Infective endocarditis due to *Streptococcus dysgalactiae*: clinical presentation and microbiological features

Anna Bläckberg¹ · Bo Nilson^{2,3} · Volkan Özenci^{4,5} · Lars Olaison^{6,7} · Magnus Rasmussen¹

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Abstract

Knowledge of infective endocarditis (IE) caused by *Streptococcus dysgalactiae* (SD) is limited. This study aimed to identify the clinical and microbiological features of SD-caused IE and to investigate any possible synergy between penicillin and gentamicin on SD isolates. Cases of IE 2008–2016 due to SD reported to the Swedish Registry of Infective Endocarditis (SRIE) were identified. Isolates were *emm* typed and synergy between antibiotics was determined in time-kill experiments. Medical records were reviewed and SD-cases were compared to cases of IE due to other pathogens reported to the SRIE. Fifty cases of SD-caused IE were confirmed. *emm* types stC74a, stG62647, and stG643 were most commonly encountered. The patients had a median age of 74 years (range 38–93) and were significantly older compared to patients with *Staphylococcus aureus*-caused IE, (65 years ($p = 0.003$)). The median time to diagnosis from symptom onset was 1 day for patients with SD-caused IE which was less compared to patients with IE due to the other pathogens (2–15 days). Embolization was seen in 46% and the in-hospital mortality was 8%. Etest-based methods did not indicate any synergy between penicillin and gentamicin whereas synergy was noted for four out of nine isolates applying time-kill assays. This is the largest study of SD-caused IE, a condition with an acute onset predominantly affecting elderly people. Synergy between penicillin and gentamicin against some SD isolates was distinguished but the potential benefit of this must be weighed against the risk of aminoglycoside side effects.

Keywords *Streptococcus dysgalactiae* · Infective endocarditis · Antibiotic susceptibility · *emm* type

Introduction

During the past years, invasive infections due to *Streptococcus dysgalactiae* (SD) have been increasingly reported worldwide [1]. Human pathogenic SD most commonly belongs to the subspecies *equisimilis* and expresses Lancefield group C, G, or infrequently group A antigen [2]. Species determination of SD has been considerably improved by the introduction of matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) [3]. Further typing of SD is based on the sequence of the 5'-part of the *emm* gene encoding the hypervariable NH₂-terminal part of the cell wall-attached M protein [4, 5]. Several molecular epidemiological studies have investigated the distribution of *emm* types among SD isolates in attempt to link different *emm* types to invasive or non-invasive infections [1, 6, 7].

SD can cause both superficial and invasive infections often with a focus in soft tissues [8]. A severe type of infection caused by SD is infective endocarditis (IE). Oppeggaard et al.

✉ Anna Bläckberg
anna.blackberg@med.lu.se

¹ Department of Clinical Sciences, Division of Infection Medicine, Lund University, BMC B14 Baravägen 27, 223 63 Lund, Sweden

² Clinical Microbiology, Labmedicin, Region Skåne, Lund, Sweden

³ Department of Laboratory Medicine Lund, Section of Medical Microbiology, Lund University, Lund, Sweden

⁴ Department of Clinical Microbiology, Karolinska University Hospital, Huddinge, Stockholm, Sweden

⁵ Division of Clinical Microbiology, Department of Laboratory Medicine, Karolinska Institutet, Stockholm, Sweden

⁶ Department of Infectious Diseases, Sahlgrenska University Hospital, Institute of Biomedicine, University of Gothenburg, Gothenburg, Sweden

⁷ Swedish Society of Infectious Diseases, Swedish Registry of Infective Endocarditis, Gothenburg, Sweden

recently described nine cases of SD-caused IE and reported the onset of symptoms to be rapid and the disease course to be severe [9]. In addition, Lother et al. identified 12 cases with group C- or G-caused IE, four cases of definitive, and eight cases of possible IE, out of 209 events of groups C and G bacteremia. Of these 12 cases, a majority had embolic events with rapid and progressive disease and considerable mortality rate [10]. Other studies have focused on all β -hemolytic streptococci (BHS) and typically the majority of cases have been attributed to group B streptococci, with no species determination performed to determine if some isolates were SD. In one such study, El Rafei et al. showed large vegetations and high rate of systemic embolization in BHS-caused IE [11]. Another study by Lefort et al. presented high rate of extra cardiac complications in IE caused by BHS [12].

