PHARMACOEPIDEMIOLOGICAL EVALUATION OF ANTIFUNGAL DRUG THERAPY USED IN HOSPITAL UNIVERSITI SAINS MALAYSIA (HUSM)

By

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DEDICATION

I dedicate my present work to my uncle Ali Hamid Awad , my mother Zainab Hamid awad, my Father Mahmoud Nasreldin, my grandmother Fatima osman , my brothers and my sister pretty Amna.

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ABBREVIATIONS

AIDS	Acquired Immune Deficiency Syndrome
NAD	National Institute of Allergy and Infectious Diseases,
IDSA	Infectious Diseases Society of America
WHO	World Health Organization,
DNA	Deoxyribonucleic acid
RNA	Ribonucleic acid
TPN	Total parenteral nutrition
CAPD	Continuous Ambulatory Peritoneal Dialysis
RF	Renal Failure
HIV	Human Immunodeficiency Virus
NNIS	National Nosocomial Infections Surveillance
IFIS	Invasive Fungal Infections
HSCT	Hematopoietic Stem Cell transplant
CKR	*Candida krusel*
CGL	*Candida glabrata*
TRB	*Trichosporon betgelll*
NCI	*Neoformans, Coccidioides immitis*
CTR	*Candida-tropicalis*
UTI	Urinary tract infection
VATC	Video-assisted thoracic surgery
AFS	Allergic Fungal Sinusitis
CRS	Chronic Rhino Sinusitis
HUSM	Hospital Universiti Sains Malaysia

SPSS	Statistical Package for the Social Sciences
ICU	Intensive Care Unit
CAN	*Candida SP*
GIT	Gastrointestinal Tract
TRU	Trichophyton Rubrum
ASP	Aspergillus spp.

PENILAIAN FARMAKOEPIDEMILOGI TERAPI DRUG ANTIKULAT YANG DIGUNAKAN DI HOSPITAL UNIVERSITI SAINS MALAYSIA (HUSM)

ABSTRAK

Pada hari ini, mengurus jangkitan kulat merupakan satu cabaran yang terpaksa dihadapi oleh doktor di seluruh dunia. Jangkitan kulat dianggap sebagai penyebab utama morbiditi dan mortaliti dalam kalangan pesakit-pesakit, terutamanya pesakit-pesakit yang yang mempunyai immunokompromi yang teruk. Dalam penyelidikan ini, kajian retrospektif telah dijalankan untuk menentukan epidemiologi dan pengurusan jangkitan kulat dalam kalangan pesakit luar dan pesakit dalam di Hospital Universiti Sains Malaysia (HUSM). Data telah dibahagikan kepada data pesakit luar dan pesakit dalam. Data pesakit dalam telah dipungut secara prospektif daripada rekod perubatan. Jumlah pesakit yang merupakan kes-kes jangkitan kulat yang disahkan berdasarkan laporan makmal terdiri daripada 290 orang. Melayu merupakan kaum yang majoritinya dikesan mengalami jangkitan kulat. Kumpulan umur 18-27 tahun mempunyai kekerapan yang tertinggi dangan jumlah 31%. Wanita (212,73%) mempunyai kekerapan yang lebih tinggi daripada lelaki (78, 26.9%). Wad obstetrik di HUSM telah menerima lebih banyak pesakit jangkitan kulat (130, 44.8%). Separuh daripada pesakit itu (145, 50%) telah dimasukkan ke hospital selama 1 hingga 4 hari. Kematian berjumlah lebih kurang 9.3% (27 pesakit). Diabetes melitus (47,18.6%) merupakan komorbiditi yang paling tinggi. Penggunaan antibiotik merupakan faktor risiko umum yang melibatkan 199 (68.6%) orang. *Candida albicans* dianggap sebagai kulat yang paling kerap dikenal pasti. Di antara pesakit-pesakit tersebut, 81 orang (27.9%) telah dirawat dengan terapi drug antikulat. Fluconazole ialah drug yang paling kerap digunakan bagi merawat pesakit-

pesakit jangkitan kulat yang dimasukkan ke hospital. Data pesakit luar telah dikumpul secara retrospektif daripada preskripsi perubatan yang diberikan. Terdapat 1090 pesakit luar yang dirawat dengan terapi drug antikulat dalam tempoh kajian ini dijalankan mulai 1 Jan. 2005 hingga 30 Jun 2005. Wanita (677, 62.1%) merupakan majoriti pesakit dalam kalangan pesakit luar. Orang Melayu (979, 89%) merupakan kumpulan etnik yang paling ramai menerima rawatan, diikuti oleh Cina (94, 8.6%), India (14, 1.3%). Klinik keluarga telah menerima bilangan pesakit yang paling banyak. Kulit (927, 85%) merupakan sistem yang paling banyak dijangkiti berbanding sistem tubuh badan yang lain. Miconazole (818, 75%) merupakan rawatan yang paling kerap diberikan kepada pesakit. Lebih kurang 97.7 % preskriber terdiri daripada pegawai perubatan. Sebagai kesimpulan, kajian ini telah mengenalpasti pola umum jangkitan kulat dan pengubatan antikulat yang digunakan bagi merawat pesakit-pesakit yang dimasukkan ke wad perubatan dan rawatan yang diberikan kepada mereka yang datang ke klinik rawatan pesakit luar di HUSM. Ciri-ciri umum jangkitan kulat dalam persekitaran kita didapati konsisten dengan spektrum kajian yang lebih luas yang dijalankan di merata dunia. Dapatan kajian ini akan membantu pembuat dasar dan pegawai perubatan agar dapat mengawal dengan lebih baik serta mengurus jangkitan kulat di Malaysia degan lebih baik.

