Expert panel

Intensive Care Medicine

Intensive Care Med (1994) 20:522–528

Management of deep *Candida* infection in surgical and intensive care unit patients

British Society for Antimicrobial Chemotherapy Working Party

Abstract. Deep *Candida* infections are increasing in incidence, especially in non-neutropenic, intensive care patients including neonates. The attributable mortality of candidaemia and *candida* peritonitis is 37–38% with a 57% overall mortality. The BSAC set up a working party to develop recommendations for management in the absence of controlled trials. These recommendations focus on the role of the microbiology laboratory, management strategies, the respective roles of amphotericin B, flucytosine and fluconazole and long-term maintenance therapy. The indications for initiation of therapy are given special consideration.

Key words: Candida – Candidaemia – Fluconazole – Amphotericin B – Flucytosine

Deep candida infections are common in the hospitalised patient [1–6] and particularly common in the following groups: patients in intensive care units, renal and cancer patients, in those who have had gastrointestinal, pancreatic or thoracic surgery [1–6] and in the premature neonate [7–9]. Groups of patients less commonly affected include those receiving total parenteral nutrition [1, 3] or with other indwelling central venous catheters for other reasons [1, 3], patients on chronic ambulatory peritoneal dialysis (CAPD) [10], neurosurgical patients with cerebrospinal fluid shunts and intravenous drug users [11]. This article will consider only deep *Candida* infections in the above patient groups and will not include CAPD patients, intravenous drug users and patient groups discussed in previous Working Party reports, including those with AIDS [12] and haematological malignancy [13].

The impact of *Candida* infections is considerable. *Candida* was reported to be the fifth most common nosocomial isolate from blood culture in the USA (1986–1990), accounting for from 7 to 22% of such blood cultures [5–6]. In one series from a tertiary care institution, candidaemia occurred in 0.5% of all medical and surgical patients [3]. Candidaemia data from the UK are lacking. Serious *Candida* infection includes peritonitis, pneumonia and endophthalmitis as well as candidaemia itself. The incidence of all deep *Candida* infections in the hospitalised patient population is rising. The recent EPIC study showed that 17% of all intensive care unit patients have deep fungal infections, almost exclusively due to *Candida* [14]; the definition of infection in this preliminary report was not stated.

In two large series of patients with documented candidaemia only 43% of patients survived, 19% died of underlying disease and 38% died as a direct result of candidaemia (attributable mortality) [3, 6]. The impact of *Candida* peritonitis in surgical patients is hardly less remarkable with an attributable mortality of 37% [15, 16].

The majority of *Candida* infections have been caused by *Candida albicans* (85–90%) but recent data (from the USA) suggest a significant shift towards a higher proportion of non-*albicans* species (37–49%) causing candidaemia [1, 3]. If this alteration in the epidemiology of deep candidosis is seen more widely it would have significant bearing on antifungal prophylaxis and therapy. The vast majority (>98%) [17] of *C. albicans* isolates are susceptible to both fluconazole and amphotericin B (Table 1). However, limited data suggest a worse outcome in patients infected with isolates less susceptible to amphotericin B [18], as does some other work correlating in-vivo and in-vitro results [19]. *C. (Torulopsis) glabrata* is

Participants: J. Cohen, Chairman, Royal Postgraduate Medical School, London; D. W. Denning, Rapporteur, North Manchester General and Hope Hospitals and University of Manchester; E. G. V. Evans, University of Leeds; R. J. Hay, United Medical and Dental Schools of Guy's and St. Thomas' Hospital, London; D. W. R. Mackenzie, London School of Hygiene and Tropical Medicine,; A. G. Prentice, Derriford Hospital, Plymouth; T. R. F. Rogers, Royal Postgraduate Medical School, London; D. C. E. Speller, University of Bristol, Bristol; D. W. Warnock, Public Health Laboratory, Bristol; R. E. Warren, Royal Shrewsbury Hospital, Shrewsbury

Correspondence to: Dr. D. W. Denning, Department of Infectious Diseases and Tropical Medicine (Monsall Unit), North Manchester General Hospital, Delaunay's Road, Manchester M8 6RB, UK

Table 1. Appropriate antifungal agents for different *Candida* spp.

