Influence of drug class and healthcare setting on systemic antifungal expenditures in the United States, 2005–15

Margaret A. Fitzpatrick, M.D., M.S., Department of Veterans Affairs, Center of Innovation for Complex Chronic Healthcare, Edward Hines Jr. VA Hospital, Hines, IL, and Department of Medicine, Division of Infectious Diseases, Loyola University Chicago Stritch School of Medicine, Maywood, IL.

Katie J. Suda, Pharm.D., M.S., Department of Veterans Affairs, Center of Innovation for Complex Chronic Healthcare, Edward Hines Jr. VA Hospital, Hines, IL, and Department of Pharmacy Systems, Outcomes and Policy, University of Illinois at Chicago College of Pharmacy, Chicago, IL.

Charlesnika T. Evans, Ph.D., M.P.H., Department of Veterans Affairs, Center of Innovation for Complex Chronic Healthcare, Edward Hines Jr. VA Hospital, Hines, IL, and Department of Preventive Medicine, Institute for Public Health and Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL.

Robert J. Hunkler, M.B.A., QuintilesIMS, Professor Relations, Fountain Hills, AZ.

Frances Weaver, Ph.D., Department of Veterans Affairs, Center of Innovation for Complex Chronic Healthcare, Edward Hines Jr. VA Hospital, Hines, IL, and Department of Public Health Sciences, Loyola University Chicago Stritch School of Medicine, Maywood, IL.

Glen T. Schumock, Pharm.D., Ph.D., M.B.A., Department of Pharmacy Practice, University of Illinois at Chicago College of Pharmacy, Chicago, IL.

Purpose. Overall and specific class trends in systemic antifungal expenditures in various U.S. healthcare settings from 2005 through 2015 were evaluated.

Methods. Systemic antifungal expenditures from January 1, 2005, through December 31, 2015, were obtained from the QuintilesIMS National Sales Perspective database, which provides a statistically valid projection of medication purchases from multiple markets throughout the United States. Summary data for total antifungal expenditures over the entire period are reported, as are growth and the percentage change in expenditures from one year to the next. Expenditures were also assessed specifically by year, class, and healthcare setting. Expenditure trends over the study period were assessed using simple linear trend regression models.

Results. Overall expenditures for the 11-year period were $9.37 billion. The greatest proportion of expenditures occurred in nonfederal hospitals (47.2%) and for triazoles (57.6%). From 2005 through 2015, total expenditures decreased from $1.1 billion to $894 million (−18.8%, p = 0.09); however, expenditures in clinics and retail pharmacies increased (202%, p < 0.01, and 13.8%, p = 0.04, respectively), a trend most pronounced after 2012. Expenditures for flucytosine also increased (968.1%, p < 0.01), particularly in clinics where there was a dramatic 6,640.9% increase (p < 0.01).

Conclusion. From 2005 through 2015, an increase in systemic antifungal expenditures was observed in community settings, despite an overall decrease in total antifungal expenditures in the United States. Large increases in flucytosine expenditures were observed, particularly in the community.

Keywords: antifungal agents, health expenditures, prescription drugs

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Antimicrobial resistance has become a global public health crisis. A recent comprehensive report commissioned by the Wellcome Trust and the U.K. Department of Health estimated that if left unchecked, antimicrobial resistance could result in an estimated 10 million deaths annually and a cumulative global cost of $100 trillion by 2050. Much emphasis has been placed on curbing antibiotic use in both community and hospital settings to decrease antimicrobial resistance and toxic effects, primarily with national initiatives to decrease inappropriate antimicrobial use through antimicrobial stewardship programs. Inappropriate antifungal use also contributes to antimicrobial resistance, with concomitant increased morbidity and mortality from infections with resistant fungi and unnecessary toxicity from antifungal medications. The prevalence of invasive fungal infections, long felt to be problematic only
in immunocompromised or oncology patients, has been increasing over the past 20 years, with **Candida** species becoming one of the most common causative pathogens of healthcare-associated bloodstream infections in many U.S. hospitals. Estimates of the proportion of inpatient systemic antifungal use that is inappropriate are scarce and variable, ranging from 13% to 70%. While few studies have specifically evaluated the impact of decreasing inappropriate antifungal use, most have reported cost containment or cost savings and decreased antifungal resistance without a significant impact on clinical outcomes. As a result, attentions are now increasingly focused on antifungal use, costs, expenditures, and stewardship.

