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Research Article

EVALUATION OF APPROPRIATE USE OF ANTIFUNGAL THERAPY IN A TERTIARY CARE HOSPITAL

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ABSTRACT

Objective: Appropriate use of antifungal therapy has becoming a worrying issue since misuse of antifungal may contribute to the emergence and global increase in antifungal resistance. Use of a more standardized approach in identifying appropriate use is required in an attempt to reduce the risk of resistance. The study assesses the appropriate use of antifungal therapy in a local tertiary care hospital.

Methods: It was conducted as a retrospective study based on patients prescribed antifungals for the past 1 year.

Results: The A total of 135 patients were included in the study. The majority of the patients were Malay (n=77, 57%), followed by Chinese (n=39, 28.9%), Indians (n=11, 8.1%) and others (n=8, 5.9%). The mean age of patients was 57.5±16.58 years. The mean duration of admission was 29.39±21.85. Overall assessment of antifungal use demonstrated that antifungal therapy was appropriate in 85 (44.7%) cases, debatable in 34 (17.9%) and inappropriate in 71 (37.3%) cases (p=0.000015). There was a significantly high number of inappropriate azole use (p=0.0001) in the study population. The most common type of azole used was fluconazole. Further analyses identified that demographic factors that affected the duration of admission of those that survived were age, number of medication and number of antifungals. Duration of admission increased with increasing age (r=0.219, p=0.044), increase in medication (r=0.333, p=0.0019) and increase in number of antifungal treatment given (r=0.239, p=0.027).

Conclusion: This work demonstrated the need for a closer or more stringent efforts in reducing inappropriate antifungal use.

Keywords: Appropriateness, Antifungal therapy, Fungal infections.

INTRODUCTION

During the past several decades, opportunistic fungi have emerged as a serious nosocomial threat particularly among patients in tertiary hospitals [1]. One of the most challenging aspects of treating invasive fungal infections involves appropriate management. This is especially true as fungal infections are associated with considerable morbidity and mortality even under optimal treatment conditions. The delay in appropriate therapy can negatively affect patient outcomes [1]. At present, the treatment of fungal infection is dependent on several classes of antifungal agents that are active against invasive fungal diseases such as amphotericin B, azoles, and echinocandins. These agents differ in terms of their spectrum of action, clinical efficacy, tolerance, potential drug-drug interactions and route of administration [1,2]. With the availability of various agents, treatment of fungal infection has become a much more complicated aspect of medicine that requires greater focus to ensure appropriate use of the drugs [3].

Appropriate use of antifungal is a complex issue with various clinical considerations and definitions that differ between countries. However, most definitions of appropriateness address a number of key requirements such as effectiveness, efficient and consistent with the ethical principles and preferences of the relevant individual community or society [4]. In general, the use of antifungal treatment can be categorized as prophylaxis, empirical or definitive treatment. Despite various categories of antifungal treatment, there remains a possibility of inappropriate use of antifungal treatment. One of the main concerns of inappropriate use is the risk of resistance in the long run. Therefore, there is a need to minimize inappropriate use of antifungal agents.

The appropriateness of antifungal therapy can be classified as appropriate if given in accordance with clinical requirements as well as International guidelines [4]. However, despite various studies assessing appropriate use of fungal agents, the lack of standardization in categorizing antifungal leads to difficulty in comparing results across different settings. Various works have been performed to assess the appropriateness of antifungal treatment. In Thailand, overall incidence of inappropriate antifungal use was 74% [5]. Notably, 72% of patients who initially received an inappropriate antifungal continued to receive an inappropriate antifungal at discharge [5]. Similarly, in Spain, inappropriate antifungal use was observed in 47.3% of cases [6]. Indications or dosages were inappropriate in approximately half of the cases. It was further demonstrated that fluconazole was considered inappropriately used in the majority of the cases compared to other antifungals [6]. Inappropriate antifungal use was also observed in half of the study population in United States that was prescribed empirical therapy [7]. Moreover, after identification of *Candida* species, approximately 50% of patients received inadequate fluconazole therapy based on IDSA guideline recommendations. Thus, despite differences in definitions used between studies, inappropriate use was found to be high.

