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Full Length Research Paper

Pulmonary and extra pulmonary manifestations of aspergillosis in clinical practice and potential challenges in management: An analysis of literature review

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With various factors causing immunosuppression among humans and tendency towards opportunistic fungal infections such as aspergillosis, this study was therefore set up to assess the associated changing clinical presentations of the disease from the developing world. The study was based on literature search from available reports on clinical presentations of aspergillosis from literature searches for a period of 20 years (1990 - 2010). The most common forms of presentations of aspergillosis documented from the 9,743 patients in 1,222 literature reviews were invasive *Pulmonary aspergillosis* 34.53% (3,365), allergic bronchopulmonary aspergillosis 18.13% (1,767), *Pulmonary aspergillomas* 15.41% (1,501) and aspergillosis of maxillary sinuses 8.05% (784). Some of the rarest presentations were aspergillus aortic embolism with stroke 0.04%, tension pneumothorax 0.07%, mycotic aneurism of descending thoracic aorta 0.06%, skull base erosion by sphenoid fungal balls 0.02%, small bowel obstruction 0.16%, perforation of large intestine 0.04%, small bowel infarction 0.03%, hypertrophic cranial pachmeningitis 0.34% and invasive generalised multi-organ aspergillosis 0.44%. Aspergillosis was found to present with various unusual surgical or medical emergencies with overall infection rates significantly higher in immunocompromised ($P < 0.0001$). In patients presenting with quite familiar clinical pictures in the developing world but proving difficult for treatment especially in the immunosuppressed but not exclusive and where facilities for diagnosis may be lacking, aspergillosis should not be completely ruled out.

Key words: Aspergillosis, clinical presentations, rare.

INTRODUCTION

Aspergillosis is an air borne disease transmitted usually by inhalation of the spores (Conidia) which eventually germinate into vegetative forms and cause symptoms of the disease. The commonest clinical forms of the disease are invasive pulmonary aspergillosis, allergic broncho-pulmonary aspergillosis and pulmonary aspergillomas which account for over 85% of its manifestations. The commonest species of clinical importance are *Aspergillus fumigatus, Aspergillus flavus* and *Aspergillus niger* (Marr et al., 2002; Cahil et al., 1997; Libanore et al., 2002).

Aspergillus sp. usually do not pose serious threat to over 98% of the immunocompetent individuals however; tissue invasion and secondary bloodstream dissemination (invasive aspergillosis) have been found to be common in various forms of immunosupression (Wiley et al., 1990; Aliff et al., 2003; Maehara et al., 2010).

Invasive aspergillosis is reported to occur in less than

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1% of patients with Human Immunodeficiency Virus (HIV) infection; in 1 - 5% of liver transplant recipients; in 3 - 7% of allogenic bone marrow transplant recipients; in about 10% of patients with haematological malignancies or lung transplants and up to 14% of heart transplant recipients (Boon et al., 1991; Ludwig et al., 2005; Vogester et al., 1997). Extension of invasive aspergillosis to the central nervous system is associated with almost 100% mortality. Treatment is usually effective with systemic itraconazole, fluconazole and caspofungin (Baddley et al., 2010; Maschmeyer et al., 2007; Dutkiewicz and Hage, 2010).

To an undergraduate trainee in Medicine and Surgery, aspergillosis may not really be a disease that should be expected to be seen often in the course of practice (Milton et al., 2010; Singh and Peterson, 2005; Hope et al., 2005). This may be attributed to, probably, a low index of suspicion of the disease among clinicians which often translates to the choice and types of investigative procedures and rigours when managing supposedly index cases (Schnitzer et al., 2009; Hayden et al., 2009; Bhagavath et al., 2009).

The actual global burden of clinical aspergillosis is not known since its epidemiology is associated with several environmental, morbid and pre-morbid conditions coupled with lack of comprehensive data from several parts of the world (Bhagavath et al., 2009; Ram et al., 2008; Attigah et al., 2008). In most parts of sub-Saharan Africa and several other parts of tropical and sub-tropical regions of the world, the often ill equipped laboratories and dearth of other diagnostic aids usually limit the degree of thoroughness patients and their specimens are handled in a bid to arrive at definitive diagnosis (Ram et al., 2008; Attigah et al., 2008).

