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A Randomized Study Comparing Fluconazole with Amphotericin B/5-Flucytosine for the Treatment of Systemic *Candida* Infections in Intensive Care Patients

Summary: In this prospective, randomized study fluconazole and amphotericin B/5-flucytosine were compared in the treatment of systemic candidiasis. Seventy-two non-neutropenic intensive care patients with systemic *Candida* infections were enrolled. Thirty-six patients were randomly assigned to receive fluconazole (400 mg on the first day then 200 mg) and 36 were randomized to amphotericin B/5-flucytosine (1.0–1.5 mg/kg body weight every other day and 3×2.5 g flucytosine/day) for 14 days following the diagnosis. There was no statistically significant difference in clinical outcome in regard to the treatment of pneumonia and sepsis: 18/28 of the patients were treated successfully with fluconazole and 17/27 with amphotericin B/5-flucytosine. For the treatment of peritonitis, however, amphotericin B/5-flucytosine was more effective than fluconazole (55% vs. 25%). Furthermore, amphotericin B/5-flucytosine was found to be superior to fluconazole with regard to pathogen eradication (86% vs. 50%). Fluconazole was associated with less toxicity than amphotericin B/5-flucytosine.

The incidence of systemic *Candida* infections is on the rise, particularly in non-neutropenic intensive care patients. According to recent data, *Candida* is the fifth most common nosocomial pathogen isolated from blood cultures in the USA [1, 2]. Serious *Candida* infection includes peritonitis, pneumonia, and candidemia. Recent data have documented mortality rates of 46–75% [3, 4] with 38% of the patients dying as a direct result of candidemia [5]. The majority of *Candida* infections are caused by *Candida albicans* (85–90%). More recent data, however, suggest a significant shift towards other *Candida* species (37–49% [2, 6]). For many years, amphotericin B has been the treatment of choice for systemic candidiasis. Results of treatment with fluconazole in neutropenic and non-neutropenic patients [7, 8] have been encouraging [9–12]. Due to its lack of toxicity, fluconazole is an interesting therapeutic alternative to amphotericin B.

We conducted a randomized, comparative multicenter study of fluconazole and amphotericin B/5-flucytosine (5-FC) in the treatment of non-neutropenic intensive care patients with systemic *Candida* infection.

Patients and Methods

Study design: This prospective, randomized study included 72 ICU patients (medical and anesthesiologic intensive care unit of the City Hospital Munich-Schwabing) aged 18–80 years with evidence of systemic *Candida* infection. Participation in the study was precluded if any of the following criteria applied: pregnancy or lactation, treatment with rifampicin, phenytoin, isoniazid, anticoagulants, anticonvulsants, oral antidiabetics or xanthine derivatives, treatment with fluconazole or amphotericin B 1 month before inclusion in the study, significant impairment of hepatic function (serum enzymes and bilirubin more than four times above the normal upper limit. All patients were observed from their admission to the ICU until the end of therapy or until they died. All patients were examined for signs and symptoms of infection at daily intervals. The hematology, biochemistry and microbiology test results (including the results of the serologic diagnosis of *Candida* infection and chest X-ray (if necessary) were evaluted at the study start, at minimum intervals of 5 days during the study and upon completion of treatment. Prior to the start, all patients were classified on the basis of their APACHE II Score (including Glasgow Scale [13]).

Written or oral informed consent was provided by all patients or their relatives. The study was approved be the Ethics Committee.

Patients: Fluconazole group: Thirty-six patients randomized into the fluconazole group were given fluconazole 400 mg on the first day and subsequently received 200 mg/day (i.v.) for the remainder of the study. The dosis was adjusted in patients with renal insufficiency. Randomization was performed on the basis of a sequential list of block-randomized assignments maintained by the principal investigator.

