# Case definition of chronic pulmonary aspergillosis in resource-limited settings: catalysing research and clinical care

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Short biography: Dr. Denning, an infectious diseases clinician who is heavily involved in postgraduate teaching and lectures worldwide, leads LIFE (Leading International Fungal Education) and is president of the Global Action Fund for Fungal Infections. His primary research interests are chronic and allergic pulmonary fungal disease, the global burden of fungal infection, and azole resistance in *Aspergillus*.

**Abstract**

Chronic pulmonary aspergillosis (CPA) is a recognized complication of pulmonary tuberculosis (PTB). In 2015, the WHO reported 2.2 million new cases of non-bacteriologically confirmed PTB; some probably have undiagnosed CPA. GAFFI convened an international expert panel to develop a case definition of CPA for resource-constrained settings. CPA is defined by illness of >3 months and all of: 1) symptoms of weight loss; persistent cough and haemoptysis; 2) chest imaging showing progressive cavitary infiltrates, and/or a fungal ball and/or pericavitary fibrosis or infiltrates or pleural thickening; and 3) a positive *Aspergillus* IgG antibody assay or other evidence of *Aspergillus* infection.

**Introduction**

Pulmonary tuberculosis (PTB) has a wide differential diagnosis including non-tuberculous mycobacterial infection, endemic fungal infections such as coccidioidomycosis and histoplasmosis, allergic bronchopulmonary aspergillosis (ABPA), and chronic pulmonary aspergillosis (CPA) (*1–7*). Sequelae of PTB such as bronchiectasis and restricted lung capacity can mimic infection relapse (*8–10*). Accurate diagnosis is essential to facilitate adequate treatment.

The 2015 World Health Organization (WHO) annual report notes that approximately 43% (~2.2 million) of 5.2 million cases of incident PTB, were clinically diagnosed or smear-negative (*11*). Only 21-40% of smear-negative PTB cases are culture positive (*12,13*). Exclusion of alternative is challenging in many lower and middle income countries (LMIC) (*14*). The WHO report comments: “Most clinical features of TB and abnormalities on X-ray or histology results generally associated with TB have low specificity, which may lead to false diagnoses of TB, and hence to people being enrolled on TB treatment unnecessarily.”

While coccidioidomycosis, histoplasmosis and paracoccidioidomycosis are regionally confined, aspergillosis has a global distribution. It has been estimated that each year 373,000 new CPA cases complicate treated PTB within12 months of completion of antituberculous therapy, with a 5-year period prevalence of 1,174,000 cases (range 397,000 to 2,088,000) (*9*). This wide range was due to several factors, notably the extrapolation of CPA diagnosis from a limited UK data set of only 544 patients with pulmonary cavities (*15*), substantial variability in the published frequency of cavitation after treatment of PTB, absence of an estimate of CPA prevalence in patients without cavities, and the lack of knowledge of the effect of concurrent HIV infection. The incidence and prevalence of CPA are not known but likely underestimated, in part because CPA occurs in patients with active PTB, as a sequela of prior PTB (*16*) or as a complication of other pulmonary disorders with similar symptoms to PTB and are incorrectly diagnosed and treated as PTB (*17*).

Diagnostic guidelines for CPA have recently been published in English and Japanese, emphasizing the central role of advanced imaging and *Aspergillus* serology (*18–20*). Unfortunately these are infrequently available in many low resource settings. The Global Action Fund for Fungal Infections (GAFFI) convened an international panel to develop an operational definition of CPA for research and clinical care in low-resource settings. Our aims were to adapt the existing European Society for Clinical Microbiology and Infectious Diseases and European Respiratory Society (ESCMID/ERS) (*19*) and Infectious Diseases Society of America (IDSA) guideline case definitions of CPA (*18*) to:

1. Promote research so that critical data will be available to inform policy and practice including surveillance; and

2. Facilitate individualized clinical care so that patients are managed optimally.

**Methods**

Literature and existing guidelines

We built on the work of two recent CPA expert panels (*19*)(*18,20*). These panels undertook comprehensive searching, appraisal and synthesis of the relevant literature, including diagnosis and case definitions. We included these papers in a package of materials relevant to diagnosis in different clinical contexts, i.e. underlying disease in patients developing CPA, CPA and clinically diagnosed PTB, radiological assessment and characteristics of CPA, and comparing laboratory diagnosis with different immunoassays.

Workshop Participants

We invited experts (n=36) from all regions of the world, based on their expertise. The experts had already implemented CPA diagnostic capacity, or were in the process of doing so. We also included experts from LMICs with active clinical and public health programs focused on respiratory disease including tuberculosis. Clinical expertises included internal medicine, pulmonary disease, infectious disease, critical care, thoracic radiology, medical microbiology, and medical mycology as well as those with various health system organizational roles and levels i.e. secondary care consultants, national reference laboratories, national research centres, and international health organizations. Of the 36 invited experts, 33 attended in person an extended day workshop in Liverpool, United Kingdom.

