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Quadruple valve infective endocarditis presenting with suspected Austrian syndrome: a case report and a case series of quadruple valve infective endocarditis

Shuwei Zheng [a,*], Jade Xiao Jue Soh [b], Humaira Shafi [c]

[a] Department of Infectious Diseases, Singapore General Hospital, Outram Road, Singapore 169608
[b] Department of General Medicine, Sengkang General Hospital, 110 Sengkang E Way, Singapore 544886
[c] Division of Infectious Diseases, Changi General Hospital, 2 Simei Street 3, Singapore 529889

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ABSTRACT

Objectives: Austrian syndrome comprises the triad of pneumonia, meningitis, and endocarditis secondary to *Streptococcus pneumonia*. We present what we believe to be the first reported case of Austrian syndrome with quadruple heart valve involvement and review the literature detailing cases of quadruple valve infective endocarditis.

Case presentation and results: A case is presented of a patient with radiographic evidence of a left lower lobe pneumonia. Sequential transthoracic followed by transesophageal echocardiogram done to evaluate the presence of a cardiac murmur revealed the presence of quadruple valve vegetations. Multiple blood cultures were persistently negative. The patient went on to develop seizures secondary to proven meningitis. Microbiological diagnosis was eventually established through positive *Streptococcus pneumoniae* antigen (Alere BinaxNOW®) from cerebrospinal fluid, establishing a presumptive clinical diagnosis of Austrian syndrome. A computerized PubMed search for reports of quadruple valve infective endocarditis and their references was collated.

A total of 22 patients were found, including our patient. The median age of presentation was 47.5 years. Five patients had a history of intravenous drug abuse, another 5 had underlying congenital heart disease, and 1 had both. Two patients (9.1%) had 2 microorganisms isolated. *Staphylococcus aureus* and *Streptococcus viridans* (3 cases, 13.6% each) were the most commonly implicated microorganism. Heart failure was the commonest complication, afflicting 11 patients (50.0%). Ten patients (45.5%) underwent surgery. Overall case fatality rate was 50.0%. Cardiac surgery was of statistical significance in predicting survival ($P = 0.009$).

Conclusion: Quadruple valve endocarditis is associated with a high mortality rate, and cardiac surgery may be protective.

1. Introduction

The triad of pneumonia, meningitis, and endocarditis secondary to *Streptococcus pneumoniae* is known as the Austrian syndrome (Taylor and Sanders, 1999). First described by Heschl in 1862 then Osler in 1881, Robert Austrian went on to describe a case series of 8 patients with pneumococcal endocarditis and rupture of the aortic valve subsequently (Austrian, 1956-1957). We present what we believe to be the first reported case of Austrian syndrome with quadruple heart valve involvement and review the literature detailing cases of quadruple valve infective endocarditis.

2. Case presentation

A 54-year-old man presented to our hospital with a 2-week history of fever, cough, and headache. He had no past medical history, denied intravenous drug abuse, and had no significant alcohol consumption. He was afebrile and hemodynamically stable on presentation. Further clinical examination revealed an early diastolic cardiac murmur with basal crackles in the left lung. Neurological examination was unremarkable.

He had leukocytosis (white blood cell count $42.5 \times 10^3/\mu L$) as well as thrombocytopenia (platelet count $50 \times 10^3/\mu L$). Urinary analysis showed the presence of microscopic hematuria without positive urinary cultures.

A chest radiograph revealed left lower lobe bronchopneumonia. He was commenced on intravenous ceftriaxone upon admission from the emergency department. Blood cultures done following antibiotics did not reveal a causative microorganism. A contrasted computed tomography (CT) scan of his chest, abdomen, and pelvis confirmed the diagnosis

* Corresponding author. Tel.: +65-6321-3479; fax: +65-6227-5247.
E-mail address: shuwei.zheng@mohh.com.sg (S. Zheng).

