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MANAGEMENT OF MYCOSES IN SURGICAL PATIENTS REVIEW OF THE LITERATURE

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Abstract: Fungal infections have been recognized as major cause of morbidity and mortality in neutropenic and non-neutropenic surgical intensive care patients. The incidence of Candida has increased: it is now the fourth most often isolated pathogen in bloodstream infections. The incidence of Aspergillus infection in transplant patients is highest in heart and lung transplants: 19-26%. Most invasive fungal infections in surgical patients are caused by Candida spp. and Aspergillus spp., less by Cryptococcus spp. and may be classified as local or organ-related, as (chronic) disseminated, and as fungemia. There is no highly specific and sensitive routine test for the diagnosis of Candida and Aspergillus infections available; clinical signs of fungal infections are rather unspecific. The significance of colonization remains undetermined. In non-neutropenic surgical patients central venous access and broad-spectrum antibiotics are independent risk factors for the development of fungal infection. Immunsuppression, e.g., transplantation, burn injury, can render patients susceptible to fungal infection. This has lead to the introduction of antifungal prophylaxis in transplant and burned patients which has reduced the mortality for Candida spp. infection significantly. There is no prophylaxis available against Aspergillus spp. and Cryptococcus spp.. Treatment of fungal infections consists of surgical and medical treatment for most organ-related infections. Recommendations for the management of fungal infections exist mostly for neutropenic patients, only few reports address the fungal infection of the surgical intensive care patient. Amphotericin B has been recommended as first line treatment for most severe fungal infections with fluconazole as follow-up treatment. In case of the development of toxic side effects of amphotericin B, mostly fluconazole or lipid formulations of amphotericin were favored. However, a shift in Candida strains towards non-albicans spp. and more resistant species was observed during recent years. This has lead to treatment failures in severe Candida and Aspergillus infections. The prognosis for invasive Aspergillus infections remains poor despite amphotericin B treatment. Newer azoles, e.g. voriconazole, demonstrated stable activity against most of these strains and may offer an option in the treatment of refractory fungal infections.

Key words: Candida; Aspergillus; Cryptococcus; surgical infection; voriconazole; disseminated infection; azoles; amphotericin B

INTRODUCTION

Candida and other fungal infections were rarely diagnosed until the 70ties. Nowadays, invasive and disseminated fungal infections pose a serious threat to surgical patients (Wright and Wenzel 1997). Not only the incidence of fungal infections has increased substantially (1.5 – 2 times) during recent years but also pathogens, which rarely caused disease in normal individuals, were more often identified, e.g., Aspergillus, Cryptococcus neoformans, and Histoplasma capsulatum (Dunn 2000). This may be due to several clinical circumstances, e.g., more patients who require surgery are elderly, critically ill, or immunosuppressed (Cone et al. 1988). The increase in fungal infections has been attributed to the increased use of immunosuppressive and antineoplastic agents, prosthetic devices and grafts, broad-spectrum antibiotics and hyperalimentation (Codish et al. 1979; Anaissie and Bodey 1989; Berbari et al. 1997). Surgical procedures such as upper gastrointestinal tract surgery, liver transplantation or procedures related to burns or acute necrotizing pancreatitis are associated with a high incidence of fungal infections (Edwards 1991; Kusne et al. 1988; Vindenes and Bjerknes 1993). While bacterial infections declined in burned patients, fungal wound infection did not (Becker et al. 1991). In organ transplant patients fungal infections, e.g., respiratory infections or primary cutaneous fungal infections, are emerging as significant problems (Crawford 1995; Benedict et al. 1992). Nosocomial infections were reported to be higher in surgical intensive care unit (SICU) patients than in medical intensive care unit patients. The SICU patients had more urinary tract infections, bacteremias, and wound infections. They were more likely to have received prior broad-spectrum antibiotics and had significantly more often endotracheal tubes, arterial lines, central venous lines, and indwelling bladder catheters (Craven et al. 1988). Inadequate antimicrobial treatment of critically ill patients with bloodstream infections has been associated with increased mortality, the presence of resistant Candida species (Ibrahim et al. 2000) and the development of drug resistance (Alexander and Perfect 1997). The changing spectrum of invasive candidiasis towards non-albicans species and the increase in antifungal resistances underscores the need for development of new anti-

fungal compounds, e.g. voriconazole, echinocandins (Singh 2001). As invasive fungal infections have become an increasing problem in older adults, the treatment with amphotericin B may have to be replaced due to toxic side effects with less toxic azoles (Kauffman 2001).

Candidiasis

Colonization

The clinical significance of Candida colonization is disputed since years. It has been demonstrated that gut colonization with candida may contribute to impairment of cell-mediated immunity in the critically ill patient (Marshall et al. 1988). Candida colonization was common in the patients who had operations, and levels were highest in those receiving antibiotics (Jarvis 1996). Candida levels in the oral cavity were highest in critically ill patients (Mitchell et al. 1982). Prophylaxis with ketokonazole resulted in a lower incidence of Candida colonization and the absence of fungal infection (Slotman and Burchard 1987). Persistent colonization with signs of sepsis, and peritoneal contamination and positive blood cultures were associated with a mortality of up to 83% (Solomkin et al. 1982). Patients colonized with Candida showed severe organ dysfunction (Marshall et al. 1993). Isolation of Candida spp. within the first week after surgery has been associated with serious mortality (55%) (Rantala et al. 1993). High risk colonized patients may not always demonstrate perioperative fungemia (Rantala et al. 1991). Critically ill patients with multiple gastrointestinal operations and wound infections often had multisite colonization together with an increased mortality. (Slotman et al. 1994) In a recent study it has been demonstrated that in a group of patients Candida colonization precede infection with a genotypical Candida spp.. A Candida colonization index demonstrated high predictive values 6 days before the clinical appearance of Candida infection (Pittet et al. 1994). Antibiotics may influence colonization. Metronidazole (D'Amelio et al. 1995), and amoxicillin-clavulanate caused a higher and more persistent increase in gastrointestinal colonization by yeasts compared to other antibiotics, e.g. ciprofloxacin, sulfamethoxazole-trimethoprim, ampicillin, cefepime or meropenem (Samonis et al. 1994; Samonis et al. 2001). The possibility of cross-transmission between patients and health-care workers has been observed for Candida albicans, but neither C. glabrata nor C. parapsilosis (Hedderwick et al. 2000). Despite frequent colonization in non-neutropenic ICU patients, invasive mycoses are rare in non-neutropenic ICU patients. In contrast to earlier studies, mortality in patients with fungal colonization in a European trial was not significantly increased compared to that in noncolonized patients. Laboratory tests, e.g., Candida HAT, Candida IFT, and the Candida Ramco Antigen Test, were not very helpful to differentiate between colonization and invasive infection (Petri et al. 1997). The prophylactic use of antifungal agents in non-neutropenic surgical patients decreased the rate of colonization but not that of fungal sepsis. Prophylactic use of these agents may be beneficial only in the high risk (>3 risk factors according to Slotman and Burchard) surgical patients (Savino et al. 1994). The efficacy of antifungal treatment in most colonized surgical patients remains undocumented (Solomkin 1996).

Invasion

A consensus committee established three levels of probability developed standard definitions for invasive fungal infections: proven, probable and possible (Ascioglu et al. 2002) (Table 1). The most specific evidence for fungal invasion is the identification of fungi in sterile tissues along with the growth of the organism in culture. Invasion of deeper tissues is commonly surmised by the clinical status along with culture of the organism at accessible sites, e.g., sputum, urine and blood (Burchard 1992). Invasive candidiasis in surgical patients may be defined by clinical signs of infection after surgery, absence of bacterial pathogens and/or failure to respond to systemic antibiotics, cultivation of Candida spp. from normally

Table 1. Definitions of invasive fungal infections.

- Proven invasive fungal infection
  - deep tissue infection
    - histopathologic/cytopathologic examination and evidence of tissue damage
    - positive culture in normally sterile tissue and clinically/radiologicially infective tissue
    - antigen positive for cryptococcus in CSF
  - fungemia
    - blood culture positive plus clinical symptoms
- Probable or possible invasive fungal infection
  - host factor
  - microbiological criterion
  - clinical criterion
- Host factors
  - neutropenia
  - persistent fever despite antibiotic treatment
  - immunosuppression
  - graft-versus-host disease
  - corticosteroid treatment
- Microbiological factors
  - positive culture for Aspergillus, Candida, Cryptococcus from different body locations
  - positive antigen test for Cryptococcus, Aspergillus
- Clinical factors (respiratory, sinus, CNS)
  - radiological evidence (major)
  - clinical symptoms (minor)
- Disseminated fungal infection
  - specific skin lesions
  - intraocular findings
- Chronic disseminated candidiasis
  - abscess in liver/spleen demonstrated by CT/MRI/US
  - increase in serum alkaline phosphatase
- Candidemia
- No clinical criteria for candidemia

(Modified according to Ascioglu 2002)

sterile sites or abundant growth in tracheal aspirate, response to antimycotic therapy, diagnostic serum antibody test (Geldner et al. 2000). Efforts have been made to discriminate fungal burn wound colonization from invasion according to the microbial status (Becker et al. 1991).

Disseminated Candidiasis

The term systemic candidiasis has been used for candida infection that invades the tissue beyond the skin and mucosa, but it does not differentiate hematogenously disseminated candidiasis from a candida infection that is spread from a local focus to the surrounding tissue. Hematogenous candidiasis has been defined as hematogenous seeding to deep organs. Chronic hematogenous disseminated candidiasis or chronic hepatosplenic candidiasis should be preferred to the term chronic systemic candidiasis. Specific reference could be made to the site of infection, e.g., candida peritonitis, candida pneumonia (Edwards and Filler 1992).

