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Invasive *Aspergillus* Infections in a Thai Tertiary-Care Hospital during 2006-2011

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Abstract

From an increase in the number of immunocompromised hosts including AIDS patients, organ transplantation, solid-organ tumor, hematological malignancy, corticosteroid use, and others underlying diseases, it leads to increasing the incidence of invasive aspergillosis (IA) as one of the most prevalent opportunistic mould infections. However, the epidemiological data are still limited. Our objective is to study the epidemiology of IA, patients' characteristics in a tertiary-care hospital, King Chulalongkorn Memorial Hospital, Bangkok, Thailand. The retrospective study of IA as principal diagnosis in both medical and laboratory records in a tertiary-care hospital, King Chulalongkorn Memorial Hospital, from January 1, 2006 to December 31, 2011, was performed. There were 69 patients who were diagnosed as IA during 2006 till 2011. They were classified as proven (45 patients), probable (3 patients), and possible (21 patients) invasive aspergillosis following the criteria of European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG), 2008. The numbers of patients in 2006 to 2011 were 3, 11, 12, 10, 10, and 23 respectively. Male patients were 58 percent. The age range was from 8 months to 87 years old. Most of patients were from Medicine ward. Others were derived from Pediatrics, Surgery, and Ear Nose Throat wards. The most common underlying disease was diabetes mellitus type 2 in the proven group. The main predisposing factors of patients were the history of pulmonary tuberculosis and using of immunosuppressive drugs. The sites of infection were lung (62%), sinus (28%), and brain (8%). *Aspergillus fumigatus* (69%) and *Aspergillus flavus* (15%) were common species from the isolated culture. The treatment used mostly was surgery and followed by amphotericin B or voriconazole. The case fatality rate of IA was 20 percent. From the epidemiological data, we can conclude that in this past ten years there is an incessant increase in the number of IA in the immunocompromised hosts especially from *Aspergillus fumigatus*, which is the most prevalent species found in IA. Diabetes mellitus and history of pulmonary tuberculosis will play the important role for IA in the future. The plan for prevention and treatment should be concerned about those underlying diseases and predisposing factors.

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Keywords

Invasive Aspergillosis, Thailand, Epidemiology, *Aspergillus*, Tertiary Hospital

1. Introduction

Aspergillus species are saprophytic filamentous fungi. This genus is characterized by the flask-shaped or cylindrical phialides on the vesicle at the apex of a conidiophore. Asexual spores or conidia are globose and various in colors. Their spores can be found in the soil, composed piles, air, animals, and humans. They can be pathogens in immunocompromised hosts such as patients with acquired immunodeficiency syndrome (AIDS), patients who had allogenic hematopoietic stem cell transplantation or solid organ transplantation, patients who received immunosuppressive drugs, patients with prolonged neutropenia, and patients with others underlying diseases. The common pathogenic *Aspergillus* species include *A. fumigatus*, *A. flavus*, *A. niger*, and *A. terreus*. *A. nidulans* can also cause infections mostly in patients with chronic granulomatous disease (CGD). There are three forms of aspergillosis: invasive aspergillosis, chronic aspergillosis, and allergic forms of aspergillosis. Chronic aspergillosis is less frequently found than the acute disease. Affected patients usually have the common underlying conditions including previous tuberculosis infection, atypical mycobacterial infection, Chronic Obstructive Pulmonary Disease (COPD), other chronic lung diseases, diabetes mellitus, and alcoholism. Allergic forms of aspergillosis include allergic sinusitis and allergic bronchopulmonary aspergillosis [1]. Invasive aspergillosis (IA) is the most concerning form for public health and also has high mortality rate [1]. IA also includes the infections of the lower respiratory system, sinuses, and skin as routes of entry. In addition, cardiovascular system, central nervous system, and other tissues could be infected from hematogenous dissemination or direct extension from adjacent infected tissues [1]. As a result of an increasing number of immunocompromised hosts, patients with IA were increasing at the same time [2]-[13]. In North America and Europe, there is an increase in IA among severely immunocompromised patients including patients with allogenic hematopoietic stem cell transplantation (HSCT) and solid organ transplantation [5] [6] [9] [12] [14]-[17]. It has been shown that after 1992 the incidence of IA increased in allograft recipients and continued high through 1990s [5]. Furthermore, the incidence of IA was mostly found in HLA (Human Leukocyte Antigen)-matched HSCT from an unrelated donor or HLA-mismatched HSCT and lung transplantation [14] [16] [18]-[20]. According to the systemic review from 50 studies [7], common underlying conditions were leukemia or lymphoma (42.6%), bone marrow transplant (25.8%), and solid-organ transplant patients (13.0%). The crude mortality rate in IA was high, more than 90% if untreated [7].