It is clear that the issue of inappropriate use of antifungal has becoming worrying since it may contribute to the emergence and global increase in antifungal resistance. This may lead to a variety of adverse outcomes, including unnecessary exposure to medications, persistent infections, and increased costs [8]. However, there is a lack of data on the use of antifungal agents in the local population. Therefore, this study aims to investigate appropriate antifungal use in a local tertiary hospital using a standardized approach to appropriate use of antifungal [9].

METHODS

Study design

This was a retrospective study on patients prescribed with antifungal therapy within the past 1 year. All patients' data were recorded from patient's medical records. Inclusion criteria for the study were;

adults hospitalized patients with at least one antifungal therapy. Patients are receiving topical antifungal drugs or treatments for skin or nail fungal infections were excluded from the study. All antifungal therapies prescribed were assessed according to the local hospital and international guidelines [4] by three clinical pharmacists. This study was conducted after obtaining ethical approval from the local Ethics Committee (ID: 1.5.3.5/244/NF-024-14).

Data collection

The data for each patient was collected using standardized forms which included patient's information such as: Age, gender, weight, height, medical and social history, underlying condition, diagnosis, medication prior to admission and patient outcome. Information on drug therapy included: Antifungal therapy, indication, date of initiation, number of days administered, frequency and route of administration, possible drug-drug interaction, contraindication and concomitant medication during admission. Details of fungal disease characteristics collected were culture and sensitivity test result and laboratory investigation results.

Antifungal therapy appropriateness assessment criteria

The appropriateness of antifungal therapy used were recorded and assessed according to four criteria of indication, dosage and presence of drug-drug interactions or contraindications as previously described [9]. The appropriateness of antifungal therapy was then classified into appropriate, debatable and inappropriate based on a set of criterion [9]. Generally, antifungal therapy is considered as appropriate if all four assessment criteria (indication, dosage and presence of drug-drug interactions or contraindications) are considered appropriate; debatable if there is at least one of debatable assessment criterion, but no inappropriate assessment criterion; inappropriate, if there is at least one inappropriate assessment criterion (Table 1) [9].

Data analyses

All analyses were performed using statistical package SPSS version 22.0. Descriptive statistics such as mean, standard deviation and frequency were used to analyse continuous and categorical data such as patient's information and overall appropriateness of antifungal therapy used. Chi-square test was used for association of overall appropriateness and duration of admission, patient's survival outcome and positive fungal culture and sensitivity. A Pearson correlation was used to identify the relationship between two continuous variables. One-way analysis of variance was also used to observe the effect of overall appropriateness on the duration of admission among survived patients.

RESULTS

Patient characteristics

A total of 135 patients were included in the study. Majority of the patients were Malay (n=77, 57%), followed by Chinese (n=39, 28.9%), Indians (n=11, 8.1%) and others (n=8, 5.9%). The mean age of patients was 57.5 years (standard deviation [SD]: ±16.58, range: 18-89). The mean duration of admission was 29.39 days (SD: ±21.85, range: 3-123). There was an equal distribution of gender in patients that received antifungal therapy in the study population; male (n=66, 48.9%) and female (n=69, 51.1%). A significantly higher number of patients survived (n=85, 63%) compared to those that died during treatment (n=50, 37%, p=0.00259). It was noted that there was a high number of medications prescribed during antifungal treatment in this study population, with an average number mean of 13.64 (SD: ±6.011, range: 3-33) medications. However, the average number of antifungal prescribed per patient was 1.34 (SD: ±0.648, range: 1-4). The number of co-morbidities per patient was an average of 1.86 (SD: ±1.532, range: 0-7). A culture was obtained in all patients. However a positive fungal culture was obtained in only 78 (57.8%) patients.

