Approach to new onset fever in admitted patient

Dr. Krutarth Kanjiya

Consultant Infection and Critical Care, Sterling hospital

DNB (Internal Medicine)

FNB (Infectious diseases, P.D.Hinduja hospital, mumbai)

TropMed (CMC, Vellore)

- 45 year old female
- Hepatitis B on tenofovir
- Multiple myeloma
- Had received 8 cycles of chemotherapy
- Admitted for BMT
- The patient was on fluconazole and acyclovir prophylaxis

- D7 post transplant patient had fever and throat pain
- O/E : Stable hemodynamically

  : Oral candidiasis present
- S/E : NAD
- Blood culture and urine routine sent

What Next??

A) CT chest and abdomen
B) Start BLBLI or Carbapenem
C) Start meropenem + teicoplanin
D) Start echinocandins
E) B+D

Define the clinical syndrome

- Neutropenic fever with oropharyngeal candidiasis in hemodynamically stable patient

Epub 2018 Jan 31.

Fluconazole non-susceptible breakthrough candidemia after prolonged low-dose prophylaxis: a prospective FUNGINOS study

Christina Orasch [1], Dominik Mertz [2], Jorge Garbino [3], Christian van Delden [3], Stephane Emonet [3], Jacques Schrenzel [4], Stefan Zimmerli [5], Lauro Damonti [6], Konrad Mühlethaler [5], Alexander Imhof [7], Christian Ruef [8], Jan Fehr [9], Reinhard Zbinden [10], Katia Boggian [11], Thomas Bruderer [12], Ursula Flückiger [13], Anna Conen [14], Nina Khanna [15], Reno Frei [16], Thomas Bregenzer [17], Frédéric Lamoth [18], Véronique Erard [19], Pierre-Yves Bochud [20], Thierry Calandra [20], Jacques Bille [21], Oscar Marchetti [22], Fungal Infection Network of Switzerland (FUNGINOS)

Collaborators, Affiliations + expand

PMID: 29378240 DOI: 10.1016/j.jinf.2017.12.018

Abstract

Objectives: Breakthrough candidemia (BTC) on fluconazole was associated with non-susceptible Candida spp. and increased mortality. This nationwide FUNGINOS study analyzed clinical and mycological BTC characteristics.

Methods: A 3-year prospective study was conducted in 567 consecutive candidemias. Species identification and antifungal susceptibility testing (CLSI) were performed in the FUNGINOS reference laboratory. Data were analyzed according to STROBE criteria.

Results: 43/576 (8%) BTC occurred: 37/43 (86%) on fluconazole (28 prophylaxis, median 200 mg/day). 21% BTC vs. 23% non-BTC presented severe sepsis/septic shock. Overall mortality was 34% vs. 32%. BTC was associated with gastrointestinal mucositis (multivariate OR 5.25, 95%CI 2.23-12.40, $p < 0.001$) and graft-versus-host-disease (6.25, 1.00-38.87, $p = 0.05$), immunosuppression (2.42, 1.03-5.68, $p = 0.043$), and parenteral nutrition (2.87, 1.44-5.71, $p = 0.003$). Non-albicans Candida were isolated in 58% BTC vs. 35% non-BTC ($p = 0.005$). 63% of 16 BTC occurring after 10-day fluconazole were non-susceptible (Candida glabrata, Candida krusei, Candida norvegensis) vs. 19% of 21 BTC (C. glabrata) following shorter exposure (7.10, 1.60-31.30, $p = 0.007$). Median fluconazole MIC was 4 mg/l vs. 0.25 mg/l ($p < 0.001$). Ten-day fluconazole exposure predicted non-susceptible BTC with 73% accuracy.

Conclusions: Outcomes of BTC and non-BTC were similar. Fluconazole non-susceptible BTC occurred in three out of four cases after prolonged low-dose prophylaxis. This implies reassessment of prophylaxis duration and rapid de-escalation of empirical therapy in BTC after short fluconazole exposure.

