Impact of the revised (2008) EORTC/MSG definitions for invasive fungal disease on the rates of diagnosis of invasive aspergillosis

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Diagnosis of invasive aspergillosis (IA) remains a challenge as the clinical manifestations are not specific, and a histological diagnosis is often unfeasible. The 2002 European Organization for Research and Treatment of Cancer (EORTC) and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (MSG) criteria for classification of cases into possible, probable or proven were revised in 2008. Our objective was to analyze the impact of these revisions on the diagnosis of IA. A retrospective analysis of 589 high risk patient-episodes revealed that 125 of 155 ‘possible’ (81%) and 12 of 16 ‘probable’ (75%) cases of IA should be changed to ‘non-classifiable’ when the new criteria were applied. We concluded, as expected, that the 2008 EORTC/MSG revised definitions reduced the number of cases classified as ‘possible’ IA, but additionally, there has been a dramatic reduction in ‘probable’ cases. These changes have significant implications on the interpretation of clinical trial data based on EORTC/MSG classifications.

Keywords invasive aspergillosis, EORTC/MSG, leukaemia, transplantation

Introduction

Invasive aspergillosis (IA) accounts for more than 80% of invasive fungal diseases (IFD) and is a potentially life-threatening opportunistic infection affecting immunocompromised patients [1,2]. The overall incidence of IA in more recent reports in those with hematological malignancies and allogeneic hematopoietic stem cell transplant recipients has been reported to range from 4.7–13.1% and have an attributable mortality of from 27–72.4% [3,4].

Early diagnosis and treatment is associated with more favorable outcomes [5]. However, specifically identifying IA remains a challenge as the clinical manifestations are not unambiguous, as well as, the current diagnostic tools described in the literature show highly variable sensitivities and specificities [6–10] and are not routinely available in many centers. Furthermore, the diagnostic gold standard of a histological study and/or recovery of the etiologic agent in culture from a tissue biopsy is rarely feasible ante-mortem as patients are too unstable to undergo invasive procedures. This diagnostic uncertainty leads to many patients being unnecessarily treated for presumed IA which could result in additional toxicities and has major cost implications. On the other hand, due to these problems many cases of IA are only discovered post mortem [11,12].

In 2002 the European Organization for Research and Treatment of Cancer (EORTC) and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (MSG) devised criteria for classification of potential cases according to the likelihood of underlying invasive fungal disease (IFD) into possible, probable and proven. These
definitions were intended for use in the context of clinical and/or epidemiological research but not for making clinical decisions [13]. To prove infections requires histological evidence or the isolation of the suspected etiologic agent in culture from a normally sterile site. Classification of cases as ‘possible’ or ‘probable’ were based on consideration of a constellation of host, clinical and microbiological criteria. Clinical criteria were further subdivided into ‘major’, i.e., referring to specific radiological changes or ‘minor’, those founded on mostly clinical symptoms and signs.

The combination of at least one host, one major or two minor clinical features and at least one microbiological characteristic, were required for the designation of a ‘probable’ infection. The combination of at least one host factor and either one major or two minor clinical criteria or one microbiological criterion were needed for classification of a case as ‘possible’. These criteria were revised in 2008 with the objective of minimizing the number of cases previously classified as ‘possible’ IFD when there was little supportive evidence. In addition, the new classification criteria were intended to expand the ‘probable’ category thus increasing the certainty of diagnoses [14]. The significant changes in 2008 included the elimination of the 2002 category of minor clinical criteria and restriction of the clinical criteria for fungal lower respiratory tract infections to very specific findings from computed tomography (CT). Furthermore, possible IFD, according to the new 2008 classification, is restricted to the combination of host and clinical factors, whereas possible infection in 2002 allowed the combination of host and clinical or host and microbiological criteria. Consequently, in the 2008 classification, the combination of host and microbiological factors would no longer result in the classification of possible IFD. Only one galactomannan (GM) positive result is required in the new definitions, whereas at least two positive results were required by the 2002 definitions. Finally, in the revised classification, fever no longer constitutes a host factor.

In order to evaluate the effect of the changes on the rate of the diagnosis of IA, we performed a retrospective analysis of 589 patient-episodes in our database and looked for evidence of IA in patients with acute leukaemia and/or undergoing allogeneic haematopoietic stem cell transplantation, scoring the episodes by both the 2002 and the 2008 criteria.

