Medical Mycology Month 2010, **Early Online**, 1–13

informa
healthcare

Invasive aspergillosis in developing countries

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To review invasive aspergillosis (IA) in developing countries, we included those countries, which are mentioned in the document of the International Monetary Fund (IMF), called the Emerging and Developing Economies List, 2009. A PubMed/Medline literature search was performed for studies concerning IA reported during 1970 through March 2010 from these countries. IA is an important cause of morbidity and mortality of hospitalized patients of developing countries, though the exact frequency of the disease is not known due to inadequate reporting and facilities to diagnose. Only a handful of centers from India, China, Thailand, Pakistan, Bangladesh, Sri Lanka, Malaysia, Iran, Iraq, Saudi Arabia, Egypt, Sudan, South Africa, Turkey, Hungary, Brazil, Chile, Colombia, and Argentina had reported case series of IA. As sub-optimum hospital care practice, hospital renovation work in the vicinity of immunocompromised patients, overuse or misuse of steroids and broad-spectrum antibiotics, use of contaminated infusion sets/fluid, and increase in intravenous drug abusers have been reported from those countries, it is expected to find a high rate of IA among patients with high risk, though hard data is missing in most situations. Besides classical risk factors for IA, liver failure, chronic obstructive pulmonary disease, diabetes, and tuberculosis are the newly recognized underlying diseases associated with IA. In Asia, Africa and Middle East sino-orbital or cerebral aspergillosis, and *Aspergillus* endophthalmitis are emerging diseases and *Aspergillus flavus* is the predominant species isolated from these infections. The high frequency of *A. flavus* isolation from these patients may be due to higher prevalence of the fungus in the environment. Cerebral aspergillosis cases are largely due to an extension of the lesion from invasive *Aspergillus* sinusitis. The majority of the centers rely on conventional techniques including direct microscopy, histopathology, and culture to diagnose IA. Galactomannan, β-D glucan test, and DNA detection in IA are available only in a few centers. Mortality of the patients with IA is very high due to delays in diagnosis and therapy. Antifungal use is largely restricted to amphotericin B deoxycholate and itraconazole, though other anti-*Aspergillus* antifungal agents are available in those countries. Clinicians are aware of good outcome after use of voriconazole/liposomal amphotericin B/caspofungin, but they are forced to use amphotericin B deoxycholate or itraconazole in public-sector hospitals due to economic reasons.

Keywords aspergillosis, epidemiology, *Aspergillus flavus,* cerebral aspergillosis, endophthalmitis

Introduction

Aspergillus species cause a wide spectrum of diseases including allergic syndrome, colonizing sinuses or cavities, acute or subacute and chronic invasive diseases. Invasive aspergillosis (IA) is a disease of concern, as it is a leading cause of death in patients with hematological malignancies and transplant recipients. With the use of broad-spectrum antifungal agents for prophylaxis in those high risk patients, the incidence and fatality rates of IA have declined in recent years, but new risk factors have emerged [1,2]. The incidence rates among patients at risk vary according to local epidemiology. Though the epidemiology of the disease and magnitude of the problem are well studied in the developed world, literature is scanty from developing countries.

Received 31 March 2010; Received in final revised form 19 June 2010; Accepted 28 June 2010

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DOI: 10.3109/13693786.2010.505206

Developing countries are home to around five-sixth of the world's population [3] and the countries are located in the tropical and sub-tropical regions of Asia, Africa, South and Central America where fungi thrive well in the hot and humid climate [4]. These countries have large numbers of poor people with few modern medical facilities at one end and rapidly developing prosperity and health care on the other end. Below-optimum hospital care practice in the economically deprived group, and modern medical intervention including transplantations in the prosperous group have led to an increase in number of invasive fungal diseases including IA in both groups [4]. Further, the large number of untrained health providers (quacks), the misuse of steroids, intravenous drug abuse, availability of spurious medical care infusion sets, are possible additional risk factors for IA in those countries [4,5]. As the number of persons at risk of IA in developing countries is huge, it is important to review the available literature on IA from these countries.

