**Global divergence of antifungal prescribing patterns: Data from the Global Antimicrobial Resistance, Prescribing, and Efficacy in Neonates and Children (GARPEC) Surveys.**

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**Abstract**

Background

Globally, invasive fungal infections (IFD) have a significant impact in human health. With an increasing paediatric population at risk of IFD, effective antifungal drugs access and affordability should be ensured universally. The aim of our study was to characterise the global antifungal drug use in neonates and children and its variability between countries in different income groups.

Methods

Data was extracted from the Global Antimicrobial Resistance, Prescribing and Efficacy in Neonates and Children (GARPEC) PPS project, consisting in one pilot and four 1-day PPS between 2015 and 2017. The data had been entered through a study-specific web-based data collection tool.

Results

From a total of 13,410 children included, 7.8% (1,048/13,410) received at least one systemic antifungal drug: 9.5% [95% CI (8.9%-10.1%)] in High income countries (HIC) vs 5.0% [95% CI (4.4%-5.6%)] in Low-middle income countries (LMIC) (p<0.01). A significant proportion of patients on antifungals belonged to high-risk group for IFD (67.4%; 706/1,048); most of these were managed in HIC (72.8%, p<0.01). The likelihood of receiving antifungals being in high-risk group was higher in HIC compared to LMIC (ratio of 5.8 vs 3.4, p<0.01). Antifungal prophylaxis was more likely prescribed in HIC [67.2% vs 30.4%, p<0.01]. Fluconazole was the most frequently prescribed drug. The proportional use of fluconazole was higher in LMIC compared to HIC.

Conclusions

A significant variability of antifungal prescribing patterns was observed. The proportional use of systemic antifungals was twice as high in HIC compared to LMIC. More detailed data on access and antifungal use in limited-resource settings should be explored.

**Introduction**

Globally, fungal infections affect more than one billion people, resulting in approximately 11.5 million life-threatening infections and more than 1.5 million deaths annually1–3. Due to a lack of routine surveillance for most fungal diseases, global data are broad estimates and do not address specifically the burden of fungal diseases in children, which remains largely unknown3–5.

There is an increasing number of paediatric patients at risk for invasive fungal disease (IFD). This includes children infected with human immunodeficiency virus (HIV), children suffering from primary or secondary immunodeficiencies due to cancer, immunosuppressive therapies, or premature neonates5,6. Evidence has shown that IFD is associated with considerable morbidity and mortality6,7, but this varies due to the differences in availability of resources to diagnose and manage IFD8.

Effective antifungal drugs may not be accessible or affordable in many countries especially in low and middle income countries (LMIC) 1,9. Moreover, antifungal drug use in children presents its own limitations such as lack of child-appropriate formulations and dosing regimens, differences in pharmacokinetics (PK) and dosing compared to adults, and the lack of phase III clinical trials.

The aims of this study were to characterize global antifungal drug use in neonates and children and to describe the variability of antifungal use between countries in different income groups. To achieve these aims, we obtained data from the Global Antimicrobial Resistance, Prescribing, and Efficacy in Neonates and Children (GARPEC) - Point Prevalence Survey (PPS) for analyses.

**Methods:**

*Data Source*

Data was extracted from the GARPEC-PPS project. Detailed methods have been described elsewhere10. Briefly, 1-day antimicrobial prescribing data were collected for neonates and children aged <19 years admitted to participating hospitals. One pilot PPS study was conducted over two months in 2015. Following the pilot study, four 1-day PPS were carried out during the periods February-March 2016, May-June 2016, September-October 2016, and December 2016-February 2017.

Patient demographic (age, gender, body weight), comorbidity, antifungal agents, dose, frequency, route of administration, empirical or targeted treatment, and reasons for treatment were collected. Information on gestational age and birthweight were collected for neonates. Denominators comprised the total number of admitted patients by ward and hospitals. In GARPEC-PPS, neonates were defined as being aged 30 days or younger and children as aged >30 days and under 19 years. A patient was considered at “high risk” for IFD if they presented with extreme prematurity (gestational aged <28 weeks), malignancy, or immunodeficiency. Antibiotic drugs were coded in accordance with WHO Anatomical Therapeutic Chemical (ATC) classification11. Prescriptions for antifungals were defined under ATC code J02. Topical use of antifungal drugs was not collected in GARPEC project. Each participating hospital obtained local ethics approval if required. Data were collected via REDCapTM (Research Electronic Data Capture, Vanderbilt University, Nashville, TN, USA), a web-based application which allowed participating hospitals entered data online. All data were anonymised without patient identifiers. Countries were stratified into high-income country (HIC) and LMIC using World Bank classification12.

