CPAnet: the challenges of gaining evidence-based knowledge in chronic pulmonary aspergillosis

Rosanne Sprute[1,2,3], **Helmut J.F. Salzer**[4] **and Danila Seidel**[1,2,3]

[1]Dept of Internal Medicine, Faculty of Medicine and University of Cologne, Excellence Center for Medical Mycology (ECMM), University of Cologne, Cologne, Germany. [2]Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Cologne, Germany. [3]German Centre for Infection Research (DZIF), Partner Site Bonn-Cologne, Cologne, Germany. [4]Dept of Internal Medicine/Pulmonology, Kepler University Hospital, Linz, Austria.

Corresponding author: Rosanne Sprute (rosanne.sprute@uk-koeln.de)

Shareable abstract (@ERSpublications)
Chronic pulmonary aspergillosis is a destructive fungal disease complicating many respiratory disorders. Evidence is scarce for clinical management decisions. CPAnet aims to improve patient care by collecting data in an international registry. https://bit.ly/3utUFH1

Cite this article as: Sprute R, Salzer HJF, Seidel D. CPAnet: the challenges of gaining evidence-based knowledge in chronic pulmonary aspergillosis. *Eur Respir J* 2022; 59: 2102879 [DOI: 10.1183/13993003.02879-2021].

Received: 7 Nov 2021
Accepted: 1 Feb 2022

The term chronic pulmonary aspergillosis (CPA) is used to describe a wide range of severe chronic fungal infections mainly occurring in non-immunocompromised patients with pre-existing lung disease [1]. CPA is a long-term infection of the lung caused by moulds of the genus *Aspergillus*. In Europe, the majority of cases are caused by *A. fumigatus*. About three million people are diagnosed with CPA globally, mostly complicating tuberculosis, allergic bronchopulmonary aspergillosis (ABPA) or sarcoidosis [2].

The probability of developing CPA within 2 years after pulmonary tuberculosis treatment is estimated to be around 20%, which is likely underreported due to lack of current studies [3]. Other respiratory disorders, including COPD or non-tuberculosis mycobacterial infection, also predispose for these infections. Impaired lung tissue provides a perfect habitat for fungal spores to be trapped. Non-functional cilia allow unobstructed passage of fungal spores into the lungs, where hyphae may grow undetected by the immune system in damaged lung areas. Patients may present with chronic and relapsing cough, dyspnoea and weight loss developing over several months to years. The overall 5-year mortality is high with rates reported up to 85%, depending on comorbidities, severity of disease and phenotype of CPA [4]. Long-term prognosis is not fully elucidated for each subgroup.

An overview of the different phenotypes of CPA is presented in figure 1 [5]. The most common phenotype is chronic cavitary pulmonary aspergillosis (CCPA) with presence of one or multiple cavities in the lung with or without a fungal ball over at least 3 months of observation [6]. CCPA may first present as unspecific pulmonary consolidation that later progresses into distinct, mostly thick-walled cavities. If left untreated, cavities may expand or new ones occur over the following months and CCPA may further progress to chronic fibrosing pulmonary aspergillosis (CFPA) characterised by chronic scarring of the lungs. *Aspergillus* nodules and single or simple aspergilloma are less common. The latter is probably the best-known phenotype. Disease may progress more rapidly within weeks or few months in moderately immunocompromised patients and presents as subacute invasive aspergillosis (SAIA; formerly chronic necrotising or semi-invasive aspergillosis). The proposed phenotypes can overlap considerably and some authors support the notion of a continuum in the clinical and radiological features of CPA rather than identifying artificial subtypes [7].

In 2015, 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) provided the first comprehensive clinical guidelines for diagnosis and management of CPA [6].

Symptoms
Pulmonary and/or systemic:
- Breathlessness
- Cough
- Fatigue
- Haemoptysis
- Weight loss

Usually for a period >3 months, often similar to underlying disease and sometimes asymptomatic

Diagnosis
- Underlying lung disease: ABPA, asthma, COPD, sarcoidosis, TBC
- Thoracic imaging: CT (preferably)
- Bronchial secretion/BAL or sputum: microscopy, culture, GM, LFD and/or PCR (when available)
- Biopsy (when possible)
- Serology: *Aspergillus* antibodies, specifically IgG and precipitins, IgE

Treatment
- Long-term antifungal medication, *e.g.* oral triazole therapy for 6 months, if tolerated
- Localised CPA: surgical resection
- In patients with haemoptysis: tranexamic acid, catheter embolisation, surgery
- Follow-up imaging in 3–6 months