To identify the list of developing countries we followed the document of the International Monetary Fund database for the Emerging and Developing Economies, 2009 [6]. A PubMed/Medline literature search was performed for IA reported during 1970 through March 2010 from these countries. Articles were searched with the following Keywords: '*Aspergillus*', 'Aspergillosis', '*A. fumigatus*', '*A. flavus*', 'Leukemia', 'Bone Marrow Transplantation', 'Transplantation', 'Infections'. Reports with allergic *Aspergillus*-related disease and superficial *Aspergillus* infection were not considered. Published literatures on IA consist mainly of case series and case reports from a few tertiary care centers located in China [7–9], India [4,5, 10–12], Thailand [13–16], Pakistan [17–21], Iran [22–35], South Africa [36–40], Saudi Arabia [41–46], Sri Lanka [47–49], Egypt [50–56], Brazil [57–59], Argentina [60–65], Barbados [66], Bangladesh [67], Bolivia [68], Central African Republic [69], Chile [70–72], Colombia [73,74], Croatia [75,76], Estonia [77], Hungary [78,79], Iraq [80], Jamaica [81], Kuwait [82–84], Lebanon [85,86], Libya [87], Lithuania [88], Mexico [89–91], Morocco [92,93], Malaysia [94], Oman [95], Poland [96–98],Tunisia [99], Turkey [100–118], Sudan [40,119–122], Senegal [123], and Zimbabwe [124]. The present review was prepared after going through each article.

Epidemiology

In developing countries the risk factors for development of IA appear similar to the developed world, though certain differences are observed due to local epidemiology including patient characteristics, cultural habit, patient care practices [4,5,8,10,15,25,33,36,49,59,60,67,76,94,125–130]. The risk factors are outlined in Table 1. Few factors including hematological malignancies, various transplantations, chronic granulomatous disease, advanced AIDS, cytomegalovirus pneumonia are well documented [11,12,34,38,45,53,57,59, 62,131,132]. In a systematic review of IA from a tertiary care hospital in Thailand, acute leukemia was the commonest underlying disease (30%); neutropenia (39%), chemotherapy (34%), and corticosteroid therapy (25%) were major predisposing factors [15]. Diabetes mellitus (17%) and systemic lupus erythematosus (15%) were found as the second and third common underlying conditions in that study.

Table 1 Risk factors for invasive aspergillosis in developing countries.

Classic factors	Non-neutropenic factors
Acquired neutrophil defect	Chronic obstructive pulmonary disease
Neoplastic disease with persistent neutropenia	Chronic and acute liver disease
High dose of corticosteroids	Intracranial surgery
Immunosuppressants	Reactive airway disease
Bone marrow and solid organ transplants	Rheumatoid arthritis
Aplastic anaemia/myelodysplastic syndrome/myelofibrosis	ICU stay
AIDS – only when CD4 <50 cells	
Primary defect of neutrophils	Newly recognized factors
Chronic granulomatous disease	
Hyper-IgE syndrome (Job's)	Intravenous infusion/drug abuse
	Diabetes mellitus
	Burn wound
	Application of tapes/ECG leads
	Allergic broncho pulmonary aspergillosis/asthma

In haemato-oncological and haematopoietic allogenic stem cell transplant (HSCT) patients, IA is consistently the commonest fungal infection, though the incidence varied between different series [11,12,16,33,59,76,79]. The incidence of invasive candidiasis was invariably lower than IA in those patients, possibly due to routine use of fluconazole prophylaxis in such patients. The studies from Iran, India, and Tunisia reported IA in ~15% patients with hematological malignancies [12,33,99]. In a hospital from Chile, IA was the commonest (63.4%) fungal infection among all fungal diseases in patients with haemato-oncological malignancy and HSCT [71]. In HSCT recipients the incidence of IA ranged between 3–15% in different studies [30,59]. In Brazil the number of patients with IA changed with structural change of a bone-marrow unit [59]. In a study from Hungary, IA was responsible for mortality in 40% of all deaths due to established infections in patients with HSCT [79]. The patients who acquire IA had a high (83%) mortality rate within 60 days of diagnosis. Indication of mortality included corticosteroid use, neutropenia at the time of diagnosis, change of antifungal agent due to toxicity, and disseminated disease [59].

IA occurs in ~13% patients with lung transplantation and is always associated with either acute rejection episode or suture damage [70]. The incidence is consistent with the observations in the developed world [2]. In contrast IA was reported at a higher rate (2–4%) in patients with renal transplantation in developing countries [28,118] compared to <1% in developed countries [2]. This finding might be related to poor hygiene and sanitation in developing countries [118]. Due to inadequate cadaveric and living related organ supply, many patients with end-stage renal disease from the developed world go to the third-world countries for living unrelated (paid) kidney transplantation and acquire IA due to below optimum hospital care practices [133]. IA also complicates the patients undergoing liver transplantation in those countries. Multiple risk factors including hepatic failure, haemodialysis, and cytomegalovirus infection act in concert to wreck the immunity of patients with liver transplantation to *Aspergillus* species [7,22,26,27,96,134]. Heart transplantation is still rare in developing countries. Experience from a few centers reported IA cases, but the infection rate is not known [98,102].