*Statistical analysis*

Descriptive analyses were performed to characterise patients, antifungal prescriptions, clinical indication, and comorbidity. Data are expressed as the mean and standard deviation (SD) or median with interquartile range (IQR), as appropriate. All analyses were stratified by age group (e.g. neonates or children), and country income level. Clinical characteristics were compared using the Mann–Whitney *U* or Kruskall-Wallis test for continuous variables, and x2 test for categorical parameters. Statistical significance was defined as P< 0.05. All statistical analyses were performed using Stata SE software version 14.0.

**Results**

*Population and country distribution*

In GARPEC-PPS project, a total of 13,410 children were included from 23 countries and 65 hospitals. Overall, 62.6% (8,397/13,410) were patients from HIC while 37.4% (5,013/13,410) were from LMIC. Data on antifungal prescriptions were provided by 56 hospitals from 20 countries, of which 6 countries (31 hospitals) were LMICs (Figure 1).

Approximately 8% (1,048/13,410) of children received at least one antifungal drug. There was a significant difference of antifungal drug use between countries. The majority of prescriptions were from HIC compared to LMIC, 76.2% (798/1,048) vs 23.8% (250/1,048) (p<0.01). The proportion of antifungals compared to total antimicrobial consumption, also varied by level of country income, 9.5% [95% CI (8.9%-10.1%)] in HIC compared to 5.0% [95% CI (4.4%-5.6%)] in LMIC (p<0.01). Figure 2 shows the distribution of antimicrobial use and proportion of antifungal use by country.

*Demographic and clinical characteristics*

Across all the antifungal prescriptions, 86% (871/1,048) were in children outside the neonatal period, defined here as the first 4 weeks of postnatal age. Antifungals prescriptions in children represented 10.5% [95% CI (9.7%-11.2%)] of all the antimicrobials prescriptions beyond the neonatal age in HIC, this proportion significantly lower for LMIC, 4.8% [95% CI (4.2%-5.5%)], p<0.01. Proportions were not different when analysing neonates, 6.0% [95% CI (4.9%-7.1%)] in HIC vs 5.3% [95% CI (4.1%-6.6%)] in LMIC, p =0.411.

The median gestational age in neonates was 28 weeks (IQR 26-33); with 43.5% (77/177) of all antifungal prescriptions issued to extreme preterm neonates with a gestational age <28 weeks. Whereas in the whole GARPEC dataset, the proportion of high-risk neonates did not differ among HIC and LMIC (p=0.129), most of the extreme preterm neonates who received antifungals were in HIC [71.4% (55/77)], p=0.035. When addressing the antifungal consumption in this specific group, antifungals represented the 17.3% [95% CI (13.2%-21.5%)] of all antimicrobials in HIC, compared to 13.4% [95% CI (8.2%-18.2%] in LMIC (p=0.26).

Almost all patients who received antifungal treatment had at least one underlying condition reported [94.2%; 982/1,048]. For those patients with available data, the most prevalent underlying conditions were: malignancy (40.2%; 395/982); hematologic or immunologic condition (25.6%; 251/982); gastrointestinal disorders (17.3%; 170/982); disorders related to prematurity and low birth weight (13.3%; 131/982); and cardiovascular conditions (5.4%; 53/982).

A significant proportion of patients (67.4%; 706/1,048) in our study belonged to patient groups considered to be at high risk for IFD. Overall, belonging to a high risk group increased nearly 5-fold the likelihood of an antifungal drug prescribed. This ratio was significantly higher in HIC compared to LMIC, 5.8 and 3.4 respectively (p<0.01). In the entire cohort of patients, 72.8% (2,396/3,292) of children with malignancy or haemato-immunological condition were managed in HIC and 27.2% (896/3,292) in LMIC (p<0.01). Of those, 22.2% (532/2,396) received antifungals for treatment in HIC, compared to 10.8% (97/896) in LMIC (p<0.01).

*Prophylaxis and treatment*

Overall, 58.4% of antifungal prescriptions (612/1,048) were prescribed for medical prophylaxis. This proportion was significantly higher compared to children receiving other antimicrobials for prophylaxis, 29.4% (3,637/12,362) (p<0.01). The use of prophylactic antifungals was more commonly prescribed among neonates compared to children [61.0% (108/177) vs 57.9% (504/871), p=0.438]. A significantly higher proportion of antifungal prophylaxis was prescribed in HIC compared to LMIC [67.2% (536/798) vs 30.4% (76/1250), p<0.01].

