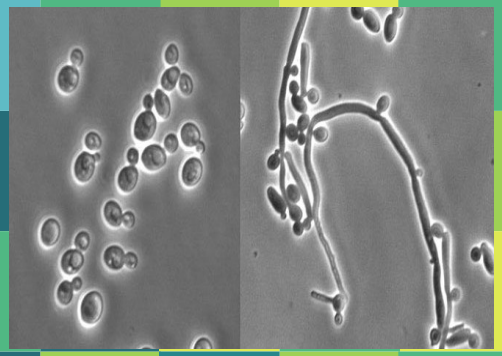
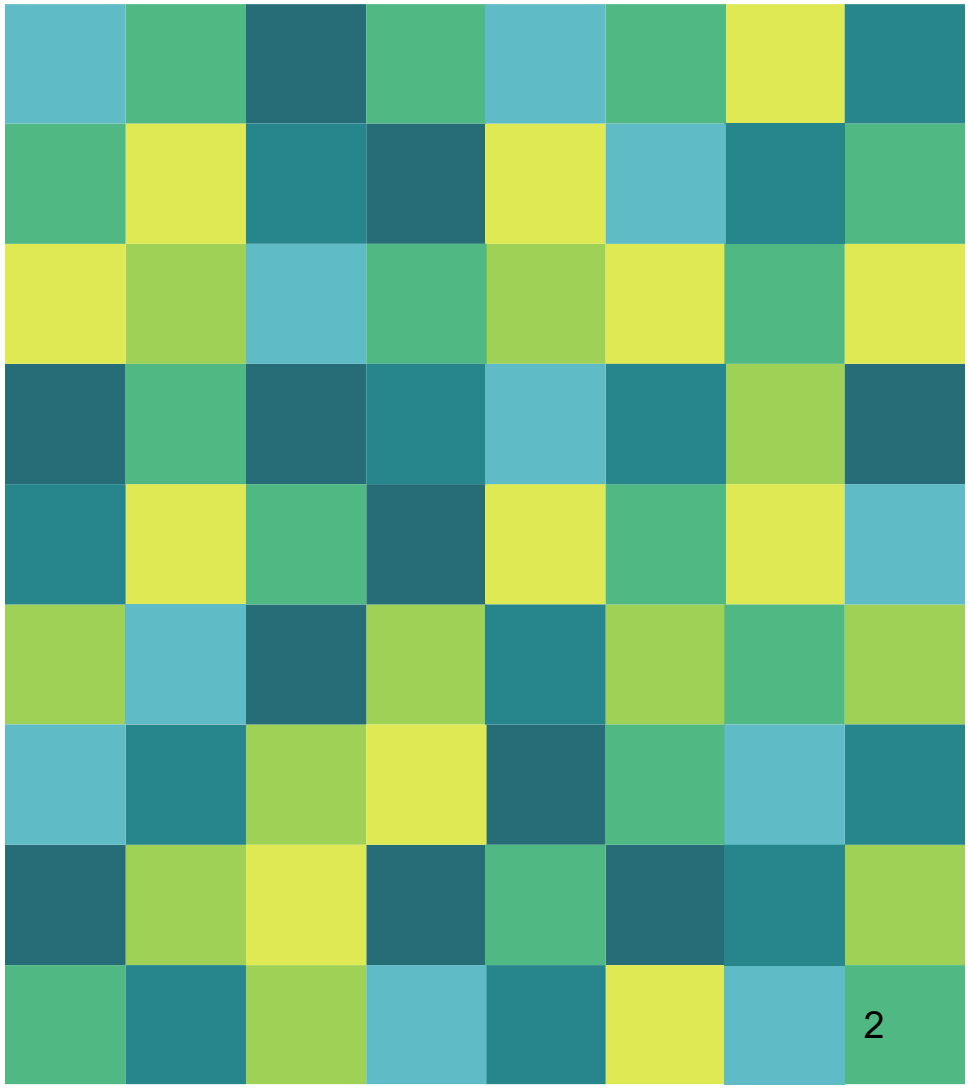
Invasive Candidiasis



Dr Z. Abtahian,
ID Specialist,
Fellowship in immunocompromised host

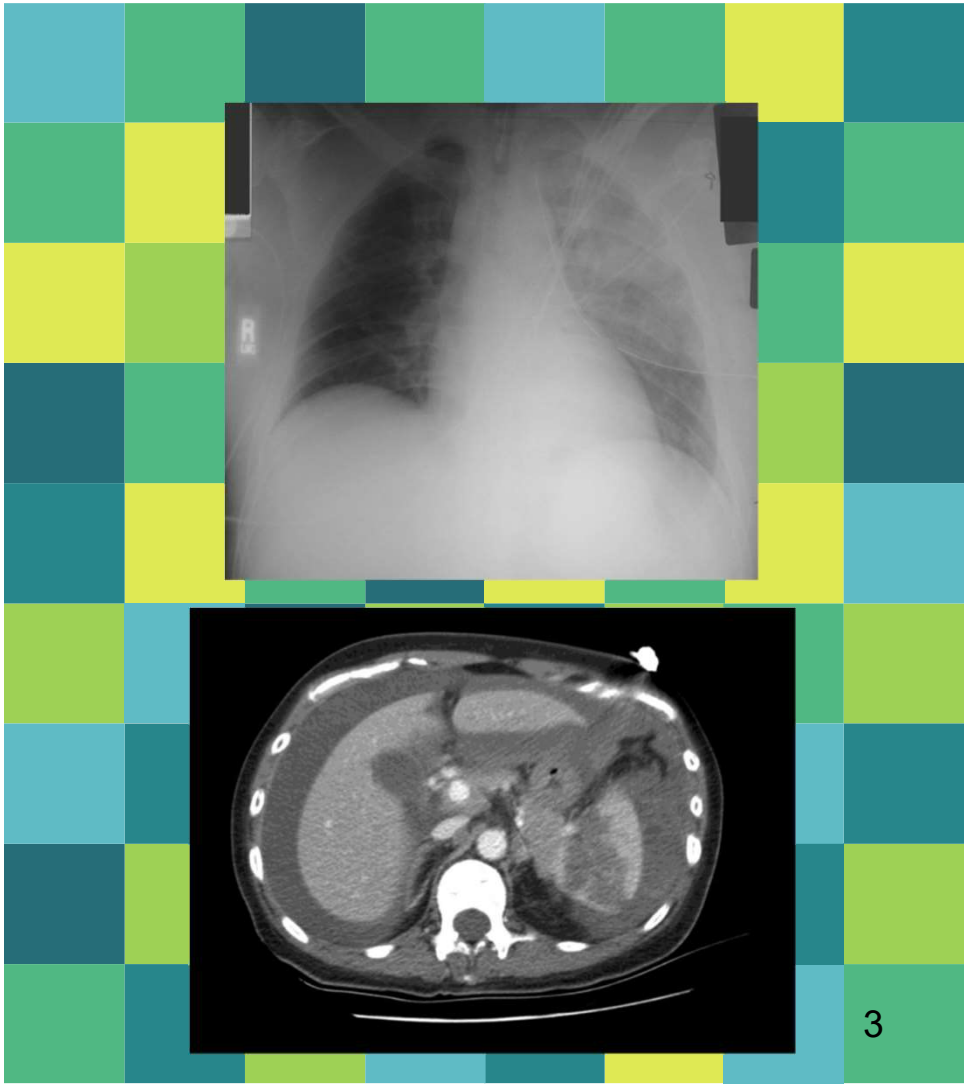
Case presentation

29 year old male with no significant past medical history who was admitted in ICU after he suffered multiple injuries secondary to road
traffic accident:



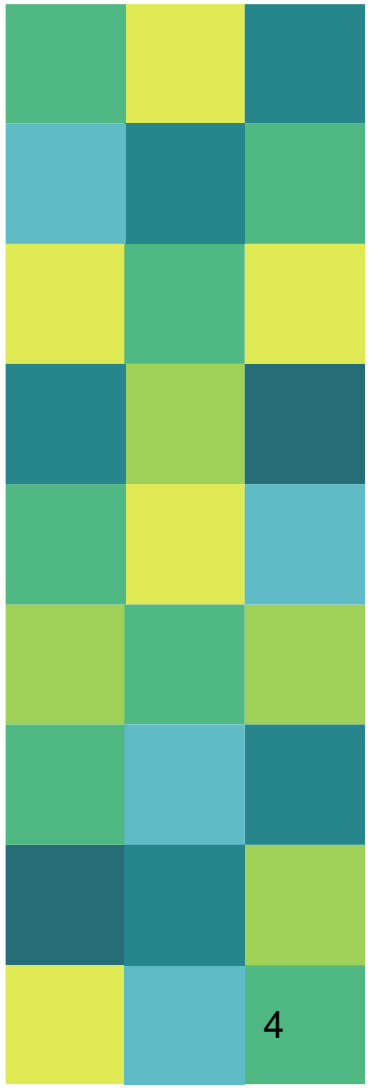
Problem list

- Left multiple rib fractures with pulmonary contusion and hemothorax, required left chest tube drainage and mechanical ventilation
- Splenic rupture with intra-abdominal bleed required splenectomy
- Intestinal injury that required resection and anastomosis



On day one

The Patient started on TPN through left sided subclavian central venous line
and
placed on:
Piperacillin/tazobactam as post surgical prophylaxis



On Day 3

Patient is still intubated and on TPN, clinically stable, without fever or leukocytosis

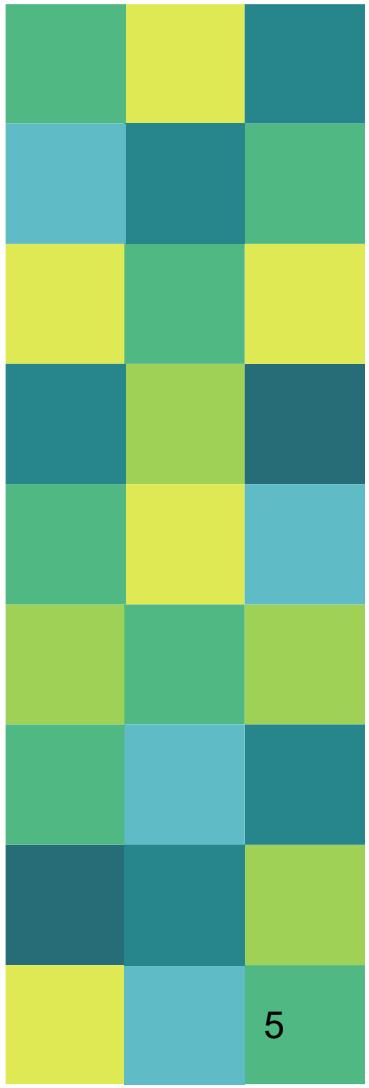
What would you do with his antibiotic regimen?

A. Continue Piperacillin/tazobactam for total of 7 days

B. Stop Piperacillin/tazobactam and start Flucanozole as antifungal prophylaxis

C. Stop Piperacillin/tazobactam and add Caspofungin as antifungal prophylaxis

D. Stop antibiotics and observe



Should Prophylaxis Be Used to Prevent Invasive Candidiasis in the Intensive Care Unit Setting?

