ASIA FUNGAL WORKING GROUP
an ISHAM working group

ISHAM
INTERNATIONAL SOCIETY FOR HUMAN AND ANIMAL MYCOLOGY

Co-organized with:

MMTN
MEDICAL MYCOLOGY TRAINING NETWORK

MMTN INDONESIA 2025

October 4 – 5, 2025
Manado, Indonesia

ASIA FUNGAL WORKING GROUP
an ISHAM working group

ISHAM
INTERNATIONAL SOCIETY FOR HUMAN AND ANIMAL MYCOLOGY

Co-organized with:

MMTN
MEDICAL MYCOLOGY TRAINING NETWORK

ATUL K PATEL *MD, FIDSA*

Infectious Diseases Consultant, Ahmedabad. India

Invasive aspergillosis – Updates in 2025

Spectrum of Aspergillosis

ABPA
Asthma with fungal sensitization

Hypersensitivity to inhaled airborne conidia

Aspergillus ball (Aspergilloma)
Chronic Pulmonary Aspergillosis (CPA)

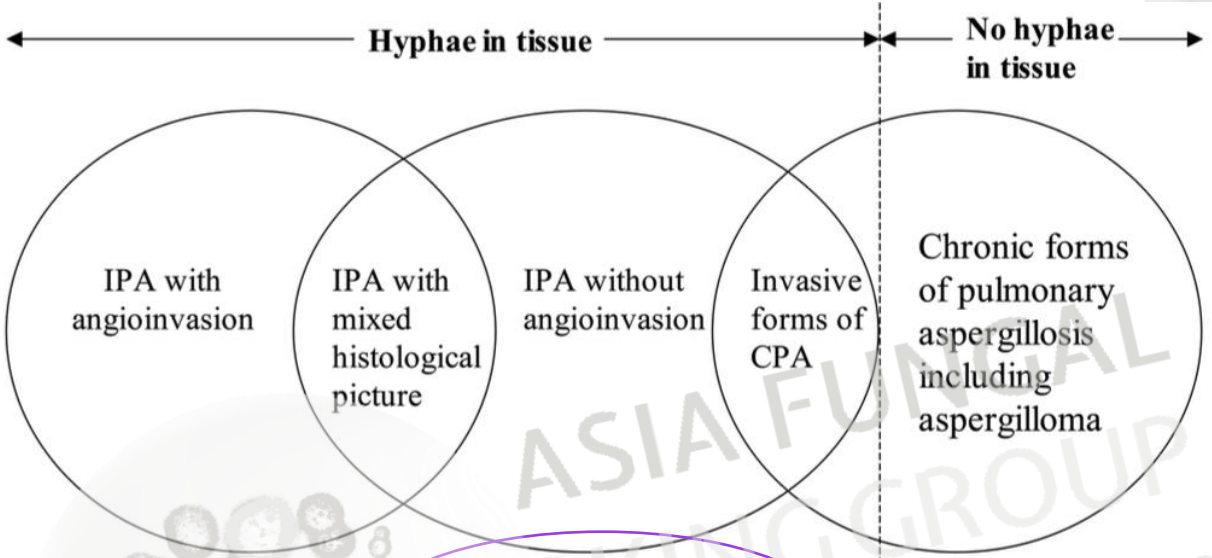
Structural lung disease

Invasive Aspergillosis

Immunocompromised

Cutaneous Disease: Trauma, burns
Ocular: traumatic, surgery
Tracheobronchitis: Lung transplant recipients, Influenza
Sinus Disease

MMTN MEDICAL MYCOLOGY TRAINING NETWORK



Pathology	Angioinvasion, coagulative necrosis, haemorrhagic infarction	No angioinvasion, pyogranulomatous inflammation, inflammatory necrosis	No angioinvasion, hyphae confined to pre-existing lung cavity
Host	Prolonged and profound neutropenia	Non-neutropenic with CGD, corticosteroid therapy, HIV/AIDS, non-neutropenic HSCT recipients, GVHD	Pre-existing structural lung disease, minor immunological defects
Time-course	Days-weeks	Weeks-months	Months-years

