Clinical and microbiological features of infective endocarditis caused by aerococci.

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Published in:
Infection

DOI:
10.1007/s15010-015-0812-8

2015

Clinical features of infective endocarditis caused by aerococci

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Running title: Infective endocarditis caused by aerococci

Abstract

Aerococci are increasingly recognized as causative agents in human infective endocarditis (IE). Information on the clinical presentation and the prognosis of IE caused by aerococci is limited. We employed the Swedish Registry of Infective Endocarditis (SRIE) to identify cases of aerococcal IE. The medical records were analysed and comparisons with cases of IE caused by other pathogens reported to the SRIE were made. Available bacterial isolates were reanalysed using matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF) and the aetiology was confirmed to be *Aerococcus urinae* in fourteen cases and *Aerococcus sanguinicola* in two cases. The bacteria were sensitive to penicillin and Etest-based synergy testing and time-kill experiments suggested synergy between penicillin and gentamicin towards some isolates. The patients had a median age of 79 years, which was significantly higher than that of patients with IE caused by streptococci or *Staphylococcus aureus*. Most patients with IE caused by aerococci had underlying urinary tract diseases and many presented with symptoms suggesting a urinary tract focus of the infection. Despite the fact that many patients with aerococcal IE presented with severe sepsis, ICU treatment was needed only in one patient and there was no fatality. Valve exchange surgery was needed in four of sixteen patients with aerococcal IE and embolization was seen in three patients. This report is by far the largest on aerococcal IE and suggests that the prognosis of aerococcal IE is relatively favourable despite the fact that the patients are old and have significant comorbidities.

Keywords: Aerococcus, infective endocarditis, prognosis, Synergy, *Aerococcus urinae*, *Aerococcus sanguinicola*.

Introduction

Aerococci have been regarded as rare causes of infective endocarditis (IE) in humans [1], but due to improved diagnostic procedures they have been increasingly reported both in IE and in other types of human infections [2]. Aerococci are easily mis-identified as streptococci, enterococci, or staphylococci and correct identification can be achieved with genetic methods [3] or more conveniently through matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF) [4,5]. *Aerococcus urinae* is the most common aerococcal species isolated in IE [6,7,8] whereas *Aerococcus sanguinicola* is more rarely encountered [9,10]. *Aerococcus viridans* was the first aerococcal species to be identified but is a rare cause of human infections [2,11]. The most common site of isolation for both *A. urinae* and *A. sanguinicola* is human urine [3,12,13,14,15,16].

From published cases, it appears that bacteremia with *A. urinae* presents as IE in approximately half of the cases and that the case fatality of *A. urinae* IE is high [2]. Patients with *A. urinae* IE are typically older males with underlying urinary tract diseases [2,6,7,8,17]. Of four described cases of IE with *A. sanguinicola*, one fatality was reported [9,10]. Several reports of putative *Aerococcus viridans* IE have been published (see [18] for references). However, correct species determination was only performed in one of these studies [19] and the aetiology in the other cases is obscure [20]. We have previously performed population-based studies which showed that only three of sixteen patients with *A. urinae* bacteremia and two of eleven patients with *A. sanguinicola* bacteremia had IE. All five patients with IE described in these studies survived their infection despite significant underlying diseases [7,10]. The optimal treatment of aerococcal IE has not been determined, but two studies have suggested

that penicillin and aminoglycosides have synergistic effect on aerococci *in vitro* [17,21] and therefore combination therapy has been used in most cases.

The Swedish Registry of Infective Endocarditis (SRIE) started in 1995, organized by the Swedish Society of Infectious Diseases. All thirty departments of infectious diseases (ID) in Sweden have participated in the registry since it´s inception. The ID departments have regional responsibility for care of patients with severe infections, and patients requiring acute surgery for IE are in most cases treated in ID departments during the pre- and/or postoperative period. During the 20-year period, 1995 – 2014, 6775 adult episodes have been registered [22]. SRIE is estimated to cover approximately 75% of all hospital treated episodes in Sweden with a diagnose of IE [23]. Here we employ the SRIE to identify cases of IE with aerococci. We reanalyse the bacterial isolates and compare the cases of aerococcal IE with cases of IE caused by staphylococci, streptococci, and enterococci reported to the same registry.

