Aspergillus Endocarditis After Cardiac Surgery

Ismail El-Hamamsy, MD, Nicolas Dürrleman, MD, Louis-Mathieu Stevens, MD, Louis-P. Perrault, MD, PhD, and Michel Carrier, MD

Research Center and Department of Surgery, Montreal Heart Institute and Université de Montréal, Montréal, Québec, Canada

Aspergillus species infections are an increasingly common occurrence in hospital wards. Aspergillus endocarditis constitutes one of the manifestations of the disease, which bears a poor prognosis in cardiac surgery patients. A review of the literature on fungal and Aspergillus endocarditis was undertaken. Valvular risk factors, indwelling intravenous catheters, prolonged antibiotics, malignancy, and intravenous drug use increase the risk. Clinical presentation is insidious, with embolic complications often representing the first manifestation of the disease. Blood cultures are typically negative. The mortality rate is almost 100%. Amphotericin B represents the mainstay of medical therapy with several possible adjuncts. Surgery is an essential part of therapy in Aspergillus endocarditis after cardiac surgery and should be undertaken as soon as the diagnosis is made. Aspergillus endocarditis is an ominous complication after cardiac surgery. A high suspicion index, early administration of appropriate antibiotics, and prompt surgical intervention should improve the prognosis, which remains dismal.

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Aspergillus is a ubiquitous mold capable of causing several diseases both in healthy humans and immunocompromised hosts. Aspergillus species endocarditis is an ominous condition whose prevalence is increasing in the hospital population and has become almost as common as Candida species endocarditis according to recent reports [1]. Several conditions predispose patients to Aspergillus infections including underlying cardiac abnormalities, prosthetic heart valves, indwelling central venous catheters, prolonged use of broad-spectrum antibiotics, and less frequently, intravenous drug use. Despite the epidemic proportions of the disease, detection of the source of the mold, diagnosis of the infection, and treatment of endocarditis remain highly challenging and often meet with little success.

Historical Perspective

The Aspergillus species was initially described by Micheli in 1729. The first case of Aspergillus disease in humans was reported in the mid 1800s. Hadorn described a case of Aspergillus aortitis in 1960. In 1964, Newman and Cordell reported the first case of Aspergillus endocarditis (AE) after mitral valvulec-tomy, which ended with the death of the patient soon after disease presentation and establishment of the diagnosis of AE postmortem. Amphotericin B has been the mainstay of therapy for the past 50 years, with reported mortality rates consistently close to 100%, and few new antifungal agents have been introduced since to improve the prognosis of the disease.

Material and Methods

We conducted a literature search using the Pubmed-Medline database. We reviewed all articles in French or English from 1970 to today. Search terms used were “Aspergillus,” “Aspergillus endocarditis,” “cardiac surgery,” and “fungal endocarditis.” All articles, including isolated case reports, were reviewed.

Epidemiology

Aspergillus endocarditis is increasingly prevalent among hospitalized patients nowadays due, in part, to the increasing use of intracardiac devices [2]. Fungal endocar-ditis affects approximately 0.1% of all prosthetic valves [3] and the Aspergillus species contributes to approximately 25% of all cases of fungal endocarditis [1], second only to the Candida species with an Aspergillus to Candida ratio of 1:3 to 1:2 [1, 4]. Men are more commonly affected than women with a peak incidence during the third and fourth decades of life [5, 6]. Numerous risk factors have been identified in the pathogenesis of AE with the most important being previous valvular surgery, reported in 40% to 50% of patients diagnosed with AE. Valvar risk factors (previous valve surgery, bacterial endocarditis, rheumatic heart disease, mitral valve prolapse) on the other hand are present in approximately two thirds of patients [1, 7]. Aspergillus-associated native valve endocarditis without prior cardiac surgery, albeit much less common, have also been reported with an equally dismal prognosis [8]. Other risk factors have been incriminated, including malignancy (18%), indwelling central venous catheters (10%), use of broad-spectrum antibiotics (10%), and intravenous drug use (the prevalence of which is decreasing) [7]. However, despite the emphasis on prior cardiac surgery in the past, according to Ellis and colleagues [1], the contribution of this risk factor has de-
increased from 1965 to 1995, probably owing to improved surgical techniques, better choice and sterilization of prostheses, and improved clean-air operating theater environment.

