Observational Study

Medicine

OPEN

A contemporary case series of *Pseudomonas aeruginosa* infective endocarditis

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Abstract

Pseudomonas aeruginosa infective endocarditis (IE) is a rare disease associated with high mortality and complications. Here, we describe a contemporary set of patients aiming to improve the understanding of risk factors, clinical features, treatments, and outcomes. This retrospective case series reviewed cases from 3 tertiary metropolitan hospitals between January 1999 and January 2019. prespecified data were collected for each case, with a review of risk factors, valve involvement, acquisition, treatment, and complications. Fifteen patients were identified over a 20 years period. All patients presented with fever, 5/15 had preexisting prosthetic valve with valvular heart disease in 7/15 patients making it the most common risk factor. Intravenous drug use (IVDU) was the source in only 6/15 cases with healthcare associated infection and left-sided valvular involvement being more common than previous reports both occurring in 9/15 cases. Complications occurred in 11/15 patients with a 30 days mortality of 13%. Surgery was performed in 7/15 patients and 9/15 patients received antibiotic combination therapy. One year mortality was higher in those with increasing age, comorbidities, left-sided valve involvement, presence of predefined complications, and antibiotic monotherapy. Development of resistance occurred in 2 cases that received monotherapy. *P aeruginosa* IE remains a rare disease with high mortality and secondary complications.

Abbreviations: CCI = Charlson comorbidity index, CIP = ciprofloxacin, EUCAST = European committee on antibiotic susceptibility testing, GEN = gentamicin, IE = infective endocarditis, IVDU = intravenous drug use, MDR = multidrug-resistant, MER = meropenem, MIC = minimum inhibitory concentration, TAZ = piperacillin/tazobactam.

Keywords: antibiotic resistance, infective endocarditis, *Pseudomonas aeruginosa*, risk factors, treatment

1. Introduction

Pseudomonas aeruginosa infective endocarditis (IE) (i.e.) is rare, accounting for approximately 1.5% of all IE cases.[1] Periodic case series can be found in the literature, and the understanding of the disease is far from complete. Earlier series reported acquisition via intravenous drug use (IVDU), with a smaller proportion of patients acquiring the infection via healthcare-associated means.[2–6] In the setting of IVDU, right-sided valve involvement has predominated.[7,8] Left-sided involvement appears to be more common in later series in patients with prosthetic or abnormal cardiac anatomy and noninjecting drug users.[2,4]

Treatment is difficult, with high rates of secondary complications, the need for surgical intervention, relapse, and mortality. The relapse of bacteremia following appropriate medical treatment was over 33% in the most recent 2 series.[2,4] Complications including embolization, intracardiac abscess formation and heart failure are common occurring in more than 50% of patients.[2,5,6] The mortality rate was over 50% in Reyes et al 1969 to 1972 case series. This was reduced to 14% in the 1972 to 1975 case series and was attributed to an increased dose of tobramycin from 5 mg/kg to 8 mg/kg in combination therapy with an antipseudomonal penicillin.[7,8]

Treatment of *P aeruginosa* in the most recently published series by Dawson et al[3] and Reyes et al[4] included at least 6 weeks of combination therapy with an antipseudomonal beta-lactam and high-dose aminoglycoside with or without surgery.[4,5] Dual therapy has been recommended by Reyes et al and Dawson et al to avoid the development of resistance during treatment and potential synergy.[3,4] The lowest mortality of any case series (10%) was reported by Reyes et al 2006 to 2008 series where cefepime and high-dose tobramycin (8 mg/kg once daily) was the most commonly used regimen.[4] antipseudomonal penicillins have been successfully used in the past as have carbapenems, with limited reports of fluoroquinolone use.[4,5,9] The emergence of resistance during therapy has been reported with piperacillin, including when used in combination with an aminoglycoside.[10,11]

This paper describes a contemporary series of patients with *P aeruginosa* IE and adds to the current knowledge regarding clinical features, prognosis, and treatment options.

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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How to cite this article: Walczak A, McCarthy K, Paterson DL. A contemporary case series of Pseudomonas aeruginosa infective endocarditis. Medicine 2023;102:13(e32662).

Received: 16 November 2022 / Received in final form: 22 December 2022 / Accepted: 27 December 2022

http://dx.doi.org/10.1097/MD.0000000000032662

2. Methods

2.1. Design

This was a retrospective case series via review of patient data at 3 Australian metropolitan tertiary hospitals between January 1st 1999 and January 1st 2019, The Royal Brisbane and Women Hospital, The Prince Charles Hospital, and Princess Alexandra Hospital, the latter 2 offering cardiothoracic surgical services.