Though IA is a common complication in patients with hematological malignancies [11,12,59], the reports of the IA in solid tumors are rare. In a study from China 45 (2.6%) of 1711 lung cancer patients had pulmonary aspergillosis [8]. On univariate analysis chemotherapy, steroid use, and stage IV diseases were found to be the significant risk factors; and on multivariate analysis only stage IV disease was the significant risk factor. Neutropenia and corticosteroid therapy correlated statistically with pulmonary aspergillosis in patients who died [8].

Apart from these classical risk factors, other factors like critically ill patients admitted in intensive care units, patients with pre-existing lung disease (emphysema, chronic obstructive pulmonary disease, healed tuberculosis cavity), and patients with liver failure are also claimed to be associated with IA in developing countries. IA in the intensive care unit patients have been reported infrequently [36,135]. However, the co-factors (multiple intravenous lines, tracheostomy, endotracheal intubation, other invasive procedures, prolonged corticosteroid and antibiotic therapy) in ICUs are either higher in numbers or misused more in developing countries due to sub-optimal protocol adherence by ICU staff [136]. Therefore, in all probability the incidence of IA is expected to be high in ICUs of developing countries. The association of liver failure and IA had been reported from centers in China [137,138]. Decompensated liver disease has been noted to be a cause of acquired immunodeficiency state, and malnourishment in hepatic failure adds to the severity of the condition. Further, frequent use of broad-spectrum antibiotics, steroids, and intensive monitoring make those patients susceptible to IA [139,140].

The elderly patients with chronic obstructive pulmonary disease are often colonized with *Aspergillus* species. They receive corticosteroids (oral or inhaled), are often critically ill and hospitalized, receive multiple antibiotics, and become susceptible to IA. Such patients were reported from China and India [125,141]. A rare case of *Aspergillus* endocarditis was reported in a patient with allergic bronchopulmonary aspergillosis (ABPA) [125]. Patients with structural lung-airway disease due to previous tuberculosis have been reported to acquire IA. Though developing countries have large number of patients with tuberculosis, IA is infrequently reported, except one autopsy series from Mumbai [126,142,143]. The autopsy series from Mumbai reported tuberculosis as a risk factor in 28% patients [126].

Recent studies reported the association of diabetes mellitus [143–146] and corticosteroid therapy [60,147,148] with IA in developing countries. Uncontrolled diabetes is a known risk factor for zygomycosis in India [149]. Possibly the decreased functional activity of macrophages in patients with diabetes predisposes the patients to IA also [143,146]. Intracranial surgery is an additional risk factor for isolated intracranial aspergillosis [61,150,151], and permanent pacemaker placement for *Aspergillus* endocarditis in immunocompetent hosts of developing countries [152]. From Argentina, a unique study reported *Aspergillus* osteomyelitis in 11% patients during childhood, which was significantly associated with chronic granulomatous disease [62].

A considerable number of IA cases in developing countries has been reported in immunocompetent host especially those with isolated cerebral aspergillosis and rhino-orbito-cerebral aspergillosis [15,21,37,41,42,75,85,87,94,111,123,150,153,154]. In a series from Thailand, 86% patients with cerebral aspergillosis had either diabetes or no known immunocompromised status [13]. This finding of interest may be due to the high spore count in the environment of tropical countries [73,99] or due to less investigation of host immunity status.

Aspergillus species

The commonest species implicated in IA is *Aspergillus fumigatus*. Other Aspergilli including *A. flavus*, *A. terreus*, *A. niger*, *A. ustus,* and *A. alliaceus* have been implicated as pathogens less commonly in patients with IA [43,45,100,101,127,155–158]. However, in developing countries *A. flavus* has been isolated comparatively at higher frequency from sino-orbital aspergillosis or *Aspergillus* eye infections [21,121,122,127,154,159,160,166–168]. Few of those series reported *A. flavus* to be the exclusive agent or several times more common than *A. fumigatus*. Higher environmental contamination due to *A. flavus* may lead to increased frequency of *A. flavus* infections in developing

countries [73,99]. *A. niger* has been reported as the etiological agent in patients with endophthalmitis [43,127,155], and endocarditis [23]. *A. terreus* [156,157] and *A. ustus* [100,107] have been isolated from patients with endophthalmitis. *A. terreus* was also isolated from a case of aortic root abscess and pseudoaneurysm post-cardiac surgery [161]. Rare cases of *A. nidulans* or *A. glaucus* isolation were reported from patients with brain abscess [85,162].

