EVALUATION OF NEPHROTOXICITY, INFUSION-RELATED ADVERSE REACTIONS AND EFFECTIVENESS OF AMPHOTERICIN B DEOXYCHOLATE ADMINISTERED OVER 24-HOUR INFUSION

JITTAWADEE KAMONPUT

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ABSTRACT

This study was an observational study performed to determine the incidence of nephrotoxicity, infusion-related adverse reactions and effectiveness due to administration of amphotericin B deoxycholate over 24-hour infusion at internal medicine wards, Asdang building, Siriraj Hospital. Fifty-three patients were evaluated during this study. Mean age was 41.74±14.99 years. The most common primary diagnoses were acute leukemia in 26 patients (49.1%) and HIV/AIDS in 12 patients (22.6%). The mean cumulative amphotericin B deoxycholate dose was 514.92±461.65 mg (ranging from 100-2,960 mg) and the total duration of amphotericin B deoxycholate therapy averaged 11.81±7.76 days (ranging from 2-39 days). Nephrotoxicity occurred in 11 patients (20.8%). The mean time to development of nephrotoxicity was approximately 6.45±3.21 days (ranging from 4-13 days). Fever was noted in 48 patients (90.6%) prior to treatment and 49 patients (92.5%) after amphotericin B deoxycholate administration. Chills/rigors, nausea/vomiting and phlebitis occurred in 5 patients (9.4%), 5 patients (9.4%) and 11 patients (20.8%), respectively. During the study period, overall mortality rate was 15 of 53 patients (28.3%). Death due to pulmonary aspergillosis occurred in 2 patients (3.8%). No patient had breakthrough fungaemia during treatment. In conclusion, amphotericin B deoxycholate administered over 24-hour infusion had a low incidence of nephrotoxicity, infusion-related adverse reactions and showed effectiveness in the treatment of fungal infection. Further studies in patients with aspergillosis are needed.

KEY WORDS: NEPHROTOXICITY / EFFECTIVENESS / AMPHOTERICIN B DEOXYCHOLATE / 24-HOUR INFUSION

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การประเมินการเกิดพิษต่อไต อาการไม่พึงประสงค์ที่สัมพันธ์กับการให้ยาและประสิทธิผลของการรักษาผู้ป่วยด้วยยาแอมโฟเทอริซินบีดีออกซีโคเลตหยดเข้าหลอดเลือดดำนาน 24 ชั่วโมง

(EVALUATION OF NEPHROTOXICITY, INFUSION-RELATED ADVERSE REACTIONS AND EFFECTIVENESS OF AMPHOTERICIN B DEOXYCHOLATE ADMINISTERED OVER 24-HOUR INFUSION)

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บทคัดย่อ

การศึกษาครั้งนี้เป็นการศึกษาเชิงสำรวจ เพื่อศึกษาอุบัติการณ์การเกิดพิษต่อไต อาการไม่พึงประสงค์ที่สัมพันธ์กับการให้ยาและประสิทธิผลของการรักษาผู้ป่วยด้วยยาแอมโฟเทอริซินบีดีออกซีโคเลตหยดเข้าหลอดเลือดดำนาน 24 ชั่วโมงในผู้ป่วยที่เข้ารับการรักษาในหอผู้ป่วยอายุรกรรม ตึกอัษฎางค์ โรงพยาบาลศิริราช

ผลการศึกษาผู้ป่วยจำนวน 53 คน พบว่ามีอายุเฉลี่ย 41.74±14.99 ปี ส่วนใหญ่ป่วยด้วยโรคเม็ดเลือดขาวมากผิดปกติเฉียบพลันจำนวน 26 คน (ร้อยละ 49.1) และเอดส์จำนวน 12 คน (ร้อยละ 22.6) ขนาดยารวมเฉลี่ย 514.92±461.65 มิลลิกรัม (ค่าพิสัยระหว่าง 100 ถึง 2,960 มิลลิกรัม) ระยะเวลาได้รับยาเฉลี่ย 11.81±7.76 วัน (ค่าพิสัยระหว่าง 2 ถึง 39 วัน) พบอุบัติการณ์การเกิดพิษต่อไตจำนวน 11 คน (ร้อยละ 20.8) เกิดหลังจากได้รับยาเฉลี่ย 6.45±3.21 วัน (ค่าพิสัยระหว่าง 4 ถึง 13 วัน) ผู้ป่วยมีอาการไข้ก่อนรับยาจำนวน 48 คน (ร้อยละ 90.6) หลังรับยาผู้ป่วยมีอาการไข้จำนวน 49 คน (ร้อยละ 92.5) ผู้ป่วยมีอาการหนาวสั่นจำนวน 5 คน (ร้อยละ 9.4) อาการคลื่นไส้อาเจียนจำนวน 5 คน (ร้อยละ 9.4) และเกิดการอักเสบของหลอดเลือดดำในผู้ป่วยจำนวน 11 คน (ร้อยละ 20.8) พบผู้ป่วยเสียชีวิตจำนวน 15 คน (ร้อยละ 28.3) ผู้ป่วยเสียชีวิตจากการติดเชื้อราชนิดแอ็สเพอจิลลัสที่ปอดจำนวน 2 คน (ร้อยละ 3.8) ไม่พบผู้ป่วยติดเชื้อราในกระแสเลือดเพิ่มขึ้นใหม่ในช่วงระยะเวลาที่ทำการศึกษา

สรุปได้ว่าการให้ยาแอมโฟเทอริซินบีดีออกซีโคเลตหยดเข้าหลอดเลือดดำนาน 24 ชั่วโมง มีอุบัติการณ์การเกิดพิษต่อไต อาการไม่พึงประสงค์ที่สัมพันธ์กับการให้ยาต่ำและมีประสิทธิผลในการรักษาการติดเชื้อรา อย่างไรก็ตามควรมีการศึกษาการให้ยาแอมโฟเทอริซินบีดีออกซีโคเลตหยดเข้าหลอดเลือดดำนาน 24 ชั่วโมงในผู้ป่วยติดเชื้อราชนิดแอ็สเพอจิลลัสเพิ่มเติม

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CONTENTS

Page

CONTENTS (CONT.)

Page

CONTENTS (CONT.)

Page

LIST OF TABLES

LIST OF TABLES (CONT.)

LIST OF TABLES (CONT.)

Table **Page**

LIST OF FIGURES

CHAPTER 1
INTRODUCTION

Over the last decade, the incidence of fungal infections have been increasing, the increase can be correlated with patients who had cancer, solid organ and bone marrow transplant (BMT) recipients due to administration of immunosuppressive therapies, increased of patients with human immunodeficiency virus (HIV) and extensive use of broad-spectrum antibiotics.

Amphotericin B deoxycholate has been a mainstay of antifungal therapy for over 40 years and still be the 'gold standard' for life-threatening fungal infections because of its broad spectrum of activity. Amphotericin B deoxycholate is an antifungal polyene antibiotics. Amphotericin B deoxycholate is isolated form *Streptomyces nodosus*, first isolated at Squibb Laboratories in 1953. The initial reports of antifungal activity published in 1956. Amphotericin B deoxycholate exerts its antifungal activity principally by binding to sterols in the fungal cell membrane. As a result of this binding, amphotericin B deoxycholate alter membrane permeability, causing leakage of cell components, with subsequent fungal cell death. The antifungal activity of amphotericin B deoxycholate may be fungistatic or fungicidal, depending on drug concentration at the site of infection and sensitivity of the organism.

The main problems during administration are the infusion-related adverse reactions (e.g. fever, chills and phlebitis) and nephrotoxicity. Nephrotoxicity leads to reduction in the daily dose of amphotericin B deoxycholate and dose reduction may result in inadequate drug levels leading to treatment failure. Patients who developed nephrotoxicity have high mortality rate than patients who did not. The standard times of amphotericin B deoxycholate infusion (4-6 hours) still occur nephrotoxicity and incidence of nephrotoxicity varies from 15-80%.

Unfortunately, the exact mechanisms involed in amphotericin B deoxycholate-induced nephrotoxicity have not been clearly defined. The two major hypotheses are amphotericin B deoxycholate-induced renal vasoconstriction, causing decrease in

renal blood flow and glomerular filtration rate (GFR), and direct toxic effect on renal tubular cells, resulting in enhanced membrane permeability with subsequent intracellular and tubular loss of electrolytes. Clinical and laboratory manifestations of amphotericin B deoxycholate-induced nephrotoxicity may include evidence of renal tubular acidosis, azotemia, oliguria, hypokalemia, hypomagnesemia, increased blood urea nitrogen (BUN) and serum creatinine (SCr) concentrations and decrease creatinine clearance (CrCl).

The different strategies are currently used to reduce nephrotoxicity. Lipid formulations of amphotericin B are less nephrotoxicity but these formulations are costly. Amphotericin B deoxycholate in lipid emulsion, data on reduced nephrotoxicity is controversial and methods for preparing have not been standardized. Stability of amphotericin B deoxycholate in lipid emulsion is not constant. Alternate times of amphotericin B deoxycholate infusion have different result of nephrotoxicity. Administration amphotericin B deoxycholate by continuous infusion over 24 hours may be reduced nephrotoxicity because the incidence of nephrotoxicity were noted from 10-16%.

Accordingly, Siriraj Hospital's policy on amphotericin B deoxycholate administration changed from infused over 4 or 6 hours to infused over 24 hours in August 2004. Thus, the purpose of this observational study were to assess the incidence of nephrotoxicity, infusion-related adverse reactions and the effectiveness of amphotericin B deoxycholate administered over 24-hour infusion at internal medicine wards, Asdang building, Siriraj Hospital, Mahidol University.

Objectives

1. To determine the incidence of nephrotoxicity due to administration of amphotericin B deoxycholate over 24-hour infusion.
2. To determine the incidence of infusion-related adverse reactions due to administration of amphotericin B deoxycholate over 24-hour infusion.
3. To determine the effectiveness of amphotericin B deoxycholate administerd over 24-hour infusion.

Expected outcomes and benefits

1. Administration of amphotericin B deoxycholate by 24-hour infusion results in low incidence of nephrotoxicity.
2. Administration of amphotericin B deoxycholate by 24-hour infusion results in low incidence of infusion-related adverse reactions and shows effectiveness in the treatment of fungal infection.

CHAPTER 2
LITERATURE REVIEW

Over the last decade, the incidence of fungal infections have been increasing. Amphotericin B deoxycholate has been a mainstay of antifungal therapy for over 40 years. The main problems during administration are the infusion-related adverse reactions and nephrotoxicity. Nephrotoxicity leads to reduction in dose of amphotericin B deoxycholate which subsequently leads to treatment failure. The incidence of nephrotoxicity due to standard infusion (4 or 6 hours) and the rapid infusion of amphotericin B deoxycholate were noted in 15-80. The exact mechanisms involed in amphotericin B deoxycholate-induced nephrotoxicity have not been clearly defined. The two major hypotheses are amphotericin B deoxycholate-induced renal vasoconstriction, causing decrease in renal blood flow and GFR, and direct toxic effect on renal tubular cells.

The different strategies are currently used to reduce nephrotoxicity: Lipid formulations of amphotericin B, amphotericin B deoxycholate in lipid emulsion and alternate times of amphotericin B deoxycholate infusion. The 24-hour infusion of amphotericin B deoxycholate studies reported the incidence of nephrotoxicity from 10-16%. Administration amphotericin B deoxycholate by continuous infusion over 24-hour infusion may be reduced nephrotoxicity.

I. Increasing of fungal infections

The increased incidence of fungal infections is a consequence of increased of immunocompromised patients due to advances in transplantation and oncology, growing numbers of patients with HIV and extensive use of broad-spectrum antibiotics. (1,2)

Beck-Sague et al. analyzed data from the National Nosocomial Infections Surveillance (NNIS) System to identify pathogens causing nosocomial fungal infections and the secular trend in their incidence in United States hospitals. The data were collected from January 1980 to December 1990 by 115 hospitals participating in the NNIS System. (3) During that period, NNIS hospitals reported 30,477 nosocomial fungal infections. The nosocomial fungal infection rate at facilities conducting hospital wide surveillance increased from 2.0 to 3.8 infections per 1,000 patients discharged. The proportion of nosocomial infections reported by all hospitals due to fungal pathogens rose from 6.0% in 1980 to 10.4% in 1990 at all major sites of infection: surgical wound infections, from 1.5% to 5.1%; lung infections, from 5.2% to 5.7%; urinary tract infections, from 6.7% to 18.7% and bloodstream infections, from 5.4% to 9.9%. *Candida albicans* was the most frequently isolated of nosocomial fungal infections (59.7%), followed by other *Candida* species (18.6%), *Torulopsis* species (7.3%) and *Aspergillus* species (1.3%). Patients with bloodstream infections receiving total parenteral nutrition or in intensive care units were more likely to have fungaemia (15.6% and 11.0%, respectively) than were those not receiving total parenteral nutrition (6.4%) or not in intensive care units (8.1%). Patients with fungaemia were more likely to die during hospitalization than were patients with bloodstream infection due to non fungal pathogens (29% and 17%; relative risk [RR], 1.8; $p<0.001$).

Morrison et al. evaluated a consecutive series of 1,186 patients who underwent BMT between 1974 and 1989 by review of the prospectively collected data for the occurrence of a non-*Candida* fungal infection in the first 180 days after BMT. (4) In this period, 129 patients (11%) developed a total of 138 significant non-*Candida* fungal infections. The primary disease diagnosis were aplastic anemia in 10 patients, acute leukemia in 54 patients, chronic myelogenous leukemia in 34 patients, immunodeficiency or metabolic disorder in 11 patients or other malignancy in 20 patients. The most common isolate was *Aspergillus* species occurred in 97 patients (70%), followed by *Fusarium* occurred in 10 patients (7%) and *Alternaria* occurred in 6 patients (4%). Fifty-four patients developed 58 episodes of disseminated non-*Candida* fungal infections. *Aspergillus* species were the most common isolates

occurred in 43 patients. A total of 106 patients (82%) died and the cause of death in 69 of the 106 cases (65%) was directly related to the non-*Candida* fungal infections.

Harvey et al. reported a retrospective studied to define the episodes of nosocomial fungaemia in a large community teaching hospital. (5) Fungaemia was considered to be nosocomial if blood cultures were positive more than 72 hours after hospital admission with no evidence of fungal infection at the time of admission. The incidence of hospital acquired fungaemia increased 8-fold during the study period. The most common fungal pathogens causing fungaemia were *C. albicans* in 28 patients (58%), *C. tropicalis* in 12 patients (25%) and *C. parapsilosis* in 7 patients (15%). The most common predisposing factors were intravenous catheter in 48 patients (100%), antibiotic administration in 47 patients (98%), central venous catheter in 40 patients (83%), urinary catheter in 39 patients (81%), blood or blood products administration in 36 patients (75%) and surgical proceders in 31 patients (65%). Thirty-nine patients (81%) received intravenous amphotericin B deoxycholate, average doses of 325 mg (range 25-1,040 mg). Patients had fully recovered in 11 patients (23%), improved but died of underlying disease in 16 patients (33%) and died of fungaemia in 12 patients (25%). Eight patients (17%) did not received intravenous amphotericin B deoxycholate and died of fungaemia.

Jarvis studied the epidemiology of nosocomial fungal infections by obtained in the NNIS system from January 1980 to April 1990. (6) A total of 27,200 fungal isolates, *Candida* species accounted for 19,621 (72.1%). *C. albicans* accounted for 76% of all isolates of *Candida* species. More specifically, 18,207 (93%) of the total number of candidal isolates from nosocomial infections were recovered from patients on the medical and surgical services. Patients appear to be at higher risk of infection due to *Candida* species include burn, trauma, cardiac surgery, oncology, general surgery and high-risk nursery patients. Nosocomial fungal infections usually occurred in patients with many invasive devices and especially common among the immunocompromised.

Horn et al. reviewed the records of 188 additional patients who had 200 episodes of fungaemia between January 1, 1978 and June 30, 1982 and compared these patients with those seen between 1974 and 1977. (7) Nine patients had more than one episode

of fungaemia with different species of yeasts. There were 30.6% more total episodes of fungaemia per year, 73% and 95% more episodes per 100 news lymphoma and solid tumor patients, respectively. *C. albicans* fungaemias were evenly distributed between patients hematologic and nonhematologic diseases. Fungaemia occurred earlier during hospitalization. The first positive blood cultures were obtained after means of 20 days of hospitalization, 11.7 days of neutropenia and 11.8 days of parenteral antibiotic therapy. Mortality in patients with fungaemia due to any species was *C. albicans* in 70 of 89 patients (79%), *C. tropicalis* in 40 of 51 patients (78%), *C. krusei* in 5 of 7 patients (71%), *C. glabrata* in 15 of 22 patients (68%) and *C. parapsilosis* in 7 of 24 patients (30%).

Anaissie et al. reported new spectrum of fungal infections in 44 patients with cancer between 1974 and 1986. (8) Thirty-four patients (77%) had a hematologic malignancy; 27 of those had acute leukemia and 10 patients (23%) had solid tumors. Thirty-eight received myelosuppressive chemotherapy, including 6 patients had undergone BMT. Thirty-four patients were profoundly neutropenia at the onset of their fungal infections. The most fungal pathogen were *Trichosporon beigelii* occurred in 23 patients and *Fusarium* species occurred in 6 patients. The most commonly involved sites were lungs in 27 patients, followed by the kidneys in 12 patients, spleen in 9 patients, skin in 8 patients, liver in 7 patients and sinuses in 4 patients. None of the patient was receiving antifungal therapy or prophylaxis at the onset of infection. Amphotericin B deoxycholate was administered to 27 patients, with a median total dose of 600 mg (range 40-2,400 mg). Therapy was initiated 1-140 days before death (mean 28 days). A total of 28 patients (64%) died; 12 patients could be directly attributed to invasive and/or disseminated fungal disease.

II. Treatment of fungal infections

As shown in Table 1, the drugs are approved by the Food and drug Administration (FDA) for the therapy of systemic fungal infections in the United States. (9) These drugs belong to 3 principal classes: polyenes, pyrimidines and azoles.

Table 1: Drugs approved for treatment of systemic fungal diseases.

Class	Name	Available formulation (s)	Year initially approved
Polyene	Amphotericin B deoxycholate	Intravenous	1958
Polyene	Amphotericin B lipid complex	Intravenous	1995
Polyene	Amphotericin B cholesteryl sulfate	Intravenous	1996
Polyene	Amphotericin B liposomal	Intravenous	1997
Pyrimidine	Flucytosine	Oral tablet	1972
Azole	Ketoconazole	Oral tablet	1981
Azole	Fluconazole	Intravenous, oral capsule, oral suspension	1990
Azole	Itraconazole	Oral solution	1992

Source: Dismukes WE. Introduction to antifungal drugs. Clin Infect Dis 2000;30:653-7

Amphotericin B deoxycholate, an antifungal polyene antibiotics has been a mainstay of antifungal therapy for over 40 years and still be the 'gold standard' for life-threatening fungal infection because of its broad spectrum of activity. The recommendation for treatment of fungal infections were shown in Table 2. (10-18)

1. Use of amphotericin B deoxycholate in aspergillosis.

Aspergillus species are saprophytic molds found worldwide. Diseases caused by *Aspergillus* species are most commonly caused by *A. fumigatus*, with *A. flavus* the second most frequently isolated pathogen. Immunocompromised patients had highly lethal related to invasive aspergillosis. Work-up must be prompt and aggressive

therapy may need to be initiated upon suspicion of the diagnosis without definitive proof. Intravenous therapy should be used, the largest therapeutic experience is with amphotericin B deoxycholate at maximum tolerated doses (e.g, 1-1.5 mg/kg/day) and should be continued, despite modest increases in SCr levels. The optimal duration of therapy is unknown and dependent on the extent of invasive aspergillosis, the response to therapy and the patient's underlying disease or immune status. (11)

Invasive aspergillosis, particularly invasive pulmonary disease. Intravenous amphotericin B deoxycholate has been the standard of treatment in invasive aspergillosis, particularly for life-threatening and severe infections. In well-characterized patients, the overall response rate has been 37% (range 14-83%). Response rates to all agents vary because of underlying diseases, extent of infection, resolution of neutropenia or underlying immunodeficiency, definition of response and duration of follow-up. (11)

Denning et al. reported therapeutic outcome in invasive aspergillosis by reviewed all published series of invasive aspergillosis that included ≥ 4 patients. (12) The dosage of amphotericin B deoxycholate was assumed to have been 0.8-1 mg/kg/day. Response to therapy as related to duration of treatment with amphotericin B deoxycholate for invasive aspergillosis. All untreated patients and all patients treated for < 8 days died. Response to therapy with amphotericin B deoxycholate for ≥ 14 days occurred in 5 of 15 patients (33%) with BMT, 44 of 81 patients (54%) with leukemia, neutropenia and aplastic anemia and 20 of 54 patients (37%) with acquired immune deficiency syndrome (AIDS).

2. Use of amphotericin B deoxycholate in cryptococcosis.

The choice of treatment for disease caused by *Cryptococcus neoformans* depends on both sites of involvement and the patient's immune status. (13)

2.1 Therapy for non-HIV associated cryptococcal pulmonary disease.

The goal of treatment is cure of the infection and prevention of dissemination of disease to the central nervous system (CNS). The desired outcome is resolution of symptoms such as cough, shortness of breath, fever and resolution or

stabilization of abnormalities on chest radiograph. Recommendations for the treatment of immunocompetent patients who are asymptomatic or present with mild to moderate symptoms should be treated with fluconazole, if oral azole therapy cannot be given or the pulmonary disease is severe or progressive, amphotericin B deoxycholate is recommended 0.5-1 mg/kg/day for a total dose of 1,000-2,000 mg.

2.2 Therapy for AIDS-related cryptococcal pneumonia.

The goal of treatment is control of the infection and prevention of dissemination of disease to the CNS. The desired outcome remains the same of non-HIV associated cryptococcal pulmonary disease. The prevention of progression to cryptococcal meningitis is the principal goal of therapy. Patients who present with mild to moderate symptoms or who are asymptomatic with a positive culture for *C. neoformans* from the lung should be treated with fluconazole for life, if fluconazole is not an option, an alternative is itraconazole for life. In patients with more severe disease, amphotericin B deoxycholate, 0.7-1 mg/kg/day should be used until symptoms are controlled, then an oral azole agent, preferably fluconazole, can be substituted.

2.3 Therapy for non-HIV associated cryptococcal CNS disease.

CNS disease usually presents as meningitis. The goal of treatment is cure of the infection, cerebrospinal fluid (CSF) sterilization and prevention of long-term CNS system sequelae. The desired outcome is resolution of abnormalities such as fever, altered mental status, meningeal signs, elevated intracranial pressure. Recommendations for the treatment are amphotericin B deoxycholate 0.7-1 mg/kg/day plus flucytosine 100 mg/kg/day for 2 weeks, then fluconazole 400 mg/day for minimum 10 weeks for consolidation therapy.

2.4 Therapy for AIDS-related cryptococcal meningitis.

The objective of treatment is eradication of the infection and control of elevated intracranial pressure. However, failing eradication, which is common in HIV disease, long-term control of infection and resolution of clinical evidence of disease are the principal goals. The desired outcome is resolution of abnormalities such as fever, headache, altered mental status, elevated intracranial pressure. The primary

objective of maintenance therapy is the prevention of relapse of cryptococcal meningitis. Recommendations for the treatment were summarized in Table 2. Oral fluconazole is the most effective maintenance therapy. Amphotericin B deoxycholate for maintenance therapy should be reserved for patients who have had multiple relapses with receiving azole therapy or who are intolerant of the azole drugs.

3. Use of amphotericin B deoxycholate in candidiasis.

Candida species are the most common cause of fungal infections, that range from non-life-threatening mucocutaneous illnesses to invasive organ. (14)

3.1 Candidemia and acute hematogenously disseminated candidiasis.

The objective of treatment is to resolve signs and symptoms of associated sepsis, to sterilize the blood stream and any clinically evident site of hematogenous disseminated. The desired outcome is clearance of bloodstream and other clinically evident sites of infection, symptomatic improvement, absence of retinal findings of *Candida* endophthalmitis and adequate follow-up to ensure that late-appearing symptoms of focal hematogenous spread are not overlooked. Initial medical therapy should invole caspofungin, fluconazole, amphotericin B deoxycholate or combination therapy with fluconazole plus amphotericin B deoxycholate. Experience with caspofungin is limited but its broad-spectrum activity against *Candida* species and low rate of treatment-related adverse events. For clinical unstable patients infected with an unspeciated isolate, amphotericin B deoxycholate ≥ 0.7 mg/kg/day is preferable because of its broad-spectrum activity.

3.2 Empirical antifungal treatment of neutropenic patients with prolonged fever despite antibacterial therapy.

The objective of treatment is to treat early occult fungal infection and prevent fungal infection in high-risk patients. The desired outcome is resolution of fever and prevention of development of clinically overt infection. Antifungal therapy is appropriate in neutropenic patients who have persistent unexplained fever, despite receipt of 4-7 days of appropriate antibacterial therapy. Therapy is continued until

resolution of neutropenia. Amphotericin B deoxycholate 0.5-0.7 mg/kg/day has been the prefered agent.

3.3 Prophylaxis in neutropenic patients.

The objective of treatment is to prevent development of invasive fungal infections, during periods of risk. The desired outcome is prevention of onset of signs and symptoms of invasive candidiasis. Prophylaxis with fluconazole or itraconazole during the period of risk for neutropenia are appropriate therapies for patients who are at significant risk for invasive candidiasis.

4. Use of amphotericin B deoxycholate in coccidioidomycosis.

Coccidioidomycosis results from inhaling the spores of *Coccidioides immitis*. The desired outcome of treatment is resolution of signs and symptoms of infection, reduction of serum concentrations of antibodies to *C. immitis* and return of function of involved organs. (15)

5. Use of amphotericin B deoxycholate in histoplasmosis.

The goal of treatment is to eradicate the infection when possible, although chronic suppression may be adequate for patients with AIDS and other serious immunosuppressive disorders. Important outcomes are resolution of clinical abnormalities and prevention of relapse. (16)

6. Use of amphotericin B deoxycholate in blastomycosis.

The desired outcome should insult in abatement of the symptoms and signs of blastomycosis and eradication of *Blastomyces dermatitidis* from involved tissue. In the immunocompromised host, a mycological cure may not be possible and long term suppressive therapy, usually with an azole, is often required to prevent relapse of disease. Amphotericin B deoxycholate is the treatment of choice for patients who are immunocompromised, have life-threatening or CNS disease or for whom azole treatment has failed. (17)

7. Use of amphotericin B deoxycholate in sporotrichosis.

Most cases of sporotrichosis are localized to the skin and subcutaneous tissues. The desired outcome of treatment include eradication of *Sporothrix schenckii* from tissues, resolution of symptoms and signs of active infection and return of function of involved organs. In patients with AIDS, eradication of the organism may not be possible but clinical resolution should be attained and subsequently maintained with suppressive antifungal therapy. (18)

Table 2: The recommendation for treatment of fungal infections.

