ASIA FUNGAL WORKING GROUP
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ISHAM
INTERNATIONAL SOCIETY FOR HUMAN AND ANIMAL MYCOLOGY

MMTN
MEDICAL MYCOLOGY TRAINING NETWORK

Sudden worsening of CXR with decompensated cirrhosis

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Disclosures

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

Thanks to Dr Wong Hei Man

- This case was presented at ID Grand Rounds by Dr Wong
- Many thanks to him for allowing me to use and modify his slides.
- The questions were invented by me, and the lit review is (almost) all mine.

Madam A.B.J, 63 yo with metabolic syndrome

Underwent elective catheterisation on 05/11/09
Findings:
LM: patent
LAD: patent, intramyocardial bridging
midLAD: NO 50% stenosis present
LCx: patent
RCA: patent, dominant
LVgram: normal LVEF

Impression:
1. Normal coronaries
2. Intramyocardial bridging

Plan:
Medical treatment, lose weight

Patient was stable on discharge.

1. Hypertension
2. Hyperlipidemia
3. Diabetes Mellitus HAB1c 4.6% Sep 2016 (diet control)
4. Chronic Kidney Disease Cr 120-140
5. ? Ischaemic Heart Disease

- 2DE 69% no RWMA in Aug 2015
- Medical therapy

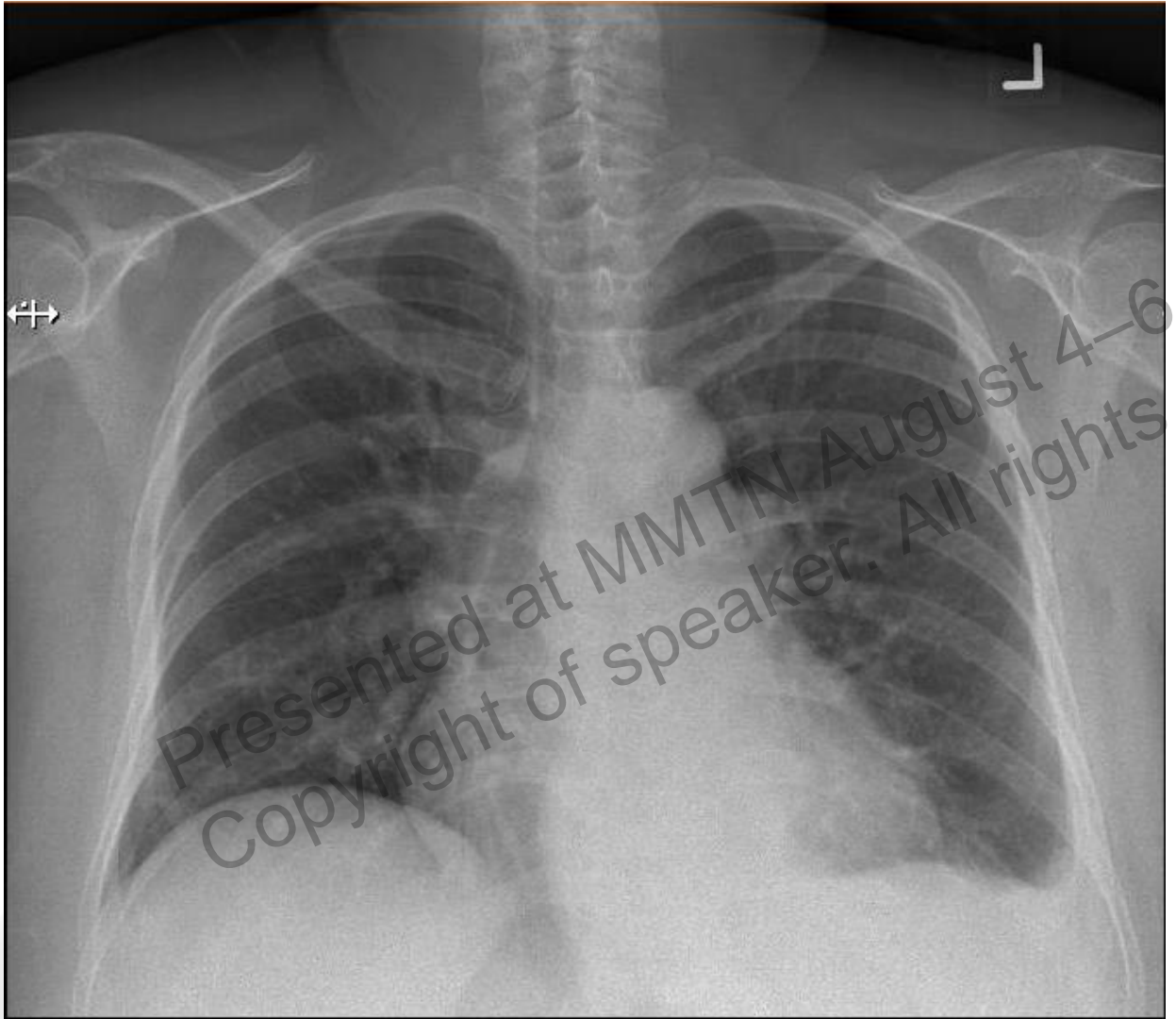
ABJ has gum bleeding, hematemesis

- First presented with gum bleeding with thrombocytopenia, 5 yrs before
- HBV, HCV and autoimmune screen negative
- NAFLD diagnosed
- Ultrasound abdomen: cirrhosis without focal lesion. Spleen is enlarged 17.1cm

- August - multiple episodes of hematemesis, abdomen found to be distended
  - Gastroscopy – oesophageal varices
  - Ascitic tap – WBC 500, culture negative
  - Child's C10; MELD 15
- Deemed suitable candidate for liver transplant
  - Swabs positive for MRSA and VRE

Admission

- 6 Nov – 17 Nov: symptomatic ascites, AOCKD and rectal variceal bleeding
- 30 Nov: now admitted for Cope loop drainage
- History:
  - Coughing for a day or two
  - No hematemesis, but abdomen getting more distended
- Physical exam
- GCS 15, well, vitals stable. Jaundiced. No asterixis. Chest clear, abdo ascites, pedal oedema