Cases were identified using International classification of diseases codes B96.5, T82.6, and I33.0. with coding Dx of *P aeruginosa* AND (infection and inflammatory reaction due to cardiac valve prosthesis OR acute and subacute IE).

2.2. Data collection

Case history and collection of predefined data was obtained from each patient, including age, sex, acquisition, medical comorbidities, Charlson comorbidity index (CCI),[12] medications, immunosuppression, modified Dukes criteria,[13] risk factors (prosthetic valve, congenital heart disease, and previous i.e.), symptoms at presentation (fever, malaise, murmur, embolic, immunological, and duration), valve involvement, echocardiographic findings, duration of bacteremia, antibiotic susceptibilities, antibiotic regimens utilized, cardiothoracic surgical treatment, and patient outcomes. Data on patient mortality at 7 and 30 days, 6 months, 1, 2, and 5 years were collected. Other outcomes included relapse and complications of congestive cardiac failure, intracardiac abscess, other abscess formation, major emboli, acute kidney injury, and neurological complications, including meningitis, encephalitis, abscess formation, or septic emboli.

2.3. Definitions

Healthcare, Nosocomial and Community acquisition definitions were as per Lin et al[2] IVDU association was defined as a confirmed or suspected recent history of this activity within the preceding 6 months. The source of bacteremia was determined primarily by the documentation of the treating team. The length of bacteremia in days was determined from the first positive to the first negative blood culture if known. Relapse was defined as repeat bacteremia with *P aeruginosa* following completion of the antibiotic treatment course within a 6-month period. Combination therapy was defined as the use of at least 2 active antipseudomonal antibiotics, including gentamicin (GEN), for a minimum of 2 weeks. However, updated European Committee on Antibiotic Susceptibility Testing (EUCAST) guidelines do not consider GEN as an adequate monotherapy.[14] Congestive cardiac failure was defined according to the Framingham criteria[15] and acute kidney injury was defined using the kidney disease improving global outcomes criteria.[16]

2.4. Microbiological methods

Microbiological data of the isolates was extracted from the hospital laboratory information system (AUSLAB). The BD BACTEC blood culture system (BD, North Ryde, Australia) (1999–2018) and BacT/ALERT 3D (bioMerieux, North Ryde, Australia) (2018–2019) were used for processing blood cultures with a standard 5 days incubation period. Organism identification was performed using the VITEK 2 system (bioMerieux, Balmes-les-Grottes, France) (1999–2012) and MALDI-TOF MS system (bioMerieux, North Ryde, Australia) (2012–2019). Susceptibility testing was performed using the VITEK 2 system (bioMerieux, North Ryde, Australia). E-test MIC was performed on 1 isolate. Susceptibility guidelines were according to the Clinical and Laboratory Standards Institute breakpoints[17] (1999–2012) and the EUCAST[18] (2012–2019) guidelines published for that year. During this period, GEN susceptibility was reported according to relevant guidelines for *P aeruginosa*.

2.5. Statistical analysis

Descriptive statistics, including the mean, median, and standard deviation, were calculated for continuous variables. Univariate analysis was performed to examine the association between mortality at 1 year and categorical variables using Fisher exact test because of the small sample size. Student *t* test was used for continuous variables. Statistical significance was set at *P* value < .05. The analysis was performed using Stata software (version 13; StataCorp LP, College Station, TX). Missing data was excluded and noted in presentation and analysis.

2.6. Ethics

Ethical approval for this study was obtained from the Queensland North Metropolitan Human Research Ethics Council - HREC/16/QRBW/619.

3. Results

Fifteen cases were identified over a 20-year period meeting modified Dukes criteria for i.e. with *P aeruginosa*.. Demographic, clinical details, treatment, and outcomes are summarized in Tables 1, 2, and 3. Age ranged from 28 to 80 years (mean, 54 years), 60% were male, with a CCI range of 0 to 7 (median 2). The universal presenting feature was fever (100%), with murmur in only 2 cases (13%) and vascular phenomena in 1 case (7%). Heart failure or immunological features were not observed in any cases at presentation; however, they occurred as subsequent complications in 2 and 3 cases, respectively. The length of bacteremia could be determined in 11 of 15 cases and varied with a range of 2 to 30 days (median, 7 days). Less than half of the patients had acquisition attributed to IVDU (40%), with the majority being healthcare-associated (60%). preexisting valvular disease was present in 47% of the cases, and only 1 case with this risk factor was it associated with IVDU.