Intravenous antibiotic treatment for several weeks is the backbone of IE treatment, but occasionally valve surgery is needed. Previous studies have implied that penicillin and aminoglycosides (AG) have a synergistic effect on SD in vitro [13]. Swedish guidelines [14] recommend β -lactam monotherapy in IE caused by BHS based on a lack of benefit from combination therapy in group B streptococcal IE [15] whereas international guidelines advocate combination therapy [16].

Aminoglycosides are well known for their nephrotoxicity and ototoxicity [17, 18] but are still recommended in BHS-caused IE [16, 19]. In a retrospective study based on 40 patients with IE caused by group G streptococci, Smyth et al. showed that patients treated with combination therapy had better outcome than single therapy [20]. Another more recent study could not demonstrate any difference in outcome for patients treated with β -lactam monotherapy compared to combination therapy in BHS-caused IE [11].

This study aimed to delineate clinical features of SD in IE, to describe which *emm* types are prevalent in the condition and to investigate the antibiotic susceptibility and possible synergistic effect between penicillin and gentamicin on SD isolates from IE.

Material and methods

Collection of bacterial isolates

In 1995, the Swedish Registry of Infective Endocarditis (SRIE) organized by the Swedish Society of Infectious Disease was established. All 30 departments of infectious diseases (ID) in Sweden have participated since its inception. The ID departments have regional responsibility for care of patients with severe infections and report cases treated at the respective clinic. In order to identify cases of IE with SD, cases caused by BHS of groups A, C, and G were identified from the SRIE between the years 2008 and 2016. Stored bacterial isolates were collected from relevant laboratories and

were cultivated on blood agar plates in 5% CO₂ at 37 °C. To determine the species identity, they were reanalyzed with Microflex MALDI-TOF MS (Bruker, Bremen, Germany) using the direct transfer or the extraction protocol described elsewhere [21] and the software FlexControl and MBT Compass 4.1, with reference database MBT-BDAL-7321 (MALDI Biotyper; Bruker). A score value above 2.0 was required for species determination.

emm typing

Typing based on the sequence of the *emm* gene was performed as described at (<http://www.cdc.gov/streplab>) and the *emm* gene sequences were compared with those in the CDC *emm* sequence database. An *emm* sequence that presented >98% identity with the CDC reference strain was identified as that certain *emm* type.

Antibiotic synergy

Minimal inhibitory concentration (MIC) was determined by broth microdilution and Etest (BioMerieux, Marcy l'Etoile, France, Sweden). Mueller-Hinton agar (MHA), with defibrinated horse blood and β -NAD, plates were used for Etest MIC determination and the Etest synergy method. Mueller-Hinton broth enriched with β -NAD and defibrinated horse blood was prepared [22] to define MIC and minimal bactericidal concentration (MBC) through the broth microdilution method [23, 24]. Antibiotics used were benzyl-penicillin (Astra Zeneca) and gentamicin (Schering-Plough). Etest synergy was performed according to the MIC:MIC ratio method and cross or 90° angle method [25]. Etest synergy methods were performed on all isolates and the summation fractional inhibitory concentration (Σ FIC) was calculated for each set of MICs as described [25]. Synergy was defined as Σ FIC $\leq$ 0.5. In order to test bactericidal synergy, the time-kill technique was applied as described by Weinstein [26] with certain modifications [27]. Synergy was defined if a >2 log₁₀ cfu/ml difference between the drugs in combination, as compared to the most effective active single antibiotic alone, at one given time point (6 or 24 h).

Data collection

Clinical information on patients with SD-caused IE and on patients with IE caused by *Staphylococcus aureus*, alpha-hemolytic streptococci, and enterococci was extracted from the SRIE. Data from the SRIE on IE caused by SD and the other pathogens were compared. In addition, detailed information on SD-caused IE was obtained from the medical records for patients that gave informed consent.

Epidemiological, clinical parameters and microbiological results were recorded.

Statistics

Fisher's exact test was applied for categorical data and comparison of continuous variables was analyzed utilizing Mann-Whitney *U* test where *p* values were adjusted according to the Bonferroni correction. Significance was defined as a *p* value less than 0.05. Microsoft Excel 2016 (Microsoft Corporation) was used for data collection and Graph Pad Prism, version 7.0b (GraphPad Software) and the SPSS software system, version 24 (SPSS) were utilized for statistical calculation.