Incidence

In the eighties an increase in surgical fungal infections from 2.5/1000 discharges to 5.6/1000 discharges was observed (Banerjee et al. 1991). The incidence of nosocomial candidemia increased from 1981 to 1984 by eight times with Candida albicans as the most frequently isolated pathogen (58%), followed by C. tropicalis (25%), C. parapsilosis (15%), C. glabrata (6%), and C. lusitaniae (2%) (Harvey and Myers 1987). Candida moved from the eighth to the fourth most common nosocomial pathogen in blood and is detected in 8% to 15% of all nosocomial bloodstream infections (Banerjee et al. 1991; Beck-Sague and Jarvis 1993). In recent surveillance reports non-albicans species, e.g., C. tropicalis, C. parapsilosis, C. krusei, C. lusitaniae, were increasingly isolated in invasive candidiasis (Pfaller et al. 1998; Wright and Wenzel 1997). Others reported a decrease in C. albicans and C. tropicalis and an increase in the rate of C. krusei and C. glabrata infections (Abi-Said et al. 1997).

Pathogenesis

Candida colonizes the mucosa of the gastrointestinal and genitourinary tract. It can exist in two forms: yeast and mycelial (dimorphism). The mycelial form is invasive. The presence of both forms is considered pathognomic of invasive infection (Dean and Burchard 1998). Krause has demonstrated the invasive potential of Candida in 1969 showing that after ingestion of Candida albicans fungemia and funguria developed (Krause et al. 1969). In autopsy studies Candida infiltration of solid organs was documented (Hickey et al. 1983; Parker et al. 1976). Heavy colonization of the upper GI tract due to previous exposure to broad-spectrum antibiotics and H2 blockers plus gut barrier failure due to mucosal disruption and impaired host immune defense may lead to Candida translocation and possibly Candida peritonitis, hepatic Kupffer cell dysfunction and candidemia. Candida can adhere to fresh surfaces and can invade epithelial and subepithelial tissues via activation of phospholipases and proteinases (Ghannoum and Abu-Elteen 1990; Calderone 1989; Inone et al. 1988; Deitch 1990). The phagocytosis of C. albicans may be pivotal in the induction of endothelial damage, which may be associated with increased prostaglandin and cytokine secretion and leukocyte adhesion molecule expression by endothelial cells (Filler et al. 1994; Filler et al. 1995; Filler et al. 1996). γ-Interferon protected endothelial cells from damage by Candida albicans by inhibiting endothelial cell phagocytosis (Fratti et al. 1996). Candidemia may be caused by endogenous Candida colonization or cross-infection (Wenzel 1995; Giamarellou and Antoniadou 1996; Cole et al. 1996). Portals of entry for Candida fungemia could be catheters, wounds, the urinary tract, and the peritoneal cavity. In up to 54% of patients with Candida sepsis portals of entry were undefined (Dyess et al. 1985). Host recognition molecules (adhesins), morphogenesis (the reversible transition between unicellular yeast cells and filamentous, growth forms), secreted aspartyl proteases and phospholipases and phenotypic switching accompanied by changes in antigen expression, colony morphology and tissue affinities in C. albicans and several other Candida spp. have been recognized as virulence factors (Calderone and Fonzi 2001).

In non-neutropenic patients, central venous catheter, Foley catheter, broad-spectrum antibiotics, total parenteral nutrition, upper GI tract surgery, burns, trauma, continuous ambulatory peritoneal dialysis, i.v. drug addiction, azotemia, and low birth weight were found to be risk factors for the development of candida infection. Prior surgery has been associated with a lowered risk for fungal infection, (Bross et al. 1989; Slotman et al. 1994) which was not confirmed by recent studies (Blumberg et al. 2001). The number of prior administered antibiotics has been regarded as the strongest risk factor (Wey et al. 1989). It is known that prolonged antibiotic treatment can suppress the normal bacterial flora enabling Candida to grow, to bind to the mucosa and to translocate. Especially in critically ill surgical patients who are prone to a diminution of the intestinal barrier, Candida has been isolated from the proximal gastrointestinal tract and the peritoneal cavity. A strong correlation between the colonization of the intestinal tract and the development of a peritoneal infection with the same species has been observed (Marshall et al. 1993; Garvey et al. 1989; Burchard 1992; Stone et al. 1974; Samonis et al. 1994; D'Amelio et al. 1995; Volkheimer and Schulte 1968). Major surgery, trauma, burn injury, cancer, bacterial sepsis, hypoperfusion, corticosteroid treatment, chemotherapy, diabetes, and transplantation may cause immunosuppression, which may render patients susceptible to Candida infections (Burchard et al. 1983; Alexander et al. 1978; Bjerknes et al. 1989; Bradley et al. 1984; McLoughlin et al. 1979; Scovill and Saba 1973; Kirkpatrick 1984; Thaler et al. 1988). Candidemia is also often associated with central lines, which have been identified as an independent risk factor for the development of fungal infection (Rex JH et al. 1994; Maid et al. 1997; Beck-Sague and

Jarvis 1993). In surgical patients severity of illness (APACHE score > 10, ventilator use > 48 hours), antibiotics, burns and immunosuppression are common risk factors (Dean and Burchard 1996).

Mortality of critically ill surgical patients with fungemia was associated with age older than 46 years, concomitant renal failure, hepatic failure, postoperative shock, or adult respiratory distress syndrome. Survival was not influenced by diabetes, chronic obstructive pulmonary disease, gastrointestinal hemorrhage, pneumonia, alcohol consumption, steroid use, enteral or parenteral nutrition. (Eubanks et al. 1993). Risk factors for candida infection in liver transplant patients were administration of preoperative steroids or antibiotics, longer posttransplant operative time, duration of antibiotic use after transplant surgery, and the number of steroid boluses administered to control rejection in the first two months after transplantation, retransplantation, risk score, intraoperative transfusion, urgent status, Roux limb biliary reconstruction, bacterial infections and vascular complications (Wajszczuk et al. 1985; Castaldo et al. 1991). This may also lead to Candida pancreatic duct infection after pancreatic transplantation (Bonatti et al. 1995). Patients suffering from Candida mediastinitis often had received prior antibiotic therapy (Clancy et al. 1997). Candida peritonitis may be a complication of peritoneal dialysis, gastrointestinal surgery or perforation of the abdominal viscus and there seems to be an increased likelihood of Candida infection in pancreatic surgery (Bayer et al. 1976, Calandra et al. 1989, Buchler et al. 2000). Patients with burns are at risk to be infected by Candida. The extent of injury may have an impact on the loss of the intestinal mucosa (Pruitt et al. 1997). There is evidence that T cell dysfunction in burned patients is accompanied by a reduction in immunoglobulin levels, phagocytic function, Interleukin-2 production and increased activity/release of immunosuppressive products. Altered polymorphonuclear neutrophilic granulocyte functions in patients with large burns lead to a reduced killing of Candida albicans by about 25% on admission (Calvano et al. 1988; Alexander et al. 1978; Bjerknes et al. 1989; Gadd et al. 1989; Constantian 1978). A recent study in trauma patients showed by logistic regression analysis that only total parenteral nutrition was an independent risk factor (Borzotta and Beardsley 1999). Patients may be classified according to their risk to develop disseminated Candida infection in high-risk and low-risk patients (Dean and Burchard 1996) (Table 2). Risk factors for the development of hematogenously disseminated candidiasis after surgery in non-neutropenic patients were associated with advanced life support, e.g. prosthetic heart valves (Seelig et al. 1974).

Resistance

Until the 90's reports on resistance in fungal infections were rare. C. lusitaniae as cause of fungemia was considered to be important because it is often resistant to amphotericin B and the azoles (Powderly et al. 1988; Blinkhorn et al. 1989; Guinet et al. 1983; Meunier-Carpentier et al. 1981). There is evidence that more and more isolates of C. glabrata and C. krusei may be resistant to amphotericin B (Martinez-Suarez and Rodriguez-Tudela 1995; Wanger et al. 1995; Fisher et al. 1989; Karyotakis et al. 1993). Recently, azole resistance in Candida albicans has been reported in critically ill patients with invasive candidiasis (Yoon et al. 1999). Susceptibility testing (NCCLS M27-A methodology) is available for fluconazole, itraconazole, and flucytosine but not for amphotericin B. Nevertheless, routine testing of susceptibility in fungal infections is not recommended (Marr et al. 1997; Rex et al. 1997; NCCLS 1997). Until recently C. glabrata was considered a relatively nonpathogenic commensal fungal organism of human mucosal tissue. However, with the increased use of immunosuppressive agents, mucosal and systemic infections caused by C. glabrata have increased which is known to have an innate resistance to azole antimycotic therapy (Fidel et al. 1999). C. glabrata has emerged a potentially antifungal resistant cause of candidemia, particularly among persons older than 65 years (Diekema et al. 2002). Fluconazole prophylaxis has been accused for increasing the rate of C. krusei in fungal infections (Girmenia et al. 2001). Voriconazole demonstrated higher activity against fluconazole-resistant Candida albicans and Candida krusei and may be an option for treatment of fluconazole- and amphotericin-resistant Candida species (Lee et al. 2000). Animal experiments indicated that voriconazole could be efficacious for the treatment of fluconazole-resistant candida krusei infection (Ghannoum et al. 1999).

Table 2. Risk factors for disseminated disease – Classification in high-risk and low-risk patients.

- acute renal failure
- age above 40
- second and third degree burns
- antibiotics for more than 7 days
- three or more antibiotics
- gram-negative sepsis
- acute peritonitis
- intra-abdominal abscess
- diabetes mellitus
- cancer
- parenteral nutrition
- multiple organ system trauma
- serum glucose above 200mg/dl
- severe head injury
- steroid medication

High risk for disseminated fungal infection three and more risk factors are present, low risk for disseminated fungal infection less than three risk factors are present.
(According to Dean 1996)

Diagnosis of Candida Infection

Laboratory diagnosis of Candida infection remains

difficult. Specimens for culture may be obtained from sputum, urine, blood, drains, stool, and wound. Unfortunately, diagnosis of Candida by blood cultures may be misleading: bacterial pathogens may interfere with recovery of Candida and only 50% of blood cultures in invasive Candida were reported to be positive (Solomkin et al. 1982; Gaines and Remington 1972). Simultaneous bacteremia and fungemia reduce the recovery of Candida (Hockey et al. 1982). Positive blood cultures do not necessarily indicate invasive or disseminated infection (Dyess et al. 1985; Stone et al. 1974; Kujath et al. 1990; Rutledge et al. 1986). Lysis centrifugation or arterial sampling has been proposed to increase the yield (Geha and Roberts 1994; Berenguer et al. 1993). Several serological laboratory tests are available to detect the following components: mannan and β-1,3 glucan (cell wall components), D-arabinitol (cell membrane metabolite), and enolase (cell cytoplasm) (Ikeda et al. 1990; Kozinn et al. 1982; Podzorski et al. 1989; Walsh et al. 1991). The latex agglutination test for Candida spp. has been announced to be a useful procedure for the rapid diagnosis of severe disseminated candidiasis with a high sensitivity and specificity (Bailey et al. 1985; DeLozier et al. 1987). Recent reports were not so optimistic. The specificity of the Cand-Tec Candida antigen assay in the diagnosis of systemic candidiasis was poor. Candida antigen titers may not be clinical useful to detect dissemination (Cabezudo et al. 1989; Pfaller et al. 1993). For the antibody and metabolite assays, results showed no difference between proven disseminated candidiasis and peripheral candidiasis (Bougnoux et al. 1990). In a large European study in intensive care units, the serological test procedures, Candida HAT (haemagglutination test), Candida IFT (immunofluorescence test) and the Candida Ramco Antigen Test had a low specificity and were not helpful in diagnosing invasive mycosis (Petri et al. 1997). Furthermore, 40% to 60% of patients with proven disseminated candidiasis have negative blood cultures (Pizzo and Walsh 1990).