PHARMACOEPIDEMIOLOGICAL EVALUATION OF ANTIFUNGAL DRUG THERAPY USED IN HOSPITAL UNIVERSITI SAINS MALAYSIA (HUSM)

ABSTRACT

Today, managing fungal infection is one of the challenges doctors have to face worldwide. Fungal infection is considered as one of the main causes of morbidity and mortality among patients, especially those who are severely immunocompromised. In the current work, retrospective study was undertaken in order to determine the epidemiology and management of fungal infection among both outpatients and hospitalized patients at Universiti Sains Malaysia Hospital (HUSM). The data were divided into outpatients and hospitalized patients. Data of hospitalized patients were collected from the medical record. The total numbers of patients with confirmed cases of fungal infection based on laboratory investigation were 290 patients. Majority of study subjects with fungal infections are Malay. The age group 18-27 years had high frequency accounting to 31%. Females (212, 73.1%) were diagnosed more for fungal infections than males (78, 26.9%) probably due to vaginal candidiasis. The obstetrics ward recorded more fungal infected patients (130, 44.8%) than other wards. Half of the patients (145, 50%) were hospitalized between 1-4 days. Death, among the fungal infected patients of this study was 27 (9.3%). Diabetes mellitus (47, 18.6%), seems to be the most frequently co-morbidity disease. Antibiotic usage was the common risk factor associated with fungal infection accounting for 199 (68.6%) patients. *Candida albicans* is the most frequent identified fungi (169, 58%). Among the patients, 81 (27.9%) were treated with antifungal drug therapy. Fluconazole was the most common drug used to treat the hospitalized fungal

infected patients. Data of outpatients was collected retrospectively from the medical prescriptions. There were 1090 outpatients treated with antifungal drug therapy during the study period from 1 Jan. 2005 to 30 of June 2005. Females (677, 62.1%) were the majority of patients among the outpatient. Malay was accounted as the most among the ethnic groups (979, 89.8%); followed Chinese (94, 8.6%), Indian (14, 1.3%). Family clinic has received most patients. Skin (927, 85%) was the most affected system compared to other body systems. Miconazole (818, 75%), was most frequently given to the patients. About 97.7% of the prescribers were medical officers according to the prescription record. The general features of fungal infection in this setting were similar to studies conducted worldwide. In conclusion, the current study has identified the general pattern of fungal infection and the use of antifungal medication given to patients admitted to the medical wards and to those who came to the outpatients' clinics of the USM Hospital.

CHAPTER ONE
INTRODUCTION

1.1 BACKGROUND

Fungi are widely distributed in nature. There are around 250,000 named species, but about 500 kinds have been recognized to cause disease (mycosis) in human (Richardson and Warnock, 2003).

Fungal infections have recently become sources of growing risk to human health, particularly in persons with a compromised immune system (National Institute of Allergy and Infectious Diseases, 2007). Normally, fungi are connected with complex disease entities in complicated medical patients (e.g. Cryptococcosis in Acquired Immune Deficiency Syndrome (AIDS) patients or Aspergillosis in bone marrow or organ transplant patients).

Pittet et al (1997) reported that the mortality rates due to fungal infections were significantly higher than those related to other organisms.

The use of a high amount of antifungal drugs can lead to drug resistance by fungi microbes, especially in hospitals, which increase the spreading of hospital-acquired infections. The recent studies have documented resistance of *Candida's* species to fluconazole and other azole and triazole drug, which are used widely in systemic fungal diseases (National Institute of Allergy and Infectious Diseases, 2007).

1.1.1 Infection

1.1.1(a) Definition of infection

According to the Infectious Diseases Society of America (IDSA, 1980), an infection was described as “the attacking of the body’s natural barriers by

microscopic organism such as bacterial, fungal, viral, or parasitic, which multiplies to make symptoms."

1.1.1 (b) Hospital-acquired infections

A hospital-acquired infection is described as one that develops at least 48 hours after the patient is admitted to the hospital, or up to 48 hours after being discharged. Outside this period, infections are considered to be community-acquired (Jamieson, 2008).

1.1.2 Significance, classification and structure of fungi

1.1.2 (a) Significance of fungi

Fungi are not always harming or transporting diseases, since they are sometimes beneficial (Talaro, 2008). Fungi are sometimes quite useful to human and play an essential role in human lives. Fungi are eukaryotes and heterotrophy that absorb their food by secreting digestive chemicals. Digesting biological substances found in the environment around fungi helps increasing the fertility of lands used in agriculture (fungi break down dead plants and animals and break down organic matter and returning essential mineral to the soil). Fungi are competing with bacteria for nutrients and space. Thus, several kinds of antibiotics are produced from fungi to fight bacterial infections (Talaro, 2008). In addition, some fungi yeast like *Saccharomyces cerevisiae are* known as baker's yeast because they are used in making bread, and they are also used to ferment beer and wine (Talaro, 2008).

