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Original article

Comparative effectiveness of fungicidal vs. fungistatic therapies for the treatment of paediatric candidaemia

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Summary

Adult data suggest that echinocandins for treatment of candidaemia are associated with decreased mortality, attributed to their fungicidal activity. There are limited data comparing antifungals in children. We compared 30-day all-cause mortality among paediatric candidaemia patients treated with fungicidal vs. fungistatic agents. All inpatients (>6 months and <19 years of age) with candidaemia between 2000 and 2012 at The Children's Hospital of Philadelphia were retrospectively identified. Definitive therapy with fungicidal (amphotericin B and caspofungin) agents was compared with fungistatic (fluconazole) agents. A propensity score model generated the inverse probability of receiving a fungicidal agent, which was included in a weighted logistic regression model. Among 203 children meeting inclusion criteria, 151 (74.4%) and 52 (25.6%) received a fungicidal and fungistatic agent, respectively. Overall, 18 (8.9%) patients died within 30 days. There was no statistically significant difference in mortality between patients started on a fungicidal or fungistatic agent (OR: 2.19, 95% CI: 0.42–11.48). In a propensity score–weighted model, definitive therapy with a fungicidal agent did not result in a significant decrease in mortality. These data suggest that both agents can be considered definitive therapy for paediatric candidaemia. The results should be interpreted with caution given the small sample size. Larger cohort studies are needed.

Key words: Candidaemia, antifungals, paediatric, comparative effectiveness.

Introduction

Candida species have been identified as one of the most common cause of nosocomial bloodstream infections and is an important cause of morbidity and mortality in children. Recent data have reported a decline in the incidence of paediatric candidaemia[1–3]; however, the mortality rates associated with paediatric candidaemia are high.[4] Additional data suggest that patients with candidaemia had increased healthcare utilisation and prolonged length of hospital stay in both adults and children compared with patients without candidaemia.[4]

Currently, there are three major classes of antifungal agents available for treatment of candidaemia: echinocandins, amphotericin B and azoles. A recent patient-level review of adult clinical trial data found that echinocandin therapy for treatment of candidaemia was associated with a decreased mortality rate and greater clinical success when compared with azoles and amphotericin B.[5] However, there is a lack of data to provide guidance for the appropriate antifungal therapy when treating candidaemia in paediatric patients. Establishing paediatric specific evidence

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for the optimal management of candidaemia could result in reduction of morbidity and mortality in children.

We aimed to compare the effectiveness of various antifungal agents as definitive therapy for paediatric candidaemia on 30-day all-cause in-hospital mortality.

Methods

Study design, data collection and definitions

We conducted a retrospective cohort study of all paediatric inpatients (>6 months and <19 years of age) diagnosed with candidaemia between 2000 and 2012 at the Children's Hospital of Philadelphia (CHOP). A subset of this cohort has been described previously.[6] Patients with candidaemia were identified through review of microbiology records. Candidaemia was defined as a positive blood culture for any *Candida* species plus clinical signs consistent with infection at the time the blood culture was obtained. Candidaemia onset was defined as the first day that microbiologic evidence of candidaemia was documented and available to the clinician (e.g. blood culture is positive for yeast). Only the first candidaemia episode per patient during the study period was included.

All data utilised for this study were abstracted from medical records. A structured data collection instrument was developed to abstract demographic, clinical and laboratory data. Information collected for each patient included age at candidaemia onset, sex, race, presence of comorbid conditions, in-hospital medication exposures, parenteral nutrition exposure and results of microbiologic testing. Information about the receipt of prophylactic antifungal therapy, defined as any systemic antifungal agent given prior to the candidaemia defining blood culture was drawn, and empiric antifungal therapy, defined as receipt of any systemic antifungal agent given from the day the candidaemia defining blood culture was obtained until candidaemia onset, was collected for each patient. In addition, underlying severity of illness information including admission to the intensive care unit (ICU), receipt of respiratory support, need for dialysis, presence of a central line and baseline immunosuppression (exposure to chemotherapy, steroids, or documented neutropenia) was collected. All data were collected for each patient from hospital admission until the end of study period. End of study period was defined as (i) 30 days from candidaemia onset, (ii) hospital discharge or (iii) in-hospital death within 30 days. Data collected through chart review were entered directly into a Microsoft Access database.

