ASIA FUNGAL WORKING GROUP
an ISHAM working group

ISHAM
INTERNATIONAL SOCIETY FOR HUMAN AND ANIMAL MYCOLOGY

MMTN
MEDICAL MYCOLOGY TRAINING NETWORK

Principles of IFI management

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Disclosures

- In the past three years, Dr Tan has served on the advisory boards of Pfizer and MSD.

Basic principles in medical mycology

- Think fungus
- Know the tests, use them well
  - (use the sophisticated investigation early)
- Befriend the microbiologist
- Treat early
  - (follow basic rules of antimicrobial therapy)
- Know the drugs
  - (beware DDIs; apply PK/PD principles)
- Follow the guidelines!
- Be an internist

Basic rules of antimicrobial therapy

- Obtain an accurate microbiological diagnosis
- Decide if you have time to wait before starting antimicrobials
- There's always time for blood cultures
- Interpret microbiology results carefully
- Don't treat Candida grown from respiratory tract
- Consider host factors in selection of antimicrobial agents
- Use therapeutic drug monitoring (TDM) if available
- Use antibiotics judiciously

Leekha S et al. *Mayo Clin Proc* 2011;86:156

Basic principles in medical mycology

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- Be an interpist

MMTN
MEDICAL MYCOLOGY
TRAINING NETWORK

Chest pain for the ID physician

- 57 yo Chinese man, 3 mth after heart tx
- Routine rv in ID clinic after bout of CMV antigenemia
- Is well, has put on weight, almost ready to go back to work
- Physical exam – NAD
- Just as he's about to leave the room, he says

I’ve got a little pain here, worse when I breathe in

What do we do next? What do we think of?

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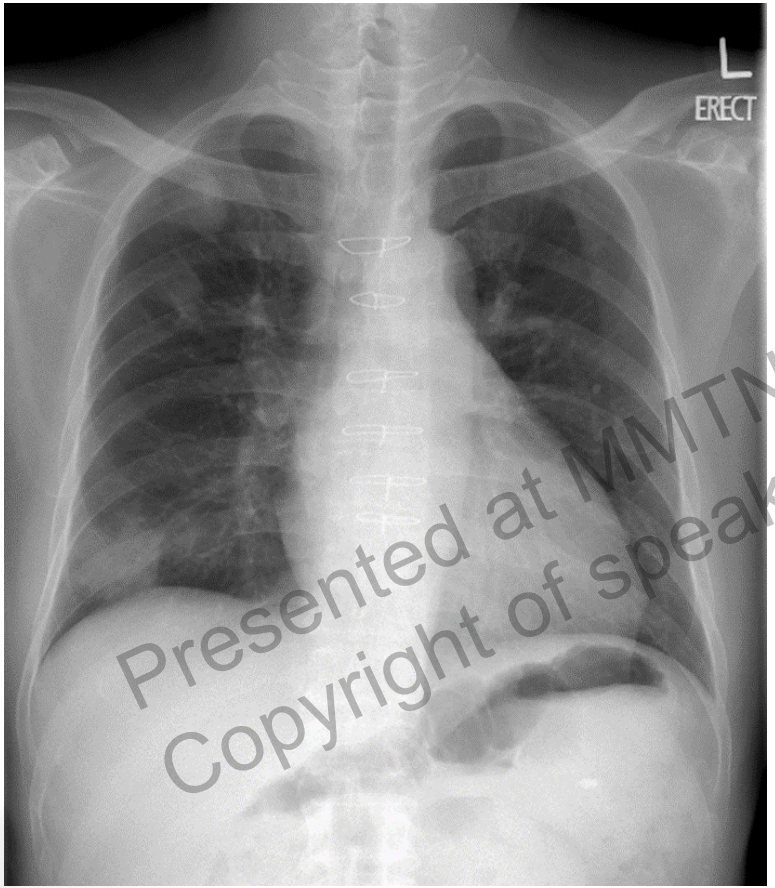
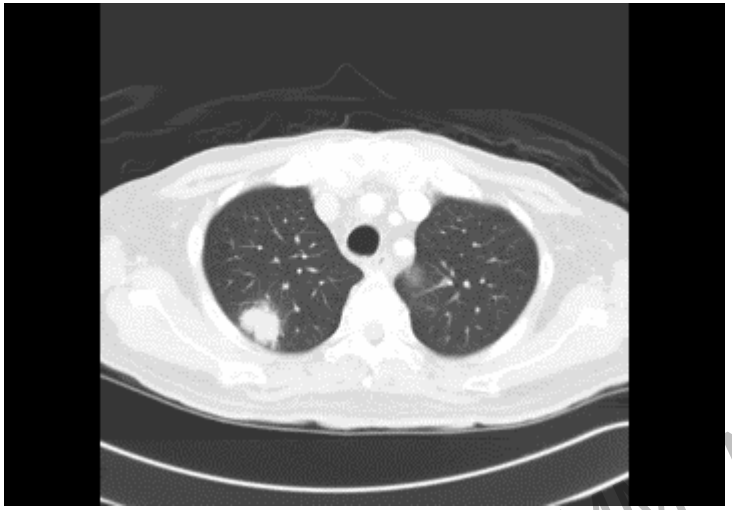
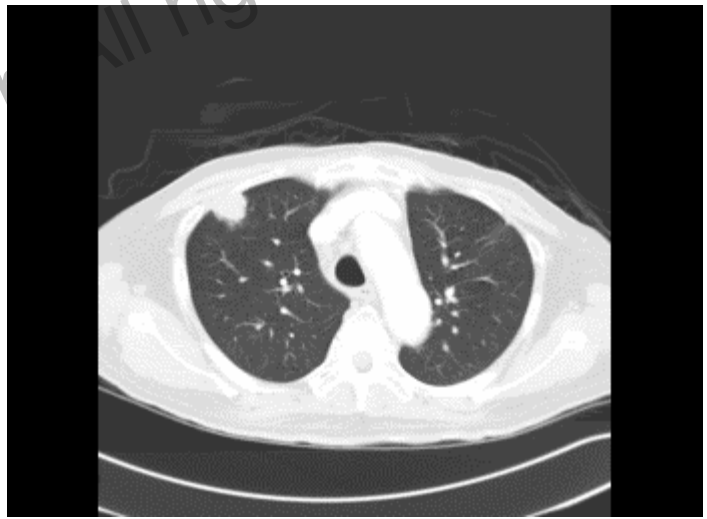
MEDICAL MYCOLOGY
TRAINING NETWORK

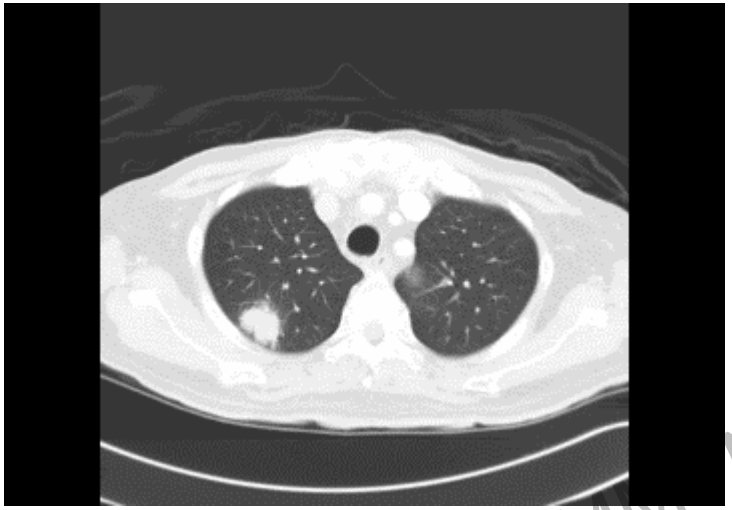


So what's the next test?

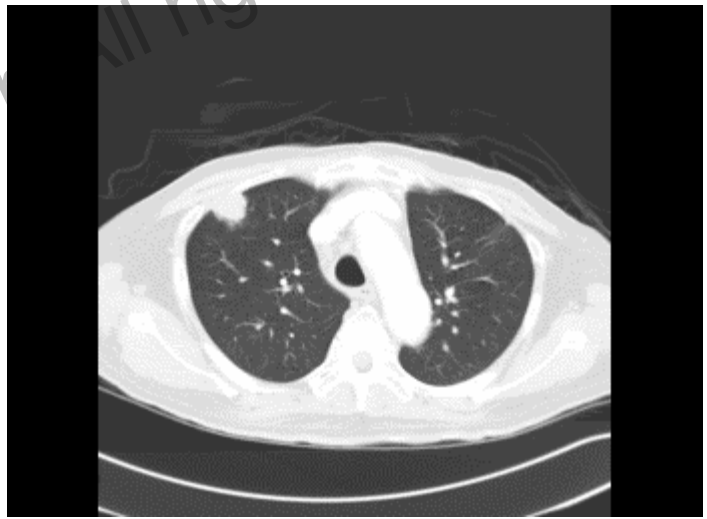




And then what?



