ASIA FUNGAL WORKING GROUP
an ISHAM working group

ISHAM
INTERNATIONAL SOCIETY FOR HUMAN AND ANIMAL MYCOLOGY

Co-organized with:

MMTN
MEDICAL MYCOLOGY TRAINING NETWORK

MMTN INDONESIA 2025

October 4 – 5, 2025
Manado, Indonesia

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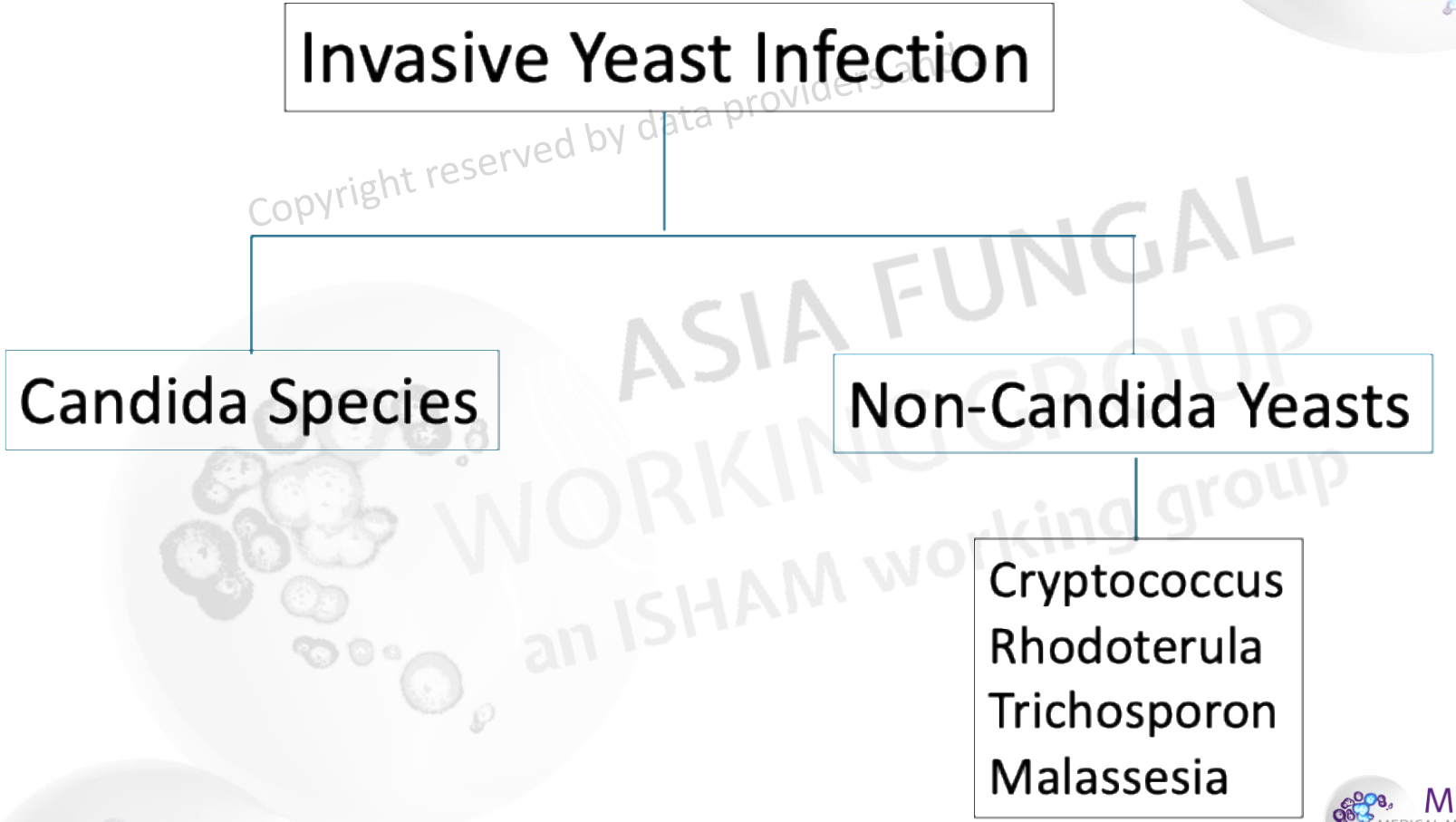
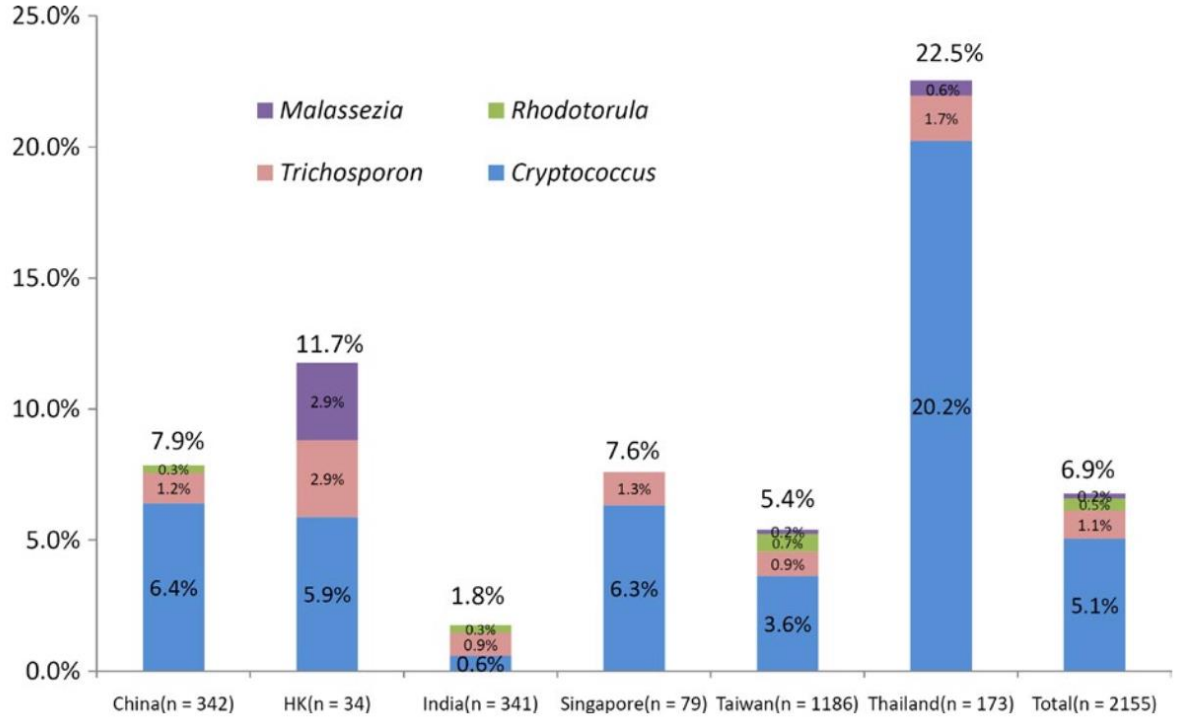
Updates in Invasive Yeast Infections



