GAFFI Fact Sheet

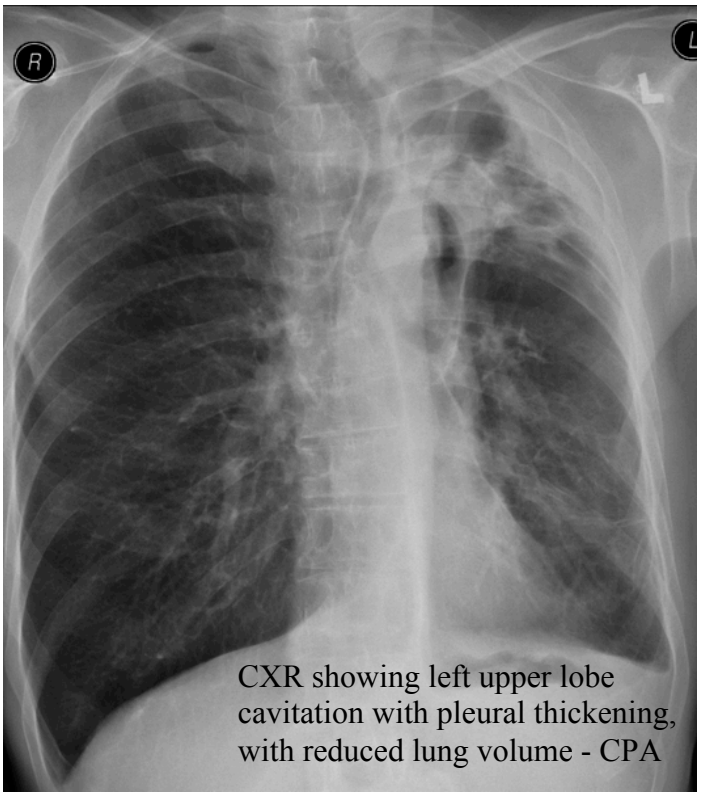
TB and its sequela chronic pulmonary aspergillosis (CPA)

Summary

CPA is a slowly destructive lung infection, with marked systemic features (weight loss, fatigue) and pulmonary features (productive cough, haemoptysis, breathlessness) almost indistinguishable from TB. CPA presents like 'smear negative TB'. It usually follows a pulmonary insult, especially TB, sarcoidosis, pneumothorax and emphysema/COPD). Most patients are not immunocompromised, although HIV infection may be present. Some patients have subtle immune defects including reduced natural killer, T helper and/or B cells and sometimes reduced gamma interferon or interleukin 12 production. Rates of progression vary, but worsening symptoms and lung destruction or fibrosis occur over many months or years. The key diagnostic features are cavitary lung lesions on radiology, sometimes containing a fungal ball (aspergilloma) and elevated serum *Aspergillus* antibody. A simple aspergilloma (<10% of cases) is best surgically removed. Antifungal therapy is effective at controlling symptoms and progression in about 60% of patients. Untreated mortality is 75-80% over 5 years, reduced to ~40% with long term antifungal therapy. Estimates suggest a prevalence of ~1.2M CPA cases after pulmonary TB, and probably ~3 million overall.

Prevalence

The prevalence of CPA is not known with confidence. In the late 1960s, one year after completion of anti-TB treatment in the UK, 25% of 544 patients with a residual cavity had *Aspergillus* antibodies and at least 14% CPA (aspergilloma) on chest Xray. On resurvey three years later, 34% of all patients had developed *Aspergillus* antibodies, >20% had CPA and 42% of these were coughing up blood. Overall 63% of patients with *Aspergillus* antibodies developed CPA with an aspergilloma within 3 years [1,2].



CXR showing left upper lobe cavitation with pleural thickening, with reduced lung volume - CPA

In Japan 20% of treated TB patients had antibodies to *Aspergillus* [3]. Two surveys in India showed *Aspergillus* antibodies in 23% and 25% of patients with "chronic lung diseases", 90% of whom had had prior TB [4,5]. In Brazil 65% patients at a tertiary chest clinic with positive *Aspergillus* antibodies had an

aspergilloma [6]. Most patients with 'recurrent TB' in Iran had *Aspergillus* antibody detectable [7].

Based on this data and global modeling of TB, the global CPA prevalence was estimated at between 0.8 and 1.37 million, after tuberculosis (Table) [8]. It does not account for cases mis-diagnosed as TB initially or CPA complicating other underlying conditions.

