RESEARCH ARTICLE

Blood culture time-to-positivity can identify *S aureus*, but not Enterococcal or Streptococcal endocarditis.

[version 1; peer review: awaiting peer review]

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v1 **First published:** 05 Sep 2025, **5**:74
https://doi.org/10.3310/nihropenres.14018.1
Latest published: 05 Sep 2025, **5**:74
https://doi.org/10.3310/nihropenres.14018.1

Abstract

Background

International guidelines for *S aureus* bacteraemia often recommend screening echocardiography irrespective clinical factors that influence the likelihood of endocarditis, but this is not the case for enterococci or streptoccoci that are also high risk organism. Time to blood culture positivity (TTP) reflects bacterial load and has the potential to identify patients at higher risk of endocarditis.

Methods

We performed a retrospective analysis of clinical data that have been performed in a tertiary hospital in England. We investigate time to positivity (TTP) as a predictor variable in our *S. aureus*, enterococci and streptococci in logistic regression models and assess non-linearity of this affect using generalised additive models. We calculate NPV for TTP beyond the median value.

Results

The odds ratio for endocarditis from *S. aureus* bacteria was 0.92 (95%CI 0.85-0.99, p = 0.02) for each hour increase in TTP, with a negative predictive value of TTP greater than the median being 90% (95% CI 85-95%). For streptococci the OR was 1.02 (95%CI 0.98-1.06, p:0.31) and enterococci 1.08 (95% CI 0.99-1.18, p = 0.1) for every

Open Peer Review

Approval Status *AWAITING PEER REVIEW*

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increase in hour of TTP.

Conclusion

Longer TTP is associated with lower risk of endocarditis in *S. aureus* bacteraemia, at 8% reduction per hour, giving an NPV of 90% beyond 13 hours. There was no evidence of association with enterococci or streptococci.

Plain Language Summary

This study looked at whether the time it takes for bacteria to grow in blood (called "time to positivity" or TTP) from patients that are generally unwell, can help predict the risk of heart valve infection (endocarditis) as opposed to other infections. We focused on three common types of bacteria: *Staphylococcus aureus*, Enterococci, and Streptococci. International guidelines, and standard practice usually recommend heart scans (echocardiography) for everyone with S. aureus infections, even if they don't have other risk factors, but this is not the case for the other two bacteria. Endocarditis treatment and investigation, has a high burden on patients, with frequent, high doses of antibiotics and invasive tests.

We studied patient records from a large hospital in England to see if TTP could help identify who is at low risk for endocarditis. We found that in patients with *S. aureus*, a longer TTP was linked to a lower chance of endocarditis. Specifically, for every extra hour before the blood culture turned positive, the risk of endocarditis dropped by about 8%. If the TTP was more than 13 hours, there was a 90% chance that the patient did not have endocarditis. However, for Enterococci and Streptococci, TTP did not help predict the risk.

This information could be helpful with determining who should be prioritised for Echocardiography with *S. aures* but not the other organisms.

Keywords
Bacteremia, Endocarditis, Diagnostic stewardship

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Competing interests: No competing interests were disclosed.

Grant information: FH is funded by the NIHR Clinical Lectureship Scheme. PW was funded by Medical Research Council grant MR/T005408/1
The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

How to cite this article: Deas G, Shuttleworth J, Carson A *et al.* **Blood culture time-to-positivity can identify *S aureus*, but not Enterococcal or Streptococcal endocarditis. [version 1; peer review: awaiting peer review]** NIHR Open Research 2025, **5**:74 https://doi.org/10.3310/nihropenres.14018.1

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Background

Staphylococcus aureus bacteremia (SAB) is a common and important cause of infective endocarditis (IE). Currently, the IDSA guidelines for SAB recommend echocardiography for all patients; however, it has been proposed that time-to-positivity (TTP) could be used to predict and stratify patients more likely to have endovascular infections such as IE[1,2]. One publication of 1703 patient episodes showed that IE reduced by 11% per hour increase in TTP and gave a negative predictive value of 96% at times beyond 13 hours[3]. Indeed, TTP, in addition to the clinical decision tool VIRSTA, improves the negative predictive value to 100%[4]. This suggests that obtaining echocardiography for all patients with SAB with a blood culture time to positivity over 13 hours without clinical evidence or specific risk factors for endocarditis may not be necessary.

