MAJOR ARTICLE

Insufficient Fluconazole Exposure in Pediatric Cancer Patients and the Need for Therapeutic Drug Monitoring in Critically Ill Children

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(See the Editorial Commentary by Cohen-Wolkowiez and Benjamin on pages 1534–6.)

Background. Fluconazole is recommended as first-line treatment in invasive candidiasis in children and infants. Although timely achievement of adequate exposure of fluconazole improves outcome, therapeutic drug monitoring is currently not recommended.

Methods. We conducted a retrospective study of critically ill children treated with fluconazole from January 2007 to October 2013 and for whom fluconazole concentrations were available. We collected demographic, clinical, and treatment data through review of the medical records and determined the correlation of clinical variables with the fluconazole concentration. Additionally, we assessed the relation between the fluconazole concentration and the time to culture conversion in patients with proven invasive candidiasis.

Results. In total, 99 pediatric patients met the inclusion criteria. The fluconazole concentration was considered subtherapeutic in 40% of the patients. Multiple linear regression analysis showed a significant, independent, and positive association of the fluconazole trough concentration with the fluconazole dose ($P < .001$), weight ($P = .009$), and the serum urea concentration ($P = .003$), and a significant, independent, and negative association with age ($P = .004$) and cancer as an underlying condition ($P = .003$). A higher fluconazole concentration was associated with a shorter time to culture conversion (hazard ratio = 1.076 [95% confidence interval, 1.017–1.138]; $P = .011$).

Conclusions. The fluconazole concentration is not sufficient in pediatric cancer patients with the currently recommended dose regimen, and a higher fluconazole dose is required to achieve adequate drug exposure. Therapeutic drug monitoring of fluconazole can be a valuable tool to detect possible underexposure in critically ill children.

Keywords. fluconazole; pediatric patients; pharmacokinetics; therapeutic drug monitoring.

Invasive candidiasis (IC) is an important cause of morbidity and mortality in critically ill pediatric patients. Despite antifungal therapy, a mortality rate of 16%–29% and a mean 21-day increase in length of hospital stay are observed in pediatric patients with IC [1–5]. Furthermore, in pediatric cancer patients with invasive fungal infections, a 5- to 26-fold increased risk of death is seen [3]. Risk factors for IC include a prolonged length of stay in an intensive care unit (ICU), the use of a central venous catheter, total parenteral nutrition, mechanical ventilation, dialysis, previous broad-spectrum antibiotic therapy, immunosuppression, and recent surgery [6, 7]. A fluconazole dose of 6–12 mg/kg/day is advised in the Summary of Product Characteristics (SPC) of fluconazole for the treatment of IC in pediatric patients [8]. The guideline of the Infectious Diseases Society of America (IDSA) for the management of

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candidiasis and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) pediatric guideline recommend the use of fluconazole as first-line therapy for (suspected) IC in children and infants. To achieve drug exposure comparable to adults, a fluconazole dose of 8–12 mg/kg/day is advised for children and a dose of 12 mg/kg/day for neonates [9, 10].

In vivo studies have demonstrated that the pharmacokinetic/pharmacodynamic parameter of fluconazole that best predicts outcome is the area under the concentration–time curve (AUC) over 24 hours in steady state divided by the minimum inhibitory concentration (MIC) [11, 12]. An AUC/MIC ratio ≥50 for *Candida* species with MIC breakpoint ≤8 mg/L corresponds with a favorable outcome, requiring an AUC of ≥400 mg × h/L [13–16]. Meanwhile, a higher AUC target of 800 mg × h/L in immunocompromised and critically ill patients with IC may be preferred [16, 17]. Although timely attainment of the target AUC improves outcome, therapeutic drug monitoring (TDM) of fluconazole is currently not recommended [10, 18], mostly due to the linear dose–concentration relationship [19, 20] and the good safety profile of fluconazole [21]. However, in critically ill patients, alterations in function of various organs and body systems may influence the pharmacokinetics and, hence, affect the serum concentration of a drug [22–26]. The purpose of this study was to determine which patient characteristics and clinical variables are associated with the serum concentration of fluconazole in critically ill pediatric patients and to identify which patient groups are at risk for underexposure of fluconazole.

