Aspergillus Flavus Endocarditis of the Native Mitral Valve in a Bone Marrow Transplant Patient

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

AEG 1 **Tolga Demir**
ABCEF 2 **Mehmet Umit Ergenoglu**
EF 2 **Abdurrahman Ekinci**
CDE 3 **Nursen Tanrikulu**
BF 1 **Mazlum Sahin**
AG 2 **Ergun Demirsoy**

1 Department of Cardiovascular Surgery, Beylikduzu Kolan Hospital, Istanbul, Turkey
2 Department of Cardiovascular Surgery, Kolan International Hospital, Istanbul, Turkey
3 Department of Anesthesiology, Kolan International Hospital, Istanbul, Turkey

Corresponding Author: Tolga Demir, e-mail: dr.tolgademir@gmail.com
Conflict of interest: None declared

Patient:	**Male, 36**
Final Diagnosis:	**Aspergillus flavus endocarditis**
Symptoms:	**Malaise • fatigue and dyspnea**
Medication:	**—**
Clinical Procedure:	**Mitral vale replacemnet**
Specialty:	**Cardiology**

Objective: Rare disease

Background: Infective endocarditis due to *Aspergillus* species is an uncommon infection with a high mortality rate. It mostly occurs after the implantation of prosthetic heart valves. Parenteral nutrition, immunosuppression, broad-spectrum antibiotic regimens, and illegal intravenous drug use are the risk factors for developing infection.

Case Report: We report a case of *Aspergillus flavus* native mitral valve endocarditis in a patient who had allogeneic stem cell transplantation in the past due to myelodysplastic syndrome.

Conclusions: Although it is rare and there is limited experience available with the diagnosis and treatment, early recognition and therapeutic intervention with systemic antifungal therapy and aggressive surgical intervention are critical to prevent further complications that may eventually lead to death. In addition, better novel diagnostic tools are needed to facilitate more accurate identification of patients with invasive *Aspergillus* and to permit earlier initiation of antifungal treatment.

MeSH Keywords: *Aspergillus flavus* • Endocarditis • Graft *vs.* Host Disease

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/892428

📄 2698   ▦ —   📊 1   📑 29

Background

Fungal endocarditis is an uncommon infection, accounting for only 1.3% to 6% of all infective endocarditis cases [1]. Prosthetic heart valves, central venous catheters, prolonged use of antibiotics, malignancy, and illegal intravenous drug use are the risk factors for developing this infection. On rare occasions, infection, which is an opportunistic disease, occurs in patients who have not had cardiac surgery. Most of these patients are immunocompromised hosts [2].

We present a case of *Aspergillus flavus* endocarditis of the native mitral valve in an allogeneic bone marrow-transplanted patient.

Case Report

A 36-year-old man was admitted to the hospital with fatigue and dyspnea. His past medical history was remarkable for allogeneic stem cell transplantation (matched related donor) due to myelodysplastic syndrome.

On the 12th post-transplant day, his early post-transplant period was complicated with acute graft-versus-host disease (GVHD) affecting skin, liver, and intestinal system. Prednisolone (1 mg/kg/day) and cyclosporine (1.5 mg/kg/day) was commenced immediately. The steroid dose was increased to 2 mg/kg/day on the 15th post-transplant day and was continued with adjusted doses until the patient died. Bacterial cultures and cytomegalovirus (CMV) antigenemia were negative. On the 15th post-transplant day, CMV and BK viruses (measured by polymerase chain reaction) were reported as positive. Ganciclovir/Valacyclovir was added to his medication. The blood cultures (4 sets of aerobic, anaerobic, and fungal) were performed and revealed negative results.

On the 42nd post-transplant day, the patient was discharged from the hospital. A week later, the patient was re-admitted to our hospital with complaints of malaise and fatigue. His admission physical examination revealed a temperature of 36.9°C, a pulse of 88 beats per minute, blood pressure of 140/80 mmHg, and a respiratory rate of 18 breaths per minute. His heart sounds were regular, and no murmur was audible. No evidence of endocarditis was found on physical examination. A neurological examination revealed no focal deficits. Laboratory tests showed a white blood cell count of $4.05 \times 10^3/\mu l$ with a demonstrated left shift (74.9% neutrophils and 13.3% bands), a hemoglobin value of 11.1 g/dl, and thrombocytopenia with platelets counts of $19 \times 10^3/\mu l$.

