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EQUAL Score Scedosporiosis/Lomentosporiosis 2021: a European Confederation of Medical Mycology (ECMM) tool to quantify guideline adherence

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Background: Invasive scedosporiosis and lomentosporiosis are life-threatening fungal infections in immunocompromised patients with complex diagnostic and treatment patterns.

Objectives: To develop a scoring tool to facilitate and quantify adherence to current guideline recommendations for diagnosis, treatment and follow-up of invasive scedosporiosis and lomentosporiosis.

Methods: Experts from European Confederation of Medical Mycology (ECMM) excellence centres reviewed current guidelines for scedosporiosis and lomentosporiosis. Recommendations for diagnosis, treatment and follow-up were summarized, assembled and weighted according to their strength of recommendation and level of evidence (strongly recommended = 3 points; moderately recommended = 2 points; marginally recommended = 1 point; recommended against = 0 points). Additional items considered of high importance for clinical management were also weighted.

Results: A total of 170 recommendations were identified. A 21-item tool was developed and embedded into the EQUAL score card. Nine items for diagnosis with 18 achievable points were assembled. For treatment, three general recommendation items with a maximal score of 9 were identified, while for specific antifungal treatment the two fungal pathogens were separated. Three and four items were established for scedosporiosis and lomentosporiosis, respectively, with a maximum achievable score of 3 due to the separation of different treatment options with the maximum point value of 3 for voriconazole-based treatment. Follow-up comprised two items (4 points maximum). Key recommendations for clinical outcome were weighted accordingly.

Conclusions: We propose the EQUAL Score Scedosporiosis/Lomentosporiosis to quantify adherence to current guideline recommendations for management of these rare infections. The score remains to be validated in real-life patient cohorts and correlated with patient outcome.

Introduction

Invasive fungal diseases (IFD) due to rare species, especially moulds, have become more frequent and cause substantial morbidity and mortality in patients.¹

Diagnosis and treatment of infections due to *Scedosporium* spp. and *Lomentospora* spp., with extremely high mortality rates, pose a particular challenge to treating physicians.^{2,3} At-risk patient groups comprise immunocompromised patients, including those

with haematological malignancy (HM), solid organ transplant (SOT), in particular lung transplant recipients, and cystic fibrosis (CF) patients and in the case of the *Scedosporium apiospermum* complex, also patients after near-drowning events.²⁻⁴ Clinical manifestations are most frequently pulmonary and cerebral, but disseminated disease with fungaemia and other forms have also been described.^{2,3,5}

Timely diagnosis with regard to the patient population at risk is the key element to avoid delays in treatment initiation and subsequently improve survival rates.⁵ However, the ideal diagnostic approach often depends on awareness of the treating physicians and the sites of infection. Furthermore, mycological diagnosis is highly complex and requires experienced laboratory-based mycologists, while in some cases appropriate samples may not even be shipped to a specialized medical mycology laboratory and pathologist.⁶

Treatment usually includes surgical debridement of infected sites, which may not always be feasible in seriously ill patients or in disseminated disease.⁷ Antifungal therapy should include an azole-based regimen and sometimes requires combination treatment due to severely compromised patients.^{2,3,8}

Guidance on clinical management of scedosporiosis and lomentosporiosis remains scarce and is largely based on retrospective analyses in this rare infection.⁹

Moreover, it is questionable whether clinicians do have guidance documents at hand and it is unknown to what extent guideline adherence affects patient outcome at all.¹⁰

As a joint initiative, European Confederation of Medical Mycology (ECMM) experts reviewed existing guideline recommendations for scedosporiosis and lomentosporiosis to quantify adherence and propose this score to improve management of patients with these infections.¹¹

Methods

Five experts [four ECMM fellows (M.L., S.C.-A.C., M.H., O.A.C.) and one aspiring ECMM fellow (J.S.)] screened available guidance publications from four scientific societies involved in the field of infectious diseases (ESCMID), medical mycology (ECMM) and haematology and transplantation (Australasian Guideline Committee; guidelines of the American Society of Transplantation Infectious Diseases Community of Practice, AST ID) on recommendations for the management of IFD due to scedosporiosis/lomentosporiosis.^{9,12-14} All recommendations were included in a first review.

Key recommendations relevant for clinical practice were selected and summarized. These were assembled into three parts: diagnosis, treatment and follow-up.

We weighted recommendations according to their strength of recommendation and level of evidence (strongly recommended = 3 points; moderately recommended = 2 points; marginally recommended = 1 point; recommended against = 0 points). Some aspects not mentioned specifically in the guidelines but of utmost clinical importance were also included as additional items in the score and weighted according to a consensus decision, such as consultation of an infectious disease physician upon diagnosis or follow-up imaging to evaluate treatment response.