METHODS

Study Design and Data Collection

This retrospective study was conducted at the University Medical Center Groningen, a university hospital in the Netherlands with a 150-bed pediatric department, including a pediatric and neonatal ICU. TDM of antimicrobial drugs is routinely performed in critically ill patients in our hospital. Patients were eligible for inclusion if the following criteria were met: (1) age 0–18 years, (2) admission to a pediatric ward or pediatric/neonatal ICU between 1 January 2007 and 30 September 2013, (3) treatment with fluconazole, and (4) at least 1 steady-state trough serum concentration of fluconazole available, which is after 2 days when a loading dose is given, and after 5 days without a loading dose [16, 27]. This study was evaluated by the local ethics committee (Institutional Review Board 2013-491) and was, according to Dutch law, allowed due to its retrospective nature.

Data were collected through review of the medical records using a standardized case report form. Demographic and clinical data were collected including age, sex, weight, underlying condition, stay in an ICU, renal function (serum urea and serum creatinine concentration), leukocyte count, *Candida* species and MIC, site of infection, and the time to culture conversion. The presence of risk factors for IC were reviewed, including the presence of a central venous catheter, total parenteral nutrition, mechanical ventilation, dialysis, previous use of broad-spectrum antibiotics, and cytostatic and immunosuppressive therapy. Medical data were collected on fluconazole dose (mg/kg/day) and route of administration, fluconazole trough concentration, dose adjustments, and interacting comedication.

Correlations With Fluconazole Concentration

Fluconazole serum concentrations were determined using a previously validated liquid chromatography–tandem mass spectrometry (LC-MS/MS) assay and externally confirmed by proficiency testing [28, 29]. Data from pharmacokinetic studies with both trough and AUC data of fluconazole in critically ill children and infants with (suspected) IC were pooled to establish the threshold for an adequate trough concentration. The adequate trough concentration was established by interpolating pharmacokinetic data from the publications of Lee et al [27] and Wade et al [16] using an AUC of 400 mg × h/L (Pearson correlation coefficient trough and AUC of 0.994; $P = .006$). A trough concentration of fluconazole >11 mg/L was defined as an adequate concentration and considered to be representative of an AUC ≥400 mg × h/L in critically ill children and infants with (suspected) IC [16, 27, 30].

We assessed the correlation of the serum concentration of fluconazole with factors that can influence the pharmacokinetics of fluconazole, such as the patients' age, weight, and renal function (serum urea and serum creatinine concentration). The correlation of the fluconazole dose with the serum concentration of fluconazole was assessed as well. Furthermore, we compared the fluconazole concentration between patient groups with different underlying conditions (solid organ transplant [SOT], cancer, surgery, and prematurity), sex, the presence of dialysis, the stay in an ICU, the route of administration of fluconazole, and interacting comedication. Finally, we performed a multiple linear regression analysis to assess the relation between the fluconazole concentration and several explanatory variables. Variables having a P value <.10 in the univariate analyses and variables that can theoretically indicate altered pharmacokinetics were included in the analysis.

Time to Culture Conversion

Time to culture conversion was defined as the time from the start of the fluconazole treatment to the first negative culture of the same matrix. Only patients with a proven invasive fungal disease, according to the 2008 definition 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 [31],

were included in the analysis. Furthermore, only the cultures that represent the focus of the infection were included in the analysis. Patients for whom no follow-up cultures were obtained by the physician within 1 week were excluded from this analysis. Cox regression analysis was performed to assess the relation between the fluconazole concentration and the time to culture conversion, thereby correcting for the leukocyte count and the MIC of the *Candida* species.

Statistical Analysis

Values are expressed as medians with interquartile range (IQR) for continuous variables and as percentages of the group from which they were derived for categorical variables. For the univariate analysis, a Spearman correlation coefficient was calculated to determine correlations between 2 continuous variables. For comparing 2 groups, the Mann–Whitney *U* test was used. Multiple linear regression was performed with backward analysis, thereby removing nonsignificant variables, starting with the one with the highest *P* value. A survival analysis (with time to culture conversion as possibly censored outcome) was performed using Cox regression with backward analysis. All statistical analyses were performed using SPSS for Windows, version 20.0 (IBM SPSS, Chicago, Illinois). A *P* value <.05 was considered statistically significant.

