Systemic Antifungal Prescribing in Neonates and Children: Outcomes from the Antibiotic Resistance and Prescribing in European Children (ARPEC) Study


Infections and up to 70% for mold infections (3, 4). The attributable mortality rates from IFI are 30 to 40% for yeast in children (5, 6). To our knowledge, PPS methodologies have patterns of antimicrobial prescribing in adults and, more recently, prevalence surveys (PPS) have provided informative data on the improvement in safe and effective prescribing. Cross-sectional point means of observing prescribing trends, linking results with microbial resistance, while the failure to initiate appropriate treatment is associated with an unacceptably high mortality rate in these vulnerable populations. In low- and extremely low-birthweight neonates, IFI is associated with an attributable mortality rate of 30 to 40% (2). The most common indications for antifungal administration in children were medical prophylaxis (n = 325), empirical treatment of febrile neutropenia (n = 122), and treatment of confirmed or suspected IFI (n = 100 [14%]). The treatment of suspected IFI in low-birthweight neonates accounted for the majority of prescriptions in the neonatal units (n = 103). An analysis of variance (ANOVA) demonstrated no significant effect of clinical indication (prophylaxis or treatment of systemic or localized infection) on the total daily dose (TDD). Fewer than one-half of the patients (n = 371) received a TDD within the dosing range recommended in the current guidelines. Subtherapeutic doses were prescribed in 416 cases (47%). The predominance of fluconazole and high incidence of subtherapeutic doses in participating hospitals may contribute to suboptimal clinical outcomes and an increased predominance of resistant pathogenic fungi. A global consensus on antifungal dosing and coordinated stewardship programs are needed to promote the consistent and appropriate use of antifungal drugs in neonates and children.

Antimicrobial agents are among the most commonly prescribed drugs in neonates and children. The widespread use of broad-spectrum antimicrobials is known to contribute to antimicrobial resistance, while the failure to initiate appropriate treatment is associated with significantly increased attributable mortality (1). The appropriate use of antifungals is of particular importance in the prevention and treatment of infection in the presence of severe intercurrent illness, prematurity, and immunosuppression. Invasive fungal infections (IFI) continue to be associated with an unacceptably high mortality rate in these vulnerable populations. In low- and extremely low-birthweight neonates, IFI is associated with an attributable mortality rate of 30 to 40% (2). In the setting of hematopoietic stem cell transplantation (HSCT), the attributable mortality rates from IFI are 30 to 40% for yeast infections and up to 70% for mold infections (3, 4).

The surveillance of antimicrobial use in hospitals is an important means of observing prescribing trends, linking results with antimicrobial resistance patterns, and identifying areas for improvement in safe and effective prescribing. Cross-sectional point prevalence surveys (PPS) have provided informative data on the patterns of antimicrobial prescribing in adults and, more recently, in children (5, 6). To our knowledge, PPS methodologies have until now not been used to describe antifungal use in children and neonates. Here, we present data on antifungal prescribing from the Antibiotic Resistance and Prescribing in European Children (ARPEC) study, a multicenter observational study investigating the current variation in antimicrobial prescription practices in hospitals.

MATERIALS AND METHODS

A single-day point prevalence study (PPS) of antifungal use was carried out in 226 centers. The details of the ARPEC study design have been outlined elsewhere (3). Briefly, the ARPEC study group was a collaborative partnership between members of the European Surveillance of Antimicrobial Consumption, European Society of Pediatric Infectious Diseases, and Global Research in Pediatrics networks. Hospital-based physicians caring for neonates or children within these networks were invited to participate. The departments within the participating centers recorded data between October and December 2012. All inpatients <18 years of age present at 8 a.m. on the day of survey were included in the...
denominator. Data were recorded for patients who were prescribed antimi-

robial agents on the day of the survey. Neonates and children receiving

antifungal agents known to have negligible bioavailability administered

via the oral route (amphotericin B, nystatin, and miconazole) were ex-

cluded from analysis. The patient exclusion criteria included emergency

admission on the day of study, patients on psychiatric wards, and patients

<18 years old admitted to an adult ward.