Materials and methods

Collection of and analysis of isolates

The SRIE was searched for cases of IE caused by aerococci reported between 2002 and 2014. Episodes had been reported on a standardized questionnaire by mail from 1995 - 2007 (3702 cases), and during 2008 - 2014 an internet-based report has been performed with a more detailed description of the episodes (2977 cases). The relevant laboratories of clinical microbiology were contacted and aerococcal isolates were collected for reanalysis in our laboratory with MALDI-TOF as described in [5]. Isolates of alpha-haemolytic streptococci, reported to the SRIE to have caused IE, were collected from selected laboratories, and reanalysed by MALDI-TOF to detect

potentially mis-identified aerococci. Bacteria were cultivated on blood agar plates in 5 % CO_2 at 37^0 C. Minimal inhibitory concentration (MIC) was determined using Etests (Biomerieux, Solna, Sweden) on Müller-Hinton agar (MHA) with defibrinated horse blood and β-NAD [24] or blood agar for three isolates not growing on the MHA. For synergy testing based on Etest methodology, the method MIC:MIC was used [25]. Fractional inhibitory concentration (FIC) was defined as (MIC for benzyl penicillin in combination) / (MIC for benzyl penicillin alone) + (MIC for gentamicin in combination) / (MIC for gentamicin alone). For bactericidal synergy testing the method described by Weinstein and Moellering [26] was used, with modification as described [27]. For the combination of benzyl penicillin and gentamicin to be considered synergistic against a given isolate, synergy, defined as a two-log difference between the combination and most effective of the individual antibiotics, had to be present at two of three samples at a given time point and antibiotic concentration.

Data collection and statistical analysis

Clinical information on patients was collected from the SRIE and from the medical records of the respective patient. Severe sepsis was defined as described in [7]. Data from the SRIE on IE caused by enterococci, alpha-haemolytic streptococci, and *Staphylococcus aureus* was extracted from the internet-based part of the Registry and compared to the corresponding data on aerococci. Differences were tested for statistical significance with Fischers exact test or the Wilcoxon rank number test using GraphPad Prism version 6.

The local research ethical committee approved of this study (reference number 2013/182).

Results

Aerococcal isolates

Twenty-nine cases of reported aerococcal IE were identified and the aetiology was reported as *A. urinae* in fifteen cases, as *A. viridans* in eight cases, as *A.* sanguinicola in one case, and as *Aerococcus sp.* in five cases. Twenty of these isolates were available for species determination with MALDI-TOF and only one of the nine isolates not available for reanalysis had been speciated with a reliable method (MALDI-TOF). Fourteen isolates (one of which was the MADLI-TOF-identified isolate not available for reanalysis) were found to be *A. urinae*, two isolates were identified as *A.* sanguinicola, whereas five isolates were identified as α-haemolytic streptococci. All scores were above 2.0. Due to the high frequency of mis-identification (5/20) we chose to exclude the eight cases where isolates were not available for MALDI-TOF analysis. We also analysed 110 isolates of α-haemolytic streptococci, reported to the SRIE to have caused IE, and no additional aerococci were identified among these isolates. Thus, for further analyses, we used the sixteen isolates securely identified as aerococci.

Aerococcal antimicrobial susceptibility

The pattern of susceptibility to relevant antimicrobials of the fifteen available isolates is given in table 1. As expected, all isolates had low MIC for penicillin and cefotaxim. Using non species-specific EUCAST breakpoints, all isolates were sensitive to penicillin, cefotaxim, and vancomycin. One isolate was resistant to clindamycin and MIC for gentamicin was in the 1-32 mg/L range. MIC to ciprofloxacin was variable and two isolates showed values above 32 mg/L. The possible synergy between

penicillin and gentamycin was tested through the MIC:MIC method and calculated fractional inhibitory concentrations (FIC) were between 0.42 and 1.75. A FIC≤0.5 is considered as synergy and using this definition, three isolates displayed synergy. There was no correlation between the FIC value and the synergistic bactericidal effect of benzyl penicillin and gentamicin. Bactericidal synergy was noted against seven of fifteen isolates (47 %). Synergy noted at 6 hours for one isolate only and for the other six at 24 hours. For some isolates synergy was not detected but could not be ruled out either (Table 1).