RESULTS

A total of 112 pediatric patients were evaluated. In 11 patients, fluconazole trough samples were obtained before steady state was reached and they were therefore excluded from the analysis. Two patients were excluded due to incomplete medical records. As a result, 99 patients were included in the study and their medical records were reviewed. The mean age of the patients was 4.7 years (range, 0–16 years), and 43 patients (43.4%) were male. The patients' characteristics are summarized in Table 1. At least 1 predisposing risk factor was present in all patients. Cytostatic therapy was used in 29 patients (29.3%), an immunosuppressant (tacrolimus, mycophenolic acid) in 17 patients (17.2%), and broad-spectrum antibiotic therapy in 98 patients (99.0%). Six patients (6.1%) were on dialysis, 81 patients (81.8%) had a central venous catheter, 29 patients (29.3%) received total parenteral nutrition, and 54 patients (54.5%) were on mechanical ventilation. Eighty-one patients (81.8%) had ≥3 predisposing risk factors. The causative pathogen was *Candida albicans* in 74 (74.7%) patients, followed by *Candida parapsilosis* (6.1%) and *Candida tropicalis* (4.0%) (Table 2). Fluconazole was administered as empirical treatment in 4 patients (4.0%) and for prophylaxis in 1 patient (1.0%).

Overall, fluconazole dosing ranged from 3.0 to 18.9 mg/kg/day. Fluconazole was dosed according to the SPC in 81 patients (81.8%) (5.5–12.5 mg/kg), 8 patients (8.1%) received a dose <5.5 mg/kg, and 10 patients (10.1%) received a dose >12.5 mg/kg. Seventy patients (70.7%) received fluconazole intravenously and 29 patients (29.3%) received oral treatment. The fluconazole serum trough concentration ranged from 2.6 to 46.5 mg/L, an adequate fluconazole trough concentration of >11 mg/L was achieved in 59 patients (59.6%). The median fluconazole dose (initial or after dose adjustment) resulting in a trough concentration of >11 mg/L was 10 mg/kg/day (IQR, 6.3–12 mg/kg/day). Two patients (2.0%) received interacting comedication with rifampicin, 5 patients (5.1%) received hydrochlorothiazide, and 43 patients (43.4%) received (es-)omeprazole as comedication. None of the patients received carbamazepine, phenytoin, or barbiturates.

Table 1. Characteristics of 99 Pediatric Patients Receiving Fluconazole

Characteristic	No. of Patients
Sex, male	43 (43.4%)
Stay in ICU	62 (62.6%)
Age	
0–1 mo	20 (20.2%)
1–24 mo	29 (29.3%)
2–12 y	33 (33.3%)
12–18 y	17 (17.2%)
Underlying condition	
Solid organ transplant	16 (16.2%)
Liver	11 (11.1%)
Lung	2 (2.0%)
Cancer	28 (28.3%)
AML	7 (7.1%)
ALL	7 (7.1%)
Lymphoma	5 (5.1%)
Neuroblastoma	3 (3.0%)
Surgery[a]	22 (22.2%)
Gastrointestinal	13 (13.1%)
Cardiovascular	6 (6.1%)
Prematurity	13 (13.1%)
Other[b]	20 (20.2%)

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ICU, intensive care unit.

[a] Surgery, other than transplant surgery or surgery related to cancer.

[b] Other: patients diagnosed with various disorders including pulmonary hypertension, renal insufficiency, liver failure, meningitis, and pneumonia.

Correlations With Fluconazole Concentration

Univariate analysis showed a significant positive correlation of the fluconazole concentration with the fluconazole dose and the serum urea and serum creatinine concentration and a significant negative correlation with age and weight of the patients (Table 3). The fluconazole trough concentration was significantly lower in patients with cancer compared with the other patient groups and significantly higher in premature neonates

Table 2. Cause and Site of Infection

Cause/Site of Infection	No. of Patients
Candida species	
C. albicans	74 (74.7%)
C. parapsilosis	6 (6.1%)
C. tropicalis	4 (4.0%)
C. lusitaniae	2 (2.0%)
C. glabrata[a]	2 (2.0%)
C. famata	1 (1.0%)
Yeast not specified	5 (5.1%)
No species isolated	5 (5.1%)
Culture material	
Blood	26 (26.3%)
Drain fluid[b]	15 (15.2%)
CVC tip	5 (5.1%)
BAL	4 (4.0%)
Sputum	8 (8.1%)
Urine	26 (26.3%)
Feces	3 (3.0%)
Throat/mouth	7 (7.1%)

Abbreviations: BAL, bronchoalveolar lavage; CVC, central venous catheter.