Kosmidis C, et al. Thorax 2015;70:270–277. doi:10.1136/thoraxjnl-2014-206291

Risk Factors: IPA

Classical Risk factors

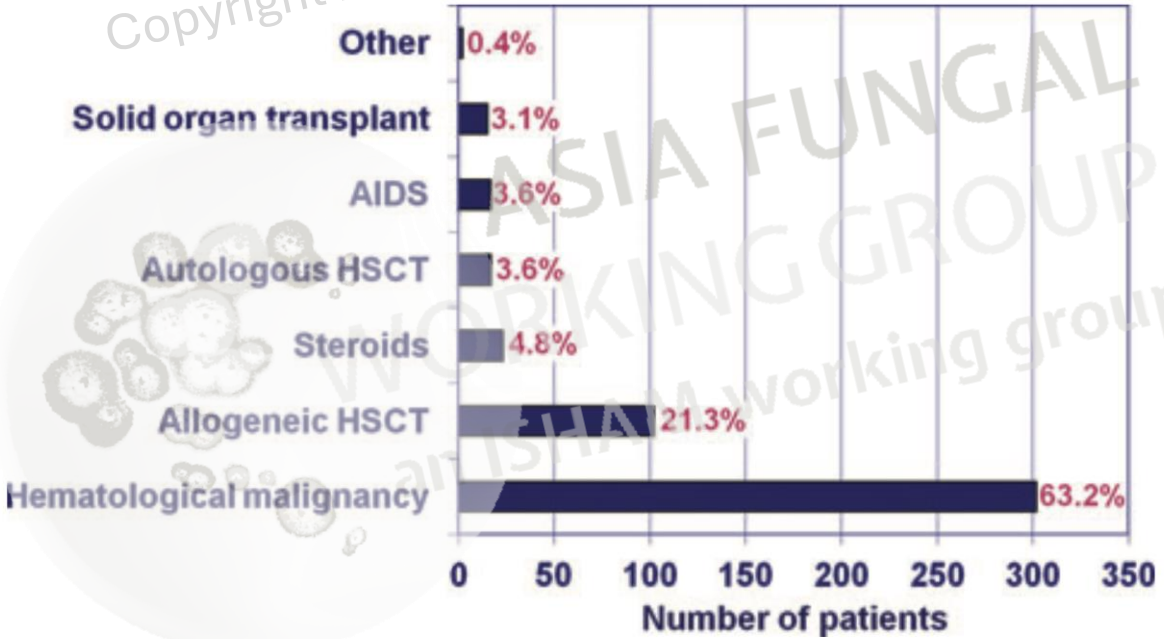
- Neutropenia
- HSCT
- GVHD
  - Steroid therapy
- SOT- Steroids/ immunosuppressive treatment
- Brutone's tyrosine kinase inhibitor (Ibrutinib)
- CART T cell therapy
  - Cytokine storm

Nontraditional risk factors

- ICU patients with COPD, ARDS receiving steroids, CLD
- Viral respiratory infections: Influenza, RSV, COVID-19

Kosmidis C, et al. Thorax 2015;70:270–277. doi:10.1136/thoraxjnl-2014-206291, Ann. N.Y. Acad. Sci. 1272 (2012) 23–30

Host factors in Voriconazole and Ambiload trials: n= 478



Cornely, O.A. (AmBiLoad trial). Clin. Infect. Dis: 2007; 44: 1289–1297. Herbrecht, R. N. Engl. J. Med.: 2002; 347: 408–415.