Results

Inclusion of patients with IE caused by SD

From 2008 to 2016, 104 cases of IE with BHS of groups A, C, and G, that potentially could be SD, had been reported to SRIE. Twenty-seven of these cases were excluded since the corresponding blood isolates were not available for reanalysis and 11 cases were excluded since they were found to be alpha-hemolytic. Sixty-six BHS isolates of groups A, C, and G

streptococci were species-determined with MALDI-TOF MS of which three strains were classified as *Streptococcus agalactiae*, *Streptococcus canis* (*S. canis*), and *Streptococcus equi* (*S. equi*). Thirteen isolates were *Streptococcus pyogenes* (all of which had group A carbohydrate). The remaining 50 cases of SD comprised the study group.

In 17, cases the SD isolate was grouped as Lancefield group C and in 33 cases as group G.

Distribution of the *emm* gene

The *emm* types of all isolates are given in Fig. 1. Isolates which expressed group G antigen were predominantly of stC74a (*n* = 6) or stG643 (*n* = 5) whereas isolates that expressed group C most often were stG62647 (*n* = 6).

Antibiotic susceptibility

The MICs, MBCs, Σ FIC, and the results of the time-kill assays for nine representative isolates of SD are given in Table 1. All isolates were susceptible to inhibition and killing action of both penicillin and gentamicin. Applying the Etest-based synergy methods gave similar results and did not indicate synergy. Σ FIC was between 0.8 and 2. Synergy was detected using the time-kill method in four out of nine isolates. Of these four

Fig. 1 The distribution of *emm* types among patients with SD-caused IE expressed as proportion of total isolates (*n* = 17 for GCS and *n* = 33 for GGS). Black bars represent GCS and white bars represent GGS

Table 1 In vitro antibiotic susceptibility of SD IE isolates ($n = 9$)

Isolate	MIC ($\mu\text{g/ml}$)		ΣFIC		MBC ($\mu\text{g/ml}$)		Log mean additional killing with combination				
	PcG	Gen	MIC:MIC	Cross	PcG	Gen	0.5 MBC PcG 6 h	0.5 MBC PcG 24 h	1 MBC PcG 6 h	1 MBC PcG 24 h	Synergy detected
1	0.008	8	1.4	1.4	0.008	8	0.3	0.2	> 2	> 2	Yes
2	0.008	16	1.2	1.4	0.008	16	1.7	0.7	1.4	ng	No
3	0.008	8	1.4	1.3	0.016	16	1.9	ng	> 2	ng	Yes
4	0.016	4	2.0	1.5	0.016	8	> 2	ng	> 2	ng	Yes
5	0.008	8	1.3	1.2	0.016	16	> 2	ng	> 2	ng	Yes
6	0.008	8	1.4	1.2	0.008	8	0.5	0.5	0.7	− 0.1	No
7	0.008	8	1.2	1.3	0.008	8	0.02	0.8	ng	1.1	No
8	0.008	8	1.2	1.2	0.008	8	1.2	0.3	1.2	ng	No
9	0.008	8	0.8	1.8	0.008	8	0.4	1.9	1.9	ng	No

SD *Streptococcus dysgalactiae*, IE infective endocarditis, MIC minimal inhibitory concentration, ΣFIC the summation of fractional inhibitory concentration, MBC minimal bactericidal concentration, PcG penicillin, Gen gentamicin, ng no growth. MIC and MBC were determined by microbroth dilution. ΣFIC was determined by Etest synergy methodology

isolates, synergy was detected at 6 h and in one case synergy was also distinguished at 24 h. In seven cases, the killing action of penicillin alone was so pronounced at 24 h that additional killing using the combination was technically difficult to detect.