[a] Sensitivity to fluconazole: 1 intermediate, 1 resistant (fluconazole started as empirical treatment).

[b] Drain fluid: 14 patients abdominal fluid, 1 patient pleural fluid.

(vs other patient groups; Figure 1 and Table 4). Furthermore, the fluconazole concentration was significantly lower in patients who received (es-)omeprazole as comedication and did not significantly differ in patients who stayed in the ICU, patients on dialysis, or patients who received fluconazole intravenously compared with patients who received oral treatment (Table 4). In the multiple linear regression analysis, variables obtained by the univariate analysis (age, weight, serum urea and serum creatinine concentration, cancer, SOT, prematurity, fluconazole dose, use of [es-]omeprazole) and variables that can theoretically indicate altered pharmacokinetics (stay in an ICU [22–24] as well as presence of dialysis [25]) were included. The multiple linear regression analysis showed a significant, independent, and positive association of the fluconazole trough concentration

Table 3. Spearman Correlations With the Fluconazole Trough Concentration

Characteristic	Correlation Coefficient	*P* Value
Age, y	−0.225	.025
Weight, kg	−0.189	.061
Fluconazole dose, mg/kg/day	0.307	.002
Serum urea, mmol/L	0.259	.011
Serum creatinine, μmol/L	0.275	.006

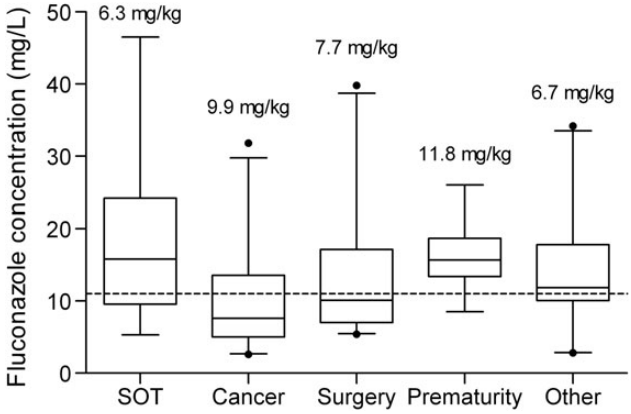

Figure 1. Median fluconazole trough concentration for different patient groups. Median box plot with interval from the 10th percentile to the 90th percentile of the fluconazole trough concentration and median fluconazole dose (mg/kg/day) for patients with different underlying conditions. The dotted line represents a trough concentration of fluconazole of 11 mg/L, which is considered to be representative of an area under the concentration–time curve of 400 mg × h/L. Abbreviations: Other, patients diagnosed with various disorders including pulmonary hypertension, renal insufficiency, liver failure, meningitis, and pneumonia; SOT, solid organ transplant; Surgery, other than transplant surgery or surgery related to cancer.

with the fluconazole dose, weight, and the serum urea concentration, and a significant, independent, and negative association with age and cancer as an underlying condition (Table 5).

Table 4. Fluconazole Trough Concentration in Different Patient Groups

Characteristic	Fluconazole Concentration, mg/L		*P* Value[a]
	Yes	No	
Sex, male	12.0 (9.0–17.5)	11.9 (7.1–17.8)	.745
Route of fluconazole administration (IV)	12.4 (8.8–17.8)	10.0 (6.0–15.6)	.138
ICU	12.6 (9.0–18.0)	10.3 (6.8–15.9)	.146
Dialysis	13.0 (4.7–27.4)	11.9 (7.6–17.6)	.957
Underlying condition			
Solid organ transplant	15.8 (9.6–24.2)	11.4 (7.4–17.0)	.082
Cancer	7.6 (5.0–13.6)	13.1 (9.7–18.0)	.002
Surgery[b]	10.2 (7.1–17.0)	12.0 (7.6–18.0)	.697
Prematurity	15.7 (12.8–18.1)	11.4 (7.1–17.1)	.020
Interacting comedication			
(Es-)omeprazole	10.3 (6.7–17.1)	13.3 (9.6–18.0)	.032
Hydrochlorothiazide	12.3 (11.9–22.4)	11.5 (7.3–17.5)	.209
Rifampicin	13.3 (11.8–13.3)	11.9 (7.5–17.7)	.757

