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HEALTH TECHNOLOGY INQUIRY SERVICE (HTIS)

Title: Empirical Therapy with Echinocandins for Suspected Candidemia and Invasive Candidiasis: A Clinical and Cost Effectiveness Review

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Context and policy issues:

Candidemia (the presence of *Candida* species in the blood) and invasive candidiasis (infection with *Candida* in various organs including the eye, kidney, heart valves, and brain) are associated with significant morbidity, mortality, increased length of hospital stay, and health-care expenditure.[1-4] Known risk factors include prior antimicrobial therapy, venous and urinary catheters, intensive care unit (ICU) admission, parenteral nutrition, major surgery, and immunosuppressive therapy for those with hematologic malignancies, recipients of solid organ or hematopoietic stem cell transplants.[1] The clinical manifestations of candidemia vary from minimal fever to life-threatening sepsis.[1] The gold standard for the diagnosis of candidemia is a positive blood culture. However, there is often a significant delay in the diagnosis of invasive candidiasis as the clinical presentation is non-specific and at least 24 hours for culturing is required. Furthermore, blood cultures are often negative in patients with disseminated candidiasis and the diagnosis is often made on clinical grounds.[1] Accordingly, early empirical therapy (before species identification and sensitivity to various antifungal agents is available) has been adopted into clinical practice for neutropenic patients with persistent fever despite broad-spectrum antibacterial therapy after 4-7 days.[5] There is evidence that earlier initiation of appropriate antifungal therapy can dramatically improve survival.[4]

Historically, amphotericin B has been the drug of choice for empiric therapy.[1] However, its use is associated with several adverse effects including nephrotoxicity, electrolyte imbalance, and infusion-related reactions prompting the search for less toxic alternatives.[1] Recently, lipid formulations of amphotericin B (including liposomal amphotericin B and amphotericin B lipid complex), and the azole antifungals (including fluconazole, itraconazole, and voriconazole) have shown to be less toxic than conventional amphotericin B but improved efficacy has been less clear.[1] Routine use of lipid formulations of amphotericin B is limited due to a high acquisition cost.[1] In addition, major concerns with the azole antifungals include extensive drug interactions

and the resistance of some *Candida* species (e.g., *C. krusei* and *C. glabrata*) to therapy with fluconazole.[1] An increasing prevalence of these resistant strains has been reported in Canada,[6] and is believed to be primarily the result of widespread use of prophylactic fluconazole.[1] Under these conditions, the echinocandins, a new class of antifungal agents, have been developed.[7,8] The echinocandins inhibit synthesis of glucans present in the fungal cell wall, leading to lysis and death of the organism.[7] Caspofungin (Cancidas®, Merck Frosst) was the first echinocandin approved by Health Canada in 2001.[9] Micafungin (Mycamine®, Astellas Pharma) and anidulafungin (Eraxis™, Pfizer) were both approved in 2007.[10,11] Caspofungin is the only echinocandin currently indicated for empirical therapy for suspected fungal infections in febrile, neutropenic adult patients. This report will review the evidence for the clinical and cost effectiveness of the echinocandins when compared with other antifungal drugs as empirical therapy for suspected candidemia and invasive candidiasis. Current guidelines will also be discussed.

Research questions:

1. What is the clinical effectiveness of echinocandins versus other antifungal agents for treating suspected candidemia and invasive candidiasis?

2. What is the cost effectiveness of echinocandins versus other antifungal agents for treating suspected candidemia and invasive candidiasis?

Methods:

A limited literature search was conducted on key health technology assessment resources, including OVID's Pre-Medline, Medline, Embase, and Biosis, Pubmed, the Cochrane Library (Issue , 2008), University of York Centre for Reviews and Dissemination (CRD) databases, CRI, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 2003 and the January 2008, and are limited to English language publications only. Filters were applied to limit the retrieval to health technology assessment, systematic reviews, guidelines, randomized controlled trial (RCT), and observational studies. This search was supplemented by hand searching the bibliographies of selected papers.

Summary of findings:

No health technology assessments, systematic reviews or meta-analyses examining echinocandins for empirical therapy were identified. Relevant randomized controlled trials (RCTs), non-controlled studies, economic evaluations and guidelines are discussed below.