Disease	Therapy
Aspergillosis	
Acute invasive aspergillosis	- Minimum 2 weeks treatment. - Amphotericin B deoxycholate 1-1.5 mg/kg/day - Amphotericin B lipid complex 5 mg/kg/day - Amphotericin B cholesteryl sulfate 3-4 mg/kg/day, up to 6 mg/kg/day - Amphotericin B liposomal 5 mg/kg/day - Itraconazole: oral 400-600 mg/day for 4 days then 200 mg twice daily or i.v. 200 mg over 1-hour infusion, 12 hours intervals for 4 doses then 200 mg/day for up to 2 weeks
Empirical treatment	- Amphotericin B deoxycholate 1 mg/kg/day
Prophylaxis	- Usefulness controversial - Itraconazole oral solution 400 mg/day or Amphotericin B deoxycholate 0.5 mg/kg/day

Table 2: The recommendation for treatment of fungal infections. (Continued)

Disease	Therapy
Cryptococcosis	
Non-HIV associated cryptococcal pulmonary disease	
- Asymptomatic	- Fluconazole 200-400 mg/day for 3-6 months
- Mild to moderate symptomatic infection	- Fluconazole 200-400 mg/day for 6-12 months - Itraconazole 200-400 mg/day for 6-12 months if oral azole cannot be given, amphotericin B deoxycholate 0.5-1 mg/kg/day for a total dose of 1,000-2,000 mg
- Severe or progressive symptomatic infection	- Amphotericin B deoxycholate 0.5-1 mg/kg/day for a total dose of 1,000-2,000 mg
HIV-related cryptococcal pneumonia	
- Asymptomatic or mild to moderate symptoms	- Fluconazole 200-400 mg/day, lifelong. - Itraconazole 400 mg/day, lifelong if fluconazole is not an option
- Severe disease	- Amphotericin B deoxycholate 0.7-1 mg/kg/day should be used until symtoms are controlled, oral azole agent, can be substituted

Table 2: The recommendation for treatment of fungal infections. (Continued)

Disease	Therapy
Non-HIV associated cryptococcal meningitis	- Amphotericin B deoxycholate 0.7-1 mg/kg/day plus flucytosine 100 mg/kg/day for 2 weeks, followed by fluconazole 400 mg/day for minimum of 10 weeks - Amphotericin B deoxycholate 0.7-1 mg/kg/day plus flucytosine 100 mg/kg/day for 6-10 weeks - Amphotericin B deoxycholate 0.7-1 mg/kg/day for 6-10 weeks - Lipid formulation of amphotericin B 3-6 mg/kg/day for 6-10 weeks
HIV-related cryptococcal meningitis	- Amphotericin B deoxycholate 0.7-1 mg/kg/day plus flucytosine 100 mg/kg/day for 2 weeks, followed by fluconazole 400 mg/day for minimum of 10 weeks - Amphotericin B deoxycholate 0.7-1 mg/kg/day plus flucytosine 100 mg/kg/day for 6-10 weeks - Amphotericin B deoxycholate 0.7-1 mg/kg/day for 6-10 weeks - Fluconazole 400-800 mg/day for 10-12 months - Itraconazole 400 mg/day for 10-12 months - Fluconazole 400-800 mg/day plus flucytosine 100-150 mg/kg/day for 6 weeks - Lipid formulation of amphotericin B 3-6 mg/kg/day for 6-10 weeks

Table 2: The recommendation for treatment of fungal infections. (Continued)

Disease	Therapy
- Maintenance therapy	- Fluconazole 200-400 mg p.o q.d, lifelong - Itraconazole 200 mg p.o b.i.d, lifelong - Amphotericin B deoxycholate 1 mg/kg i.v 1-3 times/week, lifelong - if CD_4 T-lymphocyte count increases above 100-200 cells/μl following highly active antiretroviral therapy (HAART), maintenance treatment can be discontinued
Candidiasis	
Candidemia with non-neutropenic patients	- Amphotericin B deoxycholate 0.6-1 mg/kg/day for 2 weeks - Fluconazole 400-800 mg/day for 2 weeks - Caspofungin 70 mg loading dose, followed by 50 mg/day infusion over 1 hour for 2 weeks - Amphotericin B deoxycholate 0.7 mg/kg/day plus fluconazole 800 mg/day for 4-7 days, then fluconazole 800 mg/day
Candidemia with neutropenic patients	- Amphotericin B deoxycholate 0.7-1 mg/kg/day for 2 weeks - Lipid formulation of amphotericin B 3-6 mg/kg/day for 2 weeks - Fluconazole 6-12 mg/kg/day for 2 weeks

Table 2: The recommendation for treatment of fungal infections. (Continued)

Disease	Therapy
Disseminated candidiasis	
- Acute	- Amphotericin B deoxycholate 1 mg/kg/day plus flucytosine - Fluconazole 800 mg/day or higher in less critically ill patients, dependent on species - Caspofungin 70 mg/day, followed by 50mg/day infusion over 1 hour
- Chronic	- Amphotericin B deoxycholate 0.6-0.7 mg/kg/day, followed by fluconazole 3-6 months - Lipid formulation of amphotericin B 3-5 mg/kg/day for 3-6 months - Fluconazole 400 mg/day in stable patients
Prophylaxis in neutropenic patients	- Fluconazole 400 mg/day - Itraconazole solution 2.5 mg/kg q 12 hours during the period of risk for neutropenia
Coccidioidomycosis	
Primary pulmonary	
- No dissemination risk	- Observe or fluconazole 400 mg/day for 3-6 months

Table 2: The recommendation for treatment of fungal infections. (Continued)

Disease	Therapy
- Dissemination risk	- Amphotericin B deoxycholate 0.5-0.7 mg/kg/day, followed by fluconazole 400 mg/day 6 months
Progressive pulmonary or disseminated (non-meningeal)	
- Immediately life-threatening	- Amphotericin B deoxycholate 1-1.5 mg/kg/day to achieve a total dose of 2,500-3,000 mg; switch to fluconazole when disease is under control
- Slowly progressive or stable	- Fluconazole 400-800 mg/day - Itraconazole 200 mg b.i.d
Meningitis	- Fluconazole 600-1,200 mg/day - Itraconazole 400-600 mg/day - Amphotericin B deoxycholate directly into CSF together with systemic therapy, followed by fluconazole 600-1,200 mg/day
HIV-infected	- Control infection, followed by lifelong therapy with fluconazole 400 mg/day or itraconazole 200 mg b.i.d., in meningitis: fluconazole 800 mg/day

Table 2: The recommendation for treatment of fungal infections. (Continued)

Disease	Therapy
Histoplasmosis	
Acute pulmonary	Symptoms < 4 weeks: none Persistent symptoms for > 4 weeks: - Itraconazole 200 mg/day p.o for 6-12 weeks - Amphotericin B deoxycholate 0.5-0.7 mg/kg/day, followed by itraconazole 200 mg/day p.o for 6-12 weeks - Lipid formulation of amphotericin B 3 mg/kg/day in renal impairment, followed by itraconazole 200 mg/day p.o for 6-12 weeks
Chronic pulmonary	- Itraconazole 200-400 mg/day for 12-24 months - Amphotericin B deoxycholate 0.7 mg/kg/day for 10 weeks, followed by itraconazole 200-400 mg/day for 12-24 months - Lipid formulation of amphotericin B 3 mg/kg/day in renal impairment for 12 months follow-up after discontinuation of treatment
Disseminated in non-AIDS	- Itraconazole 200-400 mg/day for 6-18 months if not tolerated, fluconazole 400 mg/day

Table 2: The recommendation for treatment of fungal infections. (Continued)

Disease	Therapy
Disseminated in non-AIDS	- Amphotericin B deoxycholate 0.7-1 mg/kg/day for 10 weeks, followed by itraconazole 200-400 mg/day for 6-18 months - Lipid formulation of amphotericin B 3 mg/kg/day in renal impairment for 12 months follow-up after discontinuation of treatment
Disseminated in AIDS - Severe disease	- Amphotericin B deoxycholate 0.7-1 mg/kg/day, followed by itraconazole 400 mg/day to complete 12 weeks total induction period if itraconazole intolerated, fluconazole 800 mg/day
- Milder disease	- Oral itraconazole 600 mg/day for 3 days, then 200 mg twice daily
- Maintenance therapy	- Itraconazole 200-400 mg/day for life if itraconazole not tolerated, fluconazole 400-800 mg/day for life - Amphotericin B deoxycholate 50 mg/week

Table 2: The recommendation for treatment of fungal infections. (Continued)

Disease	Therapy
Blastomycosis	
Pulmonary	
- Mild to moderate disease	- Itraconazole 200-400 mg/day for 6 months if intolerated, ketoconazole 400-800 mg/day or fluconazole 400-800 mg/day
- Life-threatening	- Amphotericin B deoxycholate 0.7-1 mg/kg/day to a total dose of 1,500-2,500 mg and switch to itraconazole 200-400 mg/day after the patient's condition has stabilized
Disseminated non-CNS	
- Mild to moderate disease	- Itraconazole 200-400 mg/day for 12 months if intolerated, ketoconazole 400-800 mg/day or fluconazole 400-800 mg/day
- Life-threatening	- Amphotericin B deoxycholate 0.7-1 mg/kg/day to a total dose of 1,500-2,500 mg and switch to itraconazole 200-400 mg/day after the patient's condition has stabilized
Disseminated CNS	- Amphotericin B deoxycholate 0.7-1 mg/kg/day to a total dose at least of 2 g, for patients unable to tolerate a full course of amphotericin B

Table 2: The recommendation for treatment of fungal infections. (Continued)

Disease	Therapy
Disseminated CNS	deoxycholate, consider fluconazole 800 mg/day
Immunocompromised host	- Amphotericin B deoxycholate 0.7-1 mg/kg/day to a total dose of 1,500-2,500 mg and suppressive therapy should be continued with itraconazole 200-400 mg/day, for patients with CNS disease or itraconazole intolerate, consider fluconazole 800 mg/day
Sporotrichosis	
Pulmonary	- Amphotericin B deoxycholate 1 mg/kg/day, substituted by itraconazole 400 mg/day upon improvement, for less severe disease, itraconazole 400 mg/day
Disseminated non-CNS	- Amphotericin B deoxycholate 1 mg/kg/day to a total dose of 1,000-2,000 mg, for less severe disease, itraconazole 400 mg/day
HIV-infected	- Amphotericin B deoxycholate 1 mg/kg/day to a total dose of 1,000-2,000 mg, followed by itraconazole 400 mg/day lifelong

III. Amphotericin B deoxycholate

Amphotericin B deoxycholate is antifungal antibiotic produced by *S. nodosus*. Amphotericin B deoxycholate is an amphoteric polyene antibiotics containing a hydrophilic region, made up of an hydroxylated hydrocarbon chain and a sequence of conjugated double bonds which is lipophilic. Chemical structure of amphotericin B deoxycholate as shown in Figure 1.

Amphotericin B deoxycholate binds to ergosterol and alters the permeability of the cell by forming amphotericin B deoxycholate-associated pores in the cell membrane. The pore allows the leakage of intracellular ions and macromolecules, eventually leading to cell death. Characteristics of antifungal activity of amphotericin B deoxycholate may be fungistatic or fungicidal, depending on drug concentration at the site of infection and sensitivity of the organism. (19-26)

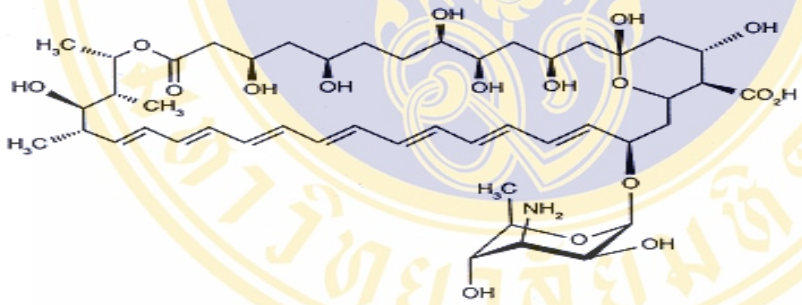

Figure 1: Chemical structure of amphotericin B deoxycholate.

1. Pharmacokinetics

Amphotericin B deoxycholate is poorly absorbed following oral administration, absorption was thought to be due to in part to the influence of mucosal irritation. Because of its irritant effect and poor absorption following intramuscular administration, this route of administration is not recommended. Distribution of amphotericin B deoxycholate is thought follow a three-compartment model. Concentrations are highest in lung and spleen, with high concentrations also detected in kidney and lung tissues. The metabolism is poorly understood because no

metabolite have been identified. Only a small amount is generally detected in the urine after 24 hours. A biphasic elimination, with rapid initial serum half-life of 24-48 hours, followed by a terminal half-life of up to 15 days. As shown in Table 3. (21)

Atkinson and Bennett studied the pharmacokinetics of amphotericin B deoxycholate in 2 patients for disseminated histoplasmosis. (27) Case 1, patient age 75 years received 3.076 g of amphotericin B deoxycholate over 50 days. For the month prior to study, patient received amphotericin B deoxycholate 70 mg daily. Case 2, patient age 45 years received 4.110 g of amphotericin B deoxycholate over 136 days. Patient had received a prior course of 2.025 g, ending 9 months before the present course. For 2 months before this investigation, patient received amphotericin B deoxycholate 70 mg every other day. In case 1, patient had volume central compartment of 26.3 L, the fast and slow peripheral compartments were 29.2 L and 187.4 L, respectively. Patient had total distribution volume of 3.71 L/kg and elimination half-life 14 days. In case 2, patient had volume central compartment of 35.4 L, the fast and slow peripheral compartments were 18.9 L and 262.6 L, respectively. Patient had total distribution volume of 4.27 L/kg and elimination half-life 16.5 days. Renal excretion related minor pathway for the elimination, accounting for only 3.1% of total elimination in case 1 and 3.5% in case 2. Renal clearance of amphotericin B deoxycholate averaged only 3% of CrCl in 2 patients.

Table 3: Pharmacokinetics of amphotericin B deoxycholate.

Parameter	Value
Absorption	
Oral	< 5%
Intramuscular	Poor
Half-life	
Initial phase	24-48 hours
Terminal phase	15 days
Apparent volume of distribution	
Overall	4 L/kg
Central compartment	0.44 L/kg
Fast compartment	0.35 L/kg
Slow compartment	3.2 L/kg
Urinary recovery at 24 hours	3%
Binding to β-lipoproteins	91-95%

Source: Gallis HA, Drew RH, Pickard WW. Amphotericin B: 30 years of clinical experience. Rev Infect Dis 1990;12:308-29

Bindschadler and Bennett studied of the concentrations of biologically active amphotericin B deoxycholate of 17 patients. (28) Six patients received only intravenous amphotericin B deoxycholate infusion every day (QD) therapy, 5 patients received only intravenous amphotericin B deoxycholate infusion every other day (QOD) and 6 patients were changed from 1 regimen to the other. Assay was

performed after the patient had received at least 3 consective infusions of the same dose of drug. Concentration in serum obtained from 15 patients without prior severe renal disease. Infusions of up to 90 mg QOD gave mean peak concentrations higher than with QD therapy of half the dose. Over the same range of doses mean valley concentrations were not significantly lower during QOD than during QD therapy. Mean peak concentrations of amphotericin B deoxycholate in serum during doses of 100 mg QOD were not significantly better than those obtained during 50 mg QD, while mean valley concentrations were significantly lower on QOD therapy. Concentrations of amphotericin B deoxycholate in serum were not everywhere directly proportional to dose. The peak concentrations during QD therapy and the valley concentrations during either schedule showed a tendency to plateau at doses exceeding 50 mg. After the same dose was given repeatedly, assays did not yield increasingly higher serum concentrations. Twenty-four hours urinary excretion of bioactive amphotericin B deoxycholate ranged from 0.51 to 4.67 mg in the 24 hours following onset of infusion. No significant difference between mean percentage of excretion of QD drug and that of QOD drug. Post-treatment elimination of amphotericin B deoxycholate obtained on 11 patients. As indicated by linearity on a log-log scale, the decline in serum concentration was rapid at first but became steadily slower as time went on. The concentration in the serum of an average patient fell by 70% during the first 24 hours but only 7% during the tenth 24 hours.

Fields et al. reported effect of rapid intravenous infusion on serum concentrations of amphotericin B deoxycholate in patients with systemic mycoses. (29) Treatment was begun with 5 mg of amphotericin B deoxycholate and gradually increased to 50 mg three times per week. Amphotericin B deoxycholate was given in an intravenous infusion of 500 ml of 5% dextrose. A total of 16 infusions of amphotericin B deoxycholate 50 mg were studies in 3 patients. Eight infusions were adminitered rapidly (45 minutes) and 8 infusions were adminitered slowly (5 hours). Serum concentrations of amphotericin B deoxycholate at 1, 18 and 42 hours after complete of infusion were obtained. The mean serum concentrations of amphotericin B deoxycholate 1 hour after the rapid infusion group was 2.02 μg/ml compared with 1.18 μg/ml in the slow infusion group, $p<0.001$. The mean serum concentrations of amphotericin B deoxycholate 18 hours after the rapid infusion group was 0.74 μg/ml

compared with 0.64 μg/ml in the slow infusion group, p>0.1. The mean serum concentrations of amphotericin B deoxycholate 42 hours after the rapid infusion group was 0.39 μg/ml compared with 0.31 μg/ml in the slow infusion group, p>0.05.

Bekersky et al. studied pharmacokinetics, excretion and mass balance of liposomal amphotericin B and amphotericin B deoxycholate by compared in a phase IV, open-label randomized paralled study in 10 healthy volunteers. (30) After a single 2-hour infusion of liposomal amphotericin B 2 mg/kg or amphotericin B deoxycholate 0.6 mg/kg, plasma, urine and feces were collected for 168 hours. All subjects who received amphotericin B deoxycholate displayed triphasic plasma amphotericin B deoxycholate concentration profiles. Mean maximum concentration of amphotericin B deoxycholate in serum (C_{max}) was 1.43±0.2 μg/ml, concentration of amphotericin B deoxycholate in serum at 24 hours was 0.25±0.03 μg/ml, the distribution half-life phase ($t_{1/2\alpha}$) was 0.17±0.4 hour, the elimination half-life phase ($t_{1/2\beta}$) was 6.8±1.6 hours and the terminal elimination half-life phase ($t_{1/2\gamma}$) was 127±30 hours. The volume of the central compartment was 136±60 ml/kg. The volume of distribution during elimination was 2,340±202 ml/kg. The volume of distribution at steady state (Vd_{ss}) was 1,807±239 ml/kg. Total clearance was 13.1±2.0 ml/kg/hr, renal clearance was 4.1±0.68 ml/kg/hr, fecal clearance was 5.4±0.91 ml/kg/hr. By the end of the 1-week study, the urinary recovery of unchanged amphotericin B deoxycholate was 20.6% and the feces recovery of unchanged amphotericin B deoxycholate was 42.5%. Metabolism plays at most a minor role in amphotericin B deoxycholate elimination. No amphotericin B deoxycholate metabolites were observed by high performance liquid chromatography (HPLC) or mass spectrometry.

Kan et al. conducted to compare safety, tolerance and pharmacokinetics of amphotericin B lipid complex and amphotericin B deoxycholate in 16 healthy male volunteers. (31) Eight volunteers received amphotericin B deoxycholate. On day 1, amphotericin B deoxycholate was given as a 1 mg test dose; after a 2-hour monitoring period, a 0.1 mg/kg was given. On day 3, dose of amphotericin B deoxycholate 0.25 mg/kg was infused. Three volunteers who received amphotericin B deoxycholate occurred somnolence, shaking chills occurred in 1 volunteer and headache occurred in 5 volunteers. In the amphotericin B deoxycholate dose 0.1 mg/kg group, C_{max} was

551±24.61 ηg/ml, elimination half-life was 30.8±4.1 hours, clearance was 0.01±0.001 L/kg/hr, Vd_{ss} was 0.5±0.05 L/kg and area under curve $_{0\text{-}24\ hours}$ ($AUC_{0\text{-}24\ hours}$) was 3,907±433 ηg.hr/ml. In amphotericin B deoxycholate dose 0.25 mg/kg group, C_{max} was 984±55.94 ηg/ml, elimination half-life was 50±11.3 hours, clearance was 0.01±0.001 L/kg/hr, Vd_{ss} was 0.74±0.13 L/kg and $AUC_{0\text{-}24\ hours}$ was 8,671±758 ηg.hr/ml. Cumulative urinary excretion of amphotericin B deoxycholate was 8% of the administered dose.

Ayestaran et al. presented a comparative prospective, open-label randomized study to compare pharmacokinetics of amphotericin B deoxycholate administered in a conventional 5% dextrose with in 20% fat emulsion formulation in 16 patients with neutropenia from May 1993 to March 1994. (32) Each 8 patients received 50 mg of amphotericin B deoxycholate infusion over 1 hour daily with random order to receive a 50 ml lipid emulsion or in 500 ml of 5% dextrose. Hydration and electrolyte supplementation were given as needed. Blood samples were obtained at 0.17, 2, 6, 12 and 24 hours after the end of the first infusion of amphotericin B deoxycholate. The C_{max} in the dextrose group was 2.83±1.17 μg/ml, the AUC was 28.98±15.46 μg.hr/ml, Vd_{ss} was 562.32±152.05 ml/kg, clearance was 33.01±14.33 ml/kg/hr, $t_{1/2\alpha}$ was 0.64±0.24 hour, $t_{1/2\beta}$ was 15.23±5.25 hours, volume of distribution of the central compartment was 328.19±151.71 ml/kg and volume of distribution of the peripheral compartment was 234.14±75.92 ml/kg.

Feldman et al. studied amphotericin B deoxycholate therapy in an anephric patient who developed candidiasis after failure of a renal transplant. (33) Amphotericin B deoxycholate therapy was begun at a dose of 20 mg (0.5 mg/kg) every 24 to 48 hours. The minimal inhibitory concentration (MIC) of drug for the organism was 0.062 μg/ml. Patient received total dose of amphotericin B deoxycholate 180 mg. Blood was taken from the patient at various times in relation to dose of amphotericin B deoxycholate during the course of therapy and for 33 days after the last dose of amphotericin B deoxycholate. During the course of amphotericin B deoxycholate therapy, patient underwent hemodialysis treatments lasting 6 hours and spaced 24 to 72 hours apart. During the course of one dialysis, hourly serum samples and 1-L samples of each hour's dialysate drainage were collected for

determination of amphotericin B deoxycholate concentration. No progressive accumulation of amphotericin B deoxycholate in serum was occurred. The serum half-life of amphotericin B deoxycholate was 43 hours. After discontinuation of therapy, the rate of decline in serum levels slowed. Values obtained on days 3, 5, 7 and 8 post-therapy were 0.23 μg/ml, 0.26 μg/ml, 0.26 μg/ml and 0.23 μg/ml, respectively. Samples taken from days 10 to 28 after therapy produced some inhibition of the test organism but values were less than 0.2 μg/ml. Samples taken from days 30 to 33 showed no evidence of antifungal activity in the patient's serum. During a 6-hour hemodialysis, serum concentration of amphotericin B deoxycholate at 0, 1, 2, 3, 4, 5, 6 hours were 0.25 μg/ml, 0.26 μg/ml, 0.22 μg/ml, 0.27 μg/ml, 0.25 μg/ml, 0.33 μg/ml and 0.22 μg/ml, respectively. Amphotericin B deoxycholate was not dialyzable with conventional hemodialysis membranes.

Block et al. assessed the efficacy of hemodialysis in removing amphotericin B deoxycholate from the blood in patients with renal failure who required chronic hemodialysis. (34) Four patients who were receiving long-term amphotericin B deoxycholate alone or in combination with flucytosine were studied. Amphotericin B deoxycholate concentrations were measured in arterial samples obtained immediately before and after a 4 or 6-hour dialysis. For patients had undergoing hemodialysis at constant blood-flow rates ranging from 175 to 300 ml/min. The clearance rate of amphotericin B deoxycholate ranged from 3-15% of the simultaneously determined creatinine. Amphotericin B deoxycholate was poorly dialyzable.

Christiansen et al. studied concentrations of amphotericin B deoxycholate in tissues obtained at autopsy from 8 patients. (35) The cumulative dose ranged from 101 to 2,688 mg. Three of patients had disseminated fungal infections at autopsy. Amphotericin B deoxycholate was measured in tissues. The liver was the major site of storage in the tissues. Highest concentrations of amphotericin B deoxycholate were detected in the liver and spleen; high concentrations were found in the kidneys and lungs. The levels in muscle and fat from all patients were much lower than other tissues. Concentrations of amphotericin B deoxycholate in the kidneys were measured in samples that included both cortex and medulla. The concentration in the cortex was

found to be about twice the level of that in the medulla. No evidence for metabolism of amphotericin B deoxycholate was observed.

2. Susceptibility testing of amphotericin B deoxycholate.

Susceptibility testing of amphotericin B deoxycholate for fungi has been brought by 3 major publications. First, there is the National Committee for Clinical Laboratory Standards (NCCLS) proposed macrobroth reference method. The NCCLS M27-P is reference method for broth dilution antifungal susceptibility testing of yeasts in 1992. The NCCLS M27-A is reference method for broth dilution antifungal susceptibility testing of yeasts in 1997. The NCCLS M38-P is reference method for broth dilution antifungal susceptibility testing of conidium-formingfilamentous fungi in 1999. This provide for the first time a standardized method for evaluating the antifungal susceptibility of yeasts. The second is a microbroth dilution method and the last one is Etest, an agar diffusion method using a strip with a predefined concentration gradient of the antimicrobial agent being tested. A problem to be addressed with amphotericin B deoxycholate susceptibility testing is that current test procedures may not be reliable for detecting resistance. There are some limitations to antifungal susceptibility testing. A viable culture is needed, the causative organism has not been isolated. The other factor is accurate identification. For yeasts, identification of infecting species may be predictive of its antifungal susceptibility pattern. Mould identification for the purposes of predicting susceptibility is difficulty as in currently lack the supporting data. (36)

The spectrum of activity of amphotericin B deoxycholate is confusing. Analysis of laboratory data, which often includes data obtained by different methods of susceptibility testing and clinical practice data or clinical experience, result of discrepancies of amphotericin B deoxycholate spectrum of activity in clinically yeasts and moulds. Resistance of amphotericin B deoxycholate is quite rare and often caused by a decrease in either the amount of ergosterol in the plasmalemma or a change in the target lipid, which leads to a decrease in the binding of amphotericin B deoxycholate (MIC > 2 mg/L). (36,37)

Espinel-Ingroff et al. conducted to evaluate the interlaboratory agreement of broth dilution susceptibility methods for 5 species of conidium-forming filamentous fungi. (38) The methods used included both macro- and microdilution methods that were adaptations of the proposed reference method of the NCCLS M27-P. The reference method testing conditions that were adopted included buffered (morpholine propanesulfonic acid; MOPS) RPMI medium incubation at 35 °C. The MICs of amphotericin B deoxycholate were determined in 6 centers by both macro- and microdilution test for 25 isolates of *A. flavus, A. fumigatus, Pseudallescheria boydii, Rhizopus arrhizus* and *S. schenckii*. All isolates produced clearly defectable growth within 1 to 4 days at 35 °C in the RPMI 1640 medium. Intralaboratory comparison of broth macro- and microdilution methods, mean agreement for 75% reduction in growth was 97% and for 50% reduction in growth was 90%. Interlaboratory agreement of microdilution method for 75% reduction in growth was 91% and for 50% reduction in growth was 87%. Interlaboratory agreement of macrodilution method for 75% reduction in growth was 87% and for 50% reduction in growth was 91%.

Rex et al. presented to identify alternative media and pH conditions for detection of amphotericin B deoxycholate-resistant *Candida* isolates because of the limited ability of the NCCLS M27-P. (39) Failure of several isolates to grow in Casitone broth at pH 7 or in Sabouraud broth at pH 5 and pH 7 makes these conditions unsuitable. YNB at pH 5 provided moderate discrimination at both 24 and 48 hours but this medium tended to elevate the MICs for all isolates. The best discrimination was obtained with Casitone broth at pH 5 and Antibiotic Medium 3 broth (Penassay broth) at both pH 5 and pH 7. An Antibiotic Medium 3 broth supported good growth of all yeast isolates and appeared to have potential for discrimination between susceptible and resistant isolates, testing isolates from the bloodstream collection at pH 5 for 218 isolated tested and pH 7 for 221 isolated tested.

Ren-Kai et al. reported the in vitro activity of amphotericin B deoxycholate against the mold forms of 304 isolates of three dimorphic fungi. (40) These comprised 100 clinical isolates each of *B. dermatitidis* and *C. immitis* and 104 clinical isolates of *Histoplasma capsulatum*. Amphotericin B deoxycholate was tested in Bacto

Antibiotic Medium 3 supplemented with 2% glucose. The MICs were determined by a broth microdilution adaptation of the NCCLS M27-A procedure. The MICs endpoints were determined after 48 hours of incubation at 35 °C or after the control tubes showed appropriate growth. The MIC was defined as the lowest concentration of drug that completely inhibited growth. The minimum fungicidal concentration (MFC) was determined and defined as the lowest concentration that allowed the growth of three or fewer colonies. This represents killing of > 97% of the original inoculum. The data were presented as MIC and MFC ranges and as the drug concentrations required to inhibit or kill 50 and 90% of the isolates of each species (MIC_{50}, MIC_{90}, MFC_{50} and MFC_{90}). Amphotericin B deoxycholate was active against *B. dermatitidis* with MIC range of ≤ 0.03 to 1 μg/ml, MIC_{50} was 0.06 μg/ml , MIC_{90} was 0.5 μg/ml and with MFC range of ≤ 0.03 to 4 μg/ml, MFC_{50} was 0.125 μg/ml , MFC_{90} was 0.5 μg/ml. For *C. immitis* with MIC range of 0.25 to 2 μg/ml, MIC_{50} was 0.5 μg/ml , MIC_{90} was 1 μg/ml and with MFC range of 0.5 to >16 μg/ml, MFC_{50} was 4 μg/ml , MFC_{90} was >16 μg/ml. For *H. capsulatum* with MIC range of ≤ 0.03 to 2 μg/ml, MIC_{50} was 0.25 μg/ml , MIC_{90} was 1 μg/ml and with MFC range of ≤ 0.03 to >16 μg/ml, MFC_{50} was 0.5 μg/ml , MFC_{90} was 2 μg/ml.

Clancy and Nguyen conducted a multicenter prospective study to express correlation between in vitro susceptibility determined by Etest and response to therapy with amphotericin B deoxycholate in candidemic patients. (41) The *Candida* isolates were recovered from 99 candidemic patients assigned to amphotericin B deoxycholate as monotherapy with dose 0.6 mg/kg/day. The isolates include were 52 of *C. albicans*, 20 of *C. glabrata*, 14 of *C. tropicalis*, 9 of *C. parapsilosis*, 3 of *C. lusitaniae* and 1 of *C. krusei.* The amphotericin B deoxycholate MIC determined by the Etest were higher for isolates associated with therapeutic failure than the MIC for those associated with therapeutic success. This finding was most pronounced at 48 hours (geometric mean MIC of 0.22 and 0.05 μg/ml, respectively; p=0.001), the difference was also significant at 24 hours (geometric mean MIC of 0.1 and 0.03 μg/ml, respectively; p=0.01). Breakpoint MIC capable of identifying amphotericin B deoxycholate-resistant isolates could be proposed. At 24 hours, 15 of 33 (46%) of the isolates for which the MIC were ≥ 0.19 μg/ml were associated with therapeutic failure compared

with 11 of 66 (17%) of those for which the MIC were < 0.19 μg/ml, p=0.005. The relative risk of therapeutic failure among patients infected with isolates for which the MIC at 24 hours were ≥ 0.19 μg/ml was 2.7-fold (95% confidence interval [95%CI], 1.5-12) greater than the risk of failure among patients infected with isolates for which the MIC were < 0.19 μg/ml. At 48 hours, 14 of 25 (56%) of the isolates for which the MIC were ≥ 0.38 μg/ml were associated with therapeutic failure compared with 12 of 74 (16%) of the isolates for which the MIC were < 0.38 μg/ml, p=0.0001. The RR of therapeutic failure among patients infected with isolates for which the MIC at 48 hours were ≥ 0.38 μg/ml was 3.5-fold (95% CI, 2.2-20.4) more than the risk of failure among patients infected with isolates for which the MIC were < 0.38 μg/ml. The Etest breakpoint MIC of ≥ 0.38 μg/ml had a sensitivity of 14 of 26 (54%), a specificity of 85% and a positive predictive value of 56%.

Wanger et al. conducted to compare Etest and the NCCLS M27-P method for antifungal susceptibility testing to detect amphotericin B deoxycholate-resistant *Candida* isolates. (42) Amphotericin B deoxycholate MIC were the lowest concentration on the Etest strip at which there was 100% inhibition of the organism. RPMI 1640 was a defined medium but it was not support good growth of all yeasts and growth was more luxuriant on antibiotic medium 3 for the majority of clinical isolates tested. Good agreement was seen between Etest and the NCCLS M27-P method with both RPMI 1640 and antibiotic medium 3. Agreement of *C. albicans* for RPMI 1640 was 96% and 98% for antibiotic medium 3, *C. parapsilosis* was 100% for RPMI 1640 and 90% for antibiotic medium 3, *C. tropicalis* was 92% for RPMI 1640 and 85% for antibiotic medium 3 and *C. glabrata* was 100% for both RPMI 1640 and antibiotic medium 3. Etest with RPMI 1640 agar and antibiotic medium 3 agar methods had to discriminated between amphotericin B deoxycholate-susceptible and resistant isolates, unlike the NCCLS reference method.

Hadley et al. examined the utility of a new method of susceptibility testing (semi-solid agar antifungal susceptibility screening; SAAS) in real-time management of invasive yeast infections in 8 immunocompromised patients. (43) Test of amphotericin B deoxycholate concentrations of 0.5 and 2 mg/L and fluconazole concentrations of 1, 8 and 40 mg/L were performed on infecting organisms included

C. albicans in 2 patients, *C. tropicalis* in 2 patients, *C. glabrata* in 1 patient, *C. krusei* in 1 patient and *Trichosporon* species in 2 patients. Comparison of MIC was made between the NCCLS M27-A broth microdilution and SAAS methods. By the SAAS test, all organisms were susceptible to amphotericin B deoxycholate and the *Candida* isolates were resistant in 5 isolates and dose-dependently susceptible in 1 isolate to fluconazole. Therapy for 2 patients were changed from amphotericin B deoxycholate to fluconazole, resulting in successful clinical and microbiological outcomes. All patients survived for 30 days after diagnosis of the invasive fungal infections (IFI) episode, with successful clinical and microbiological response. Two patients died on 39 and 47 days after IFI without evidence of recurrent infection, although no autopsies were performed. Limitations, the SAAS test has not been validated in a multilaboratory study and problems of subjective reading a results.

