EQUAL CPA Score 2022: a tool to measure guideline adherence for chronic pulmonary aspergillosis

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Received 16 August 2022; accepted 18 October 2022

Background: Chronic pulmonary aspergillosis (CPA) can complicate underlying pulmonary diseases, and clinical management of CPA is challenging. Guidelines support clinicians but due to the complexity of the disease they can be difficult to adhere to.

Objectives: To map current guideline recommendations for the clinical management of CPA into a scoring tool to facilitate and quantify guideline adherence in clinical practice.

Methods: Recommendations for diagnosis, treatment and follow-up of CPA presented in the current ESCMID/ERS/ECMM and CPAnet guidance documents were assembled and weighed on the basis of their strength of recommendation and level of evidence.

Results: Twenty-seven recommendations were identified, resulting in a total maximum EQUAL CPA Score of 51. For diagnostics ($Score_{max}$ = 27), a strong emphasis on expert consultation, culture, direct microscopy, histopathology, serology and imaging was reflected in respective points, whereas molecular techniques and susceptibility testing count into the diagnostics score to a lesser extent. Ten treatment recommendations ($Score_{max}$ = 14), including antifungal therapy, therapeutic drug monitoring and treatment duration, were identified. Surgery, where indicated, adds three points. For refractory disease or intolerance of first-line antifungal treatment, optimal second-line treatment added another two points. During follow-up ($Score_{max}$ = 10), response assessment via imaging gave three points, while culture and serology added two points each to the $Score_{max}$.

Conclusion: The EQUAL CPA Score intends to be used as a comprehensive tool for measuring guideline adherence. If adherence to current guidelines is associated with clinical outcome, this will be assessed in future studies.
Diagnosis is challenged by a heterogeneous clinical picture in several subsequent conditions, including chronic obstructive pulmonary disease, lung cancer, tuberculosis or sarcoidosis, and leads to formation of pulmonary nodules, cavities, secondary pleural thickening and fibrosis. Diagnosis is hampered by the absence of a single specific test, instead diagnosis relies on a comprehensive work-up and the exclusion of relevant differential diagnosis. Treatment aims are symptom control, preventing haemoptysis, halting disease progression and eventually cure. Triazoles remain the treatment of choice. Itraconazole has been evaluated in randomized controlled trials. High-quality evidence for other antifungals is still awaited, however, voriconazole is frequently and successfully used for treatment of CPA in clinical practice. Another challenge of CPA management is the assessment of treatment response in a consistent manner across the phenotypically diverse entities and patient populations.

The 2016 European guideline on clinical management of CPA jointly published in 2016 by the European Society for Clinical Microbiology and Infectious Diseases (ESCMID), the European Respiratory Society (ERS) and the European Confederation of Medical Mycology (ECMM) provides recommendations that are applicable to a variety of clinical settings. Two years after its publication, an international CPA research network (CPAnet) was established. CPAnet recently published consensus definitions for outcome assessment to guide clinical trial design and patient follow-up. In routine clinical work, these recommendations can be difficult to comply with.

In 2018, the ECMM introduced the EQUAL scores (ECMM scores to measure quality of disease management) to provide physicians with an easy but comprehensive guidance and to quantify guideline adherence as surrogate for the quality of diagnostic and therapeutic management. Currently, EQUAL scores are available for candidemia, invasive aspergillosis, cryptococcosis, mucormycosis, fusariosis, Scedosporium-, Lomentospora- and Trichosporon-associated infections. In several subsequent studies, guideline adherence correlated with patient outcome. Here, we present an EQUAL Score weighing recommendations from current guidelines for the management of CPA. Clinicians may find this tool useful for measuring guideline adherence and adjusting clinical practices as necessary.
Figure 1. EQUAL CPA Score 2022. Items and score points reflecting guideline recommendations and the maximum score (orange, right column) achievable depending on disease complexity. Abbreviations: BAL, bronchoalveolar lavage; h, hour; IV, intravenous; FDG-PET, [18F]-fluorodeoxyglucose positron emission tomography. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*. 