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of bronchopneumonia, and there was no radiological evidence of an underlying malignancy. A transthoracic echocardiography (TTE) showed vegetations involving both the mitral and aortic valves, with aortic regurgitation. On the fourth day of hospitalization, he developed right upper limb weakness and 2 episodes of generalized tonic–clonic seizures. Magnetic resonance imaging of the brain revealed leptomeningeal enhancement, as well as cortical infarcts in the left temporal and parietal lobes. Lumbar puncture was performed, revealing cerebrospinal fluid (CSF) white cell count of 225 U/mm^3, protein of 1.45 g/L, and CSF:serum glucose ratio of 0.23, consistent with bacterial meningitis. CSF gram stain and culture were negative. Urinary *Streptococcus pneumoniae* antigen was negative, but CSF *Streptococcus pneumoniae* antigen (Alere BinaxNow®) was positive. A diagnosis of Austrian syndrome with septic emboli to the brain was made. Antimicrobial therapy was switched to meningeal doses of vancomycin and ceftriaxone. A transesophageal echocardiography (TEE) performed on the sixth hospitalization day showed quadruple valve endocarditis (Fig. 1) complicated by aortic valvular perforation and regurgitation, as well as the presence of a small ventricular septal defect. He was planned for surgery but unfortunately developed acute renal and cardiac failure and eventually succumbed to his illness. No autopsy was performed.

3. Materials and methods

A computerized search for proven reports of quadruple valve infective endocarditis in the Medline database of the National Library of Medicine was conducted for the literature review. Only reports available in English were included. Relevant articles were identified from screening of titles and abstracts to determine final eligibility for this systematic review.

All articles published before October 2018 were used. Keywords used to select cases include "quadruple valve" OR "four-valve" OR "multiple valve" OR "multivalvular" AND "endocarditis". Relevant articles from the cited references were also retrieved for analysis if they fit our case definition of quadruple valve endocarditis.

Two authors independently performed the search and eventual decision on which article to include was based on consensus. We excluded case series of multivalvular endocarditis that included cases of quadruple valve endocarditis because these case series include little clinical details of quadruple valve endocarditis that we require for our analysis.

Fisher exact test and Mann–Whitney U test were used to analyze variables predictive of survival using SPSS software version 24.0. A *P* value not exceeding 0.05 was considered statistically significant.