TTNA yields *Aspergillus fumigatus*



The Independent Role of Cytomegalovirus as a Risk Factor for Invasive Fungal Disease in Orthotopic Liver Transplant Recipients

- 36% of those with CMV disease developed IFI
- 8% of those without CMV disease developed IFI

George MJ et al. *Am J Med* 1997;103:106

Univariate Analysis Association of Cytomegalovirus Donor/Recipient Serologic Status, CMV Isolation, CMV Viremia, or CMV Disease with Fungal Disease in Orthotopic Liver Transplant Recipients

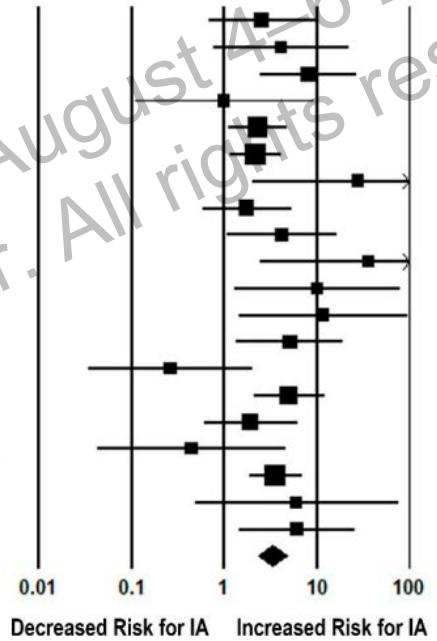
CMV Risk Factors	Fungal Disease n = 22 (%)	No Disease n = 124 (%)	Relative Risk	95% CI	*P* value
Donor/Recipient Match					
D+R−	13 (59)	26 (21)	19.1	(2.5–146.6)	<0.001*
D+R+	3 (14)	24 (19)	5.7	(0.6–55.1)	
D−R+	5 (23)	31 (25)	6.8	(0.8–58.6)	
D−R−	1 (5)	43 (35)	1.0	(reference group)	
All CMV infection†	18 (82)	64 (52)	3.6	(1.7–12.5)	0.014
CMV viremia†	16 (73)	43 (35)	4.1	(1.2–10.6)	0.002
CMV disease†	13 (59)	23 (19)	5.3	(2.3–12.4)	<0.001
CMV pneumonia†	8 (36)	9 (7)	5.3	(2.2–12.6)	<0.001

George MJ et al. *Am J Med* 1997;103:106

Post-SOT CMV ↑risk of IA (pOR 3.31, 2.3 – 4.7)

Study name	Odds ratio	Lower limit	Upper limit	*p*-Value	Relative weight (%)
Desbois 2016	2.532	0.671	9.561	0.170	5.07
Fortun 2002 (CMV infection)	4.100	0.758	22.167	0.101	3.49
Fortun 2002 (CMV disease)	8.000	2.412	26.532	0.001	5.87
Fortun 2003	1.000	0.108	9.274	1.000	2.18
Gavalda 2005 (early IA)	2.300	1.090	4.854	0.029	10.19
Gavalda 2005 (late IA)	2.200	1.162	4.165	0.015	11.66
He 2013	27.300	2.010	370.868	0.013	1.64
Heylen 2015	1.750	0.583	5.252	0.318	6.60
Husni 1998	4.200	1.068	16.511	0.040	4.85
Kato 2014	36.000	2.459	527.058	0.009	1.55
Lopez-Medrano 2016	10.000	1.280	78.122	0.028	2.50
Lopez-Medrano 2018	11.765	1.456	95.045	0.021	2.43
Monforte 2001	5.100	1.353	19.218	0.016	5.08
Munoz 2004 (asymptomatic CMV)	0.263	0.034	2.011	0.198	2.55
Munoz 2004 (CMV disease)	4.963	2.068	11.909	0.000	8.68
Munoz 2004 (CMV syndrome)	1.917	0.605	6.071	0.269	6.19
Nagao 2016	0.444	0.043	4.607	0.497	1.99
Neofytos 2018	3.600	1.839	7.048	0.000	11.19
Osawa 2007	6.000	0.479	75.200	0.165	1.73
Rosenhagen 2009	6.032	1.446	25.163	0.014	4.55
Total	3.311	2.335	4.693	0.000	

Heterogeneity: $Tau^2 = 0.166$, df = 19 (p = 0.102), $I^2 = 30\%$



George MJ et al. *Am J Med* 1997;103:106

Link between CMV & aspergillosis – in an ICU cohort too

- ICU patients; National Cheng Kung University Hospital, Tainan; Apr 2017 – May 2020
- 137 pts had influenza test, blood CMV PCR, and BAL GM

Characteristic	Invasive pulmonary aspergillosis			*p*-value[b]
	All (N = 136)	Negative (N = 115)	Positive (N = 21)	
	Number (%)	Number (%)	Number (%)	
CMV viremia	48 (35.29)	34 (29.57)	14 (66.67)	0.003
Influenza	22 (16.18)	12 (10.43)	10 (47.62)	<0.001
Detectable CMV in BAL[a] (N = 115)	72 (62.21)	59 (61.46)	13 (68.42)	1.000
Age (years), median (IQR)	65 (54.5, 74.5)	64.0 (55.0, 74.0)	66.0 (53.0, 72.0)	0.962
Age ≥65 years	68 (50.00)	57 (49.57)	11 (52.38)	1.000

Kuo C-W et al. *J Microbiol Immunol Infect* 2022;55:291

Basic principles in medical mycology

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- Follow the guidelines!

Principles of specimen collection

- The specimen should be representative of the disease process
- An adequate quantity of material should be provided to the laboratory
- Scrupulous attention must be paid to avoiding contamination
- Forward the specimen promptly to the laboratory
- Specimens should be obtained before the administration of antimicrobials

Woods GL et al. In: Mandell, Douglas & Bennett's principles and Practice of Infectious Diseases. Churchill Livingstone 1998; p169

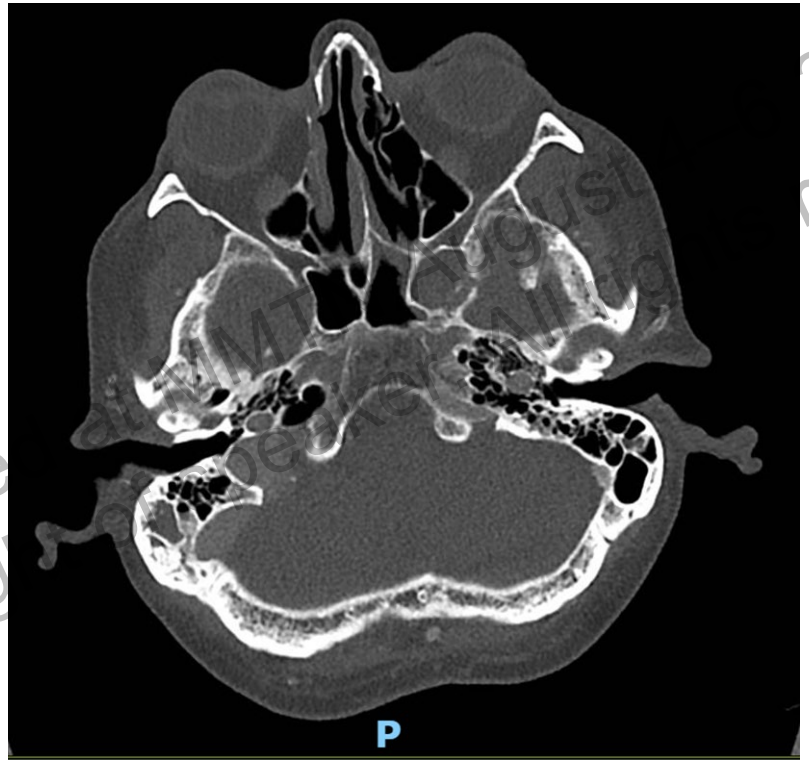
Specimen collection

- The right specimen obtained in adequate quantities promptly, without contamination, transported expeditiously to the laboratory

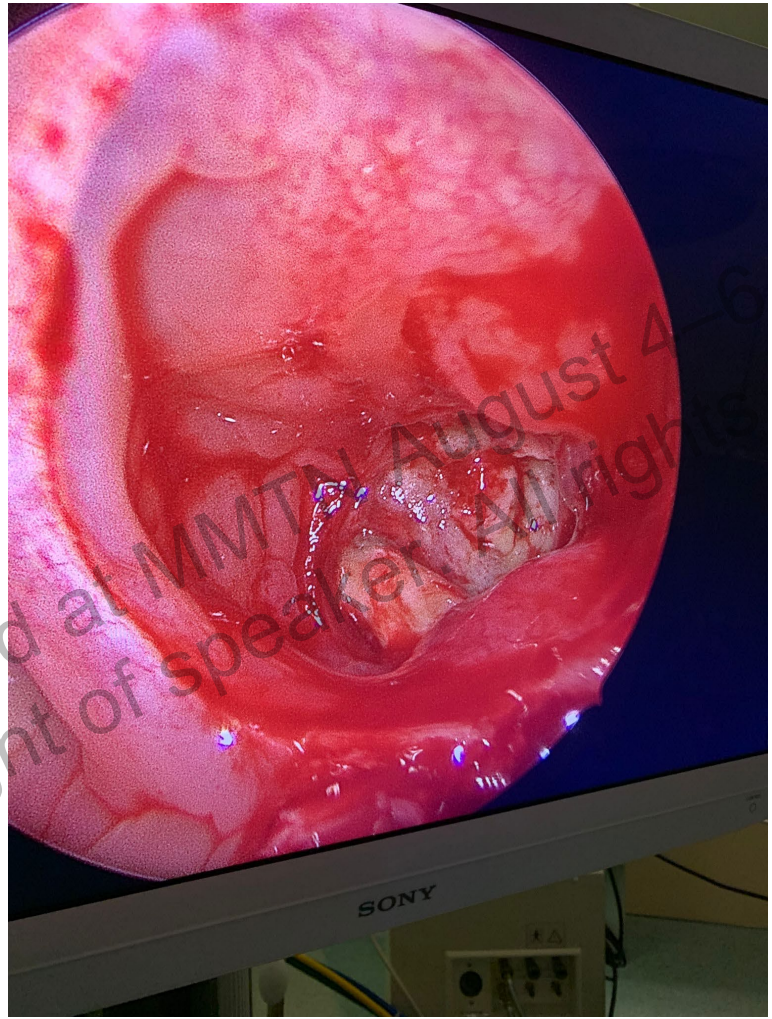
Headache for the ID physician

- 66 yo man, 3 mth after heart transplant
- Headache of 4–5 days duration
- Careful history – Pain begins just lateral to (L) eye, radiates up the temple and head; sometimes there's a shooting sensation down the side of the nose on the (L)
- No neurological deficits
- CT brain – No intracranial bleed or mass
- What is the next test?

