

## Original Article

**Aspergillus endocarditis 2003–2009**

JOE MCCORMACK &amp; JAMES POLLARD

*University of Queensland & Mater Health Services, Department of Medicine & Infectious Diseases, Brisbane, Queensland, Australia*

A retrospective study of 35 case reports of *Aspergillus* endocarditis published between 2003 and 2009 was carried out. Fifteen percent of cases presented with a new cardiac murmur, 38% with an embolus. Eighty percent of cases involved the aortic or mitral valves. Seventy-four percent of cases involved patients with a history of prior surgery, 48% of these involved a heart valve, 20% had other cardiac surgery and 32% had non-cardiac surgery. Galactomannan testing was helpful diagnostically in four out of nine cases, but PCR testing was positive in six out of six cases. Overall mortality was 68%, all eight survivors had heart valve surgery apart from one – an 8-month-old child. Seven out of eight survivors received liposomal amphotericin B, three of these in combination with other antifungals. We need to think more about the possibility of *Aspergillus* endocarditis, particularly in immunocompromised patients with recent surgery. Galactomannan and PCR testing may be used more vigorously. Valve replacement, or at least vegetectomy, should be carried out in all patients. Liposomal amphotericin B, 3–5mg/kg/day, for at least 4 weeks is the treatment of choice. Oral voriconazole should be used for at least 2 years. Posaconazole may be an alternative, however there have been no prior cases reported to suggest its efficacy. The value of combination antifungal therapy is uncertain, but consideration should be given to the use of a second agent in addition to liposomal amphotericin. While further case reports on this condition will be helpful, more definitive management guidelines will depend on a prospective study.

**Keywords** *Aspergillus*, endocarditis, surgery, antifungal therapy, galactomannan, PCR

**Introduction**

Infective endocarditis is one of the more severe forms of *Aspergillus* infection. In a 1990 review of invasive aspergillosis, endocarditis was found to be particularly associated with heart valve surgery and was sometimes a manifestation of disseminated aspergillosis. Blood cultures were noted to be rarely positive and diagnosis was most often made from embolectomy or vegetation tissue [1]. All patients treated with antifungals without surgery died. Conventional

amphotericin B was noted to have poor penetration into the heart valves and the optimal antifungal therapy regimen was not known [1]. An analysis of 270 cases of fungal endocarditis occurring over 30 years was carried out by Ellis *et al.* [2]. *Aspergillus* species were found to be the cause of endocarditis in 24% of these cases and although there was an increase in the ratio of non-*Candida albicans* *Candida* species to *Candida albicans* over the 30 years, there was no change in the relationship between *Aspergillus* and *Candida* endocarditis over that period [2]. The mean survival period for *Aspergillus* endocarditis was 11 days by comparison with *Candida* endocarditis (690 days) and *Histoplasma* endocarditis (540 days) [2]. In a further review of the topic [3] the diagnosis of *Aspergillus* endocarditis was noted to be made post-mortem in approximately one in three cases and preoperative diagnosis was made in less than half. Clinical features were found to be very non-specific

Received 3 March 2010; Received in final revised form 19 May 2010; Accepted 1 June 2010

Correspondence: Joe McCormack, University of Queensland & Mater Health Services, Department of Medicine & Infectious Diseases, 1st Floor Whitty Building, Raymond Terrace, South Brisbane, Qld, 4101, Australia. Tel: +61 7 3163 8518; fax: +61 7 3163 1548; E-mail: joe.mccormack@mater.org.au

which included fever, a murmur, emboli, focal or general neurological symptoms or signs and cardiac failure. The more traditional clinical features, e.g., clubbing, Osler's nodes and splenomegaly were rare [3]. Heart valve abnormalities were noted in approximately two out of three patients. The attributable mortality was approximately 90% [3]. Voriconazole displayed some encouraging results in the treatment of *Aspergillus* endocarditis in 11 out of 12 guinea pigs [4]. We are conducting, in the current study, an update on cases of *Aspergillus* endocarditis with the objectives of evaluating: (i) newer clinical and epidemiological features, (ii) the diagnostic role of galactomannan (GM) or polymerase chain reaction (PCR) testing, (iii) outcomes, particularly in relation to surgery, and (iv) optimal use of antifungal therapy.

## Methods

A Pubmed search was carried out of case reports between the years 2000 and 2009 inclusive using the words '*Aspergillus*' and 'endocarditis'. Case histories were examined and those between 2003 and 2009 were extracted for this study.