On the 76th post-transplant day, the patient became febrile (38.2°C to 38.9°C). A chest X-ray demonstrated consolidation in the left upper and right lower lobes of the lung parenchyma. Several sets of blood cultures were obtained and yielded *Staph epidermidis* and methicillin-resistant, coagulase-negative Staphylococci. According to *in vitro* sensitivity, intravenous Teicoplanin (6 mg/kg/day), Ceftriaxone sodium (2 g/day), and Vancomycin (1000 mg/day) were started simultaneously because the patient was immunocompromised.

A thoracic computed tomography (CT) showed multiple bilateral cavitary lesions on the lung parenchyma, suggesting pulmonary Aspergillosis. Serologic tests, blood cultures, sputum and bronchoalveolar lavage fluid specimens for fungal infection were negative. However, the serum Galactomannan antigen detection test result was highly positive (at index of 2.31; positive reference cut-off: index ≥0.5) on the 86th post-transplant day. The 1·3-β-D-glucan assay was not performed. Voriconazole (6 mg/kg IV every 12 h for the first day, followed by 4 mg/kg IV every 12 h) was started immediately. A week later, beginning with initiation of Voriconazole treatment, high levels of serum bilirubin, serum aspartate aminotransferase, and serum alanine aminotransferase (3 times during Voriconazole treatment) were measured. The all results were above the accepted reference values. Due to GVHD affecting the liver (hepatotoxicity) and the high risk of the patient, the Infectious Diseases specialist made a decision to switch from Voriconazole to liposomal Amphotericin B (AmBisome, 3 mg/kg/day). However, 2 weeks later, follow-up thoracic CT did not show any radiologic sign of improvement. At this point, on the basis of a clinical diagnosis of an Aspergillus infection and due to the severity of his condition, Caspofungin acetate (loading dose of 70 mg/day followed by 50 mg/day) was added to the current anti-fungal therapy as combination agent.

On the 94th post-transplant day, during a routine daily physical examination, a systolic cardiac murmur was noted. A transthoracic and trans-esophageal echocardiogram showed mobile vegetation (1×0.6 cm) on the anterior mitral valve leaflet with grade ¾ mitral regurgitation, supporting a diagnosis of native valve infectious endocarditis (Figure 1A). An urgent valve surgery was planned, but the patient refused surgical treatment and preferred a medical approach.

