Invasive Aspergillosis in a Tertiary-Care Hospital in Thailand†

Sasisopin Kiertiburanakul MD*,
Chittima Thibbadee MD*, Pitak Santanirand PhD**

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** Department of Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University*
*** Department of Pathology, Faculty of Medicine Ramathibodi Hospital, Mahidol University*

Background: *Invasive aspergillosis (IA) is one of the most common and serious fungal infections in immuno-compromised host. Available data regarding IA among Asian patients are limited.*
Objective: *To determine patients' characteristics, clinical presentation, treatment, and outcomes of patients with IA in a Tertiary-care Hospital in Thailand.*
Material and Method: *The authors retrospectively reviewed medical and laboratory records of adult patients with IA from January 2000 to December 2005.*
Results: *Ninety-four patients were identified and classified as proven (n = 35), probable (n = 10), and possible IA (n = 49) according to the criteria designed for cancer patients (EORTC/MSG). Mean ± SD age was 48 ± 19 (range, 17-89) years old and 54 patients (57%) were male. Acute leukemia was the most common underlying condition (30%). Major predisposing factors were neutropenia (39%), chemotherapy (34%), and receiving corticosteroid therapy (25%). Common sites of infection were lungs (68%), sinus (17%), and eyes (8%). Aspergillus fumigatus (67%) was the most frequently isolated species. Amphotericin B followed by itraconazole was the mainstay of treatment. Thirty-six patients (38%) had complete or partial response to therapy whereas 44 patients (47%) died due to aspergillosis. Multivariate analysis showed that corticosteroid therapy [hazard ratio (HR) 10.65; 95% confidence interval (CI) 1.03-110.15, p = 0.047] and pulmonary infection [HR 18.06; 95% CI 4.28-76.17, p < 0.001] were significant predictive factors of death.*
Conclusions: *Epidemiology and outcomes of IA among Thai patients were comparable to those in Western countries. Early diagnosis of IA in patients at risk is still essentially required in order to offer appropriate therapy, decrease morbidity, and mortality rate.*

Keywords: *Aspergillosis, Aspergillus spp, Fungus, Thailand*

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Aspergillus spp., a filamentous fungus, is commonly isolated from soil, organic debris, food, and indoor environment, as well as in the hospital[1,2]. The primary sites of infection are lower respiratory tract and paranasal sinus[1]. There are two major forms of aspergillosis, non-invasive form and invasive form. Invasive aspergillosis (IA) means the invasion of tissues of lung or sinuses and/or dissemination through the blood stream[3]. IA is the most common fungal infection in severe immuno-compromised patients such as in bone marrow transplant recipients and patients with hematologic malignancy receiving intensive chemotherapy[4,5]. There has been a substantial increase in the number of patients at risk of developing IA during the past decades because of many reasons, such as an increase in the number of transplantations, the development of new invasive chemotherapy regimen, increased use of immunosuppressive agents, and ac-

Correspondence to : Kiertiburanakul S, Department of Medicine, Faculty of Medicine Ramathibodi Hospital, Rama 6 Rd, Bangkok 10400, Thailand. Phone: 0-2201-1922, Fax: 0-2201-2107, E-mail: rasal@mahidol.ac.th

quired immunodeficiency syndrome patients[1,6]. IA causes a high mortality rate because of the limitation in early diagnosis, the severity of the underlying condition of the patients and insufficient effective treatment options[1]. It is estimated that IA occurs in 20-25% of leukemia patients, in whom the mortality rate is 80-90%[7-9].

After reviewing the literatures, available data especially in English regarding IA among Asian patients are still limited[10]. Only a few publications regarding IA in Thai populations were found[11,12]. It was, therefore, the authors' objective to determine patients' characteristics, clinical presentation, treatment, and outcomes of adult patients with IA in the setting of a tertiary-care hospital in Thailand.

Material and Method

The authors retrospectively reviewed medical records, microbiological records that reported the growth of *Aspergillus* spp., and pathological records of adult patients who were diagnosed IA from January 2000 to December 2005 at Ramathibodi Hospital (800-bed medical school hospital in Bangkok, Thailand). Baseline patients' characteristics, clinical manifestations, as well as clinical course, diagnosis method, treatment and outcomes were retrieved and reviewed. The present study was reviewed and approved by the Institute Review Board.