The alleged under-diagnosis and subsequent under-reportage of the disease on the African continent could as well be traced to these infrastructural challenges. This no doubt affects quality patient care with the attendant losses in man hours, human and material resources, and as in the case of aspergillosis, creating a wrong epidemiology of the disease with its own public health implications (Andres et al., 2007; Molute et al., 2007; Frei et al., 2006).

Furthermore, in sub-Saharan Africa for example and other parts of developing world, empirical treatments for infections in hospital settings very often targets non-specific bacteria and with laboratory facilities sub-sequently put in place to confirm it with often little or no provision for isolation of fungi (Jombo et al., 2006). Also in this era of HIV AIDS pandemic several fungal diseases including aspergillosis have re-defined their epidemiology and appear to be more virulent on the immune-suppressed (Van der Valden et al., 2006; Tay et al., 2003; Keller and Sax, 1997).

This study was therefore set up to review the clinical manifestations of aspergillosis in contemporary medical practice. The findings would serve as a guide to clinicians and also as a reminder on current clinical presentations of the disease. This would ensure a more prompt and efficient management of patients with similar or closely related presentations especially where facilities for its definitive diagnosis may be lacking or in short supply.

MATERIALS AND METHODS

The study was based on systematic literature search on aspergillosis for the past 20 years April 1990 - 2010. Available literature on symptoms and signs associated with aspergillosis and clinical and laboratory diagnosis of aspergillosis from scientific journals from- NCBI, MEDLINE, MESH, PUBMED, ScienceDirect-ELSEVIER, MMR-CDC, WHO, www.scielo.org, MLM Catalog, Enterez Cross, ISPUB and web med central. This consists of original research articles, letters to editors, review articles, case reports and short communications. Information obtained was on various forms of clinical presentations of aspergillosis through clinical and laboratory diagnosis with the use of facilities such as but not restricted to: Roentgenography, Computer Assissted Tomography, Positron Emission Tomography, Ultrasound scan, Magnetic resonance imaging, Tissue and Fine Needle aspiration biopsy, histology and cytology, Specific staining procedures, Serological and Chromatographic procedures, Utilization of stoichiometric parameters, Microscopy and Culture and Post mortem examinations. The scopes of investigations from the literatures were dependent on the available facilities, the purpose for diagnosis and clinical picture of the patient. Data obtained was analysed using simple descriptive methods of arithmetic mean mode and median while Epi Info 6 was used to compare association among variables where applicable (CDC, 2010).

RESULTS

From the 1,222 available and relevant literatures on clinical presentations of aspergillosis, 9,743 patients were reviewed; 6633 (68.1%) presented with usual features while 3110 (31.9%) presented with unusual forms of invasive aspergillosis. The most common forms of presentations of aspergillosis were invasive pulmonary aspergillosis 34.53% (3,365), allergic bronchopulmonary aspergillosis 18.13% (1,767), pulmonary aspergillomas 15.41% (1,501), aspergillosis of maxillary sinuses 8.05% (784) and *Aspergillus peritonitis* 6.87% (669). Other less common presentations were mimicking of pulmonary tuberculosis 3.84% (374) and cerebral abscess 0.80% (78). Some of the most life threatening presentations of aspergillosis encountered were aspergillus aortic embolism with stroke 0.04% (4), tension pneumothorax 0.07% (7) and mycotic aneurism of descending thoracic aorta 0.06% (6) (Table 1).

The species of Aspergillus associated with some of the infections among the 668 documented patients were *A. fumigatus* 27% (180), *Aspergillus niger* 26% (174), *Aspergillus flavus* 17% (114), *Aspergillus oryzae* 10% (67), *Aspergillus terreus* 9% (60), and *Aspergillus sydowii* 5% (33); there was no clear available data on organ-specie specificity (Figure 1).

Among the 7,726 patients with various forms of aspergillosis whose immune status was properly

Table 1. Clinical presentations of aspergillosis (N = 9,743).

