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Early View

Research letter

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Treatment outcome definitions in chronic pulmonary aspergillosis: a CPAnet consensus statement

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Summary
Standardized and commonly accepted treatment outcome criteria for chronic pulmonary aspergillosis (CPA) can improve patient management by better comparability and understanding of CPA treatment studies: a CPAnet consensus statement.

INTRODUCTION

Chronic pulmonary aspergillosis (CPA) is an uncommon but dreaded complication of many respiratory diseases occurring in non- or mildly immunocompromised patients [1]. CPA affects approximately three million people worldwide, an estimation which is undoubtedly affected by underreporting of this neglected disease [2]. The morbidity and mortality is high with five-year survival rates of 15-60% depending on comorbidities and age (3, 4). The diagnosis of CPA is typically established on a combination of clinical, radiological and microbiological criteria all present for at least 3 months and the absence of an alternative diagnosis [1]. The most common form of CPA is chronic cavitary pulmonary aspergillosis (CCPA), besides other disease entities, including chronic fibrosing pulmonary aspergillosis (CFPA), *Aspergillus* nodule(s) and single aspergilloma. Subacute invasive pulmonary aspergillosis (SAIA) also called chronic necrotizing pulmonary aspergillosis usually occurs in moderately immunocompromised patients and comprises a more rapidly progressive clinical course (<3 months) [1].

Treatment decisions in CPA largely depend on the pulmonary and general symptoms, and any pulmonary function loss or radiographic progression, especially in patients with CCPA. Treatment options include mostly oral triazoles with fungicidal activity against *Aspergillus* spp., such as itraconazole, voriconazole, posaconazole, and isavuconazole, of which the first two are the best documented agents in the context of CPA. Treatment duration is recommended for at least 6 months and follow-up on or off therapy is performed every 3 to 6 months, including clinical monitoring, *Aspergillus* serology and/or microbiology, chest radiographs and periodic computed tomography (CT) scans. [1, 5, 6].

Current guidelines on diagnosis and management of CPA, established by the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) in collaboration with the European Respiratory Society (ERS) and the European Confederation of Medical Mycology (ECMM), as well as those developed by the Infectious Diseases Society of America (IDSA), provide diagnostic criteria for CPA but no clear treatment outcome definitions [1, 2, 6]. This lack of standardization of endpoints parallels the limited number of available randomized controlled trials (RCTs) on antifungal treatment of CPA [7, 8], which, beside some larger retrospective and non-randomized prospective studies [9–11], leads to a scarcity of high-quality data on CPA treatment. Therefore, establishing consensus on treatment outcome definitions was considered as one of the top 4 research priorities of the Chronic Pulmonary Aspergillosis network (CPAnet), an international research collaboration established in 2017 and funded as a Clinical Research Collaboration (CRC) by the ERS in 2020 [2].

MATERIAL AND METHODS

Following two CPAnet meetings linked to the ERS conferences of Paris 2018 and Madrid 2019, a CPAnet initiative to develop a consensus statement on treatment outcome definitions for CPA was established. Well-recognized CPA experts consisting of pulmonologists, infectious disease specialists, microbiologists, and radiologists as well as a CPA patient advisory group supported by the European Lung Foundation (ELF) were invited to participate in the development of this consensus statement [2]. The methodological approach used has proven useful for other rare pulmonary infections as for multidrug-resistant tuberculosis (MDR-TB) and non-tuberculous mycobacterial pulmonary disease (NTM-PD) [12, 13]. The process involved the following 4 steps:

Step 1

Forming a CPA expert panel.

Step 2

Coordinating authors (I. Page and H. J. Salzer) proposed 15 CPA treatment outcome categories and drafted one statement for each category based on their expertise and after review of the available literature. Based on the drafted statements all co-authors were asked to provide alternative statements. All voting steps were managed by the coordinating authors using a prepared Word File (Microsoft©, Washington, USA) attached to E-mail. The coordinating authors counted all votes independently.

