New Challenges In Treatment Of Invasive Mold Infections

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Haematology patients with AML/myelodysplastic syndrome (MDS) and allogeneic haematopoietic cell transplant (HCT) recipients are traditionally considered high-risk for invasive fungal diseases (IFDs).

With new and more intense therapies for acute lymphoblastic leukemia, lymphoma and myeloma emerging, particular subgroups of these patients may also be considered at high risk of IFD.
Antifungals play an essential role in the prevention and treatment of IFD in high-risk haematology patients; however, their optimal use remains challenging in a rapidly evolving field because of: changes in the epidemiology of IFD in haematology populations with the emergence of non-Aspergillus moulds or resistant Aspergillus.
Pulmonary Aspergillosis: An Evolving Challenge for Treatment

- Aspergillus is a mold that may lead to different clinical pictures, from allergic to invasive disease, depending on the patient’s immune status and structural lung diseases.

- **Chronic pulmonary aspergillosis**: is an infection with a locally invasive presentation, reported especially in patients with chronic pulmonary disease.

- **Aspergilloma**: is typically found in patients with previously formed cavities in the lungs.

- **Allergic bronchopulmonary aspergillosis**: is due to a hypersensitivity reaction to Aspergillus antigens and is more frequently described in patients with moderate-severe asthma or cystic fibrosis.
Spectrum of Aspergillus disease

**Spectrum of Aspergillus' disease**

- Normal subject
- Cavitary lung disease
- Chronic lung disease: ABPA, COPD, lung transplantation, recurrent low respiratory tract infections, or sarcoidosis. Plus presence of cough and/or hemoptysis
- Immunocompromised host or any of the following: COPD/liver cirrhosis/ prolonged steroids treatment/influenza H1N1/prolonged ICU admission
- Any of the following: asthma/cystic fibrosis/blood eosinophil counts >500 cells/L

- No disease Possible colonization
- Aspergilloma
- Chronic pulmonary aspergillosis
- Invasive pulmonary aspergillosis
- Allergic bronchopulmonary aspergillosis
Invasive Pulmonary Aspergillosis: An Evolving Challenge for Treatment

- Invasive pulmonary aspergillosis mainly occurs in patients with neutropenia or immunodeficiency, but has increasingly been recognized as an emerging disease of non-neutropenic patients.

- The significance of this infection has dramatically increased in recent years, considering the high number of patients with an impaired immune state associated with the management and treatment of neoplasm, solid or hematological transplantation, autoimmune diseases, and inflammatory conditions.
INVASIVE PULMONARY ASPERGILLOSIS

Risk factors

- Prolonged profound neutropenia
- Neutrophil dysfunction
- Hematologic malignancies
- Allogeneic bone marrow transplantation
- SOT
- Neoplasm
- End-stage COPD requiring chronic high-dose steroid therapy
- Patients receiving immunosuppressive therapies (i.e., monoclonal agents)
Which drug has been associated with better outcomes?

Voriconazole and Isavuconazole should be considered drugs of choice for primary treatment of IA.

Liposomal amphotericin B is an alternative for primary or salvage treatment for patients who are intolerant, had hepatitis or are refractory to voriconazole or isavuconazole. Also for patients with suspected or confirmed triazole resistance, or when triazole use is not desirable due to drug interactions.
Which drug has been associated with better outcomes?

Comparing d-AmB and its lipid formulations to voriconazole, both have fungicidal activity against most fungal strains, **albeit amphotericin B has lower in vitro activity against Aspergillus nidulans, Aspergillus lentulus and Aspergillus terreus than voriconazole.**

On the other hand, emerging A. fumigatus resistance to voriconazole is a growing concern in recent years.
Which drug has been associated with better outcomes?

- Advantages of isavuconazole include:
  - moderate drug–drug interactions (compared with voriconazole and posaconazole)
  - favorable safety profile (especially, lower risk of adverse events versus voriconazole, and lack of prolongation of QT interval)

- Echinocandins, such as caspofungin or micafungin and posaconazole are not recommended as primary treatment of IA in oncohematological patients (AII), but they are an alternative as salvage therapy when other azoles and liposomal amphotericin B cannot be used (BII).
When and how often should we use therapeutic drug monitoring (TDM) for antifungal drugs in aspergillosis?

- TDM of antifungal agents is generally recommended (AII), especially where:
  - non-compliance,
  - inadequate absorption,
  - a narrow therapeutic window,
  - suspected drug interaction
  - unexpected toxicity are encountered (AI).