Clinical presentation of aerococcal IE

The features of patients with aerococcal IE are given in table 2. The patients were predominantly male (12/16) and the median age was 79 years. Two patients have been previously reported [7,10]. Fourteen patients fulfilled the revised Dukes criteria for definite IE [22] whereas two patients had possible IE. All patients had at least two sets of blood cultures positive for aerococci and in eleven cases aerococci were the only bacteria isolated from blood. In four patients, a coagulase negative *Staphylococcus* was isolated from a single flask and in one patient a single flask grew *Proteus mirabilis.* None of the patients had aerococci in urinary cultures upon admission. Eleven patients had either underlying urological conditions such as prostate cancer or urinary tract catheter. Several patients had other comorbidities such as neurological conditions (n=7), diabetes mellitus (n=4), non-urological malignancies (n=2), or conditions requiring immunosuppression (n=2). Fever was a presenting symptom in all patients and four patients had urological symptoms at presentation. At the time of admission six patients was on treatment, or had recently finished a course, with a fluoroquinolone for suspected urinary tract infection. Three

patients had been treated for aerococcal bacteremia with a short course of beta-lactam antibiotics (3-7 days i.v.) followed by peroral beta-lactams or ciprofloxacin for 5-7 days within the previous four weeks. Seven patients had severe sepsis upon admission and one patient required intensive care. All patient were subjected to trans-esophageal echocardiography (TEE) and eight were shown to have mitral valve affection whereas five had aortic valve affection. Two patients without evidence of IE at TEE had new murmurs. All patients received treatment with a beta-lactam antibiotic in combination with an aminoglycoside. Median time of treatment was 28 days (range 13-44) for the beta-lactam and 10 days (range 1-40) for the aminoglycoside. Three patients had embolic events, one had an embolus to the kidney, one had cervical spondylodiscitis (also described in [7]), and one had an occlusion of the medial cerebral artery. Surgery was needed in four patients due to progressive cardiac failure. All patients survived the hospital stay.

Comparison of IE caused by aerococci and IE caused by other bacteria

Information from the SRIE on the cases of IE caused by aerococci was compared to the information on IE caused by *S. aureus* (n=1013), alpha-haemolytic streptococci (n=722), and enterococci (n=296) (Table 3). For differences reaching significance, the p-value is given. Notably the age of the patient with aerococcal IE was significantly higher than that of patients with IE cased by streptococci or *S. aureus.* There was a higher prevalence of cancer among patients with aerococcal IE as compared to those with *S. aureus* IE. None of the cases with aerococcal IE was right-sided or occurred in patients with intravenous drug use (IVDU) and this was significantly different from the situation in *S. aureus* IE. There were no statistically significant differences between patients with aerococcal IE and those infected with the other organisms in

the proportion of patients with predisposing heart conditions or in the proportion of cases affecting the mitral and aortic valve respectively. There was a longer time from the onset of symptoms to initiation of appropriate treatment (onset of treatment in table 3) for patients with aerococcal IE compared to patients with *S. aureus* IE though the difference was not significant. Length of treatment did not vary significantly between the groups but patients with *S. aureus* IE received aminoglycosides for a significantly shorter period of time. There were no statistically significant differences in outcome measures between patients with aerococcal IE and IE with other bacteria though mortality and proportion of patients with embolization were higher among patients with *S. aureus* IE.

Discussion

From published cases on IE caused by aerococci, it appears that the condition is rare and that the prognosis is unfavourable especially for *A. urinae.* This study demonstrates that the prognosis of aerococcal IE is relatively favourable in the setting of the Swedish health care system despite the patients being very old and having significant comorbidities. Though seven of the patients presented with signs of severe sepsis, a condition generally considered to have a relatively poor prognosis, all patients survived. Despite being the largest study on aerococcal IE, the study is underpowered to detect differences in prognosis between aerococcal IE and IE with other organisms. We believe, however, that the prognosis of aerococcal IE is better than that of IE with *S. aureus* both in terms of mortality and the frequency of embolization. The unfavourable prognosis indicated by previous case reports is most likely the results of a bias to publish more dramatic presentations of disease.