Table. Relative frequency of pulmonary tuberculosis and CPA for countries with populations exceeding 50M (population 2005 and TB data 2007).

Country	**Population (2005)**	**Annual pulmonary TB cases, alive at 1 year**	**Estimated annual CPA caseload from TB**	**5 year estimated CPA prevalence from TB**	**5 year prevalence rate per 100,000 population**
Global total	6,512,276,000	5,899,619	372,385	1,173,881	18.0
China	1,312,253,000	1,052,925	67,387	212,427	16.2
India	1,130,618,000	1,297,047	83,011	261,679	23.1
USA	302,741,000	8,907	588	1,853	0.6
Indonesia	219,210,000	420,853	26,935	84,907	38.7
Brazil	186,075,000	70,789	5,663	17,852	9.6
Pakistan	165,816,000	204,955	13,117	41,350	24.9
Bangladesh	153,122,000	243361	15,575	49,098	32.1
Russia	143,470,000	116,234	7,439	23,450	16.3
Nigeria	140,879,000	299,297	19,155	60383	42.9
Japan	127,449,000	17,724	1,134	3,576	2.8
Mexico	105,330,000	15,326	981	3,092	2.9
Philippines	85,496,000	216,228	13,839	43,624	51.0
Vietnam	84,074,000	97,497	3412	10,757	12.8
Germany	82,409,000	3,339	100	316	0.4
Egypt	77,154,000	9,266	593	1,869	2.4
Ethiopia	74,661,000	124,710	7,981	25160	33.7
Turkey	71,169,000	11,042	707	2,228	3.1
Iran	70,765,000	9278	594	1,872	2.6
Thailand	65,946,000	64,566	4,132	13,026	19.8
France	61,013,000	5,517	166	522	0.9
UK	60,261,000	4,189	118	370	0.6
Congo (DR)	59,077,000	125,538	8,034	25,327	42.9
Italy	58,645,000	2,807	84	265	0.5

Since then, a cross-sectional study of TB patients in Nigeria, found both HIV positive and negative patients had CPA (8.7%), with the highest proportion (19%) in smear and GeneXpert negative, HIV negative patients[9]. In Uganda, a 2 year prospective study in 285 patients who had had TB 2-7 years earlier, found CPA present in 14 (4.9%, 95% CI 2.8–7.9%)[10]. CPA was significantly more common in those with chest radiography cavitation (26% versus 0.8%; $p<0.001$), but possibly less frequent in HIV co-infected patients (3% versus 6.7%; $p=0.177$). The annual rate of new CPA development between surveys was 6.5% in those with chest radiography cavitation and 0.2% in those without ($p<0.001$). Series of CPA patients have been reported from China and Hong Kong [11-13], India [14], Korea [15], Japan [16], Cuba [17], France [18-19], Spain [20] and UK [21] in the years 2017-2019.

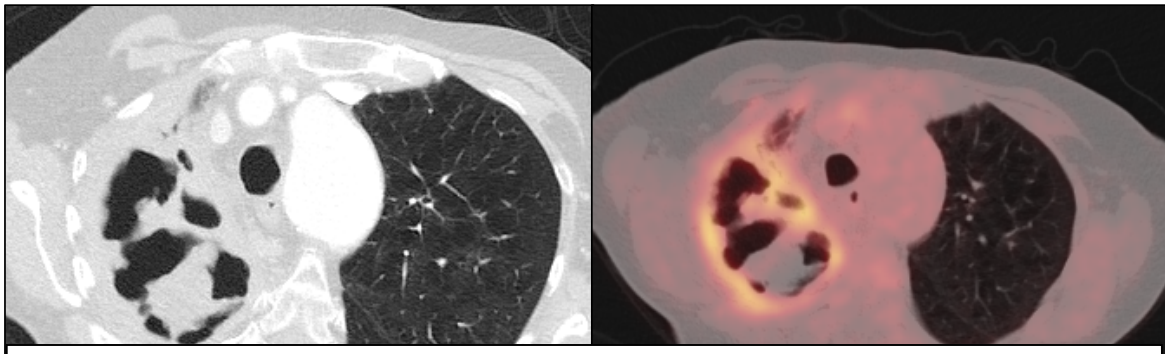
In countries with a high pulmonary TB incidence, TB is the dominant underlying disease accounting for up to 80% of cases [22]. When pulmonary TB is less frequent, other pulmonary disorders are more important, notably COPD and non-tuberculous mycobacterial infection, and prior TB was present in <20% of cases [22]. Overall therefore, a provisional prevalence estimate of 3 million CPA patients was made [23].