Lin SY, Mycoses. 2019 Feb;62(2):112-120.

Invasive Yeast Infection



ndida Yeasts

ptococcus
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chosporon
lassesia

Lin SY, Mycoses. 2019 Feb;62(2):112-120.

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Introoduction: Candidemia

- Every year 600,000 people with candidemia, with a mortality rate of 30–40%, even in high-income countries
- Invasive candidiasis (IC) without a positive blood culture exceed 900,000 every year worldwide
- IC typically occurs in patients with one or more risk factors
  - Non-neutropenic ICU and neutropenic patients

Casalini, Giacomo et al. The Lancet Microbe, Volume 5, Issue 7, 717 - 724

Introduction

- Increase in difficult to treat IC cases
  - Underlying new host factors (IL-17 inhibitors- Secukinumab, Brodalumab)
  - Emergence of antifungal resistance
    - C. Auris and fluconazole resistant C. Parapsillosis

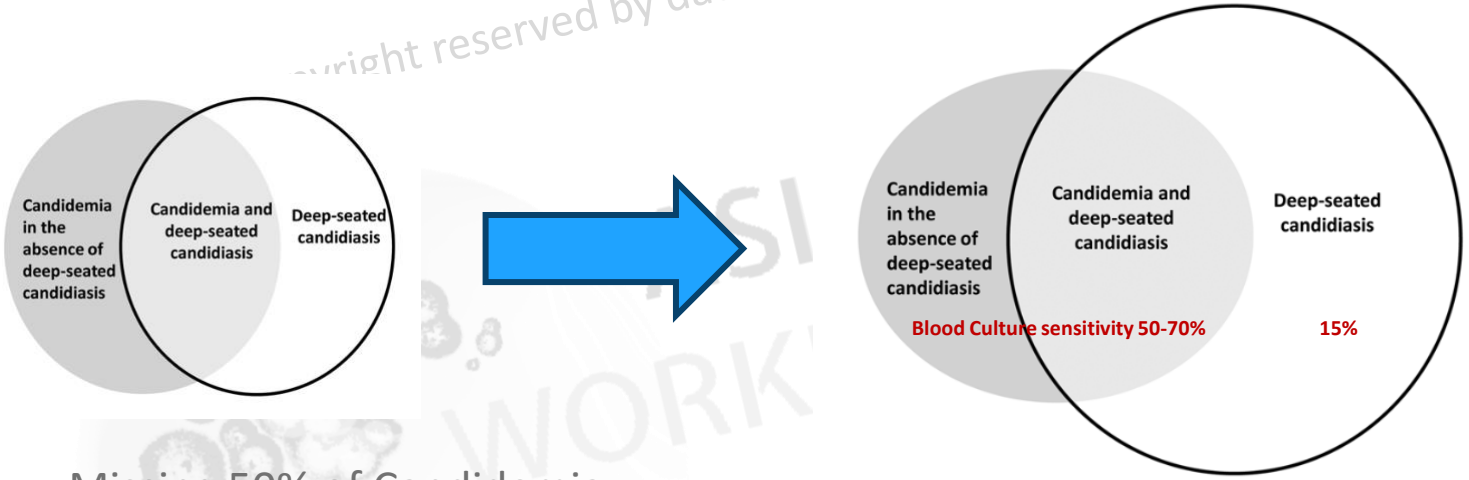
Casalini, Giacomo et al. The Lancet Microbe, Volume 5, Issue 7, 717 - 724

Updates in the epidemiology

- A global shift in species distribution
  - ***C. albicans*** no longer the predominant species in many regions
  - Non-albicans Candida species- particularly ***C glabrata***, ***C. parapsilosis***, ***C. tropicalis***, and the multidrug-resistant ***C. auris***—contributes to more than half of isolates
- Shift in species observed especially in settings with
  - High antifungal use
  - Immunocompromised
  - Critically ill patients

Ricotta EE, J Infect Dis. 2021 Apr 8;223(7):1295-1302. Bays DJ, Clin Epidemiol. 2024 Aug 28;16:549-566.

Invasive Candidiasis (IC)



Missing 50% of Candidemia

Improved diagnostics will identify more IC: Especially deep-seated candidiasis

Clancy CJ, Clin Infect Dis. 2013 May;56(9):1284-92.

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Clinical Manifestation of IC

- Non-specific:
  - Vary from minimal fever to full blown sepsis just like bacterial sepsis
- Minimal signs:
  - Skin rashes, eye involvement, less frequently muscle abscesses
- Diagnosis:
  - **Blood Cultures**
  - Non-culture based
    - BDG
    - Mannan-antimannan
    - Candida albicans germ tube antibody (CAGTA)
    - T2Candida
    - PCR

Serum Beta D Glucan

- Useful in high-risk group of patients with prevalence of invasive fungal infections at >15% (Sensitivity 81%, Specificity 60%)
- High negative predictive value (98%)
- At least two consecutive BDG should be positive to diagnose invasive candidiasis in absence of direct demonstration of fungi
- BDG test performance can vary by species
- BDG levels are significantly higher in C. Albicans as compared to non-albicans species such as C. parapsilosis and C. auris

Logan C. Intensive Care Med 2020; 46: 2001-14. Hage CA. Am J Respir Crit Care Med. 2019;200(5):535. Obayashi T. Clin Infect Dis. 2008;46(12):1864. Mikulska M, Clin Microbiol Infect. 2024 Jun;30(6):822-827. Ullah, N J. Fungi 2025, 11, 149