The majority of antifungal treatment was prescribed for empirical reasons. Seventy-one percent (303/427) of children received empirical antifungal treatment, whereas 29.0% (124/427) of children received antifungal drug as targeted treatment. Empirical antifungal treatment was more commonly prescribed to neonates compared to older children [76.8% (53/69) vs 68.1% (250/367), p=0.15]. There was no significant difference when comparing empirical and target treatment by country income; 66.8% (175/262) and 73.6% (128/174) received empiric antifungal treatment in HIC and LMIC, respectively (p=0.133).

Fluconazole was the most commonly prescribed antifungal drug, accounting for 45.8% (480/1,048) and followed by any formulations of amphotericin B (25.5%; 267/1,048). The use of different antifungals is summarised in tables 1 to 3. The proportional use of fluconazole was higher in LMIC compared to HIC, where other triazoles, amphotericin B and echinocandines were more commonly used. This prescribing pattern was even more marked when stratifying by patient risk of developing IFD and country (table 2). High-risk patients received fluconazole in 64.7% of the cases in LMIC, compared to 35.1% in HIC. The use of antifungals per rationale varied too; fluconazole was the most common agent used for prophylaxis in both LMIC and HIC but, whereas it represented 94.7% (72/76) of all the prophylaxis in LMIC, this proportion was 45.1% (243/536) in HIC, where amphotericin B and triazoles were chosen options with 27.4% (146/536) and 17.9% (96/536) of the cases respectively. Fluconazole was also most commonly used for empirical antifungal treatment in LMIC (59.2%, 77/133). This prescribing pattern is different from HIC, where amphotericin B accounted for 33.5% (61/182) of prescriptions and echinocandins for 24.4% (44/182).

**Discussion**

We analysed antifungal prescriptions from 20 countries (56 hospitals) on five consecutive 1-day PPS. Globally, antifungals accounted for 7.8% of overall antimicrobial prescriptions in the GARPEC-PPS project, with a prevalence twice as high in HIC as in LMIC. Most children at high risk for an IFD included in the cohort were treated in HIC and their use of antifungals was significantly higher in HIC compared to LMIC. The same trend was found for the use of antifungal prophylaxis. Marked differences were observed in the use of antifungal agents, with a higher proportional use of fluconazole compared to other antifungals in LMIC than in HIC.

We have previously reported our results from the ARPEC (Antibiotic Resistance and Prescribing in European Children) a single PPS study,13 which showed a similar wide variation in antifungal prescription practices. Sparse paediatric PK data and the lack of phase III clinical trials in neonates and children might be the reason for this variability. In addition, a number of studies have shown that antifungal use is dominated by prophylaxis and empirical treatment14–16. This most likely arises from the intrinsic difficulties in the management of IFD in paediatric patients with poor diagnostic tools.

We observed different antifungal prescribing patterns among HIC and LMIC, which might have been affected by the distribution of the different risk populations. This did not apply to extreme preterm neonates, but predominantly related to oncology and haemato-immunological underlying disease. In terms of paediatric cancer, approximately 85% of childhood cancer cases occur in LMIC. Nevertheless, the report from the Global Task Force on Expanded Access to Cancer Case and Control in Developing countries stated that a child diagnosed with cancer in particular LMIC has an 80% probability of dying, compared to less than 20% in most HIC17. The reasons for this poor outcome are wide-ranging. However, there is an important role for supportive care including the treatment of infectious complications amongst children with cancers. The inability to offer adequate antifungal prophylaxis and/or to treat IFD in the most optimal manner, is expected to contribute to the poor outcome of these patients in LMIC 18–20.

There were significant differences in the type of antifungal agents prescribed by country income and risk of IFD in our study population. Fluconazole was the most commonly prescribed drug, particularly in LMIC and even in the high-risk populations where an anti-mould cover might be needed both for prophylaxis and for empirical treatment. Amphotericin B was the second most commonly used antifungal drug, with almost twice as much use in HIC compared to LMIC. Echinocandines were prescribed in 12% of all the cases, with a similar high use in HIC settings. Voriconazole was the most frequently prescribed mould-active azole antifungal, with similar proportion in both groups. Data from The Global Action Fund for Fungal Infections (GAFFI), showed that fluconazole was the antifungal more extensively available globally (all of the 143 countries with data available), but variability in the price of fluconazole were observed between countries9. This report also showed that 27% of the countries surveyed (42/155), had no supply of amphotericin B9 and that the access to voriconazole varied significantly between continents. Approximately 75% (39/52) of African countries, 53.3% (24/45) of Asian and 12.5% (6/48) of American countries had either no supply of voriconazole or no data was available; this is in contrast to Europe, where almost all the countries reported availability of this drug21. Although there is no published data yet in terms of global accessibility to echinocandines, this class of antifungals is considered to be first line treatment for invasive candidiasis22,23. They are drugs with broad antifungal activity against many *Candida Sp*, as well as certain moulds, favorable toxicity profile and low susceptibility to development of resistances24,25. Costs related to the use of echinocandins may well explain the difference in prescriptions between HIC and LMIC. In some settings, such as the U.S., the administration of echinocandin exceeds amphotericin or mould-active azoles in children’s hospitals25.