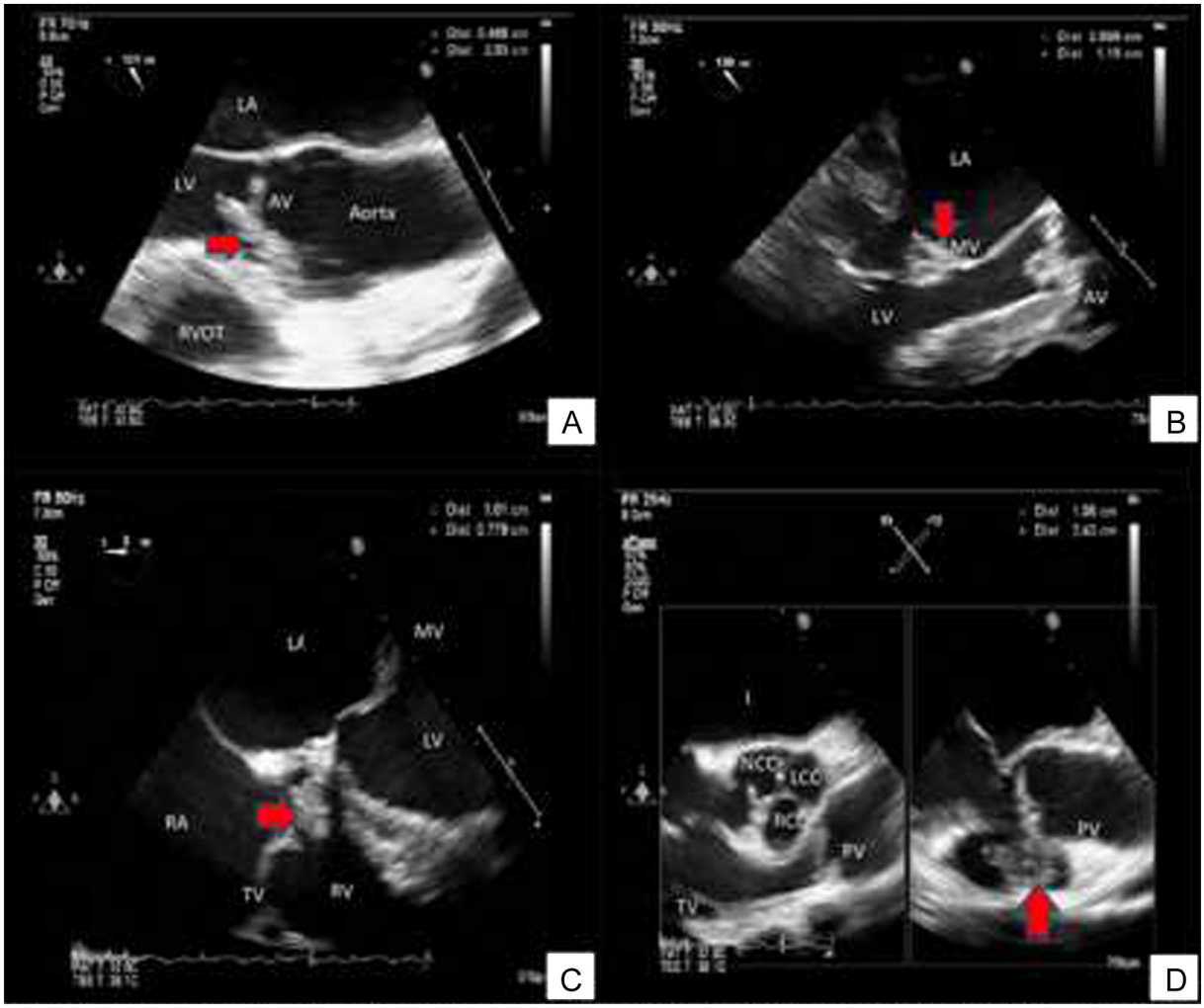

Fig. 1. Echocardiographic pictures with red arrows showing (A) aortic valve mass 2.0 × 0.4 cm (long-axis view), (B) mitral value mass 1.1 × 0.6 cm (long-axis view), (C) tricuspid valve 1.0 × 0.7 cm (4-chamber view), and (D) pulmonary valve mass 2.4 × 1.0 cm (short-axis view). LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle; MV = mitral valve; AV = aortic valve; TV = tricuspid valve; PV = pulmonary valve; LCC = left coronary cusp; RCC = right coronary cusp; NCC = noncoronary cusp.

Table 1
Literature review of quadruple valve infective endocarditis.