| Item | Score | Score summary |
|------|-------|---------------|
| **Diagnosis** | | |
| Case discussion in multidisciplinary team conference | 3 | |
| **Respiratory sample (BAL preferred)** | | 27 |
| Direct microscopy for hyphae | 3 | |
| Fungal culture | 3 | |
| Galactomannan on respiratory sample | 2 | |
| Aspergillus-specific PCR | 1 | |
| **Biopsy** | | |
| Histology | 3 | |
| Fungal culture | 2 | |
| **Susceptibility testing** | | |
| Antifungal susceptibility testing (antimycogram or PCR) | 1 | |
| **Serology** | | |
| Aspergillus-specific IgG antibody or precipitins | 3 | |
| Aspergillus-specific IgE antibody | 2 | |
| Galactomannan on serum | 1 | |
| Aspergillus-specific IgM / IgA antibody (if IgG not done) | -1 | |
| **Imaging** | | |
| Chest CT scan | 3 | |
| **Surgery** (where indicated) | 3 | 0 |
| Surgical resection | 3 | |
| **1st line treatment**<sup>a</sup> | 6 | |
| Itraconazole 200 mg q12h or voriconazole 200–300 mg q12h | 3 | |
| Posaconazole 300 mg q24h delayed release tablets | 2 | |
| Posaconazole 400 mg q12h suspension | 1 | |
| TDM and regular screening for adverse drug reactions | 3 | |
| **2nd line treatment**<sup>a</sup> (if progressive disease,azole intolerance or resistance) | | |
| Echinocandin e.g. caspofungin 50–70 mg q24h or micafungin 150 mg q24h | 2 | |
| Liposomal amphotericin B 3 mg·kg<sup>-1</sup> q24h or other lipid-based formulation | 2 | |
| Isavuconazole 200 mg q24h tablet or IV | 2 | |
| Amphotericin B deoxycholate 0.7–1.0 mg·kg<sup>-1</sup> q24h | -1 | |
| **Treatment duration** | | 3 |
| At least 6 to 12 months of antifungal therapy | 3 | |

<sup>a</sup> Combination of antifungal drugs is discouraged.
Ten treatment recommendations were identified, yielding a maximum possible score of 14 if surgical intervention was indicated and 11 points if surgery was not indicated. Surgery might be a curative option for treatment of localized disease such as simple aspergilloma. Oral triazoles are the standard of care for CPA patients and both itraconazole and voriconazole are drugs of first-line choice (three points). Posaconazole was considered an alternative first-line choice despite insufficient evidence for the treatment efficacy for CPA, whereby a tablet formulation (two points) was preferred over a suspension (one point). Monitoring plasma drug concentrations of posaconazole (any formulation) and voriconazole as well as continued screening for untoward effects of treatment have been considered highly relevant (three points).²⁹

For second-line antifungal treatment in case of intolerance to standard of care, treatment failure or disease progression during first-line antifungal treatment, caspofungin and micafungin or lipid-based amphotericin B are recommended with limited evidence for efficacy (two points), as well as isavuconazole, which authors unanimously agreed to add as an alternative second-line treatment option (two points).³⁰ As with first-line therapy, combination therapy is discouraged and does not result in the accumulation of additional points. Antifungal therapy that was continued for at least 6 months scored three points.

Follow-up of CPA patients is essential to determine treatment response and to evaluate disease progression. The first follow-up visit, including assessment of patient reported symptoms with validated scoring systems (e.g. St. George’s Respiratory Questionnaire), thorough clinical examination and pulmonary function tests at 3–6 months, was assigned three points. Additional points were assigned for follow-up radiological evaluation (three points) and microbiological work-up of respiratory samples via culture (two points) and antibody determination (two points).

Overall, a maximum EQUAL CPA Score of 51 points could be achieved. The score was higher if surgical intervention was indicated (ScoreMax = 49 for first-line treatment vs ScoreMax = 46 for first-line treatment if surgery was not indicated) or second-line treatment was indicated (ScoreMax = 51 if surgery was indicated vs ScoreMax = 48 if surgery was not indicated), reflecting more decision points and higher complexity of the disease management.

