Quantifying guideline adherence in mucormycosis management using the EQUAL score

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

Summary
Objectives: Mucormycosis is a difficult-to-diagnose life-threatening disease with high morbidity and mortality. Adherence to guidelines that lead through complex management and support clinical decisions is however rarely reported. By applying the EQUAL Score, our study evaluates the management of mucormycosis at the University Hospital of Cologne, Germany.

Methods: We performed a retrospective chart review of patients with mucormycosis at the University Hospital of Cologne. Data collection comprised items for quality assessment in mucormycosis management according to the EQUAL Mucormycosis Score and economics.

Results: Of 29 patients identified, 27 were documented retrospectively. Eight patients of 18 with neutropenia (>10 days) or receiving allogeneic stem cell transplantation (44.4%) received mould active prophylaxis. Chest CT was done in 21 patients (77.8%), while BAL and direct microscopy of BAL fluid was performed in 22 patients (81.5%), culture in 22 (81.5%) and fungal PCR in 24 (88.9%). First-line treatment was liposomal amphotericin B in 19 patients (70.4%). Isavuconazole or posaconazole with therapeutic drug monitoring was used in four (14.8%) and in one patient (3.7%), respectively. In our cohort, crude mortality was 51.9% (n = 14) with a median survival time of 113 days. During the management of the 27 patients, 450 points (53.8%) of the maximum EQUAL Mucormycosis Score were achieved (median 15 points, range 6-30).

Conclusions: We observed management of mucormycosis aligning with current guidelines and hope to encourage other groups to use the EQUAL Score in routine clinical settings. Future studies will evaluate whether guideline adherence in mucormycosis management improves patient outcome.
1 | INTRODUCTION

Mucormycosis is a difficult-to-diagnose life-threatening disease with high morbidity and mortality. Clinical patterns are diverse and span from pneumonia to sinusitis, but other organs may be involved too. Haematogenous dissemination and contiguous invasion of adjacent organs are characteristics explaining dire prognosis.1-3 Patients at highest risk are those with haematological malignancy, uncontrolled diabetes or blunt trauma.1,4-6 Diagnosis is difficult since it requires a high index of suspicion in a rare disease. Definitive proof involves tissue sampling often contraindicated by underlying factors. Treatment demands availability of experienced surgeons and early and adequate antifungal therapy. Mucormycosis management thus needs a team of experts from different disciplines rendering it a medical and organisational challenge.

Guidelines lead through the complex management pathways and support clinical decisions.7,8 However, mucormycosis guideline adherence is rarely reported. The difficulty quantifying adherence may be one reason. In 2018, the European QUALity (EQUAL) Score was derived from current guidelines and converts guideline recommendations into score points.8,9

By applying the EQUAL Score, our study evaluates the management of mucormycosis at the University Hospital of Cologne, Germany. The study is part of a teaching project at our university, as previously described.10

2 | PATIENTS AND METHODS

2.1 | Patients

We performed a retrospective chart review of patients with mucormycosis at the University Hospital of Cologne, a 1540-bed teaching hospital with a large haematology unit and allogeneic stem cell transplant programme. Medical students (FO, AB, NB, SB, FBC, JME, LP, AWR, OR, MS, JSc, AS) were trained for documentation of health records and then performed an audit of diagnostic and treatment decisions in patients with mucormycosis treated at the hospital between 1st January 2011 and 28th February 2019 (Table 1). This study was carried out in accordance with the ethical principles reflected in the Declaration of Helsinki.11

2.2 | Documentation

Available cases were retrieved from the inpatient hospital information system. International Classification of Diseases (ICD) Codes used were B46, B46.0, B46.1, B46.2, B46.3, B46.4, B46.5, B46.8 and B46.9. Data collection comprised items for quality assessment in mucormycosis management according to the EQUAL Mucormycosis Score (Table 2). Quality indicators were defined as diagnostic (max. 11 to 18 points depending on available specimen and/or biopsy), treatment (max. 8 points) and follow-up procedures (max. 6 points). The maximum EQUAL Mucormycosis Score counts thus between 25 and 32 points.9

All records were double-checked by an infectious diseases physician for missing values or inconsistency (PK and SCM), and queries were issued until resolved.