Case	Age/sex	Underlying conditions	Risk factors		Microbiological diagnosis	Echocardiography		Complications	Key antibiotics	Surgery	Outcome	Ref.
			Valvular heart disease	IVDU		Diagnostic TTE	Diagnostic TEE					
1	54 Male	VSD	Yes	No	*S. pneumoniae*	No	Yes	Embolism Multiorgan failure (including heart failure)	VAN + CEF	No	Death	NA
2	41 Male	Hepatitis C	No	Yes	Group G *Streptococcus*	NM	NM	Shock	CP + GEN	Yes	Survived	6
3	39 Female	Nil	No	Yes	Methicillin-sensitive *S. aureus*	No	Yes	Heart failure Valve perforation	CLO + GEN	Yes	Survived	7
4	58 Male	VSD	Yes	No	NM	NM	NM	Renal failure	NM	Yes	Survived	8
5	64 Male	DM, CKD, HTN	No	No	*E. faecalis*	No	Yes	Renal failure	AMP + GEN	Not mentioned	Death	9
6	76 Male	CKD, COPD, Factor XIII deficiency	No	No	*E. faecalis* *G. morbilorum*	No	Yes	Heart failure	AMP + GEN + IMI	Yes	Survived	10
7	47 Male	VSD	Yes	No	*S. pyogenes*	NM	NM	NM	NM	Yes	Survived	11[+]
8	34 Male	Hepatitis B, VSD	Yes	No	Alpha-hemolytic *Streptococcus*	NM	NM	Multiorgan failure (including heart failure)	CP + GEN + CLI	Yes	Death	12
9	7 Male	Nil	No	No	Methicillin-resistant *S. aureus*	Yes	Not done	Shock	VAN then TIG	No	Survived	13
10	46 Male	Mental retardation	No	No	*S. viridans*	Yes	Not done	Heart failure	CP	No	Survived	14
11	57 Male	Nil	No	No	*S. gallolyticus*	No	Yes	Heart failure	CEF + GEN then AMP-SUL + GEN then AMO-CLA	Yes	Survived	15
12	82 Male	Colon cancer	No	No	Methicillin-resistant *S. aureus*	No	Yes	Embolism	NM	No	Death	16
13	31 Male	Alcohol abuse	No	Yes	*Corynebacterium*	Not done	Not done	Multiorgan failure (including heart failure)	VAN + GEN + CP + TMP-SMX + ERY	No	Death[a]	17
14	56 Female	DM, CKD, HTN	No	No	*P. aeruginosa* *S. marcescens*	Not done	Not done	Heart failure Shock	NM	No	Death[a]	18
15	48 Male	Alcoholic liver cirrhosis	No	No	*S. mutans*	No	Yes	Heart failure	CP + GEN	No	Death	19
16	58 Male	Alcohol abuse	No	No	S. gallolyticus	No	Not done	Heart failure Cardiac tamponade	NM	Yes	Death	20
17	24 Male	Nil	No	Yes	*P. aeruginosa*	NM	NM	NM	NM	No	Death[a]	21
18	78 Female	Nil	No	No	*S. viridans*	NM	NM	Heart failure Pericarditis	CP + GEN	No	Death[a]	22
19	18 Male	Tetralogy of Fallot	Yes	Yes	*S. viridans*	Yes	Not done	Shock Myocardial infarction	VAN	No	Death	23
20	59 Female	VSD/ASD	Yes	No	*A. defectiva*	Yes	Yes	Heart failure	AMP + CEF	Yes	Survived	24
21	16 Female	Nil	No	No	*E. faecalis*	No	Yes	Renal failure	CP + GEN then IMI + LZD	No	Survived	25
22	32 Male	CKD	No	Yes	*S. epidermidis*	NM	NM	Heart failure	VAN + AMK	Yes	Survived	26

VSD = ventricular septal defect; DM = diabetes mellitus; CKD = chronic kidney disease; HTN = hypertension; COPD = chronic obstructive pulmonary disease; IVDU = intravenous drug user; NM = not mentioned; VAN = vancomycin; CEF = ceftriaxone; CP = crystalline penicillin; GEN = gentamicin; AMK = amikacin; CLO = cloxacillin; AMP = ampicillin; IMI = imipenem; CLI = clindamycin; TIG = tigecycline; AMP-SUL = ampicillin sulbactam; AMO-CLA = amoxicillin clavulanic acid; TMP-SMX = trimethoprim sulfamethoxazole; ERY = erythromycin; LZD = linezolid.

[a] Autopsy performed; +abstract only.

4. Results

The above search terms yielded 87 articles, with 17 articles deemed eligible. An additional 4 articles were identified from the references of these eligible articles, yielding a total of 22 cases, including our patient (case 1). In 2 case series (Xiao et al., 2016; Yao et al., 2009), 1/35 and 2/48 cases of endocarditis with quadruple valve involvement were excluded because of a lack of clinical details for the quadruple valve endocarditis cases. Two case reports were excluded as the authors only describe it as a possible case of quadruple valve endocarditis in 1 report and the other was published in Japanese (Okada et al., 2008; Tucker et al., 1987). Table 1 shows the clinical characteristics and outcomes of all the patients (Anwar et al., 2008; Bassetti et al., 2004; Berstein et al., 1993; Cao et al., 2012; Cremieux et al., 1985; Deonarine et al., 1997; Farrer, 1987; Fernandez et al., 2007; Grzywocz et al., 2018; Haghighi et al., 2014; Haranahalli et al., 2013; Henderson and Palmer, 1991; Hobbs et al., 1982; Hosseini et al., 2013; Krake et al., 2004; Kramer et al., 1977; Lam et al., 1988; Natrajsetty et al., 2015; Piran et al., 2009; Planinc et al., 2017; Seeburger et al., 2009).