	Amphotericin B	Flucytosine	Fluconazole
C. albicans[a]	yes	yes	yes
C. glabrata[b]	yes	yes	no
C. krusei[b,c]	yes	yes	no
C. lusitaniae[b]	no	yes	yes
Other *Candida* species[b]	yes	yes	yes

[a] Virtually all *C. albicans* produce germ tubes, a test that takes less than an hour
[b] No other *Candida* spp. produces germ tubes and identification takes a minimum of 48 h with the best current methods
[c] Many isolates susceptible to itraconazole

rather less susceptible to antifungal agents (Table 1). No azole should be used for treating this organism because of both intrinsic resistance and the potential for resistance to emerge [20, 21]. *C. parapsilosis* may be less susceptible to killing by amphotericin B [22]. *C. krusei* is intrinsically resistant to fluconazole [23] (Table 1). *C.lusitaniae* may be resistant to amphotericin B ab initio or may develop resistance during therapy [24, 25] (Table 1). The majority of *C. lusitaniae* isolates are susceptible to flucytosine and fluconazole. *C. tropicalis* may have more potential for invasion [26] but is usually susceptible to amphotericin B, flucytosine and fluconazole. A number of other yeasts have also been implicated in fungaemia and/or meningitis including *Rhodotorula rubra, Saccharomyces cerevisiae, Hansenula anomala* and *Malassezia (Pityrosporum)* spp. A precise mycological diagnosis of yeast infection with speciation and susceptibility studies is thus desirable for optimal treatment.

Management strategies

There are five broad approaches to the use of antimicrobial therapy which are particularly important to consider in detail with respect to antifungal therapy. These approaches are: (1) prophylaxis; (2) pre-emptive therapy; (3) empirical therapy of suspected deep candidosis; (4) treatment of established deep candidosis; (5) maintenance therapy to prevent relapse.

Prophylaxis is the preventative therapy of a whole patient population regardless of individual risk factors. The incidence of various forms of candidosis is sufficiently common in much of the neutropenic patient population to justify prophylaxis and the Working Party has produced a report on this [26]. However, there are no such data in the intensive care unit or surgical setting and the Working Party does not believe prophylaxis is indicated routinely for all patients in these settings.

Pre-emptive therapy [27, 28] is the treatment of individual patients thought to be at high risk of developing deep candidosis, identified by laboratory or clinical markers, to prevent the disease. Risk factors include multiple-antibiotic administration [1, 6], significant renal impairment (e.g. requiring active intervention) [6], central venous catheterisation [3, 6], candiduria [6], high APACHE II score [3] and serious underlying illness [3], each being particularly strong predictors of deep candidosis. However, even though clear-cut risk factors for the development of disease due to *Candida* have been identified there are no data to support this approach to management. It is possible that patients at particularly high risk (e.g. those with pancreatitis or who have undergone gastrointestinal surgery) in whom two or more of these risk factors have been identified might be candidates for pre-emptive therapy. However, this approach is essentially experimental as there are no data to indicate the most appropriate antifungal agent, the effective dosage or the duration of treatment. Therefore, at the present time we do not recommend this approach.

Empirical therapy is the treatment of patients thought to have established deep candidosis without confirmation microbiologically, histologically or serologically. The clinical presentation of focal or disseminated candidosis is rarely distinctive and confirmation of the diagnosis often elusive [3, 5]. Present blood culture systems in many hospitals, designed for culturing bacteria, are suboptimal for yeasts. Lung biopsies to diagnose pulmonary candidosis are often difficult to achieve for logistic or medical reasons and the value of serological diagnosis is still under evaluation especially in the surgical and intensive care unit patient. Thus for the foreseeable future empirical therapy will be necessary. There is clearly considerable overlap between pre-emptive therapy and empirical therapy in many cases. The therapeutic regimen selected should be as described in the treatment section. However, the following clinical indications for empirical therapy are relatively clearcut:

1. Clinically unstable or deteriorating premature neonate (very or extremely low birth weight) with any skin breaks from which *Candida* has been grown, or positive urine microscopy or culture for yeast
2. Candiduria, even if associated with bladder catheterisation of heavy colonisation at other sites, in an at-risk patient defined as above together with deteriorating clinical status.

It may be appropriate to commence empirical antifungal therapy in patients with prosthetic value endocarditis likely to be due to *Candida* but with negative blood cultures. Confirmation of the diagnosis should be possible at surgery. Management of toxicity and deciding the duration of therapy can be difficult in this context if the diagnosis is not established.