Pulmonary aspergillosis

Pulmonary aspergillosis is highly prevalent in developing countries [109,134,163]. In the series of IA reported from a tertiary care hospital in Thailand [15], the lung was involved in 68% of cases followed by sinuses (17%), eyes (8%), and brain (5%). Similarly pulmonary aspergillosis is by far the most common form of IA in transplant patients [11,59,71,79,103,118]. In an autopsy study of childhood pneumonia from Bangladesh, pulmonary aspergillosis was diagnosed in 3% of all pneumonias and 10% of necrotizing pneumonias [67]. The clinical course of pulmonary aspergillosis may be acute or chronic depending on host immune status and the amount of exposure of *Aspergillus* spore. Other than classical manifestations of pulmonary aspergillosis, certain uncommon clinical presentations have been observed in developing countries. Some of these observations include development of invasive pulmonary aspergillosis (IPA) in patients with colonizing aspergillosis (in tubercular cavity) [126,143], ABPA or aspergilloma [57,164], and bronchial asthma [8,126]. Possibly, the long period of steroid therapy allowed fungal hyphae from a cavitary lesion or localized mass lesion to invade the lung parenchyma. IPA was also found to be associated with anti neutrophilic cytoplasmic antibodies positive vasculitis [91,165]. In a series of 157 patients with vasculitis, seven (4.5%) developed IPA; two had Wegener's granulomatosis and five had microscopic polyangitis. IPA developed within 2–13 weeks of immunosuppressive therapy [165].

Isolated invasive *Aspergillus* tracheobronchitis is an uncommon clinical form of invasive aspergillosis and mostly reported in patients with severely immunocompromised status due to transplantation or haematological malignancies. Of note, 19 patients with isolated invasive *Aspergillus* tracheobronchitis were reported from China, who had impaired airway structures or defense functions rather than severely immunocompromised status. Only three (16%) patients had neutropenia. Malignancy (13 cases of solid tumor, one case of lymphoma) was the most common underlying disease. The disease could be classified into four different forms: superficial infiltrative, full layer involvement, occlusion, and mixed type [128].

Sino-orbital-cerebral aspergillosis

This clinical type is a highly prevalent disease in tropical countries, though much confusion exists regarding its categorization [92,93,109,119,121,159,160,166–168]. The most commonly accepted classification divides invasive fungal rhinosinusitis (FRS) into acute invasive FRS, granulomatous invasive FRS, and chronic invasive FRS [166]. The prevalence of acute invasive FRS is more or less similar in the developed and developing world. [168,169] However, in the developed world hematological malignancy is the commonly associated underlying disease in acute invasive FRS with higher isolation of *A. fumigatus*. In contrast uncontrolled diabetes is more commonly associated in developing countries with higher isolation of *Zygomycetes* in such a setting. This may be due to the high prevalence of uncontrolled diabetes in these countries [149]. Granulomatous invasive FRS is primarily seen in Sudan, India, Pakistan, and Saudi Arabia. The disease is described by a time course of >12 weeks with enlargement of mass in the cheek, nose, paranasal sinuses and the orbit in the immunocompetent host. Histopathologically it is characterized by granulomatous inflammation and considerable fibrosis, with presence of scanty hyphae, and *A. flavus* is the primary agent isolated [21,121,122,154,168]. In contrast, chronic invasive disease is seen in any part of the world and is characterized by dense accumulation of hyphae, presence of vascular invasion, sparse inflammatory reaction, and *A. fumigatus* isolation in patients with diabetes and on corticosteroid treatment [168,169]. It is noteworthy that *A. flavus* is the common etiological agent of all types of FRS except acute invasive type in Sudan and India [119,122,159,160,166–168].

