

The prevalence of persistent bacteraemia in patients with a non-staphylococcal infective endocarditis, a retrospective cohort study

Thomas W. van der Vaart^{a,b,*}, Marjon Stuifzand^a, S. Matthijs Boekholdt^c, Maarten J. Cramer^d, Marc J.M. Bonten^b, Jan M. Prins^a, Jan T.M. van der Meer^a

^a Department of Internal Medicine, Division of Infectious Diseases, Amsterdam UMC, University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, the Netherlands

^b Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX, Utrecht University, Utrecht, the Netherlands

^c Department of Cardiology, Amsterdam UMC, University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, the Netherlands

^d Department of Cardiology, University Medical Center Utrecht, Utrecht University, Heidelberglaan 100, 3584 CX, Utrecht, the Netherlands

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ABSTRACT

Background: Current guidelines on the management of infective endocarditis (IE) recommend follow-up blood cultures (FUBCs) to identify persistent bacteraemia, as this has prognostic value and guides treatment decisions. While persistent bacteraemia frequently occurs in *Staphylococcus aureus* bacteraemia and IE, its prevalence and impact in non-staphylococcal IE is largely unknown. We determined prevalence and prognostic value of persistent bacteraemia in non-staphylococcal IE.

Methods: We conducted a retrospective analysis of all patients diagnosed with definite non-staphylococcal endocarditis according to the modified Duke Criteria in two university hospital endocarditis registries. We determined the prevalence and prognostic value of persistent bacteraemia.

Results: Of the included 159 patients 70 (44%) had prosthetic valve endocarditis (PVE). A median number of two [IQR 1–3] FUBCs were taken during the first week, with 134/159 (84%) having at least one FUBC in the first four days. Seven patients (4.4%) had persistent bacteraemia 48 h after start of antibiotic treatment: 5/70 patients (7.1%) with PVE and 2/89 (2.2%) with native valve endocarditis. Among 97 patients with streptococcal IE, nine patients with HACEK IE and six patients with *Cutibacterium* IE, no persistent bacteraemia was observed. *Enterococcus faecalis* was the causative microorganism in five patients with persistent bacteraemia, the other two had non-HACEK Gram-negative endocarditis.

Conclusion: Persistent bacteraemia in non-staphylococcal endocarditis was rare. It was more frequently observed in PVE and was restricted to more resilient microorganisms such as enterococci and non-HACEK Gram-negative bacteria. Routine collection of FUBCs in patients with streptococcal endocarditis has a low yield and may require re-evaluation.

1. Introduction

Current international and national guidelines for the treatment of patients with infective endocarditis (IE) recommend drawing follow-up blood cultures (FUBCs) every 24 to 48 h after the start of antimicrobial therapy, until sterilization of the bloodstream has been documented (1,2). FUBCs serve a dual role, as they have prognostic value and are also used to guide treatment decisions. Persistent bacteraemia is a marker of uncontrolled infection and may lead to changes in patient management, like the duration of antimicrobial treatment, valve replacement surgery or drainage of metastatic infectious foci.

The importance of performing FUBCs is primarily based on data from patients with *Staphylococcus aureus* bacteraemia, where persistent bacteraemia is associated with increased mortality (3). Anecdotal evidence suggests that persistent bacteraemia in patients with non-staphylococcal endocarditis is relatively rare. To our knowledge, the best evidence on the yield and predictive value of FUBCs in IE is a retrospective cohort study that demonstrated that positive FUBCs were common in patients with endocarditis and were associated with in-hospital mortality (multivariate odds ratio 2.11). Forty percent of patients in this study had staphylococcal IE and this may have introduced bias, as staphylococcal (and particularly *S. aureus*) IE is associated both with persistent

* Corresponding author at: Department of Internal Medicine, Amsterdam UMC, Meibergdreef 9, Room D3-226, 1105AZ, Amsterdam, the Netherlands.

E-mail address: t.w.vandervaat@amsterdamumc.nl (T.W. van der Vaart).

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Table 1
Definition of persistent bacteraemia.

Cultures within 48 h of appropriate antimicrobial therapy	Cultures after 48 h of appropriate therapy	Classification
Positive	All negative	No persistent bacteraemia
Negative	All negative	No persistent bacteraemia
Positive	Any one positive	Persistent bacteraemia
Negative	Any one positive	Persistent bacteraemia

bacteraemia and with mortality (4). Since the prevalence and predictive value of persistent bacteraemia in patients with non-staphylococcal IE is therefore largely unknown, the value of this routine practice deserves investigation.

