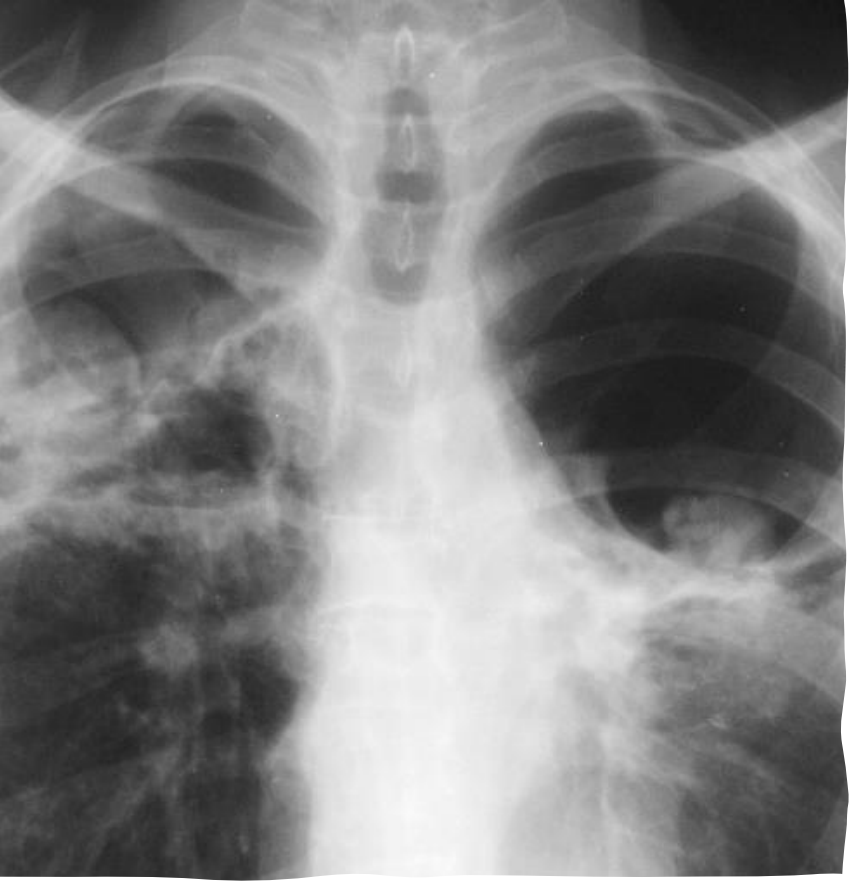
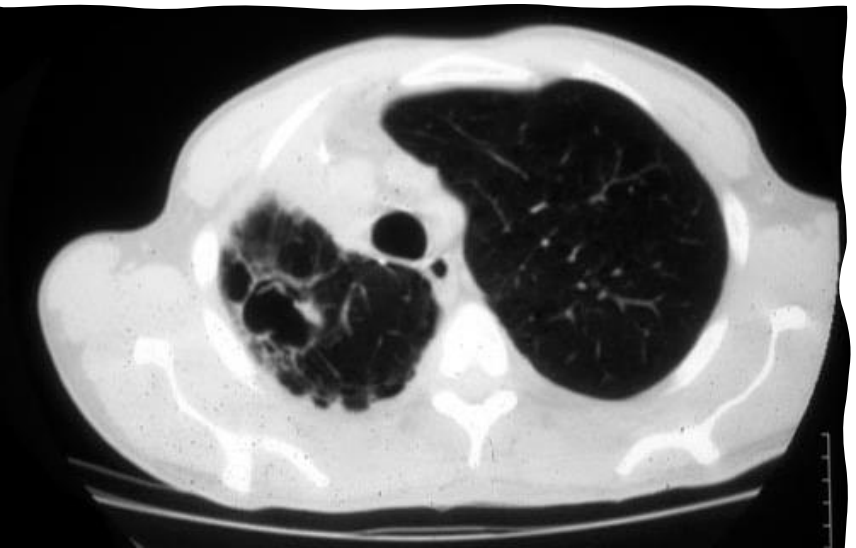


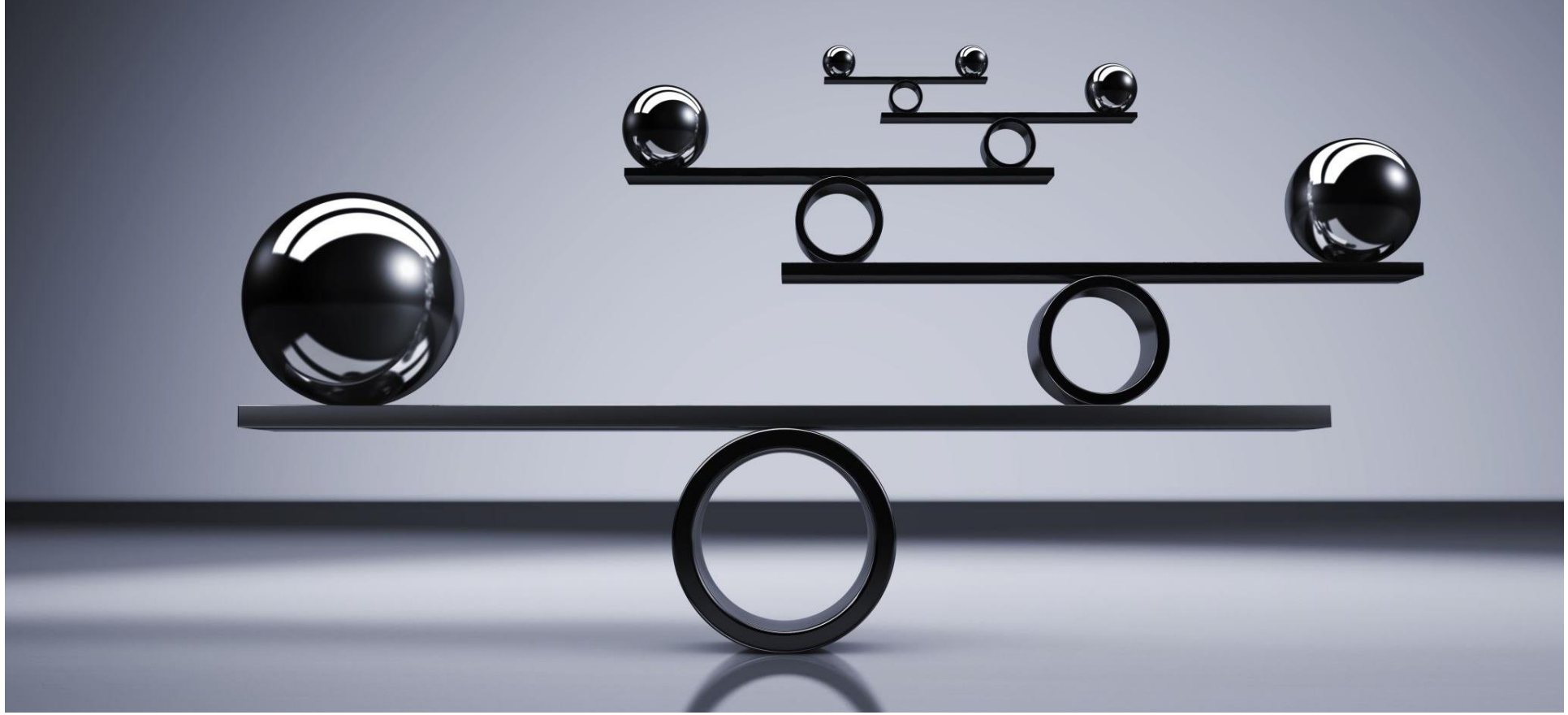


Is Chronic Pulmonary Aspergillosis A Minor Chest Problem or Can It Be Lethal?

Prof. Muhammad Irfan

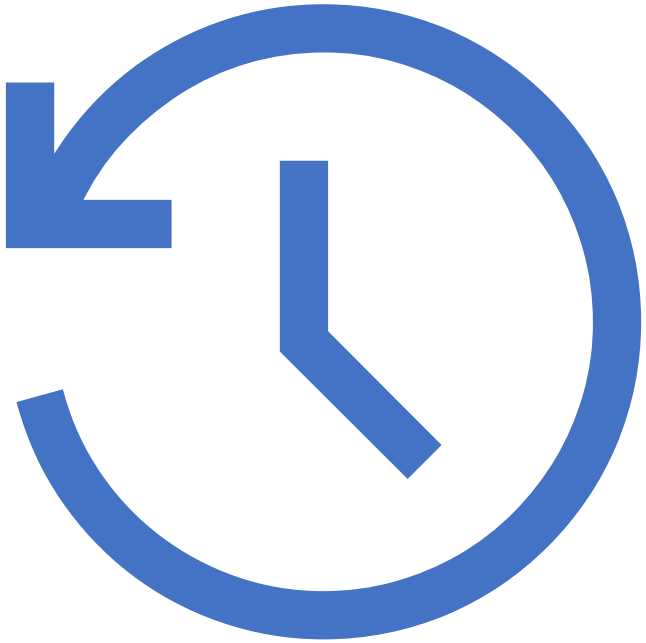
MBBS, FCPS (Med), FCPS (Pulm), FRCP(Edin), FHEA