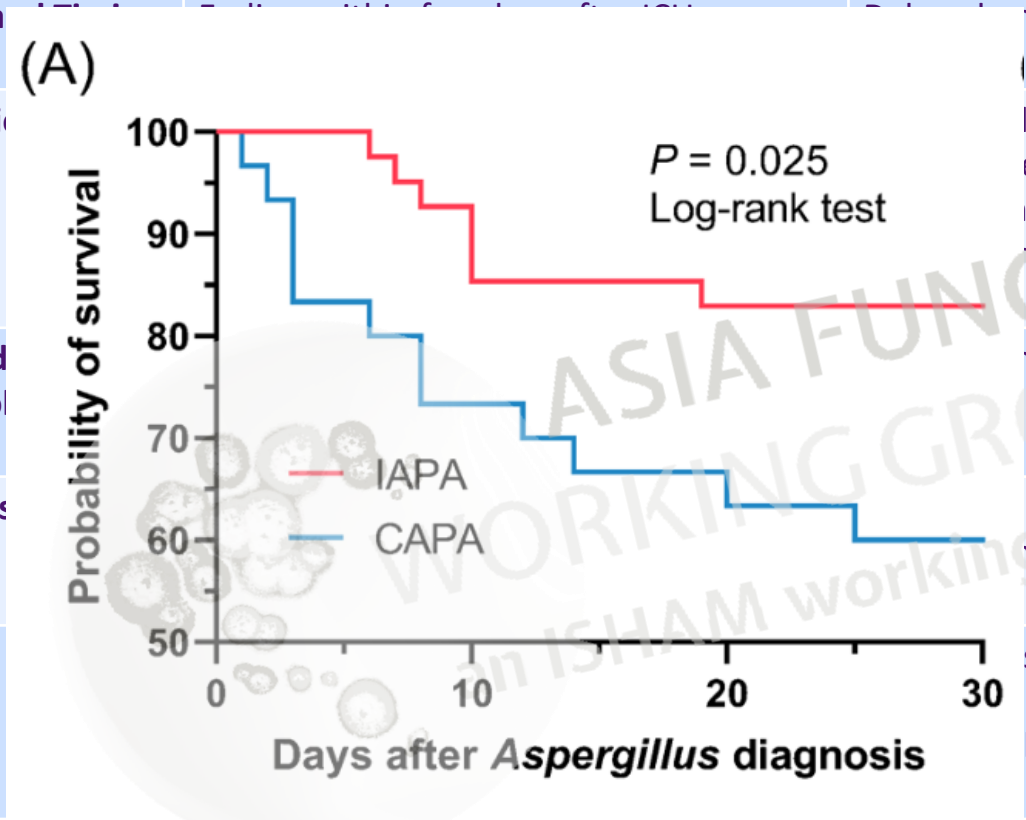
IAPA and CAPA

- IAPA and CAPA
  - Complications in critically ill patients with viral pneumonia

	IAPA	CAPA
Incidence and Timing	Earlier- within few days after ICU admission	Delayed onset- weeks
Pathophysiology	• More profound neutrophil dysfunction and early angioinvasion. • Pronounced downregulation of genes involved in antifungal effector functions compared to CAPA	• Epithelial barrier disruption • Impaired type I interferon responses, and T/B cell exhaustion • Less prominent angioinvasion
Clinical and Histopathologic Features:	• Extensive tracheobronchial involvement Early angioinvasion	• Less angioinvasion and more subtle or delayed tissue invasion
Risk Factors	• Strongly associated with pre-existing chronic pulmonary disease • Prior immunosuppression	• Linked to older age, corticosteroid or immunomodulatory therapy during COVID-19 management
Diagnosis	• Diagnostic criteria and sensitivity of mycological tests (e.g., GM in BAL) are similar • CAPA is more often classified as "putative" rather than "proven/probable" due to challenges in confirming tissue invasion	
Outcomes	Both are associated with high mortality	Higher in-hospital and 30-day mortality for CAPA compared to IAPA

Feys S, Lancet Respir Med. 2024 Sep;12(9):728-742., Zhao J, Eur J Clin Microbiol Infect Dis. 2024 Apr;43(4):683-692.

	IAPA	CAPA
Incidence a		set- weeks
Pathophysi		lial barrier disruption ed type I interferon ses, and T/B cell exhaustion ominent angioinvasion
Clinical and Histopathol Features:		gioinvasion and more or delayed tissue invasion
Risk Factors		to older age, corticosteroid unomodulatory therapy COVID-19 management
Diagnosis		sts (e.g., GM in BAL) are han "proven/probable" due
Outcomes	Both are associated with high mortality	Higher in-hospital and 30-day mortality for CAPA compared to IAPA