For Asian countries, an increased incidence of IA has been reported although the data are still limited [8]. Kiertiburanakul S., Thibbadee C., Santanirand P. (2007) showed that in Thailand between 2000 and 2005 acute leukemia was the most common underlying condition in patients with IA and *A. fumigatus* was the most common isolated species [21]. They also found that the most common site of infection was lung (68%) and corticosteroid therapy and pulmonary infection were significant predictive factors of death. The crude mortality rate of IA from this study was about 47% [21]. However, there were still very few publications regarding epidemiological data of IA in Thailand after 2005 [21]-[23]. Thus, this study showed the retrospective data of IA and patients' characteristics in a tertiary-care hospital, King Chulalongkorn Memorial Hospital (KCMH).

2. Materials and Methods

2.1. Surveillance

The authors reviewed both medical and laboratory records, including culture-based methods and galactomannan enzyme immunoassay detection, retrospectively from January 1, 2006 to December 31, 2011 at King Chulalongkorn Memorial Hospital (1479-bed medical school hospital, a tertiary-care hospital in Bangkok, Thailand). The data of patients with IA were retrieved by using principal diagnosis as invasive aspergillosis (IA) with the computer system in the hospital and the clinical microbiology laboratory.

2.2. Inclusion Criteria

The patients were categorized into three groups of invasive aspergillosis diagnosis from revised definition of

European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) in 2008 [24].

Those three categories are proven, probable, and possible diagnosis of invasive aspergillosis. Proven diagnosis of IA was defined as a culture from sterile sites with identification as *Aspergillus* spp. Probable diagnosis of IA was described as the combination of at least one host factor, one clinical feature, and one mycological evidence. Possible diagnosis was the host factors with clinical features excluding mycological evidence. We also categorized the response rates as complete response, partial response, relapse, and death [25]. Complete response was defined as the patients had no signs and symptoms related to IA and negative for consecutive cultures if any had been done. Partial response was defined as the patients recovered for the most of signs and symptoms. Relapse was defined as patients who had initial response and during follow-up had recurrence of any signs and symptoms of IA.

2.3. Fungal Identification

All specimens were observed by using 10% KOH (Potassium hydroxide) solution and Gram stain. All specimens were cultured for at least three weeks in Sabouraud dextrose agar (BD Difco™, Sparks, MD, USA), Sabouraud dextrose agar with chloramphenicol (Acumedia™, Lansing, MI, USA), Mycosel™ or Sabouraud dextrose agar with chloramphenicol and cycloheximide (BD BBL™, Sparks, MD, USA), and Sabouraud brain heart infusion agar base (BD Difco™, Sparks, MD, USA) at both 37˚C and 25˚C. All positive colonies were observed under light microscopes with lactophenol cotton blue staining.

2.4. Galactomannan Enzyme Immunoassay Test

The Platelia *Aspergillus* Ag (Bio-Rad, Redmond, WA) was used for measuring galactomannan levels following manufacturer's instructions. Bronchoalveolar lavage (BAL) and sera samples from patients were processed and mixed well. 300 µl of each sample was added to 100 µl of sample treatment solution, heated for 6 minutes in a 120˚C heat block, and then centrifuged 10 min at 10,000 *g*. Meanwhile, negative controls, cut-off controls, and positive controls were treated in the same way. Supernatant (50 µl) was mixed to 50 µl of a conjugated anti-galactomannan EBA-2 monoclonal antibody labeled with peroxidase in microplate. The microplate with a plate sealer was incubated at 37˚C for 90 minutes and then it was washed for 5 times with washing solution by an automated washer (Diagnostics Pasteur, Paris, France). After washing, wells were rapidly added 200 µl of chromogen tetramethylbenzidine solution and incubated at 25˚C for 30 minutes in the dark. Stopping solution (100 µl) containing 1N sulfuric acid was added to each well to stop reaction. Optical densities (ODs) at 450/620 nm were read in each well by a microplate reader (BioTek Instruments, Winooski, VT). Negative controls, cut-off controls, and positive controls were read at the same time in each assay. Results were determined as an index relative to the OD of the mean cut-off control (GM index = OD sample/mean cut-off control OD).

