MAJOR ARTICLE

Antifungal Prophylaxis Associated With Decreased Induction Mortality Rates and Resources Utilized in Children With New-Onset Acute Myeloid Leukemia

Brian T. Fisher,[1,2,3,4] Marko Kavcic,[5] Yimei Li,[4,5] Alix E. Seif,[3,5] Rochelle Bagatell,[3,5] Yuan-Shung Huang,[2] Theoklis Zaoutis,[1,2,3,4] Kari Torp,[5] Kateri H. Leckerman,[1] and Richard Aplenc[2,3,4,5]

[1]Division of Infectious Diseases and [2]Center for Pediatric Clinical Effectiveness, The Children's Hospital of Philadelphia; [3]Department of Pediatrics and [4]Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine at the University of Pennsylvania; and [5]Division of Oncology, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

Background. Invasive fungal infections cause significant morbidity and mortality for children with acute myeloid leukemia (AML). Data on the comparative effectiveness of antifungal prophylaxis in this population are limited.

Methods. A pediatric AML cohort was assembled from the Pediatric Health Information System database using *ICD-9* codes and pharmacy data. Antifungal prophylaxis status was determined by pharmaceutical data review within 21 days of starting induction chemotherapy. Patients were followed until end of induction, death, or loss to follow-up. Cox regression analyses compared induction mortality and resources utilized between patients receiving and not receiving antifungal prophylaxis. A propensity score accounted for variation in demographic factors, location of care, and severity of illness at presentation.

Results. Eight hundred seventy-one AML patients were identified; the induction case fatality rate was 3.7%. In the adjusted Cox regression model, patients receiving antifungal prophylaxis (57%) had a decreased hazard for induction mortality (hazard ratio [HR], 0.42; 95% confidence interval [CI], .19–.90). Children receiving prophylaxis were less frequently exposed to broad-spectrum gram-positive (incidence rate ratio [IRR], 0.87; 95% CI, .79–.97) and antipseudomonal β-lactam agents (HR, 0.91; 95% CI, .85–.96), had fewer blood cultures (IRR, 0.78; 95% CI, .71–.86), and had fewer chest CT scans (IRR, 0.73; 95% CI, .60–.88).

Conclusions. Antifungal prophylaxis in pediatric AML patients was associated with reduced induction mortality rates and supportive care resources. Further investigation is necessary to determine whether antifungal prophylaxis should include antimold activity.

Keywords. antifungal prophylaxis; pediatric; leukemia; AML.

Invasive fungal infections (IFIs) are a source of significant morbidity and mortality in children with cancer [1]. Prolonged neutropenia is the strongest risk factor for IFI in this patient population [2, 3]. Chemotherapy regimens for acute myeloid leukemia (AML) typically result in neutropenia lasting 35–49 days [4], placing this subset of cancer patients at high risk for IFI. Data from pediatric cooperative group trials report IFI incidence rates per AML chemotherapy phase ranging from 10% to 27% [5, 6]. True IFI rates in this population may be underestimated, as only microbiologically proven IFIs are captured in these estimates [7].

Adult febrile neutropenia practice guidelines have recommended routine use of fluconazole prophylaxis for adult AML patients. Posaconazole should be considered if the baseline rate of invasive aspergillosis is

Received and accepted 28 September 2013; electronically published 23 November 2013.

Correspondence: Brian T. Fisher, DO, MSCE, Division of Infectious Diseases, The Children's Hospital of Philadelphia, 34th and Civic Center Blvd, CHOP North, Rm 1515, Philadelphia, PA 19104 (fisherbria@email.chop.edu).

