The current state of antifungal stewardship among pediatric antimicrobial stewardship programs

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The current state of antifungal stewardship among pediatric antimicrobial stewardship programs

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Abstract
Objective: To characterize the current state of antifungal stewardship practices and perceptions of antifungal use among pediatric antimicrobial stewardship programs (ASPs).

Design: We developed and distributed an electronic survey, which included 17 closed-ended questions about institutional antifungal stewardship practices and perceptions, among pediatric ASPs.

Participants: ASP physicians and pharmacists of 74 hospitals participating in the multicenter Sharing Antimicrobial Reports for Pediatric Stewardship (SHARPS) Collaborative.

Results: We sent surveys to 74 hospitals and received 68 unique responses, for a response rate of 92%. Overall, 63 of 68 the respondent ASPs (93%) reported that they conduct 1 or more antifungal stewardship activities. Of these 68 hospital ASPs, 43 (63%) perform prospective audit and feedback (PAF) of antifungals. The most common reasons reported for not performing PAF of antifungals were not enough time or resources (19 of 25, 76%) and minimal institutional antifungal use (6 of 25, 24%). Also, 52 hospitals (76%) require preauthorization for 1 or more antifungal agents. The most commonly restricted antifungals were isavuconazole (42 of 52 hospitals, 80%) and posaconazole (39 of 52 hospitals, 75%). Furthermore, 33 ASPs (48%) agreed or strongly agreed that antifungals are inappropriately used at their institution, and only 25 of 68 (37%) of ASPs felt very confident making recommendations about antifungals.

Conclusions: Most pediatric ASPs steward antifungals, but the strategies employed are highly variable across surveyed institutions. Although nearly half of respondents identified inappropriate antifungal use as a problem at their institution, most ASPs do not feel confident making recommendations about antifungals. Future studies are needed to determine the rate of inappropriate antifungal use and the best antifungal stewardship strategies.

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interventions.\textsuperscript{14–17} An independent survey expert reviewed the
readability and design of the questionnaire; subsequently, the sur-
vey was pilot tested among a group of antimicrobial stewardship
physicians for relevance and content validity. The survey included
17 closed-ended questions exploring institutional antifungal stew-
dardship practices and perceptions (Supplementary Fig. 1 online).
The survey included questions about prospective audit and feed-
back (PAF) and preauthorization, since these are the core elements
of antimicrobial stewardship described in the 2016 Infectious
Diseases Society of America (IDSA) and the Society for Healthcare
Epidemiology of America (SHEA) guidelines.\textsuperscript{14} We also asked
about other antifungal stewardship elements and interventions
reported in the literature, including mandatory infectious diseases
consultations for fungemia, antifungal TDM, publication of insti-
tutional antifungal susceptibility reports, and the use of fungal
markers.\textsuperscript{16–17} Lastly, we included questions related to perceptions
around inappropriate antifungal use, antifungal stewardship,
and antifungal resistance. We used Likert-type scales, binary
options, and multiple choice answers, as appropriate, to capture
the perceptions around antifungal stewardship (Supplementary
Fig. 1 online).

The survey was distributed electronically among pediatric
ASP\textregistered s of 74 hospitals participating in the multicenter Sharing
Antimicrobial Reports for Pediatric Stewardship (SHARPS)
Collaborative. A member of the antimicrobial stewardship team
(physician or pharmacist) completed the survey at each institution.

Data were collected from December 2018 through February 2019.
Reminders were sent to nonrespondents at 2–3-week intervals dur-
ing the data collection period. The first complete survey received
was included in the study and duplicate or incomplete surveys
from the same institution were excluded. Hospitals were deidenti-
ﬁﬁed prior to analysis.

We used descriptive statistics, including frequencies and pro-
portions, to summarize the survey responses. We compared anti-
fungal stewardship strategies and perceptions based on hospital
type, hospital beds, and geographic region using the \( \chi^2 \) test.
The statistical analysis was performed with JMP version 14.1 software
(SAS Institute, Cary, NC). Informed consent was obtained from
study participants. The study was approved by the Stanford
University School of Medicine Institutional Review Board.

Results

We received 68 unique responses from 74 hospitals, for a response
rate of 92%. We received surveys from 34 states and 2 international
sites. The respondents included 37 pediatric infectious diseases
physicians (54%) and 31 pharmacists (46%). Hospital character-
istics of the participating pediatric ASP\textregistered s are summarized in Table 1.

Overall, 93% of ASP\textregistered s (63 of 68) reported that they conduct or
more antifungal stewardship activities. Of the 68 respondent ASP\textregistered s,
32 (47%) use both core stewardship strategies: PAF and preautho-
rization of antifungals. Also, 20 ASP\textregistered s (30%) require preauthorization
of antifungals alone, 11 (16%) perform PAF of antifungals
alone, and 5 (7%) do not perform any antifungal stewardship
activities.