Antifungal prophylaxis in ICU patients

- Antifungal prophylaxis in patients in the ICU have little support from clinical studies except for its use in specific HR groups

- In patients who have recent abdominal surgery and have recurrent GI perforations or anastomotic leakage, fluconazole Px has been shown to be effective

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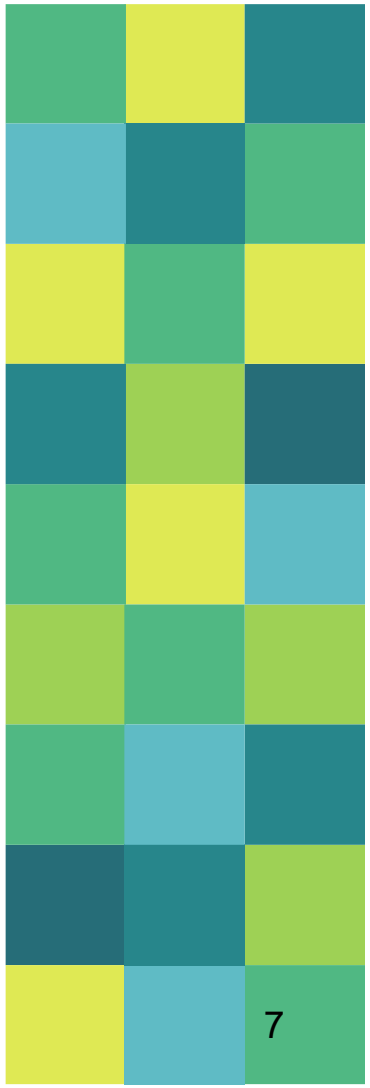
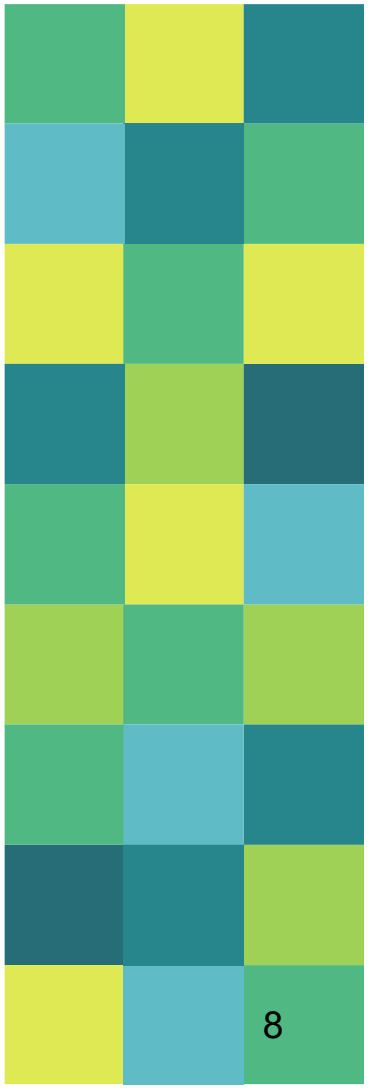


Other indications of antifungal prophylaxis in ICU patients

- Patients undergoing pancreas transplantation
- Patients undergoing small bowel transplantation
- Selected patients undergoing liver transplantation who are at HR for IC

(Prolonged or repeat OP. ,re-Tx ,RF,Ch. J ,candida colonization, high Tx requirement)

N Engl. J Med ,2015



Antifungal prophylaxis in ICU patients

- Fluconazole, 800-mg (12 mg/kg) LD, then 400 mg (6 mg/kg) daily, could be used in HR patients in adult ICUs with a high rate (>5%) of IC
  (weak recommendation; moderate-quality evidence)

- An alternative is to give an Echinocandin
  (weak recommendation; low-quality evidence)

- Daily bathing of ICU patients with chlorhexidine, which has been shown to decrease the incidence of BSIs including candidemia, could be considered

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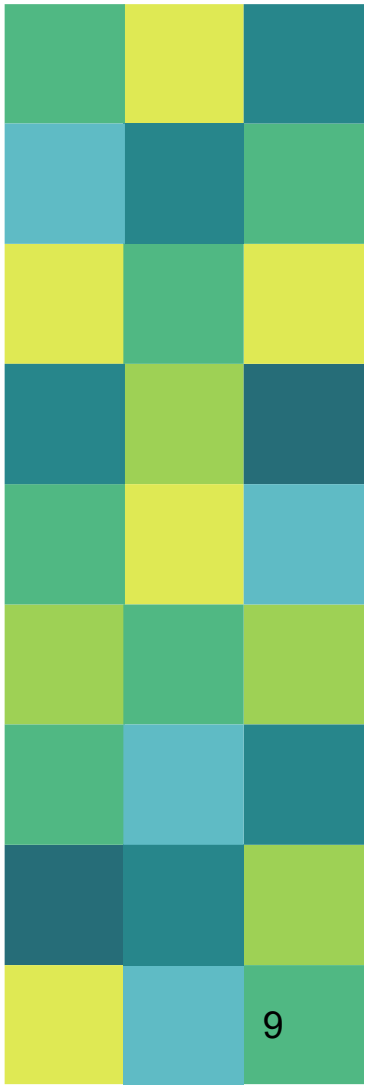

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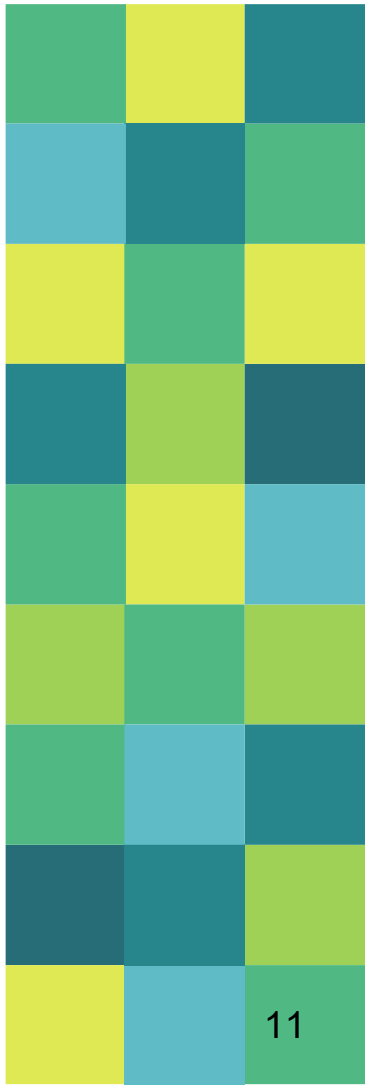
Piperacillin-tazobactam stopped and placed on fluconazole as yeast prophylaxis Because of high prevalence if IC in that center

On day 4 of his ICU admission

His chest tube removed but still intubated

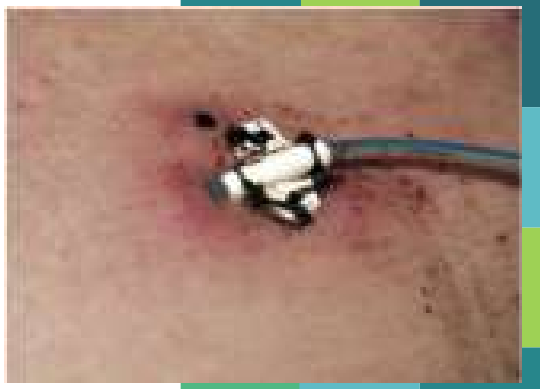
On day 6 of his ICU admission

Developed fever(AT:39.0)
as well as
hypotension (70/40 mm Hg)
and
tachycardia (120/min).



On day 6 of his ICU stay

- Physical examination is remarkable for toxic-appearing man who is intubated and sedated.
- The skin is mildly erythematous around the catheter site, but no tenderness or drainage
- The rest of his physical exam including surgical sites, were completely normal



Lab values on day 6

- CBC:
  WBC: 17,800, (90% PMN)
  Hb:11
  Plt: 120,000

- ABG: PH: 7:27 PCO2: 27 HCO3: 11

- Serum lacatate: 12mmol/ml

- BUN: 48 AST: 21

- Cr:1 ALT: 29

CXR: no evidence of any new infiltration

What would you do next?

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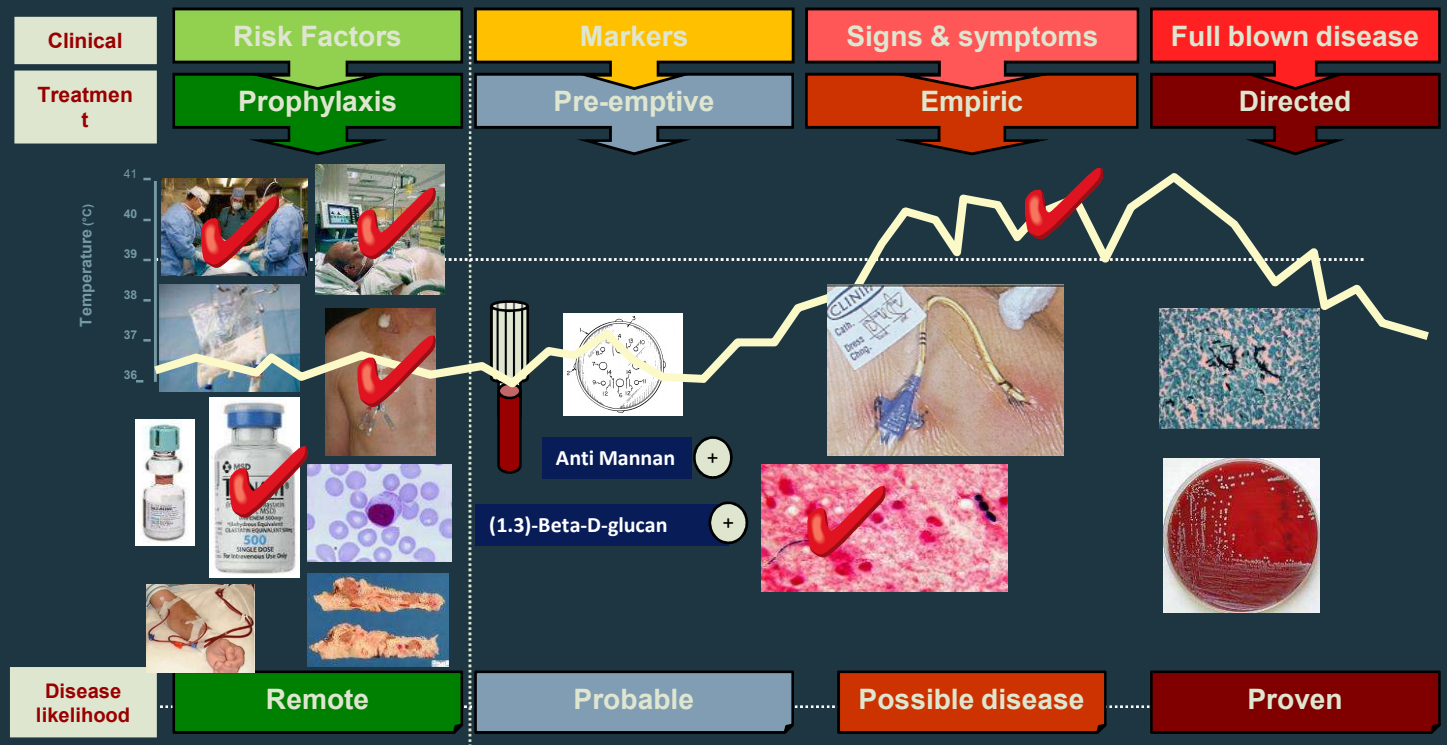
When Empiric Treatment for Suspected Invasive Candidiasis should be considered in ICU ?