Patients with aerococcal IE were, as in previous reports, old, male, and with underlying urological diseases. The higher proportion of patients with cancer in the aerococcal group is largely explained by the three cases with prostate cancer among those patients. A large proportion of the patients reported here presented with signs and symptoms which were interpreted as urinary tract infections and many had received treatment with fluoroquinolons, which have a questionable effect against aerococci [2]. Despite this, aerococci were not identified in urinary cultures which confirms findings in our previous studies [7,10]. We still believe that the urinary tract is the focus of the initial bacteremia in most cases of aerococcal IE and that more sensitive methods for detection of aerococci in urine are needed.

The combination of benzyl penicillin and gentamicin has been widely used for the treatment of aerococcal IE, including all cases described herein. The findings of this study raises the question of whether adding gentamicin is beneficial for the patient as synergy could only be shown for a minority of the isolates. Notably, synergy was not detected for the *A. sanguinicola* isolates and synergy for this species has this far not been documented. As we did not find any correlation between FIC and bactericidal synergy, there is no method that could be used in the routine clinical laboratory setting to identify which patients that should receive combination treatment. Three patients had a preceding episode of *A. urinae* bacteremia which was treated with intravenous antibiotics beta-lactam antibiotics without the addition of aminoglycosides for a shorter period of time (3-7 days) which evidently was insufficient since they had a recurrence. However, at present, we do not know how many of the patients with aerococcal bacteremia that will develop IE and possibly

many patients with aerococcal bacteremia will be cured by a shorter course of beta-lactam antibiotics. There were no recurrences after IE-treatment among our patients.

This study is by far the largest reporting IE with aerococci. We excluded thirteen patients reported to the SRIE since the species determination was incorrect (n=5) or unreliable (n=8). Of the twenty-one isolates tested with MALDI-TOF, sixteen were aerococci but five isolates were streptococci. The lack of additional aerococci among alpha-hemolytic streptococci reported to the SRIE indicates that aerococci are not very often mis-identified in Swedish laboratories, at least not in blood cultures. Eight isolates had been reported to the SRIE as *A. viridans* and this species has been implicated in many IE cases but species determination has on most occasions been inadequate [20]. This study suggests that *A. urinae* is the most common cause of aerococcal IE and that *A. viridans* is a rare cause of IE. With the introduction of MALDI-TOF, which correctly differentiates between *A. viridans* and *A. sanguinicola,* more isolates of *A. sanguinicola* will likely be identified. The use of MALDI-TOF in species determination of bacteria will likely also reveal that aerococcal IE is not so uncommon as previously thought.

We suggest that IE should be considered in all patients with aerococcal bacteremia and that the urinary tract should be considered as the point of entry of the bacteria. Before combination therapy using penicillin and an aminoglycoside is instituted, the potential risk for aminoglycoside side-effects must be carefully weighed against the potential benefit of a potential antibacterial synergy.

Acknowledgements

This work was supported by the Swedish Government Fund for Clinical Research (ALF), the Royal Physiographic Society in Lund, and the foundations of Marianne and Marcus Wallenberg, Groschinski, Crafoord, and Österlund. Dr Malin Inghammar is acknowledged for important discussions. The authors acknowledge the kind help from all participating clinical microbiology laboratories and infectious diseases clinics. The authors have no conflicting interests to declare.