Breakthrough Candida Infection

- Breakthrough Candida Infection in face of ongoing antifungal therapy suggests
  - Infected intravascular device
  - Significant immunosuppression
  - Microbiological resistance

- Therapy with an agent from a different class should be started
- Isolate should be promptly identified to the species level
- susceptibility testing should be considered
- Infected intravascular devices should be removed
- immunosuppression should be ameliorated

In our patient….

- Piperacillin tazobactam was started
- Considering the possibility of an Fluconazole resistant candida species, Micafungin was given for 10 days to which the patient responded very well.

Treatment duration for
Oropharyngeal candidiasis x 7-14 days
Oesophageal Candidiasis x 14-21 days

Ref : IDSA candida guidelines

DAY 14

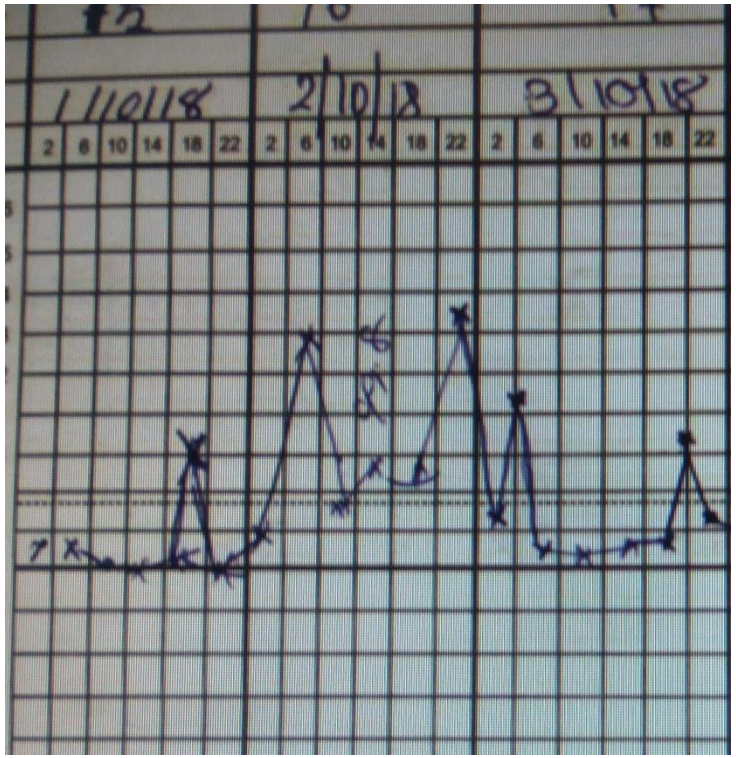
Developed fever, abdominal pain, nausea,

Loose motions

Cultures sent and patient was started on empiric meropenem and teicoplanin

Clinical deterioration with dehydration and hypotension - shifted to ICU

Hypotension responded to prompt fluid resuscitation
However fever spikes persisted



	29/9	30/9	1/10	2/10
Hb	10.4	10.3	10	10.3
WBC	570	2200	3710	7400
PC	16K	22K	27K	29K

Stool biofire – Giardia lambia

BACTERIA:

- *Campylobacter (jejuni, coli, and upsaliensis)*
- *Clostridium difficile* (toxin A/B)
- *Plesiomonas shigelloides*
- *Salmonella*
- *Yersinia enterocolitica*
- *Vibrio (parahaemolyticus, vulnificus, and cholerae)*
- *Vibrio cholerae*

DIARRHEAGENIC E. COLI/SHIGELLA:

- *Enteroaggregative E. coli* (EAEC)
- *Enteropathogenic E. coli* (EPEC)
- *Enterotoxigenic E. coli* (ETEC) *lt/st*
- *Shiga-like toxin-producing E. coli* (STEC) *stx1/stx2*
  - *E. coli* O157
- *Shigella/Enteroinvasive E. coli* (EIEC)

