Aspergillosis

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Abstract
Aspergillosis is a large spectrum of fungal diseases, which primarily affect the lungs and are caused by members of the genus Aspergillus. A. fumigatus seems to be the most frequent species. The transmission of fungal spores to the human host is via inhalation. The clinical manifestations depend upon the immunological state of the patient, and range from hypersensitivity reactions (allergic bronchopulmonary aspergillosis (ABPA)) to noninvasive colonization of previously damaged tissue (pulmonary aspergilloma) to acute or chronic limited invasive disease (chronic necrotizing pulmonary aspergillosis (CNPA)) to rapidly progressive invasive disease (invasive aspergillosis (IA)). ABPA occurs in conjunction with asthma and cystic fibrosis. CNPA is a sub-acute process most commonly associated with underlying lung disease, alcoholism, or chronic corticosteroid therapy. Aspergilloma is a fungus ball that develops in previous cavitary lung lesions. IA is an often-fatal infection that occurs in severely immunosuppressed patients, and is characterized by invasion of blood vessels. Dissemination to other organs may occur. The incidence of IA was reported to vary between 3 and 7% in bone marrow transplant (BMT) patients, 1.5 to 4% in liver transplant recipients, approximately 10% in lung transplant recipients, and 14% in patients with onco-hematological diseases and cardiac transplant recipients. Diagnosis is based on histopathological findings and immunodetection of specific antigens. Prophylaxis consists in isolating high-risk patients in laminar air flow (LAF) rooms. Voriconazole, itraconazole, the investigational azoles (posaconazole, ravuconazole, anidulafungin and micafungin) with anti-mould activity, and amphotericin B all possess a reasonably broad spectrum of activity against Aspergillus. Despite advances in therapy, the invasive forms of aspergillosis are often associated with significant morbidity and mortality.

Key-words
Aspergillosis, Allergic bronchopulmonary aspergillosis (ABPA), Chronic necrotizing pulmonary aspergillosis (CNPA), pulmonary aspergilloma, invasive aspergillosis (IA), azoles

Disease name and included diseases

- Aspergillosis
- Allergic bronchopulmonary aspergillosis (ABPA)
- Chronic necrotizing pulmonary aspergillosis (CNPA)
- Pulmonary aspergilloma
- Invasive aspergillosis (IA)

Definition

Aspergillosis is a large spectrum of fungal diseases, which primarily affect the lungs and are caused by members of the genus Aspergillus. Aspergillus species are ubiquitous molds in the environment and are especially common in the soil and decaying vegetation. The genus *Aspergillus* includes over 185 species. Around 20 species have been reported as causative agents of opportunistic infections in human beings. Among these, *A. fumigatus* is the most commonly isolated species, followed by *A. flavus* and *A. niger*, *A. clavatus*, *A. glaucus*, *A. nidulans*, *A. oryzae*, *A. terreus*, *A. ustus*, and less commonly *A. versicolor*. The transmission of fungal spores to the human host is via inhalation.

Clinical presentation of the diseases

Aspergillus can affect different organ systems. The most frequently involved organs are the lungs. The clinical manifestations of lung aspergillosis are the following: allergic bronchopulmonary aspergillosis (ABPA), chronic necrotizing pulmonary aspergillosis (CNPA), aspergilloma, and invasive aspergillosis (IA). The clinical manifestations and severity of Aspergillosis depend upon the immunological state of the patient (Cohen, 1991). In patients who are severely immunocompromised, Aspergillus may be hematogenously disseminated beyond the lung, potentially causing endophthalmitis, endocarditis, rhinosinusitis, fungemia, osteomyelitis and abscesses in the myocardium, kidney, liver, spleen and soft tissue (**Table 1**).

ABPA is a hypersensitivity reaction to A. fumigatus colonization of the tracheobronchial tree and occurs in conjunction with asthma and cystic fibrosis (Hinson *et al.*, 1952; Rosenberg *et al.*, 1977).

