Title:

Neonatal antifungal consumption is dominated by prophylactic use; outcomes from the Paediatric Antifungal Stewardship: Optimising Antifungal Prescription (PASOAP) study.

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Neonatal antifungal consumption data from PASOAP (the Paediatric Antifungal Stewardship: Optimising Antifungal Prescription) study

INTRODUCTION:

Neonates are more vulnerable to invasive candidiasis (IC) than older children and adults, and is associated with poor outcomes in terms of mortality and neurodevelopmental morbidity (1–3). Gestational age (≤ 28 weeks), birth weight (< 1000 grams) and prior abdominal surgery are the main determinants of risk for neonates and young infants to develop IC (2,4–7). Additional risk factors include the presence of central venous catheters, prolonged intubation, prolonged use of broad spectrum antibiotics, steroids and H2-blockers (4). International guidelines support the use of antifungal prophylaxis in high-risk neonates (i.e. birth weight < 1000 grams), whereas there is no strong evidence supporting neonatal antifungal prophylaxis based on other risk factors (8,9).

The management of IC in neonates and young infants represents a challenge for clinicians. The clinical presentation is indistinguishable from late-onset bacterial sepsis. Although cultures from a sterile site remain the gold standard for the diagnosis, their sensitivity is low and the experience with fungal antigen testing and PCR-based diagnostics are still very limited in this patient group (10). Pharmacokinetic studies and clinical trials in neonates are scarce and the majority of antifungal agents licensed for use in older infants and children and/or adults have no neonatal dosing recommendations (11–13).

Due to the diagnostic difficulties combined with the vulnerability of neonates to develop IC, antifungals may be prescribed prophylactically or empirically to prevent delayed treatment and a worse outcome. The drawback of these approaches is the risk of

overuse and potentially inappropriate use of antifungal drugs, all of which have side-effects. In addition, development of antifungal resistance and/or shift in *Candida* species distribution in neonates may occur. In order to obtain an improved understanding of the rationale of antifungal prescribing in this specific patient population, we performed a modified point-prevalence study (PPS).

METHODS:

A prospective modified PPS capturing prescription of antifungals to neonates and children in twelve centres in England during 26 consecutive weeks (June 2017 to January 2018) was performed. Each centre collected the data on a specific day of each week. The participating centres were: St. George´s University Hospitals NHS Foundation Trust, The Royal Marsden Hospital, Great Ormond Street Hospital for Children, St. Mary's Hospital and Evelina Children´s Hospital in London; the Children´s Hospital in Oxford; Southampton Children's Hospital; Bristol Royal Hospital for Children; Alder Hey Children´s Hospital Liverpool; Great North Children´s Hospital Newcastle; Royal Manchester Children´s Hospital and Leeds Children's Hospital. The antifungal prescribing in neonates and young infants (< 3 months of age) is described here.

Demographic, diagnostic and treatment information was collected for each patient in the registry. Changes relating to the antifungals prescribed and the likelihood of IC (suspected or proven) were captured throughout the duration of hospitalisation. The following risk factors for IC were captured at enrolment: steroid use; broad-spectrum antibiotic use > 4 days (e.g. piperacillin-tazobactam, meropenem, third or fourth generation cephalosporins); presence of central venous catheter (CVC), previous

intensive care admission, total parenteral nutrition (TPN), birth weight <1000 g, known *Candida* colonisation and abdominal surgery.

Prematurity was defined as neonates born before 37 weeks of gestation. Extremely low birth weight (ELBW) was defined as < 1000 grams. Prescription of topical nystatin in neonates ≤ 28 days of age was excluded in the analysis due to a lack of homogeneity in the data entered by the different centres.

Antifungal prescriptions counted separately new prescriptions and changes to an existing prescriptions during the antifungal prophylaxis or treatment.

