Diagnosis and management of invasive candidiasis in ICU: updated approach to an old enemy

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Diagnosis and management of invasive candidiasis in ICU: updated approach to an old enemy

Review article –

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Background

- Invasive fungal infections in ICU patients → considerable morbidity and mortality
- Candida species most common (70-90%)
- Invasive aspergillosis associated with higher morbidity and mortality rates
- Cryptococcosis, pneumocystosis and zygomycosis may also be encountered

Invasive *Candida* Infection

- *Candida* in a blood culture is never a contaminant
- Should always prompt a search for the source
- Always requires treatment with an antifungal agent

Invasive *Candida* Infection

Three subgroups:

1. Candidaemia without deep-seated or visceral involvement
2. Candidaemia with deep-seated or visceral involvement
3. Deep-seated (visceral) candidiasis without candidaemia.

Each entity responsible for 1/3 of cases.

Epidemiology

- *C albicans* most common cause of candidaemia
- Increasing isolation of non albicans species in recent years (*C. glabrata, C. parapsilosis, C. tropicalis, C. krusei*)
- Knowing local prevalence of the non albicans Candida species is important – susceptibility to antifungal agents varies among the species.
- Patients who are in ICU and/or immunocompromised at highest risk

Candidaemia in Australia

- Cases of candidaemia were evaluated by blood culture surveillance at 50 of 52 pathology laboratories in Australia from 2001-2004.
- C albicans 47.3%
- C parapsilosis 19.9%
- C glabrata 15.4%
- C tropicalis 5.1%
- C krusei 4.3%
- C dubliniensis 1.9%

Active surveillance for candidemia, Australia.. Chen S, Slavin M, Nguyen Q, Marriott D, Playford EG, Ellis D, Sorrell T; Australian Candidemia Study. Emerg Infect Dis. 2006 Oct;12(10):1508-16.

Epidemiology

- Risk factors = ICU and immunocompromised patients.

- ICU patients risk factors:

- Extremes of age
- Trauma
- Burns
- CVC
- TPN
- Broad spectrum antibiotics
- Diabetes
- High APACHE scores
- ARF, particularly if requiring haemodialysis
- Mechanical ventilation
- Abdominal surgery
- GIT tract perforations and anastomotic leaks

Pathogenesis

- Infecting strain is most often part of the host's endogenous flora, however can be nosocomial.
- Three major routes by which *Candida* gain access to the bloodstream:

1. Through the GIT mucosal barrier – most common
2. Via an intravascular catheter (increased risk with TPN)
3. From a localised focus of infection, such as pyelonephritis.

Pathogenesis

- Development of invasive *Candida* infections often preceded by extensive colonisation of skin or mucus membranes (GIT and urogenital tract).
- Degree of colonisation has been shown to be an independent risk factor for development of candidiasis.

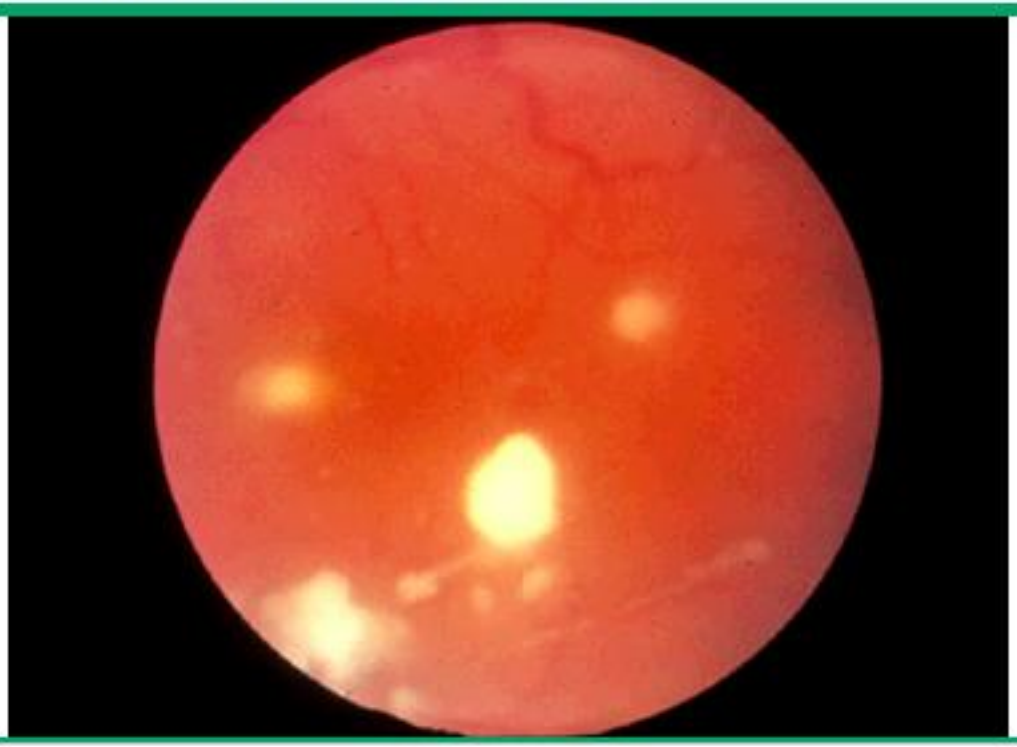
Clinical Manifestations

- Spectrum – minimal fever → full blow sepsis syndrome that is indistinguishable from severe bacterial infection.
- Haematogenous spread to multiple viscera:

- Eye (chorioretinitis, endophthalmitis)
- Kidney
- Heart valves (endocarditis)
- Brain
- Muscle abscesses
- Skin lesions

Clinical Manifestations

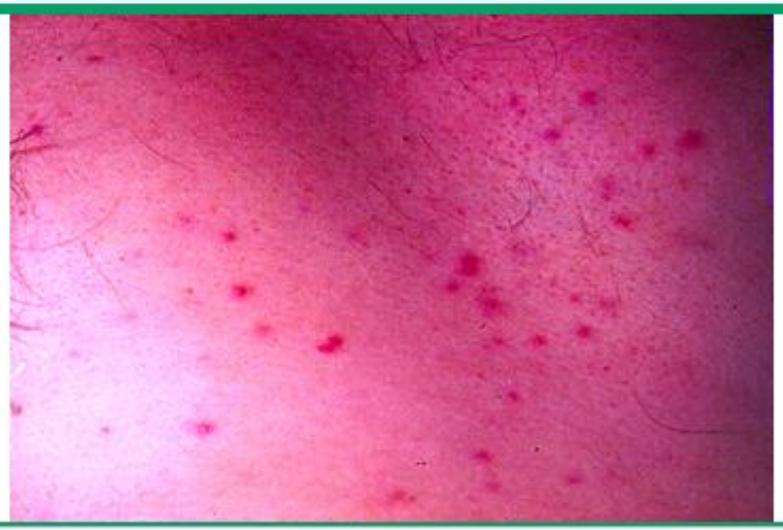
***Candida* endophthalmitis**



Endogenous *Candida* endophthalmitis with multiple focal white lesions within the choroid and extension of the two largest lesions through the retina into the vitreous.

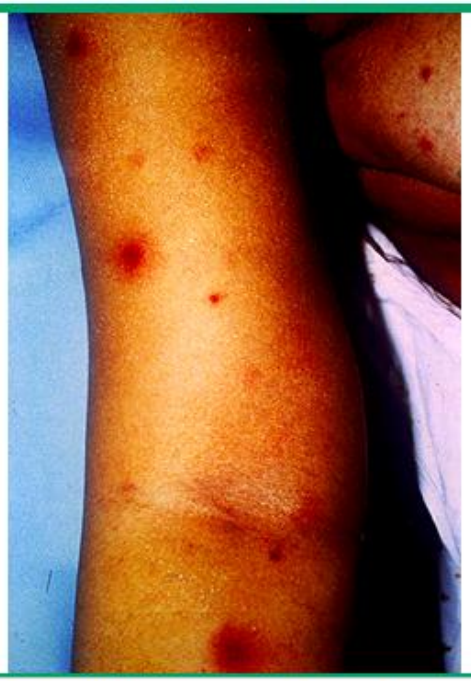
Clinical Manifestations

Skin lesions of disseminated candidiasis



Tiny pustular lesions due to the hematogenous dissemination of *Candida albicans* can be seen in this hospitalized patient with fever and signs of sepsis.