The *treatment* of established deep candidosis requires a microbiological and clinical diagnosis. It is not the primary remit of this article to describe how the diagnosis of deep candidosis is established. There are however some principles that the Working Party have used in drawing up their recommendations for clinical management which it is necessary to enunciate. The diagnosis of deep (invasive) candidosis is sufficiently established, to initiate therapy, by any of the following:

1. a single positive blood culture in an at risk patient
2. isolation of *Candida* from any sterile site (except urine)
3. positive microscopy for yeast from a sterile specimen (e.g. CSF, bone biopsy etc.) prior to culture confirmation

4. histological evidence of yeast or mycelial forms in tissue from at risk patients.

Candida antigenaemia may be suggestive of disease but the methods currently available are not yet definitive. It may be appropriate to commence therapy on the basis of a positive candida antigen test (particularly in neonates) but we would regard this as empirical therapy rather than the treatment of established disease.

Antifungal agents

Therapy of deep *Candida* infection is presently in flux. There are three established antifungal agents useful for the treatment of *Candida* infections – amphotericin B, flucytosine and fluconazole. There are other agents undergoing evaluation which include liposomal amphotericin B (AmBisome), itraconazole, and lipid complexed amphotericin B (Amphocil) [29–31]. Ketoconazole has been superseded by fluconazole. Several other potentially useful agents are emerging from the pharmaceutical industry but most are in only the earliest phases of clinical evaluation.

Table 2 gives the Working Party's current views of the appropriate therapy for deep *Candida* infections. Response rates with amphotericin B are hard to ascertain but the overall mortality from candidaemia is 55% despite amphotericin B therapy [1, 3, 6]. Underlying disease, removal of catheters and other factors significantly alter responses to therapy and thus reports of small collections of patients have yielded differing results.

The general lack of toxicity of fluconazole makes it an attractive alternative to amphotericin B. Intermediate to good results were reported with fluconazole therapy early in the drug's development [32–34]. A recent randomised trial of candidaemia in non-neutropenic adults has just been concluded [35]. This study, the first randomised study of candidaemia, showed that fluconazole 400 mg daily was equivalent to amphotericin B 0.5–0.6 mg/kg daily. The response rates were 70% and 79% respectively. There is however still some uncertainty about the optimal dose for fluconazole. For example, 30 surgical/ICU patients with candidaemia treated with 5 mg/kg had a 60% response rate whereas the next 30 patients in the same unit treated with 10 mg/kg had a 83% response rate [36]. These data need confirmation elsewhere before we can recommend the higher dose routinely and in any case exceed licensed doses in the UK. Higher doses of fluconazole are however required in patients undergoing haemofiltration as the drug is rapidly cleared by this route.

The Working Party recommend that fluconazole is indicated for the following: i) patients with candidaemia or urinary tract candidosis due to susceptible species; ii) patients failing amphotericin B and flucytosine and iii) for those with significant toxicity to amphotericin B or iv) those who need to continue with oral therapy after intravenous amphotericin B therapy.

It is not possible at present to offer definitive statements about the respective role of amphotericin B administered as a liposomal preparation (AmBisome), a lipid

Table 2. Treatment of deep candidosis[a]

Disease	First line	Second line
Candidaemia		
Neonates[b]	Amphotericin B 1 mg/kg + flucytosine[c]	Fluconazole 5 mg/kg
Other[b]	Amphotericin B 0.5–0.7 mg/kg ± flucytosine[c] Fluconazole 400–800 mg	Fluconazole 400 mg
Candida peritonitis (surgical)	Amphotericin B 0.5–0.7 mg/kg ± flucytosine[c]	Fluconazole 400 mg
Urinary tract candidiasis	Fluconazole 200 mg	Flucytosine
Candida endocarditis[d]	Amphotericin B 1 mg/kg + flucytosine[c]	AmBisome[e] 3 mg/kg + flucytosine[c] Fluconazole 400–800 mg
Candida suppurative thrombophlebitis[d]	Amphotericin B 0.5–0.7 mg/kg + flucytosine[c]	Fluconazole 400 mg
Candida meningitis[b]	Amphotericin B 1 mg/kg + flucytosine[c]	Fluconazole 400 mg
Candida endophthalmitis[f]	Intravitreal amphotericin B 5 mg + flucytosine[c] + amphotericin B 1 mg/kg	Fluconazole 400 mg
Candida arthritis or osteomyelitis	Amphotericin B 0.5–0.7 mg/kg ± flucytosine	Fluconazole 400 mg