The choice of definitive antifungal therapy was the primary exposure of interest. Definitive therapy was defined as two or more consecutive days of the same antifungal agent after candidaemia onset. The original proposal was to compare caspofungin with both fluconazole and amphotericin B. Unfortunately, there were too few caspofungin-exposed patients to perform this analysis. Therefore, the antifungal therapy exposure was dichotomised as fungistatic, inclusive of fluconazole-treated patients, and fungicidal, inclusive of amphotericin B- and caspofungin-treated patients. The 2009 IDSA guidelines for treatment of candidaemia suggested that fungicidal agents may be more beneficial for the treatment of candidaemia compared with fungistatic agents.[7] Recent adult data support that treatment with fungicidal agents (amphotericin B and echinocandins) resulted in lower mortality compared with fungistatic (triazoles) agents (mortality, 30% for fungicidal agents and 36% for fungistatic).[5] In order to evaluate the effectiveness of each antifungal agent in children, only those patients who received one antifungal agent as definitive therapy were included.

The primary outcome was all-cause in-hospital 30-day mortality, defined as death on any inpatient day up to 30 days after candidaemia onset. Patients who died within 1 day of candidaemia onset were excluded because it was concluded that the choice of definitive therapy would not have impacted early mortality events. Patients discharged prior to 30 days after candidaemia onset were classified as alive in this analysis. Subsequent readmissions were not included in the analysis.

Statistical analysis

To account for important patient differences between groups, we generated inverse probability of treatment weighting (IPTW) using constructed propensity scores. We developed a generalised propensity score that measured each patient's likelihood to receive definitive therapy with a fungicidal agent based on baseline characteristics. The propensity score was developed using measured covariates believed to impact the choice of antifungal therapy and to be associated with mortality, including age, history of malignancy or transplant, presence of a central line, underlying severity of illness, receipt of empiric or prophylactic therapy and receipt of immunosuppressive therapy within 2 weeks prior to candidaemia onset. Inverse probability weights for receiving a fungicidal agent

were generated. We weighted the study cohort by inverse probability of treatment weights derived from the propensity score. These inverse weights were included in a weighted logistic regression model to compare 30-day mortality in fungicidal vs. fungistatic definitive therapy recipients. To assess whether the propensity score model adequately balanced the covariates between the two treatment groups, means and weighted means using the IPTW were computed. All analyses were performed using Stata 13.1 (Stata Corp., College Station, TX, USA).

Results

We identified 436 incident paediatric candidaemia inpatient admissions between 2000 and 2012. Among those patients, 203 (46.9%) received only one antifungal agent as definitive therapy, survived at least 1 day after candidaemia onset, and were >6 months of age (Fig. 1). The majority of the cohort was male (56.1%) and the median age was 4 years (IQR: 1, 13). The two most commonly isolated species were *C. albicans* (50.0%) and *C. parapsilosis* (22.0%). Among the study cohort, 151 (74.4%) received a fungicidal agent, amphotericin B ($n = 134$) or caspofungin ($n = 17$), and 52 (25.6%) received fluconazole, a fungistatic agent (Table 1). Table 2 displays the baseline demographic and clinical characteristics of the study cohort by antifungal class. Overall, 18 (8.9%) patients died within 30 days of candidaemia onset, with eight of those deaths occurring in the first 2–10 days. There were two deaths (3.9%) among patients receiving fungistatic antifungal therapy and 16 deaths (10.6%) among recipients of fungicidal therapy. The mean duration of hospitalisation for the entire cohort was 18.4 days. Of the 185 patients who did not die, 127 patients (69.7%) were discharged from the hospital prior to 30 days of follow-up.