Systemic antiinfectives were 1 of the top 3 categories of drug expenditures in nonfederal hospitals in 2014 and 2015. A significant proportion of antibiotic expenditures occurs in the outpatient and community settings, and systemic antifungal expenditures may also vary by healthcare setting. Empirical and prophylactic therapy accounts for the majority of inpatient antifungal use; however, no studies have comprehensively evaluated systemic antifungal use in outpatient or community settings. Identifying specific antifungal classes and healthcare settings associated with increased expenditures can help direct future studies to develop targeted, high-impact antifungal stewardship interventions. Furthermore, the financial effect of increased use of newer and more expensive antifungals with fewer adverse effects, such as triazoles and echinocandins, has yet to be explored, nor has the impact of recent dramatic price increases for older drugs such as flucytosine been evaluated. In this study, we assessed overall trends as well as specific class and agent trends in antifungal expenditures in various U.S. healthcare settings from 2005 through 2015.

### Methods

**Study design and setting.** This retrospective study examined systemic antifungal expenditures in the United States from January 1, 2005, through December 31, 2015. Antifungal expenditure data were extracted from the QuintilesIMS National Sales Perspective (NSP) database. The NSP captures 70% of all prescription medication purchases, with data then extrapolated to a statistically valid projection of 99% of all prescription medication purchases in the United States. Although this database provides a population-level view of drug expenditures, it does not provide information on drug use or the number of prescriptions filled. Nonsystemic antifungal medications (i.e., topical nystatin, terbinafine, and ketoconazole) were excluded because we wanted to focus on expenditures for systemic oral and intravenously administered antifungals. Antifungals were stratified by class (polyenes, triazoles, flucytosine, and echinocandins) according to the QuintilesIMS Uniform System of Classification. All antifungal agents in each class were approved by the Food and Drug Administration (FDA) before December 31, 2006, with the exception of isavuconazole, a triazole antifungal approved by FDA in March 2015.

**Healthcare settings.** Expenditures from retail community pharmacies, mail service pharmacies, clinics, nonfederal hospitals, and other nonretail pharmacies were included. Retail pharmacies included standalone chain and independent stores, mass merchandisers, and food and convenience stores with a licensed pharmacy. Mail service pharmacies were licensed mail-order pharmacies affiliated with either private sector or federal facilities. Clinic expenditures included medications administered directly in the clinic and encompassed primary care and specialty physician offices and urgent care centers. Nonfederal hospitals included licensed inpatient, specialty care, and rehabilitation hospitals that were not federally owned. Other nonretail settings included federal facilities (e.g., Public Health Service and other federal hospitals, U.S. ships at sea) and other nonhospital facilities, such as long-term care facilities. Of note, beginning in 2014, QuintilesIMS did not include data from the Veterans Affairs healthcare system.

**Statistical analysis.** Summary data for total antifungal expenditures over the entire period are reported, as are growth and the percentage change in expenditures from one year to the next. Expenditures were also assessed specifically by year, class, and healthcare setting. Data were adjusted for inflation using the Consumer Price Index from the U.S. Department of Labor, Bureau for Labor Statistics, with all expenditures reported in 2015 dollars. Expenditure trends over the study period were assessed using simple linear trend regression models with an alpha level of significance set at 0.05. Stata, version 14 (StataCorp, College Station, TX), was used for statistical analysis.
Results

Overall expenditures for antifungals in all care settings for the 11-year study period were $9.37 billion. Table 1 shows annual total expenditures and annual expenditures stratified by healthcare setting. Table 1 also shows growth in expenditures (both overall and stratified by healthcare setting) over the 11-year study. As expected, the greatest percentage of antifungal expenditures occurred in nonfederal hospitals, which accounted for almost half of all expenditures ($4.4 billion, 47.2%), followed by retail (29.1%), other nonretail (13.3%), clinics (6.2%), and mail-order pharmacies (4.3%). Overall, annual total antifungal expenditures decreased each year from 2005 through 2008, remained relatively constant until 2013, and then increased slightly in 2014 and 2015. This represented an overall 18.8% decrease from $1.1 billion to $894 million between 2005 and 2015 ($p = 0.09). While expenditures in nonfederal hospitals significantly decreased (–46.5%, $p < 0.01), expenditures in clinics (202% $p < 0.01) and retail pharmacies (13.8%, $p = 0.04) significantly increased.

