Challenges in diagnosis and treatment of IFI in cancer patients

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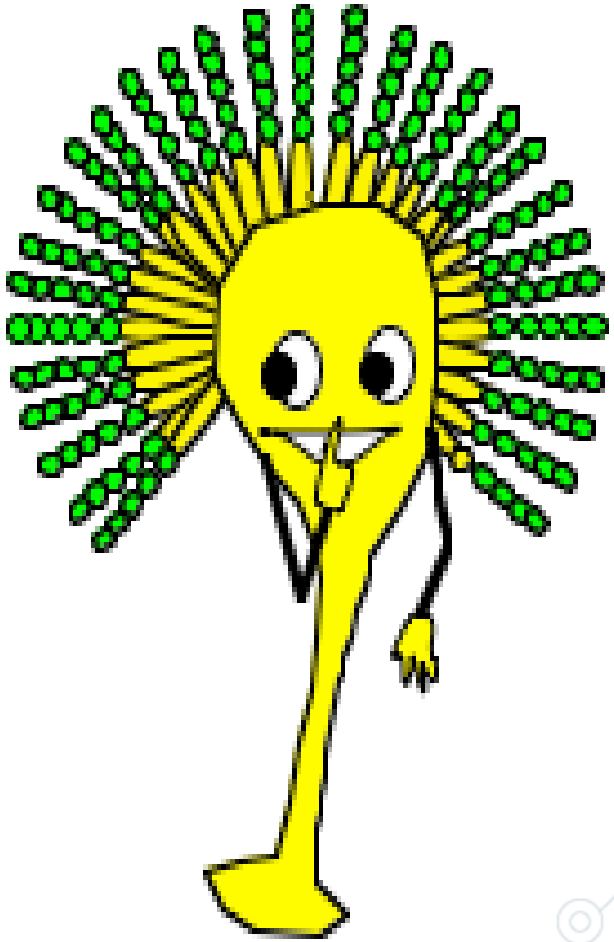


- Management of IFIs is centered on establishing an early and accurate diagnosis, as well as timely initiation of appropriate antifungal therapy
- Guidelines for the diagnosis and management of IFIs are available, yet awareness and adherence are suboptimal
- Multidisciplinary discussion/ collaboration and expert opinion provide critical guidance for many community clinicians

- Despite recent advances in the diagnosis and prevention of IFIs, in patients at highest risk of infections, the incidence of disease, treatment failure and attributable mortality remains unacceptably high.

- For example**, increasing rates of candidemia** have been reported everywhere and **candida species are an increasing cause of sepsis among non-neutropenic patients receiving intensive care**.

- **Infection and treatment failure rates** are even higher in select groups, such as those with **prolonged and persistent neutropenia** and **GVHD.**

- Early diagnosis and treatment of IFIs are associated with a better prognosis and accordingly different possible strategies has been described.

Invasive fungal infections (IFIs) are increasingly recognized in the expanding population of immunocompromised hosts such as:

1. **Transplant recipients**,
2. **People receiving immunosuppressive and chemotherapeutic agents**,
3. **Patients with HIV infection**, and
4. **Individuals at the extreme of life** (i.e., premature infants and the elderly)

Diagnostics challenges

Diagnosis of most IFIs remains a challenging task due to:

- **non-specific clinical presentation** and
- **lack of sensitivity of traditional microbiologic methods**.

- In recent years, the introduction of serologic tests such as the **GM and 1,3-BDG antigens** as well **as molecular techniques** has improved the diagnosis .

- Nevertheless, **the species of fungi responsible for disease** among immunocompromised patients **is expanding**, making the diagnosis more complicated

Diagnostics challenges

- **Histopathologic examination**, together **with culture**, is still considered the **gold standard to make a definitive diagnosis of IFIs**.