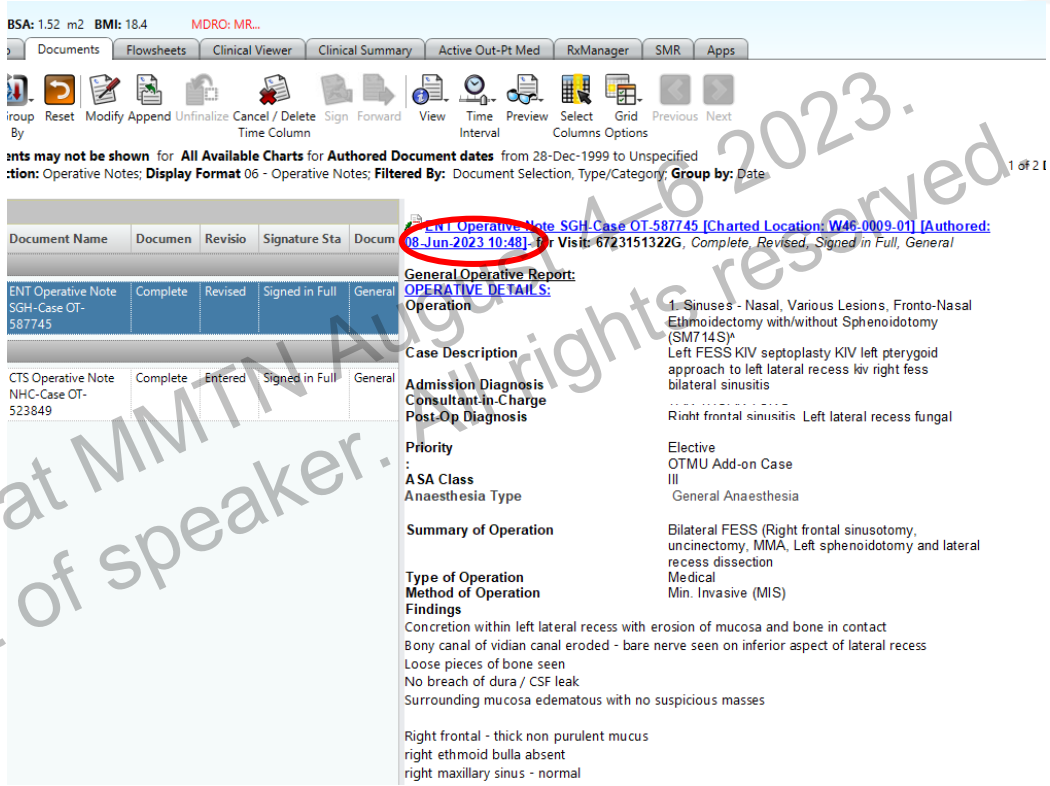
What do you see?



Nasal swab – wrong!



Look at time of surgery, time of fungal microscopy report!



Reporting Information		Date/Time : 08/06/2023 1630 SENIOR CONSULTANT : Laboratory : SGH Diagnostic Bacteriology SINGAPORE GENERAL HOSPITAL PTE LTD	Final
Received Date/Time	H	08/06/2023 1444	Final
Specimen Comment	H		Final
SOURCE : SINUS SPEC DESCRIPTION : COMMENT : DIAGNOSIS: L Sphenoid sinusitis possibly invasive fungal infection in an ICH (heart transplant)			
Microscopy, Fungal	!		Final
MYCOLOGY - MICROSCOPIC EXAM Hyphae seen 3+			

08-Jun-2023 11:07	Fungal Culture	
Received Date/Time	H	08/06/2023 1445
Specimen Comment	H	
SOURCE : SINUS SPEC DESCRIPTION : COMMENT : DIAGNOSIS: L Sphenoid sinusitis possibly invasive fungal infection in an ICH (heart transplant)		
Reporting Information	H	Date/Time : 04/07/2023 1352 SENIOR CONSULTANT : [redacted] Laboratory : SGH Diagnostic Bacteriology SINGAPORE GENERAL HOSPITAL PTE LTD
Fungal Culture	H	MYCOLOGY - UPPER RESP CUL PRELIMINARY REPORT ON 10/06/23:

Expanded Result -- Fungal Culture

MYCOLOGY - UPPER RESP CUL

PRELIMINARY REPORT ON 10/06/23:

Moulds isolated

FINAL REPORT ON 04/07/23:

ASPERGILLUS FUMIGATUS As reported on 16/06/23

DATE OF REPORTING: 04/07/23

Abnormal.

Know the tests, use them well

- Obtain an accurate microbiological diagnosis
- There's always time for blood cultures
- Interpret microbiology results carefully
  - Don't treat Candida grown from respiratory tract
- Consider host factors in selection of antimicrobial agents
- Use therapeutic drug monitoring (TDM) if available
- Use antibiotics judiciously

You've got a bit of time

Time to antibiotics

Recommendations
12. For adults with possible septic shock or a high likelihood for sepsis, we **recommend** administering antimicrobials immediately, ideally within 1 h of recognition
Strong recommendation, low quality of evidence (Septic shock)
Strong recommendation, very low quality of evidence (Sepsis without shock)

Evans L et al. *Intensive Care Med* 2021;47:1181

KEEP
CALM
AND
GET
ORGANIZED

Even more time if there's no shock

13. For adults with possible sepsis without shock, we **recommend** rapid assessment of the likelihood of infectious versus non-infectious causes of acute illness

Best Practice Statement

Remarks

Rapid assessment includes history and clinical examination, tests for both infectious and non-infectious causes of acute illness and immediate treatment for acute conditions that can mimic sepsis. Whenever possible this should be completed within 3 h of presentation so that a decision can be made as to the likelihood of an infectious cause of the patient's presentation and timely antimicrobial therapy provided if the likelihood of sepsis is thought to be high

14. For adults with possible sepsis without shock, we **suggest** a time-limited course of rapid investigation and if concern for infection persists, the administration of antimicrobials within 3 h from the time when sepsis was first recognised

Weak recommendation, very low quality of evidence

Evans L et al. *Intensive Care Med* 2021;47:1181

How useful are blood cultures for *Candida* anyway?

The right bottle may help

Role of dedicated blood culture bottle/medium for candidemia

- Habit/tradition of ordering aerobic, anerobic and fungal blood cultures (latter when indicated)
- 2-year period: 350 bottles + for Candida
- 75.7% from aerobic and/or anerobic +/- fungal bottle
- 24.3% ONLY from fungal bottle (increase is stat sig, p<0.001)
- In addition – fungal bottle gave + results earlier by one day in 27.5%, permitting speciation 1 day earlier in 23%

Zheng SW et al. *PLoS One* 2016;11:e0164668

Importance of dedicated fungal blood culture medium – in Dijon too

- Fungal bottle (MycosisIC/F lytic) was only bottle positive for a fungus in 94 of 160 (58.8%) fungemias where both aerobic/anerobic and fungal bottles were sent
- Also shorter time to positivity, in 97 of 171 cases where fungi grew in both types of bottles (ie, 56.7%)
- If fungal bottle had not been used, 56/147 fungemias would have been missed
- What might have been missed: Rhodotorula (1/1), *S. cerevisiae* (1/1), Trichoderma (1/1), *C. lusitaniae* (2/3), Fusarium (5/8), *C. guilliermondii* (3/6), *C. kefyr* (2/4)

Magallon A et al. *J Med Microbiol* 2022;32:101295

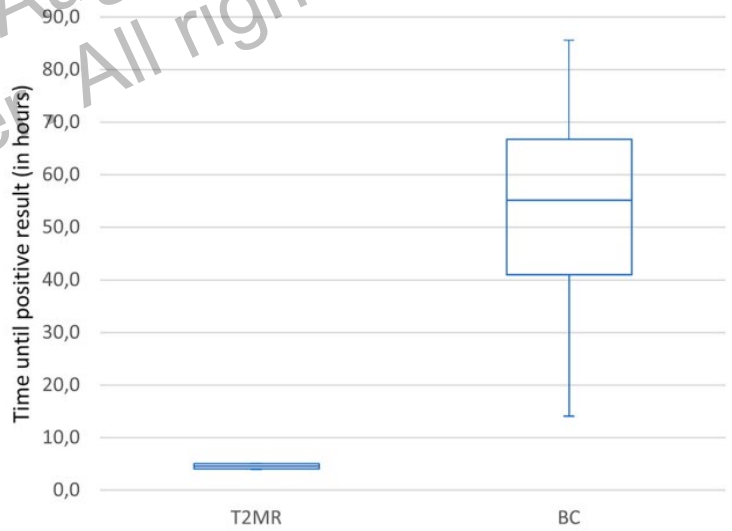
Fungal bottle may be important in polymicrobial growth

- Used Plus Aerobic F (PAF) and Mycosis IC/F (MICF) bottles of the BD Diagnostics system (Bactec 9240)
- Spiked bottles with combinations of different fungi and bacteria – 24 models studied (for fungi – 1CFU/ml; 8ml of blood inoculated per bottle)
- All bottles flagged +; however direct stain showed only bacteria from all bottles inoculated with both bacteria and fungi
- When sub-cultured on blood agar, all bottle combining Fusarium, T. asahii and C. glabrata with bacteria failed to grow the fungi
- When sub-cultured on Sabaroud's, fungi from 14 of 24 combinations failed to grow
- MICF bottle contain tobramycin, chloramphenicol, so bacteria suppressed

Oz Y et al. *J Med Microbiol* 2020;69:644

T2MR permits rapid diagnosis

- Drew blood cultures (2 bottles BACT/Alert FN) & 2 EDTA tubes for T2CandidaPanel, T2BacterialPanel when superinfection suspected among COVID-19 patients in ICU (Hospital Favoriten, Vienna)



Seitz T et al. *Microbiol Spect* 2022;10:40014022

Blood cultures missed many!

TABLE 2 Number of detected pathogens in T2MR and BC[a]

Pathogens	T2MR (*n*)	BC (*n*)
E. coli	1	1
S. aureus	1	1
K. pneumoniae	2	1
A. baumannii	0	0
P. aeruginosa	2	0
E. faecium	3	0
S. epidermidis	0	13
S. hominis	0	4
S. haemolyticus	0	1
E. cloacae	0	1
Cutibacterium spp.	0	2
No. of ESKAPE spp. detected	9	3
No. of bacteria spp. detected	9	24
C. albicans/tropicalis	8	0
C. parapsilosis	1	1
C. glabrata/*C. krusei*	0	0
No. of *Candida* spp. detected	9	1

[a]T2MR, T2 magnetic resonance; BC, blood culture.