Chronic pulmonary aspergillosis (CPA)

Single/simple aspergilloma

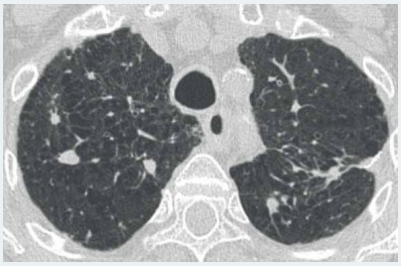
Aspergillus nodule(s)

Subacute invasive aspergillosis (SAIA)

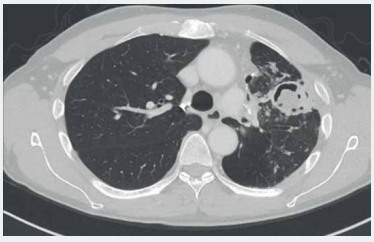
Chronic cavitary pulmonary aspergillosis (CCPA)

Chronic fibrosing pulmonary aspergillosis (CFPA)

One or more nodules which may or may not cavitate. They may mimic tuberculoma, malignoma and other diagnoses, and can only be definitively diagnosed on histology. Tissue invasion is not demonstrated, although necrosis is frequent.

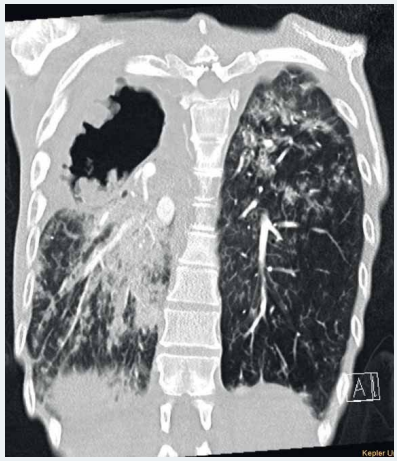


Single pulmonary cavity containing a fungal ball in immunocompetent patients with minor or no symptoms and no radiological progression over at least 3 months.



Invasive aspergillosis in mildly immunocompromised patients occurring over <3 months with variable radiological features including cavitation, nodules and consolidation. Biopsy shows hyphae in invading lung tissue. GM in serum may be positive. Diagnosis and treatment are similar to invasive aspergillosis.

Severe fibrotic destruction of at least two lobes of lung complicating CCPA leading to a major loss of lung function. Usually, the fibrosis is manifest as consolidation, but large cavities with surrounding fibrosis may be seen.



One or more pulmonary cavities (thin or thick wall) possibly containing one or more fungal balls or irregular intraluminal material with significant symptoms and overt radiological progression over at least 3 months.

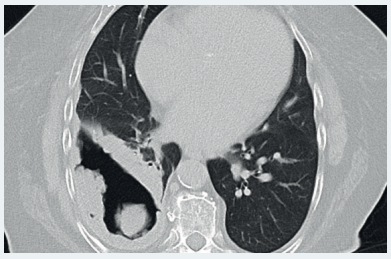


FIGURE 1 Diagnostic criteria and clinical management of chronic pulmonary aspergillosis (CPA). Considerable overlap exists in the clinical and radiological features between CPA phenotypes. CPA phenotypes and diagnostic criteria modified according to Denning *et al.* [6]. The computed tomography (CT) scan showing *Aspergillus* nodules was published in Salzer *et al.* [24]. CT scans of CPA patients were contributed with kind permission by the Department of Pulmonology, Kepler University Hospital, Linz, Austria. ABPA: allergic bronchopulmonary aspergillosis; BAL: bronchoalveolar lavage; GM: galactomannan; LFD: lateral flow device; TBC: tuberculosis complex.

The diagnosis of CPA can be established in case of suggestive radiological findings in addition to immunological or microbiological evidence of *Aspergillus* spp. and in the absence of an alternative diagnosis (figure 1) [8]. Patients may be asymptomatic, especially when having an aspergilloma or *Aspergillus* nodules. Occurrence of nodules is often associated with negative *Aspergillus*-specific IgG antibodies and *Aspergillus* precipitins; thus, diagnosis might be missed despite distinctive radiological findings [9]. If clinical symptoms are present, they are usually unspecific and often similar to those recorded for the underlying conditions (figure 1). Thus, early-stage CPA is often overlooked clinically.