Clinical presentations	Number (%)
Lungs, heart and thorax	
Invasive pulmonary aspergillosis	3,365 (34.53)
Allergic bronchopulmonary aspergillosis	1,767 (18.13)
Pulmonary aspergilloma	1,501 (15.41)
Mimicking pulmonary tuberculosis	374 (3.84)
Anterior mediastinal aspergillosis	78 (0.80)
Aspergillus endocarditis	56 (0.57)
Lung cavitation	44 (0.45)
Chronic obstructive pulmonary disease	31 (0.32)
Chronic necrotising pulmonary aspergillosis	23 (0.24)
Semi-invasive endobronchial aspergillosis	18 (0.18)
Aspergillus carditis	9 (0.09)
Tension pneumothorax	7 (0.07)
Mycotic aneurism of descending aorta	6 (0.06)
Aspergillus aortic embolism and stroke	4 (0.04)
Maxillofacial, dental, ear, nose and throat	
Aspergillosis of maxillary sinus	784 (8.05)
Ethmoido-maxillary aspergillosis	62 (0.63)
Aspergillus mycetoma of the maxillary antrum	53 (0.54)
Aspergillus mastoiditis	53 (0.54)
Primary aspergillosis of the nose	20 (0.21)
Otitis media	18 (0.18)
Aspergilloma of frontal sinus	14 (0.14)
Chronic fungal rhinitis	12 (0.12)
Aspergillosis of the frontal sinus	11 (0.11)
Aspergillus mastoiditis with progressive otalgia	7 (0.07)
Primary aspergillosis of the larynx	5 (0.05)
Sinus maxillaries mycetoma of odontogenic origin	4 (0.04)
Sinonasal teeth	2 (0.02)
Head and neck	
Intracranial granuloma	8 (0.08)
Invasive oral aspergillosis	6 (0.06)
Oesophagial aspergillosis	5 (0.05)
Mycotic intraseller abscess	4 (0.04)
Left vocal cord paralysis	2 (0.02)
Skull base erosion by sphenoid fungal balls	2 (0.02)
Primary Aspergillosis of tongue	2 (0.02)
Hard palate perforation	1 (0.01)
Abdomen	
Aspergillus peritonitis (With or without peritoneal abscess)	669 (6.87)
Small bowel infarction	32 (0.33)
Acute abdomen	18 (0.18)
Small bowel obstruction	16 (0.16)
Primary aspergillosis of digestive tract (Typhilitis with Peritonitis)	15 (0.15)
Aspergillus necrotizing colitis	11 (0.11)
Pseudoaneurism of left colic artery	5 (0.05)
Perforation of large intestine	4 (.0.04)
Mycotic aneurism of superior mesenteric artery with intestinal infarction	4 (0.04)

Table 1. Contd.

Aspergillus fatal intestinal haemorrhage	3 (0.03)
Aspergillus hepatic abscess	3 (0.03)
Pneumatosis intestinalis (caecum, ascending and transverse colon, rectum)	3 (0.03)
Bone, connective tissue and skin	
Aspergillus vertebral osteomyelitis	53 (0.53)
Aspergilloma of ethmoid	32 (0.32)
Vertebral osteomyelitis	32 (0.32)
Primary cutaneous aspergillosis	21 (0.21)
Aspergillus spondylitis of cervico-thoraco-lumbar spine	21 (0.21)
Sphenoid fungus balls	17 (0.17)
Aspergillus arthritis	16 (0.16)
Sinus aspergilloma in rheumatoid arthritis	12 (0.12)
Aspergilloma of the Frontal bone	11 (0.11)
Aspergillosis of ethmoid bone	7 (0.07)
Invasive aspergillosis of cavum	6 (0.06)
Aspergillus flavus wound infection	3 (0.03)
Aspergillosis of Masticator space and Mandibular bone	6 (0.06)
Generalised dermatitis	4 (0.04)
Osteomyelitis of the rib	3 (0.03)
Aspergillus osteomyelitis of femur	3 (0.03)
Aspergillus seller abscess	3 (0.03)
Synchronous Aspergillosis with Myospherulosis	2 (0.02)
Eye and orbit	
Haemorrhagic conjunctivitis	14 (0.14)
Primary orbital aspergilloma	10 (0.10)
Unilateral orbital aspergillosis	6 (0.06)
Mycotic abscess of the orbit	5 (0.05)
Orbital apex syndrome	5 (0.05)
Painless complete ophthalmoplegia	3 (0.03)
Mycotic abscess of the optic nerve	2 (0.02)
Brain, spinal cord and meninges	
Cerebral abscesses (Focal or multiple)	78 (0.80)
Hypertrophic cranial pachymeningitis	34 (0.34)
Primary mycotic pyocephalus	25 (0.25)
Epidural abscess	23(0.23)
Aspergillus pan meningitis	22 (0.22)
Atypical meningioma	15 (0.15)
Mycotic encephalitis	17 (0.17)
Invasive fungal granuloma of brain	9 (0.09)
General presentations	
Invasive generalized aspergillosis	44 (0.44)
Cushing's syndrome-like	8 (0.08)
Multiple myeloma-like	5 (0.05)
Budd-Chiari syndrome-like aspergillosis	1 (0.01)
Swyer-James-MacLeod syndrome-like	1 (0.01)