Seitz T et al. *Microbiol Spect* 2022;10:40014022

Problem with T2MR

T2 Biosystems, Inc.

Company plans to add multidrug-resistant Candida auris detection to its FDA-cleared T2Candida Panel

LEXINGTON, Mass., June 05, 2023 (GLOBE NEWSWIRE) -- T2 Biosystems, Inc. (NASDAQ:TTOO), a leader in the rapid detection of sepsis-causing pathogens and antibiotic resistance genes, today announced that it has submitted an application with the U.S. Food and Drug Administration (FDA) for Breakthrough Device Designation for the Company's *Candida auris* test. The Company recently announced plans to add *C. auris* detection to its FDA-cleared T2Candida® Panel.

From:T2 Biosystems Announces Submission for FDA Breakthrough Device Designation for Candida Auris Diagnostic Test (yahoo.com) accessed @2204hrs on 19072023

T2 Candida is acceptable for diagnosis of invasive candidiasis

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America | hivma hiv medicine association | OXFORD

Revision and Update of the Consensus Definitions of Invasive Fungal Disease From the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium

Candidiasis
Host factors
Recent history of neutropenia <0.5 × 10^9 neutrophils/L (<500 neutrophils/mm^3 for >10 days) temporally related to the onset of invasive fungal disease
Hematologic malignancy
Receipt of an allogeneic stem cell transplant
Solid organ transplant recipient
Prolonged use of corticosteroids (excluding among patients with allergic bronchopulmonary aspergillosis) at a therapeutic dose of ≥0.3 mg/kg corticosteroids for ≥3 weeks in the past 60 days
Treatment with other recognized T-cell immunosuppressants, such as calcineurin inhibitors, tumor necrosis factor-a blockers, lymphocyte-specific monoclonal antibodies, immunosuppressive nucleoside analogues during the past 90 days
Inherited severe immunodeficiency (such as chronic granulomatous disease, STAT 3 deficiency, CARD9 deficiency, STAT-1 gain of function, or severe combined immunodeficiency)
Acute graft-versus-host disease grade III or IV involving the gut, lungs, or liver that is refractory to first-line treatment with steroids
Clinical features
At least 1 of the following 2 entities after an episode of candidemia within the previous 2 weeks:
Small, target-like abscesses in liver or spleen (bull's-eye lesions) or in the brain, or, meningeal enhancement
Progressive retinal exudates or vitreal opacities on ophthalmologic examination
Mycological evidence
ß-D-glucan (Fungitell) ≥80 ng/L (pg/mL) detected in at least 2 consecutive serum samples provided that other etiologies have been excluded
Positive T2Candida[a]

Donelly PJ et al. *Clin Infect Dis* 2019

Know the tests, use them well

- Obtain an accurate microbiological diagnosis
- There's always time for blood cultures
- Interpret microbiology results carefully
  - Don't treat *Candida* grown from respiratory tract
- Consider host factors in selection of antimicrobial agents
- Use therapeutic drug monitoring (TDM) if available
- Use antibiotics judiciously

Do not treat Candida from a respiratory sample!

No culture-based or molecular test of respiratory specimens can distinguish between contamination, colonization and invasive disease.

Pendleton KM et al. *Pathogens & Disease* 2017;75: ftx 029

THE SIGNIFICANCE OF *CANDIDA ALBICANS* IN HUMAN SPUTUM*

GERALD L. BAUM, M.D.†

TABLE 1. *Results of Cultures of Sputum for Fungi.*

GROUP	AGE RANGE	NUMBER CULTURED	CULTURES POSITIVE		
			ALL CANDIDA SPECIES	*C. albicans*	MOLD
	yr.				
Hospital patients	24-70	55	30	15	20
Hospital employees	20-47	34	12	5	18
Medical students	20-27	30	6	4	9

The differences in these three groups are not as important as the fact that candida exists at all.

#40 of 55 pts were on antibiotics; none of control groups on antibiotics

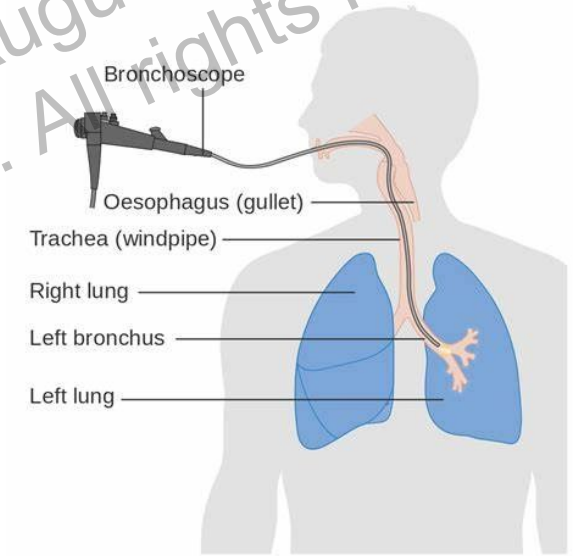
RCT: Antifungal for VAP with Candida in ETT

	Placebo	Antifungal	p	Observational
n	29	31		29
APACHE	23	22		20.9
Baseline SOFA	38	38		38
ICU LOS	11.5	13	0.35	11
Hospital LOS	29	28	0.9	29.5
28-day mortality	6 (20.7%)	7 (22.6%)	0.86	5 (17.2%)
90-day mortality	7 (24.1%)	10 (32.3%)	0.49	6 (20.7%)

Albert M et al. *Intensive Care Med* 2014;40:1313

Know the tests well

- And do the sophisticated investigation early



Early vs late BAL (HSCT)

- MDACC, unintubated HSCT recipients within 1st 100 d
- BAL fluid sent for ≈ same panel of tests
- 674 of 2,181 pts developed pulm infiltrates, 598 of 674 (88%) underwent BAL

Shannon VR et al. *BMT* 2010;45:647

Early vs late BAL (HSCT)

	Early BAL*	Late BAL
On broad-spectr abx#	98%	100%
Interval@	1.9d	6.2d
On antivirals#	23%	56%
On antifungals#	27%	87%
Diagnosed by BAL	73%	31%

*<4 days, # at time of BAL, @ btw commencement of empiric BSABx & BAL
Shannon VR et al. *BMT* 2010;45:647

Early vs late BAL (HSCT)

- Diagnostic yield α interval btw detection of pulmonary infiltrates and performance of BAL
- Within 24hrs: 75%
- At 5 days: 40%
- At 10 days: 10%

Shannon VR et al. *BMT* 2010;45:647

BAL important for Aspergillosis diagnosis outside ICH field too!

Putative invasive pulmonary aspergillosis (all four criteria must be met)

1. *Aspergillus*-positive lower respiratory tract specimen culture (− entry criterion)
2. Compatible signs and symptoms (one of the following)
   - Fever refractory to at least 3 d of appropriate antibiotic therapy
   - Recrudescent fever after a period of defervescence of at least 48 h while still on antibiotics and without other apparent cause
   - Pleuritic chest pain
   - Pleuritic rub
   - Dyspnea
   - Hemoptysis
   - Worsening respiratory insufficiency in spite of appropriate antibiotic therapy and ventilatory support
3. Abnormal medical imaging by portable chest X-ray or CT scan of the lungs
4. Either 4a or 4b
   - 4a. Host risk factors (one of the following conditions)
     - Neutropenia (absolute neutrophil count $<500/mm^3$) preceding or at the time of ICU admission
     - Underlying hematological or oncological malignancy treated with cytotoxic agents
     - Glucocorticoid treatment (prednisone equivalent, >20 mg/d)
     - Congenital or acquired immunodeficiency
   - 4b. Semiquantitative *Aspergillus*-positive culture of BAL fluid (+ or ++), without bacterial growth together with a positive cytological smear showing branching hyphae

Blot SI et al. *Am J Resp Crit Care Med* 2012;186:56

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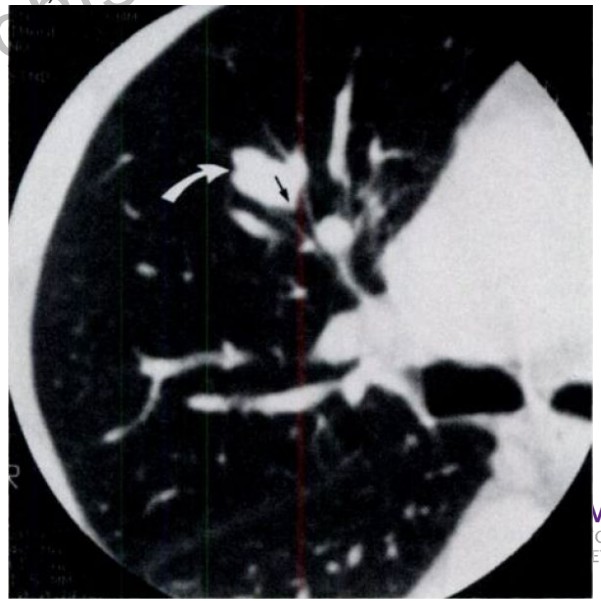
Blot SI et al. *Am J Resp Crit Care Med* 2012;186:56

Yield related to “bronchus sign”

- The presence in cross-section of a bronchus leading to or contained in the nodule or mass
- with bronchus sign: 21/35 + result* (60%)
- without bronchus sign 10/30 + result* (10%) (p=0.034)



*all with TBLB
Naidich DP et al. *Chest* 1988;93:595

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  - (use the sophisticated investigation early)
- Befriend the microbiologist
- Treat early
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Hypotension for the ID physician

- 39 yo man, transferred from another country with fulminant hepatic failure; received R lobe graft a few days after
- Intra-op – colon dusky – colostomy created
- Fluconazole prophylaxis
- POD4: Rise in WBC, caspofungin started, PipTazo converted to meropenem
- Bld c/s from POD4: C. lusitaniae
- Stable until POD13: drop in platelet, rise in liver enzymes: bld c/s repeated – *S. maltophilia*
- Now on levofloxacin, caspofungin
- POD18: New fever, BP sagging

What will you do?

