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Commentary

Antifungal stewardship: Still catching up? Commentary on "Variability in antifungal stewardship strategies among Society for Healthcare Epidemiology of America (SHEA) Research Network facilities"

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Antimicrobial stewardship programs (ASPs) are vital to limiting antimicrobial resistance, optimizing outcomes, and ensuring appropriate use of resources in the treatment and prevention of infectious diseases. To achieve these results, ASPs have incorporated not only drug-based stewardship (ie, reducing inappropriate and/or unnecessary antimicrobial use) but also disease-based strategies that aim to improve outcomes by optimizing therapy[1] and diagnostic stewardship strategies.[2] Much of this robust, multifaceted stewardship has been focused on antibacterial agents and bacterial infections. The breadth of antifungal stewardship performed by ASPs is not well described.

In this issue of *Infection Control and Hospital Epidemiology*, Fitzpatrick et al[3] attempt to characterize antifungal stewardship practices at institutions with established ASPs. In 2018, they surveyed the lead ASP pharmacists or physicians at 111 institutions in the SHEA Research Network, a consortium of hospitals collaborating on multicenter research in healthcare epidemiology.[3] In contrast to past surveys of antimicrobial stewardship practices, the investigators specifically focused their 18 questions on antifungal stewardship. Of the 45 institutions that responded, 65% were academic medical centers, and 22% were community or private hospitals. In addition, 73% of responding institutions care for hematopoietic stem cell patients and 80% of institutions care for solid-organ transplant recipients. Given the institutional makeup, it is not surprising that most of the responding institutions have large ASPs (60% with >5 members) or that 96% of institutions described using some sort of antifungal stewardship.

Drug-based practices such as prior authorization or restriction were in place at 64% of institutions, and prospective audit and feedback were reported by 73% of responding institutions. It is not clear which antifungals were the target of these practices. Only approximately half of these institutions reported having internal guidelines available for the treatment of invasive fungal infections such as candidemia. While 80% of the institutions reported offering antifungal susceptibility testing, only 60% reported incorporating susceptibilities into therapeutic interventions. The survey revealed that 69% of these institutions offered *Aspergillus* galactomannan antigen testing, 51% offered (1,3)-β-D-glucan testing, and 33% offered molecular diagnostic testing. The survey did not ascertain whether ASPs utilized such non–culture-based diagnostic tools to facilitate antifungal stewardship. Only 64% of the institutions periodically reviewed aggregate antifungal use. The survey was limited in its breadth to 45 centers and depth in that several questions remain regarding the specifics of interventions and practices. Like all surveys, this survey was also limited by accuracy concerns; respondents may interpret a question differently than intended. Despite these limitations, the results of the survey do frame current antifungal stewardship practices as rather limited.

Why is antifungal stewardship necessary? Compared to antibacterial agents, the current antifungal armamentarium is relatively miniscule. For the treatment of the most common invasive fungal infection, candidiasis, essentially 3 options are currently available: fluconazole, an echinocandin, or amphotericin B. As a result, developments like echinocandin-resistant *C. glabrata*[4] or the new species *C. auris* (of which ~90% are resistant to fluconazole and 30% are resistant to amphotericin)[5] represent enormous therapeutic challenges. Options are even more limited in the treatment of mold infections. For example, the emergence of panazole-resistant invasive aspergillosis leaves lipid amphotericin B products as preferred options.[6] As such, it is imperative that current therapies are utilized judiciously and appropriately.

What should our targets for antifungal stewardship be? The core tenets of antibacterial stewardship translate well to antifungal pharmacotherapy. First, we should start optimal therapy (in terms of agent and dose) quickly in patients with confirmed disease or with high suspicion of disease. Second, we should promptly discontinue empiric therapy if infection is shown to be unlikely. Third, we should utilize speciation and susceptibility testing to de-escalate when possible. Fourth, we should promote appropriate durations of therapy. These concepts should be embedded into institutional guidelines that not only standardize optimal therapeutic strategies but also educate to inappropriate use (eg, routine treatment of candiduria). In candidemia, these and other components of optimal therapy have been successfully incorporated into scoring tools and bundles. ASPs can facilitate such processes by identifying and intervening themselves or by facilitating consultation with infectious diseases specialists and by developing templates to ensure consistent practice. Restriction, by prospective

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audit and feedback and/or prior authorization, of broad-spectrum agents (at a minimum) is a tried-and-true principle of antibacterial stewardship that translates to antifungals.[7]

Two patient populations warrant additional attention. One is the use of early antifungals in intensive care units (ICUs). In 1 retrospective audit, almost 90% of antifungal usage in surgical ICUs was "pre-emptive" or "empiric," that is, not for proven infection.[8] However, recent randomized, controlled trials have failed to identify a patient population for whom such early therapy improves survival. Although the search continues for an optimal strategy to identify patients who would benefit from early antifungals, ASPs can point to these trials as clear, convincing evidence that broad, indiscriminate use is not supported by evidence.[9] In cases in which early antifungals are initiated due to a perceived high probability of candidiasis, programs can utilize the high negative predictive value of nonculture diagnostic adjuncts, such as (1,3)-β-D-glucan and T2 magnetic resonance, to quickly rule out invasive candidiasis and enable safe discontinuation of unnecessary antifungal therapy.[10]

Antifungal stewardship in solid-organ transplant and hematology patients is another priority. In such patients, it is well recognized that appropriate antifungal prophylaxis can significantly reduce the development of invasive fungal infections and even reduce infection-associated mortality.[11] In centers with transplant and hematology services, prophylactic use may constitute the vast majority of broad-spectrum antifungal consumption. However, not all patients with such diseases require prophylaxis and not all centers have the same epidemiology of infection. In populations like lung transplant recipients, the risk factors for infection, spectrum of prophylaxis required, and optimal duration remain largely undefined.[12] In the case of hematologic malignancies, novel therapeutic options, such as ibrutinib[13] and chimeric antigen receptor-modified T-cell therapy,[14] have confused our historical classification of patients at risk. As such, it is essential for ASPs to collaborate with their specialist colleagues to remain abreast of developments in chemotherapeutic, surgical, and immunosuppressive approaches so that prophylactic strategies are continually re-evaluated. Ideally, periodic surveillance and review of infections should be performed to update institutional epidemiology to identify opportunities for refinement.

In conclusion, Fitzpatrick et al provide important information regarding the current status of antifungal stewardship. Even in well-established ASPs, robust antifungal stewardship does not yet appear to be a priority. Given limited therapeutic options and the high associated morbidity and mortality of invasive fungal infections, it should be.

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