Nguyen et al. presented outcome for 105 patients with candidemia treated with amphotericin B deoxycholate was correlated with amphotericin B deoxycholate in vitro susceptibility results. (44) The study designed as multicenter prospective observational study. The *Candida* isolates were 53 of *C. albicans*, 19 of *C. glabrata*, 18 of *C. tropicalis*, 10 of *C. parapsilosis*, 3 of *C. lusitaniae* and 2 of *C. krusei.* All patients were treated with amphotericin B deoxycholate at a median daily dose of 0.6 mg/kg. Susceptibility testing against drug was performed by the NCCLS M27-A method. Two media were used, AM3 without glucose supplementation and without buffering (pH 6.95-6.97) and AM3 supplemented with 2% glucose (adjusted to pH 7 using 1 M phosphate buffer). The MIC was defined as the lowest concentration of amphotericin B deoxycholate that completely inhibited growth at 48 hours. The MLC was defined as the lowest concentration of drug from which the subcultures yielded < 5 colonies. There was no correlation between amphotericin B deoxycholate MIC at 24 and 48 hours and microbiologic failure. Higher amphotericin B deoxycholate MLC at 24 and 48 hours were correlated significantly with microbiologic failure. At the 48-hour reading, 14 of 18 isolates (78%) exhibiting MLC > 1 μg/ml were associated with a significantly higher likelihood of microbiologic failure than those 19 of 87 isolates (22%) exhibiting MLC ≤ 1 μg/ml, $p<0.001$. At the 24-hour reading, 6 of 11 isolates (54%) exhibiting MLC > 1 μg/ml were associated with microbiologic failure, whereas

27 of 94 isolates (29%) exhibiting MLC ≤ 1 μg/ml were associated with microbiologic failure; however, difference of 48-hour versus 24-hour MLC was not statistically different (p=0.08). All 105 isolates (100%) of MIC obtained using AM3 with glucose were within 4-fold dilution of those obtained using AM3 alone; 100 of 105 isolates of MIC were within 2-fold dilution difference. For MLC, 101 of 105 isolates (96%) of MLC obtained by AM3 with glucose were within 2-fold dilution difference of those obtained with AM3 alone.

Cook et al. examined the effects of temperature and inoculum on the agreement of macro- and microdilution broth MIC of amphotericin B deoxycholate against 6 isolates of *Candida* species. (45) Differences between macro- and microdilution broth MIC of amphotericin B deoxycholate showed significantly closer agreement between methods at the lower temperature. At 35 °C for inoculum size of 10^2 CFU/ml had mean 3.67±0.96-fold differences and for 10^4 CFU/ml had mean 4.67±1.23-fold differences. At 37 °C for 10^2 CFU/ml had mean 10±2-fold differences and for 10^4 CFU/ml had mean 9.33±2.23-fold differences. The mean difference for amphotericin B deoxycholate was more than 5-fold lower at 35 °C than at 37 °C, $p<0.004$. The magnitude of the difference between macro- and microdilution broth MIC of amphotericin B deoxycholate was comparatively large, that at 37 °C microdilution MIC averaged greater than 9-fold lower than macrodilution MIC. Inoculum size was found to affect in amphotericin B deoxycholate. Agreement was better for amphotericin B deoxycholate at 35 °C, this incubation temperature would seen preferable for standardized methods.

Pfaller et al. performed to evaluate the effect of medium, incubation time (24 and 48 hours) and temperature (30 and 35 °C) on intra- and interlaboratory variations in MIC of amphotericin B deoxycholate for *Candida* species by using a standard macrodilution protocol in 11 laboratories. (46) Four chemically defined media were evaluated, including buffered yeast nitrogen base (BYNB), synthetic amino acid medium-fungal (SAAMF), RPMI 1640 medium and high-resolution antifungal assay medium (HR). All media were buffered to pH 7 with 0.165 M MOPS. The growth rates of the test isolates were similar in 4 media. The doubling times of *Candida* species were more rapid at an incubation temperature of 35 °C than at 30 °C in each

medium except BYNB. The most rapid growth at 35 °C was observed with HR. A comparison of MIC results obtained after 24 hours of incubation versus those obtained after 48 hours of incubation at 30 and 35 °C in the four different media was given. For BYNB medium at 30 and 35 °C, agreement of MIC between 24 and 48 hours of incubation were 94% and 93%, respectively. For SAAMF medium at 30 and 35 °C, agreement of MIC between 24 and 48 hours of incubation were 92% and 100%, respectively. For RPMI 1640 and HR mediums at 30 and 35 °C, both agreement of MIC between 24 and 48 hours of incubation were 100%. The levels of interlaboratory agreement of MIC results stratified by incubation conditions and test medium were given in 5 laboratories. For BYNB, SAAMF, RPMI 1640 and HR mediums at 30 °C for 24 hours of incubation, interlaboratory agreement of MIC were 79%, 60%, 85% and 85%, respectively. For BYNB, SAAMF, RPMI 1640 and HR mediums at 30 °C for 48 hours of incubation, interlaboratory agreement of MIC were 67%, 69%, 73% and 85%, respectively. For BYNB, SAAMF, RPMI 1640 and HR mediums at 35 °C for 24 hours of incubation, interlaboratory agreement of MIC were 75%, 60%, 69% and 79%, respectively. For BYNB, SAAMF, RPMI 1640 and HR mediums at 35 °C for 48 hours of incubation, interlaboratory agreement of MIC were 76%, 67%, 81% and 79%, respectively. The highest level of agreement was observed with RPMI 1640 medium at 30 °C for 24 hours or HR medium at 30 °C for 24 and 48 hours of incubation. The incubation temperature had effect on the relative susceptibilities of amphotericin B deoxycholate when tested in BYNB medium, for which a significantly higher proportion of the data sets were in agreement with the reference rank order at 35 °C than at 30 °C, $p<0.05$.

Arikan et al. investigated microdilution susceptibility testing of amphotericin B deoxycholate against clinical isolates of *Aspergillus* and *Fusarium* species. (47) A microdilution method adopted from the NCCLS M27-A. RPMI 1640, RPMI 1640 supplemented to 2% glucose and antibiotic medium 3 supplemented to 2% glucose were used as test media. Eighty-two isolates of *Aspergillus* species: 27 isolates of *A. flavus*, 26 isolates of *A. fumigatus*, 17 isolates of *A. niger*, 9 isolates of *A. terreus* and 3 isolates of *A. nidulans* and 22 isolates of *Fusarium* species: 18 isolates of *F. solani* and 4 isolates of *F. oxysporum*. MIC were determined after 24, 48 and 72 hours. At 24

hours, sufficient growth was consistently obtained for all species except *A. nidulans*. Amphotericin B deoxycholate MIC spanned a relatively narrow range for both *Aspergillus* and *Fusarium* species. Amphotericin B deoxycholate MIC were higher for *Fusarium* isolates than for *Aspergillus* isolates. The RPMI 1640 supplemented to 2% glucose medium generated the same or slightly decreased amphotericin B deoxycholate MIC compared to the MIC generated by the reference medium, RPMI 1640 alone. The antibiotic medium 3 supplemented to 2% glucose lowered the MIC of amphotericin B deoxycholate more predominantly than RPMI 1640 supplemented to 2% glucose medium.

IV. Infusion-related adverse reactions and nephrotoxicity of amphotericin B deoxycholate.

The main problems during administration amphotericin B deoxycholate are the infusion-related adverse reactions include fever, chills and/or rigors, nausea, vomiting, phlebitis and nephrotoxicity. The incidence of nephrotoxicity varies from 15-80%, resulted from varying definitions of nephrotoxicity, differing diseases and concomitant administration of other medications.

Goodwin et al. performed a prospective study designed to determine the incidence of adverse events related of amphotericin B deoxycholate during the first 7 days of therapy from March 1988 through September 1988. (48) Three hundred ninety-seven patients who received amphotericin B deoxycholate therapy were monitored. The infusion-related adverse events most commonly reported were fever occurred in 51% of patients, chills occurred in 28% of patients, nausea occurred in 18% of patients, headache occurred in 9% of patients and thrombophlebitis occurred in 5% of patients. The onset of new infusion-related of fever and chills appeared to decrease with time, suggesting the development of tolerance to amphotericin B deoxycholate.

Ellis et al. investigated a double-blind randomized non-crossover study of the effect of infusion rates on toxicity of amphotericin B deoxycholate. (49) Eleven patients received amphotericin B deoxycholate over 45 minutes and 9 patients

received amphotericin B deoxycholate over 4 hours. Following the 7-day study period, 7 of 11 patients in the 45-minute infusion group and 8 of 9 patients in the 4-hour infusion group completed of antifungal course. The mean duration of amphotericin B deoxycholate treatment was 11.1±5.7 days (range 3-21 days) for 8 patients in the 4-hour infusion group and 26.9±20.4 days (range 7-70 days) for 7 patients in the 45-minute infusion group. The mean chill score for the total 7 day period was 173±276 for patients assigned to receive 45-minute infusion and 20±30 for patients assigned to receive 4-hour infusion, $p<0.01$. The daily mean chill score was seen to decrease with each subsequent infusion. Over the 7-day period, the mean times that patients experienced any rigor were 3.1±2.2 days in the 45-minute infusion group and 1.4±2.1 days in the 4-hour infusion group, $p=0.1$. The proportion of patients with any other side effects, mainly headache, nausea, vomiting and cramps was slightly higher in the 45-minute infusion group for the first 2 days but the difference was not significant. The mean CrCl was higher in the 45-minute infusion group but the difference was not significant. Decrease in CrCl of between 21 and 50% occurred in 6 of 11 patients (54.5%) in the 45-minute infusion group and 2 of 9 patients (22.2%) in the 4-hour infusion group. Two patients in each group had a decrease in CrCl exceeded 51%. Three patients in the 45-minute infusion group could not complete the course because of unacceptable renal toxicity. All 5 patients deaths, 4 patients in the 45-minute infusion group and 1 patient in the 4-hour infusion group.

Nicholl et al. compared 2 hours and 4 hours infusion-related adverse effects of amphotericin B deoxycholate in patients with leukemia or BMT. (50) The study designed as randomized, double-blind, 2-arm complete crossover, prospective clinical trial. The study population consisted of 25 consecutive patients who received 331 regimen infusion of amphotericin B deoxycholate. Infusion-related adverse effects of amphotericin B deoxycholate were assessed closely during each 6 hours period following the initiation of each infusion. Positive chill scores were identified in 13 infusions (8%) in the 2-hour infusion group and 12 infusions (7%) in the 4-hour infusion group. Nausea and vomiting reported in 11 infusions (7%) in the 2-hour infusion group and 19 infusions (12%) in the 4-hour infusion group and fever occurred in 5 infusions (3%) in the 2-hour infusion group and 3 infusions (2%) in the 4-hour

infusion group. Infusion-related adverse effects of amphotericin B deoxycholate were no differences between the 2-hour infusion group and the 4-hour infusion group.

Cruz et al. conducted a prospective, pilot study to determine the safety and toxicity of rapid infusions of amphotericin B deoxycholate in patients with clinical indications for antifungal therapy. (51) Twenty-five granulocytopenic adults with acute leukemia and myelodysplastic-syndromes were enrolled: 15 patients received drug infusion over 1 hour, 4 patients received drug infusion over 2 hours, each 3 patients received drug infusion over 3 hours and a standard infusion over 4 hours. Temperatures of 38 °C or greater during or within 6 hours of drug infusion occurred in 16 of 25 patients (64%): 11 patients in the 1 hour group, 2 patients in the 2 hours group, 1 patient in the 3 hours group and 2 patients in the 4 hours group. Temperatures exceeding 40 °C occurred 1 patient in the 1 hour group and 1 patient in the 2 hours group. Increases in SCr greater than 0.5 mg/dl above baseline occurred in 17 of 25 patients (68%): 10 patients in the 1 hour group, 2 patients in each the 2 hours and the 3 hours groups and 3 patients in the 4 hours group. The absolute SCr level was ≥ 2 mg/dl observed in 10 of 25 patients (40%): 6 patients in the 1 hour group, 2 patients in the 2 hours group and 1 patient in each the 3 hours and the 4 hours groups. Serum potassium levels less than 3.5 mEq/L were observed in all patients by day 10 of therapy but no patient had potassium levels below 2.5 mEq/L. Intravenous potassium supplementation was administered to all patients and exceeded 100 mEq/day in 12 of 25 patients (48%). Hypomagnesemia was observed in 24 of 25 patients (96%): 15 patients in the 1 hour group, 4 patients in the 2 hours, 3 patients in the 3 hours groups and 2 patients in the 4 hours group. One patient with a prior history of atrial fibrillation developed atrial fibrillation 6 hours after receiving amphotericin B deoxycholate over 1 hour. The patient received amphotericin B deoxycholate over 2 hours, 4 months later without complications.

Cleary et al. reported a prospectively study effect of infusion rate on amphotericin B deoxycholate-associated febrile reactions. (52) Seventeen consenting BMT recipients in whom amphotericin B deoxycholate was to be initiated for documented or suspected fungal infections were recruited. Patients were randomized to receive amphotericin B deoxycholate 0.5 mg/kg/day as either a 45-minute or 2-hour

infusion in a crossover pair design. Patients were randomized to a new treatment pair every other day for a total of four treatment pairs in eight total study days. The patients were blinded from the infusion rate delivered. After the final study day, patients returned to the standard infusion rate (2 hours) for the duration of amphotericin B deoxycholate therapy. All 17 patients completed the first pair of amphotericin B deoxycholate infusion. Eight patients received 45-minute infusion and 9 patients received 2-hour infusion as their first infusion. Ten patients did not complete all four infusion pairs. There were no significant differences in the mean temperature change for either infusion. Fever occurred in 12 of 17 patients (70.5%) and 13 of 17 patients (76.4%) for the 45-minute and 2-hour infusion groups, respectively. The mean rise in temperature was 1.7 °C (1.1-3.7) for the 45-minute infusion group and 1.7 °C (1.1-3.5) for the 2-hour infusion group ($p>0.1$). Chills were observed in 15 of 17 patients (88.2%) assigned to the 45-minute infusion group and 14 of 17 patients (82.3%) assigned to the 2-hour infusion group. The time of onset ($p>0.1$) and the duration of chills ($p=0.08$) were similar for both infusion rates. Nausea and vomiting occurred in 4 of 48 infusions monitored (8.3%) and 2 of 47 infusions monitored (4.3%) for the 45-minute and 2-hour infusion groups, respectively.

Oldfield et al. conducted a randomized, double-blind trial of 1- versus 4-hour infusions of amphotericin B deoxycholate to determine the infusion-related toxicity from January through September 1987. (53) A total of 128 maintenance infusions in 12 patients were evaluated; 62 were randomized to 1-hour infusion and 66 were randomized to 4-hour infusions. There was no significant difference between patients in two groups, $p=0.09$. Rigors or chills were noted in 15 of 62 infusions (24.1%) in the 1-hour infusion group and 12 of 66 infusions (18.1%) in the 4-hour infusion group, $p=0.4$. An increase in temperature were noted in 5 of 62 infusions (8%) in the 1-hour infusion group and 7 of 66 infusions (10.6%) in the 4-hour infusion group, $p=0.63$. The mean time to onset of an increase in temperature and rigors occurred significantly earlier in the 1-hour infusion group than the 4-hour infusion group. The mean time to onset of an increase in temperature was 120 minutes in the 1-hour infusion group and 180 minutes in the 4-hour infusion group, $p=0.018$. The mean time to onset of rigors

was 66 minutes in the 1-hour infusion group and 107 minutes in the 4-hour infusion group, p=0.02.

Pathak et al. performed a retrospective chart review to analyze the usage of amphotericin B deoxycholate with special emphasis on side effects from January 1993 to May 1996. (54) Renal insufficiency was considered to be a SCr level ≥ 1.6 mg/dl with an increase of ≥ 0.5 mg/dl during amphotericin B deoxycholate therapy. During the study period, 102 patients were treated with amphotericin B deoxycholate. The average total amphotericin B deoxycholate dosage was 162.5 mg (range 10-840 mg). Mean amphotericin B deoxycholate infusion time was 264 minutes (range 120-600 minutes). The total duration of administration averaged 8.3 days (range 1-46 days). Eighty-three percent of patients made a full recovery from documented fungal infections. Sixteen patients (14.4%) died during amphotericin B deoxycholate therapy. Most deaths were due to underlying illness. One death was directly attributable to yeast septicemia and one person died of cryptococcal meningitis and HIV disease. No patient experienced anaphylaxis due to amphotericin B deoxycholate. Chills, fever and/or nausea occurred in 25%, hypokalemia occurred in 19% and renal toxicity occurred in 15% of 102 patients. Discontinuation of amphotericin B deoxycholate occurred in 1 patient because of nephrotoxicity. This study was unable to assess the effect of infusion time since most patients were infused over 4-5 hours (94% of all patients).

Harbarth et al. performed a 9-year retrospective analysis of amphotericin B deoxycholate-associated nephrotoxicity in 494 adult patients from January 1990 through September 1998. (55) Nephrotoxicity was defined as an increase of at least 50% in the SCr level during amphotericin B deoxycholate therapy compared with the baseline value, to an absolute value ≥ 1.5 mg/dl; or moderate to severe nephrotoxicity defined as a doubling of the SCr level to ≥ 2.0 mg/dl. Overall, 139 patients (28%) experienced renal toxicity. Fifty-eight patients (12%) with moderate to severe nephrotoxicity, with the latter group including 16 patients (3%) with severe nephrotoxicity only defined as a tripling in the baseline creatinine level to ≥ 3.0 mg/dl.

Bates et al. reviewed chart of 643 patients who receiving amphotericin B deoxycholate at one tertiary care hospital between May 17, 1993 and April 22, 1997.

(56) Acute renal failure (ARF) was defined as a 50% increase in baseline creatinine with a peak ≥ 2.0 mg/dl. Acute renal failure was divided into two categories: severe, defined as a doubling of baseline creatinine values with a peak ≥ 3.0 mg/dl, and significant, meeting the definition for ARF but not the definition for severe renal failure. The overall ARF occurred in 175 patients (27%). This patients was devided for severe ARF in 67 patients (10%), while it was significant in the remaining 108 patients (17%).

Gubbins et al. studied characterizing and predicting amphotericin B deoxycholate-associated nephrotoxicity in bone marrow or peripheral blood stem cell transplant recipients. (57) Patients who received at least two doses of amphotericin B deoxycholate from January 1, 1992 through January 1, 1995 were reviewed. Nephrotoxicity was defined as a doubling of the baseline SCr value obtained on the first day of amphotericin B deoxycholate therapy. Sixty-nine patients were eligible for inclusion in the study. Nephrotoxicity occurred in 30 patients (43%). The mean time to development of nephrotoxicity was approximately 6±4.8 days (range 1-22 days). The proportion of patients who died during their hospital stay or within 30 days of hospital discharge or discontinuation of amphotericin B deoxycholate was greater among patients who developed nephrotoxicity.

Wingard et al. reviewed records of 239 immunosuppressed patients receiving amphotericin B deoxycholate for suspected or proven aspergillosis for the period January 1, 1990 through December 31, 1993. (58) Nephrotoxicity parameters assessed included a doubling of the SCr level compared with baseline (prior to start of amphotericin B deoxycholate therapy) and an increase of SCr level to > 2.5 mg/dl. The mean±SD and median durations of treatment with amphotericin B deoxycholate were 20.4±17.8 days and 15.0 days, respectively. The SCr level doubled in 53% of patients and exceeded 2.5 mg/dl in 29% of patients. One hundred forty-three (60%) of 239 patients died, 27 patients died within the first week of treatment. The mortality among patients who required dialysis greater than among those who did not (76% and 57%, p=0.039).

Bates et al. studied mortality and costs of ARF associated with amphotericin B deoxycholate therapy at a tertiary care hospital from May 17, 1993 through April 22,

1997. (59) Among 707 adult admissions were studied. The mortality rate was much higher in patients who occurred ARF than patients who did not: 115 patients (54%) versus 79 patients (16%), p=0.001. In multiple regression analyses, the mean increase in length of study associated with ARF was 8.2 days, p<0.0001. The mean adjusted total cost was $29,823 per patient, p<0.0001.

V. Risk factors for amphotericin B deoxycholate-induced nephrotoxicity.

Resulted from several studies about risk factors for amphotericin B deoxycholate-induced nephrotoxicity were differentiated.

Zager et al. assessed the incidence, risk factors and course of ARF following BMT patients who received amphotericin B deoxycholate. (60) This study designed as a retrospective study of 272 patients during 1986. The patients were assigned to one of three groups, depending on the course of their renal function. Group 1 consisted of patients who doubled their baseline SCr concentrations and required hemodialysis during their transplant hospitalization. Group 2 consisted of patients who at least doubled their baseline SCr within 21 days posttransplantation but who never required hemodialysis. Group 3 consisted of patients who did not doubled their baseline SCr within 21 days posttransplantation and never required hemodialysis. Renal insufficiency (SCr ≥ 2 times baseline) developed in 143 patients (53%), 64 patients (24%) in group 1 and 79 patients (29%) in group 2. The SCr doubling time for group 1 was 14±1 days post-BMT, with dialysis starting on day 19±2. Patients were assigned to group 3 in 129 patients (47%). Renal insufficiency patients (group 1 and 2) were contrasted with patients in group 3, amphotericin B deoxycholate use, jaundice (total bilirubin ≥ 2 mg/dl) and weight gain (≥ 2 kg) were greater for the renal insufficiency patients by univariate analysis, p<0.0001, p<0.0001 and p<0.001, respectively and by multivariate analysis, RR=9.0; p<0.001, RR=3.2; p<0.001 and RR=2.4; p<0.01, respectively. Baseline SCr and patient age were not significantly different. The development of renal insufficiency had ominous implications for patient survival. Mortality rate in group 1, 2 and 3 were 84%, 37% and 17%,

respectively. Aminoglycosides, vancomycin or cyclosporine use not correlated with the development of ARF.

Fisher et al. performed a case-control study to identify and quantify risk factors for amphotericin B deoxycholate-associated nephrotoxicity in patients who received intravenous amphotericin B deoxycholate for at least 2 days from January 1981 through December 1983. (61) Baseline SCr was defined as the lowest average of three consecutive SCr values during amphotericin B deoxycholate therapy or within 72 hours prior to its initiation. Nephrotoxicity was defined as a greater than 100% increase in SCr from the baseline value to a level above the normal range during amphotericin B deoxycholate treatment. Nephrotoxicity was considered to have occurred as soon as this threshold was met or exceeded. Cases were defined as those patients receiving amphotericin B deoxycholate who developed nephrotoxicity. Controls were those patients receiving amphotericin B deoxycholate who had less than a 50% increase in the SCr level during therapy. Controls were matched to cases by the number of days of amphotericin B deoxycholate exposure to ensure equal periods of observation. Thirty-five of the 113 evaluable patients (31%) occurred nephrotoxicity. The mean increment in SCr from baseline to the onset of nephrotoxicity was 1.3±0.5 mg/dl (range 0.6-3.2 mg/dl). The mean average daily dose of amphotericin B deoxycholate for the case group was 0.49±0.18 mg/kg/day compared with 0.34±0.17 mg/kg/day for the control group. Fungal infection in the case group were candidiasis 13 patients (37%), cryptococcosis 7 patients (20%), aspergillosis/mucormycosis 8 patients (23%) and in the control group were candidiasis 38 patients (63%), cryptococcosis 3 patients (5%), aspergillosis/mucormycosis 5 patients (8%). Neither total dose nor weight was statistically significantly related to renal failure. In a multivariate model, the risk of nephrotoxicity increased 3.7-fold (95%CI, 1.6-8.5) for each 50 mg increase in total dose for a fixed duration of therapy and patient weight. In logistic regression model, each 0.1 mg/kg/day dose increment was associated with 1.8-fold (95%CI, 1.2-2.7) increase in the risk of nephrotoxicity. Diuretic use during amphotericin B deoxycholate therapy until 3 days prior to nephrotoxicity was associated with 12.5-fold (95%CI, 1.7-94.7) increase in the risk of nephrotoxicity and abnormal baseline SCr level was associated with 12.5-fold (95%CI, 1.7-94.7) increase in the risk of nephrotoxicity.

Luber et al. assessed risk factors for amphotericin B deoxycholate-induced nephrotoxicity by reviewed retrospectively of 178 patients who received intravenous amphotericin B deoxycholate for > 3 days and a minimal total cumulative dose > 100 mg. (62) Various definitions of nephrotoxicity were used as follows. Definition 1: a change in SCr of > 46 μmol/L from baseline; definition 2: a doubling of SCr over the baseline; definition 3: a change in SCr of > 92 μmol/L from baseline; definition 4: a doubling and/or a change in SCr of > 92 μmol/L from baseline and definition 5: an increase in SCr of > 230 μmol/L from baseline. Nephrotoxicity that met any of definitions was considered mild to moderate, whereas definition 5 was considered severe. The mean age was 46±22 years, average cumulative dose of amphotericin B deoxycholate was 536±547 mg and duration of therapy was 16.6±8.2 days. Eighty-six percent of patients received amphotericin B deoxycholate for empirical therapy of febrile neutropenia. Incidences of nephrotoxicity were 50% in definition 1, 49% in definition 2, 29% in definition 3, 49% in definition 4 and 8% in definition 5. Multivariate analysis showed that nephrotoxicity was associated with a greater cumulative dose of amphotericin B deoxycholate were associated with 1.2-fold (95%CI, 1.1-1.4, p=0.0057) in definition 1, 1.2-fold (95%CI, 1.1-1.4, p=0.0065) in definition 2, 1.3-fold (95%CI, 1.1-1.5, p=0.0003) in definition 3, 1.2-fold (95%CI, 1.0-1.3, p=0.0084) in definition 4 and 1.2-fold (95%CI, 1.1-1.4, p=0.0084) in definition 5. Concomitant nephrotoxicity drugs were associated with 1.8-fold (95%CI, 1.3-2.4, p=0.0001) in definition 1, 1.5-fold (95%CI, 1.1-2.1, p=0.0092) in definition 2, 1.5-fold (95%CI, 1.0-2.2, p=0.0444) in definition 3, 1.5-fold (95%CI, 1.1-2.0, p=0.0174) in definition 4. Concomitant cyclosporine therapy was associated with 18.8-fold (95%CI, 2.3-152.2, p=0.022) in definition 5. Severe renal insufficiency was rare, occurred in 8% of patients. These patients were noted to have higher baseline creatinine values (83±64 μmol/L), received larger cumulative dose of amphotericin B deoxycholate (1,430±1,364 mg) and had a longer duration of therapy (23.9±15.2 days) than patients with mild to moderate toxicity. The time taken to reach peak creatinine levels did not differ significantly between groups, although in patients with severe renal insufficiency these times were longer than for other groups (mean 21.5±8.4 days; range 2-69 days). No clear trends were observed in time to rise in SCr levels with some patients experiencing a change within the first few days of therapy, wherease in

others it took place much later in the course of therapy. Irreversible nephrotoxicity did not occurred; however; 1 patient required hemodialysis.

VI. Management of amphotericin B deoxycholate-induced nephrotoxicity.

Today, the different strategies are currently used to reduce and management of amphotericin B deoxycholate-induced nephrotoxicity. (63)

1. Salt and electrolytes supplementation on amphotericin B deoxycholate-induced nephrotoxicity.

Branch recommendation to reduce the risk of amphotericin B deoxycholate-induced renal impairment. The first, assessed the sodium status of the patients. The second, assessed whether the patient can tolerate sodium supplementation. Otherwise healthy subjects usually tolerate a supplement of 150 mEq/day over. However, increased sodium intake may exacerbate cardiac failure, cirrhosis with ascites or renal failure. (64)

Feely et al. reported 2 patients who had nephrotoxicity after a short time on moderate dose of amphotericin B deoxycholate-associated with salt depletion. (65) The first case, palateral biopsy demonstrated *H. capsulatum*. On admission, SCr was 2.9 mg/dl, BUN 20 mg/dl, serum sodium 137 mmol/L and serum potassium 3.7 mmol/L. Amphotericin B deoxycholate was increasing from 1 mg to 25 mg/day infusion over 5 hours. Within 4 day, patient had symptomatic relief. However, BUN, SCr and potassium values rose sharphy. Therapy was discontinued after 9 days. Low serum sodium concentrations (130-135 mmol/L) were occurred. Patient was given 2 L of 0.9 mmol/L saline intravenously and diet containing 300 mEq of sodium/day. Within 2 days, BUN, SCr and potassium concentrations fell. Amphotericin B deoxycholate therapy was resumed, the dosage being rapidly increased to 25 mg/day. The concentrations of BUN and SCr continued to decrease and with complete resolution of palatal and ocular lesions. In case 2, a biopsy specimen taken at bronchoscopy revealed *C. neoformans*. Amphotericin B deoxycholate was given over 4 hours in gradually increasing doses to 25 mg/day with flucytosine 5 g daily. After 6

days of amphotericin B deoxycholate therapy, BUN and SCr values had risen and a temporary decrease in serum potassium concentration. The BUN and SCr continued to rise and 4 days later amphotericin B deoxycholate was stopped. Sodium depletion was confirmed by a 24-hour urinary sodium of only 24 mEq. A decision was made to deliberately increase sodium intake (150 mEq per 24 hours), received a high-protein diet containing 150 mEq of sodium and accept increase peripheral edema. The BUN and SCr values fell. With the patient on normal sodium diet, amphotericin B deoxycholate was restarted at 25 mg/day and continued for 7 weeks without renal deterioration. The cryptococcal lesions resolved completely. These observations suggest a critical role for sodium balance in determining the extent of amphotericin B deoxycholate nephrotoxicity.