All doses quoted as total daily dose, for adults in case of fluconazole

[a] Some therapeutic options may be poor for particular *Candida* spp.
[b] Remove, or change, intravenous catheters [35, 36] or shunts, unless impossible
[c] Flucytosine dose is 75–100 mg/kg/d in 2–4 divided doses with dosage adjustments depending on renal function and/or serum concentrations
[d] Surgery (valve replacement or removal of affected peripheral vein) essential
[e] Optimal formulation of a lipid associated amphotericin B, and dose, uncertain
[f] Partial vitrectomy essential for diagnosis and therapy, if sight threatened

complex (ABLC), a colloidal dispersion (Amphocil) or administered in Intralipid rather than glucose. Animal model and limited human therapeutic data indicate that larger doses of amphotericin B can be administered relatively safely using these mixtures of formulations but that efficacy is reduced by 2–4 fold on a mg to mg basis depending on the fungus and model system [29–31]. Further data are necessary before any of these preparations can be recommended for first line use for *Candida* infections. The mortality of established deep candidosis is such that the benefit of reducing toxicity (which is usually preventable and/or reversible) must be carefully weighed against possible loss of activity (as the minimum and optimal dose is not established).

The use of flucytosine requires facilities for monitoring serum concentrations [17]. The optimal and minimum serum concentrations of flucytosine for efficacy are not known but haematological toxicity is reduced if concentrations are maintained under 100 mg/l. Toxicity is more likely after 2 weeks of combined amphotericin B and flucytosine therapy, because of amphotericin B nephrotoxicity. There is much anecdotal evidence supporting the use of flucytosine in combination with amphotericin B, but no conclusive proof of benefit. The Working Party feel that the following are appropriate indications for the addition of flucytosine to amphotericin B i) when endophthalmitis, endocarditis, suppurative thrombophlebitis or meningitis is present; ii) in neonates (because of the 45% incidence of meningitis); iii) in *C. glabrata* or *C. lusitaniae* infections; iv) the patient is extremely ill. If the organism is later found to be resistant to flucytosine the drug should be discontinued. Little data is published on the combination of fluconazole and flucytosine.

Specific manifestations of deep candidosis

Some specific comments on the therapy of particular manifestations of deep candida infection follow.

Neonatal candidaemia

Neonates appear to tolerate amphotericin B and flucytosine well although the monitoring of flucytosine concentrations should be commenced within 48 h of initiating therapy and carried out 2–3 times a week. Flucytosine should be administered twice daily initially. The use of flucytosine is appropriate in all cases because of the high incidence of meningitis [7–9]. Complications besides meningitis include renal outflow obstruction, osteomyelitis or arthritis, cutaneous abscesses and mycocarditis/endocarditis. With appropriate therapy the mortality rate in neonates is lower than in adults, approximately 10%.

Candidaemia in adults

All patients with candidaemia require therapy, given that there is an attributable mortality of 38% [3, 6]. Therapy should be started immediately without waiting for confirmation from further cultures. Transient candidaemia is now no longer regarded as a useful clinical classification. There are however some patients who are ambulant and essentially well with candidaemia and others who are desperately ill. The intensity and duration of therapy will differ between these two groups but all patients should be commenced initially on amphotericin B or fluconazole depending in part on the infecting species. Very ill patients should also receive flucytosine with amphotericin B initially. If patients do not improve with amphotericin B alone, flucytosine should be added or therapy changed to fluconazole. If the response is rapid or the patient was only mildly ill on the initiation of therapy a switch from amphotericin B to fluconazole may be appropriate within 7–14 days. If amphotericin B is continued it should be given for at least four weeks to a total dose exceeding 1 g. Patients not responding to fluconazole often respond to amphotericin B or AmBisome.

A considerable amount of data support the need to remove or change intravenous catheters in candidosis [35, 38, 39]. Patients with persistent candidaemia despite 5 days of therapy should certainly have their venous catheters removed. Use of a guide wire to replace catheters results in immediate infection of the new catheter with the same organism.

Candida peritonitis or wound drainage in surgical patients

Candida peritonitis following extensive abdominal surgery can be insidious in onset and associated with bacterial peritonitis or positive bacterial cultures in wound drainage. Therapy is appropriate in those with positive cultures for candida from a deep collection or as a heavy growth from a drain with clinical features of sepsis. A combination of peritoneal lavage without resorting to another laparotomy (for which there is little supportive data) and amphotericin B with or without flucytosine is appropriate.