Randomized controlled trials

In 2004, Walsh *et al*. published a large, double-blind, non-inferiority, multicentre study comparing the efficacy of caspofungin with that of liposomal amphotericin B for the empiric treatment of febrile neutropenia.[12] Unlike typical superiority trials, non-inferiority trials are designed to detect if the treatment of interest is no worse than a reference treatment by more than a specified margin.[13] A total of 1095 patients with persistent fever (>38ºC despite parenteral antibacterial therapy for at least 96 hours) and neutropenia (defined as an absolute neutrophil count <500cells/mm^3 for at least 96 hours) were enrolled. On entry, patients were stratified into high- and low-risk groups and according to whether they had previously received antifungal prophylaxis. Patients who had undergone allogeneic hematopoietic stem-cell

transplantation and/or chemotherapy for relapsed acute leukemia were classified as high risk for invasive fungal infections (n=268). All other participants were considered low risk (n=827). A total of 56.3% of participants had received previous antifungal prophylaxis, mostly with fluconazole.

Patients were randomized to receive caspofungin administered as a 70 mg loading dose on day 1 followed by 50 mg once per day (n=556), or liposomal amphotericin B given 3 mg/kg/day (n=539). The median treatment times were similar between recipients of caspofungin or liposomal amphotericin B (11 versus 10 days; range 1-90 days). In patients with no evidence of baseline or breakthrough fungal infection, therapy was continued until up to 72 hours after resolution of neutropenia (to a maximum of 28 days). In patients with a documented fungal infection, therapy was continued as determined necessary by the investigator but the protocol recommended at least 14 days and for at least seven days after resolution of neutropenia and symptoms (to a maximum of 90 days). Due to the difficulty in documenting fungal infections, the authors used a composite endpoint. Treatment was considered successful if all of the following criteria were achieved: successful treatment of any baseline fungal infection, absence of any breakthrough fungal infection during therapy or within seven days of discontinuation, survival for seven days after the completion of therapy, no premature discontinuation because of drug-related toxicity or lack of efficacy, and resolution of fever (<38°C) for at least 48 hours during neutropenia. The distinction between baseline and breakthrough infections was arbitrarily defined as onset up to the second day of study therapy versus onset after the third day.

In a modified intention-to-treat analysis, caspofungin was no less effective than liposomal amphotericin B for treatment success (overall response rates 33.9% versus 33.7%). The confidence interval (CI) of the difference in overall response rates between treatments satisfied the pre-specified criteria for non-inferiority of caspofungin (difference 0.2%; 95.2% CI: -5.6 to 6.0%). In the high risk patients, 43.2% of patients receiving caspofungin and 37.7% of patients receiving liposomal amphotericin B responded (difference 5.4%; 95.2% CI: -6.3%, 17%) compared to 31% and 32.4%, respectively in low risk patients (difference –1.4%; 95.2% CI: -7.7%, 4.9%). Prior antifungal prophylaxis had no significant effect on overall response. A comparison was also made between caspofungin and liposomal amphotericin B for each component of the composite end point. Three of the components of the primary endpoint favored caspofungin over liposomal amphotericin B; namely successful treatment of baseline fungal infections (51.9% versus 25.9%, p=0.04), survival for seven days post-therapy (92.6% versus 89.2%, p=0.05) and discontinuation due to toxicity or lack of efficacy (10.3% versus 14.5%, p=0.03). The rates of breakthrough fungal infections and resolution of fever during neutropenia were similar in the two groups. There were 24 baseline infections due to *Aspergillus* species and response rates to therapy were 41.7% in patients treated with caspofungin and 8.3% in patients treated with liposomal amphotericin (p value not reported). Baseline infections caused by *Candida* species were responsible for 24 baseline infections of which 66.7% responded to caspofungin and 41.7% to liposomal amphotericin B (p value not reported).

Caspofungin was better tolerated in that significantly fewer drug-related adverse events occurred when compared with liposomal amphotericin B (54% versus 69%, p<0.001). Caspofungin was significantly less likely to be associated with nephrotoxicity (2.6% versus 11.5%, p<0.001), infusion-related events (35.1% versus 51.6%, p<0.001), or premature discontinuation of study medication due to drug-related adverse events (4.9% versus 8.2%, p=0.04) when compared with liposomal amphotericin B. The authors concluded that caspofungin is no less effective, and generally better tolerated than amphotericin B when given as antifungal therapy in patients with persistent fever and neutropenia.