Heidemann et al. reported cases of amphotericin B deoxycholate nephrotoxicity decrease by salt repletion. (66) They had previously reported 2 patients in whom amphotericin B deoxycholate nephrotoxicity developed and extended that reported with three further patients. First case, one and a half years previously, the patient had had a myocardial infarction complicated by the development of a ventricular aneurysm. Hypertension developed and was controlled with a low-sodium diet and furosemide. On admission, serum sodium was 130 mEq/L. *C. neoformans* was cultured from the blood and findings supported a diagnosis of systemic cryptococcus disease with meningeal and hepatic involvement. Amphotericin B deoxycholate was administered daily over 4 hours with an initial dose of 1 mg and optimal dose of 25 mg. Symptoms rapidly resolved within the first week. However, after 12 days of treatment, The BUN and SCr levels had increased. Amphotericin B deoxycholate therapy was discontinued for one day and the diet was liberalized to include 150 mEq of sodium per day. The BUN and SCr values returned to normal over the succeeding 12 days. Even though amphotericin B deoxycholate was readministered up to 25 mg/day. Case 2, patient had undergone thoracotomy because of *Histoplasma granuloma*. Cultures of a lung biopsy specimen and sequential sputum samples grew *H. capsulatum* and *Klebsiella pneumoniae*. Initially patient received a 10-day course of tobramycin without change in renal function. Followed by amphotericin B deoxycholate with an initial dose of 1 mg daily and increased to 25 mg/day. Within 6 days, BUN and SCr values had increased. Amphotericin B deoxycholate therapy was

discontinued, patient began receiving a diet containing 300 mEq of sodium per day. Amphotericin B deoxycholate therapy was reinstitute after 2 days at 25 mg/day for the next 15 days. Within 4 days, BUN level had returned to normal and SCr level returned to the pretreatment level at the end of the antifungal therapy. On a high-salt diet, patient tolerated the amphotericin B deoxycholate treatment and received a full course of antifungal therapy without further evidence of impaired renal function. Case 3, India ink stain revealed *C. neoformans*. Amphotericin B deoxycholate was administered with an initial dose of 1 mg daily and increased to 25 mg/day. In addition, 5-flucytosine (1.5 g/day) was administered throughout therapy. In the first few days, amphotericin B deoxycholate therapy caused nausea. Patient vomited once or twice per day and lost 5.5 pounds in weight. After 1 week of therapy, concentrations of SCr and BUN increased. Patient received a high-sodium diet, nausea and vomiting stopped. Patient rapidly returned to initial weight. Even though amphotericin B deoxycholate therapy was uninterupted, BUN level returned to normal and SCr level decrease over the next 7 days.

Stein and Alexander reported sodium protects against nephrotoxicity in neutropenic patients receiving amphotericin B deoxycholate between February 15, 1988 and December 31, 1988. (67) Patients who received ≥ 90 mEq/day of intravenous sodium during each day of amphotericin B deoxycholate therapy including 18 g/day of sodium ticarcillin (93 mEq/day of sodium) were defined as adequate sodium and ticarcillin. Patients who received ≥ 90 mEq/day of intravenous sodium on every day of amphotericin B deoxycholate therapy were classified as adequate sodium only and patients who had at least one day during amphotericin B deoxycholate therapy on which adequate sodium (90 mEq) was not administered classified as inadequate sodium. Nephrotoxicity was defined as SCr ≥ 2.0 mg/dl. Seventy-three patients entered the study, 35 patients were categorized as adequate sodium and ticarcillin, 24 patients were categorized as adequate sodium only and 14 patients were categorized as inadequate sodium. Inadequate sodium in all 14 patients due to temporary failure of intravenous access or because of physician oversight, i.e. lack of knowledge regarding the protocol on the part of house staff writing daily orders or discontinuation of ticarcillin without institution of saline. Nephrotoxicity occured 4 of 14 patients (29%) in the inadequate sodium group, 1 of 24 patients (4%)

in the adequate sodium only group and 1 of 35 patients (3%) in the adequate sodium and ticarcillin group. The incidence of nephrotoxicity in the inadequate sodium group was significantly higher than in the adequate sodium only group or in the adequate sodium and ticarcillin group, p=0.008.

Llanos et al. studied effect of salt supplementation an amphotericin B deoxycholate nephrotoxicity. (68) Twenty male patients were entered into the study and were randomized to receive either 1 L of 0.9% saline or 1 L of 5% dextrose in water, administered intravenous over 1 hour prior to amphotericin B deoxycholate administration. All patients received amphotericin B deoxycholate administered over 4 hours three times per week for 10 weeks, starting with 15, 35 and 50 mg/dose the first week and then maintenance on 50 mg/dose for the remainder of therapy. All patients responded to therapy with amphotericin B deoxycholate. The mean SCr increased over time in the dextrose group but remained unchanged in the saline group. The mean maximal increased in SCr during therapy was significant greater in the dextrose group than the saline group, p=0.01. The CrCl decreased in the dextrose group but remained unchanged in the saline group, resulting in a significantly different response over time ($p<0.05$). Baseline CrCl in the dextrose group was 111±6 ml/min and 99±5 ml/min in the saline group. At week 10, CrCl in the dextrose group was 76±7 ml/min and 91±9 ml/min in the saline group. None patient had an increased in SCr > 2 mg/dl. Four patients in the dextrose group had a ≥ 100% increased in SCr, none patient occurred in the saline group. Serum potassium level significant decrease within the first two weeks of treatment ($p<0.0001$) but no difference between groups. The saline group requiring significantly higher potassium supplements than the dextrose group ($p<0.0001$).

Barton et al. reported renal magnesium wasting associated with amphotericin B deoxycholate therapy. (69) The effect of amphotericin B deoxycholate on magnesium metabolism was studied in 10 patients with systemic fungal infections. All patients were given regular diets (estimated magnesium content 350 mg) supplemented with an additional 30 to 60 mEq of potassium/day. Laboratory measurements were made immediately prior to the administration of amphotericin B deoxycholate, during amphotericin B deoxycholate therapy at 2, 4 and 6 weeks and reevaluated 3 of 10 patients approximately one year following the discontinuation of amphotericin B

deoxycholate. At baseline, serum magnesium concentration of 2.35±0.3 mg/dl following 2 weeks of amphotericin B deoxycholate therapy, the serum magnesium level fell to 2.0±0.3 mg/dl ($p<0.01$). Following 4 weeks, the serum magnesium level continued to fall to 1.6±0.3 mg/dl, which was significant when compared with following at 2 weeks ($p<0.05$) and baseline ($p<0.001$). Following 6 weeks, the serum magnesium level was 1.6±0.2 mg/dl, which was significant when compared with baseline ($p<0.001$). At baseline, SCr level was 1.04±0.3 mg/dl following 2 weeks of amphotericin B deoxycholate therapy, the SCr level increased to 1.4±0.4 mg/dl ($p<0.05$). Following 4 weeks, the SCr level was 1.7±0.4 mg/dl, which was significant when compared with baseline ($p<0.001$). Following 6 weeks, the SCr level was 1.6±0.4 mg/dl, which was significant when compared with baseline ($p<0.01$). Approximately one year following discontinuation amphotericin B deoxycholate therapy, the serum magnesium level was 2.2±0.5 mg/dl, the SCr level was 1.2±0.5 mg/dl. The serum magnesium and SCr levels returned to baseline values and showing no significant difference from baseline.

2. Lipid formulations of amphotericin B

Available lipid formulations of amphotericin B represent a significant advance in drug delivery technology, Lipid formulations of amphotericin B are less nephrotoxicity but these formulations are expensively. Each formulations of amphotericin B shown differences in biochemical, pharmacokinetic and pharmacodynamic properties. (70-73) The biochemical and pharmacokinetic properties of amphotericin B formulations summarized in Table 4.

Table 4: Comparison of the biochemical and pharmacokinetic properties of formulations of amphotericin B.

Property	AmBd	ABLC	ABCD	L-AmB
Composition	DOC-AmB	DMPC-DMPG-AmB	Cholesteryl Sulfate-AmB	HPC-Chol-DSPG-AmB
(molar ratio)	(7:3)	(7:3:3)	(1:1)	(2:1:0.8:0.4)
AmB content (mol%)	...	33%	50%	10%
Charge of phospholipids	negative	negative	negative	negative
Shape	Micelles	Sheets	Discs	Small Unilamellar Vesicles
Diameter (μm)	<0.4	1.6-11	0.12	0.06

ABCD = amphotericin B cholesteryl sulfate; ABLC = amphotericin B lipid complex; AmB = amphotericin B deoxycholate; CHOL = cholesterol; DMPC = dimirystoylphosphatidylcholine; DMPG = dimirystoylphosphatidylglycerol; DOC = deoxycholate; DSPG = distearoylphosphatidylglycerol; HPC = hydrogenated phosphatidylcholine; L-AmB = amphotericin B liposomal.

Source: Wong-Beringer, Jacobs RA and Guglielmo BJ. Lipid formulations of amphotericin B: clinical efficacy and toxicities. Clin Infect Dis 1998;27:603-18

: Brajtburg and Bolard. Carrier effects on biological activity of amphotericin B. Clin Microb Rev 1996;9:512-31

Table 4: Comparison of the biochemical and pharmacokinetic properties of formulations of amphotericin B. (Continued)

Property	AmBd	ABLC	ABCD	L-AmB
Human tissue distribution: μg/g of tissue (% of total dose)				
Liver	93.2(26.2)	196.0		175.7(18.3)
Spleen	59.3(1.0)	290.0		201.5(3)
Lungs	12.9(3.1)	222.0		16.8(0.6)
Kidneys	18.9(0.8)	6.9		22.8(0.3)
Brain	Not studied	1.6		0.56(0.1)
Heart	3.7(0.13)	5.0		4.3(0.1)

ABCD = amphotericin B cholesteryl sulfate; ABLC = amphotericin B lipid complex; AmB = amphotericin B deoxycholate; CHOL = cholesterol; DMPC = dimirystoylphosphatidylcholine; DMPG = dimirystoylphosphatidylglycerol; DOC = deoxycholate; DSPG = distearoylphosphatidylglycerol; HPC = hydrogenated phosphatidylcholine; L-AmB = amphotericin B liposomal.

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: Brajtburg and Bolard. Carrier effects on biological activity of amphotericin B. Clin Microb Rev 1996;9:512-31

2.1 Amphotericin B lipid complex (ABLC)

Walsh et al. evaluated of safety and antifungal efficacy of amphotericin B lipid complex (ABLC) for invasive fungal infection between December 1990 and October 1995. (74) A total of 556 patients were enrolled, 292 patients (52.5%) were enrolled because of failure of previous systemic antifungal therapy (48.5% failure of

amphotericin B deoxycholate and failure of other antifungal agents in 4%), other causes for enrollment included nephrotoxicity due to amphotericin B deoxycholate occurred in 181 patients, non renal toxicities due to amphotericin B deoxycholate occurred in 30 patients, preexisting renal disease in 50 patients and toxicity due to other antifungal drugs in 3 patients. The SCr levels declined during ABLC therapy reaching statistical significance in comparison with baseline levels by the third week and continuing through the sixth week ($p<0.02$). Among 162 patients with elevated baseline SCr values ($\geq$ 2.5 mg/dl) at the start of ABLC therapy, the mean SCr values decreased significantly from the first week through the sixth week ($p\leq0.0003$). Three hundred ninety-six patients (71%) had either stable (51%) or improved (21%) in SCr levels by the end of therapy, 132 patients (24%) developed an increase in SCr level from baseline to the end of therapy and 28 patients (5%) did not have sufficient SCr values recorded by which to evaluate trends. Hypokalemia developed in 24 of 518 patients (4.6%) and hypomagnesemia developed in 65 of 369 patients (18%). The overall response rate, including complete and partial response, for all 291 evaluable fungal infections was 57%; 25% for complete response and 32% for partial response. The most common reason for discontinuation of therapy was completion of treatment occurred in 187 of 556 patients (34%). The patient's death ended therapy in 175 patients (31%). Death were progression of fungal infection in 83 patients (47%) and progression of underlying diseases in 53 patients (30%).

Menta et al. reported ABLC for the treatment of confirmed or presumed fungal infections in 64 immunocompromised patients with hematologic malignancies between May 1994 and October 1995. (75) ABLC administered intravenously with daily dose of 5 mg/kg. Patients received 68 courses of ABLC therapy for presumed fungal infection in 52 patients or proven in 16 patients. Seven patients developed febrile reaction to ABLC. The creatinine doubled during seven evaluable courses of therapy, during five of which patients were receiving concomitant therapy with one to four other nephrotoxic agents (cyclosporine, aminoglycosides, vancomycin, high-dose intravenous acyclovir, ganciclovir or foscarnet). Nephrotoxicity necessitated discontinuation of ABLC in 4 patients (6%). The overall response rate was 35 of 53 patients (66%).

Subira et al. conducted a prospective, randomized controlled trial to compare ABLC 1 mg/kg/day with amphotericin B deoxycholate 0.6 mg/kg/day for empirical antifungal therapy of neutropenic fever in 105 patients with hematologic malignancies between January 2000 and February 2002. (76) Patients were evaluable for safety if they had received at least one dose of the study drug and evaluable for efficacy if they had received the study drug for at least 3 days and neutropenia lasted a minimum of 3 days after start of therapy. Nephrotoxicity was defined as an increase in SCr > 1.5 mg/dl or an increase > 2 times baseline value. Hypokalemia defined as a serum potassium level < 3 mmol/L. The incidence of nephrotoxicity was significantly lower in the ABLC group compared with patients who received amphotericin B deoxycholate: 4 of 49 patients (8%) versus 18 of 56 patients (32%), respectively (p=0.003). Renal toxicity led to study drug discontinuation in 9 patients who treated with amphotericin B deoxycholate and 1 patient on ABLC. Hypokalemia occurred in 6 of 49 patients (12%) in the ABLC group and 18 of 56 patients (32%) in the amphotericin B deoxycholate group, p=0.01. Infusion-related adverse events were similar in both groups. Fever occurred in 27 patients (55%) in the ABLC group and 37 patients (66%) in the amphotericin B deoxycholate group, p=0.2. Chills or rigors occurred in 31 patients (63%) in the ABLC group and 33 patients (59%) in the amphotericin B deoxycholate group. Nausea or vomiting occured in 4 patients (8%) in the ABLC group and 7 patients (13%) in the amphotericin B deoxycholate group. The overall response rate for the ABLC and the amphotericin B deoxycholate groups were 72% and 48%, respectively (p=0.018).

2.2 Amphotericin B cholesteryl sulfate (ABCD)

White et al. reported a retrospective study to assess the efficacy and safety of ABCD compared with amphotericin B deoxycholate as therapy for invasive aspergillosis. (77) The case report forms of 572 patients enrolled in five open-label antifungal trials evaluating ABCD from November 1991 to June 1994 at 42 sites were reviewed. Eighty-two patients with proven or probable aspergillosis who were treated in clinical trials with ABCD were compared retrospective with 261 patients with aspergillosis who were treated with amphotericin B deoxycholate at six cancer or

transplant centers between January 1, 1990 and June 30, 1994. Nephrotoxicity was defined as a doubling of the SCr level from the baseline level, an increase in SCr level of at least 1 mg/dl from baseline or a ≥ 50% decrease of CrCl. Baseline was defined as the first day of study drug treatment. Mortality rates and follow up were assessed through 120 days after the first dose of ABCD or amphotericin B deoxycholate. Renal toxicity developed during treatment in 6 of 73 patients (8.2%) in the ABCD group and 107 of 248 patients (43.1%) in the amphotericin B deoxycholate group, p<0.001. Renal toxicity occurred significantly earlier in the amphotericin B deoxycholate group than the ABCD group, p<0.001. The response rate among the ABCD recipients was 40 of 82 patients (48.8%) compared with 61 of 261 patients (23.4%) among the amphotericin B deoxycholate recipients, p<0.001. Survival rates among the ABCD recipients was 41 of 82 patients (50%) compared with 74 of 261 patients (28.4%) among the amphotericin B deoxycholate recipients, p<0.001. Multivariated analysis revealed that treatment group was the best predictor of response, mortality and nephrotoxicity. The relative risk for complete or partial response in association with ABCD treatment compared with amphotericin B deoxycholate treatment was 3.00 (95%CI, 1.48-6.07, p=0.002). The relative risk for death in association with ABCD treatment compared with amphotericin B deoxycholate treatment was 0.35 (95%CI, 0.2-0.59, p<0.001). The relative risk of developing renal impairment associated with ABCD treatment compared with amphotericin B deoxycholate treatment was 0.13 (95%CI, 0.04-0.42, p=0.001).

White et al. conducted a prospective, randomized, double-blind multicenter study to compare ABCD with amphotericin B deoxycholate in the empirical treatment of fever and neutropenia. (78) Patients were randomized to receive therapy with ABCD 4 mg/kg/day or amphotericin B deoxycholate 0.8 mg/kg/day for ≤ 14 days. Nephrotoxicity was defined as any of the following: a doubling in the SCr level from baseline, an increase of 1 mg/dl in the SCr level from baseline or a ≥ 50% decrease of CrCl. Defervescence occurred in 54 of 101 patients (53.5%) in the ABCD group and 55 of 95 patients (57.9%) in the amphotericin B deoxycholate group, p=0.63. No significant difference between treatment groups in the median number of days to defervescence and the occurrence of sustained defervescence. Chills were noted in 87 of 109 patients (79.8%) in the ABCD group

and 68 of 104 patients (65.4%) in the amphotericin B deoxycholate group, p=0.018. Hypoxia were noted in 13 patients in the ABCD group and 3 patients in the amphotericin B deoxycholate group, p=0.013. The development of renal toxicity was more frequent in amphotericin B deoxycholate recipients than ABCD recipients; 51 patients versus 20 patients, respectively (p<0.001). A successful response was noted in 49 of 98 patients (50%) in the ABCD group and 41 of 95 patients (43.2%) in the amphotericin B deoxycholate group, p=0.31. Mortality was assessed from the first dose through 28 days after the last dose of the study drug. Twenty-nine patients died, occurred in 16 ABCD recipients and 13 amphotericin B deoxycholate recipients.

Bowden et al. performed a randomized, double-blind, multicenter controlled trial to compare ABCD with amphotericin B deoxycholate for the treatment of invasive aspergillosis in 174 immunocompromised patients from January 1993 through February 1997. (79) A total of 174 patients, 88 patients were taking ABCD of 6 mg/kg/day and 86 patients were taking amphotericin B deoxycholate 1 or 1.5 mg/kg/day. The study drug was infused over 4 hours and could be decreased to 2 hours after administration of 2 doses, if the drug was well tolerated. Nephrotoxicity was defined as either a doubling in the SCr level from baseline, an increase of 1 mg/dl in the SCr level from baseline or a ≥ 50% decrease of CrCl. Time to renal toxicity was defined as the number of days between the first infusion of study drug and the first observation of renal toxicity. Chills occurred in 47 of 88 patients (53.4%) who received ABCD and 26 of 86 patients (30.2%) who received amphotericin B deoxycholate. Fever occurred in 24 of 88 patients (27.3%) who received ABCD and 14 of 86 patients (16.3%) who received amphotericin B deoxycholate. Nausea and/or vomiting occurred in 28 of 88 patients (31.8%) who received ABCD therapy and 17 of 86 patients (19.8%) who received amphotericin B deoxycholate therapy. The incidence of nephotoxicity was almost twice as high in patients treated with amphotericin B deoxycholate compared with patients who received ABCD. Nephrotoxicity occurred in 19 patients (25%) who received ABCD and 38 patients (49.4%) who received amphotericin B deoxycholate, p=0.002. The median time to nephrotoxicity was 301 days (range 2-301 days) in the ABCD group and 22 days (range 2-47 days) in the amphotericin B deoxycholate group, p<0.001. Nephrotoxicity necessitated discontinuation of ABCD in 3 patients (3.4%) and 16 patients (18.6%)

who took amphotericin B deoxycholate, p=0.001. The rate of therapeutic response was 31 of 88 patients (35.2%) who received ABCD and 30 of 86 patients (34.9%) who received amphotericin B deoxycholate, p=0.5. Overall mortality rate was 50% versus 55% in the ABCD and amphotericin B deoxycholate groups, respectively. The rate of death due to fungal infection was similar in the ABCD and amphotericin B deoxycholate groups: 40% versus 36%, respectively (p=0.6).

2.3 Amphotericin B liposomal

Prentice et al. studied a randomized, open-label, multicenter trials comparison of liposomal amphotericin B versus amphotericin B deoxycholate of neutropenic patients. (80) One hundred thirty-four patients were randomized, 39 patients received amphotericin B deoxycholate 1 mg/kg/day, 48 patients received liposomal amphotericin B 1 mg/kg/day and 47 patients received liposomal amphotericin B 3 mg/kg/day. Nephrotoxicity was defined as a 100% or more increase in baseline of SCr. Nephrotoxicity occurred in 31% of patients who treated with amphotericin B deoxycholate, 12% of patients who treated with liposomal amphotericin B 1 mg/kg/day and 13% of patients who treated with liposomal amphotericin B 3 mg/kg/day, p=0.05. Treatment success was observed in 18 of 39 patients (46%) in the amphotericin B deoxycholate group, 23 of 47 patients (49%) in the liposomal amphotericin B 1 mg/kg/day group and 30 of 47 patients (64%) in the amphotericin B 3 mg/kg/day group, p=0.2. Time to neutrophil recovery was not differrence between groups.

Leenders et al. performed a randomized trial to compare liposomal amphotericin B 4 mg/kg/day with amphotericin B deoxycholate 0.7 mg/kg/day for 3 weeks both followed by oral fluconazole 400 mg/day for 7 weeks in the treatment of AIDS-associated cryptococcal meningitis between June 1992 and June 1995. (81) Of the 28 evaluable patients, 15 patients were assigned to liposomal amphotericin B and 13 patients were assigned to amphotericin B deoxycholate. Concerning nephrotoxicity, when increase from baseline of SCr levels at the various time-points. Chills and nausea occurred in 2 patients and 1 patient in the amphotericin B deoxycholate group, respectively. The SCr > 3 times upper limit of normal reported in

1 patient who received amphotericin B deoxycholate. Clinical response rates after the first 3 weeks of treatment were 12 of 15 patients (80%) in the liposomal amphotericin B group and 11 of 13 patients (86%) in the amphotericin B deoxycholate group. Clinical response rates at week 10 were 13 of 15 patients (87%) in the liposomal amphotericin B group and 10 of 12 patients (83%) in the amphotericin B deoxycholate group. No clinical relapses were observed during the 10-week study period. No proven clinical relapses occurred during the 6-month or further follow up.

Leenders et al. reported a randomized multicentre study comparing liposomal amphotericin B with amphotericin B deoxycholate in the treatment of documented and suspected neutropenia-associated invasive fungal infections. (82) Between January 1992 and January 1996, 32 patients were assigned to liposomal amphotericin B; 5 mg/kg/day infused over 45 minutes and 34 patients were assigned to amphotericin B deoxycholate; 1 mg/kg/day infused over 6 hours. After 2 weeks of full dose the liposomal amphotericin B and amphotericin B deoxycholate dose were reduced to 3 mg/kg/day and 0.7 mg/kg/day, respectively. Nephrotoxicity was defined as a > 100% increase of SCr baseline. Nephrotoxicity occurred in 22 of 54 patients (40%) who were treated with amphotericin B deoxycholate and 6 of 51 patients (12%) who were treated with liposomal amphotericin B, $p<0.001$. In 18 patients treated with amphotericin B deoxycholate and 2 patients treated with liposomal amphotericin B was temporarily discontinued or lowered in dose due to increase of SCr ($p<0.001$). At day 14 of therapy, overall response occurred in 15 of 30 patients assigned to liposomal amphotericin B compared with 8 of 33 patients assigned to amphotericin B deoxycholate, $p=0.04$. The overall mortality rate was 7 of 32 patients (22%) assigned to liposomal amphotericin B compared with 13 of 34 patients (38%) assigned to amphotericin B deoxycholate, $p=0.03$. Five of 7 patients assigned to liposomal amphotericin B and 10 of 13 patients assigned to amphotericin B deoxycholate were considered to have died due, or at least partly due to fungal infection.

Walsh et al. conducted a randomized, double-blind, multicentre trial to compare liposomal amphotericin B with amphotericin B deoxycholate as empirical therapy in 687 patients with persistent fever and neutropenia between January 1995 and May 1996. (83) Three hundred forty-three patients received liposomal amphotericin B; 3 mg/kg/day and 344 patients were assigned to amphotericin B

deoxycholate; 0.6 mg/kg/day. Investigators were permitted to adjust the dose. Dose of liposomal amphotericin B and amphotericin B deoxycholate were increased to intermediate doses of 4.5 mg/kg/day and 0.9 mg/kg/day, respectively or to high dose of 6.0 mg/kg/day and 1.2 mg/kg/day, respectively or reduced to 1.5 mg/kg/day and 0.3 mg/kg/day, respectively, when toxic effects occurred. Nephrotoxicity was defined as the doubling or tripling of the SCr level or by peak SCr value above 3 mg/dl. The mean daily dose throughout the study were 3.0±0.9 mg/kg/day of liposomal amphotericin B and 0.6±0.2 mg/kg/day of amphotericin B deoxycholate. The mean duration of therapy of liposomal amphotericin B was 10.8±8.9 days and 10.3±8.9 days of amphotericin B deoxycholate. Fever on day 1 occurred in 58 patients (16.9%) in the liposomal amphotericin B group and 150 patients (43.6%) in the amphotericin B deoxycholate group, $p \leq 0.001$. Chills or rigors on day 1 occurred in 63 patients (18.4%) in the liposomal amphotericin B group and 187 patients (54.4%) in the amphotericin B deoxycholate group, $p \leq 0.001$. Chills on overall treatment occurred in 129 patients (37.6%) in the liposomal amphotericin B group and 253 patients (73.5%) in the amphotericin B deoxycholate group, $p \leq 0.001$. Nephrotoxicity indicated by the SCr > 2 times from baseline occurred in 64 patients (18.7%) in the liposomal amphotericin B group and 116 patients (33.7%) in the amphotericin B deoxycholate group, $p \leq 0.001$. Nephrotoxicity indicated by the SCr > 3 times from baseline occurred in 28 patients (8.2%) in the liposomal amphotericin B group and 57 patients (16.6%) in the amphotericin B deoxycholate group, $p \leq 0.001$. The overall success treatment were similar, 172 patients (50.1%) received liposomal amphotericin B and 170 patients (49.4%) received amphotericin B deoxycholate. Breakthrough fungal infections occurred in 11 patients (3.2%) received liposomal amphotericin B and 27 patients (7.8%) received amphotericin B deoxycholate, $p<0.009$.

Johnson et al. reported safety and efficacy of liposomal amphotericin B compared with amphotericin B deoxycholate for induction therapy of moderate to severe disseminated histoplasmosis in patients with AIDS. (84) Patients were randomly assigned in a 2:1 ratio for liposomal amphotericin B : amphotericin B deoxycholate in this multicenter double-blind clinical trial at 21 sites of the U.S.. National Institute of Allergy and Infectious Diseases Mycoses Study Group. Patients were randomized to received liposomal amphotericin B 3 mg/kg/day or amphotericin

B deoxycholate 0.7 mg/kg/day for 2 weeks by intravenous infusion over 2 hours for induction therapy and received itraconazole for 10 weeks as consolidation therapy. Fifty-three patients received liposomal amphotericin B and 26 patients received amphotericin B deoxycholate. Nephrotoxicity was defined as increase in SCr level to more than twice the baseline level. Acute infusion-related toxicities occurred in 13 of 53 patients (25%) treated with liposomal amphotericin B and 15 of 24 patients (63%) treated with amphotericin B deoxycholate, p=0.002. Nephrotoxicity occurred in 5 of 53 patients (9%) treated with liposomal amphotericin B and 9 of 24 patients (37%) treated with amphotericin B deoxycholate, p=0.003. Clinical success was achieved in 45 of 51 patients (88%) treated with liposomal amphotericin B and 14 of 22 patients (64%) treated with amphotericin B deoxycholate, p=0.014. Among the 57 patients receiving itraconazole. Consolidation therapy was successul in 38 of 43 patients (88%) treated with liposomal amphotericin B and 13 of 14 patients (93%) treated with amphotericin B deoxycholate, p>0.2. There was no significant difference in time to negative cultures, p>0.2.

Cagnoni et al. studied the pharmacoeconomics of liposomal amphotericin B; 3 mg/kg/day and amphotericin B deoxycholate; 0.6 mg/kg/day in the empirical treatment of 414 persistently febrile neutropenic patients. (85) The mean duration of therapy was 10.8 days in the liposomal amphotericin B group and 10.3 days in the amphotericin B deoxycholate group. The mean cost of study medication for patients treated with liposomal amphotericin B was significant greater because of higher during regimens and higher cost of drug per 50 mg vial ($188.40 versus $16.60 per 50 mg). Hospital costs from the start of therapy to the time of hospital discharge were higher for patients treated with liposomal amphotericin B than amphotericin B deoxycholate, $48,962 in the liposomal amphotericin B group and $43,183 in the amphotericin B deoxycholate group, p=0.022.

3. Amphotericin B deoxycholate in lipid emulsion.

Data about reduced nephrotoxicity of amphotericin B deoxycholate in lipid emulsion are varies and methods for preparing have not been standardized. Stability of amphotericin B deoxycholate in lipid emulsion is not constant.

Schoffski et al. reported safety and toxicity of amphotericin B deoxycholate in 5% dextrose or 20% intralipid in neutropenic patients with pneumonia or fever of unknown origin. (86) The study was single centre stratified, prospective randomised non-blinded phase II study. Twenty-four patients were randomized to receive amphotericin B deoxycholate in 5% dextrose and 27 patients received amphotericin B deoxycholate in 250 ml intralipid 20% (Kabi-Pharmacia), with dose of 0.75 mg/kg/day for 8 days then alternate days of in both groups. Dose escalation was prohibited, but the infusion duration could be prolonged from 1-4 hours. The daily and cumulative dose of amphotericin B deoxycholate, overall duration of treatment or dose reduction due to toxicity were not significantly different. Peripheral edema was noted more often in the intralipid group, p=0.009. Significant differences between the study arms were not found for the study of the variables of renal function. Four patients, 1 patient in the dextrose group and 3 patients in the intralipid group had severe renal dysfunction. One patient in the dextrose group and 2 patients in the intralipid group underwent hemodialysis. Pulmonary symptoms occurred in 11 patients in the dextrose group and 17 patients in the intralipid group. Acute dyspnea occurred in 4 patients in the dextrose group and 11 patients in the intralipid group, p=0.083. Other pulmonary events occurred in 1 patient in the dextrose group and 8 patients in the intralipid group, p=0.029. Pulmonary events occurred when amphotericin B deoxycholate in intralipid was repeatedly given to patients with either pneumonia or fever of unknown origin and either 1 or 4-hour infusions.

Chavanet et al. studied non-blind randomized controlled trial to compare glucose versus 20% intralipid in preparation of amphotericin B deoxycholate for use in HIV infected patients with oral candidiasis from June to December 1991. (87) Amphotericin B deoxycholate 1 mg/kg/day given on 4 consecutive days as 1 hour infusion dissolved in either 5% dextrose or 20% intralipid at a final concentration of 2 g/L fat emulsion. Eleven patients were enrolled in each group. All the intralipid group were given without serious problem whereas 4 patients in the dextrose group were stopped. Clinical side effects were 36 per 38 infusions (94.7%) in the dextrose group compared with 10 per 44 infusions (22.7%) in the intralipid group, p=0.0001. Chills and fever were 25 infusions (66%) in the dextrose group and 2 infusions (4%) in the intralipid group, p=0.0001. At least one creatinine value ≥ 133 μmol/L during

observation were 4 patients among 7 patients in the dextrose group compared with 1 patient among 11 patients in the intralipid group, p=0.04. Two patients had shaking chills during the first two amphotericin B deoxycholate-dextrose infusion and 3 patients had renal impairment (a striking increase in creatinine concentration > 159 μmol/L) on day 3. All patients improved with either treatment. The reduction in clinical score of oral candidiasis was similar in two groups.