Different clinical presentations in same patient were grouped separately.

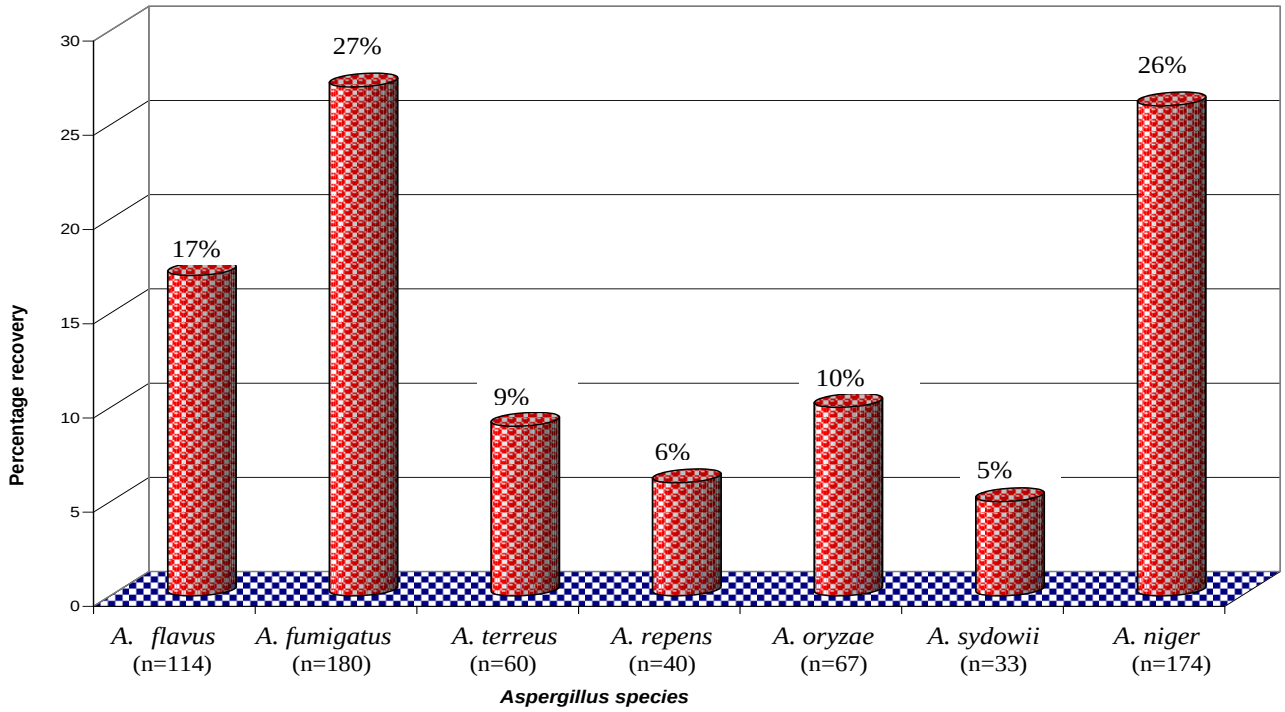

Figure 1. Species of Aspergillus recovered from various clinical presentations (N = 668).