Other organisms associated with IE include *E faecalis* (13.6%)[5] and some species of high-risk streptococci[6], but no clear clinically useful association has been reported between IE and TTP in these organisms[7,8], with one study giving an ROC AUC of 0.75 for TTP on IE diagnosis and an association with mortality rates[9]. TTP is dependent on the generation time of the organism, which is comparable across these causes[10–12]; and inoculum size, which should be consistent across the same disease process. It is reasonable to explore whether TTP can discriminate between those with and without. These organisms are common causes of bacteremia; however, currently, there is no recommendation to perform echocardiography in all patients, and the European Society of Cardiology 2023 Endocarditis guidance highlights the potential utility of clinical decision tools for the organisms[13]. With IE prevalence as high as *S. aureus*, the decision to pursue IE investigations is based on clinical suspicion.

To investigate whether these results are generalizable to cohorts in the UK and to organisms other than *S. aureus*, we retrospectively investigated our cohort of patients with bacteremia caused by *S. aureus,* high-risk streptococci and enterococci.

Methods

Patient and Public Involvement

No patient or member of the public was involved in this work

Locally, four quality improvement projects have gathered data on the risk of infective endocarditis (IE) by analyzing isolates from three bacterial genera in recent years: staphylococci (2017–2018 and 2022–2023), enterococci (2020–2023), and streptococci (2017–2024). In this report, we will refer to these by their genus names, which include the following species:

Staphylococci: *aureus*

Enterococci: *faecalis*

Streptococci: *mitis, oralis, gallolyticus, sanguinis, mutans, gordonii,* and *cristatus*.

Data were extracted from the laboratory systems of a four-hospital network in the UK that serves 2600 inpatient beds, including tertiary cardiac and cardiothoracic patients. Blood cultures were drawn and processed in line with UK SMI S12[14] and placed in automated incubators (BD BACTEC FX).

These projects collected data on blood culture results, patient comorbidities, imaging findings, treatment duration, and compliance with relevant guidelines. From these datasets, we extracted the blood culture results, time to positivity, and final diagnoses. Only the first positive blood culture in a patient in a thirty-day period was included. The diagnosis of endocarditis was made by a qualified infection specialist involved in the care of the patient.

Statistical analysis

Descriptive data of organisms were reported, including positivity rate, mean and median time-to-positivity, and number of cases. Bacteremia was excluded if the time to positivity data was missing or species identification was unavailable. Mann-Whitney tests were performed on each species for IE- and non-IE-associated bacteremia. We explored the association between TTP and IE risk in a) a logistic regression model, calculating the increased risk for each hour of growth, b) a logistic regression model, binarizing TTP at the median TTP, and c) fitting a non-linear model (GAM) to explore inflection points and potential non-linearity. The predictive value of the median TTP was calculated. As transport time to the laboratory can influence time to positivity, we used our cohorts' median TTP rather than median values reported in the literature[15].

Results

Eight hundred and fifty-six bacteraemias were included, of which 46 were removed due to missing TTP data. There were 159 cases of IE: 37 staphylococci (16.2% of 228 bacteremias), 20 enterococci (18.3% of 109), and 97 streptococci (20.5% of 473). The mean TTP was: staphylococci: 14.1 hours (median 13, IQR 10-16); enterococci 11.6 hours (median 11, IQR 9-14); streptococci 14.5 hours (median 13, IQR 10-17). The streptococcal group included *cristatus* 3, *gallolyticus* 48, *gordonii* 13, *mitis/oralis* 75, *mutans* 7, *sanguinis* 34.

The univariate logistic models (*IE ~ TTP*) produced Odds Ratios of: staphylococci 0.92 (95%CI 0.85-0.99, p:0.02) enterococci 1.08 (95%CI 0.99-1.18, p:0.1) and streptococci 1.02 (95%CI 0.98-1.06, p:0.31) for every increase in hour of TTP. Using growth below the median TTP as a binomial (cutoff) variable produced the OR: staphylococci 2.62 (95% CI 1.25-5.46, p = 0.01), enterococci 0.94 (95% CI 0.36-2.44, p:0.90) and streptococci 0.80 (95% CI 0.52-1.24, p:0.32) (Figure 1).

The negative predictive values for growth beyond the median TTP for IE is staphylococci 90% (95% CI 84-95), enterococci 80% (95%CI 68-90) and streptococci 78% (95% CI 73-83). The Generalized additive models exhibited monotonicity and no nonlinearity. These results are shown in the supplementary material.