Chronic necrotizing pulmonary aspergillosis (CNPA) is a sub-acute process usually found in patients with some degree of immunosuppression, most commonly associated with underlying lung disease, alcoholism, or chronic corticosteroid therapy (Binder *et al.*, 1982; Gefter *et al.*, 1981). Because it is uncommon, CNPA often remains unrecognized for weeks or months and causes a progressive cavitary pulmonary infiltrate.

IA is a rapidly progressing, often fatal infection that occurs in patients who are severely immunosuppressed, including those who are profoundly neutropenic, those who have received bone marrow transplant (BMT) or solid organ transplants, and patients with advanced AIDS or chronic granulomatous disease (Ascioglu *et al.*, 2002). This infectious process is characterized by invasion of blood vessels, resulting in multifocal infiltrates, which are often wedge-shaped, pleural-based, and cavitary. Dissemination to other organs, particularly the central nervous system, may occur.

Aspergilloma is a fungus ball that typically develops in the context of preexisting cavitary diseases (Fraser *et al.*, 1998; Kauffman, 1996. Aspergillomas may develop in patients with invasive aspergillosis or chronic necrotizing pulmonary aspergillosis. Underlying causes of the cavitary disease may include treated tuberculosis or other necrotizing infections, sarcoidosis, cystic fibrosis, and emphysematous bullae. The ball of fungus may move within the cavity but does not invade the cavity wall; however, it may cause hemoptysis.

Table 1: Clinical presentation of aspergillosis infections

Invasive aspergillosis	Pulmonary aspergillosis CNS aspergillosis Sinonasal aspergillosis Osteomyelitis Endophthalmitis Endocarditis Renal abscesses Cutaneous aspergillosis
Pulmonary aspergilloma	Pre-existing lung cavity
Colonization	Sinuses, lungs
Allergic bronchopulmonary aspergillosis	Sinuses, lungs
Others	Cutaneous aspergillosis Burns Post surgical wounds I.V. insertion sites Otomycosis Exogenous endophthalmitis Allergic fungal sinusitis Urinary tract fungus balls

Risk factors for Aspergillosis infections

Risk factors involved in the development of AI are hematological malignancies (Aisner *et al.*, 1979; Cowie *et al.*, 1994), exposure to steroids, agranulocytosis (intensity + duration), CMV disease, underlying pulmonary disease (Cowie *et al.*, 1994) (including COPD, interstitial lung disease, and previous thoracic surgery) and altered immune status due to chronic corticosteroid therapy (Bodey *et al.*, 1992; Denning *et al.*, 1994; Denning and Stevens, 1990), alcoholism, collagen vascular disease, or chronic granulomatous disease (Beyer *et al.*, 1994) and preexisting cavitary disease.

Patients who have undergone BMT or solid organ transplant, profoundly neutropenic after receiving chemotherapy for hematological malignancies or

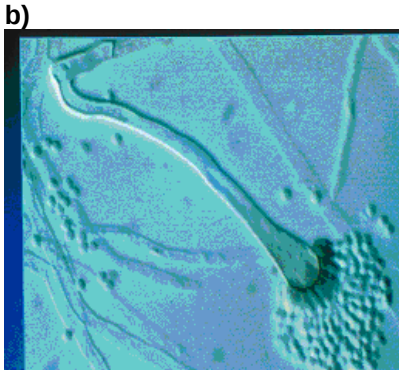
lymphoma, patients with chronic granulomatous disease, and patients with late-stage HIV are also at risk. Specific risk factors for invasive aspergillosis after BMT include prolonged neutropenia, graft versus host disease, high-dose corticosteroid therapy, disruption of normal mucosal barriers, mismatched or unrelated donor transplants, and the presence of central venous catheters.
The risk of IA is also related to the degree of exposure to Aspergillus spores (Gefter *et al.*, 1985; Gustafson *et al.*, 1983; Hofflin *et al.*, 1987; Iwen *et al.*, 1993; Janssen *et al.*, 1996).

