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The invasive and saprophytic syndromes due to *Aspergillus* spp.

W. W. HOPE*†, T. J. WALSH† & D. W. DENNING*

**University of Manchester and Wythenshawe Hospital, Manchester, UK, and †Immunocompromised Host Section, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA*

Aspergillus spp. produce a wide range of invasive and sapropytic syndromes which may involve any tissue. Within a given tissue or organ the pathology and pathogenesis varies enormously, ranging from angioinvasive disease to non-invasive saprophytic disease. The individual invasive and saprophytic syndromes in which a causative role can be attributed to *Aspergillus* spp. are detailed specifically with reference to the underlying pathology and pathogenesis, the clinical setting and features, and the manner in which a diagnosis can be established.

Keywords aspergillosis, classification, diagnosis, invasive, saprophytic

Introduction

Disease manifestations associated with *Aspergillus* spp. are protean and dependent on a complex interaction between fungus and host, making the derivation of a satisfactory classification system difficult. There have been major recent advances in the diagnosis of invasive fungal infections, including an international consensus statement from the European Organization for Research and Treatment of Cancer/Mycosis Study Group (EORTC/MSG) consortium [1]. The aim and scope of the current document is to logically partition the entire entity of invasive asspergillosis (IA) into individual pathophysiological components in which a causative role has been ascribed to *Aspergillus* spp. This document aims to be complementary and compatible with the diagnostic criteria developed by the EORTC/MSG consortium [1]; it is not a revision or critique of this widely accepted document. Most of the background material in this review derives from case reports or small case series which were included if an adequate clinical history or context was delineated and, most importantly, if the laboratory data enabled confidence that *Aspergillus* was the causative pathogen. In the case of invasive disease, the definitions and concepts that are contained within the current edition of the EORTC/MSG document were employed.

Colonization

A consensus definition of colonization does not exist but may be considered as the isolation of *Aspergillus* spp., at least once, from a mucocutaneous surface in patients without concomitant evidence of invasive, saporophytic, or allergic disease. Colonization may represent transient passage of *Aspergillus* spp. in the airway, genuine long term (benign) carriage as typically seen in patients with localized structural or functional pulmonary deficits, or finally, as a marker and indeed a necessary precedent to the development of overt invasive disease. The latter point is illustrated by a study of lung transplant recipients in which 5.7% of patients who were 'colonized' proceeded to develop some form of IA [2], as well as a report in which polymerase chain reaction (PCR) was used to identify *Aspergillus* spp. in the airway at the time of bone marrow transplantation and related to the subsequent manifestation of IA [3]. The length of follow-up period is an important consideration in the definition of colonization since invasive disease may follow the identification of *Aspergillus* spp. by as long as three months [4]. It is also important that the concept and definition of colonization is amenable to the incorporation of new diagnostic modalities as they are developed. PCR has already been used as a tool with which to

Correspondence: D. W. Denning, Education and Research Centre, Wythenshawe Hospital, Southmoor Rd., Manchester M23 9LT, UK. Tel.: +44 (0)161 291 5811; Fax: +44 (0)161 291 5806; E-mail: ddenning@manchester.ac.uk

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define colonization [3] and several recent studies have raised the possibility that quantitative PCR may be employed to distinguish colonization from disease.

IA: site unknown

This term could be used to refer to cases in which the antemortem diagnosis of invasive aspergillosis is suggested by positive serological or molecular data in blood, but the site of infection cannot be determined despite appropriate investigation. In the majority of cases the lung is undoubtedly the site of infection but other sites, such as the gut, myocardium, spleen and liver, may be implicated. Evidence of disease may not be apparent because the infectious burden is beneath the analytical sensitivity of the chosen imaging modality, or infection remains limited in the context of neutrophil recovery or following administration of prophylactic or empirical antifungal therapy.

Disseminated IA

Most definitions of disseminated IA require the demonstration of *Aspergillus* spp. at two or more non-contiguous sites with the overriding supposition that endovascular or bloodstream infection is implicit in the pathogenesis. This concept should be distinguished from local spread or extension across tissue planes (e.g., sinus aspergillosis with direct extension to the meninges and brain), multifocal disease within one organ, and situations in which there is more than one site of infection within the same organ system (e.g., coexistent invasive pulmonary aspergillosis (IPA) and tracheobronchial aspergillosis). Furthermore, infection at two primary sites, as defined as sites in which it is reasonable to suppose infection is initiated (e.g., concomitant acute invasive sinusitis and IPA), should probably not be considered as disseminated disease.

From a practical point of view, the diagnosis of disseminated IA poses a number of difficulties which relate to the combination of diagnostic data. The current EORTC/MSG criteria specifically state that, in the case of probable disease, the site at which microbiological data are acquired should be *related* to the region of tissue damage as defined clinically or radiologically. Thus, this construct would not allow a diagnosis of cerebral aspergillosis with an adequate degree of certainty in the circumstance of a high risk patient with abnormal neuroradiology and *Aspergillus* growing from a sputum sample.

The diagnosis of disseminated disease may be considered to be proven or probable. Proven disseminated IA may be defined as proven or probable IA at two non-contiguous sites (e.g., pulmonary and cutaneous disease). Probable dissemination on the other hand could be defined as proven or probable invasive aspergillosis at one site with evidence of tissue damage at a normally sterile non-contiguous site which is otherwise consistent with IA, but for which definitive evidence for both invasive aspergillosis and an alternative diagnosis is absent. The supposition (or indeed specific demonstration) of bloodstream infection with only a single site of infection (e.g., a diagnosis of endogenous endophthalmitis alone in the context of intravenous drug abuse) is probably insufficient to define disseminated disease but should obviously mandate a thorough search to exclude the possibility.

Aspergillosis of the lower respiratory tract (Table 1, Fig. 1)

Invasive pulmonary aspergillosis

There is a vast literature pertaining to IPA; the challenge is to distil its essence in a comprehensive but succinct manner. IPA is the commonest manifestation of IA; the lungs are implicated in more than 90% of cases in several large series [5,6]. IPA may be complicated by spread to contiguous structures such as the pleural space [7], pericardium [8], chest wall [9] and mediastinal structures such as the esophagus [10] and great vessels [11,12]. Dissemination from the lung is frequently observed, although the specific risk factors remain poorly elucidated.

The development of IPA is an interplay between the inoculating dose, which is not known and probably varies widely, the ability of the host to resist infection at both a local and systemic level, and the virulence of the organism [13]. There are relatively few data to address the inocuoum concentration; clearly, it is tempting to postulate that large inocula may overwhelm an otherwise adequately functioning immune system and there are certainly anecdotal reports of IPA occurring within the context of significant environmental exposure [14]. Similarly, virulence is poorly understood and could relate to factors such as growth rate [15]; it does not appear to be restricted to specific clades or genotypes [16]. A full discourse on this topic is beyond the scope of this paper.

Neutropenia is clearly the dominant risk factor for the acquisition of IA [17]; importantly, however, it also exerts a major influence on the specific pathology of IPA. Insight into the relationship between the pathology of IPA in neutropenic versus non-neutropenic hosts was derived from rabbit models in which the pulmonary pathology of IPA was assessed in the context of

Table 1 Aspergillosis of the lower respiratory tract (see also Fig. 1)

	Pathological features	Radiological features	Clinical setting	Direct evidence to implicate *Aspergillus* spp.	Indirect evidence to implicate *Aspergillus* spp.
IPA (angioinvasive)	Vascular invasion by hyphal elements, coagulative necrosis, haemorrhagic infarction. The target lesion (or mycotic sequestrum) and distal wedge shaped areas of pulmonary infarction are classical manifestations of angioinvasion	Halo sign, air crescent sign, single or multiple pulmonary nodules	Prolonged and profound neutropenia	*Aspergillus* spp. (culture/histology) from lung biopsy *Aspergillus* spp. (culture/histology) from contiguous site [PCR from lung biopsy (especially in the context of tissue infarction and necrosis)][b]	Proven/probable IA at non-contiguous site *Aspergillus* spp. (culture/cytology) from respiratory tract specimen Positive GM (x2) from blood [a,b] Positive GM from respiratory tract specimen[a,b] [Positive PCR from blood][b] [Positive PCR from respiratory tract specimen][b]
IPA (non-angioinvasive)	No evidence of vascular invasion, pyogranulomatous inflammatory infiltrate, inflammatory necrosis, cavitation (occasionally a mixed histological picture may be observed)	Non-specific abnormalities including air-space disease, nodular infiltrates and cavitation	Non-neutropenic individuals, including corticosteroid therapy, non-neutropenic HSCT, GVHD, HIV/AIDS, CGD and solid organ transplantation. Some chronic forms of pulmonary aspergillosis with progressive pulmonary cavitation and the presence of precipitating antibodies to *Aspergillus* spp. are characterised by tissue invasion	*Aspergillus* spp. (culture/histology) from lung biopsy [PCR from lung biopsy][b] *Aspergillus* spp. (culture/histology) from contiguous site (e.g. pleura or chest wall)	Proven/probable IA at non-contiguous site *Aspergillus* spp. (culture/cytology) from respiratory tract specimen[a,b] Positive GM (x2) from blood[a,b] Positive GM from respiratory tract specimen[a,b] [Positive PCR from blood][b] [Positive PCR from respiratory tract specimen][b] Precipitating antibodies in chronic forms of pulmonary aspergillosis and potentially other forms of non-angioinvasive IPA[b]
Chronic invasive forms of pulmonary aspergillosis including CNPA†, CCPA†, CFPA†	Hyphae contained within cavity with no evidence of parenchymal invasion (occasionally hyphae are observed to be directly invading tissue, thus constituting a non-angioinvasive form of IPA)	≥1 cavities, peri-cavity infiltrates, progressive enlargement of new cavities, pleural thickening, CFPA associated with fibrosis	Cough, weight loss, fatigue, haemoptysis progressive over months to years	Histological evidence of hyphae within cavity, but usually not penetrating into lung parenchyma	Positive precipitating antibodies to *Aspergillus* *Aspergillus*-specific RAST positive *Aspergillus* spp. (culture/cytology) from respiratory tract specimen or from pleural space
Aspergilloma	No evidence of parenchymal invasion by hyphal elements	Single cavity with fungal ball, radiologically stable, pleural thickening	Haemoptysis, no other pulmonary symptoms	Evidence of hyphae within cavity, but not invading lung parenchyma	Positive precipitating antibodies to *Aspergillus* spp.
Invasive bronchial aspergillosis	Invasion of large airway, pathological manifestation: superficial invasion, pseudomembrane formation and focal ulceration (especially anastomotic infection in lung transplant)	Non-specific abnormalities, atelectasis, lobar collapse	Wide range of clinical scenarios, ulcerative disease in lung transplantation	*Aspergillus* spp. (culture/histology) from bronchoscopic specimen	Nil

† CNPA, Chronic necrotizing pulmonary aspergillosis, CCPA, Chronic cavitary pulmonary aspergillosis, CFPA Chronic fibrosing pulmonary aspergillosis.
PCR data in square brackets to indicate that significant issues in assay validation and standardization remain.
[a] As per the current EORTC/MSG definitions.
[b] Evidence exists in the form of case reports or case series.

profound neutropenia versus a combination of cyclosporine A (CsA) and methylprednisolone [18]. The pulmonary pathology of neutropenic rabbits was characterised by coagulative necrosis, hemorrhagic infarction, angioinvasion, and a scant mononuclear inflammatory infiltrate. Conversely, the histopathology of rabbits treated with CsA and methylprednisolone was characterized by a pyogranulomatous inflammation and inflammatory necrosis with no evidence of angioinvasion [18]. Thus, it is reasonable to consider IPA under two broad pathophysiological headings. The first is angioinvasive disease which is characterized by tissue infarction, coagulative necrosis and is essentially restricted to neutropenic hosts. The second is characterized by a pyogranulomatous inflammatory infiltrate, inflammatory necrosis, and is observed in a wide range of non-neutropenic hosts. Occasionally a mixture of pathological appearances may be present (Fig. 1).

Angioinvasive IPA

Pathology and pathogenesis: There are two classical pathological manifestations of IPA in which angioinvasion appears to be central to pathogenesis. The first arises in the context of invasion of major proximal pulmonary arteries with resultant thrombosis and distal tissue infarction leading to a wedge-shaped lesion with the base abutting the visceral pleura. The second consists of a well circumscribed spherical nodule with a vessel in the center of the lesion which is infiltrated by hyphal elements [13]. The nodule has a pale centre which consists of an area of coagulative necrosis with extensive permeation of tissue by hyphal elements but with a relative paucity of inflammatory cells or hemorrhage. The central necrotic core is surrounded by a hemorrhagic rim comprised of congested and hemorrhagic parenchyma. From a pathological perspective, this is referred to as a target lesion or mycotic sequestrum [19]; the radiological correlate, as defined with CT, is a nodule with or without an associated halo sign [13,20]. Nodular lesions may undergo cavitation with neutrophil recovery in which case the area of central necrosis, otherwise called the sequestrum, contracts with replacement by an air-cap; the radiological correlate in this context is the air-crescent sign. The use of elastic and reticulin fiber stains enables the identification of the residual vascular and airway structures within the sequestrum, thus distinguishing cavitary disease arising from the invasion and destruction of tissue from an aspergilloma or chronic pulmonary aspergillosis in which there is colonization of a pre-existing cavity [21,22].

Clinical setting and clinical features: Angioinvasive IPA is almost exclusively seen in profound and prolonged neutropenia. Furthermore, the disease is usually rapidly progressive, evolving over a period of days. There are no specific clinical signs or symptoms but fever, dyspnea, non-productive cough, hemoptysis, and chest pain are commonly cited although none are invariably

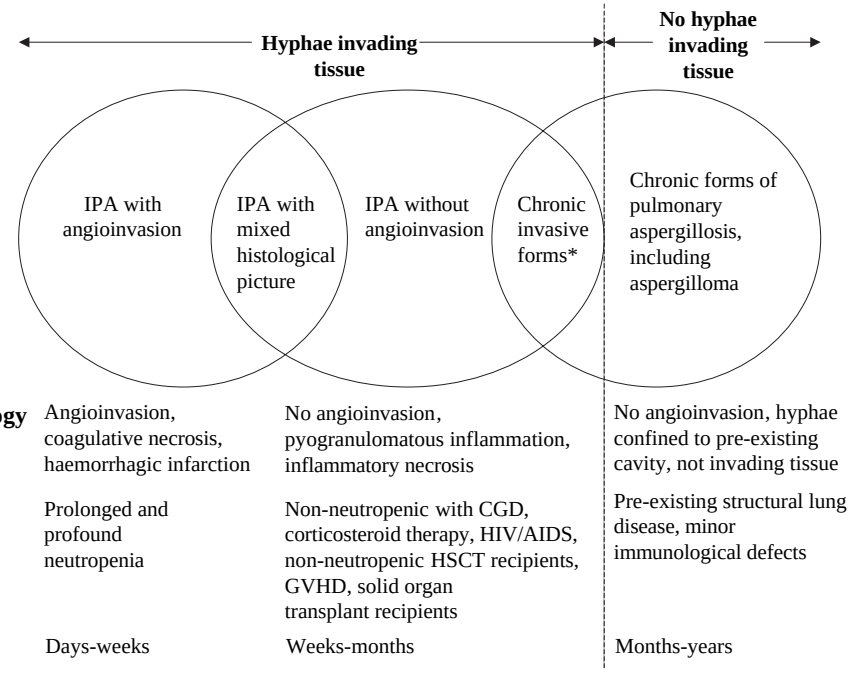

Fig. 1 The spectrum of aspergillosis of the lower respiratory tract (IPA, invasive pulmonary aspergillosis). *Chronic invasive forms including chronic necrotising pulmonary aspergillosis.

present [6,23]. Pleuritic chest pain, pleural rub and hemoptysis are suggestive of hemorrhagic infarction [6,24,25].
Diagnosis: See non-angioinvasive IPA, below.

Non-angioinvasive IPA

Pathology and pathogenesis: This entity contains a wide range of non-neutropenic hosts in whom the underlying pathology consists of a pyogranulomatous inflammatory response and inflammatory necrosis with no evidence of angioinvasion. Cavitation is frequently observed, presumably as a result of tissue necrosis. Individuals with chronic granulomatous disease (CGD) possess a unique immunological defect and pathology that is characterized by a multifocal nodular, micronodular, or a miliary infiltrate with scattered non-caseating, non-confluent granulomas containing hyphae with variable amounts of necrosis [26–28]. At least some patients with chronic necrotizing pulmonary aspergillosis (CNPA) can be classified as having non-angioinvasive IPA on the basis of invasion of pulmonary parenchyma by hyphal elements.
Clinical setting and clinical features: Non-angioinvasive IPA is observed most commonly in those exposed to corticosteroids, non-neutropenic hematopoeitic stem cell transplant (HSCT) recipients, solid organ transplant recipients, severe graft versus host disease (GVHD), and HIV/AIDS although a multitude of other non-neutropenic contexts are described. The disease may be insidious in onset and exhibit a slower clinical course than angioinvasive IPA. The term 'subacute IPA' has been coined to denote the more slowly progressive forms of IPA although the term has not been rigorously defined [29,30].
Diagnosis: The EORTC/MSG criteria [1] represent the current diagnostic benchmark but are designed in their current format only to apply to patients with cancer or HSCT. Virtually any radiological pattern may be seen with single or multiple nodular infiltrates (with or without halo sign), segmental or sub-segmental consolidation, diffuse ground glass opacification, and cavitation all being described. CT allows for the delineation of the more specific halo sign and air-crescent sign.

The diagnostic value of *Aspergillus* spp. in respiratory tract specimens is not straightforward, principally because of difficulties distinguishing colonization from disease. The specificity of the isolation of *Aspergillus* spp. in those with profound immunocompromise is high [31] and forms a central component of almost all diagnostic criteria for IPA. In patients without profound immunological deficits, the isolation of *Aspergillus* spp. is less likely to reflect underlying invasive disease and within this context significant caution should be exercised when directly extrapolating the diagnostic paradigm outlined in the EORTC/MSG document. The detection of *Aspergillus* antigen (using a sandwich ELISA employing a monoclonal antibody to galactomannan [GM], Platelia Aspergillus EIA kit, Bio-Rad Laboratories) in BAL specimens has been recently incorporated into diagnostic criteria to enable a diagnosis of probable IA in patients with cancer and HSCT [1]. The use of PCR in respiratory tract specimens is limited by specificity in much the same way as culture: quantitative PCR techniques may enable a distinction to be made between colonization and disease although this work is in its infancy.

Two positive GM results in serum have recently been incorporated into the diagnostic criteria to establish a diagnosis of probable IPA in high risk patients with cancer or post HSCT [1]. A similar case could potentially be made for PCR when issues of assay validation and standardization are overcome. Precipitating antibody to *Aspergillus* spp. has also been reported in the context of histologically proven IPA [5,32,33] although there are no reports in which antibody alone has been used to define a case of IPA.

Chronic forms of pulmonary aspergillosis including pulmonary aspergilloma

Chronic forms of pulmonary aspergillosis have been recognized for many years and have been variably referred to as pulmonary aspergillosis with cavitation, symptomatic pulmonary aspergilloma, complex aspergilloma, and chronic granulomatous aspergillosis. Subsequently, Gefter *et al.* [34] and Binder *et al.* [35] coined the terms semi-invasive pulmonary aspergillosis and chronic necrotizing pulmonary aspergillosis (CNPA), respectively. Since then, there have been considerable conceptual developments regarding the slowly progressive pulmonary syndromes due to *Aspergillus* spp. and it is likely that many early series were in fact comprised of a heterogeneous group of patients in whom the diagnosis ranged from slowly progressive forms of IPA to aspergilloma.

CNPA, CCPA, CFPA

The epithet CNPA has been widely used to apply to a syndrome complex consisting of slowly progressive cavitary lung disease, chronic respiratory symptoms, and the presence of precipitating antibodies to *Aspergillus* spp. The spectrum of disease is somewhat difficult to define; clearly, some reports of CNPA contain descriptions of direct invasion of pulmonary parenchyma by hyphal elements, thus representing a

(subacute) non-angioinvasive form of IPA [35–37]. In the majority of reports, however, there is no clear evidence of parenchymal invasion despite progressive tissue damage [34]. In this context the term chronic cavitary pulmonary aspergillosis (CCPA) has been recently proposed to account for cases in which there is formation and expansion of multiple cavities over time, and the term chronic fibrotic pulmonary aspergillosis (CFPA) to circumstances in which cavity formation is followed by a marked fibrotic reaction [30]. Furthermore, it has been proposed that the term CNPA be reserved for cases in which hyphal invasion of tissue is demonstrated (i.e., a subacute form of IPA) [30]. Thus, one is left with a collection of terms whose definition and scope varies considerably. Whether the rigorous sub-classifications of chronic pulmonary aspergillosis has more than academic importance is unclear.