Reliable evidence for strong treatment recommendations for CPA is lacking and optimal management varies depending on the clinical presentation and phenotype of the disease. Clinical stable aspergilloma, CCPA and CFPA may not require antifungal treatment and monitoring of parameters including radiology, serology and lung function may be sufficient until occurrence of symptoms or disease progression. Itraconazole and voriconazole are the drugs of choice for all forms of CPA, both requiring therapeutic drug monitoring (TDM). Both drugs demonstrated clinical improvement in small randomised controlled clinical trials (RCTs) for the majority of patients [10, 11]. Disease management is usually characterised by an interplay of antifungal treatment and watch-and-wait periods. At least 6 months of therapy is recommended for limited disease, but life-long antifungal treatment might be needed for extensive disease, if tolerated, to control symptoms and to avoid relapse after discontinuation.

In patients who fail therapy with triazoles or show intolerance, intravenous therapy with amphotericin B lipid formulations or echinocandins can be considered [6]. For echinocandins, a similar response rate with better safety profile compared to voriconazole has been shown [12]. However, comprehensive data on treatment duration and long-term prognosis are non-existent. New antifungals with alternative routes of administration and less toxicity are currently being investigated in clinical trials [13]. The orally available glucan-synthase inhibitor ibrexafungerp and the second-generation echinocandin rezafungin with prolonged half-life after intravenous application allow use in an outpatient setting [13]. The novel triazole opelconazole is designed for inhalation *via* commonly available nebulisers, limiting the potential systemic adverse effects of the triazoles [13]. These drugs may offer more advantageous treatment options for CPA patients in the future.

Surgical resection can be associated with a significant long-term response in patients with localised disease and a relatively intact lung parenchyma [14]. For simple aspergilloma or CCPA, surgery can be curative and should be considered as the preferable treatment option. However, surgical treatment is often restricted by poor respiratory function, making patients unsuitable for surgery. Post-surgical complications and potential risk of disease recurrence must be carefully considered relative to the potential benefit. There is no clear evidence or consent if itraconazole or voriconazole should be administered prior to and/or after surgery to prevent spillage of fungal material during surgery. Pleural washing with amphotericin B or taurolidine may be used in addition but could not be correlated with improved outcome so far [15].

Surgery may also be considered as treatment for severe haemoptysis. Other treatment options include tranexamic acid infusions and/or bronchial artery catheter embolisation in more severe cases, where this procedure might be life-saving [16, 17]. However, recurrence after successful embolisation is common and elective surgery as definitive treatment should then be considered [17].

For CPA, several fundamental questions remain unanswered, complicating consensus on the optimal diagnostic and therapeutic procedures, defining treatment outcomes and thereby challenging the development of clinical trials. Antibody testing is central to establish diagnosis. However, global standardisation of antibody assays has proven difficult and commercial diagnostic tools are often not validated for CPA, but cut-off values are based on data from ABPA or invasive aspergillosis patients and vary between different systems [18]. In addition, tests are generally not designed to detect antibody response to *Aspergillus* spp. other than *A. fumigatus*. Large-scale studies directly comparing and evaluating different diagnostic tests in a well-defined clinical cohort are needed. Reliable and consented diagnostic criteria are critical for future clinical trials.

Consent on an appropriate endpoint to determine treatment response in clinical trials has yet to be defined. Resolution of radiological or mycological findings, and decrease of *Aspergillus*-specific IgG antibodies have been used to describe treatment response or clinical failure, but none has been evaluated in a RCT so far. Also, defining clinical cure in CPA is complicated by the overlap of symptoms related to underlying lung disease. Consensus definitions to harmonise objective clinical, radiological and mycological treatment endpoints are urgently needed. CPAnet currently tries to reach consensus for treatment outcome definitions within the scientific CPA community, because the lack of outcome definitions parallels the limited number

