Review Article

Antifungal stewardship: What we need to know

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Abstract

Antimicrobial stewardship refers to a well-coordinated program which promotes the scientific and rational use of antimicrobials, reduces the chances of drug resistance and improves patient outcomes. A comprehensive English language literature search was done across multiple databases (PubMed, EMBASE, MEDLINE and Cochrane) for the period 1990–2022, revealing a large volume of reports of growing resistance to established antifungal therapies, against a backdrop of irrational and unscientific prescriptions. As a result of this, antifungal stewardship, a new kid on the block, has recently garnered attention. This review article is an attempt to summarise the basic concept of stewardship programs, highlighting the dire need to implement the same in the present situation of antifungal resistance and treatment failure.

Key words: Antimicrobial, antifungal, stewardship, update

Introduction

Antimicrobial stewardship is defined as a continued effort by a healthcare institution to optimise antimicrobial use for improving patient outcomes, ensuring a cost-effective therapy, and reducing adverse consequences. The benefits of antimicrobial stewardship programmes are well documented and include improved patient outcomes, reduced *Clostridium difficile* infections, and optimised resource utilisation across the continuum of care. An efficiently structured programme, while ensuring optimal antifungal usage, also curtails the undesired outcomes of antifungal use including toxicity and emergence of resistant fungi.[1–3] It potentially reduces the cost of antifungal therapy by limiting any drug overuse and encouraging a timely switch from intravenous to oral antifungals.[4]

In a systematic review published by a group of authors from the United States, it was mentioned that antifungal stewardship interventions can improve performance measures and decrease the consumption of antifungal drugs.[5] Although the review did not detect improvements in clinical outcomes, significant adverse outcomes were not reported. The principles of antifungal stewardship factor into consideration the range of antifungal activity of the drug, pharmacokinetic and pharmacodynamic properties of the drug, treatment duration and the drug administration route. The programme aims to ensure optimal selection of antimicrobials with improved doses and length of therapy.[6] Antifungals in clinical usage are divided into three primary classes: polyenes, triazoles and echinocandins. Polyenes have broad-spectrum antifungal activity against yeasts and moulds. The triazole group of drugs have varied susceptibility and are agent specific. Echinocandins will work against the most medically important species of *Aspergillus* and *Candida*.[7]

Even as antifungal stewardship shares common goals with antimicrobial stewardship like refining drug usage, streamlining appropriate drug prescription and preventing long-term resistance, there are fundamental differences between both:

- Infection sources: Bacterial infections are commonly transmitted between patients, but the patient-to-patient transmission of fungal infections is comparatively rare and infection sources include endogenous foci, environment, and hospital devices.

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- Available clinical data from antibiotics is more widely available, as compared to antifungals such that, medical graduates are more familiar with antibiotic resistance patterns.
- Antifungals have higher systemic toxicity levels and monitoring drug toxicity is an important part of antifungal stewardship programmes.
- Fewer tools are available for diagnosis and monitoring of fungal infections, and antifungal susceptibility testing. Most centres are not equipped with these tools.
- Therapeutic drug monitoring of antifungal agents is less developed.
- Generalised knowledge and information regarding antifungal usage and resistance are less common among clinicians and hospital staff.[8]

Need for antifungal stewardship

With the world battling the notorious COVID-19 nuisance, there has been a remarkable escalation in the number of diseases and deaths with coronavirus-related mucormycosis. Overall, between December 2019 to April 2021, 71% of the global cases of mucormycosis in COVID-19 have been attributed to India. Affected patients most likely had a combination of potent predisposing factors such as uncontrolled diabetes, unregulated steroid use, immunosuppression and prolonged ICU stays.[9] This underscores the need for delving into drug (steroids and antifungals) stewardship programmes, with an aim to prevent and combat unwarranted systemic mycoses.

The development of a new antimicrobial drug requires years of research. With the rampant misdirected use of antimicrobials including antifungals, the rate of increasing antifungal resistance has vastly outpaced the pharmacological development of newer antifungals. For clinicians, antifungal resistance is progressively becoming a serious cause for concern. Antifungals are one of the most prescribed over-the-counter medications. Many such prescriptions are deemed unnecessary, and a lot of antifungal prescriptions are overkill.