Pathology and pathogenesis: Structural lung disease appears to be a critical factor in pathogenesis and can be readily documented in the majority of cases [30,35], mycobacterial infection, emphysema, bullae, asthma, sarcoidosis, pneumoconiosis, thoracic surgery, lung cancer, upper lobe fibrosis complicating ankylosing spondylitis, and *Legionella* infection are all described [30,34,35,38–41]. Subtle but critical defects in systemic immunity may also be important in the pathogenesis; defects in mannose binding lectin, corticosteroid therapy, diabetes, HIV/AIDS and alcohol abuse have all been reported in this regard [30,42]. The precise mechanism of new cavity formation remains unclear. Involvement of the pleural space usually implies the presence a bronchopleural fistula which may arise in the setting of spontaneous and therapeutic pneumothoraces and lung resection surgery but most commonly in the context of past or current tuberculosis [43–46].

Clinical setting and clinical features: Patients with CCPA tend to be middle-aged [35], with a symptom complex consisting of weight loss, chronic cough, hemoptysis, fatigue and shortness of breath [30]. While the clinical signs and symptoms of chronic pulmonary aspergillosis are non-specific, their presence and severity is an important point of distinction from aspergilloma.

Diagnosis: Although the diagnosis can be inferred from a single chest radiograph, detailed and sequentially acquired radiological data may be required to confirm the typical radiological features, as well as the very slow progression that is characteristic of this entity. CT scans may be useful to further define the precise pattern and extent of disease. Radiological examination usually reveals one or more cavities, typically within the upper lobes which may or may not contain fungus balls. New cavity formation or expansion of one or more existing cavities over time is highly characteristic. Peri-cavitary infiltrates and adjacent pleural thickening are frequently observed and appear to be indicative of disease activity; these radiological abnormalities may ameliorate with appropriate therapy leaving residual thin-walled empty cavities [30].

The demonstration of precipitating antibodies to *Aspergillus* spp. is the cornerstone and prerequisite for the diagnosis [30]. When precipitins are negative in the context of an otherwise compatible illness, batch to batch variability in kit antigen and the prospect of a non-*fumigatus Aspergillus* spp. as the causative organism should be considered and appropriate testing sought. *Aspergillus* spp. may be grown from respiratory specimens from both the upper and lower respiratory tract and, on occasion, the pleural space. Other important diagnostic facets include the demonstration of elevated inflammatory markers such as ESR and CRP, and the exclusion of other infectious, neoplastic, and inflammatory entities which may mimic this syndrome [30]. There appears to be a particularly strong link with atypical mycobacteria and these infections may be active simultaneously or sequentially. There is also the possibility of a pyogenic infection in a cavity which may require drainage and appropriate antibacterial therapy.

Aspergilloma

Pathology and pathogenesis: A pulmonary aspergilloma is a rounded conglomerate of hyphae, mucus, and cellular debris contained within a fibrotic and thickened wall and occupying a pre-existing cavity. The cause of pre-existing cavity is most commonly an old tuberculous cavity but an aspergilloma may complicate a wide range of other pulmonary diseases which are associated with or characterized by cavitation such as sarcoidosis, histoplasmosis, pulmonary cysts, ankylosing spondylitis, tuberculosis, bronchiectasis, rheumatoid nodules, and adenocarcinoma [48–54]. The fungal ball is typically mobile and its size may vary with time as may the degree of adjacent pleural and cavity wall thickening. The distinction between an aspergilloma and chronic pulmonary aspergillosis may be somewhat semantic but does reflect the singularity of the aspergilloma as opposed to the multiple cavities typical of chronic pulmonary aspergillosis. Most aspergillomas are caused by *A. fumigatus* but some, especially in diabetic patients, are caused by *A. niger* in which case oxalic acid crystals may be seen in sputum and the aspergilloma if resected [55].

Clinical setting and clinical features: There are no symptoms referable to the aspergilloma other than the occurrence of hemoptysis in 50%–90% of patients. This is often infrequent and small in volume but on occasions may be massive and fatal.
Diagnosis: The appearance of a mobile fungal ball in a pulmonary cavity is highly suggestive of the diagnosis. The demonstration of precipitating antibodies to *Aspergillus* spp. is the essential diagnostic test to confirm the aetiology; rarely non-*Aspergillus* fungi may be responsible.

Invasive bronchial aspergillosis

This syndrome refers to invasive disease primarily involving the (bronchoscopically accessible) large airways. Kramer *et al.* [56] proposed the all-inclusive term 'invasive bronchial aspergillosis' (IBA) and further suggested IBA could be sub-classified on the basis of the specific endobronchial appearances as *Aspergillus* tracheobronchitis, pseudomembranous tracheobronchial aspergillosis, and ulcerative tracheobronchial aspergillosis [56]. IBA represents a spectrum of disease and this poses difficulties for sub-classification, with a plethora of morphological and functional terms making an analysis of the literature somewhat difficult.
Pathology/pathogenesis: *Aspergillus* tracheobronchitis is a term reserved for cases in which there is tracheobronchial inflammation with a mucus exudate containing *Aspergillus* spp. with no other identifiable pathogen [6,56,57]. The inflammation is superficial, the mucosa is intact, and there is no evidence of pseudomembrane formation, deep focal ulceration or other focal endobronchial abnormalities [6,56,57].

Pseudomembranous tracheobronchial aspergillosis results from necrosis and sloughing of the bronchial epithelium and the formation a pseudomembrane consisting of necrotic debris and hyphal elements. In the early stages of disease, the airway damage may manifest as a series of discontinuous focal plaques which are grey, white, or black in color, which coalesce to result in extensive, continuous and circumferential involvement of the airway over time [58–60]. The depth of infection is variable; in the majority of cases there is superficial invasion which does not extend past the bronchial cartilage [61], while in others there is involvement of the entire bronchial wall (synonymous with transmural infection and probably the term necrotising tracheobronchitis) with subsequent extension into surrounding peribronchial tissue [62,63].

Ulcerative tracheobronchial aspergillosis refers to single or multiple focal and discretely abnormal areas which manifest as endobronchial plaques, nodules, or areas of ulceration and necrosis [56,61]. The original description of this entity was in the context of lung transplantation with involvement of the anastomosis [56]. The depth of the ulcer is variable; it may extend as far as the adjacent pulmonary parenchyma and pulmonary vasculature [61]. Late sequelae of ulcerative bronchial aspergillosis include the formation of excessive granulation tissue resulting in bronchial stenosis [64,65].
Clinical features and clinical setting: Pseudomembranous *Aspergillus* tracheobronchitis has been documented to occur in a variety of clinical contexts including lung transplantation, heart-lung transplantation, post-influenza, hematological malignancy, HSCT, chronic obstructive pulmonary disease (COPD) and metastatic renal cell carcinoma [56,58,60,61,66–69]. Pseudomembranous tracheobronchitis may be clinically silent; progressive encroachment into the airway lumen leads to bronchial obstruction, distal atelectasis or lobar collapse, and manifests clinically as stridor, wheeze, respiratory failure and ultimately death [6,57,58,60–62,68].

Ulcerative tracheobronchial aspergillosis characteristically occurs in the initial six months following lung transplantation, in which case the bronchial anastomosis is the usual site of involvement [56,70]. Ulcerative tracheobronchial aspergillosis has also been observed in a limited number of other clinical contexts including HIV/AIDS [71] and solid cancers [61].
Diagnosis: A high index of suspicion is required to establish the diagnosis of invasive bronchial aspergillosis, since the associated symptoms and imaging abnormalities may be relatively minor and non-specific. The diagnosis can be established following bronchoscopic examination to assess the nature and extent of disease and also to enable the procurement of appropriate diagnostic specimens from which *Aspergillus* spp. can be identified.

Aspergillosis of the upper respiratory tract (Table 2)

The classification of sinus disease due to *Aspergillus* spp. in this document is consistent with the scheme developed by deShazo *et al.* [72]. There are a number of vital structures surrounding the sinuses, all of which may be involved with extension of disease. It is particularly worth highlighting the impressive literature on orbital aspergillosis in which case the sinuses can be invariably implicated as the primary source of infection. The orbital apex syndrome, which refers to the combination of optic neuropathy, ophthalmoplegia,

Table 2 Aspergillosis of the upper respiratory tract

	Pathological features	Radiological features	Clinical setting	Direct evidence to implicate *Aspergillus* spp.	Indirect evidence to implicate *Aspergillus* spp.
Acute invasive sinusitis	Coagulative necrosis, invasion of contiguous structures, scant inflammatory infiltrate	Sinus opacification, evidence of erosion of bony structures	Neutropenia and allogeneic HSCT recipients	*Aspergillus* spp. (culture/histology) from sinus biopsy *Aspergillus* spp. (culture/cytology) from sinus aspirate[a] *Aspergillus* spp. (culture/histology) from contiguous site (e.g. orbit, brain). [PCR from sinus biopsy][c]	Proven/probable IA at non-contiguous site. Positive GM (x2) from blood[a] [Positive PCR from blood][c]
Chronic invasive sinusitis	Infiltrative mass comprising mixed inflammatory infiltrate, inflammatory necrosis, invasion of contiguous structures	Evidence of sinusitis, bone erosion, destruction of contiguous structures	Diabetes, corticosteroid therapy, HIV/AIDS, chronic signs and symptoms	*Aspergillus* spp. (culture/histology) from sinus biopsy *Aspergillus* spp. (culture/histology) from contiguous site (e.g. orbit, brain) [PCR from sinus biopsy][c]	
Chronic granulomatous sinusitis	Infiltrative mass, florid granulomatous inflammation, spread to the orbit and brain	Evidence of pansinusitis, bone erosion and spread to contiguous structures	Immunocompetent individuals from Sudan, Middle East, Indian subcontinent	*Aspergillus* spp. (culture or histology) from sinus biopsy *Aspergillus* spp. from contiguous site (orbit, brain) [PCR from sinus biopsy]	Proven/probable IA at non-contiguous site Positive precipitating antibodies to *Aspergillus* spp.
Sinus aspergilloma	Fungal ball comprised of cheesy friable material, conglomerate of hyphae in concentric circles, no evidence of bone erosion	Maxillary sinusitis opacification with concretions or antroliths	Older person with some pre-existing sinus abnormality	*Aspergillus* spp. (culture or histology) from sinus aspirate or surgically removed material	Positive precipitating antibodies to *Aspergillus* spp.

PCR data in square brackets to indicate significant issues in assay validation and standardization remain.
[a] As per the current EORTC/MSG definitions.
[c] No current reports of diagnostic modalities being used in this context.

and proptosis due to a mass in the superior portion of the orbit, is especially characteristic.

Acute invasive Aspergillus *sinusitis*

This syndrome was originally described in 1980 [73]; synonyms include fulminant aspergillosis of the paranasal sinuses [73,74] and fulminant *Aspergillus* sinusitis [75]. The syndrome denotes a rapidly progressive disease occurring typically in patients with neutropenia and allogeneic HSCT and only appears rarely outside this setting.

Pathology and pathogenesis

Aspergillus sinusitis develops following the inhalation and deposition of conidia in the nasal passages and sinuses. The establishment of local invasion is typically followed by the development of a rapidly destructive pansinusitis, spread to contiguous structures such as the orbit, frontal bone, cavernous sinus, carotid artery, anterior and middle cranial fossae, and eventual dissemination [76–79]. The histological findings include a relatively scant acute inflammatory infiltrate, infiltration of tissue by hyphal elements, angioinvasion, and coagulative necrosis [73,75,76].

Clinical setting and clinical features

The pertinent clinical signs and symptoms include facial pain, nasal congestion, nasal discharge, epistaxis, nasal crusting, nasal ulcers and the presence of a necrotic anaesthetic eschar in the nose or on the palate [72,73,80–83].

Diagnosis

The diagnosis of acute invasive *Aspergillus* sinusitis should be considered in a patient with neutropenia or allogeneic HSCT with signs and symptoms of sinus disease. Radiological examination may show sinus opacification, destruction of bone, and evidence of orbital or intracranial extension [84]. Direct evidence that the pathological process relates to a filamentous fungus rests with the demonstration of hyphae from a tissue specimen, ideally procured from the edge of a lesion to avoid non-viable necrotic fungal elements which may reside in the centre [73,79]. Confidence that *Aspergillus* in particular is the causative pathogen then rests with positive culture data from the tissue specimen or from a sinus aspirate. Indirect evidence to implicate *Aspergillus* spp. may come from analysis of nasal swabs or nasal discharge specimens. While the acquisition of such specimens may be less invasive, they are less specific than tissue specimens and there can be less certainty about the diagnosis. The current EORTC/MSG criteria enable a diagnosis of probable disease to be established when data suggesting *Aspergillus* spp. are obtained from a sinus aspirate or if there are ≥ 2 positive GM results from blood in high risk patients with cancer or HSCT, with concomitant evidence of sinusitis as defined clinically or radiologically.

Chronic invasive Aspergillus *sinusitis*

Pathology and pathogenesis

This entity is characterized by a mass within the sinuses which is comprised of friable, necrotic, or purulent material [85,86]. There is frequently evidence of invasion of contiguous structures such as the base of the skull, orbit and brain. Histological examination reveals prominent tissue necrosis, and a sparse low grade mixed cellular infiltrate [82].

Clinical setting and clinical features

There are no specific clinical signs and symptoms, although the orbital apex syndrome is particularly characteristic [82,87,88]. Other clinical manifestations resulting from invasion of major vessels, brain, and cavernous sinuses are also well documented [82,89–91].

Diagnosis

This entity is distinguished from acute sinus aspergillosis on the basis of its insidious onset, a clinical course extending over a period of months and its tendency to affect individuals with relatively subtle defects in immunity such as those with diabetes, low dose corticosteroid use, and HIV/AIDS [82,88,89,91–94]. The diagnosis should be considered in those with a syndrome of chronic sinusitis as defined clinically and radiologically and present for at least several months, especially in the context of a subtle but nevertheless readily identifiable immunological deficit. Radiological examination shows a soft tissue mass with evidence of tissue infiltration and destruction and frequent extension to contiguous structures. The diagnosis is secured by demonstrating hyphal elements in tissue and/or *Aspergillus* spp. in culture from a tissue biopsy or sinus contents, in the context of a compatible clinical syndrome and following the demonstration of compatible histological findings of a low grade mixed inflammatory infiltrate; the latter is a point of distinction from chronic granulomatous sinusitis.

Chronic granulomatous invasive sinusitis

This entity, also called primary paranasal *Aspergillus* granuloma (PPAG) of the Sudan [95] is slowly progressive, occurs in overtly immunocompetent patients, within restricted geographical locales, and is

characterized histologically by florid granulomatous inflammation. Almost all reports come from the Sudan [95,96], Saudi Arabia [97,98], and the Indian subcontinent [99,100]. There are a limited number of reports of granulomatous sinusitis acquired in the USA which appear to almost exclusively affect African-Americans but whether this is precisely the same syndrome as PPAG is not clear [101–103]. *A. flavus* is the responsible pathogen in 90% of cases, with the remainder attributable to *A. fumigatus* and *A. niger* [91,96,98,104].

Pathology/pathogenesis

The hallmark of this syndrome is a painless, hard, irregular, relatively avascular mass which mimics malignancy [95,105]. Frequently there is direct spread beyond the confines of the sinuses to invade the brain, cavernous sinus, orbit and great vessels; intracranial involvement is seen in approximately 58% of cases at the time of diagnosis [77,91,98]. Bone erosion is a common finding [96]. The ethmoid sinuses are the most commonly affected structures and pan-sinusitis develops in the majority of individuals [96,98]. Histologically there is a florid granulomatous reaction with giant cells, histiocytes, lymphocytes and plasma cells [101]. Both fibrotic and necrotic histological variants have been described [104]. Tissue destruction occurs as a result of expansion of the mass rather than vascular invasion. The vascular appearance, nevertheless, is often abnormal; vessels are characteristically thickened with luminal narrowing due to intimal proliferation with a peri-arterial, cuff-like chronic inflammatory infiltrate progressing to concentric lamellated dense fibrous tissue without demonstrable hyphal elements [104].

Clinical setting and clinical features

Most individuals present with a unilateral proptosis [95]. Other signs and symptoms related to the sinuses and extension to contiguous structures may be present. The mean duration of symptoms before diagnosis is 18 months and the mean age at disease onset ranges from 25–38 years in a number of studies [91,96,98].

Diagnosis

The diagnosis should be considered in an immunocompetent individual from the Sudan, Indian subcontinent, or Middle East with evidence of chronic sinusitis as defined clinically and radiologically. Radiological findings include opacification of the sinuses, bone erosion, pansinusitis as well as orbital and intracranial extension [98]. A definitive diagnosis requires a biopsy to demonstrate granulomatous inflammation and the presence of *Aspergillus* spp. Hyphae are typically sparse and can only be visualised in around 50% of cases. *Aspergillus* spp. can be recovered in culture in approximately two-thirds of cases and the finding of *A. flavus* is particularly characteristic [96]. Similarly, precipitating antibodies to *Aspergillus* spp. are present in around two-thirds of cases and a positive IgG RAST to *A. flavus* is also frequently seen [95,96,101]. Serological data may be used as indirect evidence to implicate *Aspergillus* spp. when conventional data are negative or cannot be acquired.

Sinus aspergilloma

This saprophytic syndrome shares common features with both pulmonary and renal aspergilloma, including the absence of tissue invasion, occurrence in individuals without immunological impairment, and the formation of precipitating antibodies which are of diagnostic value. The term sinus mycetoma is best avoided to prevent confusion with the specific syndrome involving subcutaneous tissue and contiguous structures.

Pathology and pathogenesis

A sinus aspergilloma may develop in areas of functional or anatomical abnormalities; root-filling material has also been implicated in the pathogenesis [106–108]. The fungal mass is clearly demarcated from normal sinus tissue with no evidence of invasion of tissue, although there may be thickening or sclerosis of the sinus wall due to the effect of pressure and pressure necrosis may ensue [109,110]. The aspergilloma consists of a cheesy, friable material which is brown, tan, green, yellow or black in colour. Histologically, the antral mucosa is well preserved other than a chronic non-granulomatous inflammatory response which may be a response to the effect of pressure. The fungal ball consists of a dense conglomerate of hyphae arranged in concentric circles [76,106,110].

Clinical features and clinical setting

Chronic sinus symptoms such as nasal discharge, obstruction, facial fullness, and pain predominate although none are specific. Unilateral sinus involvement is typical; the maxillary sinuses are the most commonly affected structure followed by the sphenoids but occasionally more than a single sinus is involved [76,110–112].

Diagnosis

The diagnosis should be considered in an older person with evidence of chronic sinusitis but without clinical or radiological evidence of invasive disease. Radiologic imaging shows opacification of the sinus with

one or more round or oval radiolucent objects which are referred to as foreign bodies, concrements (or concretions) or antroliths lying centrally or toward the orifice of the antrum [106]. These calcium phosphate rich bodies probably originate from calcification of inspissated mucus and necrotic hyphal elements, although root filling material has also been implicated [113]. Specific evidence that *Aspergillus* is the responsible pathogen requires the application of conventional techniques such as histology and culture to surgically acquired specimens. The use of histological data alone may be compromised by the fact that hyphal morphology may assume atypical forms [114]. Precipitating antibodies to *Aspergillus* spp. are invariably positive and are of considerable diagnostic benefit.

Cardiovascular aspergillosis (Table 3)

Aspergillus spp. may affect both native and prosthetic valves. These entities differ significantly in terms of their etiology and pathogenesis, but have in common a tendency to form large friable vegetations, a high incidence of embolic events involving multiple organs, negative blood cultures, absence of classical clinical features of infective endocarditis, and a dismal prognosis [115,116]. The pathological consequences of *Aspergillus* endocarditis include both the development of disseminated disease (especially endophthalmitis) as well as local complications such as pancarditis [117] and cardiac rupture [118–120].

Native valve Aspergillus *endocarditis*

Native valve *Aspergillus* endocarditis (NVAE) usually occurs in the context of individuals with significant immunological impairment without preceding cardiac surgery or instrumentation. Less commonly this syndrome occurs as a complication of cardiac surgery (without insertion of prosthetic material).