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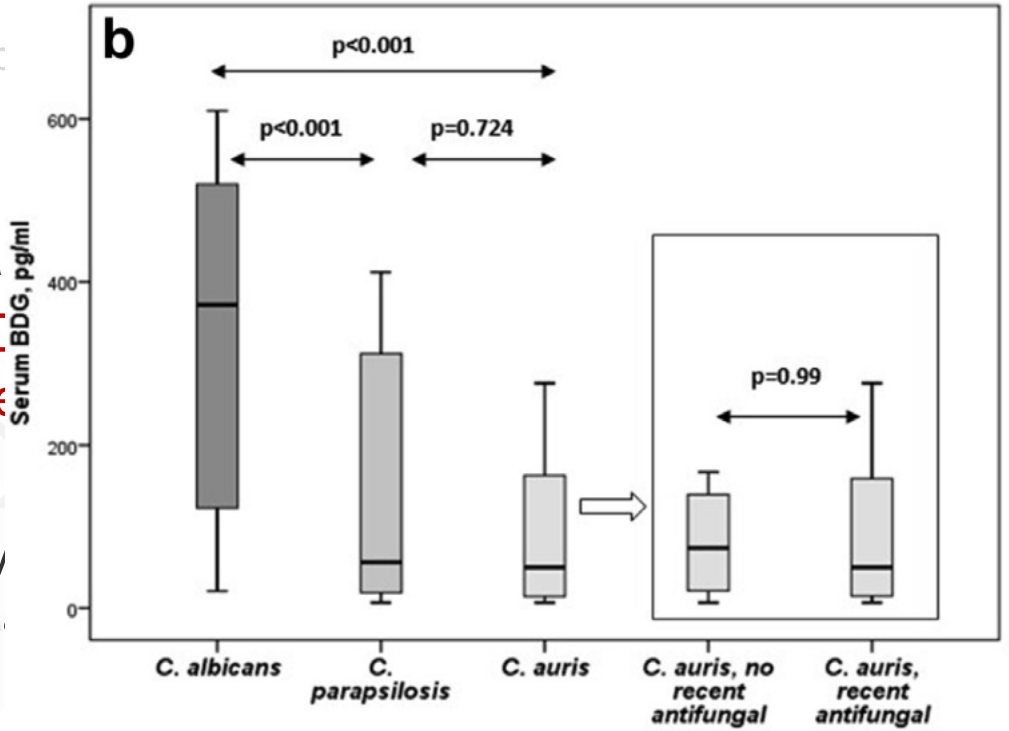

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1. *Candida* Biomarkers May Help to Identify the Origin of the **Candidemia**

CAGTA determinations in serum samples (N = 50)

In **CAGTA**-positive candidemias:

- **69%** deep seated CR candidemias, $P < .001$
- **4.7%** non-deep seated CR candidemias, $P < .001$

If CAGTA positive:

look beyond the catheter

Sensitivity of CATGA may be lower for infections caused by *C. tropicalis* than other *Candida* species

CAGTA, *C albicans* germ tube-specific antibody; CR, catheter-related.
Martínez-Jiménez MC, et al. Med Mycol. 2014;52:270-275.

2. The Number of Positive BCs Also Help to Detect CR Candidemia

- Skin and hub cultures worse than in bacterial infections
- No optimal cutoff for DTTP or MTTP
- When < 2 BCs are positive in a patient with candidemia, the probability that the CVC is the origin is low and other foci should be investigated

Sens	Spec	PPV	NPV	Accuracy
100%	62.5%	83.3%	100%	87.0%

If not all BCs positive:

look beyond the catheter

BC, blood culture; CVC, ventral venous catheter; DTTP, differential time to positivity; MTTP, minimal time to positivity; NPV, negative predictive value; PPV, positive predictive value; Sens, sensitivity; Spec, specificity.

Bouza E, et al. Clin Microbiol Infect. 2013;19:E129-E135.