Baseline antibiograms are shown in Table 4, with no antibiotic demonstrating universal susceptibility. The initial isolate that was resistant to meropenem (MER) (case 9–2011) was susceptible to colistin with a minimum inhibitory concentration (MIC) of 1 mg/L. Case 12 developed relapsed infection within 2 weeks of completing a 6-week course of piperacillin/tazobactam (TAZ) monotherapy with an isolate that was resistant to TAZ. Case 10 developed progressive resistance after initial monotherapy with ceftazidime followed by MER, and finally ciprofloxacin (CIP) before a formal diagnosis of endocarditis was made and treatment was withdrawn. The initial isolate was piperacillin-tazobactam resistant with the isolate from the 1st recurrence of bacteremia also resistant to antipseudomonal cephalosporins but susceptible to MER. The isolate from 2nd recurrence was only susceptible to GEN and CIP of the antibiotics tested.

Treatment choices varied but included at least 6 weeks of intravenous antibiotic therapy in all cases surviving beyond 30 days followed by suppressive CIP orally in 2 cases: case 9 due to prosthetic valve infection with vegectomy not replacement and case 7 due to significant native valve infection in a patient not suitable for surgical intervention. Changes in the antibiotic regimen were observed in 7 cases. In Case 1, relapse after the completion of combination therapy occurred, with a repeat 6-week course of MER monotherapy. Reason for change is unknown for Case 2 and 13. In Case 3, multiple changes (see Table 1) were made due to ongoing fever and concerns for drug-induced fever. In case 9, multiple changes (Table 1) were made due to persistent bacteremia with a multidrug-resistant (MDR) isolate. In case 12, relapse occurred with a piperacillin-tazobactam resistant isolate, and in case 15, concerns for neurological infection

Table 1

Summary of cases.

Case yr	Demographic	Valve	Antibiotics	Cardiothoracicsurgery	Follow up
1	46 M	TV	1.MER + GEN	No	Alive > 1 yr
1999	IVDU		2. MER		
2	73M	MV, AV, PPM	1. TIM + TOB	Yes	Died 6 mo after Dx from sepsis with other organism
2002			2. MER	AVR, MVR, TV repair, removal of PPM lead	
3	46 M	MV	1.TIM + GEN	No	Clinical cure
2003			2.CIP + TOB		Alive > 5 yr
			3.CAZ + CIP		
4	49 M	TV	1. TIM + TOB	Yes	Clinical cure
2003	IVDU			TV repair and vegectomy	Alive > 5 yr
5	50 F	MVR	1.MER	No	Died in hospital < 30 d from diagnosis
2005					
6	72 M	MV	1.MER	No	Clinical cure
2008					Alive > 1 yr
7	58 F	MV	1.MER + CIP	No	Alive > 2 yr
2009			2.CIP*		
8	54M	MV	1.MER	No	Alive > 5 yr
2009					
9	80 F	MVR	1.GEN, MER	Yes	Died 7 years after episode of i.e.
2011			2. COL,MER, RIF	MVR vegectomy	
			3. COL		
			4. CIP*		
10	75 M	TV + MV	1.CAZ	No	Died in hospital < 30 d from diagnosis
2012			2. MER		
			3. CIP		
11	52 F	AV	1.TAZ	Yes	Died from other bacterial, i.e., after < 6 mo
2013	IVDU			AVR	
12	40 M	MV	1.TAZ	Yes	Relapse
2014	IVDU		2.MER	MV repair	Alive > 5 yr
13	46 M	TV	1.MER + GEN	Yes	Clinical cure
2017	IVDU		2.MER + CIP	TVR	Alive > 1 yr
14	28F	PVR, PC	1. TAZ	Yes	Alive > 2 yr
2017				Closure of VSD, redo pulmonary conduit	No relapse
15	45F	AVR	1. TAZ	No	Died within 6 mo
2018	IVDU		2. FEP + TOB		
			3. MER		

AV = aortic valve, AVR = aortic valve replacement, CAZ = ceftazidime. CIP* = ciprofloxacin suppressive therapy, CIP = ciprofloxacin, COL = colistin, GEN = gentamicin, MER = meropenem, MV = mitral valve, MVR = mitral valve replacement, PC = pulmonary conduit, PPM = permanent pacemaker, RIF = rifampicin, TAZ = piperacillin/tazobactam, TIM = ticarcillin/clavulanic, TOB = tobramycin, TV = tricuspid valve, TVR = tricuspid valve replacement, VSD = ventricular septal defect.

resulted in a change from TAZ to cefepime, with a later change to MER due to a lower MIC.