Clinical presentation

Patients with chronic pulmonary aspergillosis present most commonly with weight loss, chronic productive cough, hemoptysis of variable severity, significant fatigue, and/or shortness of breath [23, 24]. Fever, night sweats and chest discomfort occur occasionally. The systemic symptoms of chronic cavitary pulmonary aspergillosis are an important point of distinction from a simple aspergilloma, in which these do not occur [25].

Radiology

Radiographic examination usually reveals one or more cavities, typically within the upper lobes, which may or may not contain fungus balls [24,26]. Pleural thickening is common.



Matching CT and PET scan from a woman with CPA showing remarkable inflammatory response in the pleura and multiple cavities with an irregular inside surface

A simple aspergilloma is a fungus ball in a single pulmonary cavity with limited surrounding inflammation, pleural thickening, or fibrosis, and few symptoms [25]. Chronic cavitary pulmonary aspergillosis usually begins as ill-defined regions of consolidation that progress to form clearly defined cavities [23,24,26]. Cavities may contain fungus balls, debris, or fluid. There are often multiple cavities of different sizes. The interior of the cavity may show marked irregularity, representing fungal growth on the cavity wall. Cavities may be thick- or thin-walled. Pleural thickening is common but not universal. New cavity formation or expansion of one or more existing cavities over time is highly characteristic, and typically occurs over months in the absence of treatment.

Some patients get *Aspergillus* nodules – which may be single or multiple, and occasionally cavitate [27]. Some are asymptomatic, others are associated with many pulmonary symptoms and haemoptysis.

Chronic fibrosing pulmonary aspergillosis [28], otherwise known as 'destroyed lung' is a late stage of disease and characterized by the same radiographic findings that occur with chronic cavitary pulmonary aspergillosis in combination with significant fibrosis.

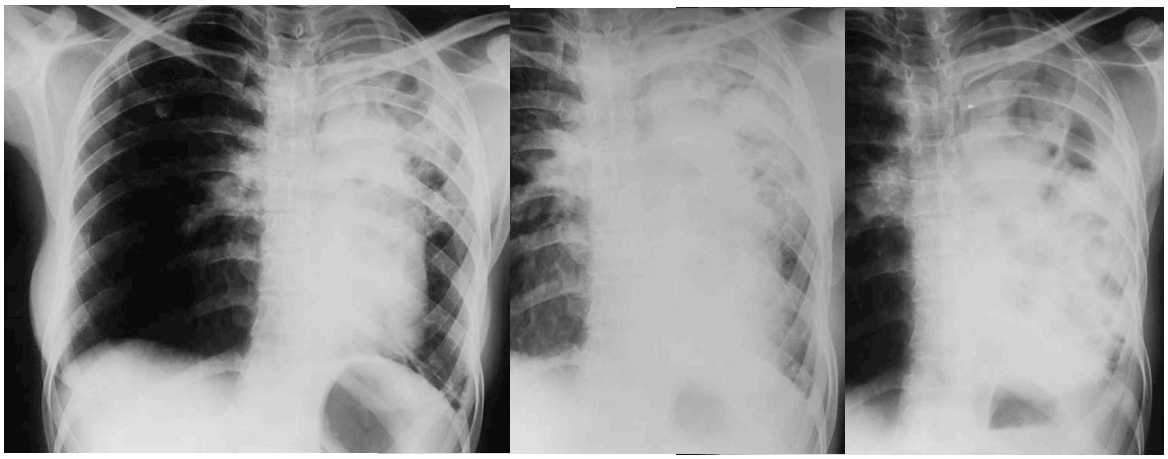
Diagnosis

The key test for CPA is a positive *Aspergillus* antibody test (precipitins) in serum [24, 26]. The best tests have >90% sensitivity and a 85% specificity [11,19,26]. An affordable new lateral flow device with excellent performance characteristics has recently been commercialized [19,29]. Raised inflammatory markers (CRP, plasma viscosity or ESR) are seen in about 50% of patients [23]. *Aspergillus* antigen is sometimes detectable in serum, but usually in bronchoalveolar lavage [14,30], and in sputum, but the cut-off is much higher [31]. Cultures are positive for *Aspergillus* spp. (usually *A. fumigatus*) in~25% of patients [24]. *Aspergillus* PCR is more often positive (~80%) [31-33]. Guidelines on diagnosis, including radiological features, are published [24], and for low resource settings an algorithm is now available for diagnosis [26].