Step 3
Co-authors were asked to select one preferred statement among the original and the alternative statements. All co-authors were blinded to the votes. The statement that received the most votes within each outcome category was selected for inclusion in the manuscript.

Step 4
Finally, co-authors were asked to indicate their agreement, disagreement or whether they preferred to abstain from a decision.

Definition Respiratory Symptom Score (RSS)
To evaluate the clinical response the RSS should be used, which is based on six items including cough, sputum production, dyspnea, hemoptoic sputum, chest tightness, and nocturnal awakening. For each symptom a simple visual analogical scale (VAS) (10-cm line) can be used comparable to the commonly established VAS to measure pain in patients. Stability is defined by a score variation between -25 and +25% (equivalent to +/- 2,5 cm on the VAS), while improvement and deterioration is defined by a decrease or increase in the score greater than 25%, respectively (Table 1) [10].

RESULTS

Twenty-nine CPA experts from nine countries in the European Region (Austria, Belgium, Denmark, France, Germany, Moldova, Serbia, Spain, UK), one country from the Eastern Mediterranean Region (Pakistan), one country from the South-East Asian region (India), two countries from the Western Pacific region (Japan, South Korea), one country from the African region (Nigeria), and one country from the Americas (US) contributed to the development of this consensus statement, 28 completed all 4 steps. A median of seven alternative statements (minimum 1; maximum 17) for a category was proposed by the co-authors during step 2. Table 1 summarizes the final definitions, including the results of voting in Step 3 and the support level achieved in Step 4.

DISCUSSION

By proposing these consensus definitions on outcome parameters for the treatment of patients with CPA, we aim to provide guidance for the design of future clinical trials in CPA, which encompass a highly unmet need [2]. Particularly RCTs, comparing different antifungal treatment regimens, are lacking, partly due to the infrequent occurrence in single centers and disease heterogeneity of CPA. The consensus statement is an essential framework for the evaluation of CPA treatment outcome measures, which should ideally be harmonized throughout clinical trial design.

The overall agreement level within the expert panel was quite high for most questions, with ultimate agreement ranging from 78-100%. The value of *Aspergillus*-specific serology in treatment response assessment was the most important matter of debate. Indeed, since most available *Aspergillus* immunoglobulin G detection kits were originally designed to detect *A. fumigatus*, these assays might have limitations in areas where non-*fumigatus* strains are epidemiologically important [14]. The wording of the question did not include quantitative changes on a linear or semi-logarithmic scale, limiting this conclusion. Treatment response was generally assessed on three levels: (i) clinical

response assessed by the RSS comprised of 6 cardinal symptoms in CPA (cough, dyspnoea, sputum, haemoptysis, chest pain, and nocturnal awakening) [10], (ii) microbiological response defined by negative fungal cultures, and (iii) radiological response through assessment of cavity wall thickness and pleural thickness [15]. In one previous study on cavitary CPA disease, regression or remission of the latter two radiological criteria during concomitant 6 months of antifungal treatment was associated with clinical improvement. Loss of fungus ball on radiological imaging (without surgery) was also associated with favourable treatment response, while increase of cavity size or assessment of number and size of nodules and tree-in-bud patterns were less concordant with clinical progression [15].

Similar to the consensus statement previously published on NTM-PD, the definition of clinical cure in CPA is complicated by any remaining symptoms relating to underlying non-CPA lung disease, and therefore based on an improvement of at least 25% in the RSS [10, 13]. In European cohorts, chronic obstructive pulmonary disease is the leading comorbidity in patients with CPA, while, while a history of tuberculosis is generally predominant in endemic countries [1, 3, 4] . The definition of cure in CPA is further hampered by the fact that there is no standard of care concerning treatment duration in CPA, except for the minimum duration of 6 months recommended in the current European and American guidelines for CCPA [1, 6]. CPA also has some underlying genetic risk factors, and cure may indeed be elusive, with long-term remission being a more appropriate status.

