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EQUAL Aspergillosis Score 2018: An ECMM score derived from current guidelines to measure QUALity of the clinical management of invasive pulmonary aspergillosis

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Abstract

Invasive pulmonary aspergillosis is a serious threat to immunocompromised and critical care patients. Recent detailed guidelines and treatment algorithms lead microbiologists and clinicians in diagnosis and treatment of invasive aspergillosis. Currently, there is no tool available that allows to

measure guideline adherence. To develop such a tool, we reviewed current guidelines provided by 5 scientific societies (European Society for Clinical Microbiology and Infectious Diseases, European Confederation of Medical Mycology, European Respiratory Society, Infectious Diseases Society of America (IDSA), and Infectious Diseases Working Party of the German Society for Hematology and Medical Oncology) and selected the strongest recommendations for management as key components for our scoring tool. We integrated diagnostic measures (chest computed tomography, bronchoalveolar lavage with galactomannan, fungal culture, fungal polymerase chain reaction analysis, species identification, susceptibility testing, histology with silver stain, Periodic acid–Schiff staining, and molecular diagnostics), treatment (antifungal choice and therapeutic drug monitoring), and follow-up computed tomography. The EQUAL Aspergillosis Score 2018 aggregates and weighs the components and provides a tool to support antifungal stewardship and to quantify guideline adherence.

Introduction

Invasive aspergillosis causes substantial morbidity and mortality.[1] Timely diagnosis is important to allow treatment early in the course of disease.[2, 3] However, there is uncertainty about the ideal diagnostic approach: clinicians may be reluctant to follow an aggressive diagnostic algorithm in a very sick patient, laboratory-based mycologists may not receive the appropriate samples [4, 5], and pathologists may not receive any sample at all, since invasive procedures are avoided. At first glance it appears obvious to choose a triazole for first line treatment,[2, 3, 6, 7] however, most patients at risk will already receive triazole prophylaxis. A switch in antifungal drug class upon presumed breakthrough aspergillosis is plausible,[7] but has not been subject to randomized clinical trials.[8]

Recent clinical guidelines on management of patients with invasive aspergillosis recommend on multiple diagnostic and therapeutic decisions. Complexity of the management of invasive aspergillosis is reflected in these guidelines. Currently, a total of 98 recommendations in the IDSA guideline,[6] and an impressive 286 recommendations in the ESCMID-ECMM-ERS guideline,[7] render the documents great resources for microbiologists and treating physicians even in very specific areas.

Depending on individual clinical situations and patient factors only a minority of all these recommendations may be decisive for a given patient. Focusing on invasive pulmonary aspergillosis as predominant form of aspergillosis in haematology and in transplant recipients, we developed a score reflecting the strongest recommendations from recent guidelines for those patient groups. The score can be used to evaluate guideline adherence in daily clinical practice and thus aims to support antifungal stewardship.

Methods

In order to provide a simplified overview we extracted key recommendations from recent guidance documents of the European Society for Clinical Microbiology and Infectious Diseases (ESCMID),

European Confederation of Medical Mycology (ECMM), European Respiratory Society (ERS), Infectious Diseases Society of America (IDSA), and the Infectious Diseases Working Party of the German Society for Hematology and Medical Oncology.[6, 7, 9] We broke down guidelines and grouped recommendations into three groups: diagnosis, treatment, follow-up. First, we selected "AI" and "AII" recommendations. Then we added aspects that are part of a complete work-up, but are either recommended with a lower grade of evidence or not specifically recommended in current guidelines.[3, 6, 7, 10] In a last step we allocated score points along the guideline levels of evidence and the clinical importance regarding complete work up.

Results

In a population of patients with (expected) neutropenia >10 days or patients undergoing allogeneic stem cell transplantation use of mould active prophylaxis[11] or galactomannan screening 2-3x/week in those not receiving prophylaxis is indicated (3 points). In patients with 72-96h of persistent fever despite broad-spectrum antibacterial treatment chest computed tomography (CT) is the imaging modality of choice (3 points).[7, 9] In case of pulmonary infiltrates a bronchoalveolar lavage is warranted.[7] Microbiologic testing of bronchoalveolar lavage fluid should comprise galactomannan index (1 point),[7] direct microscopy including fluorescent dyes (Calcofluor White™, Uvitex 2B™, or Blancophor™) (1 point),[7] culture (1 point), panfungal, *Aspergillus*-, and Mucorales-specific PCR (1 point)[7, 12]. In case of *Aspergillus* growth in culture, identification to species level (1 point) and susceptibility testing (1 point) is crucial for antifungal treatment.[7] If invasive pulmonary aspergillosis is refractory to treatment, histopathology is essential and mandatory staining comprises (Gomori's methenamine) silver stain (1 point),[7] periodic acid-Schiff (PAS) (1 point),[7] and in case of visible hyphae molecular diagnostics (1 point) should be conducted.[7]