1.1.2 (b) Classification of fungi

There are three major types of fungi: yeasts, moulds and dimorphic fungi

i. Yeasts

They are small oval or round in shape, predominantly unicellular, e.g. *Candida spp.*

ii. Moulds

Grow as branching filments which are called hyphae, and connected to form a mass, known with mycelium, e.g. *Mucor* spp. And *Ttrichophyton* spp.

iii. Dimorphic fungi

This type is capable to changing and existing in both mould and yeast forms. The yeast always forms in the body while the filamentous one forms in the environment, e.g. *Histoplasma* spp. And *Sporothrix* spp. (Richardson and Warnock, 2003)

1.1.2 (c) Structure of fungi

Fungi have defined nucleus with both DNA and RNA. They have a complex cell wall that contains sterols. Yeast is single cell organisms that reproduce by budding, whereas moulds grow by developing filamentous (Inglis, 2003).

1.1.2 (d) Morphology of pathogenic fungi

The pathogenic fungi that infect humans are non-motile eukaryotes, which are reproduced by sporulation. This organism exists in two forms viz: filamentous molds and unicellular yeast. In addition, these forms of morphology are not mutually exclusive and it depends on the growth conditions (Cleary *et al*., 2005).

1.1.3 Fungal infection

1.1.3 (a) Infectious diseases due to fungi

Fungal infection has become one of the most dangerous diseases that cause morbidity and mortality among the patients. Many reasons and factors such as advances in medical technology and the development of new diagnostic and treatment which lead to infections of fungi among the pations and increased the life expectancy of critically ill patients. On the other hand, Candidiasis remains as the most common fungal infection in immunosupressed patients. Aspergillosis, zygomycosis and others invasive filamentous fungal infections are major problem for certain groups of patients (National Foundation for Infectous Diseases 1998)

1.1.3 (b) Types of fungal infection

The general name of the disease caused by fungi in human is called Mycoses. Fungus always lives in association with humans and might be present in the environment. Until few years ago, severe superficial infections as well as systemic infections caused by fungal micro organisms were very uncommon. However, fungal infections such as foot infections, oral and vaginal thrushes were the common diseases known to individuals.

The incidence of serious systemic fungal infections has increased during the recent years. There are many factors which lead to fungal infections such as widespread use of broad-spectrum antibiotics (eliminate or decrease the non pathogenic bacterial population that normally competes with fungi). Other factors are the increase in the number of individuals with reduced immune responses due to Acquired Immunodeficiency Syndrome (AIDS), the action of immunosuppressant

drugs, or cancer chemotherapy agents. These reasons have lead to an increase in the prevalence of systemic fungal infections (Rang & Dale., 1999).

Fungi (mycoses) which cause infections disease to the human can be classified into a number of broad groups according to the initial site of infection. This classification shows the different groups of fungi and the way in which the site affected is related to the route by which the fungus enters to the body (Cleary *et al*., 2005).

i. Superficial mycoses

These types of fungal infections involve only the outer layers of the skin and hair. These infections are often harmless that patients do not recognize their condition. The most famous example for these mycoses is *Malasseziasis (Tinea versicolor)*.

ii. Cutaneous mycoses

In the case of cutaneous mycoses the fungal extend deeper into the epidermis and also may infect the nails as well. The most common example for these mycoses is dermatophytosis. (Cleary *et al*., 2005).

iii. Subcutaneous mycoses

These kinds of fungal microorganisms are chronic. It leads to localized infections of the skin and subcutaneous tissue following the traumatic implantation of the etiologic agent. The example for these mycoses is *sporotrich*. (Cleary *et al*., 2005).

iv. Systemic mycoses

This type of mycoses is caused by dimorphic fungal pathogens in the internal organs. They often overcome the physiological and cellular defenses of the normal human host by changing their morphological form. Most organs commonly affected are the lungs and gastrointestinal tract (Cleary *et al*., 2005).

v. Opportunistic mycoses

These types of mycoses cause fungal infections for the human body in the immunocompromised patients when the normal defense mechanisms are weak, an example of that is AIDS patients, more aggressive cancer and post-transplantation chemotherapy and the use of antibiotics, cytotoxins, immunosuppressive, corticosteroids and other macro disruptive procedures that result in lowered resistance of the host.

The organisms involved in these infections are cosmopolitan fungi, which have a very low inherent virulence. The increased incidence of these infections and the diversity of fungi causing them; have paralleled the emergence of AIDS, more aggressive cancer and post-transplantation chemotherapy and the use of antibiotics, cytotoxins, immunosuppressive, corticosteroids and other macro disruptive procedures that result in lowered resistance of the host. The examples for these mycoses are *Cryptococcus, Aspergillosis* and *Mucomycosis* (Cleary *et al*., 2005).

vi. Non opportunistic fungi (primary pathogens)

Usually the primary pathogens cause diseases in the immunologically normal host. The most common examples for these mycoses are *Histoplasmosis, Blastomycosis,* and *occidioidomycosis* (Cleary *et al.*, 2005).

1.1.3 (c) Pathology of fungal infection

The information of fungi are very little among the people, because many people think that the fungi, indicates only an organism that causes skin infections. However, actually fungi have major effect on the health and people life all around the world. Fungi cause a different types of clinical diseases, from simple superficial problems to very serious and harmful systemic infections (Schaechter et al., 2007).