Microbiological cure in CPA may be difficult to definitively demonstrate, since culture of *Aspergillus* species lacks both sensitivity and specificity, and is unable to distinguish colonization from infection in the absence of radiological findings [14]. Presence of *Aspergillus* species on culture from bronchoscopic specimens is more likely in infection, while sputum is usually not recommended, because of high risk of contamination/colonisation [1]. Alternative assays (antigen detection or quantitative PCR) to establish microbiological evidence for *Aspergillus* are insufficiently validated on broncho-pulmonary samples in the context of CPA [14]. Moreover, performing a bronchoscopy to obtain deep respiratory tract samples, is seldomly justifiable in an improving patient, and less available in resource-limited settings. Serum biomarkers (galactomannan, ß-D-glucan, DNA) are only occasionally detected in SAIA. Finally, while serology (specific antibody detection) is a key tool in establishing the diagnosis of CPA, its utility in the follow-up remains to be demonstrated [16]. Thus, the panel agreed on including culture as one of the criteria for cure, provided that no *Aspergillus* was grown for respiratory samples during 2 years after completion of treatment, and with at least two different negative cultures per year from a respiratory sample (e.g. sputum, bronchial secretion, bronchoalveolar lavage).

Another limitation is that radiological changes require careful evaluation and CT image quality parameters can differ (e.g. slice thickness, pixel size, dose levels). Consensus on radiological criteria is very much concentrated on a single study [15]. Further studies are needed defining the most relevant CT imaging variables for assessing treatment response.

The methodology of this step-wise process has the intrinsic limitation of being mainly expert-opinion-based, yet has been usefully applied for MDR-TB and NTM-PD therapy outcome [12, 13]. As the available evidence on CPA treatment outcomes is even scarcer, performing a systematic review of literature on CPA treatment is intrinsically challenging [2]. In conclusion, this consensus statement on treatment outcome definitions in CPA is an important first step in evolving towards more qualitative and prospective data, with the highest priority for the development of state-of-the-art randomized clinical trials investigating treatment of CPA.