Discussion

The EQUAL CPA Score 2022 is a 27-item assessment tool that summarized the diagnostic, treatment and follow-up recommendations from the current guidance documents of ESCMID, ERS and ECM and CPAnet. Equivalent to the other EQUAL scores, this tool was designed as a bedside instrument for self-assessment of management quality and to support antifungal stewardship.¹⁴–²⁰

One of the main objectives of CPA management is to reliably diagnose or rule out CPA when clinically suspected. A multidisciplinary team conference between healthcare professionals with different medical expertise is crucial for obtaining consensus on the appropriate diagnostic and therapeutic approaches in difficult to manage fungal infections. For pulmonary diseases as for CPA, a team conference should involve experts in the fields of pulmonology, infectious diseases and microbiology, as well as other specialties (e.g. immunology, radiology, thoracic surgery) as appropriate. A CPA diagnosis relies on a combination of radiological and microbiological, histopathological and serological methods. For microbiological disease evaluation, bronchoalveolar lavage is preferred over sputum samples, however, bronchoscopy might be contraindicated in some cases leaving sputum as the alternative type of sample. Comprehensive microbiological work-up including direct microscopy, culture, nucleic acid amplification testing and galactomannan assay is recommended. The usefulness of sputum galactomannan analysis remains controversial.³¹ Histopathology and culture results from biopsy or surgical resection is recommended to confirm disease stage and to exclude the numerous differential diagnoses, including other infectious diseases and malignancies. Repeated antifungal susceptibility testing informs about resistance development, especially in patients undergoing long-term antifungal treatment. In vitro susceptibility data guide treatment decisions and are useful for in-house disease surveillance and epidemiological investigations. In regions with high incidence of resistance reported for Aspergillus, in vitro susceptibility testing or alternative methods such as resistance gene sequencing especially in culture-negative cases are recommended.³²

Serum marker detection is considered the most effective method for the diagnosis of CPA; however, many different methods exist, and data on cut-off values, sensitivity and reproducibility are limited. Elevated Aspergillus-specific IgG is found in most cases of CPA but is also common in allergic bronchopulmonary aspergillosis and invasive aspergillosis, as well as in patients with lung diseases that may mimic CPA.³³ Other serological markers i.e. Aspergillus-specific IgE and galactomannan also present a considerable overlap to other forms of aspergillosis.³⁴ This underlines the necessity for a combined approach to diagnose CPA. Diagnosis of CPA is particularly complex and crucial for subsequent decisions on disease management. The complexity of the diagnostic work-up is reflected by the highest score possible to achieve in the EQUAL Score in comparison to treatment and follow-up.

Imaging is an important component for the diagnosis and response assessment for CPA. There is continuous evidence building that [18F]-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT can be used to estimate disease activity in infectious diseases including CPA.²⁰,³⁵ However, conventional diagnostics such as CT is often preferred over PET/CT as patient preparation and scanning is less time consuming and radiation dose is lower. The author group considers [18F]-FDG-PET/CT a useful alternative to CT for response assessment in CPA if appropriate baseline imaging is available. Regardless of imaging modality, histology is indispensable if radiologic features are suggestive of malignancy.

Recent advances in the understanding of antifungal pharmacokinetics are not represented in the most recent CPA guideline.¹³ For posaconazole, delayed release tablets with a more predictable pharmacokinetic profile than the oral suspension became available. The second-generation triazole isavuconazole with efficacy against a broad spectrum of fungi has been approved for treatment of invasive aspergillosis and mucormycosis. Its favourable safety profile is beneficial for the long treatment durations required in CPA patients but costs are high compared to the older triazoles. Posaconazole and voriconazole serum concentrations
have non-linear pharmacokinetics with interpatient variability influenced by various factors, thus, therapeutic drug monitoring is required during treatment.

All echinocandins are considered to demonstrate equal clinical efficacy in fungal infections.\[^{15}\] In CPA, the highest quality of evidence has been obtained with the use of micafungin.\[^{16}\] In the light of data showing an association of micafungin with the development of hepatocellular carcinoma in rats, caspofungin may be the drug of choice in the absence of contraindications.\[^{17}\]

Caspofungin and micafungin demonstrate similar efficacy to voriconazole in the treatment of CPA with a favourable safety profile, which makes them preferred second-line choices. An alternative with a less favourable safety profile is lipid-based amphotericin B, which should be preferred over amphotericin B deoxycholate. The added value of inhaled amphotericin B for treatment of CPA has not been comprehensively evaluated for all subtypes but first studies suggested a beneficial effect.\[^{18}\]

Association of in vivo efficacy of antifungal drugs and clinical outcome must be considered as an interplay with patients underling condition and its control during clinical course, as prognosis may vary widely between patient populations at risk.

In the 2016 guideline of the ESCMID, ERS and ECMM, a treatment duration of 4–6 months for initial therapy is recommended.\[^{19}\] A significant relapse rate in cases with discontinued antifungal treatment after 6 months has been described.\[^{20}\] A recent study suggests that a longer treatment duration of 12 months prevents relapses more effectively compared to 6 months of treatment.\[^{21}\]

Therefore, we consider a treatment duration of up to 12 months appropriate.