Urinary tract candidosis

Urinary tract candidosis implies candiduria and the passage of fungal balls in the urine, radiological evidence of outflow obstruction with fungal balls, a parenchymal abscess or other histological evidence of renal tract involvement. Many fungi may produce a similar clinical picture, only some of which are susceptible to fluconazole. The penetration of amphotericin B into the urine is poor and the likelihood of development of resistance to flucytosine if used alone is considerable. Thus fluconazole represents an appropriate first-line therapy if the causative species is susceptible even though this has not been shown in controlled trials. Fluconazole will not sterilise the urinary tract if the same catheter remains in place. Obstructive nephropathy with fungal balls in the pelvis and kidney may require surgical exploration and their removal. Urinary catheters and nephrostomy tubes should be changed.

Patients with persistent candiduria related to abnormal urinary tracts and long-term indwelling urinary catheters may respond to amphotericin B bladder washouts and catheter change [40]. If used, amphotericin B 5 to

10 mg with an intravesical dwell time of 2 h is appropriate once or twice a day for no longer than 2 days.

Candida endocarditis

Candida endocarditis [41, 42] is seen most commonly in the context of prosthetic valve endocarditis but may occasionally occur as a complication of candidaemia in the intensive care unit, in heroin addicts and in a few other settings. On native valves, large vegetations are usually seen or the patient may present with a large vessel embolus in which pseudohyphae may be seen histologically or *Candida* cultured. Patients with prosthetic valve endocarditis may have normal echocardiograms. All patients (except neonates [9]) with candida endocarditis require valve replacement [41–44]. Amphotericin B 1 mg/kg with flucytosine is appropriate medical therapy as the penetration of amphotericin B into vegetations is poor. It is not known if the timing of surgery is important in response. Alternative therapies include AmBisome with flucytosine or large doses of fluconazole (e.g. 10 mg/kg). There are very few data on the efficacy of these latter treatments. Relapse may occur many months after apparently successful therapy [44, 45].

Candida suppurative thrombophlebitis

In a peripheral site this requires resection of the vein or artery in addition to the therapy as administered for candidaemia [46]. If the central veins are involved resection is clearly not possible and large doses of amphotericin B and flucytosine for long periods of time are likely to be needed to eradicate the infection.

Candida meningitis

Candida meningitis [47] usually occurs in immunocompromised patients following candidaemia or in the context of neurosurgical procedures following ventriculoperitoneal shunt placement. Amphotericin B with flucytosine is appropriate in very ill patients with *Candida* meningitis. Penetration of amphotericin B into cerebrospinal fluid is poor (less than 10%) and flucytosine is therefore helpful. In mildly ill patients with neurosurgical shunt infections the removal or replacement of the shunt is critical and fluconazole therapy may be as efficacious as amphotericin B and flucytosine in this setting. The use of intraventricular amphotericin B given via shunts or Ommaya reservoirs has little to recommend it as the distribution of amphotericin B given this way is limited.

Candida endophthalmitis

Candida endophthalmitis is a common complication of candidaemia (9–22%) [48, 49]. It occurs with all species of *Candida* and may not be manifest until several days or weeks after treatment has commenced. Any ocular symptoms should be taken seriously in these patients and in all patients the pupils should be dilated and the fundi examined for the presence or absence of retinal lesions. Large, progressive or symptomatic lesions will usually require a partial vitrectomy and intravitreal dosing of amphotericin B. Patients also require systemic amphotericin B in high doses, with flucytosine, as the penetration of amphotericin B into the vitreous is not good. Subconjunctival amphotericin B probably contributes little and is unnecessary. Fluconazole may be an alternative therapy because of the good penetration of the vitreous but there are very few clinical data to support its use.

Candida arthritis

This may occur as a complication of candidaemia particularly in IV drug abusers or in the context of prosthetic joint replacements. The contribution of intra-articular amphotericin B is probably small but has not been rigorously examined. In patients with infected non-prosthetic joints systemic amphotericin B initially without flucytosine is appropriate. Flucytosine should be added if improvement is not obtained within 5–7 days, or fluconazole substituted. In patients with prosthetic joints, replacement of the joint together with the removal of all existing cement and necrotic bone tissue should be undertaken. This is often very difficult to achieve and long-term suppressive therapy may be an alternative, especially elderly.

