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Short Communication

Association of persistent positive blood cultures and infective endocarditis: A cohort study among patients with suspected infective endocarditis

André Teixeira Antunes[1], Pierre Monney[2], Georgios Tzimas[2], Piergiorgio Tozzi[3], Matthias Kirsch[3], Benoit Guery[1], Matthaios Papadimitriou-Olivgeris[1,4,*]

[1] Infectious Diseases Service, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland
[2] Department of Cardiology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland
[3] Department of Cardiac Surgery, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland
[4] Infectious Diseases Service, Cantonal Hospital of Sion and Institut Central des Hôpitaux (ICH), Sion, Switzerland

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ABSTRACT

Objectives: To ascertain whether infective endocarditis (IE) was associated with persistent bacteraemia/candidaemia among patients with suspected IE.
Methods: This study included bacteraemic/candidaemic adult patients with echocardiography and follow-up blood cultures. Persistent bacteraemia/candidaemia was defined as continued positive blood cultures with the same microorganism for 48 h or more after antibiotic treatment initiation. Each case was classified for IE by the Endocarditis Team.
Results: Among 1962 episodes of suspected IE, IE (605; 31%) was the most prevalent infection type. Persistent bacteraemia/candidaemia was observed in 426 (22%) episodes. Persistent bacteraemia was more common among episodes with *Staphylococcus aureus* bacteraemia compared to episodes with positive blood cultures for other pathogens (32%, 298/933 vs 12%, 128/1029; $P < 0.001$). Multivariable analysis demonstrated that cardiac predisposing factors (aOR 1.84, 95% CI 1.31-2.60), community or non-nosocomial healthcare-associated (2.85, 2.10-3.88), bacteraemia by high-risk bacteria, such as *S. aureus*, streptococci, enterococci or HACEK (1.84, 1.31-2.60), two or more positive sets of index blood cultures (6.99, 4.60-10.63), persistent bacteraemia/candidaemia for 48 h from antimicrobial treatment initiation (1.43, 1.05-1.93), embolic events within 48h from antimicrobial treatment initiation (12.81, 9.43-17.41), and immunological phenomena (3.87, 1.09-1.78) were associated with infective endocarditis.
Conclusions: IE was associated with persistent bacteraemia/candidaemia, along with other commonly associated factors.

Introduction

Blood cultures are the cornerstone for diagnosing infective endocarditis (IE), identifying the microbial cause in over 90% of cases [1]. The significance of blood cultures in diagnosing IE is underscored by their incorporation into all versions of the Duke criteria as a major criterion, alongside the presence of typical intracardiac lesions [1]. In inconclusive initial assessments, persistently positive follow-up blood cultures heighten the suspicion of IE [1]. Follow-up blood cultures are integral for managing intravascular infections like IE, *Staphylococcus aureus* bacteraemia, and candidaemia [1–3].

The primary objective was to ascertain whether IE was associated with persistent bacteraemia/candidaemia among patients with suspected IE.

Methods

This retrospective study was conducted at the Lausanne University Hospital in Switzerland (January 2014-June 2023), merging two cohorts: the cohort of patients suspected of IE, which included patients with blood cultures drawn and echocardiography performed specifically for the research of IE (retrospective

* Corresponding author: Matthaios Papadimitriou-Olivgeris, Infectious Diseases Service, Cantonal Hospital of Sion and Institut Central des Hôpitaux (ICH), Sion, 1951 Switzerland, Tel.: +41 27 603 47 94.
E-mail address: Matthaios.Papadimitriou-Olivgeris@hopitalvs.ch (M. Papadimitriou-Olivgeris).

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Table 1
Comparison of episodes with or without infective endocarditis.

	No infective endocarditis (n = 1357)		Infective endocarditis (n = 605)		*P*
Demographics					
Male sex	944	70%	451	75%	0.027
Age (years)	67	55-77	68	55-77	0.960
Cardiac predisposing factors[a]	208	15%	258	43%	<0.001
IV drug use	78	6%	54	9%	0.011
Congenital heart condition	24	2%	71	12%	<0.001
Prosthetic valve	93	7%	176	29%	<0.001
Prior endocarditis	30	2%	57	9%	<0.001
Cardiac implantable electronic devices	109	8%	118	20%	<0.001
Setting of infection onset					
Community or non-nosocomial healthcare-associated	771	57%	513	85%	<0.001
Nosocomial	586	43%	92	15%	
Isolated pathogen					
Bacteraemia by high-risk bacteria[b]	1015	75%	525	87%	<0.001
S. aureus	666	49%	267	44%	0.045
Streptococcus spp	279	21%	166	27%	0.001
Enterococcus spp	109	8%	83	14%	<0.001
HACEK	2	0.1%	19	3%	0.001
Coagulase-negative staphylococci	109	8%	43	7%	0.523
Gram-positive other than staphylococci, streptococci and enterococci	39	3%	13	2%	0.447
Gram-negative other than HACEK	194	14%	19	3%	<0.001
Fungi	113	8%	11	2%	<0.001
Polymicrobial bacteraemia/candidaemia	166	12%	16	3%	<0.001
>1 positive set of index blood cultures	920	68%	570	94%	<0.001
Duration of bacteraemia/candidaemia (h)	0	0-33	21	0-67	<0.001
Persistent bacteraemia/candidaemia for 48 h or more from antimicrobial	237	18%	189	31%	<0.001
treatment initiation					
Manifestations					
Fever (temperature >38 °C)	1139	84%	506	84%	0.894
Sepsis	561	41%	277	46%	0.068
Embolic events within 48h from antimicrobial treatment initiation	87	6%	246	41%	<0.001
Cerebral embolic events	12	0.9%	126	21%	<0.001
Non-cerebral embolic events	75	6%	180	30%	<0.001
Immunological phenomena	16	1%	53	9%	<0.001
Bone and joint infection[c]	250	18%	126	21%	0.215
Septic arthritis	95	7%	61	10%	0.024
Vertebral osteomyelitis	67	5%	55	9%	0.001
Non-vertebral osteomyelitis	14	1%	3	0.5%	0.299
Prosthetic osteoarticular infection	108	8%	23	4%	0.001