Calderone and Sihlar, (2002) mentioned that pathogenic fungi cause a variety of infections, which can be life-threatening. The infection can enter the human body through skin contact, inhalation, and translocation across physical barriers pursuant to host defects, accidental or iatrogenic abridgement of epithelial integrity.

1.1.3 (d) Transmission of fungal infection

Most fungi live in the soil or on plants. They are transmitted to humans by contact with fungus or its spores. They are frequently inhaled (e.g. *Aspergillus* spores and *Cryptococcus*), but they can also enter to the body through the broken skin. Some other cataneous mycoses are transmitted by contact with infected skin area, or by direct contact with a lesion on the skin of an infected human or animal (e.g. ringworm on cats (Lee and Bishop, 2002).

1.1.3 (e) Signs and symptoms of fungal infection

The signs and symptoms of fungal infection differ in accordance to the infected parts of the body. Often superficial fungal infections, such as jock itch, vaginal yeast, athlete's foot, and ringworm are typically annoying, but they are not very serious. Their symptoms generally include itchy, dry, red, scaly, or irritated skin. In addition, there are systemic fungal infections often begin in the lungs and

take time to develop. Furthermore, severe infections occur in people, whose immune systems have been weakened, allowing the infection to spread beyond the lungs to other organs. Moreover, symptoms of systemic fungal infections depend on which organs become infected and may include respiratory problems, extreme tiredness, coughing, weight loss, fever, night sweats, and headache (Human diseases and conditions, 2007)

1.1.3 (f) Factors contributing to fungal infection

There are a number of factors contributing to patient's susceptibility to infection such as medical procedures, which lead to weakness of patient's immune system. These factors are summarized by Lee and Bishop, (2002) as transplant in organ surgery with administration of immunosuppressive drugs; prolonged broad spectrum antibiotic therapy, which destroys the normal flora; other invasive therapies such as intravenous total parenteral nutrition (TPN) - this involves the use of solutions of glucose, which inhibit bacterial growth but favor the growth of fungi such as *Candida albicans*. The use of fat emulsion in TPN also encourages the growth of *Malassezia further*, an otherwise harmless superficial fungus. Other factors include Continuous Ambulatory Peritoneal Dialysis (CAPD) - this is used to haemodialyse patients with renal failure (RF), the main problem is the risk of fungal infection as well as bacterial infection through the indwelling cannulae; and from contaminated equipment or material.

1.1.4 Pharmacoepidemiolog

1.1.4 (a) Definitions

Pharmacoepidemiology was described as the study of the utilization and effects of drugs among large numbers of people

The word Pharmacoepidemiology consists of two components, one is ‘phamaco’ and the other is ‘epidemiology’.

1.1.4 (b) Epidemiology

Epidemiology can be defined as the study of the distribution and determinants of diseases in populations

1.1.4 (c) Important of Pharmacoepidemiology:

Study of pharmacoepidemiology is extremely important because there are numbers of significant and contributions that can be made by pharmacoepidemiology such as new information about the drug effects and drug costs. Moreover by applying research studies of pharmacoepidemiology can obtain large information about new adverse drug reactions and drugs safety. Reassurance about drug safety is one of the most important contributions that can be made by pharmacoepidemiology studies. Also use of pharmacoepidemiology is very useful and effect in the clinical trial method for the drugs before sending to the market. (Strom and Kimmel, 2006)

1.1.4 (d) Epidemiology of fungal infection

Fungal infections have become a major concern in our life as a result of many diseases such as nosocomial infections that is associated with significant mortality, longer hospital stays and higher health care costs (Klein and Watanakunakron, 1979; Edmond *et al*., 1999).

The study of Toscano and Jarvis (1999) from the national foundation for infectious disease, reported that throughout the few decades, researches in advances in medical technology, development of new diagnostics and treatment approaches lead to increase in the life expectancy of seriously ill patients. They added that presence of the global Human Immunodeficiency Virus (HIV) epidemic has resulted in an increase in severely ill immunocompromised hospitalized patients, accompanied by more reports of fungal infections.

The data from the National Nosocomial Infections Surveillance (NNIS) (1994) showed that *Candida* spp. now ranks as the fourth most common cause of nosocomial blood stream infections in United States, and the prevalence of systemic fungal infections has increased significantly during the past decade (Pfaller et al, 1998).

Segal et al, (2007) and Ng (1994) declared that there are a lot of factors that associated with increase of fungal infections particularly invasive fungal infections (IFIs) among many patients, due to great use of bread-spectrum antibiotics and immunosuppressive agent.

IFIs is associated with high mortality and morbidity among patients with acute leukemia and receipt of an allogeneic hematopoietic stem cell transplant (HSCT), central venous catheters, intensive care of low birth weight infections and the acquired immunodeficiency syndrome (AIDS) epidemic.

Caston-Osorio et al., (2008) revealed that the use of wide amount of azole prophylaxis for *Candida* spp. might associate with high rate of incidence of many other fungal infections, such as *Aspergillosis* spp.