Operational definitions indicator selection

The morning presentations and discussions aimed to build on prior reading material and provide all participants evidence of CPA burden, risk factors, clinical presentations, diagnostic tools, treatment options, recurrences and prior case definitions. Facilitated afternoon breakout groups (n=3) started with CPA diagnostic indicator type i.e. clinical presentation, radiology, medical microbiology-mycology-immunology, which discussed the options for diagnosis, with a focus on secondary care levels and above, for LMICs. Notes were kept by a recorder and the pros and cons of different indicators shared in a plenary session. Subsequently three cross indicator groups worked to bring the indicators together in constructing key criteria for CPA with different clinical or radiological presentations.

Case definitions development

Plenary discussion compared and contrasted the different approaches and moved towards operational definitions. Based on consolidated notes from breakout groups and plenaries, descriptions of possible, probable and confirmed CPA were synthesized to garner consensus on the most critical elements of the diagnosis. Simple graphic representations were developed, shared with breakout group leaders for feedback, and subsequently revised through iteration. Further iteration on the key elements of the algorithms to be used in the field and minimal definitional requirements were conducted online via email and file sharing services, simplifying to a single, composite definition and algorithm.

**Results**

Modern diagnostic criteria for CPA date from 2003 (*21*) and have been used in some prospective clinical trials (Table 1), and refined for specific purposes. The consensus group considered diagnostic criteria in three sections – clinical features, radiological criteria and microbiological criteria.

Clinical features

*a. Underlying diseases*

The majority of patients have prior or concurrent underlying pulmonary disease. Lung cavities in the lung caused by PTB, sarcoidosis, previous *Pneumocystis* pneumonia, bullae or lung cysts, lung abscess, pulmonary infarction, pulmonary fibrosis, healed abscess cavities, cavitary bronchogenic carcinoma, infection by non-tuberculous *Mycobacteria* are all possible risk factors for the development of CPA (*21,26–30*). In many countries, PTB was the most common prior disorder (*9*). Pulmonary mycobacterial infection is also the most common differential diagnosis.

*b. Duration*

Previous studies have used from one to six, and usually three, months as the duration of disease required to define CPA (Table 1). The consensus was to endorse a three-month duration as a criterion for diagnosis of CPA. In patients with pre-existing pulmonary disease, who often have chronic symptoms, a change in pattern or severity of clinical presentation is considered the trigger point for the three-month duration. In those with few or unchanged symptoms, documentation of 3 months duration may also be confirmed with radiographic findings of progression of cavitation, peri-cavitary infiltrates or fibrosis, development of fungal ball (which takes weeks to form), or microbiological data (see below).

*c. Symptoms*

The majority of patients with CPA have symptoms, although some patients are asymptomatic and only present with radiological progression. The most distinctive and alarming symptom is haemoptysis/haemosputum. About 12-43% of CPA patients develop haemoptysis (*23,25,31,32*), which varies from blood streaking in sputum to massive and fatal haemoptysis. Haemoptysis may be seen in tuberculosis, but is uncommon and usually not severe. Another characteristic symptom is mild but persistent chest pain, discomfort or ‘tightness’,,present in up to 37% of patients. Weight loss and fatigue are also very common, although not universal. Cough, usually productive, and dyspnea are very common, but not sufficiently distinctive to distinguish CPA from other pulmonary disorders, including PTB. Fever or pyrexia is uncommon in CPA patients, and if present, may indicate a concurrent or alternative diagnosis, or subacute invasive aspergillosis. Night or day sweats are occasionally reported, but are not discriminatory.

The consensus of the panel was that the diagnosis of CPA required the presence of one or more symptoms (as above) persisting for 3 months and radiological progression, a scenario present in most cases. Two other clinical scenarios that also qualify for the diagnosis of CPA are radiological evidence of a ‘simple’ aspergilloma, with or without symptoms, or asymptomatic but definite radiological progression.

Radiological criteria

The focus of the discussion revolved around the use of chest radiograph (CXR) alone to diagnose CPA; requirement of a CT scan that is often unavailable might delay diagnosis. Multiple studies have demonstrated that a CT scan is more sensitive than a CXR in demonstrating several features, namely: one or more fungal balls, pulmonary nodules, multiple cavities, and identifying disease in the apices and in the retro-cardiac space (*33*). Considering the limited availability of CT scanning in many health settings, the radiological criteria adopted are based solely on CXR findings. Where available, CT scan is recommended in the context of clinical and microbiological suspicion of CPA with a non-diagnostic CXR.

