The Hospital for Sick Children

Technology Assessment at SickKids (TASK)

APPENDICES

CASPOFUNGIN IN THE EMPIRIC TREATMENT OF FEBRILE NEUTROPENIA IN PEDIATRIC PATIENTS: A COMPARISON WITH CONVENTIONAL AND LIPOSOMAL AMPHOTERICIN B

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CONFLICTS OF INTEREST

The authors declare that they do not have any conflicts of interest.

TABLE OF CONTENTS

ABBREVIATIONS AND ACRONYMS

ALT	alanine aminotransferase
AML	acute myeloid leukemia
ALL	acute lymphoid leukemia
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CI	confidence interval
EMEA	European Medicines Agency
HSCT	hematopoietic stem cell transplantation
HTA	Health Technology Assessment
IDSA	Infectious Disease Society of America
IRF	impaired renal function
SD	standard deviation

APPENDIX 1 SYSTEMATIC LITERATURE REVIEW METHODOLOGY

Pubmed

Caspofungin*: caspofungin[All Fields] OR caspofungin/csa[All Fields] OR caspofungin/mk[All Fields] OR caspofungin/voriconazole[All Fields] OR caspofungin's[All Fields] OR caspofungina[All Fields] OR caspofungine[All Fields]

Cancidas: ("caspofungin"[TIAB] NOT Medline[SB]) OR "caspofungin"[Substance Name] OR cancidas[Text Word]

Echinocandin*: echinocandin[All Fields] OR echinocandin/pneumocandin[All Fields] OR echinocandine[All Fields] OR echinocandines[All Fields] OR echinocandins[All Fields]

Medline, Centre for Reviews and Dissemination, The Cochrane Library

caspofungin$.mp. OR cancidas.mp. OR echinocandin.mp.

EMBASE

exp CASPOFUNGIN/ OR cancidas.mp. OR exp ECHINOCANDIN/

Abstracts of conferences of the following societies were also searched for studies with caspofungin in pediatrics:

- Infectious Disease Society of America (IDSA)
- European Society of Clinical Microbiology and Infectious Diseases
- European Society for Paediatric Infectious Diseases
- Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)

Databases of clinical trials were also searched for study results in pediatric patients treated with caspofungin. The list of databases suggested in a publication from the Institute of Health Economics, Alberta, Canada, and the Alberta Heritage Foundation for Medical Research was adopted as the base of our search [1]. The list of the websites searched is given below:

Table 1.1 List of websites included in the search

Database	Website
CCT Current Controlled Trials	www.controlled-trials.com
CenterWatch	www.centerwatch.com
Clinical Study Results	www.clinicalstudyresults.org
ClinicalTrials.org	www.clinicaltrials.gov
IFPMA Clinical Trials Portal*	www.ifpma.org/clinicaltrials.html
National Cancer Institute of Clinical Trials Group	www.ctg.queensu.ca
National Cancer Institute (United States) Clinical Trials database	www.cancer.gov/clinical_trials
National Research Register	www.update-software.com/National
TrialsCentral	www.trialscentral.org

IFPMA = International Federation of Pharmaceutical Manufacturers and Associations

APPENDIX 2 PEDIATRIC PATIENTS, CHARACTERISTICS, EFFICACY AND SAFETY RESULTS OF NON-COMPARATIVE STUDIES

Table 2.1 Pediatric study characteristics

Study (year)	Study treatments	Inclusion criteria	Study outcomes
Cesaro et al.[2] (2004) Invasive fungal infections Refractory N=10 Prospective	***Caspofungin IV*** 50mg/m^2 max 50mg (70mg/m^2 max 70mg loading dose on day 1) ***Liposomal amphotericin B*** (5-6mg/kg/day) Voriconazole administered after treatment completion in both arms.	Proven, probable or possible invasive fungal infections* Failure** or progression§ of invasive fungal infection with empirical antifungal therapy for 7-14 days (liposomal amphotericin B 1-3mg/kg/day)	Complete response: resolution of all clinical signs and symptoms attributed to the fungal infection and complete or almost complete resolution of radiological findings. Partial response: major improvement or resolution of the attributable clinical signs and symptoms and ≥ 50% improvement in radiological signs. Favourable response: complete or partial response.
Merlin et al.[3] (2006) Invasive fungal infections 1st line or salvage therapy N=20 Retrospective	***Caspofungin IV*** ≤ 45kg: 1-4mg/kg/day (mean 1.88mg/kg > 45kg: 50mg (70mg loading dose on day 1) *Combination with:* Amphotericin B (different formulations), flucytosine, Fluconazole, voriconazole.	Probable or proven invasive fungal infection¶	> 7 days on caspofungin Successful response: complete or partial response. Safety Survival (day 7-180)
Koo et al. [4] (2007) Febrile neutropenia N=67 / Retrospective	***Caspofungin IV*** (50mg/m^2/day, maximum 70mg/day)	Patients > 2 years old Febrile despite 5-7 days treatment with broad spectrum antibiotics AML, HSCT, or intolerant to amphotericin B	Favourable overall response according to Walsh et al. criteria[5]
Groll et al.[6] (2006) Immunocompromised patients N=64 Retrospective	***Caspofungin IV*** (dose determined by the treating physician) Median maintenance dose: 1.07mg/kg/day 35 (55%): 50mg/day	< 18 year old Received at least one dose of caspofungin Treatment started before July 2004	Favourable response: complete or partial response. Absence of breakthrough fungal infection and survival at the end of treatment with caspofungin (empirical therapy) Complete resolution of

			symptoms and marked improvement in endoscopic appearance
Cesaro et al.[7] (2007) Invasive Aspergillosis N=40 Prospective	***Caspofungin IV*** 50mg/m^2 (70mg/m^2 loading dose on day 1) ***Combination therapy*** (amphotericin B, azoles)	Pediatric patients Hematology or oncological underlying conditions Proven or probable invasive aspergillosis	Favourable response Survival (100-day, overall) Safety Complete response: resolution of all clinical signs and symptoms attributed to the fungal infection and ≥90% resolution of radiological findings. Partial response: major improvement or resolution of the attributable clinical signs and symptoms and ≥ 50% improvement in radiological signs. Favourable response: complete or partial response
Walsh et al.[8] (2005) Pharmacokinetic study N=39 Prospective	***Caspofungin IV*** 2-11 year-olds: 1mg/kg/day, 50-70mg/m^2/day 2-17 year-olds: 50mg/day	Inclusion criteria 2-17 years New onset of fever (≥38C) and neutropenia (< 500 /mm^3) Exclusion criteria Proven or probable invasive fungal infection Concomitant use of cyclosporine A, rifampin, phenytoin, phenobarbital, carbamazepine, other antifungals Elevated levels of liver enzymes and INR	Pharmacokinetics Safety
Franklin et al.[9] (2003) Safety study N=25 / Retrospective	***Caspofungin IV*** ≥ 50kg: 50-75mg/day < 50kg: 0.8-1.6mg/kg/day	Pediatric patients ≥ 1 dose of caspofungin	Safety (laboratory abnormalities) graded according to the National Cancer Institute Common Toxicity Criteria
Zaoutis et al. (2007)	***Caspofungin IV***	Inclusion criteria	Success with therapy (not

N=39 / Interim results presented at a conference Invasive infections	50mg/m^2 (70mg/m^2 on day 1) Maximum dose: 70mg/day	3 months – 17 years Proven or probable fungal infections <u>Exclusion criteria</u> Liver enzymes' abnormalities or liver disease Concomitant use of cyclosporine or rifampin	defined) Safety

AML=acute myelogenous leukemia; HSCT=hematopoietic stem cell transplantation; INR=international normalized ratio
*According to international criteria.
**Persistence of fever and/or absence of ≤ 50% reduction in number and/or size of known lesions.
§Rapid worsening of clinical conditions, documented through X-ray, CT scan, ultrasound of new lesions
¶ Proven or probable infections according to the consensus committee definition of the European Organization for Research and Treatment of Cancer/Mycosis Study Group of the National Institute of Allergy and Infectious Diseases.

Table 2.2 Pediatric studies, baseline characteristics

Baseline Characteristics ANTIFUNGAL MONOTHERAPY OR COMBINATION?	**Cesaro et al.[2] N=10 COMBINATION**	**Merlin et al.[3] N=20 COMBINATION**	**Zaoutis et al. [10] N=38 MONOTHERAPY**	**Koo et al.[4] N=67 MONOTHERAPY**
Median age (range in years)	13 (6-24)	12 (0.1–16)	Mean (range): 8.5 (0.5 – 17)	8 (1-17)
Premature (neonates)	0	0	N/A	0
Haematological malignancies, n(%) Stem cell transplantation	10 (100%) 3 (30%) allogeneic	17 (85%) 5 (25%)	NR	26 (39%) -
Neutropenia	8 (80%) < 500 / mm^3	16 (80%) < 500 / mm^3	7 (18%)	67 (100%)
Invasive fungal infections Invasive candidiasis Invasive aspergillosis Other	- - 9 (90%) -	- 7 (35%) 11 (55%) -	39 (100%) 27 (71%) 10 (26%) 1 (3%)	7(10%) 3 (4.5%) 2 (3%) 2 (3%)
Prior therapy, n (%) Azoles Amphotericin B* Combination	 1 (10%) 9 (90%) -	 4 (20%) 9 (45%) -	 NR	 2 (3%) 2 (3%) -
Duration of prior therapy, days, median (range)	3 (2-10)	NR	NR	NR
Refractory to prior therapy, n (%)	10 (100%)	13 (65%)	NR	NR
Combination drugs in addition to caspofungin Caspofungin monotherapy Azoles Amphotericin B* Combination of the two	 - - 10 (100%) -	 6 (30%) 9 (45%) 8 (40%) -	 NR	 67 (100%) - - -
Concomitant cyclosporine/ tacrolimus	1 (10%)	5 (25%)	0	19 (28%)
Renal failure	NR	4 (20%) – amphotericin B or cyclosporine	NR	0
Hepatic failure	NR	1 (5%) (GVHD)	NR	0
Age, years, median	11.5 (0.4 – 17.9)	11.1 (1.2-17.9)	7.7 (2-16)	9.8 (0.3-26.2)

(range)				
Premature (neonates)	N/A	N/A	0	
Hematological malignancies Stem cell transplantation	48 (75%) 36 (56%)	37 (93%) 13 (33%)	22 (56%) 18 (46%)	- 14 (56%)
Neutropenia	33 (51%) < 500 / mm^3	31 (78%) < 500 / mm^3	39 (100%) < 500 / mm^3	13 (52%) < 500 / mm^3
Invasive fungal infections Invasive candidiasis Invasive aspergillosis Mould infections	- 8 (17%) 23 (48%) 17(35%)	40 (100%) - 40 (100%) -	Safety evaluation	Safety evaluation
Prior therapy Azoles Amphotericin B* Combination	 12 (18.7%) 27 (42.1%) 25(39%)	33 (83%) - - -	N/A	21 (84%) - - -
Duration of prior therapy, days, median (range)	19.5 (1-94)	NR	N/A	NR
Refractory to prior therapy, n (%)	38 (59%)	33 (83%)	N/A	NR
Combination drugs in addition to caspofungin Caspofungin monotherapy Azoles Amphotericin B* Combination of the two	44 (69%) 20 (31%) - - -	40 (100%) 0 9 (25%) 18 (50%) 9 (25%)	39 (100%) - - - -	 4 (16%) - 21 (84%) – liposomal amphotericin B
Concomitant cyclosporin A	19 (30%)	14 (35%) includes tacrolimus	0	NR

N/A=not applicable ; NR=not reported
*Different formulations of amphotericin B were used
**Possible, probable or proven

Table 2.3 Pediatric studies, results (invasive aspergillosis or invasive fungal infections)