Use of a short-term composite efficacy endpoint is a limitation of this study.[14,15] For this particular composite endpoint, resolution of fever during neutropenia has been shown to be a major driver of treatment effect.[15] However, other causes for fever during neutropenia can confound the true treatment effect. A sensitivity analysis of the trial revealed that response rates increased in both treatment groups compared with the primary analysis, particularly in low-risk patients when this component was either excluded from the composite endpoint or modified from the definition used in the primary analysis.[15] Furthermore, positive results obtained for the individual components of the composite endpoint may not necessarily reflect efficacy. For example, resolution of fever may reflect response to concomitant antibacterial therapy, resolution of a drug-induced fever, recovery of the neutrophil count, or successful treatment of underlying disease. Similarly, favorable survival is not necessarily a direct result of empirical antifungal efficacy. A further limitation is that the distinction between baseline and breakthrough infections was arbitrarily defined making it difficult to assess true treatment efficacy. Finally, non-inferiority trials have methodological features that differ from superiority trials making the results less robust and more difficult to interprete.[13]

No RCTs have compared caspofungin to azole antifungals for empirical antifungal therapy. Furthermore, RCTs evaluating micafungin or anidulafungin for empirical antifungal therapy have yet to be published. Ongoing RCTs are evaluating the use of caspofungin versus liposomal amphotericin B as empirical therapy in febrile, neutropenic adult patients.[16,17] The use of caspofungin[18-20] and micafungin[21] as empirical therapy in febrile, neutropenic pediatric patients is also being evaluated.

Non-controlled studies

Two non-controlled studies have examined the safety and efficacy of micafungin as empirical therapy in febrile neutropenic patients treated for hematological malignancies.[22,23]

Yanada *et al.* conducted a prospective trial in 18 febrile patients (10 with persistent fever and 8 with recurrent fever) with acute leukemia unresponsive after at least 5 days of antibacterial therapy.[22] Four patients had received previous antifungal prophylaxis with fluconazole. Patients received a once-daily intravenous infusion of micafungin at dosages between 50 mg and 300 mg per day. Therapy was continued until both resolution of fever (< 37.5°C) and absolute neutrophil counts above 500 cells/mm^3 for more than two successive days were achieved. Patients were observed for 14 days after completion of the study drug or until death. The median duration of neutropenia and drug administration was 22 days and 9.5 days, respectively. Treatment success was defined as resolution of fever during the neutropenic period, and cure of baseline invasive fungal infections, if present. Failure was defined as the presence of any of the following conditions: development of breakthrough fungal infections; discontinuation of micafungin due to serious adverse events or lack of efficacy; addition of other antifungal drugs; and death from any cause during the study period. Results revealed treatment success in 14 (78%) patients with a median duration to resolution of fever of 3 days. Treatment failure was observed in 4 (22%) patients. Adverse effects including elevation of liver enzymes, hypokalemia, and skin rash occurred in 7 (39%) patients. None of the patients required discontinuation or dose reduction due to adverse events except for one patient with severe hypokalemia which resolved upon discontinuation of micafungin.

Toubai *et al.* conducted a prospective trial in 23 patients with hematological malignancies presenting with febrile neutropenia for which antibiotic therapy was not effective.[23] Most patients (95.6%) had received previous antifungal prophylaxis with fluconazole, itraconazole, or

combinations consisting of azole antifungals and amphotericin B. Therapy with micafungin and definitions for treatment success and failure were the same as the above study. The treatment success rate was 73.9%. Treatment success in patients who had previously received antifungal prophylaxis was not significantly different from those who had not received prophylaxis. Treatment failure occurred in 6 (26%) patients due to a lack of clinical improvement resulting in the discontinuation of micafungin. Mild liver dysfunction occurred in five (27.7%) of the patients during the study, but did not result in discontinuation of micafungin. None of the patients developed documented breakthrough fungal infections and only one patient died from primary disease.

While these preliminary results are promising, both of these studies are limited by the fact that a control group was not included and by small sample size.

Economic evaluations

Two cost-effectiveness studies[24,25] and one costing study[26] were identified in the search.