Discussion

Our main findings demonstrate that *S. aurues* bacteremia with longer TTP is significantly less likely to be associated with IE (8% per hour), but this was not true for enterococci or streptococci. Here, *S. aureus* taking > 13 h to grow had a Negative Predictive Value of 90% (95% CI 85-95). Our study matches the values previously reported by Stromdahl *et al.*, despite the inability to analyze confounding factors in our cohort. This finding highlights the strength of this association. It

will be reassuring to infection specialists that patients who cannot tolerate transesophageal echocardiography or are unable to obtain timely imaging can still be risk assessed for endocarditis prior to completing the 2023 ISCVID Duke scoring.

The lack of a relationship between time-to-positivity for streptococci and enterococci may reflect the differences in IE clinical syndromes with these organisms, typically a subacute presentation as opposed to an acute presentation with *S. aureus*. This assumes that TTP is related to the bacterial density of the original inoculum, which could be due to lower circulating CFU or sample volume[16]. Notably, the risk of IE remains above 15% across all TTP values for these groups, and there is no clear relationship between the two. While the species-specific analysis of streptococci suggests that *S. sanguinis* and *S. gordonii* might have a statistical difference in TTP per IE status, there is a clear overlap in the groups, and clinical significance is not met (Figure 2).

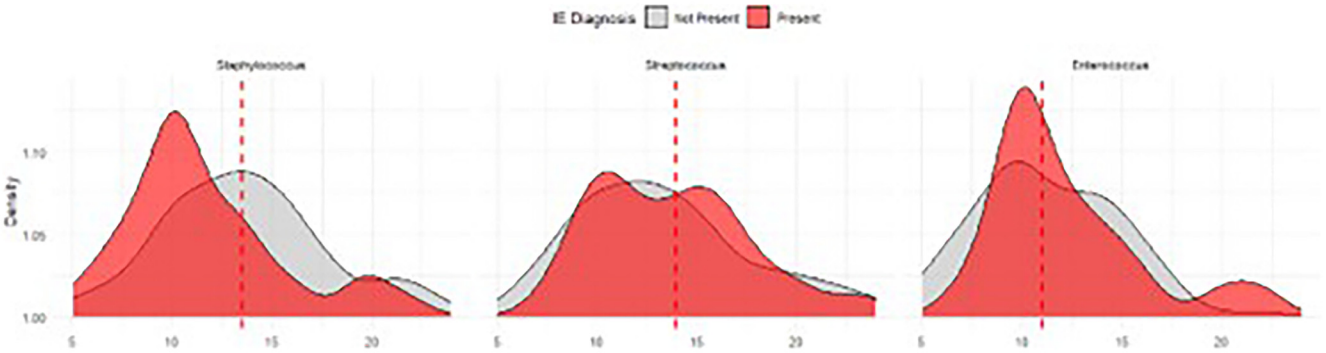

Figure 1. Relative density plots for each organism, grouped by IE status against the time to positivity in hours. The red dashed lines indicate the species-specific median TTP.