Shao et al., (2007) from Taiwan reported that the *Candida albican, Cryptococcus neoformans* and *Aspergillus* along with the use of high amount of antifungal prophylaxis, were the most causes agents of invasive fungal infections (IFIs). But today, the epidemiology of IFI has been shifted to others agents and factors of the fungal infections such as rise of non-*albicant Candida*, non-*fumigatus Asperjillus* and many others type of fungal microorganism from both main type of fungi (yeast, moulds). These new recognized fungal infections are associated with with morbidity and mortality (Shao et al., 2007)

1.1.5 Cost of antifungal drugs

Pharmacoeconomics refers to the scientific discipline that analysis cost of drugs therapy to health care system and society. It is using for determine, measures and compares the value of pharmaceutical product and services. Pharmacoeconomics study also using to evaluate the research method of cost minimization, cost-effectiveness, cost benefits, cost of illness, cost utility, and quality of life assessment (Bootman *et al*, 1991).

1.2. LITERATURE REVIEW

1.2.1 Fungal infection worldwide

There are many studies and evaluations of infectious microorganisms during the last decade. Based on the studies, fungal diseases appeared to have a higher toll as seen with increased morbidity and mortality among patients, thus considering it as outstanding. This can be seen particularly in hospitalized patients where the rate of *Candida* species' bloodstream infection has increased greatly than the previous three decades. This increase in fungal infections leads to the increase of mortality and long duration of hospitalization.

Pfaller et al, (1998) reported that the presence of new types of fungal microorganism such as *Candida krusei, Candida glabrata, Fusarium* and *Trichosporon betgelll* lead to an increase in the incidence rate of community acquired and nosocomial infections among the patients. The study showed that there was significant resistance of antifungal drugs from the nosocomial pathogen of fungal.

Goldani and Mario, (2003) reported a retrospective review of the clinical features, treatment and outcomes of 27 patients with *Candida tropicalis* fungemia which was a common cause of fungemia in Latin America. The study covered a period of 4 years at a tertiary Brazilian care hospital. *Candida tropicalis* cases were selected from 101 patients with different Candida species. Among those 101 patients, *Candida albicans* was the most frequently isolated (32.6%), followed by *Candida-tropicalis* (26.7%), and *Candida parapsilosis* (23.7%). The mortality rate among the 27 patients with *Candida tropicalis fungemia*, was 48%.

A USA data from the Surveillance and Control of Pathogens of Epidemiological Importance (SCOPE) Program indicated that *Candida* is the fourth

most common cause of nosocomial bloodstream infection, comprising 8% of bloodstream infections (Pfaller et al, 1998).

Another study showed that *Candida albicans* remained the most commonly isolated *Candida species*. But non-*albicans* species increase in frequency and often have been showing changeable degrees of antifungal susceptibility (Wisplinghoff *et al.*, 2004).

Moreover, (Simpson et al., 2004) of the University of Alberta-Canada conducted a morbidity and mortality comparative study among patients with asymptomatic funguria. The study was performed among 149 adult patients with funguria. During the study period, the incidence of funguria in all hospitalized urine specimens was found to be 3%. Laboratory testing was done for 73% of cases out of which 70% were identified as *Candida albicans*. The study revealed that the hospitalized adults patients did not benefit from treatment of asymptomatic funguria with regards to morbidity or mortality. Nevertheless, the presence of multiple risk factors for funguria or invasive fungal infections was associated with a longer duration of hospitalization, suggesting that funguria may be a sickness indicator.

A study about the incidence of Candiduria and fungal urinary tract infection (UTI) showed that infections have increased in recent years due to immunosuppressive therapy (Guglielmo *et al*., 1994).

In addition, the most frequent organism that, causes fungal UTI is still *Candida albicans* followed by *Candida (Torulopsis)glabrata, Candida tropicalis,,* and *Candida krusei* (Guglielmo *et al*., 1994). Non-*albicans Candida* and non-*Candida yeasts* are steadily increasing as the etiological cause of fungal UTI.

Krcmery, *et al.*, (1999) conducted a study on 50 patients hospitalized with fungal UTI in Slovak Republic. The numbers of males among the patients were 26,

while the total numbers of females were 24 patients. The patients mean age was 62.4years. *Candida albicans* isolated from 36 patients, followed by *Candida tropicallis* (5 patients), *Blastoschizomyces capitatus* (5 patients), and *Candida krusei* from 4 patients. Two patients had *fungaemia*, simultaneous significant bacteria were present from 20 of 50 patients with fungal UTI (40%). Fluconazole was used in 29 patients of which 25 of them were cured; ketoconazole was used in 14 patients of which 12 of them were cured. Itraconazole was used in 3 patients and all of them were cured. Systemic amphotericin B was used in the treatment of four patients with fungal infections, two of them were cured. The results also showed that 42 (84%) patients from the total number of patients were cured. The analysis result showed the significant of systemic antifungal chemotherapy in high-risk patients with fungal UTI.

Beck-Sague *et al.*, (1993) conducted study during 1980-1990. The result showed that there were 30,477 reported cases out of which 26,553 were nosocomial fungal infections. The rates of fungal infections were increased during the study period from 2.0 to 3.8 infections/1000 patients discharged.