Golan *et al.* used a cost-effectiveness decision tree model to analyze the effect of empiric versus culture-based treatment strategies using a variety of antifungal agents (standard or liposomal amphotericin B preparations, fluconazole, or caspofungin), compared to no treatment intervention for high-risk patients in the ICU.[24] All empirical therapies were started before culture results were available, were continued even if fungal culture results were negative, and were given to all patients in the ICU with fever, hypothermia, or unexplained hypotension that persisted after 3 days of antibacterial therapy. Culture-based strategies included therapy with amphotericin B, liposomal amphotericin, caspofungin, or fluconazole only when cultures were reported to grow *Candida*. Life expectancy and cost of care were analyzed for each treatment strategy. Sources for estimates included published data to May 2005, administrative ICU databases, expert estimates, and actual hospital costs. Direct costs for hospital stay, drug-related nephrotoxicity and antifungal drugs (amphotericin B, fluconazole, liposomal amphotericin, and caspofungin) were considered. The costs associated with *Candida* culture were not considered since culture was performed on all patients regardless of treatment strategy. Outcome measures were the incremental life expectancy and incremental cost per discounted life-year (DLY) saved in US dollars. The incremental cost per DLY gained was US$1,122 with culture-based fluconazole over no anti-Candida treatment, US$12,593 with empirical fluconazole therapy over culture-based fluconazole, and US$295,115 with empirical caspofungin therapy over empirical fluconazole. The authors concluded that in high-risk patients in the ICU with suspected infection who have not responded to antibiotic treatment, empirical fluconazole should reduce mortality at an acceptable cost and the use of empirical strategies in low-risk patients is not justified.

Bruynesteyn *et al.* conducted a cost-effectiveness analysis for caspofungin versus liposomal amphotericin B for the treatment of febrile neutropenic adults in the UK.[25] A decision-tree model was developed for the analysis, and effectiveness data was taken from the RCT conducted by Walsh *et al*.[12] Information on life expectancy, quality of life, medical resource consumption and costs were obtained from peer-reviewed published data. Survival data at one and five years were obtained from UK National Statistics from 1998-2001 and other published trial data. The summary measure of benefit was quality adjusted life-years (QALYs), to capture health-related quality of life and survival benefits. Direct costs were included from the UK National Health System perspective. These involved drug costs, hospitalization costs, and associated drug costs relating to adverse events including nephrotoxicity. Costs were undiscounted and indexed to 2005 UK pounds sterling. The average direct cost with caspofungin was £9,762 (95%

uncertainty level £6,955-12,577), which was £2,033 (95% uncertainty level £-2,489- £6,779) less than liposomal amphotericin B. Treatment with caspofungin resulted in 0.40 (-0.12; 0.94) additional QALYs saved in comparison with liposomal amphotericin B. Sensitivity analysis found a 95% probability of the incremental cost per QALY saved being within the generally accepted threshold for cost-effectiveness (£30,000). The authors concluded that given the underlying assumptions of this analysis, caspofungin is cost-effective compared with liposomal amphotericin B in terms of cost savings and higher QALY gains for the treatment of suspected fungal infections in the UK.

Wingard *et al*. compared the cost differences between caspofungin and liposomal amphotericin B for empirical antifungal therapy for persistent fever during neutropenia.[26] An economic model was developed to determine whether the costs of increased nephrotoxicity associated with amphotericin B would offset the higher drug costs of caspofungin. The duration of treatment with caspofungin or amphotericin B was from one week to a few months; this is consistent with the mean duration of antifungal therapy observed in the trial conducted by Walsh et al (13 days; range 1-90days)[12] and the time encompassing the occurrence and treatment of acute renal toxicity. Rates of drug use and impaired renal function were based on data from published studies. Mean acquisition costs in US dollars for the antifungal drugs were estimated using sales transaction data from nonfederal hospitals from July 2003 through December 2003. The acquisition costs per patient were US$6,942 for liposomal amphotericin B and US$3,996 for caspofungin. The estimated cost per patient for impaired renal function was US$3,173 for liposomal amphotericin B and US$793 for caspofungin. Combining drug acquisition and costs associated with renal dysfunction, the overall treatment cost per patient for caspofungin was US$5,326 less than for liposomal amphotericin B.

Guidelines

One North American guideline[27] and one European guideline[28] presenting recommendations for empirical antifungal therapy were identified.