Cardiothoracic surgical intervention occurred in 47% of the cases at variable time periods during illness. Indications for surgery varied and included aortic root abscess in 2 cases, persistent bacteremia in 1 case (30 days duration), 1 case of relapse with septic emboli, 1 with congestive cardiac failure and 2 cases due to enlarging echo-densities on echocardiogram, 1 with persistent fever, and the other with associated septic emboli. 2 of 7 valve tissues were culture positive for *P aeruginosa*, no other organisms were isolated and no further molecular testing was performed on culture negative samples.

In hospital mortality and at 30 days was 13% (2/15), increasing to 20% (3/15) at 6 months and 27% (4/15) at 1 year for the 15 cases. At 5 years, this increased to 60% (6/10); however, 2 patients were lost to follow up, and 3 patients were still alive and not yet at 5 years of follow-up. The 2 patients who died within 30 days had significant comorbidities, including immunosuppression, had nosocomial acquired infection, and received monotherapy without surgery before treatment was withdrawn.

Analysis of Mortality at 1 year compared with age, CCI, acquisition, left-sided valve involvement, surgical intervention, complications, and use of monotherapy are shown in Table 3, with *P* values derived from univariate analysis. The mean age and CCI were higher in cases with mortality at 1 year. Left-sided involvement, complications, and use of monotherapy were more frequent among patients who died at 1 year.

Relapse occurred in 2 cases, both IVDU acquired. Case 1 had tricuspid valve endocarditis initially treated with 6 weeks of MER and GEN, the relapse was successfully treated with a further 6 weeks of MER. Case 12 had mitral valve endocarditis initially treated with TAZ, relapse was treated with mitral valve repair and 6 weeks of MER due to the second isolate testing resistant to piperacillin-tazobactam. Both cases remained relapse free and survived beyond 12 months. No typing was performed to determine relatedness of blood culture isolate from primary episode and relapse.

4. Discussion

P aeruginosa IE remains rare, with only 15 cases found over a 20-year period. In comparison to earlier case series, healthcare-associated infection was more common than IVDU, with most cases having left-sided valve involvement. Successful treatment of a MDR isolate causing prosthetic valve endocarditis and the use of CIP in combination regimens and as a suppressive therapy are described. Mortality in hospital and at 30 days was 13% (2/15), increasing to 20% (3/15) at 6 months and 60% (6/10) at 5 years. This study is limited primarily by its observational nature, with small numbers over a significant period of time, given the rarity of the disease.

Table 2

Clinical characteristics of 15 cases of Pseudomonas aeruginosa infective endocarditis.

Variable	Number (n = 15)	Percentage
Risk factors		
Valvular heart disease	7	47%
IVDU	6	40%
CVL (within 14 d)	6	40%
Prosthetic valve	5	33%
Immunosuppression	4	27%
Prior i.e.	2	13%
Cardiac device	1	7%
Acquisition		
Community	6	40%
Healthcare	5	33%
Nosocomial	4	27%
Source		
IVDU	6	40%
CVL	6	40%
Unknown	3	20%
Valve involvement		
Left	9	60%
Right	4	27%
Both	2	13%
Prosthetic	4	27%
Aortic	3	20%
Mitral	8	53%
Tricuspid	3	20%
Pulmonary	1	7%
Treatment		
Antibiotic monotherapy	6	40%
Antibiotic combination	9	60%
Complications		
Any	11	73%
AKI	8	53%
Intracardiac abscess	3	20%
Major emboli	3	20%
Neurological	3	20%
Congestive cardiac failure	2	13%
Abscess formation other	2	13%

AKI = acute kidney injury, CVL = central venous line, i.e. = infective endocarditis, IVDU = intravenous drug use

Advanced age, higher CCI, left-sided involvement, and complications were more common in those who died within 1 year in our series, but without statistical significance in univariate analysis. The Reyes et al 1973 series included 23 cases and suggested that increasing age, time to appropriate therapy, monotherapy, and left-sided disease were risk factors for mortality.[7] A systematic review by Lin et al 1993 to 2003 reported age > 60 years, prosthetic device-related i.e., and relapse following appropriate therapy as risk factors for mortality in noninjecting drug users with OR of 7.58, 12.88, and 17.5, respectively ($P < .05$).[2] Renal failure was reported as a risk factor for mortality by Wieland et al 1974 to 1983 in a 10 case series of left-sided i.e.[6]

