Awareness of predictors of mortality may help improve outcome in chronic pulmonary aspergillosis

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Chronic pulmonary aspergillosis (CPA) is a severe fungal infection usually seen in immunocompetent patients with underlying respiratory disorders [1]. Estimates suggest that ~3 million people suffer from CPA globally [2]. The precise prevalence is unknown. Pulmonary tuberculosis (TB) seems to be the most relevant driver for the global burden of CPA with estimates suggesting about 1.2 million patients with CPA as a sequel to TB [3]. Given that there were 10.4 million new TB cases in 2015, CPA represents a serious sequela to pulmonary TB [4]. However, any search for CPA in the Global Tuberculosis Report of the World Health Organization (WHO) is still in vain [4]. The relative frequency of CPA after standard antituberculous treatment is estimated to be 17% after 12 months and increases to 22% after 48 months. This data, however, is based on two historic UK studies from 1968 and 1970 in which fungal evidence was confirmed by *Aspergillus* precipitins (59% sensitivity, 100% specificity) and radiological features considered only aspergilloma [3, 5, 6]. Thus, the frequency of CPA might even be higher, when using *Aspergillus*-specific IgG antibody assays, which are superior to *Aspergillus* precipitins with a sensitivity of up to 96% and a specificity of 98%, and when radiological criteria consider all CPA entities, especially chronic cavitary pulmonary aspergillosis (CCPA) [7]. Follow-up visits of TB patients, especially those with cavitary TB, should always include a diagnostic work-up for CPA. Whether CPA plays even a larger role in multidrug-resistant (MDR) and extensively drug-resistant (XDR)-TB patients is entirely unknown. MDR/XDR-TB patients experience a more progressive destruction of the lung and global rates of MDR/XDR-TB are increasing considerably [4, 8].

Diagnosis of CPA is often challenging and made late. There is no solitary test or biomarker that allows a definite diagnosis without considering other parameters. Diagnosis of CPA should rather be based upon a combination of characteristics. In 2016, the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) in cooperation with the European Respiratory Society (ERS) and the European Confederation of Medical Mycology (ECMM) published guidelines for the diagnosis and management of CPA [9]. Diagnostic criteria include one or more cavities with or without a fungal ball present or nodules on thoracic imaging, direct evidence of *Aspergillus* infection or an immunological response to *Aspergillus* spp., and exclusion of alternative diagnosis, all present for at least 3 months. In the same year the

Infectious Diseases Society of America (IDSA) also published diagnostic criteria for CPA [10], but the IDSA criteria refer only to CCPA and differ significantly in some points, which may lead to deviating conclusions with corresponding therapeutic implications [11]. Both guidelines, however, strengthen the use of *Aspergillus*-specific IgG assays to provide mycological evidence.

CPA infection results in a slow and progressive destruction of the lung with high rates of morbidity and mortality. Few studies have reported data on the outcome of CPA. Most of them indicate a 5-year survival rate between 48% and 62% [12–17]. Two studies even report a 5-year survival rate of less than 20% [18, 19]. Higher survival rates may be achieved in patients with a more localised pulmonary disease including patients with a single aspergilloma rendering surgical resection an option [20]. However, all of these studies had a retrospective study design and were conducted in high-income countries, and the vast majority of CPA patients analysed received adequate antifungal treatment.

In this issue of the *European Respiratory Journal*, Lowes *et al.* [21] present predictors of mortality in a cohort of 387 CPA patients referred to the UK's National Aspergillosis Centre for medical management of CPA between 1992 and 2012. This is a retrospective data analysis of the largest CPA patient cohort described to date, integrating objective as well as subjective variables to assess predictors of mortality. Furthermore, CPA diagnosis was consistent with the diagnostic criteria of the recently published European guideline on CPA, designating a well-defined and comprehensible patient cohort [9].