First CXR this admission

Investigations

- Cr 121 (baseline 100) HCO_3 22 Na 133 K 3.6 urea 4.9 Cl 99
- Protein 69 Albumin 35 Bio 651 ALP 105 ALT 42 AST 148 GGT75
- INR 1.9 APTT 72
- Hb 7.5 MCV 92.7 TW 9.17 Plt 101

- Throat swab for respiratory viruses multiplex: negative (influenza, RSV, parainfluenza, adenovirus, rhinovirus, metapneumovirus)

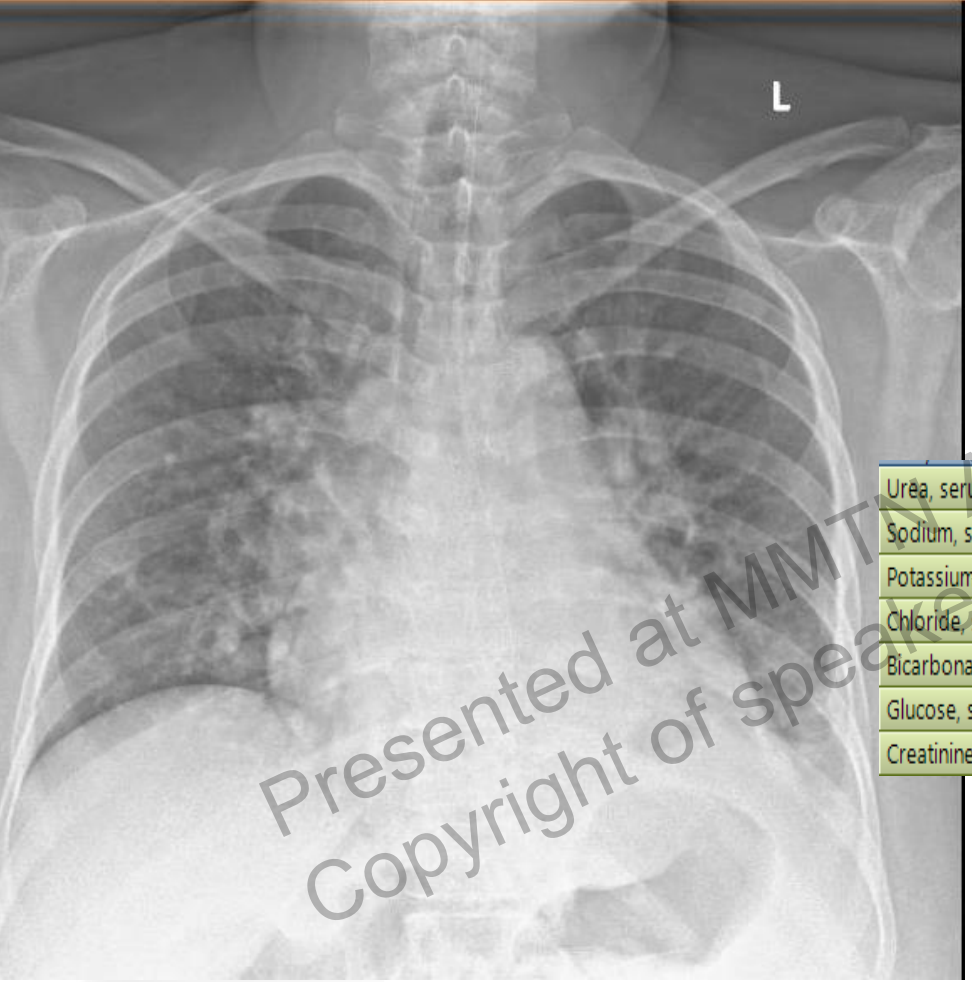
Progression

- Ultrasound guided coop loop insertion by IR on 2/12/2015 (D3)
  - SAAG>11 g/L
  - Ascitic fluid culture negative

Progression

	03Dec2015 06:01	03Dec2015 10:45	04Dec2015 09:33	04Dec2015 19:38	05Dec2015 05:44	06Dec2015 06:37	07Dec2015 05:42	08Dec2015 08:09	09Dec2015 06:47
Urea, serum	* 5.2		* 6.5		* ↑ 7.3	* ↑ 9.1	* ↑ 11.9	* ↑ 14.2	* ↑ 17.4
Sodium, serum	* ↓ 132		* ↓ 132		* ↓ 130	* ↓ 128	* ↓ 126	* ↓ 125	* ↓ 122
Potassium, serum	* ↓ 3.3		* ↓ 3.1		* ↓ 3.3	* 3.9	* ↓ 3.5	* 3.6	* 4.1
Chloride, serum	* ↓ 97		* ↓ 97		* ↓ 96	* ↓ 94	* ↓ 92	* ↓ 92	* ↓ 90
Bicarbonate, serum	* 24.8		* 22.6		* 24.1	* 23.3	* 22.9	* 22.1	* 20.4
Creatinine, serum	* ↑ 104		* ↑ 98		* ↑ 115	* ↑ 126	* ↑ 141	* ↑ 161	* ↑ 192

- Worsening of lower limb edema, more breathless
- Worsening renal function and urine output despite hydration and IV albumin and abdominal drainage
- Hepatorenal syndrome



Brought to High Dependency Unit for iv terlipressin

	10Dec2015 04:50	10Dec2015 12:07	11Dec2015 05:10	11Dec2015 14:47	12Dec2015 05:32	13Dec2015 10:34
Urea, serum	* ↑ 20.0	* ↑ 20.4	* ↑ 21.4	* ↑ 20.8	* ↑ 22.8	* ↑ 23.3
Sodium, serum	* ↓ 124	* ↓ 123	* ↓ 124	* ↓ 121	* ↓ 124	* ↓ 126
Potassium, serum	* ↓ 2.9	* ↓ 3.2	* ↓ 3.2	* 3.8	* 4.0	* 4.3
Chloride, serum	* ↓ 91	* ↓ 91	* ↓ 92	* ↓ 92	* ↓ 93	* ↓ 95
Bicarbonate, serum	* 20.0	* 20.3	* 20.0	* ↓ 17.9	* ↓ 18.6	* 19.1
Glucose, serum						
Creatinine, serum	* ↑ 167	* ↑ 155	* ↑ 133	* ↑ 132	* ↑ 132	* ↑ 129

