The Hospital for Sick Children
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EXECUTIVE SUMMARY

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.
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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 m² 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 (0.49m² – 1.7m²).

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 neutropicen 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\(^1\) 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\(^2\). No
studies comparing caspofungin and conventional amphotericin B in febrile neutropenia
were identified. Additionally, eight non-comparative caspofungin studies were identified
in pediatric patients\(^3\) \(^4\) \(^5\) \(^6\) \(^7\) \(^8\) \(^9\) \(^10\) . 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\(^1\). In total 82 patients were included in the RCT, 56 in the caspofungin group and
26 in the liposomal amphotericin B group\(^1\). The authors concluded that the rate of overall
favourable response\(^a\) to treatment was similar between caspofungin and liposomal
amphotericin B\(^1\). 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,

\(^a\) 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.
4% vs. 11%, respectively)\(^1\). 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\(^1\). 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 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\(^1\) 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.

REFERENCES