

Guidelines for the management of nosocomial *Candida* infections in non-neutropenic intensive care patients

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WA Demajo, J-G Guimond, C Rotstein, M Tweeddale and the Canadian Candidemia Advisory Group. Guidelines for the management of nosocomial *Candida* infections in non-neutropenic intensive care patients. *Can J Infect Dis* 1997;8(Suppl B):3B-9B. A consensus meeting of the Canadian Candidemia Advisory Group was held during the 16th International Symposium on Intensive Care and Emergency Medicine on March 19, 1996 in Brussels, Belgium. For this meeting, a group of 20 intensive care and infectious disease specialists were brought together to discuss the risk factors associated with *Candida* species colonization in intensive care units and the treatment of invasive candidiasis in non-neutropenic patients. Members of the consensus group assessed the evidence available and attempted to reach a consensus on the role of antifungal therapy in the intensive care unit setting.

Key Words: *Candidiasis, Guidelines, Intensive care, Non-neutropenic patients, Therapy*

Fungal pathogens of the *Candida* species, especially *Candida albicans*, have emerged as a major cause of nosocomial infections and mortality in hospitalized patients, most significantly in the intensive care environment (1). The rate of fungal infections, surveyed since 1980, increased from 2.0 to 3.8 infections/1000 discharged hospital patients, while the proportion of fungal infections among nosocomial infections rose from 6% to 10.4%, with *Candida* species accounting for 78% of

all fungal infections (2). The Canadian Invasive Fungal Disease Registry, which collected data on candidemia from March 1992 to February 1994, reported that 66% of fungal infections were due to *Candida* species. *C. albicans* was isolated in 68% of these cases, while *Candida glabrata*, *Candida krusei* and *Candida lusitanae* comprised 8.2%, 4% and 0.7% of the isolates, respectively (3). The increased incidence has affected clinical practice broadly – the frequency of candidemia has in-

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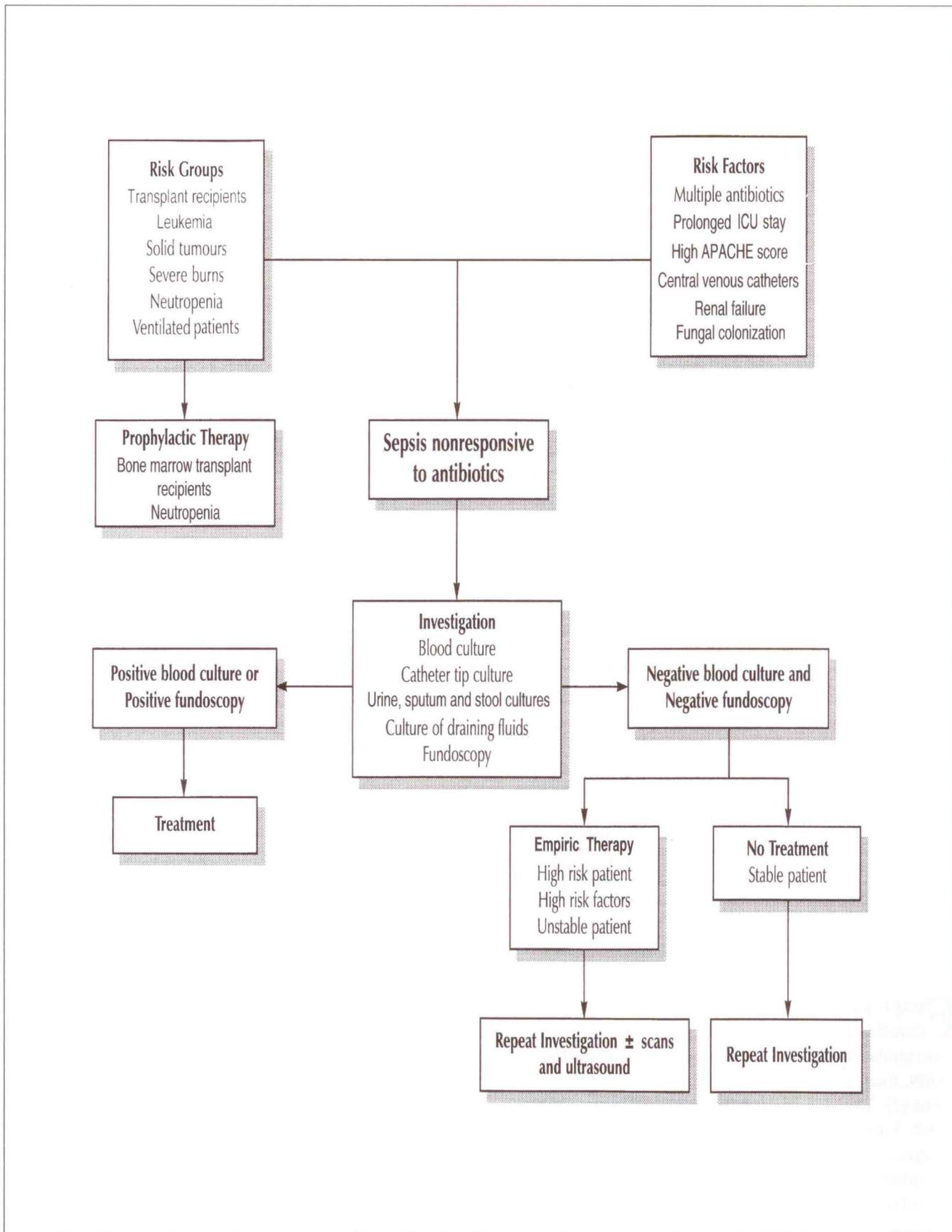


