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Candidiasis

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Candida **spp. are the most common fungal pathogens isolated in immunocompromised hosts, particularly cancer patients. Numerous clinical manifestations of candidiasis have been recognized, including localized infection such as oropharyngeal candidiasis or focal hepatic candidiasis, and disseminated infection resulting from hematogenous spread, with or without documented fungemia. Granulocytopenic patients are particularly at risk.** ***Candida albicans*** **is isolated in approximately 40 % of cases of fungemia, other** ***Candida*** **spp. now also commonly being isolated. The rate of morbidity and mortality secondary to candidiasis is still significant despite numerous attempts to develop better diagnostic techniques, and more effective means of chemoprophylaxis and therapy. Currently, new antifungal agents and galenic preparations of amphotericin B are being evaluated with the aim of improving the prognosis of candidiasis in immunocompromised hosts.**

Invasive Candidiasis: An Increasing Problem

In the last decade, an increased incidence of documented fungal infections has been reported in various groups of patients. *Candida* spp. are the organisms most frequently identified as causative agents of mycoses (1–3) in the compromised host. This paper deals with invasive candidiasis occurring mainly in immunocompromised hosts, while superficial candidiasis such as localized cutaneous infection or vaginal candidiasis will not be discussed.

A recent evaluation has demonstrated that approximately 5 % of hospitalized patients develop a nosocominal infection (4), 5 % of these infections being caused by *Candida* spp. Patients with hematological malignancies are particularly at risk (1, 3, 5); several autopsy studies have shown that 10 to 30 % of leukemic patients (and particularly those with prolonged granulocytopenia) have histopathological evidence of invasive candidiasis (1, 3, 5). In addition, such infection occurs in approximately 10 to 15 % of patients with lymphoma and in 5 % of patients with solid tumors (1, 5, 6). For many years, invasive candidiasis has been considered a terminal event, observed mainly in severely debilitated patients. The recent progress in intensive care and surgery, as well as more aggressive therapeutic approaches, including organ transplantation, and intensive antineoplastic chemotherapy result in a prolonged survival of patients with life-threatening underlying disease and poor immunological status. Previously, most of these patients died as a result of their underlying disease, bacterial infection (such as septicemia caused by gram-negative bacilli) or hemorrhage. These complications can now be either prevented or better controlled, and these patients are therefore at risk of developing opportunistic fungal infections.

Invasive candidiasis is also common in patients without neoplastic disease. A new group of patients, i.e. those with AIDS, constitutes a target population for numerous fungal infections including candidiasis. However, these patients usually have oropharyngeal or oesophageal infection, disseminated candidiasis having been demonstrated only on a few occasions (7).

Another category of patients predisposed to invasive candidiasis constitutes newborns (8), particularly premature babies requiring various invasive diagnostic and therapeutic procedures for supportive care.

Patients with extensive burns are also frequently colonized by yeasts and receive prolonged courses of antimicrobial therapy which promotes changes in the normal flora and enhances the rate of superinfection caused by *Candida* spp.

Heroin addicts represent another group of patients at risk. An unusual syndrome caused by *Candida albicans*, resulting in disseminated infection with cutaneous localisation as well as deep foci of can-

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didiasis in the bones and in the eyes has been described in those patients (9).

Colonization by *Candida* spp. occurs in 5 to 10 % of normal individuals, but proliferation of yeasts increases considerably in persons seeking medical attention, particularly hospitalized patients. Yeast colonization (which increases with the duration of hospitalization) associated with loss of defense mechanisms results in a high incidence of candidiasis.

Numerous other predisposing factors, several of them being iatrogenic, have also been reported (10). Breaches of body barriers and mucosal ulceration are major sites of colonization, invasion and dissemination of *Candida* spp. Changes in the normal flora and overgrowth of yeasts also occur secondary to administration of various medications or to hyperalimentation requiring the use of central venous catheters often inserted for prolonged periods. Bladder catheters are also frequently colonized by yeasts, particularly in diabetic patients or if an intraabdominal tumor is causing obstruction.

Polymorphonuclear leucocytes, macrophages and monocytes represent major mechanisms of defense against *Candida* spp. (1, 2, 10). The role of cell-mediated immunity has been studied particularly in patients with chronic mucocutaneous candidiasis or with AIDS (7). Humoral immunity may play a role but probably in conjunction with other mechanisms. Adherence of yeasts to the various mucosa has also been reported to be of major importance (3, 10).