Treatment of Invasive Candidiasis in ICU



Empirical treatment for suspected IC in ICU patients

Empiric antifungal therapy should be considered in:

critically ill patients

With

risk factors for invasive candidiasis

and

no other known cause of fever

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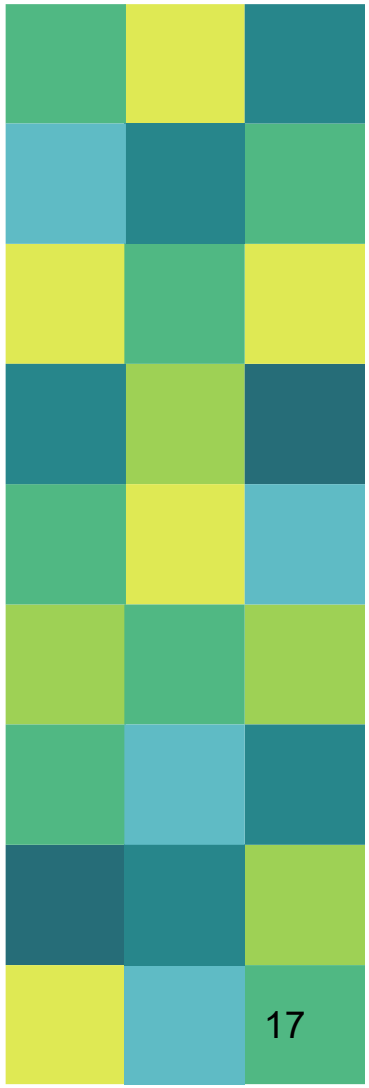


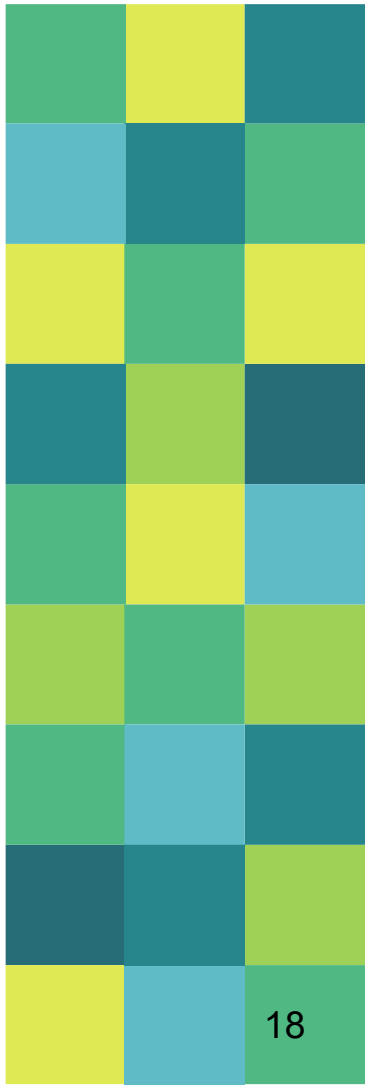
Empiric Treatment for Suspected Invasive Candidiasis

should be based on:

- ✓ **Clinical assessment of risk factors,**
- ✓ **Surrogate markers for IC,**

and/or

- ✓ **Culture data from non-sterile sites**



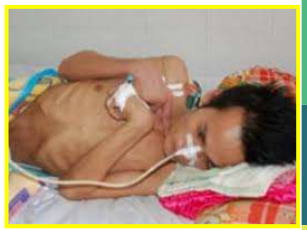
Risk factors for development of invasive candidiasis

1. Candida colonization,
2. Severity of illness,
3. Exposure to broad spectrum ABs,

4. Recent major surgery, particularly abdominal surgery,

5. Necrotizing pancreatitis,

6. Dialysis,
7. Parenteral nutrition (TPN)



8. Corticosteroids,
9. the use of CVCs

Surrogate markers in diagnosis of IC

Surrogate markers that have been evaluated in the ICU setting Include:

1-β-D-glucan

2-mannan-antimannan antibodies

3-PCR testing.

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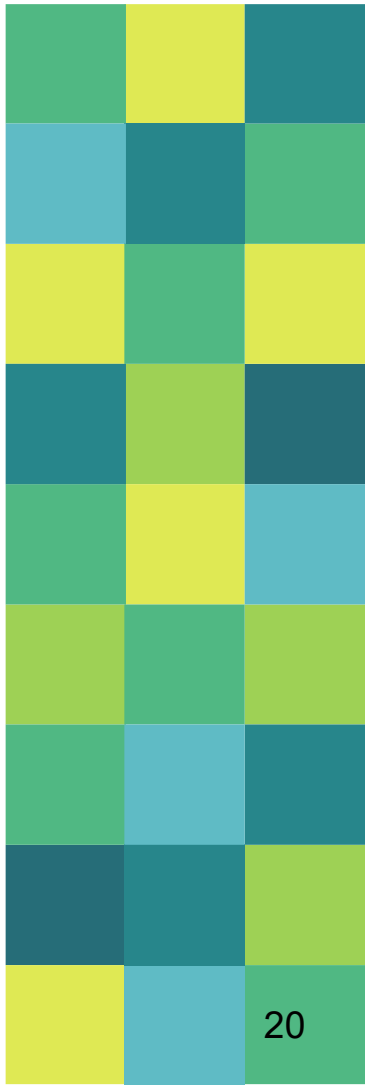

Surrogate markers in diagnosis of IC

β-D-glucan:

- The major concern about β-D-glucan detection is the potential for poor specificity and false positivity

- test will be most useful if targeted to subgroups of patients whose clinical course or RFs are particularly suggestive of invasive candidiasis or other fungal infection.

- appears to be more sensitive than Candida colonization scores or indices, but appears to have low PPV

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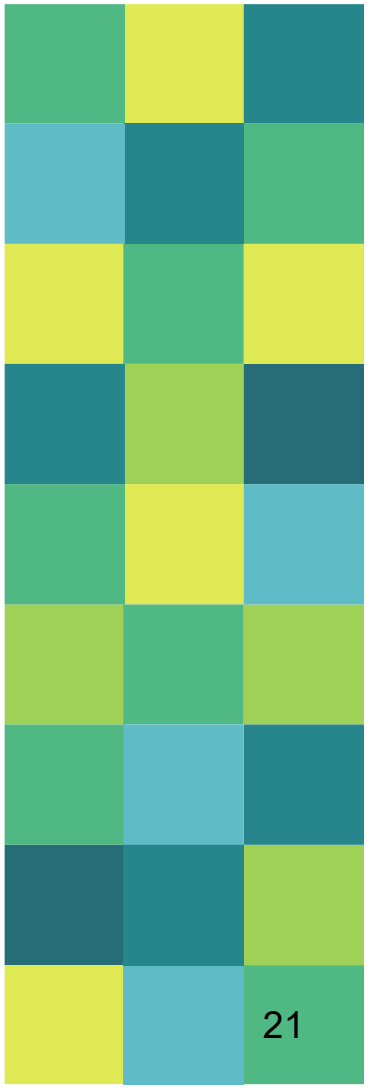
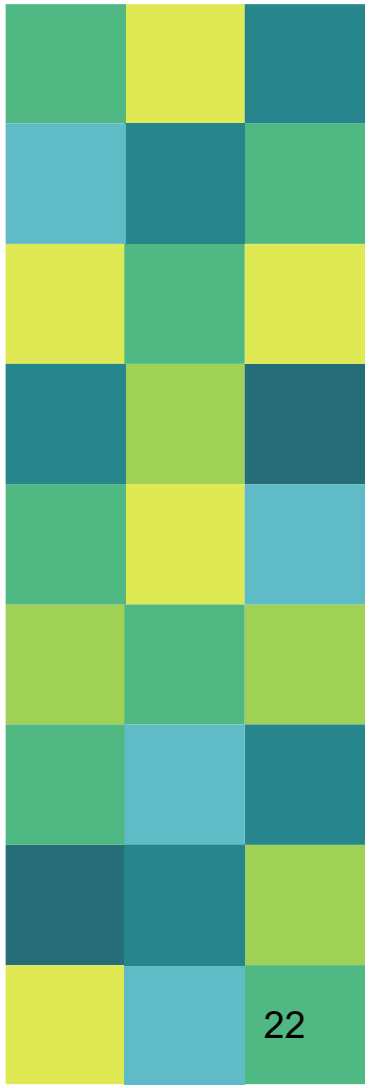


Surrogate markers in diagnosis of IC

The major benefit of β-D-glucan is its NPV for invasive candidiasis in environment in which the prevalence is low to moderate

N Engl. J Med ,2015



Empiric antifungal therapy should be started as soon as possible in patients who have mentioned risk factors and who have clinical signs of septic shock

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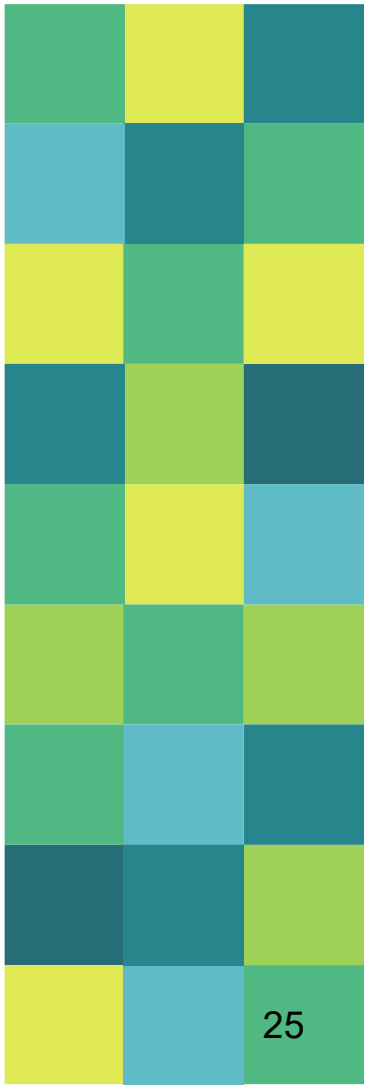
“
Which antifungal agent should be used for empirical therapy of IC in non-neutropenic ICU patients

Which antifungal agent should be used for empirical therapy of IC in non-neutropenic ICU patients

Fluconazole	Echinocandin
▪hemodynamically stable patients ▪colonized with azole-susceptible Candida species ▪who have no prior exposure to azoles	▪hemodynamically unstable patients, ▪ those previously exposed to an azole, ▪ in those colonized with azole-resistant Candida species

