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FULL REPORT

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.

ABSTRACT

Introduction

Neutropenic patients with fever that persists despite antibacterial treatment are suspected of having a fungal infection. Conventional amphotericin B may be used as empiric antifungal treatment of children with persistent febrile neutropenia, however there are concerns with its safety profile. Other antifungals are believed to have an improved safety profile, such as caspofungin and liposomal amphotericin B, however due to a higher cost, their use is often limited to circumstances where toxicity with conventional amphotericin B is a concern. There is currently a paucity of comparative clinical and economic evidence between caspofungin and other antifungals in children. Our objectives were to evaluate the efficacy, safety, and cost of caspofungin compared to conventional amphotericin B and liposomal amphotericin B in the empiric treatment of persistent febrile neutropenia in children.

Methods

Our study population consisted of febrile neutropenic children 2-17 years old with hematological malignancies or who underwent an haematopoietic stem cell transplantation and who required empiric antifungal treatment. A systematic review of the peer-reviewed and gray literature was conducted in order to identify comparative and non-comparative caspofungin studies in adult and pediatric patients with febrile neutropenia. Adult studies were used to complement the data in children where appropriate. Outcomes included in the analysis were treatment response, antifungal switches, complications, and costs. We calculated the costs of empiric antifungal treatment with caspofungin, conventional and liposomal amphotericin B from a health care system perspective. It included the drug acquisition costs, materials, and nursing and pharmacy personnel time. The analysis was based on a 14-day treatment duration and a 20 kg/0.79 m^2 child. In univariate sensitivity analyses we varied factors that may impact treatment cost such as treatment duration and patient weight. In an economic evaluation we compared the treatment costs and outcomes between caspofungin and liposomal amphotericin B. The current evidence suggests a similar efficacy between caspofungin and liposomal amphotericin B in our patient population. We created a decision model and performed a cost-minimisation analysis using probabilistic sensitivity analysis (10,000 Monte Carlo simulations). Data for the probabilistic sensitivity analyses were derived from a caspofungin randomized controlled trial (RCT) in children with febrile neutropenia presented at a conference and included the rates of complications and drug switches reported. Costs associated with these outcomes and the antifungal treatment were also included.

Results

One pediatric RCT presented at a conference and one published adult RCT comparing caspofungin and liposomal amphotericin B in febrile neutropenia were identified. In addition, 8 non-comparative studies but no systematic review, meta-analysis, or economic analysis with caspofungin in pediatric patients were identified. The pediatric RCT included 82 patients, 56 and 26 in the caspofungin and liposomal amphotericin B groups respectively. The authors concluded that the two drugs had a similar rate of overall treatment response. There was a trend towards a lower rate of some adverse events when caspofungin was compared to liposomal amphotericin B (nephrotoxicity, 6% vs. 8%, and hypokalemia, 4% vs. 11%, respectively, among others). A trend towards a higher frequency of rash (9% vs. 0%) and headache (9% vs. 0) was observed for caspofungin compared to liposomal amphotericin B, respectively. The differences were not statistically significant. The costs of empiric antifungal treatment were estimated as $2,503, $3,129 and $1,470 for caspofungin, liposomal amphotericin B and conventional amphotericin B, respectively (14 days, 20 kg/0.0.79 m^2 child). The probabilistic sensitivity analysis demonstrated a trend towards a mean cost saving of $667 per patient for caspofungin compared to liposomal amphotericin B (95% confidence interval (CI) -$3,221, + $1,802) with a 68% probability that caspofungin is less costly than liposomal amphotericin B.

Conclusion

Our analyses showed that there was a trend towards lower treatment costs with caspofungin compared to liposomal amphotericin B. Both caspofungin and liposomal amphotericin B present relatively high acquisition costs that may affect the hospital pharmacy budgets, especially if a large number of patients receive these drugs annually in a given institution. Conventional amphotericin B had lower drug acquisition costs however the monitoring, prevention, and treatment of amphotericin B-related complications may be more time and resource consuming compared to caspofungin and liposomal amphotericin B. Due to a lack of comparative data with caspofungin in pediatric patients, conventional amphotericin B could not be incorporated into the comparative analyses.

EXECUTIVE SUMMARY

Introduction

The incidence and severity of invasive fungal infections in immunosuppressed patients has been increasing in adults and children in the past decades. This is in part due to an increase in the population susceptible to these infections as a result of advances in supportive medical care and treatment. Neutropenic patients with fever that persists despite treatment with antibacterials are suspected of having a fungal infection. The most common fungal infections in this population, candidiasis and aspergillosis, usually present with a high mortality, i.e., approximately 19-31%, and 68-77%., respectively in children.

Conventional amphotericin B has been used for more than three decades and may still be used as a first-line empiric antifungal treatment of children with neutropenia and fever that persists for more than 5-7 days despite empiric antibacterial treatment. Concerns have been raised regarding adverse events associated with conventional amphotericin B, including nephrotoxicity, hypokalemia, and infusion-related reactions. However, due to a higher acquisition cost compared to conventional amphotericin B, the use of other antifungals believed to have an improved safety profile, such as caspofungin and liposomal amphotericin B, is often limited to circumstances where toxicity with conventional amphotericin B is a concern. There is currently a paucity of comparative clinical and economic evidence between caspofungin and other antifungals in children with febrile neutropenia. Our objectives were to evaluate the efficacy and safety evidence and to assess the economic impact of the use of caspofungin compared to conventional and liposomal amphotericin B in children with febrile neutropenia.

Methods

Our study population was comprised of febrile neutropenic children 2-17 years old with haematological malignancies or who underwent a haematopoietic stem cell transplantation and who required empiric antifungal treatment. The clinical evidence was based on a systematic review of the peer-reviewed and gray literature. We have included both comparative and non-comparative caspofungin studies in adult and pediatric patients with febrile neutropenia. Adult studies were used to complement pediatric data where appropriate. Pediatric studies in indications other than febrile neutropenia were also included for reporting of safety data. Outcomes included in the report were overall antifungal treatment response, antifungal-related complications, and need for a switch to a second antifungal due to intolerance or lack of efficacy with the initial antifungal.

In a cost analysis we calculated the cost of the empiric antifungal treatment with caspofungin, conventional and liposomal amphotericin B in children with febrile neutropenia from a health care system perspective. It included the acquisition costs of antifungals and of other medications used in the prevention of antifungal-related complications, drug administration materials, and nursing and pharmacy personnel time to prepare and administer the drugs. Nursing time was based on the duration of the daily infusion of each antifungal and ratio of nurses per patient in the ward, i.e., one hour for caspofungin, two hours for liposomal amphotericin B, and four hours for conventional amphotericin B. In addition, nursing time for the one-hour infusion of saline loading before the administration of conventional and liposomal amphotericin B, and the time for the administration of pre-medications to prevent antifungal complications were also included in the cost analysis. Our cost analysis was based on a 14-day antifungal treatment. The doses of medication were based on a 20 kg / 0.79 m^2 child. All unit prices were obtained from institutional or provincial sources. In univariate sensitivity analyses we varied the values of variables that may impact upon treatment costs such as the duration of treatment and patient weight. The duration of treatment was varied from 1-28 days, based on a pediatric randomized controlled trial (RCT), and patient weight was varied between 10-60 kg ($0.49m^2$ – $1.7m^2$).

No comparative studies that compared caspofungin and conventional amphotericin B were identified therefore an economic analysis comparing these two drugs was not performed.

An economic analysis was conducted to compare caspofungin and liposomal amphotericin B. It included antifungal treatment costs calculated through our cost analysis, as well as the costs of complications and antifungal switches. Rates of complications and drug switches were based on an RCT comparing caspofungin and liposomal amphotericin B in febrile neutropenic children (2-17 years) with hematological malignancies that was presented at a conference. The RCT excluded patients with a baseline fungal infection. We assumed that an absence of breakthrough fungal infections during the study due to its low rate of occurrence in the RCT. A cost-minimisation analysis was undertaken due to lack of evidence of a clinically significant difference in efficacy between the two drugs. A decision model using a probabilistic sensitivity analysis (10,000 Monte Carlo simulations) was used in the economic analysis. The probabilistic sensitivity analyses incorporated the point estimates and variance of the frequencies of complications reported, the need for antifungal dose increases, antifungal drug switches due to

intolerance or lack of efficacy with the initial antifungal, and treatment duration. Costs with the antifungal treatment, switches, and complications based on the literature and/or expert opinion were also included in the probabilistic sensitivity analysis.

Results

One RCT comparing caspofungin and liposomal amphotericin B in children with febrile neutropenia was identified. The RCT was presented at a conference and is currently not available in the peer-reviewed literature. One published adult RCT comparing caspofungin and liposomal amphotericin B in febrile neutropenia was identified. No studies comparing caspofungin and conventional amphotericin B in febrile neutropenia were identified. Additionally, eight non-comparative caspofungin studies were identified in pediatric patients. No systematic reviews, health technology assessments or economic evaluations on the use of caspofungin specific to the pediatric population were identified.

The pediatric RCT was not designed to detect a difference in efficacy between the two drugs. In total 82 patients were included in the RCT, 56 in the caspofungin group and 26 in the liposomal amphotericin B group. The authors concluded that the rate of overall favourable response to treatment[a] was similar between caspofungin and liposomal amphotericin B. There was a trend towards a lower rate of some adverse events for caspofungin compared to liposomal amphotericin B (nephrotoxicity, defined as a doubling of the baseline serum creatinine, 6% vs. 8%, respectively, and hypokalemia, 4% vs. 11%, respectively). The authors did not provide a definition for hypokalemia, or discuss the clinical significance of the abnormal results. In contrast, a trend towards a higher frequency of rash (9% vs. 0%) and headache (9% vs. 0%) was observed for caspofungin compared to liposomal amphotericin B, respectively. The differences between the two groups were not statistically significant.

In the cost analysis we calculated the cost of empiric antifungal treatment including drug acquisition cost, nursing and pharmacists' time, and materials used in antifungal treatment and

[a] Definition of overall favourable response:
All five following criteria had to be met:
1 Successful treatment of any baseline fungal infection. Criterion assessed by a blinded adjudication committee.
2. Absence of any breakthrough fungal infection during therapy or within 7 days of the end of treatment (fungal infection defined according to EORTC/MSG criteria). Criterion assessed by a blinded adjudication committee.
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.

in the monitoring and prevention of complications. Assuming a treatment duration of 14 days and a 20 kg/0.79 m^2 child, the costs were estimated as $2,503, $3,129 and $1,470 for caspofungin, liposomal amphotericin B and conventional amphotericin B, respectively. While the acquisition cost of caspofungin and liposomal amphotericin B were higher than conventional amphotericin B, due to a longer infusion period for antifungal and pre-medications, the administration of conventional amphotericin B was more resource-intensive with regards to nursing time and use of materials. Moreover, during the first hour of the conventional amphotericin B infusion, the patient needs to be monitored closely for infusion-related events which cannot be completely avoided even with the use of pre-medications. This was included in the cost analysis as nursing time during the conventional amphotericin B infusion.

Varying the duration of the empiric antifungal treatment from 1-28 days yielded antifungal treatment costs ranging from $235 - $4,946 with caspofungin, $224 - $6,258 with liposomal amphotericin B, and $105 - $2,940 with conventional amphotericin B per patient (20 kg / 0.79 m^2 child). Varying the patients weight from 10 kg – 60 kg (0.49m^2 – 1.7m^2) resulted in treatment costs ranging from $1,686 - $4,072, $1,913 - $8,011, and $1,246 - $2,366 for a 14-day treatment course with caspofungin, liposomal amphotericin B, and conventional amphotericin B, respectively.

The probabilistic sensitivity analysis demonstrated a mean cost saving of $667 per patient for caspofungin compared to liposomal amphotericin B (95% confidence interval (CI) -$3,221, + $1,802). There was a 68% probability that caspofungin was less costly than liposomal amphotericin B (20 kg/0.79 m^2). In children weighing 10-60 kg, the probability of a lower cost with caspofungin compared to liposomal amphotericin B varied between 62% and 90%.

Discussion

The authors of both adult and pediatric studies concluded that there were no differences in the overall treatment response between caspofungin and liposomal amphotericin B. In both the adult and pediatric studies there was a trend towards a lower frequency of individual adverse events with caspofungin compared to liposomal amphotericin B, which was statistically significant at times in the adult RCT. These adverse events may require changes in the course of treatment with the antifungal and other drugs that are crucial for the patient and may therefore also affect clinical outcomes.

No direct controlled study between caspofungin and conventional amphotericin B in adult or pediatric patients with febrile neutropenia was identified. For this reason, we could not compare the costs and consequences between these two drugs. An RCT in adult patients with invasive candidiasis showed a higher frequency of adverse events with conventional amphotericin B compared to caspofungin.

The probabilistic sensitivity analysis comparing caspofungin and liposomal amphotericin B was based on a single pediatric RCT that may not have had enough statistical power to detect differences between the two groups. Our probabilistic sensitivity analyses duly incorporated the imprecision in the study results. Thus, while the use of caspofungin was found on average to be cost saving compared to liposomal amphotericin B, the wide CI reveals a 32% probability of liposomal amphotericin B being less costly. The variation in CI was a result of the imprecision in the results obtained clinical study available, due to its small sample size.

Differences in treatment costs among the antifungals should be evaluated in the context of differences in clinical outcomes and safety. Complications including drug-infusion related events, rash, hypokalemia and nephrotoxicity occurred more frequently with conventional amphotericin B compared to caspofungin in adult patients with invasive fungal infections. These adverse events may not only impact clinical outcomes but also increase resource use and consequently costs. However, conventional amphotericin B could not be incorporated into the analyses due to a lack of comparative data with caspofungin in pediatric patients.

The results of our economic analyses may be generalizable to other settings as long as the assumptions used are applicable to their context. For instance, our results were based on a RCT in pediatric patients that excluded patients with baseline fungal infections. We assumed an absence of breakthrough fungal infection based on a low reported rate. Invasive fungal infections are treated according to the specific pathogen and may require long-term treatment, which would affect treatment costs. Our costs were based on the current clinical practice and costs at our institution and on antifungals currently available. As new evidence and/or new antifungal drugs become available this analysis may need to be updated.

Further research is required to address gaps in the pediatric literature mentioned above. Additionally, the long-term effects of antifungal toxicity such as nephrotoxicity with conventional and liposomal amphotericin B are not clear. According to the European Medicines Agency,

although the benefit-risk relationship of caspofungin is favourable, there are still concerns with liver and pancreatic toxicity and these events should be monitored.

Conclusions

The purported benefits of caspofungin are a better safety profile and fewer drug interactions compared to other classes of antifungals. RCTs in adults and pediatric patients with febrile neutropenia have found a similar efficacy between caspofungin and liposomal amphotericin B with a trend towards a lower frequency of important adverse events and drug withdrawal in pediatric patients. Data from adult studies suggests a similar efficacy with a better safety profile with caspofungin compared to conventional amphotericin B in invasive fungal infections.

Our analyses showed that when costs related to the antifungal treatment and complications were considered, there was a trend towards lower costs with caspofungin compared to liposomal amphotericin B.

Both caspofungin and liposomal amphotericin B present relatively high acquisition costs that may affect the hospital pharmacy budgets, especially if a large number of patients receive these drugs annually in a given institution. However, consideration must be given to other hospital resources that are affected by the use of these drugs. For example, the monitoring, prevention, and treatment of complications may consume more time of healthcare professionals especially for conventional amphotericin B compared to caspofungin, therefore preventing staff from working on other tasks during that period.

It should be highlighted that our economic analysis was based on a small RCT (n=82), which may lead to imprecision in the estimates. It is also important to note that apart from cost-effectiveness results, the choice of antifungal also needs to take into account several factors such as the fungal pathogen isolated, local antifungal drug resistance, the patient's underlying condition, potential for drug interactions, and drug safety.

