Infective endocarditis in pregnant women without intravenous drug use: a multicentre retrospective case series

Laura Escolà-Vergé, Pau Rello, Charles Declerck, Vincent Dubée, Fréderic Rouleau, Xavier Duval, Gilbert Habib, Yoan Lavie-Badie, Guillaume Martin-Blondel, Lydie Porte, et al.

▶ **To cite this version:**

Laura Escolà-Vergé, Pau Rello, Charles Declerck, Vincent Dubée, Fréderic Rouleau, et al.. Infective endocarditis in pregnant women without intravenous drug use: a multicentre retrospective case series. Journal of Antimicrobial Chemotherapy, 2022, 10.1093/jac/dkac258 . hal-03777460

HAL Id: hal-03777460
https://univ-rennes.hal.science/hal-03777460

Submitted on 21 Sep 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

JAC-2022-0428.R1-FINAL

Infective endocarditis in pregnant women without intravenous drug use: a multicentre retrospective case series

Laura ESCOLÀ-VERGÉ[1,2], Pau RELLO[3], Charles DECLERCK[4,5], Vincent DUBÉE[4,5], Fréderic ROULEAU[5,6], Xavier DUVAL[5,7], Gilbert HABIB[5,8], Yoan LAVIE-BADIE[5,9], Guillaume MARTIN-BLONDEL[5,10], Lydie PORTE[5,10], Kevin BOUILLE[5,11], François GOEHRINGER[5,12], Christine SELTON-SUTY[5,13], Cristiane da Cruz LAMAS[14], Francisco NACINOVICH[15], Nahema ISSA[16], Clémence RICHAUD[5,17], Nadjib HAMMOUDI[18], Francisco José BARRANCO[19], Benito ALMIRANTE[1,2], Pierre TATTEVIN[5,20]† and Nuria FERNÁNDEZ-HIDALGO[1,2]*†

1. Servei de Malalties Infeccioses, Hospital Universitari Vall d'Hebron, Barcelona, Spain. Universitat Autònoma de Barcelona, Barcelona, Spain;

2. CIBERINFEC, ISCIII-CIBER de Enfermedades Infecciosas, Instituto de Salud Carlos III;

3. Department of Cardiology, Hospital Universitari Vall d'Hebron, Barcelona, Spain;

4. Infectious Diseases Department, Angers University Hospital, Angers, France;

5. Association pour l'Etude et la Prévention de l'Endocardite Infectieuse (AEPEI) Study group.

6. Department of Cardiology, Angers University Hospital, Angers, France;

7. Infectious Diseases, CIC Inserm 1425, IAME, Bichat Hospital, APHP, Paris Cité University, Paris, France;

8. Cardiology Department, La Timone Hospital, Aix Marseille University, IRD, APHM, Marseille, France;

9. Heart Valve Center, Toulouse University Hospital, Toulouse, France;

10. Department of Infectious and Tropical Diseases, Toulouse University Hospital, Toulouse, France;

11. Infectious Diseases, CHU Besancon, Besancon, France;

ACCEPTED MANUSCRIPT / CLEAN COPY

12. Infectious Diseases Department, Nancy University Hospital, Nancy, France;

13. Cardiology Department, CHU Nancy, Nancy, France;

14. Infectious Diseases. Instituto Nacional de Cardiologia. Unigranrio. Instituto Nacional de Infectologia Evandro Chagas, Fiocruz, Rio de Janeiro, Brazil;

15. Infectious Diseases, Instituto Cardiovascular Buenos Aires, Buenos Aires, Argentina;

16. Infectious Diseases and ICU, Groupe Saint-André Hospital, University Hospital, Bordeaux, France;

17. Internal Medecine, Institut Mutualiste Montsouris, Paris, France;

18. Sorbonne Université, ACTION Study Group, INSERM UMR_S 1166, and Hôpital Pitié-Salpêtrière (AP-HP), Paris, France;

19. Maternal Fetal Medicine Unit, Department of Obstetrics, Vall d'Hebron Barcelona Hospital Campus, Universitat Autònoma de Barcelona, Barcelona, Spain;

20. Infectious Diseases and ICU, Pontchaillou University Hospital, Rennes, France

*Corresponding author. E-mail: nufernan@gmail.com

†These authors contributed equally to this work.