Aga Khan University, Karachi-Pakistan



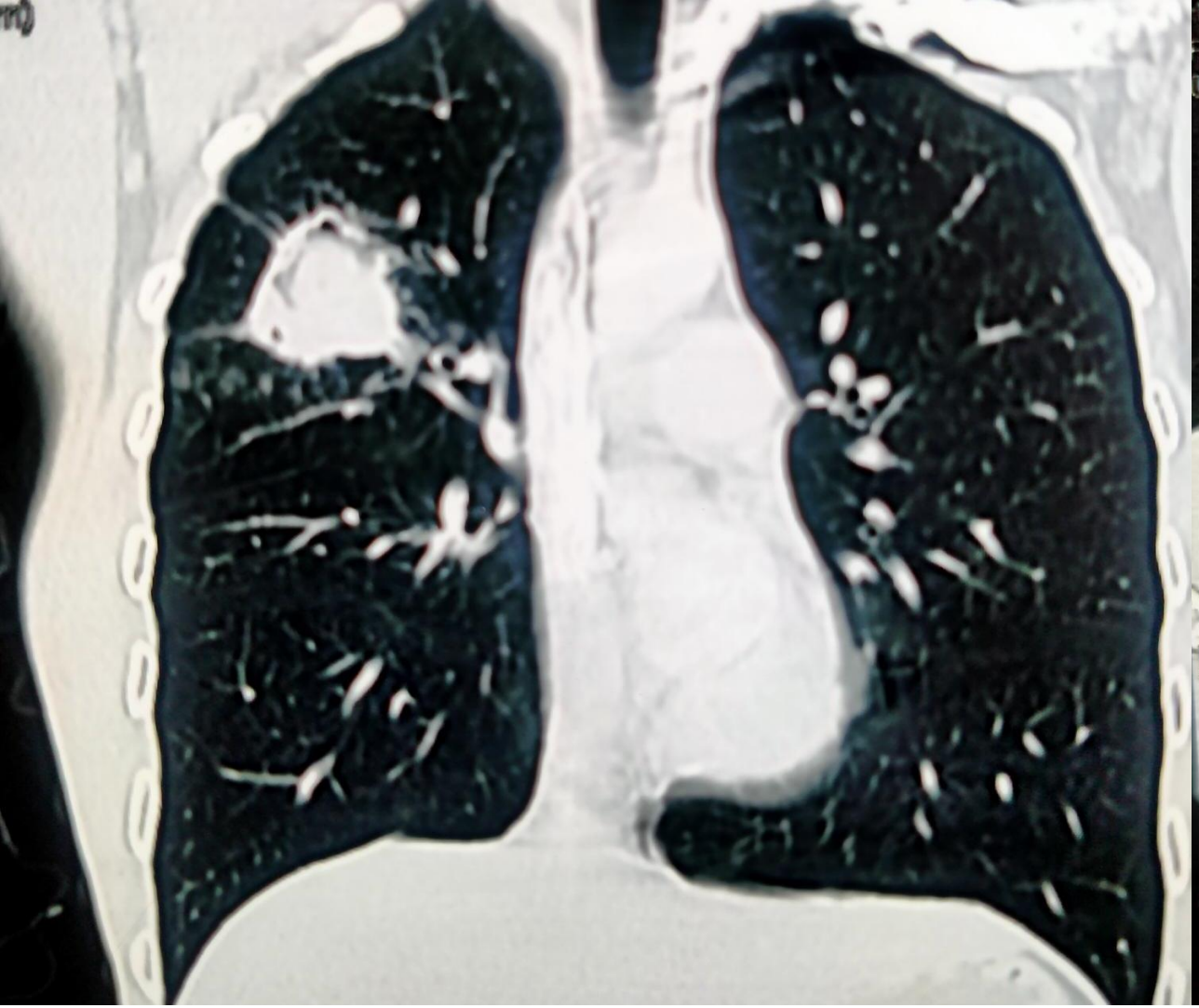
Conflict of interest

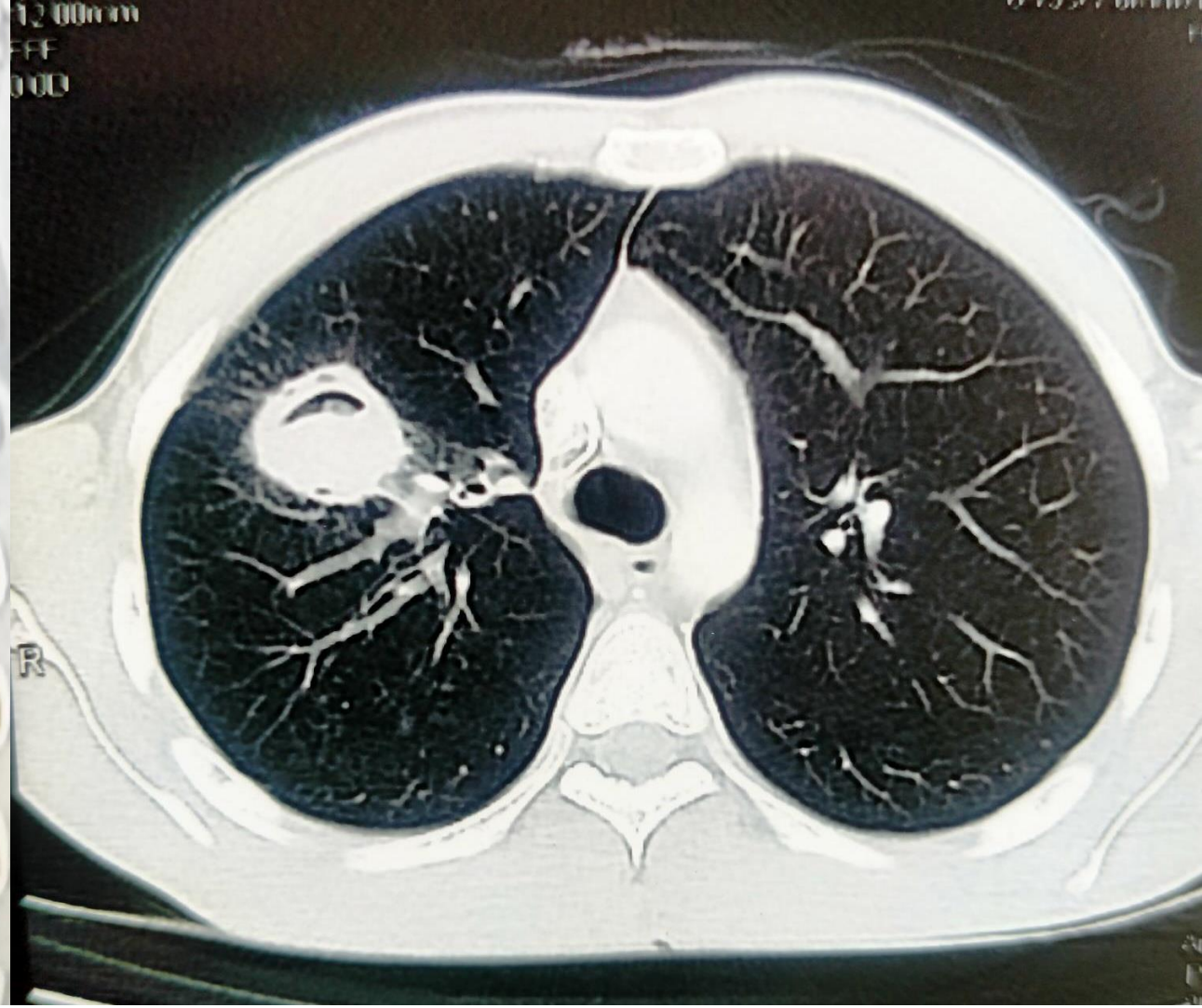
None to declare



Overview

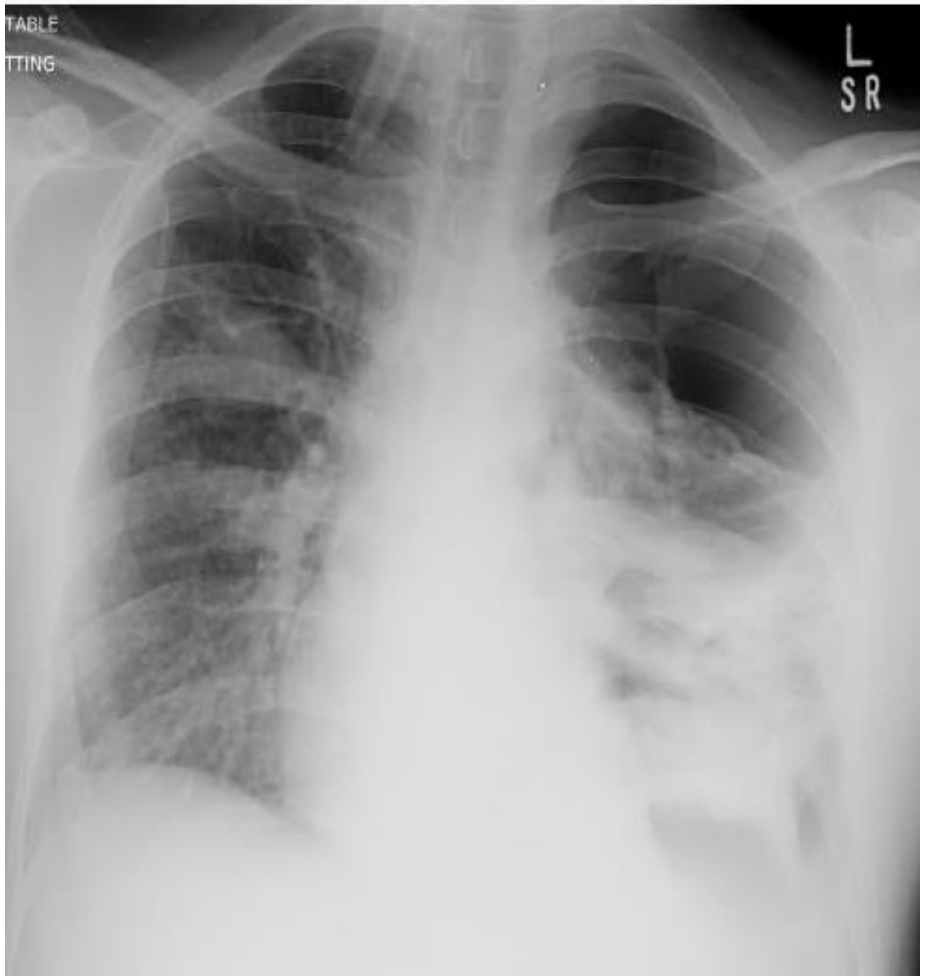
- Clinical cases
- Global burden of CPA
- Diagnosis
- Treatment
- Outcome
- Predictors of relapse & mortality