Clinical characteristics of cases of IE due to SD

Out of 50 patients with SD-caused IE identified in the registry, the episodes of 46 patients were studied in detail through the

medical records at the respective hospitals. Four patients were excluded since informed consent was not obtained and two patients were excluded as IE could be rejected after reviewing the medical records. Table 2 describes the clinical presentation of the 44 patients with SD-caused IE and a further detailed account for all patients is given in the Appendix Table 4. Twenty-nine percent of the patients ($n = 13$) were treated at the intensive care unit due to circulatory failure. Three patients with indications for surgery were not operated due to age and severe underlying diseases such as liver encephalopathy and

Table 2 Clinical and microbiological features of patients with SD-caused IE ($n = 44$) obtained from medical records

Underlying disease (n)	Dukes (n)	Type of IE (n)	Intensive care unit, treatment (n)	Operation (n)	Operation indication	In-hospital mortality (n)
CHF 19	D 36	NVE 31	CS 13	BAV 4	CHF 8	5
COPD 2	P 8	Aortic 12		BMV 7	SE 2	
SyD 5		Mitral 15		MAV 1	VP 3	
RD 3		Tricuspid 2		PE 3	PVE 3	
M 5		Unknown 2		AGE 1		
SkD 1		PVE 10				
N and/or CVI 9		Aortic 9				
		Mitral 1				
		IPE 3				

Modified Dukes criteria according to Li et al. [28] where BHS is regarded as a typical microorganism consistent with IE

SD *Streptococcus dysgalactiae*, IE infective endocarditis, CHF congestive heart failure, COPD chronic obstructive pulmonary disease, SyD systemic disease, RD renal disease, M malignancy, SkD skin disease, N neurological disease, CVI cerebrovascular insult, D definitive, P possible, NVE native valve endocarditis, PVE prosthetic valve endocarditis, IPE isolated pacemaker endocarditis, CSF cerebrospinal fluid, CS circulatory shock, BAV biological aortic valve, BMV biological mitral valve, MAV mechanical aortic valve, PE pacemaker extraction, AGE aorta graft excision, SE systemic embolization, VP vegetation on pacemaker

Categorical variables are presented as number (n)

cardiovascular disease. The in-hospital mortality among the studied patients was 11% ($n = 5$).

Comparison of IE due to SD and IE caused by other major IE-pathogens

Cases of IE due to SD were compared with cases of IE caused by *S. aureus* ($n = 1378$), alpha-hemolytic

streptococci ($n = 934$), and enterococci ($n = 414$) reported to the same registry (Table 3). The median age was significantly higher among patients with SD-caused IE compared to *S. aureus* (74 vs 65 years) ($p = 0.003$). The onset of SD-caused IE was acute as median time from onset of symptoms to initiation of treatment was only 1 day which was significantly less compared to enterococci and alpha-hemolytic streptococci (1 day vs 7–15 days) ($p < 0.0001$) but not to *S. aureus* (1 day vs 2 days). The in-hospital mortality was

Table 3 Clinical characteristics of cases of SD-caused IE compared to cases of IE due to other pathogens obtained from the SRIE

	SD $n = 50$	<i>S. aureus</i> (MSSA) $n = 1378$	Alpha-hemolytic streptococci $n = 934$	Enterococci $n = 414$
Age (years, median)	74	65 ($p = 0.003$)	69	73
Gender (% male)	60	61	72	77 ($p = 0.05$)
Underlying disease (%)				
Diabetes	20	18	11	18
Cancer	4	9	9	16
IVDU	4	26 ($p < 0.001$)	4	15
Underlying heart disease (%)				
Native valve disease	18	12	30	19
Prosthetic heart valve	28	13 ($p = 0.01$)	21	36
Previous IE	0	9	9	17 ($p < 0.001$)
Pacemaker/ICD	18	15	8 ($p = 0.05$)	18
Type of infection (%)				
NVE, left isolated	58	47	60	52
NVE right isolated	8	22	3	5
PVE	18	10	15	15
PME	6	7	2	6
Aortic valve	46	31	42	53
Mitral valve	30	32	35	31
Nosocomial	6	10	4	12
Course of disease				
Onset to hospitalization (days)	1	2	15 ($p < 0.0001$)	7 ($p < 0.0001$)
Length of stay (days)	32	32	29 ($p < 0.001$)	37
Treatment length (days)	29	28	28 ($p = 0.008$)	34
Treatment length AG (days)	1	0	14 ($p < 0.0001$)	14 ($p < 0.0001$)
Embolization (%)	46	50	27 ($p = 0.02$)	27 ($p = 0.02$)
Operation (%)	30	23	19	26
Mortality (%)	8	14	6	10