## Results

Forty-four cases were identified during the indicated period, with 35 of these reports providing good quality information in English on clinical, microbiological, diagnostic and outcome aspects were analysed. Information regarding the clinical features is presented in Table 1. The denominators in this and other tables vary because information was not always available on every aspect of the cases [5–33]. In Table 2 the role of prior surgery is defined. Of the 25 patients with prior surgery, 12 had heart valve surgery, five had other types of cardiac surgery (four transplants, one pericardial drainage) and eight had non-cardiac surgery (six transplants, one portacaval shunt surgery, one leg embolectomy) [5,6,8–16,18,23–28]. The predisposing

**Table 1** Clinical/epidemiological features of the cases of *Aspergillus* endocarditis.

Number of patients	34
Male	26 (76%)
Age (years)	
Range	8mo–75
Mean	62.9
Median	50
New murmur at presentation	5 (15%)
Embolus at presentation	13 (38%)
Site	
CNS	6 (18%)
Leg	3 (9%)
Other*	4 (12%)
Valves involved	35
Aortic	14 (40%)
Mitral	14 (40%)
Tricuspid	5 (14%)
Mixed	2 (6%)

\*One patient had splinter haemorrhages, one had Janeway lesions.

factors of the 7 patients who did not have surgery are listed in Table 2 [7,17,19,20,22,25,30].

The diagnostic value of GM and PCR testing in cases where this was reported is shown in Table 3 [5,8,10,11,13,15,17,30,31]. A 1-3-b-d glucan test was done in only one case and provided negative results [17]. Serological testing was positive in three cases by an indirect haemagglutination reaction [31,32]. Blood culture was positive in only one case in which the sample was taken through a portal vein [5]. Of 26 cases in which the etiologic agent was recovered in culture, the identifications of the fungus were indicated in 26 of them and included 16 isolates of *A. fumigatus*, three *A. niger*, two *A. flavus* and five were designated as *Aspergillus* species.

In Table 4 the initial antifungal drugs used are listed for the 22 patients where information was available. The numbers of patients and those who died versus those who survived are listed also in this table [5,6,8,9,11–15,18,20,22–24,27–29].

**Table 2** Role of prior surgery in 34 patients with *Aspergillus* endocarditis.

Number	Surgery 25 (74%)	No surgery 7 (21%)	Pacemaker/defibrillator 2 (5%)
Pre-existing conditions	Heart valve 12 (48%) Other cardiac 5 (20%) Non cardiac 8 (32%) [Transplants total 10 (40%)] Cystic Fibrosis 3 (12%) ABPA 2 (8%)	T cell lymphoma AML <sup>1</sup> , Crohn's disease Aplastic anemia AIDS <sup>2</sup> , PCP <sup>3</sup> , IDDM <sup>4</sup> Hepatitis B & C, IDU <sup>5</sup> ABPA <sup>6</sup> , steroids Asthma, steroids	

<sup>1</sup>Acute myeloid leukemia. <sup>2</sup>Acquired immunodeficiency syndrome. <sup>3</sup>Pneumocystis pneumonia. <sup>4</sup>Insulin dependent diabetes mellitus. <sup>5</sup>Injecting drug user. <sup>6</sup>Allergic broncho pulmonary aspergillosis.

**Table 3** Galactomannan (GM) and PCR testing in patients with *Aspergillus* endocarditis.

	Positive	Negative
GM	4*	5
PCR	6 <sup>+</sup>	0

\*Three serum, one bronchoalveolar lavage fluid. <sup>+</sup>Five serum, one vegetation tissue. GM and PCR testing data not reported for other known cases of *Aspergillus* endocarditis.

The outcomes in 25 patients who had surgery are described in table 5 [5–9,11–15,18,20,22–24,27–29,30,33]. Sixteen patients (64%) had valve replacements and in three of these patients replacement was required on more than one occasion. One patient had a vegectomy [11]. Seventeen patients died (68%), diagnosis was more frequently made pre-mortem than post-mortem. Only one patient [10] survived without surgical intervention. In this case it was difficult to determine total duration of initial antifungal drugs. Voriconazole treatment was begun, caspofungin was subsequently added, followed by liposomal amphotericin B (Table 6).

## Discussion

Interpretation of results from this case series was difficult due to the variability of reporting and the fact that information was not standardized. In many cases information was incomplete, e.g., regarding clinical presentation, GM or PCR testing, treatment and outcomes. The focus of these case reports often reflected the type of journal in which they appeared, e.g., those with surgical or microbiological emphasis.