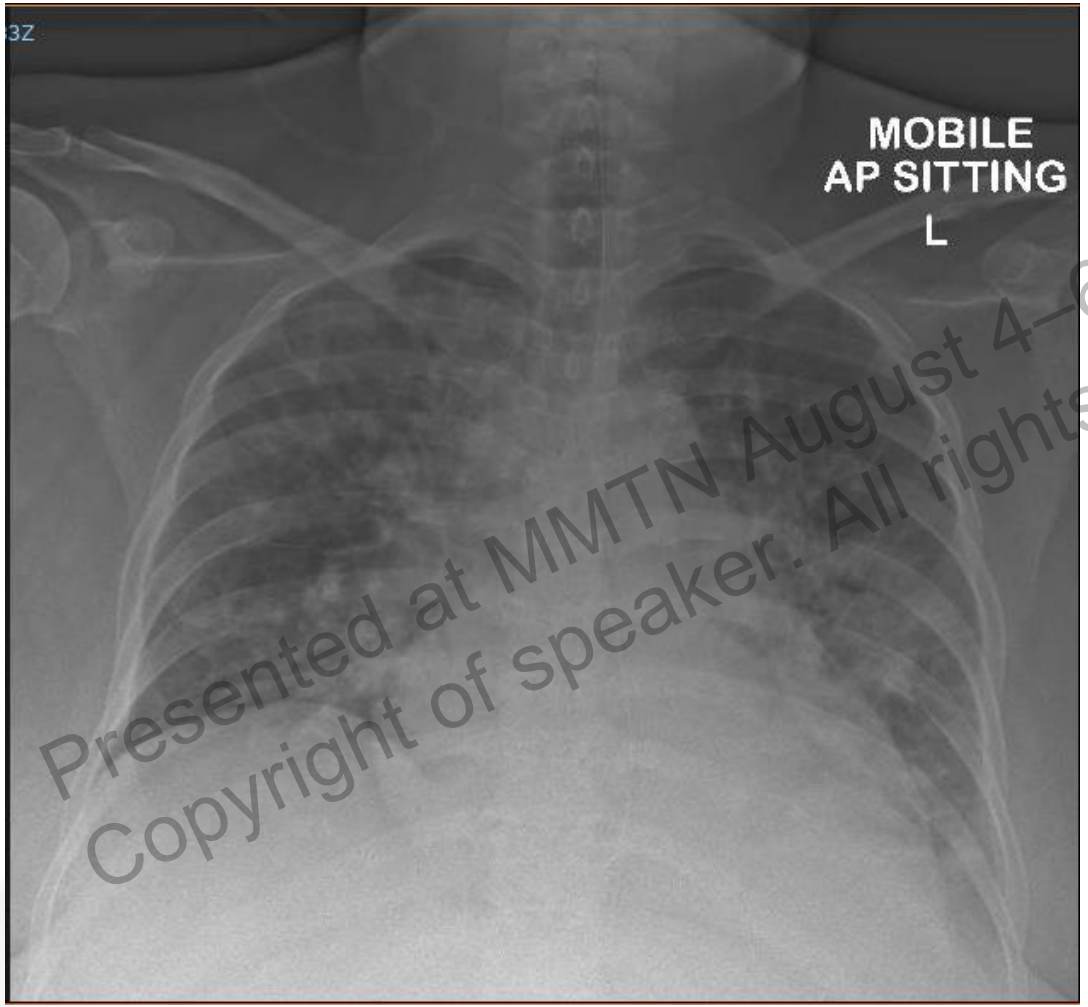
13/12/2015 (D14)

- Progressively more breathless and tachypneic clinically
- Tmax 37.7C
- 99% INO2 4L (on room air previously)
- Heart sound dual no murmurs
- Clinically bibasal crepitations with ? minimally raised JVP; rhonchi heard
- Abdomen distended
- Pedal edema

utine					
Haemoglobin	* ↓	7.6	* ↓	7.4	
WBC Count	*	7.62	* ↑	14.38	
Platelet Count	* ↓	58	* ↓	83	
RBC Count	* ↓	2.44	* ↓	2.30	
MCV	*	86.5	*	90.0	
MCH	*	31.1	* ↑	32.2	
MCHC	*	36.0	*	35.7	
RBC Distribution Width	* ↑	22.7	* ↑	24.0	
Neutrophil	* ↑	75.3	* ↑	79.0	
Lymphocyte	* ↓	10.6	* ↓	5.0	
Monocyte	* ↑	12.1	*	10.0	
Eosinophil	*	1.6	*	2.0	
Basophil	*	0.4			
Atypical Mononuclear Cell					
N. Myelocyte			* ↑	4.0	
WBC Comment					
Cell Count, peritoneal fluid					
Haematocrit	* ↓	21.1	* ↓	20.7	
Neut Absolute	*	5.74	* ↑	11.35	
Lymph Absolute	* ↓	0.81	* ↓	0.72	
Mono Absolute	* ↑	0.92	* ↑	1.44	
EOS Absolute	*	0.12	*	0.29	
BAS Absolute	*	0.03			

Protein Total, serum	* ↓	67
Albumin, serum	*	40
Bilirubin Total, serum	* ↑	669
Alkaline Phosphatase, serum	* ↑	156
Alanine Transaminase, serum	*	47
Aspartate Transaminase, serum	* ↑	118
Gamma-Glutamyl Transferase, serum	* ↑	116

Urea, serum	* ↑	23.3
Sodium, serum	* ↓	126
Potassium, serum	*	4.1
Chloride, serum	* ↓	96
Bicarbonate, serum	* ↓	18.4
Glucose, serum		
Creatinine, serum	* ↑	124