*Strength and limitations*

To our knowledge, this is the first global collaborative study to evaluate antifungal prescription in a large paediatric population, including data from LMICs. We observed a substantial variation between countries in the use of antifungals in neonates and children. Our study has limitations in common with other PPS studies10,26–28. We were unable to capture treatment duration, sequential treatment choices, and treatment outcomes. Furthermore, participating hospitals contributed data to the GARPEC network voluntarily so our study may not be generalisable to the overall global inpatient paediatric population. The use of a simple cross-sectional PPS study design allows the collection of valuable data in LMICs, where surveillance and stewardship programmes are not routinely available.

**Conclusion**

Globally, a significant variability in antifungal prescription was observed, with a proportional use twice as high in HIC compared to LMIC. The majority of prescriptions were issued for medical prophylaxis and empirical treatment in high-risk paediatric population. Accessibility and affordability of antifungal drugs is a well-known hurdle for LMICs in general. The next step is to obtain patient level data from the LMIC setting, focussing on the optimal management of high-risk groups.

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**Figure legends**

Figure 1: Countries included in the GARPEC-PPS project with data on antifungal use, number of centres at each country presented in brackets. Dark grey colour, countries classified as high-income countries (HIC) including Australia (1), Chile (1), Finland (1), Germany (5), Greece (3), Italy (4), Japan (1), Singapore (1), Slovenia (1), Spain (2), Taiwan (1), United Kingdom (11) and United States (1). Light grey colour, countries classified as middle- and low-income countries (LMIC) including Brazil (6), Gambia (1), India (9), Mexico (1), Nigeria (10, South Africa (2), and Thailand (2).

Figure 2. Distribution of antimicrobial prescriptions and proportion of antifungal prescriptions per country. Right Y axis and bars represent the total antimicrobial prescription in frequency. Left Y axis and dots represent the proportion (%) of antifungal prescriptions from the total of antimicrobials prescribed. Dotted line represents the average of antifungal use on the total sample.

**Tables**

**Table 1.** Antifungal agents prescribed in high-income countries (HICs) and low-middle income countries (LMICs)

|  |  |  |  |
| --- | --- | --- | --- |
|  | Country income level | |  |
| Antifungal drug | HIC  (n= 798) | LMIC  (n=250) | Total  (n= 1048) |
| Amphotericin B n(%) | 231 (28.4) | 43 (16.0) | 274 (26.1) |
| Fluconazole n(%) | 314 (39.2) | 167 (66.8) | 481 (45.9) |
| Mould active triazoles n(%) | 139 (17.4) | 24 (9.6) | 163 (15.5) |
| *Voriconazole* | *60 (7.5)* | *16 (6.4)* | *76 (7.3)* |
| *Posaconazole* | *32 (4.0)* | *6 (2.4)* | *38 (3.6)* |
| *Itraconazole* | *47 (5.9)* | *2 (0.8)* | *49 (4.7)* |
| Echinocandins n(%) | 111 (13.9) | 15 (6.0) | 126 (12.0) |
| *Caspofungin* | *61 (7.6)* | *8 (3.2)* | *69 (6.6)* |
| *Micafungin* | *47 (5.9)* | *7 (2.8)* | *54 (5.1)* |
| *Anidulafungin* | *3 (0.4)* | *0* | *3 (0.3)* |
| Flucytosine n(%) | 1 (0.1) | 1 (0.4) | 2 (0.2) |
| Other n(%) | 2 (0.2) | 0 | 2 (0.2) |

HIC, High Income Country. LMIC, Low Middle Income Country. Amphotericin B includes all formulations.