2.5. Statistical Analysis

Statistical analysis used in this study was shown as mean, standard deviation (SD), percent, and McNemar's test by Graph Pad Prism 5.0 software to compare risk factors leading to the death of patients. p-value at < 0.05 is significant.

This study was approved by Institutional Review Board (IRB No. 350/55), Faculty of Medicine, Chulalongkorn University.

3. Results

3.1. Demographic Data

Sixty-nine patients were diagnosed as IA from 2006 to 2011 as shown in **Figure 1**. Patients were categorized as proven IA (65.2%), probable IA (4.3%), and possible IA (30.4%) as shown in **Figure 2**. Mean age ± SD was 48.5 ± 23.1 years (range, 8 months to 87 years old). Forty patients (58%) were male as shown in **Table 1**.

3.2. Underlying Diseases and Predisposing Factors

The leading underlying diseases were diabetes mellitus (42.6%), followed by malignancy (12.8%) including

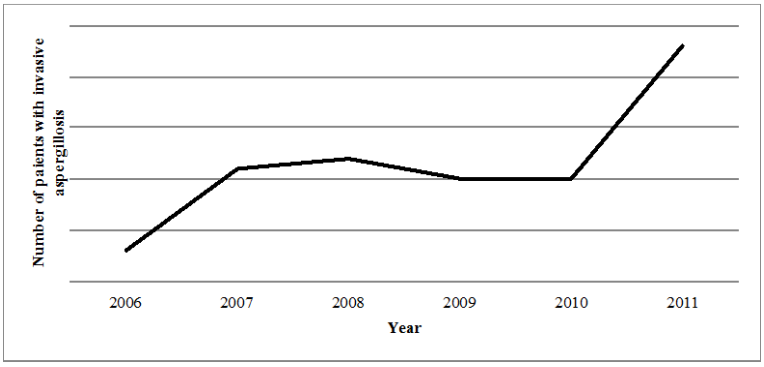

Figure 1. Number of patients with invasive aspergillosis in 2006-2011, King Chulalongkorn Memorial Hospital.

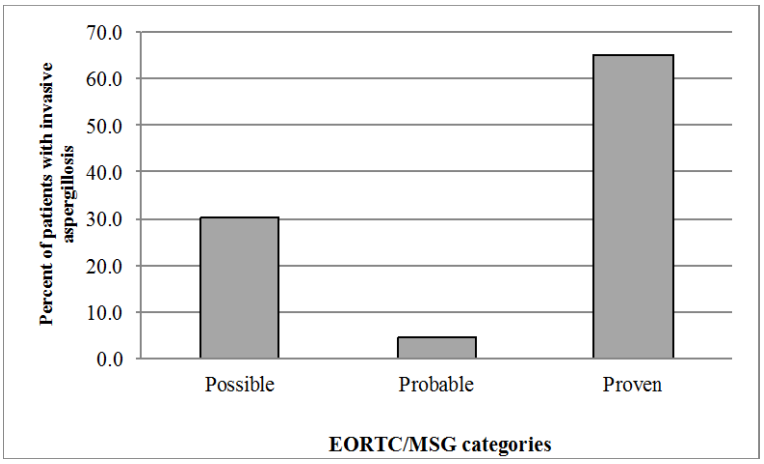

Figure 2. The percent of patients in each European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) 2008 category.

hematological malignancy and solid organ malignancy. The main predisposing factors were the history of old pulmonary tuberculosis (53.1%), and using corticosteroid (37.5%). Lungs (62.3%) were the most common sites of infection. Thirty-six patients (52.1%) were recruited from the Medicine ward. Mean length of stay in hospital ± SD was 26.9 ± 34.7 days (range, 1 to 137 days). Demographic characteristics and clinical data are provided in **Table 1**.