There was also significant variability in antifungal expenditures by class. Overall, triazoles accounted for the greatest proportion of expenditures ($5.4 billion, 57.6% of overall total expenditures), followed by echinocandins ($2.4 billion, 26.4%), polyenes ($1.3 billion, 14.1%), and flucytosine ($181 million, 1.9%). From 2005 through 2015, significant decreases were observed for expenditures for echinocandins (–59%, $p < 0.01) and polyenes (–38.6%, $p < 0.01), while expenditures increased by 10.8% for triazoles ($p = 0.03) and by 96.8% for flucytosine ($p < 0.01) (Figure 1). Even more pronounced were trends in the annual growth (percent change) in expenditures for each study year stratified by class (Figure 2). Growth in annual flucytosine expenditures steadily increased from 2005 through 2010, followed by stabilization until 2014–15 when there was a 126.1% increase (Figure 2).
We next performed a more detailed analysis of antifungal expenditures for specific classes stratified by healthcare setting. Figure 3 demonstrates how healthcare setting influenced antifungal expenditures by drug class. Retail and mail-order settings were dominated by triazole expenditures (97.4% and 95.3% of expenditures, respectively). Triazoles also comprised the greatest proportion of expenditures in clinics (64.1%), though echinocandins (18.8%) and polyenes (14.0%) made substantial contributions. Nonfederal hospital and other nonretail settings encompassed a mix of expenditures for all classes. Because clinic expenditures increased by the greatest proportion during the 11-year study, we chose to perform an additional analysis of expenditures by drug class within the clinic setting. Clinic expenditures for each antifungal class significantly increased during the study period, and this trend was most pronounced after 2012 (Table 2). Changes in annual expenditures for flucytosine widely fluctuated in clinics, with a large increase in expenditures from 2007 through 2009, a remarkable decline from 2010 through 2012, and another notable increase from 2012 through 2015. Overall, there was a dramatic 6,640.9% increase in flucytosine expenditures in the clinic setting from 2005 through 2015 (Table 2).

**Discussion**

In 2014, systemic antimicrobials were one of the top categories of drug expenditures in nonfederal hospitals. Antifungals have historically lagged behind antibacterial and antiviral drugs in overall expenditures; however, in the past decade, antifungals have garnered increasing attention as both the frequency of invasive fungal infections (IFIs) and the number of available drug classes and agents to treat IFIs have increased.

Further, with the availability of newer antifungal agents with fewer adverse effects, there has been an increased emphasis on empiric antifungal use. The clinical and economic burdens of preventing and treating IFIs in hospitals are particularly high due to increased mortality, length of stay, and costs related to IFIs. Despite this increasing attention to IFIs and antifungal use, few large-scale studies of systemic antifungal expenditures have been performed, and most have been conducted outside the United States or focused only on hospitalized patients.
In this study, we analyzed systemic antifungal expenditures from all healthcare settings in the United States and observed an overall trend toward decreased expenditures over the 11-year period, though the decrease was not statistically significant. Overall expenditures may have decreased due to increased generic availability of frequently used expensive brand agents such as voriconazole and echinocandins or because of antimicrobial stewardship programs that promote the judicious use of antifungals. It is important to note that after expenditures decreased and then remained constant from 2005 through 2013, they began to increase again in 2014 and 2015. This may represent the beginning of an upward trend in systemic antifungal expenditures that may be related to recent price increases for antifungals (e.g., flucytosine) or the increased use of more-expensive antifungal agents (e.g., posaconazole). As an example of the latter, clinical guidelines now recommend posaconazole over other agents for primary prophylaxis of invasive mold infections in certain high-risk patient groups. Only 1 prior study evaluated U.S. antifungal expenditures on a scale equivalent to that used in our study. Desai et al. examined Medicaid data for systemic and topical antifungals between 1991 and 2009 and found that utilization remained constant but antifungal expenditures increased from $93.87 million to $143.76 million. The difference in these results from our study may be related to the inclusion of topical antifungal agents (which accounted for the majority of prescriptions), the exclusive focus on the Medicaid population, and an earlier time period.