Despite the course of antifungal treatment, the patient continued to be febrile; however, serial thoracic CT scans showed that the dimensions of the lesions were not changed. On the 115th post-transplant day and while the patient was receiving combined antifungal therapy, he developed painful multiple purpuric skin lesions in the extremities. A local skin biopsy was performed, and a microscopic pathologic examination confirmed the *Aspergillus* species. On the 117th post-transplant day, the patient started to complain of right arm paraesthesia with pain arising from the right axilla. The right forearm and the distal ½ of the arm were cold compared to the
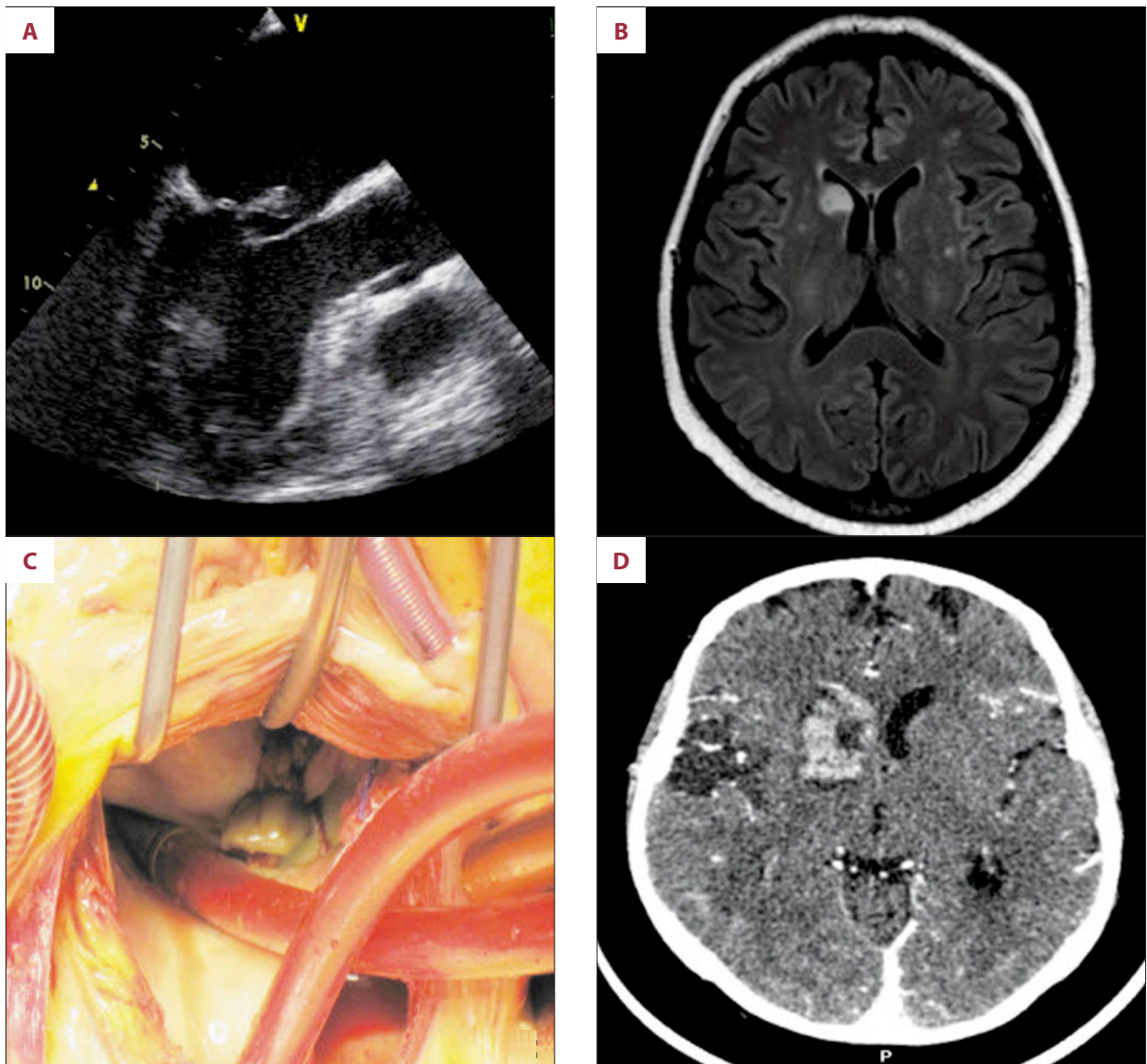
Figure 1. (**A**) Preoperative cardiac 2-D echocardiography. This shows a large mobile vegetation with an estimated size of 1×0.6 cm, on the anterior leaflet of the mitral valve. (**B**) Preoperative cerebral magnetic resonance imaging shows multiple septic emboli. (**C**) Surgical picture shows yellow-white vegetation on the anterior leaflet of the mitral valve. (**D**) Postoperative cerebral computed tomography shows a large hemorrhagic infarct.

left side. Neurologic exam results were normal. However, due to vegetation on the mitral valve and the history of embolic events, a cerebral magnetic resonance (MR) scan was performed, which revealed multiple areas compatible with septic emboli (Figure 1B).

After a long conversation with the family and medical consulting team about the risks, the patient was then referred for emergent valve surgery. On December 2010, the 118th post-transplant day, he underwent mitral valve replacement with a 29-mm bioprosthetic valve (SJM, St. Jude Medical, St. Paul, MN, U.S.A.). The explanted mitral valve revealed the presence

of yellow-white vegetations on the anterior leaflet with a ruptured papillary muscle head (Figure 1C). Microscopically, the nodule consisted of many branched septate hyphae with degenerative changes of necrosis. The fungal stain of the vegetation was consistent with Aspergillus, and the culture subsequently yielded heavy growth of *Aspergillus flavus*.