*a. Fungal ball or aspergilloma, intra-cavitary material or fluid level on CXR*

There is a limited differential diagnosis of a fungal ball in the lung: echinoccocal cyst, necrotizing bronchogenic carcinoma, acute or subacute invasive fungal infection. Occasionally a lung abscess, Rasmussen aneurysm in a tuberculous cavity, cavitating hematoma or lung infarct give similar appearances (*34*). If single and in a localized area of lung, with few or no symptoms, a simple aspergilloma is the most precise diagnosis (Figure 1), and may be resected, or observed without antifungal treatment. Although the presence of a fungal ball is highly suggestive of an aspergilloma as a manifestation of CPA, microbiological confirmation is required for a definitive diagnosis.

Occasionally cavities have a fluid level visible. Few of these cavities have been sampled with aspiration and microbiological analysis, but when this is done, they usually have a positive culture for *A. fumigatus*, or less commonly, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and other pathogens. Therefore, a fluid level in a cavity is entirely consistent with CPA, but may also represent co-infection (*35*).

*b. Cavitation*

The cardinal feature of CPA is presence of one or more cavities. These may be small or large, have thick, or less commonly thin walls, and usually abut the pleura (*33,36*). The cavities expand and may coalesce during progression of infection. In patients with extensive bullous emphysema, inflammation around a bulla may resemble cavitation. The differential diagnosis of chronic cavitary lesions includes mycobacterial infection, endemic fungal infection and malignancy (*37*). The cavities seen with CPA are often located in the upper lung zone, and may mimic tuberculosis; in non-tuberculous mycobacterial infection (NTM) and endemic fungal diseases the cavities may be located in any lung zone. A distinguishing feature of CPA is slow progression of findings over months or years, whereas active PTB infection progresses faster (*34,38*) (Figure 2). NTM infection may also present with cavitary lesions, however these are more common in older Caucasian men with underlying lung disease (*39*). Patients with residual coccidioidal or other infectious cavities are usually asymptomatic, unless complicated by aspergilloma or superinfected (*40*). Cavitary bronchogenic carcinoma usually presents with associated adenopathy, and often pleural effusion.

*c. Pleural thickening*

In the pre-CT scan era, pleural thickening was regarded as a sign of aspergilloma, and indeed pleural thickening is common in patients with CPA (*34,38*). On CT scan, ‘pleural thickening’ usually consists of two components in many patients: fibrosis of the pleura overlying a cavity or area of consolidation, and in-drawing of extra-pleural fat, typically seen in chronic inflammatory processes of the lung. This subtle distinction cannot be made readily on a CXR. Pleural thickening should be regarded as a common and useful feature of CPA. Furthermore, pleural thickening is a specific feature of CPA, and rarely seen in TB or chronic coccidioidal or other fungal cavities (*40,41*). Tuberculous empyema is usually manifest as a large pleural effusion (*42*) and commonly accompanied by interlobular septal thickening and micronodules (*43*). Cavitating bronchogenic carcinoma may invade the chest wall causing bone destruction, or cause diffuse pleural involvement, however these manifestations are distinct from the focal pleural thickening associated with CPA.

*d. Pericavitary infiltration*

The inflammatory changes seen adjacent to cavities in CPA are often marked, reflecting inflammation but not hyphal invasion. They may merge with localized areas of fibrosis and/or pleural thickening, but are usually obvious on plain CXR (*36*). They indicate active CPA disease and are a clear indication for therapy (*44*). Such pericavitary infiltrates are uncommon in reactivation TB and NTM disease, unless very extensive. Peri-cavitary consolidation may be seen in chronic fibrocavitary coccidioidomycosis (*40*).

*e. CT scan features*

One radiological aspect of CPA not characterized on a CXR is the interior of a cavity. *Aspergillus* grows inside the cavity along the wall, resulting in an irregular appearance of the inner border seen on CT. Additionally, the cavity may contain linear opacities representing mats of fungal growth that have detached from the cavity wall (*38*). These often merge to form sponge-like densities, which can be described as a fungal ball containing air (*45*). These structures may detach from the cavity wall, and may be mobile. For the purposes of the definitions outlined here, all these characteristic features are deemed to be ‘equivalent to a fungal ball’, and are illustrated in (figure 3. They resolve more readily with antifungal therapy than an aspergilloma.

One feature for which CT scan has much higher sensitivity for detection than CXR is the *Aspergillus* nodule, particularly when the nodule is small (*46*). These nodules vary in size from 5 to 50mm in maximum diameter, may be single or multiple, and may be solid or have central cavitation. Larger ‘nodules’ measuring more than 3 cm are more accurately described as masses, which may also be attributable to *Aspergillus* infection. The differential diagnosis of the *Aspergillus* nodule is broad including carcinoma (primary or secondary), coccidioidomycosis, cryptococcosis, NTM infection and others.