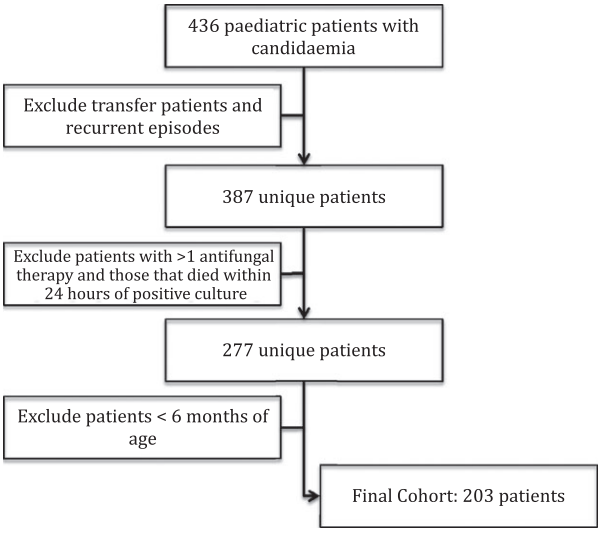

Figure 1 Paediatric candidaemia cohort assembly.

Means of the covariates between fungicidal and fungistatic groups as well as weighted means using the IPTW were computed. The means were similar between the two treatment groups after IPTW. Therefore, covariate balance between the fungicidal-treated and fungistatic-treated groups was achieved with IPTW (Fig. 2). Prior to IPTW, there was no statistically significant difference in mortality between patients started on a fungicidal or fungistatic agent (OR: 2.96, 95% CI: 0.66–16.4). In the propensity score–weighted model, initiation of definitive therapy with a fungicidal agent still did not result in a decrease in 30-day mortality (OR: 2.19, 95% CI: 0.42–11.48). As noted, there were too few caspofungin-exposed patients to perform a subanalysis of caspofungin vs. either amphotericin B or fluconazole. However, a subanalysis comparing amphotericin B- and fluconazole-exposed patients was performed. Using the same propensity score–weighted model approach as above, there was no difference identified in patients receiving amphotericin B as initial definitive therapy as compared with those receiving fluconazole (OR: 2.48, 95% CI: 0.48–12.89).

Discussion

Candidaemia causes significant morbidity and mortality in children. While recent literature suggests that the overall incidence of paediatric candidaemia is decreasing, mortality rates in these patients remain high.[4] Unfortunately, there are limited data available to provide evidence-based guidance for optimal management of paediatric candidaemia. In this retrospective observational study, we found that initiation of definitive therapy with a fungicidal agent did not result in a significant decrease in 30-day mortality using a propensity score–weighted model. Our results suggest that both fungicidal and fungistatic agents can be considered definitive therapy for treatment of paediatric candidaemia.

To our knowledge, this is the first attempt to understand the impact of the choice of definitive antifungal therapy in a purely paediatric population. Many large randomised clinical trials have compared antifungal therapies in predominantly adult patients and have been summarised in study-level meta-analyses.[8,9] A

Table 1 Demographics and clinical characteristics by antifungal type.

Characteristic	Caspofungin, $n = 17$	Amphotericin B, $n = 134$	Fluconazole, $n = 52$
Median age in years (IQR)	11.0 (3.0, 14.0)	4.0 (1.0, 13.0)	4.5 (1.5, 14.0)
Male gender	8 (47.1)	74 (55.2)	29 (55.8)
History of transplantation or malignancy	11 (64.7)	53 (39.6)	14 (26.9)
Neutropenia within preceding 2 weeks	5 (29.4)	30 (22.4)	7 (13.5)
Immune suppression[1] within preceding 2 weeks	9 (52.9)	33 (24.6)	12 (23.1)
Receipt of total parenteral nutrition within 1 week	7 (41.2)	79 (59.0)	31 (59.6)
Mechanical ventilation at time of candidemia	2 (12.5)	31 (23.1)	10 (19.2)
Central line present at onset	14 (82.4)	108 (80.6)	39 (75.0)
ICU at time of candidemia	5 (29.4)	48 (35.8)	12 (23.1)
Receipt of prophylactic therapy	10 (58.8)	47 (35.1)	27 (51.9)
Receipt of empiric therapy	9 (52.9)	28 (20.9)	25 (48.1)
30-day case fatality rate	2 (11.8)	14 (1.4%)	2 (3.9)

[1]Corticosteroids or chemotherapeutic agent.