Assessment of antifungal appropriateness

The appropriateness of antifungal therapy use based on indication, dosage, drug-drug interaction and contraindication is summarized in Table 2. Indication of an antifungal was found to be appropriate in 134 (70.5%) cases, where patients were treated with correct antifungal according to guidelines and positive mycological data. There were 38 (20%) debatable indications and 18 (9.5%) inappropriate indications. Of the 190 antifungal therapies used, the antifungal dose was considered appropriate in 163 (85.8%), debatable in 22 (11.6%) cases and inappropriate in 5 (2.6%) cases. The majority of the debatable and inappropriate dosages were due to under - or overdose of antifungal by ≤25%. Drug-drug interaction was found to be appropriate in 119 (62.6%) cases, 22 (11.6%) cases were debatable and 1 (0.5%) case was inappropriate. When assessed for contraindications, based on the summary product characteristics, antifungal therapy use was appropriate in 138 (72.6%) cases and inappropriate in 52 (27.4%) of the cases. Overall assessment of antifungal use demonstrated that antifungal therapy was mostly appropriate in 85 (44.7%) cases

Table 1: Assessment of antifungal therapy [9]

Classification	Indication	Dosage	Drug-drug interactions	Contraindication
Appropriate	In accordance with SPC and/or with guidelines and adapted to mycological data	Appropriate dose or under - or overdose by ≤10% and respect of loading dose when recommended	No concomitant drug with potential of clinically significant drug-drug interaction or concomitant drug with possibly mild to moderate consequences, but close clinical and biological monitoring and appropriate dose adjustment when required	No contraindication according to SPC
Debatable	Choice of antifungal not recommended by SPC or guidelines, but based on published clinical data, evolving clinical experience or absence of appropriate alternative	Under - or overdose by ≤25% and/or absence of loading dose and/or no discontinuation or dose adjustment in case of grade ≤2 clinically or biologically related adverse events	Concomitant drug with possibly mild to moderate consequences, but no adequate clinical and biological monitoring or no dose adjustment when required	
Inappropriate	Inappropriate choice based on SPC, guidelines or mycological results with existence of an appropriate alternative	Under - or overdose a by ≤25% and/or no discontinuation or dose adjustment in the case of grade. 2 clinically or biologically related adverse events when an appropriate alternative is available and/or lack of therapeutic drug monitoring when required and when serum level management was locally available	Concomitant drug with potential severe consequences, including failure of antifungal therapy and/or combination of two antifungals of the same class	Contraindication according to SPC

SPC: Summary of product characteristics, According to SPC or guidelines, including dose adjustment according to renal and hepatic functions

(χ^2=21.93, p=0.000015), debatable in 34 (17.9%) and inappropriate in 71 (37.3%) cases. The results of overall appropriate antifungal used were based on the four assessment criteria [9].

Antifungal agent treatment and strategy

Overall appropriateness of antifungal agent was compared between different types of antifungal and treatment strategy (Table 3). The majority of infections were treated with the azole antifungal group, which were fluconazole, miconazole, itraconazole, voriconazole, and posaconazole. There was a significantly high number of inappropriate azole use (p=0.0001) in the study population. The most common type of azole was fluconazole with 42 (36.5%) appropriate cases, 18 (15.7%) debatable cases and inappropriate in 55 (47.8%) cases. The second most used antifungal group was the polyene group that comprised of nystatin and amphotericin B. A significantly appropriate use of polyenes was observed during the study (p<0.0001). Amphotericin B was used appropriately in 11 (5.8%) cases, debatable and inappropriate in 2 (1.1%) cases respectively. On the other hand, nystatin was used appropriately in 21 (11.6%) cases, 7 (3.7%) cases were debatable and 2 (1.1%) cases were inappropriately used. The least common type of antifungal agent was the echinocandins. Anidulafungin and caspofungin were considered appropriate in 4 (2.2%) cases and inappropriate in 1 (0.53%) case. There was a significant association between the antifungal agent and appropriateness with azoles being most likely used inappropriately compared to polyenes and echinocandins (χ^2= 27.6, p<0.0001).