PARASITES:

- *Cryptosporidium*
- *Cyclospora cayetanensis*
- *Entamoeba histolytica*
- *Giardia lamblia*

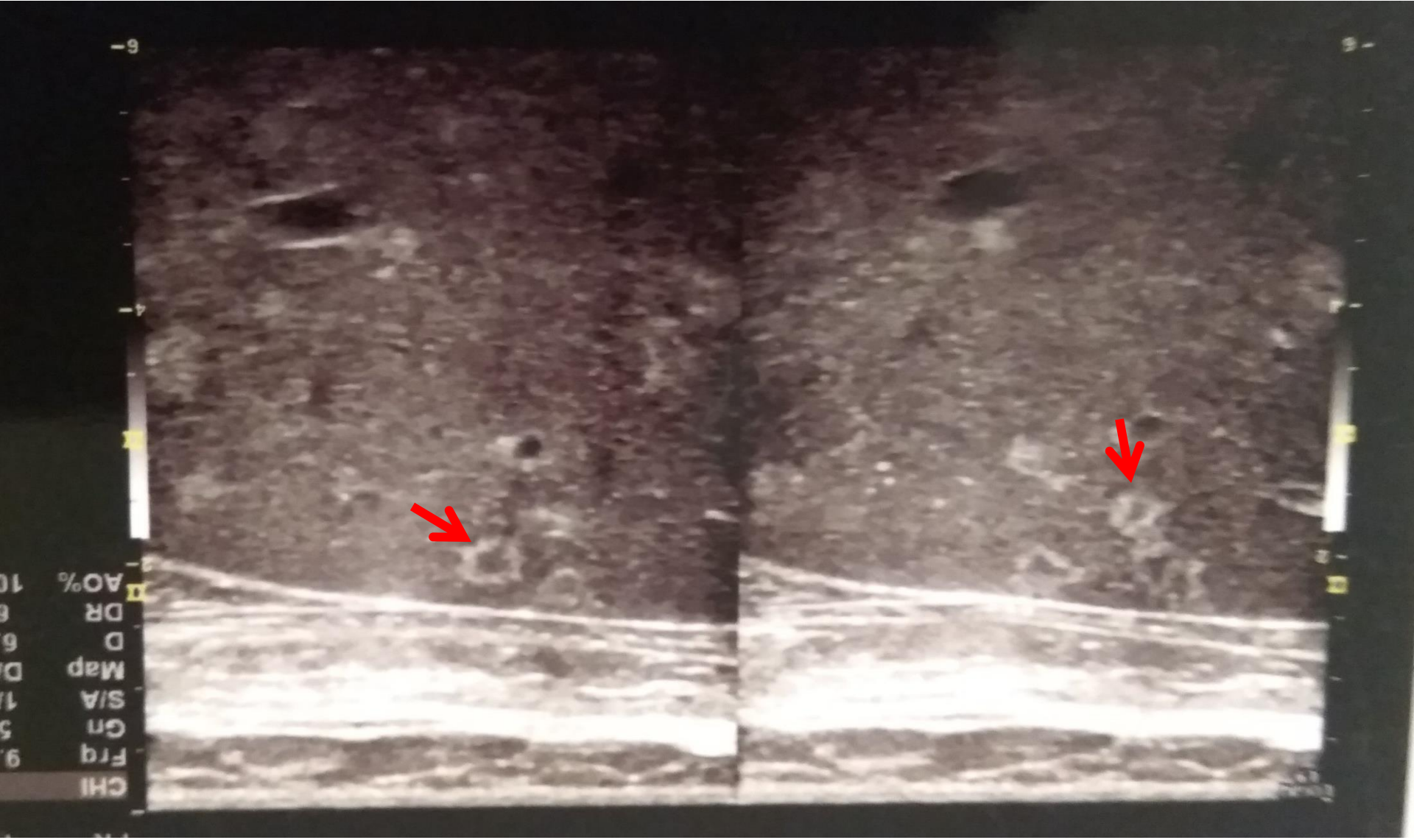
VIRUSES:

- Adenovirus F40/41
- Astrovirus
- Norovirus GI/GII
- Rotavirus A
- Sapovirus (I, II, IV, and V)

D/D

- Neutropenia, diarrhoea, mucositis, gut translocation, sepsis
- Giardia related diarrhoea with hypotension and fever
- Are we missing something…????