Amphotericin B/5-flucytosine group: Thirty-six patients randomized into the amphotericin B group received amphotericin B in combination with 5-flucytosine at doses of 1–1.5 mg/kg body weight (maximum dose 70 mg) every other day. Flucytosine was administered at daily doses of 3×2.5 g. Drug levels were monitored weekly, in patients with impaired renal function twice a week. Peak blood levels were kept between 50 and 75 mg/l and, certainly below 100 mg/l. The dose was adjusted to serum levels.

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Microbiological surveillance: The following samples were collected for quantitative cultures immediately after ICU admission and subsequently at 3-day intervals: oropharyngeal and rectal swabs, endotracheal aspirates, bronchoalveolar lavage (if possible), urine, gastric aspirates and wound secretions, blood cultures (in case of fever) and tips of indwelling catheters. All samples were examined microsopically after Gram staining. Standard methods were used for culture and pathogen identification. The serologic antibody and antigen detection was carried out by use of the hemagglutination and the Ramco Latex tests (high sensitivity [14]).

Definitions: The diagnosis of systemic candidiasis was made if the following criteria applied: histologic evidence of blastomycetes in a tissue sample, positive cultures of normally sterile sites, positive blood culture (not taken via the indwelling catheter), *Candida* lesion of the retina. *Septicaemia* was defined as the presence of *Candida* species in blood cultures or tissues and clinical evidence of infection. Pneumonia was assumed if at least one criterion from each of the following categories applied: a) clinical criteria: temperature >38.5°C, purulent tracheabronchial aspirate, WBC >12,000/mm^3, elevated alveolar arterial oxygen gradient; b) infiltrates: on chest x-ray; and c) mycological criteria: quantitative culture of tracheal aspirate or BAL positive for *Candida* species as the only microorganism >10^4 cfu/ml. Colonization was assumed when only the mycological criteria applied. Patients with signs of inflammation and a positive *Candida* culture of purulent secretions, aspirate or a biopsy were diagnosed as having soft tissue infections, abscesses, peritonitis and wound infection. Clinical cure was defined as resolution of all symptoms and clinical signs. Clinical improvement was defined as a substantial improvement of the symptoms without complete clinical resolution of the infection. Failure was defined as the absence of any substantial clinical improvement. Microbiological cure was defined as the eradication of *Candida* species during therapy with absence of growth at the posttreatment follow-up. Patients were considered to have died from fungal infection if they died with evidence of infection following isolation of *Candida* and if no significant clinical improvement had occurred; if they had cultures that were persistently positive for *Candida* or if autopsy revealed histological evidence of invasive candidiasis. The fungal infection score was determined on the basis of the following ratings (ten): positive histological finding (ten points), positive blood culture (seven points), positive culture from central venous catheter tip (five points), positive mycological findings in more than five sites (four points), positive *Candida* antigen test >1:16 (three points).

Statistical method: For the statistical analysis, the two-sided Fisher's exact test was used. The age, the time on artificial ventilation and the colonization were tested by the Mann-Whitney test. The significance level was 5% ($p < 0.05$).

Table 1: Characteristics of the patients.

Characteristics	Fluconoazole (n = 36)	Amphotericin B/5-FC (n = 36)
Age in years (SD)	58.3 (15.0)	59.7 (11.8)
Sex (male/female)	26/10	25/11
Weight in kg (SD)	70 (14)	75 (18)
Height in cm (SD)	172 (8.7)	180 (14.0)
APACHE II score (SD)	20 (2.3)	20 (2.8)
Fungal infection score (SD)	15 (4.7)	14 (5.0)
Interval colonization/therapy		
Mean in days (SD)	10.4 (7.9)	16.4 (9.2)
Underlying disease		
Cancer	5	4
Gastrointestinal disease	6	8
Cardiovascular disease	7	8
Respiratory disease	8	7
Pancreatitis	5	6
Cranial trauma	5	3
Risk factors for candidiasis		
Recent surgery	20	19
Recent use of antibiotics	35	36
Central venous catheter	34	35
Recent hyperalimentation	23	30
Diabetes mellitus	10	8
Recent use of corticosteroids	12	10
Age > 60 years	14	17

Results

A total of 72 patients (36 in the fluconazole group and 36 in the amphotericin B group) were enrolled. Their data are shown in Table 1.