Table 2 Demographics and clinical characteristics by treatment groups.

Characteristic	Fungistatic ($n = 52$)	Fungicidal ($n = 151$)
Median age in years (IQR)	4.5 (1.5, 14.0)	4.0 (1.0, 13.0)
Male gender	29 (55.8)	82 (54.3)
History of transplantation or malignancy	14 (26.9)	64 (42.4)
Neutropenia within preceding 2 weeks	7 (13.5)	35 (23.2)
Immune suppression[1] within preceding 2 weeks	12 (23.1)	42 (27.8)
Receipt of total parenteral nutrition within 1 week	31 (59.6)	86 (57.0)
Mechanical ventilation at time of candidemia	10 (19.2)	33 (22.0)
Central line present at onset	39 (75.0)	122 (80.8)
ICU at time of candidemia	12 (23.1)	53 (35.1)
Receipt of prophylactic therapy	27 (51.9)	57 (37.7)
Receipt of empiric therapy	25 (48.1)	37 (24.5)

[1]Corticosteroids or chemotherapeutic agent.

meta-analysis assessing 15 randomised controlled trials (RCT's) that compared different antifungal agents for the treatment of candidaemia reported no difference in efficacy between amphotericin B, azoles and echinocandin therapy.[8] Another meta-analysis of 11 RCTs that compared antifungal therapies for treatment of candidaemia also found no difference in efficacy between azoles, amphotericin B and echinocandin therapy.[9] More recently, a quantitative review of predominately adult patient–level clinical trial data found that echinocandin therapy for treatment of candidaemia was associated with a decreased mortality rate (OR: 0.50; 95% CI: 0.35–0.72).[5] While some characteristics of paediatric and adult candidaemia are similar, many studies have discovered key differences in the epidemiology of *Candida* species, host factors, pharmacokinetics and outcomes in children.[4,10–13] In addition, RCTs typically exclude patients within the extremes of the clinical spectrum of candidaemia and study-level meta-analyses prohibit adjustment for potential patient-level confounders.

Our study compared the effectiveness of fungicidal vs. fungistatic therapies for paediatric candidaemia at a single institution and included a statistical approach that tried to account for important patient differences between treatment groups. Using a propensity score model, we constructed inverse probability weights for receiving a fungicidal agent as definitive therapy to balance key baseline patient differences between the treatment groups. These patient characteristics included age, sex, admission to the ICU, history of malignancy or transplant, presence of central line, receipt of prophylactic therapy or empiric therapy, and recent immune suppression. Comparing the raw vs. weighted means between groups, we showed that overall IPTW improved the balance of the covariates

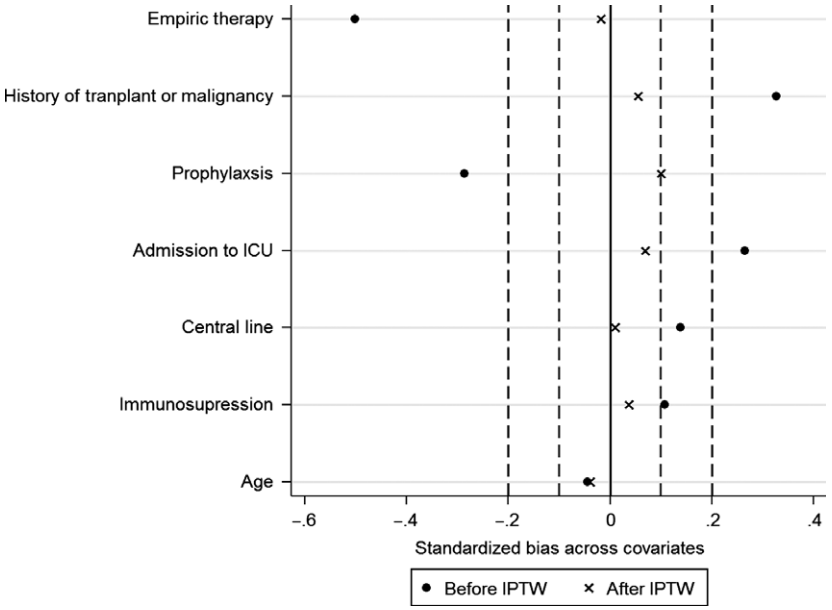

Figure 2 Covariate balance before and after inverse probability of treatment weighting. Plotted points represent the standardised mean differences for each covariate. Vertical grey and black dashed lines indicate standardised mean differences of 0.1 and 0.2, respectively.