Eligible patients were as follows: aged 15 years or older and those who met diagnostic criteria for proven, probable, or possible IA according to the definitions established by the European Organization for Research and Treatment of Cancer and the Mycosis Study Group (EORTC/MSG) of the National Institute of Allergy and Infectious Disease[13].

"Proven IA" is defined as isolation of *Aspergillus* spp. from a normally sterile site obtained by a sterile procedure (from needle aspiration or biopsy specimen) or identification of typical hyphal elements compatible with *Aspergillus* spp. with evidence of associated tissue damage from histopathological or cytological report and clinically or radiologically abnormal site consistent with infection. "Probable IA" implies at least one host factor criterion as defined by the EORTC/MSG[13] and the presence of positive culture results or cytological evidence or direct microscopic evaluation for *Aspergillus* spp. (microbiological criteria), and one major (or two minor) clinical criteria defined by the EORTC/MSG definitions[13]. If there is one microbiological criterion (as probable IA) or one major (or two minor) clinical criterion in the appropriate host setting, the patients were considered to have "possible IA". Aspergillosis was considered to be disseminated if the infection was documented at $\geq$ two noncontiguous organ sites reflecting blood-borne spread, whereas the infection was classified as multisites if the sites of infection were within one organ system[13,14].

Response to therapy was categorized as follows[15,16]: (1) complete response was defined by resolution of all clinical, laboratory and radiographic parameters, as well as the conversion of the fungal culture results from positive to negative, if results were available; (2) partial response was defined by clinically important improvements in disease activity (including $\geq$ 50% improvements in radiographic finding) or $\geq$ 50% improvement in fungal disease in patients who ultimately died, with the absence of positive results of fungal culture or histopathological examination on autopsy; (3) stable disease was defined by clinical improvement and < 50% improvement in radiographic findings; (4) failure occurred if the patient had progression of fungal infection; (5) relapse was defined by recurrence of any sign or symptom of fungal infection during follow-up after initial response; and (6) death attributed to IA was defined by positive results of fungal culture or histopathological examination on autopsy or negative results of other fungi, bacterial culture and virus detection or undefined other causes of death.

Statistical analysis

Continuous data were shown as mean and standard deviation (SD) and were compared using independent *t*-test. Categorical data were shown as frequency and percentage. Chi-square test or Fisher's exact test was used for categorical data analysis. Kaplan-Meier analysis was applied to estimate survival times. Log-rank test was used to compare the survival time among baseline characteristics factors. All analyses were performed using SPSS version 11.0. A p-value $\leq$ 0.05 was considered statistically significant.

Results

Ninety-four patients with evidence of IA were identified. Mean age $\pm$ SD was 47.9 $\pm$ 19.4 (range, 17-89) years 54 patients (57.4%) were male. There was a wide range of underlying conditions including hematological malignancy in 36 patients (38.3%), in whom acute leukemia (29.8%) was the most common. The important predisposing factors were neutropenia in

Table 1. Demographic and clinical characteristics of 94 patients with invasive aspergillosis

Characteristics	Number (%)
Mean age ± SD, years (range)	47.9±19.4 (17-89)
Gender	
Male	54 (57.4)
Female	40 (42.6)
Underlying conditions[a]	78 (83.0)
Malignancy	38 (40.4)
Hematology	36 (38.3)
Solid	2 (2.1)
Diabetes mellitus	16 (17.0)
Systemic lupus erythematosus	14 (14.7)
Human imnunodeficiency virus infection	7 (7.4)
Transplantation	5 (5.3)
Chronic obstructive pulmonary diasese	2 (2.1)
Others[b]	10 (10.5)
Predisposing factors[a]	61 (64.9)
Neutropenia	37 (39.4)
Chemotherapy	32 (34.0)
Corticosteroid	23 (24.5)
Immunosuppressive drugs[c]	14 (14.9)
Sites of infection[d]	
Lungs	68 (68.0)
Sinus	17 (17.0)
Eyes	8 (8.0)
Central nervous system	5 (5.0)
Skin	1 (1.0)
Cardiovascular system	1 (1.0)

[a] Some patients had more than one underlying disease
[b] Thalassemia, myelodysplastic syndrome, cirrhosis, multiple sclerosis, Cushing syndrome, idiopathic thrombocytopenic purpura, myasthenia gravis, aplastic anemia
[c] Cyclosporin, cyclophosphamide, tacrolimus, myclophenolate, azathiopine
[d] Some patients had more than one site of infection