Microbiology

Numerous strands of Aspergillus have been identified, and the most commonly responsible for AE include Aspergillus fumigatus (60% to 90%), Aspergillus terreus (5% to 20%), Aspergillus flavus, Aspergillus niger, and Aspergillus nidus [7]. The predominance of one of these species owes to several intrinsic characteristics that vary from one strain to the other including mass doubling time, viability at body temperature as most species do not survive at 37°C [9], production of proteases, and adherence to the fibrin-platelet matrix covering the damaged valve.

Indeed, the first step toward AE is adherence of the Aspergillus species to the damaged heart valve owing to their capacity to bind to the platelet-fibrin matrix. Aspergillus fumigatus binds laminin and fibrinogen more efficiently than other species [10, 11]. Also, Aspergillus species release several proteases allowing invasion and destruction of the endothelial cell lining creating an inflammatory milieu [12]. Furthermore, Aspergillus organisms are protected from the phagocytic activity of mononuclear cells by their ability to secrete toxic metabolites, namely gliotoxins [13]. All these pathogenic features are further aided by the avascularity of mechanical prosthetic material per se; however, adhesion to Aspergillus species, namely gliotoxins [13]. All these pathogenic features are further aided by the avascularity of mechanical prosthetic material per se; however, adhesion to the fibrin-platelet matrix covering the damaged valve.

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The Aspergillus species can colonize and infect most body organs, starting with the lungs owing to airborne transmission. Aspergillus endocarditis develops primarily intraoperatively secondary to seedling by airborne spores, although the disease may occur much less frequently in patients without prior cardiac surgery [8].

Sources and Risk Factors

Aspergillus infection may be community-acquired or may occur as a nosocomial event. The primary ecologic niche for Aspergillus species is vegetable material and soil [16, 17], but it may reside anywhere from water to food (tea, fruits, peppers, and spices) to potted plants and flowers as well as ice-making machines and air humidifiers. Air remains the principal means of transmission to patients, especially in cases of AE. Molds release an extremely high number of small-sized conidia (3 μm to 5 μm), increasing the risk of contamination in cases of colonized air environment. High concentrations are observed near farms or hay barns where counts as high as 10³/m³ can be registered [18]. In the hospital environment, the presence of demolition or construction work in the vicinity of the hospital is the most commonly incriminated factor leading to an increased incidence of aspergillosis and A. flavus can be isolated from respiratory tracts at times of nearby construction [19–21]. The spores can accumulate in air ducts and other infrequently cleaned or aerated places, creating a potential source of air contamination bursts elicited by air movements, vacuum-cleaning, or repeated door movements in the operating rooms [22]. Introduction of high-efficiency particulate air (HEPA) filtration (with or without laminar air flow systems) has consistently reduced air counts of Aspergillus spores and decreased the incidence of Aspergillus infections in epidemic areas [23, 24]. Unfortunately, sampling of Aspergillus spores in the air is impractical, making monitoring of preventive interventions a time-consuming affair [25] and warranting continued vigilance after an outbreak despite “normal” air counts.

In one report, a patient succumbed to postoperative infection of an aortic prosthetic Dacron graft with A. flavus. Since the strain from the graft showed perfect concordance with a strain from the heat exchanger [26], it is reasonable to believe that all components of the cardiopulmonary bypass circuit are potential sources of contamination.