In this retrospective cohort study, we aimed to determine the prevalence of persistent bacteraemia and its prognostic value in patients with non-staphylococcal IE.

2. Methods

2.1. Study design

We conducted an analysis of the prospectively recorded databases from the endocarditis teams of the Amsterdam University Medical Centres (Amsterdam UMC) and the University Medical Centre Utrecht (UMCU). Both hospitals act as referral centres for cardiothoracic surgery and infective endocarditis and have endocarditis teams and an endocarditis registry, as outlined in clinical guidelines (2). The endocarditis registries used different selection criteria and ran over different time periods: the Amsterdam UMC registry contained all patients discussed in the endocarditis team between 1 October 2016 and 1 March 2021 and thus included also patients without IE, whereas the UMCU registry contained only patients with proven IE or a very high suspicion of IE and covered the period from 1 January 2011 to 31 December 2018.

This project was exempt from formal approval by a Medical Ethics

Committee (MEC), as it involved a retrospective analysis of routinely collected information. The MEC of the Amsterdam UMC therefore waived the need for ethical approval (local approval code: W20_044). This study is reported using the STROBE guidelines for reporting of observational studies (5).

2.2. Study population

All adult patients with a definite diagnosis of non-staphylococcal IE according to the 2015 ESC version of the modified Duke criteria were eligible for inclusion (2,6). Patients with staphylococcal endocarditis, blood-culture negative endocarditis and patients without at least one follow-up blood culture were excluded.

2.3. Procedures

We collected the following information: age, gender, history of previous endocarditis, presence of prosthetic material, congenital heart disease, comorbidity as measured using the Charlson Comorbidity Index (CCI) (7), and antibiotic treatment given. The following clinical features were collected: fever, date of resolution of fever, presence of metastatic infectious foci (abscesses or metastatic infection diagnosed clinically or by imaging), vascular and immunological, cardiac imaging findings and localization of the endocarditis. Clinical outcome of patients (mortality, valve surgery) at day 90 was assessed using information from the electronic health record.

There was no protocol in both hospitals for collection of FUBCs after initiation of antimicrobial therapy, but collection of FUBCs was standard practice during the study period. Blood cultures were incubated using the BACTEC (Becton-Dickinson) and BacT/ALERT (Biomérieux) systems, according to manufacturer's instructions and local protocols. Blood cultures were incubated for a minimum of five days.

2.4. Definitions

The index culture was defined as the first blood culture demonstrating clinically significant bacteraemia. A FUBC was defined as a blood culture drawn after the index culture. We collected data on FUBCs