The data collection was performed in the online database REDCap™. Data were extracted into Stata 14.0 for analysis. Variables that followed a normal distribution were expressed as mean, variance and range, those that did not follow a normal distribution were expressed as medians and interquartile ranges. Categorical variables were reported as frequency of distribution or rates and expressed as 2×2 tables. Estimates were displayed using 95% confidence intervals.

RESULTS:

Clinical Characteristics

During the six-month study period, 280 neonates and infants < 3 months of age who were prescribed a systemic antifungal agent, were included. The majority were ≤ 1 month of age (n=191, 68.2%), with 114 (40.7%) being neonates ≤ 7 days of age (Table 1).

Most of the neonates and infants were admitted to neonatal wards (n=200; 71.4%). The proportion of infants receiving antifungals admitted to neonatal wards was 19.3% (95% CI 17.3 to 21.3%). Prematurity was the most frequent reported underlying

condition in 68.9% (188/273). Underlying cardiac and abdominal abnormalities accounted for 8% (22/273) and 7.3% (20/273) respectively. 7.5% infants suffered from an underlying condition not directly associated with a higher risk for IC and 2.9% had no underlying condition reported (Table 1). A microbiologically-proven diagnosis of IC was made in 15 (5.4%) patients. In 37 (13.2 %) cases, IC was suspected but not confirmed.

Risk factors

At least one risk factor was reported in 91.8% (257/280) infants. Of those, 67 (23.9%), 65 (23.2%) and 125 (44.7%) reported the presence of 1, 2, and 3 or more risk factors, respectively (Table 2). Half of the non-ELBW premature infants had just one risk factor. The most common risk factors reported were presence of CVC, administration of TPN, ELBW and prolonged use of antimicrobial agents in 197 (70.4%), 148 (52.9%), 95 (33.9%) and 82 (29.3%), respectively (Table 3). Of the neonates born prematurely, 50.5% (95/188) had a birth weight < 1000 g.

Antifungal prescriptions and rationale

A total of 369 prescriptions were registered during the study. The rationale for the antifungal prescription was prophylaxis in 291 (78.9%) and 78 (21.1%) for treatment. In only 7 (2.5%) cases was observed a change from prophylaxis to treatment. Only 23.3% of the treatment prescriptions were for proven IC. The median age for those on prophylaxis was lower than for those on treatment; 7 days [IQR 3-28] versus 33 days [IQR 15-56].

Of the 223 (79.6 %) young infants receiving antifungal prophylaxis, 40.8% (91/223) had a birth weight of < 1000 g. The distribution of risk factors based on underlying conditions for those receiving prophylaxis is summarised in Table 4.

Drug of choice

Irrespective of the rationale for the antifungal prescription, 76.7% (283/369) prescriptions were for fluconazole, 13.3% (49/369) for nystatin (all outside neonatal period), 23 (6.2%) for liposomal amphotericin B and 14 (3.8%) for another antifungal. Only three prescriptions were for echinocandins, all in infants > 28 days of age. Flucytosine was prescribed for 2 infants. There were no prescriptions reported for other formulations of amphotericin B.

The vast majority of fluconazole use was for prophylaxis, 84.8% (240/283). The mean prophylactic dose prescribed was 3.2 mg/kg/day (SD 1.9 mg/kg/day). The dosing frequency was every 24, 48 and 72 hours in 50%, 2.3% and 47.7% respectively. When fluconazole was prescribed for treatment purposes, the mean dose was 9.7 mg/kg/day (SD 3.6 mg/kg/day). The majority of the prescriptions were daily (87.7%), while 5% and 7.5% were every 48 and 72 hours respectively. Fluconazole was administered intravenously in 90.4% (255/282) and orally in 9.6% (27/282) independently of the rationale for the prescription. The ELBW neonates received fluconazole only intravenously.