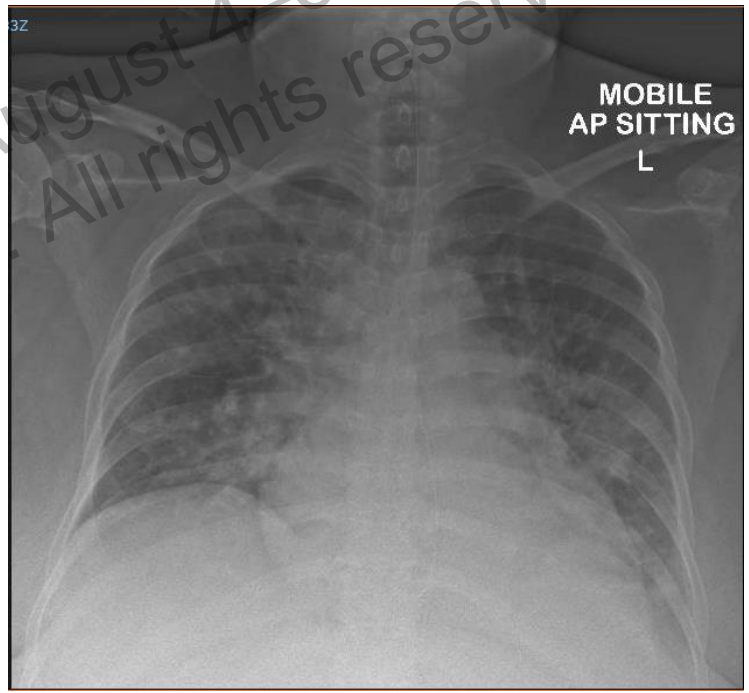


Now CXR in high-dependency unit looks like that

What is the next step?

Cirrhotic with HRS, cough, dyspnea & low-grade fever, abnormal CXR. Apart from broad-spectrum antibiotics, you would

a) Check cryptococcal antigen
b) Order CT chest
c) Intubate patient
d) Rule out Covid
e) Start Ambisome empirically