CIED, cardiac implantable electronic devices; HACEK, Haemophilus spp, Aggregatibacter spp, *Cardiobacterium hominis, Eikenella corrodens, Kingella kingae*; ISCVID: International Society of Cardiovascular Infectious Diseases.
Data are depicted as number/percentage or median/Q1-Q3.
[a] Cardiac predisposing factors as described by the 2023 European Society of Cardiology Duke criteria.
[b] *Staphylococcus aureus*, streptococci, enterococci or HACEK.
[c] Excluding chronic osteitis.

inclusion from 2014 to 2017, and prospective inclusion from 2018 onwards), and the bacteraemia/candidaemia cohort (retrospective inclusion from 2015 to 2021).

Inclusion criteria were adult patients with bacteraemia or candidaemia with clinical suspicion of IE, defined as echocardiography performed specifically for the research of IE. Exclusion criteria were the absence of follow-up blood cultures and death within 48 h from antibiotic treatment initiation without negative follow-up blood cultures. Additional exclusion criteria were written refusal to use their data and duplicate episodes.

Data regarding demographics, comorbidities, cardiac predisposing factors [1], blood culture data, systemic manifestations, type of infection, embolic events, were retrieved from patients' electronic health records.

Per internal guidelines, follow-up blood cultures among patients with suspected IE were taken every 24-48 h until clearance. Persistent bacteraemia/candidaemia was defined as continuous positive blood cultures with the same microorganism for 48 h or more from antibiotic treatment initiation, as proposed in previous study on *S. aureus* [4]. IE diagnosis was classified by the Endocarditis Team and other foci of infections were diagnosed by the infectious diseases consultant or treating physician. Antimicrobial treatment initiation was defined as the hour of administration of the first antimicrobial. Sepsis was defined based on the criteria of the Sepsis-3 International Consensus [5].

Data analysis was conducted using SPSS version 26.0 (SPSS, Chicago, Illinois, USA). Categorical variables were analysed using the chi-square or Fisher exact test and continuous variables with Mann-Whitney *U* test. Bivariable and multivariable logistic regression analyses were performed with IE being the dependent variable. Variables with $P < 0.1$ that did not contribute to multicollinearity (variance inflation factor assessment) were used in multivariable analyses. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were calculated. $P < 0.05$ was considered statistically significant.

Results

Of the 2942 episodes across both cohorts, 1962 were included (Supplementary Figure 1). The most frequently isolated pathogen was *S. aureus* (933; 48%). Sepsis was observed in 838 (43%) episodes.

IE (605; 31%) was the most prevalent infection type (Supplementary Table 1); 383 (69%) native valve, 146 (26%) prosthetic valve, and 70 (13%) CIED-lead IE. Transthoracic echocardiography, transoesophageal echocardiography, ^{18}F-Fluorodeoxyglucose

Table 2
Multivariable analysis of predictors of infective endocarditis among patients with suspected infective endocarditis.

	P	aOR (95% CI)
Male sex	0.757	1.05 (0.79-1.39)
Cardiac predisposing factors[a]	<0.001	1.84 (1.31-2.60)
Community or non-nosocomial healthcare-associated	<0.001	2.85 (2.10-3.88)
Bacteraemia by high-risk bacteria[b]	<0.001	1.84 (1.31-2.60)
>1 positive set of index blood cultures	<0.001	6.99 (4.60-10.63)
Persistent bacteraemia/candidaemia for 48 h or more from antimicrobial treatment initiation	0.022	1.43 (1.05-1.93)
Sepsis	0.936	0.99 (0.76-1.28)
Embolic events within 48 h from antimicrobial treatment initiation	<0.001	12.81 (9.43-17.41)
Immunological phenomena	<0.001	3.87 (1.81-8.25)
Septic arthritis	0.194	1.33 (0.86-2.06)
Vertebral osteomyelitis	0.134	1.44 (0.89-2.31)

aOR, adjusted odds ratios; CI, confidence interval; HACEK, *Haemophilus spp, Aggregatibacter spp, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae.*
[a] Cardiac predisposing factors as described by the 2023 European Society of Cardiology Duke criteria.
[b] *Staphylococcus aureus*, streptococci, enterococci or HACEK.