Study results **ANTIFUNGAL MONOTHERAPY?**	**Cesaro et al. [2] (2004) N=9** **COMBINATION**	**Merlin et al. [3] N=11** **COMBINATION**	**Cesaro et al. [7] N=36** **COMBINATION**	**Groll et al. [6] N=62** **COMBINATION**	**Zaoutis et al.[10] N=10** **MONOTHERAPY**
Duration of therapy, days, median (range)	17 (6-40)	35 (7-280)	29 (3-382) – any combination	37 (3-218)	42.7 (6-87) (mean, range)
Complete or partial response Relapse Mortality (related to infection) Mortality (overall)	8 (89%) 0 1 (10%) median follow-up:125 days (9-335) Overall favourable response at the end of follow-up: 80% (8/10 patients received oral voriconazole	10 (91%) 4/11 (36%) 6 (55%)	21 (53%) (100 days of diagnosis) 15 (30%) (100 days) 20 (50%) median follow-up 0.7 years, 80% had active aspergillosis	49 (79%) 25% (3 months: 30%)	5 (50%) - success

Table 2.4 Pediatric studies, results (Invasive candidiasis)

Study results **ANTIFUNGAL MONOTHERAPY?**	**Merlin et al.[3]** **N=7** **COMBINATION**	**Zaoutis et al.[10]** **N=27** **MONOTHERAPY**
Duration of therapy, days, median (range)	35 (7-280 days)	12.3 (2-42) days (mean, range)
Complete response, n(%)	4 (57%)	22 (81%) – success
Partial response, n(%)	1 (14%)	
Complete or partial response, n(%)	5 (71%)	
Relapse		
Mortality (related to infection)	2 (29%) – 90 days , 4 (57%) mean follow-up: 102 days	
Mortality (overall)		

Table 2.5 Pediatric studies, results (febrile neutropenia)

Study results **ANTIFUNGAL MONOTHERAPY?**	**Koo et al.**[4] Febrile neutropenia **MONOTHERAPY**	**Walsh et al.** [8] **MONOTHERAPY**
Duration of therapy, days, median (range)	8 (1-129)	5.5 (2-28)
Favourable response, n(%) Mortality (related to infection), n(%) Mortality (overall), n(%)	53 (79%) 0 6 (9%)	Breakthrough infections: 2 (5.1%)

Table 2.6 Pediatric studies, safety

Safety **ANTIFUNGAL MONOTHERAPY OR COMBINATION ?**	**Cesaro et al.[2]** **N=10** **COMBINATION**	**Merlin et al.[3]** **N=20** **COMBINATION**	**Zaoutis et al.** **N=39** **MONOTHERAPY**	**Koo et al.[4]** **N=67** **MONOTHERAPY**
Cyclosp./tacrol. Renal insufficiency Hepatoinsuficiency	NR NR NR	25% 20% 5%	0 NR 0	28% NR NR
Serious adverse event (drug related)	NR	NR	0	0
Drug-related clinical adverse event	NR	9 (45%)*	11 (28%)	NR
Laboratory-related adverse event	NR	NR	12 (31%)	NR
Withdrawal due to toxicity	NR	0	0	1 (1.5%) - rash
Dose adjustment, immunosuppresives	1 (100%) –dose adjusted according to blood levels	NR	NR	NR
Increase in serum creatinine	0 (>2x baseline)	0 (renal function deterioration)	NR	1 (1.5%)
Increase in liver enzymes	NR	5 (25%) mild (1 conc. Cyclosporine)	NR	1 (1.5%)
Hypokalemia	8 (80%) <2.5mEq/L** (possibly related to amphotericin B)	2 (10%) (moderate)	NR	3 (4.5%)
Increased ALT	0	NR	4 (10%)	NR
Increased AST	NR	NR	7 (18%)	NR
Increased Bilirubin	2 (20%) 2-2.5x ULN¶	NR	NR	NR
Increased BUN	NR	NR	NR	NR
Hypomagnesemia	NR	NR	2 (5%)	1 (1.5%)
Decrease in serum phosphorus	NR	NR	2 (5%)	NR
Vomiting	NR	2 (10%)*	NR	1 (1.5%)
Nausea	NR	2 (10%)*	NR	1 (1.5%)
Fever	0	NR	4 (10.3%) (1 moderate, infusion-related)	NR

Chills	0	NR	NR	NR
Thrombophlebitis thrombosis	2 (20%)	1 (5%) at the injection site	1(2.5%) –severe, infusion-related	NR
Rash	NR	NR	3 (8%)	2 (3%)
Livedo	NR	1 (5%)**	NR	NR
Decrease in eosinophils	NR	NR	2 (5%)	NR

ALT =alanine aminotransferase ; AST (aspartate aminitransferase); NR=not reported
*Possibly drug-related (Caspofungin).
**Possibly related to Liposomal amphotericin B
§ Considered as related to caspofungin (does not specify the extent, e.g possibly, probablY), however amphotericin B and/or fluconazole were being used concomitantly. The authors state that it is difficult to separate the contribution of caspofungin and other concomitant drugs or underlying conditions to the development of these events.
¶ Patients had venous-occlusive disease after treatment with gentuzomab-ozogamycin.

Table 2.7 Pediatric studies, safety

Safety **ANTIFUNGAL MONOTHERAPY?** cyclosporine/tacrolimus Renal insufficiency Hepatoinsuficiency	**Groll et al.[6]** **N=64** **COMBINATION (69%)** 30% NR NR	**Walsh et al.[8]** **N=39** **MONOTHERAPY** NR NR NR	**Franklin et al.[9]** **N=25COMBINATION (84%)** NR NR NR	**Cesaro et al.[7]** **N=40** **COMBINATION** 35% NR NR
Serious adverse event (drug related)	NR	0	0	0
Drug-related clinical adverse event	34 (53%)*	5 (12.8%)	3 (12%) possibly 0 – probable or definitely-related	NR
Laboratory-related adverse event	NR	2 (5.1%)	NR	NR
Withdrawal due to toxicity	0	0	0	0
Infusion-related event	NR	2 (5.1%)	NR	NR
Increase in serum creatinine	14 (22%) ≥1.5x baseline 3 (5%) ≥3x baseline	NR	NR	NR
Renal function deterioration	NR	6 (16.7%) creatinine clearance decreased 75% the baseline (concomitant with other kidney toxic drugs)	NR	NR
Elevated proteinuria	NR	1 (2.6%)*	NR	NR
Hypokalemia	NR	1 (2.6%)* caspofungin-related	3 (12%)* caspofungin-related	NR
Increased ALT	17 (26.5%) ≥1.5x baseline* 9 (14%) ≥3x baseline*	NR	1 (4%)*	NR
Increased AST	12 (18.7%) ≥1.5x baseline* 7 (10.9%) ≥3x baseline*	1 (2.6%)*	NR	NR

Increased Alkaline phosphatase	6 (9%) ≥1.5x baseline* 1 (1.5%) ≥3x baseline*	NR	NR	NR
Increased Bilirubin	8 (12.5%) ≥1.5x baseline* 3 (4.6%) ≥3x baseline*	NR	2 (8%)*	NR
Decreased hemoglobin	NR	NR	1 (4%)*	NR
Fever	26 (40.6%)	1 (2.6%)* (rigours)	NR	NR
Vomiting	19 (29.6%) (includes nausea)	NR	NR	NR
Chills	NR	1 (2.6%)*	NR	NR
Diarrhea	7 (10.9%)	1 (2.6%)*	NR	NR
Phlebitis	NR	1 (2.6%)*	NR	NR
Rash	4 (6.2%) (skin eruptions)	1 (2.6%)*	NR	1 (2.5%)
Headache	5 (7.8%)	NR	NR	NR

ALT =alanine aminotransferase ; AST (aspartate aminitransferase); NR=not reported
*Possibly drug-related (Caspofungin).
**Possibly related to Liposomal amphotericin B
§ Considered as related to caspofungin (does not specify the extent, e.g possibly, probablY), however amphotericin B and/or fluconazole were being used concomitantly. The authors state that it is difficult to separate the contribution of caspofungin and other concomitant drugs or underlying conditions to the development of these events.
¶ Patients had venous-occlusive disease after treatment with gentuzomab-ozogamycin.

APPENDIX 3 PEDIATRIC PATIENTS – SUMMARY OF SAFETY RESULTS OF NON-COMPARATIVE STUDIES

Altogether, a total of 304 pediatric patients were included in these studies. Some studies included patients with concomitant use of cyclosporine [2 3 4 6 7] and one study included patients with renal or hepatic failure [3].

One study reported renal toxicity measured by a 75% decrease in creatinine clearance from baseline in 6/39 (15%) patients [8]. The patients were receiving other nephrotoxic drugs such as aminoglycosides or cytotoxic chemotherapy either concomitantly or shortly preceding the caspofungin administration, therefore, it was not possible to attribute causality to caspofungin[8]. One study reported increases in serum creatinine ≥ 1.5x baseline in 14 (21.8%) patients, and ≥ 3x baseline in 3 (5%) patients[6]. The events were considered possibly related to caspofungin, however, 69% of the patients included in the study were receiving combination therapy with amphotericin B formulations (80%) and/or azoles, and 1/3 was receiving cyclosporine[6]. A study reported an increase in serum creatinine in one (1.5%) patient[4].

Hypokalemia was reported in 2.6%-16% of the patients receiving caspofungin [4 8 9]. The clinical significance of these abnormalities was not reported. One study reported hypokalemia (< 2.5 mEq) in 8/10 (80%) patients receiving a combination of caspofungin and liposomal amphotericin B[2]. In all eight cases, the hypokalemia was considered by the investigators as possibly related to liposomal amphotericin B[2].

Possibly caspofungin-related increases in liver enzymes alanine aminotransferase (ALT), alkaline phosphatase (AST), or bilirubin are shown in the table below. Patients were using caspofungin in monotherapy or combination therapy [2 3 4 6 8 9 10]. The clinical significance of these abnormalities was not discussed by the authors. Groll et al. did not observe a difference in the percentages of patients with increases in liver enzymes between patients with and without concomitant use of cyclosporine[6].

Table 3.1 Pediatric studies, frequencies of increases in liver enzymes

	Increases in Liver Enzymes				
Study	**AST**	**ALT**	**Alkaline phosphatase**	**Bilirubin**	**Liver enzymes in general**
Groll et al.[6] (> 3x baseline value) N=64	7 (10.9%)**	9 (14%)**	1 (1.5%)**	3 (4.6%)**	NR
Cesaro et al.[2] (2-2.5x ULN) N=10	NR	0	NR	2 (20%)	NR
Walsh et al.[8] N=39	1 (2.6%)¶	NR	NR	NR	NR
Franklin et al.[9] N=25	NR	1 (4%)*	NR	2 (8%)*	NR
Koo et al.[4] N=67	NR	NR	NR	NR	1 (1.5%)* (hepatotoxicity) (concomitant cyclosporine use)
Merlin et al.[3] N=20	NR	NR	NR	NR	5 (25%)* (1 patient-concomitant cyclosporine use)
Zaoutis et al.[10] N=39	4 (10%)¶	7 (18%)¶	NR	NR	NR

The magnitude of increase specified if reported in the studies.
ALT= alanine aminotransferase / AST=aspartate aminotransferase / NR=not reported / ULN=upper limit of the normal range
* considered as possibly-related to caspofungin as judged by the investigators.
** considered as potentially drug-related by the investigators
¶ - considered as caspofungin-related by the investigator

Clinical adverse events were reported in 12% to 53% of the patients treated with caspofungin in five studies [3 6 8 9 10]. Patients received the drug either as monotherapy or in combination with other antifungals, and some patients used cyclosporine concomitantly, which may explain part of the wide variation in the frequency of clinical adverse events. Common clinical events considered by the investigators as at least possibly related to caspofungin are shown in table below.