Also the study showed that the fungal infections rate increased for urinary tract infection from (9.0 to 20.5 /1000) patients discharged, for surgical wound infection from 1.0 to 3.1, and for pneumonia from 2.3 to 3.6. The nosocomial fungemia rate increase from 1.0 to 4.9. The percentage of nosocomial infection by all hospitals due to fungal pathogens increased from 6.0% in 1980 to 10.4% in 1990 at all major sites of infection. According to the study the surgical wound infections, from 1.5% to 5.1%; lung infections, from 5.2% to 5.7%; urinary tract infections from 6.7% to18.7%, and blood stream infection from, 5.4% to 9.9%. Candida albican was

the most frequently isolated fungal pathogen (59.7%), then others Candida species (18.6%), Candida albicans infection increase from (52%) in 1980 to (63%) in1990

Singh et al., (2005) conducted a study in all India Institutes of Medical Sciences, in order to do isolation of fungus from the specimen of brain tissue culture due to *Candida bantianum.* The study reported that there was a case of fungal granuloma of the brain due to C. bantianum which causes very serious infection to the patient's brain.

Fungal infections were associated with significantly higher 28-day mortality (35) % and in-hospital mortality (57%) than were infections due to another organism, the odds ratio for death within 28 days due to fungemia was 2.07 (95% in comparison with that for blood stream infections caused by other organisms (Pittet *et al.,1997)*.

Keady and Thacker, (2005) confirmed the increase in the incidence of invasive fungal infections, especially those caused by *Candida* spp. and *Aspergillus* spp. due to the increasing numbers of critically ill and immunocompromised patients.

According to Tritipwanit, *et al.*, (2005) from Thailand, *Candida albicans* remains the most commonly isolated species of candidemia, accounting for 42.9 percent of all isolations.

Lin *et al.*, (2005) from Taiwan documented a case report of 33 years old women with invasive fungal infection that has been treated firstly by glucocorticoids and prednisolone. Later on after being discharged, patient experienced chest pain and fever and returned back to hospital where she was confirmed to be suffering from invasive pulmonary *aspergillosis* and pulmonary *cryptococcosis* infections. The patient was treated by the antifungal agent amphotericin B (IV) for 20 days and fluconazole (orally) for 4 months. Latest diagnosis showed normal findings. The

authors explained that each possible infectious etiology for pulmonary lesions in immunocompromised patients is associated with a significant risk of mortality.

A study conducted by Nyirjery *et al* (1995) during the period 1991 to 1993, reflected that 74 patients out of 300 had positive fungal culture, among those patients 68% were *Candida albicans*, 32% were others' species. Fungal vaginitis remains one of the most common infections of the fungal genital tract, it has been estimated that approximately 75% of all women will at the same time in their lives, have vaginal yeast infections.

According to the report of the International Conference for the Development of a Consensus on the Management and Prevention of Severe Candidal Infections, there is an increasing incidence of *Candidial* infection and *Candida* represents the fourth most common organism isolated from the blood of hospitalized patients (Edwards *et al.*, 1997). The report also mentioned that some reasons that lead to the increase of *candida* infections were due to change in the incidence of species to non-*albicans* isolate with resistance to antifungal drugs, and the limitation of diagnostics for deep fungal infections.

A prospective surveillance study was conducted by Lopes, (2006) from January 1998 until March 2000 in the pediatric hospital in Portugal. The hospital contained units of neonatal intensive care, pediatric intensive care, general surgery, haematology, gastroenterology, pneumology/nephrology, infant medicine, general medicine and burn units. During the period of the study nosocomial fungal infection was identified in 63 children with a total of 67 reported episodes, since one patient had four different episodes and another one had two. These incidents are considered as new cases because they were spaced more than 1 month. In seven cases death was associated with nosocomial fungal infection, accounting for 10.4% of lethality. The

accumulated incidence of nosocomial fungal infections was 3.0 per 1000, with a mean annual incidence of 1.3 per 1000 populations. In this study, the incident of nosocomial fungal infections was occurred more frequently among; males (56.7%), among the less age (34.3%) and among the longer hospitalized patients (50.7%). fungal organisms which were observed most frequently among the patients were, *Candida albicans* (64.2%), followed by *Candida parapsilosis* (28.4%), *Candida tropicalis* (6.0%), and *Saccharomyces cerevisiae* (1.5%). In seven death cases associated with nosocomial fungal infection, five were happened due to *Candida albicans*, two (*Candida tropicalis)* and one (*Candida parapsilosis)*.

Patel *et al* (2005) conducted a study that analyzed 119 patients and found that 50% of them were males, and their mean age was 51.8 year (range 19-85). The study observed that the *Candida albicans* was the species that isolated most frequently (41%), followed by *Candida parapsilosis* (24%), *Candida glabrata* (20%), *Candida tropicalis* (8%), *Candida krusei* (4%), *Candida lusitamae* (2%), and *Candida gullieeromondi* (1%). Fluconazole was the initial choice therapy offered for 75% of the patients.