2.3 | Teaching

Documentation, interpretation of results and authoring of the paper were part of an established teaching concept on scientific writing at the University of Cologne embedded into the Medical School Research Track as described previously.10 Twelve students participated in this project. After documentation of mucormycosis cases, students were taught drafting an original manuscript during a one-day course. The draft was revised by PK, SCM, JSt, FO, FF, JSG, FK and OAC.

2.4 | Statistics

Categorical variables are presented as frequencies and percentages, while continuous variables are presented as median and interquartile range, as appropriate, after variable distribution was evaluated with Shapiro-Wilk test. The latter were compared using Mann-Whitney U test. A two-tailed P-value < .05 was defined as statistically significant. Statistical computation and design of Figures 1 and 2 were performed with the python libraries pandas v0.23.4 and scipy v1.2.0 and data visualisation with matplotlib v3.0.2 and seaborn v0.9.0 distributed through pypi.org under python version 3.6.6. Further statistical analyses were performed using IBM SPSS Statistics for Windows (version 25, IBM SPSS Inc). Survival probability of patients with mucormycosis was assessed by Kaplan-Meier survival plots (Figure 3A,B).

2.5 | Economics

Clinical data were merged with economic data using a hospital controlling programme (eis.TIK®; KMS AG). Economic data are based on the German Diagnosis Related Group (G-DRG) reimbursement system regulated by the Institute for the Hospital Remuneration System (InEK GmbH). No discounting was performed, and all economic data...
are expressed in Euro (€) based on respective currency rates for the years 2011 to 2019 (Table 3).

3 | RESULTS

The overall mucormycosis incidence rate of this retrospective cohort study was 0.06/1000 admissions.

3.1 | Patient characteristics

Of 29 patients identified, two were excluded due to insufficient data quality leading to 27 study participants documented retrospectively.
22.2%), pre-existing diabetes (n = 1, 11%) and solid organ transplantation (n = 1, 11.1%). With regard to malignancy, 38.9% (n = 7) of haematology patients had acute myeloid leukaemia (AML), 27.8% (n = 5) had acute lymphoblastic leukaemia (ALL) and 27.8% (n = 5) had other malignancies (lymphoma n = 2, chronic myelogenous leukaemia (CML) n = 2, chronic myelomonocytic leukaemia (CMML) plus lung adenocarcinoma n = 1, myeloma n = 1). Sites of infection were pulmonary (n = 14, 51.9%), cutaneous (n = 2, 7.4%), gastrointestinal (n = 1, 3.7%) and paranasal sinus (n = 1, 3.7%). Disseminated disease was present in nine (33.3%) patients (Tables 1 and 2).

### 3.2 | Diagnostics

Eight patients of 18 with neutropenia for longer than ten days or receiving allogeneic SCT (44.4%) received mould active prophylaxis.