In addition, water is increasingly recognized as a source of Aspergillus species inside the hospital. Indeed, a recent Norwegian study of a bone marrow transplant unit reported 49% of water samples positive for A. fumigatus [27]. In addition, Aspergillus species were recovered in 31% of samples taken from hemodialysis water in a multicenter study [28]. Immunosuppression therapy is a major risk factor for infection with Aspergillus species, making cardiac transplantation recipients a favored target. In fact, among patients undergoing heart transplantation, Aspergillus is the opportunistic infection with the highest attributable mortality [29]. Aspergillus infections in these patients can result in a variety of clinical syndromes, with invasive pulmonary aspergillosis being most frequent. Although not always as fatal as AE, the case fatality rate associated with invasive pulmonary aspergillosis was 36% in a report from the Stanford University Medical Center [29]. Cases of transmission of invasive aspergillosis from subclinically infected donors to transplant recipients have also been described. In one instance, a heart transplant recipient was diagnosed with AE 3 months after transplantation. Two kidney transplant recipients from the same donor also developed renal Aspergillus abscesses with the same strain.

Clinical Presentation

Typically, AE presents with a relative paucity of peripheral signs of endocarditis (ie, Osler’s nodes, Janeway lesions, Roth spots) [30]. No consistent or pathognomonic features characterize AE. The most common clinical features are fever, major peripheral emboli, and a changing heart murmur [5]. Less commonly, patients present with focal or generalized neurologic deficits, heart failure, or dyspnea [1].

The interval between valve replacement and onset of
infection is extremely variable, ranging from 1 day to 24 years in a recent review of fungal endocarditis cases. The distribution of early (less than 60 days) versus late fungal prosthetic valve endocarditis was almost similar [7]. Clinical manifestations are nonspecific and occur late after valve replacement. To underline the diagnostic challenges posed by AE cases, Ellis and colleagues [1] reviewed the world literature for fungal endocarditis from 1965 to 1995 and reported a mean interval of 34 days from the first symptoms to hospital admission, with an additional 17 days on average before establishment of the diagnosis. These long delays along with the extremely friable nature of Aspergillus vegetations explain the frequent initial presentation with embolic complications.

A preferential involvement of specific sites for AE is unclear, but a predilection for left-sided valve endocarditis is documented regardless of the precipitating factor (even in cases of central catheters or intravenous drug use), with the aortic valve more commonly affected than the mitral valve throughout the literature.

Complications
As already mentioned, major peripheral emboli are one of the most common presenting features of AE and occur in as many as 83% of patients with AE, averaging 68% of patients [31]. Peripheral emboli may lodge in the brain, skin, eyes, upper and lower limbs, mesenteric arteries, kidneys, and coronary artery beds, hence mimicking other pathologic conditions and contributing to delaying the diagnosis in some cases. The occurrence of emboli in a culture-negative environment should raise the suspicion of Aspergillus species infection. Neurologic complications, focal or generalized, occur in as many as 30% of patients with AE. Identification of mycotic abscesses on brain imaging studies may be helpful in establishing the diagnosis. Aspergillus species are highly angioinvasive with rapid seeding of the vascular wall creating weak areas, which lead to aneurysmal disease. These aneurysms grow very rapidly in all vascular beds (aorta, circle of Willis, peripheral), and if not detected in a timely fashion, present a great risk of rupture. Consequently, the ascending aorta should be thoroughly investigated preoperatively when a diagnosis of AE is suspected. In fact, many cases of Aspergillus aortitis have been reported in the literature [26, 32–38]. Most cases are uniformly fatal because of the associated valve endocarditis or late identification of the disease process and causal organism [32]. The usual presentation is that of aneurysmal disease, which can mimic infective endocarditis [35]. Pathology examination of the aorta is characteristic of vasculitis. Differential diagnosis includes both infectious and noninfectious etiologies, including Takayasu’s aortitis and giant cell aortitis [35]. Aortic extension of the Aspergillus disease can also present as aneurysms of the sinuses of Valsalva, valvular detachment, and paravalvular leaks [39] mandating urgent surgery associated with poor results.

Ocular complications can be very debilitating, resulting in sudden loss of vision due to Aspergillus endophthalmitis in 13% of cases. In fact, in a report by Friedman and colleagues [40], Aspergillus endophthalmitis accompanied AE in as many as 40% of cases, warranting a high clinical suspicion and thorough clinical investigation.