across treatment groups. The propensity score–weighted model found that definitive therapy with a fungicidal agent did not decrease 30-day mortality. In a similar statistical approach, treatment with an amphotericin B product did not decrease 30-day mortality as compared with treatment with fluconazole.

Our study findings should be interpreted with caution given a number of limitations. A primary concern in comparative effectiveness studies is confounding by indication. For this study, confounding by indication is possible if sicker patients are more likely to receive a fungicidal agent and more likely to have worse outcomes. Our small sample size did not allow for adjusting for confounding by indication using a traditional multivariate model. However, propensity score weighting allowed us to include many covariates to obtain a degree of balance in critical baseline patient differences between exposure groups even with a small number of events.[14] In fact, we were able to illustrate a degree of balance in the measured potential confounders between the two treatment groups when comparing the means and standardised differences before and after IPTW. Although we did not achieve substantial improvement for every covariate after IPTW, there was some improvement in the degree of balance among all of the covariates after weighting. We believe that the improved balance suggest that these results are a vast improvement over an unadjusted model. Regardless of the balance in the measured confounders between the two treatment arms using IPTW, this approach is unable to account for unmeasured confounding by indication. The point estimate of our OR was above 2.0, which may suggest that there was residual confounding by indication that could not be accounted for.

The study's small sample size had additional impact on our analyses. Ideally, we would have compared caspofungin definitive therapy to all other agents as was done in the adult patient-level quantitative review.[5] Only 17 patients received caspofungin as definitive therapy, and thus, we could not compare caspofungin with the other antifungal agents. Even with the approach of comparing fungicidal with fungistatic therapy or amphotericin B with fluconazole, we had reduced power given the relatively low event rate to detect a significant difference in the treatment groups. This as is evident in the wide confidence intervals for the comparison of fungicidal vs. fungistatic therapy (OR: 2.19, 95% CI: 0.42–11.48) and the comparison of amphotericin B with fluconazole (OR: 2.48, 95% CI: 0.48–12.89). Adult comparative effectiveness studies such as the aforementioned patient-level quantitative review by Andes *et al.* were inclusive of a population with a much higher mortality, which exceeded 30%.[5] This higher risk for mortality confers more power to establish a benefit of one agent over another. We were unable to follow-up patients beyond discharge; therefore, if a patient was discharged prior to day 30 and subsequently died, that patient may have been misclassified as alive in the analysis. As these children were well enough to be discharged from the hospital, we anticipate that such misclassification is

unlikely. Additionally, we did not include children less than 6 months in our cohort. The decision to exclude these patients was based on the fact that there are important differences relative to candidaemia in children less than 6 months. This includes differences in mortality, pharmacokinetics of antifungal therapies and recommendations for duration of therapy. Nonetheless, it is important to understand the comparative effectiveness of antifungal agents in this patient population, and thus, this should be a focus of future investigation. Finally, we did not collect dose information for any of the antifungal exposures and did not specify amphotericin B formulation administered. It is possible that choice of dose and formulation may impact outcomes, but again the small sample size and event rate would have limited the ability to include these additional factors into our multivariate models.

In conclusion, our study suggests that initiation of definitive therapy with fungicidal or fungistatic agents can be considered for management of paediatric candidaemia. Larger paediatric cohort studies are needed to confirm these findings and further compare specific antifungal therapeutic options to determine optimal treatment strategies to reduce the morbidity and mortality related to paediatric candidaemia.

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Conflict of interest

T.E.Z has received research funding from Merck and Cubist and has served as consultant for Merck, Cubist and Pfizer. B.T.F. has received research funding from Enzon and Wyeth and currently receives research funding from Merck and Pfizer Pharmaceuticals. All other authors: no conflicts.

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