C. albicans was the causative organism found most frequently, with 72% (26/36) of the fluconazole patients and 64% (23/36) of the amphotericin patients being diagnosed as having a monoinfection with *C. albicans*. Further data are shown in Table 2.

Patients randomized into the fluconazole group were treated for 14.9 (8.9) days (range 5–19 days) at a mean dose of 191.9 (87.0) mg fluconazole/day. The treatment was initiated at a mean of 10.4 (7.9) days (range 4–30 days) after demonstration of *Candida* organisms. Patients randomized into the amphotericin group were treated for 15.4 (9.4) days (range 7–22 days) at mean daily doses of 41.4 (11.0) mg amphotericin and 6.09 g (1.62) flucytosine. In this group, treatment was started at a mean of 16.4 (9.2) days after demonstration of *Candida* infection (range 5–31 days). The duration of therapy and the time to initiation of therapy did not differ significantly between the two groups.

Adverse Events

Elevations of serum creatinine were seen in 31% (11/36) of the amphotericin-treated patients and in none of the fluconazole group ($p < 0.001$ by Fisher's exact test). Chills or rigor were observed in the patients on amphotericin B only (44%; 16/36; $p < 0.001$ by Fisher's exact test). Hypokalemia developed in 6% (2/36) of the patients in the fluconazole group and in 14% (5/36) of the patients of the amphotericin group ($p > 0.05$). Elevations of liver enzymes were seen in 25% (9/36) of the patients of the fluconazole group and in 19% (7/36) of the amphotericin group ($p > 0.05$). No toxic hematologic effects were ob-

Table 2: Distribution of causative *Candida* organisms.

	Fluconazole (n = 36)	Amphotericin B/5-FC (n = 36)
Monoinfection		
Candida albicans	26 (72%)	23 (64%)
Torulopsis glabrata	0	1
Candida pseudotropicalis	1	0
Candida tropicalis	1	1
Mixed fungal infection		
Candida albicans + *Torulopsis glabrata*	1	3
Candida albicans + *Candida guilliermondii*	2	1
Candida albicans + *Candida krusei*	2	2
Torulopsis glabrata + *Candida krusei*	1	2
Torulopsis glabrata + *Candida pseudotropicalis*	0	2
Candida albicans + *Torulopsis glabrata* + *Candida krusei*	1	2
Candida albicans + *Torulopsis glabrata* + *Candida tropicalis*	0	1
Torulopsis glabrata + *Candida krusei* + *Candida tropicalis*	1	0
Total number of each species		
Total number of *Candida*	46	52
Candida albicans	32	32
Torulopsis glabrata	4	10
Candida guilliermondii	2	1
Candida krusei	5	5
Candida pseudotropicalis	1	2
Candida tropicalis	2	2

Table 3: Response to therapy.

	Fluconazole (n = 36)		Amphotericin B/5-FC (n = 36)	
Clinical response				
No. of patients	24	(67%)	25	(69%)
Early start of therapy (<8 days)*	20/24	(69%)[a]	18/23	(78%)[a]
Late start of therapy (>8 days)*	4/12	(25%)[a]	6/13	(46%)[a]
Cure	20	(56%)	22	(61%)
Improvement	4	(11%)	3	(8%)
Failure	12	(33%)	11	(31%)
Death	13	(36%)	14	(39%)
Death related to fungal infection	9	(25%)	7	(19%)
Microbiological response				
No. of *Candida* species	34/46	(74%)	45/52	(87%)
Elimination	22/46	(48%)[c]	42/52	(83%)[c]
Candida albicans	20/34	(59%)[b]	30/32	(94%)[b]
Other *Candida* species	2/12	(17%)[a]	12/20	(60%)[a]
Decrease	12/46	(26%)	2/52	(4%)
Persistence	10/46	(22%)	5/52	(10%)

* interval between detection of colonization and start of therapy; [a] $p < 0.05$; [b] $p < 0.01$; [c] $p < 0.001$.

served in patients receiving amphotericin/5-FC. However, peak blood levels of 5-FC were kept below 100 mg/l in all cases.