Although good hemodynamic support was achieved before the cardiopulmonary bypass and in the early postoperative period, the patient did not wake up in the intensive care unit. An urgent brain CT scan was performed, which revealed a large hemorrhagic infarct transformed from the previous ischemic

infarct (Figure 1D). Repeated brain CTs showed no improvement, and, unfortunately, in spite of all efforts with maximal supportive therapy, the patient died 7 days after valve surgery.

Discussion

Endocarditis with fungal etiology is an uncommon occurrence. However, *Aspergillus* species, which are associated with an extremely high mortality rate of 80–96%, cause approximately 20–30% of all fungal endocarditis cases [1,3,4]. More than 180 species within the genus *Aspergillus* have been described. Many of the species are quite rare, and only a few of them are known etiological agents of Aspergillosis in humans, such as *Aspergillus fumigatus* and *Aspergillus flavus.*

In the literature, Newman and Cordell were the first reporting *Aspergillus* endocarditis after a mitral valvulectomy in 1964. Only 28 cases of Aspergillus endocarditis were found in a MEDLINE search between 1995 and 2000, with distribution of *Aspergillus fumigatus* (54%), *Aspergillus terreus* (18%), *Aspergillus niger* (7%), and *Aspergillus flavus* (7%) [1].

There are some predisposing risk factors for the development of fungal endocarditis, such as underlying cardiac anomalies (41%), prosthetic cardiac valves (39%), malignancy (18%), solid-organ transplants (18%), and bone marrow transplants (18%) [1]. In our patient, the major predisposing risk factors appeared to be the evolving myelodysplastic syndrome, the use of steroid and cytotoxic drugs, and bone marrow transplantation with high dose of immunosuppressive therapy.

Although pre-existing valvulopathy or a prosthetic valve is another major predisposing factor for developing *Aspergillus* endocarditis, it has also been observed in patients with normal cardiac valves, as in our patient.

In this catastrophic disease, the aortic and mitral valves are the most frequent sites of infection. However, there is a predilection for left-sided valve endocarditis. The vegetations are often large and friable and carry high risk for embolization.

Aspergillosis can have a wide variety of manifestations, depending on the host response (defense) to the fungus. The most common clinical features are fever, major peripheral emboli from large friable vegetations, changing nature of the heart murmur, sub-dermal skin lesions, and endophthalmitis. Due to high risk of fatality in immunocompromised patients, clinical work-up and empirical therapy may need to be started upon suspicion, without any clue of the diagnosis. It is highly challenging to identify the source, which may not always be feasible in critically ill patients, to establish the diagnosis, and to carry out the treatment [5]. There are numerous species

of *Aspergillus* – the most common involving the heart include *Aspergillus fumigatus* (60–90%), *Aspergillus terreus* (5–20%), *Aspergillus flavus, Aspergillus niger,* and *Aspergillus nidus* [1]. In contrast to bacterial endocarditis, the pathogen can rarely be isolated from blood cultures, as occurred in our patient.

Laboratory findings are non-specific, such as anemia, leukocytosis, and elevated sedimentation and C-reactive protein. To establish the diagnosis, many serologic methods have been developed for the diagnosis of *Aspergillus* endocarditis, including testing for *Aspergillus* antigens, circulating galactomannan antigens, or polysaccharides (fungal components that are released during tissue invasion by *Aspergillus*). However, these tests have little impact on diagnosis due to their low sensitivities [6]. Galactomannan antigen detection, a recently developed test in bronchoalveolar lavage fluid, is a promising technique for detection of invasive Aspergillosis, with 88%sensitivity and 87% specificity [7]. However, false-positive results can occur in other fungal infections such as histoplasmosis, blastomycosis, cryptococcosis, and antibiotic treatment with amoxicillin-clavunate [8–10]. A promising new test to detect of *Aspergillus* DNA by polymerase chain reaction has superior sensitivity. It focuses mainly on the detection of *Aspergillus* spp. from clinical samples and can accurately detect a single gene. It offers ultrasensitive detection of pathogens in blood and respiratory specimens but has a wide range of positive and negative predictive values due to lack of standardization of specimen preparation, nucleic acid extraction, and detection. Therefore, DNA extraction and purification procedures should be standardized [11]. Branching and septating hyphae on Gomori methenamine silver or periodic acid-Schiff stains are typical for microscopic pathological diagnosis. Absolute diagnosis requires histological and tissue culture confirmation to differentiate and determine *Aspergillus* species.