Pathogenesis and pathology

The importance of pre-existing valvular abnormalities in native valve *Aspergillus* endocarditis without preceding surgery remains unknown, although in most case reports there is no history of structural cardiac disease, suggesting that the degree of endocardial damage required to initiate infection is less than is the case for other organisms [116]. Vegetations are characteristically large and friable [116]. Embolic events to major vessels such as the aorta, iliac and femoral arteries are especially characteristic [115,121,122]. Intracardiac vegetations may be of sufficient size to result in hemodynamic compromise, as illustrated by a case in an infant where vegetations were estimated to occupy 50% of the ventricular volume [123]. Large vegetations may also obstruct cardiac structures such as the superior vena cava [124] and coronary ostea, potentially leading to acute myocardial infarction in the latter scenario [117,118,125].

True mural endocarditis (mural endocarditis without a known antecedent endocardial lesion) is highly characteristic of *Aspergillus* spp; it can be documented in approximately one-third of patients with *Aspergillus* endocarditis and appears to be more likely in those patients who are significantly immunocompromised [116]. Mural endocarditis may represent contiguous involvement from an infectious focus within the myocardium or may arise *de novo* [120]. Mural vegetations are described as white-yellow-grey excrescences which average several millimetres in diameter [120]. Mural vegetations do not appear to produce large emboli: they may act, however, as a source of microemboli which may lead to the formation of peripheral metastatic infectious foci. In cases of cardiac surgery in which a prosthetic valve has not been placed, endothelial damage may result from cannulation to establish extracorporeal circulation or the construction of an aortic-graft anastomosis and this presumably provides a nidus for the initiation and subsequent development of endocardial infection [126].

Clinical setting and clinical features

NVAE without prior cardiac surgery occurs in a variety of contexts including hematological malignancy [116,127], solid organ transplantation [128–132], HIV/AIDS [116], neonates [123], exposure to corticosteroids [133], and CGD [124]. Intravenous drug use (IVDU) is also a well recognised risk factor [134–136]. There are no specific clinical features.

Diagnosis

The Duke criteria [137] provide the modern framework for establishing the diagnosis of *Aspergillus* NVAE. A diagnosis of NVAE is suggested by fever unresponsive to antibacterial agents, clinical signs of endocarditis, negative blood cultures, embolic events involving major vessels, and echocardiographic abnormalities. Approximately 78% of patients with *Aspergillus* endocarditis have demonstrable vegetations on transthoracic echocardiography. In the presence of mural vegetations, both clinical and transthoracic echocardiographic evidence of endocardial involvement may be falsely negative; transoesphageal echocardiography is likely to be more sensitive in this context but this remains to be determined [120,133,138].

Table 3 Cardiovascular aspergillosis

	Pathological features	Radiological features	Clinical setting	Direct evidence to implicate *Aspergillus* spp.	Indirect evidence to implicate *Aspergillus* spp.
Native valve endocarditis	Large friable vegetations, mural vegetations, extension to paravalvular structures, development of pancarditis	Echocardiographic evidence of endocardial abnormalities	Individual with significant immunological impairment without preceding surgery, or, recent cardiac surgery without insertion of prosthetic valves or material, WITH: fever unresponsive to antibacterial antibiotics, new or changing murmurs, peripheral stigmata of endocarditis, emboli to large vessels or disseminated IA	*Aspergillus* spp. in blood cultures *Aspergillus* spp. (culture/histology) from retrieved embolus or valve GM from blood[b] [PCR from blood][b] [PCR from resected valve or retrieved embolus][c]	Proven/probable IA at non-contiguous site
Prosthetic valve endocarditis	Vegetation causing prosthetic malfunction, valve dehiscence	Echocardiographic abnormalities including malfunction of prosthetic valve, paravalvular leak, paravalvular collection	Previous cardiac surgery with prosthetic valves or prosthetic material WITH: fever, new or changing murmurs, peripheral stigmata of endocarditis, emboli to large vessels and disseminated IA	*Aspergillus* spp. in blood cultures *Aspergillus* spp. (culture/histology) from retrieved embolus or resected valve [PCR from blood][c] [PCR from resected valve or retrieved embolus][c]	Proven/probable IA at non-contiguous site
Pericardial aspergillosis	Fibrinous or exudative pericarditis, evidence of contiguous IPA or myocardial aspergillosis	Echocardiographic evidence of pericardial disease including pericardial effusion and signs of pericardial tamponade, widened cardiac silhouette on CXR	Contiguous IPA, or, evidence of pre-existing endocarditis or myocarditis with signs of pericardial disease including pericardial rub, muffled heart sounds, signs of pericardial tamponade.	*Aspergillus* spp. (culture, cytology or histology) from pericardial biopsy or aspirate *Aspergillus* spp. (culture, cytology or histology) from a contiguous site (esp. IPA) GM from pericardial fluid[b] [PCR from pericardial fluid][c]	Proven/probable IA at non-contiguous site GM from blood[c] [PCR from blood][c]

PCR data in square brackets to indicate significant issues in assay validation and standardization remain. IPA: Invasive pulmonary aspergillosis.
[b] Evidence exists in the form of case reports or case series.
[c] No current reports of diagnostic modalities being used in this context.

Specific evidence that *Aspergillus* is the causative pathogen is more problematic. Blood cultures are frequently, although not invariably, negative which represents a significant diagnostic obstacle [116,139]. Not infrequently, *Aspergillus* spp. may be recovered from an embolus or distant site which enables the clinical diagnosis to be established with some confidence [117,130,132,135,138,140–143]. There are emerging reports of PCR in blood being used to implicate *Aspergillus* spp. as the causative organism [144–146]. There is a single report of *Aspergillus* antigen (detection method unknown) turning positive at low titre and this is potentially another way in which a microbiological diagnosis could be established [127]. *Aspergillus* antibodies are positive in a minority of patients, but whether they have any serious diagnostic role is a matter for further study [116,147].

Prosthetic valve Aspergillus *endocarditis and prosthetic device-related endocarditis*

Prosthetic valve *Aspergillus* endocarditis (PVAE) is the most common manifestation of cardiovascular aspergillosis and carries a grave prognosis [124,148–150]. Less commonly *Aspergillus* may also infect a variety of prosthetic devices such as pacemaker wires [151] and implantable defibrillators [152].

Pathogenesis and pathology

The likely pathogenesis is the direct inoculation of conidia at the time of surgery or seeding of the endocardium from the lungs in the peri-operative period at a time when normal pulmonary defenses are compromised [115]. Several studies report clustering of such *Aspergillus* prosthetic valve infections, suggesting environmental contamination as the cause of the infection [149,153,154].

The syndrome typically manifests relatively late after valve replacement with a range of 12–103 days in one small series [150]. Infection of homografts [155], xenografts [156,157], patches [158–160], prosthetic valves [115,149,161–165], annulopasty rings [166] have all been described. As with NVAE, the vegetations tend to be large and may interfere with the function of the prosthesis by obstructing the prosthetic apparatus, failure of the valve seating, or progressive valve dehiscence [141,148–150,162,167,168]. Embolization to large arteries is characteristic [153,160]. Thrombotic occlusion of the coronary arteries and resultant myocardial infarction has been described, as has obstruction of the right ventricular outflow tract and cardiac rupture [117,121,140,158,169].

Clinical setting and clinical features

Clinical evidence of endocardial involvement such as new or changing murmurs, alteration in the quality of prosthetic heart sounds, or clinical evidence of prosthetic valve dysfunction, may be present but are not specific findings.

Diagnosis

The diagnosis is suggested in the context of a prosthetic valve by clinical evidence of prosthetic valve malfunction, fever unresponsive to antibacterial agents, negative blood cultures, embolic events involving major vessels, and echocardiographic abnormalities. Again, the Duke criteria provide the construct within which this entity should be considered. The echocardiographic findings are non-specific and include compromise in the function and seating of the mechanical valve, para-valvular leak and para-valvular abscess formation [153]. Specific evidence to implicate *Aspergillus* spp. is difficult. Blood cultures with most *Aspergillus* species are typically negative [153,160]. An ante-mortem diagnosis is most frequently secured following analysis of the resected valve, other intraoperative specimens, or from a retrieved embolus [140,153,157,159].

Aspergillus *infection of vascular grafts*

Infection of vascular prostheses with *Aspergillus* spp. is uncommon. Infection of aortic grafts are well recognized in which case the proximal anastomosis is usually implicated and contiguous vertebral osteomyelitis is frequently seen (see osteomyelitis) [170,171]. *Aspergillus* infection of femoral-popliteal grafts has been reported [170]. Blood cultures are typically negative [171]. The diagnosis is most readily made from retrieved embolectomy specimens or surgical specimens obtained from the anastomotic or contiguous site.

Pericardial aspergillosis

Pericardial aspergillosis may arise from contiguous spread from either the pleura or mycocardium [6,8,172]. Post-mortem findings include a patchy or diffuse pericarditis or multiple raised nodules or plaques on one or both pericardial surfaces. Both a serofibrinous and purulent pericarditis may be seen [6,172]. Constrictive pericarditis has been described [173]. Clinical evidence of pericardial disease (pericarditis, pericardial effusion, pericardial tamponade) and other radiological and electrocardiographic abnormalities may be observed but are not invariably present [172]. Pericardial aspergillosis is not a frequent ante-mortem diagnosis but should be suspected when a

patient with known IPA develops a pericardial effusion or other evidence of pericardial disease. Culture, histology of resected pericardium, or potentially GM or PCR on aspirated pericardial fluid establishes the diagnosis.

Myocardial aspergillosis

Myocardial aspergillosis may arise from hematogenous seeding or as a result of contiguous spread from an endocardial or epicardial focus [6,125,129,174]. Myocardial involvement appears to be a frequent manifestation of disseminated aspergillosis and a spectrum of appearances is observed ranging from sub-clinical myocardial involvement with small discrete abscesses 1–3 mm in diameter up to more extensive involvement with large abscess formation, invasion of the coronary arteries, and spread to the endocardial surface to produce mural vegetations [6,175–177]. Myocarditis is most commonly clinically silent unless there is associated conduction disturbances, endocarditis, or pericarditis [174]. A definitive antemortem diagnosis of *Aspergillus* myocarditis is usually not possible for practical reasons.

Central nervous system aspergillosis (Table 4)

Infection of the CNS may follow hematogenous seeding (in which case the lung or heart are the most common primary sites [178–182]), direct inoculation into the CNS during neurosurgery, or spread from contiguous anatomical structures such as the sinuses. There is a spectrum of disease and frequently more than one pathological process may be present at a given time.

Cerebrovascular aspergillosis

The term 'cerebrovascular aspergillosis' denotes the well recognized syndrome of cerebral infarction and necrosis and/or hemorrhage without suppuration resulting from vascular invasion and thrombosis.

Pathology and pathogenesis

Cerebrovascular aspergillosis results in the majority of cases from endovascular infection, from either a septic embolus from a proximal site or cerebral vasculitis induced by primary invasion of the vascular wall [179,180,183]. Less commonly, this syndrome arises following invasion from the adventitial side of the vessel, as has been documented following meningitis [183–185] and post-surgical clipping of a berry aneurysm [186]. Vessels of all sizes may be involved and widespread arteritis, arteriolitis, and vascular thrombosis is commonly observed [179,180]. Vascular thrombosis leads to cerebral infarction within the territory of the involved vessel. Subsequently, vascular invasion by hyphal elements may lead to a loss of vessel integrity with resultant cerebral hemorrhage or hemorrhagic transformation within an area of infarction [179,187]. Histologically, tissue infarction, necrosis and hemorrhage predominate and there is little inflammatory response; when present an acute inflammatory infiltrate is seen [179,180,188]. Hyphae are typically scant [180,189]. The majority of cerebral lesions occur in the cortex, corticomedullary, and sub-cortical regions supplied by perforating arteries [179,180,187, 190]; less commonly, the cerebellum, brain stem, and spinal cord are affected [179,180,182,191]. A focal meningitis in areas contiguous with primary cerebral involvement is commonly observed [179,180,182,189].

Clinical setting and clinical features

Cerebrovascular aspergillosis occurs most frequently in patients with significant immunological impairment such as HSCT [192] or solid organ transplant recipients [180,188–190,193]. Less commonly it may occur in the context of corticosteroid therapy [194], HIV/AIDS [195], native and prosthetic valve endocarditis, and IVDU [182,196,197]. The clinical features are non-specific and typically include an acute stroke like illness with focal neurological deficits, seizures, and a progressive decline in conscious state [179].

Diagnosis

An antemortem diagnosis of cerebrovascular aspergillosis is notoriously difficult; the illness is rapidly progressive, biopsy is often precluded due to coagulopathy, and the diagnostic yield is limited by the relative paucity of hyphal elements at the site of tissue damage. By the time *Aspergillus* is entertained as a diagnostic possibility, a definitive diagnosis may only be of academic importance. The radiological appearances of cerebrovascular aspergillosis are protean and non-specific and may be normal or near normal in the early stages of infection [179,187,188]. CT may reveal single, but more commonly multiple, non-enhancing hypodense lesions with little associated mass effect. There may be radiological evidence of superimposed cerebral hemorrhage or hemorrhagic transformation within an area of cerebral infarction.

Evidence implicating *Aspergillus* as the causative organism is difficult. Since CNS disease is often a marker of disseminated aspergillosis, a definitive antemortem microbiological diagnosis may be more easily and most appropriately established using microbiological data from a non-contiguous extra-cerebral site

Table 4 Central nervous system aspergillosis

	Pathological features	Radiological features	Clinical setting	Direct evidence to implicate *Aspergillus* spp.	Indirect evidence to implicate *Aspergillus* spp.
Cerebrovascular aspergillosis	Invasion of vessels by hyphae, cerebral infarction in region of vascular territory, hemorrhagic transformation, no evidence of abscess or granuloma formation, contiguous involvement of the meninges	CT showing one or more non-enhancing hypodense region(s) consistent with cerebral infarction and/or hyperdense region(s) consistent with hemorrhage or hemorrhagic transformation	Essentially restricted to those with significant immunological impairment, IVDU, or *Aspergillus* endocarditis	*Aspergillus* spp. (culture/histology) from cerebral biopsy/aspirate Proven/probable IA at contiguous site (e.g. sinuses) Positive GM from CSF[a,b] [Positive PCR from cerebral biopsy/aspirate][c] [Positive PCR from CSF][b]	Proven/probable IA at non-contiguous site Positive GM (x2) from blood[a,b] [Positive PCR from blood][b]
Cerebral abscess	Abscess formation: central necrotic area with liquifactive necrosis surrounded by an abscess wall.	Single or multiple space occupying lesion(s) showing ring enhancement, mass effect, cerebral oedema	Patients with significant immunological impairment, IVDU, or *Aspergillus* endocarditis	*Aspergillus* spp. (culture/histology) from cerebral biopsy or abscess aspirate. Proven/probable IA at a contiguous site. Positive GM from CSF[a,b] [Positive PCR from cerebral biopsy][c] [Positive PCR from CSF][b]	Proven/probable IA at non-contiguous site Positive GM (x2) from blood[a] [Positive PCR from blood][c]
Cerebral granuloma	Solid lesion without suppuration, with florid granulomatous inflammation and hyphal infiltration	Space occupying lesion	Immunocompetent patient from Sudan, Middle East, Indian Subcontinent, patient with CGD, with longstanding signs/symptoms (months years)	*Aspergillus* spp. from a brain biopsy, aspirate Proven/probable IA with granulomatous inflammation from sinuses or orbit	Precipitating antibodies to *Aspergillus* spp.
Mycotic cerebral aneurysm	Aneurysm formation of intracranial artery, invasion of vessel wall by hyphae	Aneurysm of intracranial vessel defined at cerebral angiography	Patients with profound immunological impairment, recent neurosurgical clipping of a berry aneurysm or in the setting of *Aspergillus* meningitis with involvement of vessels at the base of the brain	Proven/probable IA at a contiguous site (e.g. sinuses or orbit)	Proven/probable IA at a non-contiguous site Positive GM (x2) from blood[a] [Positive PCR from blood][c]
Meningitis	Thick grey-white membrane overlying brain in cases of spread from sinuses, focal and contiguous meningitis in the case of cerebrovascular aspergillosis and cerebral abscess formation, meninges infiltrated by hyphae and inflammatory infiltrate, neutrophil pleocytosis, raised protein, low to normal glucose in CSF	Nil	Evidence of another CNS aspergillosis syndrome; as above Previous neurosurgery Aspergillosis of a contiguous structure (sinuses, orbit)	*Aspergillus* spp. (culture, histology) from a meningeal biopsy *Aspergillus* spp. (culture, cytology) from CSF Positive GM from CSF[a,b] [Positive PCR from CSF][b] Proven/probable IA at contiguous site (e.g. sinuses)	Positive GM x2 from blood[a,b] [Positive PCR from blood]

PCR data in square brackets to indicate significant issues in assay validation and standardization remain.
[a] As per the current EORTC/MSG definitions.
[b] Evidence exists in the form of case reports or case series.
[c] No current reports of diagnostic modalities being used in this context.
IVDU: Intravenous drug use.
CGD: Chronic granulomatous disease.

such as the lung, sinuses and skin [179,188,195]. Blood cultures are invariably negative but both PCR and GM from blood may be more sensitive markers of endovascular infection and there are several reports utilizing these techniques to establish the diagnosis [198,199]. The current EORTC/MSG criteria enable a diagnosis of probable CNS aspergillosis to be established in high risk patients with appropriate radiological abnormalities and ≥ 2 positive GM results in serum.

In the absence of specific data from blood, examination of CSF provides an alternative diagnostic avenue. Unfortunately, despite the fact that CSF findings are typically abnormal, specific evidence implicating *Aspergillus* spp. using conventional techniques is extremely uncommon [179,182,188,200]. In contrast, GM levels in CSF have been documented to be elevated in patients with probable cerebral aspergillosis [199,201] and elevated GM levels in CSF have been incorporated into the EORTC/MSG criteria to establish the diagnosis of CNS aspergillosis. PCR in CSF has also been used to confirm a presumptive diagnosis of cerebral aspergillosis, including a case in which CSF was drawn post-mortem in the setting of pulmonary aspergillosis (defined by pulmonary nodules on CT with a positive GM test in blood and consistent neuroradiological abnormalities) [198].

Cerebral abscess

Pathology/pathogenesis

This entity refers to a suppurative process within the brain caused by *Aspergillus* spp. and may arise in a variety of clinical contexts via a number of distinct mechanisms. The abscess consists of an area of central liquifactive necrosis where hyphal elements are sparse or absent and this is surrounded by an area of hemorrhagic necrosis with an acute inflammatory infiltrate interspersed with multiple hyphal elements [189,202]. In the majority of cases, cerebral abscess formation results from hematogenous seeding in the context of significant immunological impairment. Less commonly, abscess formation follows direct inoculation during neurosurgery [203] or extension from contiguous structures such as the sinuses [91,195,204–206].

Clinical setting and clinical features

Abscess formation has been documented in a wide range of scenarios. There are no specific clinical signs and symptoms. In cases in which hematogenous seeding is the likely source, patients are usually immunologically impaired as exemplified by solid organ transplant recipients [207–209], CGD [210,211], HIV/AIDS [195], and patients receiving corticosteroid therapy [212,213]. The appearance of a cerebral abscess in the early period following solid organ transplantation is especially characteristic of *Aspergillus* spp. In other cases in which an alternative pathogenic mechanism is responsible, there is a history of recent neurosurgery or clinical signs and symptoms to suggest infection in contiguous structures such as the sinuses.

Diagnosis

The diagnosis should be considered in an appropriate clinical context in those exhibiting neurological signs and symptoms with consistent radiological abnormalities; CT scans reveal single or multiple ring enhancing lesions [202]. Since drainage is frequently required for therapeutic reasons, intra-operative specimens are usually available for diagnostic purposes [214]. Alternatively, evidence that *Aspergillus* is the causative organism may be obtained by establishing a diagnosis of proven or probable IA at a non-contiguous site in the setting of consistent neuroradiological abnormalities [211,215]. The EORTC/MSG criteria suggest that a diagnosis of probable CNS aspergillosis can be established in an appropriate clinical context with the use of GM in blood or CSF; the pertinent issue for the specific diagnosis of abscess formation rests with the demonstration of consistent neuroradiological abnormalities. There are reports of serological markers such as *Aspergillus* precipitins and elevated *Aspergillus* specific IgE levels in cases of coexistent pulmonary and cerebral infection [211,215] as well as in isolated cerebral disease [216], although the diagnostic utility of such data remains unclear.

Cerebral granuloma

This entity refers to a heterogeneous collection of syndromes, arising in a number of distinct contexts, which are characterized by solid intracerebral lesions exhibiting florid granulomatous inflammation without suppuration [217,218]. This syndrome is observed in immunocompetent individuals and those with CGD and it may arise following hematogenous seeding or following extension from the sinuses [217,219] (see also chronic granulomatous sinusitis). Prior to surgery, it is often thought that the diagnosis is a malignant tumour.