- First sample (trough sample) for TDM must be obtained once the steady state has been reached (3-7 days depending on the antifungal) (AI).

- Then repeated at least once per week after dose stability is achieved (CIII).
Which levels of antifungals have been related with better outcomes in IA?

- A therapeutic range to treat IA between 1 mg/L and 6 mg/L has been defined for voriconazole (AII).

- Trough levels > 0.7 mg/L for prophylaxis and > 1.0–1.25 mg/L for treatment may be predictive of efficacy for posaconazole (AII).

  - Postmarketing experience has reported subtherapeutic serum trough concentrations in 20–30% of haematology patients.

  - Of note, it has also recently been established that secondary hypertension and hypokalemia, consistent with pseudohyperaldosteronism is associated with higher serum posaconazole concentrations, in which TDM may be useful in managing.
Which levels of antifungals have been related with better outcomes in IA?

Regarding itraconazole, a trough concentration of 0.5–1 mg/L is recommended (AII).

Isavuconazole does not appear to require TDM
Antifungal combination therapy should not be generally recommended for primary treatment of IA, but it could be considered in selected hematological patients with documented IA (BI).

In SOT recipients with severe forms of IA (i.e., CNS involvement or disseminated disease), initiating treatment with antifungal combination therapy should be considered, at least until therapeutic concentrations of voriconazole are achieved (BII).
Regarding class of antifungal compounds to be combined, combinations including triazole and echinocandin are the most commonly recommended and specifically voriconazole with anidulafungin would be the best regimen.

When echinocandins were combined with other antifungals in patients with severe or refractory IPA, better outcomes were observed.
Combination modalities may be useful when:

- The IA species is unknown
- If there are concerns for antifungal resistance, combination therapy may expand the armamentarium available until susceptibility testing is back.
- Thirdly, since voriconazole requires at least 5 days for the achievement of steady-state when a loading dose is not given and its metabolism can be highly influenced by concomitant medications, overlapping a complimentary antifungal may be prudent.

Finally, the various amphotericin B formulations, triazoles, and echinocandins exhibit different tissue penetrations based on their pharmacodynamic properties such that the choice of antifungal may depend upon the major site of infection. However, we found no significant difference in site of infection among the salvage treatment group.
First Line Treatment of IA

Table 7. ECIL-6 recommendations for first-line treatment of invasive aspergillosis.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Grade</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voriconazole*</td>
<td>A I</td>
<td>Daily dose: 2x6 mg/kg on day 1 then 2x4 mg/kg (initiation with oral therapy: C III)</td>
</tr>
<tr>
<td>Isavuconazole</td>
<td>A I</td>
<td>As effective as voriconazole and better tolerated</td>
</tr>
<tr>
<td>Liposomal amphotericin B</td>
<td>B I</td>
<td>Daily dose: 3 mg/kg</td>
</tr>
<tr>
<td>Amphotericin B lipid complex</td>
<td>B II</td>
<td>Daily dose: 5 mg/kg</td>
</tr>
<tr>
<td>Amphotericin B colloidal dispersion</td>
<td>C I</td>
<td>Not more effective than d-AmB but less nephrotoxic</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>C II</td>
<td></td>
</tr>
<tr>
<td>Itraconazole</td>
<td>C III</td>
<td></td>
</tr>
<tr>
<td>Combination voriconazole* + anidulafungin</td>
<td>C I</td>
<td></td>
</tr>
<tr>
<td>Other combinations</td>
<td>C III</td>
<td></td>
</tr>
<tr>
<td>Recommendation against use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amphotericin B deoxycholate</td>
<td>A I</td>
<td>Less effective and more toxic</td>
</tr>
</tbody>
</table>

*Monitoring of serum levels is indicated. In the absence of sufficient data for first-line monotherapy, anidulafungin, micafungin and posaconazole have not been graded.
Aspergillus resistance to antifungal drugs should be suspected in every therapeutic failure scenario and when cryptic species are identified as causative agents of invasive aspergillosis.

Commercially available test that have been standardized in multicenter studies can be used in clinical laboratories to screen for resistance; however, European Committee on Antimicrobial Susceptibility Testing (EUCAST) or Clinical Laboratory Standards Institute (CLSI) reference methods should be used to confirm antifungal resistance.
What is the best treatment for Aspergillus infections caused by azole-resistant isolates?

- Therapy of *Aspergillus* infections caused by cryptic or resistant species should be selected per *in vitro* susceptibility data, site of infection, and patient characteristics (*AIII*).