In our case, *Aspergillus* mitral valve endocarditis occurred on the 94th post-transplant day. All blood, sputum, and bronchoalveolar lavage cultures were negative for fungal disease. Blood cultures of *Aspergillus* pathogens are negative in over 50% of patients with *Aspergillus* endocarditis [12].

Echocardiography is an important initial step in establishing the diagnosis. With improved technology, transthoracic echocardiography provides valuable information for the diagnosis of *Aspergillus* endocarditis, identifying 89% of vegetations in native valve endocarditis and 77% in prosthetic valve endocarditis [1]. Ellis et al. [3] reported that the sensitivity of transthoracic and transesophageal echocardiography techniques specifically focused on fungal endocarditis reach 77%. The vegetations are large, friable, and highly mobile, with high risk of early peripheral embolization [1]. The cutaneous lesions and axillary embolism were diagnosed after the mitral valve vegetation, which was diagnosed upon echocardiographic examination,

as in our case. However, embolic episodes may be the primary manifestation of valvular disease and should prompt the physician to perform further detailed cardiac examinations.

Successful treatment of *Aspergillus* endocarditis requires the combination of antifungal therapy and surgical debridement [13]. The optimum antifungal therapy still remains debatable. Voriconazole, the drug of choice for invasive *Aspergillus*, is active against a wide spectrum of clinically important fungi, including *Candida*, *Aspergillus*, and *Fusarium*. In addition to direct antifungal activity, it also possesses immune-modulatory properties that may enhance the immune response to *A. fumigatus* [14,15]. Voriconazole is effective in hematologic malignancies with invasive candidiasis and is also effective for anti-fungal prophylaxis in patients at high risk of invasive Aspergillosis (lung and hematopoietic stem cell transplant recipients [16,17].

Amphotericin (AMP) has been the mainstay of *Aspergillus* infection treatment for more than 50 years. Despite the new technologies developed, very few advances, such as Amphotericin B, a liposomal form of the drug (AmBisome, AMB), have been introduced in the management of *Aspergillus* endocarditis. AMB is significantly less toxic than conventional AMP and can be administered at higher doses. It is especially indicated for the patient who has impaired renal function or who develops nephrotoxicity while receiving classic AMP.

Itraconazole, synthetic triazole, is the second licensed agent for the primary treatment of invasive Aspergillosis. However, it has not gained as much popularity due to its pharmacokinetic specifications. Reports in the literature show an increasing rate of resistance to the anti-*Aspergillus* triazoles [18,19]. Due to high risk of hepatotoxicity manifested by elevated serum bilirubin, alkaline phosphatase, and hepatic aminotransferase enzyme levels, Voriconazole was not the first-choice medication in our patient [20]. Available data indicate that AMBs are effective against invasive pulmonary Aspergillosis and other forms of invasive Aspergillosis [21,22].

Caspofungin, a new drug and the first echinocandin to be licensed that inhibits cell wall biosynthesis, is approved for salvage treatment of refractory *Aspergillus* infection. Echinocandins have low toxicity and limited drug interactions compared to other antifungal drugs. It is at least as effective as AMB in nonneutropenic patients with *Aspergillus* infection. Due to pharmacokinetic properties, the liver does not metabolize it and with its long half-life infrequent dosing is possible. There is preclinical evidence that echinocandins augment the efficacy of AMB against *Aspergillus* species in combination therapy [23]. Aliff et al. treated 30 leukemia patients who showed inadequate response to AMB alone and reported that 60% had a favorable response with combination therapy with caspofungin [23]. Another alternative approach for treatment could be the

combination of Voriconazole with Caspofungin, which has led to promising results, although there has been very limited experience in patients with endocarditis. In our case, as approved in the literature for salvage therapy of invasive Aspergillosis, AMB and caspofungin were preferred and used [25,26].