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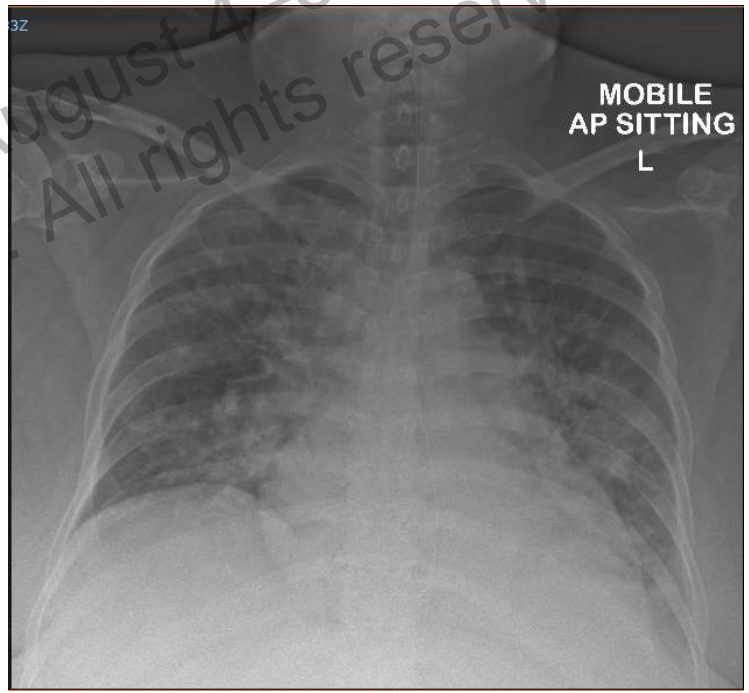
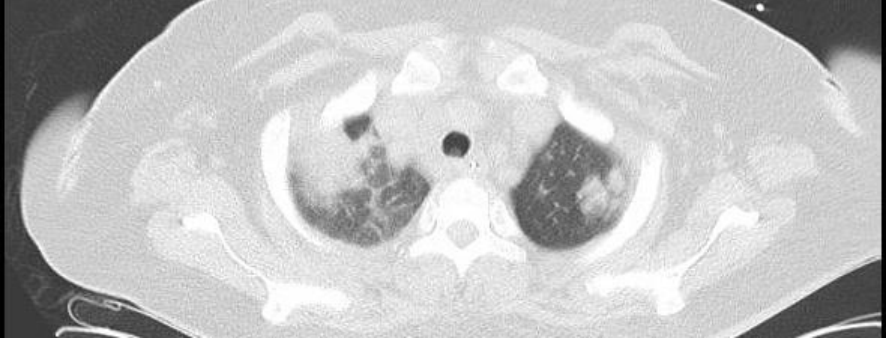
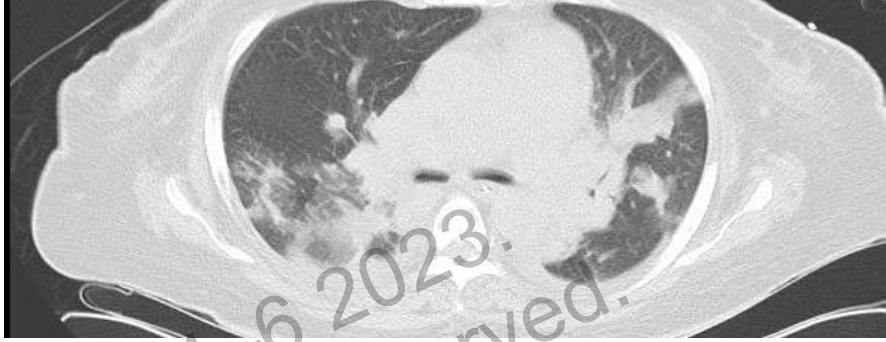
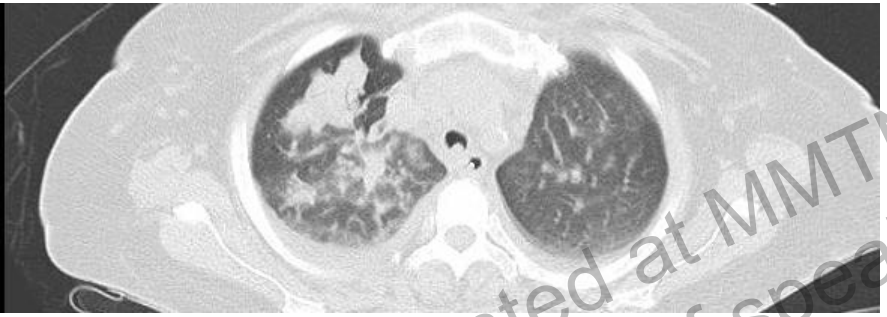
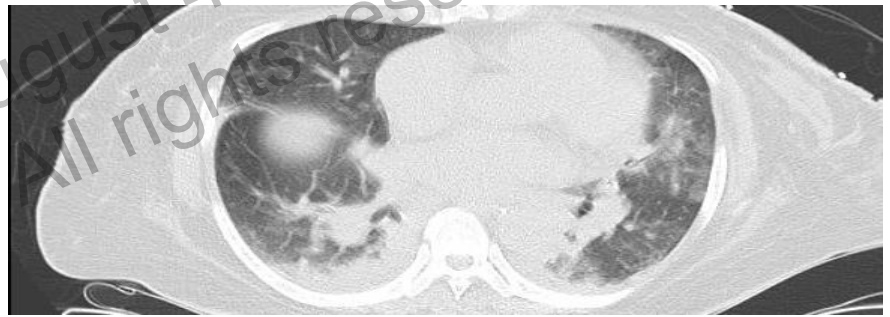
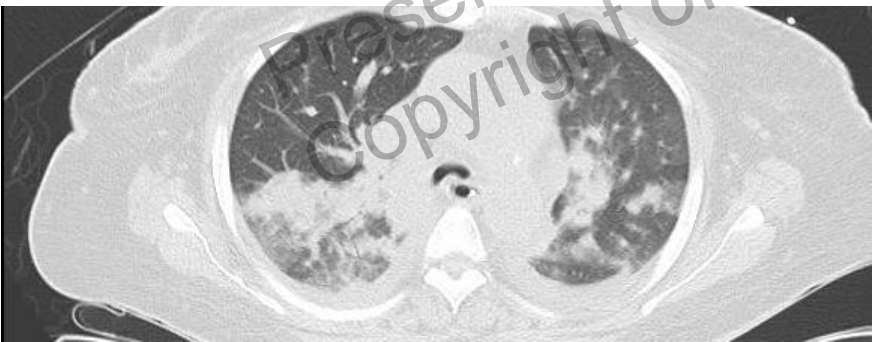
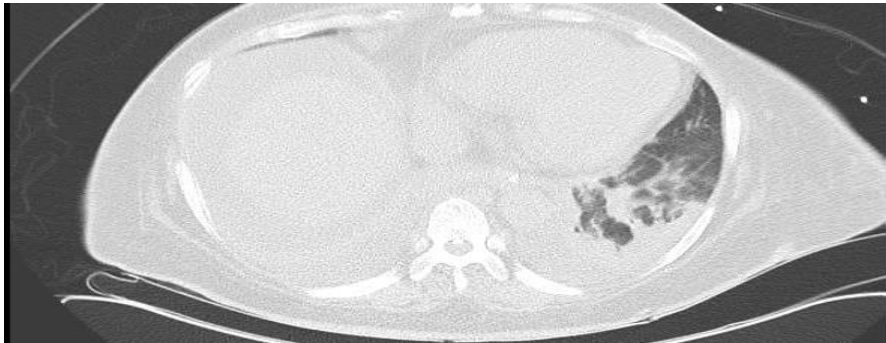
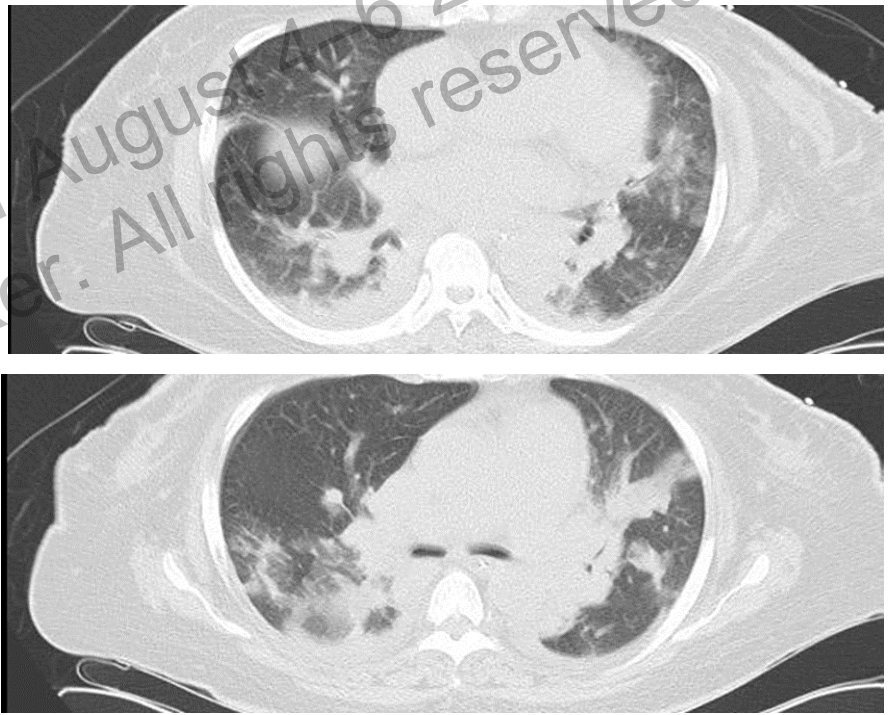


Cirrhotic with HRS, cough, dyspnea & low-grade fever, abnormal CXR, CT looking like that. What medical intervention is appropriate?