SD *Streptococcus dysgalactiae*, IE infective endocarditis, SRIE Swedish Registry of Infective Endocarditis, *S. aureus* *Staphylococcus aureus*, IVDU intravenous drug use, ICD intracardiac device, NVE native valve endocarditis, PVE prosthetic valve endocarditis, PME pacemaker endocarditis, AG aminoglycoside, Mortality death during time of hospital treatment. Categorical variables are presented as count (percentage) and continuous data as median. p value indicates any statistically significant difference in characteristics of patients with SD-caused IE compared to patients with *S. aureus*, alpha-hemolytic streptococci, or enterococci

8% and embolization was seen in 46% in patients with SD-caused IE.

Discussion

This study is the largest report of SD-caused IE and describes the clinical presentation and outcome of 50 cases of IE due to SD. The condition has an acute onset, high rate of embolization, and aggressive course often including organ dysfunction. Previous studies have demonstrated SD-caused IE as having an acute onset of illness and high mortality similar to *S. aureus*-caused IE [9, 11]. Furthermore, Lothar et al. showed that 6% of patients with GCS or GGS bacteremia developed IE with extensive need of intensive care unit treatment but of these cases only two were verified at the species level as SD [10]. As with other types of invasive SD infections [29], old males are the typical patients.

In the present study, we demonstrate synergy between penicillin and gentamicin in vitro against some SD isolates with the time-kill method. However, in the 24-h samples, there was an efficient killing action by penicillin alone resulting in difficulties in evaluating the effect of combination with aminoglycosides. Etest-based methods were not able to demonstrate synergy. Interestingly, according to the medical records, 27 of the 44 patients received treatment with aminoglycosides of which 11 patients had one dose whereas 16 patients had several dosages of aminoglycosides during time of care. There was no statistical significant difference in clinical outcome between patients treated with long-term addition of aminoglycosides and those receiving monotherapy but the study was likely under-powered to detect such difference. There is to date no firm results to guide the use of addition of aminoglycosides and potential additional killing of bacteria must be weighed against the risk of side effects.

We found SD-caused IE to be much more common than IE caused by *S. pyogenes* which is in line with previous studies [11, 12]. According to the SRIE, and also in line with previous reports, group B streptococci was the most common BHS-causing endocarditis comprising 76 cases, though these isolates were not confirmed to the species level by us. In the present study, the *emm* types stC74a and stG62647 were the most commonly encountered in SD isolates with groups G and C carbohydrate respectively. The distribution of *emm* types was similar to that described previously in Sweden [6]. A previous study has indicated that rare *emm* types are associated to poor prognosis [7] but four of the five fatal cases described here were caused by common types (stG480, stG652, stG2078, and stC74a).

This study is limited by its retrospective design and a possible bias in the inclusion of patients in the SRIE. It has previously been estimated that around 75–80% of cases of IE in Sweden are included in the SRIE [30]. When comparing the medical records to the data reported to the registry, some inaccuracies were noted. For example, the SRIE was found to contain several episodes reported as caused by BHS of group A that were instead due to alpha-hemolytic streptococci. However, we chose not to correct the SRIE data after analysis of the medical records since no corresponding corrections were possible for IE caused by the other pathogens. Thus, there are discrepancies between the information on episodes extracted from the SRIE (Table 3), the medical records (Table 2), and the Appendix Table 4.

MALDI-TOF MS can identify SD to the species level but subspecies determination can formally not be made with this method. The vast majority of human isolates of SD are *Streptococcus dysgalactiae* subspecies *equisimilis* (SDSE) but formally, we cannot exclude that we also had isolates of *Streptococcus dysgalactiae* subspecies *dysgalactiae* though such isolates generally are alpha-hemolytic [5]. There are also isolates of SDSE exhibiting alpha-hemolysis; however, this is a rare occurrence [5]. Interestingly in our study population, one isolate was *S. canis* and another isolate was *S. equi*, both of which are of animal origin and are rare causes to human infections. These species, however, have been reported as IE-pathogens [31, 32].

Conclusion

SD-endocarditis has an acute onset of symptoms and causes severe infection in elderly people. Synergy of penicillin and gentamicin could be shown in vitro but it was not distinguished utilizing Etest methodology.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical statement and informed consent The study was approved by the local ethical research committee (reference number 2013/182) with the addition (2015/81). Informed consent was obtained for the study of medical records.