In 15% of cases a new murmur was present at clinical presentation. In 38% an embolus was part of the presenting clinical features, with most emboli related to the central nervous system or leg. Seventy-four percent of patients had prior surgery, 48% involving a heart valve, 20% involving other cardiac surgery, e.g., coronary bypass grafting and

**Table 4** Initial antifungal therapy in 22 patients with *Aspergillus* endocarditis.

Drug	No	Survived/died
LAmB alone	6	4/2
LAmB + vori + caspo	4	2/2
Vori alone	3	1/2
CAmB + Itra	2	0/2
CAmB alone	2	0/2
CAmB + vori	1	0/1
LAmB + vori	1	0/1
LAmB + Anid	1	1/0
Vori + caspo	1	0/1
Caspo alone	1	0/1

LAmB, liposomal amphotericin B; CamB, conventional Amphotericin B; Vori, voriconazole; Caspo, caspofungin; Anid, anidulafungin.

cardiac transplants, and 37% of patients had non-cardiac surgery prior to the onset of the incidents of endocarditis. Overall 40% of patients developed *Aspergillus* endocarditis following transplant of an organ. Immune suppressive therapy is likely to have contributed to the development of *Aspergillus* endocarditis in these cases. Prior surgery is an important predisposing factor for this condition, although not just involving cardiac valves. The diagnostic value of GM testing was disappointing (four out of nine positive), however the diagnostic value of PCR testing was more encouraging (six out of six positive). Both of these tests require standardization and further validation, and more experience is required to understand their diagnostic roles. The overall mortality in this case series was 68%, seven out of eight patients survived with valve surgery and only one patient survived without valve surgery.

Antifungal drug use in these patients was variable, i.e., seven out of the eight survivors received liposomal amphotericin B, three of these in combination with at least one other drug. All patients who received conventional amphotericin B and/or itraconazole as their initial treatment died. There was no clear evidence to determine whether or not combination therapy was superior to liposomal amphotericin B alone. The dose of liposomal amphotericin B used was in the 3–5 mg/kg/day range. In view of the morbidity and mortality associated with *Aspergillus* endocarditis, combination therapy may be indicated. No clear pattern could be determined in relation to the optimal duration of initial antifungal treatment or of long-term secondary prophylaxis. Four weeks of initial treatment and two years of subsequent antifungals appear to represent minimal requirements.

The case reports presented here are certainly interesting and collectively add to the volume of data and information on the clinical manifestations, diagnosis and management of *Aspergillus* endocarditis. Undoubtedly more case reports will be published in the years ahead. However, in order to formulate clear guidelines regarding the management of this condition more structured studies are needed and a multicentre prospective study would be essential. It is appreciated that because of the uncommon nature of this condition such a study would be difficult to organize. This should involve the collaboration of many major centres where such cases may be more commonly seen. It may be possible to include a study of *Aspergillus* endocarditis as part of a larger prospective study of invasive aspergillosis.

**Table 5** Outcomes in 25 patients with *Aspergillus* endocarditis.

Survived with surgery	7/25 (28%)
Survived without surgery	1/25 (4%)
Died; pre-mortem diagnosis	13/25 (52%)
Died; post-mortem diagnosis	14/25 (16%)

**Table 6** Eight patients who survived following *Aspergillus* endocarditis.

Underlying conditions	Initial antifungals	Ongoing antifungals	Reference
Pericardial effusion	LAmB 6 weeks	Itra 10 weeks	[6]
Elective AVR	Vori unknown duration	Unknown	[8]
Elective AVR	LAmB unknown duration	Unknown	[12]
Lung transplant, DM	LAmB + caspo 6 weeks	Vori lifelong	[18]
Asthma, steroids, BSA	LAmB + vori 6 weeks	Vori 6 mos	[22]
AVR for Streptococcal endocarditis, BSA	LAmB + Anid	Vori lifelong	[23]
Defibrillator, recent pneumonia, BSA	LAmB 3 weeks	Itra uncertain duration followed by Vori (uncertain duration)	[29]
Liver transplant, biliary atresia, 8 mos old	LAmB + vori + caspo	Vori 20 mos	[10]*

AVR, aortic valve replacement; DM, diabetes mellitus; BSA, broad spectrum antibiotics; LAmB, liposomal amphotericin B; Vori, voriconazole; Caspo, caspofungin; Anid, anidulafungin; Itra, Itraconazole

\*Survived without surgery.