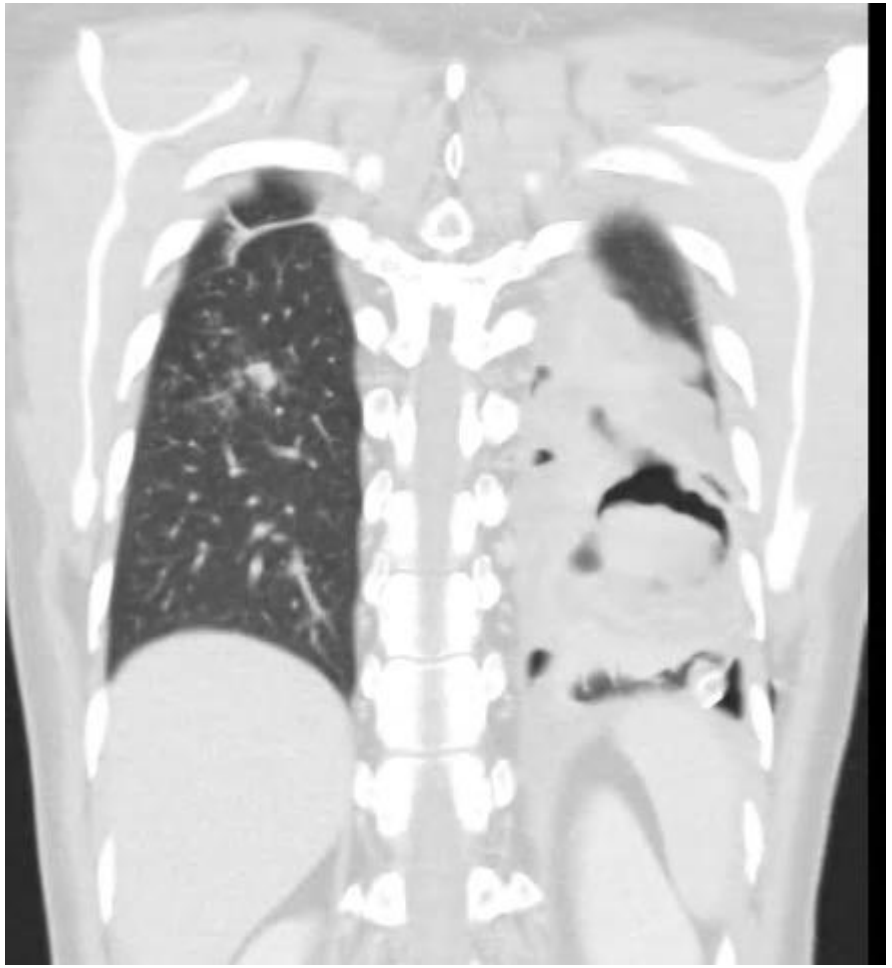




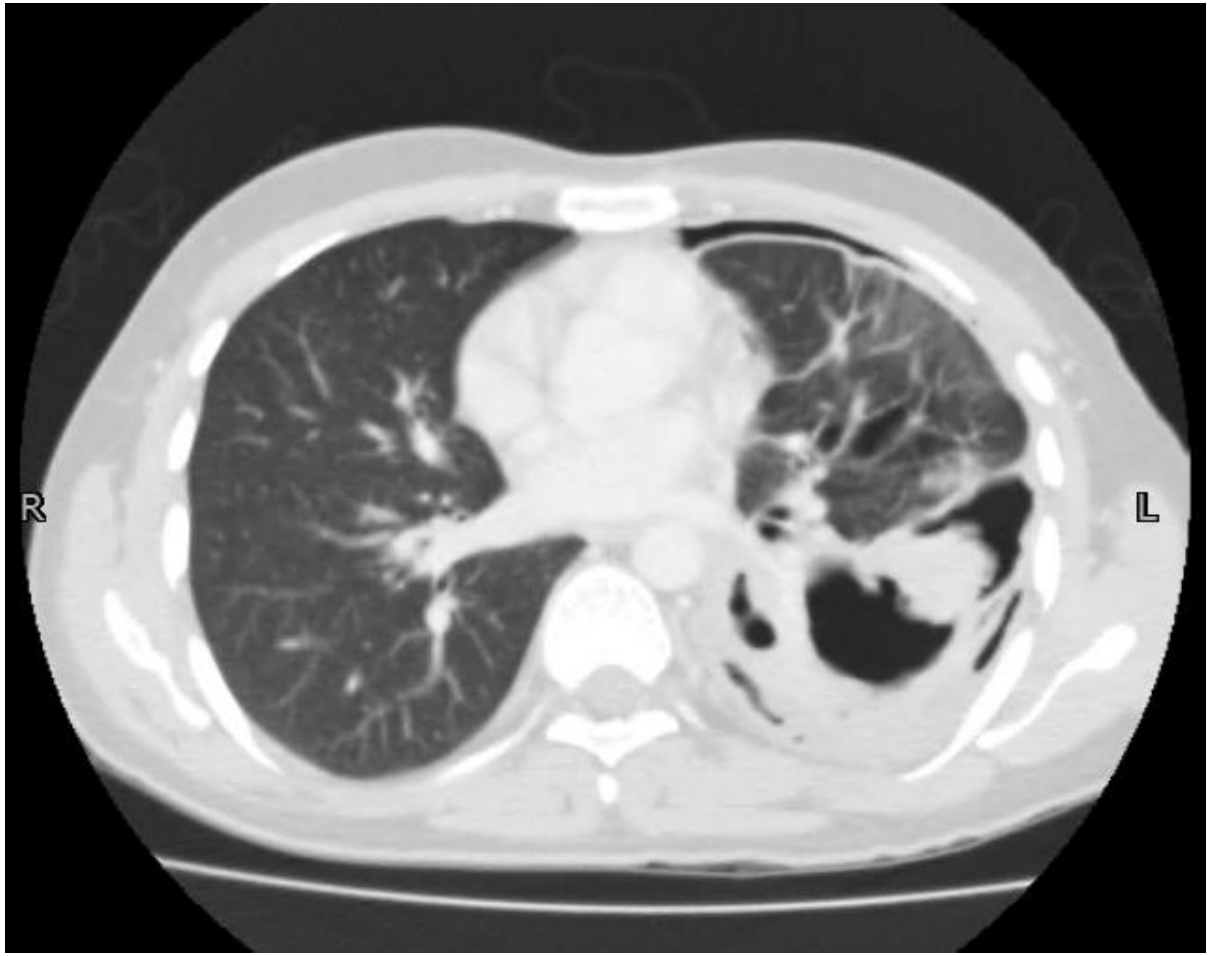
20- year male nursing student with massive hemoptysis