Appendix

Table 4 Detailed clinical features of patients with SD-caused IE ($n = 44$) obtained from medical records

Age/sex	Underlying disease	Initial symptoms	Duration of symptoms (days)	qSOFA	Organ dysfunction	Treatment	Treatment AG	Dukes
80, F	IHD	Dyspnea Fever	3	0	No	Penicillin G	1 dose	SRIE: D MR: D
74, M	No	Back-chest/pain	1	0	Yes	Penicillin G	Several doses	SRIE: D MR: P
82, M	COPD MG AF BAV pacemaker CHF	Fever Shivers	1	1	Yes	Penicillin G	Several doses	SRIE: D MR: D
76, F	DM hypertension	Fever	7	0	Yes	Penicillin G	No	SRIE: D MR: D
58, F	SLE IHD CKD HD DM MAV	Dyspnea Fever	1	2	Yes	Penicillin G	No	SRIE: D MR: D
80, F	IHD hypertension BMV	Dyspnea Fever	1	1	Yes	Penicillin G	Several doses	SRIE: D MR: D
74, F	IHD	Nausea Fever	2	0	Yes	Penicillin G	Several doses	Dukes: P MR: D
82, F	IHD MAV pacemaker AF	Cough Fever	2	2	No	Penicillin G	1 dose	SRIE: D MR: D
59, M	No	Throat pain Fever Shivers	2	0	Yes	Cefuroxime	Several doses	SRIE: P MR: D
66, M	CHF pacemaker	Fever Shivers	1	1	Yes	Penicillin G	Several doses	SRIE: D MR: D
88, F	Neurological failure	Fever	2	2	No	Penicillin G	Several doses	SRIE: D MR: D
89, M	CHF lymphoma DM	Fever Shivers	1	0	Yes	Penicillin G	No	SRIE: D MR: D
64, M	Meningitis as child, neurological sequel	Fever Shivers	1	0	Yes	Penicillin G	Several doses	SRIE: D MR: D
59, M	Skin disease RA AO	Fever Nausea	5	0	No	Penicillin G	No	SRIE: D MR: D
56, M	COPD AO	Erysipelas Dyspnea Nausea	1	3	Yes	Meropenem	1 dose	SRIE: P MR: D
77, F	No	Vomiting Fever	1	1	Yes	Penicillin G	1 dose	SRIE: D MR: D
38, M	MAV AGR	Confusion Fever Shivers	1	0	No	Penicillin G	Several doses	SRIE: D MR: D
88, F	PMR CHF	Dyspnea Fever	1	2	Yes	Cefuroxime (penicillin allergy)	1 dose	SRIE: D MR: D
58, M	No	Fever Shivers	3	0	Yes	Penicillin G	1 dose	SRIE: D MR: D
82, M	CHF IHD	Fever	5	0	No	Penicillin G	No	SRIE: P

Table 4 (continued)

