Update: New EORTC / MSG criteria for clinical trials

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Defining invasive fungal disease
Defining Opportunistic Invasive Fungal Infections in Immunocompromised Patients with Cancer and Hematopoietic Stem Cell Transplants: An International Consensus

S. Ascioglu,1 J. H. Rex,2 B. de Paauw,1 J. E. Bennett,2 J. Bille,1 F. Grokaert,1 D. W. Denning,1 J. P. Donnelly,1 J. E. Edwards,2 Z. Erjavec,1 D. Fiere,1 D. Lortholary,1 J. Maertens,1 J. F. Meis,1 T. F. Patterson,2 J. Ritter,1 D. Selleslag,1 P. M. Shah,1 D. A. Stevens,2 and T. J. Walsh,2 on behalf of the Invasive Fungal Infections Cooperative Group of the European Organization for Research and Treatment of Cancer and Mycoses Study Group of the National Institute of Allergy and Infectious Diseases

1European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group, Brussels; and 2National Institute of Allergy and Infectious Diseases Mycoses Study Group, National Institutes of Health, Bethesda, Maryland

Clinical Infectious Diseases 2002;34:7–14

2002
Original aims

To improve the ability for both clinicians and researchers:

• in comparing protocols and outcome of trials
• in assessing reports on therapeutic and diagnostic interventions
• in eliminating subjective classification
Strengths
Who uses the EORTC/MSG definitions?

Clinical trials

Liposomal Amphotericin B as Initial Therapy for Invasive Mold Infection: A Randomized Comparing a High-Loading Dose Regimen with Standard Dosing (AmBLoad Trial)

Method: A double-blind, placebo-controlled, randomized study in patients with invasive fungal disease who had not previously been treated with amphotericin B. The study compared a high-loading dose regimen with a standard dose regimen.

Diagnostic tests

Optimization of the Cutoff Value for the Aspergillus Double-Sandwich Enzyme Immunoassay

Method: The study evaluated the diagnostic performance of the Aspergillus Double-Sandwich Enzyme Immunoassay using 12 patients with invasive fungal disease and 10 controls without invasive fungal disease.
How valuable do you consider the EORTC/MSG definitions?

- 100% very useful
- 90% quite useful
- 80% don't know
- 70% not very useful
- 60% quite useless
- 50% useless
- 40% not very useful
- 30% quite useless
- 20% useless
- 10% not very useful
- 0% useless
Better communication
Strengths

EORTC/ MSG definitions

- have fostered better communication
- have been accepted by major journals
- are being applied by registration authorities
- have been adopted for therapeutic trials
- are used for approving diagnostic tests
• Why revise?
• The process
• Definitions
• Why revise?
• The process
• Definitions
Limitations
Problems

INAPPROPRIATE USE

• applied for clinical uses
• patients without cancer
Problems

INAPPROPRIATE USE

- applied for clinical uses
- patients without cancer

APPROPRIATE USE

- no criteria for endemic mycoses, fusariosis
- host factors too vague
- clinical features given equal weight
- insecurity about Aspergillus antigen
- PCR not included
Patient groups at risk of developing IFD

Haematological malignancy
Allogeneic HSCT

Invasive fungal disease
Goal of adapting definitions
Goal of adapting definitions

- Proven
- Probable
- Possible
- Present
- Future
**Question**

**Host factor**
- *neutropenic*

**Clinical features**
- Halo sign on pulmonary CT

**Mycology**
- Blood & BAL: Galactomannan -ve
- Blood: PCR positive

**Diagnosis?**
1. possible invasive aspergillosis.
2. probable invasive aspergillosis.
3. proven invasive aspergillosis.
4. possible invasive fungal infection
Answer

Host factor: neutropenic

Clinical features: Halo sign on pulmonary CT

Mycology: Blood & BAL: Galactomannan -ve

Blood: PCR positive

Diagnosis

1. possible invasive aspergillosis.
2. probable invasive aspergillosis.
3. proven invasive aspergillosis.
4. possible invasive fungal infection

4. possible invasive fungal infection
• Why revise?
• The process
• Definitions
a) the need for the rules for defining IFI to be clear and consistent was of paramount importance

b) proven invasive fungal infection (IFI) does not require the presence of a host factor as such

c) for probable IFI the host factors should be expanded to include

- solid organ transplants
- HIV infection
- hereditary immunodeficiencies
- connective tissue disorders
- low birth-weight (<1500 g) infants
- diabetes mellitus
- immunopharmacological treatments e.g. infliximab, dicluzimab, fludarabine
e) PROVEN, PROBABLE and POSSIBLE should remain as categories for IFI

f) probable IFI will continue to require that all three elements should be present and therefore is defined as host factors AND clinical features AND mycological evidence

g) the definitions for proven IFI will remain unchanged. The principle is that the criteria for proven or probable IFI have to be met in full in order to assign a level of certainty.
<table>
<thead>
<tr>
<th>Group</th>
<th>Task</th>
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<tbody>
<tr>
<td>Candidiasis</td>
<td>new criteria for candidaemia</td>
</tr>
<tr>
<td>Aspergillosis and infections due to other moulds</td>
<td>Imaging, galactomannan, BAL</td>
</tr>
<tr>
<td>Cryptococcosis</td>
<td>to review the criteria</td>
</tr>
<tr>
<td>Endemic mycososes</td>
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## Working parties - 1 year later

