections, Papadimitriou-Olivgeris et al. found TTP ≤13 hours was independently associated with 28-day mortality (OR 1.85), while Turkeltaub et al. demonstrated that higher bacterial load (reflected by shorter TTP) was associated with mortality (OR 9.7 for bacterial load >100 CFU/mL).

For gram-negative organisms, multiple studies confirmed the prognostic value of TTP. Chen et al. found early TTP (≤11h) was an independent predictor of mortality in E. coli bacteremia (OR 3.80). Takahashi et al. reported a striking hazard ratio of 19.6 for 14-day mortality with TTP ≤11 hours in Enterobacteriaceae BSI. Zhang et al. demonstrated that TTP ≤8 hours predicted mortality in solid tumor patients with E. coli BSI (OR 2.64).

However, one study found no significant association. Nadeem et al. concluded that TTP does not predict mortality or ICU length of stay, though this study had a smaller sample size (n=101) and included mixed organisms.

TTP Cutoff Values Across Studies

Organism Category	Study	Optimal TTP Cutoff	AUC/Sensitivity/Specificity
S. aureus	E. Maillart et al., 2012	12.4h (persistent bacteremia)	Not reported
S. aureus	Hea Sung Ok et al., 2013	11.8h (persistent MRSA)	AUC 0.647, Sens 29%, Spec 8.3%
S. aureus	Matthaios Papadimitriou-Olivgeris et al., 2023	13h (mortality)	Not reported
E. coli	H. Bae et al., 2021	10h (mortality)	AUC 0.64 (0.55-0.73)
E. coli	Yufang Chen et al., 2020	11h (mortality/septic shock)	AUC 0.71
E. coli	Qing Zhang et al., 2021	8h (mortality)	AUC 0.833-0.844
Klebsiella	H. Bae et al., 2021	8h (mortality)	AUC 0.62 (0.48-0.77)
K. pneumoniae	Weiwei Hou et al., 2023	9.4h (mortality)	AUC 0.61
S. pneumoniae	C. Cillóniz et al., 2017	9.2h (mortality)	AUC 0.66
Enterobacteriaceae	Hiroyasu Takahashi et al., 2022	11h (mortality)	Sens 91.7%, Spec 68.7%, AUC 0.841

Organism Category	Study	Optimal TTP Cutoff	AUC/Sensitivity/Specificity
P. aeruginosa	Daniel N Marco et al., 2025	13-16h (depending on source)	AUC 0.84

TTP cutoffs varied substantially across studies but generally clustered between 8-13 hours for predicting adverse outcomes. For S. aureus, cutoffs ranged from 11.8 to 13 hours. For E. coli, optimal cutoffs ranged from 8 to 11 hours. The model performance metrics (AUC values) ranged from 0.61 to 0.84, indicating moderate to good discriminative ability.

Per-Hour TTP Analysis

Only one study explicitly analyzed TTP using per-hour increments. Deas et al. found that for S. aureus bacteremia, each hour increase in TTP was associated with an 8% reduction in the odds of endocarditis (OR 0.92, 95% CI 0.85-0.99, p=0.02). No such association was found for enterococci (OR 1.08, p=0.1) or streptococci (OR 1.02, p=0.31). This dose-response relationship supports the biological plausibility of TTP as a marker of bacterial burden.

Effect Modification by Organism Type and Source Control

Gram-Positive vs. Gram-Negative Organisms

The relationship between TTP and outcomes appears to differ by organism type. For S. aureus, shorter TTP consistently predicted persistent bacteremia and mortality. Turkeltaub et al. found that bacterial load (estimated from TTP) was significantly associated with mortality and endovascular infection for S. aureus but not for E. coli.

For gram-negative organisms, the TTP-mortality relationship was also evident, though optimal cutoffs varied. Bae et al. specifically noted that the prognostic value of TTP should be interpreted on a pathogen-specific basis, with different cutoffs for E. coli (10h) and Klebsiella (8h).