References

1. Parker MT, Ball LC. Streptococci and aerococci associated with systemic infection in man. J Med Microbiol 1976; 9: 275–302.
2. Rasmussen M. Aerococci and aerococcal infections. J Infect 2012.
3. Cattoir V, Kobal A, Legrand P. *Aerococcus urinae* and *Aerococcus sanguinicola*, two frequently misidentified uropathogens. Scand J Infect Dis 2010; 42: 775–780.
4. Christensen JJ, Dargis R, Hammer M *et al.* Matrix-assisted laser desorption ionization-time of flight mass spectrometry analysis of Gram-positive, catalase-negative cocci not belonging to the *Streptococcus* or *Enterococcus* genus and benefits of database extension. J Clin Microbiol 2012; 50: 1787–1791.
5. Senneby E, Nilson B, Petersson AC, Rasmussen M. Matrix-assisted laser desorption ionization-time of flight mass spectrometry is a sensitive and specific method for identification of aerococci. J Clin Microbiol 2013; 51: 1303–1304.
6. Christensen JJ, Jensen IP, Faerk J *et al.* Bacteremia/septicemia due to *Aerococcus*-like organisms: report of seventeen cases. Danish ALO Study Group. Clin Infect Dis 1995; 21: 943–947.
7. Senneby E, Petersson AC, Rasmussen M. Clinical and microbiological features of bacteraemia with *Aerococcus urinae*. Clin Microbiol Infect 2012; 18: 546–550.
8. de Jong MFC, Soetekouw R, Kate ten RW, Veenendaal D. *Aerococcus urinae*: severe and fatal bloodstream infections and endocarditis. J Clin Microbiol 2010; 48: 3445–3447.
9. Ibler K, Truberg Jensen K, Ostergaard C *et al.* Six cases of *Aerococcus sanguinicola* infection: clinical relevance and bacterial identification. Scand J Infect Dis 2008; 40: 761–765.
10. Senneby E, Eriksson B, Fagerholm E, Rasmussen M. Bacteremia with *Aerococcus sanguinicola* - case series with characterization of virulence properties. Open Forum Infect Dis 2014; 1.
11. Williams RE, Hirch A, Cowan ST. *Aerococcus*, a new bacterial genus. J Gen Microbiol 1953; 8: 475–480.
12. Christensen JJ, Vibits H, Ursing J, Korner B. *Aerococcus*-like organism, a newly recognized potential urinary tract pathogen. J Clin Microbiol 1991; 29: 1049–1053.
13. Shelton-Dodge K, Vetter EA, Kohner PC, Nyre LM, Patel R. Clinical significance and antimicrobial susceptibilities of *Aerococcus sanguinicola* and *Aerococcus urinae*. Diagn Microbiol Infect Dis 2011; 70: 448–451.
14. Schuur PM, Kasteren ME, Sabbe L *et al.* Urinary tract infections with *Aerococcus urinae* in the south of The Netherlands. Eur J Clin Microbiol Infect Dis 1997; 16: 871–875.
15. Sierra-Hoffman M, Watkins K, Jinadatha C, Fader R, Carpenter JL. Clinical significance of *Aerococcus urinae*: a retrospective review. Diagn Microbiol Infect Dis 2005; 53: 289–292.
16. Senneby E, Petersson AC, Rasmussen M. Epidemiology and antibiotic susceptibility of aerococci in urinary cultures. Diagn Microbiol Infect Dis 2014.
17. Zbinden R, Santanam P, Hunziker L, Leuzinger B, Graevenitz von A. Endocarditis due to *Aerococcus urinae*: diagnostic tests, fatty acid composition

and killing kinetics. Infection 1999; 27: 122–124.
18. Zhou W, Nanci V, Jean A *et al. Aerococcus viridans* native valve endocarditis. Can J Infect Dis Med Microbiol 2013; 24: 155–158.
19. Chen L-Y, Yu W-C, Huang S-H *et al.* Successful treatment of *Aerococcus viridans* endocarditis in a patient allergic to penicillin. J Microbiol Immunol Infect 2012; 45: 158–160.
20. Rasmussen M. *Aerococcus viridans* is not a matter of opinion. Comment on: An unusual microorganism, *Aerococcus viridans*, causing endocarditis and aortic valvular obstruction due to a huge vegetation (Turk Kardiyol Dern Ars 2011;39:317-319). Turk Kardiyol Dern Ars 2012; 40: 112.
21. Skov R, Christensen JJ, Korner B, Frimodt-Møller N, Espersen F. *In vitro* antimicrobial susceptibility of *Aerococcus urinae* to 14 antibiotics, and time-kill curves for penicillin, gentamicin and vancomycin. J Antimicrob Chemother 2001; 48: 653–658.
22. Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Duke Endocarditis Service. Am J Med 1994; 96: 200–209.
23. Ternhag A, Cederström A, Törner A, Westling K. A nationwide cohort study of mortality risk and long-term prognosis in infective endocarditis in Sweden. PLoS ONE 2013; 8: e67519.
24. Matuschek E, Brown DFJ, Kahlmeter G. Development of the EUCAST disk diffusion antimicrobial susceptibility testing method and its implementation in routine microbiology laboratories. Clin Microbiol Infect 2014; 20: O255–66.
25. Pankey GA, Ashcraft DS, Dornelles A. Comparison of 3 Etest(®) methods and time-kill assay for determination of antimicrobial synergy against carbapenemase-producing Klebsiella species. Diagn Microbiol Infect Dis 2013; 77: 220–226.
26. Weinstein AJ, Moellering RC. Studies of cephalothin: aminoglycoside synergism against enterococci. Antimicrob Agents Chemother 1975; 7: 522–529.
27. Sunnerhagen T, Hammarlund P, Rasmussen M. A case of suspected infective endocarditis with *Lactococcus garvieae*: lack of in vitro synergy between ampicillin and gentamicin. JMM Case Reports 2015; 2.