Table 3.2 Pediatric studies, frequencies of common clinical adverse events considered possibly related to caspofungin

Study	Thrombophlebitis / phlebitis	Nausea / Vomiting	Diarrhea	Rash	Headache	Fever	Livedo
Cesaro et al.[2] N=10	2 (20%)	NR	NR	NR	NR	0	NR
Merlin et al.[3] N=20	1 (5%) – at injection site	2 (10%)	NR	NR	NR	NR	1 (5%)
Groll et al.[6] N=64	NR	19 (29.6%)	7 (10.9%)	4 (6.2%) skin eruptions	5 (7.8%)	26 (40.6%)	NR
Walsh et al.[8] N=39	1 (2.6%)	NR	1 (2.6%)	1 (2.6%)	NR	1 (2.6%) / rigours	NR
Cesaro et al.[7] N=40	NR	NR	NR	1 (2.5%)	NR	NR	NR
Koo et al.[4] N=67	NR	1 (1.5%)	NR	2 (3%)	NR	NR	NR
Zaoutis et al.[10] N=39	1 (2.5%) – severe, infusion-related	NR	NR	3 (8%)	NR	4 (10.3%)	NR

NR=not reported

APPENDIX 4 ADULT PATIENTS: CHARACTERISTICS, EFFICACY AND SAFETY RESULTS OF RCTS

Table 4.1 Adult studies, RCT characteristics

Study (year of publication)	Comparative treatments	Study Population	Study outcomes
Walsh et al. (2004)[5] ***Empiric therapy in persistent fever and neutropenia*** N=1,095 (caspofungin: 556 / liposomal amphotericin B: 539) Multicentre study	***Caspofungin*** IV 70mg on day 1 and 50mg once a day subsequently ***Liposomal amphotericin B*** IV 3mg/kg weight daily The dose could be increased to 70mg daily and 5mg/kg daily, respectively in case of persistent fever (≥ 5 days) and worsening of patient condition. Duration of infusion not reported. Pre-medication was allowed after day 1. Length of treatment Patients without evidence of baseline or breakthrough infections: At least 72 hours after the absolute neutrophil count > 500/mm^3. Patients with baseline or breakthrough infections: Treatment duration determined by the investigator Treatment was recommended to last at least 14 days or at least 7 days after resolution of neutropenia and symptoms.	Inclusion criteria ≥ 16 years Previous cancer chemotherapy or HSCT Absolute neutrophil count < 500/ mm^3 Fever (> 38° C) Parenteral antibiotics for ≥ 96 hours Exclusion Criteria Inadequately managed infection Karnofsky score < 30 Abnormal laboratory results for selected liver tests and platelet counts Need for use of rifampin, cyclosporine Concomitant systemic antifungals requirement	Results stratified according to risk and systemic antifungal prophylaxis. Analysis: modified intention-to-treat§ Primary outcome Favourable overall response according to five criteria*. Primary analysis: non-inferiority of caspofungin to liposomal amphotericin B (modified intention-to-treat population) Secondary outcomes Evaluation of each of the 5 components of the primary outcome. Survival times Safety Assessed daily from start of the treatment until 14 days after its completion. Main analysis: Nephrotoxicity, evaluated in patients with a creatinine clearance > 30 ml/minute

HSCT=hematopoietic stem cell transplantation
* Primary outcome criteria:
1-Successful treatment of any baseline fungal infection.
2- absence of any breakthrough fungal infection during therapy or within 7 days of the end of treatment.
3- Survival for 7 days after the end of treatment.
4- No premature discontinuation of the study therapy due to drug-related toxicity or lack of efficacy.
5- Resolution of fever during neutropenia to a temperature < 38° for at least 48 hours.
§ Randomized patients with fever and neutropenia who received at least one complete dose of the study drug.

Table 4.2 Adult RCT, baseline characteristics

Baseline characteristics	**Walsh et al.**[5] Empiric therapy of febrile neutropenia	
	Caspofungin N=556	**Liposomal amphotericin B N=539**
Female, n (%)	238 (42.8%)	247 (45.8%)
Age, yr, Median (range)	51(17-83)	49 (16-83)
Prior antifungal prophylaxis, n (%)	313 (56.3%)	304 (56.4%)
High risk, n (%)	146 (26.3%)	122 (22.6%)
Allogeneic HSCT, n (%)	36 (6.5%)	39 (7.2%)
Relapse of acute leukemia, n (%)	110 (19.8%)	83 (15.4%)
Primary diagnosis		
Acute myelogenous leukemia, n (%)	364 (65.5%)	339 (62.9%)
Acute lymphocytic leukemia, n (%)	57 (10.3%)	50 (9.3%)
Non-Hodkin's lymphoma, n (%)	58 (10.4%)	62 (11.5%)
Neutropenia	556 (100%)	539 (100%)
Neutrophil count < 100/ mm^3	400 (71.9%)	406 (75.3%)

MDS=myelodysplastic syndrome

Table 4.3 Adult RCT, clinical outcomes

Clinical Outcomes	Walsh et al.[5] Empiric treatment of persistent and neutropenia		
	Caspofungin N=556	**Liposomal Amphotericin B N=539**	**Absolute Difference, % (95% CI), p value if reported**
Duration of treatment, days	Median: 11 (range:1-90)	Median: 10 (range: 1-90)	-
Favourable overall response*			
Unstratified analysis, n (%)	190 (34.2%)	181 (33.6%)	-
Stratified analysis**, n (%)	190 (33.9%)	181 (33.7%)	0.2% (-5.6 , 6.0)
High risk patients	63 (43.2%)	46 (37.7%)	5.4% (-6.3 , 17.2)
Low risk patients	127 (31%)	135 (32.4%)	-1.4% (-7.7 , 4.9)
Antifungal prophylaxis	105 (33.5%)	100 (32.9%)	-
No antifungal prophylaxis	85 (35%)	81 (34.5%)	-
Successful treatment of baseline fungal infection	14 (51.9%)	7 (25.9%)	25.9% (0.9 , 51), p=0.04
Absence of breakthrough infection	527 (94.8%)	515 (95.5%)	-0.8% (-3.3 , 1.8), p=0.56
Survival for ≥7 days after treatment completion¦	515 (92.6%)	481 (89.2%)	3.4% (0 , 6.8), p=0.05
Resolution of fever and neutropenia	229 (41.2%)	223 (41.4%)	-0.2% (-6 , 5.6), p=0.95
Treatment discontinuation due to:	57 (10.3%)	78 (14.5%)	4.2% (0.3 , 8.1), p=0.03
lack of efficacy	30 (5.4%)	34 (6.3%)	-0.9% (-3.7 , 1.9)
toxicity	27 (4.9%)	44 (8.2%)	-3.3% (-6.2 , -0.4)
Probable or proven infections§			
Aspergillus (all)	5/12 (41.7%)	1/12 (8.3%)	-
Candida (all)	8/12 (66.7%)	5/12 (41.7%)	-

Amph amphotericin ; CI= confidence interval ; N=number
* Favourable overall response defined by:
1-Successful treatment of any baseline fungal infection.
2- Absence of any breakthrough fungal infection during therapy or within 7 days of the end of treatment.
3- Survival for 7 days after the end of treatment.
4- No premature discontinuation of the study therapy due to drug-related toxicity or lack of efficacy.
5- Resolution of fever during neutropenia to a temperature < 38ºC for at least 48 hours.
** The analysis was stratified according to patient's risk status and use of systemic antifungal prophylaxis.
¦ Deaths were due mostly to complications of the underlying diseases or infections and were distributed evenly between the two groups. Mortality rates including the period beyond 7 days after treatment completion were 10.8% and 13.7% in the caspofungin and liposomal amphotericin B, respectively, however, the number of patients dropped significantly after day 7, i.e., 547 and 523 respectively at day 7, 82 and 80 respectively at day 28, and 6 for both groups at day 63,making a comparison between the two groups, difficult.
§ Defined by histologic or microbiologic documentation for all filamentous fungal infections, microbiologic documentation for candidemia, and histologic documentation or characteristic radiologic features for chronic disseminated candidiasis. Based on the criteria defined by the European Organization for Research and Treatment of Cancer and the National Institute of Allergy and Infectious Diseases Mycosis Study Group.

Table 4.4 Adult RCT, study-drug related adverse events (possibly, probably, definitely related to the study drug as defined by the investigator)

Safety	RCT - Empiric treatment of persistent and neutropenia **Walsh et al.[5] or data reported to EMEA[11] when specified**		
	Caspofungin N=564	**Liposomal Amphotericin B N=547**	**Difference, % (95% CI)**
Serious adverse events	9 (1.6%)[11]	16 (2.9%)[11]	-1.3 (-3.1 , 0.4) [11]
Serious drug-related laboratory adverse events (source: EMEA[11]) – See table 4.5 for details	0[11]	1 (0.1%)[11]	
Withdrawal due to toxicity (table 4.5)	28 (5%)	44 (8%)	-3.1 (-6 , -0.02)
Nephrotoxicity*	2.6%	11.5%	-8.9 (-12 , -5.9)
Elevated serum creatinine	1.2%	5.5%	-4.3 (-6.4 , -2.1)
Elevated blood urea nitrogen	1.9%	3.1%	-1.2 (-3.9 , 1.5)
Events during drug infusion	35.1%**	51.6%**	-16.4 (-22.2 , -10.7)
Severe events during drug infusion[11]	5.1%	8.6%	NS
Clinical drug-related events¶	47%	59.6%	-12.6 (-18.4 , -6.8)
Fever	17%	19.4%	-2.4 (-6.9 , 2.2)
Chills	13.8%	24.7%	-10.9 (-15.5 , -6.2)
Rash	6.2%	5.3%	0.9 (-1.8 , 3.6)
Headache	4.3%	5.7%	-1.4 (-4 , 1.1)
Hypokalemia	3.7%	4.2%	-0.5 (-2.8 , 1.8)
Nausea	3.5%	11.3%	-7.8 (-10.9 , -4.7)
Vomiting	3.5%	8.6%	-5.0 (-7.8 , -2.2)
Dyspnea	2.0%	4.2%	-2.3 (-4.3 , -0.2)
Flushing	1.8%	4.2%	-2.4 (-4.4 , -0.4)
Laboratory (drug-related) events¶	22.5%	32%	-9.5 (-14.7 , -4.3)
Increased ALT	8.7%	8.9%	-0.1 (-3.5 , 3.2)
Increased AST	7%	7.6%	-0.6 (-3.7 , 2.4)
Increased alkaline phosphatase	7%	12%	-5.1 (-8.5 , -1.6)
Hypokalemia	7.3%	11.8%	-4.5 (-7.9 , -1.0)
Increased total serum bilirubin	3%	5.2%	-2.1 (-4.5 , 0.2)

ALT= alanine aminotransferase / AST=aspartate aminotransferase / EMEA=European Medicines Agency / NS=not statistically significant/ Lip. Amph. B – liposomal amphotericin B

* Defined by a doubling of the baseline serum creatinine level or an increase ≥1mg/dL in patients with elevated serum creatinine at enrollment. Patients with creatinine clearance < 30ml/minute were not included in this analysis.

** most frequently reported: fever, chills, headache, nausea, and vomiting[5]. Most difference between the two groups in chills and fever[11].

§ Defined by a doubling of the baseline serum creatinine level or an increase ≥1mg/dL in patients with serum creatinine above the upper limit of the normal range at enrollment. Patients with creatinine clearance < 30ml/minute were not included in this analysis.

¶ Events classified as either possibly, probably or definitely related to the drug[5]. Events were reported if the rate was > 2% in at least one study group, for laboratory events, only the results of tests performed in >100 patients were reported[5].