IDSA Guideline for the Management of Candidiasis;2016

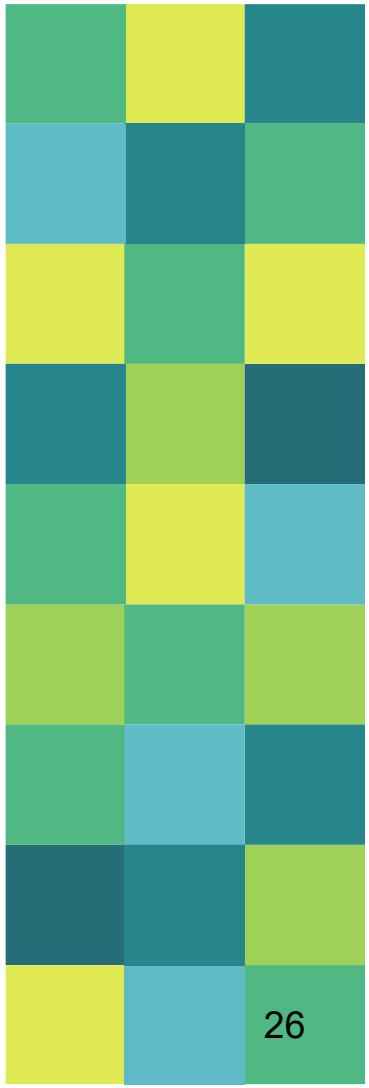


- After sending 2 sets of blood cultures (from peripheral line and CVC)

CVC removed

and
the patient placed on

Imipenem + Vancomycin
+
Fluconazole replaced with **Caspofungin**

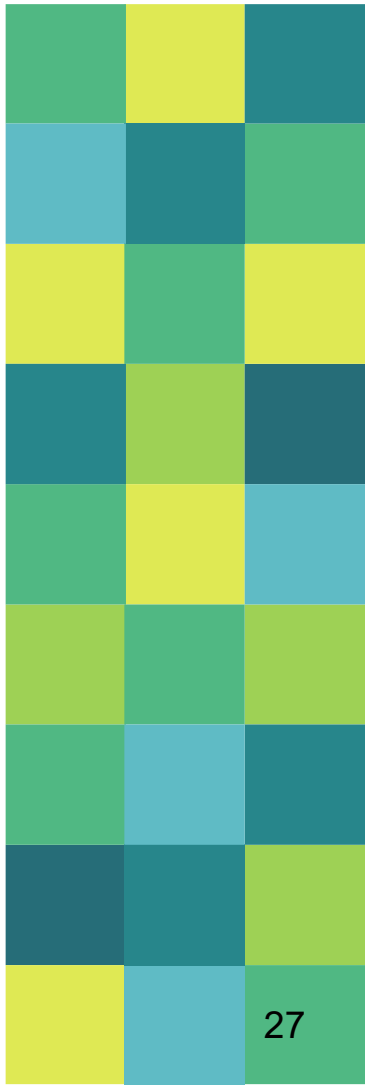


On day 8

Patient's hemodynamic return to normal but continued to be febrile

Lab values On day 8

- **CBC:**
  - **WBC: 10,000 (60% PMN)**
  - **Hb:11**
  - **Plt: 360,000**
- ***ABG: PH: 7:35 PCO2: 38 HCO3: 21***
- ***Serum lacatate: 5mmol/ml***



On day 8

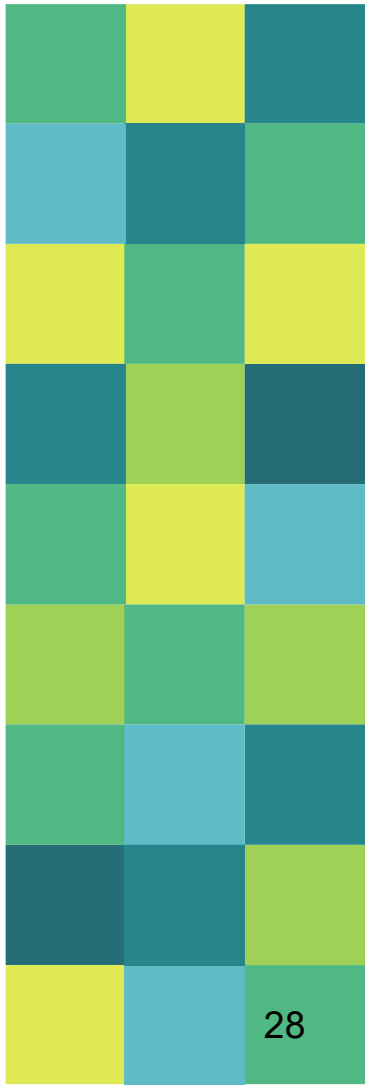
Blood Cultures taken on day 6 ,yielded ESBL producing Ecoli and *C. Parapsilosis*

Accordingly

Vancomycin discontinued

and

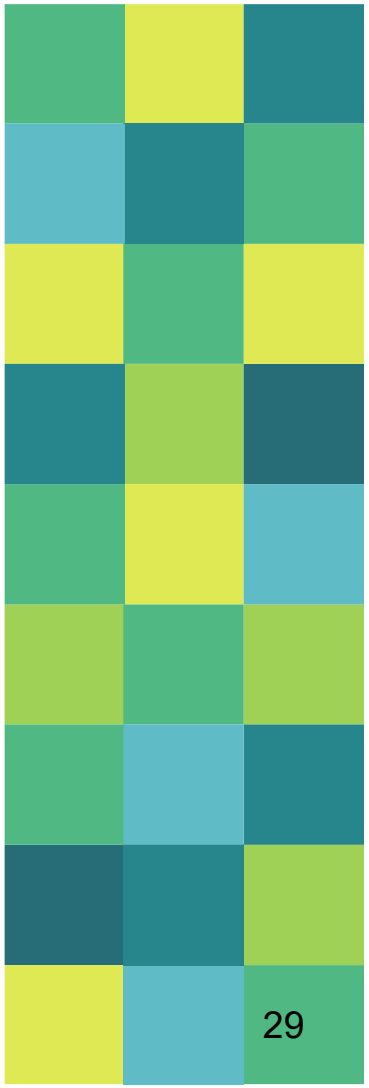
continued on Imipenem and Caspofungin



On day 12

The patient extubated
his fever persisted
but
Day by day physical examination and workups, including ophthalmological examination, ***did not revealed any localizing site of infection***

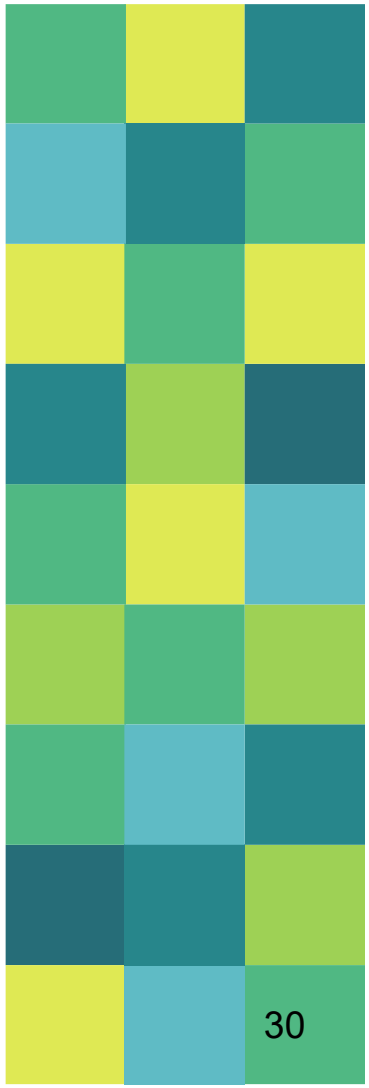
trans-thoracic echocardiography did not reveal vegetative endocardial lesions.



On day 16

- The patient continued to be febrile

- Blood culture sets drawn separately over 4 days, cultured
  C. Parapsilosis
  in 3 of samples



On day 16

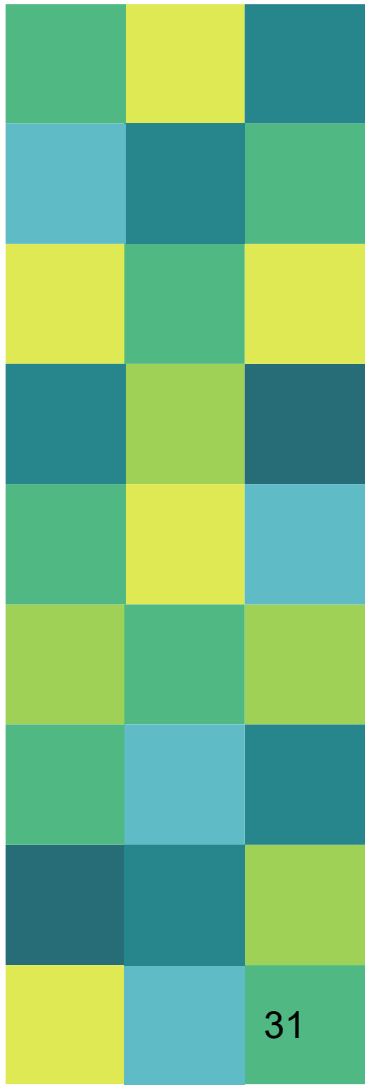
Trans-esophageal Echocardiography revealed a large vegetation on the mitral valves

subsequently

Caspofungin replaced

with

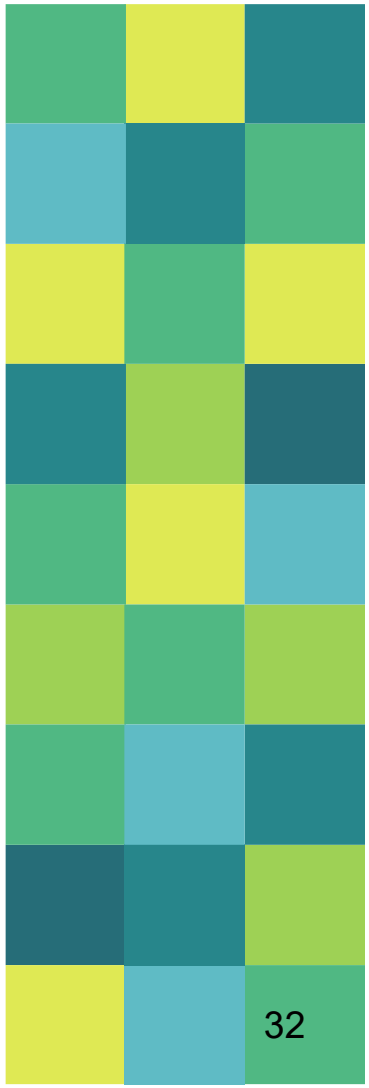
IV liposomal AmB (5 mg/kg /day)



Clinical course

the patient underwent valve-replacement surgery 10 days later.