Prevalence of candidemia in different populations, and anticipated PPVs and NPVs of non-culture tests

Prevalence	Representative Patient (Reference)	[1] BDG, Mannan/Anti-Mannan		[2] T2Candida		[3] PCR	
		PPV	NPV	PPV	NPV	PPV	NPV
0.4%	Any hospitalized patient in whom a blood culture is collected [20]	1%	99.9%	15%	>99.9%	3%	>99.9%
1%	Patient admitted to intensive care unit (ICU) [30,31]	4%	99.7%	31%	99.9%	8%	99.9%
2%	Patient with febrile neutropenia, baseline rate of candidemia prior to empiric antifungal treatment [32–35]	7%	99.5%	47%	99.8%		99.8%
3%	Patient with septic shock and > 3–7 days in ICU [30,36–38]	11%	99.2%	67%	99.7%	22%	99.7%
5%	Patient with left ventricular assist device and evidence of active infection [39,40]	17%	98.7%	70%	99.5%	32%	99.5%
10%	Patient fulfilling criteria of clinical prediction model for candidemia [41–43]	31%	97%	82%	99%	50%	99%

Clancy & Nguyen. J. Fungi 2018, 4, 27; doi:10.3390/jof4010027

Case History

- A 70/ male residing in Udaipur presented with
  - High-grade fever spikes (103°F) with chills for the last 21 days
  - Weakness, loss of appetite, and weight loss
  - Relatives also described altered sensorium with high fever spikes for the last 3-4 days
  - Frequency and urgency of urinations
- Past History
  - He was diabetic and recently diagnosed with Hodgkin disease
  - Completed three cycles of ABVD
  - The chemo port was placed 4 months ago

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Case History

- Treatment so far:
  - He was admitted elsewhere and worked up extensively
  - Urine examination and culture was unremarkable: BEP
  - His 2D echo (TTE), CT scans of the thorax and USG abdomen were unremarkable
  - Received multiple courses of antibiotics
  - MRI brain with contrast and CSF examinations for the assessment of altered sensorium; were normal
- The patient was transferred to our center for further evaluation and treatment

Summary of current presentation

An elderly diabetic man diagnosed with Hodgkin disease on ABVD chemotherapy through chemo port presented with FUO without localising symptoms and no response to multiple courses of antibiotics

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Physical Exam

- Thin built (weight 51 kg), drowsy but arousable with pallor, generalised increased skin pigmentation, and fingernails clubbing grade 2
- Heart sounds were normal, with no murmurs
- Clear breath sounds
- A non-tender spleen was palpable below the left costal margin

Differential Diagnosis

1. Fever without localising symptoms is challenging
    1. Drug fever
    2. Disease activity (Hodgkin disease)
2. Endocarditis: Fever, clubbing, splenomegaly
3. CMV reactivation
4. UTI – Prostatitis

Work up at our hospital

- Blood cultures, urine culture, and routine laboratory workups
- Empiric antibiotics (Meropenem)
- Lab: Hb: 10.8 gm/dL, WBC: 11060/cmm, 83% poly, platelet count 165000/cmm. Urine examination showed 2-4 pus cells and 1-2 RBCs with trace protein
- RA factor was **2X ULN**, creatinine **1.33** mg/dL, SGPT: **56** IU/L, K^{+}: **2.8** mEq/L, Mg^{+2}: **0.9** mg/dL, and Na^{+}: **130** mEq/L.

Hospitalisation D2: Call from Microbiology Lab

- After 23 hours of hospitalization
  - Blood culture from chemo-port grew yeast
  - Peripheral line was sterile
- Caspofungin in standard dosage was added
  - Non-candida yeasts can cause invasive infection in immunocompromised patients
  - Echinocandins are not effective against non-candida yeast (cryptococcus, trichosporon, Malassezia, and others)
- Yeast was identified by Vitek II as Candida parapsilosis
- Drug susceptibility results: fluconazole <= 0.5, voriconazole <= 0.12, caspofungin = 0.25, micafungin = 0.5, amphotericin B = 0.5, and flucytosine <= 1

Lin SY,; The epidemiology of non-Candida yeast isolated from blood: The Asia Surveillance Study. Mycoses. 2019 Feb;62(2):112-120.

Should we remove the chemo port?

