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Research Article

ANTIFUNGAL UTILIZATION AND OUTCOME EVALUATION IN A TERTIARY HOSPITAL

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ABSTRACT

Objective: The risk of fungal infection is one of the many concerns of patients admitted for chronic illness. The increase in fungal infection causes excessive morbidity and mortality. Despite the use of antifungals, the outcome of patients remains challenging. The study was performed to identify factors affecting the outcome of antifungal use.

Methods: A retrospective study was carried out in a local tertiary hospital for the past 1 year. Patients prescribed antifungals were included.

Results: A total of 145 patients who had been prescribed with antifungal agents within the past year were included in the study. It was noted that patients infected with fungi were mostly elderly patients (n=83, 57.2%). A majority of the patients (n=67, 46.2%, p<0.001) were diagnosed with or suspected to have systemic fungal infection compared to urinary fungal infection (n=31, 21.4%), oral fungal infection (n=20, 13.8%), pulmonary fungal infection (n=19, 13.1%), and others (n=8, 5.5%). As such, intravenous antifungal was the most commonly prescribed dosage form (n=88, 60.7%, p<0.001). The mortality rate of patients with fungal infection was 35.9% (n=52). No significant factors were observed to affect the clinical outcome of patients. However, factors affecting survival outcome in patients treated for fungal infection were targeted treatment (p=0.036), less number of medications (p<0.001), and a higher number of antifungals prescribed (p=0.010).

Conclusion: A more comprehensive review of medication is required to ensure appropriate treatment is given to patients with fungal infection.

Keywords: Antifungal**,** Fungal infection, Outcome.

INTRODUCTION

The recent increase in the use of antineoplastic and immunosuppressive agents, prosthetic devices, grafts, and more aggressive surgery has contributed to the increase in invasive fungal infections [1,2]. Fungal infection causes excessive morbidity and mortality in patients at risk including patients undergoing blood and marrow transplantation, solid-organ transplantation, major surgery, acquired immune deficiency syndrome, neoplastic disease, advanced age, and premature infants [3]. Apart from posing an important medical risk, fungal infection also causes an increase in financial burden due to longer use of hospital resources [4]. In view of this, the use of antifungal treatment should be done with care to ensure the optimum patient outcome.

Despite the use of antifungal agents, the outcome of fungal infection remains suboptimal and challenging [2]. The outcomes associated with invasive fungal infection are related to the severity of underlying host factors as well as the optimization of treatment-related factors [5]. Treatment-related factors include the speed of the initiation of antifungal therapy and the achievement of pharmacodynamic parameters [4]. As such, antifungal therapy should be initiated quickly to improve outcomes. However, early initiation of antifungal therapy is difficult to achieve due to relatively slow and insensitive diagnostic techniques. In addition, failures to achieve pharmacodynamic targets with the use of antifungals have also been associated with negative outcomes, and thus, dosing and appropriate serum levels also play an important role [5]. In view of the various factors that affect antifungal treatment, the effectiveness of antifungal agents is consistently being reviewed in the clinical setting in an attempt to optimize management and reduce resistance in the long run.

The high use of antifungals may expose the patient to the risk of resistance. Recent work has demonstrated that there is an increase in *Candida* resistance to first-line and second-line treatment [3,6]. Unfortunately, the available therapeutic options are limited. This poses a further problem as resistance increases additional days of admission [4]. The burden of resistance is especially a concern in immunocompromised patients. Therefore, identifying factors that optimize fungal management is vital.

Advances in medical technology, the widespread use of indwelling intravenous catheters, and the increased use of potent, broad-spectrum antimicrobial agents, have contributed to the dramatic increase in the incidence of fungal infections worldwide. Unfortunately, response rate remains suboptimal despite recent advances in antifungal therapy [4]. Although inadequate antimicrobial therapy has been shown to increase the risk for death in bacterial infections in many studies, few data investigating the effect of antifungal therapy on outcome of serious fungal disease are available [7], especially in the local setting. In view of this, it is vital to ensure that the use of antifungals is monitored closely to ensure that optimum treatment is given and problems such as the risk of resistance are minimized in the long run. This could provide vital information on measures that can be taken to improve antifungal use. Therefore, the aim of this study is to identify factors that affect the antifungal outcome in the local tertiary hospital.