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ABBREVIATIONS AND ACRONYMS

ALT alanine aminotransferase
AML acute myeloid leukemia
ALL acute lymphocytic leukemia
AST aspartate aminotransferase
BUN blood urea nitrogen
CADTH Canadian Agency for Drugs and Technologies in Health
CI confidence interval
EMEA European Medicines Agency
FDA Food and Drug Administration
HSCT haematopoietic stem cell transplantation
HTA Health Technology Assessment
IDSA Infectious Disease Society of America
IV Intravenous
RCT randomized controlled trial
SD standard deviation

PREAMBLE

Patients with prolonged fever and neutropenia that persist despite treatment with antibacterials are at a high risk for invasive fungal infections. Due to the difficulties in diagnosing invasive fungal infections and the importance of a prompt initiation of antifungal therapy, empiric treatment is usually started in these patients.

Conventional amphotericin B has been used for more than three decades and may still be used as first-line empiric antifungal treatment of children with persistent neutropenia and fever. Concerns have been raised regarding the safety profile of conventional amphotericin B. However, due to a higher treatment cost compared to conventional amphotericin B, the use of other antifungals believed to have an improved safety profile, such as caspofungin and liposomal amphotericin B, is often limited to circumstances where toxicity with conventional amphotericin B is a concern.

We have undertaken an evaluation of the clinical evidence available and the economic impact of the use of caspofungin compared to other antifungals used in our institution for the empiric treatment of febrile neutropenic children 2-17 years old with hematological malignancies or who underwent an haematopoietic stem cell transplantation (HSCT).

1.0 BACKGROUND

The incidence and severity of invasive fungal infections in immunosuppressed patients has been increasing in adults and children in the past decades[1 2]. This is in part due to an increase in the population susceptible to these infections as a result of advances in supportive medical care, cancer treatments, and stem cell and organ transplantations[1]. Patients with fever and neutropenia who present with hematological malignancies, who received chemotherapy, allogeneic stem cells or organ transplantations are at a high risk for invasive fungal infections[3 4]. Patients with acute leukemias or who received an HSCT are at an even higher risk of invasive fungal infections due to the duration and degree of neutropenia [2 3 5 6] and the intensity of chemotherapy[7].

The most common fungal infections in this population are aspergillosis and candidiasis in both adults and children[5 8]. Invasive candidiasis and invasive aspergillosis usually present with a high

mortality, i.e., approximately 19-31% and 68-77%, respectively, in children[2]. Some believe that one of the reasons for the poor prognosis of invasive fungal infections may lie in the difficulty in diagnosing the infection that may lead to delays in starting the therapy[4 6 9]. Due to the difficulty in diagnosing invasive fungal infections and to the importance of a prompt initiation of antifungal therapy, empirical treatment is usually started in patients with prolonged fever and neutropenia that persist despite treatment with antibacterials [5 10 11 12]. In the absence of a diagnosed fungal infection, antifungal treatment may be discontinued after two weeks of treatment in patients with prolonged neutropenia who are clinically well[13].

1.1 Febrile neutropenia

Severe neutropenia is usually defined as an absolute neutrophil count ≤ 500 cells/mm^3, or an absolute neutrophil count ≤ 1,000 cells/mm^3 that is expected to decrease to ≤ 500 cells/mm^3 in the subsequent 24-48 hours [14 15]. The lower the absolute neutrophil count and the longer the neutropenic period, the higher is the risk of infections[14]. Fever is usually defined as a single oral temperature ≥ 38.3°C or a temperature ≥ 38.0°C lasting for ≥ one hour [13 14 16].

Neutropenic patients with fever that persists despite treatment with antibacterials are suspected of having a fungal infection[10]. Fungal infections due to *Candida* species usually occur after the first week of neutropenia while *Aspergillus* infections normally occur with more prolonged neutropenia, i.e., greater than two-three weeks[10]. Such long periods of neutropenia are more likely to occur in patients treated for acute leukemia or who underwent HSCT[10].

1.2 Antifungal drugs available

Antifungals available for the treatment of febrile neutropenia and invasive fungal infections include amphotericin B formulations, azoles, flucytosine, and the more recently developed class, echinocandin, which includes caspofungin, the object of this report, in addition to micafungin and anidulafungin[17]. Currently in our institution, caspofungin is used as an alternative to amphotericin B for the empiric antifungal treatment of children (2-17 years) with acute leukemias or who underwent a HSCT or who presented with side effects[b] associated with amphotericin B[18]. According to the literature, liposomal amphotericin B may also be used as an alternative to conventional amphotericin B in cases of resistance or intolerance to conventional amphotericin

[b] Amphotericin B side effects defined as abnormal renal function, uncontrolled infusion-related reactions, or uncontrolled hypokalemia due to amphotericin B[18]. Koo A, Sung L, Allen U, et al. Efficacy and Safety of Caspofungin for the Empiric Management of Fever in Neutropenic Children. Pediatr Infect Dis J 2007;26(9):854-6.

B [11 19]. Some of the characteristics of these drugs, more specifically caspofungin, are summarized below.

Conventional amphotericin B is an antifungal drug with a broad spectrum of activity and a low rate of resistance[1] that has been used for more than three decades in adults and children [20 21]. It has a relatively low cost compared to other antifungal agents and may still be used as first line therapy of invasive fungal infections in children and adults[1]. However its use is limited by dose-limiting safety issues in adults and children, the most important ones being nephrotoxicity [22] and infusion-related event such as fever, chills, headache, nausea, and vomiting[21 23 24 25]. Other amphotericin B-related events include hypokalemia, hypomagnesemia, anemia, and hepatotoxicity[9 21 26 27].The extent to which hospitals currently use conventional amphotericin B is not clear.

Lipid formulations of amphotericin B [liposomal amphotericin B (Ambisome®), amphotericin B lipid complex (Abelcet®), and amphotericin B colloidal dispersion][11] were developed in the 1990's with the objective of decreasing the risk of conventional amphotericin B's common toxicities [23 28 29] while maintaining a similar efficacy[24 27 30]. Nevertheless, lipid formulations of amphotericin B are still associated (but less frequently) with common amphotericin B toxicities [26 28 31 32]. The different lipid formulations of amphotericin B, i.e., liposomal amphotericin B and amphotericin B lipid complex may have different pharmacokinetic properties[33]. The higher cost of lipid formulations compared to conventional amphotericin B[23 29] has resulted in their use being limited to cases of resistance or intolerance to conventional amphotericin B[11 19].

Other antifungal drugs that have been developed included the azole antifungals (fluconazole, itraconazole, and more recently voriconazole, posaconazole), and a less frequently used drug, flucytosine[23]. The azoles constitute therapeutic alternatives to amphotericin B as they possess a broad spectrum of activity and a lower toxicity profile[29]. One drawback of some of the azole drugs is that, being metabolized by the cytochrome P450, there is a potential for drug interactions [29 20], which may result in serious and sometimes life-threatening adverse clinical events[1 11 29 34]. This is particularly the case with itraconazole and voriconazole[1 11 29]. Drugs with which there is a potential for azole interaction include rifampin, anticonvulsants, sirolimus, tacrolimus, cyclosporine, oral anticoagulants, statins, omeprazole, protease inhibitors [5 11], and some chemotherapy drugs[9 20]. The dose of voriconazole may need to be adjusted as a result of drug interactions[8]. Adverse reactions associated with the azole class include increases in liver

enzymes, rash [20], and nausea [9], in addition to visual disturbances[1 20], hepatitis, and hallucinations with voriconazole[5].

Despite the development of new antifungals, problems with toxicity, drug interactions and fungal resistance still exist [23]. More recently, antifungals belonging to a new class, echinocandin, have been developed, including compounds such as caspofungin, micafungin, and anidulafungin [17].

1.2.1 Echinocandins

The echinocandin is a class of antifungals that include caspofungin, micafungin, and anidulafungin. The echinocandins have a different mechanism of action compared to amphotericin B and azoles, i.e., inhibition of the synthesis of an essential component of the fungal cell wall**,** whereas the azoles and amphotericin B destabilize the permeability of the fungal cell membrane[1]. Because the target of the echinocandin on the fungal wall does not exist in mammalian cells as is the case with amphotericin B and azoles, echinocandins have a lower potential for adverse reactions compared to antifungals and azoles [1 17]. In general the echinocandins are well tolerated[35]. Adverse reactions associated with the echinocandins include transient infusion-related rash, facial swelling, and vasodilation, which may occur within minutes of the initial infusion and can be treated with an anti-histamine[17]. The echinocandins are excreted mainly by the liver, and are not metabolized by the cytochrome P450, which decreases the potential for drug interactions and adverse drug reactions observed with the azoles [1]. Echinocandins are active against *Candida* species and fungistatic against *Aspergillus* species [36]. The first marketed echinocandin was caspofungin, but other drugs in this class include micafungin, and anidulafungin [36].

1.2.2 Caspofungin

Caspofungin is active against *Candida*, including *albicans* and some non-*albicans* species (C. *glabrata*, C. *krusei*) [37], and has a fungistatic effect against *Aspergillus* species[23]. Caspofungin has been reported to be better tolerated with minimal adverse effects[32] with less frequent infusion-related events compared to other classes of antifungals[38]. Caspofungin, not being metabolized by the cytochrome P450, has a lower potential for drug interactions compared to the azoles[34]. Adverse reactions associated with caspofungin are as listed above for its class, the echinocandins. Other adverse reactions include headache, fever, nausea, vomiting, flushing, and phlebitis at the site of infusion[17 39 32]. Laboratory abnormalities associated with caspofungin include increases in liver enzymes, leucopenia, and thrombocytopenia[23 35]. The dose of

caspofungin may need to be adjusted as a result of liver impairment[36]. Caspofungin may interact with tacrolimus, reducing its plasma levels by approximately 20%[1 39]. Cyclosporine increases the plasma level of caspofungin by approximately 35%, which may result in an increase in liver enzymes with the co-administration of these two drugs[17 35 40]. The concomitant use of caspofungin and rifampin, efavirenz, carbamazepine, phenytoin, nevirapine, or dexamethasone may result in reduced plasma levels of caspofungin[23 17 40] and may require dose adjustments[38].

It is recommended that the concomitant use of cyclosporine and caspofungin should be done with caution and in cases where the benefits outweigh the risks[17 34 35 41]. This recommendation stems from trials in healthy volunteers receiving caspofungin and cyclosporine concomitantly that showed that some patients developed elevations of liver function enzymes possibly related to this drug combination[42].

1.2.2.1 Regulatory Approval

Caspofungin was approved by Health Canada, the United States Food and Drug Administration (FDA), and the European Medicines Agency (EMEA) for use in adult patients in 2001[43 44 45]. The current labeled indications in Canada[42] are summarized in table 1.

Table 1. Caspofungin approved indications in Canada

Caspofungin – labeled indications in Canada[42]
Adults
- Empirical therapy for presumed fungal infections in febrile, neutropenic patients
- Invasive Candidiasis including candidemia, intra-abdominal abscesses, peritonitis and pleural space infections
- Esophageal Candidiasis
- Invasive Aspergillosis in patients who are refractory to or intolerant of other therapies
Children
- Safety and effectiveness in patients less than 18 years old have not been established.

Source: Compendium of Pharmaceutical Specialties (online version)[42] . Last Access: August 5th 2008.

A letter from the FDA dated July 29th 2008, communicated the approval of the use of caspofungin in pediatric patients (3 months – 16 years) for the same indications listed above in table 1 for adults[46].

The regulatory agency of the European Union (European Medicines Agency, EMEA) revised in 2006 the indication of caspofungin for empirical therapy for presumed fungal infections in febrile neutropenic patients as follows: “Empirical therapy for presumed fungal infections (such as Candida and Aspergillus) in febrile, neutropenic adult patients” since preliminary evidence suggests that uncommon non-Candida yeasts and non- Aspergillus moulds may not be susceptible to caspofungin[41 48]. According to a 2006 evaluation of caspofungin data available, EMEA considers that “the risk-benefit of caspofungin is positive,… however, the development of hepatitis and pancreatitis with the drug should be monitored carefully.”[48]

1.3 Choice of antifungals

The choice of antifungal drug depends on several factors such as local antifungal resistance, the patient’s immune system, organ dysfunction, potential interaction with other concomitant drugs, and drug safety[23 38 49 50]. In pediatric patients, information on the pharmacokinetics of the drug is also important[51]. Acquisition costs vary widely among these drugs and should also be taken into account when choosing an antifungal[23 49].

Most of the antifungals available do not have specific pediatric indications and limited to no clinical information in pediatric patients is available[8]. Their use in this patient population is therefore mainly based on data from adult patients[1 2 52].

1.4 Dosage and presentations of the antifungals evaluated in our report

Table 2 provides details about the presentations and the pediatric doses used.

Table 2. Presentation of antifungals included in the report and pediatric dose

Antifungal	Pediatric dose	Route of administration	Presentations available
Caspofungin	Day 1 loading dose: 70 mg/ m^2 [53] Daily dose 50 mg/m^2 (maximum: 70 mg/day) [18 35 54 55]	Intravenous infusion[42] Infusion time: 1 hour[42]	50 mg and 70 mg vials[42]
Conventional amphotericin B	1 mg/kg/day (maximum recommended: 1.5mg/kg/day)[2]	Intravenous infusion[56] Infusion time: 2-6 hours[33 56]	50 mg vials[56]
Liposomal amphotericin B	3 mg/kg/day (maximum recommended: 5mg/kg/day) [2 8]	Intravenous infusion[57] Infusion time: 2 hours[33]	50 mg vials[57]

1.5 Common antifungal-related toxicities

The most commonly reported adverse events associated with amphotericin B formulations and caspofungin in adults and children are infusion-related reactions, nephrotoxicity, hypokalemia, and increases in liver enzymes[21 26].

1.5.1 Infusion-related reactions

Infusion-related reactions such as fever, chills, rigour, hypotension, nausea, vomiting, and thrombophlebitis are common in patients treated with conventional amphotericin B (approximately 20-60%)[28 31]. They are usually transient and occur during the first few hours of the initiation of the infusion[56]. Nevertheless, if intolerable, infusion-related reactions may lead to treatment discontinuation[31]. The use of pre-medications such as diphenhydramine, acetaminophen, corticosteroid, heparin[29], and meperidine[33] may reduce the occurrence of the above mentioned infusion-related events[29], but does not always eliminate their occurrence[31 38]. Therefore conventional amphotericin B-treated patients need to be more closely monitored during the first hour of infusion[33], which lasts for approximately four hours[56]. Infusion-related events may occur less often with lipid formulations of amphotericin B compared to conventional amphotericin B[31 58]. Although expected to have a low rate of infusion-related events[38 31], caspofungin and other echinocandins may be associated with transient infusion-related rash, facial swelling, and vasodilation, which may occur within minutes of the initial infusion and can be treated with an anti-histamine[17].

1.5.2 Nephrotoxicity

Nephrotoxicity associated with conventional amphotericin B has been reported at widely varying rates of 30-80% of adult and pediatric patients[59]. This variation may be due to the use of different measures and definitions of nephrotoxicity, and possibly by heterogeneous patient populations used in these studies.