76, M	BAV	Wound right foot Fever	1	2	No	Penicillin G	Several doses	MR: P SRIE: D
67, M	CHF BAV AF hypertension	Fever Shivers Nausea	1	0	Yes	Penicillin G switch to vancomycin due to allergy	No	MR: D SRIE: D MR: D
68, M	BAV pacemaker	Fever Shivers	2	0	No	Penicillin G	Several doses	SRIE: D MR: D
81, F	CHF Pacemaker	Confusion Weakness right arm	1	1	Yes	Penicillin G	Several doses	SRIE: D MR: D
70, F	CVI	Erysipelas left leg	1	2	Yes	Penicillin G	No	SRIE: D
87, M	DM No	Confusion	<1	1	No	Post op meropenem Penicillin G	1 dose	MR: D SRIE: D
65, M	CKD BAV pacemaker ICD	Fever Shivers Fever Shivers	1	1	Yes	Penicillin G	Several doses	MR: P SRIE: D MR: D
71, F	Dementia CKD CVI DM	Nausea Vomiting	1	1	Yes	Penicillin G	No	SRIE: D MR: D
51, M	MAV AGR	Fever Shivers	3	1	Yes	Penicillin G	1 dose	SRIE: D MR: D
59, F	MAV epilepsy	Fever Shivers	7	0	No	Penicillin G	Several doses	MR: D SRIE: D
87, F	CHF aorta stenosis CVI	Fever Shivers	2	1	Yes	Piperacillin with tazobactam	No	SRIE: P MR: P
63, M	No	Fever Chest pain	1	0	No	Penicillin G	1 dose	SRIE: D MR: D
87, M	PMR CHF IHD Prostate cancer BAV	Fever Shivers	1	0	No	Penicillin G	No	SRIE: P MR: P
76, M	PMR CHF CVI prostate cancer BAV AGR	Fever Vomiting	1	2	Yes	Penicillin G	No	SRIE: P MR: D
88, F	No	Headache Weakness right arm	2	0	No	Penicillin G	No	SRIE: D MR: D
82, F	CHF breast cancer pacemaker	Fever Shivers Vomiting	3	0	Yes	Penicillin G	Several doses	SRIE: D MR: D
93, M	Asthma DM	Dyspnea	1	1	Yes	Penicillin G	No	SRIE: P MR: P
60, M	AO DM	Fever Shivers	1	1	Yes	Meropenem	1 dose	SRIE: D MR: D
81, M	CHF pacemaker	Cough	4	1	Yes	Penicillin G	No	SRIE: D MR: D
80, F	No	Joint pain Wound right foot	5	0	No	Penicillin G switch to cefotaxime due to allergy	No	MR: D SRIE: D MR: D
52, M	CVI	Fever Shivers	1	1	No		No	SRIE: P MR: P

Table 4 (continued)

Age /sex	Operation	Intensive care unit, treatment	Complication	TTE or and TEE findings	Diagnosis	Outcome
75, M	CHF IHD	Fever	1	2	Yes	1 dose
71, M	DM urine bladder cancer MAV CHF MAV	Unconsciousness Confusion	1	0	Yes	Several doses
59, M	No	Unconsciousness Fever Shivers Wound left toe	1	0	Yes	No
Penicillin G switch to cefotaxime due to "drug fever"						
					Cefotaxim	1 dose
					Penicillin G	Several doses
					Penicillin G	No
						SRIE: D MR: D SRIE: D MR: D SRIE: D MR: D
Age /sex	Operation	Intensive care unit, treatment	Complication	TTE or and TEE findings	Diagnosis	Outcome
80, F	BMV	Post op	No	MV	SRIE and MR: NMVIE	Recovered
74, M	No	No	No	Suspected TV	SRIE and MR: NTVIE	Recovered
82, M	No	Hypotension	No	PV	SRIE: NNIE MR: IPIE	Recovered Recurrent IE with <i>Streptococcus mitis</i> 4 months after discharge
76, F	No	No	Embolus	AV	SRIE and MR: NAVIE	Recovered
58, F	No	No	No	PAV	SRIE and MR: PAVIE	Recovered
80, F	No	No	Embolus Stroke	Vegetation not detected	SRIE: IE unknown infection site	Recovered
74, F	BMV	Post op complication, CS	Meningitis Embolus	MV	MR: PMIE SRIE and MR: NMVIE	Died at 26 days
82, F	No	No	Stroke	Vegetation not detected	SRIE: NAVIE MR: PAVIE	Recovered
59, M	No	Heart failure	Embolus	AV	SRIE and MR: NAVIE	Recovered
66, M	BAV and graft replacement	Post op heart failure	No	AV	SRIE and MR: NAVIE	Recovered
88, F	No	No	Embolus Stroke	Vegetation not detected	SRIE and MR: NVIE	Recovered
89, M	No	No	Embolus Stroke	MV	SRIE and MR: NMVIE	Recovered
64, M	BMV	Post op cardiogenic shock		MV	SRIE and MR: NMVIE	Recovered
59, M	BMV	Post op	Embolus	MV	SRIE and MR: NMVIE	Recovered
56, M	BAV	Post op	No	AV	SRIE and MR: NAVIE	Recovered
77, F	BMV	Post op	Embolus	MV	SRIE and MR: NMVIE	Recovered
38, M	No	No	Embolus	Aortic abscess not on MAV	SRIE and MR: NAVIE	Recovered
88, F	No	No	No	AV	SRIE and MR: NAVIE	Recovered
58, M	No	No		AV	SRIE and MR NAVIE	Recovered
82, M	No	No		Suspected vegetation on MV	SRIE and MR: NMVIE	Recovered
76, M	No	No	Embolus	AV	SRIE and MR: PAVIE	Recovered