| Quality indicator                                                                 | Score points | Overall patients | Performed in patients | Achievable score | Achieved score |
|----------------------------------------------------------------------------------|--------------|------------------|-----------------------|------------------|----------------|
| **Diagnosis**                                                                    |              |                  |                       |                  |                |
| Mould active prophylaxis*                                                        | 3            | 27/18*           | 8                     | 81/54*           | 24             |
| Chest CT in case of persistent fever (72-96hrs)                                  | 3            | 27               | 21                    | 81               | 63             |
| **In case of inverse halo:**                                                     |              |                  |                       |                  |                |
| CT/MRI staging: head, neck, abdomen                                              | 2            | 27               | 9                     | 54               | 18             |
| **BAL**                                                                          |              |                  |                       |                  |                |
| Direct microscopy, preferably using optical brighteners                           | 1            | 27               | 22                    | 27               | 22             |
| Culture                                                                          | 1            | 27               | 22                    | 27               | 22             |
| PCR (pan-fungal, *Aspergillus*, *Mucorales*)                                     | 1            | 27               | 24                    | 27               | 22             |
| **Biopsy in case of negative microbiological tests**                              |              |                  |                       |                  |                |
| Biopsy specimen culture                                                           | 2            | 27               | 12                    | 54               | 24             |
| Histopathology                                                                   | 2            | 27               | 12                    | 54               | 24             |
| Molecular-based tests                                                            | 1            | 27               | 3                     | 27               | 3              |
| Isolate growth: Identification to species level and susceptibility testing        | 2            | 27               | 5                     | 54               | 10             |
| **Total diagnosis score**                                                        |              |                  |                       |                  |                |
|                                                                                | 486/459*     | 232              |                       | 47.7%/50.5%*     |                |
| **1st line treatment**                                                           |              |                  |                       |                  |                |
| Surgical debridement                                                             | 2            | 27               | 11                    | 54               | 22             |
| With microscopically clear resection margins                                     | 1            | 27               | 7                     | 27               | 7              |
| L-AmB ≥ 5 mg/kg/d                                                                | 3            | 27               | 19                    | 81               | 57             |
| Isavuconazole with TDM                                                            | 2            | 27               | 4                     | 8                |                |
| Posaconazole with TDM                                                             | 2            | 27               | 1                     | 2                |                |
| Control of risk factors*                                                         | 2            | 27               | 25                    | 54               | 50             |
| **Total treatment score**                                                        |              |                  |                       |                  |                |
|                                                                                | 216          | 146              |                       | 67.6%            |                |
| **Follow-up**                                                                    |              |                  |                       |                  |                |
| CT scan on day 7                                                                 | 2            | 27               | 15                    | 54               | 30             |
| CT scan on day 14                                                                 | 2            | 27               | 14                    | 54               | 28             |
| Weekly CT scan until improvement                                                 | 2            | 27               | 7                     | 54               | 14             |
| **Total follow-up Score**                                                        |              |                  |                       |                  |                |
|                                                                                | 162          | 72               |                       | 44.4%            |                |
| **Total EQUAL Score**                                                            |              |                  |                       |                  |                |
|                                                                                | 864/837*     | 450              |                       | 52.1%/53.8%*     |                |

Note: Twelve patients underwent biopsy; in five patients isolates could be cultured (18.5%);
Abbreviations: BAL, bronchoalveolar lavage; CT, Computed tomography; D, day; L-AmB, liposomal amphotericin B; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; TDM, therapeutic drug monitoring.

*In case of neutropenia > 10 d or allogeneic stem cell transplantation;

*Neutropenia, hyperglycaemia, ketoacidosis, corticosteroids. In case of multiple options, for example surgical debridement with or without debridement the higher score value was chosen. Combination therapy of azole plus polyene in six patients (data not shown).
Chest computed tomography (CT) was done in 21 patients (77.8%) with persistent fever despite broad-spectrum antibiotic therapy. Nine patients (33.3%) received CT or magnetic resonance imaging (MRI) staging of head, neck and abdomen. Bronchoalveolar lavage (BAL) and direct microscopy of BAL fluid was done in 22 patients (81.5%), culture in 22 (81.5%) and fungal PCR in 24 (88.9%). Twelve
**FIGURE 3** A. Survival probability of patients diagnosed with mucormycosis. B. Survival probability of patients diagnosed with mucormycosis stratified by haematology and non-haematology patients.