Clinical Infectious Diseases 2014;58(4):502–8

DOI: 10.1093/cid/cit781

≥6% [8]. These recommendations are based on multiple randomized controlled trials (RCT) in predominantly adult populations showing the efficacy of fluconazole compared to placebo [9, 10] and posaconazole compared to fluconazole or itraconazole [11]. Pediatric oncologists have often extrapolated these adult recommendations to their AML patients. In a recent survey, >75% of pediatric oncologists noted that they prescribe antifungal prophylaxis to AML patients [12]. Furthermore, the supportive care section of the current Children's Oncology Group AML chemotherapy trial (AAML1031) recommends antifungal prophylaxis. However, there remains a paucity of pediatric-specific comparative data for the effectiveness of antifungal prophylaxis in children with AML. Therefore, we aimed to evaluate the effectiveness of antifungal prophylaxis in reducing in-hospital mortality. In addition, we evaluated the frequency of blood cultures, antibiotic exposures, and chest computed tomographic (CT) scans during the induction period.

METHODS

Study Design and Data Source

We performed a retrospective cohort study of patients with newly diagnosed AML receiving care at pediatric institutions that contribute data to the Pediatric Health Information System (PHIS). The PHIS database is a comparative pediatric database capturing inpatient data from up to 44 not-for-profit children's hospitals in the United States. These institutions are affiliated with the Children's Hospital Association (Overland Park, Kansas) and represent 17 of the 20 major metropolitan areas nationwide. PHIS data include participating hospitals' inpatient information including demographics and *International Classification of Diseases, Ninth Revision* (*ICD-9*) discharge diagnosis and procedure codes (up to 41 codes per admission). Additionally, hospitals submit data for specific resources (eg, pharmaceutical agents) by hospital day of service. Patients are assigned a unique identifier in the PHIS database that is preserved for subsequent admissions. Oversight of PHIS data quality maintenance is a joint effort between the Children's Hospital Association, Truven Health Analytics (data processing partner, Ann Arbor, Michigan), and participating hospitals. Data are deidentified at the time of submission and subjected to a number of reliability and validity checks. These audits check for valid entries (eg, valid *ICD-9* diagnosis codes) and reasonable patient information (eg, birth weight). Known data quality issues are communicated to all PHIS data users.

Study Population

This cohort was assembled from hospital-specific data in a 3-step process that has been previously described and validated [13]. In brief, all first admissions containing an *ICD-9* discharge diagnosis code consistent with AML (205.XX–208.XX) were identified. Next, patients were excluded if there was evidence of an alternative malignancy or receipt of a stem cell transplant during their index admission. Finally, an extensive manual review of chemotherapy data was performed to identify chemotherapy patterns consistent with AML induction. For the purposes of this analysis, only those patients receiving an ADE (cytarabine, daunorubicin, and etoposide) chemotherapy regimen were considered. This was done to maintain a homogeneous population with respect to chemotherapy regimen and because induction therapy with ADE is the most common regimen currently administered to AML patients [14]. Each patient was followed until the first of the following events occurred: inpatient death, loss to follow-up, or completion of induction. The induction period was determined using chemotherapy exposure data. Typical ADE induction chemotherapy includes 2 courses of chemotherapy. Therefore, the final date for induction was the day before the start of the third course of chemotherapy.

Outcome

The primary endpoint for this study was inpatient death during induction determined from disposition status at the conclusion of each inpatient admission. Secondary outcomes included rates of antibacterial exposures, blood cultures, and chest CT scans. The burden of antibiotic exposure was represented as the number of days of exposure to a specific category of antibiotics per 1000 study days. Antibiotic exposure was considered in the following groupings: broad-spectrum gram-positive agents (vancomycin, linezolid, daptomycin, quinupristin/dalfopristin), and antipseudomonal β-lactam agents (aztreonam, cefepime, ceftazidime, imipenem, meropenem, piperacillin, piperacillin-tazobactam, ticarcillin, and ticarcillin-clavulanate). The frequency of blood cultures and chest CT scans were also reported per 1000 study days.