METHODS

Study design

The study was conducted retrospectively in a local tertiary hospital. Data were collected from patients who had been prescribed with systemic antifungal agents within the past 1 year from pharmacy database and medical records. A list of antifungals available was identified from the local formulary. There were 11 antifungal agents in the formulary, which include: Nystatin, ketoconazole, itraconazole, caspofungin, amphotericin B, fluconazole, anidulafungin, flucytosine, posaconazole, voriconazole, and terbinafine. Only adult patients who had received at least one antifungal agent during this period were included in the study. Patients with incomplete data were excluded from the study. A list of patients who were prescribed these antifungals

was then generated using the pharmacy database. The following data were collected for each patient: Demographic data (name, registration number, age, gender, race, height, and weight), current medical problems, past medication history, social history, antifungal therapy, other drug therapy, laboratory investigation, culture and sensitivity test results, date of admission, date of discharge, and discharge status. Ethical approval was obtained from the local ethics committee (NF-026-14).

Study definition

Some definitions used for this study include elderly which is defined as adults aged 60-year-old and above [8]. During the study, outcomes were defined based on two areas: Clinical or survival outcome. Clinical outcome was evaluated using a few parameters which were constantly monitored during admission: Efficacy (temperature, white blood count) and safety (liver function test and renal profile) [9,10]. Survival was defined as survival or death on discharge. Treatment strategies were defined as targeted antifungal treatment after a clear diagnosis of fungal infection, empirical treatment in symptomatic patients with suspected fungal infection, and prophylaxis treatment in patients at risk without any symptoms of infection.

Data analyzes

The collected data were analyzed using Statistical Package for Social Sciences (SPSS) version 22.0. Summary statistics of mean, range, and standard deviation (SD) were presented for numerical variables. Frequency and percentage were presented for categorical variables. Continuous data were analyzed using student's T-test and ANOVA. For categorical response parameters, group comparisons were made using chi-square test. Logistic regression analysis was performed to examine the significance of individual variables in predicting the outcome of the patients. All statistical testing was two-sided with p-values <0.05 considered significant.

RESULTS

Demographic data

A total of 145 patients were included in the study. The majority of the patients (n=83, 57.2%) were elderly, with an overall mean age of 59±16.6 years old. The different ethnics observed were Malay (n=82, 56.6%), followed by Chinese (n=45, 31%), Indian (n=11, 7.6%), and others (n=7, 4.8%). Slightly more female patients (n=75, 51.7%) than males (n=70, 48.3%) were included in the study. A range of 1-4 (mean±SD: 1.27±0.568) antifungals was prescribed to the patients during their admission. In average, patients had a long duration of admission (mean±SD: 28.9±21.365 days, range 3-123 days) and received an average of 15.12±5.992 (range 4-35) medications during their admission. Patients presented a mean of 4.83±2.142 (range 1-9) comorbidities apart from fungal infection. Less than half (n=52, 35.9%) of the patients died on discharge.

The prevalence and pattern of antifungal use

Fluconazole (111 cases), nystatin (30 cases), itraconazole (15 cases), and amphotericin B (13 cases) were the four most commonly prescribed antifungal agents in the study population. Among the study population, over half of the patients (n=85, 58.6%, p=0.046) showed positive fungal culture and sensitivity results. A majority of the patients (n=67, 46.2%, p<0.001) were diagnosed with or suspected to have systemic fungal infection, followed by urinary fungal infection (n=31, 21.4%), oral fungal infection (n=20, 13.8%), pulmonary fungal infection (n=19, 13.1%), and others (n=8, 5.5%). A higher number of patients (n=88, 60.7%, p<0.001) received intravenous antifungal regimen as compared to oral route (n=37, 25.5%), intraperitoneal (n=1, 0.7%), and combination of oral and intravenous (n=19, 13.1%). There were three types of treatment strategies for fungal infection; prophylaxis, empirical, and targeted treatment. A significantly higher number of patients (n=95, 65.5%, p<0.001) were given targeted antifungal treatment after a clear diagnosis of fungal infection. Symptomatic patients with suspected fungal infection (n=37, 25.5%) were given empirical treatment. Patients at risk without any symptoms of infection (n=13, 9.0%) were given prophylaxis.

Outcome evaluation of antifungal use

Clinical outcome was evaluated based on efficacy and safety. Temperature and white blood count were used to evaluate the efficacy of antifungal use, whereas safety of antifungal use was evaluated based on liver and kidney function. In the study population, an average of 2.72±2.79 days was taken for their body temperature to be normalized. An average of 3.74±3.68 days was taken for white blood cell to return normal. On the other hand, an average of 2.63±5.24 and 1.96±2.02 days were taken for a patient taking antifungals to develop an abnormality in liver and kidney function, respectively. Patients with a higher number of antifungals administered needed more time to develop an abnormality in liver function (r=0.249, p=0.047). However, no significant association was observed between treatment outcome of antifungal use and other variables such as age, race, gender, presence of positive culture and sensitivity, treatment strategy, the total number of medications, and number of co-morbidities.