Sorkine et al. performed a prospective, randomized, controlled study to evaluate the differences in efficacy and tolerance of amphotericin B deoxycholate administered in an 20% intralipid compared with amphotericin B deoxycholate administered in 5% dextrose in the treatment of *C. albican* infection in 60 intensive care unit (ICU) patients. (88) Amphotericin B deoxycholate 1 mg/kg/day given in 3-hour infusion, administered randomly in 5% dextrose or 250 ml of 20% intralipid (Kabi-Vitrum AB). Nephrotoxicity was defined as any increase of SCr > 0.3 mg/dl/day and a decrease of CrCl to ≤ 50% from baseline values, and/or sodium, potassium and magnesium losing nephropathy occurring on day 3 or later following institution of amphotericin B deoxycholate therapy. Thirty patients were enrolled in each group. Patients receiving amphotericin B deoxycholate in lipid emulsion experienced a lower frequency rate of drug-associated adverse reaction than patients receiving amphotericin B deoxycholate in 5% dextrose. Fever occurred in 61.4% in the dextrose group and 5.8% in the intralipid group, p<0.003. Chills occurred in 54% in the dextrose group and 8.5% in the intralipid group, p<0.004. Cholesterol and triglyceride serum concentrations were not significantly different in both groups. Nephrotoxicity reported in 20 patients (66.7%) in the dextrose group and 6 patients (20%) in the intralipid group, p<0.0002. No significant hypokalemia occurred in either group. Moderate hypomagnesemia occurred in 26 patients who treated in the dextrose group and 8 patients who treated in the intralipid group, p<0.02. No patient died in both groups as a direct result of amphotericin B deoxycholate therapy. Survival to discharge from the ICU was the same in the two groups.

Joly et al. conducted a randomized, open-label clinical trial to compare the tolerability and efficacy of amphotericin B deoxycholate, prepared in 5% dextrose or 20% intralipid (Kabi-Pharmacia) in the treatment of AIDS-associated cryptococcal meningitis. (89) Ninty patients were enrolled in the study, 44 patients were assigned

to receive amphotericin B deoxycholate in 5% dextrose in a final volume of 500 ml infusion over 6 hours and 46 patients were assigned to receive amphotericin B deoxycholate in 20% intralipid in a final volume of 125 ml infusion over 2 hours. Amphotericin B deoxycholate was given daily for 14 days; the unitary dose were 0.7 mg/kg/day for amphotericin B deoxycholate in 5% dextrose and 1 mg/kg/day for amphotericin B deoxycholate in intralipid. These formulations were then given every other day for 28 days at the respective unitary doses of 1 mg/kg and 1.5 mg/kg. Fever occurred in 30 patients (68.2%) in the dextrose group and 20 patients (43.5%) in the intralipid group, p=0.02. Chills occurred in 39 patients (88.6%) in the dextrose group and 13 patients (28.3%) in the intralipid group, p=0.0001. Two patients in each group received a reduced dose of amphotericin B deoxycholate because development of nephrotoxicity. The percentage of patients with increased levels of SCr > 150 μmol/L was assessed weekly from day 0 to 42 and was significant higher in the intralipid group than the dextrose group on day 28 ($p<0.001$). Clinical efficacy showed no significant difference between two groups. Clinical cure or improvement was noted in 27 patients (69.2%) assigned to the dextrose group and 31 patients (73.8%) assigned to the intralipid group, p=0.65. The mortality associated with progressive cryptococcal disease was 6 patients (15.4%) died in the dextrose group and 7 patients (16.7%) died in the intralipid group. The difference in success rates between the treatment groups was not significant (p=0.16). Analysis of the time to the first negative CSF culture showed a nearly significant difference between treatment groups (p=0.07).

Caillot et al. performed a randomized, open controlled study to evaluate of the tolerance of amphotericin B deoxycholate infused in 5% dextrose or intralipid 20% in 42 patients with haematological malignancies from November 1991 through July 1992. (90) Twenty-one patients were included in each group. Amphotericin B deoxycholate was infused over 2 hours, initial daily dose of amphotericin B deoxycholate ranged from 1-1.1 mg/kg. Chills occurred in 16 patients of the dextrose group and 5 patients of the intralipid group, p=0.0008. The SCr increase > 75% from baseline occurred in 10 patients of the dextrose group compared with 2 patients of the intralipid group, p=0.0007. The CrCl decrease ≥ 50% was observed in 14 patients of the dextrose group compared with 7 patients of the intralipid group, p=0.025. Treatment was discontinued in 4 patients of the dextrose group as a result of renal

toxicity. No difference was found between the both groups with regard to potassium and sodium requirement. Mean duration of survival was 14±3 months in the dextrose group and 13±2 months in the intralipid group.

Moreau et al. conducted a randomized prospective study to compare renal toxicity and clinical tolerance of amphotericin B deoxycholate mixed with in 5% dextrose or 20% intralipid (Kabi-Pharmacia) in 32 neutropenic patients between February and May 1991. (91) Amphotericin B deoxycholate 0.7-1 mg/kg/day was administered infusion over 4 hours through a central venous catheter. The final concentration of amphotericin B deoxycholate varied from 0.16 mg/ml to 0.32 mg/ml. Nephrotoxicity was defined as a 100% increase of SCr from baseline value. Fever with rigors was observed in 2 patients of the dextrose group compared with 5 patients of the intralipid group, $p < 0.05$. Nephrotoxicity was observed in 9 of 16 patients (56%) of the dextrose group compared with 2 of 16 patients (12.5%) of the intralipid group, $p<0.05$. Patients who received amphotericin B deoxycholate in 5% dextrose requiring either interruption of amphotericin B deoxycholate administration or a reduction in dosage. Renal damage occurred between 4 and 13 days (mean 7 days) after the beginning of therapy.

Nucci et al. conducted a multicenter, nonblinded randomized trial to compare of the toxicity of amphotericin B deoxycholate in 5% dextrose with amphotericin B deoxycholate in fat emulsion in 61 cancer patients between February 1994 and November 1995. (92) Thirty-three patients were assigned to receive amphotericin B deoxycholate in 5% dextrose and 28 patients were assigned to receive amphotericin B deoxycholate in fat emulsion. Amphotericin B deoxycholate was dissolved in 5% dextrose to a final concentration of 0.25 mg/ml. Amphotericin B deoxycholate in fat emulsion was dissolved in 10 ml of distilled water, then added to intralipid at a proportion of 2 ml of 20% intralipid per mg of amphotericin B deoxycholate or 4 ml of 10% intralipid per mg of amphotericin B deoxycholate. Amphotericin B deoxycholate was given daily as a 1 hour infusion into either a central or a peripheral vein of 1 mg/kg for patients with documented fungal infections, the dose can be increased to 1.5 mg/kg. Nephrotoxicity was defined as a 50% or more decrease in CrCl or at least a 0.5 mg/dl increase in SCr from baseline levels. Fever was observed in 28 patients (85%) of the dextrose group compared with 19 patients (68%) of the intralipid group,

p=0.11. Hypokalemia occurred in 19 patients (58%) assigned to the dextrose group and 6 patients (21%) in the intralipid group, p=0.004. Nephrotoxicity was observed in 7 patients (32%) in the dextrose group and 4 patients (21%) in the intralipid group, p=0.44. The success rates of empirical antifungal therapy were similar in both groups: 18 of 26 patients (69%) in the dextrose group and 17 of 24 patients (71%) in the intralipid group, p=0.9.

Walker et al. studied stability, compatibility and in vitro antifungal activity of amphotericin B deoxycholate in lipid emulsion. (93) Compatibility of amphotericin B deoxycholate and intralipid were found to be dependent on the concentration of soybean oil in the intralipid and the concentration of amphotericin B deoxycholate or intralipid in the final mixture. Within 24 hours of preparation, amphotericin B deoxycholate separated from intralipid, forming a distinct lower yellow lager. The amphotericin B deoxycholate could be readily resuspended within the intralipid by shaking and the concentration of amphotericin B deoxycholate were shaken before sampling retained greater than 90% of the initial concentration for 21 days when stored at either 4 or 23 °C. In vitro antifungal activity of amphotericin B deoxycholate in intralipid indicate that the presence of intralipid did not reduce the in vitro activity amphotericin B deoxycholate against the yeast strains tested. The compatibility of amphotericin B deoxycholate with intralipid were shown in Table 5.

Table 5: The compatibility of amphotericin B deoxycholate with intralipid.

Vol (ml) of lipid in 100 ml of total mixture vol	Intralipid with 10% soybean oil-AmB at 0.6 mg/ml	Intralipid with 10% soybean oil-AmB at 1.2 mg/ml	Intralipid with 20% soybean oil-AmB at 0.6 mg/ml	Intralipid with 20% soybean oil-AmB at 1.2 mg/ml
80	Precipitate	Precipitate	Precipitate	Precipitate
70	Precipitate	Precipitate	Precipitate	Precipitate
60	Precipitate	Precipitate	Precipitate	Precipitate
50	Precipitate	Precipitate	Precipitate	Precipitate
40[a]	No precipitate	Precipitate	Precipitate	Precipitate
30[a]	No precipitate	No precipitate	No precipitate	Precipitate
20[a]	No precipitate	No precipitate	No precipitate	Precipitate
10[a]	No precipitate	No precipitate	No precipitate	No precipitate

[a] refered Mixture with 40 ml of intralipid or less than in 100 ml of the total mixture volume were evaluated after 1 hour and 24 hours

Source: Walker S, Tailor SA, Lee M, Louie L, Louie M, Simor AE. Amphotericin B in lipid emulsion: stability, compatibility, and in vitro antifungal activity. Antimicrob Agents Chemother 1998;42:762-6

Lopez et al. studied stability of amphotericin B deoxycholate in an extemporaneously prepare with fat emulsion. (94) Admixtures of amphotericin B deoxycholate 0.5, 1 and 2 mg/ml were prepared by adding 10, 20 and 40 ml of amphotericin B deoxycholate 5 mg/ml to 90, 80 and 60 ml of 20% intralipid. The admixtures were stored in glass vacuum containers at 20-25 °C and exposed to fluorescent light, 20-25 °C and protected from light or 4-8 °C and protected from light. Amphotericin B deoxycholate 0.5 mg/ml in intralipid 20% was stable for 1 week under all the storage conditions. At 2 weeks, drug loss was approximately 12% at room temperature and 10% under refrigeration. Amphotericin B deoxycholate in the 1 and 2 mg/ml admixtures was stable for up to 4 days at 20-25 °C exposed to fluorescent

light and for up to 1 week at 20-25 °C protected from light. The mean amphotericin B deoxycholate concentrations at 1 week in containers kept at room temperature were 91.9% and 91.5% of the initial values for the 1 mg/ml and 2 mg/ml admixtures, respectively; however, some individual admixtures had a > 10% loss of drug concentration. There was no evidence of incompatibility of amphotericin B deoxycholate in intralipid. No separation of phases, creaming or streaking was observed in any of the 100 ml containers. A yellow color was observed at the bottom of the container for all preparations after 4 hours; this color was consistent with amphotericin B deoxycholate sedimentation. Shaking redispered the drug and made the color of the admixtures homogeneous.

Trissel evaluated the compatibility of amphotericin B deoxycholate in fat emulsion. (95) Amphotericin B deoxycholate in intralipid was prepared by combined 1.2 ml of amphotericin B deoxycholate 5 mg/ml in duplicate with 8.8 ml of intralipid 10% and with 8.8 ml of 20% intralipid and mixed thoroughly to yield an amphotericin B deoxycholate concentration of 0.6 mg/ml. The liquids were stored undisturbed at 23 °C for 1 hour and then centrifuged at 5000 rpm for 15 minutes, which separated the two phases. After centrifugation, the lipid phase appeared above the hazy aqueous phase and a yellow precipitate appeared in the aqueous phase at the bottoms of the test tubes. A light-obscuration particle sizer-counter was used to compare the particle size and content of amphotericin B deoxycholate 0.6 mg/ml in 10% and 20% intralipid with amphotericin B deoxycholate in 5% dextrose. The liquids were stored undistured at 23 °C for 1 hour and then evaluated. Most of the particles of amphotericin B deoxycholate in 5% dextrose had a diameter of < 10 μm; relatively few of the particles were ≥ 10 μm. The amphotericin B deoxycholate in fat emulsion had substantially more particles overall and more particles of ≥ 10 μm. The precipitate in the fat emulsion, obtained by centrifuging the samples, contained particles of ≥ 10 μm (Table 6).

Table 6: The particle content of amphotericin B deoxycholate 0.6 mg/ml in various diluents.

Diluent and particle size (μm) [a]	No. Particles per milliliter [b]
5% dextrose injection	
Total	9,077±44
≥ 10	81±15
10% fat emulsion	
Total	82,951±4,323
≥ 10	8,268±336
20% fat emulsion	
Total	74,119±333
≥ 10	31,988±923

[a] Total refered particles ranging in size from 1 to 112 μm.

[b] refered Mean±S.D. of three determinations.

Source: Trissel LA. Amphotericin B dose not mix with fat emulsion. Am J Health-Syst Pharm 1995;52:1463-4

Ranchere et al. reported stability and particle size of amphotericin B deoxycholate in intralipid formulation. (96) Amphotericin B deoxycholate 50 mg were diluted in 10 ml of intralipid and 13 ml of this mixture were added to 35 ml of intralipid. A study of particle size using a coulter counter TA II (Electronics, Luton, UK). Visual examination of the solution was also recorded measurement were made at times 0, 1, 2, 3, 4 and 5 hours, and after homogenization of the emulsion at 5 and 24 hours. The solution stability was not constant with a clear yellow precipitate being formed in the lower part of the syringe, beginning immediately and increasing with time. The microscopic study did not show a modification of the lipid emulsion but there were many aggregates of large particles. The number of particles ≥ 1 μm/ml of solution is 1.5 to 4-fold higher than in intralipid without amphotericin B deoxycholate. The number of particles ≥ 2 μm/ml of solution is 10 to 25-fold higher than the original emulsion.

4. Amphotericin B deoxycholate administered over 24-hour infusion.

Administration amphotericin B deoxycholate by continuous infusion over 24 hours may be reduced nephrotoxicity.

Chabot et al. reported pharmacokinetics and toxicity of continuous infusion amphotericin B deoxycholate in cancer patients and evaluated the role of amphotericin B deoxycholate in the biochemical modulation of antineoplastic agents. (97) Twenty-six courses of continuous infusion amphotericin B deoxycholate were administered to 14 patients who had bronchogenic small cell carcinomas or metastatic sarcomas. The 24-hour continuous infusion amphotericin B deoxycholate was started at the indicated doses (0.5-0.8 mg/kg/day) diluted in 1 L of 5% dextrose in water and increased dose by 0.1 mg/kg/day after it was determined that the preceding dose level of amphotericin B deoxycholate was safe. A valley pump was used for the infusion via a central venous catheter. The solution was changed every 24 hours. The amphotericin B deoxycholate plasma levels were determined during 23 courses. The continuous infusion amphotericin B deoxycholate over the period from 52 to 120 hours maintained a plateau plasma concentration from 0.7-1.9 μg/ml for total doses ranging from 1-3.7 mg/kg. The plateau plasma concentration was directly related to the infusion rate, with a positive linear correlation ($r=0.52$, $p<0.05$). Potentially effective plateau plasma concentrations of continuous amphotericin B deoxycholate infusion were attained within 1 day and maintained within the antifungal pharmacological range (0.5-2 μg/ml) throughout the infusion time. Blood sampling at the conclusion of continuous infusion amphotericin B deoxycholate treatment allowed the determination amphotericin B deoxycholate plasma disposition was biphasic, with the first elimination half-life of 17 hours (range 8.7-25.1 hours), followed by a prolonged termination phase with a half-life of 11 days (range 9.4-13.7 days). Vd_{ss} was large, 3.2 L/kg and the total body clearance was 0.10 L/hr/kg. A pleural fluid specimen obtained on day 4 of treatment contained 0.2 μg/ml of amphotericin B deoxycholate, representing 22% of the simutaneous plasma level. The urinary excretion was consistently low, with a mean of 3.7% of the total dose (range 1.9-7.2%; n=5 patients). The SCr and BUN were obtained before treatment and weekly. Renal toxicity was

evaluated as follows: grade 1, SCr increase < 1.25 times from baseline; grade 2, SCr increase 1.25-2.5 times from baseline; grade 3, SCr increase 2.6-5 times from baseline; grade 4, SCr increase > 5 times from baseline. Patients were assessed every 4 hours for acute clinical toxicity (fever and chills). Three patients experienced mild chills and 1 patient occurred a febrile reaction. No other acute toxicities were encountered in this study. Renal toxicity was observed; grade 1 were noted in 3 courses and grade 2 were noted in 20 courses. Grade 3 and 4 were not seen. The SCr level generally returned to baseline within 1 week following the cessation of continuous infusion amphotericin B deoxycholate by day 21 or 28. Biochemical modulation of antineoplastic agents by continuous infusion amphotericin B deoxycholate was not demonstrated.

Eriksson et al. performed a randomized, controlled, non-blinded, single centre study to compare effects of amphotericin B deoxycholate infused over 4 or 24 hours in 80 mostly neutropenic patients with refractory fever and suspected or proved invasive fungal infections. (98) Patients were randomised to receive 0.97 mg/kg of amphotericin B deoxycholate by continuous infusion over 24 hours or 0.95 mg/kg by infusion over 4 hours. The drug was given in 500 ml of 5% dextrose without any additives through a separate intravenous line. To reduce nephrotoxicity from amphotericin B deoxycholate, all patients received infusion of saline as standard care. The SCr levels were measured daily during treatment. Hypokalemia was defined as a serum potassium concentration < 2.5 mmol/L and hypomagnesemia as a serum magnesium concentration < 0.5 mmol/L. Efficacy was monitored for overall mortality, mortality due to invasive fungal infections and breakthrough fungaemia during treatment. The two groups did not differ significantly with regard to treatment with aminoglycosides, vancomycin, diuretics, and granulocyte colony stimulating factor. No patient received cyclosporine. Overall duration of treatment were 12 days (range 3-51 days) in the 4-hour infusion group and 16 days (range 3-89 days) in the 24-hour infusion group. The major side effects related to infusion occurred mainly during the first 3 days of treatment were chills, fever and vomiting. Chills or rigors occurred in 25 patients (63%) assigned to the 4-hour infusion group and 8 patients (20%) assigned to the 24-hours infusion group, p=0.0001. Vomiting occurred in 24 patients (60%) assigned to the 4-hour infusion group and 11 patients (28%) assigned

to the 24-hour infusion group, p=0.004. Fever during the first days of amphotericin B deoxycholate therapy occurred in 21 patients (53%) assigned to the 4-hour infusion group and 10 patients (25%) assigned to the 24-hour infusion group, p=0.021. Nephrotoxicity occurred in 15 patients (38%) who received the 4 hours group, 11 patients (28%) had SCr increased 2 times from baseline and 4 patients (10%) had SCr increased 3 times from baseline. Treatment was discontinued in 1 patient because of severe nephrotoxicity from treatment. Nephrotoxicity occurred in 6 patients (15%) who received the 24-hour infusion group, all patients had SCr increased 2 times from baseline. No patients in the 24-hour infusion group had SCr increased 3 times from baseline. Patients who had hypokalemia or hypomagnesemia did not differ significantly between the both groups. Hypokalemia occurred in 10 patients (25%) assigned to the 4-hour infusion group and 4 patients (10%) assigned to the 24-hour infusion group. Hypomagnesemia was observed in 19 patients (47.5%) assigned to the 4-hour infusion group and 17 patients (42.5%) assigned to the 24-hour infusion group. All seven deaths during treatment occurred in the 4-hour infusion group compared with none of patient death in the 24-hour infusion group, p=0.012. Necropsy was carried out in 6 patients and severe pneumonia was found. Invasive fungi were proved in 3 patients. Breakthrough fungaemia did not occurred in any patient of both groups. After 3 months' follow-up, 12 patients died (30%) in the 4-hour infusion group compared with 4 patient died (10%) in the 24-hour infusion group, p=0.048.

Speich et al. conducted an open pilot study to assess tolerability, safety and efficacy of amphotericin B deoxycholate administered by 24-hour infusion to lung transplant recipients between November 1992 and April 2000. (99) Six out of 94 lung transplant recipients (6%) were treated with amphotericin B deoxycholate administratered by 24-hour infusion for azole-resistant candidal infection: 3 patients in *C. paraspilosis*, 2 patients in *C.glabata* and 1 patient in *C. krusei*. Patients received 1 mg/kg amphotericin B deoxycholate in 500 ml of 5% dextrose and infused over 24 hours for a median of 40 days (range 17-73 days). At least 1,000 ml of 0.9% saline was administered intravenously per day. All patients were concomitantly treated with cyclosporine A (CsA) and dosage was not reduced during amphotericin B deoxycholate treatment. In addition, 5 patients received aminoglycoside for at least 2 weeks, 4 patients received intravenous ganciclovir and 1 patient received teicoplanin.

Creatinine and electrolytes were measured on a daily basis. During the whole treatment period, no patient complained about amphotericin B deoxycholate-associated side effects such as fever, chills, headache or vomiting. There were 3 episodes of mild hypokalaemia. The CrCl decreased from 57 ml/min (range 43-73 ml/min) to a nadir of 35 ml/min (range 28-39 ml/min) during treatment, p=0.028 and recovered to 52 ml/min (range 33-60 ml/min) after cessation of therapy. The SCr levels increased from 118 μmol/L (range 88-138 μmol/L) to 183 μmol/L (range 115-252 μmol/L), p=0.0022 and recovered to 123 μmol/L (range 80-173 μmol/L). The recovered of CrCl and SCr values were not significantly different from the pre-treatment levels, p=0.14. One patient had doubled SCr level and need temporary haemofiltration for a period of 7 days but oliguric renal failure may due to inappropriate hydration and use of 150 ml contrast media. The eradication of the fungal infection was successful in 5 of 6 patients. One patient had recurrent colonisation with *C.glabata* subsequently to the early disconinuation of amphotericin B deoxycholate treatment after 16 days. Fungal colonisation was eventually eradicated 10 months later.

Furrer et al. conducted a retrospective study to assess nephrotoxicity of CsA and amphotericin B deoxycholate as continuous 24-hour infusion in patients with allogeneic stem cell transplantation between January 1998 and April 2001. (100) Amphotericin B deoxycholate was administered as a continuous 24-hour infusion in 500 ml of 5% dextrose without any additives through a separate intravenous line. To reduce nephrotoxicity, all patients received an additional 1,000 ml of normal saline over 24 hours as standard care, whenever possible. Of a total of 84 patients, 22 were treated with amphotericin B deoxycholate. The mean maximal dosage of amphotericin B deoxycholate was 1.03±0.37 mg/kg/day (range 0.6-2 mg/kg/day). The mean total dose of amphotericin B deoxycholate was 1,181±677 mg (range 378-2,655 mg) with mean duration of 22.3±22.6 days (range 3-112 days). To compare parameters of kidney function in patients undergoing amphotericin B deoxycholate therapy with patients receiving CsA alone. The SCr increasing in both groups but significantly greater increase in the group receiving amphotericin B deoxycholate. The SCr in the group without amphotericin B deoxycholate was 96.1±29.6 μg/ml and 132.0±59.6 μg/ml in the group with amphotericin B deoxycholate, p=0.0004. The

CrCl in the group without amphotericin B deoxycholate was 74.1±21.7 ml/min compared with 55.5±18.6 ml/min in the group with amphotericin B deoxycholate, p=0.0002. In both groups, none of patient had CrCl below 30 ml/min. Renal insufficiency in all patients remained in a clinically acceptable range and was reversible. The minimal potassium concentration was 3.1±0.3 mmol/L in the group without amphotericin B deoxycholate and 2.8±0.4 mmol/L in the group with amphotericin B deoxycholate, p<0.0001. One year after transplantation a significant difference in SCr level persisted, 91.9±20.2 μg/ml in the group without amphotericin B deoxycholate and 124.3±29.3 μg/ml in the group with amphotericin B deoxycholate, p<0.0001. None of the 22 patients who treated with continuous 24-hour infusion of amphotericin B deoxycholate died from a mycosis, neither during amphotericin B deoxycholate therapy nor during follow up at 3 and 6 months.

Imhof et al. performed an open-label observational study to evaluate continuous infusion of escalated dose of amphotericin B deoxycholate in 31 patients were neutropenia and 2 patients were HIV infection. (101) On day 1 of the study, 1 mg/kg of amphotericin B deoxycholate was administered in 500 ml of 5% dextrose, without additives, through a separate intravenous line and was gradually increase to 2 mg/kg/day. All patients received an additional 1,000 ml of saline every 24 hours as standard care, whenever possible. Thirty-one patients were treated with amphotericin B deoxycholate monotherapy. In 2 patients, one was treated with a combination of amphotericin B deoxycholate and flucytosine because of cryptococcal meningitis, and the other received amphotericin B deoxycholate in combination with caspofungin and flucytosine because of life-threatening aspergillosis, both patients were include in the 2 mg/kg dose group. The SCr levels were measured daily. Nephrotoxicity defined as SCr increase ≥ 2 times from baseline value. Efficacy was monitored for overall mortality and mortality due to invasive fungal infections. Of the 727 infusions administered, 129 (18%) were associated with infusion-related reactions. Seventeen patients (52%) had chills and/or rigors on day 1 or 2. Nausea occorred in 7 patients (21%) and febrile reaction was noted during treatment in 1 patient. Sixteen patients (48%) had CrCl values that were 1.5 times less than the baseline value. Five patients (15%) had CrCl values 2 times less than the baseline value. The SCr increase 2 times from baseline value occurred in 4 patients and SCr increase 3 times from baseline

value occurred in 1 patient. Overall nephrotoxicity occurred in 5 of 33 patients (15%). Supplementation with sodium bicarbonate was necessary for 21 patients (64%) because of the development of tubular acidosis. A dose-dependent increase in the daily required potassium supplementation was found and the daily amount of intravenous fluid administration increased with increasing daily amphotericin B deoxycholate dose. Hypomagnesemia requiring magnesium substitution occurred in 24 patients (73%). Nine patients (27%) died during therapy period. Invasive fungi were found at autosy in 3 patients. Two months after the end of amphotericin B deoxycholate treatment, 22 patients (67%) were still alive. Two patients died of progression of acute leukemia unrelated to fungal infection.

Peleg and Woods conducted a retrospective cohort study to assess the nephrotoxicity and efficacy of continuous 24-hour infusion compared with 4-hour infusion of amphotericin B deoxycholate in a high-risk haematology with fever and neutropenia, including BMT recipients during January 2001 to January 2003. (102) The institution's policy on amphotericin B deoxycholate administration changed from a 4-hour infusion to a 24-hour continuous infusion in January 2002. Amphotericin B deoxycholate were given in 500 ml of 5% dextrose. Patients were given an additional 500 ml of normal saline over the 24 hours period to reduce the risk of nephrotoxicity. Recommendations on amphotericin B deoxycholate dosing were: 0.6 mg/kg/day for patients with refractory fever and neutropenia and 1 mg/kg/day for suspected or proven aspergillosis. The SCr was measured daily. Renal impairment was defined as a doubling of baseline SCr. Efficacy was assessed mortality at 14 days after the initiation of amphotericin B deoxycholate, absence of breakthrough fungal infections during administration of amphotericin B deoxycholate or 7 days after completion of treatment and the successful treatment of any baseline fungal infection, if present. A total of 81 admissions from 77 patients were included in the study, 39 received the 24-hour infusion and 42 received the 4-hour infusion of amphotericin B deoxycholate. No significant difference in use of concurrent nephrotoxic drugs such as aminoglycosides, vancomycin. Nephrotoxicity occurred in 19 of 42 patients (45%) in the 4-hour group and 4 of 39 patients (10%) in the 24-hour group (odd ratio [OR], 0.14; 95%CI, 0.04-0.5, $p<0.001$). Nephrotoxicity was significantly less frequent in the 24-hour infusion group compared with the 4-hour infusion group in the subgroup of

patients who underwent allogenic transplantation. Nephrotoxicity occurred in 7% in the 24-hour infusion group and 60% in the 4-hour infusion group (OR=0.06, 95%CI, 0.01-0.6, p=0.007). In the subgroup of patients who received concurrent nephrotoxic drugs, nephrotoxicity occurred in 3% in the 24-hour infusion group and 46% in the 4-hour infusion group (OR=0.03, 95%CI, 0.001-0.3, p<0.001). No patient required dialysis. Multivariate logistic regression analysis confirmed that continuous 24-hour infusion of amphotericin B deoxycholate was the only variable to be significantly associated with renal impairment, with a protective effect (OR=0.16, 95%CI, 0.05-0.5, p=0.003). Patients who had amphotericin B deoxycholate infusion rate of ≥ 0.08 mg/kg/hr were significantly more likely to develop renal impairment compared with patients with infusion rate of < 0.08 mg/kg/hr (OR= 7.8, 95%CI, 2.3-25.8, p<0.001). Survival at 14 days after the initiation of amphotericin B deoxycholate were 37 of 39 patients (95%) in the 24-hour infusion group and 33 of 42 patients (79%) in the 4-hour infusion group (OR= 5.1, 95%CI, 1.02-25.1, p=0.003). Mortality directly due to invasive fungal infection was not significantly, 1 patient (2.6%) in the 24-hour infusion group and 2 patients (4.8%) in the 4-hour infusion group, p=1.00. The breakthrough fungal infections were 37 of 39 patients (95%) in the 24-hour infusion group compared with 40 of 42 patients (95%) in the 4-hour infusion group, p=1.00. Cure of baseline fungal infection were observed in 10 of 13 patients (77%) in the 24-hour infusion group compared with 7 of 10 patients (70%) in the 4-hour infusion group, p=1.00. As a consequence of reduced renal impairment, the total pharmacy expediture for liposomal amphotericin B decreased by $A 245,200 during the year continuous 24-hour infusion of amphotericin B deoxycholate was implemented.

Amphotericin B deoxycholate was administered by intravenous infusion. Amphotericin B deoxycholate 50 mg vial reconstitute with 10 ml of sterile water for injection without preservatives and shake until a clear colloidal dispersion was obtained. The resultant concentration was 5 mg/ml of amphotericin B deoxycholate. For infusion, amphotericin B deoxycholate must be further diluted with 5% dextrose in water with a pH above 4.2. (103) Compatibility information of amphotericin B deoxycholate shown in Appendix I.

Tipple et al. studied stability of amphotericin B deoxycholate as prepared for intravenous use in glass and PVC containers. (104) Two 1,000 ml glass bottles and

two 500 ml PVC bags containing 5 % dextrose in water. Amphotericin B deoxycholate were reconstituted and added to each container to a final concentration of approximately 0.1 mg/ml. One glass bottle and 1 PVC bag were covered to exclude light. All containers were hung approximately 4 feet below overhead fluorescent lights and kept at 25 °C. Samples were collected from each container at 0, 0.5, 1, 2, 4, 7 and 24 hours, and immediately frozen at -20 °C. Comparison of data for the covered PVC container with those for the one exposed to light for 24 hours also showed no significant differences in drug activity, p=0.50. Concentrations of amphotericin B deoxycholate solutions in covered and uncovered glass and PVC containers showed the same levels of activity at each time interval and no significant sorption of drug by the plastic container, p=0.70 and 0.90, respectively (Table 7).