Liposomal amphotericin B was prescribed in a comparable number of infants for prophylaxis (47.8%, 11/23) and treatment (52.2%, 12/23). One third were neonatal prescriptions (8/23). The daily dose of liposomal amphotericin B was variable and

ranged from 0.7 to 4 mg/kg/day. Half of the prescriptions (11/23) were 3 mg/kg/day; followed by 1 mg/kg/day used in 30.5% (7/23) and 2.5 mg/kg/day in 8.7% (2/23).

From all the nystatin prescriptions, 59.2% (29/49) were for prophylaxis outside the neonatal period. Its prophylactic use was mainly for infants with a surgical condition (13/29; 44.8%), followed by infants born prematurely (9/29; 31%). Twenty neonates and infants received nystatin therapeutically, most of them (n=16, 80%) had an underlying condition associated with an increased risk for IC.

Antifungal duration

From those with data available, 22.6% (55/243) infants were discharged home on antifungals, of which two thirds (37/55) were for prophylaxis. For those whose treatment was stopped before discharge and where the stop date was available (n=130), the median of duration was 12 days (IQR 7-25). The duration varied slightly between prophylactic and therapeutic use, median 12 days (IQR 7-26) and 16 days (IQR 7-23), respectively. ELBW infants received prophylaxis for a longer duration compared to those born with a birth weight > 1000 g; median 16 days (IQR 7-29) versus 11 days (IQR 7-19). The median of treatment duration in neonates with proven IC was 33.5 days (IQR 16-51).

DISCUSSION

This study summarises the antifungal prescribing practice for neonates and infants < 3 months of age in 12 hospitals in England. Two-third of the prescriptions were for infants < 1 month of age. Prematurity was by far the most common underlying condition (almost 70%) in those receiving antifungal drugs. Of those infants born

prematurely, almost half were ELBW infants. 44.7% of the cases presented three or more risk factors gathering a higher risk for IC, where CVC was the commonest risk factor associated with the use of antifungals. The vast majority of antifungal drugs were prescribed for prophylaxis. There was a substantial group of non-ELBW premature and infants with primary prophylaxis for IC with no or only one risk factor. Fluconazole was the most common antifungal used, with a tendency to be underdosed.

At present, antifungal prophylaxis in neonates is recommended for ELBW infants by the Infectious Diseases Society of America (IDSA) and by the European Society of Clinical Microbiology and Infectious Diseases, due to the reported high incidences of IC and poor outcome (7,8). Nevertheless, the local incidence needs to be taken into account when adopting neonatal antifungal prophylaxis as part of the clinical management strategy (9,14). Only 34% of the infants in our study being prescribed antifungal prophylaxis fulfilled this risk profile (e.g. ELBW) – there was a substantial group of non-ELBW premature neonates and infants with zero or just one risk factor for IC. Our study highlights a high number of other underlying conditions and risk factors assumed to be associated with an increased risk to develop IC. Though a combination of risk factors may be regarded as justification for starting antifungal prophylaxis (9,15–17), this did not explain the prescription in the non-ELBW and non-premature infants. ELBW infants had an additional three risk factors in 85%, while for the non-ELBW premature infants and the non-premature infants this was only the case in 7.5% and 35% respectively. *Candida* colonisation was rarely reported as a risk factor, which may be explained by the absence of active surveillance programs.

Prophylaxis accounted for the great majority of antifungal prescriptions (78.9%). This was higher than previous European data estimates in which prophylaxis accounted for 46% of the prescriptions for both neonates and children (18). Neonatal antifungal prophylaxis has become much more part of the clinical practice within the NICU's of the larger children's hospitals in England (Ferreras-Antolin L et al, in press).