Resection or biopsy is usually required for establishing a definitive diagnosis of a nodule, especially since many patients do not have elevated *Aspergillus* IgG antibodies or positive sputum cultures (*47,48*). Because these diagnostic procedures are not available in many medical centres in LMICs, we have elected to consider these separately and not include them within our operational definition here.

Culture-based and non-culture based evidence of aspergillosis

The most reliable diagnostic test for CPA is a positive Aspergillus antibody test indicative of an immune response to *Aspergillus*. The second most reliable diagnostic marker for CPA is detection of *Aspergillus* in the airways using culture, antigen and/or nucleic acid amplification (PCR).

*a. Aspergillus antibody*

Elevated circulating *Aspergillus* antibodies are present in over 95% of patients, although not in 100% of cases (*49–51*). The majority of commercial assays detect IgG antibody to *A. fumigatus*; however CPA is occasionally caused by other *Aspergillus* spp. resulting in false negative results. Additionally, some patients with CPA are subtly immunocompromised as documented with poor pneumococcal or *Haemophilus* antibody (*52*), low circulating CD4 (T helper), CD19 (B cell) or CD56 (natural killer) cell counts (*53*), and/or poor production of gamma interferon, IL17A and/or IL12 (*54*). Such patients may not mount a detectable IgG antibody response. Many patients have detectable *A. fumigatus* IgE and an elevated total IgE, in the absence of any other features of allergic *Aspergillus* disease (*21*).

*Aspergillus* serology relies mainly on the detection of IgG and precipitating antibodies (known as precipitins) which may be IgG or IgM. Precipitins detection requires immunodiffusion and electrophoresis migration methods, which lack standardization and are too laborious and time-consuming for low resource settings. Consequently, we focused on commercially available enzyme immunoassay kits that detect IgG. Up to 2015, there were few comparisons of *A. fumigatus* serology (*55*), but more recently (Table 2). Crucial to these comparisons is defining the cut off values for each assay. The control groups of patients used for such comparisons have included healthy controls or those with pulmonary disease without aspergillosis. Few data on antibody titre related to age, HIV status or ethnicity in controls are available. New lateral flow devices for *Aspergillus* antibody are in the final stages of development and, if their performance is good, could greatly facilitate diagnosis. The consensus was that any *Aspergillus* antibody test performance had to be at least 90% sensitive and 85% specific.

An elevated *Aspergillus* IgG antibody is consistent with several conditions including *Aspergillus* rhinosinusitis, ABPA, *Aspergillus* bronchitis (notably in cystic fibrosis and bronchiectasis), subacute invasive aspergillosis, recovery from invasive aspergillosis, and community acquired *Aspergillus* pneumonia. Since an elevated IgG antibody is highly sensitive but not specific for CPA, the diagnosis of CPA requires the presence of compatible symptoms and radiological abnormalities.

*b. Respiratory tract microscopy and culture*

Microscopy of sputum may show hyphae morphologically consistent with *Aspergillus* spp. If present, this finding is most consistent with CPA or *Aspergillus* tracheobronchitis (*63*). Despite the substantial burden of *Aspergillus* spp. in the cavities of patients with CPA, culture positivity from sputum samples is lower than expected ranging from 41% to 81% and is probably biased towards culture positive cases (*21,22,64–67*). One reason for this lower sensitivity is the inoculation of culture plates with very small volumes of sputum (*65,68*), as is done for bacterial culture. Perhaps negative cultures reflect an inability of the fungus to adapt to *in vitro* conditions, despite the apparent ease with which environmental contamination occurs in the laboratory.

When positive, culture has significant merits, notably in identifying the *Aspergillus* species causing infection and allowing susceptibility testing. False positive cultures do occur as a result of laboratory contamination. While the majority of CPA cases are caused by *A. fumigatus* complex (probably *sensu stricto*), *A. niger* complex and *A. flavus* complex and rare cases caused by unusual pathogenic species are reported. In countries such as India, where *A. flavus* infection is much more common, it is not clear what proportion of cases are attributable to non-*fumigatus* species. The vast majority of triazole resistant isolates of *A. fumigatus* in CPA have arisen while on therapy, probably due to large fungal loads or low drug exposure (low dose, drug interactions, poor bioavailability) (*69*). Isolates may be resistant or have intermediate susceptibility to one, two, three or four triazoles.