When analyzing survival outcome, a total of 93 (64.1%) patients survived and was discharged during the study duration. Analyzes demonstrated that there were statistically significant associations between types of treatment and mortality (p=0.036), between number of medications and mortality (p<0.001), as well as between number of antifungals prescribed with mortality (p=0.010). Patients receiving targeted treatment was associated with a lower rate of mortality compared to empirical and prophylaxis (χ=6.66, p=0.036). A number of medications taken were higher (mean±SD: 18.52±6.16) in patients that died upon discharge as compared to patients who survived (mean±SD: 13.23±5.00, p<0.001). Besides, patients who survived received more antifungals (mean±SD: 1.35±0.64) than patients who died on discharge (mean±SD: 1.12±0.38, p=0.010).

Factors affecting clinical and survival outcome

Clinical outcome was not influenced by the study factors. No statistically significant association between study variables with clinical outcome was observed. However, survival outcome was affected by three factors which included types of treatment, the number of medications and number of antifungals prescribed. Simple logistic regression was used to demonstrate how these factors affected survival outcome (Table 1). Empirical treatment was 2.179 times more likely to result in mortality than targeted treatment (p=0.049). Increasing the number of medications used was associated with an increased likelihood of death (odds ratio [OR]=1.191, p<0.001), and increasing the number of antifungal use was associated with a decreased likelihood of death (OR=0.368, p=0.022).

Further analysis using multiple logistic regression was performed to illustrate the effect of all these factors on survival (Table 2). After controlling effects of other factors, empirical treatment was 5.906 times more likely to cause death than targeted treatment (p=0.024). One unit increase in the number of medications used was associated with 1.26 times (or 26%) more likely to result in death (p<0.001). Increasing the number of antifungals was less likely to cause death (OR=0.231, p=0.007).

DISCUSSION

One of the many concerns of patients admitted for chronic illness is the risk of fungal infection, similarly observed in the current work. Interestingly, nosocomial infection significantly increases the length of hospitalization [11]. This is due to the difficulty in eradicating fungi [6]. Evidently, a significant increase in the length of hospitalization has been previously demonstrated with an increase in co-morbidity index [12]. Although the current work demonstrates a higher proportion of Malay patients compared to other races, this reflects the racial population in Malaysia [8]. In the study population, it was noted that patients infected with fungi were mostly elderly patients. Age has been known to predispose patients to fungal infection with those above 50 years

Table 1: Simple logistic regression of factors affecting survival outcome

Variables	B value	OR	95% CI	p value
Age				
Elderly	0.276	1.318	0.660-2.632	0.435
Non-elderly[a]		1.000		
Ethnic				
Malay	−0.536	0.585	0.122-2.808	0.503
Chinese	0.154	1.167	0.234-5.822	0.851
Indian	−0.693	0.500	0.068-3.696	0.497
Others[a]		1.000		
Gender				
Male[a]		1.000		
Female	−0.592	0.553	0.279-1.100	0.091
Positive fungal C and S				
Yes	0.442	1.556	0.771-3.140	0.218
No[a]		1.000		
Types of treatment				
Prophylaxis	−0.980	0.375	0.078-1.798	0.220
Empirical	0.779	2.179	1.005-4.727	0.049*
Targeted treatment[a]		1.000		
Number of medications	0.174	1.191	1.105-1.283	<0.001*
Number of comorbidities	0.106	1.112	0.946-1.307	0.197
Number of antifungals prescribed	−0.998	0.368	0.157-0.864	0.022*

CI stands for confidence interval, C and S stands for culture and sensitivity. [a]Represents the reference category, *p<0.05 considered significant, OR: Odds ratio, CI: Confidence interval

Table 2: Multiple logistic regression of all factors that affect survival outcome

Variables	B value	OR	95% CI	p value
Age				
Elderly	0.076	1.097	0.392-2.973	0.883
Non-elderly[a]		1.000		
Ethnic				
Malay	−1.008	0.365	0.051-2.635	0.318
Chinese	−0.050	0.951	0.123-7.357	0.961
Indian	−1.689	0.185	0.016-2.149	0.177
Others[a]		1.000		
Gender				
Male[a]		1.000		
Female	−0.571	0.565	0.231-1.381	0.211
Positive fungal C and S				
Yes	1.147	3.150	0.674-14.718	0.145
No[a]		1.000		
Types of treatment				
Prophylaxis	0.259	1.295	0.125-13.377	0.828
Empirical	1.776	5.906	1.269-27.487	0.024*
Targeted treatment[a]		1.000		
Number of medications	0.231	1.260	1.144-1.387	<0.001*
Number of comorbidities	−0.072	0.931	0.724-1.196	0.575
Number of antifungals prescribed	−1.466	0.231	0.080-0.667	0.007*

CI stands for confidence interval, C and S stands for culture and sensitivity. [a]Represents the reference category, *p<0.05 considered significant, OR: Odds ratio, CI: Confidence interval

being at a higher risk of fungal infection [13,14]. Fortunately, despite this, there were a significantly higher number of patients that survived as compared to patients that died during treatment for fungal infection, which demonstrates that with appropriate management, fungal infection can be treated.