Stratov *et al* (1998) conducted study in Australia on 38 patients with *Candidaemia* between 1994 and 1996. The study showed that the incidence of *Candidaemia* was 0.71 per 1000 discharged patients admitted longer than 1 day and 1.54 per 1000 of discharged who were admitted longer than 5 days. Male percentage was 63%, average ages of the patients were 66 years (range 36-80). There were underlying illnesses such as gastrointestinal disease present in 66% of the patients, solid tumour (eight patients), pancreatic (5 patients), inflammatory colitis (4 patients), and abdominal surgery (19). The number of patients who were infected with genitourinary tract disease was 5 (13%). Some diseases such as hematological

malignancies, diabetes mellitus and renal failure had 4 patients for each. Isolation of *Candida albicans* was positive in 63% of the total infections, 62% of the deaths numbers, and 75% of the complications. The study showed that 13 (34%) of the patients died, 5 from primary sepsis and 3 from treatment failure. 5 deaths were unrelated to *Candidaemia*. 62% of the deaths occurred among the patients were due to candidaemia. Out of 38 patients 8 patients did not receive antifungal therapy. 5 died septic deaths within 48 hours of blood cultures having been taken, and 3 survived the episode of *Candidaemia* with catheter removal. There were 4 complications, one each of endophthalmitis, septic pulmonary emboli, hepatic *Candidiasis* and splenic *Candidiasis*. 3 patients survived without sequelae after prolonged antifungal therapy (103, 79 and 33 days, respectively), the fourth patients died the day after all active treatments were withdrawn.

Khor and colleagues (2006) reported the epidemiology of fungal keratitis in Singapore. They concluded that *Fusarium* was most prevalent fungal keratitis and contributed to significant morbidity.

In summary, it could be deduced that most of the fungal infections studied were from *Candida* spp. The resultant infections were shown to be from nosocomial origins from different continents of the world thereby depicting its worldwide coverage. However, other fungal organisms other than *Candida* spp were also studied.

1.2.2 Fungal infections in Malaysia

Up to our knowledge, pharmacoepidemiological evaluation of fungal infection in Malaysia has not been conducted extensively. However, few studies were performed focusing more on specific types of fungal infections.

A study was conducted by Ng *et al* (1999) at the Medical Microbiology Department of Malaya University. One thousand one hundred and fourteen fungal yeasts were isolated from virus clinical specimens. The study identified a species of Candida with the high frequency of *Candida albicans* (44.2%), *Candida parapsilosis* (26.0%), *Candida tropicalis* (17.7%), *Candida globrata* (9.6%), *Candida krusis* (1.2%), *Candida rugosa* (0.6%), *Candida guilliermondii* (0.2%), *Candida lustaniae* (0.08%), and *Candida keyr* (0.8%). The most non-*albicans* was isolated from the blood, respiratory system, urine and skin. The higher number of *Candida albicans* was obtained from the vaginal swabs, then *Candida globrata* 82.2, and *Candida kurodei* was 64.2%.

A study was conducted in the National University of Malaysia (UKM) by Goh *et al*. (2005) to determine the incidence of allergic fungal sinusitis. The study involved 30 patients of immunocompetent chronic rhinosinusitis who were under surgery. Five (16.7%) of the nasal secretions specimens and 11(36.7%) of the surgical specimens taken from all patients were found to be fungal-positive. The prevalence of allergic fungal sinusitis was found to be 26.7%. It was also observed that the most common causative agent was *Aspergillus.Sp* (54.5%). All patients' results were positive in the test done for discovering the skin reactivity to the fungal allergen.

As compared to fungal studies reported in other parts of the world, few studies were reported from Malaysia. However, the few studies reported were mostly from *Candida albicans* causing vaginal candidiasis.

1.2.3 Risk factors

A study on fungal urinary tract infections was conducted by Krcmercy *et al* (1999) among 50 hospitalized patients. The study showed that the most frequent risk factors for developing of symptomatic fungal urinary tract infections were the use of antibiotic drugs with more than one agent in one week (96%), previous therapy with corticosteroids (72%), fungal infection in other parts of the body (48%), urinary catheter or nephrostomy (46%), hematological malignancies with neutropenia (30%), and diabetes mellitus(12%). The organisms which were isolated from the urinary tract were *Candida albicans* in 36 patients, *Candida tropicalis* in 5 patients, *Blastoschizomyces capitatus* in 5 patiens, and *Candida Krusei* in 4 patients.

In the previous Malaysian study that was conducted by Goh et al. (2005), asthma was recognized to be associated with allergic fungal sinusitis in 37.5% (3 out of 8 patients) of cases. 25% (2/8 patients) of cases had Aspirin intolerance, and 62.5% (5/8 patient) had elevated total immunoglobulin E levels. Other risk factors have been highlighted in section 1.1.3(f).

1.2.4 Antifungal drugs

1.2.4 (a) Classification of antifungal drugs

Based on pharmacological action, antifungal drug therapy divided into two major types, one is systemic antifungal drugs and the other is topical use of antifungal drugs.

Examples of antifungal drugs such as imidazole, triazole, and polyene can be used to treatment either systemic or topical fungal infection. Whereas, there are many superficial infections that can be treated either systemically or topically. (Bennett, 2001).

Zhang et al., (2008) showed that the antifungal drugs are classified according to the area of infection in the body into two main types, topical and systemic.

According to Zhang et al, topical and systemic antifungal drugs are divided into four subclasses; polyenes, amidazoles, triazoles and miscellaneous.