Amphotericin B-related nephrotoxicity seems to be reversible after the discontinuation of the drug[60], however it can cause permanent damage in some patients, especially in adult patients receiving a cumulative dose > 5g[22 59]. Some authors state that amphotericin B-related nephrotoxicity seems to be less severe in children compared to adults[36 59 15], possibly due to a faster elimination of the drug in children[36]. However, the magnitude of this difference is not clear. Conventional amphotericin B-related nephrotoxicity can be potentiated by the concomitant use of other nephrotoxic drugs including cyclosporine, tacrolimus, antibiotics (glycopeptides,

aminoglycosides), corticosteroids, etc[60 61]. Some medical conditions also predispose patients to nephrotoxicity such as baseline renal impairment[3], severe sepsis, and hemorrhagic shock[62]. Adult and pediatric patients undergoing HSCT are also believed to be more susceptible to the conventional amphotericin B-related nephrotoxicity[19] possibly due to the use of nephrotoxic treatments such as chemotherapy, aminoglycosides, and total body irradiation[63 64 65] .

Some authors reported that the signs of nephrotoxicity in patients using amphotericin B were seen as early as the first dose of the drug or within the first 7-14 days of treatment in both adult and pediatric patients[19 25 66 67 68 69]. Hypokalemia and hypomagnesemia may also be observed in the presence of nephrotoxicity[69 70 71].

A lot of effort has been put into understanding the risks of nephrotoxicity in patients treated with amphotericin B[12 15 19 25 59 60 70 72 73 74 75 76 77 78 79 80 81 82 83 84], mostly in adult patients. This includes a study conducted at The Hospital for Sick Children in Toronto[59], that is summarized below. The study conducted at The Hospital for Sick Children consisted of a retrospective evaluation of 90 courses of conventional amphotericin B administered at the institution[59]. Nephrotoxicity developed in 52 (58%) patients defined as a ≥ 20% decrease in creatinine clearance from baseline, and 15 (17%) patients had a decrease in creatinine clearance > 30%[59]. The authors concluded that a high rate of nephrotoxicity was observed despite preventive efforts with fluid and sodium supplementation in all patients[59]. Other studies in children reported a 11% - 52% rate of amphotericin-related nephrotoxicity[15 25 60 81 82 83]. Most studies followed the patients during hospitalization and to a maximum of 5 months thereafter. Therefore, the long-term consequences of the amphotericin B-related nephrotoxicity are poorly understood[84].

One measure to reduce the risk of nephrotoxicity is fluid and sodium supplementation[71], but its efficacy has not been proven in controlled trials[3]. If nephrotoxicity develops, it may require more frequent monitoring of the patient's renal function, a decrease or switch to another antifungal or the interruption of other important concomitant drugs[22]. Other consequences of nephrotoxicity are difficult to measure and may result from the withdrawal or reduction of the dose of amphotericin B itself[22], or other medications that are important for the treatment of the infection or underlying conditions such as antibacterials or cyclosporine[61 25 81]. The withdrawal of medications that are critical to the patient's care may potentially result in poorer outcomes[22 61 25 67].

Lipid formulations of amphotericin B may present with a risk of nephrotoxicity, although the risk is lower than with conventional amphotericin B[73 58] . Caspofungin is not expected to cause nephrotoxicity[32 39].

1.5.3 Hypokalemia

Hypokalemia (low serum potassium) has been observed with conventional amphotericin B[9 23], and to a lower extent with liposomal amphotericin B[23 29].

It may be associated with nephrotoxicity[66 69 70]. Decreases in serum potassium levels have to be monitored carefully[26 66] especially in the circumstance of fluctuating renal function[83] since it may result in cardiac arrhytmias[85] that may be fatal[66 71]. Children are very susceptible to renal potassium wasting and may experience a sudden decrease in serum potassium[72]. Therefore, in order to avoid serious clinical consequences such as heart and nerve malfunction, physicians need to monitor the serum potassium levels frequently in pediatric patients[72].

1.5.4 Increases in liver enzymes

Increases in liver enzymes (transaminases, alkaline phosphatase, bilirubin) have been reported with conventional amphotericin B, liposomal amphotericin B, and echinocandins (including caspofungin)[9 26 23 29 35], however, its clinical significance is not clear. The concomitant use of caspofungin and cyclosporine may increase the risk of increases in liver enzymes[17 35 40].

2.0 RATIONALE

Caspofungin purportedly presents a similar efficacy and an improved safety profile in the empiric treatment of children with febrile neutropenia compared to conventional amphotericin B and liposomal amphotericin B, however with higher acquisition costs, especially when compared to conventional amphotericin B.

Caspofungin may be used in our institution as an alternative to conventional amphotericin B in the patient population used in our report[18]. According to the literature liposomal amphotericin B may also be used in febrile neutropenic patients who cannot tolerate conventional amphotericin B[7 29]. There is currently a paucity of comparative clinical and economic evidence between caspofungin and other antifungals in children with febrile neutropenia. Given the increasing use

of antifungals and the high expenditures incurred by hospital pharmacies, a full health technology assessment is warranted. Our objectives were to evaluate the efficacy, safety, and cost of caspofungin compared to conventional and liposomal amphotericin B in the empiric treatment of persistent febrile neutropenia in children.

3.0 PATIENT POPULATION

Our study population is comprised of pediatric patients (2-17 years old) with hematological malignancies or who underwent a HSCT and who presented with febrile neutropenia that persisted despite 5-7 days of treatment with antibacterials.

4.0 OBJECTIVES

The objectives of this report are to evaluate the efficacy, safety, cost, and cost-effectiveness of caspofungin compared to conventional amphotericin B and liposomal amphotericin B in the empirical treatment of persistent febrile neutropenia.

5.0 METHODS

5.1 Systematic literature review

The Pubmed, Embase, Cochrane, and the Centre for Reviews and Dissemination (CRD) databases were used in our systematic literature search. Search terms are shown in Appendix 1. The reference lists of the studies identified and proceedings from conferences in the field were searched. Databases of ongoing and completed clinical trials were also searched in order to identify recently completed caspofungin studies. More details are in Appendix 1. Last search: June 2008.

The Health Technology Inquiry Service from the Canadian Agency for Drugs and Technologies in Health (CADTH) was also used in an attempt to identify additional references pertinent to this report. The websites of regulatory agencies were also searched in order to identify information on caspofungin studies that may have been reported in more detail to these agencies. The websites of the US Food and Drug Administration (FDA) and of the European Medicines Agency (EMEA) were searched.

The studies identified through the systematic literature review were included in our report as follows:

- Clinical studies comparing caspofungin with other antifungals, systematic reviews, meta-analyses, and health technology assessment reports of caspofungin in patients with febrile neutropenia were included in the efficacy and safety sections of this report.
- Due to the dearth of information available and of comparative caspofungin studies published in pediatric patients in the peer-reviewed literature, we also included in our report the safety information from non-comparative studies in pediatric patients with indications other than febrile neutropenia.
- Given the concerns of hepatotoxicity with the concomitant use of caspofungin and cyclosporine, studies identified through our search (regardless of treatment indication) that reported the effects of this drug combination on liver function in adults and children were summarized separately.
- Economic evaluations of caspofungin in febrile neutropenia were summarized in our economic evaluation section.

Case reports and non-clinical studies (animal studies, *in vitro* susceptibility studies) were excluded from our report. Studies in neonates were also excluded. No other restriction for age was applied, but adult and pediatric patients were evaluated separately. Adult studies were used to supplement data in pediatric patients where appropriate. No restrictions for dates of publication or language were used, however, only articles in English, French, Portuguese, Italian, German, and Spanish were included due to availability of translation.

The information was abstracted from the eligible studies using pre-tested standardized forms.

5.2 Outcomes evaluated

We included outcomes such as response to therapy (defined according to the studies identified), rates of antifungal switches, and antifungal-related adverse events.

5.3 Data analysis

Comparisons of percentages of clinical outcomes and complications between groups were evaluated as absolute risk differences. The standard deviation and 95% confidence intervals for percentages of events, if not provided by the authors, were calculated according to the data provided in the publication.

Results were combined in a meta-analysis if deemed appropriate using the software RevMan 4.2.1[86].

5.4 Cost and economic analyses

This health technology assessment includes a primary cost analysis and a comparative economic evaluation. In the primary cost analysis, the treatment costs of caspofungin, conventional and liposomal amphotericin B used in the empiric treatment of children with febrile neutropenia were calculated. In the economic evaluation, costs related to antifungal treatment, complications and switches were modeled for caspofungin and liposomal amphotericin B. Conventional amphotericin B could not be included in the economic evaluation due to a lack of comparative data with caspofungin in pediatric patients with febrile neutropenia. The economic evaluation is presented as a probabilistic sensitivity analysis with inputs modeled in a decision tree.

The study population consisted of children 2-17 years old with hematological malignancies or who underwent an HSCT and who presented with febrile neutropenia that persisted despite 5-7 days of treatment with antibacterials.

5.4.1 Time horizon

A short-term analysis comprising of the duration of the antifungal treatment was undertaken. Since no deaths occurred in the seven days following the antifungal treatment in the pediatric randomized controlled trial (RCT)[53], clinical information beyond the antifungal course duration was not available, and there was no evidence of long-term effects of treatment complications, we assumed that clinical outcomes would be similar among the different treatment groups after the resolution of the febrile neutropenia episode.

5.4.2 Healthcare resource use and costs

Since we are focusing on pediatric patients, we have incorporated direct healthcare resource use and costs specific to this patient population. The perspective of the analysis was that of the provincial healthcare system, which includes all costs incurred by the provincial Ministry of Health. As the time horizon is limited to the episode of febrile neutropenia which is treated in hospital, no outpatient costs were included.

We calculated the cost of empiric antifungal treatment with caspofungin and other antifungals used in our institution, i.e., conventional amphotericin B, and liposomal amphotericin B, in children 2-17 years old with hematological malignancies or who underwent a HSCT and who presented with febrile neutropenia that persisted despite 5-7 days of treatment with antibacterials. Drug acquisition costs for antifungals as well as for medications used to prevent antifungal-related complications, nursing and pharmacy personnel time, and materials used in the drug administration were included in the cost analysis.

The primary cost analysis includes only those healthcare resources incurred in the empiric antifungal treatment of patients with febrile neutropenia. Therefore it does not represent the total costs of febrile neutropenia care for any treatment group.

Doses of antifungals and other medications were calculated according to patient weight or body surface area. Our base case analyses used a 20 kg / (0.79 m^2)[87] patient, which was assumed to be the approximate weight of a seven year-old[c] (mean age in the pediatric RCT used in our analyses).

Healthcare resource use was based on the peer-reviewed literature and/or expert opinion. Resources included are as follows:

- Antifungal treatment
    - Antifungals used in the treatment, based on the usual pediatric doses (table 2).
    - Medications routinely administered before the antifungal infusion to avoid infusion-related events with conventional amphotericin B, based on the doses used in our institution.
    - Infusion of saline solution to prevent nephrotoxicity in patients receiving conventional and liposomal amphotericin B.
    - Material for the reconstitution and administration of intravenous drugs, such as IV solutions and IV bags.
    - Healthcare personnel time (pharmacy personnel and nurses) for the preparation and administration of these drugs, pre-medication and saline solution.

[c] Median weight for a 5-year old is approximately 18 kg according to the weight-for-age table of the World Health Organization (WHO)88. World Health Organization (WHO). Weight-for-age charts (Girls and Boys) http://www.who.int/nutrition/media_page/en/ (Last access: June 6th 2008)..

The duration of antifungal treatment in the absence of a documented infection is difficult to ascertain[13 89] and it is usually guided by the duration of the fever and neutropenia (in the absence of a diagnosed systemic infection)[13 90 91] and therefore, according to expert opinion, does not vary according to the antifungal used. Moreover, the length of antifungal treatment was similar between caspofungin and liposomal amphotericin B in adult and pediatric febrile neutropenia RCTs[53 92]. For this reason, hospitalization costs other than those incurred in the antifungal treatment and administration, and monitoring, prevention, and treatment of antifungal-related complications were not included in the primary cost analysis as they are believed to be identical among the groups.

Resource use and costs were based on a 14-day treatment. This was based on the guidelines from the Infectious Diseases Society of America (IDSA)[13] that suggests that assuming an absence of a breakthrough fungal infection, antifungal treatment can be discontinued after two weeks in clinically well patients with prolonged fever and neutropenia with no lesions detected by either clinical evaluation, chest X-ray, or abdominal computed tomography (CT)[13]. Additionally, the median duration of neutropenia was 11 days (interquartile range 7-20)[93] and 12 days[94] in two studies including 1792 and 64 children, respectively, mainly with hematological malignancies and who received antifungal treatment for febrile neutropenia or invasive fungal infections. This further supports the length of antifungal treatment employed in our analysis.

In a secondary cost analysis hospitalization costs for the duration of the antifungal treatment were included. Costs related to treatment, complications and inpatient care of patients with febrile neutropenia incurred during the empiric antifungal treatment were based on a study[95] performed at The Hospital for Sick Children. Costs associated with the stay in the hospital ward, included medications used (excluding chemotherapy), blood products, laboratory tests (biochemistry and microbiology), diagnostic tests (X-rays, computed tomography, ultrasound, magnetic resonance imaging, electrocardiograms, echocardiograms, glomerular filtration rate exam), physician fees, nursing, supplies, equipment, and administration fees. These costs were based on the resource use in 19 children > two years old treated with empirical antifungal treatment at The Hospital for Sick Children.

Costs with antifungal drug switches and antifungal-related complications were included in the probabilistic sensitivity analysis, as follows:

- Antifungal drug switch
    - In patients who require a switch to a different antifungal due to adverse events or lack of efficacy with the initial antifungal, the costs of the second antifungal were incorporated into the analysis. We assumed that patients who discontinued the initial antifungal drug due to lack of efficacy or adverse events were switched to a second antifungal.

- Antifungal-related complications
    - Costs of antifungal-related complications were calculated according to the type of complication. The costs of complications included drug acquisition costs, materials, healthcare personnel and physician time, laboratory tests and other diagnostic exams, and hospitalization costs[d] as applicable.

Resources incurred in the treatment of antifungal-related complications were based on expert opinion and/or data from the peer-reviewed literature.

Nursing time for the administration of the drugs was based on the length of the antifungal administration and the ratio of nurses to patients at our institution in the specific ward. The monitoring of infusion-related events of patients treated with conventional amphotericin B and liposomal amphotericin B by the nurses occurs during the administration of the antifungals. We did not cost the time spent on both tasks separately in order to avoid double-counting of resource use. Pharmacy personnel's time for the preparation of the drug infusion were based on an estimate from the pharmacy department.

The source for unit costs was The Hospital for Sick Children (not shown due to confidentiality agreements). The amount of resource use was multiplied by their unit costs in order to estimate the treatment costs. Costs are shown in 2007 Canadian dollars. As our analyses did not extend beyond 1 year, discounting of costs and outcomes was not necessary.

5.4.3 Sensitivity analyses

5.4.3.1 Univariate sensitivity analyses

[d] Based on the study performed at The Hospital for Sick Children95. Study protocol: "Nephrotoxicity: Conventional versus Liposomal Amphotericin B in Children". . described above.

Univariate sensitivity analyses were undertaken on factors that may influence the treatment costs such as the length of treatment and patient weight.

The length of the empiric antifungal treatment was varied from 1-28 days according to information from a caspofungin RCT in pediatric patients with febrile neutropenia. The authors reported that less than 8% of the patients were treated for more than 28 days[53]. In a second univariate sensitivity analysis the patient weight was varied between 10-60 kg (0.49 – 1.7 m^2) [87].

We also varied our baseline assumption that the non-used portion of each antifungal vial would be re-used, by calculating the cost of antifungal treatment assuming that the non-used portion of the vial would be discarded.

5.4.4 Economic evaluation

A decision analysis using probabilistic sensitivity analysis (10,000 Monte Carlo simulations) was undertaken since it incorporates the uncertainties related to model inputs such as the occurrence of complications and the clinical treatment pathways.