Diagnosis
AI is often difficult to diagnose especially in the early stage. However, early diagnosis is of remarkable significance for earlier initiation of antifungal therapy and reduction of mortality rates. Suspicion of AI should be based on patients with risk factors for infection.
Definitive diagnosis requires both histopathologic evidence of acute-angle branching, septated nonpigmented hyphae approximately 3.0 mm in diameter, and culture(s) yielding Aspergillus species from specimens obtained by biopsy from the involved organs (or aspiration from a solid organ) (see **Figure 2**). Blood, CSF, and bone marrow specimens rarely yield Aspergillus species. The septated hyphae of Aspergillus are best detected by Gomori methenamine silver and periodic acidSchiff stains, and it would be desirable to include these stains in the initial tissue evaluation if invasive fungal disease is suspected.
Radiographic studies may include characteristic findings such as wedge-shaped pleural-based densities or cavities on plain radiographs (both late findings). Findings on CT scans include the "halo sign" (an area of low attenuation surrounding a nodular lung lesion) initially (caused by edema or bleeding surrounding an ischemic area) and, later, the "crescent sign" (an air crescent near the periphery of a lung nodule, caused by contraction of infarcted tissue). Bronchoalveolar lavage, with assay of the fluid by smear, culture, and/or antigen detection, has excellent specificity and reasonably good positive predictive value for invasive aspergillosis in immunocompromised patients. Transbronchial biopsy or brushings are too often false negative (CIII). Biopsies of endobronchial lesions have been useful when such lesions are encountered (Stevens *et al.*, 2000a).

Figure 2 (Photos courtesy Pfizer)
- **a) Characteristic dichotomous branching of *Aspergillus sp* (45º)**
- b) **Conidial head *Aspergillus fumigatus***

a)

b)



Immunodetection
The availability of the Platelia Aspergillus, a sandwich ELISA kit that detects circulating galactomannan, an exoantigen of Aspergillus, has been a major advance for managing patients at risk for invasive aspergillosis because of the early detection of the antigen. The assay is now widely used throughout the world, including the USA. Although initial studies that assessed the performance characteristics of this assay reported high sensitivity and specificity, more recent studies show significant variation in performance. Some of the factors that might affect the release of the Aspergillus antigen bearing the epitope that reacts with the monoclonal antibody EB-A2 used in the ELISA include those relating to fungal growth and leakage of the antigens from the site of infection into the blood, and their binding to substances present in the blood (Mennink-Kersten *et al.*, 2004). Antigen may be detected in other fluids including bronchoalveolar lavage fluid and cerebrospinal fluid (Salonen *et al.*, 2000; Verweij *et al.*, 1999; Viscoli *et al.*, 2002).

Epidemiology
In the last decades, the incidence of fungal infections has been increasing. Invasive aspergillosis (IA) is the second most frequent fungal infection in cancer patients, after candidiasis (Anaissie, 1992); The incidence of IA was reported to vary between 3 and 7% in BMT

patients (Bartlett, 2000; Denning *et al.*, 1991; Fisher *et al.*, 1981; Gefter *et al.*, 1985; Groll *et al.*, 1996; Kurup *et al.*, 1991; Levy *et al.*, 1992; McWhinney *et al.*, 1993), 1.5 to 4% in liver transplantations, approximately 10% in lung transplantations, and 14% in patients with hematological neoplasia and cardiac transplantations (Anaissie, 1992; Mills *et al.*, 1994; Morrison *et al.*, 1993; Nakamura *et al.*, 1994). Mortality rate ranged from 45 to 94% (Caillot *et al.*, 1997; Opal *et al.*, 1986; Orr *et al.*, 1978) and the attributable mortality associated with IA exceeds 80% (Fisher *et al.*, 1981; Pai *et al.*, 1994). IA is invariably associated with a fatal outcome when the central nervous system is involved or when the underlying neoplasia is not cured (Bodey *et al.*, 1992; Pai *et al.*, 1994; Palmer *et al.*, 1991). The mortality rates related to different antifungal treatments according to two different studies are shown in **Table 2**:

Table 2: Effect of different drugs on survival in IA patients*

Medication	Number of patients	Mortality
Amphotericin B deoxycholate[1]	559	65%
Lipid formulations of Amphotericin B[1]	235	51%
Itraconazole po[1]	156	34%
Itraconazole[1]	156	24%
Voriconazole[2]	144	29%
Amphotericin B deoxycholate[2]	133	42%

*In this table are included only the first line treatment drugs. Other drugs, such as caspofungin, are recommended as second line choice.
[1]Lin *et al.* (2001)
[2]Herbrecht *et al.* (2002)

Treatment

The treatment and prognosis of AI depends upon the type and severity of the disease as well as the immunological status of the patient. Treatment for chronic necrotizing aspergillosis differs significantly from the treatment of ABPA and aspergilloma (Stevens *et al*, 2000a). Allergic aspergillosis has been successfully treated with corticosteroids, and itraconazole (Stevens *et al.*, 2000b).

Antifungal therapy and the use of LAF or high-efficiency particulate air (HEPA) filtration of the rooms of the patients who receive BMT and other high-risk patients may prevent invasive aspergillosis.

Invasive aspergillosis may be treated with voriconazole (Herbrecht *et al.*, 2001), amphotericin B (deoxycholate and lipid preparations), and itraconazole (Stevens *et al.*, 2000a; Denning and Stevens, 1990). However, despite advances in therapy, the invasive forms of aspergillosis are often associated with significant morbidity and mortality (Denning and Stevens, 1990).

Voriconazole, itraconazole, the investigational azoles (posaconazole, ravuconazole, anidulafungin and micafungin) with anti-mould activity, and amphotericin B all possess a reasonably broad spectrum of activity against Aspergillus and the related hyaline moulds.

Voriconazole is a new triazole structurally related to fluconazole, but with improved potency and spectrum of activity, including fluconazole-resistant strains of Candida, and most emerging fungal pathogens such as Blastomycetes, Fusarium spp. and Penicillium spp. (Arikan *et al.*, 1999; Clancy and Nguyen, 1998; Chryssanthou and Cuenca-Estrella, 2002; Espinel-Ingroff, 1998; Sanati *et al.*, 1997; Pfaller *et al.*, 2002; 2003). Parenteral administration can be followed by oral therapy. Voriconazole is currently approved in many countries for primary treatment of acute invasive aspergillosis (Herbrecht *et al.*, 2001, Denning *et al.*, 2002, Herbrecht *et al.*, 2002), and salvage therapy for rare but serious fungal infections. The recommended dosage is as follows:

	Loading dose (1 day)	Maintaining dose
i.v. formulation	6 mg/kg/12 h	4 mg/kg/12 h
Oral formulation > or = 40 kg	400 mg/12 h	200 mg/12 h
Oral formulation < 40 kg	200 mg/12 h	100 mg/12 h

The echinocandin glucan synthesis inhibitors, caspofungin, micafungin, and anidulafungin possess a narrower spectrum of activity and should only be used if the infection is known to be due to Aspergillus spp. Echinocandin is a new class of antifungals that inhibits the synthesis of 1,3-β-glucan of the cell wall. Caspofungin exhibits antifungal activity against a wide array of clinically important fungi, including Candida and Aspergillus spp. (59, Mora-Duarte *et al.*, 2002; Pfaller *et al.*, 2001; 1998).

It is generally well tolerated with minimal side effects (Keating and Jarvis, 2001; Stone *et al.*, 2002). Caspofungin has been recently licensed in the United States for the treatment of invasive aspergillosis in patients who are refractory to, or intolerant to other therapies (i.e., amphotericin B, lipid formulations of amphotericin B, and/or itraconazole) (Maertens *et al.*, 2000). The recommended dosage is 70 mg i.v./day for the loading dose (1 day), followed by 50 mg i.v./day for the maintaining dose.

Surgical treatment

In IA and chronic necrotizing aspergillosis a surgical resection is indicated for localized

diseases which failed to respond to prolonged antifungal treatment.
Aspergillomas may be treated by surgical resection (Denning and Stevens, 1990; Kauffman, 1996). However, this approach may cause significant morbidity and mortality, therefore it should be reserved for patients at high risk to develop severe hemoptysis (Glimp and Bayer, 1983, Massard *et al.*, 1992).