- Guideline strongly recommends

- It should be removed as soon as possible
  - Candidemia
  - C. parapsilosis loves plastic and readily produces biofilms

Should we change antifungal to fluconazole?

- Switching antifungals to fluconazole is an option in this case

- Echinocandins have higher MIC values for *C. parapsilosis*
  - Naturally occurring polymorphisms in the FKS region

We continued Caspofungin

- Better biofilms activity of echinocandins (L-AmB is also active in biofilm)
- No clinical studies demonstrated superiority of fluconazole over the echinocandins for the treatment of *C. parapsilosis* infections
  - Observational study from Spain: No difference in outcome among patients who received initial treatment with an echinocandin compared with those who received other regimens
- Study showed enhanced activity of micafungin against *C. parapsilosis* in the presence of human serum as compared to PK/PD targets in vitro

Beredaki MI, A new PK/PD target for assessing efficacy of micafungin against Candida parapsilosis. J Antimicrob Chemother. 2024 Jan 3;79(1):157-165.
Fernandez-Ruiz M, Initial use of echinocandins does not negatively influence outcome in Candida parapsilosis bloodstream infection: a propensity score analysis. Clin Infect Dis 2014; 58:1413–21.

Patient's relative refuses for hardware removal

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How Should I Monitor the treatment?

- Guidelines recommend: Daily blood culture till patients achieve a sterile blood culture for three consecutive days
- My way of treatment monitoring:
  - Repeat blood cultures on days 3, 7, 10 and so on to monitor response to the treatment
- Serum beta-D glucan can be used to monitor treatment response
  - Up to 20% of patients may experience intermittent rises in BDG levels without treatment failure or relapse

Träger J, Detailed β-(1→3)-D-glucan and mannan antigen kinetics in patients with candidemia. J Clin Microbiol61:e00598-23

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Case Continued

- Relatives were reluctant to remove chemo port
- Patient continued to spike fever but with reduced intensity
- The sensorium started improving
- Urine culture came back sterile
- Day three blood culture from the chemo port grew yeast after 22 hours, and peripheral line grew yeast after 46 hours
  - Vitek II identification and drug susceptibility remain the same

Possible reasons for D 3 positive blood culture

- Wrong selection of antifungal
- Failure to remove hardware
- Deep seated source

How will you approach patients whose day three blood culture is positive?

- Checked for the possible source of infection
- Deep seated infectious focus
  - Infective endocarditis
  - Vertebrodiscitis
  - Other site deep-seated, undrained focus
- Failure to remove hardware/CVC/Chemoport was a likely source for persistent candidemia

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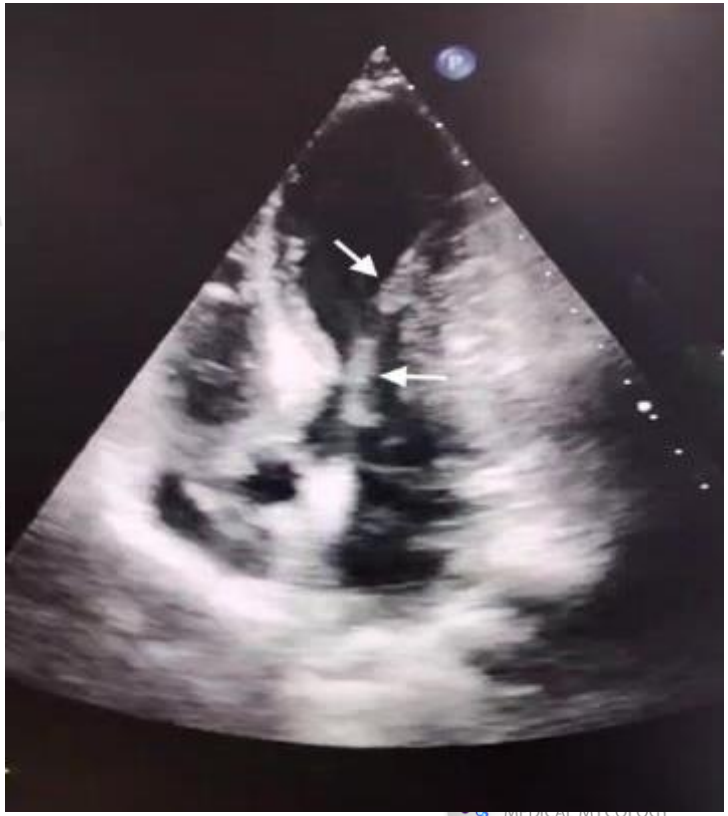
Case continued