37 patients (39.4%), receiving intensive chemotherapy in 32 patients (34.0%), and receiving corticosteroid therapy 23 patients (24.5%). Immunosuppressive drugs including myclophenolate, cyclophosphominde, cyclosporine, azathiopine, tacrolimus, and methotrexate were observed. Sixteen patients (17.0%) had no underlying conditions, and 33 patients (35.1%) did not have any predisposing factor. Median time to diagnosed IA was nine (range, 1-72) days after admission and 18 patients (19.1%) were diagnosed IA within 48 hours of hospitalization. The demographic features, underlying condition and predisposing factors are shown in Table 1.

Patients were classified as proven IA in 35 patients (37.2%), probable IA in 10 patients (10.7%), and possible IA in 49 patients (52.1%). Of 94 patients, there were totally 100 sites of infection. The most frequent sites of infection were lungs 68.0%, followed by sinus 17.0%, eyes 8.0%, central nervous system 5.0%, skin 1.0%, and cardiovascular system 1.0%. Six patients (6.4%) had disseminated infection.

Table 2. Clinical manifestations of 94 patients with invasive aspergillosis

Characteristics[a]	Number (%)
Temperature < 36°C or > 38°C	73 (77.7)
Cough	46 (48.9)
Dyspnea	45 (47.9)
Eyes pain with visual impairment	9 (9.6)
Non-massive hemoptysis	6 (6.4)
Cranial nerve palsy	7 (7.4)
Headache	7 (7.4)
Mental status change	3 (3.2)
Generalized malaise/weight loss	3 (3.2)
Pleuritic chest pain	2 (2.1)
Black necrotic lesion	2 (2.1)
Nasal discharge	2 (2.1)
Epistaxis	2 (2.1)
Nausea/vomiting	1 (1.1)
Stuffiness	1 (1.1)

[a] Some patients had more than one clinical manifestation

Table 3. Antifungal therapy and outcomes of 94 patients with invasive aspergillosis

Characteristics	Number (%)
Medication[a]	
Amphotericin B	56 (58.9)
Itraconazole	37 (39.4)
Liposomal amphotericin B	9 (9.6)
Caspofungin	5 (5.3)
Voriconazole	2 (2.1)
Response to therapy at the same admission	
Complete	26 (27.7)
Partial	10 (10.6)
Stable	6 (6.4)
Failure	1 (1.1)
Relapse	1 (1.1)
Death	43 (45.7)
Undetermined outcome	7 (13.7)
Death rate at the end of the study	75 (79.8)
Aspergillosis related	44 (46.8)
Other causes related	16 (17.1)
Undetermined cause of death	15 (16.0)

[a] Some patients received more than one antifungal agent

The most common clinical presentations were temperature less than 36°C or more than 38°C (77.7%), cough (48.9%), and dyspnea (47.9%) (Table 2). Thirteen patients (13.8%) had concurrent infections, which were granulomatous diseases (6 patients), cytomegalovirus (4 patients), non-tuberculous mycobacteria (2 patients), and *Pneumocystis jirovecii* pneumonia (1 patient).

According to isolated species, 80 patients (85%) had positive culture of 107 isolates for *Aspergillus* spp. The vast majority of isolates was *Aspergillus fumigatus* 72 isolates (67.3%), followed by *A. flavus* 26 isolates (24.3%), *A. niger* 5 isolates (4.7%), and *A. terreus* 4 isolates (3.7%). Twelve patients (15%) had more than one species isolated.

Computed tomography scan of the chest was performed in 28 patients. The most common radiological finding in patients with invasive pulmonary aspergillosis was pulmonary nodule (11 patients). Only three patients had a halo sign but none had crescent sign.

Amphotericin B followed by itraconazole was the mainstay for treatment. Antifungal therapy and outcomes are shown in Table 3. Twenty-six patients (27.7%) and 10 patients (10.6%) had complete and partial response to the treatment, respectively. Seven patients (7.4%) had stable disease or treatment failure. One patient had relapse on the twenty-second day after stopping medication.