Table 4.5. Adult RCT, serious drug-related adverse events and reasons for drug discontinuation – RCT comparing caspofungin and liposomal amphotericin B in adult patients with febrile neutropenia

Safety	**RCT - Empiric treatment of persistent and neutropenia** **Source: data reported to EMEA**[11]	
	Caspofungin N=564	**Liposomal amphotericin B N=547**
Serious drug-related adverse events	9 (1.6%)[11] - Renal failure or insufficiency (n=3) - Rash, patients recovered (n=2) - Infusion-related hypersensitivity reaction that resolved over 3 hours after the infusion (n=1) - Hyperbillirubinemia in patient with metastatic liver and lungs disease (n=1) - Congestive heart failure, hypokalemia, and extension of a myocardial infarction in a patient with AML and underlying cardiovascular disease (n=1) - Bronchiolitis obliterans with organizing pneumonia on lung biopsy done 3 days after the end of the treatment (n=1)	16 (2.9%)[11] - Respiratory system (n=3), respiratory distress, dyspnea, hipoxia - Hypersensitivity reaction (n=3) - Anaphilaxis (n=1) - Anaphilactic reaction (n=1) - Acute renal failure (n=2) - Renal insufficiency (n=1), - Hypokalemia (n=1) - Ventricular fibrillation with cardiac arrest (n=1) - Fungal infection (n=1) - Grand mal seizure (n=1) - Adverse event not clear in one case.
Serious drug-related laboratory adverse events	0[11]	1 (0.1%)[11] - Increased serum total bilirubin
Withdrawal due clinical drug-related adverse events	25 (4.4%) - Adverse events in the skin (n=10), 1 case of serious rash - Hepatobiliary system or hyperbilirubinemia (n=5) not clear in the remainder	35 (6.4%) - hypersensitivity reactions (n=4) - anaphylaxis or anaphylactic-type reactions (n=3) - fever (n=4) not clear in the remainder
Withdrawal due laboratory drug-related adverse events	3 (0.5%) - Hepatic dysfunction, increased one or more liver enzymes AST, ALT, alkaline phosphatase, total and direct bilirubin (n=3)	13 (2.4%) - Abnormal liver function tests, increased bilirubin, alkaline phosphatase, AST, ALT) (n=9) - Increased creatinine (n=4)
Deaths possibly related to the study drug	1 (0.17%) Due to a renal insufficiency considered possibly related to caspofungin	2 (0.37%) cardiac arrest (n=1) respiratory distress (n=1) considered possibly related to liposomal

		amphotericin B

ALT= alanine aminotransferase / AST=aspartate aminotransferase / EMEA=European Medicines Agency

APPENDIX 5 ADULT PATIENTS: NON-RANDOMIZED COMPARATIVE STUDIES

Table 5.1. Adult studies, non-randomized comparative studies' characteristics

Study (year of publication)	Comparative treatments	Study Population
Ellis et al.[12] Invasive fungal infections or febrile neutropenia and hematological malignancies N= 73 episodes (57 patients) Retrospective Open label Treatment allocation according to the physician's judgement	***Caspofungin IV*** 70mg loading dose and 50mg/daily (N. episodes =24, 23 patients) ***Liposomal amphotericin B*** IV (N. episodes=49, 34 patients): 3mg/kg/day in patients with non-responsive to broad spectrum antibiotics 5mg/kg/day – invasive fungal infections Dose could be increased to up to 10/mg/kg/day in progressive fungal infections Treatment was continued until fever and neutropenia resolution and if the drug had been given for at least 10 days (14 days for invasive fungal infections). Responsive patients received 14-day voriconazole treatment	Inclusion criteria - Acute hematological malignancy - Negative bacterial culture - Target organ negative febrile neutropenia unresponsive to broad spectrum antibiotics or patients with invasive fungal infection**

** Invasive fungal infection defined according to the European Organization for Research and Treatment of Cancer's Invasive Fungal Infections Cooperative Group.

Table 5.2 Adult studies, non-randomized comparative studies (baseline characteristics)

Baseline characteristics	**Ellis et al.**[12] Febrile neutropenia, invasive fungal infections	
	Caspofungin N=23	**Lipid amphotericin B N=49**
Age, yr,median /mean (range)	38.7 (SD 16)	33.1 (SD 11.3)
Primary diagnosis Hematological malignancy, n (%)	23 (100%)	34 (100%)
HSCT	NR	NR
Previous antifungal therapy	N/A	N/A
Duration of previous therapy, median (range)	N/A	N/A
Invasive candidiasis Invasive aspergillosis Febrile neutropenia	4 (17%) 4 (17%) 9 (38%)	4 (12%) 20 (41%) 14 (29%)
Renal failure	NR	NR
Use of cyclosporine Use of tacrolimus	NR	NR

HSCT=hematopoietic stem cell transplantation / N/A=not applicable / NR=not reported / SD=standard deviation

Table 5.3 Adult studies, non-randomized comparative studies (study results)

Study results	**Ellis et al.** [12] Invasive fungal infections or febrile neutropenia	
	Caspofungin **N=24**	**Liposomal amphotericin B** **N=49**
Duration of therapy, days, mean (SD)	10 7.2)	8.6 (4.9)
Favourable response*	12 (50%)	49 (90%)

CI= confidence interval / NR=not reported / SD=standard deviation
* Favourable responses were defined by the following endpoints:
1- Successful treatment of any baseline fungal infection.
2- Absence of any breakthrough fungal infection during therapy or within 7 days of the end of treatment.
3- Survival for 7 days after the end of treatment.
4- No premature discontinuation of the study therapy due to drug-related toxicity or lack of efficacy.
5- Resolution of fever during neutropenia to a temperature < 38ºC for at least 48 hours.

Table 5.4 Adult studies, non-randomized comparative studies (safety)

Safety	**Ellis et al.** [12] N=24
Serious adverse event	0
Clinical adverse events	58.3%
Withdrawal due to toxicity	8.3%
Nephrotoxicity	16.7% (elevated creatinine)
Hypokalemia	33.3%
Hepatotoxicity	20.8%
Rigour	16.7%

AST=aspartate transferase / ALT=alanine transferase / NR=not reported

The study by Marr et al. reported similar median serum levelsof liver enzymes or creatinine between the two groups[13]. Percentage of patients with increased levels was not reported[13].

APPENDIX 6 ADULT PATIENTS: SUMMARY OF STUDY RESULTS

Efficacy

Randomized controlled trials

In our report, we have concentrated on the only RCT in patients with febrile neutropenia[5] as this is the focus of our report. It consisted of a randomized, double-blind, multicentre study that evaluated the efficacy of caspofungin IV 50mg/day (loading dose 70mg on day 1) compared to liposomal amphotericin B IV (3mg/kg/day) in patients ≥ 16 years who presented with fever and neutropenia and who had undergone previous cancer chemotherapy or HSCT [5]. Some of the exclusion criteria were presence of abnormal liver function and platelet levels, and concomitant use of rifampin, cyclosporine or other systemic antifungals [5]. The study was designed to evaluate if caspofungin was not inferior to liposomal amphotericin B in the overall treatment response in the modified intention-to-treat population[1] [5].

As multiple outcomes were evaluated in the study by Walsh et al. [5], we focused on those defined as primary, as well as treatment relapse and survival if available (summarized below). Safety outcomes are discussed separately.

Empirical antifungal treatment in patients with persistent fever and neutropenia

One RCT evaluated the use of caspofungin in the empirical treatment of adult patients with persistent fever and neutropenia [5]. It consisted of a randomized, double-blind, multicentre study that evaluated the efficacy of caspofungin IV 50mg/day (loading dose 70mg on day 1) compared to liposomal amphotericin B IV (3mg/kg/day) in patients ≥ 16 years who presented with fever and neutropenia and who had undergone previous cancer chemotherapy or HSCT [5]. Some of the exclusion criteria were presence of abnormal liver function and platelet levels, and concomitant use of rifampin, cyclosporine or other systemic antifungals [5].

The study was designed to evaluate if caspofungin was not inferior to liposomal amphotericin B in the overall treatment response in the modified intention-to-treat population[5]. A favourable overall treatment response was defined by five criteria[2], all of which had to be met. The study treatment was administered for up to 72 hours after the neutrophil count reached ≥ 500/mm^3 in patients without breakthrough fungal infections, otherwise, the treating physician decided the duration of the therapy, however it was recommended to last for at least 14 days or 7 days after the resolution of the neutropenia and symptoms [5].

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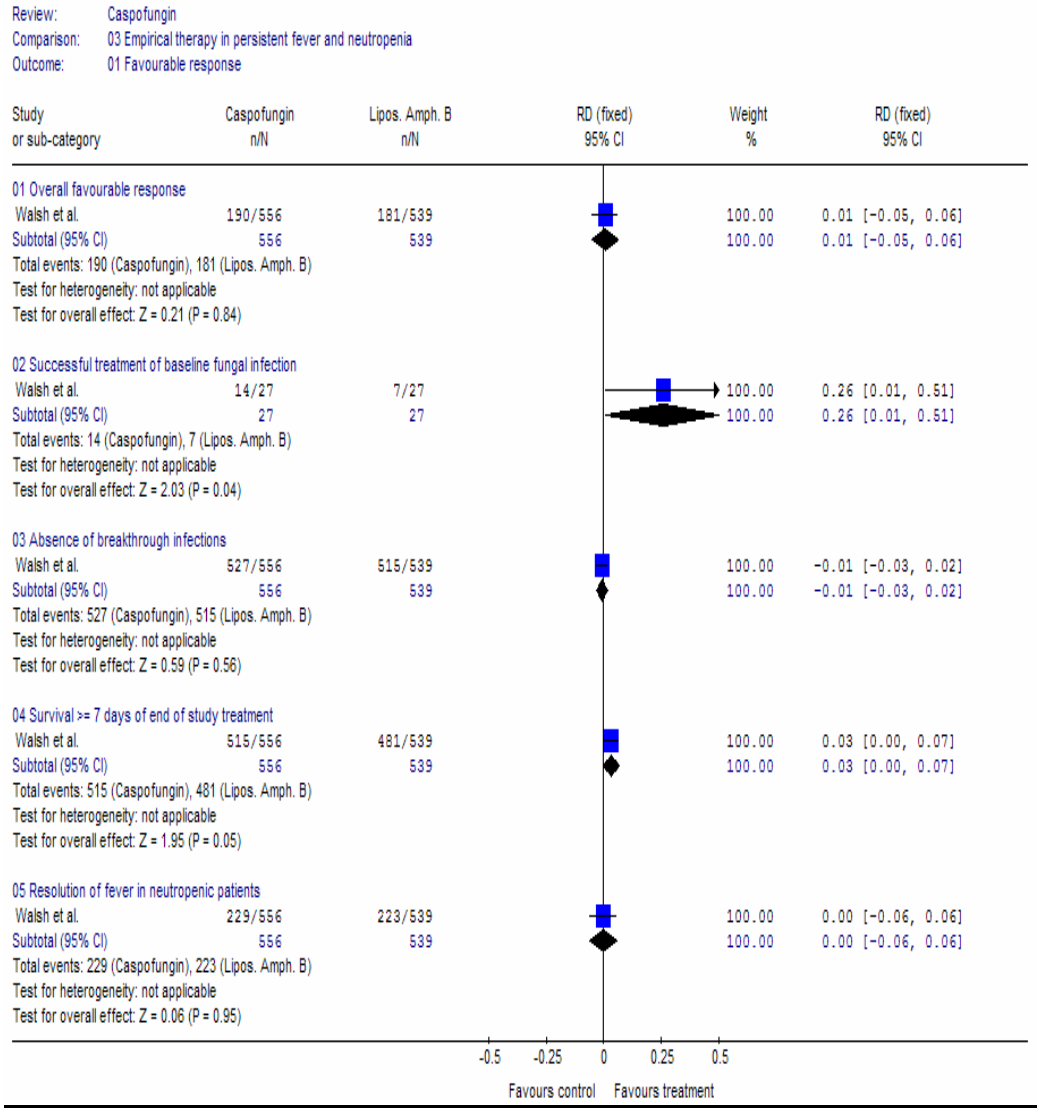
[1] randomized patients with persistent fever and neutropenia who received at least one complete dose of the study drug

[2] 1- Successful treatment of any baseline fungal infection.
2- Absence of any breakthrough fungal infection during therapy or within 7 days of the end of treatment.
3- Survival for 7 days after the end of treatment.
4- No premature discontinuation of the study therapy due to drug-related toxicity or lack of efficacy.
5- Resolution of fever during neutropenia to a temperature < 38° for at least 48 hours.