Exposure of Interest

The primary exposure was receipt of antifungal prophylaxis with any of the following agents: fluconazole, voriconazole, posaconazole, itraconazole, anidulafungin, caspofungin, micafungin, and amphotericin B products. There is no definitive way to determine from the primary data source the indication of antifungal therapy administered (ie, prophylaxis or empiric therapy). Evidence-based guidelines recommend that empiric antifungal therapy start on or after day 4 of consecutive antipseudomonal antibiotic therapy or after recurrent episodes of fever requiring antipseudomonal antibiotic therapy. Therefore, to distinguish antifungal prophylaxis from empiric therapy, we used the following a priori–defined parameters. The antifungal exposure had to happen within 14 days of initiation of induction chemotherapy, and 1 of the following conditions must

have been met: (1) antifungal treatment initiated on or before the third consecutive day of antipseudomonal antibiotic exposure; (2) if antipseudomonal antibiotic therapy was stopped and restarted, antifungal therapy must have been started on or before the second day after reinitiation of antipseudomonal therapy; (3) absence of a blood culture (surrogate marker for fever) ordered within 1 day of antifungal therapy initiation regardless of concomitant antibiotic exposures. Amphotericin B therapy was only considered prophylactic when administered every other day or 3 times a week. Patients who did not receive antifungal therapy during the first 21 days of induction or those deemed to have received empirical antifungal therapy were labeled as "no prophylaxis" patients. The final analysis was based on the intention to treat and thus any person receiving at least 1 day of a prophylactic antifungal agent was considered an antifungal prophylaxis patient. In a subanalysis, antifungal prophylaxis was subcategorized as "antimold" and "fluconazole only" prophylaxis. Patients receiving fluconazole prophylaxis comprised the fluconazole only prophylaxis group, whereas all other antifungal agents were included in the antimold prophylaxis group.

Covariates

Sex, age, race, and insurance status were determined at the time of each patient's first identified admission for AML. Age in years was considered as a continuous and categorical (0 to <1 years, 1 to <3 years, 3 to <10 years, 10 to <15 years, and 15 to <19 years) variable. PHIS data categorize race as follows: white, black, Asian, Native American, other, and missing. Insurance status includes private, government (ie, Medicare/Medicaid), self-pay, other, and unknown. For descriptive statistics, these categories were preserved; for multivariate models race was grouped as white, nonwhite, and other, and insurance was grouped as private, government, and other. The hospital where patients received their care was also documented. Finally the need for critical care resources was used as a proxy measure for a severe illness state as previously described [15]. Patients were labeled as presenting in a severely ill state if they received such resources in the first 2 hospital days of their index admission.

Propensity Score Model

In assessing the impact of antifungal prophylaxis, there was concern for confounding by indication, such that physicians may be more likely to initiate prophylaxis to patients who are severely ill at AML presentation. Alternatively, patients presenting in a severely ill state may be more likely to require early empiric antifungal therapy and thus not be eligible for prophylaxis. Confounding by center to which the patient was admitted was also of concern, as centers that commonly use antifungal prophylaxis may have increased or decreased AML mortality rates at baseline based upon other factors. Therefore, a propensity score was established from a multivariable logistic regression model to predict a patient's probability of receiving antifungal prophylaxis. The following were included in the propensity score model: age, sex, race, insurance status, hospital site, and whether a patient was severely ill in the first or second day of the index AML admission.

Statistical Analysis

Summary statistics describe demographic characteristics using frequencies and proportions for categorical data and medians and interquartile range (IQR) for continuous variables. A Cox proportional hazards model was performed to compare time to death in the induction period between patients receiving vs those not receiving antifungal prophylaxis. The propensity score was grouped into quintiles, and included as a categorical covariate to adjust for the aforementioned confounding. The Cox proportional hazards assumption was assessed graphically using log-log plots. Results from the Cox models were summarized as hazard ratios (HRs). Poisson regression models were performed to establish and to compare the rates of antibacterial exposures, blood cultures, and chest CT scans between the 2 exposure groups. The propensity score quintiles were again used in each of the Poisson models to account for baseline variations. Pearson-scale adjustment was applied to account for potential overdispersion in Poisson regression. Results from Poisson models were summarized with incidence rate ratios (IRRs).