Among pediatric ASP\textregistered s, 43 of the 68 respondents (63%) perform
PAF of antifungals and 52 (76%) require preauthorization of 1 or
more antifungal agents. The characteristics of antifungal PAF
and preauthorization are shown in Table 2. No differences in antifungal
stewardship strategies were identiﬁed based on hospital type
or hospital beds. For those who do not audit antifungals, the most
common reasons for not performing PAF are insufﬁcient time
or resources (19 of 25, 76%) and minimal institutional antifungal
use (6 of 25, 24%).

At 58 of the 68 respondent hospitals (85%), TDM of antifungals
is routinely performed, and 23 of these 58 programs (40%) have a
pharmacokinetics program to assist with this effort. Of the 58 hos-
pitals that reported antifungal TDM, all 58 (100%) perform TDM
for voriconazole and 46 (79%) perform TDM for posaconazole.
The target trough level reported for the treatment of suspected
invasive fungal infections varied across institutions (Fig. 1).
Among the responding hospitals, 10 (15%) reported that their hos-
pitals have a policy mandating pediatric infectious diseases consulta-
tion for patients with fungemia. Among hospitals without a
mandatory consult policy, most reported that pediatric infectious
diseases consultations occur with >75% of the cases of fungemia
(67%, 39 of 58). Also, 53 of 68 institutions (79%) reported using
noninvasive fungal markers when evaluating for invasive fungal
infections. The most commonly used fungal markers among these
institutions were serum aspergillus galactomannan (53 of 53,
100%) and (1,3)-β-D-glucan (41 of 53, 77%). Only 14 hospitals
(20%) reported that they include antifungal susceptibilities as part of
their institutional antibiogram.

A summary of the ASP\textregistered s perceptions about antifungal use and
resistance is shown in Figure 2, with additional details in
Supplementary Table 1 (online). Compared to children’s hospitals
within a hospital, ASP\textregistered s from freestanding children’s hospitals are
more likely to agree or strongly agree that antifungals are inap-
propriately used at their institutions (60% vs 34%, \( P = 0.03 \)).
Likewise, respondents from large-size hospitals (>300 beds) are
more likely to agree or strongly agree that antifungals are inap-
propriately used at their institution than medium- and small-sized
hospitals (67% vs 51% vs 25%, \( P = .02 \)). The perception of inappro-
priate use did not differ based on the respondent’s role. ASP\textregistered s in
hospitals that reported antifungal susceptibilities were more likely
to perceive antifungal resistance as problem at their institutions
(64% vs 35%, \( P = .04 \)). Only 25 ASP\textregistered s (37%) reported feeling very
confident in providing antifungal recommendations. Respondents

\begin{table}[h!]
\centering
\caption{Hospital Characteristics of Surveyed Pediatric Antimicrobial Stewardship Programs}
\begin{tabular}{|c|c|}
\hline
Characteristics & ASP Programs (N = 68, No. (%)) \\
\hline
Type of hospital & \\
Freestanding children’s hospital & 35 (52) \\
Children’s hospital within a hospital & 32 (47) \\
Specialist children’s hospital & 1 (1) \\
\hline
Geographic region & \\
Northeast & 10 (15) \\
Midwest & 19 (28) \\
West & 12 (17) \\
South & 25 (37) \\
International & 2 (3) \\
\hline
Hospital beds & \\
<150 & 16 (24) \\
150–350 & 37 (54) \\
>350 & 15 (22) \\
\hline
\end{tabular}
\end{table}

Note. ASP, antimicrobial stewardship.
reported that having clinical guidelines specific for antifungal use in children and better diagnostics would improve their level of confidence in making antifungal recommendations (46%, 31 of 68 and 37%, 25 of 68, respectively). Furthermore, respondents perceived hematology-oncology (32 of 68, 47%) and stem cell transplant (15 of 68, 22%) as the services most likely to benefit from antifungal stewardship interventions.

**Discussion**

Our survey revealed some of the antifungal stewardship practices and perceptions in a cohort of pediatric ASPs. Most pediatric ASPs have implemented some form of antifungal stewardship, and the strategies employed are highly variable across surveyed hospitals. Interestingly, although nearly half of respondents perceived inappropriate antifungal use as a problem at their hospital, many did not feel confident in providing antifungal recommendations. Specific stewardship strategies, including antifungal TDM and fungal susceptibility reporting, appear to be less common and may represent unique and important antifungal stewardship opportunities.