Among the 1123 randomized patients and 1111 who received treatment, 1095 patients were included in the modified intention-to-treat analysis, 556 and 539 in the caspofungin and liposomal amphotericin B groups, respectively[5]. Approximately 94% of the patients presented with a hematological malignancy, and approximately 64% with acute myeloid leukemia [5]. One-hundred and ninety (33.9%) patients in the caspofungin group and 181 (33.7%) in the liposomal amphotericin B presented an overall favourable response to therapy (difference: 0.2%, 95% confidence interval (CI): -5.6 , 6.0) [5]. Therefore, caspofungin was considered as non-inferior to liposomal amphotericin B according to pre-specified criteria [5]. Results of the overall favourable response and of its five components are shown in Appendix 4 and in the figure below. There was a trend towards a higher rate of favourable response with caspofungin compared to liposomal amphotericin B in most of these five components. The only outcome that showed a statistically significant difference between the groups was the successful treatment of baseline infection, i.e., among the 27 patients/group with an evidence of a baseline fungal infection, successful outcome was observed in 14/27 (51.9%) in the caspofungin group and 7/27 (25.9%) in the liposomal amphotericin B group (absolute difference: 25.9%, 95% CI: 0.9%, 51%) (figure below)[5]. However this result must be interpreted with caution due to 1) the multiple comparisons undertaken, which increases the chance that a statistically significant result occurs by chance, 2) the small sample size (n=27/group) of this subgroup, and 3) the fact that the study was not designed to evaluate this outcome individually (not the primary outcome).

Patient follow-up in this study was relatively short, i.e., during the treatment (median duration: 10-11 days) and for two weeks thereafter[5]. The concomitant use of drugs that may interact with caspofungin or other antifungals under evaluation such as cyclosporine, rifampin, tacrolimus, ritonazole, ritonavir among others was not evaluated in the RCTs as the co-administration of these drugs was an exclusion criterion [5].

Figure 6.1 RCT in adult patients with febrile neutropenia. Results of the primary outcome and its components.



Source: Walsh et al. [5]

Percentages may differ slightly from the publication due to rounding and due to the fact that we are showing unadjusted results.

Comparative non-randomized studies

We identified one study comparing caspofungin to liposomal amphotericin B in patients treated for febrile neutropenia[12] as described below.

A retrospective study compared caspofungin and liposomal amphotericin B in the treatment of febrile neutropenia or invasive fungal infections in adult patients with hematological malignancies [12]. Treatment assignment was done according to the treating physician's judgement[12]. A total of 57 patients were included in the study, 23 treated with caspofungin and 34 treated with liposomal amphotericin B[12]. In patients with febrile neutropenia, 3/8 (37.5%) treated with caspofungin and 7/12 (58.3%) treated with liposomal amphotericin B showed a favourable treatment response[3] (p=0.65) (unadjusted results). In patients with invasive fungal infections, favourable responses were observed in 4/12 (33.3%) and 15/26 (57.7%) in the caspofungin and liposomal amphotericin B groups respectively (p=0.16) (unadjusted results) [12]. Patients treated with caspofungin had a higher risk of mortality compared to patients in the liposomal amphotericin B group, adjusted odds ratio (OR): 7.6 (95% confidence interval (CI): 1.2, 45.5) [12]. Additional details about this study are provided in Appendix 5.

Difficulties in interpreting the results of this study arise from the small sample size and from the fact that the treatment allocation was not randomized. Although in some cases the results were adjusted for potential confounders, there is still a possibility that unmeasured or residual confounding was present.

Safety – Adult patients

Randomized controlled trial

We have summarized below the safety results of the caspofungin RCT by Walsh et al.[5] that included adult patients with febrile neutropenia. Adverse events were monitored during the study and for 14 days after its completion [5]. The investigators were responsible for ascertaining the association between the adverse events and the study drugs [5]. Adverse events considered as caspofungin- or liposomal amphotericin B- related to any degree by the investigator are summarised below, additional information can be found in Appendix 4.

[3] Defined by the following endpoints:
1. Successful treatment of any baseline fungal infection.
2. Absence of any breakthrough fungal infection during therapy or within 7 days of the end of treatment.
3. Survival for 7 days after the end of treatment.
4. No premature discontinuation of the study therapy due to drug-related toxicity or lack of efficacy.
5. Resolution of fever during neutropenia to a temperature < 38ºC for at least 48 hours.

Serious drug-related adverse events

The publication by Walsh et al.[5] did not report any drug-related serious adverse events. Drug-related serious adverse events that occurred during the same RCT (or during the 14-day follow-up) were reported to the regulatory agency of the European Union, EMEA[11], as summarized in the table below.

Table 6.1 Serious drug-related adverse events – Adult RCT comparing caspofungin and liposomal amphotericin B in adult patients with febrile neutropenia.

Safety	**RCT - Empiric treatment of persistent and neutropenia** **Source: data reported to EMEA**[11]	
	Caspofungin **N=564**	**Liposomal amphotericin B** **N=547**
Serious drug-related adverse events, n (%)	9 (1.6%) - Renal failure or insufficiency (n=3) - Rash, patients recovered (n=2) - Infusion-related hypersensitivity reaction that resolved over 3 hours after the infusion (n=1) - Hyperbillirubinemia in patient with metastatic liver and lungs disease (n=1) - Congestive heart failure, hypokalemia, and extension of a myocardial infarction in a patient with AML and underlying cardiovascular disease (n=1) - Bronchiolitis obliterans with organizing pneumonia on lung biopsy done 3 days after the end of the treatment (n=1)	16 (2.9%) - Respiratory system (n=3), respiratory distress, dyspnea, hipoxia - Hypersensitivity reaction (n=3) - Anaphilaxis (n=1) - Anaphilactic reaction (n=1) - Acute renal failure (n=2) - Renal insufficiency (n=1), - Hypokalemia (n=1) - Ventricular fibrillation with cardiac arrest (n=1) - Fungal infection (n=1) - Grand mal seizure (n=1) - Adverse event not clear in one case.
Serious drug-related laboratory adverse events	0	1 (0.1%) - Increased serum total bilirubin
Withdrawal due to clinical drug-related adverse events	25 (4.4%) - Adverse events in the skin (n=10), 1 case of serious rash - Hepatobiliary system or hyperbilirubinemia (n=5) not clear in the remainder	35 (6.4%) - hypersensitivity reactions (n=4) - anaphylaxis or anaphylactic-type reactions (n=3) - fever (n=4) not clear in the remainder
Withdrawal due to laboratory drug-related adverse events	3 (0.5%) - Hepatic dysfunction, increased one or more liver enzymes AST, ALT, alkaline phosphatase, total and direct bilirubin (n=3)	13 (2.4%) - Abnormal liver function tests, increased bilirubin, alkaline phosphatase, AST, ALT) (n=9) - Increased creatinine (n=4)

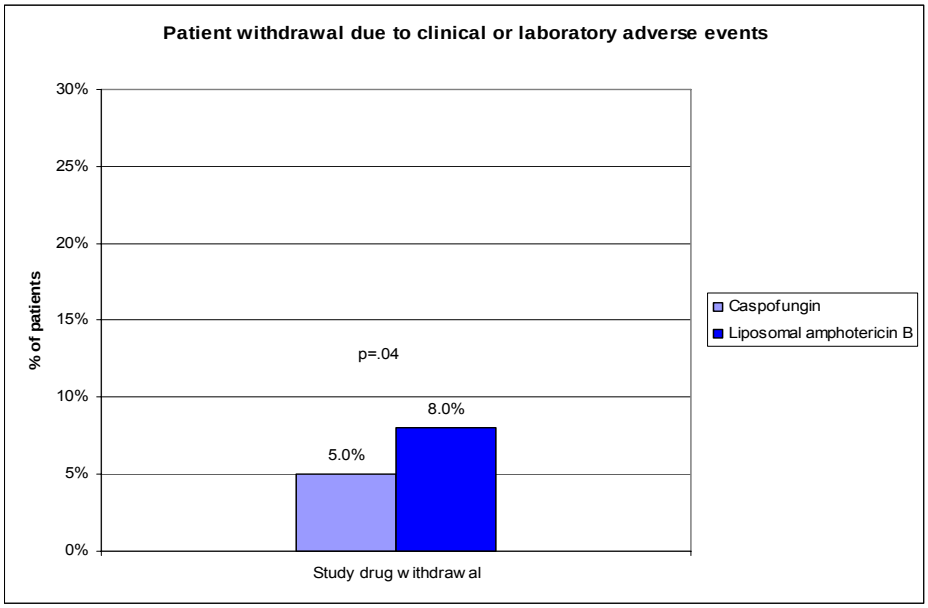
Deaths possibly related to the study drug	1 (0.17%) due to a renal insufficiency considered possibly related to caspofungin	2 (0.37%) cardiac arrest (n=1), respiratory distress (n=1) considered possibly related to the drug

ALT= alanine aminotransferase ; AST=aspartate aminotransferase ; EMEA=European Medicines Agency; AML = acute myeloid leukemia

Withdrawal of study drug due to adverse events

When caspofungin was compared to liposomal amphotericin B in 1111 adult patients with febrile neutropenia in the study by Walsh et al., a -3.1% absolute difference (95% CI: -6, -2) in treatment withdrawal due to adverse events was observed (caspofungin: 5%, liposomal amphotericin B: 8%, p=0.04) (figure below) [5].

Figure 6.2 Adult RCT, rates of withdrawal of the antifungal treatment due to adverse events



Source: Walsh et al. [5]

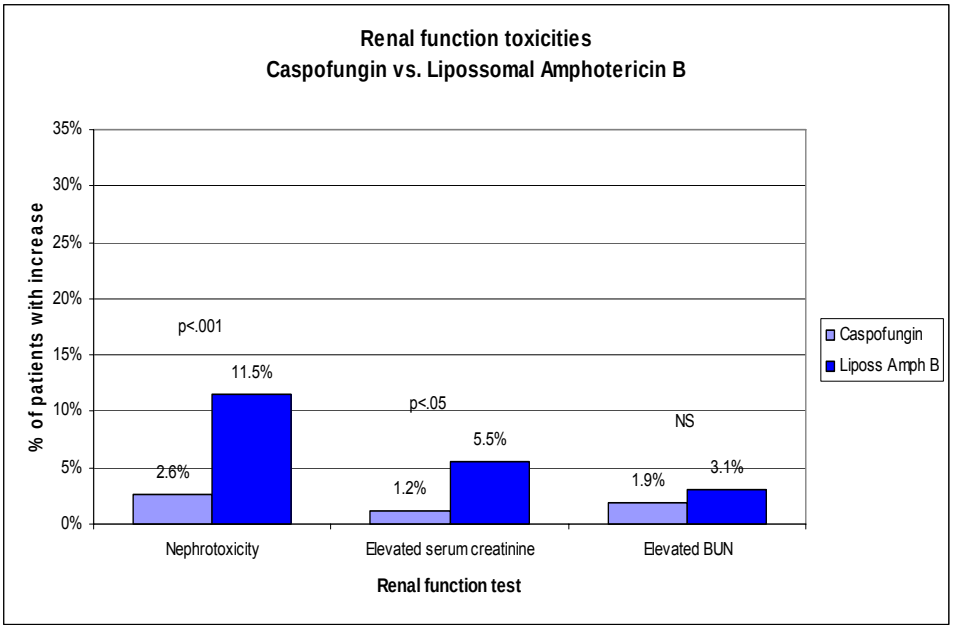
Nephrotoxicity

Nephrotoxicity defined as a doubling of the baseline serum creatinine level or an increase ≥1mg/dL in patients with elevated serum creatinine at enrollment, was measured in adult patients who had a creatinine clearance of at least 30ml/minute in the study by Walsh et al.[5]. There was a 8.9% (95% CI: -12, -5.9, p<.001) absolute difference in the frequency of nephrotoxicity between caspofungin (2.6%) and liposomal amphotericin B (11.5%) (figure 11) [5].

Elevations in serum creatinine and blood urea nitrogen (BUN), which are measures of renal function impairment, were also reported more often with liposomal amphotericin B, compared to

caspofungin [5] as shown in the figure below. The difference was not statistically significant for BUN. The clinical significance and magnitude of the increase was not specified by the authors.