Figure 1) A therapeutic algorithm for intensive care unit (ICU) patients at risk for candidiasis. APACHE Acute Physiologic Score and Chronic Health Evaluation

creased by almost 500% in large teaching hospitals and by more than 200% in smaller nonteaching hospitals since the early 1980s (4). In surgical patients, the incidence of nosocomial fungal infections jumped from 2.5 to 5.6/1000 patients discharged, and in medical patients from 3.0 to 5.2/1000 patients discharged (2). In another study, *Candida* species was the fourth most common pathogen isolated from intensive care patients (5). A one-day prevalence study of intensive care unit nosocomial infections in 17 European countries found that almost half of the patients developed sepsis – 50% of these patients acquired their infection in the intensive care unit, and 17% of the isolates were fungi (6). The mortality rate in candidemic patients is very high, ranging from 38% to 57% (7,8). Although mortality is attributed to a number of factors in these seriously ill patients, Wey et al (7) reported a mortality rate of 38%, which was directly attributed to candidemia (7). The Canadian Invasive Fungal Disease Registry reported an overall mortality rate of 46%, and 18% of deaths were directly attributable to candidemia (3).

Due to the significance of invasive *Candida* infections in intensive care patients, it is imperative that clinicians caring for such patients acquire a pragmatic and rational approach to diagnosis and therapy. This paper attempts to outline risk factors, discuss diagnostic criteria and, finally, provide Canadian guidelines for a rational approach to the management of patients in an intensive care unit setting. For purposes of this discussion, the term 'candidemia' refers to the presence of *Candida* species in blood cultures, while 'disseminated' or 'invasive' candidiasis or, more simply, 'candidiasis', is tissue infection with or without positive blood cultures.

RISK FACTORS FOR INVASIVE CANDIDIASIS

Invasive candidiasis is common in patients rendered profoundly neutropenic by immunosuppressive therapy. However, candidiasis may also occur in patients whose immune system is not impaired pharmacologically. Because positive antemortem blood cultures are obtained in only 30% to 50% of autopsy-proven candidiasis (9), it is important to be aware of clinical factors that predispose patients to an increased risk of invasive candidiasis. The major risk factors for invasive fungal infections include fungal colonization; the use of multiple, broad-spectrum antibiotics; the presence of intravascular cannulae (especially Hickman catheter); renal failure; and prolonged stay in the intensive care unit. Wey et al (7) found that prolonged use of antibiotics, especially when more than two were used, significantly increased the risk of nosocomial candidemia

(Figure 1). This study and others (2,10-12) demonstrated that the use of central indwelling catheters and the length of stay in the intensive care unit are also associated with a high risk of candidemia. Similarly, a study of the severity of underlying illness showed that high Acute Physiologic Score and Chronic Health Evaluation (APACHE) scores are good predictors of risk of invasive candidiasis and death (13). Most studies consistently report that patients with sustained candidemia had been in an intensive care unit, had a pre-existing central venous catheter and had been treated with multiple antibiotics. Many patients also had renal failure. When clinical improvement in intensive care patients is interrupted by ongoing or new infection of uncertain etiology, candidemia or invasive *Candida* infection should be suspected, and steps taken to either confirm or dismiss this diagnosis.