Clinical diagnosis of Candida infection is difficult as most symptoms are nonspecific. Fever may be present in most ICU admissions (Circiumaru et al. 1999). There is no magic test to discriminate fungal colonization and systemic infection in critically ill surgical patients; less than 50% of colonized patients developed disseminated candidiasis or candidemia. No single site of isolation was superior to others in predicting which patients are likely to develop systemic infection (Cornwell et al. 1995). Diagnostic criteria for disseminated fungal (Candida) infection are culture of fungus from tissue, the presence of endophthalmitis, burn wound invasion, and positive peritoneal culture, osteomyelitis, and candiduria in the absence of bladder instrumentation. Three or more colonized sites, two positive blood cultures at least 24 hours apart and without a central line, or two positive blood cultures with a second culture obtained more than 24 hours after removal of a central line are likely to be diagnostic for invasive fungal infection (Dyess et al. 1985; Slotman et al. 1994; Dean and Burchard 1998; Edwards et al. 1992; Fraser et al. 1992). Myalgia, skin lesions and endophthalmitis may be symptomatic for disseminated disease (Kozinn et al. 1982; Bodey and Luna 1974; Jarowski et al. 1978; Kressel et al. 1978; Donahue et al. 1994). Skin lesions, e.g., Purpura fulminans, could provide an early diagnostic sign for candida sepsis (Silverman et al. 1986). Bullous skin lesions could be a sign of disseminated candidiasis (Suster and Rosen 1987). Clinically significant candida peritonitis can be differentiated from contamination by the presence and persistence of fever, peritoneal signs, peripheral leukocytosis, positive peritoneal cultures for Candida, abnormal films of the abdomen and purulent ascites fluid (Bayer et al. 1976). If risk factors that are commonly associated with fungal infections (cardiac surgery, prolonged hospitalization, indwelling central lines, and long term antibiotic treatment) are present, fungal endocarditis is possible (Berbari et al. 1997). Common clinical manifestations of candidal mediastinitis are chest wall erythema, drainage, fever, and sternal instability. Mediastinitis is often complicated by hematogenous or contiguous spread (78%) (Clancy et al. 1997). Identification of infection in the orthotopic liver transplant recipient is often difficult due to the similarity between the clinical manifestations of rejection and those of infection. The patient's clinical status is most helpful in differentiating colonization from an infection (Colonna et al. 1988). Sometimes clinical symptoms may not allow an early identification of a Candida albicans infection of an ascending aortic prosthetic graft and a porcine aortic valve prosthesis which led to a dissecting false aneurysm of the remaining transverse and entire descending thoracic aorta (Cooley and Burnett 1993). Hepatic fungal abscess from Candida albicans or hepatosplenic candidiasis may be distinguished from the gallbladder by ultrasound or laparoscopic-guided liver biopsy (Berger et al. 1977; Anttila et al. 1997). Burn wound infection may be recognized by characteristic lesions (Becker et al. 1991, Pruitt et al. 1998).

Candidemia and Acute Hematogenously Disseminated Candidiasis

Candida bloodstream infections are often accompanied by clinical signs of sepsis and a high mortality (Wey et al. 1988). In neutropenic patients the role of the gut as source of infection is evident. The significance of catheter as source of infection in neutropenic patients is unclear with the exception for Candida parapsilosis, which has been frequently associated with catheter infection (Anaissie et al. 1998; Nguyen et al. 1995). In nonneutropenic patients removal of all existing central venous catheters is warranted (Nguyen et al. 1995; Rex et al. 1995).

Systemic treatment may be started with fluconazole or amphotericin B. Two randomized studies and 2 observational studies have demonstrated that fluconazole at 400 mg/d and amphotericin B at 0.5-0.6 mg/kg/d were equally effective (Rex et al. 1994; Phillips et al. 1997; Anaissie et al. 1998; Nguyen et al. 1995). Amphotericin B lipid complex and liposomal amphotericin B, which are causing less toxic effects, have been recommended for treatment of patients intolerant of or refractory to conventional antifungal

therapy (Walsh et al. 1998; Noskin et al. 1998; Anaissie et al. 1995). Susceptibility testing is available to identify isolates that are likely to be resistant to fluconazole or amphotericin B. Therapy for candidemia should be continued for 2 weeks after the last positive blood culture and resolution of clinical signs of infection. Fluconazole may be used to continue treatment after amphotericin B as initial treatment (Rex et al. 2000; Edwards et al. 1997). In neutropenic patients, G-CSF and GM-CSF may be administered additional to antifungal agents (Hughes et al. 1997). All patients with candidemia should have a retinal examination. Candida infection of the eye has been considered a marker for disseminated disease. Amphotericin B may be combined with flucytosine, fluconazole may be used as follow-up therapy. Treatment may be necessary for 6-12 weeks, until complete resolution of visible disease or stabilization. Occasionally vitrectomy has been performed (Rex et al. 2000; Edwards et al. 1974; Myers et al. 1973; Akier et al. 1995) (Table 3). The investigational triazoles posaconazole, ravuconazole, and voriconazole showed a high activity against all species of candida isolated from bloodstream infections, whereas a trend in decreasing susceptibility was demonstrated for fluconazole, itraconazole and amphotericin B (Pfaller et al. 2002). Voriconazole was also significantly more active than fluconazole against C. glabrata (Pfaller et al. 2001). When compared to fluconazole, itraconazole, ketoconazole, amphotericin B and flucytosine, voriconazole demonstrated the best activity against Candida species isolated from bloodstream infections (Hoban et al. 1999).

Empirical Therapy for Suspected Disseminated Candidiasis in Febrile Nonneutropenic Patients

Colonization by Candida of multiple nonsterile sites, broad-spectrum antibiotics, central venous catheters, parenteral nutrition, surgery of the gastrointestinal tract or prolonged ICU stay have been recognized as risk factors for invasive candidiasis (Pittet et al. 1994; Wey et al. 1989; Fraser et al. 1992). There is no clear recommendation for antifungal therapy in these patients. The antifungal treatment should be limited to high-risk patients with colonization at multiple sites and absence of other reasons for fever (Rex et al. 2000). In surgical high-risk patients (according to the classification of Dean and Burchard 1996) the indication for treatment may be adapted to the recommendations of the British Society for Antimicrobial Chemotherapy (Table 4).

Empirical Antifungal Therapy for Neutropenic Patients with Prolonged Fever despite Antibacterial Therapy

Neutropenic patients with persistent fever despite antibiotic treatment have a risk of approximately 20% to develop invasive fungal infection (Pizzo et al. 1982; EORTC 1989). Empirical antifungal therapy may reduce the frequency of fungal infection. Itraconazole has been introduced as an alternative therapy to amphotericin B (Walsh et al. 1991; Pizzo et al. 1982; EORTC 1989). Liposomal amphotericin B has demonstrated equivalent efficacy to amphotericin B but was superior in safety, tolerance and documented breakthrough fungal infections (Walsh et al. 1999). Amphotericin B (0.5-0.7 mg/kg/d) is the preferred antifungal agent when patients suffer from fever despite antimicrobial treatment (4-6 days). Liposomal amphotericin B (3mg/kg/d median dose) is equally effective (Rex et al. 2000). In a comparison with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever voriconazole had a similar overall success rate (30.6% versus 26%) (Walsh et al. 2002).

Chronic Disseminated Candidiasis (Hepatosplenic candidiasis)

This syndrome, which occurs mostly in patients with hematologic malignancies, is often referred to as hepatosplenic candidiasis, chronic systemic candidiasis, or chronic disseminated candidiasis. Patients usually present with non-neutropenic fever, unresponsive to antibiotics and abnormal liver function tests. In imaging studies there may be focal lesions in the liver or spleen (Kontoyiannis et al. 2000; Chun et al. 1980). The optimal treatment is not yet established. In selected cases, splenectomy or percutaneous drainage may be beneficial (Helton et al. 1986). Amphotericin B, amphotericin B lipid complex and fluconazole were equally effective in the treatment of chronic disseminated candidiasis (Thaler et al. 1988; Walsh et al. 1995; Walsh et al. 1997; Kauffman et al. 1991;

Table 3. Recommendation for therapy of candidemia and acute hematogenously disseminated candidiasis.

Clinical situation	Therapy
Stable patients without prior azole therapy	Fluconazole >6mg/kg/d
Clinically unstable patients with unknown isolate	Amphothericin B (>0.7mg/kg/d) or fluconazole
C. albicans, C. tropicalis, C. parapsilosis	Amphotericin B (0.6 mg/kg/d) or fluconazole (6 mg/kg/d)
C. glabrata	Amphotericin B as initial therapy (>0.7 mg/kg/d) or fluconazole (12 mg/kg/d)
C. krusei	Amphotericin B (1.0 mg/kg/d)
C. lusitaniae	Fluconazole (6 mg/kg/d)

(Rex JH 2000; Edwards JE 1997)

Table 4. Indication for empiric antifungal therapy.