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CONFLICT OF INTEREST

R. Agarwal has received grants from Cipla Pharmaceuticals, India outside the submitted work. A. Alastruey-Izquierdo has received honoraria for lectures from Gilead and Pfizer. O.A. Cornely reports grants or contracts from Amplyx, Basilea, BMBF, Cidara, DZIF, EU-DG RTD (101037867), F2G, Gilead, Matinas, MedPace, MSD, Mundipharma, Octapharma, Pfizer, Scynexis; Consulting fees from Amplyx, Biocon, Biosys, Cidara, Da Volterra, Gilead, Matinas, MedPace, Menarini, Molecular Partners, MSG-ERC, Noxxon, Octapharma, PSI, Scynexis, Seres; Honoraria for lectures from Abbott, Al-Jazeera Pharmaceuticals, Astellas, Grupo Biotoscana/United Medical/Knight, Hikma, MedScape, MedUpdate, Merck/MSD, Mylan, Pfizer; Payment for expert testimony from Cidara; Participation on a Data Safety Monitoring Board or Advisory Board from Actelion, Allecra, Cidara, Entasis, IQVIA, Jannsen, MedPace, Paratek, PSI, Shionogi; A pending patent currently reviewed at the German Patent and Trade Mark Office; Other interests from DGHO, DGI, ECMM, ISHAM, MSG-ERC, Wiley. D.W. Denning and family hold Founder shares in F2G Ltd, a University of Manchester spin-out antifungal discovery company; Acts or has recently acted as a consultant to Pulmatrix, Pulmocide, Zambon, Biosergen, TFF Pharmaceuticals, Bright Angel Therapeutics and Cipla; Sits on the DSMB for a SARS-CoV-2 vaccine trial; Honoraria for talks from Hikma, Gilead, BioRad, Basilea, 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. H. Flick participated in the past 3 years on advisory boards from Boehringer-Ingelheim and INSMED and has received honoraria for lectures and travel support from Boehringer-Ingelheim, MSD, Roche, Novartis, AstraZeneca, GSK, Chiesi, Pfizer and GSK. C. Godet has received honoraria for lectures and travel support from Pfizer and MSD; fees for board memberships from SOS Oxygène and Pulmatrix; grant support from Ohre Pharma, Boerhringer-Ingelheim, Pfizer, MSD, SOS Oxygène, ISIS Medical, Vivisol, Elivie, CF Sante, Oxyvie LVL Medicaland and AstraZeneca; grant to the University of Poitiers from the French Ministry of Health for NEBULAMB and CPAAARI clinical trial. C. Hennequin has received funds for basic research from MSD; received travel grants from Pfizer and Gilead and has received honoraria for talks by Gilead. M. Hoenigl has received research funds from NIH, Gilead, Euroimmune, Astellas, Pfizer, F2G and MSD. K. Izumikawa has received research funds and speakers honoraria from Astellas Pharma Inc., Pfizer Japan Inc., MSD K.K. a subsidiary of Merck & Co., Inc., Asahi Kasei Pharma Cooperation and Sumitomo Dainippon Pharma Co., Ltd. C. Lange has received honoraria for talks from Chiesi, Gilead, Novartis, Oxfordimmunotec, Janssen and Insmed. T.F. Patterson has received grant support to UT Health San Antonio from Cidara, F2G and Gilead and was a consultant or served on data review committees for Appili, Basilea, Mayne, Merck, Pfizer, Scynexis and Sfunga. A. Watanabe has received research funding from Shionogi & Co. Ltd. and Eiken Chemical Co. Ltd. E. van Braeckel, I. Page, J.R. Davidsen, C.B. Laursen, A. Barac, J. Cadranel, J.P. Gangneux, Y. Hayashi, M. Irfan, W.J. Koh, C. Kosmidis, B. Lamprecht, F. Laurent, O. Munteanu, R. Oladele, A. Chakrabarti and H.J.F. Salzer have no conflict of interest.

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Table 1. Consensus definitions established by a CPA expert panel

CPA, chronic pulmonary aspergillosis; ELISA, enzyme-linked immunosorbent assay; IgG, immunoglobulin G; [¶]: number of votes received from the 29 experts during Step 3; [#]: level of agreement/support obtained among 28 experts during Step 4; [§]: preferably computed tomography scan of the chest; *: maximal cavitary wall thickness

Outcome category	Consensus definition	Votes during Step 3[¶]	Support during Step 4[#]
1. Cure	Successful curative complete resection and/or antifungal treatment completed, with fulfilment of all of the following criteria 2 years after completion of CPA therapy: i. Sustained clinical treatment response defined by improvement in the Respiratory Symptom Score (RSS) at the end of the pre-defined antifungal treatment period or 6 months after successful curative complete resection.[10] ii. Microbiological cure defined by negative culture from respiratory specimen at the end of treatment and the following 2 years after completion of treatment with at least two negative cultures at two different time points per year. iii. Sustained radiological treatment response defined by 20% reduction in either maximum cavity wall thickness of any cavity, or maximum pleural thickness adjacent to a cavity (with a minimum change of 2 mm) after completion of CPA therapy, and no radiological deterioration elsewhere. No new CPA suspicious lesions 6 months after successful curative complete resection.	6	25 (93%)
2. Treatment completed	Successful curative complete resection and/or antifungal treatment throughout the pre-defined study period, which is (in absence of curative resection) no less than 6 months.	13	26 (96%)
3. Radiological treatment response[§]	In case of at least one cavity*: - decrease of ≥20% (with a minimum of 2 mm) of the maximal pleural thickness, OR - decrease of ≥20% (with a minimum of 2 mm) of cavitary wall thickness, OR - disappearance of a fungal ball and/or ribbons AND absence of new radiological features of CPA. In absence of cavities: - decrease of ≥1 point of a semi-quantitative visual score of ground glass opacities/consolidation/micronodules evaluating the lung volume occupied by features from 0 to 100% [15], OR - decrease of ≥50% of the volume of a macronodule (>1 cm in diameter) [15] AND absence of new radiological features of CPA.	12	25 (93%)
4. Radiological treatment deterioration[§]	In case of at least one cavity*: - increase of ≥20% (with a minimum of 2 mm) of the maximal pleural thickness, OR - increase of ≥20% (with a minimum of 2 mm) of cavitary wall thickness, OR	11	25 (93%)