Suspected sepsis, already on meropenem, echinocandin (compromised host)

- Redo septic work-up
- Review medication list
- ***Repeat blood cultures!***

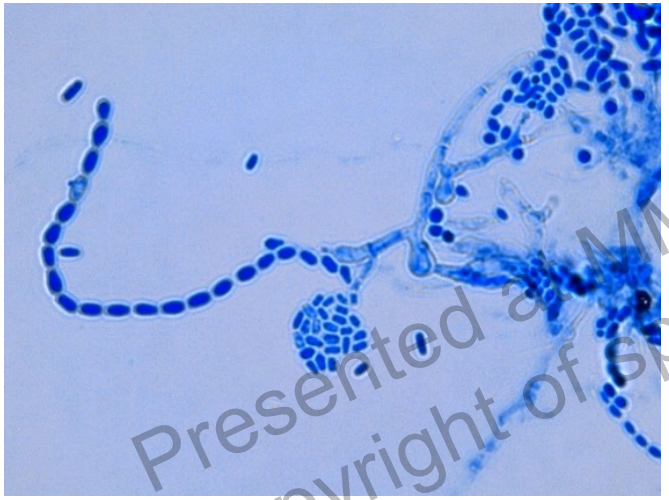
Suspected sepsis, already on meropenem, echinocandin (compromised host)

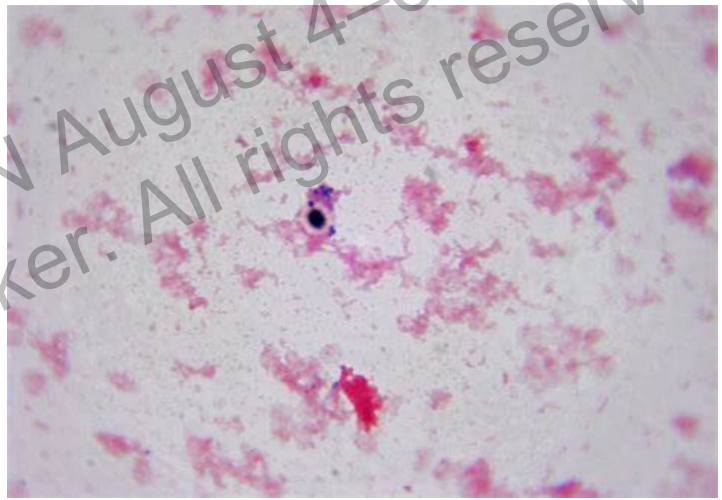
- So you order blood cultures and they're positive for "yeast"
- What do you do?

What should you do when a compromised host on meropenem and caspofungin is said to be growing yeasts in his latest blood culture?

a) Change to anidulafungin
b) Add amphotericin/lipid preparation of amphotericin
c) Speak to the microbiologist
d) Ignore the result – it is likely contaminant

Speak to the microbiologist!





Not all yeasts are echinocandin-susceptible

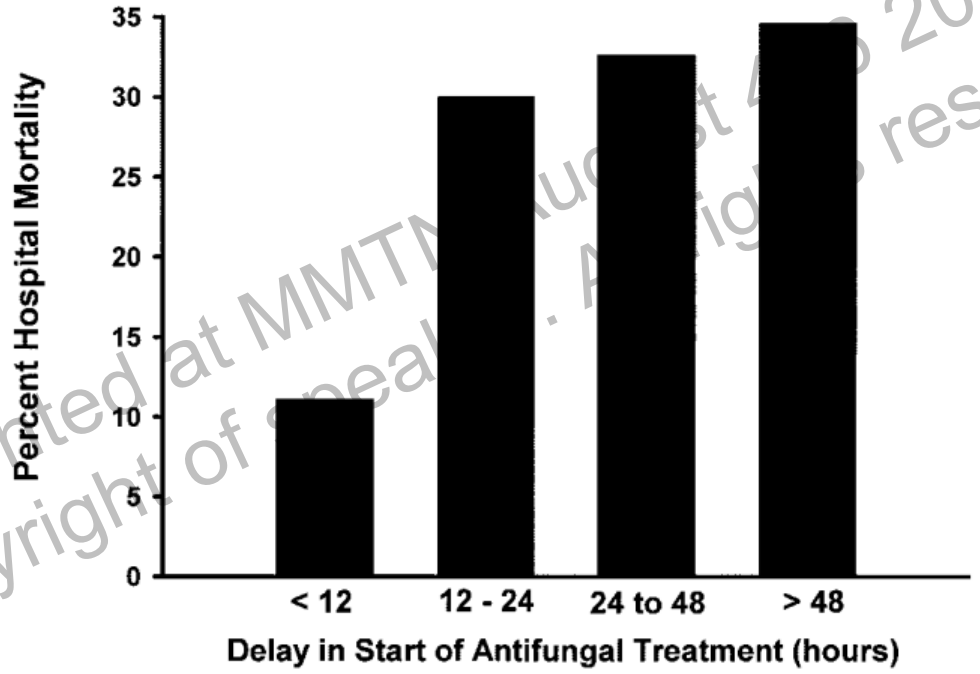
- 2,155 yeast isolates from blood cultures (6 Asian countries), 175 (ie, 8.1%) were non-*Candida* yeasts
- Most were no echinocandin-susceptible
- *Cryptococcus* (109), *Trichosporon* (23), *Rhodotorula* (10), *Malassezia* (4)

Lin S-Y et al. *Mycoses* 2019;62:112

Basic principles in medical mycology

- Think fungus
- Know the tests, use them well
  - (use the sophisticated investigation early)
- Befriend the microbiologist
- Treat early
  - (follow basic rules of antimicrobial therapy)
- Know the drugs
  - (beware DDIs; apply PK/PD principles)
- Follow the guidelines!

Candidemia – treat early!



Morell M et al. *Antimicrob Agents Chemother* 2005;49:3604

Surviving sepsis guidelines within lowest mortality window

Time to antibiotics

Recommendations

12. For adults with possible septic shock or a high likelihood for sepsis, we **recommend** administering antimicrobials immediately, ideally within 1 h of recognition

Strong recommendation, low quality of evidence (Septic shock)

Strong recommendation, very low quality of evidence (Sepsis without shock)

13. For adults with possible sepsis without shock, we **recommend** rapid assessment of the likelihood of infectious versus non-infectious causes of acute illness

Best Practice Statement

Remarks

Rapid assessment includes history and clinical examination, tests for both infectious and non-infectious causes of acute illness and immediate treatment for acute conditions that can mimic sepsis. Whenever possible this should be completed within 3 h of presentation so that a decision can be made as to the likelihood of an infectious cause of the patient's presentation and timely antimicrobial therapy provided if the likelihood of sepsis is thought to be high

14. For adults with possible sepsis without shock, we **suggest** a time-limited course of rapid investigation and if concern for infection persists, the administration of antimicrobials within 3 h from the time when sepsis was first recognised

Weak recommendation, very low quality of evidence

So it appears that we cannot wait for blood cultures to flag positive for *Candida* …

Caspofungin vs placebo for prophylaxis/ pre-emptive therapy

- Multi-centre RCT in 15 adult ICUs (US)
- Randomizable if Ostrosky-Zeichner score fulfilled

  - Mechanically ventilated &
  - With a CVC &
  - On broad-spectrum antibiotics &
- With at least one more of
  - TPN, any dialysis, any major surgery, acute pancreatitis, systemic steroids, any other immunosuppressive

Ostrosky-Zeichner L et al. *Clin Infect Dis* 2014;58;1219

Caspofungin vs placebo for prophylaxis/ pre-emptive therapy

	Proven/probable invasive candidiasis	p
Caspofungin	9.8%	0.14
Placebo	16.7%	

- Also no difference between the two arms for “all-cause mortality at 7 days”, and “length of stay”.

Ostrosky-Zeichner L et al. *Clin Infect Dis* 2014;58;1219

Consensus guidelines for the diagnosis and management of invasive candidiasis in haematology, oncology and intensive care settings, 2021

Question 5: What is the role of prophylaxis to prevent IC?

Recommendations

- Prophylactic and pre-emptive antifungal therapy is not recommended for ICU patients. Empirical antifungal therapy may be considered in patients with septic shock, multi-organ failure and at least two extra-intestinal sites of *Candida* colonisation (Moderate recommendation, Level III evidence).

Keighley C et al. *Intern Med J* 2021;51(Suppl. 7):89

- In other words, no role for prophylaxis or pre-emptive therapy in a program
- Early empiric treatment

- In other words, no role for prophylaxis or pre-emptive therapy in a program
- Early empiric treatment

Rule	Objective	Risk Factors
Colonization index[1]	Determine the role of *Candida* colonization in the development of subsequent infection in critically ill patients	• Severity of illness assessed by APACHE II score • Intensity of *Candida* colonization
Paphitou rule[2]	Identify patients at increased risk for candidal infections in the surgical ICU	• Any combination of : – Diabetes mellitus – New onset hemodialysis – Use of total parenteral nutrition – Receipt of broad-spectrum antibiotics
BAMSG rule[3]	Identify patients at risk of invasive candidiasis in the ICU	• Any systemic antibiotic (days 1-3) **OR** • Presence of a central venous catheter (days 1-3) **AND** • Plus **AT LEAST TWO** of the following: – Total parenteral nutrition (days 1-3) – Any dialysis (days 1-3) – Any major surgery (days -7–0) – Pancreatitis (days -7–0) – Any use of steroids (days -7–3)
MSG rule[4]	Identify patients at risk of invasive candidiasis in the ICU in a clinical trial setting	• Use of mechanical ventilation (days 1-3) **AND** • Use of a central venous catheter (days 1-3) **AND** • Use of any broad spectrum antibiotics (days 1-3) • Plus **AT LEAST ONE** of the following: – Use of parenteral nutrition (days 1-3) – Any type of dialysis (days 1-3) – Any major surgery (days -7–0) – Diagnosis of pancreatitis (by CT or lipase >1,000 u) (days -7–0) – Use of systemic steroids (>1 dose of prednisone equivalent to ≥20 mg/day) (days -7–0) – Use of any other immunosuppressive agents (>1 dose) (days -7–0)
León rule[5]	Obtain a score ("Candida score") for deciding early antifungal treatment when candidal infection is suspected in non-neutropenic critically ill patients	• Surgery = 1 point • Multifocal colonization = 1 point • Total parenteral nutrition = 1 point • Severe sepsis = 2 points • Score of ≥3 predictive of invasive candidiasis
Nebraska Medical Center rule[6]	Determine the likelihood of patients in the ICU to develop invasive candidiasis; this rule is more useful for identifying patients who would least likely benefit from antifungal prophylaxis rather than for identifying patients who should receive such therapy	• Currently receiving broad-spectrum antibiotics • Presence of a central venous catheter • Receipt of total parenteral nutrition • Abdominal surgery within the last 7 days • Steroid use • Length of stay in the hospital