Running title: IE in non-IVDU pregnant women

ACCEPTED MANUSCRIPT / CLEAN COPY

Objectives: To describe the clinical features and outcomes of infective endocarditis (IE) in pregnant women who do not inject drugs.

Methods: A multinational retrospective study was performed at 14 hospitals. All definite IE episodes between January 2000 and April 2021 were included. The main outcomes were maternal mortality and pregnancy-related complications.

Results: Twenty-five episodes of IE were included. Median age at IE diagnosis was 33.2 years (IQR 28.3–36.6) and median gestational age was 30 weeks (IQR 16–32). Thirteen (52%) patients had no previously known heart disease. Sixteen (64%) were native IE, 7 (28%) prosthetic and 2 (8%) cardiac implantable electronic device IE. The most common aetiologies were streptococci (*n*=10, 40%), staphylococci (*n*=5, 20%), HACEK group (*n*=3, 12%) and *Enterococcus faecalis* (*n*=3, 12%). Twenty (80%) patients presented at least one IE complication; the most common were heart failure (*n*=13, 52%) and symptomatic embolism other than stroke (*n*=4, 16%). Twenty-one (84%) patients had surgery indication and surgery was performed when indicated in 19 (90%). There was one maternal death and 16 (64%) patients presented pregnancy-related complications (11 patients ≥1 complication): 3 pregnancy losses, 9 urgent Caesarean sections, 2 emergency Caesarean sections, 1 fetal death, and 11 preterm births. Two patients presented a relapse during a median follow-up of 3.1 years (IQR 0.6–7.4).

Conclusions: Strict medical surveillance of pregnant women with IE is required and must involve a multidisciplinary including obstetricians and neonatologists. Furthermore, the potential risk of IE during pregnancy should never be underestimated in women with previously known underlying heart disease.

ACCEPTED MANUSCRIPT / CLEAN COPY

Introduction

Infective endocarditis (IE) is a rare but potentially severe disease, and it is even more uncommon in pregnant women,[1–3] with an estimated incidence of 0.00 002% among pregnant patients in a recent study.[4] The main reported risk factors are IVDU and congenital or rheumatic cardiac diseases, but in most recent series women with IVDU are the predominant group.[5–7] Although lower than previously reported, maternal and fetal mortality are still around 5%–11% and 0%–16%, respectively.[3–6,8]

Contemporary clinical characteristics and prognosis of pregnant women with IE who do not inject drugs remain unknown. The aim of this study was to describe the clinical features and outcomes of a contemporary multinational cohort of IE in pregnant women who do not inject drugs.

ACCEPTED MANUSCRIPT / CLEAN COPY

Methods

This retrospective observational study was promoted and coordinated by Hospital Universitari Vall d'Hebron, a referral centre for IE and cardiac surgery in Barcelona, Spain. We asked 64 centres whether they had cases of IE in pregnant women between 2000 and 2021 (42 centres in France, 11 in Spain, 2 in Italy, 2 in Sweden, 2 in Denmark, 1 in Argentina, 1 in Brazil, 1 in Australia, 1 in USA and 1 in Lebanon). All of the centres answered, but only 14 centres had treated pregnant women with endocarditis (11 from France, 1 from Spain, 1 from Argentina and 1 from Brazil). All of them were centres with cardiac surgery capabilities. Only adult non-IVDU pregnant women (≥18 years) with definite IE according to the current Duke criteria at the time of IE diagnosis were included. IVDU was identified through medical records and women with IVDU were excluded.

A standardized case report form was designed and sent to the participating hospitals. We collected information on patient demographics, comorbidities, predisposing factors, microbiological data, ECG findings, medical and surgical treatment, pregnancy-related complications and follow-up. Variable definitions are the same as in previous studies.[9] Main outcomes were maternal mortality and pregnancy-related complications. Pregnancy-related complications included pregnancy loss (gestational age <24 weeks), emergency Caesarean section, fetal death (gestational age ≥24 weeks) and fetal morbidity (preterm birth, Apgar score <7, neonatal intensive care admission). Data were recorded anonymously and sent to the coordinating centre where a database was created specifically for this study.

Ethics

The study was approved by the Ethics Committee of the promoting and coordinating centre (Hospital Universitari Vall d'Hebron, PR(AG)361/2021). Informed consent from patients was not required.