3.3. Galactomannan Enzyme Immunoassay (EIA) Test

Galactomannan Enzyme Immunoassay (EIA) test was performed in twelve patients as shown in **Table 2**. Specimens came from 11 sera and 1 bronchoalveolar lavage (BAL). The cut-off value was 0.5. From the data, sensitivity was 100 percent and specificity was 25 percent. Furthermore, positive predictive value was 40 percent and negative predictive value was 100 percent.

3.4. Treatments

Aspergillus fumigatus (69.2%) was the most common *Aspergillus* species isolated from patients with IA, followed by *Aspergillus flavus* (15.4%) as shown in **Figure 3**. Most patients were treated by using voriconazole (25.3%), and amphotericin B (22.7%). Forty-eight patients (69.6%) had complete response and case fatality rate of IA was 20.3 percent as shown in **Table 3**. We used McNemar's test to find the association between the factors and the death of patient with invasive aspergillosis as shown in **Table 4**. We found that only lung infection was associated with the death of patients with invasive aspergillosis significantly. Patients with complete re-

Table 1. Demographic and clinical data of 69 patients with invasive aspergillosis.

Characteristics	Number (%)
Mean age ± SD, years (range)	48.5 ± 23.1 (8 mon-87 yr.)
Gender	
Male	40 (58.0)
Female	29 (42.0)
Underlying diseases[a]	
Diabetes mellitus	20 (42.6)
Malignancy	6 (12.8)
Leukemia	4 (8.5)
Lymphoma	1 (2.1)
Malignant thymoma	1 (2.1)
Renal diseases	5 (10.6)
Systemic lupus erythematosus (SLE)	4 (8.5)
Chronic granulomatous disease (CGD)	3 (6.4)
Autoimmune hepatitis	2 (4.3)
Chronic obstructive pulmonary disease (COPD)	2 (4.3)
Others: lung transplantation, Kasabach Merritt	5 (10.6)
Syndrome, aplastic anemia, anemia of chronic disease, Multiple sclerosis	
Predisposing factors[a]	
Old pulmonary tuberculosis	17 (53.1)
Corticosteroid	12 (37.5)
Chemotherapy	3 (9.4)
Specimens[a]	
Lungs	43 (62.3)
Bronchioalveolar lavage (BAL)	3
Sputum	11
Tissue	29
Sinus	19 (27.5)
Pus	2
Tissue	17
Central nervous system	6 (8.7)
Tissue	6
Skin	1 (1.4)
Pus	1
Length of stay ± SD, days (range)	26.9 ± 34.7 (1 - 137)
Wards	
Medicine, general	25 (36.2)
Medicine, intensive care unit (ICU)	11 (15.9)
Surgery	11 (15.9)
Eye Nose Throat (ENT)	10 (14.5)
Pediatrics, general	8 (11.6)
Pediatrics, intensive care unit (ICU)	3 (4.3)
Orthopedics	1 (1.4)

SD: Standard deviation. [a]Some patients had more than one underlying diseases, predisposing factors or sites of infection.

sponse came from surgery alone (33.3%), surgery combined with antifungal agents (8.7%), and antifungal agents alone (26.0%). About a half of patients with complete response among antifungal agents alone received medications as voriconazole alone and voriconazole combined with other antifungal agents. Fourteen patients died from IA. The sites of infection from those fourteen patients came from lung (10 patients), brain (3 patients), and sinus (1 patient). Six patients who died from IA received amphotericin B alone. Two patients who died from

Table 2. Galactomannan Enzyme Immunoassay (EIA) test and culture for *Aspergillus* spp.

Galactomannan test	Culture for *Aspergillus* spp.	
	Positive	Negative
Positive	4	6
Negative	0	2

Table 3. Treatments and outcomes of 69 patients with invasive aspergillosis.