- Isolates resistant to voriconazole (MIC $>2$ mg/l) are recommended to be treated with amphotericin B (*AIII*) or the combination of voriconazole with an echinocandin (*CIII*).

- In areas with a rate of azole resistance 10%, azole monotherapy should be avoided in empirical primary treatment of severe cases of IA (*BIII*).
Should we monitor treatment response? How?

Response assessment of antifungal therapy should be based on a composite of:
- **clinical**
- **radiological**
- **mycological criteria** in an appropriate period evaluation (AI).

A follow-up chest CT scan is recommended to assess the radiological response of invasive aspergillosis to treatment after a minimum of 2 weeks of treatment (CIII).

Radiological findings may progress during the first week of treatment, mainly in neutropenic patients, with up to a 4-fold increase in patients with an otherwise favourable evolution; cavitation may appear while recovering from neutropenia.
Should we monitor treatment response? How?

Monitoring of serum galactomannan titers can be used in patients with hematological malignancies and hematopoietic stem cell transplantation recipients to assess therapeutic responses earlier and predict outcomes (AII).

Several studies are concordant with the optimal relationship between serum GM values and clinical response at 6 and 12 weeks.

There is limited data about serial determinations of BDG to predict outcome of IA, but it seems that early changes in BDG index do not correlate well with clinical responses since the decline in BDG titers is slower.
Duration of antifungal therapy is typically individualized in patients with invasive mould infection, taking into account:

- Host factors (e.g. immune status),
- Infection-related factors (e.g. type of mould infection, extent of infection)
- Response to therapy
- Duration of neutropenia
- Site of the disease

Almost all centres rely on CT-scan to guide duration of therapy.

Other tools, which are sometimes used in this indication are FDG-PET/CT (given its potential to differentiate active infection from nonactive lesions) and biomarkers (commonly, serum galactomannan).

However, as recently reviewed, there are no validated criteria that predict when it is safe to stop antifungals.
IDSA guidelines recommend that the treatment of IPA should be continued for at least 6–12 weeks, considering the clinical condition of the patient and their response to therapy; moreover, serum biomarkers and radiological follow-up with a CT scan should be considered to monitor the therapeutic response to IPA.
What is the role of adjunctive therapy in IPA?

- Doses of immunosuppressive agents should be reduced as much as possible as an adjunct to antifungal therapy (AII).

- Granulocyte transfusion therapy may be considered for neutropenic patients with refractory forms of IA and an anticipated duration of neutropenia >7 days.

- There is no indication for this type of adjunctive therapy in other populations (BII).

- Adjunctive surgery is recommended in patients with massive hemoptysis, invasive sinusitis, or infection of large vessels, bone, subcutaneous tissue, or central nervous system during treatment (BII).

- Wedge resection and lobectomy without significant loss of lung function are preferred over pneumonectomy, which should be avoided.
Treatment approaches to mucormycosis
Mucormycosis has been known to be the second- or third-most common mould infection after aspergillosis in most countries.

Mucormycetes account for up to 10% of moulds isolated from solid organ and HSCT recipients with invasive mould disease.
<table>
<thead>
<tr>
<th>Management includes antifungal therapy, surgery and control of underlying conditions</th>
<th>Grade</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antifungal therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amphotericin B deoxycholate</td>
<td>C II</td>
<td></td>
</tr>
<tr>
<td>Liposomal amphotericin B</td>
<td>B II</td>
<td></td>
</tr>
<tr>
<td>Amphotericin B lipid complex</td>
<td>B II</td>
<td></td>
</tr>
<tr>
<td>Amphotericin B colloidal dispersion</td>
<td>C II</td>
<td></td>
</tr>
<tr>
<td>Posaconazole</td>
<td>C III</td>
<td></td>
</tr>
<tr>
<td>Combination therapy</td>
<td>C III</td>
<td></td>
</tr>
<tr>
<td>Control of underlying condition</td>
<td>A II</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhino-orbito-cerebral infection</td>
<td>A II</td>
<td></td>
</tr>
<tr>
<td>Soft tissue infection</td>
<td>A II</td>
<td></td>
</tr>
<tr>
<td>Localized pulmonary lesion</td>
<td>B III</td>
<td></td>
</tr>
<tr>
<td>Disseminated infection</td>
<td>C III</td>
<td></td>
</tr>
<tr>
<td>Hyperbaric oxygen</td>
<td>C III</td>
<td></td>
</tr>
<tr>
<td>Recommendation against use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination with deferasirox</td>
<td>A II</td>
<td></td>
</tr>
</tbody>
</table>

CNS: central nervous system.