A propensity score was also established to predict the probability that a patient received fluconazole vs antimold prophylaxis among patients who received antifungal prophylaxis. Cox proportional hazards and Poisson regression models were performed to compare mortality and resource utilization, adjusting for propensity score. Due to a smaller sample size in this subanalysis, hospital site could not be included as a covariate in the propensity score model. Therefore, to account for the possibility of confounding by hospital, we decomposed the effect of prophylaxis exposure to patient level and hospital level by including the percentage of patients receiving each antifungal prophylaxis type within a hospital as a hospital-level covariate in the Cox and Poisson models [16, 17]. Data organization and analyses were performed using SAS software, version 9.2 (Cary, North Carolina).

Human Subjects Oversight

The conduct of this study was approved by the Child Healthcare Association and received an exemption status by the Committee for Protection of Human Subjects at the Children's Hospital of Philadelphia.

RESULTS

Between 1 January 1999 and 31 March 2010, 931 patients with new-onset AML from 38 children's hospitals were identified as

having received ADE induction chemotherapy. One institution did not have billing data for blood cultures and thus the definition for prophylactic antifungal exposure could not be applied. The 60 patients from this center were excluded, leaving 871patients for the final analysis. The median duration of the induction period was 73 days (IQR, 64–83 days); 32 patients (3.7%) died during this period. More than half (57%) of the cohort received antifungal prophylaxis. In patients receiving prophylaxis, fluconazole was most common (80%); the remaining 20% of patients received an antimold prophylaxis agent. Table 1 compares baseline demographic information and severe illness status at presentation. Patients who received antifungal prophylaxis were similar to those not receiving prophylaxis with respect to age, race, sex, and insurance type. Patients receiving antifungal prophylaxis were significantly less likely (3.0% vs 6.9%; $P = .007$) to be deemed severely ill during the first 2 hospital days of their index AML admission.

Table 2 displays the distribution of patients receiving and those not receiving prophylaxis into propensity score quintiles. The distribution across quintiles varies between the 2 study groups, but there is sufficient overlap of patients in each quintile between the 2 study groups to allow for inclusion of propensity score as a categorical variable in the final model. Within each quintile of propensity score, the baseline covariates are similarly distributed. The Cochran-Mantel-Haenszel tests suggest no significant association of the covariates with study group stratifying on the propensity score quintiles ($P = .8600$ for age; $P = .9488$ for sex; $P = .7112$ for race; $P = 9241$ for insurance; $P = .7023$ for severe illness state; $P = .8228$ for hospital site).

Table 3 compares the induction mortality rate and variation in specific resources utilized during the induction period between those receiving and not receiving antifungal prophylaxis. After adjustment for propensity score, patients receiving any type of antifungal prophylaxis were at significantly decreased risk of induction mortality (adjusted HR, 0.42; 95% confidence interval [CI], .19–.90). Patients receiving antifungal prophylaxis had reduced exposure to broad-spectrum

Table 1. Comparison of Demographics and Severe Illness State at Initial Acute Myeloid Leukemia Presentation Between Those Receiving and Those Not Receiving Antifungal Prophylaxis