Cerebral aspergillosis

Although *Aspergillus* spp. have a predilection for the central nervous system and many series of cerebral aspergillosis are reported from developing countries, the studies are limited by non-availability of relevant microbiological analysis. Most prevalence reports are based on surgical practice and postmortem data [144,147,150,154]. The reports of these series at least denoted high prevalence of cerebral aspergillosis in developing countries. The central nervous system involvement by *Aspergillus* species is either by haematogenous dissemination or direct inoculation of the agent during surgical procedure or spread from contiguous structures like paranasal sinuses, mastoid, and middle ear. The haematogenous dissemination leads to multiple acute necrotizing purulent lesions commonly in the parietal lobe involving the middle or anterior cerebral artery. Whereas contiguous spread occurs from granulomatous lesions in the paranasal sinuses and middle ear

leading to the development of chronic granuloma with dense fibrosis in adjacent structures of the brain like the frontal (from paranasal sinuses) or temporal lobe (from middle ear or mastoid) [144]. As FRS is a highly prevalent disease in Asia, the Middle East, and Africa [119,159,160,166–169], the paranasal source of CNS involvement is common and often results in an orbital apex syndrome or granulomatous disease of the frontal lobe [24,104,144,147,150,154,170]. The two clinical conditions (rhinocerebral granulomas and intracranial abscess) have different presentations (Table 2). The former variety occurs commonly in immunocompetent hosts in contrast to intracerebral abscess. Rhinocerebral lesions are usually diagnosed early due to easier sampling from paranasal sinuses and have less mortality. In contrast intracerebral abscess developed by haematogenous dissemination have high mortality and are diagnosed late as a clinical surprise because of subtle clinical presentations and absence of any diagnostic characteristics [150].

Although vascular invasion by *Aspergillus* species is a common finding, true mycotic aneurysm is rare. In developing countries occasionally such cases of intracranial mycotic aneurysms have been reported as a result of direct invasion of the wall of blood vessels either from the luminal or adventitial side [144,171,172]. Isolated meningitis due to *Aspergillus* spp. is a rare finding, as also is spinal cord involvement. The possibility of iatrogenic intrusion by *Aspergillus* spp. in the meninges through contaminated needles was suggested in some cases after performing spinal anaesthesia [48,49,171]. This was further supported in the outbreak of *Aspergillus* meningitis in Sri Lanka which was considered a post-tsunami effect. This outbreak occurred between 2 July and 25 July 2005, where five patients suffered from *Aspergillus* meningitis after administration of spinal anaesthesia for cesarean section. As the drug warehouses were full of donations for survivors of the tsunami, the regular supplies of the hospital were stored in a dirty and humid temporary warehouse, which possibly led to contamination of the syringes with *A. fumigatus*. After destruction of the unused syringes, the outbreak was controlled. This outbreak also proves that poor hospital practices in developing countries may lead to many cases of iatrogenic invasive aspergillosis [47].

Cardiac aspergillosis

Aspergillus endocarditis, an uncommon but life threatening entity, occurs mainly on prosthetic valves, but patients with native valve *Aspergillus* endocarditis have been described from India and Iran [1,23,54,125,152,154,173,174]. The disease has also been described as a part of disseminated aspergillosis [175]. Patients with *Aspergillus* endocarditis may present with fever, multiple embolic strokes, valve abnormalities, and arrhythmias [154,173]. The invading *Aspergillus* hyphae have a tendency to extend deep into the myocardium and pericardium producing multiple abscesses, necrosis, vasculitis, and areas of infarction [125]. The Aspergilli may further invade into the lungs [125], and even the reverse may occur where a mediastinal mass due to angioinvasive *Aspergillus* spp. may involve the pericardium and the heart [173].

Disseminated aspergillosis

Disseminated aspergillosis is a life threatening rapidly fulminant infection, involving two or more non-contiguous organs of the body, occurring in severely immunocompromised patients [7,13,57,94,154,175–178]. A rare case of disseminated aspergillosis was documented in an apparently immunocompetent host in Malaysia [94]. Lung is the common involved organ in all cases of dissemination [7,13,51,57,154,175–178]. Other involved organs include brain, heart, kidneys, liver, thyroid, and the gastrointestinal tract. Gastrointestinal aspergillosis, a rare entity, had been reported as a part of dissemination [176,177].

Table 2 Differentiating features of rhinocerebral *Aspergillus* granuloma and intracerebral *Aspergillus* abscess (modified from Sharma *et al.*) [38].