**TABLE 3** Performance and cost data

|                         | Total   | Haematology | Non-haematology |
|-------------------------|---------|-------------|-----------------|
| Cases                   | 27      | 18          | 9               |
| Cases at ICU            | 15      | 8           | 7               |
| Total reimbursement/ costs | €2,743,794.45 | €2,061,903.51 | €681,890.93 |
| Reimbursement/ costs per case, mean ± SD | €101,622.02 ± €80,299.38 | €114,550.20 ± €82,297.45 | €75,765.66 ± €63,866.59 |
| Reimbursement/ costs per case, median (IQR) [Range] | €85,428.84 (€36,389.48-€136,070.95) | €99,404.75 (€42,523.38-€146,606.06) | €78,487.05 (€20,031.94-€108,195.42) |
| Surcharges/ extra fee (included) | €813,435.29 | €736,237.02 | €77,198.27 |
| Case mix (Total points) | 597.54  | 411.35      | 186.19          |
| Case mix Index, mean ± SD | 22.13 ± 17.91 | 22.85 ± 17.77 | 20.69 ± 18.12 |
| Total length of stay/ hospitalisation (days) | 1747 | 1254 | 493 |
| Length of stay/ hospitalisation (days), mean ± SD | 64.7 ± 44.0 | 69.7 ± 43.1 | 54.8 ± 63.5 |
| Length of stay/ hospitalisation (days), median (IQR) [Range] | 44.0 (23.0-95.0) | 62.0 (34.0-97.3) | 30.0 (10.5-95.0) | 4.0-193.0 |

**Note:** Abbreviations: ICU, intensive care unit; SD, standard deviation.
patients (44.5%) were biopsied. Biopsy specimen culture for isolation of bacteria and fungi (n = 12, 100%), histopathology (n = 12, 100%) and molecular-based tests on biopsy samples (n = 3, 25%) were done. Diagnostic yield of fungal culture was 18.5% (n = 5); all these isolates were identified to species level and underwent susceptibility testing. Twelve cases were defined proven by histopathology, 15 cases probable mycological evidence by culture or PCR in non-sterile according to the current EORTC/MSGERC consensus definitions of invasive fungal diseases (IFDs).

Median score achieved for diagnosis of mucormycosis was 7.0 (IQR: 6.0-12.0) out of 18.

3.3 | Treatment

First-line treatment was liposomal amphotericin B (L-AmB) (>5 mg/kg body weight per day) in 19 patients (70.4%). Isavuconazole or posaconazole with therapeutic drug monitoring was used in four (14.8%) and in one patient (3.7%), respectively. Three patients (11.1%) did not receive antifungal therapy for mucormycosis because therapy goals had changed to palliative care. Surgical debridement with microscopically clear resection margins was achieved in seven patients (26%). In 25 patients (92.6%), predisposing factors were closely monitored and counter measures were taken. A day 7 CT was performed in 15 (55.6%) and at day 14 in 14 patients (51.8%). With regard to treatment, a median score of 5.0 (IQR: 4.0-7.0) out of 8 points was achieved.

3.4 | Follow-up

Weekly follow-up CT scans were accomplished in seven patients (26%). For follow-up, a median score of 2.0 (IQR: 0.0-6.0) out of 6 points was achieved. In our cohort, crude mortality was 51.9% (n = 14) with a median survival time of 113 days (IQR: 11.0-261.0 days). Survival probability is depicted in Figure 3A, B.

During the management of the 27 patients, 450 points (53.8%) of the maximum EQUAL Mucormycosis Score were achieved (median: 15 points; IQR: 10.0-24.0; range: 6-30). Total score points achieved for quality indicators specifying diagnostic procedures were 232 of 459 maximum points (50.5%) (Table 2), for treatment 146 of 216 points (67.6%) and for follow-up 72 of 162 points (44.4%). Boxplots showing the scores for the 27 patients subdivided by diagnosis, treatment and follow-up in haematology versus non-haematology patients are shown in Figure 1 and with regard to outcome in Figure 2.