Table 7: The concentrations of amphotericin B deoxycholate solutions in covered and uncovered glass and PVC containers.

Time (hours)	Covered glass (μg/ml)	Light-Exposed glass (μg/ml)	Covered PVC (μg/ml)	Light-Exposed PVC (μg/ml)
0	1.18	1.15	1.20	1.24
0.5	0.97	0.93	1.20	1.01
1	1.02	1.20	0.93	1.05
2	1.13	1.10	1.13	1.10
4	1.16	1.13	1.16	1.02
7	0.97	0.97	0.99	1.11
24	0.94	0.94	1.10	0.93

Source: Tipple M, Shadomy S, Espinel-Ingroff A. Stability of amphotericin B in polyvinyl chloride intravenous bags. Am Rev Respir Dis 1975;112: 145-6

Kintzel and Kennedy reported the chemical stability and physical compatibility amphotericin B deoxycholate in 5% dextrose at concentrations of 0.47, 0.66 and 0.75 mg/ml when stored at 25 °C for 4, 12 and 24 hours. (105) Amphotericin B deoxycholate were reconstituted with 10 ml of sterile water for injection, then 30, 40 and 50 mg portions of the solution were injected into 50 ml of 5% dextrose in polyolefin containers. Final concentration were 0.52, 0.67 and 0.81 mg/ml.

Significant chemical degradation was defined as a loss of > 10% of the initial amphotericin B deoxycholate concentrations. For each concentration and storage time, sample were inspected visually for signs physical incompatibility such as precipitation, turbidity, gas formation and color change. The pH was measured. The interday variability of the assay was 3.3%. Sample pH was 7.29±0.08 throughout the study. None of the samples showed evidence of precipitation, turbidity, gas formation or color change. Concentrations of amphotericin B deoxycholate remained within 3% of initial concentrations all after 4, 12 and 24 hours of storage were summarized in Table 8.

Table 8: Stability of amphotericin B deoxycholate at 25 °C.

Theoretical concentration (mg/ml)	Actual initial concentration (mg/ml) (mean±S.D.)	% initial concentration remaining (mean±S.D.)		
		4 hours	12 hours	24 hours
Storage at 25°C				
0.52	0.47±0.01	101.5±2.8	102.2±2.8	100.7±2.9
0.67	0.66±0.01	100.1±2.1	101.6±2.0	100.0±2.1
0.81	0.75±0.02	97.9±1.9	100.8±1.8	98.7±1.8

Source: Kintzel PE, Kennedy PE. Stability of amphotericin B in 5% dextrose injection at 25 °c. Am J Hosp Pharm 1991;48:1681

Kintzel and Kennedy studied of stability of amphotericin B deoxycholate in 5% dextrose at concentrations used for administration through a central venous line. (106) Amphotericin B deoxycholate with final after adjustment for total volume were 0.92±0.01 mg/ml, 1.20±0.03 mg/ml and 1.40±0.03 mg/ml, respectively. Sample were stored at 6 and 25 °C. Amphotericin B deoxycholate concentration was tested at 0, 4, 12, 24 and 36 hours. The pH was measured and the admixtures were inspected visually at each time point for precipitation, turbidity, gas formation and color change. Concentrations of amphotericin B deoxycholate remained within 3% of initial concentrations at each time point at both 6 and 25 °C (Table 9). No changes in pH

were observed. None of the admixtures showed precipitation, turbidity, gas formation or color change throughout the study.

Table 9: Stability of amphotericin B deoxycholate at 6 and 25 °C.

Theoretical concentration (mg/ml)	Actual initial concentration (mg/ml) (mean±S.D.)	% initial concentration remaining (mean±S.D.)			
		4 hours	12 hours	24 hours	36 hours
Storage at 6°C					
0.95	0.93±0.03	99.0±0.3	97.0±1.5	101.0±1.5	101.0±1.5
1.19	1.19±0.01	100.0±2.3	99.0±2.3	100.0±2.3	100.0±2.3
1.40	1.41±0.01	100.0±1.9	99.0±1.9	101.0±1.9	102.0±1.9
Storage at 25°C					
0.95	0.91±0.01	99.0±0.7	101.0±1.6	98.0±0.2	100.0±2.0
1.19	1.20±0.01	99.0±2.3	99.0±2.3	98.0±0.1	98.0±2.4
1.40	1.40±0.02	98.0±2.0	98.0±2.0	99.0±2.0	98.0±1.5

Source: Kintzel PE, Kennedy PE. Stability of amphotericin B in 5% dextrose injection at concentrations used for administration through a central venous line. Am J Hosp Pharm 1991;48:283-5

Block and Bennett reported stability of amphotericin B deoxycholate in infusion bottles. (107) Twelve 500 ml bottles of 5% dextrose in water containing either amphotericin B deoxycholate (35 or 70 mg) alone, amphotericin B deoxycholate (35 or 70 mg) and 25 mg hydrocortisone sodium succinate or amphotericin B deoxycholate (35 or 70 mg) and 1000 U of sodium heparin were prepared and studied at room temperature 25 °C. Six of the bottles were directly exposed to fluorescent room lighting and other 6 bottles were wrapped in aluminum foil. Samples were removed at 0, 1, 4 and 24 hours. Amphotericin B deoxycholate bioactivity was not significantly affected at either concentration studied by the exposure to light and/or by the presence in the infusion bottle of heparin or hydrocortisone.

Lee et al. assessed the visual compatibility and chemical stability of amphotericin B deoxycholate in 5% dextrose in PVC bags when stored protected from light at 4 °C

and when stored under fluorescent light at 25 °C for 120 hours. (108) Amphotericin B deoxycholate 50 mg diluted with sterile water and add with 5% dextrose to produce a final concentration of 0.2, 0.5 and 1 mg/ml contained in PVC. The container were stored protected from light at 4 °C and under 40-W fluorescent light at 25 °C. At 24, 48 and 120 hours, the admixtures were removed. All the admixtures were inspected visually at each time point for precipitation and turbidity. None of the samples contained any visible precipitate. However, the 1 mg/ml amphotericin B deoxycholate admixture exhibited turbidity immediately after preparation. This turbidity persisted at both at 4 °C and 25 °C throughout the study period. The visual turbidity of the 1 mg/ml admixture did not affect chemical stability. No changes in pH were detected over the 120-hour period. No significant changes in mean amphotericin B deoxycholate concentrations which were summarized in Table 10.

Table 10: Stability of amphotericin B deoxycholate at 4 and 25 °C.

Theoretical concentration (mg/ml)	Actual initial concentration (mg/ml) (mean±S.D.)	% initial concentration remaining (mean±S.D.)		
		24 hours	48 hours	120 hours
Storage at 4°C				
0.2	0.18±0.00	101.6±1.9	101.8±2.9	100.9±2.3
0.5	0.45±0.00	102.4±6.1	100.9±0.2	104.1±3.7
1.0	0.95±0.05	96.9±7.4	98.6±12.0	98.7±5.5
Storage at 25°C				
0.2	0.17±0.00	101.4±1.7	102.9±2.9	100.4±1.7
0.5	0.47±0.01	99.1±0.4	100.8±3.7	97.9±2.4
1.0	0.93±0.03	98.9±3.9	98.1±1.2	101.1±5.1

Source: Lee MD, Hess MM, Boucher BA, Apple AM. Stability of amphotericin B in 5% dextrose injection stored at 4 or 25 °C for 120 hours. Am J Hosp Pharm 1994;51:394-6

Wiest et al. investigated stability of amphotericin B deoxycholate in 5%, 10%, 15% and 20% dextrose injection. (109) The pH of each solution was determined before amphotericin B deoxycholate was added to a concentration of approximately

100 μg/ml. The bags were stored at 15-20 °C and protected from light. Samples were obtained at 0, 0.5, 1, 2, 4, 6, 8, 12 and 24 hours and was analyzed for precipitation, color and pH changes. No visual changes were observed and pH did not changes. The mean amphotericin B deoxycholate concentration remained above 90% of the initial concentration at all intervals up to 24 hours in each dextrose solution. However, amphotericin B deoxycholate concentrations in 3 of 27 samples from the admixtures with 10% dextrose and 5 of 27 samples from the admixtures with 20% dextrose were less than 90% of the initial concentration within 6 hours.

Mitrano et al. assessed chemical and visual stability of amphotericin B deoxycholate in 5% dextrose for 0.1 and 0.25 mg/ml in PVC bags stored at 4 °C and protected from light for 35 days. (110) Admixtures were also assessed for pH and visually under fluorescent light for color change, turbidity, gas evolution and precipitation. Samples were obtained at 10, 21 and 35 days. There were no appreciable changes in pH and none of the samples exhibited any sign of color change, turbidity, gas evolution or precipitation. There was no substantial loss or deterioration of amphotericin B deoxycholate during the 35-day study. At time zero and 10, 21 and 35 days, the mean concentration of amphotericin B deoxycholate remained within 4% of the concentration at time zero.

Protection from light does not seem to be necessary for amphotericin B deoxycholate in 5 % dextrose injection to ensure stability for up to 24 or even 36 hours. (111 ,112) As summarized in Table 11, the incidence of nephrotoxicity, infusion-related adverse reactions and clinical outcome of amphotericin B deoxycholate administered in the rapid infusion, standard infusion and over 24-hour infusion stydies were varies. Previous of amphotericin B deoxycholate administered over 24-hour infusion stydies showed that incidence of nephrotoxicity and infusion-related adverse reactions due to amphotericin B deoxycholate were reduced. Then amphotericin B deoxycholate infused over 24 hours may be useful to reduce nephrotoxicity and have effectiveness for treatment fungal infection.

Table 11: The incidence of nephrotoxicity, infusion-related adverse reactions and clinical outcome of amphotericin B deoxycholate administered in the rapid infusion, standard infusion and over 24-hour infusion studies.

Studies	Incidence of nephrotoxicity	Incidence of infusion-related adverse reactions	Effectiveness
Goodwin et al. (48)		Fever: 51% (202 of 397 patients) Chills: 28% (111 of 397 patients) Nausea: 18% (71 of 397 patients) Thrombophlebitis: 5 % (20 of 397 patients)	
Ellis et al. (49)	2 patients (18%) in 45-minute group 2 patients (22.2%) in 4-hour group		4 patients (36%) in 45-minute group 1 patient (11.1%) in 4-hour group
Nicholl et al. (50)		Fever: 5 infusions (3%) in 2-hour group : 3 infusions (2%) in 4-hour group Chills: 13 infusions (8%) in 2-hour group : 12 infusions (7%) in 4-hour group Nausea and vomiting : 11 infusions (7%) in 2-hour group : 19 infusions (12%) in 4-hour group	

Table 11: The incidence of nephrotoxicity, infusion-related adverse reactions and clinical outcome of amphotericin B deoxycholate administered in the rapid infusion, standard infusion and over 24-hour infusion studies. (Continued)

Studies	Incidence of nephrotoxicity	Incidence of infusion-related adverse reactions	Effectiveness
Cruz et al. (51)	17 of 25 patients (68%)		
Cleary et al. (52)		Fever: 12 patients (70.5%) in 45-minute group : 13 patients (76.4%) in 2-hour group Chills:15 patients (88.2%) in 45-minute group : 14 patients (82.3%) in 2-hour group Nausea and vomiting : 4 infusions (8.3%) in 45-minute group : 2 infusions (4.3%) in 2-hour group	
Oldfield et al. (53)		Fever: 5 infusions (8%) in 1-hour group : 7 infusions (10.6%) in 4-hour group Chills or rigors :15 infusions (24.1%) in 1-hour group : 12 infusions (18.1%) in 4-hour group	
Pathak et al. (54)	15 % -Discontinuation: 1 patient	Chills, fever and/or nausea : 25 %	16 patients (14.4%) died

Table 11: The incidence of nephrotoxicity, infusion-related adverse reactions and clinical outcome of amphotericin B deoxycholate administered in the rapid infusion, standard infusion and over 24-hour infusion studies. (Continued)

Studies	Incidence of nephrotoxicity	Incidence of infusion-related adverse reactions	Effectiveness
Harbarth et al. (55)	139 of 494 patients (28%) SCr ≥ 3 mg/dl: 16 patients (3%)		
Bates et al. (56)	175 patients (27%) SCr ≥ 3 mg/dl: 67 patients (10%)		
Gubbins et al. (57)	30 of 69 patients (43%)		
Wingard et al. (58)	127 of 239 patients (53%) SCr ≥ 2.5 mg/dl: 29 %		143 of 239 patients (60%) died
Subira et al. (76)	18 of 56 patients (32%) -Discontinuation: 9 of 56 patients (16%) Hemodialysis: 1 patient (1.8%)	Fever: 37 patients (66%) Chills or rigors : 33 patients (59%) Nausea or vomiting : 7 patients (13%)	
White et al. (77)	107 of 248 patients (43.1%)		Survival rate: 74 of 261 patients (28.4%)

Table 11: The incidence of nephrotoxicity, infusion-related adverse reactions and clinical outcome of amphotericin B deoxycholate administered in the rapid infusion, standard infusion and over 24-hour infusion studies. (Continued)

Studies	Incidence of nephrotoxicity	Incidence of infusion-related adverse reactions	Effectiveness
Bowden et al. (79)	38 patients (49.4%) -Discontinuation: 16 patients (18.6%)	Fever: 14 patients (16.3%) Chills: 26 patients (30.2%) Nausea and vomiting : 17 patients (19.8%)	-Overall mortality : 55 % -Death due to fungal infection : 36 %
Prentice et al. (80)	12 of 39 patients (31%)		Treatment success : 18 of 39 patients (46%)
Leenders et al. (82)	22 of 54 patients (40%) -Discontinuation or reduced dose: 18 patients (33%)		-Overall mortality : 13 of 34 patients (38%) -Died due, or at least partly due to fungal infectio: 10 of 13 patients
Walsh et al. (83)	Overall: 50.3 % -SCr > 2 times from baseline: 116 of 344 patients (33.7%) -SCr > 3 times from baseline: 57 of 344 patients (16.6%)	Fever on day 1: 150 of 344 patients (43.6%) Chills: 253 of 344 patients (73.5%) Nausea: 89 of 344 patients (25.9%) Vomiting: 81 of 344 patients (23.5%)	-Overall success : 170 of 344 patients (49.4%) -Breakthrough fungal infection : 27 of 344 patients (7.8%)

Table 11: The incidence of nephrotoxicity, infusion-related adverse reactions and clinical outcome of amphotericin B deoxycholate administered in the rapid infusion, standard infusion and over 24-hour infusion studies. (Continued)

Studies	Incidence of nephrotoxicity	Incidence of infusion-related adverse reactions	Effectiveness
Johnson et al. (84)	9 of 24 patients (37%)	Acute infusion-related toxicity: 15 of 24 patients (63%)	Clinical success: 14 of 22 patients (64%)
Chavanet et al. (87)	3 of 11 patients (27.3%)	Fever and chills: 25 of 38 infusions (66%)	
Sorkine et al. (88)	20 of 30 patients (66.7%)	Fever: 61.4% Chills: 54%	
Joly et al. (89)	Reduced dose due to nephrotoxicity: 2 of 44 patients (4.5%)	Fever: 30 of 44 patients (68.2%) Chills: 39 of 44 patients (88.6%)	The mortality associated with progressive cryptococcus disease: 6 patients (15.4%)
Caillot et al. (90)	14 of 21 patients (66.7%) -Discontinuation: 4 of 21 patients (19%)	Chills: 16 of 21 patients (76.2%)	
Moreau et al. (91)	9 of 16 patients (56%)	Fever with rigor: 2 of 16 patients (12.5%)	

Table 11: The incidence of nephrotoxicity, infusion-related adverse reactions and clinical outcome of amphotericin B deoxycholate administered in the rapid infusion, standard infusion and over 24-hour infusion studies. (Continued)

Studies	Incidence of nephrotoxicity	Incidence of infusion-related adverse reactions	Effectiveness
Nucci et al. (92)	7 patients (32%)	Fever: 28 patients (85%)	
24-hour infusion Chabot et al. (97)	-SCr increase < 1.25 times from baseline: 3 of 26 courses (11.5%) -SCr increase 1.25-2.5 times from baseline: 20 of 26 courses (76.92%)	Fever: 1 of 14 patients (7.1%) Mild chills: 3 of 14 patients (21.4%)	
Eriksson et al. (98)	4-hour infusion: 15 of 40 patients (38%) -SCr > 2 times: 11 of 40 patients (28%) -SCr > 3 times: 4 of 40 patients (10%) -Discontinuation: 1 patient 24-hour infusion: -SCr > 2 times: 6 of 40 patients (15%)	Fever on day 1: 4-hour infusion: 21 of 40 patients (53%) 24-hour infusion: 10 of 40 patients (25%) Chills or rigors: 4-hour infusion: 25 of 40 patients (63%) 24-hour infusion: 8 of 40 patients (20%) Vomiting: 4-hour infusion: 24 of 40 patients (60%) 24-hour infusion: 11 of 40 patients (28%)	-During therapy: 7 of 40 patients (17.5%) died in 4-hour infusion -Breakthrough fungaemia: did not occurred - 3 months' follow-up: 4-hour infusion: 12 of 40 patients (30%) died 24-hour infusion: 4 of 40 patients (10%) died

Table 11: The incidence of nephrotoxicity, infusion-related adverse reactions and clinical outcome of amphotericin B deoxycholate administered in the rapid infusion, standard infusion and over 24-hour infusion studies. (Continued)

Studies	Incidence of nephrotoxicity	Incidence of infusion-related adverse reactions	Effectiveness
Speich et al. (99)	1 of 6 patients (16%)	No patient complained about fever, chills, headache or vomiting	
Furrer et al. (100)	None of patient had CrCl below 30 ml/min		None of 22 patients died from a mycosis, neither during therapy nor follow-up at 3 and 6 months
Imhof et al. (101)	5 of 33 patients (15%) -SCr > 2 times: 4 of 33 patients (12%) -SCr > 3 times: 1 of 33 patients (3%)	Fever: 1 of 33 patients (3%) Chills and/or rigors: 17 of 33 patients (52%) Nausea: 7 of 33 patients (21%)	9 of 33 patients (27%) died
Peleg and woods	4-hour infusion: 19 of 42 patients (45%) 24-hour infusion: 4 of 39 patients (10%)		4-hour infusion: 9 of 42 patients (21%) died and 2 patients (4.8%) died due to fungal infection

Table 11: The incidence of nephrotoxicity, infusion-related adverse reactions and clinical outcome of amphotericin B deoxycholate administered in the rapid infusion, standard infusion and over 24-hour infusion studies. (Continued)

Studies	Incidence of nephrotoxicity	Incidence of infusion-related adverse reactions	Effectiveness
Peleg and woods			24-hour infusion: 2 of 39 patients (5%) died and 1 patient (2.6%) died due to fungal infection

CHAPTER 3
METHODOLOGY

I. Study design

The study was designed as observational, prospective single centre study.

II. Definition of terms

The terms used throughout the study were defined as follows:

Incidence was defined as cumulative incidence (CI)

formula used as cumulative incidence (CI) = $\frac{\text{new case during given time period}}{\text{total population}}$

Nephrotoxicity was defined as doubling of the serum creatinine level from the baseline level during administration of amphotericin B deoxycholate. (57, 82, 98)

Effectiveness consisted of overall mortality, mortality due to invasive fungal infections and breakthrough fungaemia during treatment. (98, 101)

Infusion-related adverse reactions consisted of fever, chills/rigors, nausea/vomiting, phlebitis and any other reactions that were related to infusion.

Fever was defined as an increased in temperature of 2 °C or more if the baseline temperature is ≥ 38 °C or an increased in temperature of 1 °C from a baseline temperature or less than 38 °C. (50)

Chills/rigors was defined as cold feeling with infusion-associated shivering. (51,52)

Time to renal toxicity was defined as the number of days between the first infusion of amphotericin B deoxycholate and the first observation of nephrotoxicity.

Hypokalemia was defined as the serum potassium was less than 3.5 mmol/L. (49)

Hypomagnesemia was defined as the serum magnesium was less than 1.9 mg/dl. (49)

Dehydration was defined as present of urine specific gravity increased, oliguria, BUN: Cr ratio > 20, hematocrit increased, skin turgor that determined by physician.

Sodium supplementation for reduced nephrotoxicity was defined as received sodium 75-150 mEq/day. (64-68)

III. Ethical approval

Study protocol was approved by the Human Research Ethics Committee of Faculty of Medicine, Siriraj Hospital, Mahidol University.

IV. Study population

Subjects were recruited according to the following criteria:

Inclusion criteria

1. Patients who were admitted in the internal medicine wards at Asdang building, Siriraj Hospital.
2. Patients who were treated with amphotericin B deoxycholate administered over 24-hour infusion.

Exclusion criteria

1. Patients who had a history of anaphylactic reactions or other serious, life-threatening reactions to amphotericin B deoxycholate.
2. Patients who had baseline serum creatinine levels greater than 3 mg/dl.
3. Patients who denied to participate in the study.

Sample size

Sample size calculated based on an observational study. The statistical formula used as follow:

$$n = \frac{(Z\alpha/2)^2 P (1-P)}{d^2}$$

The following terms were defined as

n = sample size

$Z_{\alpha/2}$ = 1.96

P = the prevalence of nephrotoxicity

d = allowable error

Previous 24-hour infusion of amphotericin B deoxycholate studies reported incidence of nephrotoxicity ranging from 10-16%. Literature review showed that nephrotoxicity of amphotericin B deoxycholate administered over 24-hour infusion was 15 %. (98)

$$n = \frac{(1.96)^2 (0.15) (1-0.15)}{(0.1)^2} = 49$$

Number of sample size comprised to 50 patients.

V. Period of study

Study period was during April 2004 to April 2005 or until number of sample size in the study were completed.

VI. Steps of investigation

Patients who were admitted at internal medicine wards, Asdang building, Siriraj Hospital and received amphotericin B deoxycholate over 24-hour infusion were recruited. Amphotericin B deoxycholate was given in 500-1,000 ml of 5% dextrose injection without any additives. The initial and subsequent dosage of amphotericin B deoxycholate were chosen by the physicians in charge. A clinical pharmacist was reviewed medical charts daily until discontinuation of amphotericin B deoxycholate or being referred to other hospitals or dead and monitored for nephrotoxicity, infusion-related adverse reactions such as fever, chills/rigors, phlebitis, if occurred and effectiveness. The data were recorded in data collecting form (Appendix II). Clinical pharmacist was determined the incidence of nephrotoxicity and infusion-related

adverse reactions. For the effectiveness of amphotericin B deoxycholate infusion over 24 hours, the incidence of overall mortality, mortality due to invasive fungal infections and breakthrough fungaemia during treatment were assessed. Steps of investigation were shown in Figure 2.

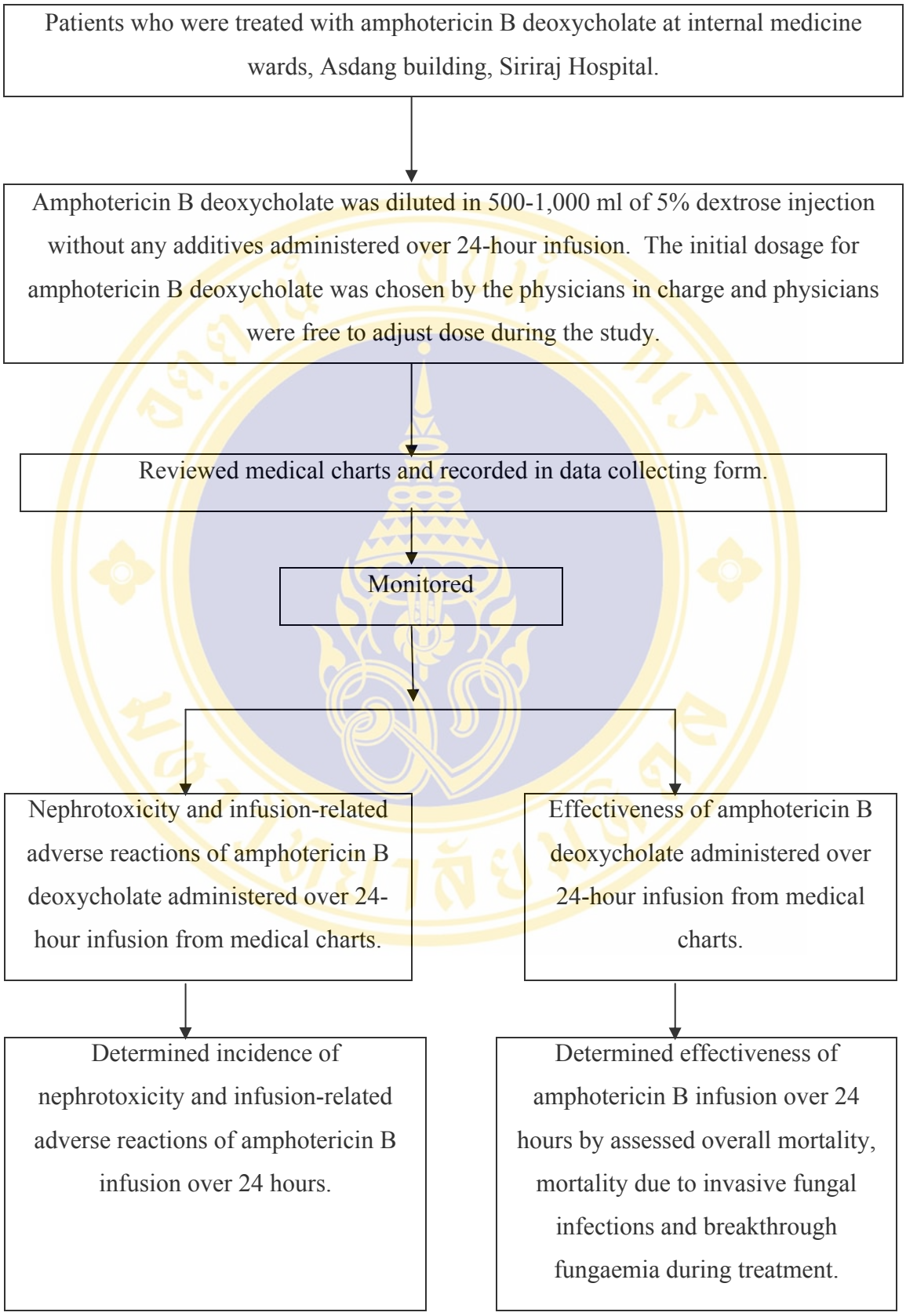

Figure 2: Steps of investigation.

VII. Data collections

The data were collected and recorded in the data collecting form as follows:

1. Demorgraphic data include:

Patient's initials, gender, age, hospital number (HN), admission number (AN), ward, admission date, study date, body weight (kg), height (cm) and underlying illness.

2. Medication profile data include:

2.1 Indication for amphotericin B deoxycholate therapy

- Febrile neutropenia
- Fungal infection (specify site & organism)

2.2 Amphotericin B deoxycholate administration

- Initial dosage of amphotericin B deoxycholate (mg/kg/day)
- Subsequent dosage of amphotericin B deoxycholate (mg/kg/day)
- Duration of amphotericin B deoxycholate treatment (days)
- Total dosage of amphotericin B deoxycholate (mg)
- Concomitant nephrotoxic agents (specify)

2.3 Risk factors of amphotericin B deoxycholate-induced nephrotoxicity

- Occurred nephrotoxicity from amphotericin B deoxycholate prior
- Does not received sodium supplementation (Na 75-150 mEq/day)
- Dehydration
- Electrolyte imbalance
- Others

2.4 Treatment of nephrotoxicity

- Discontinuation of amphotericin B deoxycholate
- Reduced dose of amphotericin B deoxycholate (mg/kg/day)

- Increased dose of amphotericin B deoxycholate and extended interval
- Supplement of electrolyte
- Hemodialysis
- Hydration
- Others (specify)

2.5 Cause of discontinuation of amphotericin B deoxycholate

- Completed treatment
- Changed to another systemic antifungal due to worsening clinical condition
- Occurred nephrotoxicity
- Death
- Refer

3. Data for assessed amphotericin B deoxycholate administered over 24 hours infusion

3.1 Primary outcome

- Nephrotoxicity

Incidence of amphotericin B deoxycholate induced nephrotoxicity were monitored of BUN, SCr, K, Mg during treatment per physicians in charge. SCr level were monotored at baseline and at least one time per week.

3.2 Secondary outcome

- Infusion-related reactions of amphotericin B deoxycholate were occurred with fever, chills/rigors, nausea/vomiting, phlebitis and any other infusion-related adverse reactions.
- Effectiveness were monitored of overall mortality, mortality due to invasive fungal infections and breakthrough fungaemia during treatment.

VIII. Data analysis

The data were analyzed by using SPSS 11.5.

The data were analyzed by descriptive statistics and inferential statistics by reported 95% confidence interval (95% CI) and set α=0.05.

1. Demographic characteristic of patients

Data were analyzed in term of gender, age and underlying illness.

2. Frequency of toxicity

- Data were analyzed in term of nephrotoxicity:
  - Number, percentage and 95% CI of patients with nephrotoxicity

- Data were analyzed in term of infusion-related adverse reactions:
  - Number, percentage and 95% CI of patients with fever
  - Number, percentage and 95% CI of patients with chills/rigors
  - Number, percentage and 95% CI of patients with nausea/vomiting
  - Number, percentage and 95% CI of patients with phlebitis

3. Frequency to assess clinical outcome

- Data were analyzed in term of overall mortality:
  - Number, percentage and 95% CI of overall mortality
- Data were analyzed in term of mortality due to invasive fungal infections:
  - Number, percentage and 95% CI of patients who died due to invasive fungal infections
- Data were analyzed in term of breakthrough fungaemia during treatment:
  - Number, percentage and 95% CI of patients who had breakthrough fungaemia during treatment

CHAPTER 4
RESULTS

The purpose of this observational study was to determine the incidence of nephrotoxicity, infusion-related adverse reactions and effectiveness due to administration of amphotericin B deoxycholate over 24-hour infusion. Fifty-three patients were included in the study. The results of this study were shown as follows:

I. Demographic characteristics of the patients

A total of 53 patients were studied. Patients' demographic data and clinical characteristics were shown in Table 12. Patients comprised of 31 male (58.5%) and 22 female (41.5%), with mean age of 41.74±14.99 years (range 17-74 years). The primary diagnosis were acute leukemia in 26 patients (49.1%), HIV/AIDS in 12 patients (22.6%), lymphoma in 5 patients (9.4%), chronic leukemia in 1 patient (1.9%), other hematologic diseases in 6 patients (11.3%) and other diseases in 3 patients (5.7%). Thirty patients (56.6%) received amphotericin B deoxycholate for empirical treatment. Proven baseline fungal infections were found in 23 patients (43.4%). Sites of fungal infection were central nervous system (CNS) in 10 patients (18.9%), lungs in 7 patients (13.2%), disseminated fungal infections in 6 patients (11.3%). The isolated fungal pathogens were *Cryptococcus neoformans* in 10 patients (18.9%), *Aspergillus* species in 7 patients (13.2%), *Penicillium maneffei* in 4 patients (7.5%), *Candida* species in 1 patient (1.9%) and *Histoplasma* species in 1 patient (1.9%). Concomitant use of nephrotoxic drugs were amikacin in 12 patients (22.6%) with mean dose of 656.82±138.79 mg/day (range 375-750 mg/day), vancomycin in 5 patients (9.4%) with mean dose of 1.63±0.48 g/day (range 1.00-2.00 g/day), amikacin and vancomycin in 5 patients (9.4%) with mean amikacin and vancomycin doses of

708.33±102.06 mg/day (range 500-750 mg/day) and 1.21±0.75 g/day (range 0.25-2.00 g/day) , respectively and cyclophosphamide 450 mg/day in 1 patient (1.9%).