Candida osteomyelitis

Candida osteomyelitis is generally a late complication of candidaemia presenting weeks after discharge from hospital. The vertebral column is most often affected although sternal osteomyelitis after cardiac surgery has been reported. Debridement of necrotic bone and bone grafting at the same procedure if necessary for stability if extensive vertebral destruction is present. Systemic amphotericin B with or without flucytosine (as used for arthritis) is appropriate therapy, with fluconazole a useful alternative.

Duration of therapy

The duration of therapy for all forms of deep candidosis is uncertain. A larger total dose and longer duration of amphotericin B therapy are associated with lower mortality [3]. Rarely should therapy be for less than 4 weeks and in very ill patients it should be for longer (e.g. 8–10 weeks). The intensity of dosing as shown on Table 1 can often be moderated after the first 2 weeks of therapy.

Maintenance therapy is only indicated occasionally for patients with serious candidal disease who are not immunocompromised. In almost all circumstances this relates to the persistent presence of foreign material infected with *Candida* which cannot be removed. Examples include Porto-cath devices, vascular grafts, artificial joints, ventriculoperitoneal shunts, etc. In general, it is desirable to remove foreign material as it is extremely difficult to eradicate candida infections without so doing but there are occasionally extenuating clinical circumstances which prohibit this course of action. In these circumstances lifelong therapy with antifungal agents may be appropriate. At present, the only agent appropriate for this use given its low toxicity and oral bioavailability is fluconazole. There are no data available as to dose but 100–200 mg

daily is probably appropriate. If the organism involved is resistant to fluconazole (*C. krusei* or *C. glabrata*) intermittent amphotericin B with or without flucytosine is one choice; ketoconazole or itraconazole 400 mg/day may be useful depending on susceptibility testing [17]. No choice is ideal because of the requirement for monitoring for toxicity or serum concentrations and, in the case of amphotericin B, problems of cumulative toxicity and those associated with intravenous access including bacteraemia. There are insufficient data to support the use of itraconazole for deep *Candida* infections even though it is effective for mucosal candidosis. In circumstances where currently available oral therapy is inadequate, early consideration of experimental therapy is appropriate. Isolates obtained from patients should also be monitored for the development of resistance [17].

Prevention

In the surgical and intensive care unit setting limited data suggest that modification of two aspects of care might reduce the incidence of serious candidal infection. The number of antibiotic classes prescribed increases the risk of candidaemia [3, 6]. Thus reducing antibiotic prescriptions and more closely targeted therapy would probably have some impact on reducing candidaemia. It is not known if the duration of antibiotic therapy is important although this appears likely. In practice therefore a judicious approach to antibiotic prescribing in these patients is appropriate.

The other factor likely to reduce candida infections is good compliance with infection control practices to reduce hospital staff transmission of *Candida*. Much careful epidemiological work using DNA typing for strain delineation has shown cross infection among patients and frequent hand carriage of *Candida* by nursing, medical and other staff. Compliance with handwashing is often poor. Several outbreaks in surgical patients or in hospital ward settings have been described, in some cases with resistant isolates.

Conclusion

Life threatening, deep *Candida* infections are increased in frequency and importance. The mortality remains high. Inadequate data exist concerning the most appropriate management strategies, the antifungal agent of choice, the dose of that antifungal agent and the merit or otherwise of combination and/or sequential therapy. More antifungal agents will be marketed in the next decade generating additional uncertainty as to their place in clinical management. Multicentre trial work is essential to address these questions.