Most candidiasis results from endogenous sources and it is now well recognized that several species of yeasts cause life-threatening infections with identical clinical manifestations. Besides *Candida albicans, Candida tropicalis, Candida krusei, Torulopsis glabrata, Candida parapsilosis* and other species of yeasts are now more commonly identified as pathogens (11–15).

Table 1: Incidence of candidiasis in immunocompromised patients.

Cancer patients	
Fungemia in patients with	
hematologic malignancy	2 %
solid tumor	1 %
Invasive candidiasis at autopsy in patients with	
acute leukemia	10–30 %
lymphoma	10 %
solid tumor	5 %
Manifestations associated with disseminated candidiasis	
cerebral microabscesses	30 %
myocarditis	50 %
skin lesions	13 %
AIDS patients	
Oropharyngeal candidiasis	90 %
Candida esophagitis	15 %
Neonates	
Disseminated candidiasis (mostly in premature neonates)	3 %

Table 2: Clinical manifestations of candidiasis in immunocompromised patients.

Disseminated infection
Fungemia
Oropharyngeal candidiasis and esophagitis
Hepatosplenic candidiasis
Urinary tract candidiasis
Endophthalmitis
Central nervous system infection
Osteo-articular candidiasis
Pulmonary infection
Endocarditis
Peritonitis
Other (infection of lymph nodes, pericardium, gall bladder)

Clinical Manifestations of Candidiasis

The incidence and the various clinical manifestations of candidiasis are summarized in Tables 1 and 2.

Disseminated Candidiasis. Disseminated candidiasis is a major cause of death in compromised patients, often occurring in granulocytopenic patients (1, 12, 14, 15). The organs commonly involved are the kidneys, liver, spleen, lungs and muscles, but other tissues (including ovaries, lymph nodes, thyroid) have occasionally been shown to be involved (1, 3). The clinical signs and symptoms of disseminated candidiasis are often non-specific, and persisting fever in predisposed patients should alert the physician. Occasionally, patients present with severe myalgia and peripheral nodular lesions suggesting emboli. These manifestations have been more frequently observed if the infection is caused by *Candida tropicalis* (12, 14, 15).

The prognosis of disseminated candidiasis is extremely poor, particularly in granulocytopenic patients, and prompt administration of antifungal therapy is mandatory. Early recognition of disseminated candidiasis is essential but too often the infection is not discovered until autopsy as it is extremely difficult to establish an accurate diagnosis at an early stage (1, 5, 6, 16). Cultures of clinical specimens can easily be false positive or false negative and are therefore difficult to interpret (3, 17–19). Due to frequent colonization of predisposed patients, interpretation of positive samples from various sites is still controversial and varies with the species isolated (17, 19). For example, the isolation of *Candida* spp.

from sputum or urine does not necessarily indicate that the patient has disseminated candidiasis. On the other hand, until five years ago only approximately 50 % of patients with disseminated candidiasis at autopsy could be shown to have blood cultures positive for yeasts prior to death (1, 3, 5, 6). Deep infection should therefore be considered even in the absence of documented candidemia. Recent developments in diagnostic techniques, particularly blood cultures, have improved the recovery of yeasts. An increased rate of isolation of yeasts as well as a shorter interval between taking of samples and detection of yeasts using the lysis centrifugation system (Dupont, USA) have been reported (20–22). Such a diagnostic approach seems extremely useful and may improve the management of immunocompromised patients.

Serological tests have also been developed to detect either candida antibodies or antigens in patients suspected of having disseminated candidiasis. Demonstration of candida antibody titers seems to be of limited value, however, due to the high rate of false positive and false negative results (16). Patients at risk for disseminated candidiasis are severely immunocompromised and usually do not produce specific antibodies. In addition, colonized patients are exposed to high amounts of antigen and may develop antibodies even in the absence of deep-seated infection. In the last ten years, several studies have been performed in an effort to detect antigens or fungal metabolites in such patients which could be indicative of disseminated candidiasis (14, 16). This approach is more promising than the detection of antibodies but is not yet available for routine use. Further research is still necessary and is currently underway.