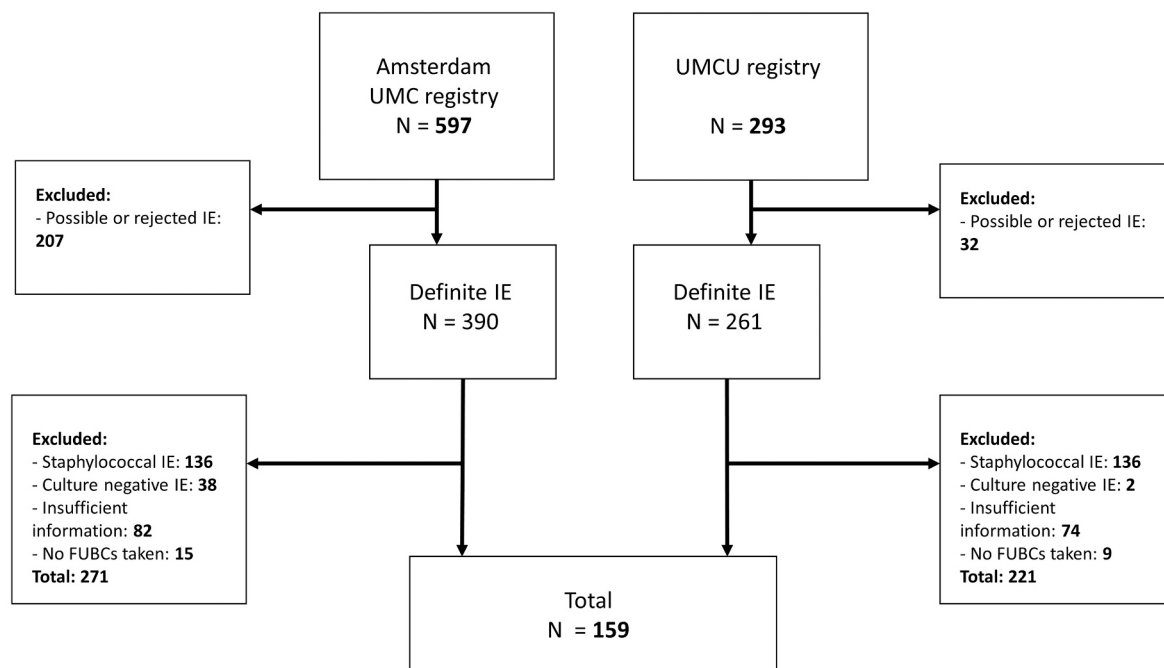


Fig 1. Flowchart of patient selection

Table 2
Demographic and clinical characteristics of included patients.

Variable	
N	159
<i>Demographics</i>	
Age (median, IQR)	67 [59–74]
Male gender	127 (80)
Coronary heart disease	24 (15)
Heart failure *	73 (46)
Diabetes mellitus	32 (20)
Charlson comorbidity index >1	79 (50)
Charlson comorbidity index (median, IQR)	1 [1–3]
<i>Predisposing cardiac conditions</i>	
Congenital cyanotic heart disease	12 (8)
Previous endocarditis	11 (7)
Prosthetic valve #	76 (48)
Implantable cardiac electronic device	26 (16)
ICD	4 (3)
Pacemaker	19 (12)
CRT-D	3 (2)
<i>Clinical signs of infection</i>	
Fever at presentation	129 (85) *
Metastatic infection	59 (37)
Vascular phenomena of endocarditis	14 (9)
Immunological phenomena of endocarditis	20 (13)
Imaging positive for endocarditis	147 (92)
Definite microbiological criterion for endocarditis	125 (79)
Type of valve involved	
Native valve endocarditis	89 (56)
Prosthetic valve endocarditis	70 (44)
CIED endocarditis ##	11 (7)
<i>Microbiology and treatment</i>	
Causative bacterium	
<i>Viridans</i> group streptococci	75 (47)
<i>Enterococcus faecalis</i>	28 (18)
β -hemolytic streptococci	18 (11)
Other bacteria ###	16 (10)
HACEK group	9 (6)
<i>Cutibacterium acnes</i>	6 (4)
<i>Streptococcus pneumoniae</i>	4 (2)
<i>Enterococcus faecium</i>	3 (2)
Time from blood culture to start of effective antimicrobial therapy - days (median + IQR)	1 [0–1]
Received antibiotics effective against causative microorganism within the first 24 h	120 (75)
Underwent cardiac surgery	64 (40)
<i>Outcomes</i>	
Time to resolution of fever – days (median, IQR)	2 [0–5]**
90-day mortality	22 (15) ^
90-day relapse	5 (4) ^^

Data are n (%) unless otherwise indicated.

Abbreviations. ICD: implantable cardioverter defibrillator, CRT-D: cardiac resynchronization therapy defibrillator, CIED: cardiac implantable electronic device, HACEK: *Haemophilus*, *Aggregatibacter*, *Cardiobacterium*, *Kingella*, *Eikenella*.

* Left ventricular ejection fraction <50%

not all patients with a prosthetic valve had proven infection of the prosthetic valve

could occur concurrently with native or prosthetic valve endocarditis

Includes: *Abiotrophia defectiva* (1), *Aerococcus urinae* (2), *Enterobacter cloacae* (1), *Escherichia coli* (2), *Granulicatella adiacens* (1), *Klebsiella pneumoniae* (2), *Lactobacillus rhamnosus* (1), *Lactococcus garviae* (1), *Neisseria elongata* (1), *Pseudomonas aeruginosa* (1), *Rothia mucilaginosa* (1) and *Salmonella enteritidis* (1).

* data missing in 7 patients

** data missing in 56 patients

^ data missing for 16 patients

^^ data missing for 18 patients

up to 7 days after the index culture and we recorded the last day with a positive FUBC.