References

1. Komshian SV, Uwaydah AK, Sobel JD, Crane LR (1989) Fungemia caused by *Candida* species and *Torulopsis glabrata* in the hospitalized patient: frequency, characteristics, and evaluation of factors influencing outcome. Rev Infect Dis 11:379–390
2. Wenzel RP, Pfaller MA (1991) *Candida* species: emerging hospital bloodstream pathogens. Infect Control Hosp Epidemiol 12:523–524
3. Fraser VJ, Jones M, Dunkel J, Storfer S, Medoff G, Dunagan WC (1992) Candidemia in a tertiary care hospital: epidemiology, risk factors, and predictors of mortality. Clin Infect Dis 15:414–421
4. Denning DW (1991) Epidemiology and pathogenesis of systemic fungal infection in the immunocompromised host. J Antimicrob Chemother 28 [Suppl B]:1–16
5. Edwards JE (1991) Invasive *candida* infections. Evolution of a fungal pathogen. N Engl J Med 324:1059–1062
6. Wey SB, Mori M, Pfaller MA, Woolson RF, Wenzel RP (1988) Hospital-acquired candidemia. The attributable mortality and excess length of stay. Arch Intern Med 148:2642–2645
7. Johnson D, Thompson T, Green T, Ferrieri P (1984) Systemic candidiasis in very low birth weight infants (<1500 g). Pediatrics 73:138–143
8. Baley J, Kleigman R, Fanaroff A (1984) Disseminated fungal infections in very low birth weight infants: Clinical manifestations and epidemiology. Pediatrics 73:144–152
9. Sanchez P, Siegel J, Fishbein J (1991) *Candida* endocarditis: successful medical management in three preterm infants and review of the literature. Pediatr Infect Dis J 10:239–243
10. British Society for Antimicrobial Chemotherapy Working Party (1987) Diagnosis and management of peritonitis in continuous ambulatory peritoneal dialysis. Lancet I:845–849
11. Leen CLS, Brettle RP (1991) Fungal infections in drug abusers. J Antimicrobial Chemother 28 [Suppl A]:83–96
12. British Society for Antimicrobial Chemotherapy Working Party on Fungal Infection (1992) Treatment of fungal infections in AIDS. Lancet 340:648–651
13. Dupont B (1991) Clinical manifestations and management of candidosis in the compromised patient. In: Warnock DW, Richardson MD (eds) Fungal infection in the compromised patient. Wiley, Chichester, pp 55–83
14. EPIC Study Group (1992) The EPIC study – preliminary results. HOST 9:12–13
15. Calandra T, Bille J, Schneider R, Mosimann F, Francioli P (1989) Clinical significance of *Candida* isolated from peritoneum in surgical patients. Lancet II:1437–1440
16. Bayer AS, Blumenkrantz MJ, Montgomerie JZ, Galpin JE, Coburn JW, Guze LB (1976) *Candida* peritonitis: report of 22 cases and review of the English literature. Am J Med 61:832–840
17. British Society for Antimicrobial Chemotherapy Working Party on Fungal Infection (1991) Laboratory monitoring of antifungal chemotherapy. Lancet 357:1577–1580
18. Powderly WG, Kobayashi GS, Herzig GP, Medoff G (1988) Amphotericin B-resistant yeast infection in severely immunocompromised patients. Am J Med 84:826–832
19. O'Day DM, Ray WA, Robinson RD, Head WS, Williams TE (1991) Differences in response in vivo to amphotericin B among *Candida albicans* strains. Invest Ophthalmol Vis Sci 32:1569–1572
20. Warnock DW, Burke J, Cope NJ, Johnson EM, von Fraunhofer NA, Williams EW (1988) Fluconazole resistance in *Candida glabrata*. Lancet II:1310
21. Vanden Bossche H, Marichal P, Odds FC, Le Jeune L, Coene M-C (1992) Characterization of an azole resistant *Candida glabrata* isolate. Antimicrob Agents Chemother 36:2602–2610
22. Seidenfeld SM, Cooper BH, Smith JW, Luby JP, Mackowiak PA (1983) Amphotericin B tolerance: a characteristic of *Candida parapsilosis* not shared by other *Candida* species. J Infect Dis 147:116–119
23. Wingard JR, Merz WG, Rinaldi MG, Johnson TR, Karp JE, Saral R (1991) Increase in *Candida krusei* infection among patients with bone marrow transplantation and neutropenia treated prophylactically with fluconazole. N Engl J Med 325:1274–1277
24. Pappagianis D, Collins MS, Hector R, Remington J (1979) Development of resistance to amphotericin B in *Candida lusitaniae* infecting in human. Antimicrob Agents Chemother 16:123–126
25. Blinkhorn RJ, Adelstein D, Spagnuolo PJ (1989) Emergence of a new opportunistic pathogen, *Candida lusitaniae*. J Clin Microbiol 27:236–240