Characteristics	Number (%)
Treatments[a]	
Surgery	33 (44)
Voriconazole	19 (25.3)
Amphotericin B	17 (22.7)
Caspofungin	4 (5.3)
Anidulafungin	1 (1.3)
Micafungin	1 (1.3)
Outcomes	
Complete response	48 (69.6)
Partial response	2 (2.9)
Relapse	5 (7.2)
Death	14 (20.3)

[a]Some patients had more than one treatment.

Table 4. McNemar's test of major factors associated with death in invasive aspergillosis patients.

Factors	95% CI	*p*-value*
Using corticosteroid	0.542 to 6.837	0.4227
Diabetes	0.274 to 1.464	0.3447
Brain infection	0.969 to 20.46	0.0614
Lung infection	0.046 to 0.535	0.0009

*p-value at < 0.05 is significant.

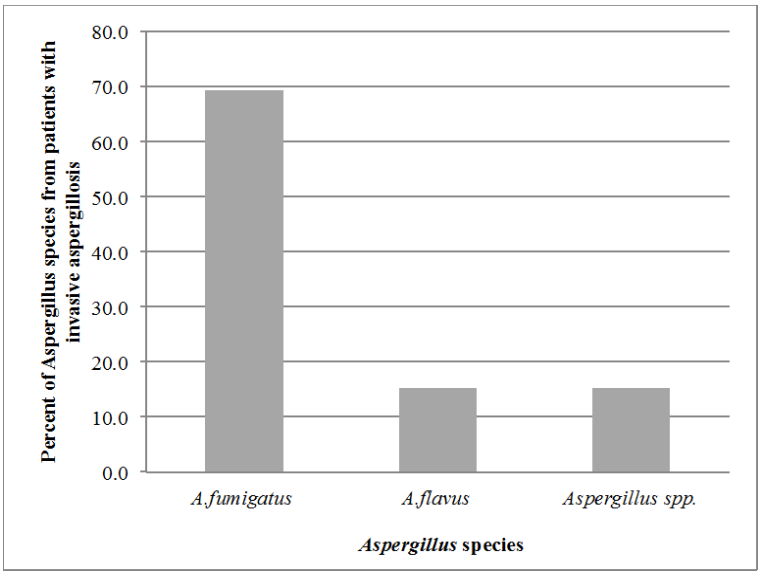

Figure 3. The percent of *Aspergillus* species isolated from patients with invasive aspergillosis.

IA received voriconazole alone and another two patients received echinocandin (caspofungin or anidulafungin) alone. The remainder received combined therapy of amphotericin B and other antifungal agents.

4. Discussion

According to the previous studies in North America [5] [6] [14]-[16], Europe [9] [17] [26], and Asia Pacific [3] [27], this study also showed the same underlying diseases and predisposing factors for patients with IA. The major risk factors for IA were prolonged neutropenia (<500 cells/μL), using corticosteroid, using chemotherapy, patients with hematologic or solid organ malignancy, patients in extensive surgery or burn, patients in ICU, patients with bone marrow and solid organ transplant, AIDS patients when CD4 < 50 cells, extremity of age, and patients with diabetes mellitus [27]. Nevertheless, hematological malignancy or transplantation was not the most common underlying disease in this study. This could be because our institute is not a transplantation center. In contrast, this study indicated that diabetes mellitus was the most common underlying diseases in these patients with IA. From previous data [28], they found an impairment of PMN response in poorly controlled diabetics and suppression of phagocytic activity with low chemotactic responses in hyperglycemic state. There were also a few case reports of diabetes and invasive aspergillosis [27] [29] [30]. All patients with IA in those case reports shared the common feature that they had no other risk factors except uncontrolled diabetes mellitus. Chakrabarti A., *et al.* [27] also classified diabetes mellitus as one of the newly recognized risk factors for invasive aspergillosis in developing countries. Diabetic patients would have a decrease in phagocytic activity of macrophages. However, diabetic patients with invasive aspergillosis are not significantly associated with mortality of patients with invasive aspergillosis. Only pulmonary infection is associated with the mortality in these patients as shown in **Table 4**.