FUNGAL COLONIZATION

The exact significance of the colonization of nonsterile body sites with fungi in the eventual development of candidiasis in the intensive care unit population is unclear. No generally acceptable definition of significant fungal colonization, defining number of sites or concentration of organism, exists. However, the authors of a number of studies (13-15,17,18) have suggested that there is a higher incidence of candidemia in patients with multiple sites colonized. *Candida* colonization has been narrowly defined as the presence of *Candida* species in three or more samples taken from the same or different nonsterile body sites on at least two consecutive screening days (13).

Pittet et al (13), using a cohort of critically ill surgical patients, showed that the intensity of colonization, quantified as the ratio of nonblood body sites colonized:sites sampled, is an independent predictor of infection. Martino et al (18), in a study of cancer patients, reported an incidence of candidemia of 22% in patients with multiple-site colonization, compared with 5% in patients with single-site colonization and absence of candidemia in patients who lacked colonized sites. Density of colonization, particularly in the gastrointestinal tract, defined as the number of organisms present in stool cultures, has been reported to be a significant risk factor for candidemia (19). The authors of other studies suggest that protracted urinary colonization is an important risk factor for invasive candidiasis (15,20). Studies using DNA typing have confirmed that systemic candidiasis usually arises from endogenous flora (15), but cross-contamination also occurs (16). Stone et al (17) demonstrated that *Candida* species can migrate across the normal gastrointestinal mucosa. When con-

centrations of 10^{15} organisms/mL were instilled into the intestinal lumen, *Candida* species migrated across the mucosa and into the portal vein (17).

The boundary between colonization and invasion in intensive care unit patients is somewhat unclear. There is a subset of febrile and clinically unwell intensive care patients with *Candida* species cultured from nonsterile body sites and in whom cultures from sterile body sites continue to be negative. These patients present evidence of systemic inflammatory response syndrome and may or may not be hemodynamically unstable. Some evidence suggests that these individuals may benefit from empiric antifungal therapy because of a high risk for invasion, and delay in instituting therapy until positive blood cultures are obtained or endophthalmitis develops results in increased mortality (21).

DIAGNOSIS OF INVASIVE CANDIDIASIS

Candidemia: Candidemia is defined by the presence of a positive blood culture for *Candida*. It is always significant and requires initiation of antifungal therapy. This may be true disseminated candidiasis, or it may signify transition from colonization to invasive candidiasis. The propensity of *Candida* species to produce metastatic foci of infection is an additional reason to initiate treatment. Thus, treatment is advisable even when candidemia is suspected to be secondary to a colonized central venous catheter. The approach of dismissing one set of positive blood cultures as benign, transient candidemia is no longer appropriate practice (1).

Disseminated candidiasis: Disseminated candidiasis, which implies the presence of deep-seated organ infection, is often difficult to diagnose because clinical presentations may vary considerably and are nonspecific. Disseminated infections can occur without positive blood cultures – approximately half of the patients with disseminated candidiasis have persistently negative blood cultures. Ophthalmological examination to detect endophthalmitis is useful in patients with suspected disseminated candidiasis because it helps in directing the choice and duration of treatment. This manifestation of disseminated candidiasis is relatively common in intensive care patients – it is present in 9% to 15% of such cases (22). Other manifestations of disseminated infection are much less common – suppurative thrombophlebitis, skin lesions and septic arthritis are rare in intensive care patients (23). Candiduria, when present persistently in concentrations of 10^7 or more colony-forming units/L, may indicate renal infection. Although Stone et al (17) identified candiduria as an indicator of systemic candidiasis, current opinion is that candiduria can be present in the absence of disseminated candidia-

sis, but that disseminated candidiasis without candiduria is unlikely. However, Dyess et al (24) found that 31 of 74 patients with candidemia did not have *Candida* species detected in the urine.

SEROLOGICAL LABORATORY INVESTIGATIONS

Serological tests for mannan and β -1-3-glucan, *Candida* species cell wall components; D-arabinitol, a cell membrane metabolite; and enolase, a cytoplasm constituent, are available with variable sensitivity and specificity spectra for the diagnosis of invasive candidiasis. Correlation of disseminated candidiasis with these antigen titres has been advocated, but routine antibody tests have not proven useful (25,26).