At present, a final diagnosis of disseminated candidiasis relies mainly on histological demonstration of yeasts and/or pseudohyphae in tissues. Unfortunately, in most cases peripheral lesions are absent. When present, these cutaneous manifestations are often non-specific (1). Samples of septic emboli may easily be taken for staining, culture and histological examination, and may be very helpful for confirming the diagnosis (1, 2). In their absence, the diagnosis of disseminated candidiasis may require invasive procedures including biopsy of tissue of deep organs (such as the liver or the spleen). Altered coagulation tests and low platelet counts frequently observed in those patients render biopsy a dangerous approach.

Fungemia. The various *Candida* spp. commonly isolated from blood cultures in cancer patients are listed in Table 3. Several clinical entities have to be considered in the diagnosis when fungemia is documented. Occasionally, a blood culture is false positive due to contamination by yeasts. However, in a febrile immunocompromised patient a single positive culture requires that further investigations be performed, and if invasive candidiasis is suspected antifungal therapy should be considered. Fungemia represents either a transient and self-limited infection or a life-threatening situation. The source of the disease is often endogenous, fungemia resulting for instance from proliferation of yeasts in the gastrointestinal tract and invasion through mucosal ulcerations secondary to antineoplastic chemotherapy. In addition, in many compromised patients, intravenous catheters are maintained in situ for prolonged periods, catheter-related fungemia therefore also being common. Catheter-related fungemia should be distinguished from other forms of the disease. Although occasionally removal of an infected catheter has meant the infection could be brought under control, severe complications such as candida endophthalmitis, arthritis, osteomyelitis or thrombophlebitis have been reported in a significant number of patients (23–28). Therefore, antifungal therapy should be administered to all patients with evidence of fungemia, particularly in immunocompromised patients, even for a short term when there is no sign of a persisting focus of infection. While removal of an infected catheter is not always necessary in the case of bacteremia (29),

Table 3: *Candida* species causing fungemia in cancer patients.

	MSKCC[a] 1974–1977	MSKCC[b] 1978–1982	Institut J. Bordet 1983–1988	Total	(%)
Number of episodes	136	200	54	390	(100)
C. albicans	53	89	27	169	(43.3)
C. tropicalis	29	51	10	90	(23.0)
T. glabrata	26	22	7	55	(14.1)
C. parapsilosis	16	23	2	41	(10.5)
C. krusei	4	7	3	14	(3.5)
Others	8	8	5	21	(5.3)

MSKCC: Memorial Sloan Kettering Cancer Center.

[a] Reference no. 11.
[b] Reference no. 12.

there is still controversy concerning the management of catheter-related fungemia and further studies are necessary. It seems prudent to initiate antifungal therapy through the catheter and to remove it if blood cultures remain positive despite treatment.

Oropharyngeal Candidiasis and Esophagitis. These manifestations are particularly frequent in cancer patients (1) and AIDS patients (7). Oropharyngeal candidiasis is painful and alters the quality of life of infected patients. In addition, extension to the esophagus or to the entire gastrointestinal tract can occur and constitutes a major source for further dissemination. It has been shown that a significant number of patients have extensive esophageal candidiasis at autopsy even if no clinical symptoms were reported prior to death (30). Accurate diagnosis of oropharyngeal candidiasis is not difficult; however, in the differential diagnosis for esophagitis, infection caused by herpes simplex virus, which is common in these patients, and less often cytomegalovirus, must also be considered. Severe complications have been reported secondary to candida esophagitis, including gastrointestinal bleeding, perforation and mediastinitis. Eradication of yeasts from the oropharynx is particularly difficult to achieve in granulocytopenic patients (1) and AIDS patients (7, 31) and the relapse rate of oropharyngeal candidiasis or esophagitis is high in these patients.

Pulmonary Candidiasis. There are few convincing studies of pulmonary infection caused by yeasts (32, 33). Isolation of yeasts from sputum or respiratory secretions is common, particularly in intensive care units. However, in most cases these isolates are not representative of the infecting agent responsible for the pulmonary infiltrates. Once again, colonized patients may have positive cultures without deep-seated infection while patients with histopathological evidence of pulmonary candidiasis do not usually have positive cultures of specimens obtained from the respiratory tract (1, 17–19, 32, 33). Pulmonary candidiasis is either a consequence of disseminated candidiasis or constitutes a localized infection secondary to aspiration. This latter entity occurs infrequently.