In this study, the prevalence of systemic fungal infections was higher compared to localized fungal infection and as such intravenous antifungal agent was the most commonly prescribed dosage form in the study population. This is due to the requirement of a more intensive antifungal treatment and more rapid action for systemic fungal infection [15]. Despite approximately half of patients not showing positive fungal infection during culture and sensitivity tests, antifungal therapy was administered as a delay in administration of appropriate antifungal treatment is associated with worsened outcomes and higher mortality rates [15]. However, it was noted that despite a large amount of antifungal prescribed without positive culture, a significantly higher number of agents were given for targeted treatment as compared to prophylaxis and empirical management. Therefore, despite not obtaining positive cultures, the treatment was guided by other clinical symptoms which deemed the use of antifungal agents being classified as targeted treatment.

Clinical outcome of patients was assessed based on efficacy and safety of the agents given. The efficacy was based on the number of days the temperature and white cell count normalized, as previously described [9,10]. It was noted that normalization of these values was observed within 2-3 days in the present work. This demonstrates a good outcome of antifungal efficacy as guidelines recommend a change of antifungal after 2-3 days if patient conditions do not improve based on body temperature and level of white cell counts [10]. However, it should be noted that body temperature and white cell counts may not be the best indicator for evaluation of antifungal therapy efficacy, due to limitations such as the presence of other infections, use of antipyretics and presence of other co-morbidities [9]. Despite this, many studies use these parameters to compare the efficacy of treatment with appropriate success [9]. On the other hand, the safety of the agents was assessed based on effects on renal and liver. This is one of the major drawbacks in using antifungal agents, as toxicity may limit its use [16]. This present work, however, demonstrated an average of 1-2 days for abnormalities in liver or renal parameters to occur. Nonetheless, it should be noted that the abnormalities may not be directly related to antifungal use, as other factors such as a number of co-morbidities, diet, age, and other medication may affect renal and liver function [17,18].

Unfortunately, in view of the complexity of treating fungal infection and the severity of diseases patients present with, there was high mortality observed in the present work. However, mortality rates in patients treated with a fungal infection in other work have shown to be higher [19,20]. Interestingly, those that survived had a significantly higher number of antifungal agents given to them for targeted treatment compared to those that died. This indicated that a more aggressive approach in the management of fungal infection is required, as previously demonstrated [15]. However, patients that died also had a higher number of other medications than those that survived, which may indicate there was a higher risk of drug interaction or adverse reaction. Polypharmacy has been shown to have negative effects and thus, limiting the use of medications to those that are important may reduce drug-drug interaction and unwanted adverse effects [21].

In view of the complexity accompanying patients with fungal infection, various works have been performed to identify factors that predispose the patients to appropriate outcome. In this study population, it was observed that of the factors studied, three factors affected survival outcome. These were types of treatment, number of medications used and the number of antifungal prescribed. It was demonstrated that empirical treatment resulted in higher rate of mortality as compared to targeted treatment by more than five-fold. A delay in initiation of appropriate antifungal therapy has been associated with increased mortality [22]. However, if effective empiric antifungal therapy is administered, the mortality rate was shown to be reduced [23]. The need for appropriate targeted treatment is, therefore, vital. Furthermore, an increase in the number of antifungals was shown to decrease mortality rate in this present work. Introducing antifungal combination therapy is another possibility to improve the outcome and prognosis in immunocompromised or severely ill patients [24]. For example, combination antifungals have been shown to be more effective than monotherapy for invasive *Aspergilosis* [25]. The response rate and mortality of a cohort receiving antifungal combination therapy were also better than those receiving antifungal monotherapy [24].

However, despite this, it should be noted that an increase in the number of medications caused an increase in mortality. The risk of toxicity and drug-drug interaction increases with the number of medications given [26]. Thus, patients treated for fungal infection should have their medications reviewed thoroughly before adding to the list of treatment.

The aim of the study to identify factors that affect treatment and survival outcome in the local population were achieved. Factors that predicted survival in the local population were the use of more than one antifungal, less number of medications, and definitive treatment of fungal infection. Generalization of the study, however, should be done cautiously, due to the limitation in the retrospective nature and use of outcome parameters in this study. Therefore, further work in a prospective setting using a more specific parameter such as a combination of clinical, radiological, and mycological responses can be used in the future.

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