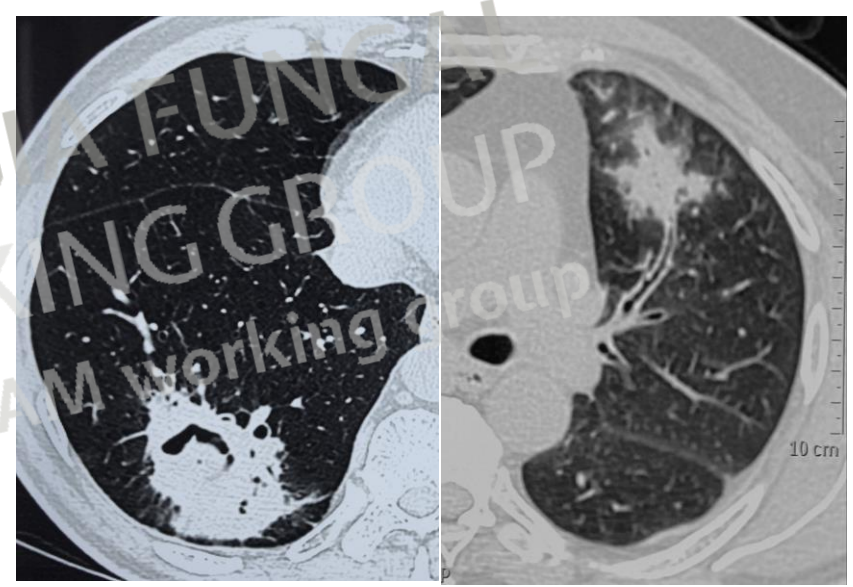
Feys S, Lancet Respir Med. 2024 Sep;12(9):728-742., Zhao J, Eur J Clin Microbiol Infect Dis. 2024 Apr;43(4):683-692.

Challenges in IA diagnosis

- Basic microbiological tests **direct microscopic exam**, **culture** and **Histopathology** are corner stone in IFI diagnosis
  - Culture is frequently sterile
  - Direct microscopy: rarely requested from the biopsy/ needle aspiration sample
  - Histopathology: Difficult to get tissue sample in hematological patients, deep seated inaccessible lesion, helpful in confirm diagnosis, need expertise and special stain
- Fungal Biomarkers
  - Interpretation of fungal biomarkers is tricky
- Molecular techniques: High sensitivity/ cost, TAT, many a times difficult to interpret, needs further standardization
- Radiology: HRCT is preferred, consider CTPA for angioinvasion

Radiological Diagnosis: Findings suggestive of IFI

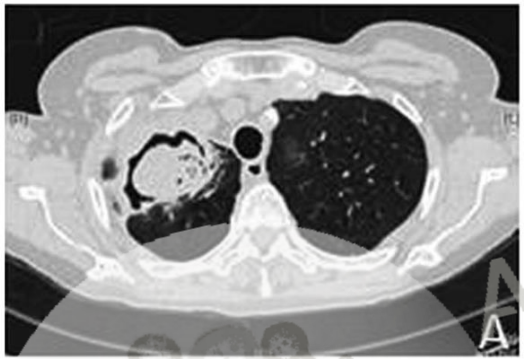
- Dense, well-circumscribed lesions (with or without halo sign)
- Cavitation
- Air crescent sign
- Wedge-shaped or lobar consolidation
- Reversed halo sign may suggest pulmonary mucormycosis



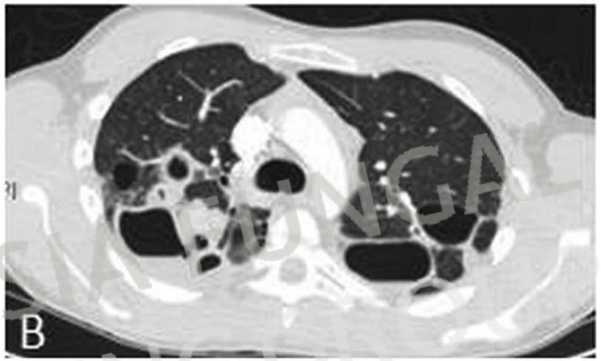
Images from personal collection

MMTN
MEDICAL MYCOLOGY TRAINING NETWORK

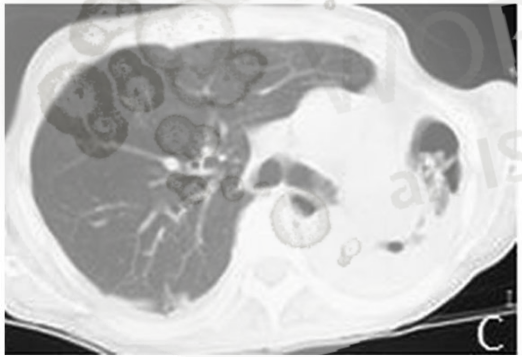
CT scans from patients with various forms of CPA