References

Aisner J, Murillo J, Schimpff SC, Steere A. Invasive aspergillosis in acute leukemia: Correlation with nose cultures and antibiotic use. Ann Intern Med 1979; 90: 4-9.
Anaissie E. Opportunistic mycoses in the immunocompromised host: Experience at a cancer center and review. Clin Infect Dis 1992; 14(Suppl 1): S43-S53.
Arikan S, Lozano-Chiu M, Paetznick V, Nangia S, Rex JH. Microdilution susceptibility testing of amphotericin B, itraconazole, and voriconazole against clinical isolates of Aspergillus and Fusarium species. J Clin Microbiol 1999; 37: 3946-3951.
Ascioglu *et al.* Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. Clin Infect Dis 2002; 34: 7-14.
Bartlett, JG. Aspergillosis update. Medicine (Baltimore) 2000; 79: 281-282.
Bennett JE. Aspergillus species, p. 2306-2310. In Mandell GL, Bennett JE, and Dolin R (ed.). Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases, 1995; 4th edition ed. Churchill Livingstone, New York.
Beyer J, Schwartz S, Heinemann V, Siegert W. Strategies in prevention of invasive pulmonary aspergillosis in immunosuppressed or neutropenic patients. Antimicrob Agents Chemother 1994; 38: 911-17.
Binder, RE, Faling, LJ, Pugatch, RD, *et al.* Chronic necrotizing pulmonary aspergillosis: a discrete clinical entity. Medicine (Baltimore) 1982; 61: 109-124.
Bodey G, Bueltmann B, Duguid W, Gibbs D, Hanak H, Hotchi M, Mall G, Martino P, Meunier F, Milliken S. Fungal infections in cancer patients: An international autopsy survey. Eur J Clin Microbiol Infect Dis 1992; 11: 99-109.
Caillot D, Casasnovas O, Bernard A, Couaillier J, Durand C, Cuisenier B, Solary E, Piard F, Petrella T, Bonnin A, Couillault G, Dumas M, Guy H. Improved management of invasive pulmonary aspergillosis in neutropenic patients using early thoracic computed tomographic scan and surgery. J Clin Oncol 1997; 15: 139-47.
Chryssanthou E, Cuenca-Estrella M. Comparison of the Antifungal Susceptibility Testing Subcommittee of the European Committee on Antibiotic Susceptibility Testing proposed standard and the E-test with the NCCLS broth microdilution method for voriconazole and caspofungin susceptibility testing of yeast species. J Clin Microbiol 2002; 40: 3841-3844.
Clancy CJ, Nguyen MH. In vitro efficacy and fungicidal activity of voriconazole against Aspergillus and Fusarium species. Eur J Clin Microbiol Infect Dis 1998; 17: 573-575.
Cohen J. Clinical manifestation and management of aspergillosis in the compromised patient. In Warnock DW, Richardson MD (eds): Fungal infection in the Compromised patient, 2nd ed. John Wiley & Sons, Chichester, United Kingdom, 1991. p.117.
Cohen MS, Isturiz RE, Malech HL, Root RK, Wilfert CM, Gutman L, Buckley RH. Fungal infection in chronic granulomatous disease. The importance of the phagocyte in defense against fungi. Am J Med 1981; 71:59-66.
Cowie F, Meller ST, Cushing P, Pinkerton R. Chemoprophylaxis for pulmonary aspergillosis during intensive chemotherapy. Arch Dis Child 1994; 70: 136-38.
Denning DW, Follansbee SE, Scolaro M, *et al.* Pulmonary aspergillosis in the acquired immunodeficiency syndrome. N Engl J Med 1991; 324: 654-662.
Denning DW, Lee JY, Hostetler JS, Pappas P, Kauffman CA, Dewsnup DH, Galgiani JN, Graybill JR, Sugar AM, Catanzaro A, *et al.* NIAID Mycoses Study Group multicenter trial of oral itraconazole therapy for invasive aspergillosis. Am J Med 1994; 97: 135-44.
Denning DW, Ribaud P, Milpied N, *et al.* Efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis. Clin Infect Dis 2002; 34: 563-571.
Denning DW, Stevens DA. Antifungal and surgical treatment of invasive aspergillosis: Review of 2,121 published cases. Rev Infect Dis 1990; 12: 1147-1201.
Espinel-Ingroff A. In vitro activity of the new triazole voriconazole (UK-109,496) against opportunistic filamentous and dimorphic fungi and common and emerging yeast pathogens. J Clin Microbiol 1998; 36: 198-202.
Fisher BD, Armstrong D, Yu B, Gold JW. Invasive aspergillosis. Am J Med 1981; 71: 571-80.
Fujimura M, Ishiura Y, Kasahara K, Amemiya T, Myou S, Hayashi Y, Watanabe Y, Takazakura E, Nonomura A, and Matsuda T. Necrotizing bronchial aspergillosis as a cause of hemoptysis in sarcoidosis. Am J Med Sci 1998; 315:56-8.
Gefter WB, Albelda SM, Talbot GH, Gerson SL, Cassileth PA, Miller W. Invasive pulmonary aspergillosis and acute leukemia. Limitations in