The current evidence shows a similar efficacy between caspofungin and liposomal amphotericin B used as an empirical antifungal treatment of febrile neutropenia in both adult[92] and pediatric patients[53], therefore the full economic evaluation consisted of a cost-minimisation analysis. Caspofungin could not be compared to conventional amphotericin B since no studies comparing the two drugs in pediatric patients were identified in the literature.

The probabilistic sensitivity analyses incorporated the point estimates and variance of the frequencies of complications reported, the need for antifungal drug dose increases, antifungal drug switches due to intolerance or lack of efficacy with the initial antifungal, and the length of treatment.

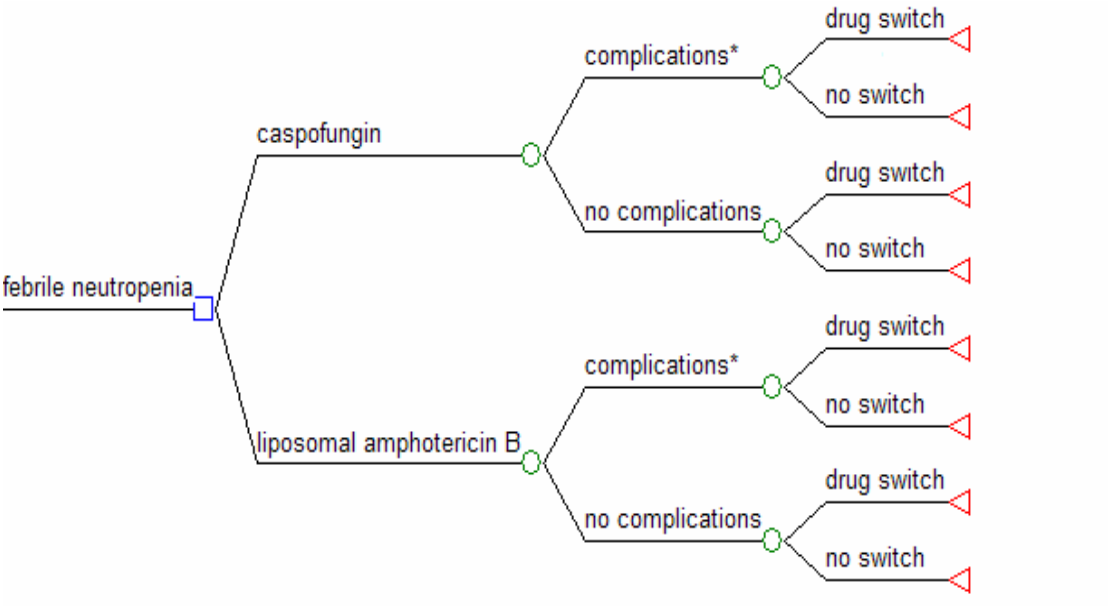
A pediatric RCT comparing caspofungin and liposomal amphotericin B in children 2-17 years with hematological malignancies and febrile neutropenia[53] presented at a conference was used as the basis for rates of drug switches, dose increases, and complications in the probabilistic sensitivity analysis. The study excluded patients with a baseline fungal infections, therefore our analysis is based on patients without such an infection. Moreover, since once a breakthrough invasive fungal infection is documented the antifungal treatment administered depends on the

organism isolated[13], and since such treatment information is not available in the pediatric RCT we restricted our population to patients who did not develop new invasive fungal infections. In fact, in the pediatric RCT, only 1 out of 82 patients (1.2%) were diagnosed with an invasive fungal infection during the course of treatment[53]. Additionally, other pediatric studies also showed a low rate of breakthrough fungal infections , i.e., no infections were diagnosed during 67 courses of caspofungin for febrile neutropenia in children at The Hospital for Sick Children[18], and 2/39 (5.1%) of patients in an open-label caspofungin study were diagnosed with breakthrough fungal infections[54]

The costs of antifungal treatment, complications and drug switches were based on the cost analysis previously described. Only the complications that required specific treatment and therefore resulted in an increase in resource use were included in our model. The clinical significance of the complications was not discussed in the RCT.

The structure of the decision model used in the probabilistic sensitivity analysis (figure 1) is based on the clinical practice and was validated by clinical experts.

Figure 1. Decision model used in the probabilistic sensitivity analysis comparing caspofungin and liposomal amphotericin B



* Antifungal-related complications included nephrotoxicity, hypokalemia, chills, nausea for liposomal amphotericin B and caspofungin. In addition, the caspofungin arm also included rash. Antifungal-related complications are shown as a general term in one branch of the tree in this figure for simplification purposes, but each complication was included as a separate branch of the tree used in the decision model.

We assumed that patients who discontinued the initial antifungal due to intolerance or lack of efficacy would receive a second antifungal (caspofungin if treatment initiated with liposomal amphotericin B and vice-versa). Conventional amphotericin B was not used a second antifungal since we assumed that the patients received caspofungin or liposomal amphotericin B due to contraindications to conventional amphotericin B.
We also assumed that patients did not present with a baseline fungal infection according to pediatric RCT[53] and that there were no breakthrough fungal infections. The incidence of breakthrough fungal infections in this population is low, i.e., 0/67 courses[18], 1.2% (1/82 courses from the pediatric RCT that was the base of our analysis[53]), and 5.1% (2/39 courses)[54].

The variance in the rates of switches or complications reported in the RCT were incorporated into the analysis using 10,000 Monte-Carlo simulations. For each parameter included in the probabilistic sensitivity analysis, a distribution defined by the point estimate and variance was incorporated. In each Monte Carlo simulation, a value was randomly drawn from each parameter distribution for each variable included in the sensitivity analysis. This process was repeated 10,000 times in order to produce a distribution of costs in each treatment group from which an estimate of the mean and of the 95% confidence interval (CI) was derived. This provided a measure of the uncertainty surrounding the cost estimate. Beta distributions were used for probabilities of drug switches defined according to the point estimate and variance reported in the study identified. Triangular distributions were used for healthcare resource parameters such as the duration of treatment as reported in the RCT. The probabilistic sensitivity analysis was stratified according to patient weight/body surface area (10-60 kg / 0.49 – 1.7m^2).The probabilistic sensitivity analyses were carried-out using the TreeAge Pro Suite 2008 program (TreeAge Software Inc.).

We assumed that patients who discontinued the initial antifungal due to intolerance or lack of efficacy were switched to a second antifungal that was administered until the end of the 14-day (1-28 days) antifungal treatment course (assuming an absence of baseline and breakthrough fungal infection).

6.0 RESULTS OF THE SYSTEMATIC LITERATURE REVIEW

In pediatric patients, one RCT comparing caspofungin and liposomal amphotericin B in febrile neutropenia was identified[53]. The study was presented at a conference and has not been published in the peer-reviewed literature. Additionally, eight non-comparative caspofungin studies[18 54 94 96 97 98 99 100] were identified in pediatric patients, one of which was presented at a conference and is not yet available in the peer-reviewed literature[100].

Studies in pediatric patients with febrile neutropenia are summarized in the efficacy and safety sections of the report. Studies in pediatric patients with invasive fungal infections were included in the safety section.

The following publications were identified in adult patients with febrile neutropenia

- One RCT of caspofungin vs. liposomal amphotericin B[92]
- One non-randomized comparative study of caspofungin vs. liposomal amphotericin B[101]
- One systematic review of RCTs of different treatment indications, including febrile neutropenia[102] .
- Two HTA reports were identified through our literature search, one from the Canadian Agency for Drugs and Technologies in Health (CADTH)[103], and one from the Institute for Clinical Effectiveness and Health Policy in Argentina[104]
- Five economic analyses comparing caspofungin to other antifungals[105 106 107 108 109].

Studies in adult patients were use to complement data in pediatric patients.

These studies are summarized in the next sections.

6.1 Study results - Pediatric patients

One RCT[53] comparing caspofungin and liposomal amphotericin B and three non-comparative studies[18 54 94] included pediatric patients with febrile neutropenia. One of the non-comparative studies prospectively evaluated the pharmacokinetics and safety of caspofungin[54], another study consisted of a retrospective chart review performed at The Hospital for Sick Children in Toronto that evaluated the efficacy and safety of caspofungin[18]. The third publication consisted of a survey done at different institutions on the use of caspofungin in pediatric patients, part of which received the medication as empiric therapy[94].

The remaining studies consisted of non-comparative retrospective[18 98 99 110] or prospective[96 97 100 111] evaluations of caspofungin alone or in combination with other antifungals as first line or salvage therapy of documented invasive fungal infections.

The studies with caspofungin in febrile neutropenia are summarized below. Additional information is provided in Appendices 2 and 3.

No meta-analyses, health technology assessment reports, or economic analyses on the use of caspofungin in pediatric patients were identified.

6.1.1 Efficacy – Pediatric Patients

6.1.1.1 Randomized controlled trial in febrile neutropenia

A multicenter RCT evaluated the efficacy and safety of caspofungin compared to liposomal amphotericin B in pediatric patients with febrile neutropenia[53]. The study was presented at a conference, and the information available is summarized below.

Eligible patients were 2-17 years old, who had received chemotherapy for leukemia, lymphoma or other malignancies, or who had undergone an HSCT, who presented with neutropenia (absolute neutrophil count < 500 cells/μL) for ≥ 96 hours, fever (> 38ºC), and who received systemic antibacterial treatment for ≥ 96 hours[53]. Patients with a documented fungal infection, who had received amphotericin B or echinocandins in the 10 days preceding the study, with abnormal hematologic and liver enzymes test results, with concomitant treatment with rifampin, cyclosporine, or other concomitant systemic antifungal treatment, not expected to survive > 5 days, or with improperly managed antibacterial infection were excluded from the study[53].

The main outcome of the study was the number of patients with ≥ 1 adverse event associated with the drug during the study or in the 14 days after the end of the study[53]. Secondary outcomes included the occurrence of drug-related serious adverse events, drug discontinuation, and overall favourable response to treatment[e 53].

Eligible patients were randomized on a 2:1 ratio to caspofungin 50 mg/m^2/day (70mg/m^2 loading dose on day 1), maximum dose: 70mg/day, or liposomal amphotericin B 3mg/kg/day[53]. The dose could be increased after five days of persistent fever[53]. The randomization was stratified according to risk status (high risk: allogeneic HSCT or relapsed acute leukemia)[53]. All 56 patients enrolled in the caspofungin group were included in the modified intention-to-treat

[e] Definition of overall favourable response to treatment:
All five following criteria had to be met:
1. Successful treatment of any baseline fungal infection. Criterion assessed by a blinded adjudication committee.
2. Absence of any breakthrough fungal infection during therapy or within 7 days of the end of treatment (fungal infection defined according to EORTC/MSG criteria). Criterion assessed by a blinded adjudication committee.
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.

analysis[53]. One out of 26 patients enrolled in the liposomal amphotericin group was excluded from the modified intention-to-treat analysis due to absence of fever > 38ºC at randomization[53]. The baseline characteristics of the patients included in the study are summarized in table 3.

Table 3. Characteristics of the patients included in the RCT in children with febrile neutropenia

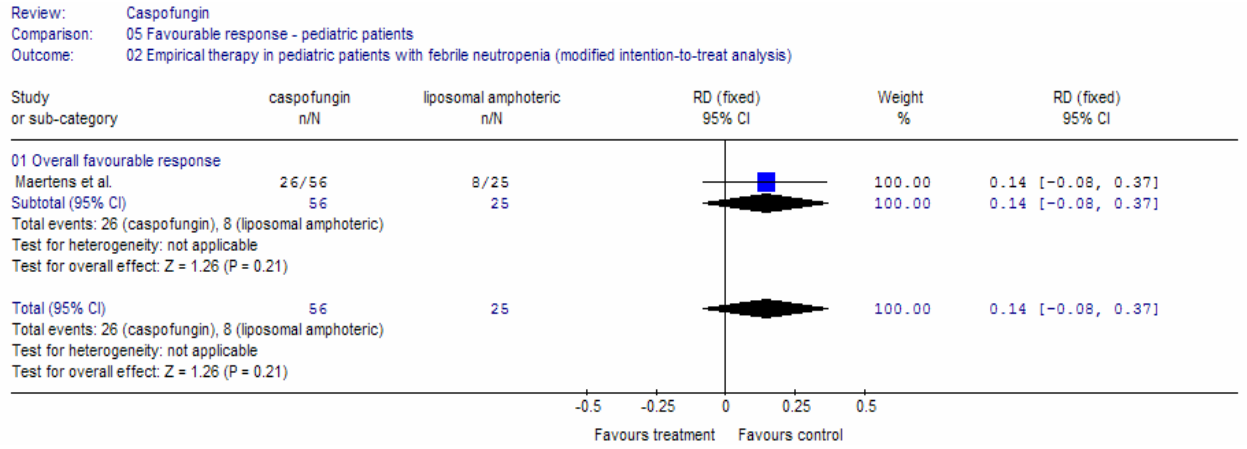
	Caspofungin (N=56)	**Liposomal amphotericin B (N=26)**
Age (years), mean (range)	7.4 (2-16)	7.4 (2–16)
Male gender, n (%)	35 (63%)	20 (77%)
Underlying disease, n (%)		
AML	18 (32%)	10 (38%)
ALL	16 (28%)	7 (27%)
Lymphoma	6 (11%)	5 (19%)
Solid tumours	16 (28%)	4 (15%)
Neutropenia, n (%)		
< 500 cells/µl	16 (28%)	7 (27%)
< 100 cellss/µl	40 (71%)	19 (73%)

ALL= acute lymphocytic leukemia / AML = acute myeloid leukemia

The mean treatment duration was 11.6 days (range 3-36, median 9) and 11.4 days (range: 1-55, median 9) in the caspofungin and liposomal amphotericin B groups, respectively[53]. One patient (2%), and two patients (8%) required an increased dose, respectively[53]. Figure 2 shows the efficacy results of the modified intention-to-treat analysis. As reported in the caspofungin product label approved by the FDA, there was a trend towards better outcomes with caspofungin compared to liposomal amphotericin B in the overall response to treatment, i.e., 26 (46.4%), and eight (32%), respectively [44].The authors of the abstracted presented at the conference concluded that the efficacy between the two treatments was similar[53].

The study drug was discontinued due to lack of efficacy in three (5%) and one (4%) patient(s) in the caspofungin and liposomal amphotericin B groups, respectively[53]. Drug-related adverse events were the cause of discontinuation in two (4%) and three (12%) patients, respectively (total: five (9%), and four (16%), respectively)[53].

Figure 2. Pediatric RCT in febrile neutropenia



The risk difference between the two groups was calculated according to the frequencies reported in the presentation and does not take into account adjustments according to stratification variables. The risk difference may consequently vary slightly from what is reported in the publication.

Source: Caspofungin product label approved by the FDA[44].

6.1.1.2 Non-comparative studies in febrile neutropenia

A retrospective study performed at The Hospital for Sick Children Toronto evaluated the use of caspofungin in the empiric treatment of febrile neutropenia[18]. Fifty-six children (67 courses) were included between June 1st 2005 and April 30th 2006[18]. Haematologic stem cell transplantation had been undertaken in 26 (39%) of the treatment courses[18]. A proven baseline fungal infection was documented in seven courses (10%) consisting of aspergillosis, (n=2), candidemia, (n=3), yeast cells, (n=1), and zygomycetes, (n=1)[18]. An overall favourable response based on five criteria[f] was seen in 53 (79%) treatment courses[18]. Responses to each individual criterion were used to define the overall favourable response as follows:

- Complete resolution of the fungal infection in patients with evidence of a baseline fungal infection: 4/7 (57%).
- Breakthrough fungal infections: None.
- Mortality within 7 days of stopping the study drug: 6 (9%), none was considered related to caspofungin or the fungal infection.
- Caspofungin discontinuation: 9 (13%) courses.