	- increase of volume of >30% of a fungal ball with or without new radiological features of CPA. In absence of cavities: - increase of ≥1 point of a semi-quantitative visual score of ground glass opacities/consolidation/micronodules evaluating the lung volume occupied by features from 0 to 100% [15], OR - increase of ≥50% of volume of a macronodule (>1 cm in diameter).[15]		
5. Clinical treatment response	Significant improvement – defined by a decrease in the RSS >25%, based on 6 items (cough, dyspnoea, sputum production, hemoptoic sputum, chest tightness, and nocturnal awakening), using a 10-cm visual analogue scale [10]. Stability is defined by score variation between -25% and +25%.	9	26 (96%)
6. Clinical treatment deterioration	Increase in the RSS >25% or occurrence of haemoptysis requiring either interventional radiology OR surgery, after having excluded all other causes capable of interfering with the evaluation of the *Aspergillus* disease.	5	26 (96%)
7. Serological improvement	Reduction in *Aspergillus*-specific IgG titre of 50%, OR return to normal levels, measured using an assay validated for use in CPA in the same laboratory.	9	21 (78%)
8. Serological deterioration	Newly positive serology, OR an increase of at least two dilutions when using a quantitative technique such as ELISA, OR an increase of ≥50% of precipitating antibody lines, with a technique validated for use in CPA in the same laboratory.	12	26 (96%)
9. Overall treatment response	Overall treatment response evaluated at 3 and 6 months is defined by clinical improvement and radiological stability OR improvement. Overall treatment response with mycological eradication is achieved if confirmed by negative mycological culture of respiratory secretion specimen. Serology should not be considered to define overall treatment response.	10	22 (82%)
10. Overall stability under treatment	Neither clinical and radiological deterioration nor improvement evaluated at 3 and 6 months. Serology should not be considered to define stability under treatment.	10	26 (96%)
11. Treatment failure	Presence of clinical OR radiological deterioration evaluated at 3 and 6 months. Treatment failure would be confirmed by a complete microbiological evaluation either in sputum or bronchial aspiration to exclude any other cause for clinical or radiological deterioration, including (myco)bacterial super-infection. Serology should not be considered to define treatment failure.	14	26 (96%)
12. Relapse after treatment	Presence of ANY of clinical OR radiological deterioration >3 months after treatment cessation in a patient considered overall responsive or stable. Relapse would be confirmed by a complete	10	26 (96%)

	microbiological evaluation either in sputum or bronchial aspiration to exclude any other cause for clinical or radiological deterioration, including (myco)bacterial super-infection. Serology should not be considered to define relapse.		
13. Died	Death due to any causes during the study or follow up period.	23	27 (100%)
14. Died due to CPA	Death assessed by two pre-defined experts, who were blinded to the study intervention, and who independently of each other determines the cause of death as being due to CPA. In case of disagreement between the two blinded experts, a third pre-defined expert, who is also blinded to the study intervention, determines whether the cause is due to CPA or another cause.	12	26 (96%)
15. Lost to follow-up	Patient no longer in follow up for more than 2 months during treatment OR at the end of the study period.	12	27 (100%)