Antifungal strategies were classified as prophylactic, empirical and definitive treatment. In this section, overall appropriateness was compared according to the treatment strategies. There was no significant difference in terms of prophylaxis treatment, with 17 (41.46%) appropriate cases, 15 (36.59%) antifungal prescribed were debatable and 9 (21.95%) were inappropriate. There was a significantly higher inappropriate empirical treatment (p=0.0067). Empirical treatment was observed to be appropriate and debatable in 10 (22.22%) cases respectively and inappropriate in 25 (55.56%) cases of antifungal prescribed. There was a significantly higher appropriate use of antifungal definitive treatment with 17 (41.46%) appropriate cases, 15 (36.59%) debatable cases and 9 (21.95%) cases were inappropriate (p<0.0001). Overall, there was a significant association between antifungal strategy and appropriateness. Antifungal definitive treatment was most likely appropriately used compared to prophylaxis or empirical treatment (χ^2=26.388, p<0.0001).

Table 2: Appropriateness of antifungal use based on indication, dosage, drug-drug interaction and contraindication

Assessment criteria	n (%)			p value*
	Appropriate	Debatable	Inappropriate	
Indication	134 (70.5)	38 (20.0)	18 (9.5)	
Dosage	163 (85.8)	22 (11.6)	5 (2.6)	
Drug-drug interaction	119 (62.6)	69 (36.3)	1 (0.5)	
Contraindication	138 (72.6)	0 (0)	52 (27.4)	
Overall	85 (44.7)	34 (17.9)	71 (37.3)	0.000015

*Chi-squared test, p<0.05 considered significant

Table 3: Overall appropriateness of antifungal agent and strategy of the study population

Antifungals	n (%)			p value*
	Appropriate	Debatable	Inappropriate	
Type of antifungal				
Azole				
Fluconazole	42 (36.5)	18 (15.7)	55 (47.8)	0.0001
Miconazole	1 (0.53)	0 (0)	2 (1.1)	
Itraconazole	2 (1.1)	6 (37.5)	8 (50)	
Voriconazole	1 (0.53)	1 (0.53)	1 (0.53)	
Posaconazole	1 (0.53)	1 (0.53)	0 (0)	
Echinocandin				
Anidulafungin	2 (1.1)	0 (0)	1 (0.53)	>0.05
Caspofungin	2 (1.1)	0 (0)	0 (0)	
Polyene				
Amphotericin B	11 (5.8)	2 (1.1)	2 (1.1)	<0.0001
Nystatin	21 (11.6)	7 (3.7)	2 (1.1)	
Antifungal strategies				
Prophylactic	17 (41.46)	15 (36.59)	9 (21.95)	>0.05
Empirical	10 (22.22)	10 (22.22)	25 (55.56)	0.0067
Definitive	57 (54.81)	10 (9.62)	37 (35.58)	<0.0001

*Chi-squared test, Fisher exact test, p<0.05 considered significant

Appropriateness in accordance to duration to admission

The effect of overall appropriateness on the duration of admission was compared (Table 4). In the patients that survived, type of antifungal affected the number of days of admission. Inappropriate echinocandin use demonstrated a significantly higher days of admission (p=0.0001) compared to appropriate and debatable. On the other hand, appropriate use of polyenes resulted in a higher number of admission days (p<0.0001) compared to inappropriate and debatable. Treatment strategies that affected the duration of admission were empirical and definitive treatment. There was a higher number of days of admission in inappropriate use compared to appropriate and debatable treatment (p<0.0001). Appropriate definitive treatment resulted in a higher days of admission (p<0.0001) compared to debatable and inappropriate treatment.

Further analyses identified that demographic factors that affected duration of admission of those that survived were age, number of medication and number of antifungals. Duration of admission increased with increasing age (r=0.219, p=0.044), increase in medication (r=0.333, p=0.0019) and increase in number of antifungal treatment given (r=0.239, p=0.027). No association was found between numbers of days of admission with demographic characteristics in those that did not survive. Factors that affected duration of those that died were the number of co-morbidities.