[f] All five following criteria have to be met:
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.

Reasons for discontinuation: rash in one case (1.5%), lack of efficacy in 8 cases (11.9%). In all cases, caspofungin was switched to amphotericin B formulations, combined with voriconazole in one case.

- Fever resolution: 57 (85%).

A study by Walsh et al. included 39 febrile neutropenic patients between 2 and 17 years of age[54]. Treatment efficacy was not reported, however the authors reported that 2/39 (5.1%) patients developed breakthrough fungal infections during the course of the study[54]. The main goal of the study was to determine the dose of caspofungin that produces plasma concentrations similar to the ones obtained in adults with a 50 mg/day regimen[54]. The study revealed that dosing based on the patients' body surface area is adequate in pediatric patients aged 2-17 years, and that a dose of 50 mg/m^2/day (up to a maximum of 70mg/day) in these patients produces plasma concentrations similar to those obtained in adults with standard dosing[54].

The multicenter survey by Groll et al. included 16 pediatric patients who received caspofungin as empiric therapy of febrile neutropenia, and 48 patients treated for possible, probable, or proven fungal infections[94]. Due to heterogeneities in the caspofungin treatment strategy compared to the other studies, i.e., the median dose patients in the empirical therapy group received was much lower than the usual dose (median: 30 mg/m^2, range 20-54), and caspofungin was combined with other antifungals in some cases, we decided to only include this study in the safety section.

6.1.2 Safety – Pediatric patients

6.1.2.1 Randomized controlled trial in febrile neutropenia

The main outcome of the study, patients with ≥ 1 drug-related adverse event, was observed in 48% of the patients in the caspofungin group and 46% in the liposomal amphotericin B group[53]. This difference was not statistically significant based on the 95% CI of these estimates (figure 2).

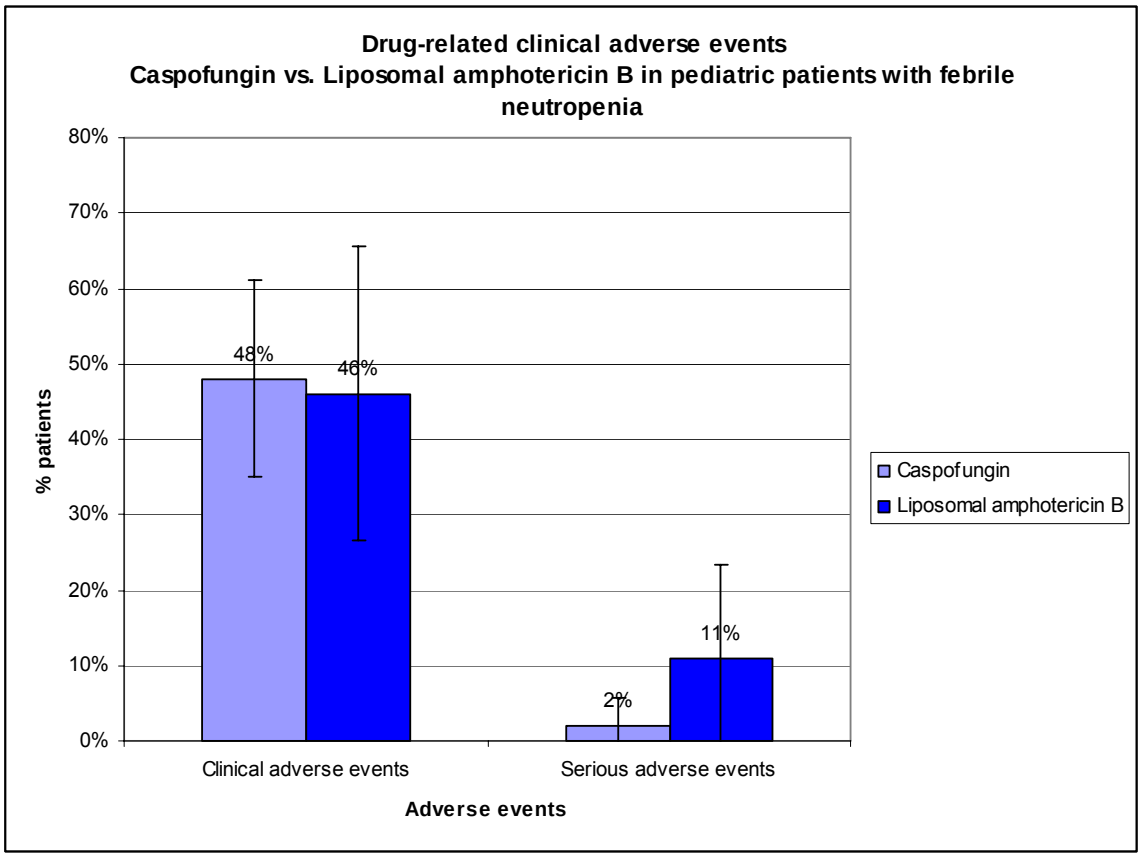
Results of the RCT showed that there was a trend to a lower frequency of some individual drug-related clinical and laboratory adverse events with caspofungin compared to liposomal amphotericin B and vice-versa[53] (Figures 3-5). However the difference between the two groups was not statistically significant judging by the overlapping 95% CI (Figures 3-5). We calculated

the 95% CI based on the number of patients and frequencies of adverse events reported by the authors. Lack of statistical significance may have been due, at least partially, to a low statistical power to detect such a difference, since the number of patients included was relatively small, i.e., 56 and 25 patients in the caspofungin and liposomal amphotericin B groups, respectively.

Two percent of the patients in the caspofungin group, and 11% of the patients in the liposomal amphotericin B group experienced serious drug-related adverse events[53], however, the types of events were not specified by the authors.

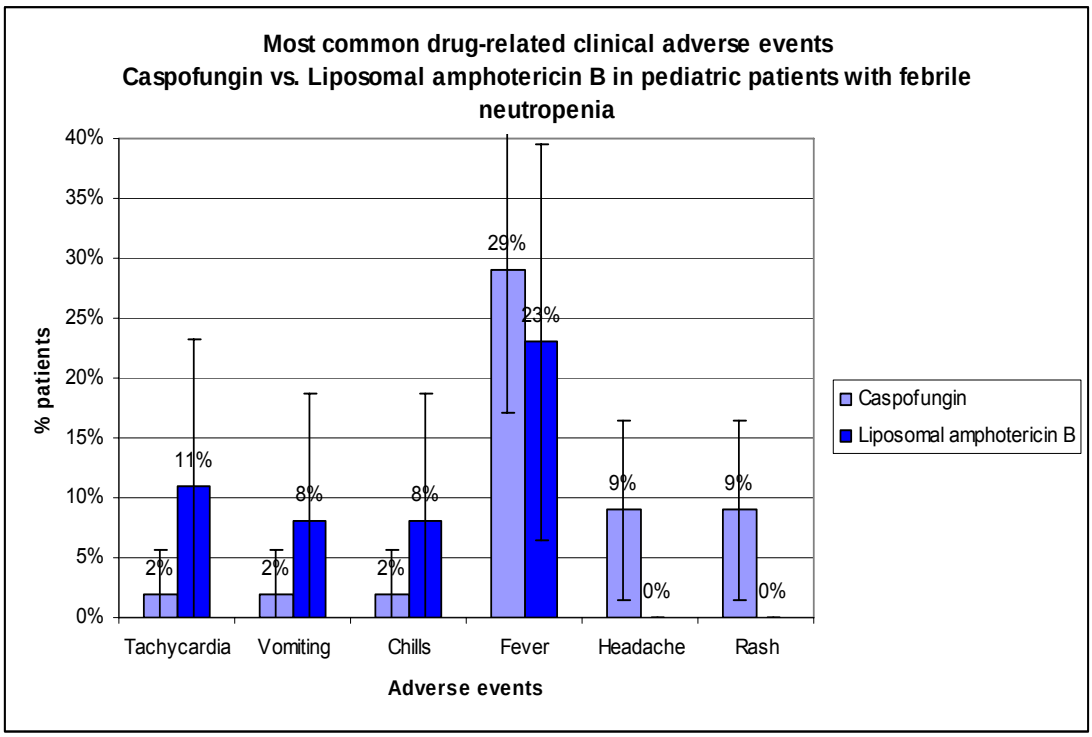
The study drug had to be discontinued due to drug-related adverse events in 4% and 12% of the patients in the caspofungin and liposomal amphotericin B groups, respectively[53].

Figure 3. Drug-related clinical adverse events reported



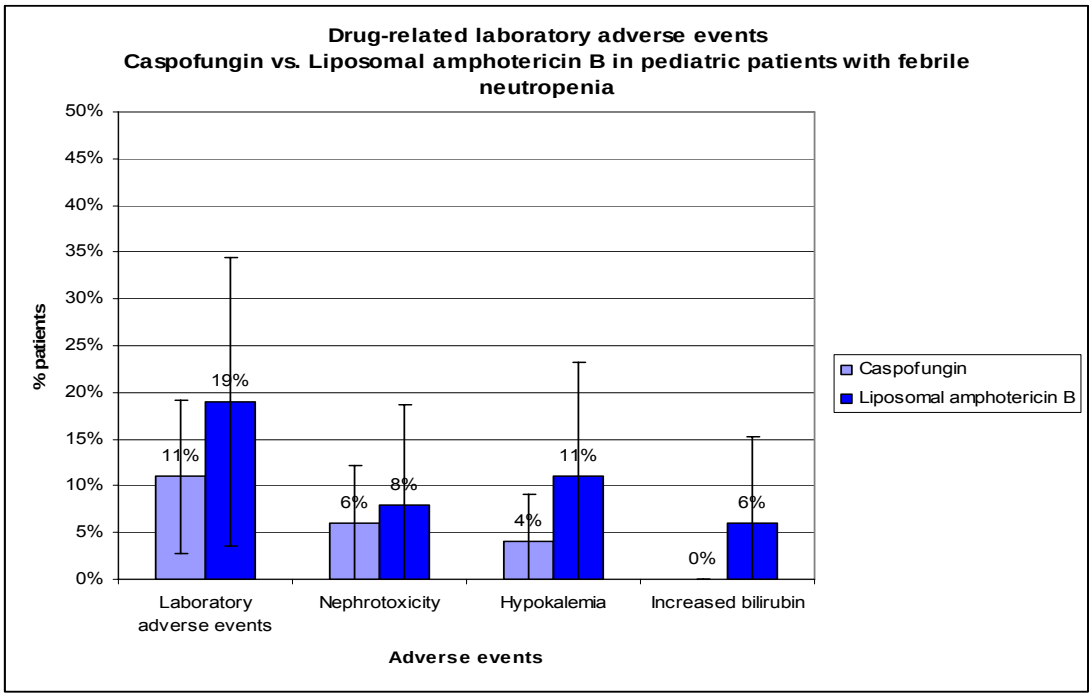
Error bars refer to the 95% confidence interval calculated based on the frequency of each adverse event and the number of patients reported by the author. Type of serious adverse events were not specified by the authors

Figure 4. Most common drug-related clinical adverse events reported



Error bars refer to the 95% confidence interval calculated based on the frequency of each adverse event and the number of patients reported by the author.

Figure 5. Drug-related laboratory events



Error bars refer to the 95% confidence interval calculated based on the frequency of each adverse event and the number of patients reported by the author.

6.1.2.2 Safety - Non-comparative studies in febrile neutropenia

In the retrospective study from The Hospital for Sick Children Toronto, ten adverse events (14.9%) were observed, 9 possibly related and one probably related to caspofungin (none definitely related)[18]. In the study by Walsh et al., five (12.8%) and two (5.1%) patients reported drug-related clinical or laboratory adverse events, respectively.

Caspofungin treatment was discontinued due to adverse events in one patient (1.5%, rash) in the study at The Hospital for Sick Children[18]. In the studies by Walsh et al.[54] and Groll et al.[94] no patient had to discontinue the treatment due to drug-related adverse events.

Adverse events considered by the investigators as possibly, probably, or definitely drug-related in the non-comparative studies in pediatric patients with febrile neutropenia are summarized in table 4.

Table 4. Drug-related adverse events. Non-comparative pediatric studies in febrile neutropenia

Adverse Events	**Koo et al.[18] Caspofungin monotherapy N=67**	**Walsh et al.[54] Caspofungin monotherapy N=39**	**Groll et al.[94] * Caspofungin alone or in combination with other antifungals / cyclosporine** (N=16)**
Rash, n (%)	2 (3%)	1 (2.6%)	Skin eruptions: 0
Nausea, n (%)	1 (1.5%)	NR	1 (6.3%) – grade III ¶
Vomiting, n (%)	1 (1.5%)	NR	
Fever, n (%)	NR	1 (2.6%) – fever/rigours	5 (31.3%) – fever grades I or II ¶
Diarrhea, n (%)	NR	1 (2.6%)	0
Phlebitis, n (%)	NR	1 (2.6%)	NR
Nephrotoxicity§, n (%)	1 (1.5%)	NR	2 (12.5%) – creatinine ≥ 3x baseline
Proteinuria§, n (%)	NR	1 (2.6%)	NR
Hypokalemia§, n (%)	2 (3%)	1 (2.6%)	NR
Hypomagnesemia§, n (%)	1 (1.5%)	NR	NR
Hepatotoxicity§, n (%)	1 (1.5%)	1 (2.6%)– increased AST	4 (25%) - AST , 5 (31.3%) – ALT, 1 (6.3%) – bilirubin, 0 – alkaline phosphatase ≥ 3x baseline

ALT = alanine aminotransferase; AST=aspartate transaminase; NR= not reported

*Only patients with febrile neutropenia were included.
** - It is not clear how many patients in this group used cyclosporine concomitantly with caspofungin. 19/64 (29.7%) patients included in the study used the combination in the study.
§ Criteria for adverse events not provided by the authors with the exception of the study by Groll et al.[94].
¶ - Grades of adverse event according to the Common Toxicity Criteria set by the United States National Cancer Institute[94].

No serious adverse events related to caspofungin or other antifungals were reported among the 304 pediatric patients included in the non-comparative studies[18 54 94 96 97 98 99 100]. The adverse events reported in the eight non-comparative caspofungin studies in pediatric patients [18 54 94 96 97 98 99 100] are provided in Appendix 3.

6.1.4 Comments - Pediatric patients

The authors of the RCT comparing caspofungin and liposomal amphotericin B in febrile neutropenic children concluded that caspofungin has a similar efficacy compared to liposomal amphotericin B with a tolerable safety profile[53] . There was a trend towards better outcomes with caspofungin compared to liposomal amphotericin B in the overall response to treatment, however this difference was not statistically significant. Due to the small sample size, lack of statistically significant differences between the two groups may have been due to insufficient statistical power to detect such differences.

Authors of non-comparative caspofungin studies in pediatric patients concluded that caspofungin alone or in combination with other antifungals presents reasonable efficacy and safety in pediatric patients with invasive fungal infections[94 96 97 98] (Appendices 2 and 3). Altogether the non-comparative studies provided information on 304 pediatric patients with treatment extending to up to 382 days.

The non-comparative and sometimes retrospective nature of the studies and the small sample sizes do not permit conclusions to be drawn regarding the efficacy of caspofungin relative to other antifungals. On the other hand, these studies did not present strict inclusion criteria and therefore permitted the evaluation of safety in situations that occur in clinical practice that would normally be excluded from RCTs, such as the concomitant use of medications such as cyclosporine, and co-morbid conditions.

Information on the transience and clinical importance of the laboratory abnormalities were often not provided in the studies. Factors that may contribute to the large variation in the frequencies of events reported among the different studies include the small sample sizes, heterogeneity of the patients included, different lengths of treatment, use of different concomitant medications,

different criteria to define the adverse events, and frequency of measurements, among other factors.