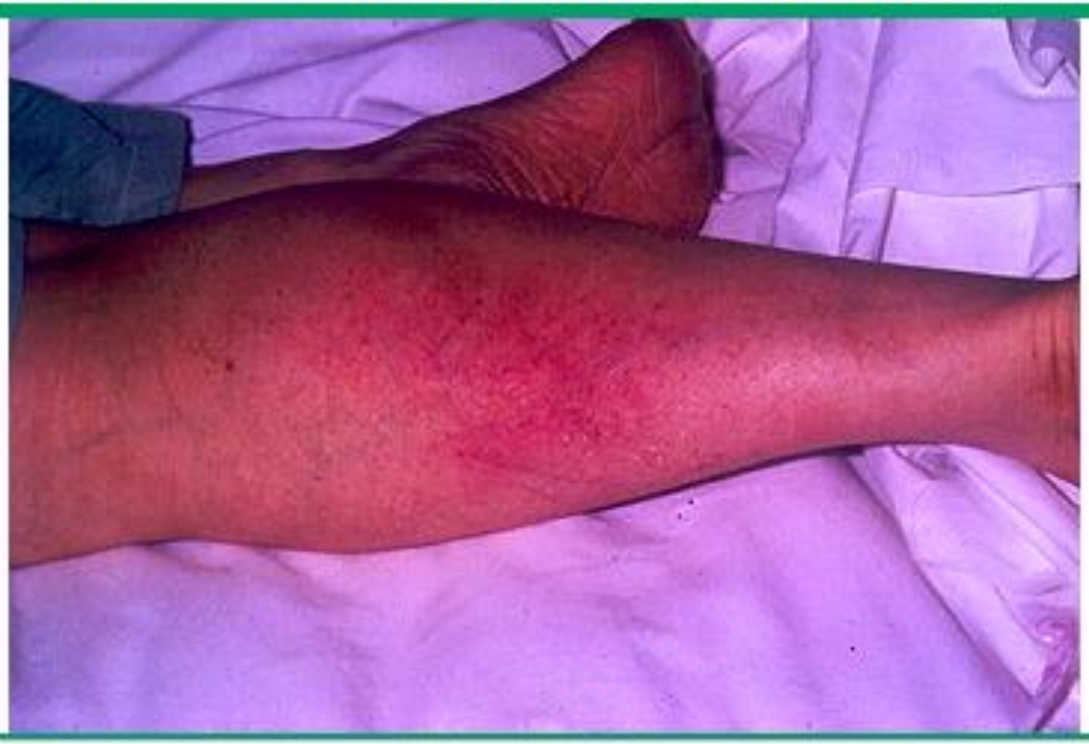
Nodules in disseminated candidiasis



Large erythematous, nodular lesions with central necrosis in a patient with acute leukemia and disseminated candidiasis.

Clinical Manifestations

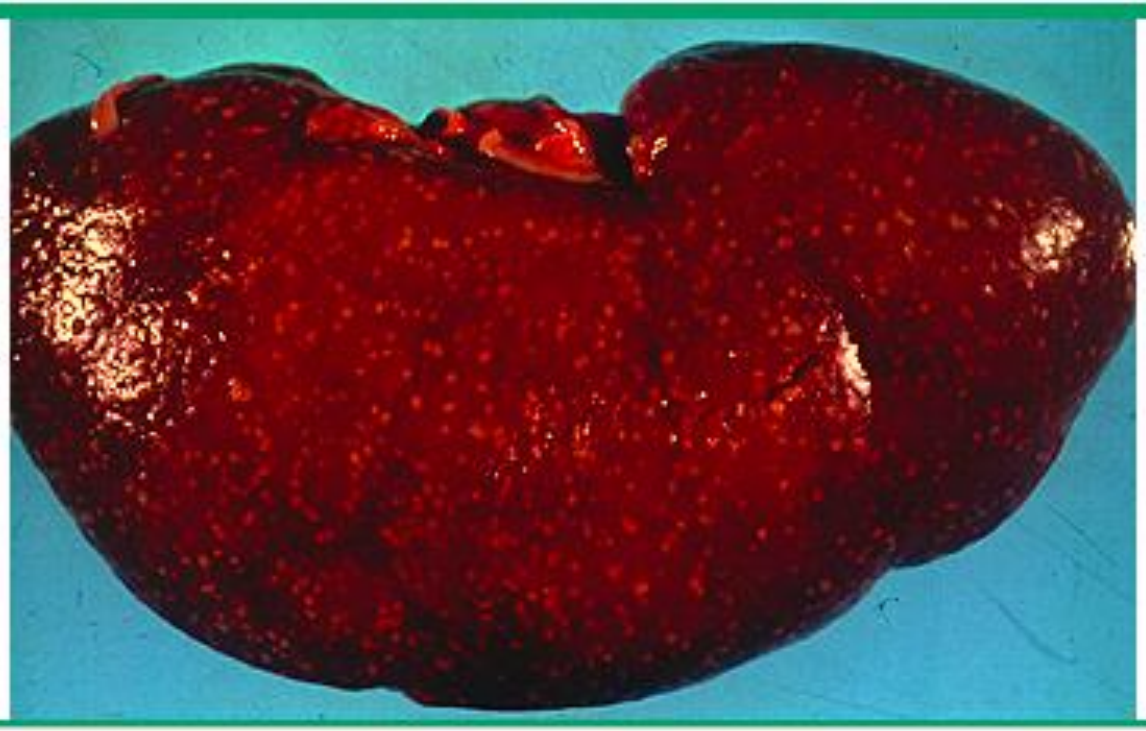
Muscle abscess in disseminated candidiasis



Erythematous, warm, tender gastrocnemius muscle in an older adult male with acute leukemia and neutropenia. Biopsy showed microabscesses containing budding yeasts and pseudohyphae.

Clinical Manifestations

Disseminated candidiasis



Numerous small abscesses can be seen studding the surface of the kidney in a patient who developed disseminated candidiasis.