There is insufficient available data on the toxicities and pharmacological interactions of antifungals due to poor awareness about antifungal usage. Widespread antifungal administration as over-the-counter drugs by pharmacists and drugstore staff fuels the likelihood of antifungal abuse and subsequent resistance. With a general increase in the proportion of the immunosuppressed population, due to multiple factors including anticancer therapy, organ transplantation, immunosuppressant use and prevalence of HIV-AIDS amongst others, the dependence on antifungals has increased. In most conditions, antifungals are actively used for both prophylaxis and treatment of infections.[10]

In the past few decades, there has been a steady and rapid increase in the incidence of invasive *Candida* infections, especially in patients undergoing chemotherapy for conditions including bone marrow transplantation.[11] Patients who are under anticancer therapy are increasingly exposed to azoles for both chemotherapy and prophylaxis. Prophylactic fluconazole is widely used for neutropenic and non-neutropenic patients in surgical intensive care units.[12] In a five-year multicentric study in Germany, Gross *et al.*[13] reported that primary consumers of antifungals for therapeutic and prophylactic use were surgical and medical intensive care units (ICU), and oncology departments.

With a steep and prominent rise in the incidence of antifungal resistance, the Centers for Disease Control (CDC) listed fluconazole-resistant *Candida* species as a serious threat in a report published in 2013.[14]

Cleveland *et al.*[15] observed an increase in fungal isolates that were also resistant to echinocandins, prominently seen with the *Candida* species, especially *Candida glabrata*.

In a study of patients with candidemia, less than 40% of patients with fluconazole susceptible isolates, who were treated with echinocandins, were de-escalated to fluconazole.[16]

Among isolates collected from critically ill patients in ICUs and among immunocompromised patients, the most common isolate is *Candida* species followed by invasive aspergillosis.[17]

In patients with serious comorbidities, such as haematological stem cell transplant recipients, candidiasis does not have a benign course, and invasive candidiasis is reported to have a 12-month mortality rate of 67%, similar to a 75% morbidity rate seen in invasive aspergillosis. A global increase has also been reflected in India with the rise in the incidence of invasive mould infections like mucormycosis in patients with uncontrolled diabetes.[18]

Now more than ever in the present pandemic, the risks of antifungal resistance are imminent among vulnerable populations. With the rise in mucormycosis among critically ill COVID19 patients and widespread unregulated drug use, growing resistance in the treatment of invasive fungal infections is likely to develop.

Oberoi *et al*[19]. reported fluconazole as the most frequently prescribed drug at a centre in India with a statistically significant correlation between yearly fluconazole use and increased isolation of *Candida* (other than *Candida albicans*). Emergence of azole resistance in *Aspergillus fumigatus* and *Aspergillus flavus* has also been noted in India.[20,21] The incidence of inappropriate antifungal usage runs high at 74% (tertiary care centre in Thailand, Sutepvarnon *et al.*[22]). The common reasons for inappropriate fungal prescriptions are incorrect dosing, needlessly prolonged therapy, and incorrect clinical indications. For instance, multivariate analyses have demonstrated that

frequently inappropriate antifungal prescriptions are for *Candida* species isolated from urine.[21,22]

A majority of these cases are due to contamination of the samples by *Candida* species, and often antifungal therapy has no benefit in the absence of signs of UTI (urinary tract infections). When *Candida* sp. is isolated from urine samples, it must be accompanied by signs and symptoms of urinary tract infection, as a suitable indication for antifungal therapy.[23] There is a significant need for the de-escalation of empirical antifungals. Often, a reluctance to de-escalate empirical therapy is seen among clinicians, even after seriously ill patients show improvement with broad-spectrum treatment.

Antifungal resistance to day-to-day antifungals has been reported in several common fungal species, which are as follows:

- Amphotericin B resistance in *Aspergillus* species.[24]
- Resistance of *Aspergillus fumigatus* to azoles.[25]
- Emergence and increased incidence of multidrug-resistant *Candida auris*.[24]
- Resistance of *Non-albicans Candida sp.* to azoles with development of multidrug transporting efflux pump proteins.[26]
- Resistance of *Trichophyton sp.* to azoles with a mutation in the azole target gene, in the context of reports of azole-resistant dermatophyte infection.[27]
- Resistance of *Trichophyton rubrum* and *Trichophyton mentagrophytes* to terbinafine.[28,29]
- Resistance of *Trichophyton rubrum* and *Trichophyton mentagrophytes*, to most antifungals except Echinocandins and liposomal amphotericin, with the mechanism of biofilm formation.[30]

Fungal epidemiology and resistance vary regionally, and in the making of an effective antifungal stewardship programme (AFSP) these factors must be considered such that the programme is designed at a local and institutional level.[6] Of special note is the sweeping number of patients with superficial dermatophytosis in India. Growing resistance to commonly prescribed antifungal agents including azoles has been noted over the last 2 decades. Superficial dermatophytosis affects almost 20–25% of the global population.[31] Reported rates of azole resistance are almost 19% in parts of the world.[31,32] With such alarming rates of incidence and prevalence of drug-resistant infections, other countries have developed antifungal susceptibility testing guidelines such as the European Committee on Antibiotic Susceptibility Testing.[33,34]