- However, **due to the many pitfalls** encountered in the **morphological diagnosis of IFIs** and **the development of highly specific molecular techniques** such as in situ hybridization(ISH) and NAT, it is clear that **a pathologist with a subspecialty expertise in infectious diseases is essential in hospitals** dealing with large numbers of immunocompromised hosts

Diagnostics challenges

- **The increasing complexity of immunocompromised patients** together with **the expanding number of pathogenic filamentous fungi which show different antifungal susceptibility** makes an **early and accurate** (genus- or species-level) **identification of the causative fungal pathogen challenging** to **optimize drug treatment**.

- **Molecular diagnostic methods** applied either to fresh or formalin-fixed paraffin-embedded (FFPE) tissue specimens have been increasingly used to help in the identification of **different fungi responsible for invasive diseases**

Diagnostics challenges

- **IMI diagnosis** relies on the use of imaging, biomarkers (e.g.,GM and PCR), and culture.
- The methods used for IA, in particular **culture, imaging, and PCR**, are **applicable** also to suspected **mucormycoses and rare mould infections**.
- The diagnosis of ***Mucorales* and other rare IMI** caused by moulds **remains challenging** because **phenotypic identification is not always possible** as cultures can remain negative and their evaluation is often possible only after a comparatively long time.

Diagnostics challenges

- The GM test has been shown to be a reliable diagnostic tool in a number of clinical trials, although a recent study has reported a **high rate of false positives** in BAL samples of **hematological and SOT patients** using the standard **cut-off value of 0.5**.

- Another problem with the use of GM testing on serum is **its low sensitivity, in particular in non-neutropenic patients.**

1-3-ß-BDG

After its introduction as a diagnostic test, 1-3-ß-BDG has received considerable attention, but based on **disappointing sensitivity**, **high workload and costs**, and **many false positives**, it **has not become a generally recommended test for IMI detection**

Diagnostics challenges

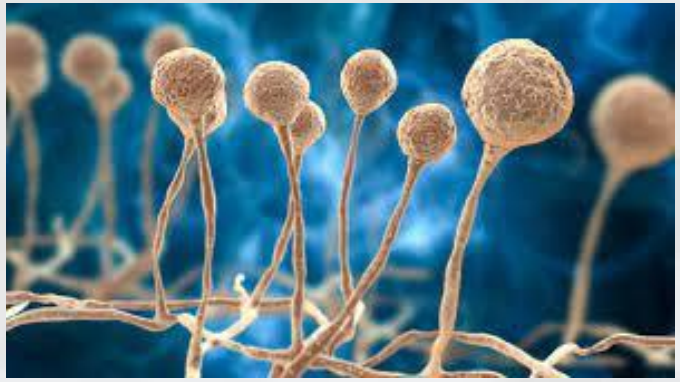
❖ PCR

PCR has the **advantage to provide a reliable species identification** in a **relatively short time**, but its **sensitivity is limited** when used on **serum** or **plasma** and, **even on GM positive BAL fluid**, the sensitivity is not optimal.

Salehi and coworkers,
using a multiple real time quantitative PCR (qPCR) targeting the ITS2 region of rDNA, found an **overall sensitivity of 64% for the identification of fungi at the species or genus level**
However, **16% of the histopathologically diagnosed cases of aspergillosis according to real-time qPCR** were **fusariosis (5) and mucormycosis (1).**

Diagnostics challenges

PCR



Mucormycosis diagnosis had important therapeutic implications since treatment of Mucormycosis differs in a substantial way from that of Aspergillosis.

In this regard, it should be highlighted that in the study by Dekio et al. conducted among immunocompromised pediatric patients with histology-proven IFIs, **the communication of histologic diagnosis resulted in changes in antifungal therapy in 64% of patients**

Diagnostics challenges

- IMI patients have been shown to have **increased levels** of **mould-reactive *Aspergillus*- or *Mucorales*-specific CD4 cells** compared to healthy controls, but scant data are available on *Mucorales*-reactive T cells, with only a small patients cohort studied so far.
- ***Mucorales*-reactive T cells producing IL-10 and IL-4** have been detected at high rates in patients with **mucormycosis** and are currently evaluated as potential surrogate diagnostic markers in the diagnosis of mucormycoses.