Differentials	Points in favour	Points against
Sepsis	Fever hypotension	Recovering WBC Persistent fever after hemodynamic stability
Giardia Infection	Diarrhoea	Fever
Disseminated candidiasis	New onset of fever with recovering Neutrophil count	

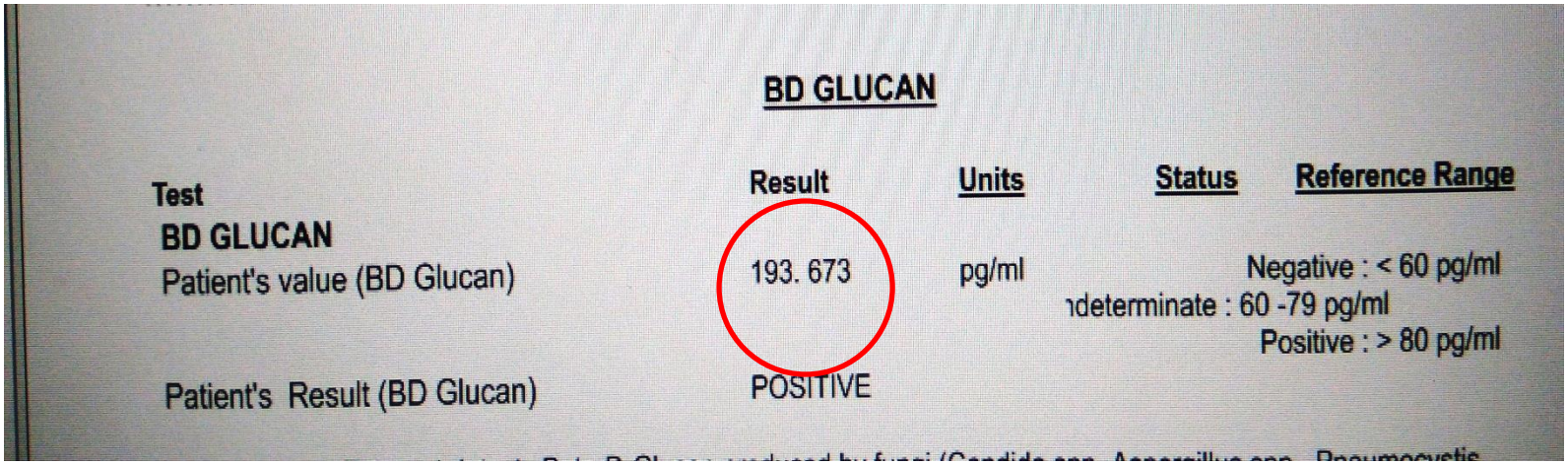


Multiple targetoid "bull`s eye" lesions with central hypoechoic and peripheral echogenic zones seen in both lobes of liver largest measuring :-

Right lobe : 8.5 x 6.3 mm and Left lobe 7.2 x 6.4 mm in size.

Blood culture – negative

Teicoplanin stopped



BD GLUCAN

Test	Result	Units	Status	Reference Range
BD GLUCAN				
Patient's value (BD Glucan)	193. 673	pg/ml		Negative : < 60 pg/ml ıdeterminate : 60 -79 pg/ml Positive : > 80 pg/ml
Patient's Result (BD Glucan)	POSITIVE			

Diagnosis of hepatosplenic candidiasis was made

Which antifungal to start?