In a tropical country like India with high infection rates, resistance is a cause for deep consternation and effective antifungal susceptibility may be instrumental in preventing resistant infections of epidemic proportions, which are of deep concern to the dermatologist. Misuse of over-the-counter antifungal drugs is also frequently seen with monilial vulvovaginitis and monilial balanoposthitis. Ferris *et al.*[35] showed that among self-diagnosed patients with vulvo-vaginal candidiasis who self-medicated with antifungals, only 33.7% actually had the infection.

With the appropriate use of antifungals, the following changes may be observed:[36,37]

- An increase in the efficacy of these drugs since the minimum inhibitory concentration (MIC) for causative organisms will not increase.
- Lower MICs reduce the need for prolonged therapy, which decreases the cost of therapy and minimises drug toxicities.
- With effective antifungal stewardship programmes, most infections can be controlled with oral medication, and intravenous therapy is minimally used. This reduces the cost of therapy and decreases drug-related toxicities.
- Restriction of the potential for the emergence of resistant fungal organisms.
- Studies involving a limited number of patients suffering from Candidemia, have reported improved mortality rates with the implementation of antifungal stewardship programmes.
- Reduction of expenditure in antifungal therapy has been noted with stoppage of treatment on time and switching to oral therapy. The reduction in expenditure was 32% in the first year and 33% in the second year of intervention.

Difficulties in implementation of antifungal stewardship programme

- For a large part of India's population, points of delivery of healthcare are primary and community healthcare centres where antifungals are generously prescribed. These basic health care centres lack the infrastructure for simpler tests like fungal culture and advanced monitoring with MIC testing and therapeutic dose monitoring. The conventional diagnostic methods for fungal infections in Indian healthcare centres have very low sensitivity. Biomarker tests for fungal infections have very limited availability in Indian laboratories.[27] An assessment of antifungal stewardship programmes in England observed that, in a majority of institutions, the shortcomings and hurdles in the programme implementation, were the unavailability of rapid diagnostics, the lack of support of clinical teams and a shortage of lab resources. Frequently, the reasons stated for not having antifungal stewardship programmes were a lack of time, the requirement of available expertise, a perceived lack of importance including indifference among most clinicians. Overall, the largest limiting factor assessed in their study was the resources required to execute the programme. Regardless of clinical expertise levels, adherence to guidelines is often very poor.[37,38]

- Munoz *et al.*[39] stated that the need for effective antifungal stewardship programme is based mainly on the difficulty of appropriate real-world use of antifungals, even among clinicians with experience and the roadblocks include poor sensitivity of microbiological tests for fungal detection, frequently elusive clinical picture of fungal infections and the morbidity risk seen with delay in starting therapy which frequently prompts unjustified use of empirical antifungals.[39]

Pre-requisites for antifungal stewardship programme

- Similar to the Infectious Diseases Society of America (IDSA) recommendations, a team including an infectious disease specialist, a microbiologist (mycologist), a hospital pharmacist focusing on antimicrobials, and a multidisciplinary group including physicians of different specialities should be formed.[38] Antifungal prescriptions by the primary treating physician should be made in accordance with the guidelines designed by the antifungal stewardship programme.
- Prior to implementation of the antifungal stewardship programme, a detailed audit of the centre's prescriptions is to be carried out to understand patterns of antifungal use in various departments. At the start of the programme, departments which show patterns of greater use of antifungals should be targeted.[39]
- Recommendations must be specific to each patient and closed feedback should be shared with the members of the antifungal stewardship programme.[40]
- Antifungal stewardship programme must include guidelines for antifungal use in:

  i. Patients requiring empirical therapy.
  ii. Treatment based on biochemical markers.
  iii. Treatment for patients with signs and symptoms of fungal infection.

- Guidelines should include clear instructions about the stoppage of antifungal treatment by:

  i. Stoppage of empirical therapy using biomarker values as a yardstick.
  ii. Changing from intravenous to the oral route of antifungal medication.
  iii. Switching from broad spectrum antifungals to specific antifungals after a specific diagnosis is made.