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<tr>
<td>Endemic mycoses</td>
<td>completed</td>
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The best laid schemes o' Mice an' Men,
Gang aft agley,
An' lea'e us nought but grief an' pain,
For promis'd joy!

(The best laid schemes of Mice and Men
often go awry,
And leave us nothing but grief and pain,
For promised joy!)

Robert Burns (1759 - 1796)
Head to head

Walsh
MSG

De Pauw
EORTC
Plan B

Three wise men?

Microbiological Criteria.doc

Proven IFI.doc

Host factors.doc
Consensus group

Consensus Group

TO ADDRESS EACH OF YOUR OBJECTIONS, WE SUCCESSFULLY WATERED DOWN THE CONCEPT BEYOND ALL RECOGNITION
Round 1
Round 2
Definitions II process

Round 1
- Ben De Pauw
- Pete Pappas
- Tom Walsh
- Tom Patterson
- Peter Donnelly
- John Perfect
- Sibel Ascioglu
- Jack Sobel
- Jacques Billé
- David Stevens
- Raoul Herbrecht
- John Wingard
- Bartjan Kullberg
- Carol Kauffman
- Olivier Lortholary
- David Denning
- Johan Maertens
- Frank Odds
- Marcus Ruhnke
- Georg Masschmeyer
- Claudio Viscoli
- Brahm Segal
- Jack Bennett
- Theo Zaoutis
- Bill Dismukes
- Angela Restrepo
- Jack Edwards
- Patrícia Munoz
- Kieren Marr
- Chris Kibbler

Round 2

Round 3

Round 4

Round 5

Round 6
Round ‘em up
• Why revise?
• The process
• Definitions
No change
Proven invasive fungal infective disease

- Tissue
- Blood culture
- Mycology
- Histology
- Culture
Defining invasive fungal disease

- Host factor
- Clinical feature
- Mycology
First change
What’s in a name?

Invasive Fungal Infection

2002
What's in a name?

Invasive Fungal Infection

Invasive Fungal Disease

2007
Second change
Definitions I - Possible invasive fungal disease

- Host factor
- Clinical features
- Mycology
- OR
- 2002
Invasive fungal disease - Definitions

- **Proven**: microcopy + tissue + culture
- **Probable**: Host factors + Clinical features + Mycology
- **Possible**: Host factors + Clinical features
- **Possible**: Host factors + Clinical features
- **Possible**: Host factors + none
- **Possible**: Host factors + none
- **Not classified**: Host factors + none

Definitions:
- **Possible**: Not classified
- **Probable**: Proven
- **Possible**: Negative or Not done
Invasive fungal disease - Definitions II

- **Probable**
  - Host factors + Clinical features + Mycology = Probable

- **Possible**
  - Host factors + Clinical features = Possible
  - Host factors + Clinical features = Possible

- **Not classified**
  - Host factors + None + Mycology = Not classified
Invasive fungal disease - Definitions II

- **Possible**
  - Host factors
  - Clinical features
  - Mycology
    - Negative or Not done

- **Probable**
  - Host factors
  - Clinical features
  - Mycology

- **Proven**
  - Host factors
  - Clinical features
  - Tissue culture
  - Microscopy

- **Not classified**
  - Host factors
  - Clinical features
  - Mycology
    - Negative or Not done
  - Microscopy
  - Tissue culture
Definitions II - Possible invasive fungal disease

- Host factor
- Clinical features

Characteristic of invasive fungal disease
BUT
no mycological evidence

2007
Third change
Definitions - Host factors

- Neutropenia: > 4 days unexplained fever despite broad spectrum antibiotics
- Graft versus Host Disease: > 3 weeks corticosteroids
- Host factor:
  - <36°C or > 38°C and
  - prior mycosis
  - AIDS
  - Immunosuppressive drugs
  - > 10 days neutropenia
- > 4 days unexplained fever despite broad spectrum antibiotics
Definitions - Host factors

- Neutropenia

- > 3 weeks corticosteroids

> 36°C or > 38°C and
  - prior mycosis
  - AIDS
  - Immunosuppressive drugs
  - > 10 days neutropenia