Furthermore, we observed interesting trends in antifungal expenditures by care setting and drug class. Substantial growth occurred in expenditures in the community setting, with clinic expenditures increasing by 202% from 2005 through 2015. Much of this growth was in expenditures for echinocandins and polyenes, and drugs in both of these classes are administered intravenously. This may suggest a growing trend in outpatient parenteral antifungal therapy administered outside of hospital settings, such as in hematology-oncology or infectious diseases clinics with associated infusion centers. As expected, triazoles represented the greatest proportion of expenditures overall and in each study year, a finding similar to prior studies conducted outside of the United States.

Figure 2. Percent change in antifungal expenditures for each study year stratified by drug class.
for echinocandins in every setting except clinics. These discordant results may be related to the fact that we included more diverse care settings (not just hospitals) and a longer time period (11 years versus 4 years for the Garey et al. study).

Perhaps the most striking class-specific trend in this study was that clinic expenditures for flucytosine increased by a staggering 6,641%. Flucytosine, a pyrimidine analog introduced in 1973, is used infrequently but is a key component of treatment for cryptococcal disease. Since 2009, the U.S. price of flucytosine has steadily increased, with a 306% increase observed in the past 2 years and a nearly 100-fold higher price now in the United States compared with Europe. As of January 2016, there was only 1 FDA-approved pharmaceutical supplier of flucytosine, Valeant Pharmaceuticals. Because the incidence of cryptococcal disease is decreasing in the United States, the use of flucytosine has likely decreased or at least remained constant; thus, the increase we observed in flucytosine expenditures was likely the direct result of price increases. Although expenditures for flucytosine remained a small proportion of the total antifungal expenditures in our study, the dramatic increase in expenditures we observed raises concern for greater issues of access to antimicrobials and appropriate pricing for older generic drugs.

This study had several limitations. Expenditures may not represent use or actual consumption of antifungal agents. Previous studies have demonstrated good correlation between antimicrobial purchasing data and dispensing data for hospital settings; however, we could not draw conclusions regarding use or consumption based on our analysis. Furthermore, our data set did not capture expenditures for systemic antifungals acquired without a prescription, though we anticipate that nonprescription use of systemic antifungals is likely to be low in the United States. Finally, for 2014 and 2015, QuintilesIMS did not include expenditures from the Veterans Affairs healthcare system, which may have led to an underestimation of expenditures for those years in other nonretail settings.

Despite these limitations, this study provides a comprehensive, national assessment of trends in antifungal expenditures over 11 years that we feel is highly valuable to those involved in public health, pharmacy, hospital administration, and antimicrobial stewardship. Although we identified an overall decrease in total

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**Figure 3.** Antifungal expenditures for each drug class as a percentage of overall total antifungal expenditures in each healthcare setting from 2005 through 2015.
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antifungal expenditures, expenditures in the community setting increased substantially, as did expenditures for specific agents (e.g., flucytosine). This suggests a need for further studies on the indications for and appropriateness of antifungal prescribing in community settings to develop strategies to promote judicious and cost-effective antifungal use, particularly for parenteral antifungals.

Conclusion

From 2005 through 2015, an increase in systemic antifungal expenditures was observed in community settings, despite an overall decrease in total antifungal expenditures in the United States. Large increases in flucytosine expenditures were observed, particularly in the community.

Disclosures

This work was supported by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Health Services Research and Development Service Postdoctoral Fellowship Award (grant number TPR 42-005), awarded to Dr. Fitzpatrick. The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the U.S. government. The statements, findings, conclusion, views, and opinions contained and expressed here are not necessarily those of QuintilesIMS or any of its affiliated or subsidiary entities. Dr. Schumock has served as a consultant for AbbVie and Baxter and a speaker for Astellas. Mr. Hunkler is an employee of QuintilesIMS. The authors have declared no other potential conflicts of interest.

References


Table 2. Trends in Antifungal Expenditures and Annual Growth by Class in the Clinic Setting

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| *p < 0.05, estimated from simple linear regression analysis of trend over time in annual growth by class.

*All expenditures adjusted for inflation and reported in 2015 dollars. All expenditures reported in dollars.

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ANTIFUNGAL EXPENDITURES