As a result of this study the following recommendations are suggested:

- (1) Although an uncommon condition, *Aspergillus* endocarditis should be considered in patients with previous surgery, not just involving heart valves. Any immunocompromising condition can also be a predisposing factor to this condition and the degree of immunocompromise does not have to be severe;
- (2) An aggressive approach to the diagnosis of *Aspergillus* endocarditis should be adopted, including the use of GM and PCR testing;
- (3) Survival without valve surgery is rare and this should be recommended in all cases;
- (4) Liposomal amphotericin B at a dose of 3–5mg/kg/day should be used as initial therapy, a 4-week minimum duration is recommended assuming a good initial response;
- (5) Combination therapy involving liposomal amphotericin B with voriconazole and an echinocandin may be used but the evidence of its superiority over liposomal amphotericin B alone is weak; and
- (6) Secondary prophylaxis with long-term oral voriconazole for at least two years is recommended, in many cases this may need to be continued lifelong. Ongoing supervision with clinical review and echocardiographic correlation should be carried out.

Taking into account galactomannan testing and the wider availability of antifungal drugs over the last five years, these recommendations represent an update on those by Denning and Stevens [1], Ellis *et al.* [2] and McCormack and Ellis [3].

**Declaration of interest:** The first author has carried out consultancies with Glaxo SmithKline, Jansen Cilag and Pfizer, has received research support from Pfizer and travel and/or accommodation support from Gilead and Astra Zeneca.

## References

- 1 Denning DW, Stevens DA. Antifungal and surgical treatment of invasive aspergillosis: review of 2,121 published cases. *Rev Infect Dis* 1990; **12**: 1147–1201.
- 2 Ellis ME, Al-Abdely H, Sandridge A, Greer W, Ventura W. Fungal endocarditis: evidence in the world literature, 1965–1995. *Clin Infect Dis* 2001; **32**: 50–62.
- 3 McCormack J, Ellis M. Endocarditis. 2007 [updated 2007]. Accessed 1 March 2010 from: <http://www.Aspergillus.org.uk/indexhome.htm?secure/treatment/endocard.php?PHPSESSID=77c7d42-main>
- 4 Ghannoum MA, Kuhn DM. Voriconazole – better chances for patients with invasive mycoses. *Eur J Med Res* 2002; **7**: 242–256.
- 5 Jensen J, Guinea J, Torres-Narbona M, *et al.* Post-surgical invasive aspergillosis: an uncommon and under-appreciated entity. *J Infect* 2009; **60**: 162–167.
- 6 Ryu KM, Seo PW, Kim SH, Park S, Ryu JW. Surgical treatment of native valve *Aspergillus* endocarditis and fungemic vascular complications. *J Korean Med Sci* 2009; **24**: 170–172.
- 7 Gupta K, Das A, Joshi K, *et al.* *Aspergillus* endocarditis in a known case of allergic bronchopulmonary aspergillosis: an autopsy report. *Cardiovasc Pathol* 2009 Feb 10 Epub ahead of print. PMID 19211274.
- 8 Badiee P, Alborzi A, Shakiba E, Ziyaeyan M, Pourabbas B. Molecular diagnosis of *Aspergillus* endocarditis after cardiac surgery. *J Med Microbiol* 2009; **58**: 192–195.
- 9 Esmailzadeh M, Parsaee M, Peighambari MM, *et al.* Late occurrence of fatal aortitis: a complication of *Aspergillus* endocarditis following coronary artery bypass graft surgery. *Eur J Echocardiogr* 2009; **10**: 165–167.
- 10 Mourier O, Durand P, Lambert V, *et al.* *Aspergillus fumigatus* endocarditis in a pediatric liver transplant recipient: favorable outcome without cardiac surgery. *Pediatr Transplant* 2009; **13**: 636–640.
- 11 Morio F, Treilhaud M, Lepelletier D, *et al.* *Aspergillus fumigatus* endocarditis of the mitral valve in a heart transplant recipient: a case report. *Diagn Microbiol Infect Dis* 2008; **62**: 453–456.
- 12 Brili S, Rokas C, Tzannos K, *et al.* Fungal ascending aortic aneurysm after cardiac surgery. *Echocardiography* 2008; **26**: 84–87.
- 13 Maher TM, Carby MR, Hall AV, *et al.* Native valve *Aspergillus* endocarditis complicating lung transplantation. *J Heart Lung Transplant* 2008; **27**: 910–913.
- 14 Rana M, Fahad B, Abid Q. Embolic *Aspergillus* endophthalmitis in an immunocompetent patient from aortic root *Aspergillus* endocarditis. *Mycoses* 2008; **51**: 352–353.
- 15 Van Meensel B, Meersseman W, Bammens B, *et al.* Fatal right-sided endocarditis due to *Aspergillus* in a kidney transplant recipient. *Med Mycol* 2007; **45**: 565–568.