	All Patients (N = 871)		No Prophylaxis (n = 376)		Prophylaxis (n = 495)		
Characteristic	No.	%	No.	%	No.	%	*P* Value
Age at start of chemotherapy							.72
<1 y	89	10.2	40	10.6	49	9.9	
1 to <3 y	170	19.5	76	20.2	94	19.0	
3 to <10 y	198	22.7	77	20.5	121	24.4	
10 to <15 y	249	28.6	108	28.7	141	28.5	
15 to <19 y	165	18.9	75	20.0	90	18.2	
Sex							.16
Male	465	53.4	211	56.1	254	51.3	
Female	406	46.6	165	43.9	241	48.7	
Race							.83
White	603	69.2	258	68.6	345	69.7	
Black	114	13.1	51	13.6	63	12.7	
Asian/Pacific Islander	33	3.8	16	4.3	17	3.4	
Native American	7	0.8	4	1.1	3	0.6	
Other	82	9.4	36	9.6	46	9.3	
Unknown	32	3.7	11	2.9	21	4.2	
Insurance at start of chemotherapy							.33
Private	318	36.5	150	39.9	168	33.9	
Government	365	41.9	150	39.9	215	43.4	
Self-pay	18	2.1	8	2.1	10	2.0	
Other	170	19.5	18	18.1	102	20.6	
Severely ill at time of AML presentation							.007
Yes	41	4.7	26	6.9	15	3.0	
No	830	95.3	350	93.1	480	97.0	

Abbreviation: AML, acute myeloid leukemia.

Table 2. Distribution of Patients Receiving and Not Receiving Antifungal Prophylaxis Across Quintiles of Propensity to Receive Antifungal Prophylaxis

Propensity Score[a] Quintile	No Prophylaxis, No. (%)	Prophylaxis, No. (%)
1	125 (33.2)	50 (10.1)
2	94 (25.0)	79 (16.0)
3	76 (20.2)	98 (19.8)
4	48 (12.8)	126 (25.5)
5	33 (8.8)	142 (28.7)
Total	376	495

[a] Predicted by age, sex, race (white, black, other), insurance status (private, government, other), hospital location, and severe illness state at presentation.

gram-positive antibiotics and β-lactam antipseudomonal antibiotics per 1000 study days and had fewer blood cultures and chest CT scans performed per 1000 study days.

In a subset analysis, patients exposed to antimold prophylaxis were compared to those receiving fluconazole prophylaxis (Table 4). After inclusion of the propensity score and adjusting for variation in antifungal prophylaxis choice by hospital, no difference in induction mortality between these 2 subgroups could be identified. There was also no statistically significant difference in the utilization of broad-spectrum gram-positive antibiotics, antipseudomonal β-lactam agents, orders for blood cultures, and orders for chest CT scans.

DISCUSSION

Our results suggest that antifungal prophylaxis for newly diagnosed pediatric AML patients is associated with reduced rates of induction mortality, a finding not previously reported for a pediatric cohort. There have been many adult RCTs investigating the impact of antifungal prophylaxis summarized in multiple meta-analyses [9, 10]. A 2007 meta-analysis by Robenshtok et al included 64 RCTs enrolling cancer patients receiving chemotherapy and recipients of hematopoietic stem cell transplant (HSCT) [10]. Among the 31 trials comparing systemic antifungal prophylaxis to placebo or nonsystemic therapy, prophylaxis reduced mortality (Relative Risk, 0.84; 95% CI, .74–.95). Only 1 of these studies focused on pediatric patients. This was a multicenter trial comparing fluconazole to nonsystemic oral polyene therapy in 502 patients with malignancy and HSCT recipients. Fluconazole was found to reduce the incidence of microbiologically documented IFI but was not associated with a statistically significant reduction in deaths [18]. A number of pediatric observational studies have suggested that the introduction of antifungal prophylaxis resulted in a reduction in IFI rates, but such studies included only historical controls or no comparator group and did not investigate the impact on mortality [3, 19–22].