Anonymized patient data were collected through a study-specific on-

one portal using a standardized data entry protocol. The project focused

on European centers. In addition, centers outside Europe that collected

and submitted data according to the same methodology during the study

periods were included in the analysis. The data collected for all patients

receiving antimicrobials included age, gender, current weight and birth-

weight, ventilation status, and the prescribed antimicrobial agents, single

unit dose, number of doses per 24 h, route of administration, and drug

indication (therapeutic or prophylaxis). To facilitate data collection on

the underlying diagnosis and reason for treatment, a predefined list of

grouped underlying conditions, acute diagnoses, and anatomical site of

infection was used and is described elsewhere (5). The individual center

and department type were recorded categorically. Neonates were defined

based on postmenstrual age at the time of participation. The classification

of the level of neonatal care was defined locally, according to previously

described predetermined categories (7). Where dose frequencies were less

than daily and an antifungal agent was subsequently prescribed but not

administered on the day of study, patients were included and doses deci-

malized to account for the frequency of administration.

Descriptive statistical analysis was carried out using Stata 10 and R

(version 2.15.3) (8, 9). An analysis of antifungal dosing was performed

using the total daily dose in 24 h (TDD). The TDDs were analyzed per

unit of current weight or estimated surface area (kg or m²), according to

the current guidance for each drug (Table 1). The following Anatomical

Therapeutic Chemical classes (version 2011) were analyzed: antymy-

cotics (ATC J02), antifungals for systemic use (ATC D01B), and intestinal

antimicrobials (ATC A07) (10). The dosing regimens were analyzed by nation

and macrogeographical regions using the United Nations geoscheme

(11).

The mean and variance of the TDDs for each antifungal agent were

compared to currently recommended regimens. The recommended daily

doses (RDD) were defined using collated guidance from the summary of

product characteristics (SPC), the European Society of Pediatric Infect-

ious Disease (ESPID), the Manual of childhood infections: the blue book,

3rd ed. (12), and Red book 2012: 2012 report of the Committee on Infec-

tious Diseases (13). Where specific dosing recommendations for pediatric

or neonatal populations could be derived from the respective SPC, these

formed the basis of the total daily dose recommendations. The dosing

recommendations are summarized in Table 1.

The upper and lower limits for recommended TDD were identified

from the range produced from the collated dosing recommendations and

used to define the maximum recommended daily doses (MaxRDD) and

minimum recommended daily doses (MinRDD). Dosing errors were de-

fined as prescription of medication at a dose meeting one of the follow-

ing criteria: (i) TDD prescribed at ≥110% of the MaxRDD, or (ii) TDD pre-

scribed at ≤90% of the MinRDD. For example, the MinRDD and

MaxRDD for voriconazole in children age 2 to 12 years were determined

as follows: the highest current recommended dosing regimen (excluding

loading doses) was 8 mg/kg of body weight every 12 h, and the lowest
dosing regimen was 4 mg/kg every 12 h (see Table 1) during the study
period (14–22). The MaxRDD and MinRDD were therefore calculated to

be 16 mg/kg and 8 mg/kg daily, respectively, and the supra- and subthera-

peutic doses were calculated to be ≥17.6 mg/kg and ≤7.2 mg/kg, respect-

ively. The doses were defined according to age categories and route of

administration (where specified in the guidelines). A full description of

this methodology is described in detail elsewhere (23). Doses exceeding

values 10-fold above the MaxRDD or below the MinRDD were considered

isolated prescribing or data entry errors and were excluded from analysis.

In accordance with European regulations, the anonymized data ob-

tained during this observational study were gathered without additional

therapy, monitoring procedures, or a change from existing clinical prac-

tices. Submission to the institutional review boards of participating cen-

ters was at the discretion of individual lead investigators.

RESULTS

Patient demographics. Data were recorded from 17,693 neonatal

and pediatric inpatients from 226 centers. The participating cen-

ters were from 19 European countries and 17 countries outside

Europe (see Table 2). A total of 1,345 inpatients from 136 centers

were prescribed at least one oral or parenteral antifungal. This

included 203 neonates and 379 children (1 month to 18 years old).

The median ages of the neonates and children in the study were 13 days

(interquartile range [IQR], 7 to 19 days) and 6.5 years (IQR, 1 to 13 years),

respectively.

Antifungal use. The most commonly prescribed agent for ne-

onates and children during the study was fluconazole, accounting

for 355 (40%) prescriptions (see Fig. 2). Second-generation tria-

zoles were less commonly prescribed (voriconazole, n = 87

[10%]; posaconazole, n = 14 [2%]). Fifteen children (6%) received

oral itraconazole. Amphotericin B deoxycholate was the second

most frequently prescribed drug. Of 262 patients prescribed am-

photericin B, 197 (75%) were prescribed amphotericin B deoxy-

cholate (DAmB). The majority of the DAmB prescriptions (n = 150

[76%]) were from European centers. Lipid amphotericin B

preparations (liposomal, lipid complex, and colloid dispersion)

were prescribed less frequently than was conventional amphoter-

icin B (n = 65 [8%]), of which 51 prescriptions (78%) were within

European centers. The use of echinocandins was less common

than that of amphotericin B formulations and azoles (caspofun-

gin, n = 55 [6%]; micafungin, n = 32 [4%]). One child received

parenteral fluconazole for the treatment of a catheter-related

bloodstream infection. Forty-two patients received combination

antifungal therapy. The most commonly prescribed drug combi-
nations used were amphotericin B-fluconazole (n = 7), amphot-

ericin B-caspofungin (n = 6), and caspofungin-voriconazole

(n = 6).