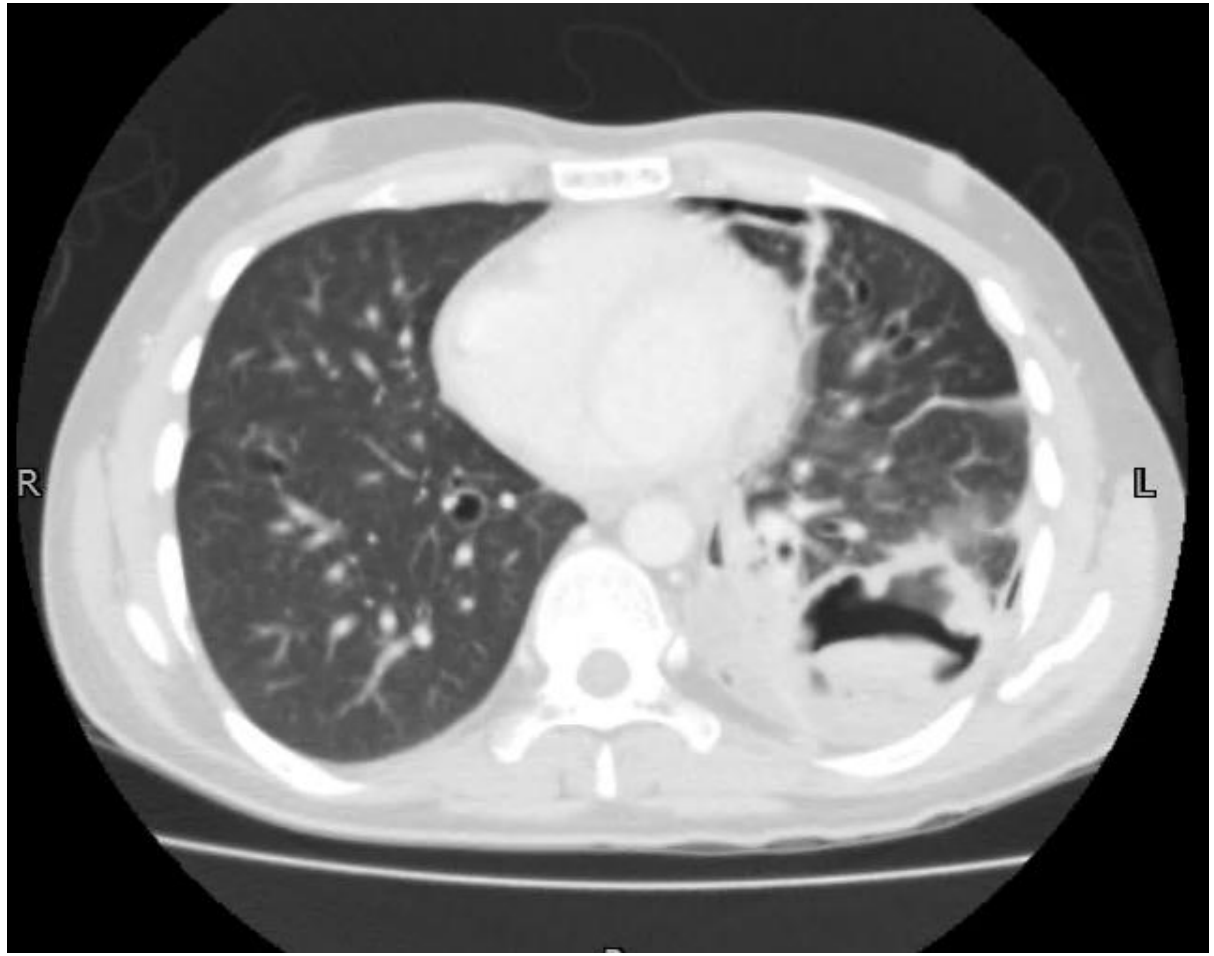
30 years male with Asthma presents with severe dyspnea and left sided chest pain



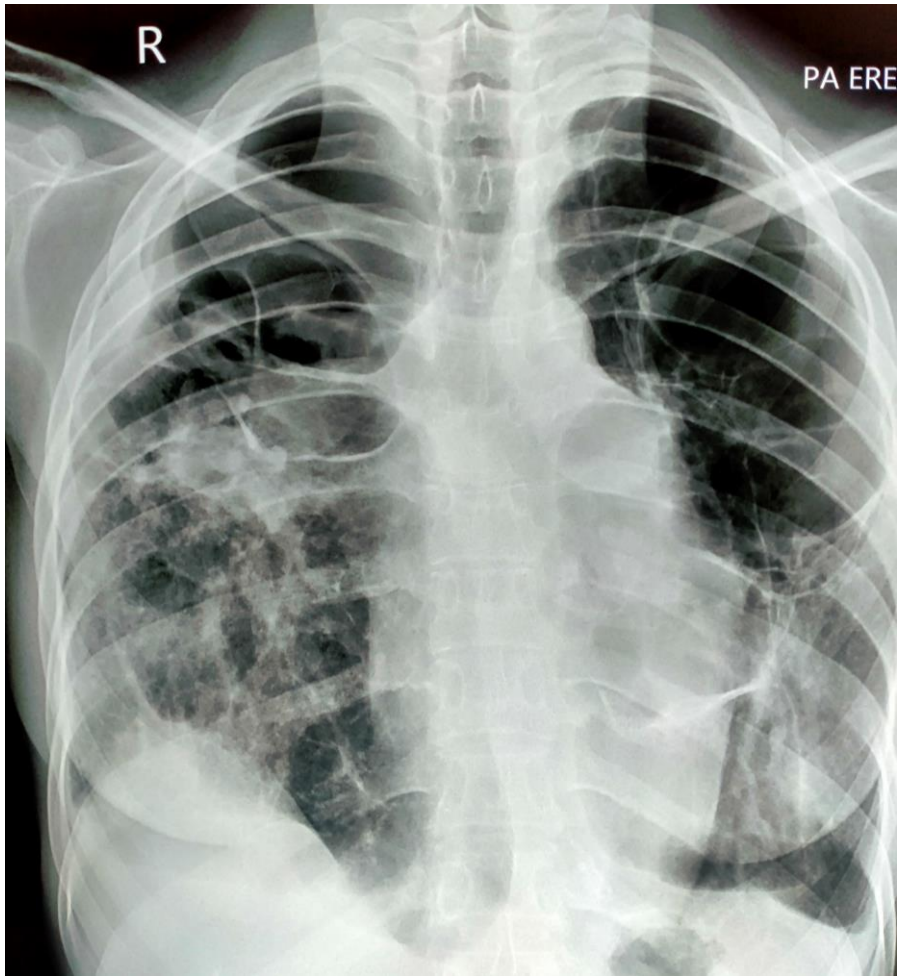


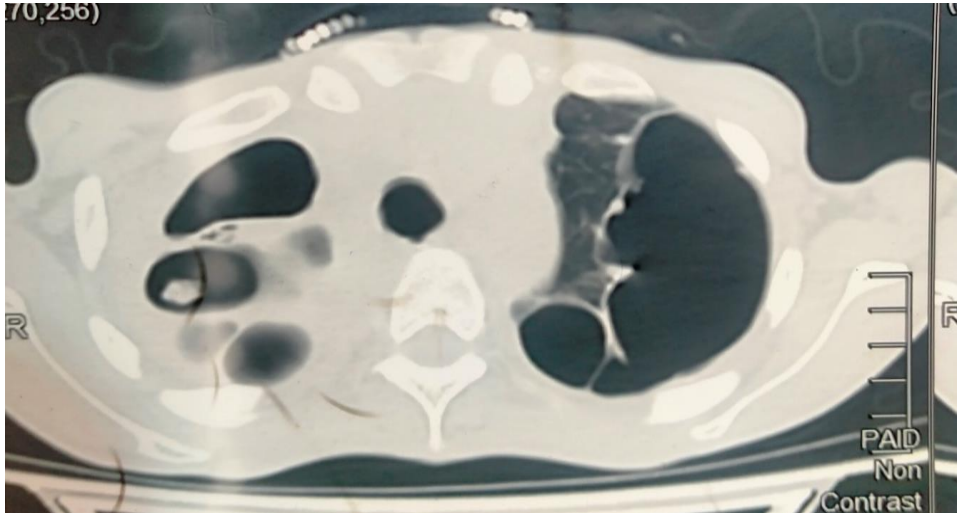
30 years male with Asthma presents with severe dyspnea and left sided chest pain

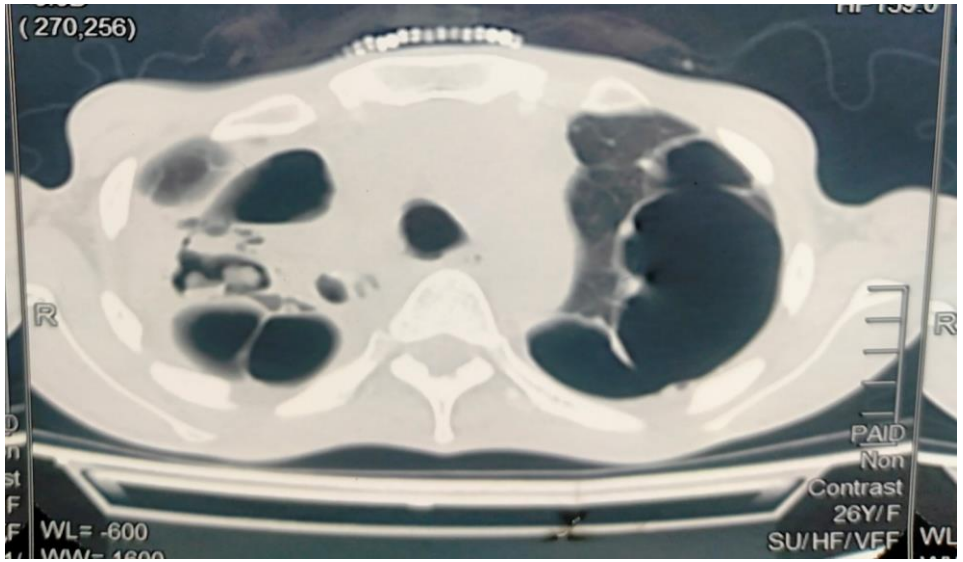




26 years female with a history of TB 5-years ago presented with Respiratory failure







CPA has now been recognized as a significant global health burden

Globally, approximately 6.1 million people suffer from CPA, with an annual incidence of 1.83 M (23.6 per 100,000 population)