the diagnostic utility of the air crescent sign. Radiology 1985; 157: 605-10.
Fraser R, *et al.* Diagnosis of diseases of the chest. 3d ed. W.B. Saunders: Philadelphia, 1998.
Gefter, WB, Weingrad, TR, Epstein, DM, *et al.* "Semi-invasive" pulmonary aspergillosis: a new look at the spectrum of Aspergillus infections of the lung. Radiology 1981; 140: 313-321.
Gerson SL, Talbot GH, Hurwitz S, Strom BL, Lusk EJ, and Cassileth PA. Prolonged granulocytopenia: the major risk factor for invasive pulmonary aspergillosis in patients with acute leukemia. Ann Intern Med 1984; 100:345-351.
Glimp RA, and Bayer AS. Pulmonary aspergilloma. Diagnostic and therapeutic considerations. Arch Intern Med 1983; 143:303-8.
Groll AH, Shah PM, Mentzel C, *et al.* Trends in the postmortem epidemiology of invasive fungal infections at a university hospital. J Infect 1996; 33: 23-32.
Gustafson TL, Schaffner W, Lavely GB, Stratton CW, Johnson HK, Hutcheson RHJ. Invasive aspergillosis in renal transplant recipients: Correlation with corticosteroid therapy. J Infect Dis 1983; 148: 230-40.
Herbrecht R, Denning DW, Patterson TF, *et al.* Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 2002; 347: 408-415.
Herbrecht R, Denning DW, Patterson TF, *et al.* Open, randomised comparison of voriconazole and amphotericin B followed by other licensed antifungal therapy for primary therapy of invasive aspergillosis. 41st Interscience Conference on Antimicrobial Agents and Chemotherapy 2001, Abstract No. J-680.
Hinson KF, *et al.* Bronchopulmonary aspergillosis. Thorax 1952; 7: 317-33.
Hofflin JM, Potasman I, Baldwin JC, Oyer PE, Stinson EB, Remington JS. Infectious complications in heart transplant recipients receiving cyclosporine and corticosteroids. Ann Intern Med 1987; 106: 209-16.
Hoffman HL, Rathbun RC. Review of the safety and efficacy of voriconazole. Expert Opin Investig Drugs 2002; 11: 409-429.
Iwen PC, Reed EC, Armitage JO, Bierman PJ, Kessinger A, Vose JM, Arneson MA, Winfield BA, Woods G. Nosocomial invasive aspergillosis in lymphoma patients treated with bone marrow or peripheral stem cell transplants. Infect Control Hosp Epidemiol 1993; 14: 131-39.
Janssen J, Strack van Schijndel R, Van der Poest Clement E, Ossenkippele G, Thijs L, Huijgens P. Outcome of ICU treatment in invasive aspergillosis. Intensive Care Med 1996; 22: 1315-22.
Kahn FW, Jones JM, England DM. The role of bronchoalveolar lavage in the diagnosis of invasive pulmonary aspergillosis. Am J Clin Pathol 1986; 86: 518-23.