- candiduria in a high-risk patient with deteriorating clinical status
- single Candida-positive blood culture in an at-risk patient
- isolation of Candida from any sterile body site (except urine)
- positive microscopy for yeast from a sterile specimen
- histologic evidence of yeast or mycelial forms in tissue from at-risk patients

(British Society for Antimicrobial Chemotherapy, Working Party Reccommendations 1994)

Anaissie et al. 1991). In stable patients fluconazole (6 mg/kg/d) is the recommended initial treatment of choice, amphotericin B (0.6-0.7 mg/kg/d) in acutely ill patients or patients not responding to fluconazole. Alternatively, an initial treatment with amphotericin B for 1-2 weeks followed by fluconazole may be acceptable. Therapy is continued until calcification or resolution of lesions (Rex et al. 2000; Edwards et al. 1997).

Urinary Candidiasis

The risk for urinary candidiasis is increased in patients with urinary tract instrumentation, antibiotic therapy and advanced age. In surgical intensive care patients Candida is the most frequent isolated pathogen in urine. However, in most instances it is only colonization (Wise and Silver 1993; Hamory and Wenzel 1978). Candiduria may be the source of dissemination or a marker of acute hematogenous dissemination (Wise et al. 1993; Ang et al. 1993; Nassoura et al. 1993). A change of urinary catheter may eliminate candiduria in only 20% of cases, whereas removal of the catheter may stop candiduria in 40% of the patients (Sobel et al 2000). Asymptomatic candiduria rarely requires therapy. Candiduria should be treated in symptomatic patients, neutropenic patients, renal transplant patients and patients with procedures in the urinary tract. Removal of catheters, whenever possible, is recommended. Fluconazole (200 mg for 7-14 days) or amphotericin B (0.3-1.0 mg/kg/d for 1-7 days) may be used for the treatment of candiduria. In the absence of renal insufficiency, oral flucytosine (25 mg/kg/q.i.d.) may be used especially in candiduria with non-albicans Candida species. Bladder irrigation is seldom indicated. Persistent candiduria warrants CT scan of the kidneys (Jacobs et al. 1996; Leu and Huang 1995; Fong et al. 1991; Rex et al. 2000). While Candida albicans and Candida tropicalis urinary isolates from 1994 to 1998 demonstrated increased resistance against fluconazole, the minimal inhibitor concentrations (MICs) for voriconazole remained constant (Baran et al. 2000).

Candida Infection of the Gallbladder, Pancreas, and Peritoneum

11 studies in surgical patients, which included mainly intra-abdominal fungal infections, reported a mortality rate of 23% - 84%. 5 studies in surgical patients were randomized controlled clinical studies mostly investigating the therapeutic effect of fluconazole (Table 5). Candida peritonitis may occur in patients with peritoneal dialysis and in association with surgery or trauma to the intestine. In the latter case Candida infection is usually part of a polymicrobial infection. Treatment of Candida is indicated in immunosuppressed patients or when Candida is part of a complex infection (Bayer et al. 1976; Solomkin et al. 1980; Calandra et al. 1989). Candida has been isolated as the second most common pathogen in surgical patients with tertiary peritonitis (Nathens et al. 1998; Rotstein et al. 1986; Marshall et al. 1988), or even as the most frequent pathogen in secondary peritonitis (Sawyer et al. 1992). The microbiology of intra-abdominal infections is different: Candida may be more often isolated from patients in surgical intensive care unit or in specimens from pancreas (Holzheimer et al. 1990). In peripancreatic sepsis Candida is much more frequently isolated than previously recognized and may be associated with a high mortality (42%) (Aloia et al. 1994). Surgical interventions and removal of infected peritoneal fluid have been the cornerstones of therapy together with short-term, low-dose systemic and/or intraperitoneally administered amphotericin B and fluconazole (Bayer et al. 1976; Goldie et al. 1996; Eisenberg et al. 1986; Levine et al. 1989; Michel et al. 1994). Fluconazole has reduced the likelihood of developing symptomatic Candida peritonitis in case of recurrent perforations of the gut or anastomotic leakage (Eggimann et al. 1999). Candida infection of the biliary tree is best treated by a combination of surgical therapy with restoration of the drainage and amphotericin B or fluconazole (Adamson et al. 1989). Recent guidelines emphasize that in catheter-associated peritonitis removal of the catheter and amphotericin B or fluconazole treatment is necessary. Candida peritonitis associated with perforation of the gastrointestinal tract or anastomotic leakage is best treated by source control, drainage and amphotericin B or fluconazole. The duration of therapy is in general 2-3 weeks, depending on the response of the patient. Antifungal prophylaxis may be beneficial in patients with recurrent gastrointestinal perforations (Rex et al. 2000).

Candida Endocarditis, Pericarditis, and Suppurative Phlebitis

Candida endocarditis, pericarditis and suppurative phlebitis are associated with a high mortality (Walsh et al. 1980). Vascular lines, non-cardiac surgery, immunosuppression and injection drug abuse are recognized as increasing risk factors for fungal endocarditis (Ellis et al. 1995). 270 cases of fungal endocarditis were reported during 30 years (1965-1995) in the literature with Candida albicans (24%), non-albicans species (24%), Aspergillus species (24%), and Histoplasma species (6%) as leading pathogens (Ellis et al. 1995). Mycotic aneurysms are rare and were detected in 12 cases of 22,792 autopsies (Parkhurst and Decker 1955).

Table 5. Studies on local, disseminated candidiasis or candidemia in surgical patients.

Author	Year	Study (Type)	Infection	Patients (n)	Mortality (%)
Dennis	1968	R	Candidemia	5	60
Bernhardt	1972	R+A	Disseminated	14	-
Rodrigues	1974	R	Candidemia	30	56.6
Ackerman	1975	R	Intra-abdominal	23	35
Bayer	1976	R	Peritonitis	31	16
Solomkin	1980	R	Peritonitis	56	71
Develoux	1982	R	Disseminated candidiasis	23	65
Solomkin	1982	R	Different	47	43-83
Solomkin	1982	R	Candidemia	63	Untreated 83 Ampho B 33
Burchard	1983	R	Candidemia	65	
Marsh	1983	R	Different	55	38
Dyess	1985	R	Candidemia	83	52 (synchronous bacteremia)
Slotman	1987	RCT	Candidemia	57	60
Verghese	1988	R	Candidemia	14	78
Alden	1989	R	Intra-abdominal	13	23
Calandra	1989	R	Intra-abdominal	49	31
Kujath	1989	P	Different	26	35
Kujath	1990	R	Peritonitis	12	67
Kujath	1990	P	Peritonitis	10	50
Rosemurgy	1990	R	Candidosis	33	18
Nolla-Salas	1992	P	Candidemia	6	0
Eubanks	1993	R	Candidemia	46	57
Kujath	1993	RCT	Different	40	Fluconazole 30 Control 25
Nassoura	1993	R+P	Candiduria Disseminated candidiasis	47	Control 53 Fluconazole 5
Aloia	1994	R	Pancreatic	17	42
Pittet	1994	P	Different	29	Infected 55 Colonized 11
Savino	1994	RCT	Different	292	14
Slotman	1994	R	Candidemia	36	47
Cornwell	1995	R	Different	129	36.3 diss. Infection
D'Amelio	1995	P	Different	32	15.6 colonized
Safran	1997	R	Different	72	44
Hoerauf	1998	R	Pancreatic	13	54
Borzotta	1999	R	Different	20	10.8
Eggimann	1999	RCT	Intra-abdominal	49	Fluconazole 30 Placebo 50
Geldner	2000	R	Intra-abdominal Pneumonia	8	12.5
Gotzinger	2000	R	Pancreatic	31	84
Rocco	2000	R	Different	137	Fluconazole 40 Without fluconazole 20
Kappe	2001	R	Different	69	20
Pelz	2001	RCT	Different	260	12

R = retrospective A = autopsy P = prospective RCT = randomized

Fungal intravascular graft infections are uncommon. In a 20-year period from 1966 to 1986 14 documented infections were reported which were mostly caused by Candida and Aspergillus species (Doscher et al. 1987). Infected valves, infected peripheral veins and infected pericardial tissue have to be replaced. Suppurative infection of the central veins may be treated with amphotericin B (Muehrcke et al. 1995;

Schrank and Dooley 1995; Strinden et al. 1985; Jarrett et al. 1978). Suppurative peripheral thrombophlebitis is best treated by removal of the infected vein and either amphotericin B or fluconazole for two weeks (Walsh et al. 1986; Rex et al. 2000). Total duration of therapy may be better in some instances longer than 6 weeks after surgery. Candida endocarditis is likely to relapse and a follow-up of more than one year is recommended (Johnston et al. 1991). Life-long therapy with fluconazole is required in cases the valve cannot be replaced (Baddour 1995). In Candida pericarditis the surgical debridement is the cornerstone of therapy together with prolonged therapy with amphotericin B or fluconazole (Rabinovici et al. 1997). Especially when immunocompromised solid organ transplant recipients are exposed to gastrointestinal endoscopic procedures there may be at a greater risk for the development of subsequent candida septicemia (Sailors et al. 1996).

Candida Meningitis

Candida meningitis is an infection, which often follows candidemia in newborns. However, it may also be associated with neurosurgical operations (Smego et al. 1984; Nguyen and Yu 1995). Amphotericin B (0,7-1,0 mg/kd/d) plus flucytosine 25 mg/kg qid has been recommended as initial therapy (Rex et al. 2000; Smego et al. 1984; Nguyen and Yu 1995; Rex et al. 2000).

Candida Pneumonia

Candida pneumonia, primary or secondary, has been associated with high mortality in patients with malignant tumors. Secondary Candida pneumonia may be observed in hematogenously disseminated candidiasis (Haron et al. 1993; Panos et al. 1988; Masur et al. 1977). Colonization of the upper airways with Candida is common which renders diagnostic results based solely on microbiological data insufficient (El-Ebiary et al. 1997). Primary Candida pneumonia may be best treated by amphotericin, Candida pneumonia due to hematogenously disseminated Candidiasis may be treated as disseminated disease (Rex et al. 2000).