3.5 | Economics

As demonstrated in Table 3, the economic analysis of the 27 coded German Diagnosis Related Groups (G-DRG) cases has shown an overall case mix (CM) of 597.54 (case mix index [CMI] 22.13 ± 17.91; median value: 18.02 [IQR: 7.90-34.36]) with an average hospitalisation of 64.7 ± 44.0 days (median value: 44 days; IQR: 23.0-95.0 days; range 4-193 days). Through the whole group, we had total costs of €2.74 million including surcharges for high-cost drugs and treatments, which are not covered by the G-DRG lump sum. The average costs per case were €101 622 ± €80 299.38, and median was €85 428 (IQR: €36 389.48-€136 070.95; range: €3390.59-€344 426.72). In group 1 (haematology, n = 18) median costs were nearly €100 000 per case (IQR: €42 523.38-€146 606.06; CMI: 22.85 ± 17.77) and in group 2 (non-haematology, n = 9) €78 487 per case (IQR: €20 031.94-€108 195.42; CMI: 20.69 ± 18.12). There was a lower average length of stay in group 2 (54.8 ± 63.5 days; group 1: 69.7 ± 43.1 days), and average CMI per case was 2 points lower than in the haematology group (CMI 22.85 ± 17.77 vs CMI 20.69 ± 18.12).

4 | DISCUSSION

In this retrospective study at the University Hospital of Cologne, Germany, the overall mucormycosis incidence rate was 0.06/1000 admissions. This concurs with the reported general incidence of mucormycosis in Europe ranging from 0.006 to 0.2/1000 admissions.

Mould active prophylaxis was performed in 44.4% of patients who either had expected neutropenia for more than 10 days, or who had received allogeneic stem cell transplantation. The rate is similar to the 45.5% in the EQUAL Score validation study.

Median score achieved for diagnosis of mucormycosis was 7.0 (IQR: 6.0-12.0) out of a maximum of 18. Most score points were achieved by imaging: 77.8% of the patients with persistent fever underwent a CT scan. BAL was performed in 77.8% of patients. Compared to a previous analysis that achieved 67.9% adherence to diagnostic guideline recommendations, our patients only reached a guideline adherence of 47.7%.

This deviation is due to fewer molecular-based tests performed on biopsies in only three (11.1%) patients, as nuclear amplification assays were introduced rather recently.

At our hospital, a management algorithm exists for patients with persistent fever and treating physicians are well aware of diagnostic steps. In addition, treating physicians are well supported by an infectious disease consulting service. This may explain the rate of appropriate CT scans.

Patients achieved a median score of 5.0 (IQR: 4.0-7.0) out of 8 points for treatment. Out of 27 patients, 19 (70.4%) received L-AmB as first treatment, while only 11 patients (40.7%) had surgical debridement. Debridement is not always feasible due to health conditions of our patients, specifically in the haematological/oncological setting. In addition, three patients died before surgery could be performed.

Regarding follow-up, a median score of 2.0 (IQR: 0.0-6.0) out of 6 points was achieved. A CT scan on day 7 was performed in 15 patients of whom 13 (86.6%) also received CT follow-up on day 14.
Three of 27 patients (11.1%) died within seven days after diagnosis, eight within the first months—accounting for a total mortality of 48.1%. This is in accordance with previously reported studies showing 44% to 72.2%.9,15

We conclude that the EQUAL Score may not be an appropriate tool for patients who die within the first days after diagnosis. In these patients, treatment and follow-up management cannot be evaluated.

Cost data and economic analysis have shown higher resource consumption in the haematology group associated with higher average length of stay. Due to different main diagnosis and resource utilisation in both groups, we identified wide ranges of costs per case. There is an apparent need for detailed cost and reimbursement evaluations for such patients.

Results of this study are limited due to its retrospective character and relatively small patient number compared to other case series.1,4,16 However, first application of the EQUAL Score within a small case series facilitates experience of its feasibility and insights in management at our own hospital. We decided to only include patients with electronic case files, which were introduced in 2011 at our hospital. Lacking reference populations for comparison are a further limitation as the score has not been applied to other patients yet. Studies with greater sample sizes are needed to verify our results in the future.