A hypothetical patient should be followed along the aggregated items to facilitate and quantitate quality of patient management.

Results

A total of 118 recommendations from the ECMM guideline were identified (13 of those for children only).⁹ Additionally, 39

Scedosporium and *Lomentospora*-specific recommendations from the 2014 ESCMID-ECMM guideline, 6 from the AST ID (treatment only) and 7 (for treatment only) from the Australasian Guideline Committee were identified, resulting in an overall number of 170 recommendations.¹²⁻¹⁴

A 21-item tool was developed as an EQUAL score card and assembled as displayed in Figure 1.

Nine items for diagnosis with 18 achievable points were identified. Diagnosis should be based on culture and histopathology. Molecular and proteomic techniques are recommended but lack accuracy due to still incomplete databases for reference sequences and are therefore only marginally recommended. Antifungal susceptibility testing (AFST) using EUCAST or CLSI methodology should inform epidemiological purposes, but not guide antifungal treatment in general and a recommendation is supported with moderate strength in the current ECMM guideline due to missing clinical breakpoints.⁹ Imaging of all suspected sites of infection should be performed to evaluate the extent of IFD.

For treatment, three general recommendations with a maximal score of 9 were developed, while for specific antifungal treatment the two pathogens were separated. For scedosporiosis, three items, and for lomentosporiosis, four items were formulated, respectively. Appropriate first-line treatment comprises only one item with 3 points (voriconazole-based regimen), therefore this is the maximum achievable score for treatment. If voriconazole is not used, the total achievable score reduces to 7 for scedosporiosis and 8 for lomentosporiosis, respectively, as 3 points for strongly advised therapeutic drug monitoring (TDM) for voriconazole will drop out.

Surgical debridement of all sites involved in invasive infection remains the cornerstone for successful treatment, as well as antifungal therapy with a voriconazole-based regimen. For lomentosporiosis, terbinafine 500-1000mg/day should be added. Amphotericin B monotherapy is not recommended and should be avoided. Immediate treatment initiation is not explicitly mentioned in guidelines, but any delay can be considered malpractice in such a rapidly progressive disease.

Follow-up measures comprise two items with a maximum of 4 points, including regular imaging and the reconstitution of immune competence of the patient. No recommendations for specific antifungal prophylaxis were identified. This results in a maximum score of 34 points, while it decreases to 29 and 30 points for scedosporiosis and lomentosporiosis, respectively, if voriconazole is not the first-line treatment (Figure 2).

Discussion

The EQUAL Scedosporiosis/Lomentosporiosis Score is a 21-item card for management of patients with IFD due to *Scedosporium* spp. and *Lomentospora* spp., derived from current guidelines, aggregating and weighting the recommendations according to their strength.

Antifungal prophylaxis to prevent scedosporiosis/lomentosporiosis was not addressed since infections due to these agents remain too rare to propose specific prophylaxis. However, general recommendations for mould-active prophylaxis in high-risk patients should be followed.¹⁵ In other patient groups, such as colonized CF, lung transplant or near-drowned patients,

EQUAL Scedosporiosis/Lomentosporiosis Score 2021		
Diagnosis ¹	- Imaging incl. CNS to document the extent of disease	2
	- ID and/or mycological reference laboratory consultation	3
	Infected tissue(s) or body fluids:	
	- Culture from BAL or any other tissue/fluid ² (morphology, physiology)	3
	- Direct microscopic examination with calcofluor white staining	2
	- Blood cultures (to rule out haematogenous dissemination)	2
	- Species complex/species identification (morphology, ITS-1/2)	1
	- Further molecular and/or proteomic analysis of clinical specimens or cultures (MALDI-TOF, β-tubulin sequencing, pan-fungal PCRs)	1
	- Histopathological examination of biopsy (Grocott's/PAS stain)	3
	- Antifungal susceptibility testing	1
Treatment	- Immediate treatment initiation	3
	- Surgical debridement of suspected infected sites (if possible)	3
	<i>Scedosporium (apiospermum)</i>	
	- Voriconazole-based therapeutic regimen (Day 1: 2 × 6 mg/kg/day; from Day 2: 2 × 4 mg/kg/day)	3
	- Isavuconazole- or posaconazole-based treatments	1
	- Amphotericin B (liposomal or lipid complex) monotherapy	-1
	<i>Lomentospora (prolificans)</i>	
	- Voriconazole + terbinafine 500–1000 mg/day ± other antifungals	3
	- Voriconazole monotherapy	2
	- Isavuconazole or posaconazole in combination with other antifungal classes	1
- Amphotericin B (liposomal or lipid complex) monotherapy	-1	
- Therapeutic drug monitoring for voriconazole	3	
Follow-up	- Weekly response assessment via imaging of infected body site	2
	- Consider reducing immunosuppression	2

¹Consider mould-active antifungal prophylaxis in patients with neutropenia >10 days or allogeneic HSCT and recipients of donor lungs colonized with *Scedosporium* spp. or *Lomentospora* spp.