Candida Osteomyelitis, Mediastinitis, and Arthritis

Hematogenous spread of Candida may be responsible for Candida osteomyelitis, which may also be found secondary to postoperative wounds, as a late complication of fungemia, or sometimes as rib osteomyelitis in children and young adults (Gathe et al. 1987; Ferra et al. 1994; Bishara et al. 2000). Osteomyelitis was also discovered as complication in liver transplant patients. Medical treatment with Amphotericin B and flucytosine was successful (Jonnalagadda et al. 1996). The mortality rate has been reported to be 15%. (Miller and Mejicano 2001). Candida mediastinitis, which may be caused by esophageal perforation and trauma, is a rare disease; 39 cases of Candida mediastinitis after cardiac operation have been described until 1990. Aggressive surgical management with mediastinal drainage, sternal debridement, early wound closure with vascularized flaps is best combined with amphotericin B or fluconazole treatment. The mortality rate was 55% in the postoperative setting (Glower et al. 1990; Clancy et al. 1997; Lew et al. 1995). According to recent recommendations cases with nonpurulent sternomediastinitis and no soft tissue or bone necrosis (type I) may be treated with reopening, drainage, sternal stabilization, and primary closure. Virulent infections with tissue necrosis (type II) may be best handled with reopening, several days of open management, and debridement then secondary closure with viable tissue (usually muscle flaps). Chronic smoldering infections (type III) are usually best managed with debridement and muscle-flap coverage (Robicsek et al. 2000). Osteomyelitis is best treated by surgical debridement initially. Amphotericin B (0.5-1,0 mg/kg/d) for 6-10 weeks or fluconazole (6 mg/kg/d) for 6-12 months were both successfully used; fluconazole may be used as follow-up therapy after treatment with amphotericin B (Almekinders and Greene 1991; Ferra et al. 1994; Hennequin et al. 1996; Sugar et al. 1990; Tang 1993; Rex et al. 2000). Candida arthritis may require resection arthroplasty with removal of the prosthetic joint. Drainage is often a cornerstone of successful therapy (Weers-Pothoff et al. 1997; Tunkel et al. 1993).

Oropharyngeal and Esophageal Candidiasis

Candida esophagitis has been described as an occasional complication in patients with compromised immune system such as malignancy of the hematopoetic system or diabetes. (Mathieson and Dutta 1983). Presence of oropharyngeal candidiasis and symptoms of esophagitis were predicitive of esophageal candidiasis (Wilcox et al. 1995). Oral thrush may be a reliable marker for esophageal candidiasis in cancer patients reserving routine endoscopy for patients with persistent thrush and symptoms despite antifungal therapy (Samonis et al. 1998). There was a 2.3% incidence of candida esophagitis in patients undergoing renal transplantation in diabetic patients and 0.7% in nondiabetic patients. Perforation of the esophagus was treated surgically followed by discontinuation of immunosuppressive drugs and aggressive treatment with oral and parenterally absorbed fungal agents (Jones et al. 1982). Despite nystatin prophylaxis, Candida esophagitis was diagnosed in 2.2% of renal transplant patients (Frick et al. 1988). With the increased use of antibiotics and immunosuppressive agents oropharyngeal candidiasis is becoming more common. This infection was associated with chemotherapy and organ transplantation and with HIV infection (Epstein and Polsky 1998).. In patients with either AIDS or esophageal cancer C. albicans, alone or in mixed culture, remains the most often isolated species when Candida esophagitis is present (Bhatia et al. 1989; Sangeorzan et al. 1994). Recently C. glabrata and C. krusei have been detected as causative organisms (Phillips et al. 1996). In case of oropharyngeal candidiasis treatment may be started with clotrimazole or nystatin. Oral fluconazole (100 mg/d for 7-14 days) or itraconazole solution (200 mg/d 7-14 days) are equally effective. Amphotericin B may be

used in refractory disease. In esophageal candidiasis systemic treatment with either fluconazole (100 mg/d orally for 14-21 days) or itraconazole solution (200 mg/d orally) are recommended. Ketoconazole or itraconazole capsules are less effective. Intravenous amphotericin B (0.3-0.7 mg/kg/d) may be used in refractory disease. (Rex et al. 2000; Lake et al. 1996). In a randomized, double-blind trial in the treatment of esophageal candidiasis in immunocompromised patients voriconazole (200 mg, b.i.d.) demonstrated at least equal effectiveness compared to fluconazole (Ally et al. 2001).

Candida Infection in Burns

In 15 studies on fungal infections in burned patients from 1972 to 2001 the mortality rate decreased from 80-100% to approximately 10% in recent studies (Table 6). 30% - 63% of patients with burns were reported to have positive cultures for Candida. Candidemia occurred in 3%-5% burned patients with a crude mortality rate ranging from 50%-70% (MacMillian et al. 1972; Spebar and Pruitt 1981). Before the introduction of prophylaxis with nystatin, invasive Candida sepsis was associated with a high mortality (up to 80%). It has been suggested that judicious use of broad-spectrum antibiotics and expeditious closure of the burn wound may reduce the incidence of burn wound infection (Spebar and Pruitt 1981; Prasad et al. 1987; Jarrett et al. 1978). A steady increase in non-candidal infection from 40.8 to 67% has been reported with a stable mortality of approx. 80% in the Candida spp. and a significant drop in mortality to 25% for non-candidal species in 1978. Local surgical control of the infected portion of burn wounds was considered to be an effective way of improving survival in noncandidal burn wound infections; surgical excision of burn wound did not alter the poor prognosis of patients with Candida invasion (Spebar et al. 1982). With early recognition of burn wound invasion by routine biopsies, wound swabs, and early amphotericin therapy, the mortality has been reduced to 14% and Candida burn wound infections were almost completed wiped out (Desai et al. 1987; Desai and Herndon 1988, Heggers et al. 1989, Desai et al. 1992). Aggressive early burn excision and grafting, avoidance of invasive monitoring and central hyperalimentation lines together with enteral nystatin and a judicious use of antibiotics lead to the assumption that Candida no longer was a problem for the burned patients (Grube et al. 1988). Yet, wound cleaning and staged early excision in patients with large burns may induce bacteremia or fungemia (Vindenes and Bjerknes 1993). Despite wide surgical excision 10% of burned patients died of disseminated fungal disease (Becker et al. 1991). Not all prophylactic regimens (Polymyxin E, Tobramycin, Amphotericin B) were successful in decreasing bacterial colonization and infectious episodes in burned patients (Barret et al. 2001).

Candida Infections in Transplant Patients

The prevalence of invasive fungal infections in solid organ transplant patients ranges from 5% to 50% in kidney and liver transplants, respectively. Candida species and Aspergillus spp. account for approx. 80% of fungal episodes in both solid organ transplants and bone marrow transplants (Dictar et al. 2000). Orthotopic liver transplantation is prone to severe fungal infection, with a reported incidence of 16% to 45%. Candida species accounted for approximately 80% and Aspergillus for 20% (Kusne 1988; Castaldo et al. 1991) (Table 7). Liver transplant patients are often colonized with Candida (Ascher et al. 1988). However, the role of fungal infections has been in dispute when compared to technical problems, rejection and bacterial sepsis. (Schröter et al. 1977). Opportunistic fungal infections resulted in a 100% mortality in other studies (Kirby et al. 1987). During a 50-month period, Castaldo et al. recorded 91 episodes of fungal infection, mostly Candida (83.5%) in 72 liver transplant recipients (23%). Clinical patterns of infection included disseminated infection (19), peritonitis (17), pneumonitis (15), multiple sites of colonization (13), fungemia (11), and other sites (16). Fungal infections were successfully treated with amphotericin B in 63 cases (74.1%) and were associated with increased mortality (50% versus 16.5%) Retransplantation, risk score, roux limb biliary reconstruction, steroid dose, bacterial infections and antibiotic therapy, and vascular complications were identified as risk factors for the development of fungal infection (Castaldo et al. 1991). Patients who had two and more risk factors (retransplantation, creatinine of > 2.0 mg/dL, choledochojejunostomy, intraoperative use of (40 units of blood products, fungal colonization within the first three days after transplantation) were at increased risk for invasive fungal infections (Karchmer et al. 1994; Hadley et al. 1995; Collins et al. 1994). In 26 patients with candidemia, the overall mortality rate was 81%, 71% of which were related to candidemia. Hyperglycemia that required insulin and exposure to more than three antibiotics were the factors associated with the development of candidemia in liver transplants (Nieto-Rodriguez et al. 1996). Four independent variables predicted fungal infection: low pre-transplantation hemoglobin, high pre-transplantation bilirubin, return to surgery, and prolonged therapy with ciprofloxacin (Wade et al. 1995). Amphotericin B (10-20 mg/d), liposomal amphotericin B (AmBisome 1 mg/kg/d), and fluconazole (400 mg/d) may reduce the fungal colonization and the risk for serious fungal infection (Kung et al. 1995; Tollemar et al. 1995). Liposomal amphotericin B plus oral itraconazole versus i.v. fluconazole + oral itraconazole prophylaxis did not change single organ or systemic infection rate in liver transplant patients (Biancofiore et al. 2001), nor did selective bowel decontamination with gentamicin, polymyxin E, nystatin (Arnow et al. 1996; Colonna et al. 1988). In heart transplants, an infection rate of up to 57.6%, with an infection-related mortality of 5.2%, has been reported (Linder 1988). Especially a disruption of the aorta at the anastomotic site caused by Candida may be associated with a 100% mortality rate (Dowling et al. 1990). Acalculous cholecystitis mostly caused by Candida has been reported in 15 cases with a 40% mortality as complication of heart transplantation.

Table 6. Fungal infections in burn injury.

Author	Year	Study	Infection	Patients	Mortality
Law	1972	R	Disseminated	15	100
MacMillan	1972	R	Disseminated	22	63.6
Gauto	1977	R	Disseminated	15	7
Jarrett	1978	P	Candida infection	20	-
Spebar	1981	R	Candida sepsis	52	76.9
Spebar	1982	R	Candida infection - versus non-candida infection	Candida infection:	1973-1977 83.3 1978 87.5 non-candida infection: 1973-1977 87.4 1978 25
Desai	1987	R	Candida sepsis	21	14.3
Prasad	1987	R	Candida sepsis	173	15.7
Desai	1988	R	Candida sepsis	472 with nystatin prophylaxis	No burn wound infection
Grube	1988	R	Candida sepsis	3	33%
Heggers	1989	P	Candida sepsis	90	No candida sepsis
Becker	1991	R	Disseminated	209	10%
Desai	1992	R	Candida infection	34/496	38% candida sepsis but no candida related death
Vindenes	1993	P	Fungemia	28	21.4
Barret	2001	RCT	Candida infection	23	SDD not effective

R = retrospective P = prospective RCT = randomized

Table 7. Incidence of fungal infection, organisms, and mortality in solid-organ transplant patients.