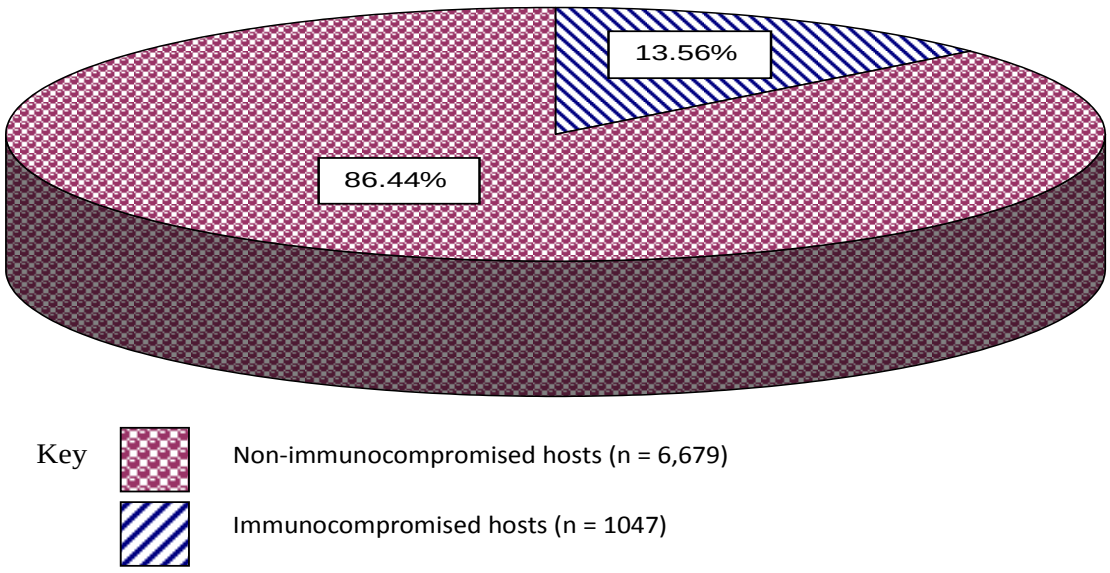

Figure 2. Rate of clinical aspergillosis among the immunocompromised and non-immunocompromised hosts (N = 7,726). X^2 (Mantel-Haenszel) = 38.16, OR = 3.34 - 13.33, RR = 2.36 - 6.86, P < 0.0001. Emphasis was on original research works where immune status was clearly defined.

documented, 86.44% (6,679) were immunocompromised while 13.56% (1047) were non-immunocompromised (P < 0.0001) (Figure 2).

There was no correlation between multiple presentations of aspergillosis and various forms of the disease from the available reports (SST = 29228.083, df = 2, MST = 14614.042, F = 0.943). There has been however an increasing number of documented unusual clinical presentations of histoplasmosis over the past 20 years; there were significantly more unusual clinical findings in the last decade compared to the former (68.0%, 2115/3110 vs 32.0%, 995/3110), while 31.3% (973) of the

Table 2. Antimicrobial susceptibility profile of *Aspergillus* species.

Aspergillus species	Caspofungin	Fluconazole	Itraconzole	Amphotericin B	Echinocandin	Voriconazole	Posaconazole
A. fumigatus (n=180)	100	100	97	83.2	-	79.5	100
A. terreus (n=60)	100	78.6	100	66.6	88.0	100	-
A. repens (40)	100	-	100	-	-	100	75.5
A. oryzae (n=67)	100	-	100	-	100	63.4	56.0
A. sydowii (n=33)	100	-	-	43.7	100	92.8	-
A. niger (n=174)	100	88.6	-	78.5	100	76.4	100
A. flavus (n=144)	100	100	100	88.4	-	92.1	100

Report not available, n= number of isolates with susceptibility reports.

cases were reported in the last five years alone (SST = 896293.500, df = 1, MST = 896293.500, F = 0.015).

Antimicrobial susceptibility profile of *Aspergillus species* from cases of invasive aspergillosis showed that caspofungin was active against all the isolates tested. Fluconazole was active against 78.6% of *A. terreus*, and amphotericin B active against 83.2, 66.6 and 43.7% of *A. fumigatus*, *A. terreus* and *A. sydowii* respectively (Table 2).