According to our survey results, the core antimicrobial stewardship strategies, PAF and preauthorization, have been expanded to include antifungals in most pediatric ASPs. Although these antifungal stewardship interventions have been shown to successfully reduce antifungal consumption in hospitalized patients, the best approach to antifungal stewardship remains unknown. This lack of comparative data has likely led to the very heterogeneous and hospital-specific approaches illustrated in this study. Some studies have proposed that PAF and more intensive stewardship strategies like daily PAF in combination with preauthorization and formulary restriction, may be more effective in decreasing antibiotic utilization. Whether the same is true for antifungals is unknown. In our study, the use of preauthorization was more common than PAF, which is considered relatively labor intensive. Similar to prior reports evaluating antibiotic stewardship strategies, respondents reported that the biggest barrier to implementing antifungal PAF was a lack of time and resources. The frequency of antifungal monitoring varied widely, with <10% of programs performing daily PAF. Whether the absence of daily PAF reflects a lack of sufficient resourcing or is a purposeful choice is uncertain; however, it may result in missed opportunities to intervene and improve antifungal prescribing. These findings highlight the importance of identifying effective antifungal stewardship interventions to better utilize and optimize current resources.

The characteristics of antifungal PAF and preauthorization varied across hospitals. For example, the survey detected differences in the types of antifungals monitored as part of PAF and restricted as part of preauthorization programs. Broad-spectrum triazoles, including voriconazole, posaconazole, and isavuconazole, were commonly targeted as part of antifungal stewardship efforts. ASPs may focus their efforts on these antifungals given the need for TDM, potential toxicities, and their higher costs. However, fluconazole may represent an important antifungal stewardship target because it accounts for ~70% of antifungal prescriptions in children and has been associated with inappropriate prescribing in neonates and children.

The TDM of azole medications is an important strategy to ensure the appropriate use of antifungals and mitigate adverse events. Most institutions responding to this survey routinely monitor azole levels; however, TDM was the least commonly monitored parameter among ASPs performing PAF of antifungals, and only a few institutions reported having a pharmacokinetics program to assist with antifungal TDM. These findings suggest that most clinicians conduct TDM of antifungals without expert

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**Table 2. Characteristics of Antifungal Stewardship Strategies Among Pediatric Antimicrobial Stewardship Programs**

<table>
<thead>
<tr>
<th>Antifungal Stewardship Strategies</th>
<th>ASP Programs (N = 68), No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antifungal prospective audit and feedback</td>
<td>43 (63)</td>
</tr>
<tr>
<td>Antifungal monitored</td>
<td></td>
</tr>
<tr>
<td>Posaconazole</td>
<td>43 (100)</td>
</tr>
<tr>
<td>Echinocandins</td>
<td>42 (98)</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>41 (95)</td>
</tr>
<tr>
<td>Amphotericin B (liposomal)</td>
<td>38 (88)</td>
</tr>
<tr>
<td>Isavuconazole</td>
<td>37 (86)</td>
</tr>
<tr>
<td>Amphotericin B (deoxycholate)</td>
<td>37 (86)</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>32 (74)</td>
</tr>
<tr>
<td>Parameters monitored</td>
<td></td>
</tr>
<tr>
<td>Indication</td>
<td>43 (100)</td>
</tr>
<tr>
<td>Route</td>
<td>39 (91)</td>
</tr>
<tr>
<td>Pathogen–drug mismatch</td>
<td>39 (91)</td>
</tr>
<tr>
<td>Dose</td>
<td>38 (88)</td>
</tr>
<tr>
<td>Therapeutic drug monitoring</td>
<td>32 (74)</td>
</tr>
<tr>
<td>Most common recommendations</td>
<td></td>
</tr>
<tr>
<td>Stop antifungal</td>
<td>23 (53)</td>
</tr>
<tr>
<td>Convert intravenous to oral</td>
<td>21 (49)</td>
</tr>
<tr>
<td>Infectious diseases consult</td>
<td>21 (49)</td>
</tr>
<tr>
<td>Clarify indication</td>
<td>18 (42)</td>
</tr>
<tr>
<td>Therapeutic drug monitoring</td>
<td>17 (40)</td>
</tr>
<tr>
<td>Change dose</td>
<td>13 (30)</td>
</tr>
<tr>
<td>Switch drug</td>
<td>11 (25)</td>
</tr>
<tr>
<td>Frequency of monitoring</td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Monday–Friday</td>
<td>32 (74)</td>
</tr>
<tr>
<td>3 d per week</td>
<td>5 (12)</td>
</tr>
<tr>
<td>Once weekly</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Antifungal preauthorization</td>
<td>52 (76)</td>
</tr>
<tr>
<td>Antifungal restricted</td>
<td></td>
</tr>
<tr>
<td>Isavuconazole</td>
<td>42 (80)</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>39 (75)</td>
</tr>
<tr>
<td>Anidulafungin</td>
<td>32 (61)</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>25 (48)</td>
</tr>
<tr>
<td>Micafungin</td>
<td>25 (48)</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>23 (44)</td>
</tr>
<tr>
<td>Amphotericin B (liposomal)</td>
<td>21 (40)</td>
</tr>
<tr>
<td>Amphotericin B (deoxycholate)</td>
<td>13 (25)</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>3 (6)</td>
</tr>
</tbody>
</table>