#### Methods

The department of Haematological Oncology at St Bartholomew’s Hospital maintains a database on infectious complications of patients receiving treatment for hematological malignancies, with a particular focus on fungal infections. Information from 589 patient-episodes which occurred between September 2005 and June 2009 were retrieved and analyzed to assess the diagnostic probability of IA by both the 2002 and 2008 criteria. A patient-episode was defined as admission: (i) for induction or consolidation chemotherapy for acute leukaemia, (ii) for transplant conditioning and transplantation, and (iii) with an infectious complications while receiving intensive chemotherapy or in the post transplant period. These 589 episodes occurred in 325 patients of who 58% were male \(n = 341\) and 42% female \(n = 248\) which represents an average of 1.8 episodes per patient, with a range from 1–7 episodes per patient. The underlying conditions and the treatments administered during admissions are summarised in Table 1.

All patients, unless they had specific contraindications, received antibacterial, antiviral and antifungal prophylaxis as per departmental guidelines. Clinically, IFD was suspected in patients who remained febrile after 72 h despite administration of broad spectrum antibiotics and were investigated with a CT of the chest (while high-resolution CT was performed in most cases, recent practice is to perform a volumetric acquisition with thin-slice reconstruction). Based on the results of the CT imaging and the clinical pictures, respiratory opinions and targeted bronchoscopies were requested. Routine, twice weekly testing for the presence of serum GM antigen was introduced in 2008, whereas previously this test was only performed in selected cases. A value of 0.5 or above was considered positive.

#### Table 1: Patient characteristics.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>341</td>
<td>58%</td>
</tr>
<tr>
<td>Female</td>
<td>248</td>
<td>42%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA</td>
<td>3</td>
<td>0.6%</td>
</tr>
<tr>
<td>ALL</td>
<td>64</td>
<td>10.9%</td>
</tr>
<tr>
<td>AML</td>
<td>416</td>
<td>70.6%</td>
</tr>
<tr>
<td>CLL</td>
<td>8</td>
<td>1.3%</td>
</tr>
<tr>
<td>CML</td>
<td>3</td>
<td>0.6%</td>
</tr>
<tr>
<td>L</td>
<td>39</td>
<td>6.7%</td>
</tr>
<tr>
<td>MDS</td>
<td>22</td>
<td>3.5%</td>
</tr>
<tr>
<td>MF</td>
<td>6</td>
<td>1.0%</td>
</tr>
<tr>
<td>MM</td>
<td>28</td>
<td>4.8%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment received</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allograft</td>
<td>109</td>
<td>18.5%</td>
</tr>
<tr>
<td>Autograft</td>
<td>25</td>
<td>4.2%</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>423</td>
<td>71.9%</td>
</tr>
<tr>
<td>Sepsis management</td>
<td>32</td>
<td>5.4%</td>
</tr>
<tr>
<td></td>
<td>589</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

AA, Aplastic Anaemia; ALL, Acute Lymphoblastic leukaemia; AML, Acute Myeolcytic leukaemia; AML+ALL, Biphenotypic; APML, Acute Premyelocytic Leukaemia; CLL, Chronic Lymphocytic leukaemia; CML, Chronic Myelocytic leukaemia; L, Lymphoma; MDS, Myelodisplastic Syndrome; MF, Myelofibrosis; MM, Multiple Myeloma. Allograft, allogeneic hematopoietic stem cell transplant; Autograft, autogenic hematopoietic stem cell transplant.
positive, which in conjunction with persistent fever, triggered a diagnostic work-up for IFD.

For the purposes of this analysis, the scoring of CT scans was performed by two designated radiologists with a special interest in IFD who were blinded to the clinical and laboratory finding and their consensus opinions were recorded. The overall scoring and designation of infections as possible, probable or proven, using both the old and new EORTC/MSG criteria, were performed independently by two members of the team with 100% reproducibility.

Results

By applying the 2002 definitions, there was some evidence of IA in 175 episodes (30% of the total 589 episodes), of which 155 (88.5%) were ‘possible’, 16 (9%) were ‘probable’ and four cases (2.3%) were ‘proven’. By applying the 2008 revised criteria, there was a 78% reduction in all three categories of IA to just 38 cases (6.45%). Of these, 38 cases, 30 (79%) were ‘possible’ (80.6% reduction), four (10.5%) were ‘probable’ (75% reduction) and four (10.5%) remained ‘proven’ infections. There was no case where the probability of IA was higher when the 2008 criteria were applied.

Possible infections

The identification of 117 of the 155 possible IA cases employing the 2002 criteria was established on the basis of host and two or more minor clinical criteria, whereas eight cases were based on only host and microbiological factors. Microbiological factors included positive cultures obtained from sputum or bronchoalveolar lavage (BAL) specimens or positive serum GM test results. Lack of major clinical criteria accounted for the reduction of all episodes. The 30 cases that had major clinical criteria remained as possible cases when the 2008 criteria were applied.

Probable infections

A major clinical criterion was noted in only four of the 16 probable cases using the old definitions. In the 2008 definitions, the combination of host and microbiological factors no longer constitutes the basis for the diagnosis of possible infections, so all the remaining 12 cases were downgraded from probable infection to non-classifiable (Fig. 1).