Many patients have some degree of impaired immunity. Low T helper, B cell and/or natural killer cells are frequent [34]. Low pneumococcal and *Haemophilus* antibodies are frequent and usually partially responsive to conjugate vaccine [35]. Poor production of gamma interferon or interleukin 12 (which is required to produce gamma interferon) is common in the more complex patients. Multiple genetic variants are also described.

Typical untreated example

An example of a Gujerati woman who had had TB and developed CPA was diagnosed in 1992 [23]. Without treatment, she lost the function of her whole left lung (chronic fibrosing pulmonary aspergillosis) over 5 years and subsequently died. In contrast other patients have remained well on treatment for 20+ years.



1992 1994 1997

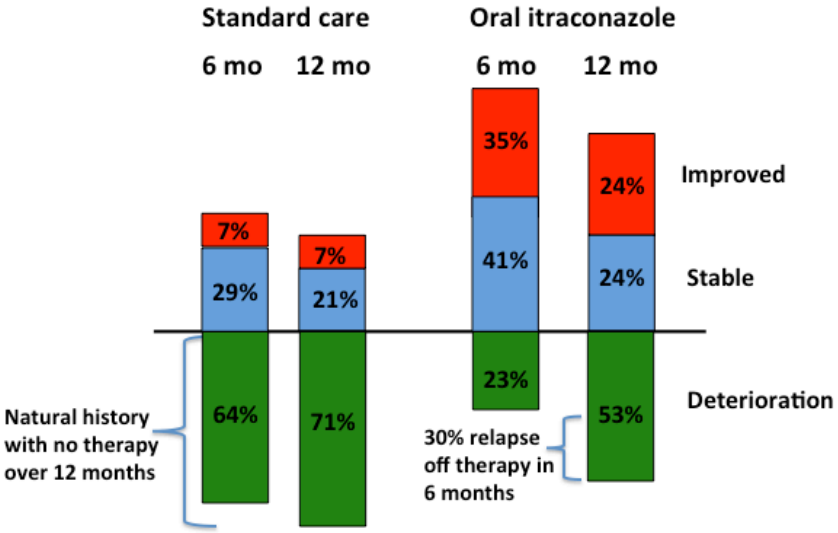
Management

Simple aspergilloma should be resected, usually requiring a lobectomy [36]. Survival rates after such surgery is excellent, if patients are carefully selected [12,36-38]. About 5% of patients with CPA are immediately suitable for resection surgery. Recurrence does occur in >25% of cases [39]. Surgery in patients with multicavity disease who are

systemically unwell, has a considerable mortality and morbidity, and is rarely curative.

Antifungal therapy with oral itraconazole is about 60-70% effective in improving or stabilising symptoms and arresting progression [16,21,24,]. Response and deterioration rates documented in an RCT comparing oral itraconazole (400mg daily) with standard care over 6 months, followed by 6 months of follow up [40] is shown in the figure below. Of those on standard care, 61% deteriorated at 6 months and 71% at 12 months. In contrast, 76% of patients improved or stabilized on itraconazole. Discontinuation of itraconazole lead to a 30% relapse rate 6 months later. Voriconazole therapy is probably slightly superior in terms of later deterioration [16,41] and a reduced rate of azole resistance emergence [21], especially in those with large fungal balls.

Response can be assessed by symptom reduction, weight gain, reduced fatigue, falling inflammatory markers and *Aspergillus* IgG antibody titre [21,24], and reduction in pleural thickening on CT scanning or chest radiograph [42].