Lowes *et al.* [21] report 1-, 5- and 10-year survival rates of 86%, 62% and 47%, which is in line with previously published data, except for one study from Japan which reported a 5-year survival rate of just 17.5% [18]. The reasons were not discussed by those authors, but might be explained by a significantly higher age of CPA patients (75.1±11.3 years) and by the distribution of underlying pulmonary conditions with a higher number of patients with TB (50%) and nontuberculous mycobacterial (NTM) infection (35.7%). Both higher age (HR 1.053 (1.03–1.07)·year^{-1} increase, p<0.001) and NTM infection (HR 2.07 (1.22–3.52), p<0.001) were significantly associated with an increased mortality in the study by Lowes *et al.* [21]. Previous studies have shown that 4–17% of NTM patients develop CPA, especially those with a cavitary type of NTM pulmonary disease [22–24]. A recent study from Nagasaki, Japan directly compared the outcome of NTM patients without CPA (n=82) to NTM patients coinfected with CPA (n=9), and to CPA patients without NTM infection (n=41) [16]. Although the number of NTM patients coinfected with CPA was limited, the study indicates that CPA coinfection predicts the outcome in NTM patients. The authors suggested giving priority to the treatment of CPA. This is now supported by the study of Lowes *et al.* [21], which showed that NTM patients coinfected with CPA had a significantly poorer outcome with a 2-year survival rate of 62% compared to 81% without CPA. The outcome was even worse when compared to CPA patients with chronic obstructive pulmonary disease (COPD), which, after NTM, was the second underlying respiratory disorder to reach statistical significance by multivariate analysis (HR 1.57 (1.05–2.36), p=0.029). Interestingly, TB infection was not identified as a predictor of mortality, which contrasts the Nagasaki study [16]. More information on the TB patient cohort would be useful to interpret these findings as TB patients differ significantly in disease severity, ranging from pulmonary *restitutio ad integrum* to severe destruction of the lung with persistent cavities and loss of functional capacity. Other independent predictors of mortality that reached statistical significance by multivariate analysis were a lower albumin count (HR 0.92 (0.87–0.96)·g^{-1}·L^{-1}, p<0.001), and lower activity (HR 1.021 (1.01–1.03) per point increase in St. George's Respiratory Questionnaire Activity Domain, p<0.001). Pleural involvement, bilateral cavitary disease or aspergilloma was also associated with worsening 2-year survival rates.

Almost all patients analysed in detail (98% of 108 patients) received antifungal treatment and 81% of these received treatment for at least 1 year (77% itraconazole, 15.2% voriconazole, 7.6% posaconazole). Positive sputum cultures for *Aspergillus* were obtained in 48 (12%) patients. 19% of isolates were pan-azole resistant, while the other isolates showed a reduced susceptibility to at least one azole. CPA patients with a susceptible *Aspergillus* isolate had a better outcome than those with a resistant or intermediate *Aspergillus* isolate, but comparison did not reveal statistical significance. In times of highly recommended *Aspergillus*-specific IgG antibody testing to establish CPA diagnosis, the direct evidence of *Aspergillus* for susceptibility testing is still compulsory and should be commonly implemented in disease management. Data regarding the cause of death are limited and were available in 40 (10%) patients. In 67.5% CPA was listed as either direct cause of death or at least contributing to death. However, most patients died at other centres and the cause of death is commonly difficult to interpret in retrospective data analysis.

In conclusion, Lowes *et al.* [21] report several factors that influence the outcome of CPA including NTM infection, COPD, higher age, lower albumin, lower activity and the level of pulmonary involvement in the largest CPA patient cohort described to date. These findings may be used to identify patients at increased risk for a more progressive course of CPA at an early stage of disease and may help to improve disease management and outcome.

The study contributes to a better understanding of factors that influence the outcome of CPA. However, data on CPA in low- and middle-income countries is scarce. Lack of diagnostic resources and limited treatment options will have to be taken into account. A recent survey on global access to antifungal therapy showed that at least 78 million people have no access to itraconazole [25]. Although it is a most needed drug for the fight against CPA, itraconazole is not yet listed by the WHO as an essential medication [26]. Between countries where itraconazole is available, the price varies remarkably ranging from US$1 to US$102. Other effective drugs for CPA such as voriconazole, posaconazole or micafungin are probably unaffordable for most CPA patients and healthcare systems [25]. Recently, the Global Fungal Infection Forum 2 was held in Liverpool, UK with the aim to develop an operational definition of CPA for future epidemiological research and clinical care in low- and middle-income countries. CPA plays a central role in the agenda of the Global Action Fund for Fungal Infections (GAFFI) (www.gaffi.org), with the overall goal of ensuring that 95% of people with serious fungal diseases are diagnosed and 95% are treated by 2025 [27].

Growing awareness led to the development of the new ESCMID/ERS/ECMM guideline on diagnosis and management of CPA [9]. The diagnostic criteria offer consistent CPA diagnosis for the first time. This momentum calls for the implementation of an international CPA registry to collect data on the epidemiology, clinical characteristics, diagnostic methods, disease management and outcome of CPA as done *e.g.* for rare invasive fungal diseases by FungiScope™ (NCT01731353; www.fungiscope.net). Furthermore, there is an urgent need for multicentre prospective studies in all fields of CPA, which could be supported for example on the platform of a research network to promote clinical research similar to the TBnet collaboration on mycobacterial infections (www.tb-net.org).

CPA is an under-rated disease of global health dimensions and further commitment is needed to tackle this neglected fungal infection.