ACCEPTED MANUSCRIPT / CLEAN COPY

Results

After excluding two cases (one due to IVDU and one because it was a postpartum IE), 25 episodes of IE in 25 pregnant patients were included in the present study. Table 1 summarizes demographic, clinical characteristics and outcomes of the 25 episodes of IE. Table S1 (Table S1 is available as Supplementary data at *JAC* Online) describes in detail each included patient. Median age at IE diagnosis was 33.2 years (IQR 28.3–36.6) and median gestational age at diagnosis was 30 weeks (IQR 16–32). Median Charlson Comorbidity Index was 0 (IQR 0–0). Thirteen (52%) patients had no previously known heart disease. Seven out of 12 remaining patients had prosthetic valves and three had cardiac implantable electronic devices (CIED). A detailed description of heart conditions is depicted in Table 1.

The most common symptoms were fever (*n*=24, 96%), asthenia (*n*=8, 32%) and dyspnoea (*n*=6, 24%). Sixteen (64%) patients were native valve IE, 7 (28%) were prosthetic IE and 2 (8%) were CIED IE. The mitral valve alone (10 patients, 40%) and the aortic valve alone (6 patients, 24%) were the most frequent affected.

The most common microorganisms were viridans streptococci (*n*=10, 40%), staphylococci (*n*=5, 20%), HACEK group (*n*=3, 12%) and *Enterococcus faecalis* (*n*=3, 12%).

A transthoracic ECG was performed in all patients and a transoesophageal ECG in 17 (68%). Most common echocardiographic findings were vegetations (*n*=23, 92%), new moderate or severe valvular regurgitation (*n*=16, 64%) and perivalvular abscess (*n*=4, 16%). A previously unknown heart disease was diagnosed in two patients (a bicuspid aortic valve and a mitral valve prolapse).

Twenty (80%) patients presented at least one IE complication. The most common complications were heart failure (*n*=13, 52%) and symptomatic embolism other than stroke (*n*=4, 16%). Twenty-one (84%) patients had surgical indication according to current ESC guidelines and surgery was performed when indicated in 19 (90%) of those patients. In one case, surgery was not performed due to a high risk for the fetus (in this woman the indication was prevention of embolism) and in another one due to a surgical procedure that was presumed difficult (IE on a CIED implanted 15 years before).

There was one maternal death that occurred during surgery. Sixteen (64%) patients presented pregnancy-related complications, including 11 with more than one

ACCEPTED MANUSCRIPT / CLEAN COPY

complication. There were 3 pregnancy losses (2 in the first trimester of pregnancy and 1 in the second), 9 emergency Caesarean sections and 2 urgent Caesarean sections (9 Caesarean sections were performed prior surgery), 1 fetal death and 11 preterm births (2 required neonatal intensive care admission).

Median hospital stay was 32.5 (IQR 24–41.5) days and median follow-up duration after hospital discharge was 3.1 (IQR 0.6–7.4) years. Two patients presented a relapse during follow-up (one patient with *Staphylococcus aureus* CIED IE who was not operated despite surgical indication relapsed at 27 days after antibiotic treatment discontinuation, and one patient with streptococcal prosthetic IE without surgical indication initially relapsed at Day 7 after antimicrobial treatment discontinuation): both had favourable outcomes with a new course of antibiotic treatment and cardiac surgery. Two other patients also required valve surgery during follow-up (one 14 months after valvuloplasty due to recurrence of severe mitral regurgitation and the other 10 years after bioprosthesis implantation due to prosthesis degeneration).

ACCEPTED MANUSCRIPT / CLEAN COPY

Discussion

This multinational retrospective study demonstrates that: (i) IE in non-IVDU pregnant women is very uncommon, as only 14 out of 64 hospitals had a case, with only 25 cases collected over 21 years; (ii) IE in non-IVDU pregnant patients usually affects women with previous heart disease, sometimes undiagnosed before IE; (iii) the most common responsible microorganisms are the same as for non-pregnant patients;[1] and (iv) IE complications occur in most cases and frequently require surgery with a high rate of pregnancy-related complications.

Previous studies focused on IE in pregnant women with IVDU,[5–7] and found that the most common aetiology was staphylococci, with a predominance of right-sided IE, and no need for surgical treatment in most cases.[5,6] In the study reported herein, we found mostly left-sided IE, with streptococcal predominance and a high rate of cardiac surgery, probably related to the fact that IVDU women were excluded.