Kauffman CA. Quandary about treatment of aspergillomas persists. Lancet 1996; 347:1640.
Keating GM, Jarvis B. Caspofungin. Drugs 2001; 61: 1121-1129.
Kurup VP, Kumar A. Immunodiagnosis of aspergillosis. Clin Microbiol 1991; Rev 4: 439-56.
Levy H, Horak DA, Tegtmeier BR, Yokota SB, Forman S. The value of bronchoalveolar lavage and bronchial washings in the diagnosis of invasive pulmonary aspergillosis. Respir Med 1992; 86: 243-48.
Lin SJ, Schranz J, Teutsch SM. Aspergillosis case-fatality rate: systematic review of the literature. Clin Infect Dis. 2001; 32: 358-66.
Loudon KW, Burnie JP, Coke AP, Matthews RC. Application of polymerase chain reaction to fingerprinting Aspergillus fumigatus by random amplification of polymorphic DNA. J Clin Microbiol 1993; 31: 1117-21.
Maertens J, Raad I, Sable CA, Ngai A, Berman R, Patterson TF, Denning D, Walsh T. Multicenter, noncomparative study to evaluate safety and efficacy of caspofungin in adults with aspergillosis refractory or intolerant to amphotericin B, amphotericin B lipid formulations, or azoles. 40th Interscience Conference on Antimicrobial Agents and Chemotherapy 2000, Abstract No. 1103.
Massard G, Roeslin N, Wihlm JM, Dumont P, Witz JP, and Morand G. Pleuropulmonary aspergilloma: clinical spectrum and results of surgical treatment [see comments]. Ann Thorac Surg 1992; 54:1159-64.
McWhinney PH, Kibbler CC, Hamon MD, Smith OP, Gandhi L, Berger L, Walesby RK, Hoffbrand AV, Prentice H. Progress in the diagnosis and management of aspergillosis in bone marrow transplantation: 13 years' experience. Clin Infect Dis 1993; 17: 397-404.
Mennink-Kersten MA, Donnelly JP, Verweij PE. Detection of circulating galactomannan for the diagnosis and management of invasive aspergillosis. Lancet Infect Dis. 2004 4:349-57.
Mills W, Chopra R, Linch DC, Goldstone AH. Liposomal amphotericin B in the treatment of fungal infections in neutropenic patients: A single-center experience of 133 episodes in 116 patients. Br J Haematol 1994; 754-60.
Mora-Duarte J, Betts R, Rotstein C, *et al.* Comparison of caspofungin and amphotericin B for invasive candidiasis. N Engl J Med 2002; 347: 2020-2029.
Morrison VA, Haake RJ, Weisdorf D. The spectrum of non-Candida fungal infections following bone marrow transplantation. Medicine (Baltimore) 1993; 72: 78-89.
Morrison, VA, Haake RJ, and Weisdorf DJ. The spectrum of non-Candida fungal infections

