SickKids

## The Hospital for Sick Children
## Technology Assessment at SickKids (TASK)

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

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## REPORT HIGHLIGHTS

*The Report Highlights consists of a summary of the full report with the same name and should be evaluated in conjunction with the full report and its appendices. Full documents are available for download at the website:*

***http://lab.research.sickkids.ca/task/reports-theses/***

## Authors

Vania Costa, MSc, Research Associate, Child Health Evaluative Sciences

Wendy Ungar. MSc, PhD, Senior Scientist, Child Health Evaluative Sciences

## Collaborators

Upton Allen, MD, *Chief, Division of Infectious Diseases, The Hospital for Sick Children*

John Doyle, MD, *Haematology/Oncology, The Hospital for Sick Children*

Lee Dupuis, MSc, *Pharmacy, The Hospital for Sick Children*

Shinya Ito MD, Clinical Pharmacology and Toxicology, The Hospital for Sick Children

Ahmed Naqvi, MD, *Haematology/Oncology, The Hospital for Sick Children* Toronto

Christopher Parshuram, MD, *Critical Care Medicine, The Hospital for Sick Children*

Lillian Sung, MD, *Haematology/Oncology, The Hospital for Sick Children*

## External reviewer

Janet Martin, PharmD, MSc(HTA&M), Director, High Impact Technology Evaluation Centre (HiTEC), Co-Director, Evidence-Based Perioperative Clinical Outcomes Research Group (EPiCOR), London Health Sciences Centre, London, Ontario



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## Conflicts of interest

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

# Introduction

The incidence and severity of invasive fungal infections in immunosuppressed patients has been increasing in adults and children in the past decades.

Patients with fever and neutropenia and who present with acute leukemias or who received an allogeneic hematopoietic stem cell transplantation (HSCT) are at a high risk of invasive fungal infections due to the duration and degree of neutropenia.

## 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 next 24-48 hours. The lower the absolute neutrophil count and the longer the neutropenic period, the higher the risk of infections. Fever is usually defined as a single oral temperature ≥ 38.3°C or a temperature ≥ 38.0°C for ≥ 1 hour.

Neutropenic patients with fever that persists despite treatment with antibacterials are suspected to have a fungal infection.

**Key Messages**

- Small RCT in children with febrile neutropenia showed similar efficacy between caspofungin and liposomal amphotericin B (LAMB).
- Trend to lower rate of some adverse effects with caspofungin compared to LAMB such as hypokalemia, increased bilirubin, tachycardia.
- Trend to higher rate of rash and headache with caspofungin compared to LAMB.
- Caspofungin and LAMB have relatively high acquisition costs that may affect the hospital pharmacy budgets.
- Conventional amphotericin B has lower treatment costs compared to caspofungin and LAMB, however it was associated with more intense use of healthcare professional time in the prevention, monitoring, and treatment of complications.
- Trend towards lower treatment costs with caspofungin vs. LAMB.
    - Caspofungin has 68% chance of being less costly than LAMB
    - Imprecision stemming from small sample in RCT

# Antifungal treatments available

Antifungals available for the treatment of febrile neutropenia and invasive fungal infections include:

- Amphotericin B formulations (conventional amphotericin B, liposomal amphotericin B, amphotericin B lipid complex)
- Azoles (fluconazole, itraconazole, voriconazole, posaconazole)
- Caspofungin, part of the echinocandin class which also includes micafungin and anidulafungin

## Characteristics of antifungals

### Conventional amphotericin B

- Broad spectrum of activity and a low rate of resistance
    - Has been used for more than 3 decades in adults and children
- Use is limited by dose-limiting safety issues in adults and children
    - Most important: nephrotoxicity, and infusion-related events (fever, chills, headache, nausea, and vomiting)
    - Also: hypokalemia, hypomagnesemia, anemia, and hepatotoxicity
- Relatively low cost compared to other antifungal agents

### Lipid formulations of amphotericin B

- Include liposomal amphotericin B (Ambisome®), amphotericin B lipid complex (Abelcet®), and amphotericin B colloidal dispersion (Amphotec®)
- Developed with the objective of decreasing the risk of conventional amphotericin B's common toxicities while maintaining a similar efficacy
- May present with a lower rate of adverse events compared to conventional amphotericin B
- Higher cost has resulted in their use being limited to cases of resistance or intolerance to conventional amphotericin B

### Azoles

- Fluconazole, itraconazole, voriconazole, posaconazole among others
- Broad spectrum of activity and a low toxicity profile
- Adverse reactions

    - Increases in liver enzymes, rash, nausea, in addition to visual disturbances, and hallucinations with voriconazole
- During metabolism there is a potential for drug interactions, which may result in serious and sometimes life-threatening adverse clinical events

### Caspofungin

- Active against *Candida*, including *albicans* and some non-*albicans* species (*C. glabrata*, *C. krusei*), and has a fungistatic effect against *Aspergillus* species
- Seems to be better tolerated with less frequent adverse effects including infusion-related events compared to other classes of antifungals
- Adverse reactions 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
    - Headache, fever, nausea, vomiting, and phlebitis at the site of infusion
    - Laboratory abnormalities include increases in liver enzymes, leucopenia, and thrombocytopenia
- The dose of caspofungin may need to be adjusted as a result of liver impairment.
- Drug interactions: tacrolimus, cyclosporine among others.
- Regulatory Approval:
    - Caspofungin use in pediatric patients is approved in the United States[1] however it is not currently approved in Canada for any pediatric indications.