Site of Infection

In the amphotericin group, 25% (9/36) of the patients suffered from pneumonia (histologically proven in five cases), 50% (18/36) of the patients had fungemia and 25% (9/36) peritonitis (histologically proven in all cases). In the fluconazole group, 31% (11/36) developed pneumonia (histologically proven in two cases), 47% (17/36) had fungemia and 22% (8/36) suffered from peritonitis (histologically proven in all cases). One patient with histologically proven pneumonia (amphotericin group) suffered from underlying rheumatoid arthritis. This patient had developed legionellosis and subsequent fungal pneumonia during treatment with corticosteroids. Another three patients with histologically proven pneumonia had an underlying chronic respiratory tract disease which required corticosteroid treatment. Following pneumonia due to *Pseudomonas aeruginosa,* the patients developed *Candida* pneumonia. The remaining three cases of histologically proven pneumonia (one each in the fluconazole and the amphotericin group) were patients who developed pneumonia secondary to severe alcoholism and compromised host defense (Table 4).

Outcome

In the treatment of pneumonia and sepsis/fungemia no significant difference was found between the groups with regard to clinical and microbiologic response or elimination rate. In the treatment of peritonitis, however, amphotericin B/5-FC was better than fluconazole (Table 3).

Treatment Failures

A total of 27 (38%) patients did not survive their *Candida* infection, with 14 (39%) in the amphotericin group and 13 (36%) in the fluconazole group. Seven patients (19%) of the amphotericin group died as a direct result of *Candida* infection (Table 5). In three of these patients, mixed fungal infections were present, involving *C. albicans. Candida krusei* and *Torulopsis glabrata* in one patient

Table 4: Response to therapy related to the site of infection.

	Fluconazole (n = 36)	Amphotericin B/5-FC (n = 36)
Sepsis/Fungemia		
No. of patients	17 (47%)	18 (50%)
Age (SD)	59 (14.8)	56 (13.9)
APACHE II score (SD)	20 (2.1)	20 (2.4)
Fungal infection score (SD)	19 (4.3)	20 (5.0)
Clinical cure	10 (59%)	11 (61%)
Death	3 (18%)	2 (11%)
Pneumonia		
No. of patients	11 (31%)	9 (25%)
Age (SD)	57 (13.8)	62 (12.9)
APACHE II score (SD)	20 (2.1)	20 (2.4)
Fungal infection score (SD)	19 (4.8)	20 (4.7)
Clinical cure	8 (73%)	6 (67%)
Death	1 (9%)	2 (22%)
Peritonitis		
No. of patients	8 (22%)	9 (25%)
Age (SD)	56 (12.8)	62 (12.4)
APACHE II score (SD)	21 (2.7)	20 (2.9)
Fungal infection score (SD)	22 (4.9)	20 (4.6)
Clinical cure	2 (25%)*	5 (56%)*
Death	5 (63%)*	3 (33%)*

* not significant.

(histologically proven pneumonia), *C. albicans, Candida tropicalis* and *T. glabrata* (sepsis), and *Candida tropicalis, C. krusei* and *T. glabrata* (sepsis) in the other two patients. The remaining four patients died of the sequelae of an infection with two *Candida sp.* (two each of peritonitis and of histologically proven pneumonia). In the fluconazole group, nine patients died of fungal infection. One patient, who suffered from diabetes mellitus, renal insufficiency and cardiovascular disease, had been admitted with severe sepsis and died after 3 days despite maximal therapy. The postmortem examination revealed *C. albicans, C. tropicalis* and *T. glabrata.* Another patient, who suffered from alcoholism and respiratory tract diseases, died of histologically proven pneumonia 10 days after initiation of therapy. Three patients died of sepsis and the remaining patients died of peritonitis. Patients who had a monoinfection with *C. albicans* had a better prognosis than patients with infections caused by more than one *Candida* species. All patients with mixed candidiasis (three species) died, and of the ten patients in the amphotericin group in whom *T. glabrata* was identified, seven (70%) died as a direct result of their fungal infection. In the fluconazole group three out of the four patients infected by *T. glabrata* also died as a direct result of their fungal infection.