Positron Emission Tomography/Computed Tomography and cardiac CT were performed in 1835 (94%), 933 (48%), 312 (16%), and 55 (3%) episodes, respectively

Persistent bacteraemia/candidaemia for 48h or more was observed in 426 (22%) episodes (Supplementary Figure 2), and was more prevalent among IE episodes compared to those without (31% vs 18%; $P < 0.001$). Among 933 patients with *S. aureus* bacteraemia, 298 (32%) had positive follow-up blood cultures for 48 h or more after the initiation of antimicrobial treatment (Supplementary Table 2). This percentage was higher compared to the rate of episodes exhibiting positive blood cultures for other pathogens, which stood at 12% (128 out of 1029 cases; $P < 0.001$). Table 1 provides an overview of factors associated with IE. Multivariable analysis (Table 2) demonstrated that cardiac predisposing factors ($P < 0.001$; aOR 1.84, 95% CI 1.31-2.60), community or non-nosocomial healthcare-associated infection ($P < 0.001$; aOR 2.85, 95% CI 2.10-3.88), bacteraemia by high-risk bacteria, such as *S. aureus*, streptococci, enterococci or HACEK ($P < 0.001$; aOR 1.84, 95% CI 1.31-2.60), two or more positive sets of index blood cultures ($P < 0.001$; aOR 6.99, 95% CI 4.60-10.63), persistent bacteraemia/candidaemia for 48 h or more from antimicrobial treatment initiation ($P = 0.022$; aOR 1.43, 95% CI 1.05-1.93), embolic events within 48 h from antimicrobial treatment initiation ($P < 0.001$; aOR 12.81, 95% CI 9.43-17.41), and immunological phenomena ($P < 0.001$; aOR 3.87, 95% CI 1.09-1.78) were associated with infective endocarditis.

Discussion

Our findings revealed that among patients with suspected IE, persistent positive blood cultures lasting at least 48 h from antimicrobial treatment initiation was common (22%) and associated with IE, alongside other factors commonly associated with IE, such as bacteraemia by typical microorganisms, non-nosocomial bacteraemia/candidaemia, embolic events, and immunological phenomena, most of them being part of the Duke clinical criteria for the diagnosis of IE [1].

Due to the association between IE and persistent bacteraemia/candidaemia, the persistently positive blood cultures for typical pathogens figure in the major microbiological Duke criterion [1]. Thus, in cases where the initial assessment for diagnosis of IE is inconclusive, the presence of persistently positive follow-up blood cultures should increase the suspicion of IE, by prompting clinicians toward more thorough diagnostic investigations, including echocardiography to identify intracardiac lesions specific to IE [3,6–9], or thoracoabdominal or cerebral imaging to detect indirect signs of IE, such as embolic events or metastatic complications like bone and joint infections typically associated with IE [6,7,10].

The primary observation was the predominant association of *S. aureus* with persistent bacteraemia (32%), whereas this occurrence was less frequent in enterococcal (14%) and notably rare in streptococcal bacteraemia (2%). This association between persistent bacteraemia and IE in *S. aureus* bacteraemic patients led to its inclusion in different prediction rules for diagnosing IE, such as VIRSTA, PREDICT, and LAUSTAPHEN [3,8,9]. Another study also associated *S. aureus* with persistent bacteraemia, while streptococci showed a higher likelihood of bacteraemia clearance [11]. These findings challenge the current practice of routinely collecting follow-up blood cultures until clearance in all patients with IE suspicion, even those with non-staphylococcal IE patients.

Our study has several limitations. Firstly, many patients were included retrospectively and it was conducted at a single center, thereby impacting the generalizability of the results. Secondly, even if the intervals of follow-up blood culture varied (every 1-2 days until clearance), all patients underwent their initial follow-up blood cultures within 48 h of the index blood cultures. Thirdly, due to prospective inclusion in the cohort of patients with suspected IE from 2018 onwards, a higher percentage of patients (17%) did not or were unable to sign the informed consent.

In summary, many patients with suspected IE exhibited persistent bacteraemia/candidaemia, a condition associated with IE. While follow-up blood cultures are indispensable among patients with *S. aureus* bacteraemia and IE suspicion, this might not be the case among those with streptococcal bacteraemia and IE suspicion, as 98% of them clear their bacteraemia within 48 h from antimicrobial treatment initiation.

Declarations of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethical approval

Ethical approval for the study was obtained from the ethics committee of the Canton of Vaud (CER-VD 2021-02516, CER-VD 2017-02137).

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Author contributions

MPO, PM and BG conceived the idea. ATA, PM, GT, PT, MK, BG and MPO collected the patients' data. MPO supervised the project. MPO performed the analysis and interpreted the results. ATA wrote the manuscript. All authors contributed to manuscript revision and read and approved the submitted version.

Data statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2024.107022.

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