Diagnostics

Immune parameters as promising tool…

- Immune parameters for potentially more specific diagnoses have so far been given little consideration but they are likely to provide directions about diagnosis, **when a decision needs to be made regarding the use of a mould-active prophylaxis**, **the start of empirical antifungal treatment**, **early escalation**, or **switch to a more appropriate antifungal agent**.

- Several cytokines may allow improving IMI diagnosis. **Serum CRP and IL-6 levels** are **increased at the time of diagnosis** and **decline in case of response to antifungal treatment.**

- **IL-1*β***, **IL-6, IL-8**, **IL-17A**, **IL-23**, and **TNF*α*** were significantly increased among patients with IPA, **confirming that the combination of specific cytokines with other biomarkers such as GM may not only facilitate diagnosis but also improve the ability to predict the disease outcome**

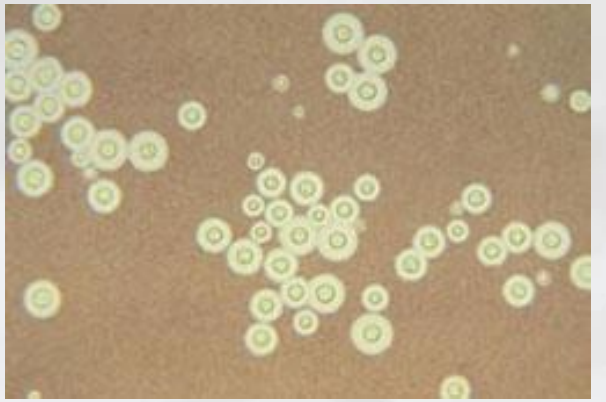
Diagnostics challenges

Cryptococcosis

Cryptococcosis represents one of the most common opportunistic invasive fungal disease **worldwide** with the highest burden among **HIV/AIDS patients** and patients **receiving immunosuppressive drugs.**

- The morphology of Cryptococcus spp. is that of a **spherical to oval encapsulated yeast with a narrow-based budding.**

- The **polysaccharide capsule is stained by mucicarmine, PAS**, and alcian blue whereas **GMS stains the fungal wall**.