Cryptococcal antigen is negative

a) Add Ambisome
b) Add voriconazole
c) Serum GM
d) Bronchoscopy, BAL
e) TTNA



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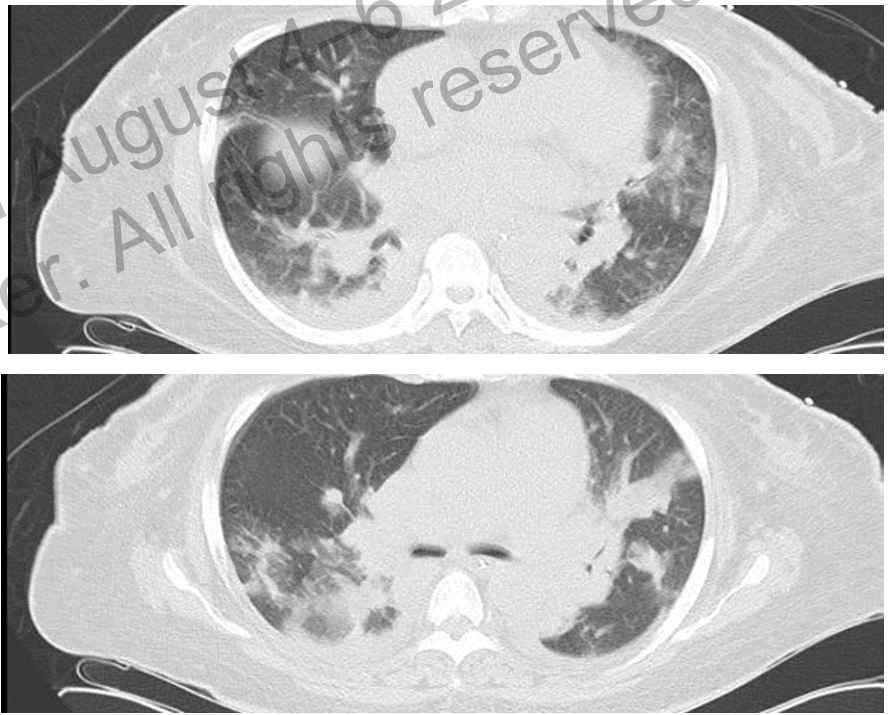
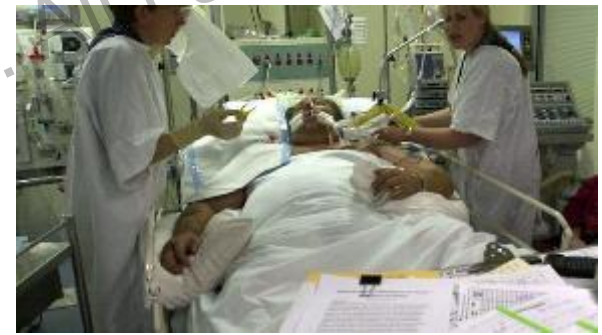


What the team did

- Transferred to MICU for high-risk diagnostic BAL KIV intubation
- Was already on piperacillin-tazobactam, so switched to meropenem,
- Added vancomycin, Ambisome



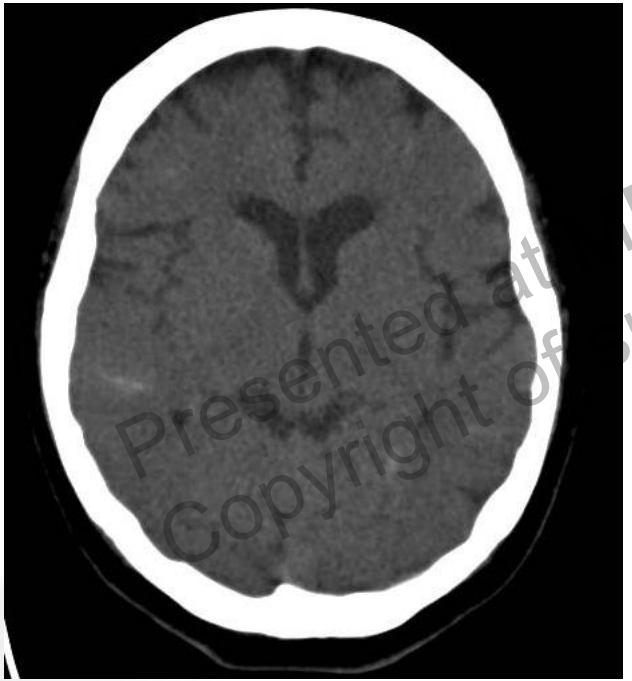
BAL results

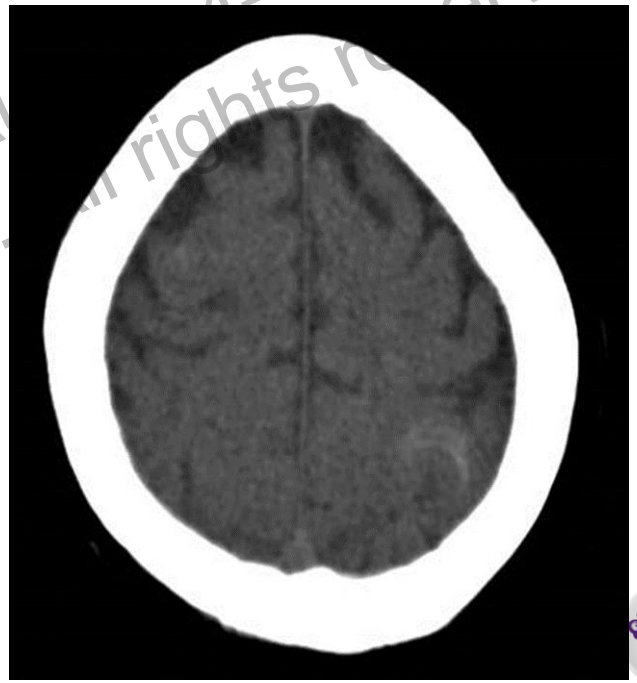
- Serum GM 0.8
- BAL also grew MRSA

Galactomannan Antigen, BAL (for Aspergillus)		
Reporting Information	Date/Time : Microbiologist : Laboratory : SGH Immunology SINGAPORE GENERAL HOSPITAL	
Received Date/Time		
Specimen Comment SPECIMEN: BAL CLINICAL DIAGNOSIS: Severe Pneumonia		
Galactomannan Antigen, BAL (for Aspergillus)	0.81 ↑	[0-0.49 AG INDEX]
Interpretation: < 0.5 : Negative > or = 0.5 : Positive		

Progress

Consciousness dropped





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Should cirrhotics undergo GM or *Aspergillus* PCR screening?