Forty-three patients (45.7%) died from IA at the same admission period. The authors did not know the outcome of the seven patients (13.7%) because they were discharged against advice. At the end of the present study, 75 patients had died (79.8%), 44 patients whom were IA related. The survival rate at the end of study was 17%. Median survival for patients who died from all causes of death was approximately 30 days (95% confidence interval [CI], 0-62.30). Median survival for patients who died from IA was approximately 15 days (95% CI, 0-30.56) after the diagnosis.

Univariate analysis showed that corticosteroid therapy (hazard ratio [HR] 10.28; 95% CI, 1.25-84.43; p = 0.013) and pulmonary infection (HR 17.7; 95% CI, 4.66-67.40; p < 0.001) were statistically significant predictive factors of death. In multivariate analysis, corticosteroid therapy (HR 10.65; 95% CI 1.03-110.15, p=0.0470), and pulmonary infection (HR 18.06; 95% CI, 4.28-76.17; p <0.001) were also statistically significant predictive factors of death (Table 4, 5). Median survival of patients who received and did not receive corticosteroid therapy was 6 days (95% CI, 0.7-11.30) and 30 days (95% CI, 0.95-36), respectively (p <0.001). Fur-

Table 4. Univariate analysis of risk factors associated with death in 94 patients with invasive aspergillosis

Factors	Death (%)	Hazard ratio (95%CI)	p-value
Age ≥ 65 years	32 (72.7)	1.55 (0.49-4.88)	0.55
Male gender	23 (63.9)	0.05 (0.16-1.57)	0.27
HIV/AIDS	3 (60.0)	0.62 (0.95-4.06)	0.63
Diabetes mellitus	8 (72.7)	1.55 (0.49-4.88)	1.00
Malignancies	13 (76.5)	1.57 (0.43-5.65)	0.55
Neutropenia	13 (72.2)	1.77 (0.3-3.9)	1.00
Corticosteroid therapy	16 (94.1)	10.28 (1.25-84.43)	0.013
Chemotherapy	10 (71.4)	1.10 (0.29-4.08)	1.00
Immunosupressive drugs	9 (90.0)	4.60 (0.54-39.44)	0.23
Pulmonary infection	38 (88.4)	17.70 (4.66-67.4)	<0.001

AIDS; acquired immunodeficiency syndrome, CI; confidence interval, HIV; human immunodeficiency virus

Table 5. Multivariate analysis of risk factors associated with death in 94 patients with invasive aspergillosis

Factors	Death (%)	Hazard ratio (95%CI)	p-value
Corticosteroid therapy	16 (94.1)	10.65 (1.03-110.15)	0.047
Pulmonary infection	38 (88.4)	18.06 (4.28-76.17)	<0.001

CI; confidence interval

thermore, median survival of patients with and without pulmonary infection was 9 days (95% CI, 5.15-12.85) and > 1,776 days, respectively (p = 0.001).

Discussion

To the authors' knowledge, the present study is the largest study regarding IA in Asian populations and in Thailand. The presented data indicated that IA was common and could cause lethal fungal infection in immunocompromised host and even in a normal host. In clinical practice, there are problems for the IA diagnosis and it remains an underdiagnosed disease[17]. Clinical symptoms and signs are not specific and the diagnosis is based on clinical presentations, radiological and microbiological data[1]. Although the recommended definitions for clinical researchers have been developed[13], there are still uncertainty and controversy regarding the best methods for establishing the diagnosis of IA. Most of our patients were diagnosed as nosocomial infection; approximately 20% of patients were diagnosed as within 48 hours after admission. IA can be occurred as community-acquired infection as well.

According to the review of publications regarding IA from 50 studies (1,941 patients), the most common underlying conditions were leukemia or lymphoma (42.6%), followed by bone marrow transplant (25.8%) and solid-organ transplant recipients (13.0%)[7]. Risk factors for IA including underlying lung diseases, prolonged neutropenia, immunosuppressive therapy, corticosteroid therapy and graft-versus-host disease are also well established[7]. These underlying conditions and factors were comparable to that in the presented patients. Furthermore, diabetes mellitus and systemic lupus erythematosus were found as the second and the third common underlying conditions in the patients of the present study. Although our institute is not a transplantation center, there were roughly 85 recipients for bone morrow transplantation and 350 recipients for kidney or liver transplantation during the present study period. Only five bone marrow or organ transplant recipients were noted. Of 94 patients, 17% of them had no underlying conditions suggesting that other factors may further contribute to infections.