**Table 2.** Antifungal agents by country income and type of underlying condition

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Country income level | | | |  | | |
|  | HIC  (n= 798) | | LMIC  (n=250) | | Total  (n= 1048) | | |
| Antifungal drug | High risk  (n=587) | Standard risk (n=211) | High risk  (n=119) | Standard risk (n=131) | High risk  (n=706) | | Standard risk  (n=342) |
| Amphotericin B n(%) | 196 (33.4) | 35 (16.6) | 20 (16.8) | 23 (19.3) | 216 (30.6) | | 58 (16.9) |
| Fluconazole n(%) | 206 (35.1) | 108 (51.2) | 77 (64.7) | 90 (68.7) | 282 (39.9) | | 198 (57.9) |
| Mould active triazoles n(%) | 111 (18.9) | 28 (13.3) | 15 (12.6) | 9 (6.9) | 130 (18.4) | | 37 (10.8) |
| *Voriconazole* | *50 (8.5)* | *10 (4.7)* | *9 (7.6)* | *7 (5.3)* | | *59 (8.4)* | *17 (5.0)* |
| *Posaconazole* | *28 (4.7)* | *4 (1.9)* | *4 (3.4)* | *2 (1.5)* | *32 (4.5)* | | *6 (1.9)* |
| *Itraconazole* | *33 (5.6)* | *14 (6.6)* | *2 (1.7)* | *0* | *35 (5.0)* | | *14 (4.1)* |
| Echinocandins n(%) | 72 (12.3) | 39 (18.5) | 7 (5.9) | 8 (6.1) | 87 (12.3) | | 46(13.4) |
| *Caspofungin* | *40 (6.8)* | *21 (9.9)* | *5 (4.2)* | *3 (2.3)* | *45 (6.4)* | | *24 (7.0)* |
| *Micafungin* | *30 (5.1)* | *17 (8.0)* | *2 (1.7)* | *5 (3.8)* | *32 (4.5)* | | *22 (6.4)* |
| *Anidulafungin* | *2 (0.3)* | *1 (0.5)* | *0* | *0* | *2 (0.3)* | | *0* |
| Flucytosine n(%) | 1 (0.2) | 0 | 0 | 1 (0.8) | 1 (0.1) | | 1 (0.3) |
| Other n(%) | 1 (0.2) | 1 (0.5) | 0 | 0 | 1 (0.1)) | | 0 |

HIC, High Income Country. LMIC, Low Middle Income Country. High risk for invasive fungal infection was considered when the neonate was extreme preterm or the children had an underlying malignancy or immunodeficiency. Amphotericin B includes all formulations.

**Table 3.** Antifungal agents by country income and rational of treatment

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Country income level | | | | | |  | | |
|  | HIC  (n= 798) | | | LMIC  (n=250) | | | | | |
| Antifungal drug | Prophylaxis  (n=536) | Empiric. (n=182) | Target  (n=80) | | Prophylaxis (n=76) | | Empiric  (n=130) | | Target  (n=44) |
| Amphotericin B n(%) | 146 (27.4) | 61 (33.5) | 21 (26.2) | | 0 | | 31 (23.8) | 12 (27.3) | |
| Fluconazole n(%) | 243 (45.1) | 42 (23.1) | 28 (35.0) | | 72 (94.7) | 77 (59.2) | | 16 (36.4) | |
| Mould active triazoles n(%) | 96 (17.9) | 26 (14.3) | 15 (18.7) | | 4 (5.5) | | 9 (6.9) | 11 (25.0) | |
| *Voriconazole* | *38 (7.1)* | *10 (5.5)* | *11 (13.7)* | | *0* | *9 (6.9)* | | *7 (15.9)* | |
| *Posaconazole* | *19 (3.5)* | *10 (5.5)* | *2 (2.5)* | | *2 (2.6)* | | *0* | *4 (9.1)* | |
| *Itraconazole* | *39 (7.3)* | *6 (3.3)* | *2 (2.5)* | | *2 (2.6)* | | *0* | *0* | |
| Echinocandins n(%) | 50(9.3) | 44 (24.2) | 16 (20) | | 0 | | 11 (8.5) | 4 (9.1) | |
| *Caspofungin* | *34 (6.4)* | *21 (11.5)* | *5 (6.2)* | | *0* | | *4 (3.1)* | *4 (9.1)* | |
| *Micafungin* | *15 (2.8)* | *21 (11.5)* | *11 (13.7)* | | *0* | | *7 (5.4)* | *0* | |
| *Anidulafungin* | *1 (0.4)* | *2 (1.1)* | *0* | | *0* | | *0* | *0* | |
| Flucytosine n(%) | 0 | 0 | 0 | | 0 | | 0 | 1 (2.3) | |
| Other n(%)  Missing data n(%) | 1 (0.4)  0 | 1 (0.5)  7 (3.8) | 0  0 | | 0  0 | | 0  2 (1.5) | 0  0 | |

HIC, High Income Country. LMIC, Low Middle Income Country. High risk for invasive fungal infection was considered when the neonate was extreme preterm or the children had an underlying malignancy or immunodeficiency. Amphotericin B includes all formulations.

**Figures**

**Figure 1**



**Figure 2**

