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

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*Aspergillus* spp. produce a wide range of invasive and saprophytic 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

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**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 aspergillosis (IA) into individual pathophysiologic 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, saprophytic, 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
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., co-existent 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 known 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**

*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 inoculum 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...
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Note: PCR data in square brackets to indicate that significant issues in assay validation and standardization remain.

As per the current EORTC/MSG definitions.

Evidence exists in the form of case reports or case series.

† CNPA, Chronic necrotizing pulmonary aspergillosis, CCPA, Chronic cavitary pulmonary aspergillosis, CFPA, Chronic fibrosing pulmonary aspergillosis.

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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
Invasive and saprophytic aspergillosis

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 hematopoetic 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 are 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 plural 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 exsudative 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

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<tr>
<th>Pathological features</th>
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</tr>
</thead>
</table>
| **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) \(^c\)  
[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) \(^c\) [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] \(^c\) | 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

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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 lumenal 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. Radiographic 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 pancytaditis [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 ostia, 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; transoesophageal echocardiography is likely to be more sensitive in this context but this remains to be determined [120,133,138].
### Table 3  Cardiovascular aspergillosis

<table>
<thead>
<tr>
<th>Pathological features</th>
<th>Radiological features</th>
<th>Clinical setting</th>
<th>Direct evidence to implicate <em>Aspergillus</em> spp.</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Native valve endocarditis</td>
<td>Large friable vegetations, mural vegetations, extension to paravalvular structures, development of pancarditis</td>
<td>Echocardiographic evidence of endocardial abnormalities</td>
<td><em>Aspergillus</em> spp. in blood cultures from retrieved embolus or valve GM from blood&lt;sup&gt;b&lt;/sup&gt; [PCR from blood]&lt;sup&gt;c&lt;/sup&gt; [PCR from resected valve or retrieved embolus]&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Proven/probable IA at non-contiguous site</td>
</tr>
<tr>
<td>Prosthetic valve endocarditis</td>
<td>Vegetation causing prosthetic malfunction, valve dehiscence</td>
<td>Echocardiographic abnormalities including malfunction of prosthetic valve, paravalvular leak, paravalvular collection</td>
<td><em>Aspergillus</em> spp. in blood cultures from retrieved embolus or resected valve [PCR from blood]&lt;sup&gt;c&lt;/sup&gt; [PCR from resected valve or retrieved embolus]&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Proven/probable IA at non-contiguous site</td>
</tr>
<tr>
<td>Pericardial aspergillosis</td>
<td>Fibrinous or exudative pericarditis, evidence of contiguous IPA or myocardial aspergillosis</td>
<td>Echocardiographic evidence of pericardial disease including pericardial effusion and signs of pericardial tamponade, widened cardiac silhouette on CXR</td>
<td><em>Aspergillus</em> spp. (culture, cytology or histology) from pericardial biopsy or aspirate [PCR from pericardial fluid]&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Proven/probable IA at non-contiguous site</td>
</tr>
</tbody>
</table>

<sup>b</sup> Evidence exists in the form of case reports or case series.

<sup>c</sup> No current reports of diagnostic modalities being used in this context.

PCR data in square brackets to indicate significant issues in assay validation and standardization remain. IPA: Invasive pulmonary aspergillosis.
Specific evidence that \textit{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, \textit{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 \textit{Aspergillus} spp. as the causative organism [144–146]. There is a single report of \textit{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]. \textit{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].

\textbf{Prosthetic valve \textit{Aspergillus} endocarditis and prosthetic device-related endocarditis}

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

\textbf{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 \textit{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].

\textbf{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.

\textbf{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 \textit{Aspergillus} spp. is difficult. Blood cultures with most \textit{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].

\textbf{Aspergillus infection of vascular grafts}

Infection of vascular prostheses with \textit{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]. \textit{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.