Fever was defined as a temperature of 38 °C or higher. We defined the time to resolution of fever as the interval between the start of appropriate antimicrobial therapy and the first of three consecutive days

with a temperature <38 °C. Persistence of fever was defined as time to resolution of fever of seven days or more (2). Antimicrobial therapy was considered effective if the antimicrobial agent had in vitro activity against the cultured micro-organism. We defined persistent bacteraemia as any blood culture growing the same microorganism as the index culture ≥ 48 h after start of effective antimicrobial treatment. Thus, patients with a positive culture within 48 h but a negative culture thereafter were classified as not having persistent bacteraemia. Patients with a negative culture after 48 h but a positive culture at 72 h were classified as having persistent bacteraemia (Table 1). This 48 h cut-off after start of antimicrobial treatment is in line with recommendations for defining persistent bacteraemia for *S. aureus* bacteraemia and is similar to the definition used by Lopez et al. (3,4).

2.5. Analysis

2.5.1. Primary and secondary outcomes

Primary outcome was the prevalence of persistent bacteraemia. The secondary outcomes were 90-day mortality and predictive value of persistent bacteraemia on mortality.

Categorical variables are reported as absolute values and percentage, continuous variables as the mean and standard deviation or median and inter-quartile range, where appropriate. To determine the effect of bacterial species, a breakdown of prevalence of persistent bacteraemia is provided by bacterial species group (streptococci, enterococci, HACEK group, non-HACEK Gram-negative bacteria and others). Prevalence (proportion of patients with persistent bacteraemia) is reported with 95% exact binomial confidence intervals. For comparisons between categorical variables we used the χ^2 -test.

The prognostic value of persistent bacteraemia was evaluated using multiple logistic regression, controlling for type of valve (native or prosthetic), microorganism and age. Missing data was handled using complete case analysis. Since the outcomes of the FUBCs were the primary outcome of the study, we refrained from using statistical imputation methods to account for missing culture results. All statistical analyses were performed by using R software environment (R3.6.0, R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2013).

3. Results

3.1. Participants

A total 890 records were screened, 597 from the Amsterdam UMC and 293 from the UMCU. Of these, 159 patients were eligible for inclusion (Fig. 1, patient selection). Main reasons for exclusion were possible or rejected IE (239 patients), staphylococcal IE (272 patients) and insufficient information on the results of FUBCs or moment of start of antimicrobial therapy (156 patients). Only 24 patients were excluded because no FUBCs had been drawn.

3.2. Characteristics of patients

Demographic and clinical features of included patients are summarized in Table 2. Endocarditis was caused by *viridans* group streptococci in 47%, and by beta-hemolytic streptococci in 11%. Prosthetic valve endocarditis was present in 44% of patients, and 7% of patients had an infection related to a cardiac implantable electronic device. Of 159 patients, 75% (120 patients) received antimicrobial therapy effective against the causative microorganism within 24 h of the first culture, which increased to 89% (142 patients) within 48 h of the index culture. Among patients with streptococcal IE, the first appropriate antibiotic used was high dosed penicillin G in 40% (39/97), ceftriaxone in 26% (25/97) and amoxicillin in 16% (16/97) of patients. For enterococcal IE, 47% (15/31) received amoxicillin combined with ceftriaxone, 6% (2/31) received amoxicillin with gentamicin and 34% (11/31) received