Guidelines prepared by the Infectious Diseases Society of America (IDSA) were published in 2004.[27] A summary of treatment options in patients with empirical therapy in patients with febrile neutropenia is provided in Table 1. The guidelines recommend the use of empiric antifungal therapy among patients with neutropenic fever which persists for 4-7 days despite appropriate broad-spectrum antibacterial coverage as the standard of care. The guidelines list amphotericin B, liposomal amphotericin B, and caspofungin as first-line options but do not provide a clear recommendation as when to select one over the other. As evidence for caspofungin was not yet available at the time of publishing, the guidelines state the role of caspofungin and other echinocandin antifungal agents is uncertain. Fluconazole is recommended as an alternative option to be used if the patient is at low risk for either invasive aspergillosis or infection with azole-resistant isolates of *Candida* (including those who have not received prophylaxis with an azole antifungal). Due to evidence that voriconazole may be superior to liposomal amphotericin B for the prevention of breakthrough infections in high-risk patients but slightly inferior in efficacy for other patient groups, the guidelines recommend that voriconazole should be limited to allogeneic bone marrow transplant recipients and individuals with relapsed leukemia. No recommendations are provided for the other azole antifungals. The guidelines did not provide a recommendation as to choice of antifungal agent for febrile non-neutropenic patients. An update to these guidelines will be published in Fall 2008.

Table 1: Summary of IDSA guidelines for empirical antifungal treatment of febrile neutropenic patients[27]

First choice	Alternative Options	Duration
Amphotericin B 0.7-1.0 mg/kg/day iv **Lipid formulation amphotericin B** 3.0-6.0 mg/day/day **Caspofungin** 70 mg loading dose followed by 50 mg iv	**Fluconazole** 6-12 mg/kg/day iv or po	14 days after last positive blood culture and resolution of signs and symptoms of infection and resolved neutropenia

iv=intravenously, po=orally

Another guideline developed by the Fungal Infection Network of Switzerland (FUNGINOS) was published in 2006.[28] The guidelines provide an approach to empiric therapy based on clinical setting and level of risk. Recommendations are rated according to a standard scoring scheme to illustrate the strength of the supporting evidence. For empiric therapy of *Candida* bloodstream infection, fluconazole is the drug of choice in non-neutropenic patients with no evidence of severe sepsis or recent exposure to azoles (Grade AI; based on good quality evidence from RCTs). In the non-neutropenic patients with previous exposure to azole antifungals, amphotericin B or caspofungin are recommended (Grade BI; based on moderate quality evidence from RCTs). In neutropenic patients, empiric therapy with amphotericin B is considered as the first choice (Grade CIII; based on poor quality evidence from a case series or expert opinion). However, in patients with severe sepsis and septic shock, caspofungin is the drug of first choice on the basis that nephrotoxic agents should be avoided in this patient population (Grade CIII).

Limitations

Evidence for the safety and efficacy of echinocandins for empirical antifungal therapy is limited to one non-inferiority RCT and two small non-controlled studies. As a result of the paucity of published evidence, current North American guidelines do not provide clear recommendations for the judicious use of antifungals for empirical therapy in different settings and patient populations. Results from available economic evaluations are limited by the fact that efficacy data for models were derived from the single published RCT. Generalizability of results from the available clinical and economic evaluations cannot be confirmed until further studies are conducted in various clinical practice settings and in different patient subgroups. Longer-term cost assessments may uncover additional economic considerations.

Conclusions and implications for decision or policy making:

In summary, limited evidence from a non-inferiority trial suggests that empirical therapy with caspofungin in patients with febrile neutropenia appears to be no less effective and better tolerated than liposomal amphotericin B. However, there is no conclusive evidence that one antifungal is clearly superior for empirical therapy in terms of efficacy and cost-effectiveness. Until such evidence is available, earlier microbiological and clinical markers of candidemia are needed to guide early empirical antifungal therapy and improve clinical outcomes.[29]

In lieu of conclusive evidence that one antifungal agent is clearly more efficacious than another, several factors may help clinicians when selecting empirical therapy. These include institutional

nosocomial infection patterns, prior exposure to antifungal therapy, disease severity (e.g., presence of sepsis or septic shock), population- and infection site-specific efficacy data, presence of underlying comorbidities that may affect drug metabolism or increase the risk for drug-related toxicities, and cost.[2] The development of sensitive and specific diagnostic assays to rapidly differentiate various *Candida* species[2,14] should also help guide the selection of less expensive antifungal empiric therapy in the future. A better definition of the risk factors predisposing patients to fungal infection should help to identify the population most likely to benefit from the empirical approach.[30] Until such tools are in place, most clinicians will continue to depend upon clinical judgment to guide initiation and choice of empirical antifungal therapy.

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