- 16 Downey BC. *Aspergillus* prosthetic valve endocarditis causing functional aortic stenosis: initial case report. *Inv Cardiol* 2007; **19**(5): [www.invasivecardiology.com/article/7111](http://www.invasivecardiology.com/article/7111).
- 17 Saitoh T, Matsushima T, Matsuo A, *et al.* Small-bowel perforation accompanied by *Aspergillus* endocarditis in a patient with angioimmunoblastic T-cell lymphoma. *Ann Hematol* 2007; **86**: 71–73.
- 18 Saxena P, Clarke B, Dunning J. *Aspergillus* endocarditis of the mitral valve in a lung-transplant patient. *Tex Heart Inst J* 2007; **34**: 95–97.
- 19 Fraser JF, Mullany D, Natani S, Chinthamuneedi M, Hovarth R. *Aspergillus flavus* endocarditis – to prevaricate is to posture. *Crit Care Resusc* 2006; **8**: 46–49.
- 20 Petrikkos GL, Skiada A, Samonis G, Mavroudis D, Daikos GL. Native valve *Aspergillus* endocarditis in two patients with aplastic anaemia. *Scand J Infect Dis* 2006; **38**: 916–920.
- 21 Leong R, Gannon BR, Childs TJ, Isotalo PA, Abdollah H. *Aspergillus fumigatus* pacemaker lead endocarditis: a case report and review of the literature. *Can J Cardiol* 2006; **22**: 337–340.
- 22 Vassiloyanakopoulos A, Falagas ME, Allamani M, Michalopoulos A. *Aspergillus fumigatus* tricuspid native valve endocarditis in a non-intravenous drug user. *J Med Microbiol* 2006; **55**: 635–638.
- 23 Reis LJ, Barton TD, Pochettino A, *et al.* Successful treatment of *Aspergillus* prosthetic valve endocarditis with oral voriconazole. *Clin Infect Dis* 2005; **41**: 752–753.
- 24 Scherer M, Fieguth HG, Aybek T, *et al.* Disseminated *Aspergillus fumigatus* infection with consecutive mitral valve endocarditis in a lung transplant recipient. *J Heart Lung Transplant* 2005; **24**: 2297–2300.
- 25 Xie L, Gebre W, Szabo K, Lin JH. Cardiac aspergillosis in patients with acquired immunodeficiency syndrome: a case report and review of the literature. *Arch Pathol Lab Med* 2005; **129**: 511–515.
- 26 Sherman-Weber S, Axelrod P, Suh B, *et al.* Infective endocarditis following orthotopic heart transplantation: 10 cases and a review of the literature. *Transpl Infect Dis* 2004; **6**: 165–170.
- 27 El-Hamamsy I, Durrleman N, Stevens LM, Perrault LP, Carrier M. *Aspergillus* endocarditis after cardiac surgery. *Ann Thorac Surg* 2005; **80**: 359–364.
- 28 Verghese S, Maria CF, Mullaseri AS, *et al.* *Aspergillus* endocarditis presenting as femoral artery embolism. *Mycoses* 2004; **47**: 252–256.
- 29 Cook RJ, Orszulak TA, Nkomo VT, *et al.* *Aspergillus* infection of implantable cardioverter-defibrillator. *Mayo Clin Proc* 2004; **79**: 549–552.
- 30 McCracken D, Barnes R, Poynton C, *et al.* Polymerase chain reaction aids in the diagnosis of an unusual case of *Aspergillus niger* endocarditis in a patient with acute myeloid leukaemia. *J Infect* 2003; **47**: 344–347.
- 31 Thuny F, Fournier PE, Casalta JP, *et al.* Investigation of blood culture negative early prosthetic valve endocarditis reveals high prevalence of fungi. *Heart* 2010 **96**(10) 733–4.
- 32 Raoult D, Casalta JP, Richet H, *et al.* Contribution of systematic serological testing in diagnosis of infective endocarditis. *J Clin Microbiol* 2005; **43**: 5238–5242.
- 33 Millar BC, Jugo J, Moore JE. Fungal endocarditis in neonates and children. *Pediatr Cardiol* 2005 **26**(5) 517–36. <http://www.springerlink.com/content/0lywdwg02nclcdkj/fulltext.html>

This paper was first published online on Early online on 7 July 2010.