As our data set included resource data, this cohort also represented an opportunity to investigate the impact of antifungal prophylaxis relative to resource utilization. We found that patients receiving antifungal prophylaxis had reduced exposure to broad-spectrum antimicrobial agents, less frequent blood culture sampling, and less frequent orders for chest CT scans. It is difficult to know to what degree these reductions can be attributed to antifungal prophylaxis. Patients receiving antifungal prophylaxis were noted to be less severely ill at baseline (3.0% vs 6.9%; $P = .007$) and thus they may have been less likely to both receive antibiotics and die during the induction period. However, this imbalance in illness severity at presentation was accounted for within the quintiles of the propensity score model. Alternatively, it is possible that patients receiving

Table 3. Comparison of Induction Mortality Rates and Resource Utilization Between Those Receiving Prophylaxis and Those Not Receiving Prophylaxis

Resource	No Antifungal Prophylaxis	Antifungal Prophylaxis	Unadjusted IRR (95% CI)	Adjusted IRR (95% CI)
Death during induction, No. (%)	20 (5.32)	12 (2.42)	0.46[a] (.23–.95)	0.42[a] (.19–.90)
Specific resources, days exposed per 1000 study days				
Broad gram-positive coverage[b]	258.7	215.9	0.83 (.76–.92)	0.87 (.79–.97)
β-lactam anti-*Pseudomonas* coverage[c]	456.9	407.8	0.89 (.84–.94)	0.91 (.85–.96)
Blood culture	184.1	136.9	0.74 (.68–.81)	0.78 (.71–.86)
Chest CT scan	14.1	11.8	0.83 (.70–.99)	0.73 (.60–.88)

Abbreviations: CT, computed tomography; IRR, incidence rate ratio.

[a] Values shown are hazard ratios; adjusted using propensity score.

[b] Includes vancomycin, linezolid, daptomycin, and quinupristin/dalfopristin.

[c] Includes ceftazidime, cefepime, piperacillin/tazobactam, ticarcillin/clavulanate, meropenem, imipenem, and aztreonam.

Table 4. Comparison of Induction Mortality Rates and Resource Utilization Between Those Receiving Antimold Prophylaxis and Those Receiving Fluconazole Prophylaxis

Resource	Antimold Prophylaxis (n = 99)	Fluconazole Prophylaxis (n = 396)	Unadjusted IRR (95% CI)	Adjusted IRR (95% CI)
Death during induction, No. (%)	4 (4.0)	8 (2.0)	1.0[a] (.39–5.62)	0.78[a] (.11–5.66)
Specific resources, days exposed per 1000 study days				
Broad gram-positive coverage[b]	251.0	207.1	1.21 (1.04–1.72)	1.02 (.80–1.29)
β-lactam anti-*Pseudomonas* coverage[c]	445.4	398.4	1.12 (1.02–1.23)	0.91 (.78–1.05)
Blood culture	135.5	137.3	0.99 (.85–1.15)	0.93 (.74–1.17)
Chest CT scan	10.07	12.18	0.83 (.59–1.15)	0.66 (.41–1.08)

Abbreviations: CT, computed tomography; IRR, incidence rate ratio.

[a] Values shown are hazard ratios; adjusted using propensity score and mean use of prophylaxis type by hospital.

[b] Includes vancomycin, linezolid, daptomycin, and quinupristin/dalfopristin.

[c] Includes ceftazidime, cefepime, piperacillin/tazobactam, ticarcillin/clavulanate, meropenem, imipenem, and aztreonam.

antifungal prophylaxis also received antibacterial prophylaxis, which could have accounted for some of the decrease in mortality and resource utilization. There are data to suggest that this is not the case. In a survey of Children's Oncology Group member institutions, Lehrnbecher et al found that 77% of centers utilize antifungal prophylaxis but only 13% prescribe antibacterial prophylaxis [12]. Thus, it is reasonable to conclude that a portion of the reduction in mortality and resources was attributable to the antifungal prophylaxis. Furthermore, initiation of antifungal prophylaxis may indirectly reduce toxicities inherent in exposure to CT imaging and broad-spectrum antibiotic agents and in turn reduce healthcare costs.