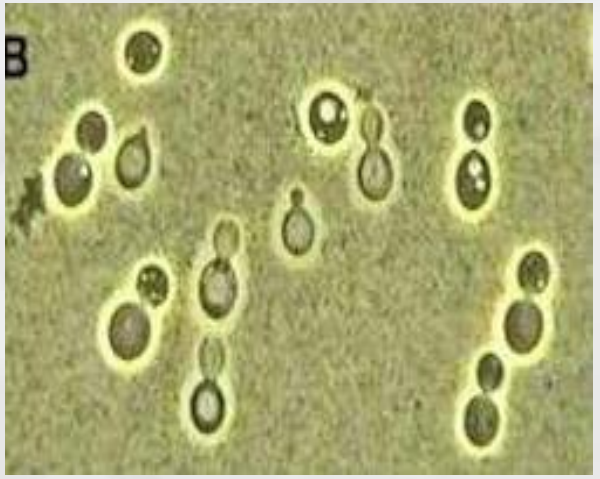
Diagnostics challenges

Cryptococcosis

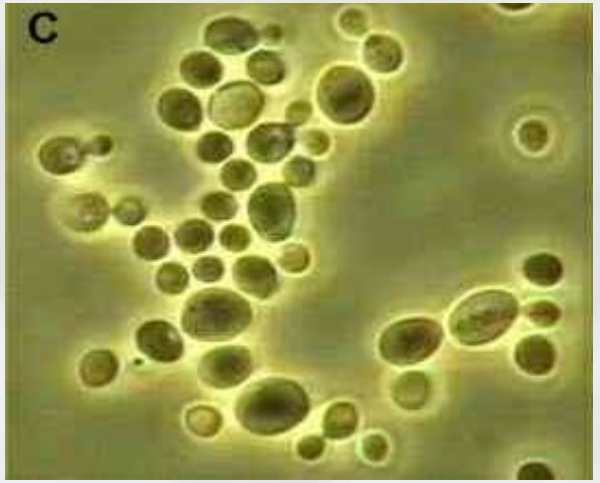
- In general, diagnosis of cryptococcal meningitis or disseminated disease in immunocompromised patients is easily achieved by using **India ink stain** (on CSF), **culture and latex agglutination**, ***EIA,*** or lateral flow assays **(LFA)** (as point-of care) **targeting the cryptococcal antigen.**

- The latter shows high sensitivity and specificity but may be negative in localized infections and **in the presence of acapsular cryptococci.**

- Moreover, **when the mucin capsule is absent**, it can be **difficult to distinguish Cryptococcus from Candida glabrata and Histoplasma capsulatum**, especially in necrotic tissues.



Cryptococcus



Candida

Therapeutic challenges

Emerging and innate resistance in Aspergillus species

- The last decade has seen an **abrupt increase in the isolation of azole-resistant *Aspergilli.***
- Overall, cases have occurred in many countries with varying prevalence, and infections are often observed in patients **without** prior azole exposure.
- **Occurrence of resistant strains seem also to be tightly linked to the local epidemiology**: for example; in The Netherlands, a gradient has been observed that seems to be correlated with the extent of flower cultivation,89 thus supporting the hypothesis that azole resistance in *Aspergillus* is correlated with fungicide use in agriculture.

Therapeutic challenges

- An important issue with relevant therapeutic implications about aspergillosis is related to the diffusion of **azole-resistant Aspergillus spp.**

- Voriconazole has been established as the first-choice treatment for IA.

- **Detection of azole-resistant aspergillosis** is complicated by the fact that **cultures are negative in up to 50% of patients with pulmonary lesions** and **in vitro susceptibility testing are not routinely available**.

- In this context, van den Linden and coworkers demonstrated the feasibility of **rapid detection of the more frequent mutation associated with azole resistance directly on FFPE tissue specimens by a specific real-time PCR**

Therapeutic challenges

Emerging and innate resistance in Aspergillus species

- **Azole resistance in A. fumigatus** develops **mainly during exposure of the fungus to azoles in the natural environment and not in the patient**,but resistance is also apparently associated with the use of long term azole therapy and **switching between antifungal azoles in patients** with chronic pulmonary aspergillosis and in immunocompromised patients requiring long term antifungal prophylaxis

Therapeutic challenges

Emerging and innate resistance in Aspergillus species

The impact of the occurrence of azole resistant *Aspergillus* isolates on the patient outcome is not yet entirely clear, but high mortality rates, up to 2.7 times higher than in nonresistant IA, have been reported.

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Therapeutic challenges

- No clinical data on the best therapeutic approach are available, and there may be a need to develop new treatment strategies, considering that **Echinocandins might not be sufficiently effective in patients with continued immunosuppression**.

- The use of upfront azoles in combination with L-AmB or an echinocandin if **local resistance rates exceed 10%** has been suggested, but **no clinical evidence exists to support this recommendation.**