6.2 Study results – Adult patients

6.2.1 Efficacy - Adult patients

6.2.1.1 Randomized controlled trial in febrile neutropenia

We have included the only caspofungin RCT in patients with febrile neutropenia[92] as this is the focus of our report. The RCT consisted of a randomized, double-blinded, 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[92]. 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[g 92].

Out of a total of 1123 randomized adult patients, 1111 received treatment[92]. A total of 1095 adult patients were included in the modified intention-to-treat analysis, 556 and 539 in the caspofungin and liposomal amphotericin B groups, respectively[92]. 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)[92]. Therefore, caspofungin was considered as non-inferior to liposomal amphotericin B according to pre-specified criteria[92].

Additional information on study characteristics and study results can be found in Appendices 4 and 6.

6.2.2 Safety – Adult patients

6.2.2.1 Randomized controlled trial

The safety results of the caspofungin RCT by Walsh et al.[92] in 1111 adult patients with febrile neutropenia are summarized in Appendices 4 and 6. Adverse events were monitored during the study and for 14 days after its completion[92]. The investigators were responsible for ascertaining the association between the adverse events and the study drugs[92]. Adverse events considered

[g] Modified intention-to-treat definition: randomized patients with persistent fever and neutropenia who received at least one complete dose of the study drug.

as caspofungin- or liposomal amphotericin B-related to any degree by the investigator were included.

The publication by Walsh et al.[92] 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[112], as summarized in table 5.

Table 5. Serious drug-related adverse events – 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**[112]	
	Caspofungin **N=564**	**Liposomal Amphotericin B** **N=547**
Serious drug-related adverse events, n(%)	9 (1.6%)[112] - 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%)[112] - Respiratory system (n=5), respiratory distress, dyspnea, hypoxia - Hypersensitivity reaction, anaphylaxis, anaphylactic reaction (n=3) - Acute renal failure or renal insufficiency (n=3) - Hypokalemia (n=1) - Ventricular fibrillation with cardiac arrest (n=1) - Fungal infection (n=1) - Grand mal seizure (n=1) 1 adverse event not accounted for in the publication.
Serious drug-related laboratory adverse events, n (%)	0[112]	1 (0.1%)[112] (Increased serum total bilirubin)
Deaths possibly related to the study drug, n(%)	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

*Chills, rigours, chest tightness, tachypnea, nausea, and high fever[112].

Withdrawal of study drug due to adverse events occurred in 5% and 8% of the patients in the caspofungin and liposomal amphotericin B groups, respectively (p=0.04)[92]. Patients treated with caspofungin had a lower rate of some drug-related adverse events such as nephrotoxicity and infusion-related events compared to patients who received liposomal amphotericin B[92].

Additional information is provided in Appendices 4 and 6.

6.2.3 Comments – Adult patients

Clinical and laboratory adverse events in the adult RCT were generally evaluated in the short term, i.e., during treatment and up to two weeks thereafter. The magnitude and clinical significance of the laboratory abnormalities considered to be associated with the study drugs were often not discussed by the authors.

Serious caspofungin-related adverse events were reported in < 2% of the adult patients included in the RCT. In general there was a trend towards a lower rate of clinical and laboratory adverse events with caspofungin compared to liposomal amphotericin B, which was statistically significant at times.

No RCT in febrile neutropenic patients compared the safety of caspofungin to conventional amphotericin B. However, an RCT comparing the two drugs in invasive candidiasis showed that conventional amphotericin B had a statistically significantly higher frequency of adverse events such as nephrotoxicity (24.8% vs. 8.4%, p=0.02), hypokalemia (23.4% vs. 9.9%, p=0.04), and infusion-related events (48.8% vs. 20.2%, p=0.002) compared to caspofungin[113]. A higher proportion of patients in the conventional amphotericin B group had to withdraw the antifungal treatment due to adverse events compared to caspofungin, (23.2% vs. 2.3%, p=0.003)[113].

6.3 Safety - Combination of caspofungin and cyclosporine in adult and pediatric patients

Nine studies identified during the literature review process reported results of the effects of the concomitant use of caspofungin/cyclosporine in hepatic toxicity in adult and pediatric patients[18 94 114 115 116 117 118 119 120]. These studies are summarized in Appendix 7.

Limitations in study design such as sample size (n=8-19 patients /study) and retrospective nature among others do not permit definite conclusions to be drawn regarding the safety of the concomitant use of these two drugs.

Most authors believe that when used in a population in which the potential benefits outweigh the potential risks, the caspofungin/cyclosporine combination either seemed tolerable or presented a low risk of hepatotoxicity[115 94 114 116 117 120]. Authors of another publication believe that the combination can be considered but that the patients' hepatic function should be monitored[118]. Some authors pointed out that larger prospective studies are necessary[115 114 116]. Morrissey et al. pointed out that while transient increases in liver enzymes may occur with the concomitant use of caspofungin and cyclosporine, clinically significant hepatotoxicity has not been observed, and drug discontinuation was seldom necessary[119]. 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)][18].

7.0 PUBLISHED ECONOMIC ANALYSES, HEALTH TECHNOLOGY ASSESSMENT REPORTS, AND SYSTEMATIC REVIEWS

Two Health Technology Assessments (HTAs)[103 104] were identified in the literature. One report was published by the Canadian Agency for Drugs and Technologies in Health (CADTH) in 2001 and constituted a short report on the use of caspofungin in patients with invasive aspergillosis refractory or intolerant to other antifungals[103]. The authors concluded that when the report was being prepared, the evidence for the use of caspofungin in this indication was scarce[103]. A more recent report (2004) from the Institute for Clinical Effectiveness from Argentina concluded that caspofungin seemed to have a similar efficacy compared to conventional amphotericin B or liposomal amphotericin B for the treatment of invasive fungal infections, with a more favourable side-effect profile[104]. These conclusions were based on studies in adult patients.

One systematic review published in 2007 evaluated the efficacy and safety of caspofungin compared to other antifungals in adult patients[102]. Febrile neutropenia was one of the indications included in the review[102]. The authors of the systematic review concluded that caspofungin has a better cure rate and fewer adverse events than conventional amphotericin B but mentioned that limitations of their systematic review were the inclusion of patients with different doses of

the study drug, different lengths of treatment, and different treatment indications[102]. Antifungals with different side-effects' profiles used in different treatment indications were pooled into one comparator group which renders the results difficult to interpret.

Five economic analyses comparing caspofungin with liposomal amphotericin B in adult patients with febrile neutropenia were identified[105 106 107 108 109]. In four of these analyses, antifungal treatment and complication costs were incorporated and the authors concluded that caspofungin was cost-effective compared to liposomal amphotericin B[105 106 107 108]. The fifth analysis compared different treatment strategies in the empirical antifungal treatment of patients with febrile neutropenia[109]. Additional information is provided in Appendix 8.

8.0 USE OF CASPOFUNGIN AT THE HOSPITAL FOR SICK CHILDREN TORONTO

In our institution, caspofungin is used as an alternative to amphotericin B for the empiric antifungal treatment of children (2-17 years) with acute leukemias or who underwent an HSCT or who presented with side effects associated with amphotericin B[18]. Side effects associated with amphotericin B include abnormal renal function, uncontrolled infusion-related reactions, or uncontrolled hypokalemia [18].

Approximately 85 to 90 patients undergo bone marrow transplantations and approximately 60 patients are treated for acute leukemia annually at The Hospital for Sick Children (personal communication, Ms. Judy Van Clieaf, Child Health Services Director, Haematology/Oncology Division). This is the population that is the most susceptible to the development of prolonged febrile neutropenia and therefore may receive empiric antifungal treatment according to the literature[3 5 10 11 12].

8.1 Cost of empiric antifungal treatment in patients with febrile neutropenia at The Hospital for Sick Children

An analysis of the cost of febrile neutropenia was performed based on a study conducted at The Hospital for Sick Children[95]. It included 19 children 2-17 years old who received conventional amphotericin B used either as empiric treatment or as therapy for a documented fungal infection[95]. Only the costs incurred during the period in which the patients received the antifungal treatment were included. The median age of the patients was 10 years (2-17) and 16

(84%) patients had acute leukemia or had undergone an HSCT[95]. Three (16%) patients had a documented fungal infection at baseline[95]. The median length of antifungal treatment was 13 days [mean: 16.3 (3-50)]. Ten (53%) patients switched from conventional amphotericin B to a second antifungal, amphotericin B lipid complex[95]. The mean treatment cost per patient was $20,786 ($3,900 - $57,879)[95]. These costs included hospitalization costs (nursing, administration, materials, equipment), medications, physician consultations, diagnostic and laboratory tests, and blood products[95]. The mean cost of antifungals was $3,326 ($83-$14,118) which represented 16% of the total treatment costs[95]. The mean cost per day of treatment was $1,275, or $1,071 excluding antifungals[95], which was used as a base for daily hospitalization costs in our report.

9.0 COST AND ECONOMIC ANALYSES – THE HOSPITAL FOR SICK CHILDREN

9.1 Cost analysis of antifungals used in the treatment of febrile neutropenia

In a primary analysis, the costs of empiric antifungal treatment with caspofungin, conventional amphotericin B, and liposomal amphotericin B were calculated. Our analysis included resources incurred during the period of the antifungal treatment. Resources incurred in the antifungal treatment, monitoring and prevention of antifungal-related complications were included in our cost analysis (table 6).

The daily antifungal costs were estimated as $174.5 ($234.5 on day 1), $223.5, and $102 with caspofungin, liposomal amphotericin B, and conventional amphotericin B, respectively (20 kg/0.79 m^2 child[87] - table 6).

Table 6. Cost of individual antifungal treatments including drugs and saline solution used to prevent complications

Drug	A - Drug acquisition costs per day (0.79 m^2/20 kg patient)	B - Solution for reconstitution** / saline loading	C - Nursing cost (1/3 of infusion time¦)	D - Pharmacist cost (preparation of infusion)	Antifungal cost /day (A + B + C + D)	Antifungal cost / episode (14 days §)
Caspofungin‡	50mg/m^2/day $150 (assuming re-use of vial*) $222 (no re-use of vial) §§ 70mg/m^2 (day 1) $210 (assuming re-use of vial*) $222 (no re-use of vial) §§	$0.19 (260.5ml 0.9% NaCl)[42] $4.00 (IV bag)	$10.3 (1 hour ÷3)	$10	Cost/day (with re-use) $174.5 (50mg/$m^2$) $234.5 (70mg/$m^2$) - day 1 Cost/day (no re-use) $242.5 (50mg/$m^2$) $242.5 (70mg/$m^2$)	With vial re-use $2,503 No vial re-use $3,395
Liposomal amphotericin B	3 mg/kg/day $174 (assuming re-use of vial*) $242 (no re-use of vial)	Drug reconstitution $0.35 (12ml sterile water, 12ml 5% dextrose solution)[57] $4.00 (IV bag) Saline loading (10ml/kg) ¶¶ $0.24 (200ml 0.9% NaCl solution) + $4.00 (IV bag)	$20.6 (2 hours[33] ÷3) $10.3 (1 hour ÷3)	$10	Cost/day (with re-use) $223.5 (3 mg/kg/day) Cost/day (no re-use) $291.5 (3 mg/kg/day)	With vial re-use $3,129 No vial re-use $4,081
Conventional amphotericin B	1 mg/kg/day $32 (assuming re-use of vial*) $66.67 (no re-use of vial)	Drug reconstitution $0.25 (500ml 5% dextrose solution + 10ml sterile water)[56] $4.00 (IV bag) Saline loading (10ml/kg) ¶¶ $0.24 (200ml 0.9% NaCl solution) + $4.00 (IV bag)	$41.2 (4 hours[28] ÷3) $10.3 (1 hour ÷3)	$10	Cost/day (with re-use) $102 Cost/day (no re-use) 132.7 Pre-medication cost + $6.0 for ½ the duration of treatment	With vial re-use $ 1,470 No vial re-use $1,900 (includes pre-medication)
Pre-medication¶	Acetaminophen(10-15mg/kg/dose)¦¦ $0.17 for 1 dose of 10mg/kg Diphenhydramine (1.25/mg/kg/dose) ¦¦ $0.4 for 1 dose Meperidine (1mg/kg/dose) ¦¦ $0.29 for 1 dose	0	$5.1 (30 minutes ÷3) for conventional amphotericin B	0	Cost/day $6.0	Included above as applicable

Daily drug acquisition and saline loading costs are based on a 20kg child (0.79m^2 of body surface area).

‡ Caspofungin costs were calculated based on a 70 mg vial since both 50 and 70 mg vials have the same cost.

* We assumed that the non-used portion of the drug that remained in the reconstituted drug vials would be kept for use by other patients as per our institutions procedures (personnal communication, Ms. Lee Dupuis, Pharmacy Department, The Hospital for Sick Children). We have nevertheless increased the drug use by 20% in order to account for possible drug waste.

**Based on the product label

¦ - Based on the fact that the nurse-patient ratio in the hospital ward where these patients are treated is 1:3 (8A ward – information from Ms. J. Van Clieaf, The Hospital for Sick Children).

§ Based on Infectious Diseases Society of America (IDSA) guidelines[13] and expert opinion.

¶ - The published literature recommends the use of pre-medication to prevent the appearance of infusion-related reactions with conventional amphotericin B[38]. We have assumed that all three medications acetaminophen, diphenhydramine, and meperidine would be administered before the infusion of conventional amphotericin B. Since pre-medications can be tapered off and discontinued in the absence of infusion-related events, we have assumed that pre-medication would be used in half of the duration of the treatment. We have assumed that the non-used portion of the vial could be used later (allowing for a 20% drug waste).

¦¦ - Doses used, personal communication with Ms. Lee Dupuis (Pharmacy, The Hospital for Sick Children, Toronto)
§§ - The cost per 50 mg caspofungin vial is the same as for a 70 mg caspofungin vial, therefore the cost of caspofungin treatment per day does not vary whether the patient is receiving a 50mg or a 70mg dose if no drug re-use is considered.
¶¶ - According to the literature saline loading is recommended before each administration of conventional and lipid formulations of amphotericin B[66]. Saline loading dose according to guidelines from the Hospital for Sick Children.

Assuming a treatment duration of 14 days, the cost of empirical antifungal treatment per child (20 kg / 0.79 m^2) was estimated as $2,503, $3,129 and $1,470 for caspofungin, liposomal amphotericin B and conventional amphotericin B, respectively (table 6). The antifungal treatment cost with caspofungin was $626 lower than with liposomal amphotericin B, and $1,033 higher than conventional amphotericin B.