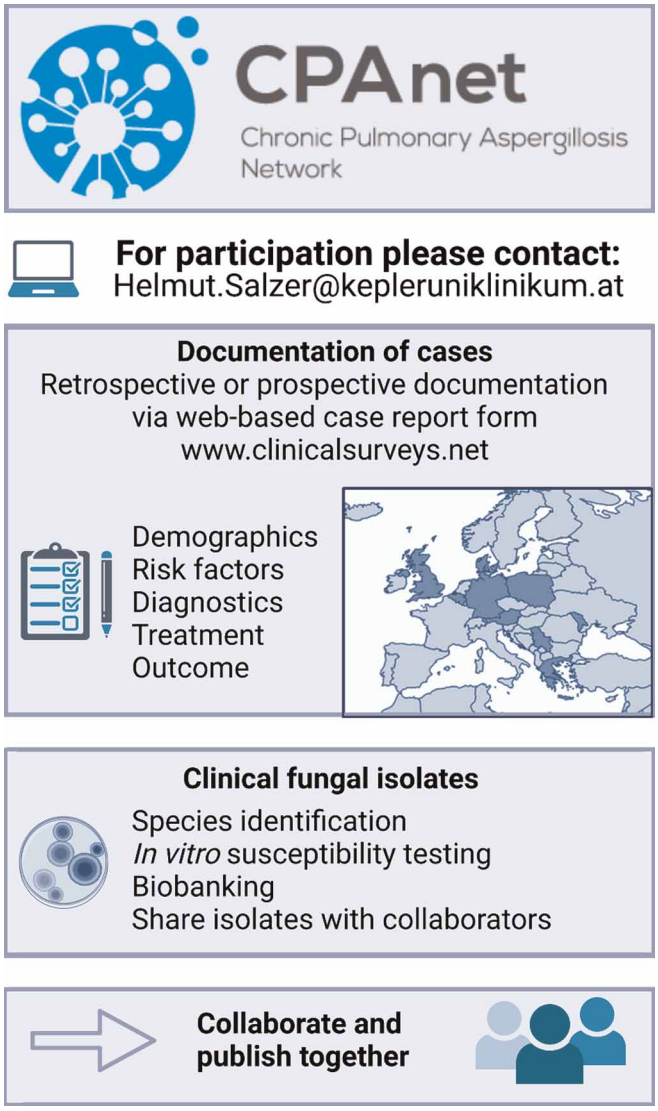


FIGURE 2 How to get involved in the of chronic pulmonary aspergillosis (CPA) research network. The CPAnet was established as a unique network for clinician scientists and experts in translational research across the globe to facilitate collaborations geared towards improved clinical management and evidence on CPA. The CPAnet registry is an international multicentre collaboration open for retrospective and prospective case entries and aiming to gather comprehensive data on a large study population. The depicted map displays countries with currently participating sites. Everyone interested in the epidemiology, pathophysiology and clinical management of CPA is strongly encouraged to join the international effort and become an active partner of the CPAnet.

of available RCTs. In particular, global RCTs comparing different antifungal treatment regimens are urgently required to fill the gaps of knowledge on the efficacy of different treatment options. The disease heterogeneity and the low frequency of CPA in single centres add to the complexity of planning and conducting those trials.

Prospective registry-type studies may be suitable to systematically broaden our knowledge on CPA. The methodological approach of registries for rare conditions has proven valuable to spearhead novel evidence for other respiratory diseases. One successful example is the ERS Clinical Research Collaboration (CRC) EMBARC registry, a pan-European prospective registry for bronchiectasis [19].

The CPA Research Network (CPAnet) was founded in 2017 and funded as a CRC by the ERS in 2020 [20, 21] with the goal of coordinating expertise in the field (figure 2). As one of the four defined research

priorities of the CPAnet, a global registry for the centralised collection of clinical cases was launched in 2018 [22]. The case report form was developed jointly by an expert panel including the steering committee of the CPAnet. The web-based questionnaire was designed using the clinicalsurveys.net survey tool (Questback GmbH, Cologne, Germany). The registry allows for retrospective and prospective case entry. Adult patients with the diagnosis of CPA based on the diagnostic criteria described by Denning *et al*. [6], including radiological and mycological evidence of *Aspergillus*-related pulmonary infection for at least 3 months and exclusion of differential diagnoses can be documented. Demographic, epidemiological, microbiological and clinical data are requested. A follow-up of at least 10 years for each patient is intended, with an intermittent update on treatment and response at 6 months and 2 years after diagnosis of CPA for prospectively enrolled subjects. For joint analyses, datasets will be made available among CPAnet members through the designated lead investigators [22, 23]. If clinical isolates are available, they can be collected in participating reference laboratories for further research on the causative pathogens. The registry study is approved by the institutional review board and ethics committee of the University Hospital Cologne (ID 17-263), Cologne, Germany and the local ethics committees of participating centres.