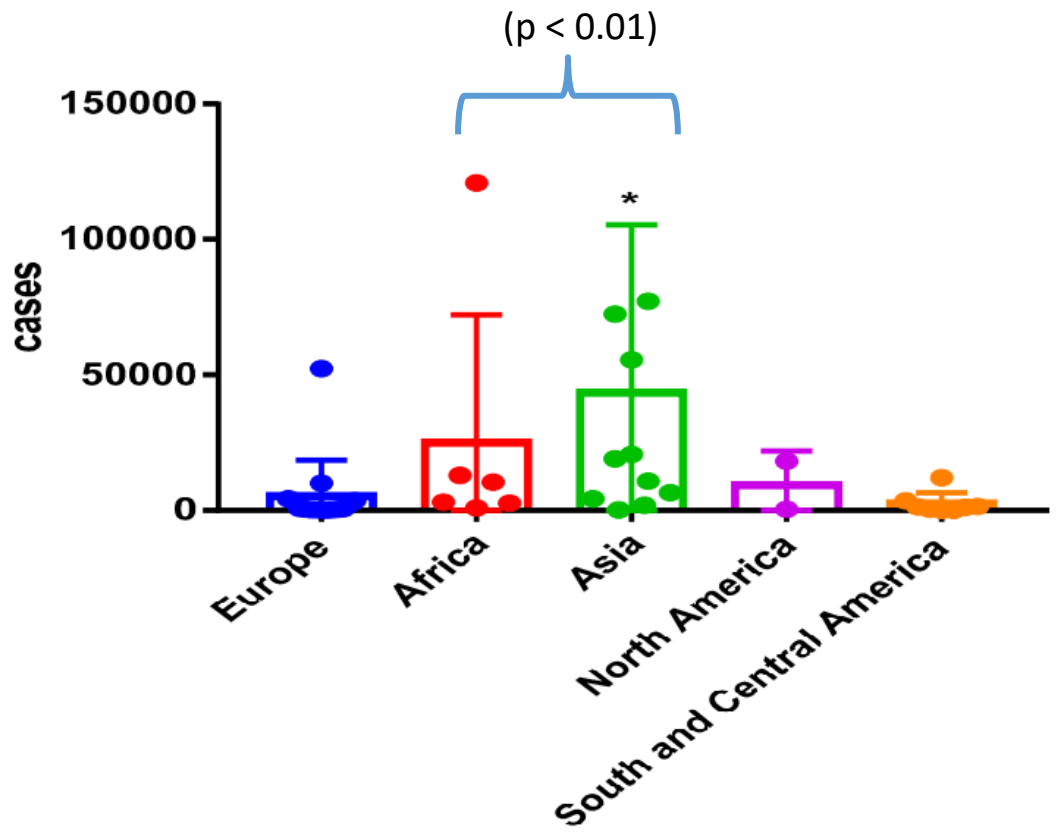
The annual estimated crude mortality : 340,000

Attributable death: 204,000

If untreated 50-80% of patients with CPA will die within 5 years

Denning DW lancet ID; 2024 (In press).
Ekeng BE et al. J Fungi . 2022; 8: 460

Global Burden of CPA



- The highest burden of CPA has been reported in India (209,147) followed by Nigeria (120,753), Philippines (77,172), Pakistan (72,438) and Vietnam (55,509)

Bongomin F, Denning D et al J. Fungi 2017, 3, 57

Risk Factor/ Underlying Disease

TB	76 (21.0)
NTM	37 (10.2)
COPD	145 (40.1)
Asthma	73 (20.2)
ABPA	44 (12.2)
Pneumonia	79 (21.8)
Pneumothorax	52 (14.4)
Bronchiectasis	55 (15.2)
Sarcoidosis	22 (6.1)
Inflammatory arthritis	34 (9.4)
Thoracic surgery[#]	56 (15.4)
Lung cancer survivor	22 (5.7)
Other	25 (6.9)

Lowes et al, Eur Resp J 2017 49: 1601062

Frequency of TB underlying CPA - globally

- Japan: 50% (Ohba et al 2011)
- China: 71% (Chen et al 2012)
- Korea: 81% (Jhun et al 2011)
- UK: 21% (Lowes et al2017)
- Senegal: 100% (Ba et al 2000)
- Pakistan: 86.6% (Iqbal et al 2020)

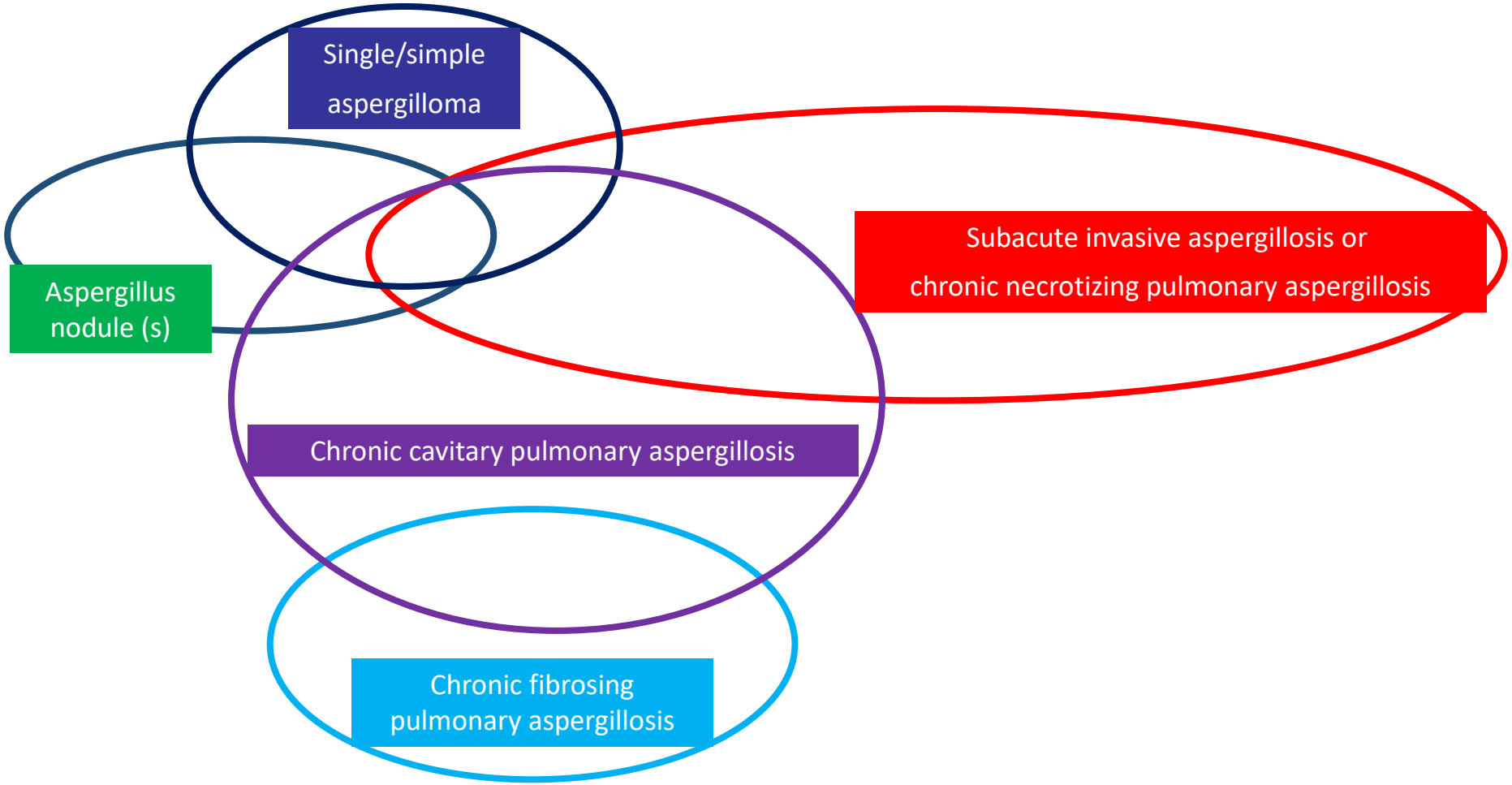
CPA - symptoms

- **<u>Common symptoms</u>**
- Cough
- Weight loss
- Tiredness
- Hemoptysis
- Chest pain / discomfort
- Shortness of breath

Some patients have no symptoms or minimal symptoms – CPA can be a very 'quiet' condition

- **<u>Occasionally</u>**
- Fever
- Severe chest pain
- Recurrent chest infections

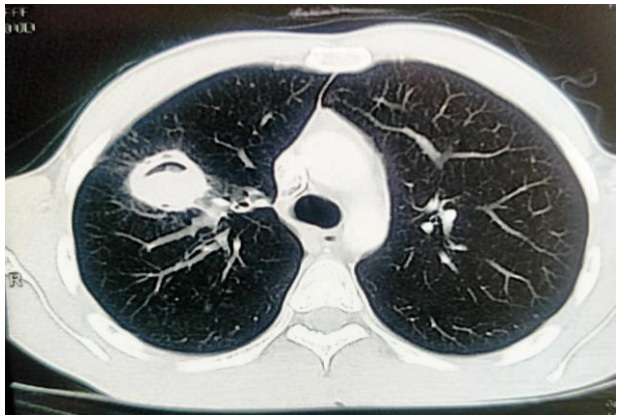
Different forms of CPA



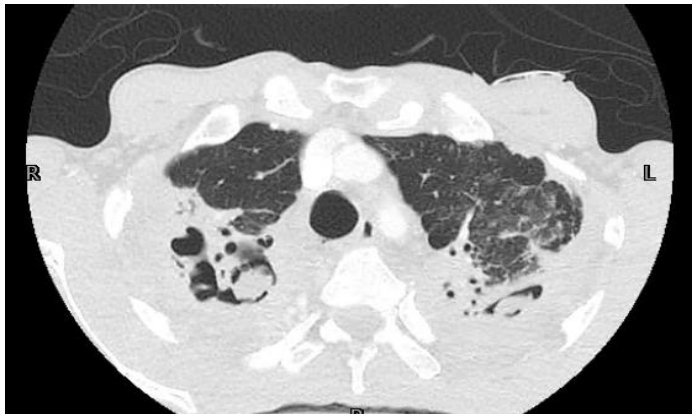
Denning et al. Eur Respir J. 2016 Jan;47:45-68