DISCUSSION

Some of the most rare and life threatening presentations of aspergillosis encountered from 9,743 patients reviewed were *Aspergillus* aortic embolism with stroke 0.04%, tension pneumothorax 0.07%, mycotic aneurism of descending thoracic aorta 0.06%, skull base erosion by sphenoid fungal balls 0.02%, small bowel obstruction 0.16%, perforation of large intestine 0.04%, small bowel infarction 0.03%, hypertrophic cranial pachmeningitis 0.34%, and invasive generalised multi-organ aspergillosis 0.44%.

In the present global disease pattern especially in the tropical and sub-tropical regions of the world where malaria, typhoid fever, pyogenic meningitis and tuberculosis are still endemic, initial symptoms on onset may be similar and hence affect appropriate thought direction towards effecting prompt and timely diagnosis (Jombo, et al, 2007; 2008; 2010). This becomes more challenging where laboratory facilities are inadequate or lacking to establish a definitive diagnosis and empirical treatment, with its obvious imperfections, is heavily relied upon for patient management (Akopian et al., 2004).

Improvement in medical technology due to availability of facilities for successful organ transplantation, immunosuppressive therapy, cytotoxic therapy in addition to immunosuppressive infections were found to have significantly increased the burden of aspergillosis worldwide (Blenow et al., 2010; Gerlach et al., 2009; Mensin et al., 2009). In Switzerland aspergillosis was found to be present as typhilitis (Eggimann et al., 2008), in Sri Lanka as acute meningitis (Rodrigo et al., 2007) and in Panicuik as intracranial granuloma (Degleish et al., 2006). In Michigan, USA (Andres et al., 2007), Belgium (Op de Beeck et al., 2009), United Kingdom (Hayden et al., 2009), India (BNN et al., 2010) and South Korea (Son et al., 2007) the infection manifested respectively as, necrotizing colitis, pneumatosis intestinalis, small bowel obstruction, vertebral osteomyelitis and spondylitis. These as well as several other life threatening clinical presentations posed diagnostic dilemmas for health personnel managing the respective patients (Braun et al., 1997; Sakamato et al., 1997; Krennmair et al., 1993).

The finding of *Aspergillus* vocal cord paralysis in Japan (Nakahira et al., 1999), *Aspergillus* multiple brain abscess in Croatia (Marinovic et al., 2007) and invasive pulmonary and central nervous system aspergillosis in The Netherlands, all in immunocompetent individuals clouds further the index of suspicion and full exercise of clinical intuition among clinicians when confronted with such cases (Leroy et al., 2006). This would no doubt hinder or slow down the utilization of specific diagnostic procedures required for its definitive diagnosis (Khemiri et al., 2009; Boutarbouch et al., 2009).

Availability of cutting edge laboratory and other diagnostic procedures no doubt has improved quality of healthcare services globally although, it has not substantially addressed the medical challenge thrown up by *Aspergillus* infections. In Safat, Kuwait, in spite of the well articulated and prompt management outline of a patient with cerebral aspergillosis, the patient still died due to unintended delay in arriving at diagnosis (Khan et al., 2007); in Madrid, Spain several cases of invasive aspergillosis could only be established at necropsies (Gongalez et al., 1999) and in Ghana, aspergillosis presented with generalised dermatitis which was also only diagnosed at post mortem (Aleksenko and Gyasi, 2006). The rapidly progressive fatal aspergillosis commonly seen in immunocompromised hosts which has been found to be not uncommon in immunocompetent individuals have severally affected prompt diagnosis and management of these patients (Hansen et al., 2010; Segan and Gozdziuk, 2010; Salgado et al., 2010). In several cases, diagnoses are only established at necropsies (Salgado et al., 2010; Camus et al., 2010;

Glockner and Karthaus, 2010). The fact that immunocompetent individuals are not completely exempted from invasive aspergillosis as widely documented; such unexpected clinical encounters are capable of influencing the line of thought of physicians in the course of patient management and should be adequately noted (Camus et al., 2010; Glockner and Karthaus, 2010; Gullo, 2009).