*c. Aspergillus antigen and β-1,3-D-glucan detection*

Galactomannan is a detectable carbohydrate antigen produced by the growth of *Aspergillus* spp. Galactomannan detection is useful in the diagnosis of invasive aspergillosis, as it is often detectable in serum and bronchoalveolar lavage fluid (BAL). As tissue invasion does not occur in CPA and so galactomannan is not usually detectable in the serum of these patients. In patients with CPA, galactomannan is usually detectable in BAL fluid only (*59,70*). This is of limited utility in LMICs as fiberoptic bronchoscopy is infrequently done. Galactomannan is detectable in sputum or tracheal secretion/aspirate but the cut-off for positivity is not established (*71*).

A new simple lateral flow assay for different protein antigens specific to *A. fumigatus* has been commercialized but there are no data available on sputum detection or its utility in CPA. It is unlikely to be useful in serum, because of antibody masking, but may be useful in BAL fluid (*72,73*).

β-1,3-D-glucan is released by *Aspergillus* spp. (and many other fungi) during infection, but is less specific and likely not more sensitive than serum galactomannan in patients with CPA.

*d. Molecular detection of Aspergillus*

Detection of *Aspergillus* spp. in sputum by PCR is significantly more sensitive than culture in patients with CPA (*63*). However, the quality and possibly quantity of the sputum sample influences PCR performance (*71*). Furthermore, studies have shown that the sensitivity of PCR for detection of *Aspergillus* is ~ 80%. Depending on the cutoff value used, low specificity may also be an issue. Molecular assays for *Aspergillus* spp. are not routinely available in most medical centres worldwide, especially in LMIC.

Consensus definition and proposed algorithm

The definition of CPA recommended for use in low resource settings in shown in Table 3. In a patient presenting with symptoms over 3 months consistent with chronic *Aspergillus* infection, a CXR should be obtained (Figure 4). If a CXR is not possible, then PTB should be excluded. The CXR appearance determines the next course of action. If the CXR is normal, the symptoms may be caused by bronchiectasis or systemic disease. If the CXR shows consolidation without cavitation, then other diagnoses such as lung malignancy, airway obstruction, or endemic fungal infections should be considered. If the CXR shows cavitation, then work-up for possible PTB should be initiated according to national practice and standards. A positive result for PTB should lead to appropriate treatment. If the PTB results are negative, and especially if the radiographic findings include pleural thickening, fungal ball, and/or pericavitary fibrosis or infiltrates, a serum IgG antibody test for *Aspergillus* should be performed (Figure 4). If the *Aspergillus* IgG antibody test is negative (or unavailable), then sputum microscopy for hyphae or fungal culture should be performed – yield is higher with multiple specimens tested. If the sputum microscopy for hyphae or fungal culture is negative, then other diagnoses should be considered, such as atypical mycobacterial infection or endemic fungal infection. If the sputum microscopy for hyphae or culture is positive, or if serum *Aspergillus* antibody test is positive, then CPA is confirmed and treatment with itraconazole or voriconazole is advised (*19*).

**Conclusions**

We present adapted recommendations to diagnose CPA for clinical use and public health surveillance in resource constrained settings. The adapted definition relies on a combination of symptoms, chest X-ray features, and serological evidence of *Aspergillus* infection, and is applicable to almost all patient groups in which CPA may be found. Prospective evaluation of the proposed definition and associated algorithms will be important, in different geographical and HIV and PTB burden contexts (*74*). We believe that the proposed operational definition of CPA in LMICs will facilitate advancements in research & practice (clinical, laboratory, radiological and public health) and policy (health services and public health), both in LMICs as well as globally in resource constrained settings.

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**Declaration of interests:**

DWD and family hold Founder shares in F2G Ltd, a University of Manchester spin-out antifungal discovery company. He acts or has recently acted as a consultant to Astellas, Sigma Tau, Basilea, Scynexis, Cidara, Biosergen, Quintiles, Pulmatrix, Fujifilm, Zambon and Pulmocide. In the last 3 years, he has been paid for talks on behalf of Astellas, Dynamiker, Gilead, Merck, Mylan and Pfizer. He is a longstanding member of the Infectious Disease Society of America Aspergillosis Guidelines group, the European Society for Clinical Microbiology and Infectious Diseases Aspergillosis Guidelines group and the British Society for Medical Mycology Standards of Care committee. IDP has received research grants and / or test kit donations from Astellas, Siemens, Dynamiker, Serion/Virion, OLM Medical and Genesis. JC none, KJ, none; CMJ is a consultant to Canon Medical Research USA and author of UpToDate, Inc; MC has been paid for talks on behalf of Astellas, Gilead, and Pfizer; AAI has received grants from Gilead Sciences, Scynexis and F2G; she has been paid for talks on behalf of Gilead; FB, none; PB is a co-founder of Alergenetica SL, an immunotherapeutics company and Syngenics Ltd., a food diagnostics company and has current grant support from Medical Research Council, Fungal Infection Trust, EU Framework 7 and National Institutes of Health, AC, none; SG, none; JG, none; BH, none; MH has received a research grant from Gilead and served on the speakers’ bureau of Gilead, Basilea and Merck; MI, none; NI, none; KI has received research grant and honorarium from Pfizer Japan Inc., MSD K.K., Astellas Pharma, Inc., and Dainippon Sumitomo Pharma Co.; BK, none; VM, none; SM, none; ROO has received honorarium from Pfizer, Nigeria; MDR acts as a consultant for Gilead Sciences, MSD, Pfizer, Astellas, Basilea and Pulmocide and is a member of the European Society for Clinical Microbiology and Infectious Diseases Aspergillosis Guidelines Group; JLRT, none; AR, none; HJFS received honorarium from Chiesi and travel grants from Gilead; RS, none; NFS, none; AS, none; CS has received grant or conference support from Fungal Infection Trust, European Society for Clinical Microbiology and Infectious Diseases and MSD; FS, none; BAPW, none; DCC, none; HG, none.