Gastrointestinal Candidiasis and Hepatic Candidiasis. Overgrowth of yeasts in the gastrointestinal tract has been documented, particularly in patients receiving corticosteroids or broad-spectrum antibiotics, and seems to be a major source of dissemination (3, 10). Invasion of gastric and duodenal ulcers has been documented occasionally (30).

Recently, a new clinical syndrome, focal hepatic candidiasis, has been recognized in immunocompromised patients (34–36). This syndrome usually occurs in patients who were previously granulocytopenic but regained an adequate granulocyte count (PMN $> 1{,}000/\mu l$). Patients present with fever, loss of appetite, nausea, vomiting, diarrhea and abnormal liver function tests (mainly increased alkaline phosphatases). On computerized tomography scans, numerous microabscesses are demonstrated, and histopathological examination of biopsy material shows fungal elements including yeasts and pseudohyphae. However, the organism usually does not grow in cultures of specimens (36). Successful treatment is difficult; a high dose of amphotericin B seems necessary to eradicate the infection. It is often difficult to decide whether antineoplastic chemotherapy should be pursued under these circumstances but control of the underlying disease is of major importance. Administration of antifungal agents during granulocytopenia is recommended if further antineoplastic chemotherapy is necessary, since complete eradication of hepatic candidiasis is rarely achieved.

Another form of gastrointestinal candidiasis presents as a fungus ball localized in the biliary tract and causing total obstruction (37, 38). These cases are rare and cause numerous diagnostic problems. Candida peritonitis and intraabdominal abscess also constitutes a distinct form of candidiasis, relatively rare in patients with neoplastic disease, occurring mainly in patients undergoing dialysis or after extensive gastrointestinal surgery (39–43).

Urinary Tract Infections. Candida urinary tract infections can be localized to the lower urinary tract or involve the kidneys. While candida urethritis is relatively rare, bladder infections are more frequent, particularly in patients with indwelling catheters or with obstructive neoplasms in the pelvis (2). The symptoms related to candiduria are usually mild and non-specific. Proliferation of yeasts in the urinary tract may occasionally be responsible for formation of a fungus ball in the ureters and anuria may also occur in such circumstances (44–46). Endoscopy reveals widespread characteristic lesions of the bladder mucosa. There is controversy concerning the diagnostic value of counts of yeast colonies recovered in the urine (47–50). Invasive candidiasis may occur even in the presence of low numbers of yeast colonies in the urine. Whether or not pseudohyphae are observed on smears does not seem to be of value in assessing the degree of invasion.

Kidney involvement is characteristic of disseminated infection and usually results from haematogenous spread leading to microabscesses. In febrile patients predisposed to invasive candidiasis, detection of yeasts in the urine, particularly in the absence of a Foley catheter, is suggestive of deep-seated candidiasis (5, 26, 47), and further investigations should be performed.

Osteo-Articular Candidiasis. Osteo-articular candida infection results most often from a hematogenous source (24, 25). Single or multiple joints may be involved (51). These complications are, however, relatively rare (52) and may occur several weeks or months after what was considered a transient fungemia. The classical syndrome described in heroin addicts is of particular interest (9). In some instances, lesions localized to one joint have been reported in patients in whom blood cultures were not positive for yeasts (24, 25). Articular candidiasis usually occurs in large joints such as the knee and the hip, the clinical signs and symptoms being non-specific. Occasionally, subacute or chronic infection may occur several weeks after documented or occult fungemia, even in leukemic patients (53). Contiguous spread after surgery leading to osteomyelitis has also been described in a recent review of the literature (54).

Candidiasis of the Central Nervous System. Central nervous system candidiasis seems to be more common than previously thought (55), the mortality rate being as high as 55 %. The clinical signs and symptoms as well as abnormalities seen on examination of the cerebrospinal fluid (CSF) are non-specific. The yeast inoculum in the CSF is usually low and it has therefore been recommended that a large quantity of CSF is cultured (55). Clinically, the patients usually demonstrate fever, confusion or other non-specific neurological findings. Cerebral abscesses may also occur, usually as a result of hematogenous dissemination. Debilitated children seem to be particularly predisposed to candidiasis of the central nervous system (56, 57). Diagnosis prior to death is rare. Inoculation during lumbar puncture has been suggested as source (58).