Table 1. Antibiotic susceptibility and synergy-testing of 15 aerococcal IE isolates

	MIC									Log median additional killing with combination				
Isolate	PcG[1]	Ctx	Van	Gen	Clm	Cip	FIC	MBC PcG	MBC Gen	0.5 MBC PcG 6h	0.5 MBC PcG 24h	1 MBC PcG 6h	1 MBC PcG 24h	Synergy
91M	0.012	0.098	0.75	3	0.064	0.19	0.69	0.063	8	0.69	0.3	0.85	>0	No
91M*	0.004	0.008	0.25	16	0.13	32	1.8	0.016	16	0.12	2.1	0.022	>2	Yes
86M	0.004	0.032	0.5	32	0.25	0.19	0.75	0.0078	32	-0.18	0.087	-0.025	2.1	Yes
83M	0.012	0.064	0.75	24	0.19	0.25	0.75	0.031	32	>1	-	>0	-	No
80F	0.008	0.047	1	16	0.13	2	0.88	0.031	8	0.78	>1	1.05	>1	No
77M	0.012	0.098	1.5	6	0.38	0.25	0.42	0.031	2	1.6	>1	2.3	>0	Yes
75M	0.004	0.064	1	16	0.047	0.75	1.3	0.0078	8	0	>2	0.22	>1	Yes
74M	0.008	0.064	0.75	16	0.13	0.75	1.1	0.031	16	0.8	>1	1.6	0.6	No
65M	0.02	0.25	1	8	0.5	0.25	0.6	0.063	16	0.6	>2	0.94	>3	Yes
53M	0.016	0.19	1	24	0.19	0.19	0.64	0.063	32	0.07	>2	0.04	>2	Yes
49F	0.002	0.023	1	24	0.13	0.094	0.66	0.0078	32	0.42	>2	0.24	>1	Yes
*85M**	*0.047*	*0.19*	*0.5*	*12*	*1*	*32*	*1.4*	*0.063*	*16*	*-0.22*	*0.54*	*-0.12*	*0.76*	*No*
54M	*0.047*	*0.25*	*0.75*	*32*	*0.5*	*3*	*0.51*	*0.031*	*32*	*0*	*1.8*	*0.25*	*>1*	*No*
81M	0.016	0.064	1	16	0.38	4	0.5	0.125	64	0.45	1.1	0.42	1.3	No
74F	0.004	0.032	0.75	4	0.032	2	0.5	0.016	8	0.7	1.4	0.89	>0	No

[1]Abbreviations used are PcG; penicillin G, Ctx; cefotaxim, Van; vancomycin, Gen; gentamicin, Clm; clindamycin, Cip; ciprofloxacin, FIC; fractional inhibitory concentration, 91M indicates the isolate from the 91 years-old man in table 2. The asterisk (*) indicate the isolates described previously [7, 10] and the italics indicate the two isolates of *A. sanguinicola.*

Table 2. Features of patients with IE caused by *A. urinae* (n=14) and *A. sanguinicola* (n=2)