Figure 6.3 Adult RCT, frequencies of renal function toxicity

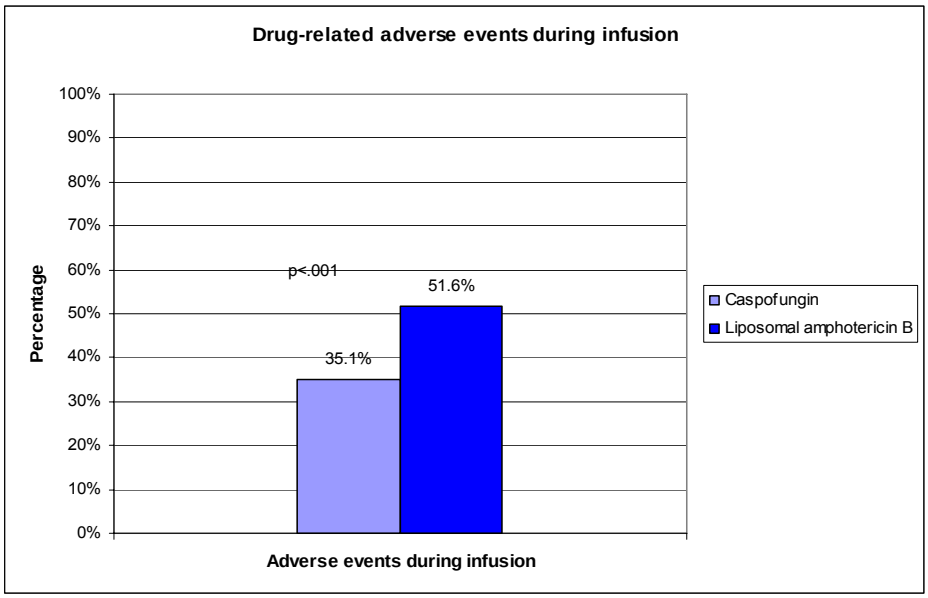


Source: Walsh et al. [5]
Nephrotoxicity was defined as a doubling of the baseline serum creatinine level or an increase ≥1mg/dL in patients with elevated serum creatinine at enrollment [5]. Patients with creatinine clearance < 30ml/minute were not included in this analysis[5].
NS=not statistically significant

Drug infusion-related events

The frequency of drug infusion-related events was lower with caspofungin compared to liposomal amphotericin B [5]. The figure below shows the results reported. The most frequently reported infusion-related events were fever, chills, headache, nausea, and vomiting [5].

Figure 6.4 Adult RCT, frequencies of adverse events during drug infusion

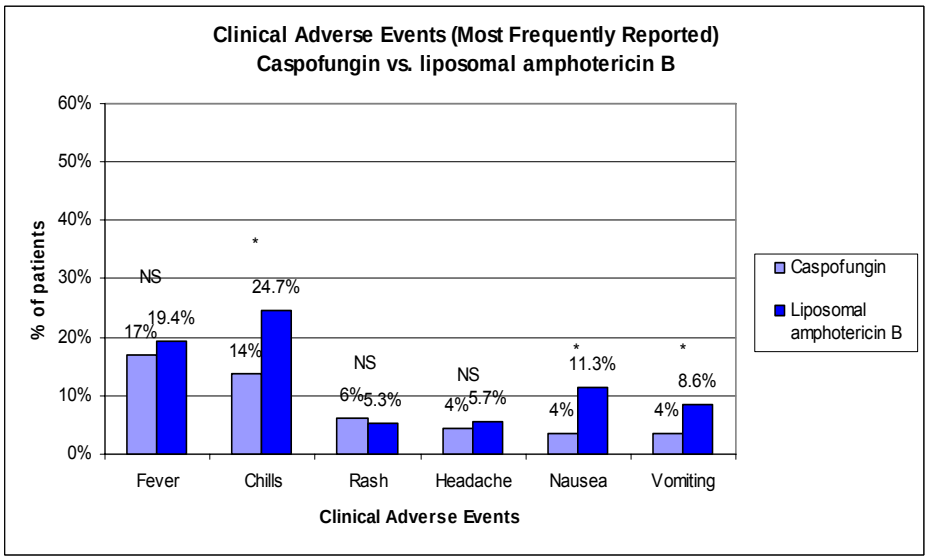


The most frequently reported infusion-related events were fever, chills, headache, nausea, and vomiting [5]
Percentages values are rounded up.

Clinical drug-related adverse events

The most common clinical drug-related adverse events reported were fever, chills, rash, headache, nausea, vomiting, and phlebitis (figure 13). There was a trend towards a lower rate of these events with caspofungin compared to liposomal amphotericin B (figure below) [5].

Figure 6.5 Adult RCT, frequencies of clinical adverse events

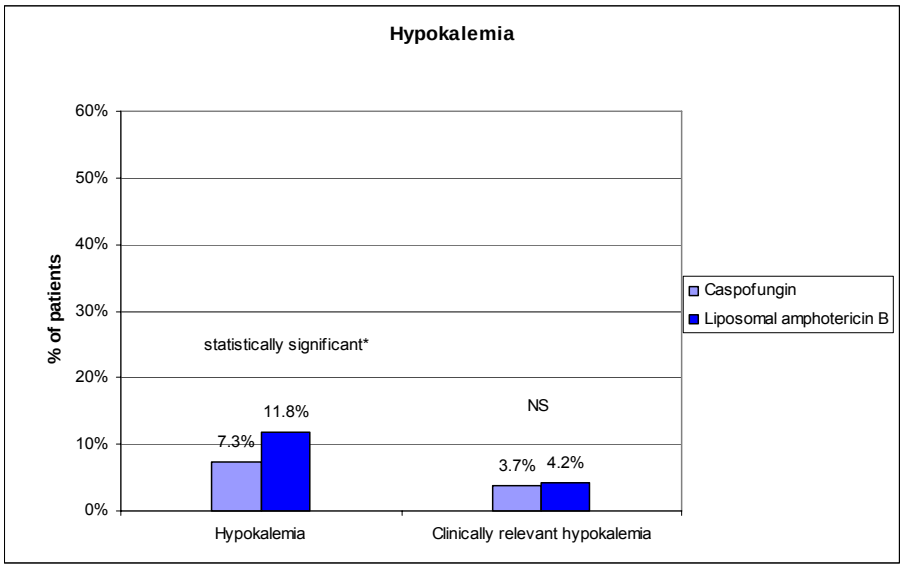


Source: Walsh et al. [5]. * Statistically significant / NS= not statistically significant
Statistical significance was based on the 95% confidence interval of the absolute difference between the two groups.

Hypokalemia

A lower frequency of hypokalemia with caspofungin (7.3%) compared to liposomal amphotericin B (11.8%) (difference: -4.5%, 95% CI: -7.9 , -1.0) was also observed (figure below) [5]. The frequency of clinically relevant hypokalemia was similar between the two groups, i.e., 3.7% and 4.2%, respectively (absolute difference: -0.5% (95% CI: -2.8 , 1.8) [5].

Figure 6.6 Adult RCT, frequency of hypokalemia

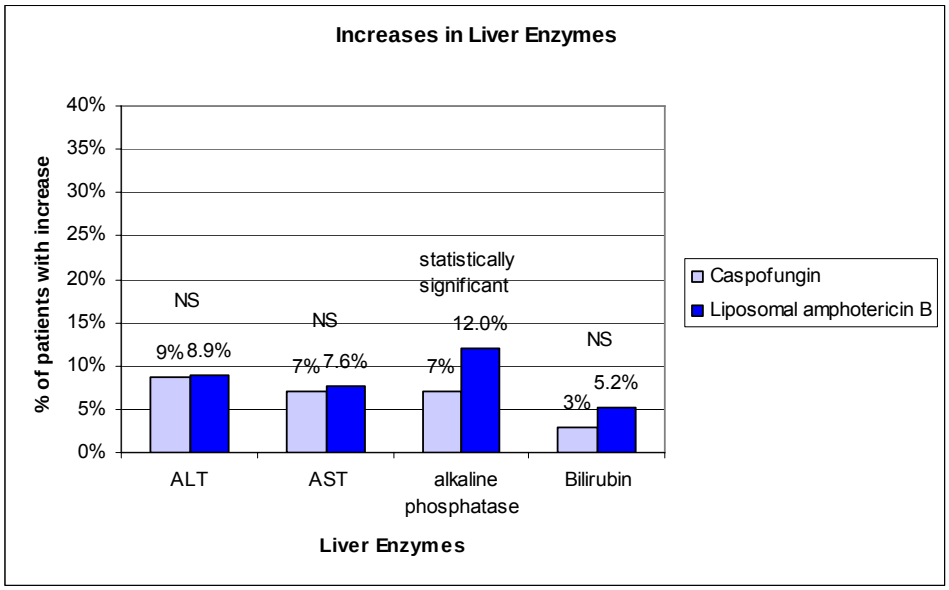


Sources: Walsh et al. [5].
NS=not statistically significant
*Statistical significance based on the 95% confidence interval of the absolute difference between the two groups

Liver enzymes abnormalities

Caspofungin showed a similar frequency of liver enzyme elevations compared to liposomal amphotericin B (statistically significantly lower for alkaline phosphatase) [5] (Figure below).

Figure 6.7 Adult RCT, frequency of increases in liver enzymes



Source : Walsh et al. [5]. NS=not statistically significant
Statistical significance based on the 95% confidence interval of the absolute difference between the two groups
ALT= alanine aminotransferase / AST=aspartate aminotransferase

APPENDIX 7 SAFETY- CASPOFUNGIN USED CONCOMITANTLY WITH CYCLOSPORINE

Due to the nature of the underlying diseases of patients with invasive fungal infections, the co-administration of cyclosporine and antifungals is common[14]. Since trials in healthy volunteers receiving caspofungin and cyclosporine concomitantly showed that some patients developed elevations of liver function enzymes possibly related to this drug combination, co-administration of the two drugs is recommended to be used only in situations where the benefits outweigh the risks[15]. Some investigators evaluated the hepatotoxicity in patients with the use of caspofungin concomitantly with cyclosporine in adult and pediatric patients [4, 6, 14, 16 17 18 19 20 21]. Most of the patients in these studies were adults who had undergone HSCT or solid organ transplants [14, 16 17 18]. The rates of hepatotoxicity with the combination are reported in these studies are summarized in the table below.

The authors of a retrospective chart review of 20 patients who underwent stem cell transplantation concluded that the concomitant use of caspofungin and cyclosporine results in a low hepatic toxicity in the patient population as shown by a transient increase in liver enzymes during treatment[18] (table below). During the concomitant treatment with caspofungin and cyclosporine that lasted for a median of 16.5 days (5-42), there was an increase in the median level of liver enzymes to above the upper normal level with most enzymes [18]. Given the large standard error of the mean (SEM) and graphs provided[18] there was a large variation in the change in the level of liver enzymes experienced by the patients. In a retrospective observational study performed at The Hospital for Sick Children (Toronto), among 19 patients who received cyclosporine concomitantly with caspofungin, there was one event of hepatotoxicity (1.5%) [increase in aspartate aminotransferase (AST)][4].

In general, the authors concluded that when used in a population in which the potential benefits outweight the potential risks, the caspofungin/cyclosporine combination seemed tolerable[14 16 17 21], but that larger prospective studies are necessary [14 16 17]. The authors of the retrospective chart review that included 20 patients concluded that the concomitant use of caspofungin and cyclosporine resulted in a low hepatic toxicity in patients who underwent an allogeneic stem cell transpant[18]. A multicenter survey showed a trend towards a higher frequency of a ≥ 3-fold increase in liver enzymes from baseline in patients receiving the combination compared to those who didn't (table) [6]. The authors concluded that they did not observe overall differences between patients who used (n=19) and those who did not use the combination (n=45)[6]. Similarly, Glasmacher et al. did not observe a harmful interaction in patients using caspofungin concomitantly wit cyclosporine (n=14) and concluded that the concomitant use of the two drugs may be considered, however, close monitoring of the hepatic function is recommended in these

patients[19]. The figures provided by the authors suggest an increase in enzyme levels measured during the treatment for ALT and gama GT which decreases after the end of treatment (individual statistical tests not provided) [19]. Morrissey et al. believe that although there may be an increase in liver enzyme levels when the combination caspofungin-cyclosporine is used, clinically significant hepatotoxicity has not been reported and drug discontinuation is seldom necessary[20].