For the diagnostic strategies of IA, the gold standard is the tissue biopsy but it is very invasive and could cause other complications such as bleeding in high-risk patients. Positive blood culture for IA is rare and the main difficulty of interpretation the positive culture from respiratory and other specimens is the lack of sensitivity and difficulty in distinguishing between infection and colonization. Galactomannan EIA test is an assay to detect galactomannan (GM) antigen, which is the main component of *Aspergillus* cell wall, using a rat anti-GM monoclonal antibody, EB-A2. It will recognize the 1,5-*β*-D-galactofuranoside sidechains. This test shows high specificity (>90%) and variable sensitivity (70% - 97%) for the detection of IA [31]. The reasons for the variability in sensitivity among many studies could be derived from the stage of IA, the use of prophylaxis, preemptive therapy with antifungal drugs, *Aspergillus* species, the number of sera and the cut-off. Possible false positive results of the test occur from cross reactivity with antigens in foods (e.g. pasta, rice, sauerkraut), other genera of fungi (e.g. *Penicillium, Paecilomyces, Alternaria, Geotrichum, Histoplasma*) or bacteria (e.g. bifidobacteria) and antibiotics (e.g. piperacillin/tazobactam, amoxicillin /clavulanic acid) [31]. From the result of galactomannan EIA test, the sensitivity of the test and negative predictive value were both 100 percent. This test can be used as a tool for excluding IA. However, the limitation of this study is that there were a small number of patients who performed the test (17.0%).

Aspergillus species isolated from patients with bone marrow transplant and solid organ transplant in North America were generally *Aspergillus fumigatus* [5]. In contrast, the most common *Aspergillus* species from patients with IA in India were *Aspergillus flavus* [8]. For this study, the major isolated species were *Aspergillus fumigatus* in the same way as North America, which is also consistent with previous report in our country [21].

For the treatment options of IA, it is dependent on many factors including host factors, underlying diseases, concomitant infections, and degree and duration of immunosuppression [1]. In some conditions of IA, surgical resection of the infected area is necessary [1]. This study showed that even surgery alone (33.3%) could save patients from IA. This would reflect that multidisciplinary approach for IA treatment is crucial. Voriconazole, targeting ergosterol biosynthesis of the fungi, is the antifungal agent of choice according to the IDSA guideline [1] for treatment of IA. It has been shown that voriconazole had a higher response rate in the treatment of IA compared to amphotericin B. However, limitation of the resource in our country and the presence of multiple comorbidities such as liver failure would complicate the voriconazole use. Amphotericin B is a polyene antifungal agent that can bind to the ergosterol on the cell membrane of the fungi leading to the formation of the ion channels and fungal cell death. However, it can also bind to cholesterol that could cause severe side effect to patients especially nephrotoxicity [1]. It can be used as an alternative drug in case of limitation of voriconazole use or refractory disease. Echinocandins are a new class of antifungal agent that can inhibit 1,3-*β*-glucan synthesis

leading to loss of cell wall integrity. This group includes caspofungin, micafungin, and anidulafungin. It can be used as an alternative drug against IA, as well [1]. From our result, it showed that voriconazole was the most effective agent especially when combined with surgery or alternative drugs.

Crude mortality rate for IA in North America was about 58 percent in 1995-1999 [13]. In Europe, the crude mortality rate was 27 percent [9] while in Thailand the crude mortality rate in previous report was 47 percent [3]. From this study, the case fatality rate was about 20.3%, which could reflect the improvement of treatment and early detection of the IA.

This study has some limitations. There could be some missing data from the misdiagnosis. It also had small sample size that might not represent the Thai population. Further studies that combine the data from every tertiary-care hospital in Thailand are necessary to be performed to understand the IA situation in Thai population.

In conclusion, the epidemiological data of Thai patients were similar to other countries. Although in this study, the vast majority of underlying disease was diabetes mellitus, it could not definitely conclude that diabetes mellitus was the only patients' risk factor to IA. This is because more than 790 people per 100,000 Thai population had diabetes mellitus as underlying disease in 2011 [2]. However, it raises our concerns that in both ketoacidosis and non-ketoacidosis diabetic patients presented with compatible IA manifestations, physicians should be aware of this infection. Further studies in the association between diabetes mellitus and IA will be inevitably necessary.

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