Diagnosis
The most critical step in the treatment of AE is establishing the diagnosis in a timely fashion, a difficult task that hampers therapeutic success. Several complementary methods can be used to establish the diagnosis of AE.

Microbiology
Whereas positive blood cultures figure among the major criteria in the Duke criteria for bacterial endocarditis, when AE is suspected, blood cultures are not a reliable means of establishing or ruling out the diagnosis, and negative blood cultures are insufficient to eliminate this disease [41]. In fact, most blood cultures are usually negative in cases of active AE because fungemia is intermittent and filamentous forms (including Aspergillus, Histoplasma, and Phycomyces) seldom grow on conventional blood culture medium. In one review, blood cultures were positive in only 11% of cases of AE [30].

Culture of the embolic material whenever possible is a reliable means of establishing the diagnosis with a high yield, and is presently considered the best process for identifying the pathogen before surgery [31].

The final determination of AE is achieved with a combination of tissue cultures and histologic examination of the samples obtained intraoperatively, emphasizing the need for more accurate serologic testing before surgery.

Serology
Many serologic assays have been developed to establish the diagnosis of Aspergillus disease, including testing for Aspergillus antigens, circulating galactomannan antigens, or polysaccharides, but have had little clinical application because of their low sensitivities [42]. A new generation of tests using novel technologies including detection of circulating 1,3-α-glucan and detection of Aspergillus DNA by polymerase-chain reaction are promising and have a superior sensitivity but require further testing to be included in the routine mycologic laboratory procedures [43–46].

Histology
The detection of hyphal invasion of tissue combined with positive cultures from the same organ or distal emboli is considered definite evidence of the disease [47]. Special stains increase the sensitivity of microscopic evaluation (eg, calcofluor white, a fluorescent brightener).

Echocardiography
Echocardiographic assessment of suspected AE is critical in establishing the diagnosis. Fortunately, echocardiographic techniques have improved along with their sensitivity, and the large size of Aspergillus vegetations make them readily visible on echocardiography. According to
Pierotti and colleagues [7], transthoracic echocardiography identified 89% of vegetations in patients with fungal native valve endocarditis and 77% in prosthetic valve endocarditis. Transesophageal echocardiography was positive in 92% and 61% of such cases, respectively. The sensitivity of both echocardiographic techniques reaches 77% according to Ellis and colleagues [1] and others [5] with a 20% to 30% false-negative rate. The high rate of false negatives is primarily associated with prosthetic valve endocarditis cases owing to prosthetic valve reflectivity and the endocardial location sometimes mistaken for mural thrombi [48].

**Treatment**

Another stumbling area of modern medicine in the management of AE pertains to the therapeutic strategy to adopt in the face of such a complication. Therapeutic management conventionally consists of combined medical and surgical approaches whenever possible. However, despite years of wrestling with the disease with dismal results, very few advances have been introduced in the management of AE, and mortality rates remain extremely high.

**Medical Treatment**

Amphotericin B has been the mainstay of *Aspergillus* infection treatment for more than 50 years [49]. Although nephrotoxic effects have been largely reduced by the introduction of the liposomal form of the drug [50], its efficacy in the treatment of AE has remained disappointingly low; and the optimal dosage, total dose, and length of therapy have not been established despite the long experience. The failure of amphotericin B to penetrate vegetations and fibrin clots, possibly because of a high serum protein binding capacity (approximately 93%), may explain in part the low success rate [51, 52]. The recommended total dosage of amphotericin B is 2.5 to 3.0 g (or 50 mg/kg), based on retrospective data of rare survival cases [53]. However, high dosages do not guarantee high penetration into vegetations or a survival benefit [8]. Increasing dosages up to four times using the liposomal form (as much as 5 mg/kg daily) [51] may theoretically improve the penetration of vegetations. The duration of therapy is also not well established; while most authors agree on a minimum of 6 weeks of therapy [8], some advocate life-long prophylactic therapy to avoid recurrences.