Indication. Systemic antifungal treatment was reported in 174

neonates. Extremely low-birthweight neonates accounted for

the majority of antifungal prescriptions (n = 103 [60%]). The most

common indications for systemic antifungal treatment in neo-

nates were medical prophylaxis in 80 cases (46%) and treatment of

suspected IFI in 77 cases (44%). The treatment of localized infec-

tion was uncommonly reported (cardiac infection, n = 2; central

nervous system [CNS] infection, n = 4; genitourinary tract infec-

tion, n = 3; lower respiratory tract infection, n = 2; other/infective

source unknown, n = 4). An ANOVA demonstrated no signifi-

cant effect of clinical indication (prophylaxis or treatment of sys-

temic or localized infection) on TDD (F = 1.1, P = 0.342).

The most common indication for antifungal administration in

children was medical prophylaxis (n = 325 [46%]), followed by

empirical treatment of febrile neutropenia (n = 122 [17%]) and

treatment of confirmed or suspected IFI (n = 100 [14%]). Anti-

fungal treatment of a localized infection was less commonly re-
ported (respiratory tract, n = 41; skin and soft tissue, n = 15; urinary tract, n = 14; gastrointestinal, n = 12; CNS, n = 4; joint and bone, n = 4; cardiac, n = 4). In 70 cases, the indication for treatment was not known or recorded.

Route of administration. Systemic antifungals were administered via the oral route in 58% and the parenteral route in 42% of children. The majority of prescriptions in neonates were administered via the parenteral route (n = 154 [89%]). Twenty neonates received oral fluconazole. In children, oral administration accounted for 108/254 (43%) of the fluconazole prescriptions and 50/87 (57%) of the voriconazole prescriptions. The mean TDD for children receiving fluconazole via the oral route was significantly lower (X = 1.8 mg/l kg−1 day; standard deviation [SD], 8.3) than that via the intravenous route (X = 3.5 mg/l kg−1 day; SD, 6.2;...
TABLE 2 Number of children and neonates from participating centers by country

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<th>Location</th>
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<th>No. of neonatal patients (n = 174)</th>
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<th>1093 Children assessed for eligibility</th>
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FIG 1 Study flowchart and reasons for patient data eligibility/exclusion.

P = <0.001). Similarly, the mean TDD for children receiving oral voriconazole was lower (X̄ = 6.1 mg⁻¹ kg⁻¹ day; SD, 4.9) than that for intravenous voriconazole (X̄ = 7.3 mg⁻¹ kg⁻¹ day; SD, 5.8; P = 0.257).

Dosing. The proportions of patients receiving doses outside the MinRDD and MaxRDD for each antifungal agent in neonates and children are shown in Fig. 2. Overall, fewer than one-half of the patients (n = 371 [42%]) received a TDD within the dosing range recommended in current guidelines. Subtherapeutic doses (<90% of the MinRDD) were prescribed in 416 cases (47%). The most commonly prescribed drug, fluconazole, was prescribed at subtherapeutic doses in 242/384 (63%) cases (Fig. 3). Amphotericin B deoxycholate was prescribed at a subtherapeutic TDD in 83/200 (42%) cases. Two neonates received amphotericin B lipid complex at a dose of 5 mg⁻¹ kg⁻¹ day. Recently, the efficacy and population pharmacokinetics of amphotericin B lipid complex (ABLC) have been described in neonates, and a dose of 2.5 to 5 mg⁻¹ kg⁻¹ day was incorporated into European guidelines for the treatment of invasive candidiasis (24).

Center and department categories. The majority of neonatal antifungal prescriptions occurred in tertiary (level III) neonatal units (n = 146 [84%]). For the pediatric population, antifungals were prescribed most frequently in hematology-oncology wards (n = 352 [50%]) and pediatric intensive care units (n = 121 [17%]). Less frequently, antifungal prescriptions were recorded in surgical transplant units (n = 75), general pediatric wards (n = 73), surgical wards (n = 32), cardiac wards (n = 16), and other specialist pediatric wards (n = 42).