Fluconazole was the most commonly prescribed antifungal drug. It has been reasonably well studied in neonates, although it was not until recently that it was shown that higher dosages were needed to reach adequate exposure (19–24). The dosing of prophylactic fluconazole in our study was adequate according to guidelines and available PK data (8,9,21,22,25,26). Treatment prescriptions were under-dosed. PK data demonstrate that fluconazole dosing in neonates and infants, including premature infants, should be 12 mg/kg/day. A loading dose of 25 mg/kg may be required to achieve rapidly adequate concentrations (19,27). Although the BNFc (British National Formulary for children) still maintains treatment dose from 6 to 12 mg/kg/dose, international guidelines already advocate for 12 mg/kg/dose with a higher loading dose (8). In general, higher fluconazole dosages were prescribed compared to those reported by the ARPEC study, which showed fluconazole to be prescribed in sub-therapeutic doses in 63% (18). A recent epidemiological study (EUROCANDY) has shown low incidence of fluconazole resistant *C. albicans* and *C. parapsilosis*, as well as low incidence of *Candida spp* with intrinsic resistances to fluconazole (28).

Echinocandins were not prescribed in neonates and only three prescriptions were counted in those > 28 days of life. Micafungin is currently the only echinocandin licensed for neonatal use by the European Medicines Agency and requires higher

dosing than older children, up to 10 mg/kg/day, with a good efficacy and safety profile (29–31).

Liposomal amphotericin B accounted for only 6.2% of the prescriptions, both for prophylaxis and treatment in neonates and infants > 28 days of life, and with variable dosing. Limited pharmacokinetic data exist regarding dosing of liposomal amphotericin B in neonates and young infants, the optimal dosing is lacking and its use is not licensed in neonates in the first month of life and prophylaxis (8,32).

Antifungal duration and the end of the period at risk, is poorly defined and is often based on individual appreciations, which were not addressed in this study. The recommended neonatal prophylaxis duration for ELBW infants is between 4 to 6 weeks (22). In our study, there was significant variation in the duration of prophylactic treatment (median 12 days, IQR 7-26). Treatment for proven IC was longer than expected (median 16 days, IQR 7-23), although we did not record information regarding disseminated disease and organ involvement. For isolated candidemia, recommended duration is 14 days after the first negative blood culture, with longer duration tailored to specific organ involvement (8,9,30).

Although this study shows unique data about neonatal antifungal use in England, there are a few limitations which bear mentioning. The study had a PPS format and was not designed to record the clinical details of each individual case, hence clinical information considered in the decision-making process to prescribe an antifungal may have been missed. As part of a bigger data set, gestational age and birthweight were not specifically recorded which would have been of use in the individual analysis of

this subgroup of patients. Neonatal use of nystatin was not considered in the final analysis, and may have led to even a higher number neonates and infants receiving antifungal prophylaxis.

In summary, the results of our 26 weeks PPS show that neonatal antifungal prophylaxis is commonly prescribed outside the recommendations by international guidelines ~~based on risk profiles~~; that fluconazole for treatment is under-dosed in neonates and infants; and that there is sporadic use of prophylactic liposomal amphotericin B. The development of a national Antifungal Stewardship (AFS) programme should take these observations into consideration to optimize antifungal prescription and preventing overuse of antifungals. The number of microbiologically-proven IC in the study group included in the PPS was low, 5.4%. It remains unclear if this indicates that a substantial number of neonates and infants received unnecessary antifungal treatment, or the effect aimed for by~~of~~ current prophylactic practices, ~~in this particular population~~ or if this low number is related to the fact no causative diagnosis could be made with the current diagnostic modalities.

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TABLES

Table 1. Characteristics of the neonates and infants receiving antifungal drugs as prophylaxis or treatment, stratified by age.

	Age 0-30 days (n= 191)	Age 31-90 days (n= 89)	Total (n= 280)
Age in days (median, IQR)	6 (3-13)	49 (40-69)	12 (4-40)
Gender, male (%)	102 (53.74)	53 (59.65)	155 (55.54)
Underlying condition			
Prematurity (%)	158 (84.582.7)	30 (34.933.7)	188 (68.967.1)
PID (%)	1 (0.5)	7 (8.17.8)	8 (2.9)
Malignancy (%)	2 (1.10)	3 (3.54)	5 (1.8)
Surgical condition (%)	16 (8.496)	25 (298.1)	41 (15.2114.6)
Other (%)	9 (54.87)	21 (23.64.4)	30 (11.2010.7)
Not Specified (%)	5 (2.6)	3 (3.4)	8 (2.9)
Admitted to Nneonatal Departmentward (%)	170 (89.0)	30 (33.7)	200 (71.4)
Admitted to NICU (%)	169 (99.488.5)	26 (86.729.2)	195 (97.569.6)

PID Primary Immunodeficiency (2 chronic granulomatous disease, 5 severe combined immunodeficiency and one unspecified); NICU Neonatal Intensive

Care Unit.