Although our data support the benefits of antifungal prophylaxis, it is not clear whether antimold prophylaxis is superior to prophylaxis that does not have antimold coverage. Cornely et al identified a reduction of IFI events and mortality in adult AML patients receiving posaconazole compared to fluconazole or itraconazole [11]. Their results support the superiority of broader antimold prophylaxis therapy in adults with AML but cannot be generalized to children. In an attempt to answer this question, we explored the impact of antimold prophylaxis vs fluconazole prophylaxis in the subset of patients who received antifungal prophylaxis. In propensity score–adjusted models, there was no difference in induction mortality rates or in resources utilized between these 2 groups. However, the number of patients in our cohort on antimold prophylaxis was small and the number of mortal events few, resulting in wide confidence intervals and limited power to detect a potential benefit of antimold therapy over fluconazole.

Our results should be interpreted in the context of certain limitations. First, identification of patients with newly diagnosed AML for this cohort was done in a retrospective manner using *ICD-9* code and pharmaceutical data rather than pathology results. Previous validation efforts by our group documented a high sensitivity and positive predictive value of this process for identifying AML patients, limiting this concern [13]. Second, misclassification of antifungal prophylaxis status may have occurred. To minimize this, we used a conservative definition for designating antifungal therapy as prophylaxis. Third, we were not able to measure the impact of other supportive care interventions. Most notably, we were unable to operationalize a process for identifying antibacterial prophylaxis. However, as noted previously, administration of antibacterial prophylaxis to children with AML is not common in pediatric institutions. Fourth, although a propensity score was used to balance measurable confounders, it is possible that additional unmeasured confounding existed. Finally, the PHIS database lacks microbiology data and therefore a microbiologically defined IFI outcome could not be evaluated. Nonetheless, the identification of a reduction in induction mortality is compelling even in the absence of IFI outcome data.

The lack of pediatric prospective comparative effectiveness data of antifungal prophylaxis has been highlighted in prior reviews [23]. However, owing to the increased risk of IFI in pediatric AML patients and knowing the adult RCT data, some form of antifungal prophylaxis has often been recommended for this patient population [1, 23]. These recommendations make it unlikely that future controlled trials comparing antifungal prophylaxis to placebo or no prophylaxis will be performed. Therefore, observational studies such as this are the only mechanism to measure the impact of antifungal prophylaxis. Our study provides comparative effectiveness results that support the use of antifungal prophylaxis in pediatric AML patients as standard of care. Currently the Children's Oncology Group is enrolling patients in a randomized trial comparing caspofungin to fluconazole prophylaxis for reducing proven or

probable IFI (clinical trials identifier: NCT01307579). Such RCTs will help to define optimal antifungal prophylaxis therapy.

Notes

Financial support. This work was supported by the National Institutes of Health (R01CA133881 to R. A.) and the Slovenian Ministry of Science (J3-4220 to M. K.).