Sl. no.	Characters	Rhinocerebral *Aspergillus* granuloma	Intracerebral *Aspergillus* abscess
1	Duration of lesion	>3 months	<3 months
2	Mode of spread	Contiguous	Haematogenous dissemination
3	Site of brain lesion	Commonly frontal lobe	Commonly parietal lobe
4	Clinical presentation	Frontal lobe symptoms with sinusitis	Raised intracranial pressure, seizures
5	Dura involvement	Common	Uncommon
6	Imaging	Hyperdense with mild enhancement	Mixed density with patchy or rim enhancement
7	Pathology (gross)	Tough – requires knife to cut	Soft
8	Pathology (microscopy)	Granuloma with fibrosis	Abscess with necrosis
9	Diagnosis	Early by samples from sinuses	Delayed till craniotomy
10	Differential diagnosis	Malignancy	Tubercular or pyogenic abscess
11	Prognosis	Low mortality though prolonged morbidity	High mortality
12	Recurrence	Common	Uncommon

Aspergillus endophthalmitis

Aspergillus endophthalmitis is an emerging problem in developing countries [5,43,100,127,156,157,179–182]. In fact, the largest series of fungal endophthalmitis (including 31 patients with *Aspergillus* endophthalmitis) from a single center was reported from India [127]. Trauma (45%) and ocular surgery (48%) are the major predisposing factors for such infections. Postoperative *Aspergillus* endophthalmitis may be seen in clusters due to the use of contaminated irrigation solution, intraocular lenses, donor cornea, ventilation system, and hospital construction activities [107,127,183,184]. An outbreak of *A. ustus* endophthalmitis from Turkey confirmed the same fact [100]. Contamination of operation theatre due to less stringent infection control practices coupled with poor quality care in rural eye camp settings are responsible for unusually high number of cases of post-operative *Aspergillus* endophthalmitis in developing countries [127,182]. Post traumatic *Aspergillus* endophthalmitis usually occurs after injury due to contaminated wires, wooden sticks, and hypodermic needle [127]. Infection develops within 4 weeks of cataract surgery or trauma [127]. Endogenous *Aspergillus* endophthalmitis is reported rarely as a part of dissemination in IA. However, the unique outbreak of endogenous *Aspergillus* endophthalmitis in India after a single intravenous administration of presumably contaminated dextrose infusion fluid possibly highlights the unusual scenario prevailing in developing countries [5].

Invasive cutaneous aspergillosis

This is another emerging problem in developing countries especially in the tropical areas. Primary cutaneous aspergillosis is observed in special risk groups like burn victims, neonates, HIV-infected populations, and solid organ transplant recipients [65,185]. In contrast, the secondary cutaneous aspergillosis, a comparatively rare disease accounting for $<5\%$ of cases of disseminated aspergillosis, is confined to hematopoietic stem cell transplant (HSCT) recipients [17,186,187]. In developing countries poor intravascular catheter care, use of contaminated arm boards, adhesive tapes, and occlusive dressings are the possible reasons for higher incidence [185]. However, in a study from Iraq it was pointed out that fungal infections were more common in burn patients with open dressings (25.5%) than with occlusive dressings (16%) [80].

Uncommon presentations of invasive aspergillosis

The literature from developing countries has documented rare cases of *Aspergillus* myositis [177], *Aspergillus* polyarthritis [19], and primary renal aspergillosis [7,130], *Aspergillus* osteomyelitis (including those of the vertebral column) [45,131] and hepatic abscess [53,131].

Experience at our center

From our Institute, a tertiary care centre (~1500 beds) in north India, systemic fungal infection was detected in 2.4% of all autopsies performed (15,040 deaths autopsied over 26 years) and IA was detected in 49% of those fungal positive cases (means 1.2% of all autopsy cases). Further, between 1994 and 2008, systemic fungal infection was demonstrated in 34 (9%) of 374 autopsies having liver failure (224 cirrhosis and 150 acute failure), and 59% of those cases had IA. Comparison of these two series (2.4% vs. 9% systemic fungal infections; 1.2% vs. 5.3% IA) indicates strong association of underlying liver failure with systemic fungal infections particularly with IA (unpublished observation by author AD).

ABPA is the most frequently recognized manifestation in allergic aspergillosis at our center [188]. In a rare case of ABPA from our Institute, the patient succumbed to his illness after the development of multilobular consolidation and multi-organ dysfunction. On autopsy invasive pulmonary aspergillosis with extensive dissemination to the thyroid, both kidneys and colon were observed (Figs 1–3) (discussed at the Clinic-pathological Conference in September 2007 at our Institute).