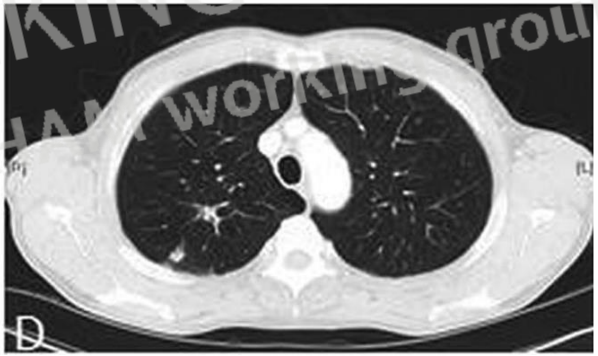
(A) Simple aspergilloma;



(B) Chronic cavitary pulmonary Aspergillosis



(C). Chronic fibrosing pulmonary aspergillosis



(D) Aspergillus nodule.

Kosmidis C, et al. Thorax 2015;70:270–277. doi:10.1136/thoraxjnl-2014-206291

Diagnosis of IPA: Case vignette

- 38 years female, post renal transplant (2 years),
  - Stable immunosuppression (pred 5mg, TAC and MMF)
  - Developed DM after Tx
- Admitted with Lt MZ multiple nodular, conglomerating lesions
- Persistent fever, cough with scant expectoration despite Ceftriaxone/Azithro for 5 days

Case continued

- Further laboratory work up : WBC: 5700, DC: 82/14/2/2, CRP 3 X ULN, SGPT 47 IU/L, Creatinine: 1.38 mg/dL
- S. Galactomannan: 0.4 index
- S. BDG: 104 pg/ml (Fungitell)

- ID reference was done?

Galactomannan in non-neutropenic

- **Serum GM:**
  - Meta-analysis (27 studies): Overall sensitivity of **S. GM of 71% and specificity of 89%**
  - Sensitivity and specificity of the test **dropped to 22% and 84%,** when onco- hematological patients were excluded
  - IA in non- neutropenic patients: a sensitivity of serum GM of 37.8% and a specificity of 87.1%, with a positive predictive value of 60.8%

Pfeiffer CD, Clin Infect Dis. 2006;42:1417–27, Zhou W, Li H, Zhang Y, et al. J Clin Microbiol. 2017;55:2153–61, Guinea J, Mycopathologia. 2014;178:403–16.

Meta-analysis of S. GM in different subgroups

Subgroups	Sensitivity	Specificity	PLR	NLR
Cutoff				
0.5	0.78–0.79	0.85–0.86	5.20–5.64	0.24–0.26
1.0	0.65–0.71	0.90–0.94	6.50–11.83	0.31–0.39
1.5	0.48–0.63	0.93–0.95	6.86–12.60	0.39–0.56
Population				
HM	0.58	0.95	11.60	0.44
HSCT	0.65	0.65	1.86	0.54
SOT	0.41	0.85	2.73	0.69

Mercier T. Galactomannan Thresholds in Invasive Fungal Disease Clin Infect Dis 2021:72 (Suppl 2), S89

Meta-analyses of the BAL GM in Subgroups

Subgroups	Sensitivity	Specificity	PLR	NLR
Cutoff				
0.5	0.82–0.87	0.89–0.92	7.45–10.88	0.14–0.20
1.0	0.75–0.86	0.94–0.95	12.50–17.20	0.15–0.27
1.5	0.70–0.92	0.95–0.98	14.00–46.00	0.08–0.32
2.0	0.61–0.84	0.95–0.96	12.20–21.00	0.17–0.41
HM				
Yes	0.85	0.91	9.44	0.16
No	0.87	0.89	7.91	0.15
Antifungal Rx/Prophylaxis				
Yes	0.76–0.85	0.89	6.91–7.73	0.17–0.27
No	0.91	0.88	7.58	0.10