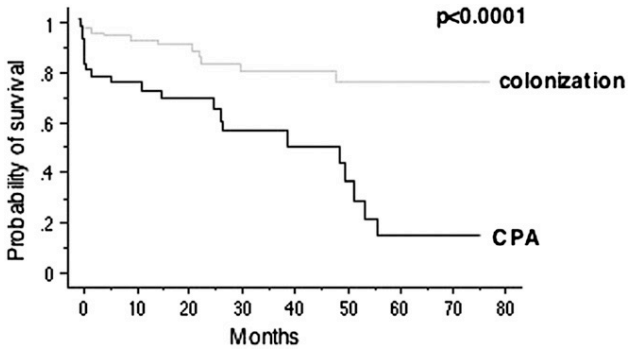


Similar response rates are seen with IV amphotericin B (short term), IV micafungin (short term), IV caspofungin (short term), oral voriconazole, oral posaconazole and oral isavuconazole [24]. Therapy needs to be long term (> 6 months) [21]. Drug interactions are problematic, especially rifampicin, anticonvulsants, some anti-retroviral agents and cardiac drugs. Itraconazole and pan-azole resistance in *A. fumigatus* occurs in some patients, and this is difficult to treat [24].

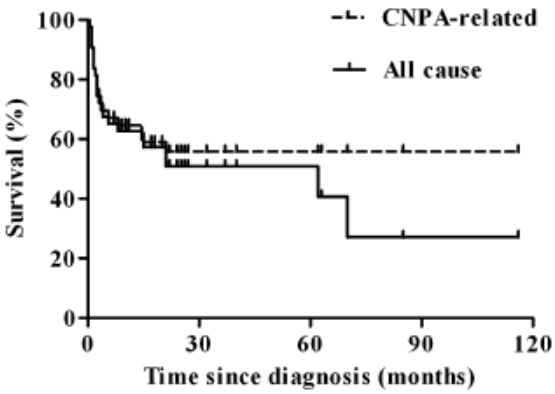
Outcome

Recent series indicate a steep mortality shortly after presentation, with stabilization over time [43,44], probably because of antifungal therapy and a less severe phenotype (slower progressors). Continuous antifungal therapy with emergence of resistance probably prolongs survival [45].

Japanese mortality data [43]

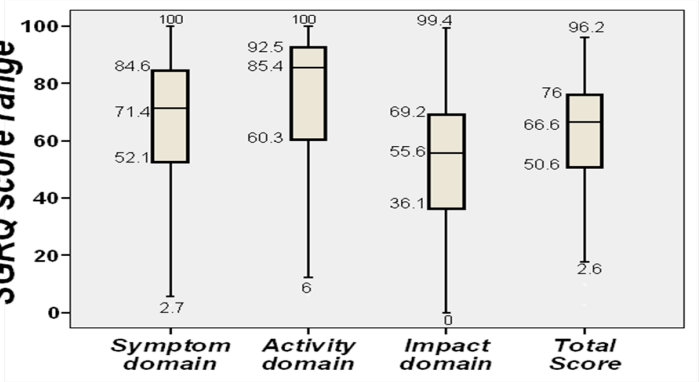


Korean mortality data [44]



Morbidity impact

The impact of CPA on quality of life is can be measured with the St George's Respiratory Score which ranges from 1 (excellent health) to 100 (extremely ill). The spread of scores is shown in this prospectively collected data from a large cohort of UK patients (n=88) [41]. Responders get good improvements in their quality of life [21].



Key questions and observations:

- CPA is a global disease but prevalence data show some variability in frequency, depending in part on local pulmonary TB incidence and probably COPD prevalence. More prevalence studies are required.
- The impact of HIV infection on prevalence and diagnosis is not well studied.
- Substantial numbers of smear negative TB cases don't have TB but have CPA, but this is not yet well assessed.
- Dual mycobacterial (TB and NTM) infections are difficult to manage and need more study and new non-interacting antifungal agents.
- A new lateral flow assay for *Aspergillus* IgG antibody is now available and could transform diagnosis.
- Oral antifungal therapy is partially successful (~60%), but azole resistance is an issue.
- Progression rates vary and some patients need really aggressive therapy, others are stable for long periods.

David Denning
The University of Manchester and GAFFI
August 2019

References

1. Research Committee of the British Tuberculosis Association. Aspergillus in persistent lung cavities after tuberculosis. Tubercle 1968;49:1-11

2. Research Committee of the British Tuberculosis Association. Aspergilloma and residual tuberculous cavities--the results of a resurvey. Tubercle 1970; 51:227.