	Kidney	Pancreas/kidney-pancreas	Liver	Heart	Lung/lung-heart
Invasive fungal infections	4.8-6	19-35	7.5-42	4.2-20	14-35.7
Type of organism					
C. spp.	18-63	100	18-100	0.03-26	42-100
Aspergillus spp.	2-26	NR	1.5-23	70-74	20-50
Cryptococcosis	0.5-47	NR	1-3	0.03	3.5-20
Mortality					
C. spp.	23-71	Unknown	10.5-59	NR	27
Aspergillus spp.	20-100	-	50-100	32-64	21-100

(According to Hadley and Karchmer 1995)

Surgical therapy consisted of drainage or cholecystectomy (Mandak et al. 1995). Mycotic aortic aneurysm after heart transplantation was reported in 10 cases until 1996. Surgical treatment consisted of pericardium patch or allograft. 1 patient died (Knosolla et al. 1996). Constrictive pericarditis due Candida was associated with a high mortality despite surgical drainage and pericardiectomy (Canver et al. 1998). In lung transplantation, anastomotic infection is an infrequent complication, but may be caused predominantly by fungal pathogens, despite fluconazole prophylaxis (Hadjiliadis et al. 2000; Horvath et al. 1993). After pancreatic transplantation an infection rate of 33% has been reported with Staphylococcus epidermidis and Candida as the leading organisms. Deep and combined wound infection led to allograft loss

despite subsequent salvage procedures. Deep wound infection should be an indication for removal of the allograft. Antifungal prophylaxis, stringent donor criteria, and delayed primary wound closure should lower the incidence of wound infection (Everett et al. 1994; Hesse et al. 1986). Candida infection may also involve the pancreatic duct (Bonatti et al. 1995). Fluconazole (400 mg/d) prophylaxis in pancreatic transplant patients reduced the rate of intra-abdominal fungal infections from 10% to 6%. Patients without infection had a significant improvement in 1-year graft survival and overall survival (Benedetti et al. 1996). There has been reported an 8.8% incidence of pulmonary infection in renal transplant patients (Russo and Marks 1976). Pathogenic specimens were obtained by bronchial washing, brushing, or transbronchoscopic biopsy (Chatterjee et al. 1978). In a more recent study, 19/224 renal transplant patients suffered from pneumonia. Fungal infections were caused by Candida and Aspergillus. The majority of patients who died had Candida pneumonia (Hesse et al. 1986).

Invasive Aspergillosis

Aspergillus is a monomorphic mycelial fungus, e.g., A. fumigatus, A. flavus, A. niger, A. nidulans, A. terreus. Aspergillus infection has been classified according to Bodey et al. (1989) as disease in the normal host, infection associated with tissue damage or foreign body, and infection in the immunocompromised host (Table 8). Even in the normal host aspergillus infection may involve the central nervous system, the eyes, the cardiovascular and respiratory system, the bones, or structures in the thorax, or it may be disseminated. Invasive aspergillosis may follow surgical procedures or trauma (Table 9) (Bodey et al. 1989).

Incidence

The incidence of invasive aspergillosis in heart and lung transplantations may range from 19-26%, in liver transplantation 1.5-10%, in heart and renal transplantation 0.5-10%, severe combined immunodeficiency 3.5% and burns 1-7% (Denning 1994; Harousseau et al. 2000; Menichetti et al. 1999; Morgenstern et al. 1999). In a recent series of fungemia during neutropenia, 7.6% of all episodes were due to Aspergillus (Duthie and Denning 1995). Liver transplant patients are at risk to suffer from lethal Aspergillus infection (Wajsczuk et al. 1985). A 14-fold increase in invasive aspergillosis has been observed during recent years (Groll et al. 1996) paralleled by an increase in the intensity of immunosuppressive and myelosuppressive anticancer treatment (Bow 2001).

Pathogenesis

Most species of Aspergillus do not grow at 37°C, which may distinguish pathogenic species from non-pathogenic species (Pitt 1994). Growth rate is likely to be a key determinant of the progression of the disease and pathogenicity. The most rapidly growing species is A. fumigatus. Hydrocortisone has been shown to enhance the growth rate of A. fumigatus and A. flavus by 30-40% (Ng et al. 1994). The small pore size of A. fumigatus, which enables it to penetrate into the lung tissue, and the protection of spores against extraordinary atmospheric conditions, seems to support the pathogenicity (Penalver et al. 1996). The ability to adhere to tissue by binding of laminin and fibrinogen (Tronchin et al. 1993; Bouchara 1993) and various other factors, e.g., proteases, ribotoxin, phospholipases, hemolysin, gliotoxin, aflatoxin, phthioic acid, and other toxins, may enhance the virulence of this pathogen (Markaryan et al. 1994; Reichard et al. 1997; Arruda et al. 1992; Latge et al. 1991; Smith et al. 1993; Birch et al. 1996; Ebina et al. 1994; Müllbacher et al. 1985; Sutton et al. 1996; Waring 1990; Denning 1987; Birch et al. 1997). Macrophages, monocytes, neutrophils ingest and kill Aspergillus or kill hyphae extracellularly (Schaffner et al. 1982; Diamond et al. 1978; Roilides et al. 1994; Kozel et al. 1989). The histological reaction to the invasion of Aspergillus may be granulomatous in case of a few organisms up to extensive necrosis in case of extensive hyphae networks. (Denning 1998). The killing of Aspergillus is impaired by corticosteroids (Roilides et al. 1993). In the host defense against Aspergillus further factors may be involved, e.g., GM-CSF, IFN-gamma, T-cells, IL-4, (Roilides et al. 1996; Rex et al. 1991) leading to a

Table 8. Classification of Aspergillus infection.

1. Disease in the normal host
   - a. Allergic
     - i. Asthma
     - ii. Saprophytic bronchopulmonary aspergillosis
     - iii. Extrinsic allergic alveolitis
     - iv. Allergic bronchopulmonary aspergillosis
   - b. Superficial
     - v. Cutaneous
     - vi. Otomycosis
     - vii. Sinusitis
     - viii. Tracheobronchitis
   - c. Invasive
     - ix. Single organ
     - x. Disseminated
2. Infection associated with tissue damage or foreign body
   - d. Keratitis and endophthalmitis
   - e. Burn wound infection
   - f. Osteomyelitis
   - g. Prosthetic valve endocarditis
   - h. Vascular graft infections
   - i. Aspergilloma
   - j. Empyema and pleural aspergillosis
   - k. Peritonitis
3. Infection in the immunocompromised host
   - l. Primary cutaneous aspergillosis
   - m. Sino-orbital infection
   - n. Pulmonary aspergillosis
     - xi. Invasive tracheobronchitis
     - xii. Chronic necrotizing pulmonary aspergillosis
     - xiii. Acute invasive pulmonary aspergillosis
   - o. Central nervous system aspergillosis
   - p. Disseminated aspergillosis

(according to Bodey GP 1989)

Table 9. Invasive aspergillosis following surgical procedures or trauma.

Aspergillus infection	Surgical procedure or trauma
Endocarditis	Valvuloplastomy, prosthetic valve
Pseudo-aneurysm	Aortic bypass, coronary artery bypass
Infected prosthesis	Mammary implants
Wound infection	Abdominal surgery
Osteomyelitis	Trauma, surgery
Lumbar disk infection	Laminectomy
Chronic meningitis	Ytrium 90 pituitary implants
Basilary artery aneurysm	Trans-sphenoidal hypophysectomy
Cerebral granuloma	Trauma, craniotomy
Pneumonia	Carotid endarterectomy
Empyema	Thoractomy tube, pneumonectomy
Keratitis, endophthalmitis	Trauma
Disseminated	Prosthetic valve

(According to Bodey GP 1989)

pronounced TH 2 cell response (de Repentigny et al. 1993). Aspergillus has been found in pepper and spices, and in showerheads and hot water faucets (Beyer et al. 1994), or has been distributed during construction work in the hospital (Walsh and Dixon 1989; Pittet et al. 1996).

Prophylaxis

No study has yet demonstrated that prophylaxis is completely successful (Denning 1998). Neither administration of aerosolized amphotericin B, intravenous amphotericin B, the use of itraconazole has achieved full protection (Conneally et al. 1990; Rousey et al. 1991). Humoral immunity is not a major player in the defense against Aspergillus; therefore vaccine may not be available soon (Denning 1998).

Clinical Features

Port of entrance could be the respiratory tract, damaged skin, operative wounds, the cornea, the ear, or the gastrointestinal tract. In transplant patients invasive aspergillosis may occur within 4 weeks of transplantation with involvement of the lung, brain, wound or hematogenously dissemination. As reported for Candida, it is difficult to distinguish colonization of the airways from true Aspergillus infection. Invasive aspergillosis often occurs after treatment for rejection after heart and kidney transplantation. Signs of infection in the lung may appear rather late. In burn patients invasive aspergillosis has been observed within 2 months of severe burns, mostly as superficial infection with a tendency to disseminated disease. There is a progress over 5-10 days to death, which is often unresponsive to medical treatment (Denning 1998; Mayer et al. 1992).