26. British Society for Antimicrobial Chemotherapy Working Party on Fungal Infection (1993) Antifungal prophylaxis in leukaemia and transplantation. J Antimicrob Chemother 32:5–21
27. Rubin RH (1991) Preemptive therapy in immunocompromised hosts. N Engl J Med 324:1057–1058
28. Schmidt GM, Horak DA, Niland JC et al (1991) A randomized, controlled trial of prophylactic ganciclovir for cytomegalovirus pulmonary infection in recipients of allogenic bone marrow transplants. N Engl J Med 324:1005–1011
29. Brajtburg J, Powderly WG, Kobayashi GS, Medoff G (1990) Amphotericin B: delivery systems. Antimicrob Agents Chemother 34:381–384
30. Clark JM, Whitney RR, Olsen SJ, George RJ, Swerdel MR, Kunselman L, Bonner DP (1991) Amphotericin B lipid complex therapy of experimental fungal infections in mice. Antimicrob Agents Chemother 35:615–621
31. Clemons KV, Stevens DA (1992) Efficacies of amphotericin B lipid complex (ABLC) and conventional amphotericin B against murine coccidioidomycosis. J Antimicrob Chemother 30:353–363
32. Van't Wout JW, Mattie H, Van Furth R (1988) A prospective study of the efficacy of fluconazole (UK-49,858) against deep-seated fungal infections. J Antimicrob Chemother 21:665–672
33. Ikemoto H (1989) A clinical study of fluconazole in the treatment of deep mycoses. Diagn Microbiol Infect Dis 12:S329–S247
34. Nolla-Salas J, León C, Torres-Rodríguez JM, Martín E, Sitges-Serra A (1992) Treatment of candidemia in critically ill surgical patients with intravenous fluconazole. Clin Infect Dis 14:952–954
35. Rex JH, Bennett JE, Sugar AM et al (1993) Fluconazole (FLU) vs. Amphotericin B (AMB) for treatment of candidemia: results of a randomized, multicenter trial. 33rd Interscience Conference on Antimicrobial Agents and Chemotherapy, October 17–20, 1993. American Society for Microbiology: Abstract 805
36. Graninger W, Presteril E, Schneeweiss B, Teleky B, Georgopoulos A (1992) Treatment of *Candida albicans* fungaemia with fluconazole. J Infect 26:133–146
37. Kujath P, Lerch K (1989) New antimicrobial agents under clinical investigation. Secondary mycosis in surgery: treatment with fluconazole. Infection 12:111–117
38. Eppes SC, Troutman JL, Gutman LT (1989) Outcome of treatment of candidemia in childen whose central catheters were removed or retained. Pediatr Infect Dis J 8:99–104
39. Dato VM, Dajani AS (1990) Candidemia in children with central venous catheters: role of catheter removal and amphotericin B therapy. Pediatr Infect Dis J 9:309–314
40. Sanford JP (1993) The enigma of candiduria: Evolution of bladder irrigation with amphotericin B for management – from anecdote to dogma and a lesson from Machiavelli. Clin Infect Dis 16:145–147
41. Walsh TJ, Hutchins GM, Bulkley BH, Mendelsohn G (1980) Fungal infections of the heart: analysis of 51 autopsy cases. Am J Cardiol 45:357–366
42. Rubinstein E, Noriega ER, Simberkoff MS, Holzman R, Rahal JJ (1975) Fungal endocarditis: analysis of 24 cases and review of the literature. Medicine 54:331–344
43. Weems JJ (1992) *Candida parapsilosis*: Epidemiology, pathogenicity, clinical manifestations and antimicrobial susceptibility. Clin Infect Dis 14:756–766
44. Rudd RM, Hill PR, Kopelman P, Parker DJ (1980) Fungal endocarditis after homograft valve replacement: difficulties in diagnosis and treatment. Thorax 35:686–689
45. Galgiani JN, Stevens DA (1977) Fungal endocarditis: need for guidelines in evaluating therapy. J Thorac Cardiovasc Surg 73:293–296
46. Walsh TJ, Bustamente CI, Vlahov D, Standiford HC (1986) Candidal suppurative peripheral thrombophlebitis: recognition, prevention, and management. Infect Control 7:16–22
47. Lipton SA, Hickey WF, Morris JH, Loscalzo J (1984) Candidal infection in the central nervous system. Am J Med 76:101–108
48. Brooks RG (1989) Prospective study of *Candida* endophthalmitis in hospitalized patients with candidemia. Arch Intern Med 149:2226–2228
49. Schmid S, Martenet AC, Oelz O (1991) *Candida* endophthalmitis: Clinical presentation, treatment and outcome in 23 patients. Infection 19:21–24