The median age was 47.5 years (interquartile range, 32–58). There were more men (77.3%) than women (22.7%). Five patients had a history of intravenous drug abuse, another 5 had underlying congenital heart disease, and 1 had both.

Out of 13 cases with information on availability of echocardiography results, only 4/13 (30.8%) were diagnostic for quadruple valve involvement using TTE. Among the remaining 9 cases, 8 (88.9%) cases were diagnosed through TEE. The last case did not have any TEE done, and involvement of all 4 cardiac valves was diagnosed at time of surgery.

Two patients (9.1%) had 2 microorganisms isolated. *Staphylococcus aureus* and *Streptococcus viridans* (3 cases, 13.6% each) were the most commonly implicated microorganism. Heart failure was the commonest complication, with 11 patients (50.0%) diagnosed. Ten patients (45.5%) underwent surgery.

Overall, 11 patients died, giving a case fatality rate of 50.0%. Correlations between demographic and clinical factors with mortality are shown in Table 2. Cardiac surgery was of statistical significance in predicting survival ($P = 0.009$). Endocarditis was diagnosed only at postmortem in 2 cases (9.1%).

Table 3 shows the surgical findings and outcomes of the 10 patients who underwent surgery. Among the 10 patients who underwent surgery, 8 (80.0%) survived. Three (30.0%) patients underwent valve replacement for all 4 valves, 2 (20.0%) patients underwent triple valve replacement, 3 (30.0%) patient underwent dual valve replacement, 1 (10.0%) patient underwent single valve replacement, and 1 (10.0%) patient underwent vegetectomy only.

Table 2
Predictors of mortality.

	Survivors ($n = 11$)	Deceased ($n = 11$)	*P* value
Demographics			
Median age in years	46 (32–58)	54 (31–64)	0.511
Male	8 (72.7%)	9 (81.8%)	1.0
Predisposing conditions			
Congenital heart disease	3 (27.3%)	3 (27.3%)	1.0
Alcohol abuse	0 (0.0%)	3 (27.3%)	0.214
Intravenous drug user	3 (27.3%)	3 (27.3%)	1.0
Comorbidities			
Chronic liver disease	1 (9.1%)	2 (18.2%)	1,0
Chronic kidney disease	2 (18.2%)	2 (18.2%)	1.0
Microbiology			
Polymicrobial bacteremia	1 (9.1%)	1 (9.1%)	1.0
Gram positive organism	3 (27.3%)	2 (18.2%)	1.0
Complications			
Multiorgan failure	0 (0.0%)	3 (27.3%)	0.214
Heart failure	7 (63.6%)	7 (63.6%)	1.0
Acute renal failure	2 (18.2%)	3 (27.3%)	1.0
Embolism	0 (0.0%)	2 (18.2%)	0.476
Shock	2 (18.2%)	4 (36.4%)	0.635
Surgical intervention	9 (81.8%)	2 (18.2%)	**0.009**

5. Discussion

We report the first case of quadruple valve infective endocarditis most likely secondary to *Streptococcus pneumoniae*, occurring in a patient with suspected Austrian syndrome and newly diagnosed ventricular septal defect. Based on the modified Duke Criteria for infective endocarditis, our patient fulfilled 1 major (evidence of endocardial involvement) and 4 minor criteria (predisposition, fever, vascular phenomena, and immunologic phenomena). A contrasted CT scan of the chest, abdomen, and pelvis failed to suggest the presence of any malignancy, making marantic endocarditis less likely. Repeated blood cultures and a cerebrospinal fluid culture did not yield positive growth, likely as a result of prior administration of broad-spectrum antibiotics, a common reason for culture-negative endocarditis (Liesman et al., 2017). In such instances, adjunctive non–culture-based tests, such as the highly sensitive and specific immunochromatographic test in our case, are important to achieve microbiological diagnosis.