Table 12: Demographic data and clinical characteristics of the study patients.

Characteristics	Number (%)
Gender	
Male	31 (58.5%)
Female	22 (41.5%)
Age (years)	
Range	17-74
Mean±S.D.	41.74±14.99
Median	38
Primary diagnosis	
Acute leukemia	26 (49.1%)
HIV/AIDS	12 (22.6%)
Lymphoma	5 (9.4%)
Chronic leukemia	1 (1.9%)
Other hematologic diseases [a]	6 (11.3%)
Other diseases [b]	3 (5.7%)
Indication for therapy	
Empirical therapy	30 (56.6%)
Documented infection	23 (43.4%)

[a] Aplatic anemia were in 5 patients and idiopathic myelofibrosis was in 1 patient.

[b] Diabetes mellitus, hypertension and nephrotic syndrome occurred, each in 1 patient.

Table 12: Demographic data and clinical characteristics of the study patients. (Continued)

Characteristics	Number (%)
Sites of fungal infection	
CNS	10 (18.9%)
Lungs	7 (13.2 %)
Disseminated fungal infections	6 (11.3 %)
No identified sites of fungal infection	30 (56.6 %)
Organisms	
Cryptococcus neoformans	10 (18.9%)
Aspergillus species	7 (13.2%)
Penicillium maneffei	4 (7.5%)
Candida species	1 (1.9%)
Histoplasma species	1 (1.9%)
No organisms identified	30 (56.6 %)
Concomitant use of nephrotoxic drugs	
Amikacin (mean 656.82±138.79 mg/day)	12 (22.6%)
Vancomycin (mean 1.63±0.48 g/day)	5 (9.4%)
Amikacin (mean708.33±102.06 mg/day) and vancomycin (mean 1.21±0.75 g/day)	5 (9.4%)
Cyclophosphamide (450 mg/day)	1 (1.9%)
No concomitant use of nephrotoxic drugs	30 (56.6 %)

II. Administration of amphotericin B deoxycholate

Data of amphotericin B deoxycholate administered over 24-hour infusion were shown in Table 13. Initial, subsequent and cumulative doses of amphotericin B deoxycholate were varied due to indications of therapy. The mean initial dose of amphotericin B deoxycholate was 0.74±0.16 mg/kg/day (range 0.50-1.21 mg/kg/day). The mean subsequent dose of amphotericin B deoxycholate was 0.80±0.16 mg/kg/day (range 0.50-1.21 mg/kg/day). The mean cumulative amphotericin B deoxycholate dose was 514.92±461.65 mg (range 100-2,960 mg). Total duration of administration averaged 11.81±7.76 days (range 2-39 days). Only five patients (9.4%) received sodium supplementation.

Table 13: Administration of amphotericin B deoxycholate over 24-hour infusion.

Administration of amphotericin B deoxycholate	Overall (n=53)
The initial dose (mg/kg/day)	
Range	0.50-1.21
Mean±S.D.	0.74±0.16
Median	0.70
The subsequent dose (mg/kg/day)	
Range	0.50-1.21
Mean±S.D.	0.80±0.16
Median	0.78
The cumulative dose (mg)	
Range	100-2,960
Mean±S.D.	514.92±461.65
Median	400

Table 13: Administration of amphotericin B deoxycholate over 24-hour infusion. (Continued)

Administration of amphotericin B deoxycholate	Overall (n=53)
Duration of amphotericin B deoxycholate therapy (days)	
Range	2-39
Mean±S.D.	11.81±7.76
Median	12

III. Laboratory values

Overall patients had mean BUN level of 16.08±15.04 mg/dl (range 4-73 mg/dl), mean SCr level of 0.84±0.38 mg/dl (range 0.40-2.40 mg/dl), mean potassium level of 3.35±0.66 mmol/L (range 1.80-4.90 mmol/L), mean magnesium level of 1.79±0.38 mg/dl (range 0.80-2.50 mg/dl) and mean sodium level of 133.96±5.99 mmol/L (range 124-153 mmol/L). At baseline, hypokalemia occurred in 26 patients (49.1%), hypomagnesemia occurred in 17 patients (32.1%) and hyponatremia occurred in 32 patients (60.4%). Laboratory values for patients in a study of amphotericin B deoxycholate administered over 24-hour infusion were shown in Table 14.

During amphotericin B deoxycholate treatment, mean maximal BUN level was 26.31±19.39 mg/dl (range 5-94 mg/dl), mean maximal SCr level was 1.24±0.59 mg/dl (range 0.60-2.70 mg/dl). Hypokalemia occurred in 44 patients (83.0%) and mean time to development of hypokalemia was 3.80±1.89 days (range 2-8 days). Hypomagnesemia occurred in 36 patients (67.9%) and mean time to development of hypomagnesemia was 7.58±4.96 days (range 2-20 days). Hyponatremia occurred in 38 patients (71.7%) and mean time to development of hyponatremia was 4.83±2.62 days (range 2-11 days).

At the end of amphotericin B deoxycholate therapy, mean BUN level was 23.30±19.71 mg/dl (range 5-94 mg/dl), mean SCr level was 1.14±0.56 mg/dl (range 0.30-2.70 mg/dl), mean potassium level was 3.50±0.86 mmol/L (range 1.70-5.80

mmol/L), mean magnesium level was 1.87±0.44 mg/dl (range 1.00-3.30 mg/dl) and mean sodium level was 135.19±5.79 mmol/L (range 121-149 mmol/L). Hypokalemia occurred in 27 patients (50.9%), hypomagnesemia occurred in 24 patients (45.3%) and hyponatremia occurred in 22 patients (41.5%). Minimum SCr level monitoring was 1 time/week. Mean SCr level monitoring was 2.94±1.28 times, 2.38±1.13 times, 2.00±0.85 times, 2.75±0.96 times and 1.50±0.71 times at week 1, 2, 3, 4 and 5, respectively.

Table 14: Laboratory values for patients in the study of amphotericin B deoxycholate administered over 24-hour infusion.

Values	Baseline	End of treatment
BUN level (mg/dl)		
Range	4-73	5-94
Mean±S.D.	16.08±15.04	23.30±19.71
Median	11	16
SCr level (mg/dl)		
Range	0.40-2.40	0.30-2.70
Mean±S.D.	0.84±0.38	1.14±0.56
Median	0.80	1.0
Hypokalemia, number (%)	26 (49.1%)	27 (50.9%)
Potassium level (mmol/L)		
Range	1.80-4.90	1.70-5.80
Mean±S.D.	3.35±0.66	3.50±0.86
Median	3.40	3.40

Table 14: Laboratory values for patients in the study of amphotericin B deoxycholate administered over 24-hour infusion. (Continued)

Values	Baseline	End of treatment
Hypomagnesemia, number (%)	17 (32.1%)	24 (45.3%)
Magnesium level (mg/dl)		
Range	0.80-2.50	1.00-3.30
Mean±S.D.	1.79±0.38	1.87±0.44
Median	1.80	1.80
Hyponatremia, number (%)	32 (60.4%)	22 (41.5%)
Sodium level (mmol/L)		
Range	124-153	121-149
Mean±S.D.	133.96±5.99	135.19±5.79
Median	133	136

IV. Adverse drug reaction and effectiveness

1. Nephrotoxicity of amphotericin B deoxycholate administered over 24-hour infusion.

Renal toxicity occurred in 11 out of 53 patients (20.8%). Table 15 summarized patients' demographic data and clinical characteristics of patients who developed nephrotoxicity. Patients comprised of 3 male (27.3%) and 8 female (72.7%), with mean age of 32.73±11.16 years (range 17-47 years). The primary diagnosis were acute leukemia in 9 patients (81.8%) and HIV/AIDS in 2 patients (18.2%). Eight patients (72.7%) received amphotericin B deoxycholate for empirical treatment. Proven baseline fungal infections were found in 3 patients (27.3%). Sites of fungal infection were CNS in 2 patients (18.2%) and disseminated fungal infections in 1 patient (9.1%). The isolated fungal pathogens were *Cryptococcus neoformans* in 2 patients (18.2%) and *Candida* species in 1 patient (9.1%). Concomitant use of

nephrotoxic drugs were amikacin in 3 patients (27.3%) with dose of 750 mg/day in all 3 patients, vancomycin in 2 patients (18.2%) with mean dose of 1.75±0.35 g/day (range 1.50-2.00 g/day), amikacin and vancomycin in 3 patients (27.3%) with amikacin dose of 750 mg/day in all 3 patients and vancomycin dose of with 1.08±0.88 g/day (range 0.25-2.00 g/day) and cyclophosphamide 450 mg/day in 1 patient (9.1%).

Table 15: Demographic data and clinical characteristics of patients occurred nephrotoxicity.

Characteristics	Number (%)	95 % CI
Gender		1.41-2.04
Male	3 (27.3%)	
Female	8 (72.7%)	
Age (years)		25.23-40.23
Range	17-47	
Mean±S.D.	32.73±11.16	
Median	33	
Primary diagnosis		1.55-2.09
Acute leukemia	9 (81.8%)	
HIV/AIDS	2 (18.2%)	
Indication for therapy		0.96-1.59
Empirical therapy	8 (72.7%)	
Documented infection	3 (27.3%)	
Sites of fungal infection		-0.20-2.20
CNS	2 (18.2%)	
Disseminated fungal infections	1 (9.1 %)	
No identified sites of fungal infection	8 (72.7 %)	

Table 15: Demographic data and clinical characteristics of patients occurred nephrotoxicity. (Continued)

Characteristics	Number (%)	95 % CI
Organisms		-0.17-1.45
Cryptococcus neoformans	2 (18.2%)	
Candida species	1 (9.1%)	
No organisms identified	8 (72.7 %)	
Concomitant use of nephrotoxic drugs		0.93-2.71
Amikacin (750 mg/day)	3 (27.3%)	
Vancomycin (mean 1.75±0.35 g/day)	2 (18.2%)	
Amikacin (750 mg/day) and vancomycin (mean 1.08±0.88 g/day)	3 (27.3%)	
Cyclophosphamide (450 mg/day)	1 (9.1%)	
No concomitant use of nephrotoxic drugs	2 (18.2 %)	

As presented in Table 16, the development of renal toxicity occurred in 11 out of 53 patients (20.8%). The mean time to development of nephrotoxicity was approximately 6.45±3.21 days (range 4-13 days). The mean initial dose of amphotericin B deoxycholate was 0.77±0.16 mg/kg/day (range 0.54-1.05 mg/kg/day). The mean subsequent dose of amphotericin B deoxycholate was 0.79±0.16 mg/kg/day (range 0.54-1.05 mg/kg/day). The mean cumulative amphotericin B deoxycholate dose was 399.09±150.16 mg (range 120-590 mg). An average total duration of amphotericin B deoxycholate therapy was 10.36±3.88 days (range 3-15 days).

Table 16: Nephrotoxicity of amphotericin B deoxycholate administered over 24-hour infusion.

Result	nephrotoxicity	95 % CI
Nephrotoxicity, number (%)	11 (20.8%)	0.09-0.32
Time to development of nephrotoxicity (days)		4.30-8.61
Range	4-13	
Mean±S.D.	6.45±3.21	
Median	5	
The initial dose (mg/kg/day)		0.66-0.87
Range	0.54-1.05	
Mean±S.D.	0.77±0.16	
Median	0.73	
The subsequent dose (mg/kg/day)		0.68-0.89
Range	0.54-1.05	
Mean±S.D.	0.79±0.16	
Median	0.77	
The cumulative dose (mg)		298.21-499.97
Range	120-590	
Mean±S.D.	399.09±150.16	
Median	420	

Table 16: Nephrotoxicity of amphotericin B deoxycholate administered over 24-hour infusion. (Continued)

Result	nephrotoxicity	95 % CI
Duration of amphotericin B deoxycholate therapy (days) Range Mean±S.D. Median	 3-15 10.36±3.88 12	7.76-12.97

At baseline of therapy, patients who developed nephrotoxicity had mean BUN level of 8.82±3.52 mg/dl (range 4-16 mg/dl), mean SCr level of 0.68±0.21 mg/dl (range 0.40-1.00 mg/dl), mean potassium level of 3.34±0.48 mmol/L (range 2.60-4.30 mmol/L), mean magnesium level of 1.77±0.47 mg/dl (range 1.10-2.50 mg/dl) and mean sodium level of 135.73±6.56 mmol/L (range 126-147 mmol/L). Hypokalemia occurred in 6 patients (54.5%), hypomagnesemia occurred in 4 patients (36.4%) and hyponatremia occurred in 5 patients (45.5%).

At detection of nephrotoxicity, mean BUN level was 16.00±8.67 mg/dl (range 8-40 mg/dl), mean SCr level was 1.57±0.56 mg/dl (range 0.90-2.50 mg/dl), mean potassium level was 3.26±1.43 mmol/L (range 1.90-5.80 mmol/L), mean magnesium level was 1.92±0.57 mg/dl (range 1.20-2.90 mg/dl) and mean sodium level was 131.55±6.04 mmol/L (range 121-145 mmol/L). Hypokalemia occurred in 8 patients (72.7%), hypomagnesemia occurred in 5 patients (45.5%) and hyponatremia occurred in 8 patients (72.7%).

At the end of amphotericin B deoxycholate therapy, mean BUN level was 17.09±12.41 mg/dl (range 6-42 mg/dl), mean SCr level was 1.51±0.56 mg/dl (range 0.80-2.60 mg/dl), mean potassium level was 3.25±1.14 mmol/L (range 1.70-5.80 mmol/L), mean magnesium level was 1.82±0.63 mg/dl (range 1.30-3.30 mg/dl) and mean sodium level was 133.20±7.01 mmol/L (range 121-146 mmol/L). Hypokalemia occurred in 6 patients (54.5%), hypomagnesemia occurred in 8 patients (72.7%) and hyponatremia occurred in 6 patients (54.5%). Laboratory values for patients with

nephrotoxicity in a study of amphotericin B deoxycholate administered over 24-hour infusion were presented in Table 17.

Table 17: Laboratory values for patients with nephrotoxicity in the study of amphotericin B deoxycholate administered over 24-hour infusion.

Result	Baseline	At detection of nephrotoxicity	End of treatment
BUN level (mg/dl)			
Range	4-16	8-40	6-42
Mean±S.D.	8.82±3.52	16.00±8.67	17.09±12.41
Median	8	16	12
SCr level (mg/dl)			
Range	0.40-1.00	0.90-2.50	0.80-2.60
Mean±S.D.	0.68±0.21	1.57±0.56	1.51±0.56
Median	0.70	1.70	1.40
Hypokalemia, number (%)	6 (54.5%)	8 (72.7%)	6 (54.5%)
Potassium level (mmol/L)			
Range	2.60-4.30	1.90-5.80	1.70-5.80
Mean±S.D.	3.34±0.48	3.26±1.43	3.25±1.14
Median	3.20	2.70	3.20
Hypomagnesemia, number(%)	4 (36.4%)	5 (45.5%)	8 (72.7%)
Magnesium level (mg/dl)			
Range	1.10-2.50	1.20-2.90	1.30-3.30
Mean±S.D.	1.77±0.47	1.92±0.57	1.82±0.63
Median	1.75	1.85	1.50

Table 17: Laboratory values for patients with nephrotoxicity in the study of amphotericin B deoxycholate administered over 24-hour infusion. (Continued)

Result	Baseline	At detection of nephrotoxicity	End of treatment
Hyponatremia , number (%)	5 (45.5%)	8 (72.7%)	6 (54.5%)
Sodium level (mmol/L)			
Range	126-147	121-145	121-146
Mean±S.D.	135.73±6.56	131.55±6.04	133.20±7.01
Median	135	130	133

Management of amphotericin B deoxycholate-induced nephrotoxicity were hydration and electrolyte supplementation in 9 patients (81.8%), decrease dose of amphotericin B deoxycholate from 0.93 mg/kg/day to 0.7 mg/kg/day in 1 patient (9.1%), decrease dose of amphotericin B deoxycholate from 0.73 mg/kg/day to 0.5 mg/kg/day with hydration and electrolyte supplementation in 1 patient (9.1%). No patient needed hemodialysis or discontinued amphotericin B deoxycholate therapy due to nephrotoxicity. Management of amphotericin B deoxycholate-induced nephrotoxicity were shown in Table 18.

Table 18: Management of amphotericin B deoxycholate-induced nephrotoxicity.

Management of nephrotoxicity	Number (%)
Hydration and electrolyte supplementation	9 (81.8%)
Decrease dose of amphotericin B deoxycholate	1 (9.1%)
Decrease dose of amphotericin B deoxycholate with hydration and electrolyte supplementation	1 (9.1%)

2. Infusion-related adverse reactions of amphotericin B deoxycholate administered over 24-hour infusion.

Prior to amphotericin B deoxycholate treatment, fever was noted in 48 patients (90.6%) and after amphotericin B deoxycholate administered over 24-hour infusion, fever was noted in 49 patients (92.5%). Fever in patients receiving amphotericin B deoxycholate administered over 24-hour infusion were displayed in Table 19. Chills or rigors were noted in 5 patients (9.4%). Mean time to development of chills or rigors was 4.20±3.56 days (range 1-10 days). Nausea or vomiting were noted in 5 patients (9.4%) and mean time to development of nausea or vomiting was 3.40±2.19 days (range 2-7 days). Phlebitis was noted in 11 patients (20.8%) and mean time to development of phlebitis was 6.64±3.38 days (range 2-13 days). Three patients (5.7%) were alter amphotericin B deoxycholate infusion times over 24 hours to infused over 4 or 6 hours because phlebitis. Infusion-related adverse reactions of amphotericin B deoxycholate were summarized in Table 20.

Table 19: Fever in patients receiving amphotericin B deoxycholate administered over 24-hour infusion.

Result	Pre-administration number (%)	After-admintration number (%)
Fever	48 (90.6%)	49 (92.5%)

Table 20: Infusion-related adverse reactions in patients receiving amphotericin B deoxycholate administered over 24-hour infusion.

Result	Infusion-related adverse reactions	95 % CI
Chills/rigors, number (%)	5 (9.4%)	0.01-0.18
Time to development of chills/rigors (days)		-0.22-8.62
Range	1-10	
Mean±S.D.	4.20±3.56	
Median	3	
Nausea/vomiting, number (%)	5 (9.4 %)	0.01-0.18
Time to development of nausea/vomiting (days)		0.68-6.12
Range	2-7	
Mean±S.D.	3.40±2.19	
Median	2	
Phlebitis, number (%)	11 (20.8%)	0.09-0.32
Time to development of phlebitis (days)		4.36-8.91
Range	2-13	
Mean±S.D.	6.64±3.38	
Median	6	

3. Effectiveness of amphotericin B deoxycholate administered over 24-hour infusion.

Overall mortality rate during amphotericin B deoxycholate was 28.3% (15 patients), 10 male (66.7%) and 5 female (33.3%). Mean age was 47.07±18.12 years (range 27-74 years). The primary diagnosis were acute leukemia in 7 patients (46.7%), HIV/AIDS in 3 patients (20.0%), lymphoma in 3 patients (20.0%) and other hematologic diseases in 2 patients (13.3%). Eight patients (53.3%) received amphotericin B deoxycholate for empirical treatment. Proven baseline fungal infections were found in 7 patients (46.7%). Sites of fungal infection were CNS in 2 patients (13.3%), lungs in 4 patients (26.7%), disseminated fungal infections in 1 patient (6.7%). The isolated fungal pathogens were *Cryptococcus neoformans* in 2 patients (13.3%), *Aspergillus* species in 4 patients (26.7%) and *Histoplasma* species in 1 patient (6.7%). Concomitant use of nephrotoxic drugs were amikacin in 4 patients (26.7%), vancomycin in 2 patients (13.3%), amikacin and vancomycin in 2 patients (13.3%). Demographic data and clinical characteristics of dead patients were summarized in Table 21.

Table 21: Demographic data and clinical characteristics of dead patients.

Characteristics	Number (%)
Gender	
Male	10 (66.7%)
Female	5 (33.3%)
Age (years)	
Range	27-74
Mean±S.D.	47.07±18.12
Median	39

Table 21: Demographic data and clinical characteristics of dead patients. (Continued)

Characteristics	Number (%)
Primary diagnosis	
Acute leukemia	7 (46.7%)
HIV/AIDS	3 (20.0%)
Lymphoma	3 (20.0%)
Other hematologic diseases [a]	2 (13.3%)
Indication for therapy	
Empirical therapy	8 (53.3%)
Documented infection	7 (46.7%)
Sites of fungal infection	
CNS	2 (13.3%)
Lungs	4 (26.7 %)
Disseminated fungal infections	1 (6.7 %)
No identified sites of fungal infection	8 (53.3%)
Organisms	
Cryptococcus neoformans	2 (13.3%)
Aspergillus species	4 (26.7%)
Histoplasma species	1 (6.7%)
No organisms identified	8 (53.3 %)
Concomitant use of nephrotoxic drugs	
Amikacin	4 (26.7%)
Vancomycin	2 (13.3%)
Amikacin and vancomycin	2 (13.3%)
No concomitant use of nephrotoxic drugs	7 (46.7 %)

[a] Aplatic anemia was in 1 patient and idiopathic myelofibrosis was in 1 patient.

The mean initial dose of amphotericin B deoxycholate was 0.74±0.16 mg/kg/day (range 0.50-1.00 mg/kg/day). The mean subsequent dose of amphotericin B deoxycholate was 0.82±0.17 mg/kg/day (range 0.50-1.05 mg/kg/day). The mean cumulative amphotericin B deoxycholate dose was 432.33±405.18 mg (range 100-1,550 mg). Total duration of administration averaged 9.47±8.25 days (range 2-31 days). Administration of amphotericin B deoxycholate over 24-hour infusion in dead patients were shown in Table 22.

Table 22: Administration of amphotericin B deoxycholate over 24-hour infusion in dead patients.

Administration of amphotericin B deoxycholate	Overall (n=15)
The initial dose (mg/kg/day)	
Range	0.50-1.00
Mean±S.D.	0.74±0.16
Median	0.73
The subsequent dose (mg/kg/day)	
Range	0.50-1.05
Mean±S.D.	0.82±0.17
Median	0.85
The cumulative dose (mg)	
Range	100-1,550
Mean±S.D.	432.33±405.18
Median	250

Table 22: Administration of amphotericin B deoxycholate over 24-hour infusion in dead patients. (Continued)

Administration of amphotericin B deoxycholate	Overall (n=15)
Duration of amphotericin B deoxycholate therapy (days)	
Range	2-31
Mean±S.D.	9.47±8.25
Median	6

As presented in Table 23, patients' death due to fungal infection occurred in 2 patients (3.8%) and death from other causes in 13 patients (24.5%). Both patients who died due to fungal infection received amphotericin B deoxycholate for treatment pulmonary aspergillosis. Case 1, patient had underlying disease with lymphoma, received initial dose of amphotericin B deoxycholate 25 mg/day (0.5 mg/kg/day) for 2 days and had subsequent dose for 50 mg/day (1 mg/kg/day). The total amphotericin B deoxycholate dose was 150 mg. Case 2, patient had underlying disease with acute leukemia. Patient received initial dose of amphotericin B deoxycholate 30 mg/day (0.75 mg/kg/day) on first day and had subsequent dose for 40 mg/day (1 mg/kg/day). The total amphotericin B deoxycholate dose was 270 mg.

Three patients who had underlying disease with HIV died. First case found disseminated fungal infections. Treatment of amphotericin B deoxycholate for proven *Candida* species. The total dose of amphotericin B deoxycholate was 100 mg and duration of treatment was 2 days. Patient died from empyema thoracic and septicemia. Case 2, *Cryptococcus neoformans* was identified from CSF. Amphotericin B deoxycholate was administered 0.85 mg/kg/day. The total dose of amphotericin B deoxycholate was 120 mg and duration of treatment was 3 days. This patient died from cerebral toxoplasmosis. Case 3, *Cryptococcus neoformans* was identified from CSF. Amphotericin B deoxycholate was administered 1.00 mg/kg/day. The total amphotericin B deoxycholate dose was 1,550 mg and duration of treatment was 31 days. Result of CSF was improved. Patient died from bacterial meningitis. None of patient had breakthrough fungaemia during treatment.

Other 10 dead patients, 6 patients had underlying disease with acute leukemia, 2 patients had underlying disease with lymphoma and 2 patients had underlying disease with other hematologic disease.

Table 23: Mortality in patients during treatment with 24-hour infusion of amphotericin B deoxycholate.

Characteristics	Number of patients (%)	95 % CI
Mortality:		
Overall	15 (28.3%)	1.59-1.84
Death due to invasive fungal infections	2 (3.8%)	1.67-2.06
Death from other causes [a]	13 (24.5%)	0.94-1.33

[a] Acute leukemia with septicemia were in 3 patients, septicemia due to other gram negative organisms were in 2 patients and septicemia due to *Hemophilus influenzae*, septicaemia with empyema thoracic, septicemia with severe pneumonia, septicaemia with *Klebsiella pneumoniae*, septicemia with Methicillin-resistant *Staphylococcus aureus* (MRSA), idiopathic aplastic anemia with septicemia, cerebral toxoplasmosis, bacterial meningitis, each in 1 patient.

CHAPTER 5
DISCUSSION

The incidence of fungal infections have been increasing, amphotericin B deoxycholate has been a mainstay of antifungal therapy for over 40 years and still be the 'gold standard' for life-threatening fungal infections because of its broad spectrum of activity. Nephrotoxicity is the main problem leading to dose reduction which subsequently leads to treatment failure. (1-18)

Accordingly, this present study was performed at internal medicine wards, Asdang building, Siriraj Hospital, Mahidol University to determine the incidence of nephrotoxicity, infusion-related adverse reactions and effectiveness due to administration of amphotericin B deoxycholate over 24 hours.

I. Demographic characteristics of the patients

Demographic data and clinical characteristics of patients in the previous 24-hour infusion of amphotericin B deoxycholate studies and the present study were summarized in Table 24. In the present study, patients were young then they were likely to have low incidence of nephrotoxicity and high survival rate. Age of patients in the present study were comparable with the previous 24-hour infusion of amphotericin B deoxycholate studies (98, 100, 102) but they were younger than the patients in Imhof et al. (101) study. Therefore, the patients in the present study should have lower incidence of nephrotoxicity and mortality rate than ones in Imhof's study.

Table 24: Demographic data and clinical characteristics of patients in the previous 24-hour infusion of amphotericin B deoxycholate studies compared with the present study.

Characteristics Number (%)	Eriksson et al. (98)	Furrer et al. (100)	Imhof et al. (101)	Peleg and woods (102)	Present study
Age (years)					
Range	17-74	18-54	15.8-70.3		17-74
Mean±S.D.		33.63±9.16		49±14	41.7±14.99
Median	47		54.4		38
Primary diagnosis					
Acute leukemia	30 (76%)	16 (73%)	27 (81.8%)	23 (59%)	26 (49.1%)
HIV/AIDS	2 (5%)		2 (6.1%)		12 (22.6%)
Indication for therapy					
Proven fungal infection	7 (17.5%)		9 (27.3%)	9 (23.1%)	23 (43.4%)
Concomitant use of nephrotoxic drugs					
Amikacin	22 (55%)			25 (64%)	12 (22.6%)
Vancomycin	11 (28%)	11 (50%)	7 (21.2%)	28 (72%)	5 (9.4%)
Amikacin and Vancomycin					5 (9.4%)
Cyclosporine		22 (100%)	2 (6.1%)		
Cyclophosphamide					1 (1.9%)

In the present study, most frequent diagnosis was acute leukemia which was similar to the previous 24-hour infusion of amphotericin B deoxycholate studies as mentioned above. (98, 100-102) Acute leukemia increased risk of nephrotoxicity because the patients had several drugs used for febrile neutropenia such as vancomycin. By contrast, the present study had patients with HIV/AIDS more than ones in the previous 24-hour infusion of amphotericin B deoxycholate studies. (98, 101) Nephrotoxicity rate in the present study may be greater than the previous studies because the patients with HIV/AIDS needed high dose of amphotericin B deoxycholate for treatment of cryptococcosis. Considering effectiveness, the majority of our patients had acute leukemia and used amphotericin B deoxycholate for febrile neutropenia, then they should have low risk of mortality compared to ones with aspergillosis. However, the present study also comprise of 7 patients with aspergillosis.

The current study had percentage of patients with proven baseline fungal infections more than ones in the previous 24-hour infusion of amphotericin B deoxycholate studies as mention above (98, 101, 102) then the patients in the current study was likely to have worse prognosis than ones in previous 24-hour infusion studies.

Among previous conventional administration of amphotericin B deoxycholate studies, concomitant use of nephrotoxics drugs had various results for risk of amphotericin B deoxycholate-induced nephrotoxicity. Harbarth et al. (55) found that use of cyclosporine or amikacin increased the risk of amphotericin B deoxycholate-induced nephrotoxicity, concomitant use of cyclosporine had hazard ratio (HR) of 2.4 (95%CI, 1.3-4.3) or amikacin had HR of 4.8 (95%CI, 1.7-13.7). Whereas use of vancomycin was not on independent variable of renal toxicity. Bates et al. (56) reported in multivariate analyses, concomitamt use of cyclosporine had odds ratio (OR) of 2.6 (95%CI, 1.5-4.8). Gubbins et al. (57) showed that concomitant cyclosporine treatment associated with amphotericin B deoxycholate-induced nephrotoxicity (OR=11.6, 95%CI, 1.91-71.0, p=0.008). By contrast, Zager et al. (60) reported neither aminoglycosides, vancomycin nor cyclosporine use were associated with development of acute renal failure. In addition, Fisher et al. (61) showed that

aminoglycosides, vancomycin were not correlated with development of nephrotoxicity in their study.