Discussion

This study was conducted to compare fluconazole and amphotericin B/5-flucytosine in the treatment of 72 patients with systemic *Candida* infections.

The use of this combination is standard therapy in Europe [15–17]. According to literature data [15] the success rates are reported to be superior to the monotherapy with amphotericin B which is mainly used in the USA (30% vs. 70%). The alternative day regimen which was proven to be as potent as the daily regimen was chosen to minimize the side effects of amphotericin B [18].

Orginally, the study was intended to have a double-blind design. In view of the unfavorable side effect profile associated with amphotericin B, however, it was decided to conduct the study with an open design for ethical reasons. Since risk factors such as central venous catheters, extensive treatment with broad spectrum antibiotics, prolonged hyperalimentation and surgical procedures or prolonged hospitalization were present in the majority of the study participants; most of the patients studied in the context of this trial belonged to the top risk group for acquiring severe *Candida* infection.

No statistically significant differences were seen when comparing amphotericin B and fluconazole in the treatment of pneumonia or sepsis neither with regard to the clinical response rate (fluconazole 67% vs. amphotericin 69%) nor the cure rate (56% vs. 61%) or the mortality rate (37% vs. 39%). At the same time, fluconazole was better tolerated and had a better side effect profile. These results confirmed the data from the literature. Two recent publications have also reported comparable therapeutic effects of fluconazole and amphotericin B in the treatment of surgical patients with systemic *Candida* infections [19] and in non-neutropenic patients with candidemia [8]. In patients with peritonitis, however, amphotericin was found to be superior to fluconazole (56% vs. 25%). These results do not agree with recent publications [11, 19] in which higher success rates were reported. Our poor results might been explained by the late start of anti-*Candida* therapy and/or the high number of mixed fungal infections.

As previously described [5], early diagnosis and prompt initiation of treatment are associated with a less severe course of the disease and better response rates (69% in the fluconazole and 78% in the amphotericin group). Of the 39 patients (across the groups) who received treatment within 1 week after the onset of the disease, cure was achieved in 29 (74%), whereas only 20 out of the 33 patients in whom treatment was initiated more than 1 week after the onset of their infection were cured or improved (51%).

A better clinical course was seen in patients with monoinfections with *C. albicans* than in those suffering from infections with more than one *Candida* species, with the course in patients with infections involving three or more *Candida* species being particularly unfavorable. All of the

Table 5: Characteristics of patients who died.