However, combination therapy is controversial and more data are needed. Pierroti et al. found no improvement in survival between antifungal therapies alone or combined therapy, with an overall mortality rate greater than 90% [1]. Nevertheless, Ellis et al. recommended surgical treatment to significantly improve the chance of survival [3].

Surgical therapy is imperative for the survival of almost all cases of *Aspergillus* endocarditis. Kalokhe et al. conducted a literature review including 53 case reports of *Aspergillus* endocarditis and found that only 4% of these cases were treated successfully with antifungal therapy alone [13]. Even with surgical therapy, the survival rate is 32%. This poor outcome may be in part due to the immunocompromised status of the host, delay in diagnosis, and rapidity of embolization. In our case the necessity of prolonged administration of steroids due to GVHD could have had a role in the development and prognosis of this infection. We assume that endocarditis was the cause of the ongoing pyrexia of our patient. According to the Duke's criteria, surgery is indicated after the detection of valvular dysfunction. Earlier echocardiography during this pyrexia phase could have been helpful in the detection of a small vegetation before the valvular destruction occurs; therefore, earlier surgical treatment of the endocarditis potentially could have changed the prognosis of our patient [27]. The fact that an embolic episode occurred while the patient was under antifungal treatment convinced us that emergent surgery was needed. Usually in such a condition, septic emboli may occur, as the friable and necrotic vegetations are not easily accessible by AMB, which penetrates poorly into these vegetations. The combined medical and surgical treatment modality that was undertaken in our patient was consistent with results in the literature. Mortality reaches 100% among those who receive medical treatment alone; therefore, an early and aggressive surgical approach is recommended before the onset of valvular destruction, fatal embolic attacks, or chordae rupture causing acute mitral valve insufficiency [28]. The radical debridement of necrotic tissue with valve replacement using biomaterials is recommended. The recurrence rate is very high, with fatal prognosis. However, a few reports of positive results have been published in the literature [29].

Conclusions

We conclude that, although it is rare and there is limited experience available with the diagnosis and treatment, early

recognition and therapeutic intervention with systemic anti-fungal therapy and aggressive surgical intervention is critical to prevent further complications that eventually lead to death. New promising antifungal agents with improved activity and reduced toxicity are needed to improve outcomes in critically ill patients diagnosed with invasive fungal infections. Better novel diagnostic tools are needed to facilitate more accurate identification of patients with invasive *Aspergillus* and to permit earlier initiation of antifungal treatment.

Statement

No potential conflict of interest relevant to this article was reported. There were no external funding sources for this study.

References:

1. Pierrotti LC, Baddour LM: Fungal endocarditis, 1995–2000. Chest, 2002;122: 302–10

2. Rana M, Fahad B, Abid Q: Embolic *Aspergillus* endophthalmitis in an immunocompetent patient from aortic root *Aspergillus* endocarditis. Mycoses, 2008; 51: 352–53

3. Ellis ME, Al-Abdely H, Sandridge A et al: Fungal endocarditis: evidence in the world literature, 1965–1995. Clin Infect Dis, 2001; 32: 50–62

4. Demaria RG, Durrleman N, Rispail P et al: *Aspergillus flavus* mitral valve endocarditis after lung abscess. J Heart Valve Dis, 2000; 9: 786–90

5. Rubinstein E, Lang R: Fungal endocarditis. Eur Heart J, 1995; 16(Suppl.B): 84–89

6. Weiner MH: Antigenemia detected by radioimmunoassay in systemic aspergillosis. Ann Intern Med, 1980; 92: 793–96

7. Meersseman W, Lagrou K, Maertens J et al: Galactomannan in bronchoalveolar lavage fluid: a tool for diagnosing aspergillosis in intensive care unit patients. Am J Respir Crit Care Med, 2008; 177: 27–34

8. Zandijk E, Mewis A, Magerman K, Cartuyvels R: False-positive results by the platelia *Aspergillus galactomannan* antigen test for patients treated with amoxicillin-clavulanate. Clin Vaccine Immunol, 2008; 15: 1132–33