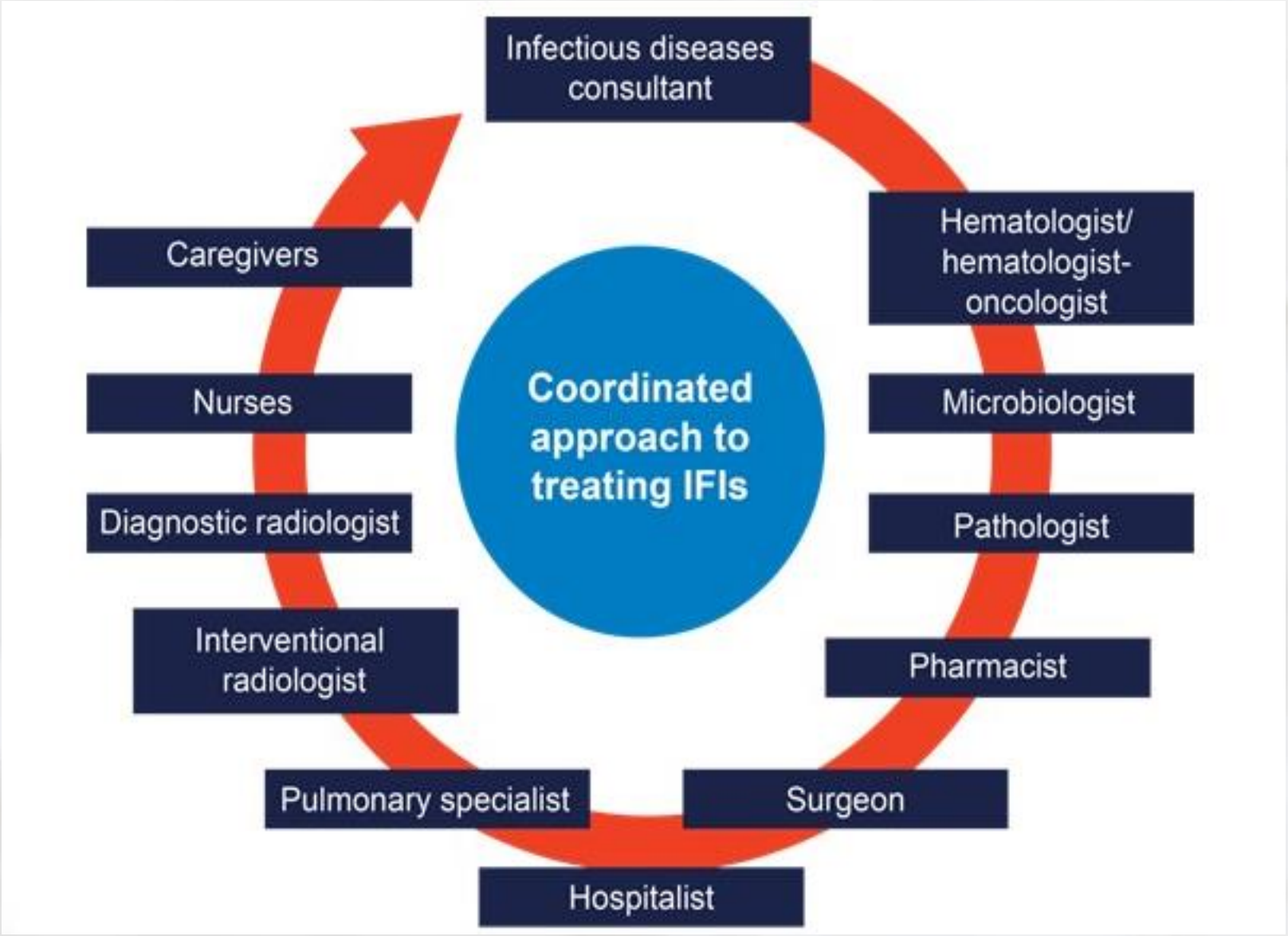
- **A guideline from The Netherlands recommends** the use of voriconazole combined with L-AmB or an echinocandin as first line therapy **until resistance has been excluded**, but clinical data on efficacy and safety of these combinations are limited.

- **Until additional data are available**, *azole monotherapy remains the treatment of choice*, and there is **no agreed threshold for local resistance rates to define an alternative**.

Therapeutic challenges

Studies are currently underway to
define a sensible threshold when **primary monotherapy with an azole is no longer acceptable**
and
to **determine an appropriate diagnostic and therapeutic scheme in the presence of high azole resistance prevalence**

Managing IFI in cancer patients required a multidisciplinary approach



“Thank you for your kind attention”