After aggressive tissue debridement and valve excision, replacement with leaflet mechanical valves was performed



Clinical course

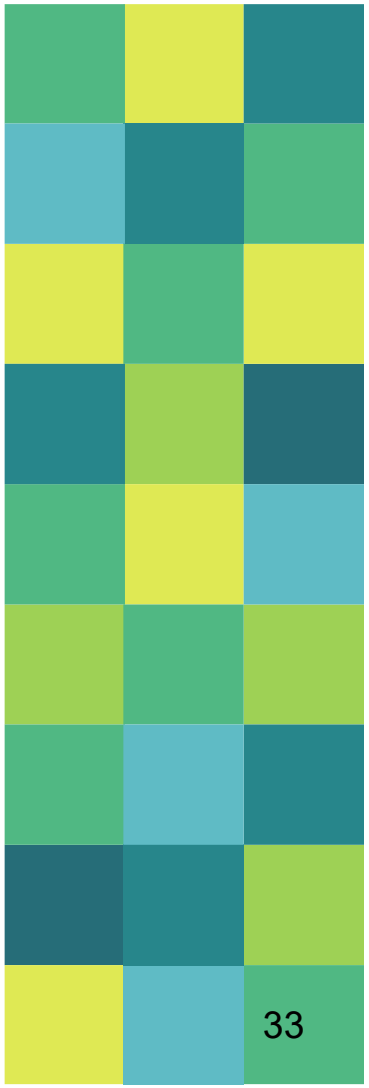
On post op day 4

the patient's fever stopped and his general condition was much better

All of his follow up cultures reported negative

his antifungal treatment continued for 6 wks afterward

and the patient discharged on day 50



Key points in treatment of candida infections

General susceptibility patterns of *Candida* species

Species	Fluconazole	Itraconazole	Voriconazole	Posaconazole	5FC	AmB	Echinocandins
C. albicans	S	S	S	S	S	S	S
C. tropicalis	S	S	S	S	S	S	S
C.parapsilosis	S	S	S	S	S	S	S to R[1]
C. glabrata	S-DD to R	S-DD to R	S-DD to R	S-DD to R	S	S to I	S
C. krusei	R	S-DD to R	S	S	I to R	S to I	S
C. lusitaniae	S	S	S	S	S	S to R	S

AmB = amphotericin B; 5-FC = flucytosine; I = intermediate susceptibility; R = resistant; S = susceptible; S-DD = susceptible dose-dependent.

[1] *C. parapsilosis* isolates resistant to echinocandins are uncommon.

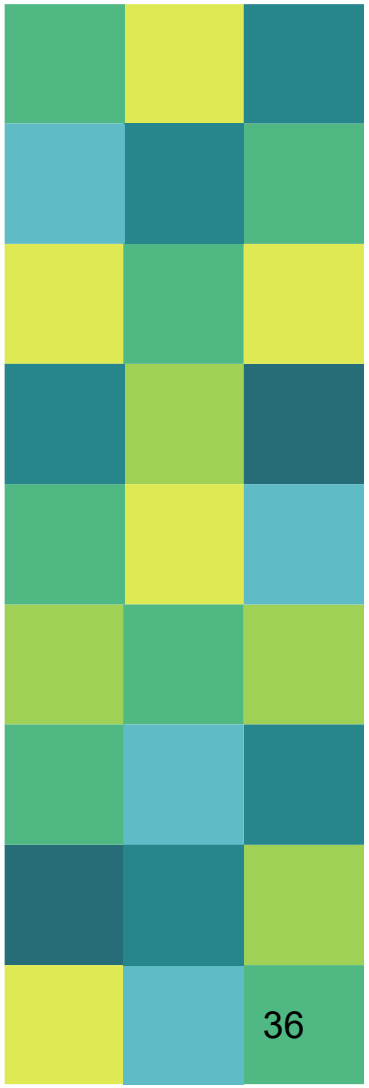
NOTE

- **Azoles are less active against C. Krusei and C. glabrata**

- **C. parapsilliosis is less responsive to Echinocandins and is related to TPN**

- **Recent case series have described treatment failure associated with resistant strains of C. glabrata to Echinocandins**

-Dannaoui E et al. Candida spp. with acquired echinocandin resistance, France, 2004–2010. Emerg Infect Dis 2012;
-Shields RK et al. Anidulafungin and micafungin MIC breakpoints are superior to that of caspofungin for identifying FKS mutant Candida glabrata strains and echinocandin resistance. Antimicrob Agents Chemother 2013.



SO

- **Testing for azole susceptibility** is recommended for all bloodstream and other clinically relevant **Candida isolates**.
- **Testing for Echinocandin susceptibility** should be considered in patients:

  1-who have had **prior treatment with an Echinocandin**

  2-among those who have infection with **C. glabrata or C. parapsilosis**

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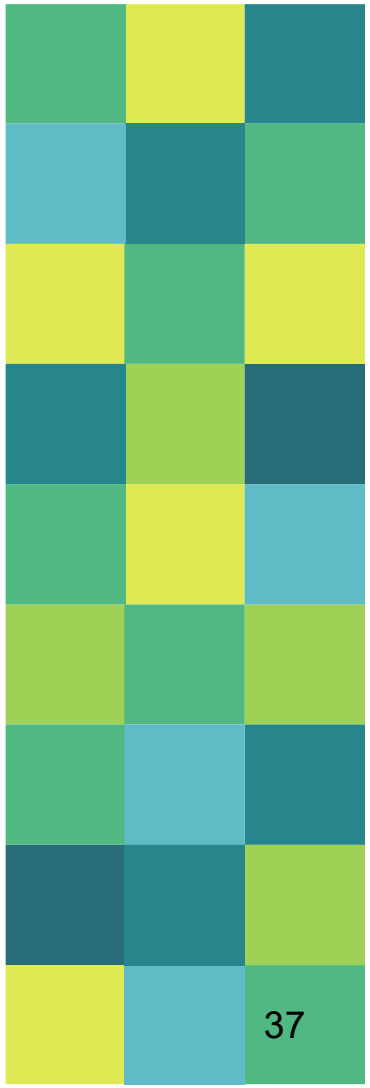
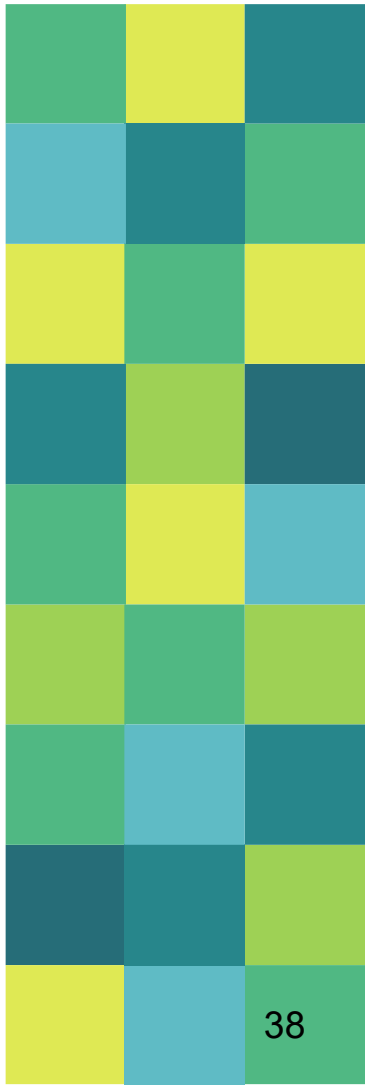


Treatments for Candidemia

- An Echinocandin is recommended as initial Rx

- Echinocandins achieve therapeutic concentrations in all infection sites with the exception of the eye, CNS, and urine

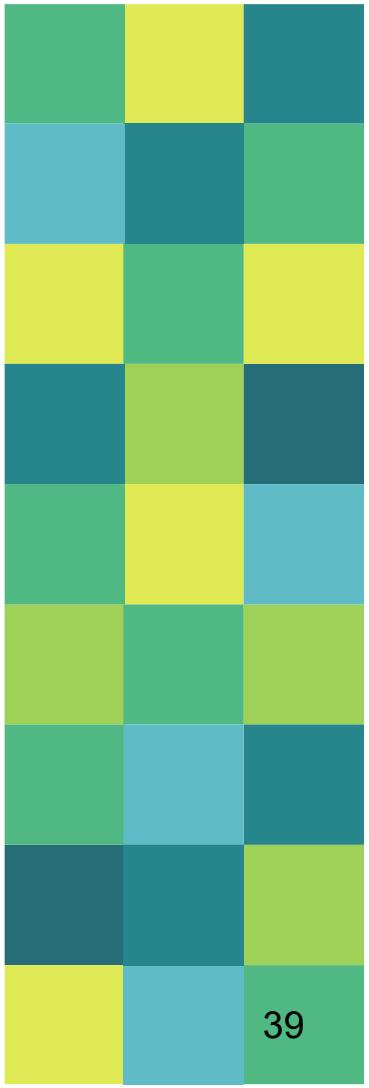
- Fluconazole, is an acceptable alternative to an Echinocandin as initial therapy in selected patients, including those who are not critically ill and who are considered unlikely to have a fluconazole-resistant Candida species



Treatments for Candidemia

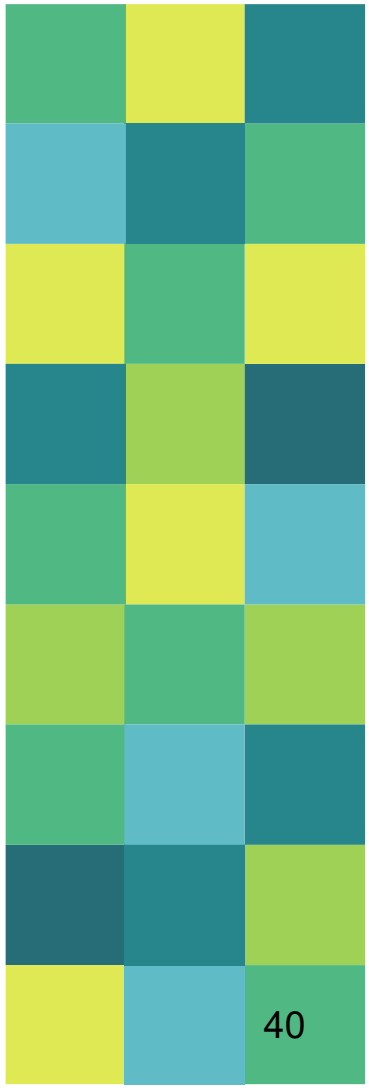
- **Transition from an Echinocandin to fluconazole** (usually within 5–7 days) is recommended for patients who are clinically stable, have isolates that are susceptible to fluconazole (eg, C. albicans), and have negative repeat blood cultures following initiation of antifungal therapy

- For infection due to **C. glabrata**, transition to higher-dose fluconazole 800 mg (12 mg/kg) daily or voriconazole 200–300 (3–4 mg/kg) twice daily should only be considered among patients with fluconazole-susceptible or voriconazole-susceptible isolates



Treatments for Candidemia

Lipid formulation amphotericin B (AmB) (3–5 mg/kg daily) is a reasonable alternative if there is intolerance, limited availability, or resistance to other antifungal agents



Duration of treatment of candidemia

- Follow-up BCs should be performed every day or every other day to establish the time point at which candidemia has been cleared
- Recommended minimum duration of therapy for candidemia without metastatic complications is 2 wks after documented clearance of Candida from the bloodstream, provided neutropenia and symptoms attributable to candidemia have resolved