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|  | **Publications (first author, date)** | | | | | |
| **Parameter** | **Denning 2003 21** | **Kohno 2010 22** | **Cadranel 2012 23** | **Ohba 2012 24** | **Jhun 2013 25** | **Denning 2016 19** |
| Symptoms | At least one of the following for 3 months:-   * weight loss * productive cough * haemoptysis   plus absence of ‘overt immunosuppression’ | At least one of the following (no duration specified):-   * Fever * Weight loss * Sputum * Cough * Haemoptysis * Fatigue * Shortness of breath | Performance status 1-2 | All of the following required for 1-6 months:-   * Fever * Cough * Sputum production * Weight loss | At least one of the following for 3 months:-   * weight loss * productive cough * haemoptysis   plus absence of ‘overt immunosuppression’ | "Significant pulmonary and / or systemic symptoms for 3 months or more”  No specific symptoms listed. |
| Radiology | At least one of the following:-   * cavitary lesion with paracavitary fibrosis * New or expanding cavity on serial imaging | At least one of the following:-   * New infiltrates * Cavity formation * Expansion of pre-existing cavities   With or without the following   * Peri-cavitary infiltrates * Adjacent pleural thickening | Compatible chest CT scan or photographically confirmed endoscopic lesion | Cavitary pulmonary lesion with evidence of paracavitary infiltrates and adjacent pleural thickening with/without fungal ball | At least one of the following:-   * Cavitary lesion with paracavitary fibrosis * New or expanding cavity on serial imaging | Both of the following required:-   * One or more pulmonary cavities with either thick or thin wall, possibly containing aspergilloma or irregular intra-luminal material * Overt radiological progression over 3 months or more required (new cavities, increasing pericavitary infiltrates or increasing fibrosis) |
| *Aspergillus* antibody / culture | Either:-   * Positive precipitins * Culture from pulmonary or * pleural cavity | At least one of the following:-   * Platelia serum galactomannan index >1.0 * Positive precipitins * Positive (1,3)-β-D-glucan * Evidence of *Aspergillus* spp. by molecular diagnosis, culture or pathological findings | Positive serological test required by both of the following:-   * Precipitins by CIE with at least 2 lines * Second serological test positive by any method   AND  Microbiological evidence by one of the following sources from BAL or sputum samples:-   * 2 or more positive cultures * One positive culture and positive microscopy | Culture from sputum or BAL mandatory, antibodies not required | Either:-   * Raised *Aspergillus*-specific IgG * Culture from pulmonary or * pleural cavity | If fungal ball present either *Aspergillus*-IgG / precipitins or “other evidence of *Aspergillus*”.  If no fungal ball but one or more cavities then any of the following acceptable   * *Aspergillus-*specificIgG * *Aspergillus* precipitins * “Strongly positive” *Aspergillus* antigen or DNA in respiratory fluids * Percutaneous or excision biopsy showing fungal hyphae on microscopy * Growing *Aspergillus* “from a cavity”   The following tests on “respiratory samples” are not sufficient in isolation: Culture, PCR, microscopy |
| Inflammatory markers | Raised levels of either:-   * CRP * ESR * Plasma viscosity | At least one of the following raised:-   * WBC count * CRP * ESR | Not required | Not required:- | Raised levels of either:-   * CRP * ESR | Not required |
| Exclusion of other pathogens | Required with the following listed examples:-   * Mycobacteria * Endemic mycoses | Lack of improvement with at least 3 days of broad spectrum antibiotics required  Patients with infectious diseases other than aspergillosis excluded | Not required | Required with the following listed examples:-  TB  other mycoses  Wegener’s  ABPA  invasive aspergillosis  simple aspergilloma | Not specifically required | Required, with the following listed examples:-   * Tuberculosis * Atypical mycobacteria * Necrotising lung cancer * Pulmonary infarction * Vasculitides * Rheumatoid nodule * Histoplasmosis / coccidioidomycosis / paracoccidioidomycosis in those with a relevant travel history |
| Comment |  |  |  | This definition includes CNPA cases with 1-3 months symptoms  Note precipitins sensitivity even lower than culture  Pleural thickening appears to be a mandatory criteria |  |  |