Pathology and pathogenesis

The mass is firm, indurated, and there is no clear demarcation with normal brain. The lesions are described as firm, rubbery, and gritty; histologically there is florid granulomatous inflammation and fibrinous tissue interspersed with hyphal elements

[196,205,220]. Vascular invasion is not observed in the context of CGD [217].

Diagnosis

This diagnosis should be considered in an immunocompetent individual, from the Sudan, Indian subcontinent, or Middle East with radiological evidence of an enhancing mass lesion with associated cerebral oedema and mass effect [221]. The diagnosis should also be considered in the context of CGD. The diagnosis then rests with a cerebral biopsy showing granulomatous inflammation with concomitant evidence to implicate *Aspergillus* spp. from a positive culture or the visualization of hyphae consistent with *Aspergillus* spp. The diagnosis may also be inferred if there are consistent radiological abnormalities in the context of an established diagnosis of granulomatous *Aspergillus* sinusitis.

Mycotic cerebral aneurysm due to Aspergillus *spp.*

While vascular invasion by *Aspergillus* spp. is common, true mycotic aneurysm formation due to *Aspergillus* spp. is rare [222]. The following discussion is limited to infiltration and destruction of the vessel wall by *Aspergillus* spp. with subsequent aneurysm formation.

Pathology and pathogenesis

Mycotic cerebral aneurysm results from direct invasion of the vessel wall, either from the luminal or advential side of the vessel. Invasion appears to proceed directly [223,224]. Endovascular infection leads to initiation of infection from the luminal surface [223] whereas infection from the adventitial aspect usually occurs in the context of an infectious process surrounding the vessel such as in meningitis [87,89,184,185,223,225, 226]. Progressive invasion of the vascular wall leads to a loss of vascular integrity and aneurysm formation. The aneurysm may rupture or leak, which usually manifests as bleeding into the subarachnoid space [182,185,222,223,225–228]. In contrast to bacterial mycotic aneurysms, fungal aneurysms tend to be fusiform in shape and involve longer and more proximal segments of intracranial vessels [89]. The basilar, middle and posterior cerebral arteries are characteristically involved [222,223,225,226,228]. The aneurysm wall is friable with areas of necrosis, fibrosis and an inflammatory infiltrate with numerous hyphae. There may be intra-luminal clot formation which may cause vascular thrombosis and cerebral infarction or serve as a source of emboli [222,228].

Diagnosis

The ante-mortem diagnosis of a mycotic aneurysm due to *Aspergillus* spp. is usually only considered in the context of a high-risk individual with a non-fatal subarachnoid hemorrhage. The opportunities to secure a diagnosis at an earlier point in time are limited by the absence of specific symptoms and the requirement for cerebral angiography. These difficulties are further compounded by the fact that the disease is progressive, meaning that serial angiographic examination may be required to establish the diagnosis, define the extent of disease, and examine the available therapeutic options [222]. The role of magnetic resonance angiography remains unclear but does have the advantage of being a less invasive modality.

Specific evidence to implicate *Aspergillus* is even more problematic. Biopsy of the involved vessel is inappropriate and examination of CSF is unlikely to be rewarding. A microbiological diagnosis may be established from sampling a contiguous or non-contiguous site [222]. Conceptually, evidence of endovascular infection in the form of a positive PCR or GM result could be useful, although there are no reports employing these modalities at the current time.

Aspergillus *meningitis*

An isolated or pure meningitis due to *Aspergillus* spp. is highly unusual: more commonly, meningeal involvement represents a complication of another *Aspergillus*-related syndrome. Meningitis may induce a vasculitis within major arteries at the base of the brain which may lead to vascular thrombosis as well as mycotic aneurysm formation.

Pathology and pathogenesis

Aspergillus meningitis may result from inoculation at the time of neurosurgery [186,189,218,226,229–234] with the clinical manifestation of infection between eight days and one year postoperatively [189,226,232]. Infection of the basilar meninges is characteristic of direct extension from the sinuses in which case a thick grey-white membrane overlying the brain is seen at autopsy [87,183,185,189,200,205,206,219,228,230,235–239]. Both cerebrovascular aspergillosis and cerebral abscess are often associated with a focal meningitis adjacent to areas of parenchymal infection (see above). Following histological examination, the meninges are infiltrated by both inflammatory cells and hyphae [235,240].

Clinical setting and clinical features

There are no specific clinical signs and symptoms to implicate *Aspergillus* as the cause of a meningitis.

Diagnosis

Irrespective of the primary *Aspergillus* syndrome, CSF abnormalities are typically modest and certainly non-specific; there is usually only a relatively modest neutrophil pleocytosis, a low to normal glucose concentration, and mild to moderate elevations in protein concentration. Radiological abnormalities within the meninges are usually absent [187]. Unfortunately, examination of CSF using conventional techniques for *Aspergillus* spp., regardless of the clinical context, is frequently unrewarding. Both PCR and GM have been used to specifically implicate *Aspergillus* as the causative organism and the current EORTC/MSG criteria enable the use of GM in CSF to establish a diagnosis of CNS aspergillosis [1,199,201,241].

Cutaneous aspergillosis

Cutaneous aspergillosis has been reviewed [242,243]. The definition of primary and secondary cutaneous aspergillosis in this document is consistent with the majority of the published literature and is made with reference to the underlying pathogenesis. Primary cutaneous aspergillosis (PCA) refers to cases in which the initial infection begins in the skin due to direct inoculation, whereas secondary cutaneous aspergillosis is due to hematogenous seeding or spread from contiguous structures. The distinction between primary and secondary disease is not always easy or straightforward especially when there is no clear history of inoculation or obvious compromise in skin integrity.

Primary cutaneous aspergillosis

The most common setting of PCA is infection beginning in the skin in the context of relatively trivial injuries in those with significant local and systemic immunological impairment. It is also appropriate that *Aspergillus* infection complicating significant burns, surgical wounds, and other traumatic injuries in otherwise immunocompetent individuals are viewed as variants of PCA. PCA is not a trivial entity; it may lead to significant local tissue destruction, extension to contiguous structures and disseminated infection [243–247].

Pathology and pathogenesis

An interplay between the extent of the breech in skin integrity, local and systemic defects in immunity, and the size of the inoculum determines whether PCA develops in a given scenario [243]. In immunocompromised individuals, relatively trivial defects in skin integrity may lead to PCA. Thus, skin maceration under arm boards, adhesive tape and occlusive dressings used to secure intravenous lines, or endotracheal tubes have all been associated with the development of PCA in neonates and in those with significant immunological impairment [243,245,248–263]. Similarly, PCA complicating sialastic intravenous catheters is especially characteristic in the context of prolonged neutropenia and HIV/AIDS [244,247,261,262,264,265]. The infection directly involves the exit site, subcutaneous tunnel, and catheter vascular entry site [247]. In other cases, PCA develops in the contiguous skin or soft tissue at the site of a removed intravenous catheter [245,266].

Less frequently, PCA occurs in immunocompetent hosts who have suffered a more significant breech in skin integrity as exemplified by patients with severe burn injury, trauma, and surgery [267,268]. Surgical site infection due to *Aspergillus* spp. is rare and has been documented in a number of contexts including free muscle flap placement [269], surgical debridement of necrotising fascitis [270], infection of abdominal and sternal wounds [271], reconstruction of an AV fistula [272], and following orthoptic liver transplantation [273]. In certain situations it may be difficult to determine whether infection is superficial or involves deeper structures and a biopsy and histological examination may be required in this situation [274].

Clinical setting and clinical features

The clinical manifestations of PCA are protean and non-specific. Typically, the lesions begin as erythematous, violaceous indurated plaques which progress to necrotic ulcers with central eschar formation [255,257]. Less commonly, hemorrhagic vesicles or bullae, subcutaneous nodules, granulomas, pustular lesions and vegetating plaques are observed [245,262,275,276].

Diagnosis

The diagnosis of PCA should not present significant difficulties using culture and histology, providing adequate and appropriate diagnostic specimens are obtained. There may be some difficulties on occasions in distinguishing PCA from SCA; this is frequently a matter of clinical judgement and opinion.

Secondary cutaneous aspergillosis

Cutaneous involvement arising due to hematogenous seeding is a well recognized feature of disseminated

aspergillosis and usually occurs in the setting of significant immunological impairment. Typically there are multiple skin lesions in anatomically unrelated sites. A variety of clinical appearances similar to PCA are described, including erythematous to violacaeous nodules, plaques and papules with necrotic ulcerative, and suppurative tendencies [277,278]. As with PCA, the diagnosis of secondary cutaneous disease should not present difficulties using histology and culture providing appropriate biopsies are taken. A specific diagnosis of secondary disease requires the demonstration or inference of IA at a non-contiguous site and a temporal sequence which is consistent with the hypothesis that dissemination has occurred from this site. The possibility that PCA may itself disseminate means that a positive GM (or PCR) in blood as sole adjunctive evidence to define SCA.

Ocular aspergillosis (Table 5)

The ocular mycoses have been recently reviewed [279]. The individual syndromes may arise via a number of mechanisms, including hematogenous seeding (endogenous endophthalmitis, uveitis and scleritis), extension from the sinuses, or as a result of traumatic or iatrogenic inoculation (exogenous endophthalmitis, uveitis, scleritis and keratitis).

Endogenous endophthalmitis

Pathogenesis and pathology

Endogenous endophthalmitis specifically implies hematogenous dissemination to the eye and is frequently a component of disseminated disease [280–285]. Invasion of retinal and choroidal vessels induces vascular thrombosis which leads to retinal necrosis, hemorrhage, and exudate formation. There is an associated inflammatory infiltrate within the retina, sub-retinal space and choroid [280]. Ultimately the edematous and necrotic retina detaches and useful vision cannot be salvaged [286]. The pathological hallmark of endogenous endophthalmitis is the invasion of the retina and choroid by hyphae and the development of a secondary vitritis [280]. Hyphal elements may be visualised in the inner retinal layers either in isolation or within retinal abscesses [286].

Clinical setting and clinical features

Endogenous endophthalmitis has been reported to occur in a wide range of clinical scenarios, although curiously there is a relative paucity of reports in those patients with profound immunological impairment. More commonly, endogenous endophthalmitis is documented in solid organ transplant recipients [281,282,284,287], patients receiving corticosteroid therapy [280], neonates [285,288], and in the context of IVDU [289–295]. Furthermore, around 40% of cases of endogenous endophthalmitis have underlying endocarditis and the syndrome is frequently observed in the context of disseminated disease [280,286,296,297].

Endogenous endophthalmitis presents with sudden visual loss. The predominant clinical findings are confined to the posterior segment of the eye [298] and include chorioretinitis, vitritis, retinal haemorrhage, retinal artery occlusion, and chorioretinal abscess formation. Signs within the anterior segment are usually only observed in the context of considerable posterior segment involvement [281,284,286].

Diagnosis

The diagnosis should be considered in an individual with visual signs and symptoms in a variety of clinical contexts but especially IVDU, *Aspergillus* endocarditis, and disseminated IA. There may be considerable problems in obtaining evidence that *Aspergillus* is the causative pathogen prior to enucleation. Vitreal aspirates or vitrectomy specimens are the most appropriate diagnostic specimen but the confinement of hyphal elements to retinal and sub-retinal structures means that histology and cultures may be falsely negative [280,286,299]. In circumstances in which hyphae are visualized but cultures are negative, confidence that *Aspergillus* is the causative organism is limited by the frequent observation of unusual and bizarre forms within the vitreus [297]. PCR on surgically obtained specimens is potentially of value but further data are required. While there are no data on the diagnostic value of PCR and GM in blood within an appropriate clinical context, this would also seem a reasonable diagnostic approach. The demonstration of *Aspergillus* spp. at a non-contiguous site may be of considerable diagnostic value in the presence of an otherwise consistent clinical syndrome and context.

Exogenous endophthalmitis

Exogenous endophthalmitis, due to the direct inoculation of viable organisms may be accidental or iatrogenic and has been documented following penetrating ocular wounds as well as post cataract surgery [300–303].

Scleritis

Scleritis due to *Aspergillus* spp. is very uncommon. It most commonly reflects direct inoculation following accidental or traumatic [304] scleral injury but may also arise from hematogenous seeding. In the case of the

Table 5 Ocular aspergillosis

	Pathological features	Radiological features	Clinical setting	Direct evidence to implicate *Aspergillus* spp.	Indirect evidence to implicate *Aspergillus* spp.
Endogenous endophthalmitis	Hyphae within retinal and subretinal structures, chorioretinal abscess formation, secondary vitritis, retinal vessel thrombosis and rupture, retinal detachment	Ocular ultrasound may reveal intraocular abnormalities	Patient with significant immunological impairment, IVDU, *Aspergillus* endocarditis or disseminated IA WITH: chorioretinitis, secondary vitritis, thrombosis and rupture of retinal vessels, retinal detachment	*Aspergillus* (culture /histology) from an intraocular specimen [Positive PCR from intraocular specimen][c]	Proven/probable IA at non-contiguous site. GM from blood[c] [PCR from blood][c]
Exogenous endophthalmitis	Ocular abnormalities may not necessarily be confined to the posterior globe	Ocular ultrasound may reveal intraocular abnormalities	History of injury or surgery	*Aspergillus* (culture /histology) from intraocular specimen [Positive PCR from intraocular specimen][c]	Nil
Scleritis	Infiltration of the sclera by hyphae most commonly in the context of recent surgery or scleral injury	Nil	Recent ocular surgery or trauma, IVDU	*Aspergillus* (culture /histology) from vitreal aspirate	Nil
Keratitis	Stromal infiltrate, stromal abscess formation, hyphal invasion, coagulative necrosis	Nil	History of injury or surgery	Corneal culture (as *Fusarium* and other moulds which may mimic *Aspergillus* spp. may be seen).	Nil

PCR data in square brackets to indicate significant issues in assay validation and standardization remain.
IVDU: Intravenous drug use.

former, *Aspergillus* scleritis has been documented to complicate pterygium excision [305], scleral buckling [306], cataract surgery [307], and trabeculectomy [308]. The diagnosis requires the demonstration of *Aspergillus* spp. in swabs, scrapings and biopsy of the affected site.

Keratitis

The keratomycoses have been recently reviewed [279]. *Aspergillus* keratitis arises in situations in which the integrity of the cornea has been disrupted as in the case of surgery, trauma, or contact lens use. The findings that are consistent with fungal keratitis include a firm elevated lesion often with slough which may be dry, hyphate lines extending out from the lesion, multifocal granular and grey-white satellite stromal infiltrates, minimal cellular infiltration in the adjacent stroma, and a mild iritis [279]. Histological examination reveals a stromal inflammatory infiltrate, stromal abscess formation and coagulative necrosis.

Diagnosis

The inherent limitations on the amount of tissue which can be procured for diagnostic purposes compromises the ability to achieve a diagnosis of *Aspergillus* keratitis. Samples from the cornea may be obtained by swabs, scrapings or biopsy; the latter can be associated with risk of corneal perforation. Direct examination, while particularly important, is relatively insensitive; options include a wet preparation using KOH, Gram staining, and the application of specific fungal stains or fluorescent brighteners such as calcofluor, blankophor and Uvitex 2B. The specimen can be plated directly into a number of solid media and placed in liquid culture media. A specific diagnosis of *Aspergillus* keratitis is complicated by the fact that this syndrome can be produced by other filamentous fungi such as *Fusarium* spp.; a definitive diagnosis of *Aspergillus*-related disease is perhaps best achieved by culture data alone or the combination of histology and culture.

Osteoarticular aspergillosis

Osteomyelitis

The classification of osteomyelitis due to *Aspergillus* spp. has been considered by a number of authors and has generally been conceived in terms of the mechanism of acquisition. Such a scheme reflects the organization of the majority of the available literature and has been adopted in this document [309–311]. Thus, osteomyelitis may be observed in a wide range of

clinical contexts and arise as a result of direct inoculation, spread from contiguous structures, or via haematogenous seeding.

Pathology and pathogenesis

Aspergillus osteomyelitis arising from direct inoculation may be traumatic or iatrogenic but both are highly uncommon. There are a number of cases of sternal osteomyelitis and adjacent osteochondritis of the ribs manifesting 2–6 months post-sternotomy [312–315], infection of the vertebral bodies and intervertebral discs manifesting 2–16 weeks following lumbar surgery [316–319], and a single case of femoral osteomyelitis three months after operative fixation [320].

Osteomyelitis due to direct spread from a contiguous focus is similarly rare, although there are a number of highly characteristic syndromes that arise in this context. Infection involving the proximal Dacron aortic graft anastomosis with contiguous involvement of the adjacent vertebrae has been described more than two years post surgery [321–323]. Similarly, vertebral osteomyelitis involving the thoracic spine in the setting of chronic pulmonary aspergillosis with clear evidence of direct spread has been described [36,310,324–327]. Contiguous spread from the lung to adjacent ribs and vertebral bodies is also characteristic of CGD (or cases highly suggestive of CGD prior to the recognition of the syndrome) [215,328–332]. Finally, base of skull osteomyelitis and mastoiditis complicating infections within the external auditory canal or sinuses is well described [77,333–336].

Hematogenous seeding most frequently results in infection of the axial skeleton with the intervertebral discs and adjacent vertebral bodies most commonly the affected sites; there is a single report of sternal osteomyelitis arising in this manner [337]. Discitis with vertebral osteomyelitis and epidural abscess formation has been described in the setting of haematological malignancy [230,338,339], solid organ transplantation [309,338–346], IVDU [347–349], CGD [350], COPD [351,352], underlying pulmonary aspergillosis [325,353], and corticosteroid exposure [338, 354–356]. Less commonly, hematogenous dissemination results in infection within the articular skeleton and this has been documented in the context of CGD [357], chemotherapy [358], and liver transplantation [359].

Diagnosis

The diagnosis of osteomyelitis classically and most appropriately rests with positive histology and/or culture from appropriately collected surgical specimens or percutaneous biopsies of affected bone or contiguous soft tissue structures.

Septic arthritis

Septic arthritis due to *Aspergillus* spp. is relatively uncommon for reasons which are unclear [360] it may result from hematogenous seeding or following direct inoculation. It is often difficult to ascertain whether the septic arthritis is primary or represents inoculation after instrumentation of the joint. A diagnosis can be established using culture or microscopy of synovial fluid or histology of synovial biopsies.

Genitourinary aspergillosis

Renal aspergillosis

This entity results from hematogenous seeding and is most typically an incidental finding within the context of disseminated disease.

Pathology and pathogenesis

The kidneys (renal vessels and parenchyma) are frequently involved as a result of haematogenous seeding and a number of distinct pathological processes are observed, ranging from vascular involvement with tissue infarction to renal abscess formation. Involvement of the renal vasculature results in multiple areas of renal infarction and ischemic and papillary necrosis [6]. The renal vein may also be involved with complications which include renal vein thrombosis and renal infarction [361]. In other cases single or multiple abscesses are the predominant finding, where the lesions are typically several millimetres in diameter, firm and nodular, and surrounded by a rim of hyperaemic congestion [6,362,363]. Less commonly, single large solid abscesses are seen [364,365]. Infection most commonly occurs in the context of structurally normal kidneys although infection within polycystic kidneys has been described [366].

Clinical setting and clinical features

This entity is usually seen in individuals with significant immunological impairment such as those with hematological malignancy, CGD [361], or HIV/AIDS [363,367,368]. The disease is most often clinically silent.

Diagnosis

There are relatively few diagnostic options. Ultrasound or CT may suggest areas of abscess formation of infarction; abscesses may be amenable to percutaneous aspiration and drainage which may also provide a useful diagnostic avenue. Hematuria, pyuria, and

proteinuria are frequently present although positive cultures for *Aspergillus* are typically negative [6,365]. *Aspergillus* precipitins have been documented to be positive, although it remains unclear whether they are of any diagnostic value [365,367].

Renal aspergilloma

This entity, also referred to as a *Aspergillus* bezoars of the urinary tract [369], was initially described in 1962 by Comings *et al.* [370] and refers to the finding of an aspergilloma within the renal collecting system. This entity is analogous to the formation of fungal balls in the lung and sinuses. The renal pelvis is the most common site; there is a single case of fungus ball formation in the bladder [371].

Pathology and pathogenesis

A predisposing cause is usually documented and diabetes is particularly common [369,370,372]; IVDU [369,373,374], corticosteroid use, hematological malignancy [375,376], previous urological surgery [377,378], renal transplantation [379], and previous obstructive uropathy [374] represent other scenarios in which this entity has been described. The fungal ball is comprised of grey, brown or cheesy material which completely fills and occludes the pelvis and other components of the collecting system [370,380,381]. Not infrequently, fragments are passed spontaneously which are useful for diagnostic purposes. Typically the renal parenchyma is uninvolved [377] although ascending infection has been documented [381,382]. Some degree of pre-existing structural abnormality is important in the pathogenesis, perhaps by providing a nidus about which infection can establish and progress.