Mercier T. Galactomannan Thresholds in Invasive Fungal Disease Clin Infect Dis 2021:72 (Suppl 2), S89

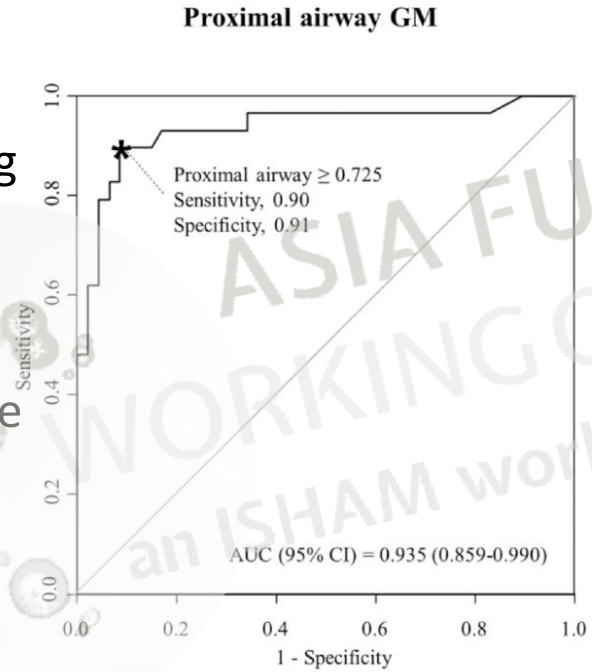
Non neutropenic settings

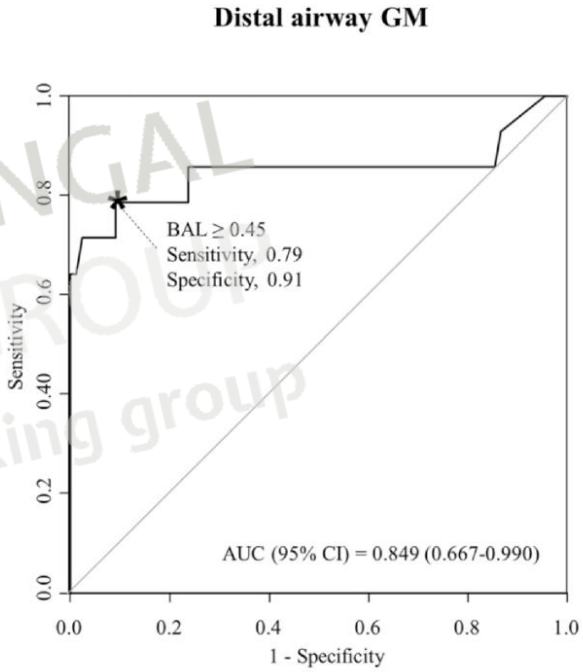
- BAL galactomannan is desirable

- Sputum examination: 25-30 pus cells, KOH: no fungal elements, Fungal and bacterial culture sterile at 48 hours
- Sputum Galactomannan: 2.63 index

Can we perform Galactomannan from Sputum?

Overall sensitivity & specificity of GM testing using proximal airway (induced sputum and tracheal aspirate) samples are comparable to distal airway (BAL) samples





Chun, June Young et al. Journal of Infection, Volume 88, Issue 6, 106159, Nuh A, J Fungi (Basel). 2022 Feb 14;8(2):188.

MMTN
MEDICAL MYCOLOGY TRAINING NETWORK

Is this Pulmonary Aspergillosis?