²Respiratory samples from CF patients: SceSel+ medium, incubation time minimum 7 days up to 14 days.

Figure 1. EQUAL Scedosporiosis/Lomentosporiosis Score with items and weights reflected by guideline recommendations. ID, infectious diseases; BAL, broncho-alveolar lavage; ITS, internal transcribed spacer; PAS, periodic acid Schiff; CF, cystic fibrosis. This figure appears in colour in the online version of JAC and in black and white in the print version of JAC.

prophylaxis may be considered, but has not received a general guideline recommendation so far due to lack of clinical studies assessing a potential benefit.¹⁶ Of note, for respiratory samples of CF patients, SceSel+ agar should be used with longer incubation times.^{17,18} However, the score is not designed to differentiate colonization and infection in this patient population.

Diagnosis seems over-represented in this score, with 18 points achievable. However, as correct diagnosis with determination of the causative pathogen is crucial to respond to such rapidly progressive IFD, this weighting seems reasonable when assuming

that diagnosis will be followed by immediate targeted treatment. AFST may inform epidemiology of scedosporiosis and lomentosporiosis and can be of information for clinicians if empirical or first-line antifungal treatment fails.¹⁹ Serological assays for diagnosis are not generally recommended, and only marginally recommended for in-house tests.⁹

Novel laboratory-based diagnostic tools have become available more broadly and reference sequence databases for PCR-based identification of *Scedosporium* spp. and *Lomentospora* spp. have improved and may enhance diagnosis.²⁰

Maximum score			
		Scedosporiosis	Lomentosporiosis
Diagnosis		18	
Treatment		9	
If voriconazole is not used		6	
First-line treatment	3	3	3
Second-line treatment (if first line not available)	1/2	1	2
Follow-up		4	
Total	34 (36)	34 ¹	34 ²
Comments			
¹ Reduces to 29 points, if voriconazole is not used as first-line treatment.			
² Reduces to 30 points, if voriconazole is not used as first-line treatment.			

Figure 2. Maximum score achievable for scedosporiosis and lomentosporiosis. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

Scedosporium (apiospermum) and *Lomentospora (prolificans)* were separated regarding treatment due to their different susceptibility profiles and outcomes.^{5,9}

The score point value for treatment results were rather low compared with diagnostics, which is due to the lack of treatment options and the lack of randomized studies regarding this rare disease, therapeutic concepts therefore mostly being based on retrospective studies.^{3,21} Treatment with voriconazole has been shown to improve outcomes compared with other regimens.²² For lomentosporiosis, the combination of voriconazole and terbinafine showed a higher survival probability compared with other antifungal combinations.²¹ In the case of progressive disease, combinations with other antifungal classes have been tried, but with lower success rates.³ A combination of azoles with terbinafine seems more recommendable than implementation of echinocandins.

It must be emphasized that one single misconception in treatment, such as ignoring recommendations of voriconazole TDM when drug levels are low, can lead to adverse outcomes. We therefore strongly encourage always consulting a reference laboratory or a clinical mycologist/infectious disease specialist once *Scedosporium spp.* or *Lomentospora prolificans* is identified in a clinically significant context. We included this aspect in the score even though this recommendation was not given in guidelines as it is considered a key element by leading mycologists.²³

Follow-up focuses on evaluation of treatment response and reducing immunosuppression if possible. Granulocyte-colony stimulating factor (G-CSF) for the reconstitution of immune competence of the infected patient has been discussed but remains controversial.²⁴ A final brain scan after stabilization of the patient and before treatment termination may be of use since CNS involvement often occurs later during the IFD course.

Limitations of the score comprise the overweighting of points for diagnostic items compared with treatment items, partially caused by the methodology of point value distribution of the EQUAL Scores and partially inherent to limited guideline recommendations. Furthermore, the score still needs to be applied in the clinical setting and to be validated independently. Additionally, the score is designed for invasive infection and does not display

guidance for other entities, such as allergic bronchopulmonary mycosis due to *Scedosporium spp.*⁶

EQUAL score cards have been developed for other IFDs such as candidaemia, invasive aspergillosis, mucormycosis, cryptococcosis and fusariosis and translated into 22 languages with open access availability.^{25–30} These scores have been validated by several research groups, based on real-life patient data, with reasonable results regarding their correlation with patient outcome.^{31–37}

We here present an additional EQUAL score card for scedosporiosis and lomentosporiosis to improve patient management of rare invasive fungal infections.

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