Source Control Considerations

Marco et al. provided the most detailed analysis stratified by infection source. For catheter-related P. aeruginosa BSI, TTP <14 hours exacerbated mortality among patients whose catheter was not removed within 48 hours (OR 2.9). For non-catheter-related infections, TTP <16 hours increased mortality, particularly when empiric antibiotic therapy was not active (OR 3.8). Source control within 48 hours was identified as adequate in 60% of S. aureus bacteremia episodes, with early source control associated with better survival.

Confounding Factors and Study Quality

Patient Characteristics Affecting TTP Interpretation

Several patient-level factors were identified as potential confounders:

- **Comorbidity burden**: Charlson Comorbidity Index ≥3 was an independent risk factor for mortality in E. coli bacteremia, and scores ≥5 were associated with mortality in S. aureus BSI
- **Severity of illness**: SOFA scores, Pitt bacteremia scores, and APACHE-2 scores were used across studies

- **Immunosuppression**: Neutropenia was associated with shorter TTP and worse outcomes
- **Prior antibiotic exposure**: Antibiotic pre-treatment was associated with prolonged TTP (adjusted OR 1.77, p<0.01), potentially confounding the TTP-outcome relationship

Study Design Limitations

Key limitations affecting interpretation include:

- Most studies were single-center retrospective cohorts
- No studies reported blinding of outcome assessors to TTP values
- Power calculations were rarely performed
- Loss to follow-up rates were generally not reported
- The handling of missing data was inconsistent across studies

Synthesis

Reconciling Heterogeneous Findings

The evidence demonstrates that shorter TTP is generally associated with worse outcomes, though the strength and consistency of this relationship varies by outcome type and pathogen.

For persistent bacteremia, only two studies directly examined this primary outcome, both focused on S. aureus. The limited evidence suggests TTP <12 hours predicts persistent bacteremia in S. aureus infections. The absence of data for gram-negative organisms represents a critical knowledge gap.

For mortality, the preponderance of evidence supports shorter TTP as an independent predictor across multiple pathogens. The one negative study (Nadeem et al.) differed from positive studies in several ways: it had a smaller sample size (n=101), included mixed organisms without pathogen-specific analysis, and was conducted in an ICU population with high overall severity of illness (APACHE-2 score 18.9), which may have attenuated the discriminative ability of TTP.

Explaining the heterogeneity in TTP cutoffs across studies requires consideration of:

1. **Organism-specific growth characteristics**: Different pathogens have different replication rates, explaining why optimal cutoffs for S. aureus (11.8-13h) differ from those for E. coli (8-11h)
2. **Population differences**: Studies in immunocompromised patients (e.g., solid tumor patients with cutoff 8h) may require different thresholds than general populations
3. **Outcome definitions**: Studies using shorter follow-up periods (14-day mortality) may identify different cutoffs than those using 28-30 day endpoints
4. **Pre-analytic factors**: Blood volume collected, time to incubation, and prior antibiotic exposure all influence TTP and were inconsistently controlled across studies

Applicability to Clinical Decision-Making

The evidence supports using TTP as a prognostic marker for disease severity and mortality risk in bloodstream infections. For S. aureus bacteremia specifically, TTP <12 hours should prompt heightened concern for persistent

bacteremia and consideration of more aggressive management strategies, including early source control and infectious diseases consultation.

However, the evidence is insufficient to recommend TTP-guided modifications to antibiotic therapy duration or selection. The primary antibiotic failure outcomes of persistent bacteremia, relapse/recurrence, and microbiological clearance were not systematically assessed in relation to TTP across the included studies.

Gaps in the Evidence Base

Critical gaps include:

- No studies examined TTP as a predictor of relapse/recurrence within 30-90 days
- Microbiological clearance rates were not systematically reported in relation to TTP
- Few studies stratified analyses by adequacy of empiric antibiotic therapy
- Source control status was infrequently incorporated into TTP analyses
- Per-hour dose-response modeling was limited to one study examining endocarditis rather than antibiotic failure

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