Age	Sex	Dukes	Organism	UT-focus	Other medical conditions	Severe sepsis	TEE finding	Surgery/Complication/ Comment
91	M[1]	D	Au	PC, UC	CVI, DM		MV	-
91*	M	D	Au	BPH, KC	CC, PM		MV	Cervival spondylitis, Bacteremia 3w before
89	F	D	Au		CHF, MI		MV	Bacteremia 3w before
86	M	D	Au	PC, US, dysuria	CC	RF	AV	CNS embolus
83	M	D	Au	US, CIC			MV,	BVP, PM
80	F	D	Au		CVI	CF	MV	-
77	M	D	Au		LF	TP, HP	AV	-
75	M	D	Au	BPH, HU		HP	MV	BVP
74	M	D	Au	SPC	MS, DM	Resp, TP, HP	-	-
65	M	D	Au	UC, dysuria	CVI, COPD	-	MV	Bacteremia 4w before
53	M	D	Au	Dysuria	DM	HT, HP	AV, ARA	BVP
49	F	D	Au	CIC, dysuria			AV	MVP
85*	M	D	As	PC	Dementia	HT, resp, HP	Sclerosis	ICU-treatment
54	M	D	As		DM, BSD		AV	immunosupression
81	M	P	Au	UC	Dementia, PAV		MV	nosicomial
74	F	P	Au	KTP	Dementia, PAV		-	immunosupression

[1]Abbreviations used are M; male, F; female, D; definite, P; possible, Au; *Aerococcus urinae*, As; *Aerococcus sanguinicola*, PC; prostate cancer, UC; urinary catheter, BPH; benign prostate hyperplasia, KC; kidney carcinoma, US; urethral stricture, CIC; chronic intermittent catheterization, HU; hematuria, SPC; suprapubic catheter, KTP; kidney trasplant, CVI; cerebrovascular insult, DM; diabetes mellitus, CC; colon cancer, PM; pacemaker, CHF; congestive heart failure, MI; mitral valve insufficiency, LF; liver failure, MS; multiple sclerosis, COPD; chronic obstructive pulonary disease, ARA; aortic root abscess, BSD; blistering skin disease, PAV; prosthetic aortic valve, RF; renal failure, CF; confusion, TP; trombocytopenia, HP; hypoperfusion, Resp; respiratory failure; HT; hypotension, MV; mitral valve vegitation,

AV; aortic valve vegitation, BVP; biological valve prosthesis, MVP; mechanical valve prosthesis, ICU; intensive care unit. The asterisk (*) indicates the isolates described previously [7, 10].

Table 3. Comparison of IE caused by aerococci and other pathogens

	Aerococci	*S. aureus*	Alpha-hemolytic streptococci	Enteroccci
	n=16	n=1013	n=722	n=296
Age, (years, median)	79	66 (p=0.006)	69 (p=0.02)	73
Gender (% male)	75	61	71	75
Underlying disease				
Diabetes (%)	25	17	11	18
Cancer (%)	25	8.5 (p=0.04)	9.2	14
IVDU[1] (%)	0	25 (p=0.02)	4.0	14
Underlying heart disease				
Native valve disease (%)	29	12	31	21
Prosthetic heart valve (%)	13	13	20	31
Previous IE (%)	0	8.7	8.1	17
Pacemaker/ICD (%)	6.2	14	7.8	16
Type of infection				
NVE, left, isolated (%)	75	49 (p=0.04)	64	53
NVE, right, isolated (%)	0	24 (p=0.04)	3.6	3.1
PVE (%)	15	11	14	22
PME (%)	0	9.6	2.1	6.1
Aortic valve (%)	44	31	41	52
Mitral valve (%)	56	32	36	32
Nosocomial (%)	7.1	13	4.0	13
Course of disease				
Onset to hospitalization (days)	4	2	15	16
Length of stay (days)	33	33	28	36
Treatment length (days)	32	30	28	34
Treatment length AG (days)	12	0 (p<0.0001)	14	14
Embolization (%)	19	48	27	27
Operation (%)	25	23	19	24
Death (%)	0	15	6.1	11

[1]Abbreviations used are; IVDU; intravenous drug use, ICD; intracardiac device, NVE; native valve endocarditis, PVE; prosthetic valve endocarditis, PME; pacemaker endocarditis, AG; aminoglycoside.