9. Narreddy S, Chandrasekar PH: False-positive *Aspergillus galactomannan* (GM) assay in histoplasmosis. J Infect, 2008; 56: 80–81

10. Cummings JR, Jamison GR, Boudreaux JW et al: Cross-reactivity of non-*Aspergillus fungal* species in the *Aspergillus galactomannan* enzyme immunoassay. Diagn Microbiol Infect Dis, 2007; 59: 113–15

11. Perlin DS, Zhao Y: Molecular diagnostic platforms for detecting *Aspergillus*. Med Mycol, 2009; 47(Suppl.1): S223–32

12. Rubinstein E, Noriega ER, Simberkoff MS et al: Fungal endocarditis: analysis of 24 cases and review of the literature. Medicine (Baltimore), 1975; 54: 331–34

13. Kalokhe AS, Rouphael N, El Chami MF et al: *Aspergillus* endocarditis: a review of the literature. Int J Infect Dis, 2010; 14: 1040–47

14. Walsh TJ, Anaissie EJ, Denning DW et al: Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis, 2008; 46: 327–60

15. Herbrecht R, Denning DW, Patterson TF et al: Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med, 2002; 347: 408–15

16. Husain S, Paterson DL, Studer S et al: Voriconazole prophylaxis in lung transplant recipients. Am J Transplant, 2006; 6: 3008–16

17. Siwek GT, Pfaller MA, Polgreen PM et al: Incidence of invasive aspergillosis among allogeneic hematopoietic stem cell transplant patients receiving voriconazole prophylaxis. Diagn Microbiol Infect Dis, 2006; 55: 209–12

18. Denning DW, Venkateswarlu K, Oakley KL et al: Itraconazole resistance in *Aspergillus fumigatus*. Antimicrob Agents Chemother, 1997; 41: 1364–68

19. Verweij PE, Mellado E, Melchers WJ: Multiple-triazole-resistant aspergillosis. N Engl J Med, 2007; 356: 1481–83

20. Boucher HW, Groll AH, Chiou CC, Walsh TJ: Newer systemic antifungal agents: pharmacokinetics, safety and efficacy. Drugs, 2004; 64: 1997–2020

21. Ng TT, Denning DW: Liposomal amphotericin B (AmBisome) therapy in invasive fungal infections. Evaluation of United Kingdom compassionate use data. Arch Intern Med, 1995; 155: 1093–98

22. Herbrecht R, Letscher V, Andres E, Cavalier A: Safety and efficacy of amphotericin B colloidal dispersion. An overview. Chemotherapy, 1999; 45(Suppl.1): 67–76

23. Arikan S, Lozano-Chiu M, Paetznick V, Rex JH: *In vitro* synergy of caspofungin and amphotericin B against *Aspergillus* and *Fusarium* spp. Antimicrob Agents Chemother, 2002; 46: 245–47

24. Aliff TB, Maslak PG, Jurcic JG et al: Refractory *Aspergillus pneumonia* in patients with acute leukemia: successful therapy with combination caspofungin and liposomal amphotericin. Cancer, 2003; 97: 1025–32

25. Caillot D, Thiebaut A, Herbrecht R et al: Liposomal amphotericin B in combination with caspofungin for invasive aspergillosis in patients with hematologic malignancies: a randomized pilot study (Combistrat trial). Cancer, 2007; 110: 2740–46

26. Cesaro S, Giacchino M, Locatelli F et al: Safety and efficacy of a caspofungin-based combination therapy for treatment of proven or probable aspergillosis in pediatric hematological patients. BMC Infect Dis, 2007; 7: 28

27. Thuny F, Grisoli D, Collart F et al: Management of infective endocarditis: challenges and perspectives. Lancet, 2012; 10: 965–75

28. Denning DW, Stevens DA: Antifungal and surgical treatment of invasive aspergillosis: review of 2,121 published cases. Rev Infect Dis, 1990; 12: 1147–201

29. Gumbo T, Taege AJ, Mawhorter S et al: *Aspergillus* valve endocarditis in patients without prior cardiac surgery. Medicine (Baltimore), 2000; 79: 261–68