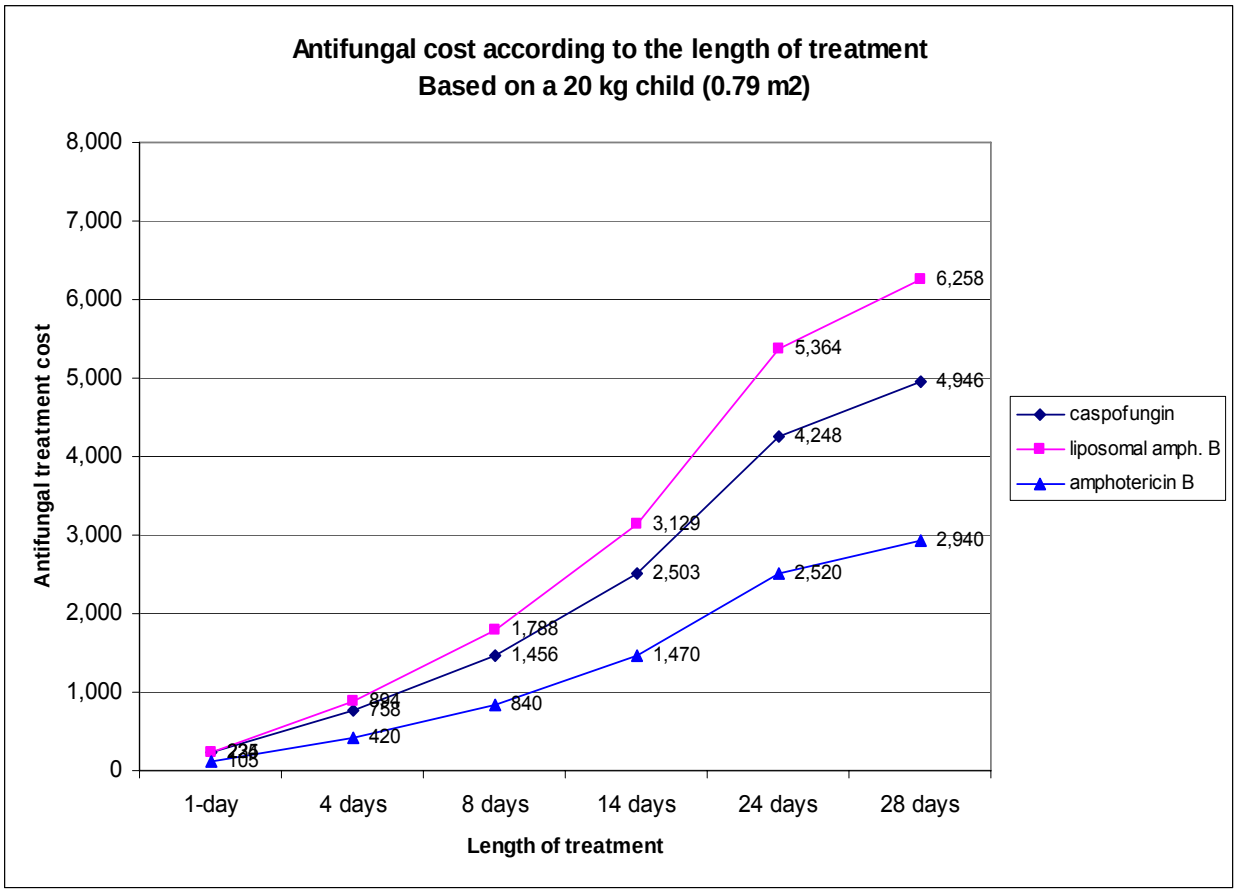
The mean daily cost of hospitalization in this patient population obtained from pediatric patients receiving empirical antifungal treatment for febrile neutropenia at our institution was estimated as $1,071 (excludes antifungal costs, section 8.1). The total hospitalization cost for the duration of the empiric antifungal treatment of febrile neutropenia in our patient population is therefore $17,497 ($1,071 x 14 + $2,503) with caspofungin, $18,123 with liposomal amphotericin B, and $16,464 with conventional amphotericin B. The difference in overall treatment cost between the antifungals did not change when hospitalization costs were included since the length of antifungal treatment and other resources used are believed to be similar between the groups.

With regards to daily drug acquisition costs, caspofungin and liposomal amphotericin B have a higher cost compared to conventional amphotericin B (table 6). On the other hand, while caspofungin is infused over one hour, both conventional amphotericin B and liposomal amphotericin B are infused over a longer period of time, i.e., four and two hours, respectively, in addition to 1 hour for the infusion of saline solution, and 30 minutes for pre-medication infusion (conventional amphotericin B) (table 6). Moreover, during the first hour of the infusion of conventional amphotericin B, the patient needs to be monitored for infusion-related events[33] which cannot be completely avoided even with the use of pre-medications[38 31]. Therefore the administration of conventional amphotericin B especially is more resource-intensive with regards to healthcare personnel time compared to caspofungin.

9.2 Univariate sensitivity analyses

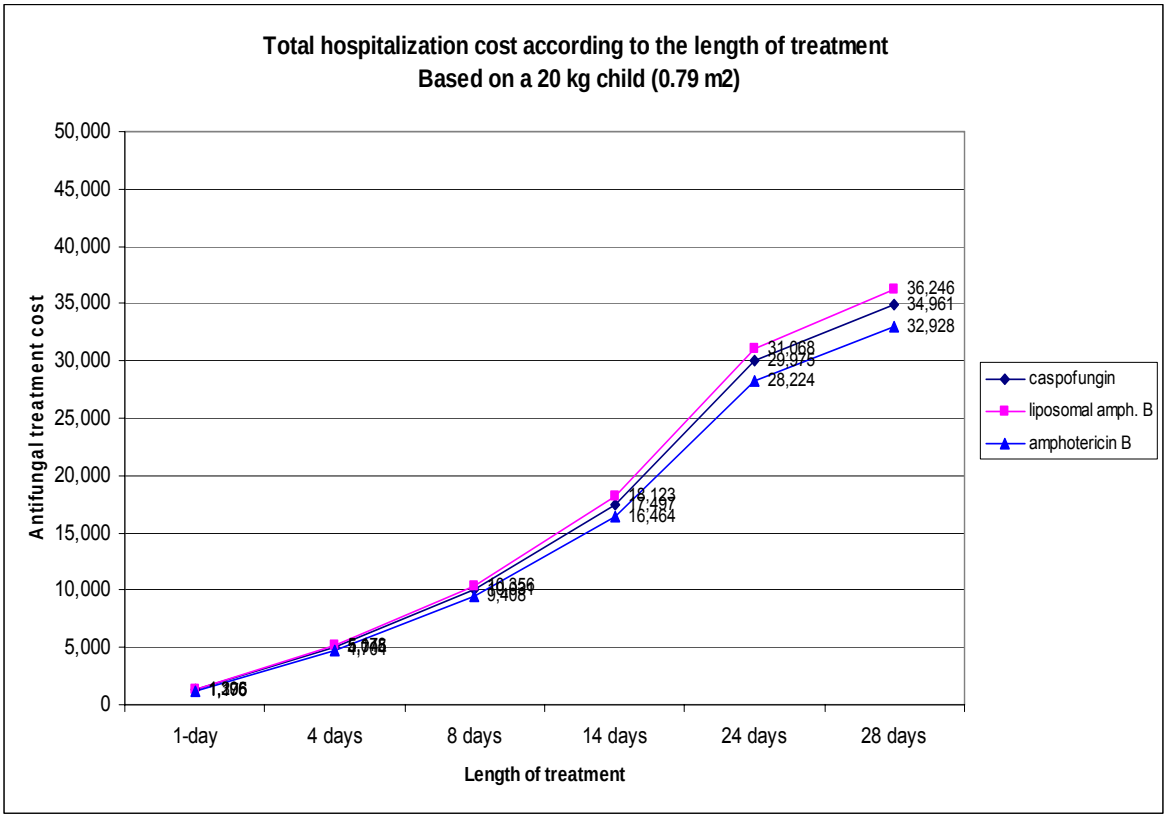
The results of a sensitivity analysis varying the treatment duration from 1-28 days and with and without hospital costs are shown in figures 6 and 7. These analyses do not take into account the probabilities of drug switch and the cost of antifungal-related complications.

Figure 6. Univariate sensitivity analysis – The impact of length of antifungal treatment on the antifungal treatment costs



Costs with antifungals used in the empiric treatment of febrile neutropenia based on a 20 kg child (0.79 m^2).
Costs include: antifungal acquisition cost, IV solution for drug reconstitution and materials, and nursing and pharmacy personnel time (table 6). Does not include cost of treatment switches and antifungal-related complications.

Figure 7. Univariate sensitivity analysis – The impact of length of antifungal treatment on the hospitalization costs



Costs with antifungals used in the empiric treatment of febrile neutropenia based on a 20 kg child (0.79 m^2).
Costs include: antifungal acquisition cost, IV solution for drug reconstitution and materials, and nursing and pharmacy personnel time (table 6), and hospitalization costs. Does not include cost of treatment switches and antifungal-related complications.

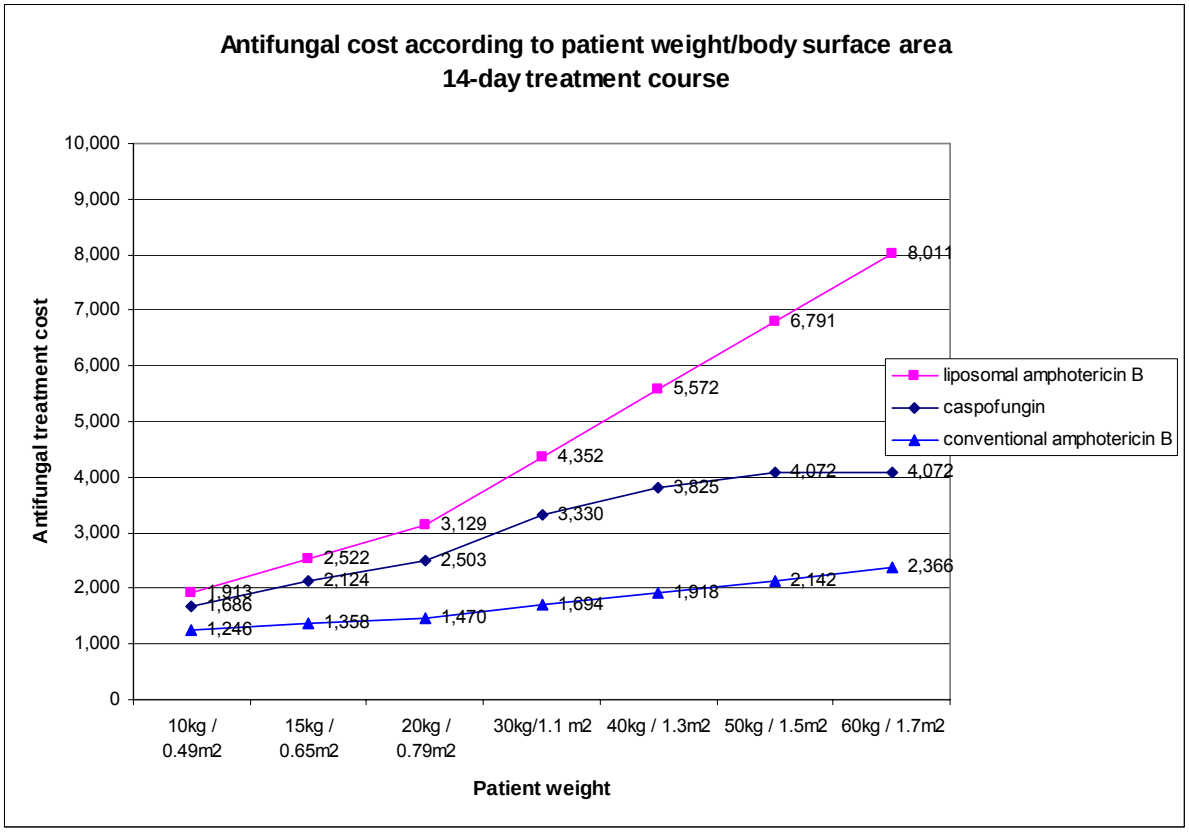
Utilization of unused portions of drug vials seems to be standard practice in hospitals, nevertheless, we have calculated the cost of antifungal treatment when the non-used portion of the antifungal vials is discarded. Table 6 shows the results for each antifungal with and without vial re-use.

Antifungal doses are calculated according to patient weight or body surface area. Our base case analyses used a 20 kg / 0.79 m^2 patient, which was assumed to be the approximate weight of a seven year-old[h] (mean age in the pediatric RCT was used in

[h] Median weight for a 5-year old is approximately 18 kg according to the weight-for-age table of the World Health Organization (WHO)88. World Health Organization (WHO). Weight-for-age charts (Girls and Boys)

our analyses). Univariate sensitivity analyses varying weight and body surface area were carried-out. The results obtained are shown in Figure 8. Costs were based on a 14-day course and included antifungal acquisition cost, IV solution for drug reconstitution and materials, and nursing and pharmacy personnel time. A maximum daily dosage of 70mg is recommended for patients treated with caspofungin, therefore, its curve plateaus after a certain level of patient weight (1.4m^2 / 44-48kg[87]) whereas the curves of conventional and liposomal amphotericin B continue to increase (figure 8). Since drug acquisition costs do not represent the largest part of the conventional amphotericin B treatment costs (table 6), its curve is less steep than the curve of liposomal amphotericin B (figure 8).

Figure 8. Univariate sensitivity analysis varying patient weight and body surface area



Costs with antifungals used in the empiric treatment of febrile neutropenia based on a 20 kg child (0.79 m^2).
Costs include: antifungal acquisition cost, IV solution for drug reconstitution and materials, and nursing and pharmacy personnel time (table 6). Does not include treatment switches and antifungal-related complications.

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http://www.who.int/nutrition/media_page/en/ (Last access: June 6th 2008).

9.2 Economic analysis

Since the current evidence suggests a similar efficacy between caspofungin and liposomal amphotericin B and conventional amphotericin B in the empiric treatment of febrile neutropenia or invasive fungal infections, a cost-minimization analysis was conducted. The patient population of our economic analyses was children (2-17 years) with haematological malignancies or who underwent HSCT, with persistent fever and neutropenia despite 5-7 days of antibacterial treatment.

Decision analytic modeling through probabilistic sensitivity analysis was used in the cost-minimization analysis. The probabilistic sensitivity analysis incorporated the point estimates and variance of antifungal switch, dose increase, complications, and duration of treatment and was carried out through Monte Carlo simulation (10,000 simulations). The parameters and the distributions used in the probabilistic sensitivity analysis are given in table 7. The costs included in the probabilistic sensitivity analysis are those that differed between the groups such as those incurred in the antifungal treatment, monitoring, prevention and treatment of complications (Appendix 9), and the costs of antifungal switch (based on antifungal costs, table 6).

The source of data was an RCT comparing caspofungin and liposomal amphotericin B in pediatric patients with febrile neutropenia was used as a source of the frequencies of antifungal switch and complications[53]. Complications reported in the RCT[53] were included in our analysis such as nephrotoxicity (doubling of serum creatinine), hypokalemia, rash, chills/rigour, and nausea/vomiting (Appendix 9). The RCT from where the data were derived did not provide detailed definition of the complications other than nephrotoxicity.

The study population of this analysis consists of the population included in the pediatric RCT that was used as the source in our analysis[53], i.e., children (2-17 years) with persistent fever and neutropenia without a documented invasive baseline fungal infection who received empiric antifungal treatment with caspofungin or liposomal amphotericin B[53]. Due to the low incidence of breakthrough fungal infections during the empiric antifungal course in different publications [0/67 caspofungin courses[18], 1/82 (1.2%) patients in the pediatric RCT[53] mentioned above, 2/39 (5.1%)[54] patients treated with caspofungin developed a breakthrough fungal infection] we assumed that there

were no a breakthrough fungal infections during the empiric antifungal treatment of the febrile neutropenia episode.

