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CONCISE COMMUNICATION

Variability in Antifungal and Antiviral Use in Hospitalized Children

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We analyzed antifungal and antiviral prescribing among high-risk children across freestanding children's hospitals. Antifungal and antiviral days of therapy varied across hospitals. Benchmarking antifungal and antiviral use and developing antimicrobial stewardship strategies to optimize use of these high cost agents is needed.

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Antimicrobial stewardship programs (ASPs) have primarily focused on the optimization of antibiotic therapy, whereas the use of antifungal therapy and antiviral therapy has been relatively ignored.[1] Antifungal and antiviral medications are often used for both treatment and prophylaxis for high-risk conditions like those in oncology and transplant patients. Furthermore, these agents are frequently associated with adverse drug effects, and they are costly. Hospitalized patients receiving these agents demand closer scrutiny to improve patient outcomes and potentially reduce hospital expenditures.[2] The 2016 Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America ASP guidelines recommend that stewardship should expand to include antifungal therapy.[3] Although prescribing trends of antifungal and antiviral drugs among children are relatively unknown, data suggest that their use is increasing.[4] The objectives of this study were (1) to characterize antifungal and antiviral prescribing for hospitalized children including comparison between high-risk and non–high-risk groups and (2) to describe variability of antifungal and antiviral prescribing among high-risk children to determine whether there are potentially important pediatric stewardship targets.

METHODS

We performed a retrospective cohort study of antifungal and antiviral prescribing in high risk hospitalized patients <18 years of age discharged between January 1 and December 31, 2015. Data were obtained from the Pediatric Health Information System database, a clinical and administrative database that contains inpatient demographic, diagnosis, and prescribing charge data from 47 freestanding children's hospitals across the United States. We a priori identified children considered to be at the highest risk for fungal or viral infections, including those coded with an All Patient Refined Diagnosis Related Group (APR-DRG; version 32) for oncology, bone marrow transplant, or solid organ transplant (Table 1).

Antifungal therapy included fluconazole, voriconazole, posaconazole, itraconazole, amphotericin, caspofungin, micafungin, anidulafungin, flucytosine, or terbinafine; antiviral therapy included charges for acyclovir, cidofovir, famciclovir, foscarnet, ganciclovir, oseltamivir, peramivir, ribavirin, rimantadine, valacyclovir, valganciclovir, or zanamivir. Data regarding age, race, gender, and receipt of any systemic antifungal or antiviral therapy were collected. Total days of antifungal or antiviral therapy (DOT) were standardized per 1,000 patient days. Summary statistics were constructed using frequencies and proportions for categorical data and medians and interquartile ranges (IQR) for continuous variables. Analyses were performed with SAS version 9.4 software (SAS Institute, Cary, NC) and Stata version 14.2 software (StataCorp, College Station, TX). This study was not considered human subject research by the Children's Hospital of Philadelphia Institutional Review Board.

RESULTS

In 2015, there were 784,240 inpatient discharges from the 47 hospitals included in our analysis; 35,211 (4.5%) of these patients were classified as oncology, bone marrow transplant, or solid organ transplant by APR-DRG. These high-risk patients were predominately male (56%) and Caucasian (63%), with a median age of 7.9 years (interquartile range [IQR], 3.6–13.6). Among this high-risk cohort, chemotherapy was the most common APR-DRG (54%), followed by major hematologic/immunologic diagnosis (21%), acute leukemia (7%), and bone marrow transplant (4%). Solid organ transplants including heart, lung, liver, and kidney accounted for approximately 3% of the total high-risk population.

Across all hospitalized patients, only 3% received antifungal or antiviral therapy. In comparison, among the high-risk patients, 19% received antifungal therapy and 12% received antiviral therapy. These high-risk patients received 50% of all antifungal DOT and 46% of all antiviral DOT despite comprising <5% of all hospital discharges. Overall, high-risk patients received 10 times more DOT than non–high-risk patients: 389 antifungal DOT per 1,000 patient days versus 30 DOT, and 244 antiviral DOT per 1,000 patient days versus 22 DOT, respectively.