Note. ASP, antimicrobial stewardship.
guidance from pharmacists or ASP team members, which may increase the risk for medication errors and suboptimal dosing. Antifungals can be particularly challenging to use in children given their unique pharmacokinetic and pharmacodynamic characteristics. For example, studies have shown that up to 50% of antifungals are inadequately dosed and that certain antifungals require multiple dose adjustments to achieve therapeutic levels.5,28,30,31 Our study revealed variability in the target therapeutic levels reported across institutions, which suggests a lack of consensus in current practices and an important opportunity for standardization. Many of the survey respondents reported a lack of confidence in making antifungal recommendations. This important finding could be related to the limited diagnostic information available to guide antifungal stewardship recommendations. Indeed, almost 40% of the respondents in our survey reported that having better diagnostics would improve their level of confidence in making antifungal recommendations. The absence of microbiological data may limit the ability of ASPs to identify opportunities for discontinuation or de-escalation of antifungals and contribute to prolonged courses of prophylactic or empiric antifungals. Previous surveys have shown that de-escalation of broad-spectrum antibiotic therapy on the basis of culture results is one of the most common antibiotic stewardship interventions.23 In contrast, our study found that the recommendation to switch antifungals (ie,
de-escalate therapy) was one of the least commonly reported interventions. As a surrogate for culture data, the use of noninvasive fungal markers was common among the surveyed hospitals. Prior studies have evaluated the use of noninvasive fungal markers for the surveillance of invasive fungal infection in stem cell transplant patients in an effort to shift from a prophylactic to a preemptive approach and decrease potentially unnecessary antifungal exposure.32–34 Further studies exploring the safety and utility of these tests as part of antifungal stewardship interventions in the pediatric population are warranted.

Inappropriate and unnecessary antifungal use was considered a problem by most pediatric ASPs in this study. Oncology and stem cell transplant were reported as the services that would benefit the most from antifungal stewardship, likely because of the disproportionately higher antifungal utilization described in this population.7 Also, most ASPs in this cohort identified antifungal resistance as a national problem, and to a lesser extent, an institutional problem. This perception may be due to the recent emergence of multidrug-resistant Candida auris outbreaks in hospitals across the United States.35 Most of these cases have been reported in adults; therefore, respondents of this study may consider issues of antifungal resistance as a national, rather than local, problem. Only 20% of the hospitals reported antifungal susceptibilities as part of the institutional antibiogram, and ASPs in these hospitals were more likely to perceive antifungal resistance as a problem at their institution. Possibly, therefore, resistant fungal organisms are underreported or ASP team members are not aware of institutional antifungal susceptibility trends. The emergence of antifungal resistance has been increasingly recognized, and understanding the local epidemiology is essential to developing institutional guidelines for antifungal prophylaxis and the empiric treatment of fungal infections.

Our study has several limitations. First, these results may not be generalizable to all pediatric hospitals. Although our response rate was high, we only surveyed ASPs participating in the SHARPS Collaborative, in which members are actively involved in identifying best practices for the use of antimicrobials. Therefore, we may be overestimating the extent to which antifungal stewardship practices are occurring. However, we were able to capture responses from both freestanding children’s hospitals and children’s hospitals within a larger adult hospital. In addition, ASPs from all 4 geographic regions in the United States and 2 international sites in Europe were represented in our cohort. Another limitation is that some of the responses may have been influenced by the respondent’s familiarity with their institution’s resources and practices and may represent perception rather than fact. Finally, we did not evaluate the effectiveness of different antifungal stewardship interventions, which should be further explored in future studies.

Although implementing antifungal stewardship has challenges, it has the potential to decrease unnecessary and suboptimal antifungal use, to reduce toxicities associated with inappropriate antifungal use, and to prevent the emergence of antifungal resistance. Currently, PAF and preauthorization are the main strategies used by pediatric ASPs to perform antifungal stewardship. Future studies should evaluate the effectiveness and clinical impact of such interventions. Optimization of antifungal dosing and TDM via ASPs represent key components of antifungal stewardship in pediatrics. Thus, future antifungal stewardship efforts should focus not only on reducing unnecessary use but also on improving the quality of antifungal prescribing.

**Supplementary material.** To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2020.306

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