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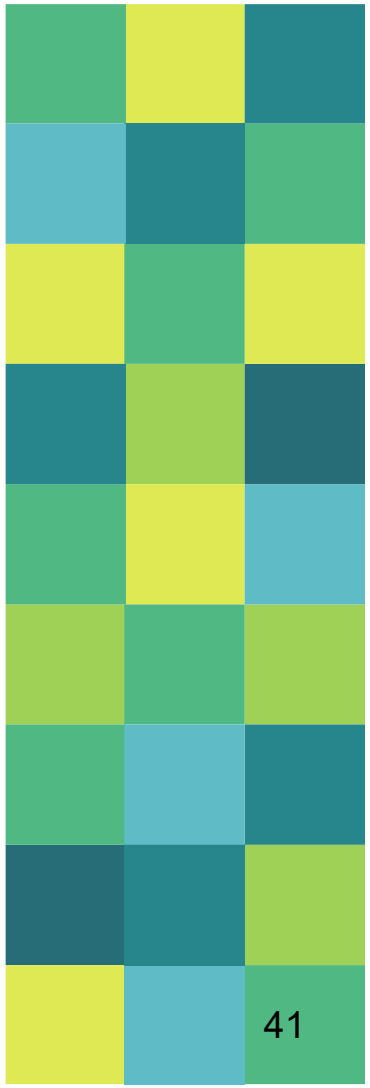
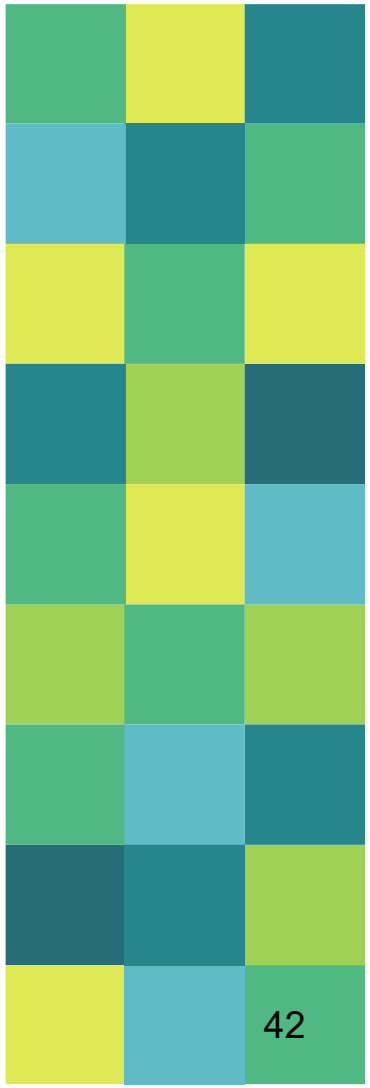


Duration of Empirical Rx for IC

- There are no data guiding the appropriate duration of empiric antifungal therapy among patients who have a clinical response to therapy, but it is logical that it should not differ from the treatment of documented candidemia.

- Conversely, therapy can be stopped after several days in the absence of clinical response if cultures and surrogate markers are negative.

IDSA Guideline for the Management of Candidiasis;2016

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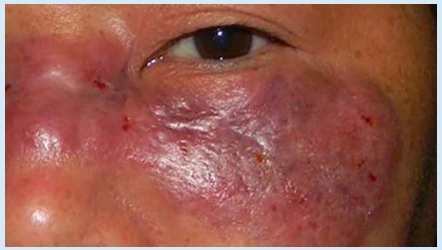
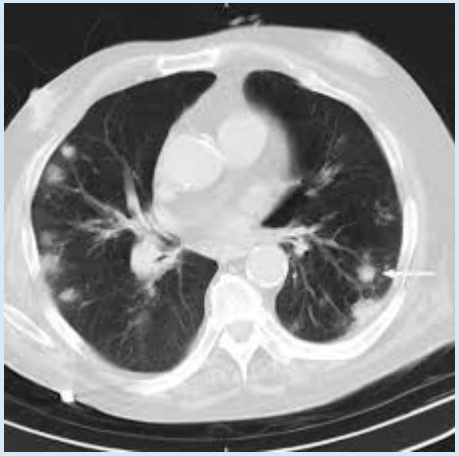
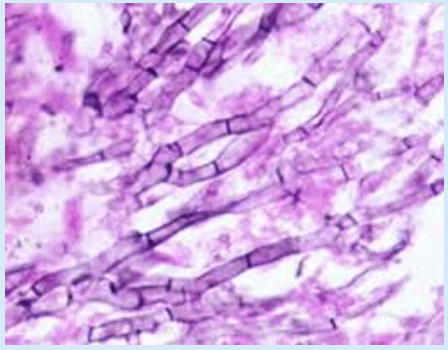


Invasive Fungal Infection in cáncer patients





Dr Z. Abtahian,
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Fellowship in immunocompromised host

Hypothetical Case

A 35-year-old man presented with a one-month history of fatigue and gingival bleeding.

Because of low CBC with peripheral blasts, underwent BM examination and immunophenotyping confirmed the diagnosis of AML-M5

Case presentation

-Accordingly, Induction chemotherapy was introduced with the "3+7" scheme:

Daunorubicin (during 3 days) and Cytarabine (during 7 days)

-Simultaneously,Ciprofloxacin,Acyclovir and Itraconazole started as prophylactic regimen

Antifungal prophylaxis(NCCN)

ALL	**Fluconazole or Micafungin** AMB products (cat. 2B)	Until resolution of neutropenia
AML & MDS (Neutropenic) receiving induction & re-induction CT	**Posaconazole (cat. 1)** Voriconazole, Fluconazole or Micafungin, AMB products (all cat. 2B)	Until resolution of neutropenia (role of PAP during consolidation CT has not been evaluated
Autologous HCT with mucositis	Fluconazole or Micafungin (both cat. 1)	Until resolution of neutropenia
Allogenic HCT	Fluconazole or Micafungin (both cat. 1) Voriconazole, Posaconazole or , AMB products (all cat. 2B)	Continue during neutropenia and for at least 75d after tenasplant
Significant GVHD	**Posaconazole (cat. 1)** Voriconazole, EC, AMB(all cat. 2B)	Until resolution of significant GVHD

Recommendations for PAP in Allogeneic HSCT Patients(GITMO)

Early Phase after Transplantation (Day 0-40)	
High risk	1-Active AL at the time of Tx(AII), 2-CB Tx (AII), 3-Grade III-IV a-GVHD after any type of Tx (AII), 4-Tx from MMRD or UD and ≥1of the following additional RF: -grade II a-GVHD, -steroid dose 2 mg/kg/day for at least 1 week, -CMV disease, recurrent CMV infection, -prolonged neutropenia (PMN< 500/mL for >3 weeks), -Iron overload (BIII), 5-Steroid refractory/dependent a-GVHD after any type of Tx(AIII).
Standard risk	All remaining patients not included in the HR category (AI).
Low risk	No patient may be considered at low risk for IFD during this phase

Recommendations for PAP in Allogeneic HSCT Patients(GITMO)

Late Phase after Transplantation (Day 41-100)	
HR	1-Grade III-IV a-GVHD after any type of Tx (AII), 2-Tx from MMRD or UD and ≥ of the following additional RF: -grade II a-GVHD, -steroid dose 2 mg/kg/day for at least 1 week, -CMV disease, recurrent CMV infection, -prolonged neutropenia (PMN< 500/mL for >1 wks), 3-Steroid refractory/dependent a-GVHD after any type of Tx(AIII).
Standard risk	All remaining patients not included in the HR category (AI).
LR	No patient may be considered at low risk for IFD during this phase

Recommendations for PAP in Allogeneic HSCT Patients (GITMO)

Very Late Phase after Transplantation (Day >100)	
HR	1. Persistent or late-onset grade III-IV a-GVHD (AII), 2. Persistent or late-onset steroid refractory/ dependent a-GVHD after any type of Tx (AII), 3. Persistent or late-onset grade II a-GVHD after Tx from MMRD or UD (BIII), 4. Extensive c-GVHD when preceded by an a-GVHD (AII)
Standard risk	Limited c-GVHD in patients who receive only a nonsteroid IS and "de novo" c-GVHD (BIII)
LR	Absence of any type of GVHD and no steroid therapy (AII).

GITMO guideline for Allogenic HSCT

- High risk patients should receive mold active agent for PAP
- Standard risk patients should receive candida active agent for PAP
- Low risk patients don't require PAP

Back to Case

-On the fifth day of chemotherapy, developed fever without any other complain

Physical examination

The patient was ill but not toxic and oriented with time, place and person

V/S:

OT: 38.7°C, PR: 86, BP: 110/70 RR: 18

- All of his general physical examination including, oral mucosa, perianal area, Indwelling catheter sites were normal

Initial laboratory values

CBC:

WBC : 200 cells/ μ l, (ANC:100)

Hb: 9.2 ,

Platelets: 6,000

BUN: 38 Cr:0.7 Na: 138 K: 4

AST:21 ALT: 25 ALP: 258

On day one of neutropenic fever

According to patient's clinic and initial paraclinic

,

,after obtaining to sets of Blood culture,

Ciprolfoxacin discontinued

And

he placed on

Meropenem (1gr/IV/q8h)

On day 4

The patient continued to be febrile

Complained of dry cough

On P/E:

- V/S: OT: 39 PR:90 RR: 20 BP: 100/70

- Fine rales in lower zone of RT lung

On day 4

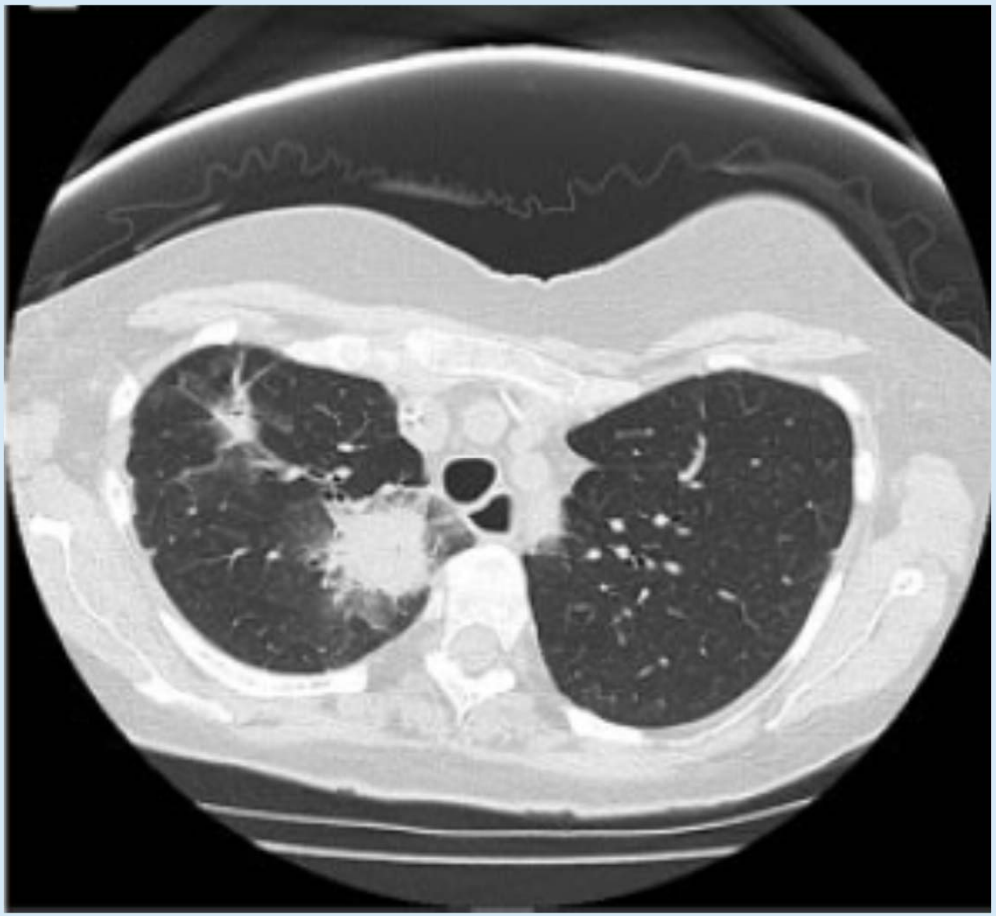
Diagnostic workup:

1. Lung CT

2. Serum 1,3-βDG & GM for 3 consecutive days

3. Tow sets of Blood cultures

Chest CT Scan



Major etiologies of pulmonary Nodules/nodular infiltrates

Infectious

- Gram +ve and Gram –ve bacteria
- *Nocardia*
- Chronic/inactive infectious granulomata
- Aspergillus
- Mucormycosis agents
- Other molds
- Toxoplasmosis
- Strongyloidiasis

Non-Infectious

- Primary lung cancer
- Lymphomas, Hodgkin lymphoma
- PTLD
- Thromboembolism
- Leukemic infiltrates

Management of a Neutropenic Patient with a Localized Infection

Initial clinical finding	evaluation	Addition to initial empiric regimen
Lung infiltrate	1-BC, Sputum culture 2-Consider depending on risk: A-Nasal wash for respiratory virus,rapid test B-Legionella urine Ag test C-Serum GM or βDG in PT at risk for IMI (IR, HR) D-Chest CT to better defining infiltrates E-Consider BAL including GM, particularly if no response to initial therapy or if diffuse infiltrates present F-Consider diagnostic lung Bx	1-Add Azithromycin or FQ to cover atypical bacteria 2-Consider adding: A-Mold active antifungal agent (in IR & HR patients) B-Antiviral Rx during peak influenza season in local area C-TMP/SMX if PJ is a possible etiology D-Vancomycin or Linezolid if MRSA is suspected 3-Re-evaluate for ability to de-escalate

On day 4

Considering that the patient:

- Is non-responding but clinically stable
- HR for invasive mold infection(AML with prolonged neutropenia)
- On anti-mold prophylaxis
- With nodular infiltration on chest CT

On day 4

- Itraconazole replaced with

  liposomal Amphotricin(3mg/kg)

- Antibacterial regimen changed to

  HD Imipenem with EI + Tubramycin + Vancomycin

- The patient planned for diagnostic bronchoscopy

Considering antifungal therapy in patient without localizing sign

Timing to add empiric antifungal therapy

Persistently febrile neutropenic patient after ≥4 day broad spectrum AB therapy

Diagnostic workup
1. Lung CT (repeat at least 1/wk, unless clinical signs or acute deterioration)
2. Serum GM & βDG for 3 consecutive days
3.BCs

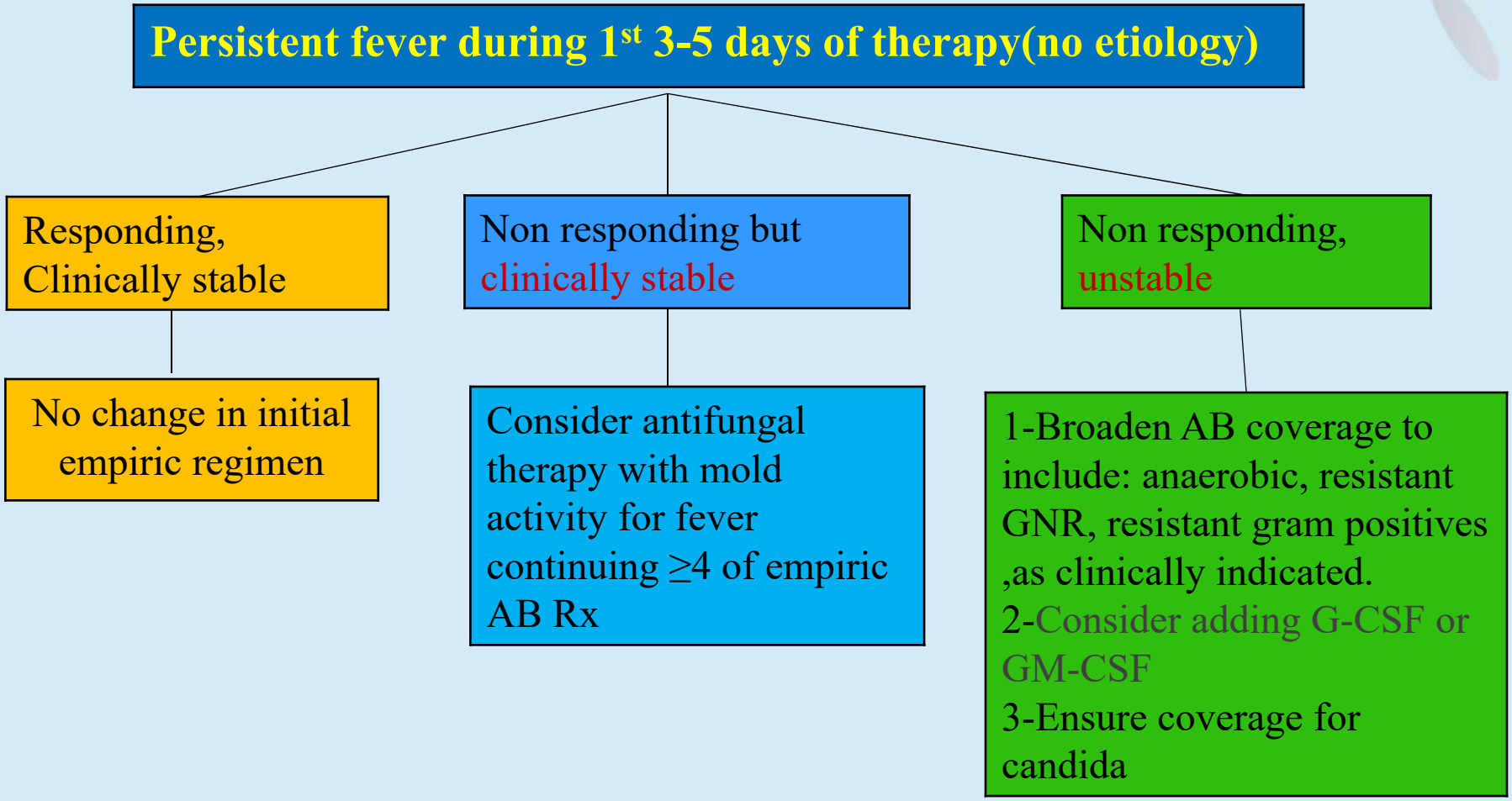
HR for IMI:
eg, Allo-HSCT recipients,
Neutropenia lasting>10day,
Treatment with HD corticosteroid

Add Anti-mold after >4day
IF was not on anti-mold Px

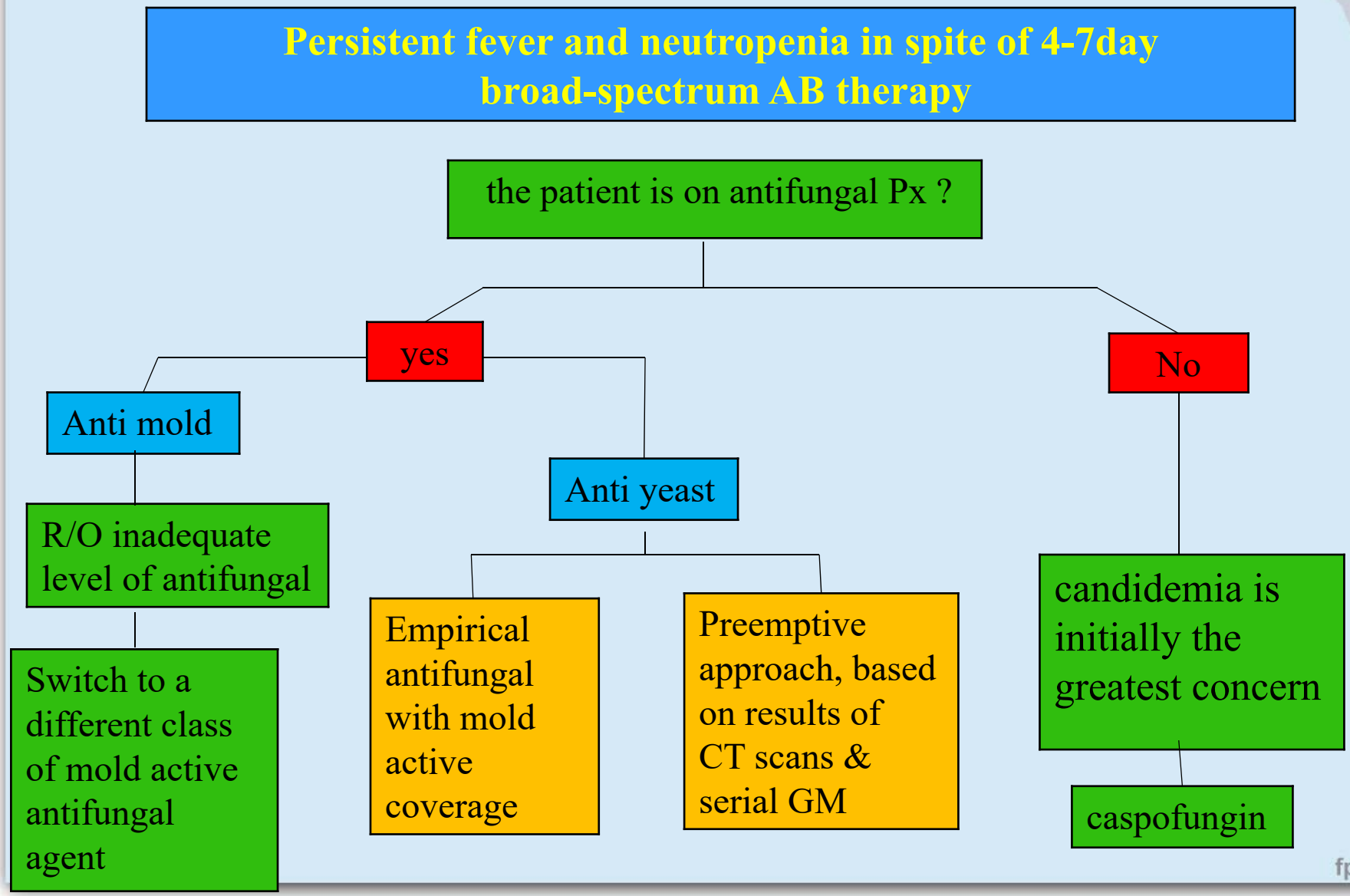
Not HR for IMI

Add antifungal agent after 7-10 days of persistent NF

Persistent fever during 1st 3-5 days of therapy (no etiology)