The highest percentage of prescribed antifungals (% total DOT) occurred in patients hospitalized for bone marrow transplant (20%), chemotherapy (10.5%), and acute leukemia (6.5%). The highest percentage of prescribed antiviral (% total DOT)

TABLE 1. Antifungal and Antiviral Therapy Prescribing Among High-Risk Children in 47 Freestanding Children's Hospitals

		Antifungal Therapy		Antiviral Therapy	
All Patient Refined Diagnosis Related Group Title	Total Patients	Patients Prescribed, %	DOT per 1,000 days	Patients Prescribed, %	DOT per 1,000 days
Chemotherapy	18,884	12	257	5	70
Major hematologic/immunologic diagnosis except sickle cell crisis & coagulopathy	7,474	20	306	11	148
Acute leukemia	2,431	34	460	11	100
Bone marrow transplant	1,323	93	845	80	685
Nervous system malignancy	772	6	66	3	25
Other or prophylaxis for lymphatic/hematopoietic/other neoplasms	500	19	434	7	92
Musculoskeletal malignancy & related pathological fractures	488	4	36	4	45
Lymphoma, myeloma & nonacute leukemia	459	19	279	10	80
Major or prophylaxis for lymphatic/hematopoietic/other neoplasms	434	26	443	6	94
Kidney transplant	363	21	116	88	656
Heart &/or lung transplant	362	41	125	83	308
Kidney & urinary tract procedures for malignancy	336	4	41	0	0
Liver transplant &/or intestinal transplant	332	71	459	94	626
Radiotherapy	274	2	101	1	31
Lymphatic & other malignancies & neoplasms of uncertain behavior	264	10	131	5	62
Malignancy of hepatobiliary system & pancreas	115	9	151	3	11
Kidney & urinary tract malignancy	100	4	30	1	5
Ear, nose, mouth, throat, cranial/facial malignancies	93	9	110	2	23
Respiratory malignancy	78	6	55	8	36
Digestive malignancy	44	16	233	9	141
Uterine & adnexa procedures for ovarian & adnexal malignancy	39	0	0	0	0
Female reproductive system malignancy	26	15	250	4	73
Malignancy, male reproductive system	15	0	0	7	34
Uterine & adnexa prophylaxis for nonovarian & nonadnexal malignancy	5	40	159	0	0

NOTE. DOT, days of therapy.

was used for children hospitalized for bone marrow transplant (24.1%), heart and/or lung transplant (4.8%), and liver and/or intestinal transplant (4.2%). Children hospitalized with a bone marrow transplant were prescribed 845 DOT per 1,000 patient days of antifungal therapy (range, 664–1194) and 685 DOT per 1,000 patient days of antiviral therapy (range, 358–1,048) (Table 1).

Examination by drug class revealed total DOT rates among high-risk patients as follows: fluconazole, 135 DOT per 1,000 patient days; echinocandins, 127 DOT per 1,000 patient days; voriconazole, 84 DOT per 1,000 patient days; and amphotericin, 24 DOT per 1,000 patient days. Antiviral drugs targeting herpes viruses (ie, acyclovir, cidofovir, famciclovir, foscarnet, ganciclovir, ribavirin, valacyclovir, or valganciclovir) were prescribed 241 DOT per 1,000 patient days. The prevalence and total use of antifungal and antiviral therapy among high-risk patients varied widely across hospitals (Figure 1): antifungal use ranged from 75 to 608 DOT per 1,000 patient days and antiviral use ranged from 18 to 451 DOT per 1,000 patient days across centers. The correlation between AFT and AVT DOT rates across hospitals was 0.58 ($P < .001$).

DISCUSSION

We examined antifungal and antiviral use among a high-risk pediatric population admitted to 47 children's hospitals. Our results revealed (1) that this immune-compromised population accounts for most antifungal and antiviral prescribing in hospitals and (2) that variability in the use of these agents exists, even when examining this relatively homogenous cohort.

Variability in antimicrobial exposure has been observed in high-risk pediatric patients, though previous work has focused on antibacterial therapy.[5] Antifungal and antiviral agents