**Table 1**: Published diagnostic features and criteria for chronic pulmonary aspergillosis

\*BAL = bronchoalveolar lavage

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Reference | Study Population | Assay | Cut-off | Sensitivity (%) | Specificity (%) | ROC/AUC  [95%IC] |
| Kitasato  2009 (*56*) | 28 CPA | DD Microgen | --- | 89.3 | --- | --- |
|  |  | Bio-Rad  galactomannan | GM index >0.5 | 50 | --- | --- |
| Guitard  2012 (*57*) | 51 CPA and 341 Controlsa | Biorad Platelia  Aspergillus IgG | 10 AU/ml | 90.2 | 89.6 | --- |
|  |  | Serion/Virion  ELISA classic Aspergillus IgG | 70 AU/ml | 88.8 | 84.4 | --- |
| Jhun  2013 (*25*) | 49 Simple aspergilloma | IBL Culture  Filtrate ELISA | --- | 99 | --- | --- |
|  |  | Bio-Rad  galactomannan | GM index >0.5 | 23 | --- | --- |
| Baxter  2013 (*58*) | 116 CPA | Biorad Platelia  Aspergillus IgG | 10 AU/ml | 86 | --- | --- |
|  |  | ThermoFisher Scientific Immunocap | 40 mg/l | 85 | --- | --- |
|  |  | DD |  | 56 | --- | --- |
| Shin  2014 (*59*) | 168 CPA | Bio-Rad  galactomannan | GM index >0.5 | 23% | --- | 0.538  [0.496-0.580] |
|  |  | DD | --- | 98% | --- | --- |
| Oliva  2015 (*60*) | 89 CPA,  10 aspergilloma and,  212 blood healthy donors | Aspergillus  Western blot IgG kit | --- | CPA: 91.0  Aspergilloma: 90.0 | --- | --- |
| Page  2016b (*49*) | 241 CPA and  100 Ugandan blood donors | Dynamiker | 65 AU/ml | 77 | 97 | 0.918  [0.89-0.946] |
|  |  | Genesis Aspergillus IgG ELISA Kit | 20 AU/ml | 75 | 99 | 0.902  [0.871-0.933] |
|  |  | Immulite Siemens | 10 mg/l | 96 | 98 | 0.991  [0.982-1] |
|  |  | ThermoFisher Scientific Immunocap | 20 mg/l | 96 | 98 | 0.996  [0.992-1] |
|  |  | Serion / Virion ELISA classic Aspergillus IgG | 35 AU/ml | 90 | 98 | 0.973  [0.96-0.987] |
|  |  | Precipitins (Microgen) | --- | 59 | 100 | --- |
| Dumollard  2016 (*50*) | 17 simple aspergilloma,  62 CPA, 25 CNPA, and 205 controlsc | Bordier | OD > 1 | Simple aspergilloma: 95.6  CPA: 97.4  CNPA: 100 | 90.3 | 0.997  [0.962-0.991] |
|  |  | Biorad Platelia  Aspergillus IgG | 10 AU/ml | Simple aspergilloma: 95.6  CPA: 97.4  CNPA: 100 | 91.3 | 0.951 [0.928-0.974] |
|  |  | Serion / Virion ELISA classic Aspergillus IgG | 70 AU/ml | Simple aspergilloma: 78.3  CPA: 82.0  CNPA: 82.9 | 81.5 | 0.897 [0.863-0.931) |
| Fujiuchi  2016 (*51*) | 51 possible CPA,  96 proven CPA and,  122 controlsd | ThermoFisher Scientific Immunocap | 50 mg/l | Possible CPA: 39.2  Proven CPA: 97.9 | --- | 0.94 [0.912-0.972] |
| Page 2018a (61) | 241 CPA cases  152 healthy Dutch controls | Siemens Immulite | 25 mg/L | 92.9 | 99.3 | 0.948 [0.921-0.975] |
|  | 241 CPA cases  141 healthy Belgian controls | Thermo Fisher Scientific ImmunoCAP | 50 mg/L | 83.8 | 95.6 | 0.956 [0.937-0.974] |
|  | 241 CPA cases  222 healthy French controls | Serion | 50 U/ml | 84.2 | 91 | 0.944 [0.925-0.964] |
|  | 118 CPA cases  222 healthy French controls | Bio-Rad | 1.5 AU/ml | 93.2 | 98.2 | 0.955 [0.922-0.988] |
| Page 2018b (62) | 241 CPA cases  299 healthy Ugandan controls | Siemens Immulite | 15 mg/L | 94.6 | 98 | 0·984 [0·972-0·997] |
|  | 241 CPA cases  398 Ugandans with treated tuberculosis | Siemens Immulite | 15 mg/L | 94.6 | 94.5 | 0·972 [0·959–0·985] |
|  | 241 CPA cases  234 Ugandans with treated tuberculosis, radiologically screened for CPA | Siemens Immulite | 25 mg/L | 92.9 | 98.7 | 0·979 [0·967–0·992] |