Which antifungal agent to use



Back to Case

- An AML patient with persistent neutropenic fever and nodular lesion in right lung

Placed on

L-AMB + Imipenem+Tubramycin+ Vancomycin

On day 7

- The patient's fever stopped and his overall general condition was much better

Lab results:

- Serial galactomannan antigen tests on the patient's blood reported as follows:

0.7→ 0.9 →1.1

- Blood cultures reported negative

On day 7

- *The patient continued on same regimen*

- *Bronchoscopy was performed and bronchial lavage taken for:*
  - *Bacterial & mycobacterial smear & culture*
  - *Tuberculosis PCR & culture*
  - *galactomannan*
  - *cytology*

On day 10

- GMI in bronchial lavage : 1.8

Collectively,
according to chest findings,
GMI in serum and BAL
and
obvious clinical response,

with a diagnosis of probable IPA,
Liposomal AMB changed to Voriconazole

ECIL-6 recommendations for first-line treatment of invasive aspergillosis

Voriconazole	**AI**	**Daily dose: 2x6 mg/kg on day 1 then 2x4 mg/kg (initiation with oral therapy: C III)**
Isavuconazole	**AI**	**As effective as voriconazole and better tolerated**
Liposomal amphotericin	B I	Daily dose: 3 mg/kg
Amphotericin B lipid complex	B II	Daily dose: 5 mg/kg
Amphotericin B colloidal dispersion	C I	Not more effective than d-AmB but less nephrotoxic
Caspofungin	C II	
Itraconazole	C III	
Combination vorico + anidulafungin	C I	
Other combinations	C III	

On day 20 of his admission

- He received his responding antibacterial regimen for 14 days
- A control bone marrow biopsy showed hematological remission of the AML.
- follow up Chest CT showed resolving pattern in pulmonary lesion
- Discharged with PO Voriconazole, with a normal blood count

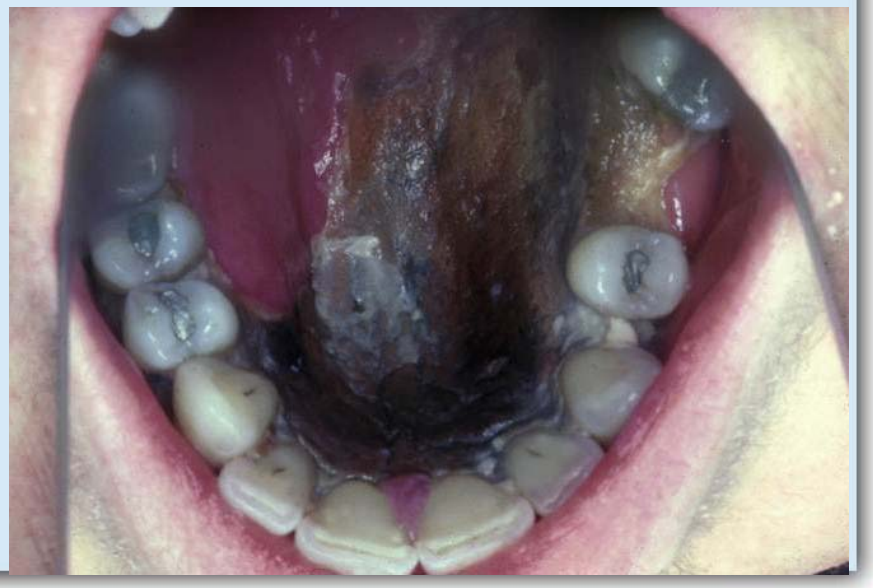
One month later

- The patient received HiDAC (high dose Ara-C) for consolidation therapy over 5 days and discharged without any complication

- During this period the patient was on Voriconazole therapy

One week after discontinuation of HiDAC

- The patient referred to ED with a 2-day history of fever, oral pain and Left facial swelling.
- On examination, a black necrotic patch was noted on the left hard palate without ulcerations.



Emergency Lab Values

CBC: WBC:3000 (ANC:1000 , bast:5%)

Hb: 7

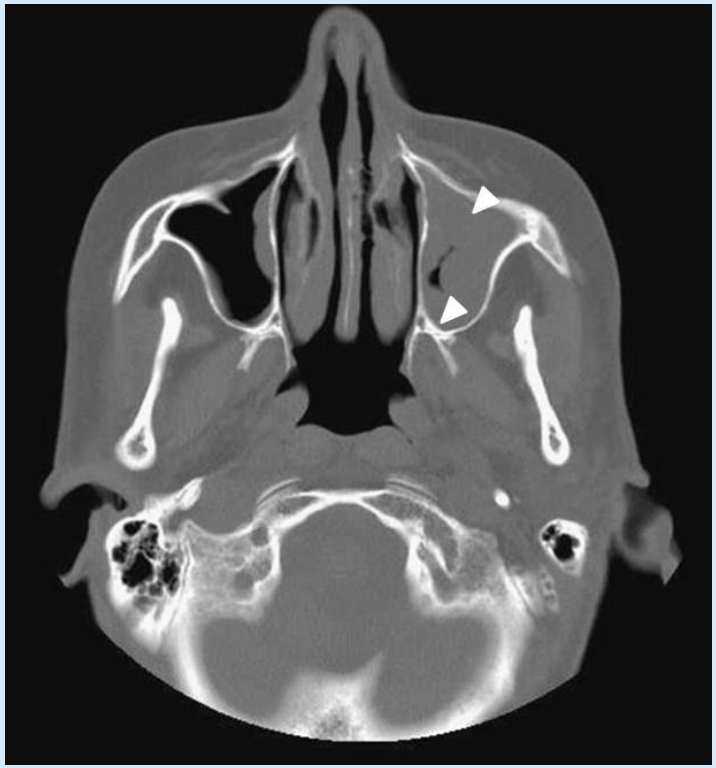
Plt: 30,000

BUN: 40 Cr: 0.9 Na:138 k:3.5

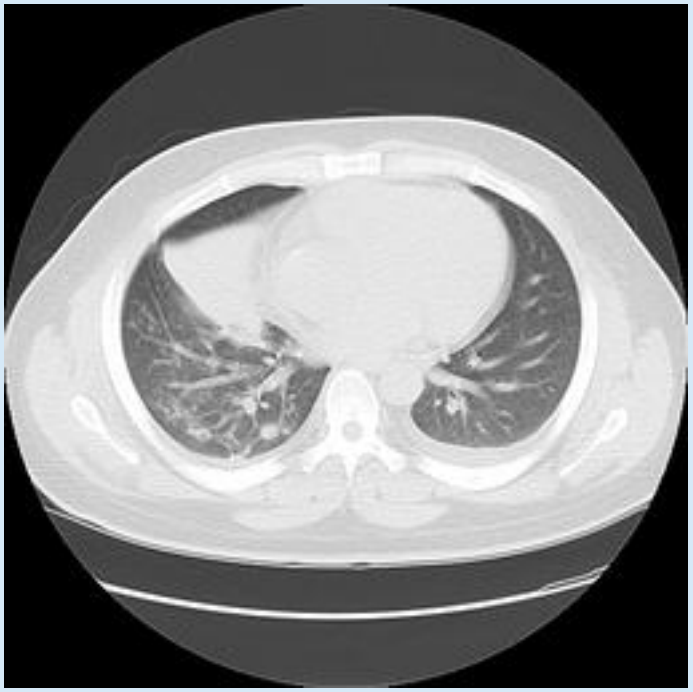
AST:19 ALT:21 ALP: 286

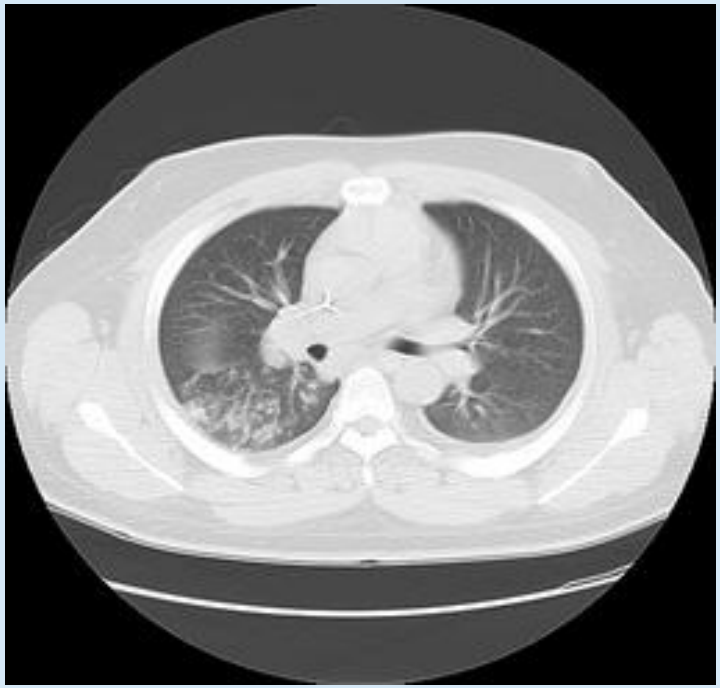
PNS CT Scan

near total opacification of the left maxillary sinus with soft tissue swelling but no evidence of bone involvement.



Lung CT Scan





Irregular nodules in the RLL and wedged shapped airspace density RML

Accordingly

- Emergency ENT consult requested
- 10 unit platelet and 2unit packed cell transfused

The patient placed on:

Imipenem

and

Voriconazole replaced with

Liposomal Amphotericin B (5mg/kg)

Fortunately

In Repeated CBC,30 minutes after transfusion , platelet raised to 55,000 and allowed undergoing debridement surgery, and the patient underwent emergent surgery.

sinus surgery showed bone necrosis in the margin of the left anterior maxillary rim for which he received debridement of the necrotic bone with resection of the inferior turbinate

The removed material was sent for culture and histopathologic studies which revealed;

broad, **right angle branching**, **non-septate**, **ribbon-like hyphae** consistent with a Zygomycete

But

cultures remained negative.

Hospital course

- 3 days post operation, his fever stopped
- On postoperative day 5, a second endoscopic look showed complete viable tissue without any necrosis,
- Imipenem stopped after 14 days
- Ambisome continued for a total duration of 12 wk after 2 completely clear second looks

ECIL-6 recommendations for first-line therapy of mucormycosis

Management includes: **1-antifungal therapy,** **2-surgery** **3-control of underlying conditions**	**AII**
Amphotericin B deoxycholate	CII
Liposomal amphotericin B	BII
Amphotericin B lipid complex	BII
Amphotericin B colloidal dispersion	CII
Posaconazole	CIII
Combination therapy	CIII
Control of underlying condition	AII

ECIL-6 recommendations for salvage therapy of mucormycosis

Management includes: *-Antifungal therapy* *-Control of underlying disease* *-Surgery*	*AII*
Posaconazole	*B II*
Combination of lipid amphotericin B and caspofungin	*B III*
Combination of lipid amphotericin B and posaconazole	*B III*

ECIL-6 recommendations for maintenance therapy of mucormycosis

Posaconazole (BIII):

- Overlap of a few days with first-line therapy to obtain appropriate serum levels.
- Monitoring of serum levels might be indicated


Thank you for your
patience