3. Iwata H, Miwa T, Takagi K. [Tuberculosis sequelae: secondary fungal infections]. Kekkaku 1990; 65: 867–71.

4. Kurhade, A.M. et al., 2002. Mycological and serological study of pulmonary aspergillosis in central India. Indian J Med Microbiol 2002;20:141–4.

5. Shahid, M., Malik, A. & Bhargava, R., 2001. Prevalence of aspergillosis in chronic lung diseases. Indian J Med Microbiol 2001;19:201–5.

6. Ferreira-Da-Cruz MF, Wanke B, Pirmez C, Galvão-Castro B. *Aspergillus fumigatus* fungus ball in hospitalized patients with chronic pulmonary disease. Usefulness of double immunodiffusion test as a screening procedure. Memórias do Instituto Oswaldo Cruz 1988;83: 357–60.

7. Hedayati MT, Azimi Y, Droudinia A, Mousavi B, Ahmadi A, Khalilian A, Hedayati N, Denning DW. Prevalence of chronic pulmonary aspergillosis in patients with tuberculosis from Iran. Eur J Clin Microbiol Infect Dis 2015;34:1759-65.

8. Denning DW, Pleuvry A, Cole DC. Global burden of chronic pulmonary aspergillosis as a sequel to tuberculosis. Bull WHO 2011;89:864-72.

9. Oladele RO, Irurhe NK, Foden P, Akanmu AS, Gbaja-Biamila T, Nwosu A, Ekundayo HA, Ogunsola FT, Richardson MD, Denning DW. Chronic pulmonary aspergillosis as a cause of smear-negative TB and/or TB treatment failure in Nigerians. Int J Tuberc Lung Dis 2017;21:1056-1061.

10. Page ID, Byanyima R, Hosmane S, Onyachi N, Opira C, Opwonya J, Sawyer R, Richardson MD, Sawyer R, Sharman A, Denning DW. Chronic pulmonary aspergillosis commonly complicates treated pulmonary tuberculosis with residual cavitation. Eur Resp J 2019 53: 1801184.

11. 1: Li H, Rui Y, Zhou W, Liu L, He B, Shi Y, Su X. Role of the Aspergillus-Specific IgG and IgM Test in the Diagnosis and Follow-Up of Chronic Pulmonary Aspergillosis. Front Microbiol. 2019 Jun 25;10:1438.

12. He B, Wan C, Zhou W, Rui Y, Shi Y, Su X. Clinical profile and surgical outcome for different types of chronic pulmonary aspergillosis. Am J Transl Res. 2019;11:3671-3679.

13. Chan JF, Lau SK, Wong SC, To KK, So SY, Leung SS, Chan SM, Pang CM, Xiao C, Hung IF, Cheng VC, Yuen KY, Woo PC. A 10-year study reveals clinical and laboratory evidence for the 'semi-invasive' properties of chronic pulmonary aspergillosis. Emerg Microbes Infect 2016;5:e37.

14. Sehgal IS, Dhooria S, Choudhary H, Aggarwal AN, Garg M, Chakrabarti A, Agarwal R. Utility of Serum and Bronchoalveolar Lavage Fluid Galactomannan in Diagnosis of Chronic Pulmonary Aspergillosis. J Clin Microbiol 2019;57(3). e01821-18.

15. Jhun BW, Jung WJ, Hwang NY, Park HY, Jeon K, Kang ES, Koh WJ. Risk factors for the development of chronic pulmonary aspergillosis in patients with nontuberculous mycobacterial lung disease. PLoS One 2017;12:e0188716.

16. Tashiro M, Takazono T, Saijo T, Yamamoto K, Imamura Y, Miyazaki T, Kakeya H, Ando T, Ogawa K, Kishi K, Tokimatsu I, Hayashi Y, Fujiuchi S, Yanagihara K, Miyazaki Y, Ichihara K, Mukae H, Kohno S, Izumikawa K. Selection of oral antifungals for initial maintenance therapy in chronic pulmonary aspergillosis: A longitudinal analysis. Clin Infect Dis. 2019 Apr 9. pii: ciz287. doi: 10.1093/cid/ciz287.

17. Beltrán Rodríguez N, San Juan-Galán JL, Fernández Andreu CM, María Yera D, Barrios Pita M, Perurena Lancha MR, Velar Martínez RE, Illnait Zaragozí MT, Martínez Machín GF. Chronic Pulmonary Aspergillosis in Patients with Underlying Respiratory Disorders in Cuba-A Pilot Study. J Fungi (Basel) 2019;5: 18.