The EQUAL CPA Score should be used considering its limitations. With the paucity of comprehensive studies on CPA, strong guideline recommendations are still awaited. Given the low level of scientific evidences available to support recommendations for clinical management of CPA, the correlation between the score and patient outcome remains unknown and will be assessed in future studies. In addition, the diagnosis of CPA requires a high level of clinical suspicion, and when CPA is considered as a differential diagnosis, this is usually because of a high level of expertise in the respective centre. Therefore, the differences in clinical management are unlikely to be as pronounced as in more common infections such as candidemia. Furthermore, we did not differentiate the management of the proposed CPA subtypes in detail, as subtypes overlap and evolve over time, making it difficult to build on high-quality evidence.

Our scoring tool includes recommendation that cannot be found in currently used guidance documents. Despite the overall aim to provide a tool to quantify guideline adherence, our scoring system is intended to be used as a bedside tool for self-assessment that may affect the clinical practice. For educational purposes and to ensure optimal patient management, aspects considered relevant by experts in the field that did not find their way into guidelines yet should be considered.

An update of the EQUAL CPA Score is necessary if new evidence becomes available; this may include data for new antifungal agents that are currently in late-stage clinical development, including drugs with enhanced pharmacokinetic properties such as the second-generation echinocandin rezafungin or novel antifungals with oral route of administration such as fosmanogipix or ibrexafungerp.\[^{22}\]

Conclusion

The EQUAL CPA Score provides a tool for clinicians to easily follow current guideline recommendations for the clinical management of patients with CPA. Adherence to guidelines is particularly challenging for complex diseases such as CPA that are therefore often left undiagnosed and untreated if expertise in a health care facility is limited. The EQUAL CPA Score may be used as an easy self-assessment tool in clinical practice.

Funding

This study was carried out as part of our routine work.

Transparency declarations

RS reports lecture honoraria from Pfizer, outside the submitted work. EB received travel support and speaker fees, all paid to her institution, from Pfizer, Gilead and MSD. HF received travel support and speaker fees from Pfizer, Gilead, Astellas, Roche, Boehringer Ingelheim, Chiesi, Actelion, Merck/MSD, Actavis, AstraZeneca, BMS, GSK, INSmed, Novartis and Sandz. MH reports grants and personal fees from Astellas, Pfizer, Gilead, MSD, Pulmocide, F2G, Mundipharma, Scynexis and Euroimmun.

JRD reports personal fees from Roche, Boehringer Ingelheim and Chiesi for lectures, and has received support for congresses, attending meetings and travel, all outside the submitted work. RA reports receiving grants from Cipla Pharmaceuticals, India, outside of the submitted work. JRD reports personal fees from Roche, Boehringer Ingelheim and Chiesi for lectures, and has received support for congresses, attending meetings and travel, all outside the submitted work. OAC reports grants or contracts from Amplyx, Basilea, BMBF, Cidara, DZIF, EU-DG RTD (101037867), F2G, Gilead, Matinas, MedPage, MSD, Mundipharma, Octapharma, Pfizer, Scynexis; Consulting fees from Abbvie, Amplyx, Biocon, Biosys, Cidara, Da Volterra, Gilead, IQVIA, Janssen, Matinas, MedPage, Menarini, Molecular Partners, MSG-ERC, Noxxon, Octapharma, Pardes, Pfizer, PSI, Scynexis, Seres; Honoraria for lectures from Abbott, Abbvie, Al-Jazeera Pharmaceuticals, Astellas, Gilead, Grupo Bioteconco/United Medical Knight, Hikma, Medscape, MedUpdate, Merck/MSD, Mylan, Noscondo, Pfizer, Shionogi; Payment for expert testimony from Cidara; Participation on a Data Safety Monitoring Board or Advisory Board from Actelion, Allegra, Cidara, Entasis, IQVIA, Janssen, MedPage, Paratek, PSI, Pulmocide, Shionogi, The Prime Meridian Group; A patent at the German Patent and Trade Mark Office (DE 10 2021 113 007.7); Stocks from CoRe Consulting; Other interests from DGH0, DGI, ECMM, ISHAM, MSG-ERC, Wiley. DS reports grants and lecture honoraria from Pfizer outside the submitted work. CK and CBL have nothing to disclose.

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