Clinical setting and clinical features

Typically symptoms are acute in onset and consist of renal colic with macroscopic hematuria due to obstruction of the urinary tract by the fungal ball [362,370]. Systemic symptoms are not observed.

Diagnosis

The diagnosis of renal aspergilloma is usually not considered in the differential diagnosis since the entity is rare and the clinical presentation is non-specific. An intravenous pyelogram usually shows filling defects, hydronephrosis, and a delayed or absent pyelogram [362,370,378]. Retrograde pyelography may outline the fungus ball more reliably [362]. Urine cultures are frequently negative and this may delay the diagnosis [362,383]. A specific and unexpected diagnosis frequently follows examination of a mucoid mass which is passed spontaneously or is retrieved intra-operatively [373,378,384]. The presence of precipitating antibodies to *Aspergillus* spp. has been described and may be useful from a diagnostic perspective in much the same manner as for pulmonary and sinus aspergilloma [373,375,378].

Miscellaneous genitourinary syndromes

There are rare cases of prostatic aspergillosis described and reported in the context of benign prostatic hypertrophy [385,386] as well as complicating AIDS [364] and renal transplantation [387]. In several of these cases there is a preceding history of instrumentation or catheterisation [387]. *Aspergillus* orchitis has been described [6,388] as well as a tubo-ovarian abscess [389].

Gastrointestinal aspergillosis

Aspergillosis of the gut

Pathology/pathogenesis

In the majority of cases, upper and the lower gut aspergillosis arises from hematogenous seeding and occurs as a component of disseminated infection [6,390,391]. Potentially the gut may be primarily infected, especially in the setting of mucositis where the integrity of the gut lining is compromised. Hematogenous seeding results in thrombosis and vasculitis of the mesenteric vessels [392]. The macroscopic pathology consists of focal areas of ulceration of variable depth and abscess formation. Histopathological sections show hyphal infiltration of the intestinal wall, arteritis and thrombus formation within intramural vessels [393].

Clinical presentation/clinical setting

Upper gastrointestinal tract disease may be asymptomatic or result in abdominal pain or melena; similarly, lower gastrointestinal disease may by asymptomatic or result in bloody diarrhea, abdominal pain, peritonitis, and ileus [175,394].

Diagnosis

There are limited opportunities to secure the diagnosis prior to surgical excision. Confirmation of an ischemic etiology may come in the form of selective angiography [392].

Miscellaneous gastrointestinal syndromes

A number of relatively uncommon syndromes related to *Aspergillus* include stomatits, hepatosplenic asper-

gillosis, and peritonitis secondary to chronic ambulatory peritonitis.

Aspergillus stomatitis appears to be a rare entity occurring in the context of profound and prolonged neutropenia. These lesions begin as violaceous discoloration of the gingiva, necrotic ulceration with an overlying grey membrane and the subsequent invasion of alveolar bone. Other clinical signs and symptoms include gingival pain, facial swelling and excessive salivation [395]. *Aspergillus* spp. may cause hepatosplenic abscess formation (hepatosplenic aspergillosis) [396,397]. *Aspergillus* spp. may complicated chronic ambulatory peritonitis in which case culture is usually negative and GM of the peritoneal dialysate may be useful [398–400].

Conclusion

We have delineated the main disease syndromes caused by *Aspergillus* spp. on the basis of pathology and pathogenesis. The lung is the organ most commonly affected and the lower respiratory tract syndromes the most challenging to classify. The major difficulty of any diagnostic classification scheme is that a continuous spectrum of disease manifestations is present. It is our purpose to establish in one document a framework for disease classification and the criteria for the diagnosis of each entity. As concepts and diagnostic data evolve revisions will be required.

References

1 Ascioglu S, Rex JH, de Pauw B, *et al*. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. *Clin Infect Dis* 2002; **34**: 7–14.
2 Singh N, Husain S. *Aspergillus* infections after lung transplantation: clinical differences in type of transplant and implications for management. *J Heart Lung Transplant* 2003; **22**: 258–266.
3 Einsele H, Quabeck K, Muller KD, *et al*. Prediction of invasive pulmonary aspergillosis from colonisation of lower respiratory tract before marrow transplantation. *Lancet* 1998; **352**: 1443.
4 Birch M, Nolard N, Shankland G, Denning DW. DNA typing of epidemiologically-related isolates of *Aspergillus fumigatus*. *Infect Epidemiol* 1995; **114**: 161–168.
5 Fisher BD, Armstrong D, Yu B, Gold JW. Invasive aspergillosis. Progress in early diagnosis and treatment. *Am J Med* 1981; **71**: 571–577.
6 Young RC, Bennett JE, Vogel CL, Carbone PP, DeVita VT. Aspergillosis. The spectrum of the disease in 98 patients. *Medicine (Baltimore)* 1970; **49**: 147–173.
7 Albelda SM, Gefter WB, Epstein DM, Miller WT. Bronchopleural fistula complicating invasive pulmonary aspergillosis. *Am Rev Respir Dis* 1982; **126**: 163–165.
8 van Ede AE, Meis JF, Koot RA, Heystraten FM, de Pauw BE. Pneumopericardium complicating invasive pulmonary aspergillosis: case report and review. *Infection* 1994; **22**: 102–105.
9 Caligiuri P, MacMahon H, Courtney J, Weiss L. Opportunistic pulmonary aspergillosis with chest wall invasion. Plain film and computed tomographic findings. *Arch Intern Med* 1983; **143**: 2323–2324.
10 Mineur P, Ferrant A, Wallon J, Otte JB, Michaux JL. Bronchoesophageal fistula caused by pulmonary aspergillosis. *Eur J Respir Dis* 1985; **66**: 360–366.
11 Kessler R, Massard G, Warter A, Wihlm JM, Weitzenblum E. Bronchial-pulmonary artery fistula after unilateral lung transplantation: a case report. *J Heart Lung Transplant* 1997; **16**: 674–677.
12 Wells WJ, Fox AH, Theodore PR, *et al*. Aspergillosis of the posterior mediastinum. *Ann Thorac Surg* 1994; **57**: 1240–1243.
13 Fraser RS. Pulmonary aspergillosis: pathologic and pathogenetic features. *Pathol Annu ; 28 Pt* 1993; **1**: 231–277.
14 Pittet D, Huguenin T, Dharan S, *et al*. Unusual cause of lethal pulmonary aspergillosis in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996; **154**: 541–544.
15 Paisley D, Robson GD, Denning DW. Correlation between growth rate and murine LD90 for a variety of *Aspergillus fumigatus* isolates, *Med Mycol* 2005; in press.
16 Debeaupuis JP, Sarfati J, Chazalet V, Latge JP. Genetic diversity among clinical and environmental isolates of *Aspergillus fumigatus*. *Infect Immun* 1997; **65**: 3080–3085.
17 Gerson SL, Talbot GH, Hurwitz CA, *et al*. Prolonged granulocytopenia: the major risk factor for invasive pulmonary aspergillosis in patients with acute leukemia. *Ann Intern Med* 1984; **100**: 345–351.
18 Berenguer J, Allende MC, Lee JW, *et al*. Pathogenesis of pulmonary aspergillosis. Granulocytopenia versus cyclosporine and methylprednisolone-induced immunosuppression. *Am J Respir Crit Care Med* 1995; **152**: 1079–1086.
19 Kibbler CC, Milkins SR, Bhamra A, *et al*. Apparent pulmonary mycetoma following invasive aspergillosis in neutropenic patients. *Thorax* 1988; **43**: 108–112.
20 Meziane MA, Hruban RH, Zerhouni EA, *et al*. High resolution CT of the lung parenchyma with pathological correlation. *Radiographics* 1988; **8**: 27–54.
21 Curtis AM, Smith GJ, Ravin CE. Air crescent sign of invasive aspergillosis. *Radiology* 1979; **133**: 17–21.
22 Ascah K, Hyland R, Hutcheon M, *et al*. Invasive aspergillosis in a "healthy" patient. *Can Med Assoc J* 1984; **131**: 332–335.
23 Denning DW. Invasive aspergillosis. *Clin Infect Dis* 1998; **26**: 781–803.
24 Albelda SM, Talbot GH, Gerson SL, Miller WT, Cassileth PA. Pulmonary cavitation and massive haemoptysis in invasive pulmonary aspergillosis. *Am Rev Respir Dis* 1985; **131**: 115–120.
25 Panos RJ, Barr LF, Walsh TJ, Silverman HJ. Factors associated with fatal hemoptysis in cancer patients. *Chest* 1988; **94**: 1008–1013.
26 de Sevaux RG, Kullberg BJ, Verweij PE, *et al*. Micrograniulomatous aspergillosis in a patient with chronic granulomatous disease: cure with voriconazole. *Clin Infect Dis* 1998; **26**: 996–997.
27 Seeborg FO, Paul ME, Abramson SL, *et al*. A 5-week-old HIV-1-exposed girl with failure to thrive and diffuse nodular pulmonary infiltrates. *J Allergy Clin Immunol* 2004; **113**: 627–634.
28 Chusid MJ, Sty JR, Wells RG. Pulmonary aspergillosis appearing as chronic nodular disease in chronic granulomatous disease. *Pediatr Radiol* 1988; **18**: 232–234.

29 Marr KA, Patterson T, Denning D. Aspergillosis. Pathogenesis, clinical manifestations, and therapy. *Infect Dis Clin North Am* 2002; **16**: 875–894.

30 Denning DW, Riniotis K, Dobrashian R, Sambatakou H. Chronic cavitary and fibrosing pulmonary and pleural aspergillosis: case series, proposed nomenclature change, and review. *Clin Infect Dis* 2003; **37**(Suppl 3): S265–280.

31 Yu VL, Muder RR, Poorsattar A. Significance of isolation of *Aspergillus* from the respiratory tract in diagnosis of invasive pulmonary aspergillosis. Results from a three-year prospective study. *Am J Med* 1986; **81**: 249–254.

32 Jariwalla AG, Smith AP, Melville-Jones G. Necrotising aspergillosis complicating fulminating viral pneumonia. *Thorax* 1980; **35**: 215–216.

33 Ahmad M, Weinstein AJ, Hughes JA, Cosgrove DE. Granulomatous mediastinitis due to *Aspergillus flavus* in a nonimmunosuppressed patient. *Am J Med* 1981; **70**: 887–890.

34 Gefter WB, Weingrad TR, Epstein DM, Ochs RH, Miller WT. "Semi-invasive" pulmonary aspergillosis: a new look at the spectrum of *Aspergillus* infections of the lung. *Radiology* 1981; **140**: 313–321.

35 Binder RE, Faling LJ, Pugatch RD, Mahasaen C, Snider GL. Chronic necrotizing pulmonary aspergillosis: a discrete clinical entity. *Medicine (Baltimore)* 1982; **61**: 109–124.

36 Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 11-1991. A 65-year-old man with a vertebral and disk lesion after a pulmonary operation for *Aspergillus* infection. *N Engl J Med* 1991; **324**: 754–763.

37 Yousem SA. The histological spectrum of chronic necrotizing forms of pulmonary aspergillosis. *Hum Pathol* 1997; **28**: 650–656.

38 Hafeez I, Muers MF, Murphy SA, *et al*. Non-tuberculous mycobacterial lung infection complicated by chronic necrotising pulmonary aspergillosis. *Thorax* 2000; **55**: 717–719.

39 Kato T, Usami I, Morita H, *et al*. Chronic necrotizing pulmonary aspergillosis in pneumoconiosis: clinical and radiologic findings in 10 patients. *Chest* 2002; **121**: 118–127.

40 Elliott JA, Milne LJ, Cumming D. Chronic necrotising pulmonary aspergillosis treated with itraconazole. *Thorax* 1989; **44**: 820–821.

41 Caras WE, Pluss JL. Chronic necrotizing pulmonary aspergillosis: pathologic outcome after itraconazole therapy. *Mayo Clin Proc* 1996; **71**: 25–30.

42 Crosdale DJ, Poulton KV, Ollier WE, Thomson W, Denning DW. Mannose-binding lectin gene polymorphisms as a susceptibility factor for chronic necrotizing pulmonary aspergillosis. *J Infect Dis* 2001; **184**: 653–656.

43 Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 38-1983. Empyema 40 years after a thoracoplasty. *N Engl J Med* 1983; **309**: 715–722.

44 Krakowka P, Rowinska E, Halweg H. Infection of the pleura by *Aspergillus fumigatus*. *Thorax* 1970; **25**: 245–253.

45 Hillerdal G. Pulmonary *Aspergillus* infection invading the pleura. *Thorax* 1981; **36**: 745–751.

46 Manning LK, Robertson L. A case of aspergillosis treated with nystatin. *Br Med J* 1959: 345–346.

47 Franquet T, Gimenez A, Cremades R, Domingo P, Plaza V. Spontaneous reversibility of "pleural thickening" in a patient with semi-invasive pulmonary aspergillosis: radiographic and CT findings. *Eur Radiol* 2000; **10**: 722–724.

48 Butz RO, Zvetina JR, Leininger BJ. Ten-year experience ith mycetomas in patients with pulmonary tuberculosis. *Chest* 1985; **87**: 365–358.

49 Wollschlager C, Khan F. Aspergillomas complicating sarcoidosis. *Chest* 1984; **86**: 585–588.

50 Stiksa G, Eklundh G, Riebe I, Simonsson BG. Bilateral pulmonary aspergilloma in ankylosing spondylitis treated with transthoracic instillations of antifungal agents. *Scand J Resp Dis* 1976; **57**: 163–170.

51 Procknow JJ, Loewen DF. Pulmonary aspergillosis with cavitation secondary to histoplasmosis. *Am Rev Respir Dis* 1960; **82**: 101–111.

52 Case Records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 45-1990. *N Engl J Med* 1990; **323**: 1329–1335.

53 McConnochie K, O'Sullivan M, Khalil JF, Pritchard MH, Gibbs AR. *Aspergillus* colonization of pulmonary rheumatoid nodule. *Respir Med* 1989; **83**: 157–160.

54 McGregor DH, Papasian CJ, Pierce PD. Aspergilloma within cavitating pulmonary adenocarcinoma. *Am J Clin Pathol* 1989; **91**: 100–103.

55 Severo LC, Geyer GR, Porto NS, Wagener MB, Londero AT. Pulmonary *Aspergillus niger* intracavitary colonization. Report of 23 cases and a review of the literature. *Rev Iberoam Micol* 1997; **14**: 104–110.

56 Kramer MR, Denning DW, Marshall SE, *et al*. Ulcerative tracheobronchitis after lung transplantation. A new form of invasive aspergillosis. *Am Rev Respir Dis* 1991; **144**: 552–556.

57 Denning DW. Commentary: unusual manifestations of aspergillosis. *Thorax* 1995; **50**: 812–813.

58 Tasci S, Schafer H, Ewig S, Luderitz B, Zhou H. Pseudomembraneous *Aspergillus fumigatus* tracheobronchitis causing life-threatening tracheobronchial obstruction in a mechanically ventilated patient. *Intensive Care Med* 2000; **26**: 143–144.

59 Angelotti T, Krishna G, Scott J, Berry G, Weinacker A. Nodular invasive tracheobronchitis due to *Aspergillus* in a patient with systemic lupus erythematosus. *Lupus* 2002; **11**: 325–328.

60 Tait RC, O'Driscoll BR, Denning DW. Unilateral wheeze caused by pseudomembranous *Aspergillus* tracheobronchitis in the immunocompromised patient. *Thorax* 1993; **48**: 1285–1287.

61 Clarke A, Skelton J, Fraser RS. Fungal tracheobronchitis report of 9 cases and review of the literature. *Medicine (Baltimore)* 1991; **70**: 1–14.

62 Ahn MI, Park SH, Kim JA, Kwon MS, Park YH. Pseudomembranous necrotizing bronchial aspergillosis. *Br J Radiol* 2000; **73**: 73–75.

63 Pervez NK, Kleinerman J, Kattan M, *et al*. Pseudomembranous necrotizing bronchial aspergillosis. A variant of invasive aspergillosis in a patient with hemophilia and acquired immune deficiency syndrome. *Am Rev Respir Dis* 1985; **131**: 961–963.

64 Nunley DR, Gal AA, Vega JD, *et al*. Saprophytic fungal infections and complications involving the bronchial anastomosis following human lung transplantation. *Chest* 2002; **122**: 1185–1191.

65 Nathan SD, Shorr AF, Schmidt ME, Burton NA. *Aspergillus* and endobronchial abnormalities in lung transplant recipients. *Chest* 2000; **118**: 403–407.

66 Ducreux D, Chevallier P, Perrin C, *et al*. Pseudomembranous *Aspergillus* bronchitis in a double-lung transplanted patient: unusual radiographic and CT features. *Eur Radiol* 2000; **10**: 1547–1549.

67 Boots RJ, Paterson DL, Allworth AM, Faoagali JL. Successful treatment of post-influenza pseudomembranous necrotising bronchial aspergillosis with liposomal amphotericin, inhaled amphotericin B, gamma interferon and GM-CSF. *Thorax* 1999; **54**: 1047–1049.

68 Routsi C, Kaltsas P, Bessis E, *et al*. Airway obstruction and acute respiratory failure due to *Aspergillus* tracheobronchitis. *Crit Care Med* 2004; **32**: 580–582.

69 Nicholson AG, Sim KM, Keogh BF, Corrin B. Pseudomembranous necrotising bronchial aspergillosis complicating chronic airways limitation. *Thorax* 1995; **50**: 807–808.

70 Mehrad B, Paciocco G, Martinez FJ, *et al*. Spectrum of *Aspergillus* infection in lung transplant recipients: case series and review of the literature. *Chest* 2001; **119**: 169–175.

71 Kemper CA, Hostetler JS, Follansbee SE, *et al*. Ulcerative and plaque-like tracheobronchitis due to infection with *Aspergillus* in patients with AIDS. *Clin Infect Dis* 1993; **17**: 344–352.

72 deShazo RD, O'Brien M, Chapin K, *et al*. A new classification and diagnostic criteria for invasive fungal sinusitis. *Arch Otolaryngol Head Neck Surg* 1997; **123**: 1181–1188.

73 McGill TJ, Simpson G, Healy GB. Fulminant aspergillosis of the nose and paranasal sinuses: a new clinical entity. *Laryngoscope* 1980; **90**: 748–754.

74 Verschraegen CF, van Besien KW, Dignani C, *et al*. Invasive *Aspergillus* sinusitis during bone marrow transplantation. *Scand J Infect Dis* 1997; **29**: 436–438.

75 Brandwein M. Histopathology of sinonasal fungal disease. *Otolaryngol Clin North Am* 1993; **26**: 949–981.

76 deShazo RD, Chapin K, Swain RE. Fungal sinusitis. *N Engl J Med* 1997; **337**: 254–259.

77 Breen DJ, Clifton AG, Wilkins P, Uttley D, Westmore G. Invasive aspergilloma of the skull base. *Neuroradiology* 1993; **35**: 216–217.

78 Adler SC, Isaacson G, Sasaki CT. Invasive aspergillosis of the paranasal sinuses and orbit: can you save the eye? *Am J Otolaryngol* 1997; **18**: 230–234.

79 Byard RW, Bonin RA, Haq AU. Invasion of paranasal sinuses by *Aspergillus oryzae*. *Mycopathologia* 1986; **96**: 41–43.

80 Talbot GH, Huang A, Provencher M. Invasive *Aspergillus* rhinosinusitis in patients with acute leukemia. *Rev Infect Dis* 1991; **13**: 219–232.

81 Choi SS, Milmoe GJ, Dinndorf PA, Quinones RR. Invasive *Aspergillus* sinusitis in pediatric bone marrow transplant patients. Evaluation and management. *Arch Otolaryngol Head Neck Surg* 1995; **121**: 1188–1192.

82 deShazo RD. Fungal sinusitis. *Am J Med Sci* 1998; **316**: 39–45.

83 Berlinger NT. Sinusitis in immunodeficient and immunosuppressed patients. *Laryngoscope* 1985; **95**: 29–33.

84 Saah D, Drakos PE, Elidan J, *et al*. Rhinocerebral aspergillosis in patients undergoing bone marrow transplantation. *Ann Otol Rhinol Laryngol* 1994; **103**: 306–310.

85 Milroy CM, Blanshard JD, Lucas S, Michaels L. Aspergillosis of the nose and paranasal sinuses. *J Clin Pathol* 1989; **42**: 123–127.