In comparison with cases included in the recent ESC-EORP EURO-ENDO registry, in our study there was a lower proportion of acute renal failure (4% versus 17.7%), but a higher rate of heart failure (52% versus 14.1%).[10] This may be related, respectively, to the younger age and morbidity of the patients, and to the cardiovascular and haemodynamic changes related to pregnancy that may favour heart failure.

Cardiac surgery and cardiopulmonary bypass are associated with significant fetus and mother mortality.[11] In our series, Caesarean section was performed in nine cases prior surgery. Only one woman died, during surgery, with fetal loss. Two other fetal losses occurred at 3 and 4 days after surgery, respectively, confirming the high risk of cardiac surgery during pregnancy and suggesting that may be Caesarean section or vaginal delivery should be performed whenever possible prior to valve surgery.

Maternal mortality has decreased in comparison to old series,[5,6] probably due to a higher prevalence of IVDU patients who are usually younger and have right-sided IE, both being associated with a better prognosis. However, in our series that does not include IVDU patients, maternal mortality is also lower. A recent national cohort study from the USA found that IE during pregnancy was not associated with additional risks for adverse outcome when compared with IE in non-pregnant women.[4] Unfortunately, the absence of a control group of non-pregnant women with IE in the same age range does not allow us to verify this data in our cohort. In the US study, pregnant women

ACCEPTED MANUSCRIPT / CLEAN COPY

with IE had worse maternal and fetal outcomes than pregnant women without IE,[4] in line with the high fetal mortality observed in our cohort.

This study has several limitations, such as the small sample size, the possible variability of patient management between centres and the absence of a control group. In addition, our method of case ascertainment is limited by provider recollection and provider presence at that facility over the entire study period. Finally, the retrospective nature of the study does not allow us to assess if obstetric complications are related to the maternal condition. However, the multicentre nature of the study is a remarkable strength. Furthermore, although IE in pregnant woman is a very rare disease and pregnancy is a variable absent in many databases, most investigators in this field remember these patients due to the associated high emotional impact.

In conclusion, in our series IE in pregnant patients who do not use intravenous drugs is frequently associated with IE complications, requires cardiac surgery in most of the cases and is associated with high fetal mortality. Therefore, strict medical surveillance of pregnant women with IE is required and must involve a multidisciplinary team, including not only cardiologists, surgeons and infectious diseases specialists with expertise in IE but also obstetricians and neonatologists, in order to improve both maternal and fetal prognosis. Furthermore, the potential risk of IE during pregnancy should never be underestimated in women with previously known underlying heart disease. These patients should receive prophylactic antibiotics when indicated, and blood cultures should be early performed in case of unexplained fever.

ACCEPTED MANUSCRIPT / CLEAN COPY

Acknowledgements

Participating sites and Investigators

Argentina: Francisco Nacinovch, MD (Instituto Cardiovascular Buenos Aires, Buenos Aires).

Brasil: Cristiane da Cruz Lamas, MD, PhD (Instituto Nacional de Cardiologia. Instituto Nacional de Infectologia Evandro Chagas, Fiocruz, Rio de Janeiro, Brazil).

France: Charles Declerck, MD, Vincent Dubée, MD, PhD, Fréderic Rouleau, MD (Angers University Hospital, Angers); Kevin Bouiller, MD, PhD (Besançon University Hospital, Besançon), Nahema Issa, MD (Bordeaux University Hospital, Bordeaux); Gilbert Habib, MD, PhD (La Timone Hospital, Marseille); François Goehringer, MD, Christine Selton-Suty, MD (Nancy University Hospital, Nancy); Xavier Duval, MD, PhD (Bichat Hospital, Paris); Clémence Richaud, MD, MS (Institut Mutualiste Montsouris, Paris); Nadjib Hammoudi, MD, PhD (Hospital Pitié-Salpêtrière, Paris); Pierre Tattevin, MD, PhD (Pontchaillou University Hospital, Rennes); Yoan Lavie-Badie, MD, Guillaume Martin-Bondel, MD, PhD, Lydie Porte MD (Toulouse University Hospital, Toulouse).

Spain: Benito Almirante, MD, PhD, Laura Escolà-Vergé, MD, PhD, Rubén Fernández, MD, Nuria Fernández-Hidalgo, MD, PhD, MSc, Maria Teresa Gonzàlez-Alujas, MD, Olga Maisterra, MD, PhD, María Nazarena Pizzi, MD, PhD, Pau Rello, MD, Remedios Ríos, MD, Albert Roque, MD, Antonia Sambola, MD, PhD, Toni Soriano, MD, Carlota Vigil, MD, Antònia Pijuan MD, PhD (Hospital Universitari Vall d'Hebron, Barcelona).