Proven infections

The proven infections were not re-classified by the 2008 criteria and in all, Aspergillus fumigatus was found to be the etiologic agent. Of interest is the fact that in two of these cases no major clinical criteria were met and one was only discovered post-mortem.

The role of serum GM

Our data on GM antigen are limited as routine testing was only introduced in October 2008. Of the 30 cases that met host and major clinical criteria and were classified as possible infections by both the old and the new definitions, a proportion may have been upgraded to probable infections if GM testing had been performed.

There were three cases that had two positive GM results and thus fulfilled the microbiological criterion by the 2002 definitions and two of which would have been classified as ‘possible’ by these older criteria. Re-scoring the episodes using the revised 2008 definitions – where only one positive

Fig. 1. Re-classification of cases of invasive aspergillosis (IA) by application of the EORTC/MSG 2008 criteria. Pie charts show EORTC/MSG classification of IFD using the 2002 and 2008 criteria. NB: all downgraded ‘probable’ cases get reduced to ‘non-classifiable’.
GM result is required – yielded a total of 17 cases that now fulfilled the microbiological criterion. However, all these cases (including the two episodes previously classified as ‘possible’) were non-classifiable by the 2008 definitions due to the absence of major clinical criteria.

**Discussion**

One of the aims of the 2008 revision of the EORTC/MSG diagnostic criteria was to reduce the number of cases classified as ‘possible’ and thus tightening the diagnosis of IA. This single centre retrospective analysis demonstrated an 80.6% reduction of cases previously classified as ‘possible’ IA. GM antigen data were only available for a limited group of patients as routine testing was only introduced in October 2008. Nevertheless, this limitation did not influence the reduction of possible cases, as all were due to the absence of major clinical criteria (e.g., specific CT findings). Therefore, positive GM result in such cases would equate to host plus microbiological factors by 2008 criteria (i.e., non-classifiable). Indeed, where GM data was available, no cases were upgraded as a result of the 2008 revision and, paradoxically, cases with positive GM were reduced to non-classifiable due to the absence of major clinical criteria. The somewhat surprisingly high number of possible cases that were recategorised could indeed indicate that the 2002 definitions were too permissive. Our findings show that the major contributing factor to the reduction is the elimination of the minor clinical criteria and the emphasis placed on specific CT findings.

We also found a 75% reduction of cases previously classified as ‘probable’ IA and as the combination of host and microbiological factors no longer factors in the establishment of possible infection, all downgraded probable cases were reduced to non-classifiable. The total number of probable cases is too small to draw any firm conclusions but it appears that the elimination of the minor clinical criteria had a considerable impact on the rate of diagnosis of probable IA, as well as possible cases. A substantial reduction in the number of cases classified as ‘probable’ would lead to difficulties in interpreting previous studies where the 2002 definitions were used. For example, a 2008 Cochrane library review [9] on the use of GM for proven and probable infections showed a mean sensitivity between 57 and 69% (depending on the cut-off value) and a mean specificity of 85–93% in studies in which the EORTC 2002 definitions were applied. Given the impact of the 2008 criteria as per our data, it is likely that the conclusions of the Cochrane review would significantly change due to the reduced number of cases classified as ‘probable’. Furthermore, using the 2008 EORTC/MSG revision for the design of future studies will be problematic, as power calculations will be based on earlier trials using 2002 criteria. Similarly, comparing data from studies using 2002 versus 2008 criteria may be impossible for anything other than proven infections.

It is important to remember that the EORTC/MSG definitions are intended for research purposes only and not for clinical decisions. The clinical management of IFD continues to rely on a high index of suspicion and clinical acumen. The low levels of EORTC/MSG probable/proven cases in our cohort of patients, contrasts with 44% of patients who were receiving antifungal treatment for suspected IFD. It is clear that a major challenge of IFD in hemato-oncology remains making a definitive diagnosis. The EORTC/MSG criteria were not designed to be used in clinical practice and there is clearly an urgent need for new diagnostic assays.

**Conclusion**

The EORTC/MSG criteria constitute a diagnostic tool for clinical research. The 2008 revision has led to a stricter definition of cases, resulting in a significant reduction of ‘possible’ and ‘probable’ cases, with an anticipated improvement in its specificity, but a potentially lower sensitivity. The role of the revision in the setting of clinical trials will have to be validated in future studies.

**Authorship contribution**

SGA designed project and co-authored the paper, DT collected and analyzed data and co-authored the paper, AM, SA, BM, GJ, MW and SD collected data, SV, SE and TS collected and interpreted data. All authors have seen and approved the manuscript.

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