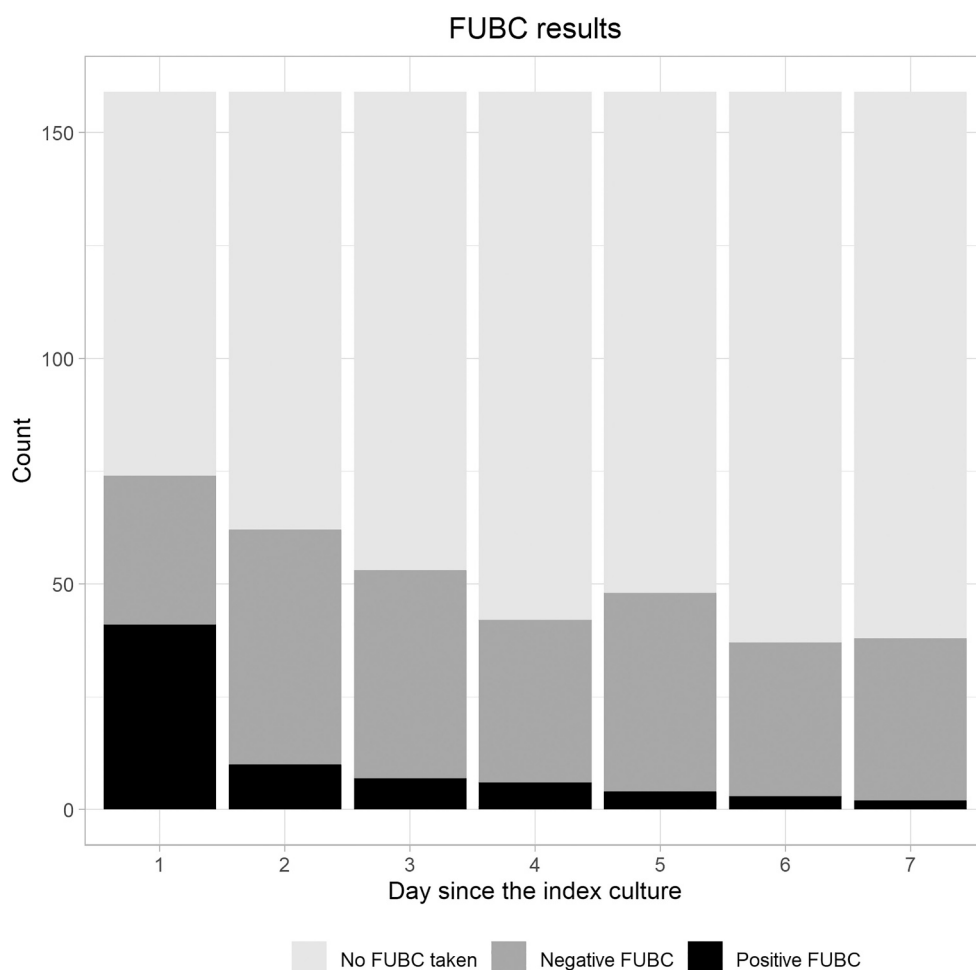


Fig. 2. Overview of FUBC results

vancomycin as first appropriate treatment. Half (80/159) of the patients were referrals from other hospitals. There were no differences between the two hospitals in prevalence of causative bacteria (χ^2 3.06, $p = 0.21$) or in proportion of patients transferred for academic care (χ^2 0.02, $p = 0.89$). Forty percent of patients underwent cardiac surgery (64/159).

3.3. Prevalence of positive follow-up blood cultures

Among the 159 included patients, a median of two [IQR 1–3] follow-up cultures were taken during the first week. Fig. 2 shows the culture results per day as counted since the index culture. In 84% of these patients at least one FUBC was taken within four days of the index culture. There was no significant difference between the two hospitals in percentage of patients who had at least one FUBC taken (χ^2 0.26, $p = 0.61$). Performance of at least one FUBC in the first four days was not different between streptococci, enterococci and other bacteria (χ^2 0.44, $p = 0.68$). Out of 159 patients, only seven (4.4%) had a positive blood culture after 2 days of effective antimicrobial therapy, meeting our definition of persistent bacteraemia: 5/70 patients (7.1%) with prosthetic valve endocarditis and 2/89 (2.2%) with native valve endocarditis ($p = 0.24$). Two of these patients also had persistent fever under antimicrobial treatment. Five out of seven patients with persistent bacteraemia had *Enterococcus faecalis* endocarditis, the other two had endocarditis by non-HACEK-gram-negative bacteria (*Pseudomonas aeruginosa* and *Enterobacter cloacae*). A more detailed description of the seven patients with persistent bacteraemia is provided in Table 3. Of note, of 97 patients with streptococcal endocarditis, none had persistent bacteraemia, while 18% (5/28) of patients with *E. faecalis* endocarditis had persistent

bacteraemia (Table 4).

3.4. Secondary outcome and prognostic value of persistent bacteraemia

Mortality and relapse rate at 90 days were 15% and 4%, respectively. The low prevalence of persistent bacteraemia (7/159 patients) precluded a meaningful statistical evaluation of its prognostic value for mortality.