The current study had lower percentage of patients who concomitantly used nephrotoxics drugs than ones in the studies by Eriksson et al. (98), Furrer et al. (100) and Peleg and Woods (102) then the patients in the present study was likely to have lower incidence of nephrotoxicity than ones in the previous studies (98, 100, 102). By contrast, the patients in the current study had concomitant use of nephrotoxics drugs more than ones in the study by Imhof et al. (101) then the patients in the present study was likely to have high incidence of nephrotoxicity than ones in Imhof's study.

In summary, taken into the considering of demographic characteristics of the patients in the present study, the patients were young. However, they still had risk of nephrotoxicity because 23 patients (43.3%) concomitantly used nephrotoxic drugs. Furthermore, the patients with HIV/AIDS needed high dose of amphotericin B deoxycholate. Patients had defect of immunes'system and 23 patients (43.4%) had proven baseline fungal infections which may lead to high mortality rate.

II. Administration of amphotericin B deoxycholate

Administration of amphotericin B deoxycholate in the previous 24-hour infusion of studies and the present study were shown in Table 25. In the present study, the mean initial and subsequent doses of amphotericin B deoxycholate were therapeutic dose for fungal infection but less than the previous 24-hour infusion of amphotericin B deoxycholate studies (98, 100, 101) then the patients in the present study was likely to have lower incidence of nephrotoxicity than ones in the previous studies. (98, 100, 101) However, these initial and subsequent doses of amphotericin B deoxycholate were too low for treatment of aspergillosis which placed them at high risk of treatment failure and was likely to have higher mortality rate than ones in the previous studies. (98, 100, 101)

Table 25: Administration of amphotericin B deoxycholate in the previous 24-hour infusion studies compared with the present study.

Administration	Eriksson et al. (98)	Furrer et al. (100)	Imhof et al. (101)	Peleg and woods (102)	Present study
Dose (mg/kg/day)					Subsequent:
Range	0.5-1.5	0.6-2.0	1.41-2.28		0.50-1.21
Mean±S.D.		1.03±0.37		0.79±0.2	0.80±0.16
Median	0.96		1.72		0.78
Cumulative (mg)					
Range	1.8-89.0	378-2,655	370-7,995		100-2,960
Mean±S.D.		1,181±677			514.92±461.65
Median	14.3 mg/kg		2,245		400
Duration (days)					
Range	3-89	3-112	7-72		2-39
Mean±S.D.		22.3±22.6			11.81±7.76
Median	16		22	10.0±6.7	12

The mean cumulative amphotericin B deoxycholate dose in the present study was less than the previous 24-hour infusion of amphotericin B deoxycholate studies (100, 101) that was likely to have lower incidence of nephrotoxicity than ones in the previous 24-hour infusion of amphotericin B deoxycholate studies. (100, 101) However, cumulative amphotericin B deoxycholate dose in the present study was consistent with the previous conventional administration of amphotericin B deoxycholate studies which were observed nephrotoxicity. As shown in Table 26.

Table 26: The cumulative dose and duration of amphotericin B deoxycholate in the previous conventional infusion studies which were observed nephrotoxicity.

Studies	Cumulative dose (mg)	duration of therapy (days)
Pathak et al. (54)	mean 162.50 (range 10-840)	8.3 (range 1-46)
Gubbins et al. (57)	median 286 (range 330-2,440)	12.5 (range 2-71)
Bowden et al. (79)	median 857 (range 55-6,271)	14.5 (range 1-87)
Leenders et al. (82)	median 850 (range 216-3,836)	13 (range 3-76)
Sorkine et al. (88)	mean 535 (range 226-873)	12 (range 6.2-18)

The previous conventional administration of amphotericin B deoxycholate studies showed duration of amphotericin B deoxycholate which were occurred nephrotoxicity. (Table 26) Total duration of amphotericin B deoxycholate tharapy in the present study was similar with Peleg and Woods (102) study but less than the other previous 24-hour infusion of amphotericin B deoxycholate studies (98, 100, 101) which may lead to lower incidence of nephrotoxicity than ones in the studies by Eriksson et al. (98), Furrer et al. (100) and Imhof et al. (101). However, total duration of amphotericin B deoxycholate tharapy in the present study was consistent with the previous conventional administration of amphotericin B deoxycholate studies which were found nephrotoxicity. (54, 57, 79, 82, 88)

Branch (64) recommended to reduce the risk of amphotericin B deoxycholate-induced renal impairment by assessing patients' sodium status. Previous studies (65-68) showed that salt supplementation reduced risk of amphotericin B deoxycholate-induced nephrotoxicity. Feely et al. (65) reported 2 patients who had nephrotoxicity after a short time on moderate dose of amphotericin B deoxycholate-associated with salt depletion. Heidemann et al. (66) reported cases of amphotericin B deoxycholate nephrotoxicity decreased by salt repletion. Stein and Alexander (67) reported sodium

protected against nephrotoxicity in neutropenic patients receiving amphotericin B deoxycholate. Llanos et al. (68) studied effect of salt supplementation on amphotericin B deoxycholate nephrotoxicity, the mean SCr level remained over time during amphotericin B deoxycholate therapy. Among previous 24-hour infusion of amphotericin B deoxycholate studies (98-102), the patients received infusion of saline as standard care to reduce the risk of nephrotoxicity. Only 5 patients (9.4%) in the present study received sodium supplementation. Saline infusion was not a standard of care in the present study, therefore, it might place risk of nephrotoxicity.

Conclusively, in the present study, mean initial and subsequent doses were in therapeutic range of fungal infection. However, the patients who received amphotericin B deoxycholate for treatment of aspergillosis might be a risk of treatment failure and likely had high mortality rate since these initial and subsequent doses of amphotericin B deoxycholate were too low. Mean cumulative amphotericin B deoxycholate dose was not high and duration of treatment was not long then the patients in the present study should have low incidence of nephrotoxicity. However, cumulative amphotericin B deoxycholate dose and duration of amphotericin B deoxycholate therapy in the current study still had the potential of inducing nephrotoxicity. Furthermore, saline infusion was not a standard of care in the present study, then it might place risk of amphotericin B deoxycholate-induced nephrotoxicity.

III. Laboratory values

The mean baseline SCr levels of overall patients was similar to the previous 24-hour infusion of amphotericin B deoxycholate studies. Laboratory values for patients in the previous 24-hour infusion of amphotericin B deoxycholate studies and the present study were summarized in Table 27. During amphotericin B deoxycholate treatment in the present study, mean BUN and SCr levels increased and at the end of amphotericin B deoxycholate therapy, mean BUN level increased to 23.30±19.71 mg/dl (range 5-94 mg/dl) and mean SCr level increased to 1.14±0.56 mg/dl (range 0.30-2.70 mg/dl). Consistent with Furrer et al. (100) reported, mean SCr level at the

end of amphotericin B deoxycholate therapy increased to 135.5±52.8 µg/dl (range 59-282 µg/dl).

Table 27: Laboratory values for patients in the previous 24-hour infusion of amphotericin B deoxycholate studies compared with the present study.

Laboratory values	Eriksson et al. (98)	Furrer et al. (100)	Imhof et al. (101)	Peleg and woods (102)	Present study
Baseline SCr level	µmol/L	µg/ml	µM	µmol/L	mg/dl
Range	54-165	52-177	44-95		0.4-2.4
Mean±S.D.		83.7±27.5		73±32	0.84±0.38
Median	78		63		0.80
Electrolye imbalance during treatment					
Hypokalemia	4 (10%)				44 (83%)
Hypomagnesemia	17 (43%)				36 (67.9%)
Hyponatremia					38 (71.7 %)
Hypernatremia	2 (5%)				

The patients in the present study had electrolytes imbalance prior to amphotericin B deoxycholate treatment, hypokalemia occurred in 26 patients (49.1%), hypomagnesemia occurred in 17 patients (32.1%) and hyponatremia occurred in 32 patients (60.4%). The patients with hyponatremia in the present study should have nephrotoxicity. Consistent with the previous studies by Feely et al. (65), Heidemann et al. (66) and Stein and Alexander (67) showed that hyponatremia might be a risk of amphotericin B deoxycholate-induced nephrotoxicity.

During amphotericin B deoxycholate therapy, electrolytes imbalance were increased. Hypokalemia occurred in 44 patients (83.0%), hypomagnesemia occurred

in 36 patients (67.9%) and hyponatremia occurred in 38 patients (71.7%) that might be resulted from amphotericin B deoxycholate-induced direct toxic effect on renal tubular cells and enhanced membrane permeability with subsequent intracellular and tubular loss of electrolytes. Previous studies showed that electrolytes imbalance were noted during amphotericin B deoxycholate therapy. Bowden et al. (79) found that hypokalemia occurred in 20 patients (23.3%) and hypomagnesemia occurred in 12 patients (14%). Nucci et al. (92) reported hypokalemia occurred in 19 patients (58%). Subira et al. (76) found hypokalemia occurred in 18 patients (32%). Among previous 24-hour infusion of amphotericin B deoxycholate study, Eriksson et al. (98) found hypokalemia occurred in 4 patients (10%) and hypomagnesemia was observed in 17 patients (43%). Furthermore, Eriksson et al. (98) found hypernatremia occurred in 2 patients (5%) and none of the patient had hyponatremia. In the present study, hyponatremia were found more than ones in the Eriksson's study that may contribute to more nephrotoxic patients than ones in Eriksson's study.

IV. Adverse drug reaction and effectiveness

1. Nephrotoxicity of amphotericin B deoxycholate administered over 24-hour infusion.

The total of 11 nephrotoxic patients were young (mean age 32.73±11.16 years) and most indication for therapy was empirical therapy but they still had risk of nephrotoxicity because 9 patients (81.8%) were acute leukemia and all of these patients were concomitantly used with nephrotoxic drugs. Two patients (18.2%) were HIV/AIDS and they received amphotericin B deoxycholate therapy with high dose for treatment of *Cryptococcus neoformans*.

Although, initial and subsequent doses of amphotericin B deoxycholate in the present study were therapeutic dose for fungal infection (mean 0.77±0.16 mg/kg/day and 0.79±0.16 mg/kg/day, respectively), cumulative dose of amphotericin B deoxycholate was not high (mean 399.09±150.16 mg) and total duration of amphotericin B deoxycholate therapy was not long (mean 10.36±3.88 days) but

cumulative dose and total duration of amphotericin B deoxycholate therapy in the current study still had the potential of inducing nephrotoxicity according to the previous studies. (54, 57, 79, 82, 88)

At baseline, mean SCr level of the nephrotoxic patients was 0.68±0.21 mg/dl (range 0.40-1.00 mg/dl). These SCr levels were within normal SCr level but electrolytes imbalance were observed prior to amphotericin B deoxycholate treatment. At detection of nephrotoxicity, the number of nephrotoxic patients with electrolytes imbalance were increased, hypokalemia occurred in 8 patients (72.7%), hypomagnesemia occurred in 5 patients (45.5%) and hyponatremia occurred in 8 patients (72.7%). Mean sodium level was 131.55±6.04 mmol/L. Hyponatremia in the present study might have the potential of inducing nephrotoxicity, as has been shown in the previous studies by Feely et al. (65), Heidemann et al. (66) and Stein and Alexander (67).

As shown in Table 28, nephrotoxicity may occurred during early treatment with amphotericin B deoxycholate. The mean time to development of nephrotoxicity in the present study was 6.45±3.21 days (range 4-13 days). This result was similar to the previous studies.

Table 28: Time to development of nephrotoxicity in the previous conventional infusion studies.

Studies	Time to development of nephrotoxicity
Wingard et al. (58)	7 days
Zager et al. (60)	6.6±0.8 days
Fisher et al. (61)	2-3 days
Gubbins et al. (57)	6.0±4.8 days (range 1-22)
Moreau et al. (91)	7 days (range 4-13)

The present study illustrated that nephrotoxicity occurred in 11 out of 53 patients (20.8%). Incidence of amphotericin B deoxycholate-induced nephrotoxicity in the present study was noted to be less than ones in the previous standard infusion (4 or 6 hours) and the rapid infusion of amphotericin B deoxycholate studies.

Among previous 24-hour infusion of amphotericin B deoxycholate studies, Eriksson et al. (98) found nephrotoxicity occurred in 6 of 40 patients (15%), Speich et al. (99) showed nephrotoxicity occurred in 1 of 6 patients with lung transplant (16%), Imhof et al. (101) found overall nephrotoxicity occurred in 5 of 33 patients (15%) and Peleg and Woods (102) reported nephrotoxicity occurred in 4 of 39 patients (10%).

Incidence of nephrotoxicity in the present study was greater than the previous 24-hour infusion of amphotericin B deoxycholate studies (98-102) that might be resulted from baseline hyponatremia and no saline infusion in the present study.

In the present study, the management of amphotericin B deoxycholate-induced nephrotoxicity were hydration and electrolyte supplement in 9 patients (81.8%), decrease dose of amphotericin B deoxycholate in 1 patient (9.1%) and decrease dose of amphotericin B deoxycholate with hydration and electrolyte supplementation in 1 patient (9.1%). None of the patient needed hemodialysis or discontinued amphotericin B deoxycholate therapy due to nephrotoxicity. In contrast with the previous standard infusion (4 or 6 hours) and the rapid infusion of amphotericin B deoxycholate studies. Bowden et al. (79) showed discontiuation of amphotericin B deoxycholate because renal toxicity occurred in 16 of 86 patients (18.6%). Caillot et al. (90) reported that amphotericin B deoxycholate treatment was discontinued in 4 of 21 patients (19%) resulted from renal toxicity. Subira et al. (76) found renal toxicity led to amphotericin B deoxycholate discontinuation in 9 of 56 patients (16%) and hemodialysis was required in 1 of 56 patients (1.8%). Leenders et al. (82) found 18 patients was temporarily discontinued or lowered in dose due to increase of SCr level.

The present result correlated with the previous amphotericin B deoxycholate 24-hour infusion studies. Imhof et al. (101) and Peleg and Woods (102) showed that none of the patient required hemodialysis. Amphotericin B deoxycholate 24-hour infusion had low incidence of nephrotoxicity and well tolerable worsening of renal function.

2. Infusion-related adverse reactions of amphotericin B deoxycholate administered over 24-hour infusion.

Prior to amphotericin B deoxycholate treatment, fever was observed in 48 of 53 patients (90.6%) and after amphotericin B deoxycholate administered over 24-hour infusion, fever was noted in 49 of 53 patients (92.5%). The previous standard infusion (4 or 6 hours) and the rapid infusion of amphotericin B deoxycholate studies had various results of fever. The previous 24-hour infusion of amphotericin B deoxycholate studies, Eriksson et al. (98) found fever on day 1 was noted in 10 of 40 patients (25%) and fever within 24 hours before treament was documented for 22 of 40 patients (55%). Imhof et al. (101) found a febrile reaction was observed during treatment in 1 of 33 patient. (3%).

Patients with fever on day 1 in the present study were noted to be greater than ones in the previous studies that may be a result from most patients had fever prior to amphotericin B deoxycholate treatment and response to antifungal agent needed time. Therefore, patients who received first dose of amphotericin B deoxycholate therapy still had fever that may interfere the real incidence of fever-related amphotericin B deoxycholate administered over 24-hour infusion in the present study.

In the present study, chills/rigors in the present study were noted in 5 of 53 patients (9.4%) and nausea/vomiting were in 5 of 53 patients (9.4%). The present study showed that chills/rigors and nausea/vomiting were noted to be less than ones in the standard infusion (4 or 6 hours) and the rapid infusion of amphotericin B deoxycholate studies. Furthermore, the present study showed chills/rigors and nausea/vomiting were noted to be less than ones in the previous 24-hour infusion of amphotericin B deoxycholate studies. (98, 101)

Phlebitis in the present study was noted in 11 of 53 patients (20.8%). Among previous conventional administration of amphotericin B deoxycholate study by Goodwin et al. (48) found phlebitis occurred in 20 of 397 patients (5%). Goodwin et al. (48) study was observed phlebitis less frequent than ones in this present study. However, the study by Goodwin et al. found that 45.1% of patients received amphotericin B deoxycholate through peripheral lines and 53.4% of patients received amphotericin B deoxycholate through central venous catheters and patients were

monitored for only the first 7 days of therapy. No previous 24-hour infusion of amphotericin B deoxycholate study reported incidence of phlebitis.

Although, the exact mechanism of infusion-related adverse reactions of amphotericin B deoxycholate was not known. Amphotericin B deoxycholate was a trigger of proinflammatory response by activating different cytokines. Continuous infusions may be better tolerated because of delayed induction or release of mediators. The previous 24-hour infusion of amphotericin B deoxycholate studies showed that infusion-related adverse reactions of amphotericin B deoxycholate administered well tolerance than ones in the standard infusion (4 or 6 hours) and the rapid infusion of amphotericin B deoxycholate studies. This result was confirmed by the present study. Furthermore, the present study reported few chills/rigors and nausea/vomiting than ones in Eriksson et al. (98) and Imhof et al. (101) studies. These might be resulted from the previous 24-hour infusion of amphotericin B deoxycholate studies which had higher median daily dose and duration of amphotericin B deoxycholate treatment longer than the present study.

3. Effectiveness of amphotericin B deoxycholate administered over 24-hour infusion.

During of amphotericin B deoxycholate therapy, 15 patients death. Although, dead patients were young (mean 47.07±18.12 years) but 6 of them (40%) were ≥ 60 years. Furthermore, the patients had comorbidity with defect of immunes's system and had severe diseases. Four dead patients (26.7%) received amphotericin B deoxycholate for pulmonary aspergillosis, 2 dead patients (13.3%) were cryptococcosis and 1 dead patient (6.7%) was disseminated fungal infections.

Overall mortality rate during amphotericin B deoxycholate in the present study was 28.3% (15 out of 53 patients). Only 2 patient died (3.8%) due to fungal infection, while 13 patients (24.5%) died from other causes.

In the present study, dead patients were less than ones in the previous standard infusion (4 or 6 hours) and the rapid infusion of amphotericin B deoxycholate studies. Although, mortality rate in the present study was greater than the previous 24-hour infusion of amphotericin B deoxycholate studies that might be resulted from the

patients in the previous 24-hour infusion of amphotericin B deoxycholate studies (98, 100, 101) received high median daily amphotericin B deoxycholate dose more than ones in the present study. Furthermore, the patients with proven fungal infection in the present study were more than ones in the previous 24-hour infusion of amphotericin B deoxycholate studies. (98, 101, 102) Proven baseline fungal infections in the present study were found in 23 of 53 patients (43.4%), while the previous 24-hour infusion of amphotericin B deoxycholate studies by Eriksson et al. (98), Imhof et al. (101) and Peleg and Woods (102) showed that proven baseline fungal infections were found in 7 of 40 patients (17.5%), 9 of 33 patients (27.3%) and 9 of 39 patients (23.1%), respectively. However, only 2 dead patients in the present study was proven to be cause by fungal infection.

None of patient had breakthrough fungaemia during treatment in the present study. Among previous conventional administration of amphotericin B deoxycholate study, Walsh et al. (83) found breakthrough fungal infection occurred in 27 patients (7.8%) who received amphotericin B deoxycholate 0.6 mg/kg/day for empirical therapy in persistent febrile neutropenic patients. The result in the present study was similar to the previous 24-hour infusion of amphotericin B deoxycholate studies, Eriksson et al. (98) reported breakthrough fungaemia was not occurred in any patient during treatment.

Today, the pharmacokinetics and pharmacodynamics of amphotericin B deoxycholate were not completely understood. Serum levels following intravenous administration of amphotericin B deoxycholate may be related to dose, frequency and rate of infusion. Therapeutic amphotericin B deoxycholate concentration was 0.5-2 μg/ml. Chabot et al. (97) reported pharmacokinetics of amphotericin B deoxycholate. The 24-hour continuous infusion amphotericin B deoxycholate was started at the indicated doses (0.5-0.8 mg/kg/day). The continuous infusion amphotericin B deoxycholate over the period from 52 to 120 hours maintained a plateau plasma concentration from 0.7-1.9 μg/ml for total doses ranging from 1-3.7 mg/kg. Potentially effective plateau plasma concentrations of continuous amphotericin B deoxycholate infusion were attained within 1 day and maintained within the antifungal pharmacological range (0.5-2 μg/ml) throughout the infusion time. Highest concentrations of amphotericin B deoxycholate were detected in the liver and spleen,

high concentrations were found in the kidneys and lungs. (35) CSF concentrations of amphotericin B deoxycholate are approximately 2%-4% of concurrent serum concentrations after intravenous administration. (19-22)

The previous 24-hour infusion of amphotericin B deoxycholate studies showed that 24-hour infusion of amphotericin B deoxycholate may be at least as effective as the standard infusion and supported by the present study. The present study found hematologic with febrile neutropenia and HIV with cryptococcosis patients were well effective. Although, the patients with pulmonary aspergillosis still had high mortality rate and 2 patients died due to pulmonary aspergillosis. Therefore, 24-hour infusion of amphotericin B deoxycholate may be appropriate in hematologic with febrile neutropenia and HIV with cryptococcosis patients. Treatment of aspergillosis with 24-hour infusion of amphotericin B deoxycholate still need further studies.

CHAPTER 6
CONCLUSION

A total of 53 patients were studied. The development of renal toxicity occurred in 11 of 53 patients (20.8%). The mean time to development of nephrotoxicity was approximately 6.45±3.21 days (range 4-13 days). No patient needed hemodialysis or discontinued amphotericin B deoxycholate therapy due to nephrotoxicity. Amphotericin B deoxycholate administered 24-hour infusion in the present study had low incidence of nephrotoxicity and well tolerable worsening of renal function. However, saline infusion was importance to reduce amphotericin B deoxycholate-induced nephrotoxicity. Infusion-related adverse reactions of amphotericin B deoxycholate administered over 24-hour infusion in the present study were well tolerated, chills/rigors and nausea/vomiting were noted to be low incidence. Although, incidence of fever was high, this might be resulted from high incidence of fever prior to amphotericin B deoxycholate treatment. Phlebitis was noted in 11 patients (20.8%). Overall mortality rate during amphotericin B deoxycholate was 15 of 53 patients (28.3%), 2 of 15 patients (3.8%) were considered to have dead-related to fungal infection and 13 of 15 patients (24.5%) were considered to died due to other causes. None of patient had breakthrough fungaemia during treatment.

Pharmacokinetics of amphotericin B deoxycholate has not been fully elucidated and the relations among serum levels, antifungal activity and outcome at the clinical site of infection were still poorly understood. The previous studies found concentrations of amphotericin B deoxycholate at the lungs were more than at the CNS but in the percentage of patients with CNS infection died less than ones with lungs infection and all 4 dead patients with lungs infection received amphotericin B deoxycholate treatment for pulmonary aspergillosis. The present study found hematologic with febrile neutropenia and HIV with cryptococcosis patients were well effective. Although, the patients with pulmonary aspergillosis still had high mortality rate and 2 patients died due to pulmonary aspergillosis. In conclusion, amphotericin B

deoxycholate administered over 24-hour infusion had low incidence of nephrotoxicity and saline infusion was importance to reduce amphotericin B deoxycholate-induced nephrotoxicity, infusion-related adverse reactions were well tolerated and 24-hour infusion of amphotericin B deoxycholate showed effectiveness to treatment of fungal infection in the hematologic with febrile neutropenia and HIV with cryptococcosis patients. However, 24-hour infusion of amphotericin B deoxycholate may be not appropriate in the patients with pulmonary aspergillosis.

Limitation of the study

1. Nephrotoxicity defined as doubling of the serum creatinine level from the baseline level during administration of amphotericin B deoxycholate but minimum SCr level monitoring was one time/week that the time to detected incidence of nephrotoxicity may be not the real time of nephrotoxicity.

2. There was the limitation to determine the incidence of infusion-related adverse reactions due to administration of amphotericin B deoxycholate over 24-hour infusion from medical chart.

3. This study was a descriptive one. Comparative study with conventional administration of amphotericin B deoxycholate may be needed to demonstrate the different of the incidence of nephrotoxicity, infusion-related adverse reactions and effectiveness due to administration of amphotericin B deoxycholate.

Suggestion

1. SCr level monitoring should be monitor 3-4 times/week for detected real time and incidence of nephrotoxicity.

2. Determine the incidence of infusion-related adverse reactions due to administration of amphotericin B deoxycholate over 24-hour infusion should be evaluated by standardised questionnaire daily, assessed by Naranjo's algorithm and should be interviewe patients directly until the end of the study.

3. For proven the benefits of amphotericin B deoxycholate administration over 24-hour infusion, further studies should be conducted experimental desiged as multicenter setting.

4. Further studies should predict odds ratio, evaluate economic outcome, the satisfaction of patients and nursing staffs about amphotericin B deoxycholate administration over 24-hour infusion and others humanistic outcome to assess the patient's health-related quality of life with the Short Form 36-item Health Survey (SF-36).

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APPENDIX

Compatibility information

Source: Trissel LA. Handbook on injectable drugs. 12th ed, 2003.

Solution compatibility

Solution	Remarks
Dextrose 5% in water	Physically compatible and drug concentration unchanged after 48 hours
Dextrose 10, 15 and 20% in water	Visually compatible with no amphotericin B deoxycholate loss by HPLC in 24 hours at 15 to 20 °C
Dextrose 5% in Sodium chloride 0.9%	Precipitate forms within 2 hours. Drug concentration of 30 to 70% of initial amount in 2 hours
Dextrose 5% in Ringer's injection lactated	Precipitate forms in 30 minutes. Drug concentration of 50% of initial amount in 30 minutes
Fat emulsion 20% intravenous	Yellow precipitate forms in 2 hours. HPLC found cumulative delivery of only 56% of the total dose
Ringer's injection, lactated	Precipitate forms within 2 hours. Drug concentration of 80% of initial amount in 2 hours
Sodium chloride 0.9%	Physically incompatible, precipitate forms within 2 hours. Drug concentration of 43% of initial amount in 2 hours
Amino acids 4.25%, dextrose 25%	Turbidity and fine yellow particles form

Compatibility information (continued)

Source: Trissel LA. Handbook on injectable drugs. 12th ed, 2003.

Additive compatibility

Drug	Concentration of additive drug (Conc/L)	Concentration of amphotericin B deoxycholate (Conc/L)	Remarks
Amikacin sulfate	5 g	100 mg	Immediate precipitate
Calcium chloride	4 g	200 mg	Haze develops over 3 hours
Calcium gluconate	4 g	200 mg	Haze develops over 3 hours
Chlorpromazine HCl	200 mg	200 mg	Immediate precipitate
Cimetidine HCl	600 mg	100 mg	Immediate haze formation. Precipitate observed at 24 hours at room temperature
Diphenhydramine HCl	80 mg	100 mg	Physically incompatible
Dopamine HCl	800 mg	200 mg	Immediate precipitate
Gentamicin sulfate	320 mg	200 mg	Haze develops over 3 hours
Heparin sodium	2000 units	70 and 140 mg	Bioactivity not significantly affected over 24 hours at 25 °C with or without light exposure
Magnesium sulfate	2 and 4 g	40 and 80 mg	Physically incompatible in 3 hours at 24 °C with decreased clarity and development of supernatant. Total loss of amphotericin B deoxycholate in supernatant by HPLC

Compatibility information (continued)

Source: Trissel LA. Handbook on injectable drugs. 12th ed, 2003.

Additive compatibility

Drug	Concentration of additive drug (Conc/L)	Concentration of amphotericin B deoxycholate (Conc/L)	Remarks
Penicillin G sodium	20 million units	100 mg	Physically incompatible
Potassium chloride	100 mEq	100 mg	Physically incompatible
Ranitidine HCl	100 mg	200 mg	Color change and particle formation
Sodium bicarbonate	2.4 mEq	50 mg	Physically compatible for 24 hours

Compatibility information (continued)

Source: Trissel LA. Handbook on injectable drugs. 12th ed, 2003.

Y-Site injection compatibility (1:1 Mixture)

Drug	Concentration of additive drug	Concentration of amphotericin B deoxycholate	Remarks
Aztreonam	40 mg/ml	0.6 mg/ml	Yellow turbidity forms immediately and becomes flocculent precipitate in 4 hours
Cefepime HCl	20 mg/ml	0.6 mg/ml	Heavy yellow flocculent precipitate forms immediately
Filgrastim	30 μg/ml	0.6 mg/ml	Yellow turbidity forms immediately and becomes flocculent precipitate
Fluconazole	2 mg/ml	5.0 mg/ml	Cloudiness and yellow precipitate
Ondansetron HCl	1 mg/ml	0.6 mg/ml	Immediate pale yellow turbidity and precipitation
Piperacillin sodium-tazobactam sodium	40+5 mg/ml	0.6 mg/ml	Heavy yellow flocculent precipitate forms immediately
Tacrolimus	1 mg/ml	5.0 mg/ml	Visually compatible for 24 hours at 25 °C

Amphotericin B deoxycholate administered over 24-hour infusion at Asdang building, Siriraj Hospital-Data Collecting Form.

Patient's Initials.....……Gender □ M □ F Age.....years
HN...…….....….....AN……Ward.....…….....
Admission date .....…Study Date .....…….....
Body Weight .....(kg) Height. .....(cm)

Underlying illness
□ No
□Yes.....…

Indication for Amphotericin B deoxycholate therapy
□ Febrile neutropenia

□ Fungal Infection (specify site & organism)
□ Site……..…...……. □ Organism…….....….....……

Amphothericin B deoxycholate Administration

□ Initial dosage of amphotericin B deoxycholate ..... mg/kg/day

□ Subsequent dosage of amphotericin B deoxycholate ..... mg/kg/day

□ Duration of amphotericin B deoxycholate treatment ..... days

□ Total dosage of amphotericin B deoxycholate ..... mg

□ Concomitant nephrotoxic agents
□ No
□ Yes (specify) .....……

Risk Factors of Amphotericin B deoxycholate-induced nephrotoxicity

□ Occurred nephrotoxicity from amphotericin B deoxycholate prior

□ Does not received sodium supplementation (Na 75 – 150 mEq/d)

□ Dehydration

□ Electrolyte imbalance

□ Others.....

Nephrotoxicity of amphotericin B deoxycholate infused over 24 hours

Date	BUN	Cr	Na	K	Mg	HCO_3	Cl	other	other

Infusion-related adverse reactions of amphotericin B deoxycholate infused over 24 hours

Date	Fever	chills/rigors	Nausea/vomiting	Phlebitis	other

Treatment of nephrotoxicity

□ Discontinuation of amphotericin B deoxycholate

□ Reduced dose of amphotericin B deoxycholate ..... mg/kg/day

□ Increase dose of amphotericin B deoxycholate and extended interval

□ Supplement of electrolyte (specify) .....

□ Hemodialysis

□ Hydration

□ Others (specify) .....

Cause of discontinued amphotericin B deoxycholate

□ Complete treatment

□ Change to another systemic antifungal due to worsening clinical condition

□ Occurred nephrotoxicity

□ Death

□ Refer

Outcome of Treatment with amphotericin B deoxycholate

□ survival

□ Breakthrough fungaemia during treatment

□ Death from fungal infection

□ Death from other cause (specify) .....

BIOGRAPHY

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