From: Penn State Hershey College of Medicine

www.peerview.com/y/c30

The Candida score ("Leon score")

Table 3. Results of multivariate analysis: Risk factors for proven candidal infection in 1,669 adult patients

Variable	Proven Candidal Infection %	*p* Value	Crude Odds Ratio (95% Confidence Interval)	Adjusted Odds Ratio (95% Confidence Interval)
Surgery on ICU admission				
No	6.9			
Yes	16.5	<.001	2.69 (1.76–4.10)	2.71 (1.45–5.06)
Total parenteral nutrition				
No	2.8			
Yes	15.5	<.001	6.46 (3.48–11.98)	2.48 (1.16–5.31)
Severe sepsis				
No	4.5			
Yes	28.8	<.001	8.63 (5.49–13.56)	7.68 (4.14–14.22)
Candida species colonization				
No	4.2			
Yes	12.3	<.001	3.20 (1.85–5.53)	3.04 (1.45–6.39)

Leon C et al. *Crit Care Med* 2006;34:730

Higher Leon Score, increased risk of invasive candidiasis

Table 4. Rates of invasive candidiasis according to the *Candida* score

Cutoff Value	Incidence Rate (%) (95% CI)	Relative Risk (95% CI)
<3	2.3 (1.1–3.5)	1
3	8.5 (4.2–12.7)	3.7 (1.8–7.7)
4	16.8 (9.7–23.9)	7.3 (3.7–14.5)
5	23.6 (12.4–34.9)	10.3 (5.0–21.0)

CI, confidence interval.

Leon C et al. *Crit Care Med* 2009;37:1624

Higher Leon Score, increased risk of invasive candidiasis

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4	16.8 (9.7–23.9)	7.3 (3.7–14.5)
5	23.6 (12.4–34.9)	10.3 (5.0–21.0)

CI, confidence interval.

- So you can decide – I'll start if the patient scores at least 3 points

Leon C et al. *Crit Care Med* 2009;37:1624

Is Leon (Candida) score too simple?

- Lots of ICU patients have “severe sepsis”, have had an abdominal op, and are on TPN!

Weiss E. *Ther Adv Infect Dis* 2014;2(5-6):105

Australian experience with rules

Table 2 Performance characteristics of risk predictive models applied to study cohort

	Clinical prediction rule 1[a]	Clinical prediction rule 2[b]	Colonisation index ≥0.5[c]	Corrected colonisation index ≥0.4[d]
Proportion of cohort meeting model (%)	21	49	42	11
Sensitivity (%)	47	80	87	60
Specificity (%)	79	51	60	90
PPV (%)	5.3	4	5.1	13
NPV (%)	98	99	99	99
LR (positive test)	2.2	1.6	2.1	6.0
LR (negative test)	0.7	0.4	0.2	0.4
Area under ROC curve (95% CI)	0.63 (0.47–0.78)	0.66 (0.53–0.78)	0.74 (0.62–0.84)	0.75 (0.60–0.90)

Note the very low PPVs!

Playford EG et al. *Intensive Care Med* 2009;35:2141

Colonization is important

Table 3 Performance characteristics of clinical prediction rules 1 and 2 with/without addition of Candida colonisation parameters

	Clinical prediction rule 1[a]				Clinical prediction rule 2[b]			
	Without colonisation	With any colonisation	With colonisation index ≥0.5[c]	With corrected colonisation index ≥0.4[c]	Without colonisation	With any colonisation	With colonisation index ≥0.5[c]	With corrected colonisation index ≥0.4[c]
Proportion of cohort meeting model (%)	21	17	11	3.4	49	38	23	8
Sensitivity (%)	47	47	47	33	80	80	73	53
Specificity (%)	79	84	90	97	51	63	78	94
PPV (%)	5.3	6.7	10.5	23.8	4.0	5.1	7.8	17.0
NPV (%)	98	98	99	98	99	99	99	99
LR (positive test)	2.2	2.9	4.7	12.5	1.6	2.2	3.4	8.2
LR (negative test)	0.7	0.6	0.6	0.7	0.4	0.3	0.3	0.5
Area under ROC curve	0.63 (0.47–0.78)	0.66 (0.50–0.81)	0.69 (0.52–0.84)	0.65 (0.49–0.82)	0.66 (0.53–0.78)	0.72 (0.60–0.84)	0.76 (0.63–0.89)	0.73 (0.58–0.89)

See the improvement

Playford EG et al. *Intensive Care Med* 2009;35:2141

Using Sepsis3.0 definition of septic shock improved predictive value of Candida score

Table 3 Discriminatory powers of *Candida* score 2009 and *Candida* score 3.0 in the validation cohort

Validation cohort	CS-2009 ≥3	CS 3.0 ≥3
Area under ROC curve (95% CI)	0.789 (0.765–0.813)	0.804 (0.782–0.827)
Sensitivity	75.2%	77.3%
Specificity	74.3%	74.3%
Predictive positive value	6.9%	7.1%
Predictive negative value	99.2%	99.2%
Relative risk for invasive candidiasis	8.799 (7.061–10.966)	9.866 (7.865–12.375)

ROC, receiver operating characteristic; CS, *Candida* score; CI, confidence interval.

Li D et al. *Ann Transl Med* 2020;8:917

Developing a New Definition and Assessing New Clinical Criteria for Septic Shock:

For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

"Septic shock" if

need for vasopressors to maintain MAP≥65mmHg
serum lactate >2mmol/L after fluid resuscitation

Shankar-Hari M et al. *JAMA* 2016;315:775

Approach to possible candidemia

- Need to treat early (“early empiric therapy”)
- Knowledge of risk factors; prediction rules may help
- Blood cultures before anti-microbials, please

Basic principles in medical mycology

- Think fungus
- Know the tests, use them well
  - (use the sophisticated investigation early)
- Befriend the microbiologist
- Treat early
  - (follow basic rules of antimicrobial therapy)
- Know the drugs
  - (beware DDIs; apply PK/PD principles)
- Follow the guidelines!

But not echinocandins

Echinocandin breakthroughs

18yo male, failing HSCT, with IPA, now 2nd HSCT with VRC as 2⁰ proph

- Switched to CSP on D7 (LFT abnormalities); no WBC recovery
- D48, fever → bld c/s done → *C. parapsilosis*

46yo male undergoing HSCT with FLUC prophylaxis

- CSP started on D6 empirical treatment for FN
- Severe GVHD → multiple immunosuppressives → CMV infection
- On d58 - 60, fever → daily bld c/s →all *C. parapsilosis*

32yo male, HSCT while on FLUC prophylaxis; with WBC engraftment D21

- GVHD → multiple immunosuppressives →CMV infection, bacteremia
- D95: switched from FLUC to CSP (LFT abnormalities)
- D118: fever → bld c/s → *C. guilliermondii*

Kabbara N et al. *Haematologica* 2008;93:639

ORIGINAL ARTICLE

Fatal *Trichosporon* fungemia in patients with hematologic malignancies

Kei Suzuki[1], Kazunori Nakase[1,2], Taiichi Kyo[3], Tadahiro Kohara[4], Yumiko Sugawara[1], Tetsunori Shibazaki[1], Kouji Oka[5], Tetsuya Tsukada[6], Naoyuki Katayama[1]

- 33 cases of trichosporon fungemia in haematologic patients (5 hospitals)
- 30 were “breakthrough” infections
- **18 were on micafungin at the time of the breakthrough**
- 25 died (mortality 76%)

Survival assoc with

✓ Granulocyte recovery
✓ Absence of hyperglycemia
✓ Use of azoles

European Journal of Haematology 84 (441–447)

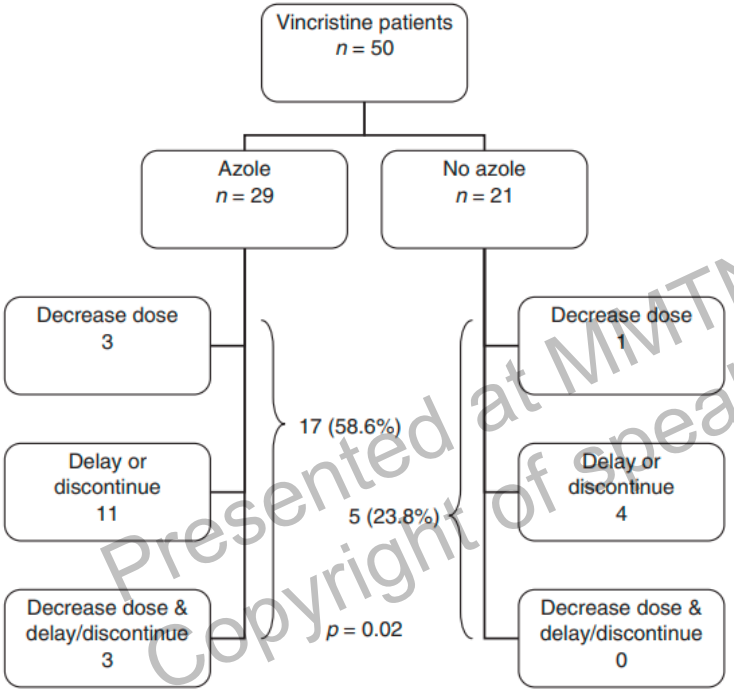
Limb weakness on chemotherapy for ALL

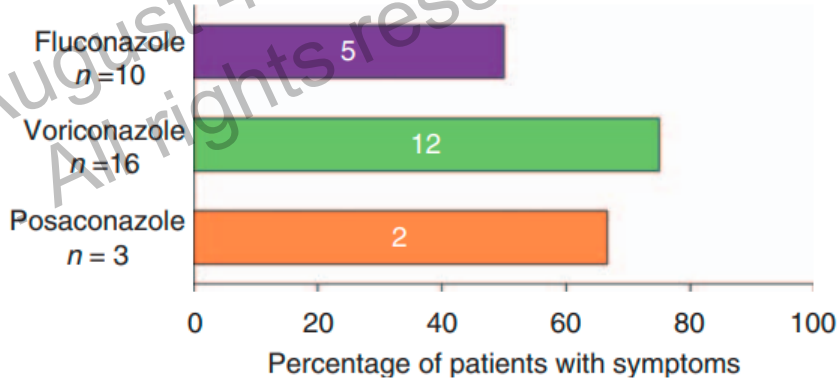
- 4 of 14 patients on prednisolone, vincristine, daunorubicin for ALL developed lower limb weakness
- All were on itraconazole prophylaxis (PO 400 mg om)

