approach to fungal infections in patients with Neutropenic fever

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Prophylaxis in Cancer Patients

- Based on risk assessment
- (high risk for mold or yeast)
**an individualized approach in AML patients**

<table>
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<tr>
<th>High Risk</th>
<th>Intermediate Risk</th>
<th>Low Risk</th>
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| • Prior aspergillosis  
  • Salvage for refractory/relapsed leukaemia  
  • Remission-induction for newly diagnosed acute leukaemia:  
    - prolonged and profound neutropenia  
    - low CR probability  
    - age ≥ 65 years  
    - pulmonary dysfunction | • Not meeting criteria for high or low risk | ✓ Newly diagnosed  
  ✓ young patients (≤ 45 years)  
  ✓ undergoing 1\textsuperscript{st} remission-induction/consolidation therapy  
  ✓ without risk factors for IFDs |
| Mold-activeazole prophylaxis | Fluconazole prophylaxis + serial biomarker monitoring | (Fluconazole prophylaxis) No serial biomarker monitoring |
• **ALL**: anti yeast (in patients undergoing remission-induction therapy)

• In other phase of chemotherapy: cautious use of anti yeast prophylaxis may be considered

  - **MDS**: anti fungal PX ☠️ low risk for IFD{ <0.2} (unless in patients with intensive AML-like regimen)

  - **CML**: anti fungal PX ☠️ (unless intensive AML-like chemotherapy for accelerated/blast phase)
- **MM:** Anti fungal PX X

- **CLL:** Anti fungal PX X (in patients with prolonged neutropenia { more than 6 m} and elderly with advanced and unresponsive disease, might be considered)

- **Lymphoma:** Anti fungal PX X

- **Autologous HSCT:** Anti fungal PX X (Anti yeast for mucosal candidiasis in neutropenic phase)
Allo HSCT:

- In pre-engraftment phase:
  - Anti mold In H.R patients:
    - Acute leukemia, cord blood transplantation
    - Prolonged neutropenia before transplantation (AA, MDS, Fanconi A.)
    - Previous fungal infection,
  - Anti yeast in L.R patients

- In post-engraftment phase:
  - Anti mold In H.R patients:
    - Acute GVHD grade III, IV and grade II in alternative donor,
    - Secondary neutropenia, recurrent CMV in alternative donor
  - Anti yeast in L.R patients:
    - Acute GVHD grade II respondent to treatment
Novel targeted cancer therapy

- **Tyrosine kinase inhibitors** in particular inhibitors of bruton TK, mTOR, JAK and phosphatidylinositol 3 kinase (PI3K) delta: Increase of risk of IFI.
  - It remains unclear, if antifungal prophylaxis is indicated

- **Inhibition of immune checkpoints**, e.g. (PD1) or (CTLA4):
  - More data is needed.

- **Hypomethylating** agents such as **Azacitidine**:
  - Antifungal PX could be considered according other risk factors.
• **Anti CD20 (Rituximab):**
  - Antifungal prophylaxis should only be considered in case of additional risk factors.

• **Further antibodies target CD19, CD33 or IL-2:**
  - Low evidence on risk of IFI

• **CD52 antibody (Alemtuzumab)**
  - Mold directed prophylaxis should be considered.

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- Given the high attributable mortality of IFI, the individual risk of patients treated with the drug classes above should be evaluated, and **antifungal prophylaxis prescribed on case by case basis.**
Neutropenic fever

Neutropenia:
- < 500 PMN/mcl
- or
- < 1000 PMN/mcl and a predicted decline to < 500/mcl over the next 48 h

Fever
- Single temperature ≥ 38.3°C
- Or T to ≥ 38°C over 1-h period
Antifungal therapy strategies in a febrile neutropenic patient

- Empirical Therapy
- Preemptive therapy
- Hybrid (mix)
empirical anti-fungal therapy

- Administration antifungal drug in a persistently febrile neutropenic cancer patient after a variable period of empirical antibacterial therapy (usually 4–7 days), in the absence of any clinical, microbiologic, or radiologic documentation of a fungal infection.