Different forms of CPA

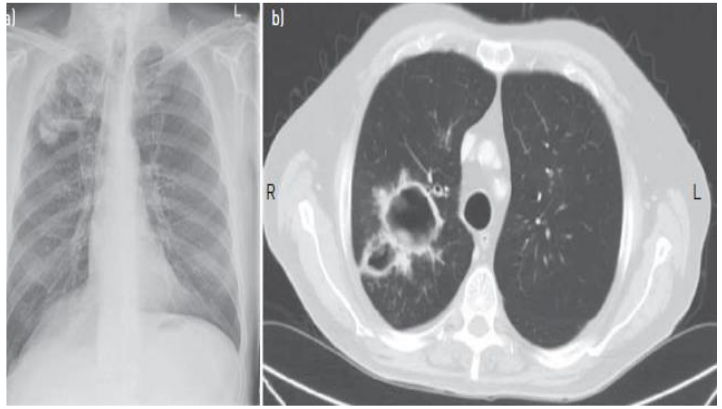
Single/simple aspergilloma



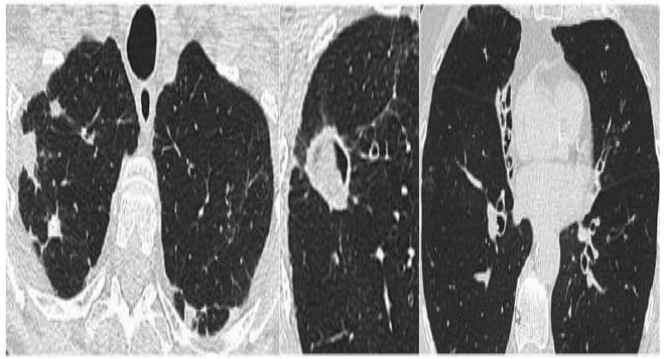
Chronic cavitary pulmonary aspergillosis



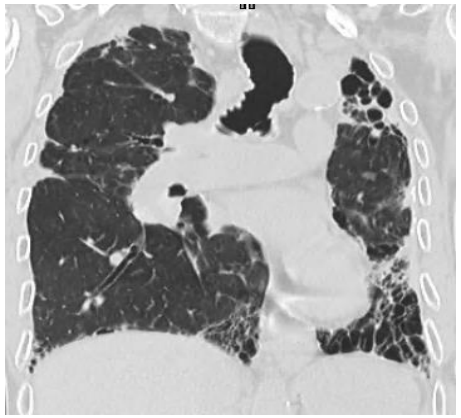
Subacute invasive aspergillosis

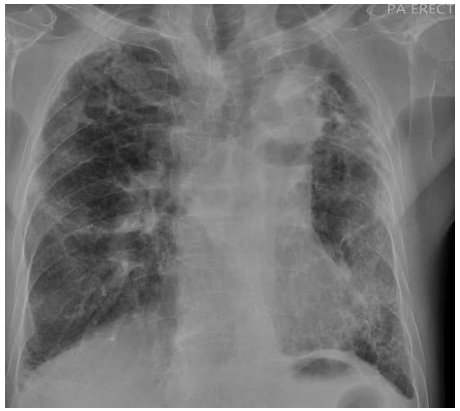


Aspergillus nodule



Chronic fibrosing pulmonary aspergillosis





Denning et al. Eur Respir J. 2016 Jan;47:45-68

Guidelines for Diagnosis and Management

IDSA

Clinical Infectious Diseases

IDSA GUIDELINE

IDSA Infectious Diseases Society of America | hivma hiv medicine association

Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America

Thomas F. Patterson,[1,a] George R. Thompson III,[2] David W. Denning,[3] Jay A. Fishman,[4] Susan Hadley,[5] Raoul Herbrecht,[6] Dimitrios P. Kontoyiannis,[7] Kieren A. Marr,[8] Vicki A. Morrison,[9] M. Hong Nguyen,[10] Brahm H. Segal,[11] William J. Steinbach,[12] David A. Stevens,[13] Thomas J. Walsh,[14] John R. Wingard,[15] Jo-Anne H. Young,[16] and John E. Bennett[17,a]

[1]University of Texas Health Science Center at San Antonio and South Texas Veterans Health Care System; [2]University of California, Davis; [3]National Aspergillosis Centre, University Hospital of South Manchester, University of Manchester, United Kingdom; [4]Massachusetts General Hospital and Harvard Medical School, and [5]Tufts Medical Center, Boston, Massachusetts; [6]University of Strasbourg, France; [7]University of Texas MD Anderson Cancer Center, Houston; [8]Johns Hopkins University School of Medicine and the Sidney Kimmel Comprehensive Cancer Center, Baltimore, Maryland; [9]Hennepin County Medical Center and University of Minnesota, Minneapolis; [10]University of Pittsburgh, Pennsylvania; [11]University at Buffalo Jacobs School of Medicine and Biomedical Sciences, and Roswell Park Cancer Institute, New York; [12]Duke University Medical Center, Durham, North Carolina; [13]California Institute for Medical Research, San Jose; [14]New York–Presbyterian Hospital/Weill Cornell Medical Center, New York; [15]University of Florida, Gainesville; [16]University of Minnesota, Minneapolis; [17]Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Disease, National Institutes of Health, Bethesda, Maryland

It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. IDSA considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

Keywords. aspergillosis; invasive aspergillosis; allergic aspergillosis; chronic aspergillosis; fungal diagnostics; azoles; echinocandins; amphotericin.

EXECUTIVE SUMMARY

Background

Aspergillus species continue to be an important cause of life-threatening infection in immunocompromised patients. This at-risk population is comprised of patients with prolonged neutropenia, allogeneic hematopoietic stem cell transplant (HSCT), solid organ transplant (SOT), inherited or acquired immunodeficiencies, corticosteroid use, and others. This document constitutes the guidelines of the Infectious Diseases Society of America (IDSA) for treatment of aspergillosis and replaces the practice guidelines for *Aspergillus* published in 2008. Since that publication, clinical studies evaluating new and existing therapies including combination therapy for the management of *Aspergillus* infection have been conducted and the data on use of non-culture-based biomarkers for diagnosing infection have been expanded. The objective of these guidelines is to summarize the current evidence for treatment of different forms of aspergillosis. This document reviews guidelines for management of the 3 major forms of aspergillosis: invasive aspergillosis (IA); chronic (and saprophytic) forms of aspergillosis; and allergic forms of aspergillosis. Given the clinical importance of IA, emphasis is placed upon the diagnosis, treatment, and prevention of the different forms of IA, including invasive pulmonary aspergillosis (IPA), *Aspergillus* sinusitis, disseminated aspergillosis, and several types of single-organ IA.

Summarized below are the 2016 recommendations for the management of aspergillosis. Due to the guidelines' relevance to pediatrics, the guideline has been reviewed and endorsed by the Pediatric Infectious Diseases Society (PIDS). The panel followed a guideline development process that has been adopted by IDSA, which includes use of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system, a systematic method of grading both the strength of the recommendation (weak or strong) and the quality of evidence (very low, low, moderate, and high) (Figure 1). The guidelines are not intended to replace clinical judgment in the management of individual patients. A detailed description of the methods, background, and evidence summaries that support each recommendation can be found in the full text of the guideline.

EPIDEMIOLOGY AND RISK FACTORS FOR INFECTION

I. How Can the Most Susceptible Patients Be Protected From Aspergillosis, and Which Patients Are Most Susceptible?

What Are Sources of Exposure to Aspergillus, and How Can Exposure Be Decreased? Is Environmental Surveillance Useful?

Received 7 May 2016; accepted 11 May 2016; published online 29 June 2016.

[a]T. F. P. and J. E. B. served as co-chairs for the IDSA *Aspergillus* Guidelines Committee.
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Clinical Infectious Diseases® 2016;63(e1–e60)

DOI: 10.1093/cid/ciw326

ESCMID/ERS/ECMM

Chronic pulmonary aspergillosis: rationale and clinical guidelines for diagnosis and management

David W. Denning[1], Jacques Cadranel[2], Catherine Beigelman-Aubry[3], Florence Ader[4,5], Arunaloke Chakrabarti[6], Stijn Blot[7,8], Andrew J. Ullmann[9], George Dimopoulos[10] and Christoph Lange[11–14] on behalf of the European Society for Clinical Microbiology and Infectious Diseases and European Respiratory Society

Affiliations: [1]The National Aspergillosis Centre, University Hospital of South Manchester, The University of Manchester and the Manchester Academic Health Science Centre, Manchester, UK. [2]Service de Pneumologie, AP-HP, Hôpital Tenon and Sorbonne Université, UPMC Univ Paris 06, Paris, France. [3]Dept of Diagnostic and Interventional Radiology, University Hospital CHUV, Lausanne, Switzerland. [4]Dept of Infectious Diseases, Hospices Civils de Lyon, Lyon, France. [5]Centre International de Recherche en Infectiologie (CIRI), INSERM U1111, CNRS UMR5308, Lyon, France. [6]Center of Advanced Research in Medical Mycology, Dept of Medical Microbiology, Postgraduate Institute of Medical Education & Research, Chandigarh, India. [7]Dept of Internal Medicine, Ghent University, Ghent, Belgium. [8]Burns, Trauma and Critical Care Research Centre, The University of Queensland, Brisbane, Australia. [9]Dept of Internal Medicine II, Division of Infectious Diseases, University Hospital Würzburg, Julius-Maximilians-University, Würzburg, Germany. [10]Dept of Critical and Respiratory Care, University Hospital Attikon, Medical School, University of Athens, Athens, Greece. [11]Division of Clinical Infectious Diseases and German Center for Infection Research (DZIF) Tuberculosis Unit, Research Center Borstel, Borstel, Germany. [12]International Health/Infectious Diseases, University of Lübeck, Lübeck, Germany. [13]Dept of Medicine, Karolinska Institute, Stockholm, Sweden. [14]Dept of Medicine, University of Namibia School of Medicine, Windhoek, Namibia.