Laboratory Diagnosis of Invasive Aspergillosis

Invasive aspergillosis occurs in many different patients with unspecific and varying clinical symptoms. Lack of experience to diagnose this infection and missing specific and sensitive tests have been accused for a delay in diagnosis (Denning 1998). It may be helpful to combine microscopy and culture obtained by bronchoalveolar lavage, bronchial lavage or endotracheal aspiration to improve the diagnostic results by 15% - 20% (Levy et al. 1992; Fischler et al. 1997). Cultivation of Aspergillus may be more successful in bronchoalveolar lavage (BAL), the Aspergillus antigen detection in bronchial lavage (Seyfarth et al. 2001). As microscopy does not allow unequivocal diagnosis of invasive aspergillus infection, immunohistochemistry may be added. Diagnosis of invasive aspergillosis is based on histological proof of hyphae and a positive culture for Aspergillus. Culture of Aspergillus from an infected sterile site is considered to be a definite proof of disease (Jenssen et al. 1997). Serologic methods, e.g., ELISA, G-test, which detects 1,3-β-D-glucan, for detecting invasive aspergillosis have shown promising results but are not yet specific and sensitive enough. Testing for antibodies has been used in transplant patients as an adjunct to identify patients at risk (Obayashi et al. 1995; Tomee et al. 1996). Several studies showed promising results, but did not recommend the molecular diagnostic approach as routine in clinical search for aspergillosis (Einsele et al. 1997; Tang et al. 1993; Bretagne et al. 1995). More recent studies demonstrated a higher sensitivity and specificity of up to 80-100% to detect Aspergillus by PCR (Jones et al. 1998; Kawamura et al. 1999; Kami et al. 2001; Raad et al. 2002). Several problems remain to be solved. High levels of Aspergillus antigen were detected in a subphrenic abscess, but circulating antigen and aspergillus DNA were undetectable in the serum (Verweij et al. 2000). The PCR assay did not differentiate between infection and colonization (Hayette et al. 2001; Raad et al. 2002). Recombinant mitogillin may be used to improve serodiagnosis of invasive Aspergillus infection (Weig et al. 2001).

Acute Invasive Pulmonary Aspergillosis

In 25-33% of patients there are no characteristic symptoms. There may be cough, fever, chest pain,

pleural rub, hemoptysis, and dyspnea. The prognosis of focal disease is better than that of diffuse or bilateral disease (Weiland et al. 1983; Denning 1998). Vocal cord paralysis has been reported to be a primary manifestation of invasive pulmonary aspergillosis in nonimmunocompromised patients (Nakahira et al. 1999). Laboratory parameters are rather unspecific. On plain chest radiographs cavitation, wedge-shaped lesions, nodular shadows are typical presentations of invasive disease. Plain radiographs are often false negative whereas CT scans can reveal the invasive disease (halo and air crescent signs) (Singh N et al. 1993; End et al. 1995; Guillemain et al. 1995; Yelandi et al. 1995; Westney et al. 1996; Blum et al. 1994). The halo sign in computed tomography of the lung is highly suggestive of early angioinvasive pulmonary aspergillosis (Collins 2001) and early thoracic computed scan allowing earlier diagnosis of invasive pulmonary aspergillosis could improve the prognosis dramatically when combined antifungal and surgical treatment are available (Caillot et al. 1997). Demonstration of Aspergillus from the respiratory tract after lung transplantation does not necessarily reflect invasive pulmonary aspergillosis (Diederich et al. 1998). Focal invasive pulmonary aspergillosis, persisting lung shadows before bone marrow transplantation or before more aggressive chemotherapy, significant hemoptysis, and lesions in the neighborhood of great vessels or major airways may be an indication for surgical treatment (McWhinney et al. 1993; Caillot et al. 1997; Denning and Stevens 1990; Hoover et al. 1997; Robinson et al. 1995). In focal disease the treatment of choice may be resection; this option may not be available in patients with bilateral or extensive disease (Denning et al. 1998). Resection of focal lesions has not been recommended in view of high mortality reported from the surgery of aspergillomas in the past. Surgery has been reserved for patients with invasive pulmonary aspergillosis and hemoptysis (Wong et al. 1992). Recent studies favor early surgical intervention for pulmonary aspergillosis. A clearance of infection in up to 70% of cases has been reported (Young et al. 1992; Wex et al. 1993; Moreau et al. 1993; Robinson et al. 1995; Bernard et al. 1997; Baron et al. 1998; Salerno et al. 1998; Reichenberger et al. 1998; Pidhorecky et al. 2000; Yeghen et al. 2000; Caillot et al. 2001). For debilitated and immunocompromised patients with focal lesion thoracoscopic resection (wedge resection and lobectomy) has been successfully applied (Gossot et al. 2002). In case the native lung is affected by aspergillosis pneumonectomy may be an escape in lung transplant patients with progressive refractory angioinvasive aspergillosis (Sandur et al. 1999). In spite of antifungal treatment with amphotericin B and mechanical ventilation in the intensive care unit, all patients with chronic obstructive pulmonary disease complicated with invasive pulmonary disease died (Bulpa et al. 2001). Invasive pulmonary aspergillosis may be further complicated by pneumomediastinum and pneumopericardium (Odev el a. 2002), mycotic pseudoaneurysm of the aortic arch (Koral and Hall 2000; Wells et al. 1994), and pericarditis with tamponade (Le Moing et al. 1998). Voriconazole has been successfully tested in several animal models of invasive aspergillosis (George et al. 1996; Chandrasekar et al. 2000). In case of therapeutic failure of amphotericin B in surgical patients with invasive aspergillosis voriconazole has been introduced (Kujath et al. 2000). A. terreus has been considered to be refractory to amphotericin B therapy but no resistance to voriconazole was observed (Sutton et al. 1999). Voriconazole retained good activity against itraconazole- or amphotericin B-resistant strains of A. fumigatus (Abraham et al. 1999). Good responses with voriconazole were observed in 60% of invasive pulmonary or tracheobronchial aspergillus infections (Denning et al. 2002). Recently it has been suggested to rethink control measures and prevention against invasive aspergillosis in high-risk patients (Hajjeh and Warnock 2001).

Chronic Invasive Pulmonary Aspergillosis

Chronic invasive pulmonary aspergillosis is less common than acute disease. AIDS, chronic granulomatous disease, diabetes mellitus, alcoholism, and corticosteroid therapy may be the underlying disease. Often there is no immunocompromising factor identified (Denning and Stevens 1990; Palmer et al. 1991; Karam and Griffin 1986; Karim et al. 1997). Symptoms in relatively immunocompetent patients are rather prominent: cough, hemoptysis, fever, malaise and weigh loss. There may be extension of the disease into the chest wall, brachial plexus, or vertebral column. It may be difficult to distinguish an aspergilloma from chronic invasive pulmonary aspergillosis on a chest film. Definitive diagnosis is ensured by the isolation of Aspergillus hyphae in lung tissue and a culture-positive respiratory specimen (Yousem et al. 1997).

Aspergillus Tracheobronchitis

It occurs mostly in patients with AIDS and in lung transplant patients. However, 25% of infected patients are not immunosuppressed. The infection may range from mild tracheobronchitis until ulcerative tracheobronchitis. In lung transplant patients it may be difficult to distinguish colonization from true infection (Kramer et al. 1991; Flume et al. 1994; Biggs et al. 1994). Although 80% of patients are symptomatic, symptoms may be not characteristic: cough, fever, dyspnea, chest pain, hemoptysis, wheeze, and stridor (Tait et al. 1993). Chest radiograph may not be helpful in diagnosis of the disease; in the CT scan there may be peribronchial consolidation and centrilobular nodules (Logan et al. 1994). Bronchoscopy with bronchial biopsy, microscopy and culture is the tool of choice to make the diagnosis. Therapy with an azole may be superior to amphotericin B (Kramer et al. 1991). In laryngeal infection, surgical debridement or excision together with antifungal treatment may be crucial for successful outcome. A mycelial mass in the trachea may be best removed by bronchoscopic procedure (Stevens et al. 2000).

Invasive Aspergillus Sinusitis

Invasive aspergillus sinusitis is uncommon in solid

organ transplant patients. Chronic invasive aspergillus sinusitis has been observed in healthy or only mildly immunocompromised patients (Iwen et al. 1997; Washburn et al. 1988). In acute invasive aspergillus rhinosinusitis early symptoms, e.g., fever, cough, epistaxis, headache, nasal discharge, sinus pain, sore throat, may be nonspecific. There may be local extension to the palate, orbit or brain as well as concurrent pulmonary aspergillosis. Plain films are not sensitive enough; CT scans demonstrate fluid opacification of the sinuses, bony destruction and spread into adjacent tissues (Talbot et al. 1991; Zinreich et al. 1988). In case of typical clinical and radiographic features together with positive culture or the demonstration of characteristic hyphae in the tissue confirms the diagnosis. Chronic invasive aspergillus sinusitis may occur in patients suffering diabetes mellitus, alcohol abuse, AIDS but many patients may not have any sign of immunosuppression. Symptoms are not characteristic for a long period of time. In case of progressive disease there may be visual symptoms, e.g., diplopia, unilateral blindness, pain in the eye, and proptosis. Surgical debridement and prolonged antifungal therapy is required; however, surgery may not offer an advantage as severe complications may be involved (Denning and Stevens 1990; Kennedy et al. 1997). Surgical debridement and drainage may be achieved by endoscopic surgery (Stammberger 1985). Aspergillus sphenoid sinusitis may be accompanied by major complications, e.g., major visual disturbance, brain abscess, stroke, invasion of carotid artery (Lin and Hung 1993). Due to a lack of response to oral itraconazole voriconazole has been successfully used for treatment of skull base osteitis following aspergillus fumigatus sinusitis (Swift and Denning 1998). Treatment should combine medical with surgical approaches in sinonasal aspergillus infections. Fungus ball or mycetoma is best treated by surgery; the role of systemic antifungal therapy is unclear (Stevens et al. 2000).

Disseminated Aspergillosis

Disseminated aspergillosis has been demonstrated at autopsy in many patients who died of aspergillosis with and without clinical diagnosis of disseminated disease. Diagnosis is often delayed due to nonspecific symptoms (Bodey et al. 1992; Kusne et al. 1988; Gurwith et al. 1971). Early recognition of aspergillus endophthalmitis with bedside fundoscopic examination in liver transplant recipients susceptible to Aspergillus infection may help to identify disseminated Aspergillus infection (Hunt and Glasgow 1996). Voriconazole demonstrated good efficacy in animal models of disseminated aspergillosis (Kirkpatrick et al. 2000).