- The best approach in H.R patients for IFD
- This approach has become common practice in many cancer centers worldwide (specially when reliable tests are not available)
- The aim of empirical therapy is to treat as early as possible both candidiasis and aspergillosis.
Preemptive Therapy

- Treating a fungal disease when highly suggestive, although not conclusive.
- Clinical considerations, biologic markers (GM) in serum and imaging data (CTscan), are combined together to obtain the highest possible diagnostic likelihood of Aspergillosis and consequently to start therapy.
Hybrid (mix) therapy

Anti yeast prophylaxis + preemptive approach for mold infection
Indications for empirical anti-fungal therapy in patients with neutropenic fever

- Septic shock
- Pneumonia with focal pattern in imaging
- Acute sinusitis
- Persistent fever (usually 4-7 days after empirical antimicrobial therapy) in the absence of any documentation of fungal infection
In persistent fever in neutropenic patients:

- **For empirical therapy:**
  - Start an anti mold agent + active diagnostic workup
    (B/Cs, GM, CTscan of lung and sinus,...)

- **If fever stops after starting antifungal treatment without specific source (with or without neutropenia remaining):**
  - Discontinue the antifungal agent, 14 days after the fever stops
In persistent fever despite empirical antibacterial and antifungal therapy (and the patient is not in shock state):

- Evaluation to find the cause of fever
- Do not change medications or add any other drug

- If the patient develops a fever with an increase in PMN, the risk of fungal infection is higher.
Pneumonia: Empirical therapy to cover organisms in HAP (less common CAP) +

1. In focal infiltration (nodule):
   Treatment to Cover Legionella and mold too

2. In diffuse infiltration:
   Treatment to Cover Legionella and PCP too
In persistent fever despite empirical antibacterial and antifungal therapy in pneumonia:

- Do not change medications or add any other drug

- in patient with neutropenic fever and lung nodules:
  - broncoscopy and BAL
  - TBLB

✓ follow-up chest CT scan to assess the response of IPA to treatment: after a minimum of 2 weeks of treatment (earlier assessment is indicated if the patient clinically deteriorates)
Molecular assays

- *Aspergillus* PCR is more sensitive than culture in blood and respiratory fluids.

- Sensitivity of 84% and specificity of 76% in serum
- Sensitivity of 77% and specificity of 94% in BAL
  - The high NPV of BAL PCR (usually ≥95%) suggests a role in ruling out IPA.

- PCR on nonblood and extrapulmonary body fluid and fresh tissues demonstrate sensitivity of 86% and specificity of 100%.
Molecular assays

- PCR is not able to differentiate colonization from disease or to distinguish different *Aspergillus* spp.

- Molecular assays have not been standardized nor cleared by FDA for clinical use.

✓ When PCR assays are used, results should be considered in conjunction with other diagnostic tests (serum and BAL GM) and the clinical context.
Galactomannan

- GM is not recommended for routine blood screening in patients receiving mold-active antifungal therapy or prophylaxis, but can be applied to bronchoscopy specimens from those patients.

- Sensitivity (approximately 70%) in serum of patients with hematological malignancy or allogeneic HSC.T

- Sensitivity > 70% in BAL fluid (more sensitive than in serum)
Cut off for positive result

- In serum (alone): >1
- In BAL (alone): >1

- In combination of serum and BAL:
  - Serum GM > ./7
  - BAL GM > ./8
(1 → 3)-β-D-glucan

- Slightly more sensitive than GM for IA, but is limited by its poor specificity.
Microscopy

- Tissue samples from patients should be examined by mycological culture and microscopy.

- **Yeast**, if found in sputum or BAL fluid, should be regarded as contamination or colonisation until invasive disease is proven.

- Recovery of **molds from sputum** in patients with clinical signs suggestive for IFD and prolonged neutropenia should be regarded as a possible indicator of fungal pneumonia.
No histopathologic finding can definitively diagnose the pathogen, and confirmation by culture or nonculture technique is necessary to distinguish Aspergillus from other filamentous fungi such as Fusarium and Scedosporium.
Thanks!