The TDDs for children receiving therapeutic dosing regimens of fluconazole varied substantially between centers and by department type; these are shown in Fig. 3. The mean TDDs were significantly lower in general pediatric wards (n = 18; X̄ = 3.9 mg⁻¹ kg⁻¹ day; SD, 4.9), hematology-oncology units (n = 50; X̄ = 3.6 mg⁻¹ kg⁻¹ day; SD, 5.4), and surgical transplant units (n = 12; X̄ = 6.1 mg⁻¹ kg⁻¹ day; SD, 3.7) than that in the pediatric intensive care unit (PICU) (n = 28; X̄ = 7.1 mg⁻¹ kg⁻¹ day; SD, 3.3), cardiac wards (n = 5; X̄ = 6.1 mg⁻¹ kg⁻¹ day; SD, 7.9), and surgical units (n = 15; X̄ = 6.3 mg⁻¹ kg⁻¹ day; SD, 7.5; P < 0.001) (Fig. 3). The mean therapeutic fluconazole TDDs were low in both level III (n = 67; X̄ = 2.2 mg⁻¹ kg⁻¹ day; SD, 6.3) and level I/II units (n = 6; X̄ = 3.5 mg⁻¹ kg⁻¹ day; SD, 3.9).

Amphotericin B was most frequently prescribed on hematology-oncology units and in the PICU. Overall, amphotericin B deoxycholate (DAmB) was prescribed more frequently than lipid formulations of amphotericin B (liposomal amphotericin B [LAmB]), accounting for 200 and 62 prescriptions, respectively. The mean TDDs for therapeutic amphotericin B were significantly lower in general pediatric wards (n = 35; X̄ = 0.6 mg⁻¹ kg⁻¹ day; SD, 2.0), hematology-oncology units (n = 78; X̄ = 0.7 mg⁻¹ kg⁻¹ day; SD, 2.8), and level I/II neonatal units (for DAmB, n = 10; X̄ = 0.4 mg⁻¹ kg⁻¹ day; SD, 3.2) than those in the PICU (for DAmB, n = 27; X̄ = 1.3 mg⁻¹ kg⁻¹ day; SD, 4.1), level III neonatal units (for DAmB, n = 28; X̄ = 1.2 mg⁻¹ kg⁻¹ day; SD, 0.8), surgical transplant units (for DAmB, n = 14; X̄ = 1.1 mg⁻¹ kg⁻¹ day; SD,
0.7), and other specialty medical wards (for DAmB, \( n = 11 \); \( \bar{X} = 1.2 \text{ mg}^{-1} \text{ kg}^{-1} \text{ day} \); SD, 2.0; \( P < 0.001 \)).

**DISCUSSION**

This prospective observational study has provided a detailed description of the current prescribing practices of systemic antifungals for hospitalized neonates and children. Significant underdosing within the participating centers was identified, with fewer than one-half of the recorded prescriptions delivering a daily dose within the ranges recommended in current international guidelines and SPCs. The lowest mean daily therapeutic doses were reported in general pediatric and hematology-oncology units. The dosing varied across countries and regions, but no specific relationship was found between geographical distribution and the proportion of patients receiving subtherapeutic doses. A similar striking variability in dosing has been identified in the treatment of invasive fungal infections in pediatric cancer patients (25). Recent observational studies have also identified that suboptimal dosing of antibacterial and antiviral drugs in children is similarly prevalent. Saxena et al. (26), reporting prescribing surveillance data from the United Kingdom, identified that children and adolescents prescribed oral penicillin received doses below the national recommendations in 40% and 70% of cases, respectively. Menson et al. (27) described the widespread suboptimal dosing of antiretroviral drugs in children and identified several potential causes of error, including the inadequacy of pharmacokinetic-pharmacodynamic (PK-PD) data. Evidence-based dosing recommendations for the older and more commonly prescribed antifungal agents in this study are extremely limited for neonates and children. Optimal doses have never been specifically defined for fluconazole and amphotericin B deoxycholate in pediatric populations, despite their widespread use. Many of the more recently introduced antifungal agents, such as echinocandins and second-generation triazoles, have been specifically studied and differentially licensed for use in neonates and children (28–31). Well-designed prospective PK-PD studies in clinical settings, in conjunction with modeling and simulation based on preclinical data, are the best tools for establishing equivalent evidence-based optimal dosing regimens for these older agents (32).