following bone marrow transplantation. Medicine (Baltimore) 1993; 72:78-89.
Nakamura H, Shibata Y, Kudo Y, Saito S, Kimura H, Tomoike H. [Detection of Aspergillus fumigatus DNA by polymerase chain reaction in the clinical samples from individuals with pulmonary aspergillosis.] Rinsho Byori 1994; 42: 676-81.
Opal SM, Asp AA, Cannady PB Jr, Morse PL, Burton LJ, Hammer PG. Efficacy of infection control measures during a nosocomial outbreak of disseminated aspergillosis associated with hospital construction. J Infect Dis 1986; 153: 634-37.
Orr DP, Myerowitz RL, Dubois PJ. Patho-radiologic correlation of invasive pulmonary aspergillosis in the compromised host. Cancer 1978; 41: 2028-35.
Pai U, Blinkhorn RJ Jr, Tomashefski JF. Invasive cavitary pulmonary aspergillosis in patients with cancer. A clinicopathologic study. Hum Pathol 1994; 25: 293-303.
Palmer LB, Greenberg HE, Schiff M. Corticosteroid treatment as a risk factor for invasive aspergillosis in patients with lung disease. Thorax 1991; 46: 15-20.
Pfaller MA, Diekema DJ, Messer SA, Boyken L, Hollis RJ, Jones RN. In vitro activities of voriconazole, posaconazole, and four licensed systemic antifungal agents against candida species infrequently isolated from blood. J Clin Microbiol 2003; 41: 78-83.
Pfaller MA, Marco F, Messer SA, Jones RN. In vitro activity of two echinocandin derivatives, LY303366 and MK-0991 (L-743,792), against clinical isolates of Aspergillus, Fusarium, Rhizopus, and other filamentous fungi. Diagn Microbiol Infect Dis 1998; 30: 251-255.
Pfaller MA, Messer SA, Hollis RJ, Jones RN. Antifungal activities of posaconazole, ravuconazole, and voriconazole compared to those of itraconazole and amphotericin B against 239 clinical isolates of Aspergillus spp. and other filamentous fungi: report from SENTRY Antimicrobial Surveillance Program, 2000. Antimicrob Agents Chemother 2002; 46: 1032-1037.
Pfaller MA, Messer SA, Mills K, Bolmstrom A, Jones RN. Evaluation of E-test method for determining caspofungin (MK-0991) susceptibilities of 726 clinical isolates of Candida species. J Clin Microbiol 2001; 39: 4387-4389.
Rosenberg M, *et al.* Clinical and immunologic criteria for the diagnosis of allergic bronchopulmonary aspergillosis. Ann Intern Med 1977; 86: 405-14.
Salonen, J., Lehtonen OP, Terasjarvi MR, Nikoskelainen J. Aspergillus antigen in serum, urine and bronchoalveolar lavage specimens of neutropenic patients in relation to clinical outcome. Scand J Infec Dis 2000; 32:485-490.
Sanati H, Belanger P, Fratti R, Ghannoum M. A new triazole, voriconazole (UK-109,496), blocks sterol biosynthesis in Candida albicans and Candida krusei. Antimicrob Agents Chemother 1997; 41: 2492-2496.
Severo LC, Geyer GR, and Porto NS. Pulmonary Aspergillus intracavitary colonization (PAIC). Mycopathologia 1990; 112:93-104.
Stanley MW, Deike M, Knoedler J, and Iber C. Pulmonary mycetomas in immunocompetent patients: diagnosis by fine-needle aspiration. Diagn Cytopathol 1992; 8:577-9.
Stevens DA, Kan VL, Judson MA, Morrison VA, Dummer S, Denning DW, Bennett JE, Walsh TJ, Patterson TF, and Pankey GA. Practice guidelines for diseases caused by Aspergillus. Clin Infect Dis 2000a; 30:696-709.
Stevens DA, Schwartz HJ, Lee JY, Moskovitz BL, Jerome DC, Catanzaro A, Bamberger DM, Weinmann AJ, Tuazon CU, Judson MA, Platts-Mills TAE, DeGraff AC Jr., Grossman J, Slavin RG, Reuman P. A randomized trial of itraconazole in allergic bronchopulmonary aspergillosis. N Engl J Med 2000b; 342:756-762.
Stone JA, Holland SD, Wickersham PJ, *et al.* Single- and multiple-dose pharmacokinetics of caspofungin in healthy men. Antimicrob Agents Chemother 2002; 46: 739-745.
Verweij PE, K. Brinkman, H. P. H. Kremer, B. J. Kullberg, and J. Meis. Aspergillus meningitis: Diagnosis by non-culture-based microbiological methods and management. J Clin Microbiol 1999; 37:1186-1189.
Viscoli C, Machetti M, Gazzola P, De Maria A, Paola D, Van Lint MT, Gualandi F, Truini M. Aspergillus galactomannan antigen in the cerebrospinal fluid of bone marrow transplant recipients with probable cerebral aspergillosis. J Clin Microbiol 2002; 40:1496-1499.