Fluconazole concentrations expressed as median with interquartile range.

Abbreviations: ICU, intensive care unit; IV, intravenous.

[a] Determined by using the Mann–Whitney *U* test.

[b] Surgery, other than transplant surgery or surgery related to cancer.

Table 5. Multiple Linear Regression Model of Factors Significantly Correlated With Fluconazole Trough Concentration

Factor	Effect	95% CI	*P* Value
Serum creatinine, μmol/L	0.043	−.006 to .092	.085
Fluconazole dose, mg/kg/day	0.805	.403 to 1.208	<.001
Age, y	−0.899	−1.502 to −.296	.004
Weight, kg	0.249	.063 to .436	.009
Serum urea, mmol/L	0.637	.224 to 1.050	.003
Cancer	−5.019	−8.334 to −1.704	.003

R^2 of the model = 0.443, R^2 change = −0.007, compared with the model with all variables included.

Abbreviation: CI, confidence interval.

Time to Culture Conversion

In total, 46 patients had a proven invasive fungal infection, of whom 33 were included in the survival analysis. Patients excluded from the analysis were 13 patients for whom no follow-up cultures were obtained within 1 week. In 8 of the 33 included patients, negative cultures were never found. In these patients, no further follow-up cultures were obtained while previous cultures were still positive, or the patient died before cultures became negative. These 8 patients were included as censored data in the analysis. The median number of follow-up cultures from the start of fluconazole until the first negative culture was 1 culture per 2 days (IQR, 1 culture per 5 days–1 culture per day) for a median period of 5 days (IQR, 3–11 days) for the patients included in the survival analysis. The fluconazole trough concentration was significantly associated with the time to culture conversion, when corrected for the leukocyte count. A higher fluconazole concentration was associated with a shorter time to culture conversion (hazard ratio [HR] = 1.076 [95% confidence interval {CI}, 1.017–1.138]; $P = .011$). Because the HR is >1.0, an increase in fluconazole concentration reduces the time to a negative culture. In 21 of the 33 patients, the MIC of the *Candida* species was available. When corrected for the leukocyte count and the *Candida* MICs, an HR of 1.052 (95% CI, 1.003–1.103; $P = .036$) was found.

Fifteen patients deceased during the hospitalization period in which fluconazole was administered. Five of these 15 patients had a proven IC; however, this number was too small to perform statistical analysis.

DISCUSSION

Pediatric cancer patients had a lower fluconazole serum concentration compared with the other patient groups, corrected for age, weight, renal function, and the fluconazole dose. Furthermore, the fluconazole concentration was <11 mg/L and hence subtherapeutic in 40% of all pediatric patients, and the fluconazole concentration was negatively correlated with the time to culture conversion.