Cutaneous Aspergillosis

It may be a manifestation of disseminated aspergillosis; however, mostly it occurs in neutropenic patients with intravenous catheters (Allo et al. 1987; Larkin et al. 1996). The clinical appearance is similar to that of pyoderma gangrenosum with raised erythema and ulceration. On histological examination there may be invasion of blood vessels and infarction of the skin (Denning et al. 1998). Aspergillus may invade burn wounds, surgical wound and other wounds (Carlson et al. 1996; Levenson et al. 1991; Bruck et al. 1971; Stone et al. 1979; Becker et al. 1991; Pla et al. 1992). Surgical excision may be necessary when local infection cannot be controlled in neutropenic patients or in burned patients (Bodey 1994; Pruitt et al. 1998).

Cerebral Aspergillosis

Cerebral aspergillosis accounts for 10-20% of all cases of invasive aspergillosis. Depending on the status of the immune system the clinical symptoms may include alteration in mental status, seizures, headache, fever, and rarely meningism. On CT scan there are hypodense, well-demarcated lesions that are usually deep seated and not easily available for surgery. Surrounding edema and midline shift may become visible with contrast enhancement (Shapiro and Tabaddor 1975; Britt et al. 1981; Boon et al. 1990; Torre-Cisneros et al. 1993; Martinez and Ahdab-Barmada 1993; Darras-Joly et al. 1996; Selby et al. 1997; Yuh et al. 1994). It may present as single or multiple cerebral abscesses, meningitis, epidural abscess, or a subarachnoid hemorrhage (Walsh et al. 1985). In liver transplant patients Aspergillus accounts for most infections of the brain, and often the clinical situation does not allow biopsy or aspiration of a cerebral lesion (Boon et al. 1990; Torre-Cisneros et al. 1993). Surgical removal of necrotic tissue and stereotactic procedure for abscess drainage has been successfully applied (Henze et al. 1982; Goodman and Coffey 1989; Casey et al. 1994). Invasive CNS aspergillosis has been cured with amphotericin B, itraconazole and radical surgery (Coleman et al. 1995). A decline of the galactomannan antigen titer in the cerebrospinal fluid during treatment with intravenous and intraventricular amphotericin B and voriconazole corresponded with the clinical response to the treatment (Verweij et al. 1999; Machetti et al. 2000). In epidural abscess surgical drainage along with systemic antifungal therapy is indicated (Stevens et al. 2000).

Unusual Forms of Invasive Aspergillosis

The surgeon may see in patients who are not immunosuppressed unusual forms of invasive aspergillosis. Sites of infection may include bronchial stump, endocarditis, vascular graft, pericardium, gastrointestinal tract, peritoneum, liver, thyroid, kidney and bones (Denning et al. 1990; Bodey et al. 1989). Aspergillus bone infections may be caused by direct extension, traumatic or surgical inoculation or hematological spread. Surgical debridement should be combined with antifungal treatment, which may include amphotericin B plus itraconazole (Barnwell et al. 1985; Holmes et al. 1988; Stevens and Lee 1997). Prosthetic valve endocarditis may be best treated by early valve replacement together with perioperative amphotericin (Carrizosa et al. 1974; Demaria et al. 2000). Pericarditis is a rare complication of disseminated

disease with a poor prognosis. Pericardiectomy, pericardial drainage and systemic antifungal treatment are recommended (Denning and Stevens 1990; Sergi et al. 1996; Carrel et al. 1991). Hepatosplenic aspergillosis may have a poor outcome despite treatment with amphotericin B. Itraconazole, lipid amphotericin or voriconazole which may attain higher concentrations in the liver may be used instead of amphotericin B (Stevens et al. 2000). Aspergillus peritonitis may be a complication of chronic ambulatory peritoneal dialysis and removal of the catheter is the cornerstone for eradication of the infection (Tanis et al. 1995). Involvement of the esophagus, colon and small bowel is mostly observed in disseminated aspergillosis. Perforation of the gut is likely and associated with a high mortality despite systemic antifungal treatment (Denning and Stevens 1990; Cohen and Heffner 1992).

Medical Treatment

In case of untreated invasive aspergillosis the mortality reaches nearly 100%. In liver transplant patients there may be only 10-14 days from the onset of clinical symptoms and radiographic appearances to death. (Denning 1996) Amphotericin B and itraconazole were until recently the only two antifungal agents available for treating invasive aspergillosis. The overall success rate for amphotericin B was rather low – 34%. Similar results have been published for itraconazole and the lipid-associated forms of amphotericin B (Denning 1998; Denning et al. 1994; Sanchez et al. 1995; Meunier et al. 1991; Mills et al. 1994) (Table 10). In vitro and in vivo resistance of A. fumigatus to itraconazole has been demonstrated; the clinical aspect has yet to be determined (Denning et al. 1997). In a recent study amphotericin B was superior to itraconazole in the treatment of invasive pulmonary aspergillosis in heart transplant recipients (Nanas et al. 1998), but the inhalation of aerosolized amphotericin B may be poorly tolerated and does not prevent invasive pulmonary aspergillosis in neutropenic patients (Erjavez et al. 1997). Despite the evidence that steroid therapy is considered a risk factor for the development of invasive aspergillosis (Palmer et al. 1991; Conesa et al. 1995) steroid pulse therapy has been successfully used for a life-threatening pulmonary insufficiency in a patient following invasive aspergillosis (Okano et al. 1999). Successful treatment of cerebral aspergillosis with voriconazole has been reported (Schwartz et al. 1997; Verweij et al. 1999; Machetti et al. 2000). Voriconazole had fungicidal activity against most Aspergillus spp. and may play an important role in the treatment of fungal infections, for which the mortality rate is high despite treatment with amphotericin B (Espinel-Ingroff et al. 2001).

Cryptococcal Disease

Before 1950, cryptococcal infection has been rarely diagnoses and patients with disseminated cryptococcal disease usually died. The introduction of amphotericin B reduced the mortality rate to approximately 40%. The addition of flucytosine to amphotericin B reduced the duration of treatment from 10 weeks to 4-6 weeks (Bennett et al. 1979). Recently, the incidence of cryptococcal infection increased mainly due to the occurrence of AIDS and the increasing number of solid organ transplant patients with immunosuppressive therapy (Dromer et al. 1996).

Pulmonary and Non-CNS Cryptococcal Infection

Pulmonary cryptococcosis may present with asymptomatic nodules in the lung to acute respiratory distress syndrome (ARDS). There may be cough, fever, sputum production or pleural symptoms. The lung is usually the entrance for the pathogen. A positive serum cryptococcal antigen titer is associated with deep tissue invasive and disseminated disease. There is a predilection for the CNS, but the pathogen may be detected in every part of the body (Kerkering et al. 1981). All patients with pulmonary or extrapulmonary cryptococcal disease should therefore have a lumbar puncture to rule out CNS infection (Saag et al. 2000). Prompt surgical intervention and systemic antifungal therapy, e.g., amphotericin B, is considered to be the treatment of choice in necrotizing fasciitis caused by Cryptococcus neoformans (Marcus et al. 1998). Patients with chronic rejection are more likely to have late infection (>6 months), which may be due to Aspergillus or Cryptococcus (Patterson 1999) and Cryptococcus may cause a lethal pulmonary infection in renal transplant patients (Russo and Marks 1976). Prophylaxis is not available against Cryptococcus infection (Paya et al. 2001). Asymptomatic immunocompetent patients having a positive lung culture for C. neoformans may be observed or treated with fluconazole (200-400 mg/d) for 3-6 months. Immunocompetent patients with mild to moderate symptoms should receive fluconazole (200-400 mg/d) for 6-12 months. The use of flucytosine is limited due to the development of resistance (Dismukes et al. 1987; Dromer et al. 1996; Yamaguchi et al. 1996; Saag et al. 2000). Itraconazole (200-400 mg/d) for 6-12 months may be an alternative therapy. In case fluconazole is not an option, amphotericin B (0.4-0.7 mg/kg/d) for a total dose of 1000 – 2000 mg may be given in severe disease (Saag et al. 2000). Voriconazole was the most active compound against Cryptococcus neoformans isolates from bloodstream infections when compared to fluconazole, itraconazole, ketoconazole, amphotericin B and flucytosine (Hoban et al. 1999).

CNS Cryptococcal Infection

Meningitis or rarely single or multiple focal mass lesions (cryptococcomas) may be found in CNS disease with or without concomitant pneumonia or disseminated disease. Combination therapy of amphotericin B and flucytosine will eradicate the pathogen from the CSF within 2 weeks of treatment in 60-90% of patients. Most immunocompetent patients will be treated successfully within 6 weeks (Dismukes et al. 1987; Bennett et al. 1979). For induction or consolidation therapy amphotericin B (0.7-1.0 mg/kg/d)

Table 10. Therapy with antifungal agents for invasive aspergillosis.

Agent		Initial dose	Comments
Amhotericin B deoxycholate		0.8-1.25 mg/kg/d, iv	First-line, high failure rate >50%, nephrotoxic, cyclosporine interaction
Itraconazole		200 mg t.i.d. for 4d then 200 mg b.i.d., p.o.	Patient must eat; intestinal absorption; level measurement, cyclosporine interaction
Amphotericin B colloidal dispersion		4-6 mg/kg/d, iv	Less nephrotoxic
Liposomal amphotericin B		1-5 mg/kg/d, iv	Less nephrotoxic
Amphotericin B lipid complex		5 mg/kg/d, iv	Less nephrotoxic
Voriconazole	Loading dose	400mg maintenance dose 200 mg (oral)	
	Loading dose	2 x 6mg/kg 12 hours apart maintenance dose 3mg/kg every 12 hours (iv)	
Caspofungin	Loading dose	70mg/d maintenance dose 50mg/d (iv)	

(Modified according to Denning DW CID 1998)

plus flucytosine (100 mg/kg/d) for 2 weeks, and then fluconazole (400 mg/d) for a minimum of 10 weeks is recommended. Amphotericin B (0.7-1 mg/kg/d) plus flucytosine (100 mg/kg/d) may be used for 6-10 weeks. Lipid formulation of amphotericin B (3-6 mg/kg/d) for 6-10 weeks may be an alternative treatment (Dismukes et al. 1987; Bennett et al. 1979; Saag et al. 2000). The potential role of voriconazole for the treatment of cryptococcal meningitis in non-HIV-infected patients is undetermined (Pappas 2001).

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