No.	Sex	Age	APACHE score	Underlying diseases	Fungal infection	Fungal species	Duration of therapy
Fluconazole							
1*	Male	60	19	Cardiovascular disease, amputation	Sepsis	*Candida albicans, Candida tropicalis, Torulopsis glabrata*	4 days
2*	Male	57	24	Necrotizing pancreatitis	Peritonitis	*Candida albicans, Candida krusei, Torulopsis glabrata*	20 days
3*	Male	78	21	Duodenal ulcer	Peritonitis	*Candida albicans, Candida krusei*	14 days
4*	Female	72	23	Perforated cholelithiasis	Peritonitis	*Candida albicans, Torulopsis glabrata*	14 days
5*	Male	70	20	Respiratory disease	Pneumonia	*Candida albicans*	10 days
6	Male	45	18	Respiratory disease, alcoholic disease	Pneumonia	*Candida albicans*	16 days
7	Female	62	18	Cranial bleeding, cranial surgery	Sepsis	*Candida albicans*	10 days
8	Male	52	18	Cardiomyopathy, respiratory disease	Sepsis	*Candida albicans*	14 days
9	Female	58	22	Polytrauma, alcoholic disease	Pneumonia	*Candida albicans*	7 days
10*	Female	80	19	Gastric perforation	Peritonitis	*Candida tropicalis*	10 days
11*	Male	49	23	Necrotizing pancreatitis	Peritonitis	*Candida albicans*	10 days
12*	Female	53	18	Cardiovascular disease, heart surgery	Sepsis	*Candida albicans*	10 days
13*	Female	33	20	Cancer	Sepsis	*Candida albicans*	5 days
Amphotericin B/5-Flucytosine							
1*	Male	70	27	Heart failure, cardiac surgery	Sepsis	*Candida albicans, Candida tropicalis,* Torulopsis glabrata	10 days
2*	Male	56	20	Global heart failure, respiratory disease	Pneumonia	*Candida krusei, Torulopsis glabrata, Candida albicans*	14 days
3*	Male	81	21	Cardiovascular disease, respiratory disease	Sepsis	*Torulopsis glabrata, Candida krusei, Candida tropicalis*	20 days
4	Male	64	20	Respiratory disease	Pneumonia	*Torulopsis glabrata, Candida albicans*	10 days
5*	Male	53	19	Necrotizing pancreatitis	Peritonitis	*Candida albicans, Torulopsis glabrata*	9 days
6*	Male	43	25	Respiratory disease	Pneumonia	*Candida albicans, Torulopsis glabrata*	20 days
7	Male	74	18	Necrotizing pancreatitis	Peritonitis	*Candida albicans, Candida krusei*	9 days
8	Female	74	23	Necrotizing pancreatitis	Peritonitis	*Candida albicans, Candida krusei*	16 days
9*	Female	74	20	Gastric perforation	Peritonitis	*Candida glabrata, Candida krusei*	5 days
10*	Male	57	25	Respiratory disease, alcoholic disease	Pneumonia	*Candida albicans, Torulopsis glabrata*	10 days
11	Male	67	25	Abscess right shoulder, *S. aureus* sepsis	Sepsis	*Candida albicans*	4 days
12	Female	67	22	Heart failure, cardiac surgery	Sepsis	*Candida albicans*	10 days
13	Male	70	19	Cancer	Sepsis	*Candida albicans*	10 days
14	Male	56	19	Cancer	Sepsis	*Candida albicans*	10 days

* death related to fungal infection.

five patients with mixed fungemia (three species) died of the sequelae of that infection. The prognosis for *T. glabrata* infections or infections involving *T. glabrata* were equally unfavorable: of the ten patients in the amphotericin B group suffering from such infections, seven died of the sequelae, despite the fact that the amphotericin dose was increased to 1 mg/kg of body weight/day. Other studies have also shown *T. glabrata* fungemia to be as-

sociated with elevated mortality rates [20]. It has yet to be determined whether a further increase to amphotericin 1.5 mg/kg of body weight as practiced in the treatment of *Aspergillus* infections – would improve the outcome in *T. glabrata* infections as well.

Proper diagnosis continues to be a problem in fungal infections especially of the respiratory tract. Sepsis and fungemia were easy to diagnose since evidence of *Candida* in blood cultures is highly suggestive of these conditions. The deep *Candida* mycoses were diagnosed by way of histologic examination of intraabdominal tissue samples. The diagnosis of *Candida* pneumonia, however, is difficult and requires histologic confirmation obtained by biopsy, a method which is not always readily available in clinical practice.

In the context of our study, patients with suspected pneumonia were treated for pneumonia if the following criteria applied: demonstration of *Candida* via BAL ($>10^4$/ml) plus the clinical and radiological signs of pneumonia described above. Most of these patients had *Candida* pathogens isolated at several sites of the body and moreover showed an elevation of the *Candida* antigen titer (>1:16 up to 1:128). These findings further supported the suspected diagnosis of systemic *Candida* infection (17). Histologic evidence of pneumonia was found during autopsy or biopsy in six of the 20 patients who had received antifungal treatment for suspected pneumonia. In the remaining 14 cases, confirmation of the suspected diagnosis could not be obtained.