Table 4 (continued)

67, M	No	No	AV	SRIE and MR: PAVIE	Recovered
68, M	Pacemaker extraction	No	PV	SRIE and MR: IPIE	Recovered
81, F	Pacemaker extraction	No	PV	SRIE and MR: IPIE	Recovered
70, F	BMV	Postop complication, ARDS	MV	SRIE: NTVIE MR: NMVIE	Recovered
87, M	No	No	Suspected vegetation MV,	SRIE and MR: NMVIE	Recovered
65, M	Pacemaker extraction	No	AV and PV	SRIE and MR: PAVIE	Recovered
71, F	No	No	MV	SRIE and MR: NMVIE	Died at 18 days
51, M	Graft extraction	Post op organ dysfunction	AV	SRIE and MR: PAVIE	Recovered
59, F	Replacement of MAV and graft to BAV	Post op	AV graft infection	SRIE and MR: PAVIE	Recovered
87, F	No	No	Suspected vegetation on MV	SRIE and MR: NMVIE	Recovered
63, M	BAV	Post op	AV	SRIE and MR: NAVIE	Recovered
87, M	No	No	Suspected aorta abscess	SRIE and MR: PAVIE	Recovered
76, M	No	Organ dysfunction	Vegetation not detected	SRIE and MR: PAVIE	Recovered
88, F	No	No	AV	SRIE and MR: NAVIE	Recovered
82, F	No	Hypotension	TV	SRIE and MR: NTVIE	Recovered
93, M	No	No	Suspected vegetation on AV and MV	SRIE: NIE MR: NLIE	Recovered
60, M	No	Organ dysfunction	MV	SRIE and MR: NMVIE	Died at 64 days
81, M	No	No	AV	SRIE and MR: NAVIE	Recovered
80, F	No	No	AV	SRIE and MR: NAVIE	Recovered
52, M	No	No	Chorda rupture with MI	SRIE and MR: NMVIE	Recovered
75, M	No	Septic shock	MV	SRIE and MR: NMVIE	Died at 23 days
71, M	MAV-died during surgery	Organ dysfunction	AV	SRIE: NAVIE MR: PAVIE	Died at 44 days
59, M	BMV	Thrombolysis right foot	MV	SRIE and MR: NMVIE	Recovered
	Transfemoral amputation due to septic embolization	shock			

SD Streptococcus dysgalactiae, *IE* infective endocarditis, *qSOFA* quick sepsis-related organ failure, *AG* aminoglycoside, *TTE* transthoracic echocardiogram, *TEE* transesophageal echocardiogram, *F* female, *IHD* ischemic heart disease, *SRIE* Swedish Registry of Infective Endocarditis, *MR* medical records, *D* definitive, *BMV* biological mitral valve, *MV* mitral valve vegetation, *NMVIE* native mitral valve *IE*, *M* man, *P* possible, *TV* tricuspid valve vegetation, *NTVIE* native tricuspid valve *IE*, *COPD* chronic obstructive pulmonary disease, *MG* myasthenia gravis *AF* atrial fibrillation, *BAV* biological aortic valve, *PV* pacemaker valve vegetation, *IPIE* isolated pacemaker *IE*, *DM* diabetes mellitus, *AV* aortic valve vegetation, *NAVIE* native aortic valve *IE*, *SLE* systemic lupus erythematosus, *CKD* chronic kidney disease, *HD* hemodialysis, *MAV* mechanical aortic valve, *PAV* prosthetic aortic valve vegetation, *PAVIE* prosthetic aortic valve *IE*, *PMIE* prosthetic mitral valve *IE*, *CS* circulatory shock, *CHF* congestive heart failure, *NVIE* native valve *IE*, *RA* rheumatoid arthritis, *AO* alcohol overconsumption, *AGR* aortic graft reconstruction, *PMR* polymyalgia rheumatic, *CVI* cerebrovascular insult, *ARDS* acute respiratory distress syndrome, *ICD* implantable cardioverter defibrillator, *NIE* native valve *IE*, *NLIE* native left-sided valve *IE*, *MI* mitral insufficiency

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