> 4 days unexplained fever despite broad spectrum antibiotics

- Graft versus Host Disease

- 2007
Definitions - Host factors

- Host factors
- Graft versus Host Disease

- <36°C or > 38°C and
  - prior mycosis
  - AIDS
  - Immunosuppressive drugs
  - > 10 days neutropenia

- > 4 days unexplained fever despite broad spectrum antibiotics

- > 3 weeks corticosteroids

- Host factor

- 2007
Definitions - Host factors

- Neutropenia
- > 3 weeks corticosteroids
- Allogeneic HSCT recipient
- Treatment with other recognized T-cell immune suppressants
- Inherited severe immunodeficiency

2007
Patients at risk of developing IFD

Haematological malignancy
Allogeneic HSCT

Invasive fungal disease

2002
Patients at risk of developing IFD

- Haematological malignancy
- Allogeneic HSCT
- CGD
- Steroids
- Liver
- Lung
- Heart
- Transplant
- ICU
- Renal

Invasive fungal disease

2007
Fourth change
Definitions - Clinical features

**MAJOR**

- Lower respiratory tract infection
  - Halo sign
  - Air-crescent sign
  - Cavity

- Sinonasal infection
  - Radiological evidence

- CNS infection
  - Radiological evidence

- Chronic disseminated candidiasis
  - Bull’s eye lesions in liver or spleen

- Disseminated fungal infection
  - Unexplained papular or nodular skin lesions
  - Chorioretinitis
  - Endophthalmitis

**2002**
Definitions - Clinical features

Lower respiratory tract infection
- Cough, chest pain, haemoptysis, dyspnoea
- Physical finding of pleural rub
- Any new infiltrate not fulfilling major criterion

CNS infection
- CSF: No pathogens, no malignant cells, abnormal biochemistry, abnormal cell count
- Focal neurological: seizures, hemiparesis, cranial nerve palsy
- Mental changes
- Meningeal irritation

Sinonasal infection
- Nasal discharge, stuffiness
- Nose ulceration, eschar or epistaxis
- Periorbital swelling
- Maxillary tenderness
- Black necrotic lesions or perforation of the hard-palate

Clinical feature

MINOR
- = 2

2002
Definitions - Clinical features

- Lower respiratory tract IFD
- Sinonasal IFD
- CNS IFD

Clinical feature

Chronic disseminated candidiasis

No more major and no more minor

2007
Definitions - Clinical features

- Lower respiratory tract IFD
- Sinonasal IFD
- CNS IFD
- Clinical feature

Chronic disseminated candidiasis

No more major and no more minor

2007
Definitions - Clinical features

A) the presence of one of the following “specific” imaging signs on CT:

- Well defined nodule(s) with a halo sign
- Well defined nodule(s) without a halo sign
- Wedge-shaped infiltrate
- Air crescent sign
- Cavity
Specific pulmonary infiltrates on CT scan

- Nodules
- Halo sign
- Cavity
- Air crescent sign
B) the presence of a new non-specific focal infiltrate
PLUS at least one of the following:

• Pleural rub
• Pleural pain
• Hemoptysis

2007
Fifth change
Definitions - Mycology

Culture of mould from tissue, aspirate BAL or sputum

Mould seen in sinus aspirate

Fungi seen in tissue or sterile body fluids

Antigen in blood, BAL, CSF

2002
Definitions - Mycology

Culture of mould from tissue, aspirate BAL or sputum

mould seen in sinus aspirate

Fungi seen in tissue or sterile body fluids

antigen in blood, BAL, CSF

Beta-D-glucan in BAL, CSF or blood

2007
Definitions - Mycology

- Culture of mould from tissue. aspirate BAL or sputum
- mould seen in sinus aspirate
- Fungi seen in tissue or sterile body fluids
- Beta-D-glucan in BAL, CSF or blood
- antigen in blood, BAL, CSF

2007
Definitions - Mycology

- Culture of mould from tissue, aspirate BAL or sputum
- Mould seen in sinus aspirate
- Fungi seen in tissue or sterile body fluids
- Beta-D-glucan in BAL, CSF or blood
- Antigen in blood, BAL, CSF
- PCR to detect nucleic acid

Not until a PCR system is developed that has been externally validated for blood, tissue, or BAL fluid
Towards a European standard for Aspergillus PCR

ISHAM
INTERNATIONAL SOCIETY FOR HUMAN AND ANIMAL MYCOLOGY

Laboratory Working party
Jurgen Loeffler
Stephane Bretagne
Willem Melchers
Lewis White
Niklas Finnström