TREATMENT OF INVASIVE CANDIDIASIS

Three indications are suggested for antifungal therapy: prophylaxis; early presumptive, empiric therapy; and definitive therapy for microbiologically documented systemic infection. Prophylaxis is the use of antifungal agents in patients at risk of developing candidiasis, without evidence of colonization or invasion. Presumptive therapy is the initiation of treatment after documentation of colonization when the clinical scenario is compatible with invasive disease. Definitive treatment is the treatment of documented candidemia and/or dissemination. Benefit from prophylactic therapy has been reported in bone marrow transplant recipients (27), but no conclusive evidence of benefit is available for intensive care patients. The evidence for benefit from presumptive therapy is encouraging but not conclusive, and further studies are required. Slotman and Burchard (21) reported that once daily treatment with ketoconazole 200 mg significantly reduced colonization, and none of the patients treated by them developed invasive candidiasis. Savino et al (28), using the same treatment, showed no benefit. Nassoura et al (20) reported an incidence of disseminated candidiasis of 63% and a mortality rate of 33% in patients with candiduria treated with amphotericin bladder irrigation, while in a similar group treated systemically with fluconazole, the incidence of disseminated candidiasis was 0% and the mortality rate was 5% (20).

ANTIFUNGAL AGENTS

With the exception of 5-fluorocytosine, which is an antimetabolite, antifungal drugs are targeted to the cell membrane. Amphotericin B and fluconazole are available as intravenous preparations, and, hence, are useful in intensive care patients (a trial of an intravenous formulation of itraconazole began recently). These will be discussed in more detail below. However, in addition to

antifungal therapy, the successful treatment of fungal infections requires ancillary drainage and debridement of infected tissue, and removal of vascular access catheters and other prosthetic material.

AMPHOTERICIN B

Amphotericin B is a polyene that produces its effect by binding with ergosterol in the fungal cell membrane. Resistance is rare, and it has been the standard treatment for *Candida* infections. It is still recommended for patients who fail to improve with less toxic agents or for the most critically ill patients. It is relatively toxic because it also binds to cholesterol, the sterol present in mammalian cell membranes. Renal toxicity, hypokalemia and hypomagnesemia are the primary side effects. An acute infusion-related reaction characterized by fever, hypotension and tachycardia has been reported in 20% of cases, possibly due to cytokine release (29). Some practitioners give a 1 mg dose to test for hypersensitivity reactions, but most do not currently give a test dose (30), and start with the maximum daily dose of 0.5 to 0.7 mg/kg and continue treatment based on clinical assessment. In patients with endophthalmitis, duration of therapy is determined by clearance of fungal infiltrates. In cases of persistent infiltrates, amphotericin B is used in combination with 5-fluorocytosine for a synergistic effect (when absorption by the enteral route is feasible). In infections with *C lusitanae*, which may develop resistance to amphotericin B, 5-fluorocytosine is very active (31).

New formulations of amphotericin B with improved toxicity profiles are being investigated. Amphotericin B lipid complex (Abelcet; The Liposome Company, New Jersey), amphotericin B colloid dispersion and other liposomal amphotericin B formulations have been demonstrated to be less toxic than amphotericin B. Clinical experience is, however, limited, and trials continue (32). Only amphotericin B lipid complex has been licensed in the United States, while in Canada, the newer formulations are only available for compassionate release.

FLUCONAZOLE

Fluconazole is a triazole agent available in both oral and intravenous preparations. It is excreted in the urine unchanged, and dose adjustments are necessary when renal function is impaired. Side effects are rare. Drug interactions, including increased levels of warfarin, cyclosporine, digoxin and oral hypoglycemic agents, have been reported but are less frequent than those experienced with ketoconazole and miconazole. Triazoles interfere with cell membrane formation through inhibi-

tion of ergosterol synthesis and are fungistatic. Resistance to *C glabrata*, *C krusei* and *C albicans* has been reported (26,33). In a recent study by Rex et al (34), amphotericin B and fluconazole had equal efficacy (in 206 candidemic patients), and there was less toxicity with fluconazole. Preliminary results from a Canadian trial (35) comparing amphotericin B with fluconazole in 106 non-neutropenic candidemic patients are consistent with those found by Rex et al (34). Overall, therapeutic success is currently 50% with fluconazole and 58% with amphotericin B, with mortality rates of about 20% in each group. Patients are given an 800 mg loading dose followed by a dose of 400 mg/day, with the duration of therapy determined by clinical assessment.