- Patient's relatives agree for chemo port removal
  - Tip gram stain showed gram-positive yeast cells
  - Culture grew C. parapsilosis (flush method) same drug susceptibility as the first isolate
- TEE
  - Large, elongated, freely mobile structure in the right atrium distinct from the tricuspid valve
- Treatment
  - Meropenem was stopped on day 7
  - Caspofungin 50 mg/day continued
  - Progressive clinical improvement, became afebrile, started eating food, and felt a sense of wellbeing



Follow up

- Repeat blood culture (one set) after 7th day remained sterile

- Patient was discharged on 14th Hospitalisation day on Caspofungin for one more week followed by oral fluconazole 400mg/day
- Fluconazole MIC: <= 0.5, (AUC/MIC= 800)

Is this Candida Endocarditis?

- Satisfied two major criteria
  - TEE showing typical freely mobile vegetation
  - Blood culture growing candida species in patient with intracardiac device (chemo port tip)
- Two minor criteria
  - Fever
  - Positive RA factor

How to Treat Candida Endocarditis?

- Guideline Suggested
- Antifungal Agent
  - Caspofungin
  - L-AmB with or without 5 FC
  - Fluconazole (6–12 mg/kg) is a step-down therapy for infections caused by susceptible candida species that have achieved sterile blood culture and are clinically stable
  - IDSA guideline: higher dosage of echinocandins (Caspo 150, Mica 150, Anidula 200mg)
- Surgical Treatment
  - Removal of Cardiac devices
  - Valve resection, Vegetectomy

How long should we continue antifungal treatment for this patient?

- At least 6 weeks following valve replacement surgery
- Long-term suppressive therapy is recommended for those who can't undergo valve replacement

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Case continued

- We chose prolong therapy for a total of 12 weeks
  - We could achieve source control by removing the chemo port
  - Valves were free from vegetations
  - We gave 3 weeks of caspofungin 50 mg/day,
  - Followed by 9 weeks of oral fluconazole 400 mg/day
- The patient responded well to the treatment with weight gain and a feeling of well-being
- Repeat TTE after two months of antifungal medication was normal, and his serum beta-glucan levels were 65 pg/mL.

Newer Agents for the Treatment of IC

- **Rezafungin**
  - A next-generation echinocandin with an extended half-life, allowing for once-weekly intravenous dosing
  - Active against most *Candida* species, including *C. auris*
  - FDA-approved for candidemia and invasive candidiasis in adults
  - Retains activity against many echinocandin-resistant isolates
- **Ibrexafungerp**
  - Oral triterpenoid glucan synthase inhibitor,
  - Activity against most *Candida* species, including some echinocandin-resistant strains and *C. auris*
  - Currently approved for acute vulvovaginal candidiasis and is under investigation as oral step-down therapy for invasive candidiasis
- **Fosmanogepix**
  - Gwt1 inhibitor that impairs fungal cell wall mannoprotein synthesis
  - Potent in vitro and in vivo activity against a broad range of *Candida* species, including multidrug-resistant *C. auris*
  - In late-stage clinical trials for invasive candidiasis
  - Oral and IV formulations and favorable tissue penetration profile make it a promising option for deep-seated or refractory infections

Ordaya EE, Mycopathologia. 2023 Dec;188(6):937-948. Kriegl L, Clin Microbiol Infect. 2025 Jun;31(6):922-930.

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Take Home message

- Changing epidemiology of species distribution
- Blood culture remains a gold standard for the diagnosis
- Non-culture-based diagnostics have high negative predictive values
- Look for the deep-seated focus in patients with repeat blood culture is positive
- Blood cultures and BDG are useful to monitor candidemia treatment
- Newer Agents: Ibrexafungerp, Fosmanogepix and Rezafungin are promising for the treatment of IC

- Thank You

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