Table 2. Risk factors reported in the included neonates and infants stratified by prematurity and by ~~the risk factor~~ ELBW (birth weight <1000 g).

Number of Risk Factors	Non-premature Infants (%) n=92	Premature Infants (%) Non-ELBW n=93	Premature Infants (%) ELBW n=95	Total (%) n=280
0	17 (18.5)	6 (6.5)	0	23 (8.2)
1	16 (17.4)	47 (50.5)	4 (4.2)	67 (23.9)
2	29 (31.5)	26 (28.0)	10 (10.5)	65 (23.2)
≥3	30 (32.6)	14 (15.01)	81 (85.3)	125 (44.7)
~~Total~~	~~92 (100)~~	~~93 (100)~~	~~95 (100)~~	~~280 (100)~~

~~RF Risk Factors;~~ ELBW Extreme Low Birth Weight.

Table 3. Frequency of individual risk factors in neonates and infants receiving antifungal prophylaxis or therapy, stratified by prematurity and by ~~risk factor~~ ELBW (birth weight <1000 g).

Risk factors	Non-premature infants (%) n = 92 (%)	Premature infants (%)		Total (%) n = 280
		Non-ELBW n = 93	ELBW n = 95	
CVC	57 (62.0)	61 (65.6)	79 (83.2)	197 (70.4)
BSA	36 (39.1)	25 (26.9)	21 (22.1)	82 (29.3)
TPN	25 (27.2)	44 (47.3)	79 (83.2)	148 (52.9)
Abd surgery	21 (22.8)	13 (14.0)	16 (16.8)	50 (17.9)
Previous ICU	13 (14.1)	1 (1.1)	2 (2.1)	16 (~~7~~5.7)
Colonisation	5 (5.4)	3 (3.2)	3 (3.2)	11 (~~4~~3.9)
Steroid use	4 (4.4)	0	1 (1.1)	5 (1.8)
Others*	18 (19.6)	1 (1.1)	0	19 (6.8)

BSA Broad-spectrum Antibiotics; CVC Central Venous Catheter; TPN Total

Parenteral Nutrition; ICU Intensive Care Unit; ELBW Extreme Low Birth Weight. *Other: chemotherapy, immunosuppressive therapy, transplant, Graft vs Host Disease.

Table 4. Risk factors distribution in neonates and infants on antifungal prophylaxis at inclusion, stratified by prematurity and by ~~risk factor~~ ELBW (birth weight <1000 gr).

Number of Risk Factors	Non-premature infants (%) n=53 ~~(%)~~	Premature infants (%)		Total (%) N=223 ~~(%)~~
		Non-ELBW n=79 ~~(%)~~	ELBW n=91 ~~(%)~~	
0	6 (11.3)	4 (5.1~~0~~)	0	10 (~~3.5~~4.5)
1	9 (17.0)	44 (~~50~~55.7)	4 (4.4)	57 (~~20~~25.6~~3~~)
2	19 (35.8)	25 (31.6)	10 (11.0)	54 (~~19.3~~24.2)
≥3	19 (35.8)	6 (7.~~5~~6)	77 (84.6)	102 (~~36.4~~45.7)
~~Total (%)~~	~~53 (100)~~	~~79 (100)~~	~~91 (100)~~	~~223 (100)~~

~~RF Risk Factors;~~ ELBW Extreme Low Birth Weight.