- Guidelines may be postulated from international recommendations, but they should be locally developed to tailor to the local epidemiology of fungal infections.[3] In a 2017 collaborative workshop by Indian medical microbiologists on the importance of antifungal stewardship programme, the use of automated systems to detect fungal resistance was recommended, these findings would then be confirmed by the gold standard microbroth dilution method.
- Fruitful antifungal stewardship programme relies on improved diagnostics, with a diagnostic-driven strategy that uses non-culture-based tests like galactomannan assay and *Aspergillus* polymerase chain reaction (PCR). The strength of these non-culture-based tests is appropriate for excluding invasive aspergillosis. Studies have successfully utilised the negative predictive value of PCR as a screening tool in haematological stem cell transplant patients to regulate antifungal therapy without any increase in mortality. Other effective diagnostic methods include Matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF) for rapid and reliable identification of *Candida* and *Aspergillus* species. Ultrasensitive Real Time *Aspergillus* PCR has been used for rapid identification of azole resistance. Regular audits are mandatory to assess the adherence and outcome of antifungal stewardship programme with a cyclical check on the methodology outcome and benefits of the programme, with regard to prevention and management of infections. The benefits of the programme are to be demonstrated to the hospital administrators, clinicians, and key members of the institution. Valerio *et al.*[37] recommended performing an audit for every 100 antifungal prescriptions to evaluate the prescribing conditions, and recommended the use of a scoring system that grades from 0 to 10 and conducting periodic assessment of the improvement of these scores over time.[27,37,38]
- Among the primary core activities of antifungal stewardship programme is post-prescription review and feedback. Any inadequacy in the prescriptions must be noted by the stewardship team and requisite feedback and education can be given to the prescribing department. Ananda-Rajah *et al.*[6] recommend reviewing of all prescription approvals within 24–48 hours, ideally.

Suggestions for antifungal stewardship programme

- Inclusion in the programme is voluntary, rather than compulsory, as suggested by Lopez Medrano *et al.*[41] A sudden compulsory regulation of prescriptions may be perceived by clinicians as undermining the autonomy of their clinical decision-making. In the beginning, antifungal stewardship programmes may include only a few departments where most antifungal prescriptions come from. An effective programme has been seen to not only positively affect the involved clinical departments, but an overall reduction in antifungal prescriptions has also been noted. The direct and personal involvement of the treating physicians' aids in the success of the programme.[38,39]
- For an antifungal stewardship programme to be

successful at an institution, the quality of healthcare provisions must also be otherwise efficient. During their programme, Loprez Medrano *et al.*[41] did not observe any increase in the incidence of yeast or mould infections or any change in the prognosis of affected patients. An efficient setup reduces the incidence of nosocomial and opportunistic fungal infections thereby restricting the use of antifungals and ensuring better implementation of the programme.[42]

- More than only educating clinicians on their prescribing behaviour, it has been seen that restrictions on prescribing medicines and prescription approvals, can be three times more effective. Delegation of responsibilities to each member of a clinical team, such that the antifungal stewardship programme members need not take daily ward rounds; however, concerns about antifungal use are looked after by the assigned member of each team. Installation of computer systems that require prescribing departments to substantiate the fungal prescription and include reminders about drug intake and the cost of antifungal therapy. Conducting larger surveys among under-graduate and post-graduate residents, and consultant specialists to assess the knowledge, attitude, and practice of antifungal usage.
- Wattal *et al.*[27] recommended the involvement of the national government via the Ministry of Health and Family Welfare with the development of national consensus guidelines that elaborate the diagnostic criteria, prophylaxis and treatment guidelines including specific details of when and how to de-escalate therapy, how to switch from intravenous to oral therapy and when to stop therapy. Formation of these consensus guidelines may be done a year after antifungal stewardship programme has been up and running at different centres in the country and adequate data has been collected from these centres to be analysed to form a concrete set of guidelines.[27]

Evidence for antifungal stewardship

A study at a university hospital in Spain reviewed 636 prescriptions over a period of six years. A high compliance rate of 88% was noted. Patient outcomes were favourable in 75% with invasive aspergillosis and 87% with invasive candidiasis. The total cost of antifungals was also found to be stable.[42] Another study, at a tertiary care centre in France, targeting high-cost antifungals over a period of one year, provided clinical advice during the review of 45 (88.2%) micafungin, 70 (78.7%) voriconazole, 78 (62.4%) liposomal amphotericin B and 3 (27.3%) caspofungin prescriptions. Except for voriconazole, around 50% of all the treatments reviewed were either terminated or altered, resulting in huge savings of antifungals, as compared to the previous year.[43] Similarly, a Spanish programme demonstrated a significant reduction in antifungal drug expenditures without any increase in the incidence of invasive fungal infections or mortality in patients with filamentous fungal infections.[44]