Candida Endocarditis. Candida endocarditis is relatively rare but the incidence has increased recently, probably as a result of more aggressive therapeutic approaches in various severe underlying diseases (59). The prognosis of this entity remains extremely poor. The classical signs and symptoms include fever, a new murmur and occasionally peripheral manifestations of septic emboli. Associated disorders include glomerulonephritis, pyelonephritis, intravascular coagulation, splenomegaly, and microabscesses in the liver and numerous other parts of the body including the central nervous system. Diagnosis prior to death is usually made in only 60 % of cases. Progression of the disease is either rapid, with shaking chills and formation of emboli, or subacute. Occasionally, extensive candida endocarditis is demonstrated at autopsy while signs and symptoms were mild or even absent before death. It should be pointed out that none of the mentioned clinical signs and symptoms are specific for candida endocarditis. However, fungal emboli often involve large blood vessels. Occasionally, peripheral blood smears show the presence of yeasts and/or pseudohyphae which is helpful for the diagnosis.

Other Manifestations of Candidiasis. A serious complication of invasive candidiasis is endophthalmitis. Candida endophthalmitis may be asymptomatic for a prolonged period in some circumstances (23). It is rare in granulocytopenic patients but common in patients who are hospitalized in intensive care units or have undergone major surgery. The prognosis of this infection is relatively poor and the risk of visual loss is high. Candida endophthalmitis has been reported to occur as long as six months after an episode of fungemia considered transient or insignificant (2, 23, 26). Infection of the eyes with fungal elements is now also commonly diagnosed in patients after ophthalmic surgery but usually remains localized (23). Other rare cases of localized candidiasis have been reported affecting the thyroid, adrenals, spleen, ovaries, lymph nodes and gall bladder (1, 3, 37, 38). Foci of candidiasis in the myocardium have also been reported and may be responsible for arrythmias (3). These lesions are more frequently demonstrated in patients with disseminated infection (1).

Recent Developments in Treatment

Optimal management of invasive candidiasis is difficult to achieve, particularly in immunocompromised hosts, the prognosis often being related to success in treatment of the underlying disease. Until recently, very few antifungal agents were available commercially for systemic therapy. Amphotericin B is poorly water soluble and is administered by the intravenous route as a complex with deoxycholate (Fungizone). This agent is still considered the standard therapy (60). However, the cases of both treatment failure and relapse are numerous. Moreover, administration of amphotericin B can be associated with side-effects including fever, chills, hypotension and hypertension (61). Electrolyte disturbances and nephrotoxicity may prevent administration of high doses of the agent (60, 62). There is still major controversy as to the total dose of amphotericin B that can be administered and the optimal duration of therapy (60, 63). In some diseases, such as focal hepatic candidiasis, total doses of more than 6 or 8 g have been administered in adults (34–36). Generally, transient fungemia, such as catheter-related infection without signs or symptoms of widespread infection, can be treated successfully with a low dose of amphotericin B, such as 500 mg in an adult (2, 60). However, if multiple blood cultures are positive, the patient usually requires a total dose of amphotericin B ranging between 1 g and 2 g (14, 60). It should be emphasized that these regimens are still arbitrarily recommended.

Whether all episodes of fungemia require administration of amphotericin B is subject to discussion (26), and whether amphotericin B is the agent of choice in such circumstances is being questioned now that new and effective alternative agents are available (3, 60, 63).

In recent years, new methods of administration of amphotericin B, mainly by incorporation in lipid vehicles such as liposomes, have been evaluated (64–67). Data obtained in clinical trials using various galenic preparations of amphotericin B are encouraging. These preparations seem to be tolerated better than the deoxycholate-amphotericin B complex and to be less toxic (64–67). However, there is not yet a commercially available preparation, and randomized comparative clinical trials are necessary to determine the efficacy of this form of administration compared to the deoxycholate-amphotericin B complex.

Topical administration of amphotericin B has been suggested mainly in ventricular reservoirs in the case of fungal meningitis with ventriculitis (3, 60). Bladder irrigation with amphotericin B would seem to be effective in some circumstances, particularly in patients with Foley catheters (2, 60). Peritoneal administration (39, 42) has been shown to be beneficial in some patients, but is poorly tolerated and this possibility is therefore difficult to pursue, likewise intra-articular injections (51). Amphotericin B does not penetrate the vitreous; occasionally intra-ocular administration of amphotericin B has been recommended in patients with candida endophthalmitis (23).