4. Discussion

Persistent bacteraemia was present in only seven of 159 patients (4.4%) with a non-staphylococcal IE. Five of seven cases involved prosthetic valve endocarditis and in five of seven cases *E. faecalis* was the causative microorganism. No persistent bacteraemia was observed in 97 patients with streptococcal IE.

Our study challenges the dogma that follow-up blood cultures are necessary in all patients with non-staphylococcal infective endocarditis. Supporting evidence for the collection of FUBCs stems mainly from one study, by Lopez et al., reporting that persistent bacteraemia was associated with increased mortality (4). Also in that study, persistent bacteraemia was more common with prosthetic valve endocarditis (PVE) compared to native valve endocarditis (NVE). However, approximately 20% of patients with streptococcal IE had persistent bacteraemia, a finding which strongly contrasts our 0% prevalence in a comparable population. Their prevalence of persistent bacteraemia in enterococcal IE was also higher than in our study (50% versus 18%). Part of the difference might be explained by the fact that the study by Lopez used

Table 3

Detailed information on patients with persistent bacteraemia.

Patient	Age and gender	Valve involved	Causative microorganism	Metastatic infection sites	Duration of bacteraemia (days)	Duration of fever after start AT* (days)	Antimicrobial treatment**	Underwent surgery	Outcome
1	78, female	TAVI	<i>Enterococcus faecalis</i>	No	4	1	Day 1–3: vancomycin Day 3–46: amoxicillin and ceftriaxone	no	Alive after one year, no relapse
2	62, male	Bioprosthetic aortic valve, native mitral valve, pacemaker	<i>Enterococcus faecalis</i>	Yes, small soft tissue abscesses, embolization to mesenteric artery	6	7	Day 1–8: vancomycin and gentamicin Day 8–22: amoxicillin and ceftriaxone	no	Presented with septic emboli and aortic root abscesses, situation considered too unstable for surgery. Died on day 24 from rupture of aortic root abscesses. Alive after one year, no relapse
3	79, male	Native aortic valve	<i>Enterococcus faecalis</i>	Yes, vertebral osteomyelitis without abscesses	4	No fever	Day 1–46: amoxicillin and ceftriaxone	Yes, implantation of bioprosthetic aortic valve on day 50 Indication: heart failure	no
4	67, female	Bioprosthetic aortic valve	<i>Pseudomonas aeruginosa</i>	No	25	21	Day 0: ceftriaxone and gentamicin Day 1–5: piperacillin/tazobactam Day 5–7: piperacillin/tazobactam and tobramycin Day 7–30: ceftazidime and tobramycin Day 30–77: meropenem and tobramycin Day 0–21: meropenem Day 2–53 (planned): ciprofloxacin	no	Relapse after 120 days from index culture. Surgery subsequently performed: bioprosthetic aortic valve replacement 46 days after relapse. Died 9 days after surgery. Cause of death unknown.
5	84, male	No positive imaging, high risk of endocarditis with bioprosthetic aortic valve and pacemaker	<i>Enterobacter cloacae complex</i>	No	8	unknown	Day 0–21: meropenem Day 2–53 (planned): ciprofloxacin	no	Lost to follow-up after day 24 while still on antimicrobial therapy.
6	76, male	Mechanical mitral valve and native aortic valve	<i>Enterococcus faecalis</i>	No	4	No fever	Day 3–7: vancomycin Day 7–84: amoxicillin and ceftriaxone	Yes, re-do mitral valve surgery and implantation of mechanical aortic valve on day 46	Died of unknown causes five months after cessation of antimicrobial therapy.
7	56, female	Bicuspid aortic valve	<i>Enterococcus faecalis</i>	No	3	No fever	Day 0: amoxicillin and ceftriaxone	Yes, bioprosthetic aortic valve implantation and aortic root reconstruction on day 4	Alive two months after cessation of antimicrobial therapy, no relapse.

Abbreviations: AT: Antimicrobial treatment, TAVI: Transcatheter aortic valve implantation.