86 Larranaga J, Fandino J, Gomez-Bueno J, *et al*. Aspergillosis of the sphenoid sinus simulating a pituitary tumor. *Neuroradiology* 1989; **31**: 362–363.

87 Hedges TR, Leung LS. Parasellar and orbital apex syndrome caused by aspergillosis. *Neurology* 1976; **26**: 117–120.

88 Lee LR, Sullivan TJ. *Aspergillus* sphenoid sinusitis-induced orbital apex syndrome in HIV infection. *Aust N Z J Ophthalmol* 1995; **23**: 327–331.

89 Hurst RW, Judkins A, Bolger W, Chu A, Loevner LA. Mycotic aneurysm and cerebral infarction resulting from fungal sinusitis: imaging and pathologic correlation. *AJNR Am J Neuroradiol* 2001; **22**: 858–863.

90 Dyken ME, Biller J, Yuh WT, *et al*. Carotid cavernous sinus thrombosis caused by *Aspergillus fumigatus*: magnetic resonance imaging with pathologic correlation – a case report. *Angiology* 1990; **41**: 652–657.

91 Clancy CJ, Nguyen MH. Invasive sinus aspergillosis in apparently immunocompetent hosts. *J Infect* 1998; **37**: 229–240.

92 Chang T, Teng MM, Wang SF, *et al*. Aspergillosis of the paranasal sinuses. *Neuroradiology* 1992; **34**: 520–523.

93 Johnson TE, Casiano RR, Kronish JW, *et al*. Sino-orbital aspergillosis in acquired immunodeficiency syndrome. *Arch Ophthalmol* 1999; **117**: 57–64.

94 Mylonakis E, Rich J, Skolnik PR, De Orchis DF, Flanigan T. Invasive *Aspergillus* sinusitis in patients with human immunodeficiency virus infection. Report of 2 cases and review. *Medicine (Baltimore)* 1997; **76**: 249–255.

95 Milosev B, el-Mahgoub S, Aal OA, el-Hassan AM. Primary aspergilloma of paranasal sinuses in the Sudan. A review of seventeen cases. *Br J Surg* 1969; **56**: 132–137.

96 Yagi HI, Gumaa SA, Shumo AI, Abdalla N, Gadir AA. Nasosinus aspergillosis in Sudanese patients: clinical features, pathology, diagnosis, and treatment. *J Otolaryngol* 1999; **28**: 90–94.

97 Dawlatly EE, Anim JT, Sowayan S, el-Hassan AY. Primary paranasal *Aspergillus* granuloma in Saudi Arabia. *Trop Geogr Med* 1988; **40**: 247–250.

98 Alrajhi AA, Enani M, Mahasin Z, Al-Omran K. Chronic invasive aspergillosis of the paranasal sinuses in immunocompetent hosts from Saudi Arabia. *Am J Trop Med Hyg* 2001; **65**: 83–86.

99 Ramani R, Hazarika P, Kapadia RD, Shivananda PG. Invasive maxillary aspergillosis in an otherwise healthy individual. *Ear Nose Throat J* 1994; **73**: 420–422.

100 Surya Prakash Rao G, Mann SB, Talwar P, Arora MM. Primary mycotic infection of paranasal sinuses. *Mycopathologia* 1984; **84**: 73–76.

101 Currens J, Hutcheson PS, Slavin RG, Citardi MJ. Primary paranasal *Aspergillus* granuloma: case report and review of the literature. *Am J Rhinol* 2002; **16**: 165–168.

102 Green WR, Font RL, Zimmerman LE. Asperillosis of the orbit. Report of ten cases and review of the literature. *Arch Ophthalmol* 1969; **82**: 302–313.

103 Weller EA, Joseph DJ, Hora JF. Deep mycotic involvement of the right maxillary and ethmoid sinuses, the orbit and adjacent structures. Case report evaluating the use of mycostatin locally and amphotericin B (fungizone) intravenously against *Aspergillus flavus*. *Laryngoscope* 1960; **70**: 999–1016.

104 Veress B, Malik OA, el-Tayeb AA, *et al*. Further observations on the primary paranasal *Aspergillus* granuloma in the Sudan: a morphological study of 46 cases. *Am J Trop Med Hyg* 1973; **22**: 765–772.

105 Oates J, Clark DR, Chiodini P. Intracranial extension of paranasal sinus aspergillosis. *J Laryngol Otol* 1987; **101**: 188–190.

106 Beck-Mannagetta J, Necek D. Radiologic findings in aspergillosis of the maxillary sinus. *Oral Surg Oral Med Oral Pathol* 1986; **62**: 345–349.

107 Beck-Mannagetta J, Necek D, Grasserbauer M. Solitary aspergillosis of maxillary sinus, a complication of dental treatment. *Lancet* 1983; **ii**: 1260.

108 Gonty AA, Page LR. Aspergillosis of the maxillary sinus. Review of the literature and report of a case. *Oral Surg Oral Med Oral Pathol* 1977; **43**: 350–356.

109 Bratton RL, Brazis PW, Hellinger WC, Wharen RE, Jr, Broderick DF. Aspergillosis related to long-term nasal corticosteroid use. *Mayo Clin Proc* 2002; **77**: 1353–1357.

110 Ferreiro JA, Carlson BA, Cody DT, 3rd. Paranasal sinus fungus balls. *Head Neck* 1997; **19**: 481–486.
111 Lavelle WG. Aspergillosis of the sphenoid sinus. *Ear Nose Throat J* 1988; **67**: 266, 268–269.
112 Klossek JM, Peloquin L, Fourcroy PJ, Ferrie JC, Fontanel JP. Aspergillomas of the sphenoid sinus: a series of 10 cases treated by endoscopic sinus surgery. *Rhinology* 1996; **34**: 179–183.
113 Stammberger H, Jakse R, Beaufort F. Aspergillosis of the paranasal sinuses x-ray diagnosis, histopathology, and clinical aspects. *Ann Otol Rhinol Laryngol* 1984; **93**: 251–256.
114 McGinnis MR, Buck DL, Jr, Katz B. Paranasal aspergilloma caused by an albino variant of *Aspergillus fumigatus*. *South Med J* 1977; **70**: 886–888.
115 Rubinstein E, Noriega ER, Simberkoff MS, Holzman R, Rahal JJ, Jr. Fungal endocarditis: analysis of 24 cases and review of the literature. *Medicine (Baltimore)* 1975; **54**: 331–334.
116 Gumbo T, Taege AJ, Mawhorter S, *et al*. *Aspergillus* valve endocarditis in patients without prior cardiac surgery. *Medicine (Baltimore)* 2000; **79**: 261–268.
117 Kuijer PM, Kuijper EJ, van den Tweel JG, van der Lelie J. *Aspergillus fumigatus*, a rare cause of fatal coronary artery occlusion. *Infection* 1992; **20**: 45–47.
118 Ross EM, Macher AM, Roberts WC. *Aspergillus fumigatus* thrombi causing total occlusion of both coronary arterial ostia, all four major epicardial coronary arteries and coronary sinus and associated with purulent pericarditis. *Am J Cardiol* 1985; **56**: 499–500.
119 Hurley J, McGovern E. Rupture of a sinus of Valsalva aneurysm due to *Aspergillus* endocarditis. *J Cardiovasc Surg (Torino)* 1994; **35**: 75–77.
120 Walsh TJ, Hutchins GM. *Aspergillus* mural endocarditis. *Am J Clin Pathol* 1979; **71**: 640–644.
121 Walsh TJ, Hutchins GM, Bulkley BH, Mendelsohn G. Fungal infections of the heart: analysis of 51 autopsy cases. *Am J Cardiol* 1980; **45**: 357–366.
122 Vo NM, Russell JC, Becker DR. Mycotic emboli of the peripheral vessels: analysis of forty-four cases. *Surgery* 1981; **90**: 541–545.
123 Luke JL, Bolande RP, Gross S. Generalized aspergillosis and *Aspergillus* endocarditis in infancy. *Pediatrics* 1963; **1**: 115–122.
124 Casson DH, Riordan FA, Ladusens EJ. *Aspergillus* endocarditis in chronic granulomatous disease. *Acta Paediatr* 1996; **85**: 758–759.
125 Laszewski M, Trigg M, de Alarcon P, Giller R. *Aspergillus* coronary embolization causing acute myocardial infarction. *Bone Marrow Transplant* 1988; **3**: 229–233.
126 Sanchez-Recalde A, Mate I, Merino JL, Simon RS, Sobrino JA. *Aspergillus* aortitis after cardiac surgery. *J Am Coll Cardiol* 2003; **41**: 152–156.
127 Demaria RG, Durrleman N, Rispail P, *et al*. *Aspergillus flavus* mitral valve endocarditis after lung abscess. *J Heart Valve Dis* 2000; **9**: 786–790.
128 Paterson DL, Dominguez EA, Chang FY, Snydman DR, Singh N. Infective endocarditis in solid organ transplant recipients. *Clin Infect Dis* 1998; **26**: 689–694.
129 Rueter F, Hirsch HH, Kunz F, *et al*. Late *Aspergillus fumigatus* endomyocarditis with brain abscess as a lethal complication after heart transplantation. *J Heart Lung Transplant* 2002; **21**: 1242–1245.
130 Marin P, Garcia-Martos P, Garcia-Doncel A, *et al*. Endocarditis by *Aspergillus fumigatus* in a renal transplant. *Mycopathologia* 1999; **145**: 127–129.
131 Viertel A, Ditting T, Pistorius K, *et al*. An unusual case of *Aspergillus* endocarditis in a kidney transplant recipient. *Transplantation* 1999; **68**: 1812–1813.
132 Gilbey JG, Chalermskulrat W, Aris RM. *Aspergillus* endocarditis in a lung transplant recipient. A case report and review of the transplant literature. *Ann Transplant* 2000; **5**: 48–53.
133 Lim ML, Oliver DH, Barasch E. *Aspergillus* mural vegetation identified by transesophageal echocardiography. *Echocardiography* 1997; **14**: 283–286.
134 Henochowicz S, Mustafa M, Lawrinson WE, Pistole M, Lindsay J, Jr. Cardiac aspergillosis in acquired immune deficiency syndrome. *Am J Cardiol* 1985; **55**: 1239–1240.
135 Petrosillo N, Pellicelli AM, Cicalini S, *et al*. Endocarditis caused by *Aspergillus* species in injection drug users. *Clin Infect Dis* 2001; **33**: e97–99.
136 Light JT, Jr, Hendrickson M, Sholes WM, *et al*. Acute aortic occlusion secondary to *Aspergillus* endocarditis in an intravenous drug abuser. *Ann Vasc Surg* 1991; **5**: 271–275.
137 Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Duke endocarditis service. *Am J Med* 1994; **96**: 220–222.
138 Lang DM, Leisen JC, Elliott JP, *et al*. Echocardiographically silent *Aspergillus* mural endocarditis. *West J Med* 1988; **149**: 334–338.
139 Schett G, Casati B, Willinger B, *et al*. Endocarditis and aortal embolization caused by *Aspergillus terreus* in a patient with acute lymphoblastic leukemia in remission: diagnosis by peripheral-blood culture. *J Clin Microbiol* 1998; **36**: 3347–3351.
140 Corrigan C, Horner SM. *Aspergillus* endocarditis in association with a false aortic aneurysm. *Clin Cardiol* 1988; **11**: 430–432.
141 Lawrence T, Shockman AT, MacVaugh H, 3rd. *Aspergillus* infection of prosthetic aortic valves. *Chest* 1971; **60**: 406–414.
142 Caplan HI, Frisch E, Houghton JD, Climo MS, Natsios GA. *Aspergillus fumigatus* endocarditis. Report of a case diagnosed during life. *Ann Intern Med* 1968; **68**: 378–385.
143 Swensson EE, Willman VL, Peterson GJ. Acute aortic occlusion from aspergillosis in a healthy patient with survival. *J Vasc Surg* 1986; **4**: 187–191.
144 Kanda Y, Akiyama H, Onozawa Y, *et al*. *Aspergillus* endocarditis in a leukemia patient diagnosed by a PCR assay. *Kansenshogaku Zasshi* 1997; **71**: 269–272.
145 McCracken D, Barnes R, Poynton C, *et al*. Polymerase chain reaction aids in the diagnosis of an unusual case of *Aspergillus niger* endocarditis in a patient with acute myeloid leukaemia. *J Infect* 2003; **47**: 344–347.
146 Grijalva M, Horvath R, Dendis M, Erny J, Benedik J. Molecular diagnosis of culture negative infective endocarditis: clinical validation in a group of surgically treated patients. *Heart* 2003; **89**: 263–268.
147 Khan ZU, Sanyal SC, Mokaddas E, *et al*. Endocarditis due to *Aspergillus flavus*. *Mycoses* 1997; **40**: 213–217.
148 Khan TH, Kane EG, Dean DC. *Aspergillus* endocarditis of mitral prosthesis. *Am J Cardiol* 1968; **22**: 277–280.
149 Gage AA, Dean DC, Schimert G, Minsley N. *Aspergillus* infection after cardiac surgery. *Arch Surg* 1970; **101**: 384–387.
150 Petheram IS, Seal RM. *Aspergillus* prosthetic valve endocarditis. *Thorax* 1976; **31**: 380–390.
151 Acquati F, Semeraro F, Respighi E, *et al*. *Aspergillus flavus* infection of a pacemaker wire: continuing evidence for active management of infected pacemakers. *G Ital Cardiol* 1987; **17**: 467–468.

152 Cook RJ, Orszulak TA, Nkomo VT, *et al*. *Aspergillus* infection of implantable cardioverter-defibrillator. *Mayo Clin Proc* 2004; **79**: 549–552.

153 El-Hamamsy I, Durrleman N, Stevens LM, *et al*. A cluster of cases of *Aspergillus* endocarditis after cardiac surgery. *Ann Thorac Surg* 2004; **77**: 2184–2186.

154 Mehta G. *Aspergillus* endocarditis after open heart surgery: an epidemiological investigation. *J Hosp Infect* 1990; **15**: 245–253.

155 Doshi R. *Aspergillus fumigatus* endocarditis of an aortic homograft with aneurysm of the ascending orta. *J Pathol* 1971; **103**: 263–265.

156 Moore RS, Hasleton PS, Lawson RA, Stanbridge TN. *Aspergillus niger* endocarditis complicating aortic tissue valve replacement. *Thorax* 1984; **39**: 76–77.

157 Drexler L, Rytel M, Keelan M, Bonchek LI, Olinger GN. *Aspergillus terreus* infective endocarditis on a porcine heterograft valve. *J Thorac Cardiovasc Surg* 1980; **79**: 269–274.

158 Navabi MA, Ajami H, Amirghofran A, Peyravian F. *Aspergillus* endocarditis: rare but serious *Aspergillus* ball obstructing the pulmonary artery. *Eur J Cardiothorac Surg* 1998; **14**: 530–532.

159 Hosking MC, MacDonald NE, Cornel G. Liposomal amphotericin B for postoperative *Aspergillus fumigatus* endocarditis. *Ann Thorac Surg* 1995; **59**: 1015–1017.

160 Barst RJ, Prince AS, Neu HC. *Aspergillus* endocarditis in children: case report and review of the literature. *Pediatrics* 1981; **68**: 73–78.

161 Jones T, Meshel L, Rubin IL. *Aspergillus* endocarditis superimposed on aortic valve prosthesis. *N Y State J Med* 1969; **69**: 1923–1928.

162 Galrinho A, Tavares J, Caria R, Veiga C. Fungal endocarditis with atypical localization in patients with aortic prosthesis. *Rev Port Cardiol* 2000; **19**: 1045–1047.

163 Kreiss Y, Vered Z, Keller N, *et al*. *Aspergillus niger* endocarditis in an immunocompetent patient: an unusual course. *Postgrad Med J* 2000; **76**: 105–106.

164 Aslam PA, Gourley R, Eastridge CE, Pate JW. *Aspergillus* endocarditis after aortic valve replacement. *Int Surg* 1970; **53**: 91–96.

165 Newman WH, Cordell AR. *Aspergillus* endocarditis after open-heart surgery. Report of a Case and Review of Literature. *J Thorac Cardiovasc Surg* 1964; **48**: 652–660.

166 Wagner DK, Werner PH, Bonchek LI, Shimshak T, Rytel MW. Successful treatment of post-mitral valve annuloplasty *Aspergillus flavus* endocarditis. *Am J Med* 1985; **79**: 777–780.

167 Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 39-1976. *N Engl J Med* 1976; **295**: 718–724.

168 Leffert RL, Hackett RL. *Aspergillus* aortitis following replacement of aortic valve. *J Thorac Cardiovasc Surg* 1967; **53**: 866–874.

169 Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 24-1973. *N Engl J Med* 1973; **288**: 1290–1296.

170 Collazos J, Mayo J, Martinez E, Ibarra S. Prosthetic vascular graft infection due to *Aspergillus* species: case report and literature review. *Eur J Clin Microbiol Infect Dis* 2001; **20**: 414–417.

171 Aguado JM, Valle R, Arjona R, Ferreres JC, Gutierrez JA. Aortic bypass graft infection due to *Aspergillus*: report of a case and review. *Clin Infect Dis* 1992; **14**: 916–921.

172 Walsh TJ, Bulkley BH. *Aspergillus* pericarditis: clinical and pathologic features in the immunocompromised patient. *Cancer* 1982; **49**: 48–54.

173 Denning DW, Tucker RM, Hanson LH, Stevens DA. Treatment of invasive aspergillosis with itraconazole. *Am J Med* 1989; **86**: 791–800.

174 Mikulski SM, Love LJ, Bergquist EJ, *et al*. *Aspergillus* vegetative endocarditis and complete heart block in a patient with acute leukemia. *Chest* 1979; **76**: 473–476.

175 Hori A, Kami M, Kishi Y, *et al*. Clinical significance of extrapulmonary involvement of invasive aspergillosis: a retrospective autopsy-based study of 107 patients. *J Hosp Infect* 2002; **50**: 175–182.

176 Cornet M, Mallat H, Somme D, *et al*. Fulminant invasive pulmonary aspergillosis in immunocompetent patients – a two-case report. *Clin Microbiol Infect* 2003; **9**: 1224–1227.

177 Babbin BA, Greene JN, Vega R, *et al*. Pathologic manifestations of invasive pulmonary aspergillosis in cancer patients: the many faces of *Aspergillus*. *Cancer Control* 2000; **7**: 566–571.

178 Torre-Cisneros J, Lopez OL, Kusne S, *et al*. CNS aspergillosis in organ transplantation: a clinicopathological study. *J Neurol Neurosurg Psychiatry* 1993; **56**: 188–193.

179 Boes B, Bashir R, Boes C, *et al*. Central nervous system aspergillosis. Analysis of 26 patients. *J Neuroimaging* 1994; **4**: 123–129.

180 Boon AP, Adams DH, Buckels J, McMaster P. Cerebral aspergillosis in liver transplantation. *J Clin Pathol* 1990; **43**: 114–118.

181 Hagensee ME, Bauwens JE, Kjos B, Bowden RA. Brain abscess following marrow transplantation: experience at the Fred Hutchinson Cancer Research Center, 1984–1992. *Clin Infect Dis* 1994; **19**: 402–408.

182 Walsh TJ, Hier DB, Caplan LR. Aspergillosis of the central nervous system: clinicopathological analysis of 17 patients. *Ann Neurol* 1985; **18**: 574–582.

183 McCormick WF, Schochet SS, Jr, Weaver PR, MacCrary JA, 3rd. Disseminated aspergillosis. *Aspergillus* endophthalmitis, optic nerve infarction, and carotid artery thrombosis. *Arch Pathol* 1975; **99**: 353–359.

184 Corvisier N, Gray F, Gherardi R, *et al*. Aspergillosis of ethmoid sinus and optic nerve, with arteritis and rupture of the internal carotid artery. *Surg Neurol* 1987; **28**: 311–315.

185 Nenoff P, Kellermann S, Horn LC, *et al*. Case report. Mycotic arteritis due to *Aspergillus fumigatus* in a diabetic with retrobulbar aspergillosis and mycotic meningitis. *Mycoses* 2001; **44**: 407–414.

186 Endo T, Tominaga T, Konno H, Yoshimoto T. Fatal subarachnoid hemorrhage, with brainstem and cerebellar infarction, caused by *Aspergillus* infection after cerebral aneurysm surgery: case report. *Neurosurgery* 2002; **50**: 1147–1150; discussion 1150–1141.

187 DeLone DR, Goldstein RA, Petermann G, *et al*. Disseminated aspergillosis involving the brain: distribution and imaging characteristics. *AJNR Am J Neuroradiol* 1999; **20**: 1597–1604.