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ABSTRACT Chronic pulmonary aspergillosis (CPA) is an uncommon and problematic pulmonary disease, complicating many other respiratory disorders, thought to affect ~240 000 people in Europe. The most common form of CPA is chronic cavitary pulmonary aspergillosis (CCPA), which untreated may progress to chronic fibrosing pulmonary aspergillosis. Less common manifestations include: *Aspergillus* nodule and single aspergilloma. All these entities are found in non-immunocompromised patients with prior or current lung disease. Subacute invasive pulmonary aspergillosis (formerly called chronic necrotising pulmonary aspergillosis) is a more rapidly progressive infection (<3 months) usually found in moderately immunocompromised patients, which should be managed as invasive aspergillosis. Few clinical guidelines have been previously proposed for either diagnosis or management of CPA. A group of experts convened to develop clinical, radiological and microbiological guidelines. The diagnosis of CPA requires a combination of characteristics: one or more cavities with or without a fungal ball present or nodules on thoracic imaging, direct evidence of *Aspergillus* infection (microscopy or culture from biopsy) or an immunological response to *Aspergillus* spp. and exclusion of alternative diagnoses, all present for at least 3 months. *Aspergillus* antibody (precipitins) is elevated in over 90% of patients. Surgical excision of simple aspergilloma is recommended, if technically possible, and preferably *via* video-assisted thoracic surgery technique. Long-term oral antifungal therapy is recommended for CCPA to improve overall health status and respiratory symptoms, arrest haemoptysis and prevent progression. Careful monitoring of azole serum concentrations, drug interactions and possible toxicities is recommended. Haemoptysis may be controlled with tranexamic acid and bronchial artery embolisation, rarely surgical resection, and may be a sign of therapeutic failure and/or antifungal resistance. Patients with single *Aspergillus* nodules only need antifungal therapy if not fully resected, but if multiple they may benefit from antifungal treatment, and require careful follow-up.

@ERSpublications
ERS and ESCMID guideline for the management of chronic pulmonary aspergillosis released http://ow.ly/Tzlsu

Received: April 13 2015 | Accepted after revision: Aug 18 2015

Case definition for LMICs

ONLINE REPORT

Case Definition of Chronic Pulmonary Aspergillosis in Resource-Constrained Settings

David W. Denning, Iain D. Page, Jeremiah Chakaya, Kauser Jabeen, Cecilia M. Jude, Muriel Cornet, Ana Alastruey-Izquierdo, Felix Bongomin, Paul Bowyer, Arunaloke Chakrabarti, Sara Gago, John Guto, Bruno Hochhegger, Martin Hoenigl, Muhammad Irfan, Nicholas Irurhe, Koichi Izumikawa, Bruce Kirenga, Veronica Manduku, Samihah Moazam, Rita O. Oladele, Malcolm D. Richardson, Juan Luis Rodriguez Tudela, Anna Rozaliyani, Helmut J.F. Salzer, Richard Sawyer, Nasilele F. Simukulwa, Alena Skrahina, Charlotte Sriruttan, Findra Setianingrum, Bayu A.P. Wilopo, Donald C. Cole, Haileyesus Getahun

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DOI: https://doi.org/10.3201/eid2408.171312

Chronic pulmonary aspergillosis (CPA) is a recognized complication of pulmonary tuberculosis (TB). In 2015, the World Health Organization reported 2.2 million new cases of nonbacteriologically confirmed pulmonary TB; some of these patients probably had undiagnosed CPA. In October 2016, the Global Action Fund for Fungal Infections convened an international expert panel to develop a case definition of CPA for resource-constrained settings. This panel defined CPA as illness for ≥3 months and all of the following: 1) weight loss, persistent cough, and/or hemoptysis; 2) chest images showing progressive cavitary infiltrates and/or a fungal ball and/or pericavitary fibrosis or infiltrates or pleural thickening; and 3) a positive *Aspergillus* IgG assay result or other evidence of *Aspergillus* infection. The proposed definition will facilitate advancements in research, practice, and policy in lower- and middle-income countries as well as in resource-constrained settings.

The differential diagnosis for pulmonary tuberculosis (TB) is wide and includes nontuberculous mycobacteria (NTM) infection, endemic fungal infections such as coccidioidomycosis and histoplasmosis, allergic bronchopulmonary aspergillosis, and chronic pulmonary aspergillosis (CPA) (*1–7*). Sequelae of pulmonary TB, such as bronchiectasis and restricted lung capacity, can mimic infection relapse (*8–10*). Accurate diagnosis is essential for adequate treatment.

The 2015 World Health Organization annual report notes that ≈2.2 million (≈43%) of 5.2 million cases of incident pulmonary TB were clinically diagnosed or smear-negative (*11*). Only 21%–40% of smear-negative pulmonary TB cases are culture positive (*12,13*). Exclusion of alternatives is challenging in many lower- and middle-income countries (*14*). The World Health Organization report comments, "Most clinical features of TB and abnormalities on X-ray or histology results generally associated with TB have low specificity, which may lead to false diagnoses of TB, and hence to people being enrolled on TB treatment unnecessarily" (*11*).

Consensus Definition/Diagnosis- CPA

- **Symptoms** for 3 moths or longer (haemoptysis, persistent cough, and/or weight loss) (other symptoms are common, but not required, notably fatigue, chest pain and sputum production)

AND

- **Radiological features** (progressive cavitation on chest X-ray AND/OR paracavitary fibrosis / fungal ball / pleural thickening adjacent to cavities on CT thorax)

AND

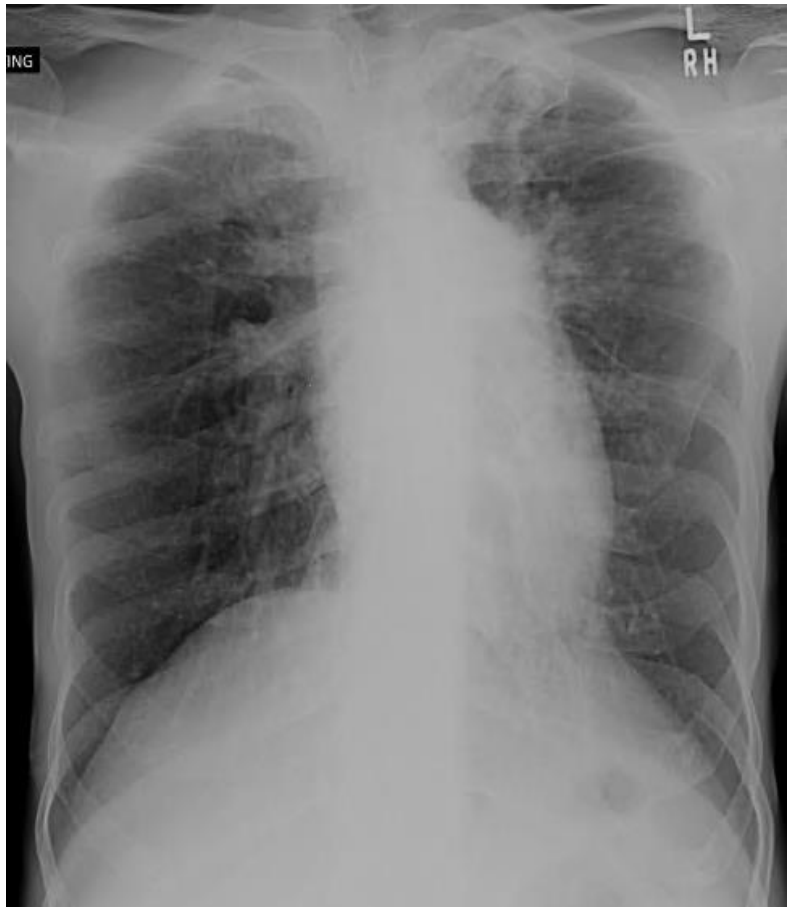
- **Microbiological evidence of *Aspergillus* infection** (positive *Aspergillus*-specific IgG and/or *Aspergillus* growth on 2 or more sputum or other respiratory sample cultures)