Multiple linear regression analysis showed that the fluconazole concentration was significantly associated with the fluconazole dose. A higher maintenance dose of fluconazole can be administered to achieve a therapeutic serum concentration of fluconazole. In 2012, our hospital guideline was revised in accordance with the IDSA and ESCMID guideline and a fluconazole dose of 12 mg/kg/day was recommended, instead of the 6–12 mg/kg/day advised in the SPC of fluconazole. This 12 mg/kg/day dosing regimen is most likely a better approach to achieve a sufficient fluconazole exposure. Besides the fluconazole dose, the age and weight of the patient were significantly associated with the fluconazole concentration. Developmental changes in renal function, and to a lesser extent, the gastrointestinal tract and volume of distribution can contribute to the varying fluconazole concentration with age [32, 33]. Even though the fluconazole dose was corrected for weight, heavier patients generally had a higher fluconazole concentration. Because fluconazole is a highly hydrophilic drug and is administered based on total body weight, patients who are overweight receive a proportionally higher fluconazole dose. As expected, the serum urea concentration and the serum creatinine concentration were both correlated with the fluconazole concentration. Finally, patients with cancer had a significantly lower fluconazole concentration. Because the renal function was included in the analysis, the observed lower fluconazole concentration in cancer patients is most likely the result of an enlarged volume of distribution. The large volume of distribution is probably the result of a shift in body water reservoirs. The shift in body water can be the result of the underlying illness or treatment with chemotherapy [26, 33]. The administration of hyper-hydration during chemotherapy can also lead to an enlarged volume of distribution, although most patients did not receive hyper-hydration at the time the fluconazole trough levels were obtained. Of the patients with cancer, 18 of the 28 patients received fluconazole through intravenous treatment, which makes the presence of vomiting or diarrhea not likely as a cause of the low fluconazole concentration in this patient group. Furthermore, low drug concentrations in cancer patients are also seen with antimicrobial agents such as aminoglycosides, vancomycin, and teicoplanin, which are also highly hydrophilic drugs, and higher doses of these drugs are recommended in cancer patients [26, 34, 35]. Hence, this patient group is currently underdosed and a higher fluconazole dose than currently recommended is required to achieve an adequate drug exposure. A prospective dose-finding study of fluconazole in pediatric cancer patients should be carried out to determine a more appropriate fluconazole dose for this patient group.

A limitation of this study is its retrospective nature, possibly introducing selection bias and suffering from incomplete data

in the medical records. Because fluconazole concentrations were measured routinely in our hospital in critically ill pediatric patients, and not just when efficacy or safety were in question, we expect selection bias to be limited. In addition, we used strict criteria for completeness of the data for analysis with respect to clinically relevant endpoints. Furthermore, MIC values of the *Candida* species were only available for patients with positive blood cultures. A significant association between the fluconazole concentration and culture conversion was still found when corrected for the MIC of the organism. However, the number of patients was small, the MIC values of the patient group showed a narrow distribution, and were all below the susceptibility breakpoint. When the MIC is <8 mg/L (CLSI breakpoint), an AUC of fluconazole <400 mg × h/L is sufficient to reach an AUC/MIC of 50. This emphasizes the importance of susceptibility testing to prevent unnecessary dose increase. However, in case of empirical treatment, the MIC of the *Candida* species is not known at the start of the fluconazole treatment. Then, the strategy would be to acquire at least adequate exposure to cover *Candida* species with a MIC of 8 mg/L. Rapid target attainment by increasing the dose of fluconazole to reach an AUC of >400 mg × h/L is not likely to cause adverse drug reactions as fluconazole has a good safety profile [21].

Based on the results of our study, we believe that the current opinion of TDM not being of added value for fluconazole should be reevaluated. TDM can help to ensure timely target attainment of fluconazole in critically ill pediatric patients who are at risk of underexposure, in particular in cancer patients. Preferably, new dosing recommendations should be developed for these patients, reducing the need for TDM. However, TDM of fluconazole is of potential added value in critically ill children who do not respond adequately to the fluconazole therapy. Because the mortality of IC in pediatric patients is still up to 29% with antifungal treatment, TDM can help to optimize the treatment with fluconazole. With the use of LC-MS/MS analysis, a sample volume of only 10 μL serum or plasma is required for the analysis. From the sample obtained for clinical chemistry, this volume can be easily spared to perform a fluconazole concentration measurement.

In conclusion, the fluconazole concentration was insufficient in pediatric cancer patients compared with other patient groups, and a higher fluconazole dose than currently recommended is required to achieve adequate drug exposure in this patient group. Furthermore, the fluconazole concentration was negatively correlated with the time to culture conversion. TDM can be a valuable tool to detect possible fluconazole underexposure in critically ill pediatric patients failing to respond to therapy. Subsequently, dose adjustment of fluconazole to achieve therapeutic fluconazole concentrations can lead to an increased efficacy of the antifungal treatment and a better outcome of IC.

Note

Potential conflicts of interest. All authors: No potential conflicts of interest.

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.

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