The CPAnet and the registry are open to everyone who is interested in researching CPA and treats respective patients. Only through a joint effort of reference centres around the world sufficient data will become available to identify suitable diagnostic and therapeutic approaches and improve the respective measures for future patient care. Within the growing network first results have been collaboratively published, presenting on risk factors and management of 74 CPA cases [23]. In addition, a Europe-wide analysis of clinical fungal isolates from CPA patients is currently being conducted and preliminary results reveal a heterogeneity of causative *Aspergillus* species in this cohort (J.C. Soto-Debran; personal communication, October 2021). The network and the registry are seeking for further reference centres to join the international effort and become an active partner of the CPAnet to increase the number of patients for comprehensively investigating management strategies for CPA.

Acknowledgements: This article was written on behalf of all CPAnet members. We thank the ERS for being selected as an ERS Clinical Research Collaboration.

Author contributions: All authors contributed equally.

Conflict of interest: All authors have nothing to disclose.

References

1 Schweer KE, Bangard C, Hekmat K, *et al.* Chronic pulmonary aspergillosis. *Mycoses* 2014; 57: 257–270.
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 Lowes D, Al-Shair K, Newton PJ, *et al.* Predictors of mortality in chronic pulmonary aspergillosis. *Eur Respir J* 2017; 49: 1601062.
5 Denning DW, Riniotis K, Dobrashian R, *et al.* Chronic cavitary and fibrosing pulmonary and pleural aspergillosis: case series, proposed nomenclature change, and review. *Clin Infect Dis* 2003; 37: Suppl 3, S265–S280.
6 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.
7 Godet C, Laurent F, Béraud G, *et al.* Phenotyping chronic pulmonary aspergillosis by cluster analysis. *Eur Respir J* 2015; 46: 1509–1512.
8 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.
9 Bongomin F, Asio LG, Baluku JB, *et al.* Chronic pulmonary aspergillosis: notes for a clinician in a resource-limited setting where there is no mycologist. *J Fungi (Basel)* 2020; 6: 75.
10 Dupont B. Itraconazole therapy in aspergillosis: study in 49 patients. *J Am Acad Dermatol* 1990; 23: 607–614.
11 Cadranel J, Philippe B, Hennequin C, *et al.* Voriconazole for chronic pulmonary aspergillosis: a prospective multicenter trial. *Eur J Clin Microbiol Infect Dis* 2012; 31: 3231–3239.
12 Kohno S, Izumikawa K, Ogawa K, *et al.* Intravenous micafungin *versus* voriconazole for chronic pulmonary aspergillosis: a multicenter trial in Japan. *J Infect* 2010; 61: 410–418.
13 Hoenigl M, Sprute R, Egger M, *et al.* The antifungal pipeline: fosmanogepix, ibrexafungerp, olorofim, opelconazole, and rezafungin. *Drugs* 2021; 81: 1703–1729.
14 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.

15 Sagan D, Goździuk K. Surgery for pulmonary aspergilloma in immunocompetent patients: no benefit from adjuvant antifungal pharmacotherapy. *Ann Thorac Surg* 2010; 89: 1603–1610.
16 Moen CA, Burrell A, Dunning J. Does tranexamic acid stop haemoptysis? *Interact Cardiovasc Thorac Surg* 2013; 17: 991–994.
17 Shin B, Koh WJ, Shin SW, *et al.* Outcomes of bronchial artery embolization for life-threatening hemoptysis in patients with chronic pulmonary aspergillosis. *PLoS One* 2016; 11: e0168373.
18 Page ID, Richardson M, Denning DW. Antibody testing in aspergillosis—quo vadis? *Med Mycol* 2015; 53: 417–439.
19 Aliberti S, Polverino E, Chalmers JD, *et al.* The European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) ERS Clinical Research Collaboration. *Eur Respir J* 2018; 52: 1802074.
20 Brightling C, Genton C, Bill W, *et al.* ERS Clinical Research Collaborations: underpinning research excellence. *Eur Respir J* 2018; 52: 1801534.
21 van den Berge M, Genton C, Heuvelin E, *et al.* Success and continuous growth of the ERS clinical research collaborations. *Eur Respir J* 2021; 58: 2102527.
22 Godet C, Alastruey-Izquierdo A, Flick H, *et al.* A CPAnet consensus statement on research priorities for chronic pulmonary aspergillosis: a neglected fungal infection that requires attention. *J Antimicrob Chemother* 2018; 73: 280–286.
23 Laursen CB, Davidsen JR, Van Acker L, *et al.* CPAnet Registry—an international chronic pulmonary aspergillosis registry. *J Fungi (Basel)* 2020; 6: 96.
24 Salzer HJ, 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.