The proportional higher isolation of *A. flavus* from patients with IA in developing countries led us to conduct an environmental surveillance of our hospital. Air samples were collected from the centrally air-conditioned portion of wards and non-air conditioned portion of the hospital every month for one year to evaluate the predominant *Aspergillus* spore in the air in those areas. In the

Fig. 1 Both lungs with cavitary lesions present bilaterally and dilated bronchi filled with mucus in the lower lobes.

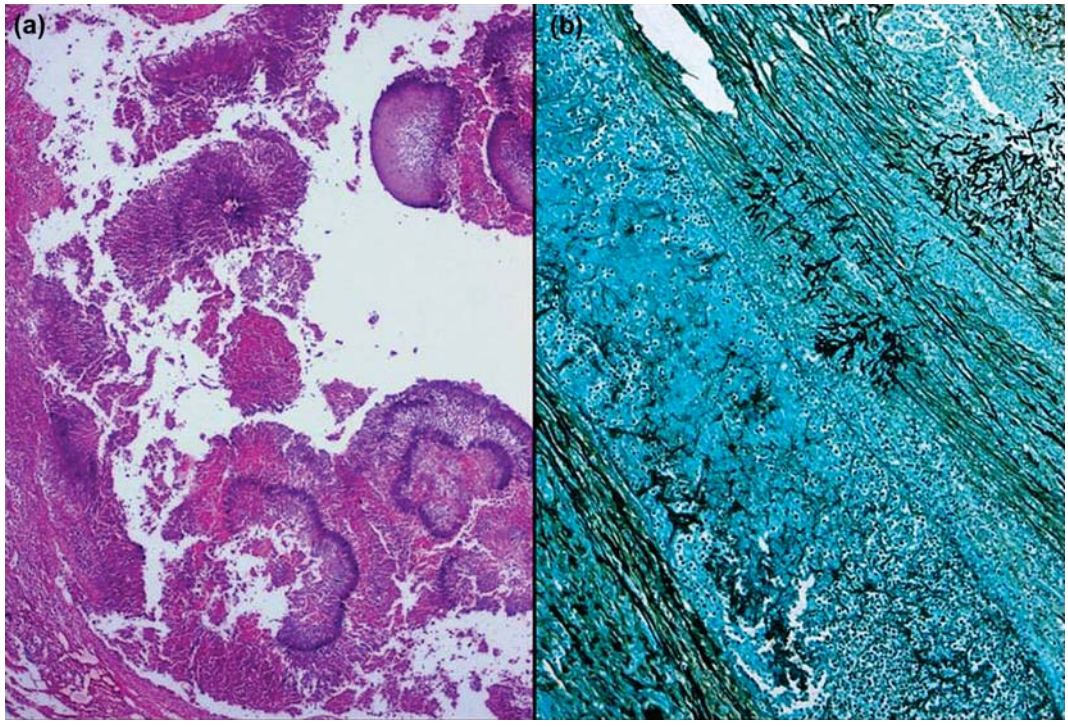

Fig. 2 (a) Bronchiectatic cavities with *Aspergillus* balls (H & E × 100). (b) Grocott's stain highlighting the fungal hyphae invading the bronchiectatic airway wall (H & E ×100).

air-conditioned wards *A. flavus* was the predominant agent isolated in all seasons except in the summer months, when *A. niger* outnumbered *A. flavus*. However, in non-air conditioned areas, *A. flavus* was the predominant species isolated only during winter and spring (January to March), *A. fumigatus* in summer and *A. niger* in autumn (unpublished observation).

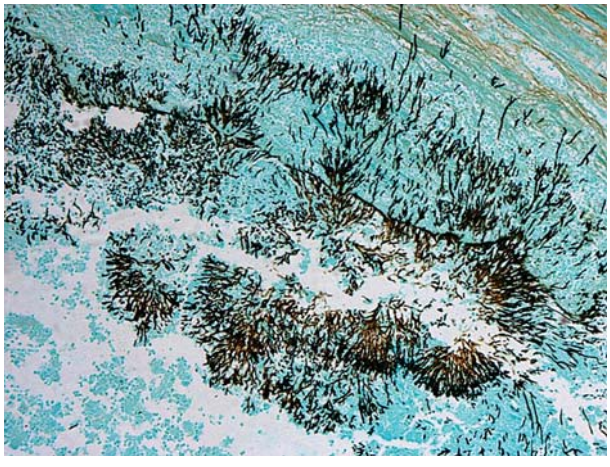

Fig. 3 Grocott's stain highlighting the *Aspergillus* hyphae (H & E × 200).