Table 7. Parameters used in the probabilistic sensitivity analysis

Parameter	Point estimate	Source	Distribution
Probability of drug switch with caspofungin*	0.09 (SD 0.038)	RCT of caspofungin vs. liposomal amphotericin B in pediatric patients[53]	Beta distribution
Probability of drug switch with liposomal amphotericin B*	0.16 (SD 0.073)	RCT of caspofungin vs. liposomal amphotericin B in pediatric patients[53]	Beta distribution
Duration of treatment with antifungal§	14 days (range 1-28) (antifungal switch at 7 days if it is the case¶)	Length of treatment according to the IDSA guidelines[13] and expert opinion. Range according to RCT[53]	Triangular distribution
Dose increase Caspofungin (to 70mg/m^2/day) Liposomal amphotericin B (to 5mg/kg/day)¦	 2% (SD 1.9%) 8% (SD 5.4%)	RCT of caspofungin vs. liposomal amphotericin B in pediatric patients[53]	Beta distribution
Probability of nephrotoxicity (doubling of serum creatinine) Caspofungin Liposomal amphotericin B	 0.06 (SD 0.032) 0.08 (SD 0.054)	RCT of caspofungin vs. liposomal amphotericin B in pediatric patients[53]	Beta distribution
Probability of hypokalemia** Caspofungin Liposomal amphotericin B	 0.04 (SD 0.026) 0.11 (SD 0.063)	RCT of caspofungin vs. liposomal amphotericin B in pediatric patients[53]	Beta distribution
Probability of Rash Caspofungin Liposomal amphotericin B	 0.09 (SD 0.038) 0	RCT of caspofungin vs. liposomal amphotericin B in pediatric patients[53]	Beta distribution
Probability of Chills Caspofungin Liposomal amphotericin B	 0.02 (SD 0.019) 0.08 (SD 0.054)	RCT of caspofungin vs. liposomal amphotericin B in pediatric patients[53]	Beta distribution
Probability of Nausea/Vomiting Caspofungin Liposomal amphotericin B	 0.02 (SD 0.019) 0.08 (SD 0.054)	RCT of caspofungin vs. liposomal amphotericin B in pediatric patients[53]	Beta distribution

IDSA = Infectious Disease Society of America / SD=standard deviation

Standard deviation (SD) was calculated based on the event frequency and the number of patients presented in the publication.
* We assumed that patients who initiated the empiric antifungal treatment with caspofungin would be switched to liposomal amphotericin B, and those initiating with liposomal amphotericin B would be switched to caspofungin. We assumed that patients using liposomal amphotericin B or caspofungin would not be switched to conventional amphotericin B since it is usually administered to patients who are unable to receive conventional amphotericin B[11].
§ According to expert opinion, the duration of empiric antifungal treatment in patients with febrile neutropenia remains the same regardless of the occurrence of antifungal switch in the absence of a documented fungal infection, i.e., treatment duration should extend for 14 days (Dr. Upton Allen, personal communication).
¶ We have assumed that the antifungal switch would occur halfway through the estimated duration of treatment, i.e., at 7 days.
¦ In case of liposomal amphotericin B dose increase, we have assumed that amphotericin B lipid complex would be used due to a lower treatment cost compared to liposomal amphotericin B at a dose of 5mg/kg.
** Definition of hypokalemia not provided by the authors.

Complications reported in the RCT comparing caspofungin to liposomal amphotericin B in pediatric patients were included in our model. These included nephrotoxicity, hypokalemia, chills (rigours), rash, and nausea/vomiting. The cost of treatment of each complication included hospitalization costs, diagnostic and laboratory tests, and healthcare professional fees where applicable. The calculation of the costs of these complications is provided in Appendix 9.

The results obtained in the probabilistic sensitivity analysis are presented in table 8. Our analysis showed that in pediatric patients (2-17 years) with haematological malignancies or who underwent HSCT, the empiric antifungal treatment of an episode of febrile neutropenia with caspofungin may result in a mean cost saving of $667 compared to treatment with liposomal amphotericin B. However, the 95% confidence interval indicates that the difference in cost may range between a saving of $3,221 up to an incremental cost of $1,802 per episode with caspofungin compared to liposomal amphotericin B. The probabilistic sensitivity analysis has shown that there is a 68% probability that caspofungin is less costly than liposomal amphotericin B.

Table 8. Probabilistic sensitivity analysis. Includes drug switches and treatment of complications in pediatric patients with febrile neutropenia

Initial treatment	Mean antifungal treatment cost (95% CI)	Mean differences in antifungal treatment cost (95% CI)	Probability that initiating treatment with caspofungin is less costly
Caspofungin	$2,875 (1,327 , 4,493)	-$667 (-3,221 , +1,802)	68%
Liposomal amphotericin B	$3,542 (1,686 , 5,486)	Reference	-

CI=Confidence Interval

Negative sign indicates cost savings

The results of the probabilistic sensitivity analysis according to patient weight/body surface area are shown in table 9.

Table 9. Probabilistic sensitivity analysis varying patient weight. Includes drug switches and treatment of complications in pediatric patients with febrile neutropenia.

Initial treatment	Mean antifungal treatment cost (95% CI)	Median differences in antifungal treatment cost (95% CI)	Probability that initiating treatment with caspofungin is less costly than liposomal amphotericin B
10 kg / 0.49 m^2			
Caspofungin	$1,948 (907 , 3,039)	-$272 (-1,879 , +1,307)	62%
Liposomal amphotericin B	$2,220 (1,080 , 3,401)	Reference	-
15 kg / 0.65 m^2			
Caspofungin	$2,438 (1,131 , 3,804)	-$432 (-2,508 , +1,592)	65%
Liposomal amphotericin B	$2,870 (1,386 , 4,414)	Reference	-
20 kg / 0.79 m^2			
Caspofungin	$2,889 (1,332 , 4,516)	-$656 (-3,215 , +1,820)	68%
Liposomal amphotericin B	$3,545 (1,688 , 5,487)	Reference	-
30 kg / 1.1 m^2			
Caspofungin	$3,797 (1,736 , 5,945)	-$1,008 (-4,464 , +2,315)	70%
Liposomal amphotericin B	$4,805 (2,279 , 7,459)	Reference	-
40 kg / 1.3 m^2			
Caspofungin	$4,384 (1,975 , 6,886)	-$1,671 (-5,939 , +2,415)	77%
Liposomal amphotericin B	$6,056 (2,829 , 9,448)	Reference	-
50 kg / 1.5 m^2			
Caspofungin	$4,717 (2,135 , 7,388)	-$2,560 (-7,553 , +2,185)	84%
Liposomal amphotericin B	$7,272 (3,364 , 11,414)	Reference	-
60 kg / 1.7 m^2			
Caspofungin	$4,717 (2,135 , 7,388)	-$3,755 (-9,360 , +1,573)	90%
Liposomal amphotericin B	$8,472 (3,868 , 13,363)	Reference	

CI=Confidence Interval
Negative sign indicates cost savings

9.3 Comments – Economic analysis at The Hospital for Sick Children

Our primary analysis which included only the resources incurred in the antifungal acquisition and administration showed that caspofungin and liposomal amphotericin B have a higher cost compared to conventional amphotericin B.

In a probabilistic sensitivity analysis we incorporated both the probabilities of antifungal-related complications and the need for antifungal switch in case of intolerance or lack of efficacy with caspofungin and liposomal amphotericin B based on a pediatric RCT.

The probabilistic sensitivity analysis incorporated not only the probability of these events occurring but also the variance, providing thus an estimate of the uncertainty surrounding the results. The small sample size included in the RCT and the lack of statistically significant differences between the two drugs are reflected in the wide confidence intervals in the probabilistic sensitivity analysis. As a consequence, we have observed a trend towards mean cost savings with caspofungin compared to liposomal amphotericin B, however, there was a 32% probability that liposomal amphotericin B may be less expensive than caspofungin.

It is important to mention that these results should be interpreted cautiously given the small sample size of the study from which outcomes were derived, that lead to imprecision in the results. Moreover, it is not possible to ascertain if there is a difference in adverse events between the two drugs since the lack of statistically significantly differences may have been due to insufficient statistical power to detect such differences. The pediatric RCT was presented at a conference and a full publication in the peer-reviewed literature is not presently available.

No other economic analysis on caspofungin in pediatric patients was identified. Economic analyses in adult patients with febrile neutropenia generally concluded that caspofungin is cost-effective when compared to liposomal amphotericin B (Appendix 8). Differences in the numerical results obtained between our report and these studies may stem from differences in treatment costs between children and adults since drug dose is based on patient weight in pediatric patients, changes in drug acquisition costs

and/or differences in drug acquisition costs in different countries, differences in the cost of nephrotoxicity used (see Appendices 9 and 10) among other factors.

Patient weight may affect both treatment costs and the cost differences between the different antifungals as shown in the sensitivity analyses. The results for different patient weights are shown separately in our analyses.

No direct controlled study between caspofungin and conventional amphotericin B in pediatric patients with febrile neutropenia was identified. For this reason, we could not compare the costs and consequences (drug switch, nephrotoxicity, hypokalemia among others) between these two drugs in pediatric patients.

The use of healthcare personnel with conventional amphotericin B compared with caspofungin may require hiring of additional personnel, however there may be an opportunity cost as it results in nurses and doctors having less time available for other tasks. It has been mentioned in the literature that despite having a lower drug acquisition cost, conventional amphotericin B may not have a lower administration cost compared to other antifungals[38]. Other authors agree that the prevention and management of conventional amphotericin B-related renal failure and electrolyte imbalances can be time and resource-consuming[26].

10.0 DISCUSSION

The systematic review revealed a paucity of evidence on the costs and benefits associated with the use of caspofungin in children with in febrile neutropenia. The pediatric and adult RCTs comparing caspofungin and liposomal amphotericin B in patients with febrile neutropenia were not designed to detect a difference in treatment response between the two drugs and their efficacy was considered similar by the authors. In both the adult and pediatric studies there was a trend towards a lower frequency of individual adverse events related to caspofungin compared to liposomal amphotericin B[53 92]. This was statistically significant at times in the adult RCT[92]. There was a 1.6% and 2.9% rate of serious adverse events possibly, probably or definitely-related to caspofungin and liposomal amphotericin B, respectively, that occurred in the adult febrile neutropenia RCT as reported to the European regulatory agency[112]. The pediatric RCT reported a 2% and 11% rate of serious drug-related adverse events with

caspofungin and liposomal amphotericin B, respectively (statistical significance not provided)[53]. Importantly, the RCT in adults showed that caspofungin had a statistically significantly lower rate of some drug-related adverse events compared to liposomal amphotericin B, such as nephrotoxicity and infusion-related events. A similar trend was observed in the pediatric RCT[53], however the difference was not statistically significant, which may have been due to a smaller sample size compared to the adult RCT. The clinical tolerance for serious adverse events in the pediatric population may differ from adults. These adverse events may require changes in the course of treatment with the antifungal and other drugs that are crucial for the patient and may therefore also affect clinical outcomes[22 25 26 81 67 79]. A trend towards a higher frequency of rash (9% vs. 0%) and fever (29% vs. 23%) was observed for caspofungin compared to liposomal amphotericin B, respectively.

No RCTs comparing caspofungin to conventional amphotericin B in adult or pediatric patients with febrile neutropenia were identified. An RCT in patients with invasive candidiasis showed a higher frequency of adverse events in adult patients treated with conventional amphotericin B compared to caspofungin[113]. In this study, a statistically significantly higher proportion of patients in the conventional amphotericin B groups presented with adverse events such as nephrotoxicity, hypokalemia, infusion-related events among others compared to the caspofungin group[113]. Additionally, a statistically significantly higher proportion of patients in the conventional amphotericin B group had to discontinue the antifungal treatment due to adverse events, compared to caspofungin[113].

No systematic reviews, health technology assessments or economic evaluations on the use of caspofungin specific to the pediatric population were identified.

Our cost analysis showed that the cost of antifungal treatment of an episode of febrile neutropenia with caspofungin and liposomal amphotericin B was higher than conventional amphotericin B i.e., $2,503, $3,129, and $1,470, respectively, for a 14-day treatment course, 20 kg/0.79 m^2 child. A probabilistic sensitivity analysis comparing caspofungin and liposomal amphotericin B included all costs related to treatment administration, drug switches and complications. The analysis showed a trend towards a mean lower cost with caspofungin compared to liposomal

amphotericin B, -$667 (95% CI: -$3,221 , +$1,802), and a 68% chance that caspofungin would cost less than liposomal amphotericin B. The use of a probabilistic sensitivity analysis incorporates the variance in the parameter estimates, consequently showing the uncertainty surrounding the cost estimates.

Both caspofungin and liposomal amphotericin B present relatively high acquisition costs that may affect the hospital pharmacy budgets, especially if a large number of patients receive these drugs annually in a given institution. However, consideration must be given to other hospital resources that are affected by the use of these drugs. For example, the monitoring, prevention, and treatment of complications may consume more time of healthcare professionals especially for conventional amphotericin B compared to caspofungin, therefore preventing staff from working on other tasks during that period.

Differences in treatment costs among the different antifungals should be evaluated in the context of differences in clinical outcomes and safety. Important antifungal treatment complications with conventional amphotericin B could not be factored into the cost analyses due to the lack of comparative data between caspofungin and conventional amphotericin B in pediatric patients. These include drug-infusion related events, hypokalemia and nephrotoxicity, which may not only impact clinical outcomes but also increase resource use and consequently costs.

The results of our economic analyses may be generalizable to other settings as long as the assumptions used are applicable to their contexts. For instance our results were based on an RCT in pediatric patients that excluded patients with baseline fungal infections. Based on the low rate of breakthrough invasive fungal infections observed in the RCT and the difficulties in determining the antifungal treatment required, we assumed that no such infection would be developed during the antifungal treatment. Invasive fungal infections are treated according to the specific pathogen and may require a long treatment, which would have an impact on treatment costs. Our costs were based on the current clinical practice and on the antifungals currently available. As new evidence and/or new antifungal drugs become available this report may need to be updated.

Other gaps in the literature remain, especially in pediatric patients. For instance, the pediatric RCT comparing caspofungin and liposomal amphotericin B may not have had sufficient statistical power to detect differences between the two drugs. According to the European regulatory agency, although the risk-benefit of caspofungin is favourable, there are still concerns with liver and pancreatic toxicity with the drug, and these events should continue to be monitored. Therefore it is important to continue to monitor the outcomes and safety of these drugs used in the less controlled setting of the clinical practice. This is especially true for pediatric patients given the scarcity of evidence in this patient population and the sensitivity around the acceptance of severe adverse events in children. Some of the consequences of toxicity such as withdrawal of important concomitant medications (antibiotics, immunosuppressives etc.) due to either nephrotoxicity or drug interactions have not been objectively reported in the literature and therefore were not included in our analyses.

11.0 CONCLUSIONS

Only one randomized clinical trial comparing caspofungin to other antifungals in pediatric patients with febrile neutropenia was identified. No health technology assessments or economic analysis compared caspofungin to other antifungals in children with febrile neutropenia.

The purported benefits of caspofungin are a better safety profile and fewer drug interactions compared to other classes of antifungals. RCTs in adults and pediatric patients with febrile neutropenia have found a similar efficacy between caspofungin and liposomal amphotericin B with a trend towards a lower frequency of important adverse events and drug withdrawal in pediatric patients. Data from adult studies suggest a similar efficacy with a better safety profile with caspofungin compared to conventional amphotericin B in invasive fungal infections.

Our analyses showed a trend towards lower treatment costs with caspofungin compared to liposomal amphotericin B. These results may be generalizable to other settings as long as the assumptions used are applicable to their contexts.

Both caspofungin and liposomal amphotericin B present relatively high acquisition costs that may affect the hospital pharmacy budgets, especially if a large number of

patients receive these drugs annually in a given institution. However, consideration must be given to other hospital resources that are affected by the use of these drugs. For example, the monitoring, prevention, and treatment of complications may consume more time of healthcare professionals especially for conventional amphotericin B compared to caspofungin, therefore preventing staff from working on other tasks during that period.

It should be highlighted that our economic analysis was based on a small RCT (n=82), which may lead to imprecision in the estimates. It is also important to notice that apart from cost-effectiveness results, the choice of antifungal also needs to take into account several factors such as the fungal pathogen isolated[13], local antifungal drug resistance, the patient's underlying conditions, potential for drug interactions, and drug safety[23 38 49].

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