Case no.	1	2	3	4
Patient characteristics				
Sex	m	f	f	f
Age (years)	24	29	16	18
Treatment				
Body surface (m^2)	2.1	1.7	1.7	1.7
Absolute dose (mg)				
Vincristine	4	4	4	4
Vinblastine	10	16	16	—
Itraconazole (mg/day)	400	400	400	400
Neurotoxic symptoms				
Extremities (WHO)	2	4	2	2
Days after start of VCR	11	7	11	8
Follow-up	CR	PR	CR	CR
Paralytic (sub)ileus (WHO)	3	4	3	4
Days after start of VCR	13	13	11	15
Follow-up	CR	CR	CR	CR
Laryngeal nerve paresis				
Days after start of VCR		60		
Follow-up		CR		

Bohme A et al. *Ann Hematol* 1995;71:311

The azole-vincristine interaction





Harnicar S et al. *J Oncol Pharm Pract* 2009;15:175

From the FDA – beware drug interactions of voriconazole

The systemic exposure of the following drugs is significantly increased or is expected to be significantly increased by coadministration of voriconazole and their use is contraindicated:

***Sirolimus* (CYP3A4 substrate):** Repeat dose administration of oral voriconazole (400 mg Q12h for 1 day, then 200 mg Q12h for 8 days) increased the C_{max} and AUC of sirolimus (2 mg single dose) an average of 7-fold (90% CI: 5.7, 7.5) and 11-fold (90% CI: 9.9, 12.6), respectively, in healthy male subjects. **Coadministration of voriconazole and sirolimus is contraindicated** (see CONTRAINDICATIONS, PRECAUTIONS - Drug Interactions).

***Terfenadine, astemizole, cisapride, pimozide and quinidine* (CYP3A4 substrates):** Although not studied *in vitro* or *in vivo*, concomitant administration of voriconazole with terfenadine, astemizole, cisapride, pimozide or quinidine may result in inhibition of the metabolism of these drugs. Increased plasma concentrations of these drugs can lead to QT prolongation and rare occurrences of *torsade de pointes*. **Coadministration of voriconazole and terfenadine, astemizole, cisapride, pimozide and quinidine is contraindicated** (see CONTRAINDICATIONS, PRECAUTIONS - Drug Interactions).

***Ergot alkaloids*:** Although not studied *in vitro* or *in vivo*, voriconazole may increase the plasma concentration of ergot alkaloids (ergotamine and dihydroergotamine) and lead to ergotism. **Coadministration of voriconazole with ergot alkaloids is contraindicated** (see CONTRAINDICATIONS, PRECAUTIONS - Drug Interactions).

From: Vfend (voriconazole) i.v., tablets and suspension label (fda.gov) accessed @1604hrs on 24062023

Pfizer

Find VFEND® medical information: e.g. Absorption Search

Everolimus (CYP3A4 Inhibition)	Not Studied *In Vivo* or *In Vitro*, but Drug Plasma Exposure Likely to be Increased	Concomitant administration of voriconazole and everolimus is not recommended.

From: VFEND®Drug Interactions (voriconazole) | Pfizer Medical Information – US accessed @1545hrs on 11062023

OPEN

Emerging Microbes & Infections (2016) 5, e98; doi:10.1038/emi.2016.95
www.nature.com/emi

LETTER TO THE EDITOR

Cryptococcosis and tuberculosis co-infection in mainland China

Min Chen[1,*], Abdullah MS Al-Hatmi[2,3,*], Yuchong Chen[4,*], Yang Ying[5,*], Wenjie Fang[1], Jianping Xu[6], Ferry Hagen[7], Nan Hong[1], Teun Boekhout[1,3], Wanqing Liao[1] and Weihua Pan[1]

Treating cryptococcosis in patients with TB

- AIDS patients, diagnosed with cryptococcal meningitis → managed with conv amB and fluconazole 400mg om (200 mg om when csf culture-neg)
- Some already on rifampicin (& other drugs) for TB
- Compared with those on fluconazole alone, concomitant rif
  - ↑ elimination rate constant by 39%
  - Cut elimination T1/2 by 28%
  - ↓ AUC by 22%
  - ↓ max concentration by 17% (all stat sig)

Ayudhya DPN et al. *Clin Pharmacokinet* 2004;43:725

Voriconazole TDM – what the BSMM says

Recommendation 5: TDM should be performed in the majority of patients receiving voriconazole

Recommendation 6: A minimum lower target concentration for TDM for treatment of established disease is a trough concentration of >1 mg/L or a trough:MIC ratio of 2–5

Recommendation 7: A trough concentration to minimize drug-related toxicity is <4–6 mg/L

Recommendation 8: Voriconazole concentrations should be measured in the first 5 days of therapy and regularly thereafter

- PK variability of VCZ is extensive → many pts on fixed weight-based regimens have levels that are a/w low probability of success, high probability of toxicity
- Concentration-effect, concentration-toxicity relationships have been reported consistently → therapeutic range is established
- Dosage adjustments a/w less toxicity, and (perhaps) improved clinical response

Ashbee HR et al. *J Antimicrob Chemother* 2014;69:1162

Basic principles in medical mycology

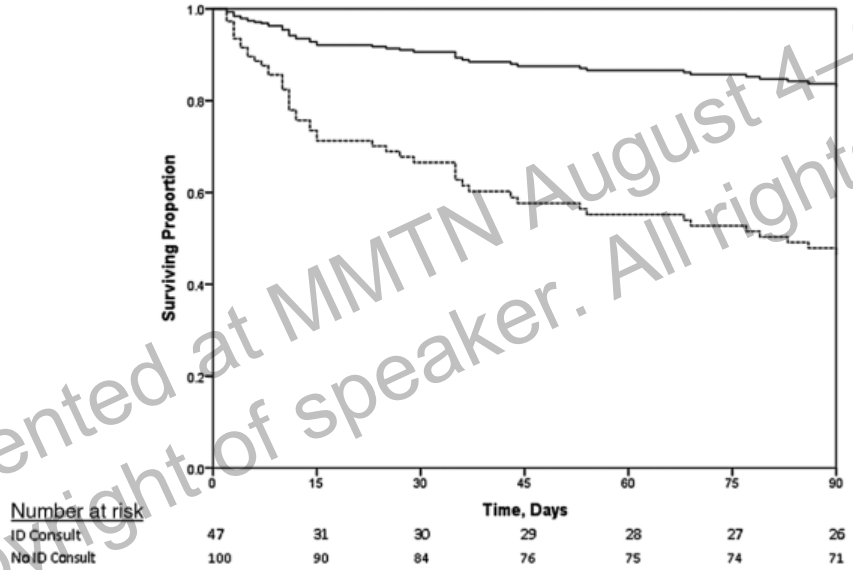
- Think fungus
- Know the tests, use them well
  - (use the sophisticated investigation early)
- Befriend the microbiologist
- Treat early
  - (follow basic rules of antimicrobial therapy)
- Know the drugs
  - (beware DDIs; apply PK/PD principles)
- Follow the guidelines!
- Be an interpist

Cryptococcal management – ID docs, guideline adherence

Treatment	ID Consult (n = 100)	No ID Consult (n = 47)	*P* Value	Total Cohort (N = 147)
LP performed when indicated	79/92 (86)	12/37 (33)	<.001	91/129 (71)
LP performed when not indicated	2/8 (25)	3/10 (30)	.81	5/18 (27.8)
No. of LPs performed among those who had at least 1, median (range)	2 (1–18)	1 (1–3)	.048	2 (1–18)
Neurosurgical intervention for ICP management[a]	8 (8)	0 (0)	.042	8 (5.4)
AmB administered when indicated	81/93 (87)	11/45 (24)	<.001	76/138 (55)
Duration of AmB therapy when indicated, d, median (IQR)	14 (16)	11 (9)	.050	14 (14.5)
5-FC administered when indicated	53/93 (57)	7/45 (16)	<.001	60/138 (44)
Duration of 5-FC therapy when indicated, d, median (IQR)	7.5 (13)	1 (1)	<.001	4 (14)