Aspergillosis is acquired primarily from inhalation. Spores are deposited deep in the lungs leading to a variety of clinical syndromes[2]. A common presentation of IA among the presented patients was pulmonary infections (68%). Invasive pulmonary aspergillosis was difficult to make a diagnosis, especially in the early stage of its course, because respiratory symptoms and signs are non-specific[18]. Chest radiography provides little information at the early stage of the disease because of a high incidence of normal and nonspecific findings[18]. Computed tomography (CT) is the most useful radiological examination[1,19]. However, CT of the chest was performed in only 30% of the presented patients. Although the halo sign and the crescent sign on CT are suggestive of IA[20], only a small proportion of patients with nodule lesion(s) and halo sign were found from the present study. The authors could not find the crescent sign, which is a late feature and usually occurs after 2-3 weeks of treatment when the patients had no neutropenia, because the physicians did not routinely perform CT at the later period as a follow up tool.

Brain, skin and heart valve are the most frequent sites of dissemination[1,19]. Nevertheless, few of the presented patients had central nervous system and skin infections presented as disseminated infections. The authors also found six postmortem cases that did not receive the diagnosis and therapy, four patients had pulmonary infection, whereas the others had disseminated infection.

Only a few of *Aspergillus* spp. of approximately 200 species are known to be pathogenic for humans[2]. *A. fulmigatus* is the most common etiology, being responsible for 80-90% of human infections[8,21,22]. Common isolated species in the present study were *A. fumigatus* (67%), *A. flavus* (24%), and *A. niger* (5%).

The authors found that some patients had concurrent granulomatous disease. This was different from other studies, in which cytomegalovirus infection was more common than granulomatous disease[23]. Pulmonary injury caused by previous respiratory infections with *Mycobacterium tuberculosis* may be a possible predisposing factor for pulmonary aspergillosis as reported in patients with *Pneumocystis jirovecii* or cytomegalovirus infections[24].

Despite advance in new antifungal agents, amphotericin B followed by oral irtaconazole was the mainstay treatment in the presented patients. Its efficacy may be limited by adverse effect, such as renal impairment and infusion reaction to amphotericin B and poor bioavailability of itraconazole capsule. Limitations of options for antifungal treatment for the presented patients were the high cost of lipid formulation of amphotericin B and other new drugs as well as the availability of new azoles and echinocandins at the beginning of the study period.

The reported mortality varies from 30-90%

[4,7,8]. The crude mortality in IA is high, more than 90% if untreated, and strongly associated with the underlying condition, stage of the underlying diseases, the extent of the aspergillosis and antifungal treatment[4,7,8]. Patients with central nervous system involvement, disseminated infections, and bone marrow transplant with pulmonary aspergillosis, including liver transplant recipients and patients with AIDS had a high mortality rate[1,7,21]. The mortality rate of IA were 99%, 86% and 66% for cerebral, pulmonary and sinus aspergillosis, respectively[8]. The present data shows that IA caused the high mortality. Patients with pulmonary infection and corticosteroids therapy had a significantly higher risk of death. Corticosteroid therapy is associated with an increased IA because it impairs human immune function and the conidicidal activity of human macrophage. Increasing growth rate of *Aspergillus* spp. by hydrocortisone was reported as an additional mechanism[25]. The authors also observed that neutropenia was the most common predisposing factor but it did not predict survival.

The present study had some limitations. First, there were some missing data and this was not unexpected in view of the nature of a retrospective study. Second, it had small sample size. Last, the authors reported approximately half of the patients as possible category of IA according to the EORTC/MSG criteria. IA was difficult for diagnosis because many patients who were at risk for IA also had conditions that might preclude invasive diagnosis procedures.

In summary, patients' characteristics, clinical presentations, and treatment outcomes among Thai patients were comparable to those in Western countries. Patients with IA had a high mortality rate. The development of new diagnostic tools and powerful antifungal agents with less toxic and low cost may reverse the increasing incidence and fatality rate of IA in patients at risk.