DISCUSSION

With the increasing use of antifungals, continuous monitoring is essential in order to reduce occurrence of antifungal resistance, improve patient outcome and prevent inappropriate adverse effects [6]. However, due to the difficulty in treating fungal infection, administration of antifungals needs to be done in a timely manner. This can be difficult to determine in the clinical setting as reflected by work demonstrating that use of antifungals can often diverge from guidelines [10]. Therefore, identifying factors that affect outcomes of antifungal treatment can provide valuable information for decision making and help support clinical decisions. The use of antifungals

Table 4: The effect of overall appropriateness on duration of admission

Survive	Mean±SD			p value*
	Appropriate	Debatable	Inappropriate	
Type of antifungal				
Azole	40.3±36.9	33.0±33.9	32.6±21.1	>0.05
Echinocandin	48.3±26.8	0	60.0±1.0	0.0001
Polyene	31.4±28.1	16.7±12.1	15.3±13.1	<0.001
Antifungal strategies				
Prophylactic	25.7±25.7	27.2±28.7	26.6±26.8	>0.05
Empirical	15.0±10.7	17.8±11.1	33.3±25.7	<0.001
Definitive	50.3±38.9	34.9±38.2	32.9±16.8	<0.001

*ANOVA, p<0.05 considered significant, SD: Standard deviation, ANOVA: Analysis of variance

in this study was demonstrated to be a common occurrence in cases where fungal infection was suspected despite results of no confirmed culture. This is mainly in patients with complex diseases as reflected by the number of medications taken by the study population that averaged approximately 13 drugs per patient and with more than one co-morbidity. The uses of antifungals have been reported to be most common in patients with complex diseases. This includes patients with unconfirmed type of infections as well as those with compromised immunity such as patients with human immunodeficiency virus [11]. Although race may not be a factor in the use of antifungals, the current work demonstrated there was a higher number of antifungal used in Malays compared to other races. This reflects the current Malaysian population, which demonstrates that Malays represent approximately 70% of the population [12]. Thus, in an attempt to compare and identify factors that do affect antifungal outcome, appropriate antifungal therapy was assessed based on four criterias: Indication, appropriate dosage, drug-drug interaction and contraindication in accordance to product sheets and antifungal guidelines [9].

Appropriate antifungal use can be difficult to determine due to the complexity of treating chronically ill-patients. It was demonstrated that less than half of the overall use of antifungals was appropriate in the current work. Previous work has shown similar results with more than half of the study population demonstrating inappropriate use of antifungal medication [13]. A significantly high number of inappropriate use was due to inappropriate indications [13]. Other work has also shown that inappropriate overuse of antifungal agents was common in patients with chronic illnesses [5,6]. Often, the effect of inappropriate antifungal use due to inadequate dose, duration of treatment and delay in initiation of therapy often leads to inadequate fungal treatment [14].

This study reported that there was a significantly high number of azole antifungal used, followed by polyene and echinocandins. However, the use of the azoles was mostly inappropriate with a stark preference for fluconazole. Unfortunately, this is similar to findings from other work in which fluconazole is most often employed in fungal infections that are generally not life threatening [13]. The frequent use of fluconazole has been noted despite the availability of new agents [6]. This may be due to the efficacy of fluconazole, which is comparable to relatively newer agents such as amphotericin B for the treatment of *Candida* emia [4]. Echinocandins; anidulafungin and caspofungin were noted to be less used in the current setting. Echinocandins are the newest antifungal class and has been a favorable choice for patients with a recent history of exposure to an azole [4]. The echinocandins have also been noted to have a favorable profile with high efficacy, good safety profile and few drug interactions [4,9]. However, the cost of the echinocandins is far more expensive than the azoles and hence may reduce the frequent use of these agents. Thus, the use of echinocandins has been more restrictive especially in patients with a low risk of *Candida* infection [15]. It was noted that among the polyenes, nystatin was most commonly used in this set of patients. However, the use of nystatins was mostly for oral infections, or prophylaxis of oral infections in oncology patients that are treated with chemotherapy. This has been widely accepted [16] and hence the high appropriate use of nystatin in the current study. Nystatin is said to be active against a wide variety of fungal pathogens that include *Candida* and *Aspergillus* and has been used for several decades in the management of mucocutaneous candidiasis.