Steering committee
J Peter Donnelly

Clinical Working party
Rosemary Barnes
Werner Heinz
Lena Klingspor
Johan Maertens
Catherine Cordonnier
Slicing the cake
Separating the chaff from the wheat

patients at risk

proven/ probable I FD
Separating the chaff from the wheat

patients at risk

proven/probable IFD

Host factors
Separating the chaff from the wheat

patients at risk

Host factors
clinical
proven/probable IFD
Separating the chaff from the wheat

**Host factors**

**Mycology**

**Clinical**

**Proven/probable IFD**

**Patients at risk**
Screening test for a potentially fatal disease with a low prevalence

- Controls
- Tests

- not ruled out start treatment
- ruled out withhold treatment
Do you apply EORTC/ MSG definitions in daily practice?
Scheme for managing high-risk patients
Scheme for managing high-risk patients

Clinical evidence of IFD

Patient

yes

no
Scheme for managing high-risk patients

- Clinical evidence of IFD
  - Microbiological evidence of IFD
    - Culture
    - Galactomannan
  - Patient
    - yes
    - no
Scheme for managing high-risk patients

Patient

Clinical evidence of IFD

Microbiological evidence of IFD

“Probable” IFD

Culture +

Galactomannan +

yes

no
Scheme for managing high-risk patients

Clinical evidence of IFD

Microbiological evidence of IFD

“Probable” IFD

“Possible” IFD

Culture

Galactomannan

Patient

Yes

No

Yes

No

+ +
Scheme for managing high-risk patients

Clinical evidence of IFD

Microbiological evidence of IFD

Culture +

Galactomannan +

“Probable” IFD

“Possible” IFD

“Unlikely” IFD
EORTC/MSG definitions - aspergillosis

Host factor

Clinical features

Halo sign on CT scan

Mycology

antigenaemia

HSCT

Probable
EORTC/MSG definitions - aspergillosis

- Host factor: HSCT
- Clinical features: Halo sign on CT scan
- Mycology: none

Probable (modified criteria)
EORTC/MSG definitions - aspergillosis

- Host factor: HSCT (Nonenone)
- Clinical features: Halo sign on CT scan (Possible)
- Mycology: None

Possible diagnosis
Liposomal Amphotericin B as Initial Therapy for Invasive Mold Infection: A Randomized Trial Comparing a High-Loading Dose Regimen with Standard Dosing (AmBiLoad Trial)

Oliver A. Cornely, Johan Maertens, Mark Bresnik, Ramin Ebrahimi, Andrew J. Ullmann, Emilio Bouza, Claus Peter Heussel, Olivier Lortholary, Christina Rieger, Angelika Boehme, Mickael Aoun, Heinz-August Horst, Anne Thiebaut, Markus Ruhnke, Dietmar Reichert, Nicola Vianelli, Stefan W. Krause, Eduardo Olavarria, and Raoul Herbrecht, for the AmBiLoad Trial Study Group

(See the editorial commentary by Anaissie on pages 1298–1306)
Table 2. Favorable overall responses among all patients and subsets of patients.

<table>
<thead>
<tr>
<th>Patient group or characteristic</th>
<th>Percentage of patients with favorable overall response by liposomal amphotericin B dosage</th>
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<tr>
<td></td>
<td>3 mg/kg per day</td>
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<tr>
<td>All patients(^a)</td>
<td>50</td>
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<tr>
<td>All patients with aspergillosis</td>
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</tr>
<tr>
<td>Patients with aspergillosis diagnosed by presence of halo sign only</td>
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</tr>
<tr>
<td>Allogeneic stem cell transplantation</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>47</td>
</tr>
<tr>
<td>No</td>
<td>50</td>
</tr>
<tr>
<td>Hematological malignancy</td>
<td></td>
</tr>
<tr>
<td>Controlled</td>
<td>53</td>
</tr>
<tr>
<td>Uncontrolled</td>
<td>48</td>
</tr>
<tr>
<td>Neutropenia at baseline</td>
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<td>Yes</td>
<td>43</td>
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<tr>
<td>No</td>
<td>67</td>
</tr>
<tr>
<td>Pulmonary infection</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Extrapulmonary infection</td>
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\(^a\) Difference, %

CID 2007:44 (15 May) • Cornely et al.
**Table 2. Favorable overall responses among all patients and subsets of patients.**

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At risk population

- Proven
- Probable
- Possible
- Unclassified
Currently eligible

- Proven
- Probable
Eligible for future studies

- Proven
- Probable
- Possible
Conclusion

• The revised definitions should make trials simpler and more representative.

• Much still needs to be done in the ICU.

• PCR needs to come into line. Failure to meet the definitions does NOT mean there is no IFD ....

  only that the criteria for defining IFD have not been met.

• Valid until 2009?