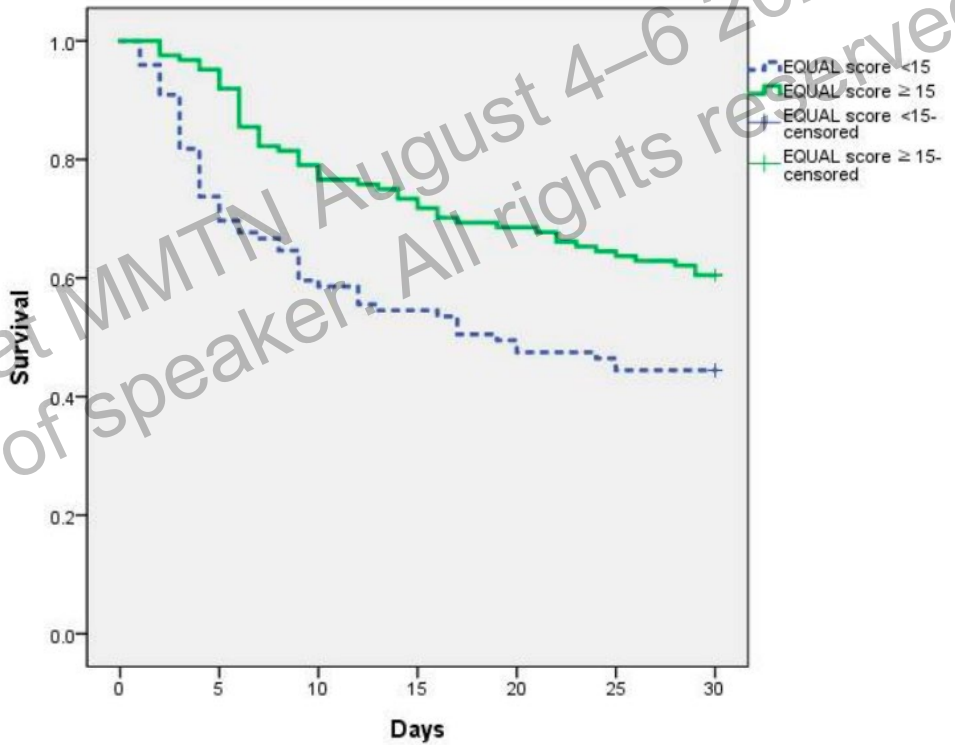
Spec A et al. *Clin Infect Dis* 2017;64:558

Cryptococcosis – Following the book lowers mortality



Spec A et al. *Clin Infect Dis* 2017;64:558

Candidemia management – adherence to guidelines cuts mortality



Kim JH et al. *J Fungi* 2021;7:275

How well are you managing candidiasis?

Candida EQUAL score

Quality indicator	Score	
	Patients with CVC	Patients without CVC
Initial blood culture (40 mL)[6,28]	3	3
Species identification[6,28]	3	3
Susceptibility testing[6,28]	2	2
Echocardiography[6,22]	1	1
Ophthalmoscopy[22,31]	1	1
Echinocandin treatment[6,22]	3	3
Step down to fluconazole depending on susceptibility result[6,22]	2	2
Treatment for 14 days after first negative follow-up culture[6,22]	2	2
CVC removal[6,22,41]		n/a
≤24 hours from diagnosis	3	
>24 < 72 hours from diagnosis	2	
Follow-up blood culture (at least one per day until negative)[6,22]	2	2
Maximum score	22	19

Mellinghoff SC et al. *Mycoses* 2018;61:326

Candidemia bundle checklist

Check for sepsis and septic shock

Presence of ocular symptoms

Presence of cardiac murmur or intravascular device

Previous azole use

Drug-drug interaction

Reviewing the previous microbiologic cultures

Choose the adequate antifungal drug according to clinical condition and previous cultures

Check for adequate antifungal dosage according to weight, renal and hepatic function

Request all necessary microbiologic and radiologic tests

Check for the number of CVC and peripheral catheters, as their status. Support all device withdrawal when unnecessary

If necessary, CVC withdrawal and adequate control of other sources

Day +1

Microbiologic adjustment according to E-test and MALDI-TOF results

Performance of follow-up blood cultures

Request echocardiography

Request ophalmoscopy

Request central venous echography if a clinical suspicion of thrombophlebitis is present

Day +3

Check for definitive antifungal susceptibility testing

Check if antifungal serum concentration is adequate, if clinically necessary

Check for negativity of previous follow-up blood cultures. If positive, request new blood culture sets

Check for results of all previous microbiologic cultures

Check for adequate source control of the infections

Day +5

Check for toxicity, drug-drug interactions and renal and hepatic functions

Check for negativity of previous follow-up blood cultures. If positive, request new blood culture sets

If possible, step-down therapy

Day +7

Check for ophthalmoscopy and echocardiography results

Check for negativity of previous follow-up blood cultures. If positive, request new blood culture sets

Day +14

Check for all microbiologic cultures, ophthalmoscopy and echocardiogram results

Check for renal and hepatic function

Establish length of antifungal therapy

Vena A et al. *Infect Dis Ther* 2020;9:119

Candidemia bundle checklist – 6 items for survival analysis

- Tracked during pre- and post-intervention period:
- Early (<72hr) adequate antifungal therapy
- Early (<72hr) source control, if necessary
- Follow-up blood cultures
- Ophthalmologic examination
- Echocardiography
- Adequate duration of therapy, according to complexity of the infection

Vena A et al. *Infect Dis Ther* 2020;9:119

Compliance with bundle reduced mortality

- Pre-intervention adherence 48.2%
- Post-intervention adherence 81.1%
- 3 components that were improved statistically significantly $p=0.01$
  - Early antifungal therapy
  - Early source control
  - Adequate duration of therapy

	Alive (14 days)	Dead (14 days)	
All bundle elements complied with	69.9%	31.3%	$p=0.004$

- HR for 14-day mortality 0.08 (0.01-0.45) for post-intervention group

Vena A et al. *Infect Dis Ther* 2020;9:119

MMTN MEDICAL MYCOLOGY TRAINING NETWORK

Basic principles in medical mycology

- Think fungus
- Know the tests, use them well
  - (use the sophisticated investigation early)
- Befriend the microbiologist
- Treat early
  - (follow basic rules of antimicrobial therapy)
- Know the drugs
  - (beware DDIs; apply PK/PD principles)
- Follow the guidelines!
- Be an internist

65 yo woman

- AMI → cardiogenic shock → IABP → CABG → weaned off IABP
- 8th POD referred to ID for anti-fungal therapy because of rising WBC despite meropenem
- This is her FBC. The resident says DRE showed no blood, no melaena

ID referral for commencement of anti-fungals (rising WBC)

	Pre-op	1st POD	3rd POD	5th POD	7th POD	9th POD
Hb	11.2	8.5	6.7	7.0	7.1	8.6
WBC	10.5	12.4	15.3	17.8	21.1	25.0
Plt	296	189	175	161	235	318

Cefazolin

PipTazo

Vancomycin & meropenem

Blood transfusion

Extubated 1st POD

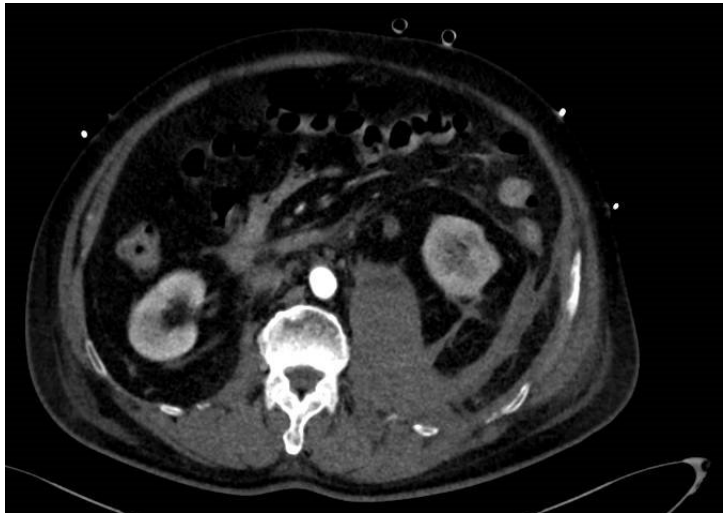
Started eating 3rd POD

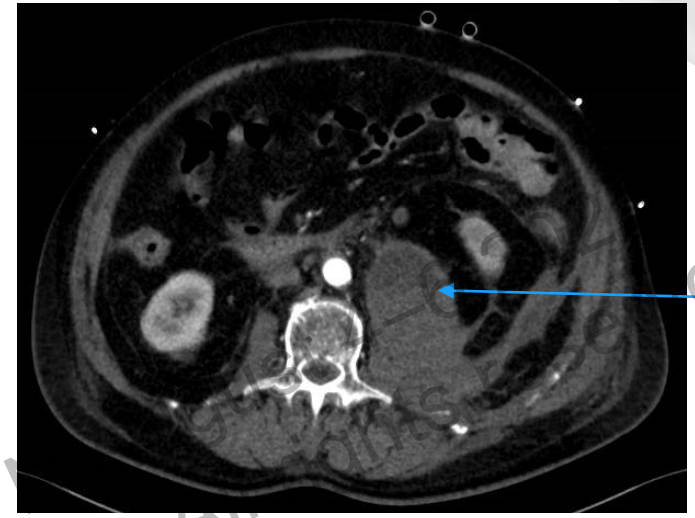
Asked to leave ICU 4th POD

Started PT (walking within ICU room) 4th POD evening

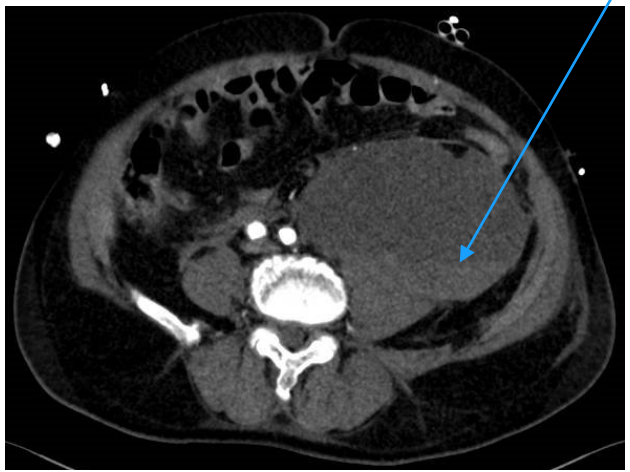
MMTN MEDICAL MYCOLOGY TRAINING NETWORK

Examine the patient!





Note the fluid-fluid lvl



Yes – note the retroperitoneal hematoma

Basic principles in medical mycology

- Think fungus
- Know the tests, use them well
  - (use the sophisticated investigation early)
- Befriend the microbiologist
- Treat early
  - (follow basic rules of antimicrobial therapy)
- Know the drugs
  - (beware DDIs; apply PK/PD principles)
- Follow the guidelines!
- Be an internist
  - (you might just be an anti-fungal steward!)

Thank you