Data collected in this retrospective analysis represents a real-life scenario of clinical routine care. As performed previously,10 we were able to combine our scientific approach with medical student teaching.

We observed management of mucormycosis aligning with current guidelines and hope to encourage other groups to use the EQUAL Score in routine clinical settings. Ultimately, we may learn whether guideline adherence in mucormycosis management improves patient outcome.

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CONFLICT OF INTEREST
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REFERENCES
1. Vehreschild JJ, Birtel A, Vehreschild MJ, et al. Mucormycosis treated with posaconazole: review of 96 case reports. Crit Rev Microbiol. 2013;39:310-324.
2. Skia da A, Pagano L, Groll A, et al. Zygomycosis in Europe: analysis of 230 cases accrued by the registry of the European Confederation of Medical Mycology (ECMM) Working Group on Zygomycosis between 2005 and 2007. Clin Microbiol Infect. 2011;17:1859-1867.
3. Koehler P, Reimer R, Wahba R, Schomig-Markiecka B, Cornely OA. Transdiaphragmatic Mucormycosis. *Clin Infect Dis*. 2019. https://doi.org/10.1093/cid/ciz533. [Epub ahead of print].

4. Roden MM, Zaoutis TE, Buchanan WL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. *Clin Infect Dis*. 2005;41:634-653.

5. Petrikos G, Skiada A, Lortholary O, Rolildes E, Walsh TJ, Kontoyiannis DP. Epidemiology and clinical manifestations of mucormycosis. *Clin Infect Dis*. 2012;54(Suppl 1):S23-34.

6. Chakrabarti A, Das A, Mandal J, et al. The rising trend of invasive zygomycosis in patients with uncontrolled diabetes mellitus. *Med Mycol*. 2006;44:335-342.

7. Tissot F, Agrawal S, Pagano L, et al. ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients. *Haematologica*. 2017;102:433-444.

8. Cornely OA, Alastrauey-Izquierdo A, Arenz D, et al. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. *Lancet Infect Dis*. 2019;19(12):405-421. https://doi:10.1016/S1473-3099(19)30312-3. Epub 2019 Nov 5.

9. Koehler P, Mellinghoff SC, Lagrou K, et al. Development and validation of the European QUALity (EQUAL) score for mucormycosis management in haematology. *J Antimicrob Chemother*. 2019;74:1704-1712.

10. Mellinghoff SC, Hartmann P, Cornely FB, et al. Analyzing candidemia guideline adherence identifies opportunities for antifungal stewardship. *Eur J Clin Microbiol Infect Dis*. 2018;37:1563-1571.

11. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310:2191-2194.

12. Donnelly JP, Chen SC, Kauffman CA, et al. Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. *Clin Infect Dis*. 2019. https://doi:10.1093/cid/ciz1008. [Epub ahead of print].

13. Kontoyiannis DP, Wessel VC, Bodey GP, Rolston KV. Zygomycosis in the 1990s in a tertiary-care cancer center. *Clin Infect Dis*. 1990s;30:851-856.

14. Torres-Narbona M, Guinea J, Martínez-Alarcón J, Muñoz P, Peláez T, Bouza E. Workload and clinical significance of the isolation of zygomycetes in a tertiary general hospital. *Med Mycol*. 2008;46:225-230.

15. Kyvernitakis A, Torres HA, Jiang Y, Chamilos G, Lewis RE, Kontoyiannis DP. Initial use of combination treatment does not impact survival of 106 patients with haematologic malignancies and mucormycosis: a propensity score analysis. Clinical microbiology and infection : the official publication of the. *Eur Soc Clin Microbiol Infect Dis*. 2016;22:811.e1-e8.

16. Lanternier F, Dannaoui E, Morizot G, et al. A global analysis of mucormycosis in France: the RetroZygo Study (2005-2007). *Clin Infect Dis*. 2012;54(Suppl 1):S35-S43.

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