* Days counted from the index culture, where day 0 is the day of the index culture.

start of antimicrobial therapy and not start of effective antimicrobial therapy to determine the duration of bacteraemia. Selection bias is an additional risk in their study, as 41% of eligible patients were excluded because no follow-up cultures were collected. A recent study among patients with streptococcal bacteraemia found that 12.5% (5/40) of patients with streptococcal IE had persistent bacteraemia, but this study did not take timing of antimicrobial therapy into account (8). In another retrospective cohort study that also did not take timing of antimicrobial therapy into account, only 3% (3/86) of patients with streptococcal

bacteraemia had persistent bacteraemia, compared to 20% (20/102) of patients with enterococcal bacteraemia, which supports our finding that persistent bacteraemia is more common in enterococcal IE (9). These data illustrate the difficulty of comparing studies on this topic, because of differences in the definition of persistent bacteraemia, varying practices in the collection of FUBCs and often limited information about the proportion of patients in whom no FUBCs were collected.

In our cohort, persistent bacteraemia was found only in patients with *E. faecalis* and non-HACEK-gram negative micro-organisms. *E. faecalis* is

Table 4

Prevalence of persistent bacteraemia per microorganism.

Causative bacterium	Patients with persistent bacteraemia (n/N)	Percentage (95% CI) of patients with persistent bacteraemia
Viridans group streptococci	0/75	0 (0–6.1)
β-haemolytic streptococci	0/18	0 (0–21.9)
<i>Streptococcus pneumoniae</i>	0/4	0 (0–60.0)
<i>Enterococcus faecalis</i>	5/28	17.8 (6.8–37.6)
<i>Enterococcus faecium</i>	0/3	0 (0–69.0)
HACEK-group	0/9	0 (0–37.1)
<i>Cutibacterium acnes</i>	0/6	0 (0–48.3)
Other bacteria [#]	2/16	12.5 (2.2–39.6)

[#] Includes: *Abiotrophia defectiva* (1), *Aerococcus urinae* (2), *Enterobacter cloacae* (1), *Escherichia coli* (2), *Granulicatella adiacens* (1), *Klebsiella pneumoniae* (2), *Lactobacillus rhamnosus* (1), *Lactococcus garviae* (1), *Neisseria elongata* (1), *Pseudomonas aeruginosa* (1), *Rothia mucilaginosa* (1) and *Salmonella enteritidis* (1).

a microorganism notably tolerant to killing by β-lactam antibiotics and may require prolonged treatment before blood culture sterilization occurs (1,10). *P. aeruginosa* and *E. cloacae* are notably difficult to treat (11,12). It is possible that the limited penetration of antibiotics into biofilm partially explains the persistent bacteraemia seen in these patients. Extensive perivalvular biofilm formation may also explain why persistent bacteraemia was more common in patients with PVE than in patients with NVE (13,14).

The primary limitation of this study is the retrospective design: blood culture collection was not standardized, and although the vast majority of IE patients had a FUBC collected in the first days, we cannot exclude the possibility that some patients with persistent bacteraemia may have been missed. Additionally, we had to exclude a significant number of patients ($N = 156$) due to missing information on blood culture results. These were mostly patients transferred from other hospitals, in whom the referral letter did not specify the results of FUBCs. We theorize that these limitations are more likely to bias our study results to over-estimation of the prevalence of persistent bacteraemia, as FUBCs are more likely to omitted in patients with a favourable clinical response, and negative cultures are more likely to be left out of a referral letter than positive blood cultures. Another limitation of our study is that due to the low prevalence of persistent bacteraemia: we were unable to perform a meaningful statistical analysis of the prognostic value of persistent bacteraemia. Finally, although we found no persistent bacteraemia in patients with IE caused by HACEK-group bacteria and *C. acnes*, we included too few patients with these bacteria to draw a conclusion for these microorganisms.

In conclusion, our findings demonstrate that persistent bacteraemia 48 h after start of effective antimicrobial therapy is uncommon. We found no persistent bacteraemia in patients with streptococcal IE, and therefore routine collection of FUBCs in patients with streptococcal endocarditis has a low yield. The cases with persistent bacteraemia had either enterococcal or non-HACEK Gram-negative bacillus IE and were predominantly PVE. More data are necessary to determine the prevalence of persistent bacteraemia in rarer causes of IE, and to examine the prognostic effect of persistent bacteraemia.

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Author contributions

TvdV, MS, JvdM, MB and JP designed the study. SMB and JMC provided access to the endocarditis team databases. TvdV and MS collected and analyzed the data and wrote the manuscript. JvdM, MB, JP, SMB and JMC reviewed the manuscript. JvdM supervised the study and manuscript writing. TvdV and MS contributed equally.

Declaration of Competing Interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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