188 Britt RH, Enzmann DR, Remington JS. Intracranial infection in cardiac transplant recipients. *Ann Neurol* 1981; **9**: 107–119.

189 Beal MF, O'Carroll CP, Kleinman GM, Grossman RI. Aspergillosis of the nervous system. *Neurology* 1982; **32**: 473–479.

190 Bonham CA, Dominguez EA, Fukui MB, *et al*. Central nervous system lesions in liver transplant recipients: prospective assessment of indications for biopsy and implications for management. *Transplantation* 1998; **66**: 1596–1604.

191 Koh S, Ross LA, Gilles FH, Nelson MD, Jr, Mitchell WG. Myelopathy resulting from invasive aspergillosis. *Pediatr Neurol* 1998; **19**: 135–138.

192 Baddley JW, Salzman D, Pappas PG. Fungal brain abscess in transplant recipients: epidemiologic, microbiologic, and clinical features. *Clin Transplant* 2002; **16**: 419–424.

193 Montero CG, Martinez AJ. Neuropathology of heart transplantation: 23 cases. *Neurology* 1986; **36**: 1149–1154.

194 Chang SC, Hsieh BS, Luh KT, *et al*. Aspergillosis of the brain: report of an autopsy proven case. *Taiwan Yi Xue Hui Za Zhi* 1987; **86**: 1287–1292.

195 Mylonakis E, Paliou M, Sax PE, *et al*. Central nervous system aspergillosis in patients with human immunodeficiency virus infection. Report of 6 cases and review. *Medicine (Baltimore)* 2000; **79**: 269–280.

196 Kaufman DM, Thal LJ, Farmer PM. Central nervous system aspergillosis in two young adults. *Neurology* 1976; **26**: 484–488.

197 Burston J, Blackwood W. A case of *Aspergillus* infection of the brain. *J Pathol Bacteriol* 1963; **86**: 225–229.

198 Kami M, Shirouzu I, Mitani K, *et al*. Early diagnosis of central nervous system aspergillosis with combination use of cerebral diffusion-weighted echo-planar magnetic resonance image and polymerase chain reaction of cerebrospinal fluid. *Intern Med* 1999; **38**: 45–48.

199 Roilides E, Pavlidou E, Papadopoulos F, *et al*. Cerebral aspergillosis in an infant with corticosteroid-resistant nephrotic syndrome. *Pediatr Nephrol* 2003; **18**: 450–453.

200 Mukoyama M, Gimple K, Poser CM. Aspergillosis of the central nervous system. Report of a brain abscess due to *A. fumigatus* and review of the literature. *Neurology* 1969; **19**: 967–974.

201 Viscoli C, Machetti M, Gazzola P, *et al*. *Aspergillus* galactomannan antigen in the cerebrospinal fluid of bone marrow transplant recipients with probable cerebral aspergillosis. *J Clin Microbiol* 2002; **40**: 1496–1499.

202 Cox J, Murtagh FR, Wilfong A, Brenner J. Cerebral aspergillosis: MR imaging and histopathologic correlation. *AJNR Am J Neuroradiol* 1992; **13**: 1489–1492.

203 Kim DG, Hong SC, Kim HJ, *et al*. Cerebral aspergillosis in immunologically competent patients. *Surg Neurol* 1993; **40**: 326–331.

204 Shuper A, Levitsky HI, Cornblath DR. Early invasive CNS aspergillosis. An easily missed diagnosis. *Neuroradiology* 1991; **33**: 183–185.

205 Lowe J, Bradley J. Cerebral and orbital *Aspergillus* infection due to invasive aspergillosis of ethmoid sinus. *J Clin Pathol* 1986; **39**: 774–778.

206 Perlmutter I, Perlmutter D, Hyams PJ. Fungal infection of the brain: an increasing threat. *South Med J* 1980; **73**: 499–501.

207 Polo JM, Fabrega E, Casafont F, *et al*. Treatment of cerebral aspergillosis after liver transplantation. *Neurology* 1992; **42**: 1817–1819.

208 Green M, Wald ER, Tzakis A, Todo S, Starzl TE. Aspergillosis of the CNS in a pediatric liver transplant recipient: case report and review. *Rev Infect Dis* 1991; **13**: 653–657.

209 Iemmolo RM, Rossanese A, Rotilio A, *et al*. Cerebral aspergillosis in a liver transplant recipient: a case report of long-term survival after combined treatment with liposomal amphotericin B and surgery. *J Hepatol* 1998; **28**: 518–522.

210 Saulsbury FT. Successful treatment of *Aspergillus* brain abscess with itraconazole and interferon-gamma in a patient with chronic granulomatous disease. *Clin Infect Dis* 2001; **32**: E137–139.

211 Kloss S, Schuster A, Schroten H, Lamprecht J, Wahn V. Control of proven pulmonary and suspected CNS *Aspergillus* infection with itraconazole in a patient with chronic granulomatous disease. *Eur J Pediatr* 1991; **150**: 483–485.

212 Wiggins RE, Jr. Invasive aspergillosis. A complication of treatment of temporal arteritis. *J Neuroophthalmol* 1995; **15**: 36–38.

213 Sanchez C, Mauri E, Dalmau D, *et al*. Treatment of cerebral aspergillosis with itraconazole: do high doses improve the prognosis? *Clin Infect Dis* 1995; **21**: 1485–1487.

214 Goodman ML, Coffey RJ. Stereotactic drainage of *Aspergillus* brain abscess with long-term survival: case report and review. *Neurosurgery* 1989; **24**: 96–99.

215 Gentile M, Venditti M, Tozzi MC, *et al*. Intracerebral lesion in a chronic granulomatous disease child with *Aspergillus* chest infection. *Haematologica* 1991; **76**: 81–82.

216 Kerkmann ML, Blaschke-Hellmessen R, Mikulin HD. Successful treatment of cerebral aspergillosis by stereotactic operation and antifungal therapy. *Mycoses* 1994; **37**: 123–126.

217 Dean AF, Janota I, Thrasher A, Robertson I, Mieli-Vergani G. Cerebral aspergilloma in a child with autosomal recessive chronic granulomatous disease. *Arch Dis Child* 1993; **68**: 412–414.

218 Shapiro K, Tabaddor K. Cerebral aspergillosis. *Surg Neurol* 1975; **4**: 465–471.

219 Yanai Y, Wakao T, Fukamachi A, Kunimine H. Intracranial granuloma caused by *Aspergillus fumigatus*. *Surg Neurol* 1985; **23**: 597–604.

220 Mathews MS, Chandy MJ. Cerebellar granuloma caused by *Aspergillus fumigatus*: first report from India. *Trans R Soc Trop Med Hyg* 1995; **89**: 83–84.

221 Elgamal EA, Murshid WR. Intracavitary administration of amphotericin B in the treatment of cerebral aspergillosis in a non immune-compromised patient: case report and review of the literature. *Br J Neurosurg* 2000; **14**: 137–141.

222 Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 7-1988. A 27-year-old man with acute myelomonocytic leukemia in remission and repeated intracranial hemorrhages. *N Engl J Med* 1988; **318**: 427–440.

223 Horten BC, Abbott GF, Porro RS. Fungal aneurysms of intracranial vessels. *Arch Neurol* 1976; **33**: 577–579.

224 Ahuja GK, Jain N, Vijayaraghavan M, Roy S. Cerebral mycotic aneurysm of fungal origin. Case report. *J Neurosurg* 1978; **49**: 107–110.

225 Visudhiphan P, Bunyaratavej S, Khantanaphar S. Cerebral aspergillosis. Report of three cases. *J Neurosurg* 1973; **38**: 472–476.

226 Mielke B, Weir B, Oldring D, von Westarp C. Fungal aneurysm: case report and review of the literature. *Neurosurgery* 1981; **9**: 578–582.

227 Suzuki K, Iwabuchi N, Kuramochi S, *et al*. *Aspergillus* aneurysm of the middle cerebral artery causing a fatal subarachnoid hemorrhage. *Intern Med* 1995; **34**: 550–553.

228 Davidson P, Robertson DM. A true mycotic (*Aspergillus*) aneurysm leading to fatal subarachnoid hemorrhage in a patient with hereditary hemorrhagic telangiectasia. Case report. *J Neurosurg* 1971; **35**: 71–76.

229 Morioka T, Tashima T, Nagata S, Fukui M, Hasuo K. Cerebral aspergillosis after burr-hole surgery for chronic subdural hematoma: case report. *Neurosurgery* 1990; **26**: 332–335.

230 Casey AT, Wilkins P, Uttley D. Aspergillosis infection in neurosurgical practice. *Br J Neurosurg* 1994; **8**: 31–39.

231 Letscher V, Herbrecht R, Gaudias J, *et al*. Post-traumatic intracranial epidural *Aspergillus fumigatus* abscess. *J Med Vet Mycol* 1997; **35**: 279–282.

232 Galassi E, Pozzati E, Poppi M, Vinci A. Cerebral aspergillosis following intracranial surgery. Case report. *J Neurosurg* 1978; **49**: 308–311.

233 Feely M, Steinberg M. *Aspergillus* infection complicating transsphenoidal strontium-90 pituitary implant. Report of two cases. *J Neurosurg* 1977; **46**: 530–532.

234 Diengdoh JV, Barnard RO, Thomas DG. Aspergillosis of the nervous system. Report of two cases. *Neuropathol Appl Neurobiol* 1983; **9**: 477–484.

235 Lammens M, Robberecht W, Waer M, Carton H, Dom R. Purulent meningitis due to aspergillosis in a patient with systemic lupus erythematosus. *Clin Neurol Neurosurg* 1992; **94**: 39–43.

236 Haran RP, Chandy MJ. Intracranial *Aspergillus* granuloma. *Br J Neurosurg* 1993; **7**: 383–388.

237 Bradley SF, McGuire NM, Kauffman CA. Sino-orbital and cerebral aspergillosis: cure with medical therapy. *Mykosen* 1987; **30**: 379–385.

238 Carrazana EJ, Rossitch E, Jr, Morris J. Isolated central nervous system aspergillosis in the acquired immunodeficiency syndrome. *Clin Neurol Neurosurg* 1991; **93**: 227–230.

239 Mohandas S, Ahuja GK, Sood VP, Virmani V. Aspergillosis of the central nervous system. *J Neurol Sci* 1978; **38**: 229–233.

240 Palo J, Haltia M, Uutela T. Cerebral aspergillosis with special reference to cerebrospinal fluid findings. *Eur Neurol* 1975; **13**: 224–231.

241 Peacock JE, Jr, McGinnis MR, Cohen MS. Persistent neutrophilic meningitis. Report of four cases and review of the literature. *Medicine (Baltimore)* 1984; **63**: 379–395.

242 van Burik JA, Colven R, Spach DH. Cutaneous aspergillosis. *J Clin Microbiol* 1998; **36**: 3115–3121.

243 Walsh TJ. Primary cutaneous aspergillosis – an emerging infection among immunocompromised patients. *Clin Infect Dis* 1998; **27**: 453–457.

244 Krol TC, O'Keefe P. Brachial plexus neuritis and fatal hemorrhage following *Aspergillus* infection of a Hickman catheter. *Cancer* 1982; **50**: 1214–1217.

245 Jones NF, Conklin WT, Albo VC. Primary invasive aspergillosis of the hand. *J Hand Surg [Am]* 1986; **11**: 425–428.

246 Bretagne S, Bart-Delabesse E, Wechsler J, *et al*. Fatal primary cutaneous aspergillosis in a bone marrow transplant recipient: nosocomial acquisition in a laminar-air flow room. *J Hosp Infect* 1997; **36**: 235–239.

247 Allo MD, Miller J, Townsend T, Tan C. Primary cutaneous aspergillosis associated with Hickman intravenous catheters. *N Engl J Med* 1987; **317**: 1105–1108.

248 Groll AH, Jaeger G, Allendorf A, *et al*. Invasive pulmonary aspergillosis in a critically ill neonate: case report and review of invasive aspergillosis during the first 3 months of life. *Clin Infect Dis* 1998; **27**: 437–452.

249 Woodruff CA, Hebert AA. Neonatal primary cutaneous aspergillosis: case report and review of the literature. *Pediatr Dermatol* 2002; **19**: 439–444.

250 Amod FC, Coovadia YM, Pillay T, Ducasse G. Primary cutaneous aspergillosis in ventilated neonates. *Pediatr Infect Dis J* 2000; **19**: 482–483.

251 Papouli M, Roilides E, Bibashi E, Andreou A. Primary cutaneous aspergillosis in neonates: case report and review. *Clin Infect Dis* 1996; **22**: 1102–1104.

252 Perzigian RW, Faix RG. Primary cutaneous aspergillosis in a preterm infant. *Am J Perinatol* 1993; **10**: 269–271.

253 Smith WF, Wallace MR. Cutaneous aspergillosis. *Cutis* 1997; **59**: 138–140.

254 Stanford D, Boyle M, Gillespie R. Human immunodeficiency virus-related primary cutaneous aspergillosis. *Australas J Dermatol* 2000; **41**: 112–116.

255 Prystowsky SD, Vogelstein B, Ettinger DS, *et al*. Invasive aspergillosis. *N Engl J Med* 1976; **295**: 655–658.

256 Mowad CM, Nguyen TV, Jaworsky C, Honig PJ. Primary cutaneous aspergillosis in an immunocompetent child. *J Am Acad Dermatol* 1995; **33**: 136–137.

257 Magid ML, Prendiville JS, Esterly NB. Violaceous nodules on the arm of a child with acute lymphocytic leukemia. Primary cutaneous aspergillosis (*Aspergillus flavus*). *Arch Dermatol* 1988; **124**: 122, 125–126.

258 Lucas GM, Tucker P, Merz WG. Primary cutaneous *Aspergillus nidulans* infection associated with a Hickman catheter in a patient with neutropenia. *Clin Infect Dis* 1999; **29**: 1594–1596.

259 Estes SA, Hendricks AA, Merz WG, Prystowsky SD. Primary cutaneous aspergillosis. *J Am Acad Dermatol* 1980; **3**: 397–400.

260 Carlile JR, Millet RE, Cho CT, Vats TS. Primary cutaneous aspergillosis in a leukemic child. *Arch Dermatol* 1978; **114**: 78–80.

261 Arikan S, Uzun O, Cetinkaya Y, *et al*. Primary cutaneous aspergillosis in human immunodeficiency virus-infected patients: two cases and review. *Clin Infect Dis* 1998; **27**: 641–643.

262 van Burik JA, Colven R, Spach DH. Itraconazole therapy for primary cutaneous aspergillosis in patients with AIDS. *Clin Infect Dis* 1998; **27**: 643–644.

263 Hunt SJ, Nagi C, Gross KG, Wong DS, Mathews WC. Primary cutaneous aspergillosis near central venous catheters in patients with the acquired immunodeficiency syndrome. *Arch Dermatol* 1992; **128**: 1229–1232.

264 Romero LS, Hunt SJ. Hickman catheter-associated primary cutaneous aspergillosis in a patient with the acquired immunodeficiency syndrome. *Int J Dermatol* 1995; **34**: 551–553.

265 Girmenia C, Gastaldi R, Martino P. Catheter-related cutaneous aspergillosis complicated by fungemia and fatal pulmonary infection in an HIV-positive patient with acute lymphocytic leukemia. *Eur J Clin Microbiol Infect Dis* 1995; **14**: 524–526.

266 Goldberg B, Eversmann WW, Eitzen EM, Jr. Invasive aspergillosis of the hand. *J Hand Surg [Am]* 1982; **7**: 38–42.

267 Golladay ES, Baker SB. Invasive aspergillosis in children. *J Pediatr Surg* 1987; **22**: 504–505.

268 Gene J, Azon-Masoliver A, Guarro J, *et al*. Cutaneous infection caused by *Aspergillus ustus*, an emerging opportunistic fungus in immunosuppressed patients. *J Clin Microbiol* 2001; **39**: 1134–1136.

269 Lai CS, Lin SD, Chou CK, Lin HJ. Aspergillosis complicating the grafted skin and free muscle flap in a diabetic. *Plast Reconstr Surg* 1993; **92**: 532–536.

270 Falsey AR, Goldsticker RD, Ahern MJ. Fatal subcutaneous aspergillosis following necrotizing fasciitis: a case report. *Yale J Biol Med* 1990; **63**: 9–13.

271 Frank KA, Merz WG, Hutchins GM. Sclerotium formation in an *Aspergillus flavus* wound infection. *Mycopathologia* 1988; **102**: 185–188.

272 Langlois RP, Flegel KM, Meakins JL, *et al*. Cutaneous aspergillosis with fatal dissemination in a renal transplant recipient. *Can Med Assoc J* 1980; **122**: 673–676.

273 Pla MP, Berenguer J, Arzuaga JA, *et al*. Surgical wound infection by *Aspergillus fumigatus* in liver transplant recipients. *Diagn Microbiol Infect Dis* 1992; **15**: 703–706.