Until now, yeasts have been considered sufficiently susceptible to amphotericin B, except in a few cases of fatal infection caused in particular by *Candida lusitaniae* (68–70). However, recent studies in hematological units have demonstrated an increased incidence of other species of yeasts also resistant to polyenes (71–74). Amphotericin B tolerance has been reported for *Candida parapsilosis* (75).

Another antifungal agent available for systemic therapy by the intravenous or oral route is 5-fluorocytosine. This agent is very active against yeasts, including *Candida* spp., however the susceptibility of clinical isolates to this agent varies (76). Moreover, the emergence of resistance strains of *Candida* spp. during therapy with 5-fluorocytosine alone precludes administration of the drug alone except in very few circumstances such as urinary tract infection (60). 5-fluorocytosine is excreted in the urine, and penetration of the drug into the CSF is satisfactory (60). Another common problem encountered with administration of 5-fluorocytosine (mainly in combination with amphotericin B) is increased toxicity leading to bone marrow aplasia, particularly if renal insufficiency occurs (62). Serum concentrations of 5-fluorocytosine should be monitored in patients receiving the combined regimen and should not exceed 100 μg/ml. Severe gastrointestinal disturbances have been reported with 5-fluorocytosine, comprising mainly nausea and vomiting, but perforation of the bowel has also been reported (60).

Imidazoles are a new class of antifungal agents, and several are now available for clinical use. Clotrimazole is active against yeasts, but due to induction of hepatic enzymes, use of this agent is restricted to topical administration (1). Miconazole is available only for intravenous administration due to poor gastrointestinal absorption after oral administration. The indications for treatment with miconazole are still unclear, particularly in immunocompromised patients (63). However, results of a recent study using placebo controls (77) suggest that administration of miconazole in febrile granulocytopenic patients receiving broad-spectrum antibiotics leads to a reduced incidence of fungemia.

Ketoconazole is the first imidazole available for oral administration in systemic therapy (63). This agent is highly effective in the treatment of chronic mucocutaneous candidiasis (78), oral thrush and candida esophagitis, even in immunocompromised patients such as those with cancer, bone marrow transplantation or AIDS (3, 60, 63, 79, 80). The compliance of patients receiving ketonazole is usually satisfactory. However, there are numerous problems related to prolonged administration of ketoconazole, particularly in immunocompromised patients (3). There is great individual variation in the gastrointestinal absorption and monitoring of the serum concentrations of ketoconazole thus seems mandatory, particularly in patients receiving antacids and cimetidine. Occasionally, severe hepatotoxicity has been observed and this should be taken into consideration in patients who are already receiving other hepatotoxic drugs. Numerous interactions have been reported between ketoconazole and various drugs administered to patients predisposed to candidiasis, such as theophyllin, warfarin, cyclosporin and rifampin (3, 81–84). In addition, inhibition of the secretion of testosterone and adrenocorticosteroids has been documented in patients receiving ketoconazole (3, 60, 85, 86). Furthermore, prolonged administration of ketoconazole seems to select *Torulopsis glabrata*, another species of yeasts known to be pathogenic in immunocompromised hosts (11).

Recently, new agents, mainly triazoles such as itraconazole and fluconazole, have been extensively evaluated (87, 88). Little information is available on the potential role of itraconazole in the treatment of documented candidiasis (89). This agent can only be administered orally and seems more effective than other imidazoles or triazoles against *Aspergillus* spp. Several studies have been performed using fluconazole in the treatment of oropharyngeal candidiasis in

cancer patients (90) and AIDS patients (91). Pharmacokinetically, fluconazole has several advantages over ketoconazole and can be administered by the oral and intravenous route. The latter is particularly useful in patients with severe underlying disease who have difficulty absorbing oral medications. In addition, no interaction with cyclosporin or adrenocorticosteroids has been reported with this triazole.