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โรคราแอสเพอร์จีลัสชนิดรุกรานในโรงพยาบาลที่เป็นตติยภูมิในประเทศไทย

ศศิโสภิณ เกียรติบูรณกุล, จิตติมา ธิบดี, พิทักษ์ สันตนิรันดร์

***ภูมิหลัง**: โรคราแอสเพอร์จีลัสชนิดรุกรานเป็นหนึ่งในการติดเชื้อราที่พบได้บ่อยที่สุด และเป็นการติดเชื้อราที่มีความรุนแรงในผู้ป่วยที่มีภูมิคุ้มกันบกพร่อง ข้อมูลที่เกี่ยวกับโรคราแอสเพอร์จีลัสชนิดรุกรานในชาวเอเชียมีน้อย*

***วัตถุประสงค์**: เพื่อศึกษาลักษณะของผู้ป่วย อาการแสดงทางคลินิก การรักษาและผลการรักษาในผู้ป่วยที่เป็นโรคราแอสเพอร์จีลัสชนิดรุกรานในโรงพยาบาลที่เป็นทุติยภูมิในประเทศไทย*

***วัสดุและวิธีการ**: ทำการศึกษาจากเวชระเบียนในระหว่างปี พ.ศ. 2543 – พ.ศ. 2548*

***ผลการศึกษา**: มีผู้ป่วยทั้งหมด 94 ราย ได้รับการวินิจฉัยว่าเป็นโรคราแอสเพอร์จีลัสชนิดที่พิสูจน์ได้แน่นอน (35 ราย) ชนิดที่มีความเป็นไปได้ (10 ราย) และชนิดที่อาจจะเป็นได้ (49 ราย) ตามเกณฑ์การวินิจฉัยในผู้ป่วยมะเร็ง มีอายุเฉลี่ย 48 ปี (ค่าเบี่ยงเบนมาตรฐาน 19) ผู้ป่วย 54 ราย (ร้อยละ 57) เป็นเพศชาย โรคมะเร็งเม็ดเลือดขาวเป็นโรคประจำตัวที่พบบ่อยที่สุด (ร้อยละ 30) ปัจจัยอื่นที่พบร่วมด้วยคือ เม็ดเลือดขาวชนิดนิวโทรฟิลต่ำ (ร้อยละ 39) ได้รับยาเคมีบำบัด (ร้อยละ 34) และได้รับยากลุ่มสเตียรอยด์ (ร้อยละ 25) ตำแหน่งที่พบว่ามีการติดเชื้อได้บ่อยที่สุดคือ ปอด (ร้อยละ 88) ไซนัส (ร้อยละ 17) และตา (ร้อยละ 8) เชื้อแอสเพอร์จีลัส ฟูมิกาตัส (ร้อยละ 67) เป็นสายพันธุ์ที่แยกได้บ่อยที่สุด แอมโฟเทอริซิน บี ตามด้วยไอทราโคนาโซล เป็นยาหลักที่ใช้บ่อยที่สุดในการรักษา ผู้ป่วย 36 ราย (ร้อยละ 38) มีการตอบสนองต่อการรักษาดีหรือบางส่วน ในขณะที่ผู้ป่วย 44 ราย (ร้อยละ 47) เสียชีวิตจากการติดเชื้อแอสเพอร์จีลัสชนิดรุกราน ผู้ป่วยที่ได้รับยากลุ่มสเตียรอยด์มีความเสี่ยงที่จะเสียชีวิตมากกว่า 10.65 เท่า (ร้อยละ 95 ความเชื่อมั่น 1.03-110.15) และการติดเชื้อที่ปอดมีความเสี่ยงที่จะเสียชีวิตมากกว่า 18.06 เท่า (ร้อยละ 95 ความเชื่อมั่น 4.28-76.17) อย่างมีนัยสำคัญทางสถิติ*

***สรุป**: ระบาดวิทยาและผลการรักษาของผู้ป่วยที่มีโรคราแอสเพอร์จีลัสชนิดรุกรานในประเทศไทยไม่มีความแตกต่างกับข้อมูลของประเทศกลุ่มตะวันตก มีความจำเป็นในการที่จะวินิจฉัยโรคราแอสเพอร์จีลัสชนิดรุกรานตั้งแต่เริ่มแรกในผู้ป่วยที่มีความเสี่ยงสูง เพื่อให้การรักษาที่เหมาะสม ซึ่งจะส่งผลให้อัตราทุพพลภาพและอัตราตายลดลง*