Funding

L.E.-V. has a Juan Rodés contract in the call 2020 Strategic Action Health from Instituto de Salud Carlos III of Spanish Health Ministry for the years 2021–24.

Transparency declarations

None to declare.

ACCEPTED MANUSCRIPT / CLEAN COPY

Supplementary data

Table S1 is available as Supplementary data at *JAC* Online.

ACCEPTED MANUSCRIPT / CLEAN COPY

References

1. Habib G, Lancellotti P, Antunes MJ *et al*. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC)Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J* 2015; **36**: 3075–128.

2. Ramlakhan KP, Johnson MR, Roos-Hesselink JW. Pregnancy and cardiovascular disease. *Nat Rev Cardiol* 2020; **17**: 718–31.

3. Yuan S-M. Infective Endocarditis during pregnancy. *J Coll Physicians Surg Pak* 2015; **25**: 134–9.

4. Dagher MM, Eichenberger EM, Addae-Konadu KL *et al*. Maternal and fetal outcomes associated with infective endocarditis in pregnancy. *Clin Infect Dis* 2021; **73**: 1571-9.

5. Adesomo A, Gonzalez-Brown V, Rood KM. Infective Endocarditis as a Complication of Intravenous Drug Use in Pregnancy: A Retrospective Case Series and Literature Review. *AJP Rep* 2020; **10**: e288–93.

6. Sinner GJ, Annabathula R, Viquez K *et al*. Infective endocarditis in pregnancy from 2009 to 2019: the consequences of injection drug use. *Infect Dis* 2021; **53**: 633-9

7. Morelli MK, Veve MP, Shorman MA. Maternal Bacteremia Caused by *Staphylococcus Aureus* With a Focus on Infective Endocarditis. *Open Forum Infect Dis* 2020; **7**: ofaa239.

8. Kebed KY, Bishu K, Al Adham RI *et al*. Pregnancy and Postpartum Infective Endocarditis. *Mayo Clin Proc* 2014; **89**: 1143–52.

9. Escolà-Vergé L, Fernández-Hidalgo N, Larrosa MN *et al*. Secular trends in the epidemiology and clinical characteristics of *Enterococcus faecalis* infective endocarditis at a referral center (2007–2018). *Eur J Clin Microbiol Infect Dis* 2021; **40**: 1137-48.

ACCEPTED MANUSCRIPT / CLEAN COPY

10. Habib G, Erba PA, Iung B *et al.* Clinical presentation, aetiology and outcome of infective endocarditis. Results of the ESC-EORP EURO-ENDO (European infective endocarditis) registry: a prospective cohort study. *Eur Heart J* 2019; **40**: 3222–32.

11. Weiss BM, von Segesser LK, Alon E *et al*. Outcome of cardiovascular surgery and pregnancy: a systematic review of the period 1984-1996. *Am J Obstet Gynecol* 1998; **179**: 1643–53.

ACCEPTED MANUSCRIPT / CLEAN COPY

Table 1. Demographic features, comorbidities, presumed source of infection, echocardiography findings, complications, surgical treatments, and maternal and fetal outcomes of 25 definite episodes of IE in pregnant patients

	Patients, *N*=25
Participant country	
France	20 (80)
Spain	3 (12)
Argentina	1 (4)
Brazil	1 (4)
Demographics	
Age (years), median (range)	33.5 (19.7–41.1)
Country of origin	
France	15 (60)
Spain	2 (8)
Nigeria	2 (8)
Guinea Conakry	1 (4)
India	1 (4)
Argentina	1 (4)
Brazil	1 (4)
Morocco	1 (4)
Unknown	1 (4)
Comorbidities	
Charlson comorbidity index, median (range)	0 (0–1)
Rheumatic heart disease	6 (24)
Prosthetic valve	4
Congenital heart disease	2 (8)
Prosthetic valve	1
CIED	1
Bicuspid aortic valve	2 (8)
Prosthetic valve	2
Congenital atrioventricular block	2 (8)