References

1. Smith NL, Denning DW. Underlying conditions in chronic pulmonary aspergillosis including simple aspergilloma. *Eur Respir J* 2011; 37: 865–872.
2. Brown GD, Denning DW, Gow NA, *et al.* Hidden killers: human fungal infections. *Sci Transl Med* 2012; 4: 165rv13.
3. Denning DW, Pleuvry A, Cole DC. Global burden of chronic pulmonary aspergillosis as a sequel to pulmonary tuberculosis. *Bull World Health Organ* 2011; 89: 864–872.
4. World Health Organization (WHO). Global Tuberculosis Report 2016. www.who.int/tb/publications/global_report/en/ Date last updated: 2016.
5. Aspergilloma and residual tuberculous cavities–the results of a resurvey. *Tubercle* 1970; 51: 227–245.
6. Research Committee of the British Tuberculosis Association. *Aspergillus* in persistent lung cavities after tuberculosis. A report from the Research Committee of the British Tuberculosis Association. *Tubercle* 1968; 49: 1–11.
7. Page ID, Richardson MD, Denning DW. Comparison of six *Aspergillus*-specific IgG assays for the diagnosis of chronic pulmonary aspergillosis (CPA). *J Infect* 2016; 72: 240–249.
8. Salzer HJ, Wassilew N, Kohler N, *et al.* Personalized medicine for chronic respiratory infectious diseases: tuberculosis, nontuberculous mycobacterial pulmonary diseases, and chronic pulmonary aspergillosis. *Respiration* 2016; 92: 199–214.
9. Denning DW, Cadranel J, Beigelman-Aubry C, *et al.* Chronic pulmonary aspergillosis: rationale and clinical guidelines for diagnosis and management. *Eur Respir J* 2016; 47: 45–68.
10. Patterson TF, Thompson GR 3rd, Denning DW, *et al.* Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2016; 63: e1–e60.
11. Salzer HJF, Heyckendorf J, Kalsdorf B, *et al.* Characterization of patients with chronic pulmonary aspergillosis according to the new ESCMID/ERS/ECMM and IDSA guidelines. *Mycoses* 2017; 60: 136–142.
12. Nam HS, Jeon K, Um SW, *et al.* Clinical characteristics and treatment outcomes of chronic necrotizing pulmonary aspergillosis: a review of 43 cases. *Int J Infect Dis* 2010; 14: e479–e482.
13. Jhun BW, Jeon K, Eom JS, *et al.* Clinical characteristics and treatment outcomes of chronic pulmonary aspergillosis. *Med Mycol* 2013; 51: 811–817.
14. Nakamoto K, Takayanagi N, Kanauchi T, *et al.* Prognostic factors in 194 patients with chronic necrotizing pulmonary aspergillosis. *Intern Med* 2013; 52: 727–734.
15. Camara B, Reymond E, Saint-Raymond C, *et al.* Characteristics and outcomes of chronic pulmonary aspergillosis: a retrospective analysis of a tertiary hospital registry. *Clin Respir J* 2015; 9: 65–73.
16. Takeda K, Imamura Y, Takazono T, *et al.* The risk factors for developing of chronic pulmonary aspergillosis in nontuberculous mycobacteria patients and clinical characteristics and outcomes in chronic pulmonary aspergillosis patients coinfected with nontuberculous mycobacteria. *Med Mycol* 2016; 54: 120–127.
17. Chan JF, Lau SK, Wong SC, *et al.* A 10-year study reveals clinical and laboratory evidence for the 'semi-invasive' properties of chronic pulmonary aspergillosis. *Emerg Microbes Infect* 2016; 5: e37.
18. Ohba H, Miwa S, Shirai M, *et al.* Clinical characteristics and prognosis of chronic pulmonary aspergillosis. *Respir Med* 2012; 106: 724–729.
19. Tomlinson JR, Sahn SA. Aspergilloma in sarcoid and tuberculosis. *Chest* 1987; 92: 505–508.
20. Jewkes J, Kay PH, Paneth M, *et al.* Pulmonary aspergilloma: analysis of prognosis in relation to haemoptysis and survey of treatment. *Thorax* 1983; 38: 572–578.
21. Lowes D, Al-Shair K, Newton PJ, *et al.* Predictors of mortality in chronic pulmonary aspergillosis. *Eur Respir J* 2017; 49: 1601062.
22. Zoumot Z, Boutou AK, Gill SS, *et al. Mycobacterium avium* complex infection in non-cystic fibrosis bronchiectasis. *Respirology* 2014; 19: 714–722.

23 Ishikawa S, Yano S, Kadowaki T, *et al.* [Clinical analysis of non-tuberculous mycobacteriosis cases complicated with pulmonary aspergillosis]. *Kekkaku* 2011; 86: 781–785.

24 Fujiuchi S, Sakunami M, Yamamoto Y, *et al.* [Analysis of chronic necrotizing pulmonary aspergillosis (CNPA) cases complicated with non-tuberculous mycobacteriosis (NTM)]. *Kekkaku* 2008; 83: 573–575.

25 Kneale M, Bartholomew JS, Davies E, *et al.* Global access to antifungal therapy and its variable cost. *J Antimicrob Chemother* 2016; 71: 3599–3606.

26 World Health Organization. 19th WHO Model List of Essential Medicines. www.who.int/medicines/publications/essentialmedicines/EML2015_8-May-15.pdf Date last updated: April 2015.

27 Denning DW. The ambitious '9595 by 2025' roadmap for the diagnosis and management of fungal diseases. *Thorax* 2015; 70: 613–614.