## Choice of antifungal

The choice of antifungal depends on several factors such as local antifungal resistance, the patient's immune system, organ dysfunction, potential interaction with other concomitant drugs, drug safety, and pharmacokinetics in pediatric patients.

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 hematopoietic stem cell transplantation (HSCT) or who presented with side effects associated with amphotericin B. 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.

## Rationale

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

## Objectives

To evaluate the efficacy, safety, and cost of caspofungin compared to conventional amphotericin B and liposomal amphotericin B in the empirical treatment of persistent febrile neutropenia.

## Patient population

Pediatric patients (2-17 years old) with hematological malignancies or who underwent a HSCT and who present with febrile neutropenia that persisted despite 5-7 days of treatment with antibacterials.

## Methods

**Systematic literature review**

Included the peer-reviewed and gray literature

**Cost analysis**

Antifungal treatment costs included:

- Antifungal treatment [based on a 20 kg (0.79 $m^2$) patient]
    - Drug acquisition costs for antifungals
    - Medications routinely administered before the antifungal infusion to avoid infusion-related events with conventional amphotericin B

- 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.

Resource use and costs were based on a 14-day treatment.

The length of treatment of an episode of febrile neutropenia is usually guided by the duration of the fever and neutropenia (in the absence of a diagnosed systemic infection), and therefore according to expert opinion, the length of treatment does not vary according to the antifungal used.

Univariate sensitivity analyses evaluated the impact on costs of varying the treatment duration and patient weight.

## Economic analysis

- A cost-minimization analysis was conducted through probabilistic sensitivity analysis
  - Current evidence suggests a similar efficacy between caspofungin and liposomal amphotericin B
- The probabilistic sensitivity analyses
  - used 10,000 Monte Carlo simulations
  - incorporated the point estimates and variance of the frequencies of complications and drug switches reported in the literature as well as costs of antifungal treatment and complications
- RCT comparing caspofungin and liposomal amphotericin B in pediatric patients with febrile neutropenia was used in the economic analysis
  - Patients with documented baseline invasive fungal infections were excluded from the RCT
  - It was also assumed that patients would not develop a breakthrough fungal infection during the antifungal treatment course

Caspofungin could not be compared to conventional amphotericin B since no studies comparing the two drugs in pediatric patients were identified in the literature.

# Clinical results

**Pediatric RCT**

*Clinical outcomes*

- In pediatric patients, one RCT comparing caspofungin and liposomal amphotericin B in febrile neutropenia demonstrated similar efficacy[2]

*Safety*

- There was a trend towards a lower rate of some adverse events when caspofungin was compared to liposomal amphotericin B (nephrotoxicity, 6% vs. 8%, respectively, and hypokalemia, 4% vs. 11%, respectively, among others)[2]
- In contrast, a trend towards a higher frequency of rash (9% vs. 0%), headache (9% vs. 0), and fever (29% vs. 23%) was observed for caspofungin compared to liposomal amphotericin B, respectively[2]
- The differences between the two groups were not statistically significant

# Economic analysis

**Antifungal treatment cost (2008 $CDN)**

- Costs of empiric antifungal treatment including drug acquisition costs, nursing and pharmacists' fees, and materials (14-day treatment course, 20kg/0.79$m^2$)
    - Caspofungin: $2,503
    - Liposomal amphotericin B: $3,129
    - Conventional amphotericin B: $1,470

**Univariate sensistivity analyses**

- Results of varying treatment duration from 1-28 days (20 kg / 0.79 $m^2$ child)
    - Caspofungin: $235 - $4,946
    - Liposomal amphotericin B: $224 - $6,258
    - Conventional amphotericin B: $105 - $2,940

- Results of varying patient weight 10 kg – 60 kg (0.49$m^2$ – 1.7$m^2$), 14-day treatment
    - Caspofungin: $1,686 - $4,072
    - Liposomal amphotericin B: $1,913 - $8,011
    - Conventional amphotericin B: $1,246 - $2,366

**Probabilistic sensitivity analysis (includes drug switches and complications)**

- Results for 20kg/0.79$m^2$ patient

| 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 savings

- Varying patient weight from 10 kg to 60 kg resulted in a probability of 62% to 90% that caspofungin would be less costly than liposomal amphotericin B.

## 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[2] [3] with a trend towards a lower frequency of important adverse events and drug withdrawal with caspofungin compared to liposomal amphotericin B in pediatrics[2].
- Our analyses showed 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.

- 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.

- Our economic analysis was based on a small RCT (n=82), which may have 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 conditions, potential for drug interactions, and drug safety

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 a RCT in pediatric patients that excluded patients with baseline fungal infections. We also assumed that there were no breakthrough fungal infections. Invasive fungal infections are treated according to the specific pathogen and may require a longer treatment course, which would affect treatment costs. Our costs were based on the current clinical practice and on antifungals currently available. As new evidence and/or new antifungal drugs become available this analysis may need to be updated.

## REFERENCES


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