18. Uzunhan Y, Nunes H, Jeny F, Lacroix M, Brun S, Brillet PY, Martinod E, Carette MF, Bouvry D, Charlier C, Lanternier F, Planès C, Tazi A, Lortholary O, Baughman RP, Valeyre D. Chronic pulmonary aspergillosis complicating sarcoidosis. Eur Respir J.2017;49(6).

19. Piarroux RP, Romain T, Martin A, Vainqueur D, Vitte J, Lachaud L, Gangneux JP, Gabriel F, Fillaux J, Ranque S. Multicenter Evaluation of a Novel Immunochromatographic Test for Anti-aspergillus IgG Detection. Front Cell Infect Microbiol 2019;9:12.

20. Aguilar-Company J, Martín MT, Goterris-Bonet L, Martinez-Marti A, Sampol J, Roldán E, Almirante B, Ruiz-Camps I. Chronic pulmonary aspergillosis in a tertiary care centre in Spain: A retrospective, observational study. Mycoses 2019;62:765-772.

21: Bongomin F, Harris C, Hayes G, Kosmidis C, Denning DW. Twelve month outcomes of 206 patients with chronic pulmonary aspergillosis. PLoS One 2018;13: e0193732.

22. Smith N, Denning DW. Underlying pulmonary disease frequency in patients with chronic pulmonary aspergillosis. Eur Resp J 2011;37:865-72.

23. Global Action Fund for Fungal Infections. 95-95 by 2025. Improving outcomes for patients with fungal infections across the world; A roadmap for the next decade. May 2015 www.gaffi.org/roadmap/

23. Denning DW, Riniotis K, Dobrashian R, Sambatakou H. Chronic cavitary and fibrosing pulmonary and pleural aspergillosis: Case series, proposed nomenclature and review. Clin Infect Dis 2003;37 (Suppl 3):S265-80.

24. Denning DW, Cadranel J, Beigelman-Aubry C, Ader, F, Chakrabarti A, Blot S, Ullman A, Dimopoulos G, Lange C, European Society for Clinical Microbiology and Infectious Diseases and European Respiratory Society. Chronic pulmonary aspergillosis – Rationale and clinical guidelines for diagnosis and management. Eur Resp J 2016; 47:45-68.

25. Kosmidis C, Denning DW. Aspergilloma. http://www.aspergillus.org.uk/content/aspergilloma-0

26. Denning DW. Page ID, Chakaya J, Jabeen K, Jude CM, Cornet M, Alastruey-Izquierdo A, Bongomin F, Bowyer P, Chakrabarti A, Gago S, Guto J, Hochhegger B, Hoenigl M, Irfan M, Irurhe N, Izumikawa K, Kirenga B, Manduku V, Moazam S, Oladele RO, Richardson MD, Rodriguez TudelaJL, Rozaliyani A, Salzer HJF, Sawyer R, Simukulwa NF, Skrahina A, Sriruttan C, Setianingrum F, Wilopo BAP, Cole DC, Getahun H. Case definition of chronic pulmonary aspergillosis in resource-constrained settings**.** Emerg Infect Dis 2018;24(8).

27. Muldoon EG, Sharman A, Page ID, Bishop P, Denning DW. Aspergillus nodules; another presentation of chronic pulmonary aspergillosis. BMC Pulm Med 2016; 16:123.

28. Kosmidis C, Newton PJ, Muldoon EG, Denning DW. Chronic fibrosing pulmonary aspergillosis: a cause of „destroyed lung" syndrome. Infect Dis (Lond). 2017;49:296-301.

29. Stucky Hunter ES, Richardson MD, Denning MD. Evaluation of LD Bio Aspergillus ICT lateral flow assay for IgG and IgM antibody detection in chronic pulmonary aspergillosis. J Clin Microbiol 2019;57:e00538-19.

30. Kitasato Y, Tao Y, Hoshino T, Tachibana K, Inoshima N, Yoshida M, Takata S, Okabayashi K, Kawasaki M, Iwanaga T, Aizawa H. Comparison of Aspergillus galactomannan antigen testing with a new cut-off index and *Aspergillus* precipitating antibody testing for the diagnosis of chronic pulmonary aspergillosis. Respirology 2009;14:701-8.