The need for antifungal stewardship programmes in the context of dermatophytosis

Superficial dermatophytosis has acquired an epidemic-like proportion, which has been attributed to a number of factors including a shift towards *Trichophyton mentagrophytes*, misuse of topical steroids, irrational steroid-antifungal combinations, resistance to terbinafine and many other unknown reasons.[45–48] Physicians have been shown to resort to unscientific prescriptions (irrational combinations of antifungals and non-pharmacological doses) to combat this menace. Voriconazole, which is considered to be a saviour drug for invasive fungal infections, is being prescribed unscrupulously for the treatment of dermatophytosis. The most important step before prescribing such molecules is the acquisition of antifungal susceptibility testing data.[48,49] Besides, itraconazole is recently being marketed as a topical formulation (alone, and in combination with steroids and antibiotics). Itraconazole should never be formulated as a topical agent as that may lead to the rapid development of itraconazole resistance as has been the case with several other antifungal drugs. The most irrational and dangerous of these itraconazole-containing creams is a fixed dose combination (FDC) comprising itraconazole, clobetasol propionate, ornidazole and ofloxacin. The emergence of drug-resistant dermatophytes and increasing prescriptions of unscientific molecules highlights the need for antifungal susceptibility testing, antifungal stewardship, and the development of a strong antifungal policy to aid clinicians in instituting appropriate antifungals empirically and to change if needed after antifungal sensitivity testing results become available.

Suggested roadmap for addressing growing antifungal resistance:

1. Awareness among the public:
   - Building awareness among the public through various public service announcements and campaigns with conventional media and social media.
   - Using the awareness campaigns to address the side effects of unregulated antifungal usage and growing resistance of common infections to established antifungals with effective messages and relatable patient stories and practical anecdotes.
   - Individual counselling of patients by physicians in the outpatient department and educating patients with written pamphlets.
   - Increased availability of publication information resources like websites in colloquial languages.
2. Awareness among clinicians:
   - Education about the rise of antifungal resistance and its implications among under-graduate and

post-graduate students of medicine and dentistry as a part of their training curriculum.
- Continuing expansion of this awareness among practising clinicians with clinical seminars, workshops, conferences, video modules and continuing medical education programmes. This could be implemented by organisational bodies at a state and national level and by various institutions and departments.
- Training of health care workers should include appropriate identification of scenarios where antifungals are required with pertinent drug selection.
- Training of pharmaceutical representatives to deliver these messages with clarification of indications and dosages while engaging with individual practitioners for their sales.

3. Encourage and implement optimal antifungal usage:
   - Establishment of antifungal stewardship programme that develop guidelines which can be used as a tool by clinicians in their daily practice.
   - Regular auditing of departmental prescriptions in hospitals to identify prescription practices in different departments and any lacunae in guidelines or their implementation.
   - Building tools to educate practitioners through public health associations, healthcare facility associations, various state and national organisations and academic institutions.
   - Use of smartphone applications, brief electronic mail messages and text messages to send regular tips to clinical practitioners.
4. Addressing irregular antifungal sales:
   - Illegalising the sale of category H drugs, without prescriptions via stringent national and state laws.
   - Firm implementation of these laws against pharmacies and unqualified quacks that dispense antifungals to gullible patients. Blacklisting of such businesses, organisations and individuals to prevent future practices.
   - Building awareness about the issue of illegal drug sales among the public by various media.
   - Individual counselling of patients by their physicians about the risks of using such medications without a prescription.

Current scenario

Literature and evidence in support of antifungal stewardship programmes are scarce. Studies focusing on such programmes have been mostly published after 2010, which explains the emergence and familiarisation of this novel concept.[50,51] Unfortunately, most of the studies are non-randomised and primarily single centre based with low sample sizes. In this background, it is prudent to mention that we need to conduct prescription audits to understand the pattern of prescription of antifungals, sensitise the physicians regarding the need for performing antifungal stewardship programmes and conduct well-designed studies to establish the significance of these programmes, conclusively.

Conclusion

An effective antifungal stewardship programme aims to set high standards for prescribing antifungals while ensuring patient safety, improved clinical outcomes, and minimising drug-related adverse effects and at the same time, warrants the use of the most effective antifungal drug. With an expansion in the size of the population, suffering from diabetes, using immunosuppressants, and suffering from long-term immunosuppression like HIV-AIDS, the proportion of at-risk individuals for fungal infections has escalated. Presently, fungal infections (both superficial and deep) may have a lower institutional incidence as compared to multidrug-resistant bacterial infections, but the health and financial liabilities of antifungal resistance are grave. Under such circumstances, antifungal stewardship programme is the need of the hour, which may exonerate us from the burden of growing antifungal resistance.

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Conflict of interest

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