**Table 9. ECIL-6 recommendations for first-line therapy of mucormycosis.**
<table>
<thead>
<tr>
<th></th>
<th>Grade</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Salvage therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Management includes</td>
<td>A II</td>
<td></td>
</tr>
<tr>
<td>antifungal therapy,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>control of underlying</td>
<td>B II</td>
<td></td>
</tr>
<tr>
<td>disease and surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posaconazole</td>
<td>B III</td>
<td></td>
</tr>
<tr>
<td>Combination of lipid</td>
<td>B III</td>
<td>Overlap of a few days with first-line therapy to obtain appropriate serum</td>
</tr>
<tr>
<td>amphotericin B and</td>
<td></td>
<td>levels. Monitoring of serum levels might be indicated*</td>
</tr>
<tr>
<td>caspofungin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination of lipid</td>
<td>B III</td>
<td></td>
</tr>
<tr>
<td>amphotericin B and</td>
<td></td>
<td></td>
</tr>
<tr>
<td>posaconazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Maintenance therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posaconazole</td>
<td>B III</td>
<td></td>
</tr>
</tbody>
</table>

*Both comments apply to the oral solution but may not apply to the solid oral formulation.
high-dose liposomal amphotericin B given at 10 mg/kg/day ???

- what is your opinion?
- Do you recommend?
In the absence of a consensus definition of secondary prophylaxis, we defined it as either:

- continued treatment in a patient who had been diagnosed with mucormycosis and responded to treatment, or
- restarted treatment in a patient with successful disease control now immunocompetent, but scheduled for a new period of immunosuppression, e.g. HSCT.

The evidence base for treatment decisions, for example for transitioning to posaconazole, or isavuconazole to facilitate outpatient treatment, is sparse.
Surgical treatment for mucormycosis

Various authors have reported higher cure and survival rates through surgical interventions. It should be noted that many patients may be too sick to undergo surgery.

Surgical treatment is important for local control of mucormycosis, but multiple sites of infection can be present in disseminated infection.

- Surgery can be separated into major groups:
  - debridement of the skin and soft tissue,
  - debridement of rhino-orbito-cerebral mucormycosis,
  - orbital exenteration,
  - lung resection,
  - debridement of bone, and visceral resections in for example liver, spleen, peritoneal structures, or transplanted organs.
### Adjunctive treatments for mucormycosis

<table>
<thead>
<tr>
<th>Iron homeostasis</th>
<th>Augmentation of host response</th>
<th>Reducing host vulnerability</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Administration of iron or deferoxamine to patients with mucormycosis is <strong>discouraged</strong>, and a conservative approach to blood transfusions may be warranted given the risk of free iron release during transfusions.</td>
<td>- The guideline group moderately supports G-CSF to augment host response against mucormycosis in patients with ongoing neutropenia</td>
<td>- <strong>controlling hyperglycaemia and ketoacidosis</strong></td>
</tr>
<tr>
<td>- <strong>Adjunctive deferasirox</strong>?</td>
<td></td>
<td>- Rapidly taper glucocorticosteroid dose to discontinue, if feasible, or reduce dose to minimum required.</td>
</tr>
</tbody>
</table>
Hyperbaric oxygen exposure ???

- what is your opinion ?
- Do you recommend ?
Figure 5: Optimal treatment pathways for mucormycosis in adults

Suspected and confirmed mucormycosis are emergencies and require rapid action

Surgical debridement with clean margins
for 3 purposes: (1) disease control, (2) histopathology, (3) microbiological diagnostics
Plus Immediate treatment initiation

Avoid slow escalation of doses
Liposomal amphotericin B 5-10 mg/kg per day from day 1

If brain involvement
Avoid slow escalation of doses
Liposomal amphotericin B 10 mg/kg per day from day 2

If SOT
Avoid slow escalation of doses
Liposomal amphotericin B or amphotericin B lipid complex 10 mg/kg per day from day 1

Posaconazole oral suspension 4-200 mg per day

Liposomal Amphotericin B <5 mg/kg per day

Avoid Amphotericin B deoxycholate Any dose

Response assessment (eg weekly imaging)

Progressive disease
Posaconazole oral suspension 4-200 mg per day
Liposomal amphotericin B 10 mg/kg per day from day 1
Amphotericin B lipid complex or liposomal amphotericin B 5 mg/kg per day from day 1
Combination with posaconazole

Toxicity
Posaconazole oral suspension 4-200 mg per day
Amphotericin B lipid complex or liposomal Amphotericin B 5 mg/kg per day from day 1
Thank You