For targeted first line treatment of invasive pulmonary aspergillosis isavuconazole [13-16] or voriconazole with therapeutic drug monitoring (TDM) is recommended (5 points).[7] Voriconazole target plasma trough range is 1-5.5 mg/L.[7] Voriconazole use without TDM leads to reduced scoring (-1 point).[7] In patients receiving mould prophylaxis, [11, 17] who develop breakthrough aspergillosis, liposomal amphotericin B or caspofungin is indicated (5 points).[7]

Follow-up chest CT in invasive pulmonary aspergillosis is advisable on day 7 post initiation of treatment (2 points),[10] day 14 (3 points),[10] and in case of clinical deterioration on day 21, but in case of clinical success on day 28 (2 points) to document course of treatment.[2, 3] CT scans should be done at optimized, i.e. as low as reasonably achievable dose.[10]

The maximum achievable EQUAL Aspergillosis Score 2018 ranges from 22 to 27 points, and depends on the specific patient course: The diagnostic score is higher in patients with positive fungal culture and in those with refractory disease, thus reflecting more decision points and higher case management complexity.

Discussion

The EQUAL Aspergillosis Score 2018 is a 16-item scoring-tool, derived from current guidelines and management path publications, to inform about quality of clinical invasive pulmonary aspergillosis care.[3, 6, 7, 10] From these documents we weighed the strongest recommendations on diagnosis, treatment, and follow-up.

It has been questioned whether diagnosis is overrated with a maximum of 10 to 15 points achievable, while treatment and follow-up add maximum scores of 5 and 7 points, respectively. However, a high percentage of recommendations given in infectious diseases consulting services center on proper diagnosis. Incomplete diagnostic tests are a frequent short-coming which ranges from delayed testing to not ordering individual assays at all. Clinically important and readily available test methods are thus individually listed as part of the EQUAL Aspergillosis Score. Once the true diagnosis is established, treatment is more readily facilitated. Mistakes or omissions early in the course, i.e. in the diagnostic period impact treatment initiation and course and can hardly be corrected at a later point. Diagnosing disease equals obtaining a usable search term which will identify the appropriate guidance document, and appropriate treatment strategies.

Treatment of invasive pulmonary aspergillosis, if diagnosed early in the course, is not very complex, this is in part due to the very limited number of available antifungal drugs.[7] It may gain complexity with the advent of new compounds requiring updates of the EQUAL Aspergillosis Score along diagnostic or therapeutic innovation.[18]

Follow-up is important because it determines the duration of treatment of invasive pulmonary aspergillosis. Main uncertainties concern timing of follow-up imaging and of treatment cessation.[10] Both aspects are not specifically addressed in current guidelines, which reflects the lack of published literature.[6, 7, 19] Most recommendations narrow down to advising individualized follow-up. A more science-based approach is clearly desirable.

A limitation is that the score can only be applied to invasive aspergillosis of the lung. While this is the most frequent invasive form, it would be inappropriate to apply the score in patients with disseminated disease or chronic forms of aspergillosis.

For ease of use we summarized the EQUAL Scores on laminate pocket cards, published at the Search Portal for Life Sciences Livivo *(DOI: 10.4126/FRL01-006407329)*.[20-22] The EQUAL scores may be used as simple tools to assess guideline adherence. However, it is currently unclear whether guideline adherence per se impacts prognosis of the individual patient. The EQUAL Aspergillosis Score 2018 may help align patient management with the current guidelines and improve comparability between single center studies.

Conflicts of Interest

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Figure 1. EQUAL Aspergillosis Score 2018 Items and Weights

EQUAL Aspergillosis Score 2018

Diagnosis

Item	Weight
Neutropenia >10d or alloHSCT → mould active prophylaxis <u>or</u> GM screening 2-3x/week	3
72-96h of persistent fever → CT scan	3

<u>Lung infiltrate → BAL</u>
- Galactomannan — 1
- Direct microscopy incl. fluorescent dyes: Calcofluor white, Uvitex 2B, or Blancophor — 1
- Culture — 1
- Fungal PCR (pan, Aspergillus, Mucorales) — 1

<u>Aspergillus grows in culture</u>
- Identification to species level — 1
- Susceptibility testing — 1

<u>Refractory cases → histology</u>
- Silver stain — 1
- PAS — 1
- Visible hyphae → molecular diagnostics — 1

Treatment

<u>1st-line treatment:</u>
- Isavuconazole <u>or</u> voriconazole <u>or</u> – after prior mould prophylaxis – liposomal amphotericin B or caspofungin — 5
- Voriconazole without TDM (target trough range 1-5.5mg/L) — 4

Follow-up
- CT scan on day 7 — 2
- CT scan on day 14 — 3
- CT scan on day 21 or 28 — 21

Figure 2. EQUAL Aspergillosis Score 2018 – Maximum Achievable Score Depends on Diseases Complexity

Maximum Score		If positive culture	If refractory disease	If positive culture and refractory disease
Diagnosis	10	12	13	15
Treatment		5		
Follow-up		7		
Total	22	24	25	27