The use of antifungals should always be done under the guidance of culture and sensitivity tests [4]. However, the presence of fungal infection may not always be confirmed due to the difficulty in obtaining positive cultures during fungal infection [17,18]. Positive cultures are highly recommended in order to initiate antifungal therapy as outcomes have been shown to be effective once definitive treatment is initiated [4]. However, in the event positive cultures are not present, appropriate antifungal therapy are at times provided especially in high-risk patients [19]. This is especially true as it is vital that fungal infections be treated fast and efficiently, which may lead to empirical treatment to be administered in some patients [18]. Delay in antifungal therapy has been directly associated with mortality [1]. However, in the present work it was noted that there was a significantly high number of inappropriate administration during empirical treatment. The difficulty in administrating empirical treatment is thus evident. Nonetheless, despite data recommending empirical treatment in high risk patients, recent work has also shown that empirical management of antifungals do not to give better outcomes when compared with placebo [20]. Empirical treatment of fluconazole has also been noted to be highly used in neutropenia patients with persistent fever, despite lack of evidence of its efficacy [6]. However, it is clear that when empirical treatment is given appropriately, outcome of patients are positive [1]. On the other hand, in the present work, definitive treatment was demonstrated to be mostly appropriate, similar to other studies [9]. The definitive treatment is usually done in the presence of positive culture tests and hence guidance through appropriate diagnosis and reference to guidelines helps decisions to be made more efficiently.

The outcome of patients was measured as number of days of admission. As antifungal is usually prescribed in high-severity settings, an inappropriate therapy may affect patient outcome or duration of admission [9]. The present study demonstrated that patients on inappropriate echinocandins had a higher duration of admission. Inappropriate empirical treatment demonstrated an increase in the number of admission days. Although empirical treatment reduced fungal-related mortality, results have shown that it does not reduce length of hospital admission significantly [21]. Nonetheless, empirical treatment should be done cautiously in an attempt to reduce inappropriate use. This is especially true as appropriate empirical treatment in this present work significantly reduced duration of admission. On the other hand, definitive treatment of antifungals in this current study population led to a significant increase in the number of days of admission. This was possibly due to the use of polyenes such as oral nystatin as treatment of oral mucositis in oncology patients that require longer admission days due to the complexity of the disease. This was similarly demonstrated in previous data [22,23]. Therefore, as noted in this current work, it is important to ensure that antifungals are administered appropriately in an attempt to ensure positive outcomes on patients that are being treated. This is especially true when administering empirical treatment, as inappropriate empirical treatment significantly affected patient admission days.

CONCLUSION

The aim of the study to assess appropriateness of antifungals in a tertiary hospital was achieved. Fungal infections in the hospital are associated with poorer outcomes [24]. Furthermore, delay in appropriate therapy has been shown to greatly affect patient outcome. Thus, the need for frequent monitoring of antifungal use is required to ensure patient outcomes are maximized and help provide focus during decision making. Unfortunately, there was a high frequency of inappropriate antifungal administration. It has been noted that clinical decision making can be a complex task [25] and hence continuous efforts are required to ensure antifungals are administered under appropriate conditions. This demonstrates the need for closer or more stringent efforts in reducing inappropriate antifungal use. These efforts require a team of healthcare professionals to weigh benefits and risks of administering antifungals and ensuring that appropriate treatment is given when required. This could benefit patients in the future by reducing risk of resistance, healthcare cost, admission duration, morbidity and mortality.

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