ACCEPTED MANUSCRIPT / CLEAN COPY

CIED	2
Gestational age at diagnosis (weeks), median (IQR)	30 (16–32)
Type of acquisition	
Community acquired	22 (88)
Non-nosocomial healthcare-associated infection	2 (8)
Nosocomial healthcare-associated infection	1 (4)
Presumed source of infection	
Unknown	9 (36)
Oral	9 (36)
Skin	3 (12)
Genitourinary	2 (8)
Gastrointestinal	1 (4)
Catheter-related bacteraemia	1 (4)
Duration of symptoms before IE diagnosis (days), median (IQR)	21 (4–55)
N=23	
Type of IE	
Native valve IE	16 (64)
Prosthetic valve IE	7 (28)
CIED IE	2 (8)
Localization of IE	
Mitral	10 (40)
Aortic	6 (24)
Aortic and mitral	4 (16)
Tricuspid	1 (4)
Pulmonary	1 (4)
Endocardium	1 (4)
Aortic and pulmonary	1 (4)
Unknown	1 (4)
Aetiologies	
Streptococcus spp.[a]	10 (40)
Staphylococcus spp.[b]	5 (20)
HACEK group[c]	3 (12)
Enterococcus faecalis	3 (12)

ACCEPTED MANUSCRIPT / CLEAN COPY

Unknown	2 (8)
Candida albicans	1 (4)
Lactobacillus spp.	1 (4)
Echocardiographic findings[d]	
Vegetations	23 (92)
New moderate or severe valve regurgitation	16 (64)
Perivalvular abscess	4 (16)
Prosthetic obstruction (*N*=7)	2/7 (29)
Valve perforation	1 (4)
Fistula	1 (4)
Mitral chordae rupture	1 (4)
IE complications (some patients had >1 complication)	20 (80)
Heart failure	13 (52)
Symptomatic embolisms (other than CNS)[e]	5 (20)
Symptomatic CNS complications[f]	3 (12)
New renal failure	1 (4)
Septic shock	1 (4)
Surgery indicated	21 (84)
Indications for surgery according to current ESC guidelines (some patients had >1 indication), *N*=21	
Heart failure	11/21 (52)
Prevention of embolisms	9/21 (43)
Uncontrolled infection	5/21 (24)
Infected CIED	2/21 (10)
Surgery performed during the active phase of infection (if indicated), *N*=21	18/21 (86)
Maternal death	1 (4)
Pregnancy-related complications (some patients ≥1 complication)	16 (64)
Pregnancy loss	3 (12)
Emergency Caesarean section	9 (36)
Urgent Caesarean section	2 (8)
Fetal death	1 (4)
Preterm birth[g]	11 (44)

ACCEPTED MANUSCRIPT / CLEAN COPY

Overall duration of antibiotic treatment (days), median (IQR)	34 (30–45)
Duration of antibiotic treatment in survivors (days), median (IQR), *N*=24	35.5 (30–46.5)
Duration of hospitalization (days), median (IQR), *N*=24[h]	32.5 (24–41.5)
Duration of follow-up after hospital discharge (survivors) (years), median (IQR), *N*=23[i]	3.1 (0.6–7.4)
Surgery during follow-up (survivors), *N*=23[i]	2/23 (9)
Relapse during follow-up (survivors), *N*=23[i]	2/23 (9)

ESC, European Society of Cardiology.

Data are expressed as *n* (%).

[a]*Streptococcus oralis* (*n*=3), *Streptococcus mitis* (*n*=2), *Streptococcus sanguinis* (*n*=2), non-specified viridans group streptococci (*n*=2) and *Streptococcus mutans* (*n*=1).

[b]*S. aureus* (*n*=3) and *S. epidermidis* (*n*=2).

[c]*Haemophilus parainfluenzae* (*n*=2) and *Cardiobacterium hominis* (*n*=1).

[d]A previously unknown heart disease was diagnosed in two patients by echocardiography (a bicuspid aortic valve and a mitral valve prolapse).

[e]In two cases in the lungs, one in the spleen, one in the kidneys and spleen, and one in the right coronary artery (post-operative).

[f]Two an ischaemic stroke and one a mycotic aneurysm.

[g]Two preterm newborns required ICU admission.

[h]One patient was transferred to a hospital from another country and the date of discharge is not known.

[i]One patient lost to follow-up and one died during the index hospitalization.

ACCEPTED MANUSCRIPT / CLEAN COPY