274 Frank L, Alton OM. Aspergillosis: a case of postoperative skin infection. *JAMA* 1933; **100**: 2007–2008.

275 Isaac M. Cutaneous aspergillosis. *Dermatol Clin* 1996; **14**: 137–140.
276 Miele PS, Levy CS, Smith MA, *et al*. Primary cutaneous fungal infections in solid organ transplantation: a case series. *Am J Transplant* 2002; **2**: 678–683.
277 Findlay GH, Roux HF, Simson IW. Skin manifestations in disseminated aspergillosis. *Br J Dermatol* 1971; **85**: 94–97.
278 Gercovich FG, Richman SP, Rodriguez V, *et al*. Successful control of systemic *Aspergillus niger* infections in two patients with acute leukemia. *Cancer* 1975; **36**: 2271–2276.
279 Thomas PA. Current perspectives on ophthalmic mycoses. *Clin Microbiol Rev* 2003; **16**: 730–797.
280 Rao NA, Hidayat A. A comparative clinicopathologic study of endogenous mycotic endophthalmitis: variations in clinical and histopathologic changes in candidiasis compared to aspergillosis. *Trans Am Ophthalmol Soc* 2000; **98**: 183–193; discussion 193–184.
281 Naidoff MA, Green WR. Endogenous *Aspergillus* endophthalmitis occurring after kidney transplant. *Am J Ophthalmol* 1975; **79**: 502–509.
282 Cattelan AM, Loy M, Tognon S, *et al*. An unusual presentation of invasive aspergillosis after lung transplantation. *Transpl Int* 2000; **13**: 183–186.
283 Demicco DD, Reichman RC, Violette EJ, Winn WC, Jr. Disseminated aspergillosis presenting with endophthalmitis. A case report and a review of the literature. *Cancer* 1984; **53**: 1995–2001.
284 Graham DA, Kinyoun JL, George DP. Endogenous *Aspergillus* endophthalmitis after lung transplantation. *Am J Ophthalmol* 1995; **119**: 107–109.
285 Paradis AJ, Roberts L. Endogenous ocular aspergillosis. Report of a case in an infant with cytomegalic inclusion disease. *Arch Ophthalmol* 1963; **69**: 765–769.
286 Friedman AH, Chishti MI, Henkind P. Endogenous ocular aspergillosis. *Ophthalmologica* 1974; **168**: 197–205.
287 Papanicolaou GA, Meyers BR, Fuchs WS, *et al*. Infectious ocular complications in orthotopic liver transplant patients. *Clin Infect Dis* 1997; **24**: 1172–1177.
288 Sihota R, Agarwal HC, Grover AK, Sood NN. *Aspergillus* endophthalmitis. *Br J Ophthalmol* 1987; **71**: 611–613.
289 Roney P, Barr CC, Chun CH, Raff MJ. Endogenous *Aspergillus* endophthalmitis. *Rev Infect Dis* 1986; **8**: 955–958.
290 Lance SE, Friberg TR, Kowalski RP. *Aspergillus flavus* endophthalmitis and retinitis in an intravenous drug abuser. A therapeutic success. *Ophthalmology* 1988; **95**: 947–949.
291 Leen CL, Brettle RP. Fungal infections in drug users. *J Antimicrob Chemother* 1991; **28**(Suppl A): 83–96.
292 Doft BH, Clarkson JG, Rebell G, Forster RK. Endogenous *Aspergillus* endophthalmitis in drug abusers. *Arch Ophthalmol* 1980; **98**: 859–862.
293 Elliott JH, O'Day DM, Gutow GS, Podgorski SF, Akrabawi P. Mycotic endophthalmitis in drug abusers. *Am J Ophthalmol* 1979; **88**: 66–72.
294 Sugar HS, Mandell GH, Shalev J. Metastatic endophthalmitis associated with injection of addictive drugs. *Am J Ophthalmol* 1971; **71**: 1055–1058.
295 Wilmarth SS, May DR, Roth AM, *et al*. *Aspergillus* endophthalmitis in an intravenous drug user. *Ann Ophthalmol* 1983; **15**: 470–472, 474–476.
296 Walinder PE, Kock E. Endogenous fungus endophthalmitis. *Acta Ophthalmol (Copenh)* 1971; **49**: 263–272.
297 Darrell RW. Endogenous *Aspergillus* uveitis following heart surgery. *Arch Ophthalmol* 1967; **78**: 354–357.
298 Stenson S, Brookner A, Rosenthal S. Bilateral endogenous necrotizing scleritis due to *Aspergillus oryzae*. *Ann Ophthalmol* 1982; **14**: 67–72.
299 Litricin O. Endogenous fungus endophthalmitis (probably *Aspergillus*). *Ophthalmologica* 1979; **179**: 42–47.
300 Ho PC, Tolentino FI, Baker AS. Successful treatment of exogenous *Aspergillus* endophthalmitis: a case report. *Br J Ophthalmol* 1984; **68**: 412–415.
301 Hanish SJ, Perlmutter JC, Boucher C, Bohigian G, Grand MG. Exogenous *Aspergillus* endophthalmitis. *Ann Ophthalmol* 1984; **16**: 417–419.
302 Oxford KW, Abbott RL, Fung WE, Ellis DS. *Aspergillus* endophthalmitis after sutureless cataract surgery. *Am J Ophthalmol* 1995; **120**: 534–535.
303 Das T, Vyas P, Sharma S. *Aspergillus terreus* postoperative endophthalmitis. *Br J Ophthalmol* 1993; **77**: 386–387.
304 Hemady R, Sainz de la Maza M, Raizman MB, Foster CS. Six cases of scleritis associated with systemic infection. *Am J Ophthalmol* 1992; **1992**: 1.
305 Huang FC, Huang SP, Tseng SH. Management of infectious scleritis after pterygium excision. *Cornea* 2000; **19**: 34–39.
306 Kim JE, Perkins SL, Harris GL. Voriconazole treatment of fungal scleritis and epibulbar abscess resulting from scleral buckle infection. *Arch Ophthalmol* 2003; **121**: 735–737.
307 Carlson AN, Foulks GN, Perfect JR, Kim JH. Fungal scleritis after cataract surgery. Successful outcome using itraconazole. *Cornea* 1992; **11**: 151–154.
308 Bernauer W, Allan BD, Dart JK. Successful management of *Aspergillus* scleritis by medical and surgical treatment. *Eye* 1998; **12**: 311–316.
309 Castelli C, Benazzo F, Minoli L, *et al*. *Aspergillus* infection of the L3-L4 disc space in an immunosuppressed heart transplant patient. *Spine* 1990; **15**: 1369–1373.
310 Barnwell PA, Jelsma LF, Raff MJ. *Aspergillus* osteomyelitis. Report of a case and review of the literature. *Diagn Microbiol Infect Dis* 1985; **3**: 515–519.
311 McKee DF, Barr WM, Bryan CS, Lunceford EM, Jr. Primary aspergillosis of the spine mimicking Pott's paraplegia. *J Bone Joint Surg Am* 1984; **66**: 1481–1483.
312 Sachs MK, Paluzzi RG, Moore JH, Jr, Fraimow HS, Ost D. Amphotericin-resistant *Aspergillus* osteomyelitis controlled by itraconazole. *Lancet* 1990; **335**: 1475.
313 Wellens F, Potvliege C, Deuvaert FE, Primo G. *Aspergillus* osteochondritis after median sternotomy. Combined operative treatment and drug therapy with amphotericin B. *Thorac Cardiovasc Surg* 1982; **30**: 322–324.
314 Barzaghi N, Emmi V, Mencherini S, *et al*. Sternal osteomyelitis due to *Aspergillus fumigatus* after cardiac surgery. *Chest* 1994; **105**: 1275–1277.
315 Attah CA, Cerruti MM. *Aspergillus* osteomyelitis of sternum after cardiac surgery. *N Y State J Med* 1979; **79**: 1420–1421.
316 Schubert M, Schar G, Curt A, Dietz V. *Aspergillus* spondylodiscitis in an immunocompetent paraplegic patient. *Spinal Cord* 1998; **36**: 800–803.
317 Mawk JR, Erickson DL, Chou SN, Seljeskog EL. *Aspergillus* infections of the lumbar disc spaces. Report of three cases. *J Neurosurg* 1983; **58**: 270–274.
318 Peters-Christodoulou MN, de Beer FC, Bots GT, *et al*. Treatment of postoperative *Aspergillus fumigatus* spondylodiscitis with itraconazole. *Scand J Infect Dis* 1991; **23**: 373–376.
319 Tack KJ, Rhame FS, Brown B, Thompson RC, Jr. *Aspergillus* osteomyelitis. Report of four cases and review of the literature. *Am J Med* 1982; **73**: 295–300.

320 Cimerman M, Gunde-Cimerman N, Zalar P, Perkovic T. Femur osteomyelitis due to a mixed fungal infection in a previously healthy man. *J Clin Microbiol* 1999; **37**: 1532–1535.

321 Glotzbach RE. *Aspergillus terreus* infection of pseudoaneurysm of aortofemoral vascular graft with contiguous vertebral osteomyelitis. *Am J Clin Pathol* 1982; **77**: 224–227.

322 Brandt SJ, Thompson RL, Wenzel RP. Mycotic pseudoaneurysm of an aortic bypass graft and contiguous vertebral osteomyelitis due to *Aspergillus fumigatus*. *Am J Med* 1985; **79**: 259–262.

323 Anderson J, Kron IL. Treatment of *Aspergillus* infection of the proximal aortic prosthetic graft with associated vertebral osteomyelitis. *J Vasc Surg* 1984; **1**: 579–581.

324 Dietz R, Huber G, Thetter O, Volkmer I. Aspergillosis of the lung with osteoclasis and paraplegia. *Neuroradiology* 1982; **23**: 219–221.

325 Nasca RJ, McElvein RB. *Aspergillus fumigatus* osteomyelitis of the thoracic spine treated by excision and interbody fusion. *Spine* 1985; **10**: 848–850.

326 Wagner DK, Varkey B, Sheth NK, DaMert GJ. Epidural abscess, vertebral destruction, and paraplegia caused by extending infection from an aspergilloma. *Am J Med* 1985; **78**: 518–522.

327 Seres JL, Ono H, Benner EJ. Aspergillosis presenting as spinal cord compression. Case report. *J Neurosurg* 1972; **36**: 221–224.

328 Gaisie G, Bowen A, Quattromani FL, Oh KS. Chest wall invasion by *Aspergillus* in chronic granulomatous disease of childhood. *Pediatr Radiol* 1981; **11**: 203–206.

329 Wolfson JJ, Kane WJ, Laxdal SD, Good RA, Quie PG. Bone findings in chronic granulomatous disease of childhood. A genetic abnormality of leukocyte function. *J Bone Joint Surg Am* 1969; **51**: 1573–1583.

330 Redmond A, Carr'E IJ, Biggart JD, Mackenzie DW. Aspergillosis (*Aspergillus nidulans*) involving bone. *J Pathol Bacteriol* 1965; **89**: 391–395.

331 Kawashima A, Kuhlman JE, Fishman EK, *et al*. Pulmonary *Aspergillus* chest wall involvement in chronic granulomatous disease: CT and MRI findings. *Skeletal Radiol* 1991; **20**: 487–493.

332 Rassa M. Vertebral aspergillosis with preservation of the disc. *Br J Radiol* 1977; **50**: 918–920.

333 Hanna E, Hughes G, Eliachar I, Wanamaker J, Tomford W. Fungal osteomyelitis of the temporal bone: a review of reported cases. *Ear Nose Throat J* 1993; **72**: 532, 537–541.

334 Hall PJ, Farrior JB. *Aspergillus* mastoiditis. *Otolaryngol Head Neck Surg* 1993; **108**: 167–170.

335 Shelton JC, Antonelli PJ, Hackett R. Skull base fungal osteomyelitis in an immunocompetent host. *Otolaryngol Head Neck Surg* 2002; **126**: 76–78.

336 Menachof MR, Jackler RK. Otogenic skull base osteomyelitis caused by invasive fungal infection. *Otolaryngol Head Neck Surg* 1990; **102**: 285–289.

337 Bianchi R, Chekikian G, Ciboddo G, *et al*. Primary sternal osteomyelitis caused by *Aspergillus fumigatus*. *Br J Rheumatol* 1994; **33**: 994–995.

338 Cortet B, Richard R, Deprez X, *et al*. *Aspergillus* spondylodiscitis: successful conservative treatment in 9 cases. *J Rheumatol* 1994; **21**: 1287–1291.

339 Bridwell KH, Campbell JW, Barenkamp SJ. Surgical treatment of hematogenous vertebral *Aspergillus* osteomyelitis. *Spine* 1990; **15**: 281–285.

340 Ingwer I, McLeish KR, Tight RR, White AC. *Aspergillus fumigatus* epidural abscess in a renal transplant recipient. *Arch Intern Med* 1978; **138**: 153–154.

341 Grossman M. Aspergillosis of bone. *Br J Radiol* 1975; **48**: 57–59.

342 Delmas Y, Merville P, Dousset V, *et al*. A renal transplant recipient with acute paraparesis due to an *Aspergillus* epidural abscess. *Nephrol Dial Transplant* 1997; **12**: 2185–2187.

343 Byrd BF, 3rd, Weiner MH, McGee ZA. *Aspergillus* spinal epidural abscess. *JAMA* 1982; **248**: 3138–3139.

344 Williams RL, Fukui MB, Meltzer CC, *et al*. Fungal spinal osteomyelitis in the immunocompromised patient: MR findings in three cases. *AJNR Am J Neuroradiol* 1999; **20**: 381–385.

345 Taillandier J, Alemanni M, Cerrina J, Le Roy Ladurie F, Dartevelle P. *Aspergillus* osteomyelitis after heart-lung transplantation. *J Heart Lung Transplant* 1997; **16**: 436–438.

346 Tang TJ, Janssen HL, van der Vlies CH, *et al*. *Aspergillus* osteomyelitis after liver transplantation: conservative or surgical treatment? *Eur J Gastroenterol Hepatol* 2000; **12**: 123–126.

347 Brown DL, Musher DM, Taffet GE. Hematogenously acquired *Aspergillus* vertebral osteomyelitis in seemingly immunocompetent drug addicts. *West J Med* 1987; **147**: 84–85.

348 Seligsohn R, Rippon JW, Lerner SA. *Aspergillus terreus* osteomyelitis. *Arch Intern Med* 1977; **137**: 918–920.

349 Holmes PF, Osterman DW, Tullos HS. *Aspergillus* discitis. Report of two cases and review of the literature. *Clin Orthop* 1988; **Jan**(226): 240–246.

350 Pollack IF, Pang D, Schuit KE. Chronic granulomatous disease with cranial fungal osteomyelitis and epidural abscess. Case report. *J Neurosurg* 1987; **67**: 132–136.

351 Chee YC, Poh SC. *Aspergillus* epidural abscess in a patient with obstructive airway disease. *Postgrad Med J* 1983; **59**: 43–45.

352 Beckers EA, Strack van Schijndel RJ. *Aspergillus* spondylodiskitis in a patient with chronic obstructive pulmonary disease 2002; **13**: 139–142.

353 Padhye AA, Godfrey JH, Chandler FW, Peterson SW. Osteomyelitis caused by *Neosartorya pseudofischeri*. *J Clin Microbiol* 1994; **32**: 2832–2836.

354 Assaad W, Nuchikat PS, Cohen L, Esguerra JV, Whittier FC. *Aspergillus* discitis with acute disc abscess. *Spine* 1994; **19**: 2226–2229.

355 Vinas FC, King PK, Diaz FG. Spinal *Aspergillus* osteomyelitis. *Clin Infect Dis* 1999; **28**: 1223–1229.

356 Morgenlander JC, Rossitch E, Jr, Rawlings CE, 3rd. *Aspergillus* disc space infection: case report and review of the literature. *Neurosurgery* 1989; **25**: 126–129.

357 Heinrich SD, Finney T, Craver R, Yin L, Zembo MM. *Aspergillus* osteomyelitis in patients who have chronic granulomatous disease. Case report. *J Bone Joint Surg Am* 1991; **73**: 456–460.

358 Flynn PM, Magill HL, Jenkins JJ, 3rd, *et al*. *Aspergillus* osteomyelitis in a child treated for acute lymphoblastic leukemia. *Pediatr Infect Dis J* 1990; **9**: 733–736.

359 Kaneko J, Sugawara Y, Makuuchi M. *Aspergillus* osteomyelitis after liver transplantation. *Liver Transpl* 2002; **8**: 1073–1075.

360 Alvarez L, Calvo E, Abril C. Articular aspergillosis: case report. *Clin Infect Dis* 1995; **20**: 457–460.

361 Myerson DA, Rosenfield AT. Renal aspergillosis: a report of two cases. *J Can Assoc Radiol* 1977; **28**: 214–216.

362 Bibler MR, Gianis JT. Acute ureteral colic from an obstructing renal aspergilloma. *Rev Infect Dis* 1987; **9**: 790–794.

363 Heussel CP, Kauczor HU, Heussel G, Thelen M, Jahn B. Multiple renal *Aspergillus* abscesses in an AIDS patient: contrast-enhanced helical CT and MRI findings. *Eur Radiol* 1999; **9**: 616–619.

364 Cervero M, Marco J, Fernandez-Ballesteros A, *et al*. Prostatic and renal aspergillosis in a patient with AIDS. *Am J Med* 1999; **106**: 123.
365 Hartman BJ, Coleman M, Brause BD, Saletan S. Localized renal aspergillosis with hairy cell leukemia: a review of urinary tract aspergillosis in malignant and nonmalignant conditions. *Cancer Invest* 1984; **2**: 199–202.
366 Nadu A, Hoznek A, Salomon L, *et al*. Laparoscopic retroperitoneal nephrectomy for *Aspergillus*-infected polycystic kidney. *J Endourol* 2002; **16**: 237–240.
367 Rey D, de Mautort E, Saussine C, *et al*. Isolated renal *Aspergillus* abscess in an AIDS patient with a normal CD4+ cell count on highly active antiretroviral therapy. *Eur J Clin Microbiol Infect Dis* 1999; **18**: 137–141.
368 Martinez-Jabaloyas J, Osca JM, Ruiz JL, *et al*. Renal aspergillosis and AIDS. *Eur Urol* 1995; **27**: 167–169.
369 Irby PB, Stoller ML, McAninch JW. Fungal bezoars of the upper urinary tract. *J Urol* 1990; **143**: 447–451.
370 Comings DE, Turbow BA, Callahan DH, Waldstein SS. Obstructing *Aspergillus* case to the renal pelvis. Report of a case in a patient having diabetes mellitus and Addison's disease. *Arch Intern Med* 1962; **110**: 255–261.
371 Sakamoto S, Ogata J, Sakazaki Y, Ikegami K. Fungus ball formation of *Aspergillus* in the bladder: an unusual case report. *Eur Urol* 1978; **4**: 388–389.
372 Warshawsky AB, Keiller D, Gittes RF. Bilateral renal aspergillosis. *J Urol* 1975; **113**: 8–11.
373 Perez-Arellano JL, Angel-Moreno A, Belon E, *et al*. Isolated renoureteric aspergilloma due to *Aspergillus flavus*: case report and review of the literature. *J Infect* 2001; **42**: 163–165.
374 Chmel H, Grieco MH. Cerebral mucormycosis and renal aspergillosis in heroin addicts without endocarditis. *Am J Med Sci* 1973; **266**: 225–231.
375 Urrutia Avisrror M, Montero Gomez J, Silva Abuin J, Gomez Zancajo VR. Solitary *Aspergillus* mycetoma of the kidney. *Eur Urol* 1983; **9**: 119–121.
376 Marchand R, Ahronheim GA, Patriquin H, *et al*. Aspergilloma of the renal pelvis in a leukemic child. *Pediatr Infect Dis* 1985; **4**: 103–105.
377 Eisenberg RL, Hedgcock MW, Shanser JD. *Aspergillus* mycetoma of the renal pelvis associated with ureteropelvic junction obstruction. *J Urol* 1977; **118**: 466–467.
378 Davies SP, Webb WJ, Patou G, Murray WK, Denning DW. Renal aspergilloma – a case illustrating the problems of medical therapy. *Nephrol Dial Transplant* 1987; **2**: 568–572.
379 Guleria S, Seth A, Dinda AK, *et al*. Ureteric aspergilloma as the cause of ureteric obstruction in a renal transplant recipient. *Nephrol Dial Transplant* 1998; **13**: 792–793.
380 Godec CJ, Mielnick A, Hilfer J. Primary renal aspergillosis. *Urology* 1989; **34**: 152–154.
381 Flechner SM, McAninch JW. Aspergillosis of the urinary tract: ascending route of infection and evolving patterns of disease. *J Urol* 1981; **125**: 598–601.
382 Hadaya K, Akposso K, Costa de Beauregard MA, *et al*. Isolated urinary aspergillosis in a renal transplant recipient. *Nephrol Dial Transplant* 1998; **13**: 2382–2384.
383 Baird RW, Lancaster DJ. Diabetic ketoacidosis as the presentation of renal aspergilloma. *Am J Med* 1988; **85**: 453–454.
384 Salgia P, Mani MK. Renal aspergillosis – case report. *Nephron* 1985; **40**: 376–378.
385 Khawand N, Jones G, Edson M. Aspergillosis of prostate. *Urology* 1989; **34**: 100–101.
386 Abbas F, Kamal MK, Talati J. Prostatic aspergillosis. *J Urol* 1995; **153**: 748–750.
387 Kaplan-Pavlovcic S, Masera A, Ovcak Z, Kmetec A. Prostatic aspergillosis in a renal transplant recipient. *Nephrol Dial Transplant* 1999; **14**: 1778–1780.
388 Singer AJ, Kubak B, Anders KH. Aspergillosis of the testis in a renal transplant recipient. *Urology* 1998; **51**: 119–121.
389 Kim SW, Nah MY, Yeum CH, *et al*. Pelvic aspergillosis with tubo-ovarian abscess in a renal transplant recipient. *J Infect* 2001; **42**: 215–217.
390 Yoo JH, Shin WS, Kim YR, *et al*. Esophageal aspergillosis in a patient with acute leukemia. *Leukemia* 1995; **9**: 1599–1600.
391 Choi JH, Yoo JH, Chung IJ, *et al*. Esophageal aspergillosis after bone marrow transplant. *Bone Marrow Transplant* 1997; **19**: 293–294.
392 Foy TM, Hawkins EP, Peters KR, Shearer WT, Ferry GD. Colonic ulcers and lower GI bleeding due to disseminated aspergillosis. *J Pediatr Gastroenterol Nutr* 1994; **18**: 399–403.
393 Catalano L, Picardi M, Anzivino D, *et al*. Small bowel infarction by *Aspergillus*. *Haematologica* 1997; **82**: 182–183.
394 Kami M, Hori A, Takaue Y, Mutou Y. The gastrointestinal tract is a common target of invasive aspergillosis in patients receiving cytotoxic chemotherapy for hematological malignancy. *Clin Infect Dis* 2002; **35**: 105–106.
395 Myoken Y, Sugata T, Kyo T, *et al*. Invasive *Aspergillus* stomatitis in patients with acute leukemia: report of 12 cases. *Clin Infect Dis* 2001; **33**: 1975–1980.
396 Johnson JD, Raff MJ. Fungal splenic abscess. *Arch Intern Med* 1984; **144**: 1987–1993.
397 Shirkhoda A, Lopez-Berestein G, Holbert JM, Luna MA. Hepatosplenic fungal infection: CT and pathologic evaluation after treatment with liposomal amphotericin B. *Radiology* 1986; **159**: 349–353.
398 Carpenter JL, Foulks CJ, Weiner MH. Peritoneal dialysis complicated by *Aspergillus flavus* peritonitis: a role for fungal antigen serodiagnosis. *Nephron* 1982; **32**: 258–260.
399 Bibashi E, Papagianni A, Kelesidis A, Antoniadou R, Papadimitriou M. Peritonitis due to *Aspergillus niger* in a patient on continuous abulatory peritoneal dialysis shortly after kidney graft rejection. *Nephrol Dial Transplant* 1993; **8**: 185–187.
400 Miles AV, Barth RH. *Aspergillus* peritonitis: therapy, survival, and return to peritoneal dialysis. *Am J Kid Dis* 1995; **26**: 80–83.