Various publications supporting its use for the diagnosis of pneumococcal meningitis cite high sensitivity and specificity when using the immunochromatographic *S. pneumoniae* antigen BinaxNOW® assay, which was the modality used in our patient (Jayaraman et al., 2018; Moisi et al., 2009; Samra et al., 2003). Samra et al. described their experience in the use of BinaxNOW® assay in CSF in 519 patients with suspected meningitis in 2 centers in Israel (Samra et al., 2003). In this study, the direct antigen test was 95.4% sensitive and 100% specific in the CSF using cultures as the gold standard. Moisi et al. also described excellent sensitivity and specificity of 99% each in 1173 CSF samples compared with culture in a multicenter study using the same assay (Moisi et al., 2009). In a large study of CSF samples from 2081 children in a multicenter study in India, the BinaxNOW® assay has 100% sensitivity and 95.3% specificity for the detection of *S. pneumoniae* in CSF using culture as a gold standard for comparison (Jayaraman et al., 2018). In another study of 25 patients with acute bacterial meningitis where 48% is due to *S. pneumoniae* proven by either culture or polymerase chain reaction, the BinaxNOW® assay was positive in 88% on days 1–3, 90% on days 4–6, and 75% on days 7–10, suggesting that prior antibiotic therapy did not affect the diagnostic yield of this assay in diagnosing pneumococcal meningitis, especially within the first week of treatment (Brink et al., 2015).

These promising data lend credence to our diagnosis of pneumococcal meningitis in our patient who has significant CSF pleocytosis and leptomeningeal enhancement on MRI. With the fulfillment of 1 major and 4 minor criteria of the modified Duke Criteria for infective endocarditis and radiological evidence of bronchopneumonia, we believe that this constitutes a strong case for Austrian syndrome as a unifying diagnosis even though we acknowledge the limitation from a lack of a positive culture.

Since the advent of penicillins, the prevalence of *S. pneumoniae* infective endocarditis has decreased tremendously. In a systematic review by de Egea et al. of 111 cases from 2000 to 2013, 26.1% had complete Austrian syndrome, and this seems to be a poor prognostic factor, evident by its presence in 43.5% of the mortality cases in this series (de Egea et al., 2015). Majority of these 111 cases were left-sided, and 27.0% had involvement of more than 1 valve. In our series of quadruple valve endocarditis, the commonest microbiological agents were *Staphylococcus aureus* and *Streptococcus viridans*.

TEE exhibits superior diagnostic utility over TTE in our series, where TTE was only 30.8% sensitive for quadruple valve endocarditis, with the remaining cases diagnosed through TEE if it had been performed. In the study by Yao et al., only 50.0% of the cases of multivalvular endocarditis were diagnosed by TTE, with an additional 35.4% confirmed by TEE (Yao et al., 2009).

Table 3
Patients who underwent surgery.

