

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

**ABSTRACT**

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

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*

**Report No. 2008-01**

**Date: September 26<sup>th</sup> 2008**

**Available at:**

**<http://pede.ccb.sickkids.ca/pede/task.jsp>**

## **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

## **ACKNOWLEDGEMENTS**

We thank the following individuals for their assistance in this report:

Beverley Hales, Pharmacy, The Hospital for Sick Children

Angela Trope, Pharmacy, The Hospital for Sick Children

Judy Van Clieaf, Child Health Services Director, The Hospital for Sick Children

Dinsie Williams, Department of Health Policy Management & Evaluation, University of Toronto

Funding for this research was provided by the Hospital for Sick Children Research Institute.

## **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<sup>2</sup> 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<sup>1</sup> and one published adult RCT<sup>2</sup> comparing caspofungin and liposomal amphotericin B in febrile neutropenia were identified. In addition, 8 non-comparative studies<sup>3 4 5 6 7 8 9 10</sup> 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<sup>1</sup>. The authors concluded that the two drugs had a similar rate of overall treatment response<sup>1</sup>. 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)<sup>1</sup>. 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<sup>1</sup>. 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<sup>2</sup> 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.

## **REFERENCES**

1. Maertens J, Madero L, Reilly A, et al. A Randomized, double-blind, multicenter trial of caspofungin vs. liposomal amphotericin B for empirical therapy of persistently febrile neutropenic pediatric patients. Presented at the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) 2007.
2. Walsh TJ, Teppler H, Donowitz GR, et al. Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. *N Engl J Med* 2004;351(14):1391-402.
3. 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.
4. Merlin E, Galambrun C, Ribaud P, et al. Efficacy and safety of caspofungin therapy in children with invasive fungal infections. *Pediatr Infect Dis J* 2006;25(12):1186-8.
5. Franklin JA, McCormick J, Flynn PM. Retrospective study of the safety of caspofungin in immunocompromised pediatric patients. *Pediatr Infect Dis J* 2003;22(8):747-9.
6. Natarajan G, Lulic-Botica M, Rongkavilit C, Pappas A, Bedard M. Experience with caspofungin in the treatment of persistent fungemia in neonates. *J Perinatol* 2005;25(12):770-7.
7. Cesaro S, Giacchino M, Locatelli F, et al. Safety and efficacy of a caspofungin-based combination therapy for treatment of proven or probable aspergillosis in pediatric hematological patients. *BMC Infect Dis* 2007;7:28.
8. Cesaro S, Toffolutti T, Messina C, et al. Safety and efficacy of caspofungin and liposomal amphotericin B, followed by voriconazole in young patients affected by refractory invasive mycosis. *Eur J Haematol* 2004;73(1):50-5.
9. Zaoutis T. Prospective, multicenter study of caspofungin for treatment of documented fungal infections in pediatric patients. Presented at the 45th Annual Meeting of the Infectious Diseases Society of America (IDSA) <http://www.idsociety.org/WorkArea/showcontent.aspx?id=7926> - Last access: January 14th 2007 2007.
10. Odio CM, Araya R, Pinto LE, et al. Caspofungin therapy of neonates with invasive candidiasis. *Pediatr Infect Dis J* 2004;23(12):1093-7.