Diagnosis of invasive aspergillosis

Many cases of IA remain undiagnosed until it is too late to save the patient [24] or diagnosed only at autopsy in developing countries [125,126,129]. Conventional direct microscopy, histopathology, and culture methods are the only available techniques in most centers to diagnose IA due to the non availability of galactomannan or beta-glucan tests assay. Therefore, most patients with IA reported from developing countries are proven cases, though few centers reported probable and possible aspergillosis cases as well [11,15,59,71,99,118]. A bone-marrow transplant center in Hungary had reported that despite the regular use of galactomannan antigen and imaging, antemortem diagnosis could be established in only 40% of cases with IA [79]. Polymerase chain reaction (PCR) has been successfully used to diagnose *Aspergillus* endophthalmitis in a few centers [51,189–191]. PCR technique had also been used to diagnose other forms of IA occasionally, but the test requires further validation [32].

Treatment of invasive aspergillosis

Despite the recommendation of Infectious Disease Society of America to use voriconazole as the primary therapy of IA [192], and better outcome reported while using

voriconazole as compared to amphotericin B [1], amphotericin B or itraconazole is the first line therapy in the majority of patients with IA in developing countries possibly due to the higher cost of other anti-*Aspergillus* effective drugs [11,13,15,47,57,59,118,128,131,146–148,150,193]. The scenario is comprehensively reviewed in the study of a tertiary care hospital in Thailand where amphotericin B deoxycholate was prescribed as the first line therapy in 59% patients with IA, followed by itraconazole (39%), liposomal amphotericin B (10%), caspofungin (5%), and voriconazole (2%) [15]. The authors in that study summed up the use of amphotericin B followed by itraconazole as the mainstay of treatment due to the higher cost of other antifungal agents. Similarly, in the Brazilian study, 91.6% HSCT recipients with IA received amphotericin B due to economic reasons, though 37.5% of them needed to change this first choice, principally because of nephrotoxicity (55.6%) and failure (33%) [59]. The cost of the drug is an important hurdle in the management of IA in those countries, as patients may be unable to complete the therapy despite the initial good response using voriconazole [146]. Only a few studies could evaluate the response to voriconazole or liposomal amphotericin B or caspofungin in IA, when patients could afford such therapy [13,15,82,118,146]. Nebulized amphotericin B has also been successfully used with voriconazole for treatment of *Aspergillus* tracheobronchitis [14]. The response to amphotericin B or itraconazole is good in immunocompetent patients [128,194]. However, the response in immunosuppressed or neutropenic patients is not encouraging (mortality up to 87.5%) [13,15,59,118]. Delay in admission to the hospital, diagnosis, and start of antifungal therapy are the other possible reasons of high mortality in those patients. In a study on patients with cerebral aspergillosis, it was observed that the median duration of symptoms prior to hospital admission was 60 days (range 8–180 days) and the median time taken to get the clinical diagnosis and treatment after admission was 8 days (range 5–30 days). High mortality (87.5%) was reported in that study in spite of extensive surgery and antifungal therapy in the majority of the patients [13]. During management of invasive fungal sinusitis, therapy with an amphotericin B formulation (active against both *Aspergillus* and Zygomycetes) is desirable until confirmation of etiology on culture or histopathology [1,42,153,160]. To manage *Aspergillus* endophthalmitis, the combination of parsplana vitreoctomy and intra-vitreal amphotericin B with or without itraconazole was recommended [127].

Conclusion

The frequency of IA in developing countries is expected to be high, though the disease is under-reported or reported late. Besides usual presentations of IA, certain peculiarities have been observed in those countries regarding risk factors, clinical presentations, and the *Aspergillus* spp. isolation. Apart from the classical risk factors, patients with pre-existing lung diseases, liver failure and diabetes are associated with IA. Sino-orbital or cerebral aspergillosis and *Aspergillus* endophthalmitis are highly prevalent diseases and *A. flavus* is isolated at a higher frequency compared to *A. fumigatus* from these patients. Though early diagnosis and therapy is desirable to manage IA, antifungal medication is frequently delayed leading to high mortality. Amphotericin B deoxycholate followed by itraconazole are the most commonly prescribed drugs to treat IA in developing countries due to economic constraints.

Acknowledgements

We acknowledge the help of Dr Kirti Gupta, Histopathology Department for the histopathology photographs, and Ms Manpreet Dhaliwal, Microbiology Department, PGI, for reference management.

Declaration of interest: The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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This paper was first published online on Early online on 20 August 2010.