a Control population included 26 patients with *Aspergillus* bronchial colonization, 44 patients with a single positive *Aspergillus* culture considered as colonization, 49 patients with negative microbiological results and 222 pregnant women.

b ROC/AUC results for ImmunoCAP are reported according to the cut off of 40mg/l.

c Control groups: 14 patients colonized with *Aspergillus* and 191 patients with respiratory symptoms.

d Possible CPA: *Aspergillus* precipitin negative and a persistently elevated inflammation marker; Proven CPA: *Aspergillus* precipitin positive and a persistently elevated inflammation marker; Controls: Other chronic respiratory disease (any Aspergillus precipitin and temporary elevated inflammation marker).

**Table 2: Performance of commercially available *Aspergillus* serology diagnostic tests in CPA.**

CPA: Chronic Pulmonary Aspergillosis, CNPA: Chronic Necrotising Pulmonary aspergillosis, DD: double diffusion (precipitins), IgG: immunoglobulin G, ELISA: enzyme immunoassay, GM: Galactomannan, ROC/AUC: Receiver operator Curve/Area under curve, IC: interval of confidence, OD: Optical Density.

**Table 3**

**Final consensus definition**

Consensus was built around the following definition of CPA in resource limited settings was agreed through participant consensus:

1 - Symptoms for 3 months or longer (haemoptysis and/or persistent cough, and/or weight loss) (other symptoms are common, but not required, notably fatigue, chest pain and sputum production)

AND

2 - Radiological features (progressive cavitation on chest imaging AND/OR intracavitary fungal ball AND/OR pleural thickening or pericavitary fibrosis or infiltrates all adjacent to cavities)

AND

3 - Microbiological evidence of *Aspergillus* infection (positive *Aspergillus*-specific IgG and/or sputum microscopy showing hyphae consistent with *Aspergillus* and/or *Aspergillus* growth on 2 or more sputum or other respiratory samples)

AND

4. Mycobacterial infection should be ruled out with smear, GeneXpert and/or mycobacterial culture. It is possible for mycobacterial infection and CPA to be present concurrently, but this diagnosis requires characteristic radiological findings on CT scan that are not present with PTB including pleural thickening, a fungal ball or other intra-cavitary material, or marked peri-cavitary infiltrates in addition to a positive *Aspergillus* IgG antibody test.

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**Figure legends:**

Figure 1. Early features of fungal ball formation in pulmonary cavities.

A. Two left lower lobe posterior thick-walled cavities, one with a fluid level. B. Two right apical cavities, the larger with an irregular interior wall, most consistent with fungal growth. C. Left apex replaced by an irregular thick walled cavity with multiple areas of fungal growth on the interior surface of the cavity. D. Significant volume loss in the right upper lobe with replacement by a small anterior cavity and larger crescent-shaped cavity with both pleural thickening and fat indrawing along the pleural surface posteriorly. The cavity shows marked irregularity consistent with fungal growth. E. A right upper lobe thin walled cavity containing 2 areas of fungal growth, one of which has detached from the wall as a thick mat of mycelial growth with a larger ‘lump’ in the cavity interior. F. Multiple cavities in both upper lobes, with wall irregularity in the left upper lobe cavity consistent with surface fugal growth. The right upper lobe cavity shows both pleural thickening and in-drawing of fat posteriorly.

Figure 2. Aspergilloma (fungal ball) in the left upper lobe. Axial CT image shows increased density in an irregular left apical cavity that was a sequela of PTB, consistent with an aspergilloma.

Figure 3. Chronic pulmonary aspergillosis (CPA). A. Left upper lobe thick-walled cavity, with associated pleural thickening. B. Several months later, there is progression of cavitation with increased peri-cavitary consolidation and formation of a fungal ball within the cavity. Aspergilloma formation is a late feature of CPA.

Figure 4. Diagnostic algorithm incorporating the chest radiographic appearance and result of rapid TB investigations with the case definition of chronic pulmonary aspergillosis.