There has been a general increase in the number of reported cases of unusual clinical presentations of aspergillosis over the past two decades. The HIV/AIDS which has assumed a global epidemic correspondingly over the past 20 years may similarly be a significant contributory factor (Libanore et al., 2002). Also, the corresponding technological revolution in clinical practice over the same period with the emergence of diagnostic equipments with higher accuracy and precision and also to establish retrospective and post mortem diagnosis with such cutting edge precision may have as well boosted clinical diagnosis of aspergillosis (Coley et al., 1999; Kami et al., 1999 Ostrosky-Zeichner et al., 2005). Introduction of high-efficiency particulate air (HEPA) filters at the organ transplantation units in Japan was accompanied by a zero percent incidence of invasive aspergillosis among the recipients (Maehara et al., 2010). This also stresses the need for improvement in precautions as well as containments in addition to increased vigilance when managing such high risk groups (Verweij et al., 1999).

RECOMMENDATIONS

In view of the general difficulty associated with both clinical and laboratory diagnosis of aspergillosis (Chionh et al., 2005; Gao et al., 2010), strong sense of clinical intuition should be exercised by clinicians so as to complement available diagnostic facilities towards establishing early diagnosis and subsequent prompt treatment.

In hospitals and clinics with adequate facilities for clinical and laboratory diagnosis of aspergillosis, extra curiosity by clinicians in assessment of patients' prognosis should be exercised so as to take note of early signs of treatment failure in order to promptly take on other available options for management of the patients; since the disease has been known to beat both the clinical expertise and investigative rigour and skills in highly standard centres (Mennink-Kersten et al., 2006; Rodriguez et al., 1992; Caillot et al., 2001).

In developing countries and centres where facilities may be insufficient or lacking to establish both clinical and laboratory diagnosis as well as diagnosis by exclusion, sound clinical judgement, frequent patient evaluation and a culture of not looking at any 'common ailment' as really common and utilization of discretionary therapeutic trials may prove helpful (Verghese et al., 2008; Barto and Flume, 2010; Karthaus, 2010). This measure may inadvertently arrest cases of the disease that could have ultimately proven fatal due to poor infrastructure. This is contrary to developed settings where availability of facilities may not require this extreme vigilance which may still be helpful (Boon et al., 1991; Kami et al., 1999 and Baddley et al., 2010).

To the undergraduate and postgraduate trainees in medicine and surgery, medical and allied sciences, from the epidemiological point of view it should be noted that, extrapulmonary manifestations of aspergillosis are extensively diverse, complex and not too rare. This study may probably not have been able to assemble all the documented rare presentations of the disease due to the time bound sampling method, extent of experience of health personnel and availability of adequate investigative tools from where data were generated; there exist a possibility of other unreported or unknown unique and rare presentations as the disease may still be far from completing the course of its clinical evolution (Neumiester et al., 1994; Brown et al., 1994; Knuttgen et al., 2009).

Drugs that could be used in the treatment of aspergillosis in the absence of a susceptibility report and in the order of preference on the majority of the species are caspofungin, voriconazole, itraconazole, posaconazole, fluconazole, amphotericin B and echinocandin LY303.

The authors wish to note that the data presented on aspergillosis in the present study is subject to certain variables and may not represent the most accurate up to date information on the disease. These include underdiagnosis of the disease due to probably poor infrastructure from the developing world, under-reporting from health institutions due to varying degrees of com-petence in data management, unwillingness or inability to publish scientific findings and also authors' preference of specific data on the disease to present with greater clarity and accuracy in journal articles. These limitations are nevertheless well noted and should also be considered in the utilization of this piece of clinical information.

Conclusion

The present study has shown that aspergillosis could be classified as an emerging infectious disease and has the potential of presenting as either medical or surgical emergencies of the head, neck, thorax and abdomen with rapidly fatal outcomes in addition to the well known chronic pulmonary and soft tissue manifestations. Physicians should therefore be on the watch especially in sub-Saharan Africa and other developing parts of the world that, patients presenting with familiar lesions or clinical pictures but unresponsive to ongoing treatments could turn out to be another case of aspergillosis. Caspofungin, Itraconazole and voriconazole could be considered for therapeutic trials where aspergillosis is strongly suspected.

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