Table 7.1 Rates of hepatotoxicity in patients treated with caspofungin concomitantly with cyclosporine

Study	N / Treatment / Median duration	Baseline Hepatotoxicity	Hepatotoxicity during treatment
Sanz-Rodriguez et al.[3, 16] Retrospective (chart review	N=14 (1 pediatric) Caspofungin concomitant with Cyclosporine IV* Duration: not clear	10 (71%)	10 (71%) ALT and/or AST > ULN 1 (7%) – related to caspofungin (transient and not clinically significant), therapy not discontinued
Saner et al. [17] Prospective	N=12 adults Caspofungin concomitant with Cyclosporine IV Duration: median: 14 days (range: 8-14)	All patients underwent liver transplantation	1 (8%), ALT and AST: 11-fold increase Clinically significant Not believed to be related to caspofungin/cyclosporine combination
Marr et al. [14] Retrospective (database study)	N=40 (2 pediatrics) Caspofungin concomitant with Cyclosporine* Duration: median: 17.5 days (range: 1-290)	12 (30%)	4 (10%) – discontinued treatment due to hepatotoxicity, 2 (5%) possibly due to caspofungin/cyclosporine** 24 (60%) – increased liver enzymes§, 6 (15%) possibly due to caspofungin/cyclosporine** , not clinically relevant
Christopeit et al.[18] Retrospective chart review	N=20 Caspofungin concomitant with cyclosporine Duration: 16.5 days (5-42) - caspofungin Length of concomitant treatment – not given Patients with concomitant azole drugs excluded	Not reported	Median enzyme levels (SEM) before / during / after caspofungin treatment ALT: 0.39 (0.65) / 0.77 (17) / 0.56 (0.77) µmol/L (upper normal: 0.74) AST: 0.28 (0.45) / 0.71 (26.26) / 0.60 (0.84) µmol/L (upper normal: 0.58) GGT:1.27 (1.78) / 2.33 (3.41) / 1.77 (4.32) µmol/L (normal: 0.92) Bilirubin: 23 (19.69) / 38 (55.41) / 20 (67.23) µmol/L (normal: 17)
Koo et al. [4] Retrospective chart review	N=19 (pediatrics) Caspofungin concomitant with cyclosporine Treatment duration: not	Not reported	1/19 (5.3%) – possibly related to caspofungin Hepatotoxicity not defined

	reported		
Groll et al. [6] Retrospective multicenter survey	N=64 (pediatrics) 19 / 45 with and without combination. Median duration of caspofungin therapy: 37 days – duration of combination not provided	Not reported	With combination / without Increase ≥ 3x baseline AST: 3 (16%) / 4 (7%) p=0.42 ALT: 3 (16%) / 6 (13%) p=1 Alkaline phosphatase: 1 (6%) / 0 p=0.3 Bilirubin: 0 / 3 (9%) p=0.5
Glasmacher et al.[19] Prospective multicenter study	N=14 (adults), 104 did not use the combination. Caspofungin treatment duration: median: 15 days – duration of combination not provided	Not reported	Differences were statistically significant when enzyme levels before, during, and after concomitant treatment were compared, however, not when before and after were compared. Values not given, figures suggest an increase in enzyme levels measured during the treatment for ALT and GGT which decreases after the end of treatment.
Morrisey et al. [20] Prospective study	N=8 (adults) Median duration: 15 days (combination)	10 (18.5%) – pre-existing liver disease	3/8 (38%) – elevation in liver enzymes ≥ 3x baseline / ≥ 5x upper normal limit . No clinical hepatotoxicity.
Trenschel et al.[21] Retrospective study	N=14 (adults) / 28 historic controls Caspofungin treatment duration: median: 13 days – duration of combination not provided	Not reported	Only mean difference in bilirubin before and after treatment was statistically significantly higher in patients using caspofungin-cyclosporine compared to historic control.

ALT=alanine amino transaminase; AST=aspartate amino transaminase; GGT=gama glutamyl transferase; IV=intravenous / SEM=standard error of the mean
* Concomitant use for at least 1 day
** The authors stated that other causes of hepatotoxicity other than the caspofungin/cyclosporine combination were possible [14].
§ - > 3x baseline or > 5x upper limit of normal[14].

APPENDIX 8 SYSTEMATIC REVIEWS, HEALTH TECHNOLOGY ASSESSMENT REPORTS, AND ECONOMIC ANALYSES

Systematic Reviews

A systematic review published in 2007 included 5 RCTs and 1 sub-study and evaluated the efficacy and safety of caspofungin compared to other antifungals in adult patients[22]. Studies on different treatment indications such as the empiric treatment of febrile neutropenia, invasive candidiasis, oropharyngeal and/ or esophageal candidiasis using different comparators such as different formulations of amphotericin B, fluconazole, and itraconazole were included [22]. The authors compared the caspofungin results with the pooled results obtained with different antifungals and different patient populations[22]. The rates of overall success were 52.6% and 44.7% with caspofungin and the pool of antifungals, respectively, and 13.8% vs. 16.9%, respectively for overall mortality (no measure of variation was provided) [22]. Safety outcomes were combined in random or fixed effects meta-analyses[22]. These included discontinuation of therapy due to drug toxicity (OR: 0.25, 95% confidence interval (CI) 0.07 . 0.85), nephrotoxicity (doubling of serum creatinine or ≥ 1mg/dL serum creatinine elevation if the level was elevated at baseline) (OR 0.23, 95% CI: 0.14 , 0.36), hypokalemia (OR: 0.3, 95% CI: 0.12, 0.76) and fever (OR: 0.26, 95% CI: 0.08 , 0.79) for caspofungin vs. the other antifungals[22]. The authors concluded that caspofungin has a better cure rate and less adverse effects than amphotericin B but mentioned that their systematic review had limitations such as the inclusion of different caspofungin doses, different lengths of antifungal treatment, and different treatment indications[22]. Moreover, different antifungals with different risks of adverse events were pooled into one comparator group which renders the results difficult to interpret.

Health Technology Assessment (HTA) Reports

Two HTA reports were identified in our systematic reviews, one published in 2001 by the Canadian Agency for Drugs and Technologies in Health (CADTH)[23], and one published in 2004 by the Institute for Clinical Effectiveness and Health Policy in Argentina[24].

The report from CADTH was published as an Emerging Drug List report on the use of caspofungin for the treatment of invasive aspergillosis in patients refractory or intolerant to other antifungals such as amphotericin B and itraconazole[23]. The authors concluded that the evidence available was scarce as no RCTs had been fully published and therefore the benefits and role of the drug could not be evaluated at that point[23].

The report from the Institute for Clinical Effectiveness and Health Policy in Argentina published in 2004 evaluated the efficacy and costs of caspofungin in patients with fungal infections[24]. It was based on five RCTs that included patients with febrile neutropenia invasive candidiasis, and

esophageal or oropharyngeal candidiasis. The authors concluded that caspofungin is not inferior in efficacy to amphotericin B in immunodeficient patients with invasive candidiasis and aspergillosis, and presents a lower incidence of adverse events, however with a higher cost[24]. The authors believe that caspofungin could be an alternative in cases where liposomal amphotericin B would be prescribed and it would be the only alternative in cases of fungal infections refractory to other antifungals[24].

Economic Analyses

Five economic analyses comparing caspofungin to liposomal amphotericin B in adult patients with febrile neutropenia [25] [26] [27] [28] [29] were identified in the literature. The clinical outcomes of these analyses were derived from published RCTs in adult patients.

A study by Wingard et al. evaluated the cost-effectiveness of caspofungin vs. liposomal amphotericin B in febrile neutropenic patients[25]. The clinical outcome consisted of the rate of impaired renal function (IRF)[4] and was based on the data from an adult RCT[25]. Costs included antifungal drug acquisition costs and those associated with treating IRF[25]. Drug acquisition costs were based on hospital prices in the United States [25]. Costs with IRF were based on published literature that evaluated the total hospitalization costs in patients who suffered nephrotoxicity compared to those without nephrotoxicity while on treatment with amphotericin B formulations[25]. Costs are shown in 2003 US dollars[25]. The costs per full-course of antifungal treatment used were $6,942 and $3,996 for liposomal amphotericin B and caspofungin, respectively and the cost per IRF episode was $26,440[25]. A short-term cost-effectiveness analysis was undertaken based on the duration of the antifungal treatment (mean 13 days, range 1-90) [25]. The authors reported cost savings of $5,236/patient treated with caspofungin compared to lipossomal amphotericin B[25]. The IRF costs were based on differences in total hospitalization costs rather than costs incurred specifically due to the renal impairment. In general in the studies in which IRF costs were based patients who developed nephrotoxicity also seemed to have a higher rate of more severe underlying diseases than patients who did not develop nephrotoxicity, which may have resulted in an overestimation of the IRF costs. Although some of these studies adjusted the IRF cost differences for patient characteristics there are still risks of residual or unmeasured confounding, which is corroborated by one of the authors[30] and other publications[31]. For instance in a study by Bates et al., used as one of the sources of IRF cost, the additional cost of treating nephrotoxicity alone was estimated at $8,947 with an additional length of stay of 2.5 days compared to those not experiencing nephrotoxicity, whereas in the same study the additional total hospital cost (used in the caspofungin pharmacoeconomics analysis by Wingard et al.) was $29,823 with an additional

[4] Defined by a doubling of the baseline serum creatinine level or an increase ≥1mg/dL in patients with elevated serum creatinine at enrollment. Patients with creatinine clearance < 30ml/minute were not included in this analysis.

length of stay of 8.2 days[30] in patients that experienced nephrotoxicity compared to patients who didn't. Even though the cost-effetiveness analysis by Wingard et al. included sensitivity analyses with the objective of testing the robustness of the IRF costs these analyses did not lower the IRF costs enough to reach the cost of treating nephrotoxicity alone reported in the study by Bates et al.. Therefore it is not possible to infer what the cost-effectiveness results would be if nephrotoxicity costs alone were used as a base for IRF costs.

An economic analysis by Kaskel et al. yielded a cost saving of €96 (95% CI: €352 , incremental €113) per patient treated with caspofungin compared to liposomal amphotericin B as an empirical therapy for suspected fungal infection when the cost of nephrotoxicity was taken into account[27].

An economic analysis from the UK compared the long-term cost-effectiveness of caspofungin compared to liposomal amphotericin B in adult patients with suspected fungal infections[26]. The patients' lifetime was employed as the time horizon[26]. Short-term clinical outcomes used in the analysis were obtained from an adult RCT and included treatment efficacy, probabilities of adverse effects associated with each drug, and mortality 1 week after treatment completion[26]. Long-term mortality was extrapolated according to the life expectancy of the different underlying diseases presented by the RCT patients based on published literature[26]. Quality-adjusted life-years were calculated based on preferences scores from the Registry from the Harvard School of Public Health 1997-2000[26]. Costs included antifungal drugs' acquisition costs, costs to treat the treatment complications, and hospitalization costs and were calculated in 2005 sterling pounds[26]. The analysis yielded a 0.55 (95% CI: 0.1 , 0.97) life years gained and 0.4 QALY (95% CI: 0.13 , 0.97) with caspofungin compared to liposomal amphotericin B[26]. The mean total direct costs were CDN$19,506 ($13,896 , $25,129) [5] and CDN$23,566 (95% CI: $17,786 , $29,419) with caspofungin and liposomal amphotericin B, respectively[26]. An acceptability curve showed that at willingness-to-pay values of CDN$39,960 (£$20,000) and CDN59,940 (£$30,000) there is a 95% chance that caspofungin is cost-effective compared to amphotericin B.