Itraconazole is the second licensed agent with activity against *Aspergillus*. Although itraconazole is more efficacious than amphotericin B in animal models [54, 55], it has not gained as much popularity for several reasons. First, until recently, only oral formulations of the antifungal were available. Second, a multitude of drug interactions, especially with cytochrome P-450 inducers, prohibits its use for critically ill patients. Finally, its intestinal absorption is variable between patients and is highly dependent on the intestinal tropism. Hence, although itraconazole is considered adequate first-line therapy for carefully selected patients, it remains less frequently used than amphotericin B.

Flucytosine (5-FC) is another agent often considered in the treatment of AE. Used alone, it had no effect on death or survival time [55] and is therefore used in combination with amphotericin B because of demonstrated in vitro synergism [56]. Blood levels of the drug should be monitored closely and adjusted to avoid the risk of hepatic or bone marrow toxicity.

Rifampin is also used in combination with amphotericin B in the treatment of fungal disease, especially *Candida* species, and has synergistic effects with amphotericin B when given simultaneously [56] but has no activity against aspergilli when given alone.

Voriconazole is a promising broad-spectrum second-generation fluconazole in the primary therapy of aspergillosis. In a recent randomized trial of 277 patients receiving either voriconazole or amphotericin B for invasive aspergillosis, the former improved survival with fewer side effects [57]. Voriconazole also proved superior to itraconazole in the treatment of AE in a guinea pig model [58] but further human studies are needed to determine the efficacy in humans.

**Surgical Therapy**

Surgery as an adjunct to the medical treatment of AE is recommended in all cases, considering the near 100% mortality rate observed in such cases. Radical debridement of necrotic tissue with valve replacement using biomaterials (bioprosthesis or homografts) with or without aortic root replacement is the recommended procedure. Lavage of the endocardium with a solution of amphotericin B has not proven efficacious and has been abandoned from the surgical technique. Surgical results are disappointing for several reasons. First, patients amenable to surgery often suffer from advanced disease, increasing their operative risk. Second, despite the radical surgical strategy, a recurrence rate as high as 40% is observed and has a dismal prognosis. Only few reports of positive results have been published. In the review by Gumbo and colleagues [8] of 61 cases of AE in patients without prior cardiac surgery over a period of 18 years, only 3 survivors who had undergone surgery in addition to medical therapy were reported. Muehrcke and colleagues [3] reported an intermediate survival rate of 50% with surgery and life-long antifungal therapy in prosthetic valve fungal endocarditis. Because of the scarcity of AE cases in the literature and the incomplete follow-up in many cases, the exact role of surgery on short- and long-term outcome after AE is elusive. Pierotti and colleagues [7] found no improvement in survival between antifungal therapy alone or combined therapy with an overall mortality rate greater than 90%. On the other hand, Ellis and colleagues [1] recommend surgical treatment to significantly improve chances of survival.

**Antifungal Prophylaxis**

The high rate of relapse associated with AE (30% to 40%) regardless of therapeutic strategy [3, 52] underscores the need for long-term antifungal therapy after treatment of
AE. A minimum of 2 years of treatment is recommended using itraconazole or the newer agent voriconazole. Life-long therapy is increasingly advocated, considering the fatal consequences of a recurrence after initial remission [7, 51, 59].

Conclusion

Aspergillus endocarditis is an ominous complication after cardiac surgery with a dismal prognosis despite better understanding of the etiology of the disease. Its detection and eradication from the hospital environment, its diagnosis in patients, and the therapeutic arsenal available remain major limiting factors for obtaining better short- and long-term results. A multidisciplinary approach is therefore warranted when outbreaks of AE are encountered to act swiftly on the primary prevention of the disease. Surgery has become a mainstay in the management of patients with AE. With the advent of newer and more efficacious antifungal agents and sterilization of the infected milieu, it is hoped that the treatment of AE will become more successful.

References