31. Fayemiwo S, Moore CB, Foden P, Denning DW, Richardson MD. Comparative performance of Aspergillus galactomannan ELISA and PCR in sputum from patients with ABPA and CPA. J Microbiol Method 2017;140:32-39.

32. Denning DW, Park S, Lass-Florl C, Fraczek MG, Kirwan M, Gore R, Smith J, Bueid A, Bowyer P, Perlin DS. High frequency triazole resistance found in non-culturable *Aspergillus fumigatus* from lungs of patients with chronic fungal disease. Clin Infect Dis 2011;52:1123-9.

33. Urabe N, Sakamoto S, Sano G, Suzuki J, Hebisawa A, Nakamura Y, Koyama K, Ishii Y, Tateda K, Homma S. Usefulness of Two Aspergillus PCR Assays and Aspergillus Galactomannan and β-d-Glucan Testing of Bronchoalveolar Lavage Fluid for Diagnosis of Chronic Pulmonary Aspergillosis. J Clin Microbiol 2017;55:1738-1746.

34. Bongomin F, Harris C, Foden P, Kosmidis C, Denning DW. Innate and adaptive immune defects in chronic pulmonary aspergillosis. J Fungi 2017;2:26.

35. Kosmidis C, Powell G, Borrow R, Morris J, Alachkar H, Denning DW. Response to pneumococcal polysaccharide vaccination in patients with chronic and allergic aspergillosis. Vaccine 2015;33:7271-5.

36. Kim YT, Kang MC, Sung SW, Kim JH. Good long-term outcomes after surgical treatment of simple and complex pulmonary aspergilloma. Ann Thorac Surg 2005;79:294-8.

37. Lejay A, Falcoz PE, Santelmo N, Helms O, Kochetkova E, Jeung M, Kessler R, Massard G. Surgery for aspergilloma: time trend towards improved results? Interact Cardiovasc Thorac Surg 2011;13:392-5.

38. Chen QK, Jiang GN, Ding JA. Surgical treatment for pulmonary aspergilloma: a 35-year experience in the Chinese population. Interact Cardiovasc Thorac Surg 2012;15:77-80.

39. Farid S, Mohammed S, Devbhandari M, Soon S, Jones MT, Krysiak P, Shah R, Kneale M, Richardson MD, Denning DW, Rammohan KS. Surgery for chronic pulmonary aspergillosis, risk stratification and recurrence - A National Centre's experience. J Cardiothorac Surg 2013; 8:180.

40. Agarwal R, Vishwanath G, Aggawal AN, Garg M, Gupta D, Chakrabarti A. Itraconazole in chronic cavitary pulmonary aspergillosis: a randomized controlled trial and systematic review of the literature. Mycoses 2013:56:559-70.

41. Al-shair K, Atherton GTW, Harris C, Ratcliffe L, Newton P, Denning DW. Long-term antifungal treatment improves health status in patients with chronic pulmonary aspergillosis; a longitudinal analysis. Clin Infect Dis 2013;57:828-35.

42. Godet C, Laurent F, Bergeron A, Ingrand P, Beigelman-Aubry C, Camara B, Cottin V, Germaud P, Philippe B, Pison C, Toper C, Carette MF, Frat JP, Béraud G, Roblot F, Cadranel J; ACHROSCAN study group. Computed Tomography Assessment of Response to Treatment in Chronic Pulmonary Aspergillosis. Chest. 2016;150:139-47.

43. Ohba H, Miwa S, Shirai M, Kanai M, Eifuku T, Suda T, Hayakawa H, Chida K. Clinical characteristics and prognosis of chronic pulmonary aspergillosis. Respir Med 2012;106:724-9.

44. Nam HS, Jeon K, Um SW, Suh GY, Chung MP, Kim H, Kwon OJ, Koh WJ. Clinical characteristics and treatment outcomes of chronic necrotizing pulmonary aspergillosis: a review of 43 cases. Int J Infect Dis 2010;14:e479-82.

45. Lowes D, Al-Shair K, Newton PJ, Morris J, Harris C, Rautemaa-Richardson R, Denning DW. Predictors of mortality in chronic pulmonary aspergillosis. Eur Resp J 2017;49:1601062.