An economic analysis comparing the use of caspofungin and liposomal amphotericin B uses as empirical treatment in adult patients with febrile neutropenia in Italy was published[28]. The patients' lifetime was used as the time horizon for the analysis[28]. Clinical outcomes were based on the RCT by Walsh et al.[5] which was complemented by the life-expectancy of the patients alive at the end of the treatment and multiplied by the utility value based on the underlying conditions[28]. Costs of treatment during the hospital stay were included in the model[28]. Antifungal costs before and after switch if it was the case, costs of treatment of complications, and costs of hospital stay were

[5] Values reported in sterling pounds: mean direct costs: 9,763 (95% CI: 6955 , 12577) with caspofungin, and $11,795 (95% CI: $8902 , 14724) with liposomal amphotericin B.

included in the model[28]. Costs were based on Italian sources[28]. The results showed that treatment with caspofungin resulted in 0.70 life-years lost (0.52-0.89), and 1.05 (0.84 – 1.29) with liposomal amphotericin B[28]. QALYs lost were 0.50 (0.31-0.7) and 0.75 (0.47-1.03) respectively[28]. Total treatment costs were estimated as €$ 8,351 (7,801 – 8,903) and €$11,821 (11,168 – 12,494) with caspofungin and liposomal amphotericin B, respectively[28].

An economic evaluation of different treatment strategies used in the empiric antifungal treatment of adult patients with a high risk of developing invasive fungal infections in Spain was published[29]. Voriconazole and caspofungin were compared to liposomal amphotericin B and amphotericin B lipid complex[29]. The time horizon consisted of the course of antifungal treatment[29]. Clinical outcomes such as response to treatment, treatment switches, and treatment complications were based on an observational study done in the hospital where the economic evaluation was done[29]. Antifungal costs before and after switch if it's the case, diagnostic and laboratory tests, and hospitalization costs were included in the analysis and were based on costs from the hospital[29]. Costs with treatment complications were not included[29]. A total of 107 patients were included in the analysis, 53 treated with amphotericin B lipid complex group, 25 with liposomal amphotericin B, 25 with caspofungin, and 6 with voriconazole[29]. The mean length of treatment was 10 days in the amphotericin B lipid complex and voriconazole groups, 8 in the liposomal amphotericin B group and 16 in the caspofungin group[29]. The results showed that voriconazole was the most effective of the drugs evaluated with the lowest cost[29]. The authors did not discuss the possible causes of differences in treatment duration among the groups. The comparability between the groups in the view of non-randomized treatment assignment and small sample sizes especially in the voriconazole group was also not discussed.

APPENDIX 9 COST OF ANTIFUNGAL-RELATED COMPLICATIONS

Complications reported in the RCT comparing caspofungin to liposomal amphotericin B in pediatric patients that are expected to either increase treatment costs and/or result in clinical consequences were included in our model. These included nephrotoxicity, hypokalemia, chills (rigour), rash, and nausea.

The RCT from which the data were derived did not provide a detailed definition of the complications other than nephrotoxicity. The clinical significance of these complications was not provided in the RCT.

The costs of treatment of each complication was estimated based on the literature and expert opinion and included hospitalization costs, diagnostic and laboratory tests, and healthcare professional fees as applicable.

Table 9.1 Resource use and cost of treatment of nephrotoxicity (doubling of serum creatinine*)

Resource	Unit cost	Quantity	Cost
Additional hospital stay	$1,071** per day	2.5 days based on a study by Bates et al.§ (range 0 to 2.5 days)	$ 2,677 (range $0-$ 2,677)
Medical consultations	$29.20	2.5 (1 per additional day in hospital) (range 0-2.5)	$73 (range $0 - $73)
Total cost	-	-	$2,750 (variation $0-2,750)

*Doubling of serum creatinine was the definition of nephrotoxicity adopted in the RCT study used as a source for our economic analysis[32].

**Based on the daily treatment of a sample of febrile neutropenic patients included in a study conducted in our institution[33] described in session 8.1 of the report.

§Although several studies in adult patients have shown that nephrotoxicity increases the length of hospitalization from 0 to 8.2 days, we have decided to use the estimate of one of the studies that reported the increase in length of stay (LOS) specifically associated with nephrotoxicity, 2.5 days (vs. overall increase in LOS of 8.2 days) [30] or zero (study which was restricted to patients with HSCT with cancer[34]). The other studies compared the difference in LOS between patients without nephrotoxicity and with nephrotoxicity even though patients with nephrotoxicity also had more severe underlying diseases (bone marrow transplantation, cancer, acute leukemia etc.) which may have contributed to the increased LOS [35] [36] [37] [38]. By using the data from studies that calculated the increased LOS associated with nephrotoxicity we believe that we avoided overly inflating the cost antifungal-related nephrotoxicity with costs that may be associated with more severe underlying diseases. The fact that a study that evaluated the impact of amphotericin B-related nephrotoxicity in the hospital LOS in a population restricted to patients with high risk of nephrotoxicity (HSCT with cancer) found no difference in LOS between patients who developed nephrotoxicity and those who didn't corroborates our point [34].

We assumed that no additional laboratory tests such as creatinine measurement would be necessary as a result of nephrotoxicity since it is already measured on a daily basis during the antifungal treatment.

Table 9.2 Resources and cost of treatment of hypokalemia

Resource	Quantity	Cost/day
Potassium IV infusion (20 kg child)	1 mmol / kg over 4 hours[33]	$0.53 (20 kg x 1 mmol + 20% wasting)
Serum potassium measurements	2 additional serum potassium measurements/day*	$6.24
Medical consultations	1 additional medical consultation per day to evaluate serum potassium level.*	$29.2
ECG¶	1 ECG exam for every 2 patients	$8.25
Total cost/day	-	$44.22

* Serum potassium measurements and physician reassessment of potassium infusion are necessary during an episode of hypokalemia according to our institutions guidelines[39].
¶ - Some patients experiencing hypokalemia ≤ 3 mmol/L are put on a cardiac monitor, an ECG may be requested if deemed necessary according to our institutions guidelines[39].

Table 9.3 Resources and cost of treatment of chills / rigour

Adverse Event	Quantity	Cost/day
Meperidine IV (20 kg child)	0.5 mg/kg/dose [40]	$0.145 (10mg x 1.2 (20% wasting) x $0.6/50mg)
Total cost/day		$0.145

IV=intravenous

Table 9.4 Resources and cost of treatment of rash

Adverse Event	Quantity	Cost/day
Dyphenhydramine IV (20 kg child)	1 mg/kg 1 to 2 times/day	$0.69 (20mg x1.2 (20% wasting) x 2 doses of $0.72/50mg)
Total cost/day		$0.69

IV=intravenous

Table 9.5 Resources and cost of treatment of nausea

Adverse Event	Quantity	Cost/day
Dimenhydrinate IV (20 kg child)	1 mg/kg/dose 3 doses*	$2.04
Or Dyphenhydramine IV (20 kg child) – used more often than dimenhydrinate	1 mg/kg 3 doses*	$1.04 (20mg x 1.2 (20% wasting) x 3 doses $0.72/50mg)
Total cost/day		$1.04 or $2.04

IV=intravenous
* Medications to treat nausea may be administered up to every 4 hours, depending on the patient's need. We have assumed that 3 doses per day would be administered

We assumed that patients who experience the complications above (except nephrotoxicity) would receive treatment for the complication for seven days.

Other complications reported in the RCT such as increases in liver enzymes, tachycardia, fever, and headache were not included in our model since they were not expected to increase the resource use/cost of treatment as explained below and since the RCT did not report any clinical consequences of these complications.

Patients with increases in liver enzymes do not receive a specific treatment, however the antifungal treatment may be switched to a different antifungal as a result of the hepatotoxicity [11 41 42] . We have assumed that cases where treatment switch due to hepatotoxicity is necessary would have been indirectly accounted for in the model in the arm drug switch. No additional treatment switch was assigned due to hepatotoxicity alone.

Patients who experience tachycardia may be put on a cardiac monitor according to expert opinion. The cost of using a cardiac monitor could not be quantified and given that a large number of patients may use the machine every year, we considered that its inclusion in the analysis would not impact the results.

Costs of treatment of fever and headache were not included since the treatments used for these complications may coincide with those used as a treatment of other complications. In order to avoid double-costing, and considering that the costs of treatment of fever and headache would be negligible and would not change our results, we decided not to include the cost of fever and headache in our analyses.

APPENDIX 10 AMPHOTERICIN B NEPHROTOXICITY COSTING STUDIES

Table 10.1 Amphotericin B nephrotoxicity costing studies, study characteristics and results

Study	Drugs used	Adults or pediatrics	N	Indication	Underlying conditions	Increases in LOS in patients with nephrotoxicity vs. no nephrotoxicity	Difference in costs in patients with nephrotoxicity	Comments	Nephro toxicity definition	Method of control for confounding
Wingard et al. [35](US - retrospective)	Amphotericin B	Adults and adolescents (14-85)	239	Invasive aspergillosis	HSCT - 37% / SOT - 26%	-	-	Patients who had nephrotoxicity also had more severe underlying disease / BMT which may have contributed to increased costs and LOS	2x baseline serum creatinine	-
Ullman et al. [36](4 European countries) - prospective	Conventional and lipid formulations of amphotericin B - observational retrospective	Adults (mean age:49 y)	419	Suspected FI: 56% Possible, probable, proven: 44%	HSCT: 23% / SOT: 0.5%	Additional LOS in hospital 5.3 days extra overall	-	Adjusted for possible confounding	50% increase in baseline peak serum creatinine	Cox proportional hazards

Cagnoni et al. [37](US)	Conventional and liposomal amphotericinliposomal amphotericin B . Resource use and cost data collected prospectively	Adults? (Mean age: 41 y)	414	Febrile neutropenia with prior chemotherapy	HSCT: 51%	Additional LOS in hospital 7 days all patients / -0.6 in BMT	US$ 25,206 (all patients 1996 $)	Patients who had nephrotoxicity also had more severe underlying disease / BMT which may have contributed to increased costs and LOS. Amph B had higher nephrotoxicity than LAMB (34% vs. 19%), however LOS between 2 groups was similar	2x baseline serum creatinine and > 1.2mg/dl	No adjustment
Bates et al. [30](US)	Amphotericin B (retrospective data collection)	Adults (mean age: 46 y)	707	Not provided	HSCT: 25% (31% in acute renal failure, 22% no acute renal failure)	Additional LOS after start of therapy 10 days (unadjusted) , 8.2 days (adjusted) Extra LOS associated with nephrotoxicity 2.5 days	$44,557 (US$, year ?) (unadjusted), $29,823 (adjusted), $8,947 (associated with nephrotoxicity)	Multivariate analysis through linear models - can you adjust for non-normally distributed outcomes ? Authors state that residual confounding by indication and severity of illness may still be present despite adjusted analyses. LOS associated with nephrotoxicity given	Acute renal failure: 50% increase in baseline serum creatinine with a peak >= 2.0 mg/dl (severe >= 3.0 mg/dl)	Univariate and multivariate analyses

Gubbins et al. [34](US)	Amphotericin B (retrospective data collection)	Adults (mean: 51 y)	69	Empirical or prophylactic use, or documented infection	HSCT and multiple myeloma 100% (saline hydration: 60%)	Additional LOS in hospital 2 days, p=0.69 (no difference according to authors) LOS after amph B started 0 days (from median)	-	High-risk patients, all had HSCT and cancer - less prone to confounding by severity of illness	2x baseline serum creatinine	Study sample restricted to patients with high risk of nephrotoxicity , i.e., HSCT with cancer
Harbarth et al.[38] (US)	Amphotericin B (retrospective data collection) year of treatment: 1990-1998	Adults (mean: 52 y)	494	Not provided	Leukemia, lymphoma or malignancy : 39%	Additional LOS after amphotericin B started 4 days (from median), NS	$14,500 (1998 US$) (unadjusted) - adjustments did not change statistical significance for cost ratio (values not provided)		2x baseline serum creatinine up to an absolute value >= 2.0 mg/dl	Multivariate analysis - Cox proportional hazard

BMT=bone marrow transplantation / FI-fungal infection / HSCT =hematopoietic stem cell transplantation / LOS=length of stay / SOT=solid organ transplant

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