Diagnosis – not always easy

- Blood cultures

- Positive in only 50-70% of cases, rarely positive in patients with deep seated Candidiasis

- If focal findings → biopsy for staining, culture and histopathologic evaluation

- Beta-D-glucan assay

Beta-D-Glucan (BDG) Assay

- BDG is present in the cell wall of fungi
- Not a specific assay for Candida
- Can be a useful adjunct to blood cultures and biopsy, and is useful in patients with deep-seated invasive candidiasis
- Not available through Pathwest

Management - Antifungals

- Antifungal agent options:

- Echinocandins (caspofungin, micafungin, anidulafungin)
- Azoles (fluconazole, voriconazole)
- Polyenes (amphotericin B)

Antifungals

- Fluconazole no longer considered 1st line for invasive candidiasis

→ Now Echinocandins (caspofungin, anidulafungin)

→ Broader spectrum of activity, fungicidal activity, excellent safety profile and fewer drug-drug interactions.

→ Penetrate well into biofilm formed on vascular devices.

Therapeutic Guidelines (Aust)

Candida species

For severe sepsis caused by *Candida* species, seek expert advice. Treatment choice should be based on local susceptibility data. If the infection is associated with an intravascular catheter, the catheter must be removed to prevent relapse.

Until the *Candida* species is identified and the results of susceptibility testing are available, use initially:

1 anidulafungin 200 mg IV, for the first dose, then 100 mg IV, daily

OR

1 caspofungin 70 mg (child younger than 3 months: 25 mg/m^2; child 3 months or older: 70 mg/m^2 up to 70 mg) IV, for the first dose, then 50 mg (child younger than 3 months: 25 mg/m^2; child 3 months or older: 50 mg/m^2 up to 50 mg) IV, daily [Note 22].

Therapeutic Guidelines (Aust)

Fluconazole is an alternative in patients who are haemodynamically stable [Note 23], are not neutropenic, have not had recent exposure to azoles, and are likely to have infection with *C. albicans* or other susceptible strains. Use:

> fluconazole 800 mg (child: 12 mg/kg up to 800 mg) IV, for the first dose, then 400 mg (child: 6 mg/kg up to 400 mg) IV, daily [Note 24].

Alternatively, amphotericin B desoxycholate or lipid formulations may be used.

Following clinical improvement, for susceptible species, continue treatment with:

> fluconazole 400 mg (child: 6 mg/kg up to 400 mg) orally, daily for a total treatment course of at least 14 days.

For non-susceptible species, seek expert advice.

Neutropenic patients with hepatosplenic candidiasis need prolonged therapy—seek expert advice.

All patients with candidaemia require an ophthalmological examination to exclude endophthalmitis, which requires prolonged therapy.

Antifungals

- Drug dosing can be challenging in critical illness due to pathophysiological changes.
- Fluconazole dosing is particularly challenging in ICU patients.

→ In sepsis, interstitial fluid concentrations of fluconazole in tissues are 50% lower than those in plasma.

→ If receiving RRT, high drug clearances of fluconazole occurs.

- Voriconazole – unpredictable dosing requirements, and many drug-drug interactions

Antifungals

- Echinocandins:

- Less pharmacokinetic changes in critically ill patients
- Not greatly influenced by RRT
- Protein bound, therefore hypoalbuminaemia could alter PK

Antifungals

- Use of therapeutic drug monitoring is likely to play an increasingly important role in antifungal dosing decisions.

Table 1 Summary guidance for antifungal dosing in different critically ill patient subpopulations

	ARC	AKI	RRT	ALF
Amphotericin	Unchanged	Unchanged	Unchanged	Unchanged
Fluconazole	Increase	Decrease	Increase	? Unchanged
Voriconazole	TDM	TDM	TDM	TDM
Itraconazole	TDM	TDM	TDM	TDM
Posaconazole	TDM	TDM	TDM	TDM
Caspofungin	Unchanged	Unchanged	Unchanged	Decrease
Micafungin	Unchanged	Unchanged	Unchanged	Unchanged
Anidulafungin	Unchanged	Unchanged	Unchanged	Unchanged
Flucytosine	TDM	TDM	TDM	TDM

AKI **acute kidney injury,** ***ALF*** **acute liver failure,** ***ARC*** **augmented renal clearance,** ***RRT*** **renal replacement therapy,** ***TDM*** **therapeutic drug monitoring**

Conclusion

- Fungal infections are associated with considerable morbidity and mortality in ICU patients.
- Therapies often started late because fungal infections are difficult to diagnose.
- Until rapid susceptibility testing is available – empiric therapy should be commenced based on:
  - Patient risk factors
  - Local fungal microbiology patterns
  - Hospital setting
  - Site of infection
- Dosing of antifungals are different in ICU compared to non-ICU patients.