Potential conflicts of interest. B. T. F. currently receives research funding from Pfizer Pharmaceuticals. T. Z. has done consultancy work for Merck, Pfizer, Astellas, and Cubist. B. T. F. and T. Z. are members of the study committee for the current Children's Oncology Group trial comparing caspofungin to fluconazole prophylaxis (NCT01307579), for which Merck Pharmaceuticals provides the caspofungin. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Dvorak CC, Fisher BT, Sung L, et al. Antifungal prophylaxis in pediatric hematology/oncology: new choices and new data. Pediatr Blood Cancer **2012**; 59:21–6.
2. Lehrnbecher T, Phillips R, Alexander S, et al. Guideline for the management of fever and neutropenia in children with cancer and/or undergoing hematopoietic stem-cell transplantation. J Clin Oncol **2012**; 30: 4427–38.
3. Wiley JM, Smith N, Leventhal BG, et al. Invasive fungal disease in pediatric acute leukemia patients with fever and neutropenia during induction chemotherapy: a multivariate analysis of risk factors. J Clin Oncol **1990**; 8:280–6.
4. Cooper TM, Franklin J, Gerbing RB, et al. AAML03P1, a pilot study of the safety of gemtuzumab ozogamicin in combination with chemotherapy for newly diagnosed childhood acute myeloid leukemia: a report from the Children's Oncology Group. Cancer **2012**; 118:761–9.
5. Sung L, Lange BJ, Gerbing RB, Alonzo TA, Feusner J. Microbiologically documented infections and infection-related mortality in children with acute myeloid leukemia. Blood **2007**; 110:3532–9.
6. Sung L, Gamis A, Alonzo TA, et al. Infections and association with different intensity of chemotherapy in children with acute myeloid leukemia. Cancer **2009**; 115:1100–8.
7. De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis **2008**; 46: 1813–21.
8. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis **2011**; 52:e56–93.
9. Bow EJ, Laverdière M, Lussier N, Rotstein C, Cheang MS, Ioannou S. Antifungal prophylaxis for severely neutropenic chemotherapy recipients: a meta analysis of randomized-controlled clinical trials. Cancer **2002**; 94:3230–46.
10. Robenshtok E, Gafter-Gvili A, Goldberg E, et al. Antifungal prophylaxis in cancer patients after chemotherapy or hematopoietic stem-cell transplantation: systematic review and meta-analysis. J Clin Oncol **2007**; 25:5471–89.
11. Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med **2007**; 356:348–59.
12. Lehrnbecher T, Ethier MC, Zaoutis T, et al. International variations in infection supportive care practices for paediatric patients with acute myeloid leukaemia. Br J Haematol **2009**; 147:125–8.
13. Kavcic M, Fisher BT, Torp K, et al. Assembly of a cohort of children treated for acute myeloid leukemia at free-standing children's hospitals in the United States using an administrative database. Pediatr Blood Cancer **2013**; 60:508–11.
14. Kavcic M, Fisher BT, Li Y, et al. Induction mortality and resource utilization in children treated for acute myeloid leukemia at free-standing pediatric hospitals in the United States. Cancer **2013**; 119: 1916–23.
15. Fisher BT, Gerber JS, Leckerman KH, et al. Variation in hospital antibiotic prescribing practices for children with acute lymphoblastic leukemia. Leuk Lymphoma **2013**; 54:1633–9.
16. Localio AR, Berlin JA, Ten Have TR, Kimmel SE. Adjustments for center in multicenter studies: an overview. Ann Intern Med **2001**; 135: 112–23.
17. Begg MD, Parides MK. Separation of individual-level and cluster-level covariate effects in regression analysis of correlated data. Stat Med **2003**; 22:2591–602.
18. Ninane J. A multicentre study of fluconazole versus oral polyenes in the prevention of fungal infection in children with hematological or oncological malignancies. Multicentre Study Group. Eur J Clin Microbiol Infect Dis **1994**; 13:330–7.
19. Dvorak CC, Steinbach WJ, Brown JMY, Agarwal R. Risks and outcomes of invasive fungal infections in pediatric patients undergoing allogeneic hematopoietic cell transplantation. Bone Marrow Transplant **2005**; 36: 621–9.
20. Hovi L, Saxen H, Saarinen-Pihkala UM, Vettenranta K, Meri T, Richardson M. Prevention and monitoring of invasive fungal infections in pediatric patients with cancer and hematologic disorders. Pediatr Blood Cancer **2007**; 48:28–34.
21. Kaya Z, Gursel T, Kocak U, Aral YZ, Kalkanci A, Albayrak M. Invasive fungal infections in pediatric leukemia patients receiving fluconazole prophylaxis. Pediatr Blood Cancer **2009**; 52:470–5.
22. Bochennek K, Tramsen L, Schedler N, et al. Liposomal amphotericin B twice weekly as antifungal prophylaxis in paediatric haematological malignancy patients. Clin Microbiol Infect **2011**; 17:1868–74.
23. Tragiannidis A, Dokos C, Lehrnbecher T, Groll AH. Antifungal chemoprophylaxis in children and adolescents with haematological malignancies and following allogeneic haematopoietic stem cell transplantation: review of the literature and options for clinical practice. Drugs **2012**; 72:685–704.