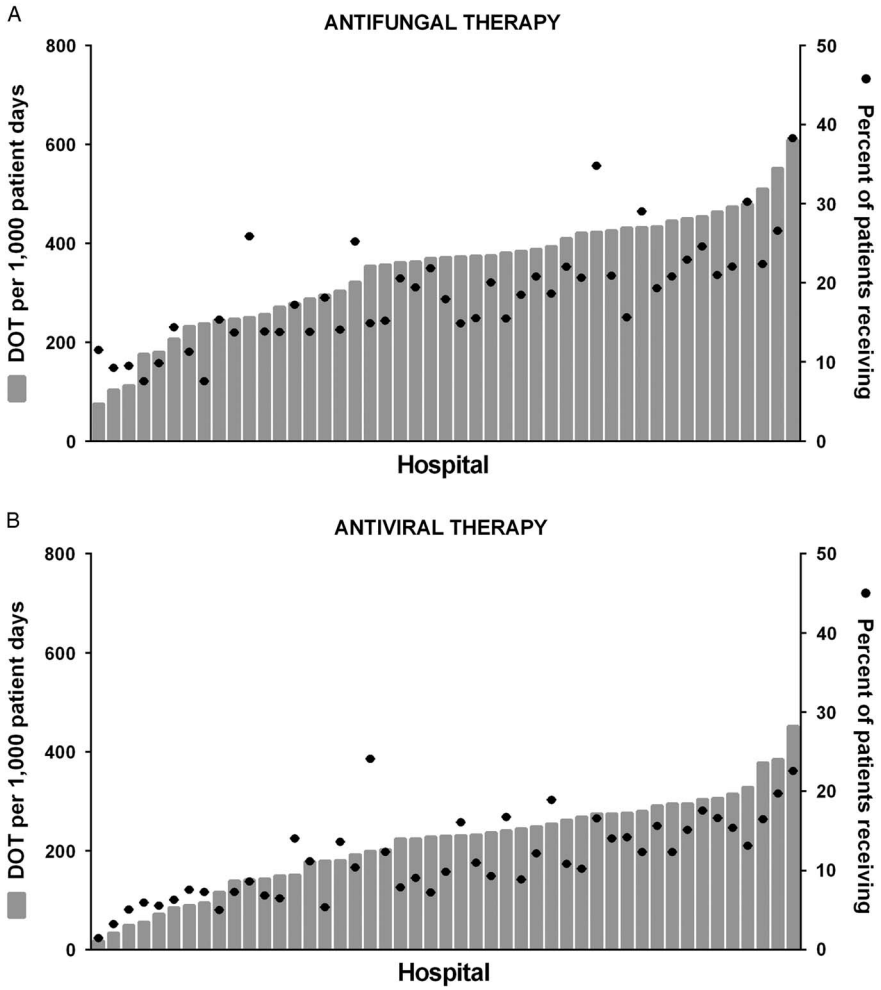

FIGURE 1. Variability in antifungal and antiviral therapy prescribing among high-risk children in 47 freestanding children's hospitals. Panel A: antifungal therapy. Panel B: antiviral therapy. Gray bars: left y-axis depicts DOT per 1,000 patient days. Black dots: right y-axis depicts percentage of patients who were prescribed therapy. DOT, days of therapy.

represent important stewardship targets because they (1) are often used for the treatment or prevention of relatively high-risk infections, (2) can be associated with a relatively high rate of adverse drug effects, (3) often require challenging therapeutic drug monitoring, and (4) are disproportionately costly relative to utilization.[2,6,7] Although guidelines have been developed to address antifungal and antiviral therapy in oncology and transplant patients,[8,9] our data demonstrate that prescribing variability exists and more can be done to standardize practice and minimize unnecessary use.

Antimicrobial stewardship programs have been shown to enhance judicious antibacterial prescribing practices, improve clinical outcomes, and reduce healthcare costs.[3] Antifungal stewardship can be effective by optimizing therapy and decreasing unnecessary use resulting in cost savings.[10] Currently, the available antifungal and antiviral therapies are limited, making stewardship critically important, as efforts to avoid the development of drug resistance and unnecessary adverse drug effects are needed. Invasive fungal and viral infections in the immunocompromised host can be devastating, resulting in high rates of morbidity and mortality. Selecting the most effective therapeutic agent, optimizing therapeutic dosing, and using therapeutic drug monitoring when available are all potentially effective points for stewardship interventions in this vulnerable population.

Our study has limitations. This study was limited to freestanding children's hospitals and may not be generalizable to other clinical settings. We were unable to discriminate between treatment and prophylaxis, and we did not assess appropriateness of use. Antifungals and antivirals were determined using charge data, not medication administration information. Nonetheless, antifungal and antiviral use varied broadly across hospitals, even when comparing use in similar, high-risk patients. Benchmarking antifungal and antiviral is an important step in identifying targeted stewardship strategies to enhance judicious antimicrobial prescribing.

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