\textbf{Pericardial aspergillosis}

Pericardial aspergillosis may arise from contiguous spread from either the pleura or myocardium [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 nonspecific 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 nonspecific 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>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Cerebrovascular aspergillosis</strong></td>
<td>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</td>
<td>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</td>
<td>Essentially restricted to those with significant immunological impairment, IVDU, or <em>Aspergillus</em> endocarditis</td>
<td>Proven/probable IA at non-contiguous site Positive GM (x2) from blood(^{a,b}) [Positive PCR from cerebral biopsy/aspirate](^{f}) [Positive PCR from CSF] (^{b})</td>
</tr>
<tr>
<td><strong>Cerebral abscess</strong></td>
<td>Abscess formation: central necrotic area with liquifactive necrosis surrounded by an abscess wall.</td>
<td>Single or multiple space occupying lesion(s) showing ring enhancement, mass effect, cerebral oedema</td>
<td>Patients with significant immunological impairment, IVDU, or <em>Aspergillus</em> endocarditis</td>
<td>Proven/probable IA at non-contiguous site Positive GM (x2) from blood (^{a,b}) [Positive PCR from cerebral biopsy/aspirate] (^{f}) [Positive PCR from CSF] (^{b})</td>
</tr>
<tr>
<td><strong>Cerebral granuloma</strong></td>
<td>Solid lesion without suppuration, with florid granulomatous inflammation and hyphal infiltration</td>
<td>Space occupying lesion</td>
<td>Immunocompetent patient from Sudan, Middle East, Indian Subcontinent, patient with CGD, with longstanding signs/symptoms (months years)</td>
<td><em>Aspergillus</em> spp. from a brain biopsy, aspirate Proven/probable IA with granulomatous inflammation from sinuses or orbit Precipitating antibodies to <em>Aspergillus</em> spp.</td>
</tr>
<tr>
<td><strong>Mycotic cerebral aneurysm</strong></td>
<td>Aneurysm formation of intracranial artery, invasion of vessel wall by hyphae</td>
<td>Aneurysm of intracranial vessel defined at cerebral angiography</td>
<td>Patients with profound immunological impairment, recent neurosurgical clipping of a berry aneurysm or in the setting of <em>Aspergillus</em> meningitis with involvement of vessels at the base of the brain</td>
<td>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,b}) [Positive PCR from cerebral biopsy]</td>
</tr>
<tr>
<td><strong>Meningitis</strong></td>
<td>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.</td>
<td>Nil</td>
<td>Evidence of another CNS aspergillosis syndrome; as above Previous neurosurgery <em>Aspergillus</em>osis of a contiguous structure (sinuses, orbit)</td>
<td>Positive GM x2 from blood (^{a,b}) [Positive PCR from blood]</td>
</tr>
</tbody>
</table>

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 liquefactive 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 suppurration [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 fibrous tissue interspersed with hyphal elements

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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].

**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].

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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. 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 breach 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 breach 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 violaceous nodules, plaques and papules with necrotic ulcerative, and suppurrative 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
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 keratomycores 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...

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**Table 5: Ocular aspergillosis**

<table>
<thead>
<tr>
<th>Pathological features</th>
<th>Clinical setting</th>
<th>Radiological features</th>
<th>Direct evidence to implicate <em>Aspergillus</em> spp.</th>
<th>Indirect evidence to implicate <em>Aspergillus</em> spp.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endogenous endophthalmitis</td>
<td>Hyphae within retinal and subretinal structures, choroidal abscess, secondary vitritis, retinal vessel thrombosis and rupture, retinal detachment</td>
<td>Ocular ultrasonography may reveal intraocular abnormalities</td>
<td><em>Aspergillus</em> (cultural/histological) from intraocular specimen</td>
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<td><em>Aspergillus</em> (cultural/histological) from intraocular specimen</td>
</tr>
<tr>
<td>Keratitis</td>
<td>Stromal infiltrate, stromal abscess formation, hyphal invasion, coagulative necrosis</td>
<td>Nil</td>
<td><em>Aspergillus</em> (culture/histology) from vitreal aspirate</td>
<td><em>Aspergillus</em> (culture/histology) from vitreal aspirate</td>
</tr>
</tbody>
</table>

**PCR data**

PCR data in square brackets to indicate significant issues in assay validation and standardization remain.

**IVDU:** Intravenous drug use.

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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 contiguous involvement of the adjacent vertebrae has been described more than two years post surgery [321–323]. 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 context 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 haematological 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 preceeding 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 stomatitis, 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.

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Invasive and saprophytic aspergillosis


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