Due to the poor prognosis of candidiasis in immunocompromised patients and the lack of effective means to diagnose invasive candidiasis at an early stage, empiric antifungal therapy has been advocated and shown to be effective in patients with suspected candidiasis. Amphotericin B has been used for this purpose, and the results of comparative studies suggest a potential benefit upon early administration in a limited number of febrile granulocytopenic patients not responding to broad spectrum antibiotics (92, 93). Obviously, not all febrile granulocytopenic patients have occult fungal infection and it seems necessary to define the patients who would benefit most from such empiric therapy. A large-scale study of the EORTC International Antimicrobial Therapy Cooperative Group showed that early administration of amphotericin B is of benefit in adult patients who had not previously received prophylactic antifungal therapy and who had a clinically documented infection (i.e. infection was found on physical examination but no pathogen was isolated from samples), or in patients who were granulocytopenic over a prolonged period (data to be published, American Journal of Medicine). In a study comparing amphotericin B and ketoconazole in therapy of fungal infections in neutropenic patients the overall rate of response to the drugs was similar (94). However, in patients with infection caused by *Candida tropicalis* and in patients with pulmonary infiltrates (which are mainly caused by *Aspergillus* spp. in this population), amphotericin B was significantly better than ketoconazole. Therefore, empiric administration of ketoconazole may be considered, although with reservations, since most of these patients are predisposed to infection with *Candida* spp., *Aspergillus* spp. or other fungal pathogens.

Recent Development in Prophylaxis

There have been numerous attempts to decrease the incidence of invasive candidiasis in patients at risk, however the optimal chemoprophylactic agent remains controversial (95). Clinical studies have been performed mainly with polyenes such as amphotericin B and nystatin, which are not absorbed after oral administration. One of the major problems with these two agents is that compliance of the patients is poor. Another is that high doses of polyenes are required to decrease colonization of the gastrointestinal tract by yeasts and such doses are rarely tolerated in humans. In addition, eradication of yeasts from the mouth seems more difficult to achieve than from the stools. Furthermore, documented fungemias have been observed in patients receiving amphotericin B or nystatin prophylactically (14). Clotrimazole has also been tested in prophylaxis of oropharyngeal candidiasis. Excellent compliance of patients taking clotrimazole lozenges has been observed, but the clinical outcome varied with the category of patients (96). Ketoconazole has been extensively tested in such patients and high doses (400 to 800 mg per day) were found to decrease the incidence of both colonization and invasive candidiasis in compromised patients (95, 97–100). However, the potential problems described above with ketoconazole preclude its widespread administration for prolonged periods in patients at risk. In addition, patients predisposed to invasive candidiasis are also predisposed to aspergillosis and none of the previously mentioned prophylactic regimens reduces the incidence of invasive aspergillosis in these patients. A preliminary evaluation from the MD Anderson Cancer Center in Houston suggests the potential role of fluconazole in decreasing oropharyngeal colonization and preventing oropharyngeal candidiasis in non-granulocytopenic cancer patients (data to be published). Several questions concerning the optimal means of prophylaxis in invasive candidiasis remain unanswered. The exact value of surveillance culture is still controversial: whether the isolation of *Candida albicans* or other *Candida* spp. is significant and has a predictive value for candidiasis remains a matter of discussion (17–19). However, surveillance cultures are of major importance in evaluation of new antifungal agents and should be performed for research purposes, even if the results are of little help in the management of immunocompromised patients. Finally, it should not be overlooked that complete eradication of yeasts in compromised patients hospitalized for prolonged period and treated with broad spectrum antibiotics may be impossible.

Conclusion

The increased incidence of invasive candidiasis in numerous categories of patients, including neonates, cancer patients, AIDS patients and patients who have undergone organ transplantation, is cause for concern in the medical community. The manifestations of candidiasis are numerous and various clinical entities such as localized and disseminated infection have to be considered separately. Several species of yeasts can be responsible for similar manifestations of infection. Granulocytopenic

patients are at high risk of acquiring life-threatening candidiasis. Extensive studies are in progress to establish accurate and rapid diagnostic methods, to develop more effective therapy, and to find the optimal means of prevention. Until now, amphotericin B has been considered the agent of choice for treatment of most forms of invasive candidiasis, but alternatives such as itraconazole, fluconazole or new galenic preparations of amphotericin B are currently under investigation and results are encouraging. Eradication of yeasts in the immunocompromised host remains difficult to achieve however. The above-mentioned current efforts combined with better control of the underlying diseases should improve the prognosis of immunocompromised patients with invasive candidiasis.

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