ITRACONAZOLE

Itraconazole is also a triazole that acts on the cell membrane. It is available in oral formulation, but an intravenous preparation is undergoing trials. It is the drug of choice for treating histoplasmosis and blastomycosis and can also be used to treat candidiasis, but clinical trials are lacking. A comparative trial of intravenous itraconazole with fluconazole in the treatment of candidemia has recently commenced in North America. Oral absorption is increased by foods and decreased by antacids but is not influenced by H₂ blockers. The pharmacokinetics of itraconazole are not affected by renal impairment or hemodialysis (36). Adverse effects include gastrointestinal intolerance, increases in transaminases and rare endocrine effects. Drug interactions are more frequent with itraconazole than with fluconazole, particularly with terfenadine and astemizole.

CONCLUSION

The standard treatment of documented candidemia and disseminated candidiasis has been amphotericin B, which, because of its relative toxicity, tended to be restricted to life-threatening infections. Hence, empiric use in potentially life-threatening fungal infections was not considered. Fluconazole, available since 1990, has offered a less toxic alternative to amphotericin B for the treatment of candidemia. Fluconazole has been found to be useful in most nosocomial candidal infections, but until recently, no comparative studies of its effectiveness in non-neutropenic patients with invasive candidiasis had been published.

In the past, management of nosocomial fungal infections with amphotericin B was based on the assessment of risk/benefit factors, and, thus, some conditions were not treated because of potentially significant amphotericin B toxicity. Although new clinical evidence has

demonstrated that fluconazole is as effective as amphotericin B, there is a variety of opinions about the choice of agent in cases requiring treatment, and in some situations it is unclear whether any therapy should be instituted. Thus, Canadian guidelines for rational therapeutic approaches to fungal infections in the intensive care unit setting are desirable. The conclusions following the panel deliberations are noted below.

PANEL CONCLUSIONS

1. Prophylactic therapy

Antifungal prophylaxis should be discouraged in intensive care unit patients, except for special situations of bone marrow transplant and neutropenic patients.

2. Empiric therapy

Early empiric treatment should be instituted in patients who have a persistent systemic inflammatory response and are unresponsive to four to seven days of treatment with broad spectrum antibiotics with significant risk factors for *Candida* infection (Figure 1).

3. Treatment of candidemia or disseminated candidiasis

Treatment of patients with candidemia or disseminated candidiasis is mandatory, irrespective of context of infection or species of *Candida* isolated.

4. Treatment regimens

i) Hemodynamically unstable patients should be treated initially with amphotericin B. Conversion to fluconazole is acceptable once hemodynamic instability has resolved and culture results indicate sensitivity. In hemodynamically stable patients, therapy with fluconazole is preferred based on superior tolerability, lower incidence of side effects and equivalent efficacy.

ii) Amphotericin B should be started immediately in doses of 0.5 to 0.7 mg/kg/day, intravenously. A test dose to exclude hypersensitivity is not necessary. Fluconazole should be prescribed as an 800 mg loading dose followed by 400 mg/day, intravenously. Fluconazole may be administered orally when clinical improvement has occurred, provided that the gastrointestinal tract is functioning normally. The dose of fluconazole, but not that of amphotericin B, needs to be adjusted to renal function. It was agreed that drug therapy should be continued at least until signs of sepsis abate, preferably for 10 to 14 days after the disappearance of signs and symptoms of infection.

Lack of response would necessitate definition of the species of *Candida* involved, sensitivity and consideration of alterations to therapy.

5. Ancillary measures in suspected or proven candidemia or candidiasis:

i) Surveillance cultures should be taken from blood, stools, sputum, urine, draining wounds and bronchoscopic alveolar lavage fluid.

ii) Ophthalmoscopic examination should be performed by an ophthalmologist and repeated weekly for patients with positive funduscopy findings.

iii) Central venous catheters and dialysis catheters should be removed, and semiquantitative cultures done. The majority opinion was that new catheters should be inserted over a wire at the old site if the puncture wound appears clean. Some members opted for a new insertion site.

iv) There was no consensus on the management of long term indwelling venous catheters. The majority opinion was to retain them but to monitor response – lack of improvement would advise removal. Removal was also recommended if there is suspicion of, or clinical evidence for, endovascular infection such as septic thrombophlebitis or endocarditis.

v) Arterial and peripheral venous catheters may be retained.

vi) Bladder irrigation with amphotericin B, in cases with candiduria, was not recommended because, although a high local clearance rate is achieved, the benefit in reduction of invasive candidiasis has not been well studied.

Finally, the panel was of the opinion that assiduous attention to the use of antibiotics in intensive care unit patients is an integral part of any protocol for control of fungal infections.

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