However, the presence of BAL cultures yielding $>10^4$ fungal organisms/ml and of clinical signs of inflammation should always be regarded as strongly suggestive of *Candida* infection. Even though colonization of the bronchial system with *Candida* does not necessarily indicate pneumonia, such presence of *Candida* in the bronchial system may constitute a source for further dissemination, possibly resulting in systemic *Candida* infection, which means that in case of clinical deterioration, these patients require antifugal treatment. In view of the lower rate of adverse events associated with fluconazole, fluconazole may prove to be preferable to amphotericin B in the treatment of patients with these conditions.

In conclusion, we found that amphothericin B/5-FC and fluconazole are not significantly different in the treatment of *Candida* pneumonia and sepsis or fungemia. In the treatment of peritonitis, however, amphotericin B/5-FC was found to be more effective than fluconazole.

Zusammenfassung: Studie zur Wirksamkeit von Fluconazol im Vergleich zu Amphotericin B/5-Flucytosin bei Intensivpatienten mit systemischen Mykosen. In dieser prospektiven, randomisierten Studie wurde die Wirksamkeit von Fluconazol (400 mg am ersten Tag der Therapie, dann 200 mg) gegenüber der Kombination von Amphotericin B/5-Flucytosin (1–1.5 mg/kg Körpergewicht Amphotericin B jeden zweiten Tag und 3×2.5 g 5-Flucytosin/die) verglichen. Es wurden 72 Patienten (36 in die Fluconazol-Gruppe und 36 in die Amphotericin-Gruppe) aufgenommen und mindestens 14 Tage lang nach der Diagnosestellung behandelt. Bei der Behandlung der Sepsis und Pneumonie ergaben sich in beiden Gruppen keine signifikanten Unterschiede in bezug auf die Heilungsrate (63% in der Fluconazol-Gruppe und 64% in der Amphotericin-Gruppe). Bei der Therapie der Peritonitis war Amphotericin B/5-Flucytosin überlegen (55% vs. 25%). Außerdem war unter der Kombinationstherapie die Keimelimination höher (86% vs. 50%). Während der Therapie mit Fluconazol traten weniger oft Nebenwirkungen auf.

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Book Review

D. Wilks, M. Farrington, D. Rubenstein (eds.)
The Infectious Diseases Manual
347 pages, numerous figures and tables
Blackwell Science, Oxford 1995
Price: £ 16.95

After a short introduction about notifiable diseases, isolation and microbiological specimens, this book comprises the essential facts about infectious diseases. It follows a clear structure by dividing the contents into four main sections.
Section 1: "Clinical Infectious Diseases," gives a concise summary of this vast field. Well placed tables make it easy to find your special interest quickly, while figures draw your attention to special topics such as the pathogenesis of infections.
In Section 2: "Microbiology," clinically important microorganisms are introduced by their systematics. Chapters about bacteria are followed by short but complete texts on virology, protozoa, helminths and fungi. Subdivisions for pathogenesis, epidemiology, spectrum of disease, laboratory diagnosis, treatment and prevention enhance the reader's understanding.
Section 3: "Antibiotic Therapy," deals with aspects of the classification of important antibiotics, the theory, use and abuse of antibiotics and antibiotic doses. By this concentration on the vital facts, an astonishing amount of information is contained in comparatively few pages. Tables also make it easier to focus on the essentials. In the appendices in Section 4, the immunisation schedules according to the British Department of Health and a glossary can be found.
In short, this book is a valuable companion for both the medical student and the practitioner and clinician interested in infectious diseases. Its size and well defined structure make it especially suitable for everyday use. The "Infectious Diseases Manual" is an interesting addition to standard textbooks on this topic, and should not be missing in any medical library.

A. Georgopoulos
Vienna

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