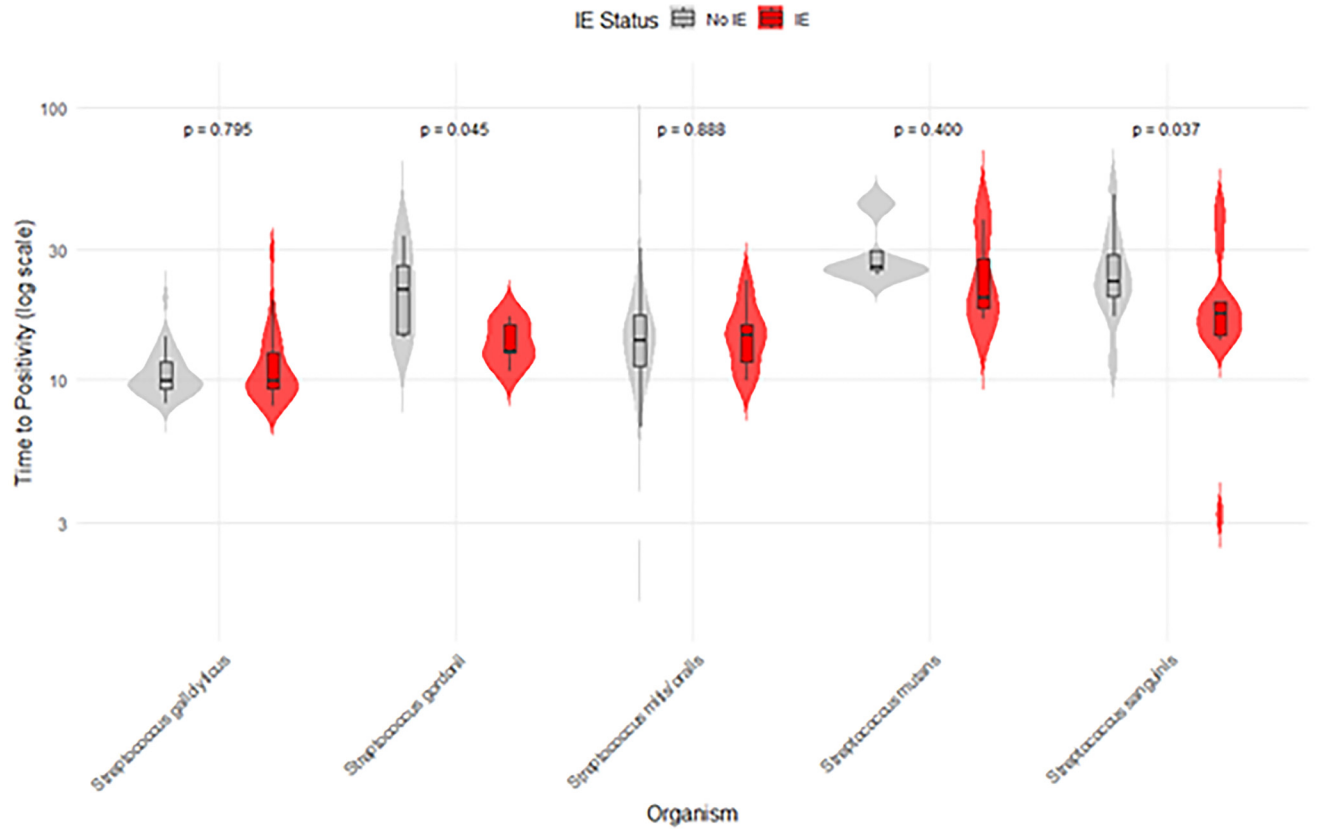

Figure 2. Violin plots of time to positivity for each *Streptococcus* species, with mean time to positivity for IE status compared by Wilcoxon ranked sum testing and p values displayed above. *S cristatus* removed due to low numbers of positive cases.

We were not able to control for antibiotic exposure prior to sampling, and we were only able to duplicate the culture results from within the hospital network. IE was diagnosed by an infection specialist in all cases, but 2023 ISCVID Duke's criteria were not extracted in this study.

Conclusion

A longer TTP is associated with lower rates of IE in *S. aureus* bacteremia at 8% reduction per hour, giving an NPV of 90% beyond 13 hours. There was no evidence of an association with enterococci or streptococci.

Ethics

Four reviews of bacteremias were undertaken as part of quality improvement projects and granted local permission to collect patient identifiable data for these purposes (North Bristol Trust, and University Hospitals Bristol and Weston). Data taken from these reviews included only the TTP results and IE diagnosis. Therefore, formal ethics approval was not required.

Data availability

Data is available as deidentified participant data and analysis code. Request should be made to the lead author at gavin.deas@nbt.nhs.uk. Local IRB approval will be required for any data sharing. Data will be available to any researcher whose proposed use of the data has been approved with investigator support and fully executed data use agreement. Supplementary material: Deas, G. (2025, August 9). Time to positivity and endocarditis. Retrieved from osf.io/w5cqg