Case	Detailed morphological findings	Nature of surgery	Timing of surgery	Outcome
2	Echocardiographic findings: Severe AV regurgitation with vegetation causing left ventricular outflow tract obstruction "Large" TV vegetation "Small" MV/PV vegetations	AV replacement (homograft) TV vegetectomy	Emergent (10 days after admission)	Survived
3	Echocardiographic findings: Vegetations on all 4 valves and 2 chambers MV perforation with severe regurgitation Operative findings: Extensive valvular destruction of all valves	Quadruple valve replacement (mechanical valves for AV/MV, bioprosthetic valves for PV/TV) Excision of ventricular vegetations	Emergent (10 days after admission)	Survived
4	Echocardiographic findings: 2 MV vegetations (max size 1.5 × 0.5cm^2), severe regurgitation 3 AV vegetations (max size 1 × 0.5cm^2), mild–moderate regurgitation TV vegetations (max size 2.2 × 0.75cm^2) PV vegetations (max size 1.75 × 0.9cm^2) Perimembranous VSD (0.7 cm^2) with vegetation	Triple valve replacement at another center (site and nature of valve replacement not specified)	Not known	Survived
6	Echocardiographic findings: Severe AV/TV/PV regurgitation, moderate MV regurgitation Operative findings: >1 cm vegetations on all 4 valves	Quadruple valve replacement (mechanical valves) Epimyocardial pacemaker lead insertion	Emergent (after 10 days of conservative treatment)	Survived
7	Operative findings: Right ventricular outflow tract obstruction Anterior MV leaflet vegetation (2 cm) and chordal rupture, scattered posterior MV leaflet vegetations Perforated anterior TV leaflet with vegetation (1 cm) AV leaflet erosion and vegetation (0.7 cm) PV scattered vegetations Perimembranous VSD (2 cm)	Quadruple valve replacement (mechanical valves) VSD repair	Emergent	Survived
8	Not stated	AV/MV/TV replacement (bioprosthetic valves) PV repair VSD repair	Emergent (after failing 7 days of conservative treatment)	Death
11	Echocardiographic findings: Severe AV regurgitation, mild–moderate MV/TV/PV regurgitation	AV/MV replacement (nature of valve replacement not specified) MV/TV valvuloplasty	Semielective (8 weeks after conservative treatment)	Survived
16	Not stated	PV vegetectomy	Not mentioned	Death
20	Echocardiographic findings: Posterior MV vegetation (0.8 × 0.6 cm), left coronary cusp AV vegetation (1.2 × 1.0 cm), septal leaflet of TV vegetation (0.6 × 0.7 cm), left cusp of PV vegetation (1.2 × 1.1 cm); all valves had moderate-to-severe insufficiency Operative findings: ASD and VSD	MV vegetectomy and annuloplasty, TB annuloplasty, PV/AV replacement (bioprosthetic valves), ASD/VSD closure	Emergent (after a month of antimicrobial treatment)	Survived
22	Echocardiographic findings: Severe MV/TV regurgitation, mild PV regurgitation; vegetations on all four valves (TV >30 mm, MV >15 mm, PV 10 mm, AV 5 mm) Operative findings:	MV replacement (mechanical valve), TV replacement (bioprosthetic valve)	Semielective (6 weeks after conservative treatment)	Survived

AV = aortic valve; MV = mitral valve; PV = pulmonary valve; TV = tricuspid valve.

We report a high mortality rate of 50.0% in our series. Multivalvular infective endocarditis has a reported mortality ranging from 12.5% to 21% (Haranahalli et al., 2013; Kim et al., 2000; Mihaljevic et al., 2001; Selton-Suty et al., 2010), but most cases in these series did not report quadruple valve involvement. Multivalvular lesions are predictive of higher risk of complications and more complex surgical therapy. Our results show that performance of cardiac surgery was of statistical significance in predicting survival. Yet, while the need for surgical intervention is clear in most cases, the choice of intervention and valvular substitute remains controversial and guided by the extent of tissue destruction. In fact, the review by Selton-Suty et al. suggests that multivalvular infective endocarditis is associated with more heart failure cases than for univalvular infective endocarditis, resulting in more surgeries performed in the analyzed cohorts (Selton-Suty et al., 2010). In our series, majority (45.5%) required surgical intervention, and of these, 80.0% had multivalvular valve replacement.

Our study is limited by its small numbers and its retrospective nature. Unfortunately, many of the case reports that we reviewed had not explained why some of these patients had not undergone surgical intervention in spite of the presence of heart failure and large vegetations, which are common indications for valvular surgery in the setting of infective endocarditis. We acknowledge that it is likely that many of these patients did not undergo surgery because they were too ill to be operated upon and could also have exsanguinated before any definitive planned surgical intervention, suggesting an element of selection bias. We postulate that early TEE, with its superior diagnostic utility, could possibly have identified this cohort of multivalvular endocarditis patients earlier, thereby allowing early surgical intervention before further clinical deterioration. While there have been several publications on the topic of multivalvular endocarditis, none have attempted to look at the unique entity of quadruple valve involvement, which our study have tried to address from an observation viewpoint.

In conclusion, while quadruple valve endocarditis remains rare, mortality is extremely high. Clinicians need to be cognizant of the additional benefit of a TEE in the setting of a diagnosed case of infective endocarditis as early surgery may be the most crucial factor in predicting survival in this clinical entity.

Disclosure

Part of the contents of this manuscript was presented as an abstract at the 2016 ID Week at New Orleans, Louisiana.

Conflict of interest

Nil

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Nil

Ethical approval

No ethical approval was sought as additional cases included are compiled from published cases reports from other institutions.

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