The use of combination therapy in this series was 60%, with a higher rate of death at 1 year in the monotherapy group and 75% versus 36% without statistical significance in univariate analysis ($P = .282$). Beta-lactam monotherapy as the first and only regimen was successful in 4 cases. Both patients who developed resistant isolates received beta-lactam monotherapy. Recent EUCAST changes have removed GEN breakpoints for *P aeruginosa* and considered it an inadequate monotherapy for this infection.[14]

Three patients received CIP as a second agent in a combination regimen instead of aminoglycosides, and in 2 cases, long-term suppressive CIP was continued following the initial 6-week course of intravenous therapy. These cases all survived beyond 12 months. This has not been previously reported in other case series.

Case 9 involved a MDR isolate that caused prosthetic valve infection. Despite advanced age and comorbidities, they had a successful outcome and survived for > 5 years. The case involved the longest duration of bacteremia of any case at 30 days, requiring surgery to provide source control. Prolonged bacteremia without clinical deterioration may also suggest a fitness cost for the multi-resistant phenotype.

P aeruginosa endocarditis with MDR isolates is exceedingly rare, with only a few case reports in the literature. Three case reports have documented success with the use of newer beta-lactam agents, such as ceftolozane/tazobactam[19,20] and cefiderocol[21] in combination regimens with other agents. Poor outcomes were reported in an earlier series with use of colistin based regimens.[22] The additional benefit of MIC testing and therapeutic drug monitoring influencing drug choice and dosing in the setting of *P aeruginosa* endocarditis and MDR isolates is unclear.

Previous studies have reported improved outcomes with surgery. The rates of surgery were similar in those who died within 12 months and those who survived in this series. Reyes et al (2009) suggested microbiological surgical indications of persistent bacteremia (2 weeks in right sided and 7 days in left side) or relapse following completion of antibiotic therapy.[4] The general recommendations for surgical intervention for IE by the American Association for Thoracic Surgery should be considered when managing patients with endocarditis.[23] The European Society of Cardiology guidelines also suggest infection caused by MDR organisms and prosthetic valve endocarditis caused by gram-negative bacteria as recommendations for urgent/elective surgery and are based on expert opinion and small studies.[24]

Relapse occurred in 2 cases, both in patients with IVDU and native valve involvement: 1 initially treated with monotherapy and the other with combination therapy. One case underwent surgical intervention, and both remained relapse free and alive beyond 12 months following second antibiotic course.

Table 3

Mortality at 1 yr.

	Death at 1 yr Mean or N (%) (n = 4)	Alive at 1 yr Mean or N (%) (n = 11)	*P* value
Age	62.5 ± 13.33	51.27 ± 14.51	.20
CCI	3.25 ± 0.96	2.72 ± 2.37	.55
IVDU	2 (50)	4 (36)	1
Healthcare associated*	2 (50)	7 (64)	1
Left sided valve involvement	4 (100)	7 (64)	.52
Complication	4 (100)	7 (64)	.52
Monotherapy†	3 (75)	4 (36)	.28
Surgical intervention	2 (50)	5 (45)	1

CCI = Charlson comorbidity index, IVDU = intravenous drug use.

*Healthcare and nosocomial.

†As initial regimen.

Table 4

Baseline antibiogram of isolates.

Antibiotic	Susceptible isolates N = 15 (%)
Meropenem	14 (93%)
Gentamicin	13 (87%)
Ciprofloxacin	12 (80%)
Piperacillin/tazobactam	11 (73%)
Ceftazidime	10 (67%)
Cefepime	10 (77%)*

*Cefepime susceptibility was performed for only 13 isolates.

5. Conclusion

P aeruginosa IE remains a rare disease but may be seen increasingly in the future in patients with high levels of healthcare exposure, as represented in our series. It is associated with significant secondary complications and a high mortality rate. The optimal antibiotic and surgical management remain unclear. This study provides additional information about this rare disease in a contemporary context, with healthcare acquisition and left-sided valve involvement more commonly than historical IVDU and right-sided involvement.

Author contributions

Conceptualization: Kate McCarthy, David L. Paterson.
Data curation: Andrew Walczak.
Investigation: Andrew Walczak.
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