References

1. Siméon S, Le Moing V, Tubiana S, *et al.*: **Time to blood culture positivity: an independent predictor of infective endocarditis and mortality in patients with *Staphylococcus aureus* bacteraemia.** *Clin Microbiol Infect.* 2019; **25**(4): 481–488.
PubMed Abstract | Publisher Full Text
2. Kahn F, Resman F, Bergmark S, *et al.*: **Time to blood culture positivity in *Staphylococcus aureus* bacteraemia to determine risk of infective endocarditis.** *Clin Microbiol Infect.* 2021; **27**(9): 1345.e7–1345.e12.
PubMed Abstract | Publisher Full Text
3. Strömdahl M, Hagman K, Hedman K, *et al.*: **Time to *Staphylococcus aureus* blood culture positivity as a risk marker of infective endocarditis: a retrospective cohort study.** *Clin Infect Dis.* 2025; **80**(4): 727–734.
PubMed Abstract | Publisher Full Text | Free Full Text
4. Simos PA, Holland DJ, Stewart A, *et al.*: **Clinical prediction scores and the utility of time to blood culture positivity in stratifying the risk of infective endocarditis in *Staphylococcus aureus* bacteraemia.** *J Antimicrob Chemother.* 2022; **77**(7): 2003–2010.
PubMed Abstract | Publisher Full Text
5. Danneels P, Chabrun F, Picard L, *et al.*: ***Enterococcus faecalis* endocarditis risk assessment in patients with bacteremia: external validation of the DENOVA score.** *J Infect.* 2023; **87**(6): 571–573.
PubMed Abstract | Publisher Full Text
6. Chamat-Hedemand S, Dahl A, Østergaard L, *et al.*: **Prevalence of infective endocarditis in streptococcal bloodstream infections is dependent on streptococcal species.** *Circulation.* 2020; **142**(8): 720–730.
PubMed Abstract | Publisher Full Text
7. Oldberg K, Thorén R, Nilson B, *et al.*: **Short time to blood culture positivity in *Enterococcus faecalis* infective endocarditis.** *Eur J Clin Microbiol Infect Dis.* 2021; **40**(8): 1657–1664.
PubMed Abstract | Publisher Full Text | Free Full Text
8. Krus D, Kahn F, Nilson B, *et al.*: **Blood culture time to positivity in non-β-hemolytic streptococcal bacteremia as a predictor of infective endocarditis–a retrospective cohort study.** *Eur J Clin Microbiol Infect Dis.* 2022; **41**(2): 325–329.
PubMed Abstract | Publisher Full Text | Free Full Text
9. Michelson K, Löffler B, Höring S: **Time to positivity as a prognostic factor in bloodstream infections with *Enterococcus spp.*** *Diagn Microbiol Infect Dis.* 2021; **101**(3): 115396.
PubMed Abstract | Publisher Full Text
10. Beckers HJ, van der Hoeven JS: **Growth rates of *Actinomyces viscosus* and *Streptococcus mutans* during early colonization of tooth surfaces in gnotobiotic rats.** *Infect Immun.* 1982; **35**(2): 583–7.
PubMed Abstract | Publisher Full Text | Free Full Text
11. Szafrańska AK, Junker V, Steglich M, *et al.*: **Rapid cell division of *Staphylococcus aureus* during colonization of the human nose.** *BMC Genomics.* 2019; **20**(1): 229.
PubMed Abstract | Publisher Full Text | Free Full Text
12. Lam MMC, Seemann T, Tobias NJ, *et al.*: **Comparative analysis of the complete genome of an epidemic hospital sequence type 203 clone of vancomycin-resistant *Enterococcus faecium*.** *BMC Genomics.* 2013; **14**: 595.
PubMed Abstract | Publisher Full Text | Free Full Text
13. Delgado V, Ajmone Marsan N, de Waha S, *et al.*: **2023 ESC guidelines for the management of endocarditis.** *Eur Heart J.* 2023; **44**(39): 3948–4042. Erratum in: Eur Heart J. 2023 Dec 1;44(45):4780. doi: 10.1093/eurheartj/ehad625. Erratum in: Eur Heart J. 2024 Jan 1;45(1):56. doi: 10.1093/eurheartj/ehad776. Erratum in: Eur Heart J. 2025 Mar 13;46(11):1082. doi: 10.1093/eurheartj/ehae877.
PubMed Abstract | Publisher Full Text
14. UK Health Security Agency: **UK SMI S12i1.1: sepsis and systemic or disseminated infections.** London: UK Health Security Agency, April 24, 2025.
Reference Source
15. Deas G, Hamilton F, Williams P: **Less haste, more speed: does delayed blood culture transport time lead to adverse incubation times or yield?** *J Infect.* 2025; **91**(1): 106520.
PubMed Abstract | Publisher Full Text | Free Full Text
16. Hamilton F, Evans R, Ghazal P, *et al.*: **Time to positivity in bloodstream infection is not a prognostic marker for mortality: analysis of a prospective multicentre randomized control trial.** *Clin Microbiol Infect.* 2022; **28**(1): 136.e7–136.e13.
PubMed Abstract | Publisher Full Text