- Yes
- No
- Don’t know

slido

Should cirrhotics undergo GM or Aspergillus PCR screening?

ⓘ Start presenting to display the poll results on this slide.

Invasive aspergillosis in critically ill patients without malignancy

- University Hosp, Leuven, 1/1/2000 – 1/1/2003
- 1700-bed hospital
- 1850 admissions to ICU during study period, 528 deaths (28%)
- 357 of deaths autopsied (68%)
- Aspergillus found in 52 cases (15% of all autopsies)

Meerssemann W et al. *Am J Resp Crit Care Med* 2004;170:621

Invasive aspergillosis in critically ill patients without malignancy

- 38 pts with underlying malignancy (37 haem malig)
  - Mortality 100%
  - Autopsy 30/38
- Invading hyphae seen in 25/30 (83%) autopsies

- 89 pts without malignancy
  - COPD 35 (42%)
  - SOTx 9 (10%)
  - AI disease, with IS 17 (19%)
  - Cirrhosis 6 (7%)
  - Miscellaneous 22 (25%)
    (14/22 – colonization only)

- Mortality 71 (80%)
- Autopsy 46/71
- Invading hyphae (59%) 25/46

Meerssemann W et al. *Am J Resp Crit Care Med* 2004;170:621

Disseminated Aspergillosis Complicating Hepatic Failure

Thomas J. Walsh, MD, Stanley R. Hamilton, MD

(*Arch Intern Med* 1983;143:1189-1191)

- Described 3 cases of disseminated aspergillosis in patients with hepatic failure
  - 9yo boy with unknown etiology; PO prednisolone 20mg for 28 days
  - 50yo lady with halothane induced hepatitis; IV 100mg hydrocortisone for 13 days
  - 66yo lady with alcohol induced hepatitis; PO prednisolone 40mg OM unknown duration
- All died of **pulmonary** and **CNS aspergillosis**

Risk Factors for Invasive Pulmonary Aspergillosis and Hospital Mortality in Acute-On-Chronic Liver Failure Patients: A Retrospective-Cohort Study

Zhejiang U, Hangzhou
1/12/2008 – 1/5/2012

787 pts with ACLF
39 with IPA
48 controls (no pneumonia)

ACLF – defined by APASL guide
IPA -- defined by EORTC guide

	-IPA	+IPA	
Age	37*	43	
HBV	91%	94%	
Hep enceph	61%		4%*
Ascites	32%*	82%	
BSAb	62%*	89%	
Steroids#	25%*	89%	

Logistic regression:
independent risk factors

Age,
Hepatic encephalopathy,
Steroids

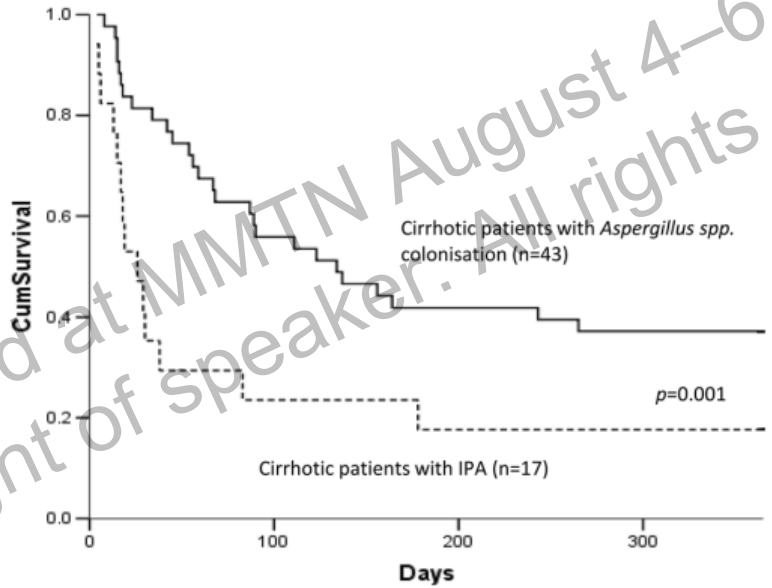
Chen J et al. *Int J Med Sc* 2013;10:1625

10-year experience of IA in cirrhotics in ICU

- Jan 2005 – Dec 2015, Henri Mondor Hosp
- 986 cirrhotics admitted to ICU, 60 had Aspergillus grown from respiratory samples
- 17 (28% of 60) diagnosed with proven/putative IA (Blot criteria)
- 28/986 = 2.8%
- Proven cases diagnosed by lung biopsy, these 2 pts also had cerebral abscesses on CT head
- CT chest – none had halo (whether proven/putative or colonization)
- Serum GM + in 10/12 (83%) of proven/putative cases, 4/30 (13% - 3 of them on PipTazo) of colonized pts
- Concomitant COPD predictive of IA in multivariate analysis
- Survival – see next pg

Levesque E et al. *Ann Intensive Care* 2019;9:31

Cirrhotics with IPA do poorly



Levesque E et al. *Ann Intensive Care* 2019;9:31

GM screening in cirrhotics

- Graz, Austria
- 2x/wk serum GM for all cirrhotics (compensated, decompensated)
- Only 2 “probable” cases

	IA prevalence	Sensitivity	Specificity	Negative predictive value	Positive predictive value
Overall study cohort (n = 150)	2/150 (1.3%)	0.5 (0.09–0.91)	0.97 (0.92–0.99)	0.99 (0.96–0.99)	0.17 (0.01–0.64)
Patients with respiratory symptoms (n = 39)	1/39 (2.6%)	0	0.92 (0.78–0.98)	0.97 (0.84–1)	0
Clinical suspicion for IA (n = 13)	2/13 (15.4%)	0.5 (0.03–0.99)	0.9 (0.54–0.99)	0.9 (0.54–0.99)	0.5 (0.03–0.98)

Prattes J et al. *Med Mycol* 2017;55:803

GM not for screening, for clinical suspicion

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Prattes J et al. *Med Mycol* 2017;55:803

Routinely adding GM to BAL in ICU?