1. Polyenes: includes amphotericin and nystatin
2. Amidazoles: such as clotrimazole, ketoconazole, miconazole, econazole, fenticonazole, sulconazole, and tioconazole.
3. Triazoles: fluconazole, itraconazole
4. Miscellaneous**:** flucytosine, griseofulvin, terbinafine

i. Topical antifungal drugs

The topical antifungal drugs are generally used for the treatment of superficial fungal infections, unless the infection is widespread, involve an extensive area, or is resistant to initial therapy (Zhang et al., 2008; Bennett, 2001).

ii. Systemic antifungal drugs

These types of antifungal drugs are often used for the treatment of *Onychomycosis, Tinea capitis*, superficial and systemic candidiasis. In addition, the systemic antifungal drugs are used for prophylaxis and treatment of invasive fungal infections (Zhang et al., 2008).

Zhang et al (2008) mentioned that the incidents of invasive fungal infections have increased in immunocompromised patients due to the development of resistant fungi. In addition to that the study mention that several new antifungal drugs have confirmed significant therapeutic benefits and have broadened clinicians' choices in the treatment of superficial and systemic invasive fungal infections.

A study done to identify the prophylaxis and treatment of fungal infection in patients with haematological malignancies reported that the polyene macrolides, the imidazoles and the triazole were the most frequently classes of antifungal drugs that are used for prophylaxis and treatment of fungal infections (Ascioglu *et al.*, 2000).

Usually polyene macrolides contain nystatin and amphotericin B. The polyene macrolides causes death of the microorganism’s cell by binding to ergosterol in cell membranes, and increased membrane permeability.

The imidazole antifungal agents - ketoconazole and miconazole -were used less frequently. The imidazole inhibits production of fungal cytochrome P450 (CYP) 14α-demethylase, thereby disallowing the production of ergosterol. Furthermore, the triazole fluconazole and itraconazole have the same mechanism of action as the imidazoles. These agents can be found in different formulations for use through different routes (Ascioglu *et al.*, 2000).

1.2.4 (b) Cost of antifungal drugs

Study conducted in adults' patients in USA by Aryun Kim et al, (2010) to determine cost of Aspergillosis fungal infection among hospitalization patients in United state of America hospital during years from 2000 to 2006. The study was looked to the general hospital costs which included length of stay and cost of antifungal treatment. The total patients were 1835, from the analysis the total cost for 1835 patients was $52 803, the researcher mention that the cost of antifungal drugs was reduced during years 2005- 2006, more over they mention that the use of intravenous voriconazole was associated with reduced the total hospitalization costs. Also they found that the using of amphotericin B or caspofungin independently associated with a reduced length of hospital stay.

Study conducted in Italy by stam WB, et al, (2008) to evaluate and compare the cost treatment of caspofungin with liposomal amphotericin B antifungal drugs using for treatment patients of neutropenic fever. From the analysis the researcher reprted that the using of caspofungin antifungal drug was cost-effective compare to liposomal amphotericin B in treatments of patients with neutropenic fever.

In general there are lack of previous studies regarding the cost of antifungal drug, moreover, cannot compare the previous limit study with this study because the current study looked only to the cost of antifungal therapy only.

1.3 PROBLEM STATEMENT

Recently, the incidence of fungal infections is raising a great deal of concern among researchers, hospital management and even individuals. In view of these concerns that have resulted in high morbidity and mortality among patients commonly hospitalized, researchers in the western world have dwelt into research to find a solution to these problems. On the other hand, Malaysia is not 100 percent free of fungal infections in its environment and the hospital in particular. However, little studies so far has been carried out and published. In fact, the studies carried out are mostly limited to a particular strain of fungus. This study, therefore, aims to investigate the epidemiology of fungal infections, types of fungal microbes, to determine the prevailing conditions that promoted the spread of fungal microorganisms, and to determine the extent of diagnosis and treatment methods used in patients in Hospital Universiti Sains Malaysia.

1.4 RATIONALE OF THE STUDY

Fungal infections are important causes of morbidity and mortality worldwide, particularly among immunocompromised patients. As a result of increased cases of fungal infection among immunocompromised patients such as cancer and HIV in the hospitals, the research aims to investigate the causes of such prevailing condition. Moreover, the increased cases of nosocomial fungal infections among patients in the hospitals boosted the zeal for such study.

In addition, patients from different walks of life come down with fungal infections and are constantly being treated, but the prevalence of the infection is not decreasing rather growing at an alarming rate. Due to this unprecedented scenario, the study aims to look into the epidemiology of fungal disease in the area under

study. In conclusion, there is limited studies conducted on fungal infections in Malaysia in general and HUSM in particular.

1.5 STUDY OBJECTIVES

1.5.1 General objective

This study was conducted to study epidemiology of fungal infections and to determine the patterns of antifungal drugs use among patients admitted to HUSM within 2005 to 2006.

1.5.2 Specific objectives

This research was conducted specifically to determine;

1. Prevalence of fungal infection and patterns of antifungal drugs that were used in the outpatient's clinic of University Sains Malaysia during the period from January 2005 to June 2005.
2. The prevalence and types of fungal infections and patterns of antifungal drugs that were used among the patients who were admitted to the hospital USM during the period from January 2006 to December 2006.
3. The demographic characteristics of the patients who were admitted to the hospital USM during the stated period (i.e. outpatients and inpatients).
4. The factors and co-morbidities associated with fungal infections.
5. The outcome statistics of death among hospitalized patients.
6. The cost of antifungal therapy for the hospitalized patients.
7. To evaluate the relationships between demography, types of fungal infection, types of antifungal drugs, co-morbidities, risk factors and patient's outcomes (i.e survival statistics).