1. Fluconazole
2. Amphotericin B
3. Echinocandins
4. Voriconazole

Recommendations

32. Fluconazole at a dosage of 400 mg (6 mg/kg) daily is recommended for clinically stable patients (A-III). LFAmB at a dosage of 3–5 mg/kg daily or AmB-d at a dosage of 0.5–0.7 mg/kg daily can be used to treat acutely ill patients or patients with refractory disease (A-III). Induction therapy with AmB for 1–2 weeks, followed by oral fluconazole at a dosage of 400 mg (6 mg/kg) daily, is also recommended (B-III).

33. Anidulafungin (loading dose of 200 mg, then 100 mg daily), micafungin (100 mg daily), or caspofungin (loading dose of 70 mg, then 50 mg daily for 1–2 weeks) are alternatives for initial therapy, followed by oral fluconazole when clinically appropriate (B-III).

- The patient was started on inj micafungin for 3 weeks followed by posaconazole

THEARAPEUTIC DRUG MONITORING AND TOXICOLOGY

Test			Result	Units	Status	Reference Range
POSACONAZOLE		Conventional	1.00	mg/l		
Plasma	*HPLC*	S.I.	1.43	umol/l		

Comments : Invasive Fungal Infection (IFI) Prophylaxis = > 0.7 mg/l
Treatment of Invasive Fungal Infection (IFI) = > 0.7 mg/l , increased to 1.25 mg/l if response is poor.
Reference: 1) Michael J.Dolton et al. 2012 . Posaconazole exposure-response relationship: Evaluating the utility of therapeutic drug monitoring. Antimicrob Agents and Chemother.56: 2806-2813

Repeat BDG after 2 months

BD GLUCAN

Test	Result	Units	Status	Reference Range
BD GLUCAN				
Patient's value (BD Glucan)	< 7.812	pg/ml		Negative : < 60 pg/ml ıdeterminate : 60 -79 pg/ml Positive : > 80 pg/ml
Patient's Result (BD Glucan)	NEGATIVE			

Review of Literature

Chronic disseminated candidiasis

- Occurs in patients with hematologic malignancy who have recently recovered from an episode of neutropenia

The temporal association of fever and neutrophil counts is an important clue in suspecting disseminated candidiasis

Risk factors

- Acute leukemia
- Prolonged neutropenia (<500 neutrophils/microL for ≥10 days)
- Administration of broad-spectrum antibiotics
- Mucosal barrier disruption
- Presence of an indwelling intravascular catheter
- Administration of total parenteral nutrition

Clinical Features

- Fever that fails to respond to broad-spectrum antibacterial therapy (M.C.)
- Right upper quadrant tenderness
- Hepatomegaly
- Splenomegaly
- Nausea, vomiting, and anorexia

Lab Findings

- Elevated serum alkaline phosphatase
- Less common laboratory abnormalities include mildly elevated aspartate aminotransferase, alanine aminotransferase, and bilirubin, as well as leucocytosis
- Blood cultures - typically negative

Diagnosis

- **Presumptive diagnosis**
  - Clinical history
  - Elevated liver function tests
  - Radiographic imaging demonstrating hypodense nodular lesions in the liver and/or spleen

- **Definitive diagnosis via biopsy**

Treatment

Initial treatment - for at least two weeks:

- A lipid formulation of amphotericin B (3 to 5 mg/kg intravenously [IV] daily)

OR

- -Caspofungin – 70 mg loading dose, then 50 mg IV once daily
- -Anidulafungin – 200 mg loading dose, then 100 mg IV once daily
- -Micafungin – 100 mg IV once daily

Step-down therapy

- Oral fluconazole (400 mg [6 mg/kg] orally once daily) should be administered
- For patients with infection due to a fluconazole-resistant isolate (wi*th C. glabrata or C. krusei*), we give step-down therapy with voriconazole or posaconazole

Treatment duration

- **Guided by imaging** – Follow-up imaging should be obtained every two to three months

- Antifungal therapy should be continued until there is persistent resolution or calcification of the lesions on imaging, which usually takes approximately **six months**

Thank You