- Hospital Universite Techniscen Munchen
- Study period – all ICU admits who were ventilated underwent BAL (routine GM part of BALF testing protocol); all non-ventilated pts had GM screening 2x/wk
- 84 cirrhotics, 12 (14%) with probable IA (all + in BAL, mean 3.6, range 1.7 – 5.7)
- BAL GM sensi 90%, spec 95%
- IPA group – more likely to need RRT, more likely to have had broad-spectrum antibiotics
- In this study, cirrhotics in ICU with IPA – 100% mortality

Lahmer T et al. *Sc Rep* 2019;9:11919

How to manage IA in patients with poor hepatic function?

- IDSA guidelines 2016, ESCMID-ECMM 2018 guidelines do not mention patients with liver disease

Treating IA in liver disease pts

- ✓ Nanfang Hosp, Guanzhou
- ✓ 20 probable IPA
- ✓ Criteria – EORTC 2008
- ✓ VRC 200mg BD loading, then 100mg OM
- ✓ Troughs 1 – 5
- ✓ 90-day survival 75% (6 of 8 treated)

Gao J et al. Sc Rep 2018;8:876

- ✓ Univ Hosp, Graz
- ✓ 2 "probable" IA
- ✓ Criteria – centre-designed
- ✓ VRC at standard doses
- ✓ Most trough values within range (1 – 5.5)
- ✓ Both survived

Prattes J et al. Med Mycol 2017;55:803

- ✓ Hospital Universite Technischen, Munchen
- ✓ 12 probable IPA
- ✓ Criteria – EORTC 2008
- ✓ 11 pts received LamB, 1 received VRC
- ✓ No mention of trough VRC values
- ✓ 100% mortality

Lahmer T et al. Sc Rep 2019;9:11919

Safer to use lower doses?

- 78 pts with Child's B or C cirrhosis on voriconazole
- Group 1 – manufacturer's recommended dosing or 200mg BD
- Group 2 – 100mg BD
- C_{min} >5: 68% in Group 1, 28% in Group 2
- Incidence of AEs: 26.5% in Group 1, 15.9% in Group 2

Wang T et al. *Int J Infect Dis* 2018;72;49

VRC produces LFT abnormalities in pts with liver disease

- 1999 – 2009, Kings College
- Looked for pts with MELD score >9 who received ≥4 days of VRC
- 29 such pts found (MELD 12 mean); for controls they found 29 similar pts who received LamB
- 20/29 pts (69%) developed LFT changes after staring VRC
- Elevated transaminases in 35%, cholestasis in 17%, mixed pattern in 45%
- ALP rises first, then transaminases, with ALP plateauing or falling (predominant)
- Clinical manifestations: none (8), new-onset rash (5), new-onset jaundice (5), fever (2). 9/20 had eosinophilia >500/uL.
- Likelihood by RUCAM score – high probability
- But none had worsening liver failure (ie, no worsening INR, albumin or encephalopathy)
- In LamB group, only 3 had abnormal LFTs (graded 1 or 2 in terms of severity)

Solis-Munoz P et al. *J Infect* 2013;66:80

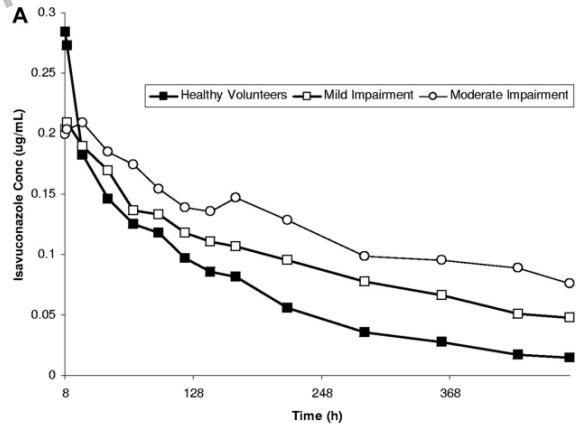
Be very careful with VRC in liver disease

We suggest that even though voriconazole is considered the drug of choice for IA it should be used with caution in patients with severe liver disfunction. We advocate regular monitoring of LFT's. Alternatively, starting treatment with other antifungal agents, such as liposomal amphotericin B, should be considered. There is a clear need for further prospective trials regarding the safety of voriconazole use in this subpopulation and in critical care patients in general.

Solis-Munoz P et al. *J Infect* 2013;66:80

Is isavuconazole an option in cirrhotics?

- Possibly, with TDM[1]
- Clearance decreased, half-life prolonged in pts with liver disease[2]
- There is accumulation with time (trough levels rose to 17 in one study)[1]



From Ref 2.

1 Cojutti PG et al. *Ther Drug Monit* 2023;45:140
2 Schmitt-Hoffmann A et al. *Antimicrob Agents Chemother* 2009;53:4885

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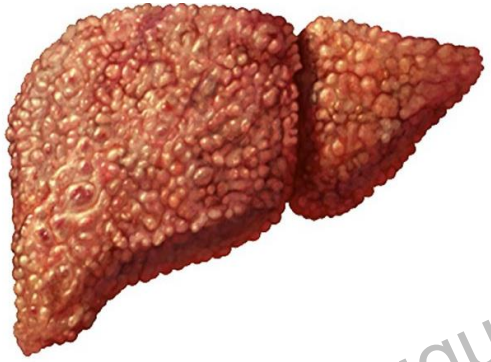

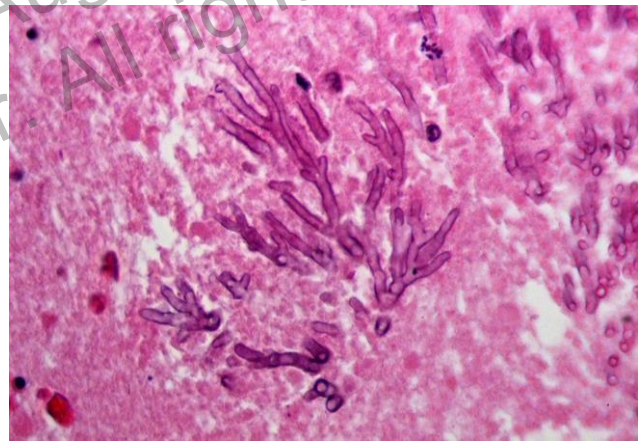

Thank you