As in previous observational studies, systemic antifungals were most frequently prescribed for the prevention and treatment of IFI in immunosuppressed children and preterm neonates (33–35). Indication-specific dosing was recently described for fluconazole use in neonates. In the treatment of suspected or confirmed IFI in neonates, a minimum daily dose of fluconazole of 12 mg kg\(^{-1}\) day in the first 90 days of life results in comparable exposure to adults receiving 800 mg daily and achieves an area under the concentration-time curve (AUC)/MIC ratio of \( \geq 50 \) (36). This study observed a large proportion of patients receiving prophylactic treatment and no significant differences between the mean daily doses of fluconazole prescribed for prophylaxis versus therapeutic use. This suggests a lack of awareness of indication-specific dosing in clinical practice and may reflect the difficulties associated with diagnosing IFI in children.

In conjunction with an improved evidence base to underpin antifungal dosing, a global consensus between key organizations issuing dosing recommendations (including those representing specialized high-risk populations) is needed for the treatment and prevention of IFI in pediatrics. An excellent example of such a consensus is the unification of pediatric antiretroviral guidelines published by the WHO, CDC, and Pediatric European Network for Treatment of AIDS (PENTA), which have resulted in consol-
validated international guidelines for the treatment of HIV (37, 38). The harmonization of existing international pediatric antifungal guidelines (for example, the European Conference on Infections in Leukaemia [ECIL] and the European Society of Clinical Microbiology and Infectious Diseases [ESCMID]) should similarly aim to select pragmatic dosing and monitoring schedules while accounting for differences in PK across children and neonates of different sizes and developmental stages (25, 39).

Antimicrobial stewardship programs (ASP) have been shown to increase appropriate antimicrobial prescribing practices, improve individual patient outcomes, and reduce health care costs (40). Recently, ASPs incorporating antifungal stewardship have been described in adults. These programs have identified key components of antifungal stewardship, which include (i) the utilization of appropriate antifungal drugs, including consideration and monitoring of local resistance patterns, (ii) appropriate antifungal doses based on published guidelines, with considerations of patient-specific PK-PD, (iii) clinical considerations, including the removal of intravenous catheters, adequate diagnostics (serial blood culture, antigen testing, and imaging techniques), and the performance of examinations to investigate disseminated disease, and (iv) a clear distinction between prophylactic and therapeutic antifungal use, with appropriate use and duration of therapy based on explicit clinical criteria in these settings (41–44).

Antibacterial ASPs in pediatric centers worldwide have recently been reported (45–47). However, as in the adult population, the relative infrequency of antifungal use compared with the use of antibacterial drugs has led to the development of antifungal stewardship being less forthcoming. The integration of antifungal stewardship within existing ASPs that currently focus predominantly on antibacterial use seems to be a pragmatic way forward to stimulate and improve appropriate antifungal prescribing practices.

PPS studies provide a large volume of information from a wide range of clinical settings at one time, and the participation rates in this study were excellent compared with those in equivalent studies. A great strength of such a PPS study is the opportunity to collect data on dosing and specific indications without relying on subjective questionnaire-based studies. The opportunistic sampling technique does, however, mean that the prescribing practices reported in this study may not be representative of centers and/or countries that did not take part. Additionally, dosing episodes for rare indications or of antifungal agents that are infrequently prescribed may be omitted on the day of study. Further systematic observational studies should aim to increase the number of participating centers in a variety of global settings (including high- and low-income countries) in order to further describe geographical variations, center-specific outcomes, and patient-related trends in antimicrobial use. A significant proportion of centers reported therapeutic antifungal use. Further data about infective organism and resistance patterns will yield important information to guide antifungal stewardship programs. Furthermore, this study did not gather qualitative information, such as clinician rationale (for example, a consideration of renal and/or hepatic impairment) and team member involvement in clinical decisions regarding drug and dose selection. Repeated and/or longitudinal surveys within participating institutions may gather such data and identify prescribing trends over time.

Overall, variability in antifungal prescriptions and widespread systematic suboptimal prescription of antifungals appears to be significant problems in neonates and children. Well-designed clinical studies in conjunction with PK modeling and simulation to inform guidelines, as well as the incorporation of antifungal

FIG 3 Total daily dosing of fluconazole prescribed as treatment for invasive fungal infection in pediatric patients by macrogeographical regions (A) and center type (B). Interquartile range (IQR), median, 1.5 times the IQR, and outlying data points are represented by boxes, central lines, whiskers, and open circles, respectively. The minimum and maximum recommended daily doses are indicated by the dashed lines.
stewardship into current and future ASPs, are urgently needed to improve prescribing practices and clinical outcomes.

ACKNOWLEDGMENTS

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REFERENCES