- Yes
- No
- May be
- Not Sure

MMTN
MEDICAL MYCOLOGY
TRAINING NETWORK

Clinical Infectious Diseases
MAJOR ARTICLE

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

J. Peter Donnelly,[1] Sharon C. Chen,[2] Carol A. Kauffman,[3] William J. Steinbach,[4] John W. Baddley,[5] Paul E. Verweij,[6] Cornelius J. Clancy,[7] John R. Wingard,[8]

Proven IFD

Fungus	Microscopy: Sterile material	Culture Sterile material	Serology	Molecular testing
Mold	Histo/Cyto/Direct microscopic exam of material obtained by biopsy/ needle aspiration, fungus +/- tissue damage	Culture from a material obtained from a sterile site with clinical/ radiological evidence of disease, Excluding BAL, PNS, Mastoid and urine	NA	From Formalin fixed paraffin block
Yeast	Same as above except mucous membrane	Same/ blood culture	CrAg	Same as above
PCP	Tissue, BAL and expectorated sputum	NA	NA	NA
Endemic Mycosis	Specimen from affected site	Specimen from affected site/ blood culture	NA	NA

Peter Donnelly. Clin. Infect. Dis 2020:71 (15 September) ;1367-76

Probable IFD: EORTC/MSG

Host Factor	Clinical Features	Mycological Features
• Immunocompromised Neutropenic, Hematological malignancy, HSCT, SOT • Immunosupp. treatment T cell/B cell depletion (Ibrutinib) • Primary immune deficiency: CGD, STAT-3, Severe combined immunodeficiency	CT scan features for IPA/PM Tracheobronchitis Sino-Nasal disease CNS Infection: FND/ MRI features	Any mold grew or direct microscopy positive from BAL, Sputum, Tracheal Aspirate Positive Galactomannan from Serum/plasma, BAL, CSF Single GM > 1.0 Aspergillus PCR Two consecutive PCR positive from blood/ BAL One each from Blood/ BAL

Peter Donnelly. Clin. Infect. Dis 2020:71 (15 September) ;1367-76

Our patient's diagnosis

- **Host factor:** SOT
- **Clinical features:** Yes
- **Mycological features:** Sputum GM, negative direct microscopy, culture sterile

- **Final diagnosis:** Probable invasive pulmonary Aspergillosis in Post Renal Tx patient

IFI Diagnosis

- **Combining diagnostic assays**: Overcome the limitations of any individual test
- **High Risk patients:** Weekly serum galactomannan testing or a serum or whole-blood PCR assay
  - Single positive result : S. GM testing, 92%; PCR assay, 84% sensitivity
  - When the two tests were used concurrently and either one was positive, the sensitivity increased to 99%
  - When both tests were positive in the same patient, the specificity increased to 98%

Thompson GR 3rd. N Engl J Med. 2021 Oct 14;385(16):1496-1509.

Prognosis of Invasive Aspergillosis

- **Baseline S. GM and GM kinetics**: Prognostic value
- Increased mortality: S. GM higher than the baseline and remains elevated over time
- Increase in S. GM index of more than 0.25 from baseline suggestive of poor outcomes

Thompson GR 3rd. N Engl J Med. 2021 Oct 14;385(16):1496-1509.

Antifungal Resistance

- Rising azole resistant A. Fumigatus in Europe
- Variable susceptibility to antifungal agents
- A. terreus is infrequently susceptible to amphotericin B
- A. calidoustus and A. lentulus are resistant to multiple antifungal agents, including amphotericin B and voriconazole.

Thompson GR 3rd. N Engl J Med. 2021 Oct 14;385(16):1496-1509.

Treatment of Aspergillosis

- Voriconazole, isavuconazole, and posaconazole
- Both isavuconazole and posaconazole are non-inferior to voriconazole
- TDM is required for the voriconazole and posaconazole
- Lipid formulation amphotericin B: Reserved agent
- Echinocandins are **NOT** recommended as initial monotherapy
  - Can be consider as a combination therapy with voriconazole in selected cases
- Newer Agents: SUBA itraconazole, Rezafungin, Fosmanogepix, Olorofim, ibrexafungerp
- Azole resistant: Lipid formulation of Amphotericin B, Echinocandins in combination, newer agents

Thompson GR 3rd. N Engl J Med. 2021 Oct 14;385(16):1496-1509.

Take home message

- Aspergillosis have different presentations in different hosts
- Diagnosis of IA is challenging
- Combination of tests improves the sensitivity and specificity
- EORTC/MSG diagnostic criteria are also useful in clinical practice
- Azoles (Voriconazole/ Isavuconazole) are drug of choice
- Azole resistant Aspergillus is reported from Europe and other parts of the world

Thank you.

MMTN
MEDICAL MYCOLOGY
TRAINING NETWORK