AND

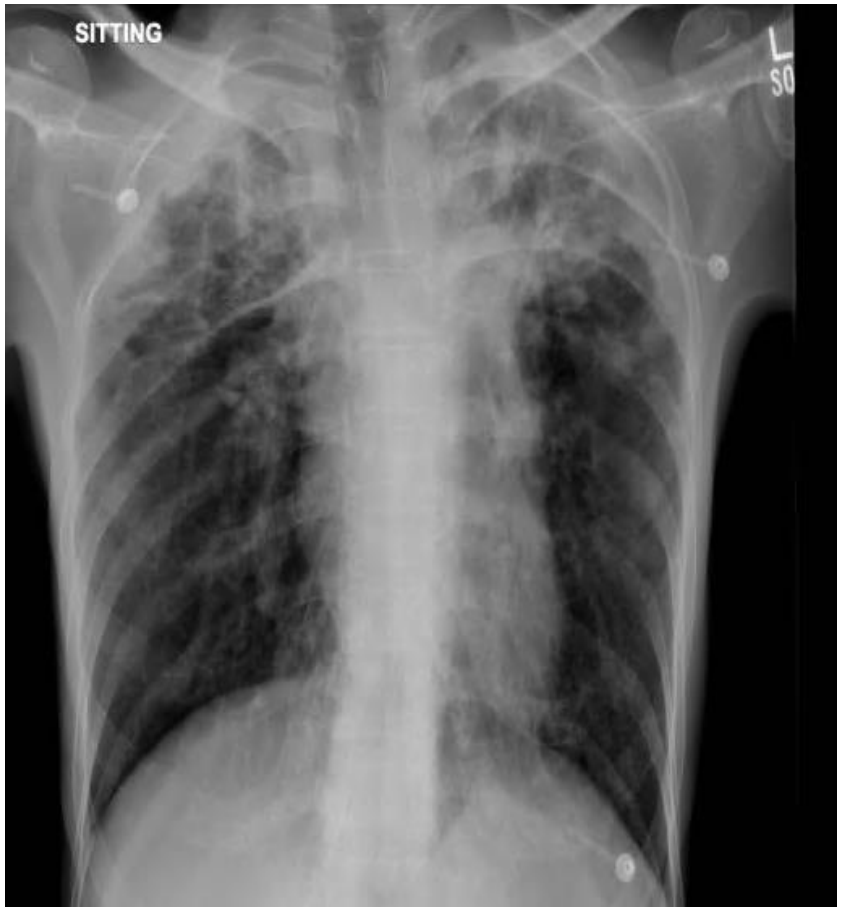
- **Mycobacterial infection should be ruled out** with smear, GeneXpert and/or mycobacterial culture

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 24, No. 8, August 2018

45 male with history of TB in 2017

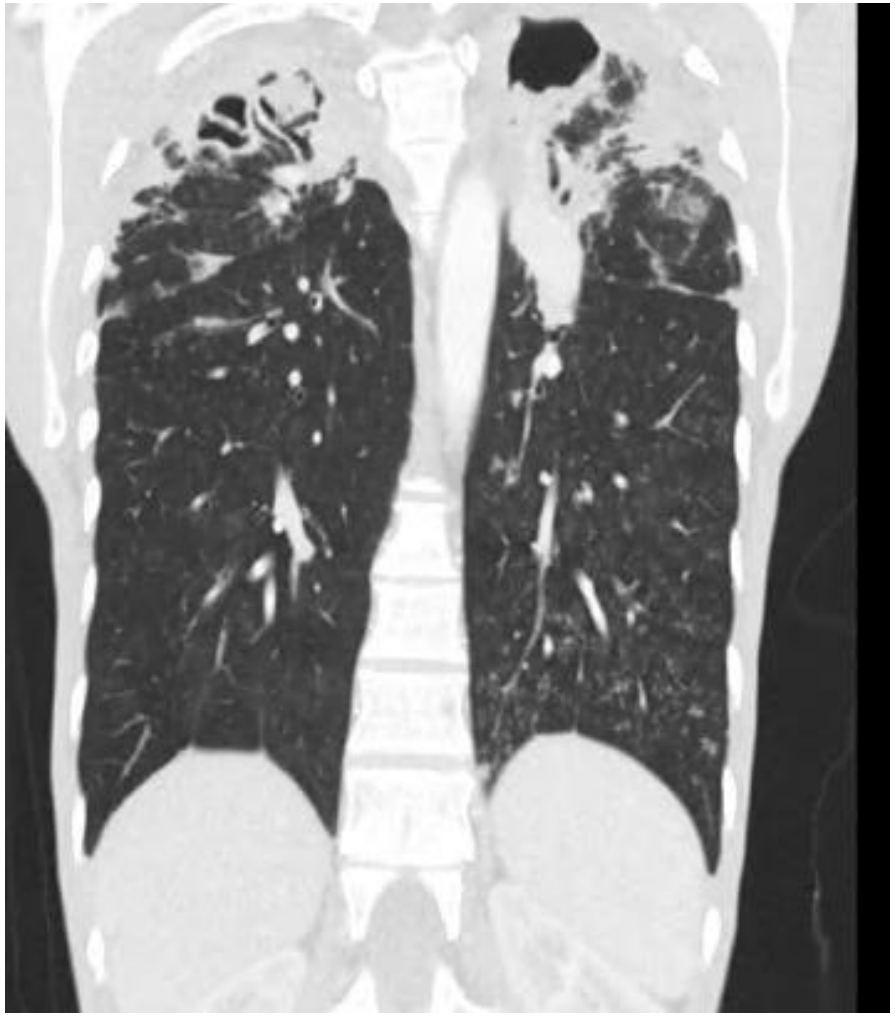


August 2017



August 2022

45 male with history of TB in 2017



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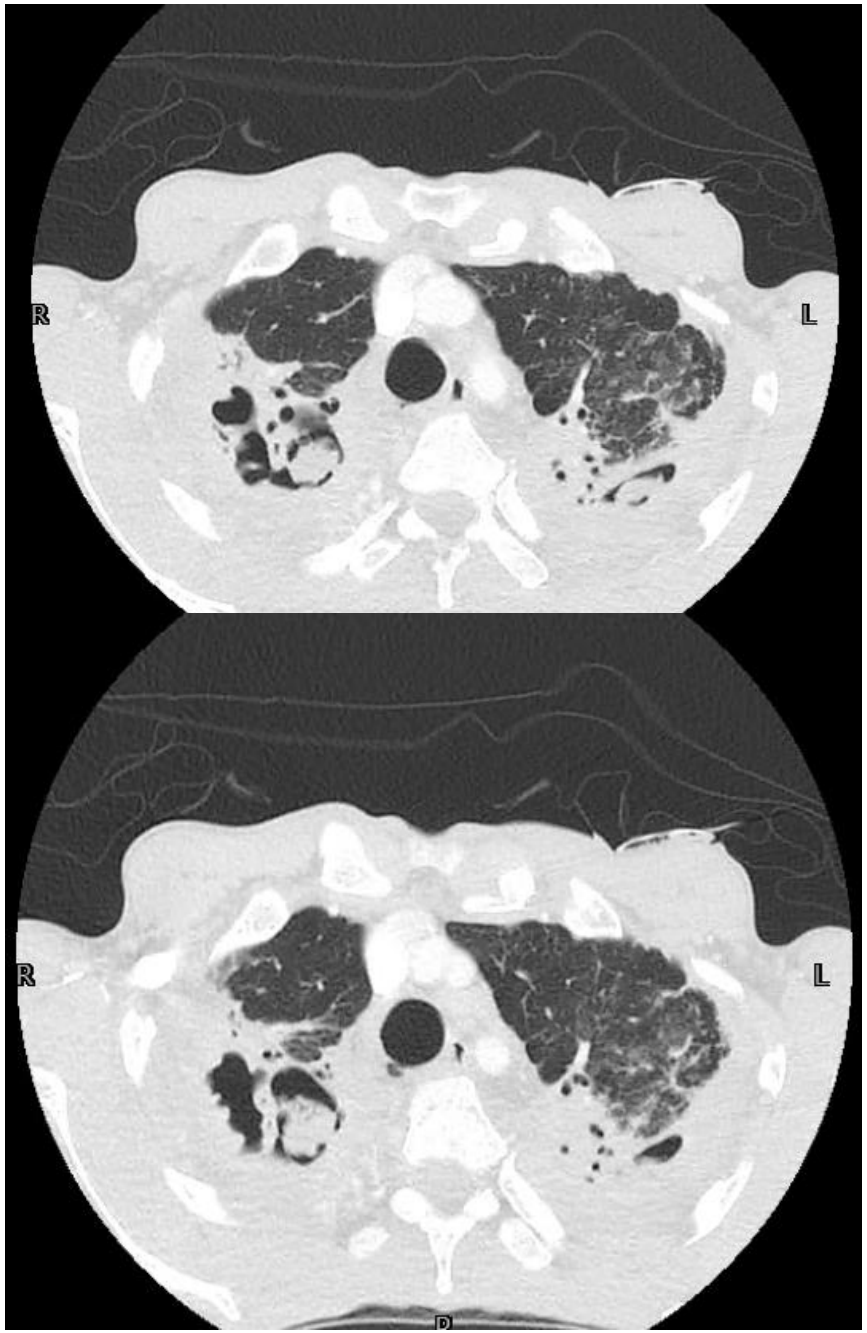


Goal of CPA treatment

Very ill patients:

- Save their lives with (usually) IV and then oral therapy

Quite ill patients:

- Improve quality of life by minimising symptoms
- Prevent further haemoptysis
- Stop progression of disease
- Prevent the emergence of antifungal resistance
- Avoid antifungal toxicity

Patients with few symptoms

- Stop progression of scarring in the lung
- Prevent the emergence of antifungal resistance
- Avoid antifungal toxicity

CPA Treatment: Oral Antifungals

Treatment	SoR	QoE
Iatraconazole 400mg/day	A (strongly)	II
Voriconazole 300-400mg/day	A (strongly)	II
Posaconazole 300mg/day tab	B (moderate)	II
Isavuconazole	-	-

Denning et al. Eur Respir J. 2016 Jan;47:45-68

Contents lists available at ScienceDirect

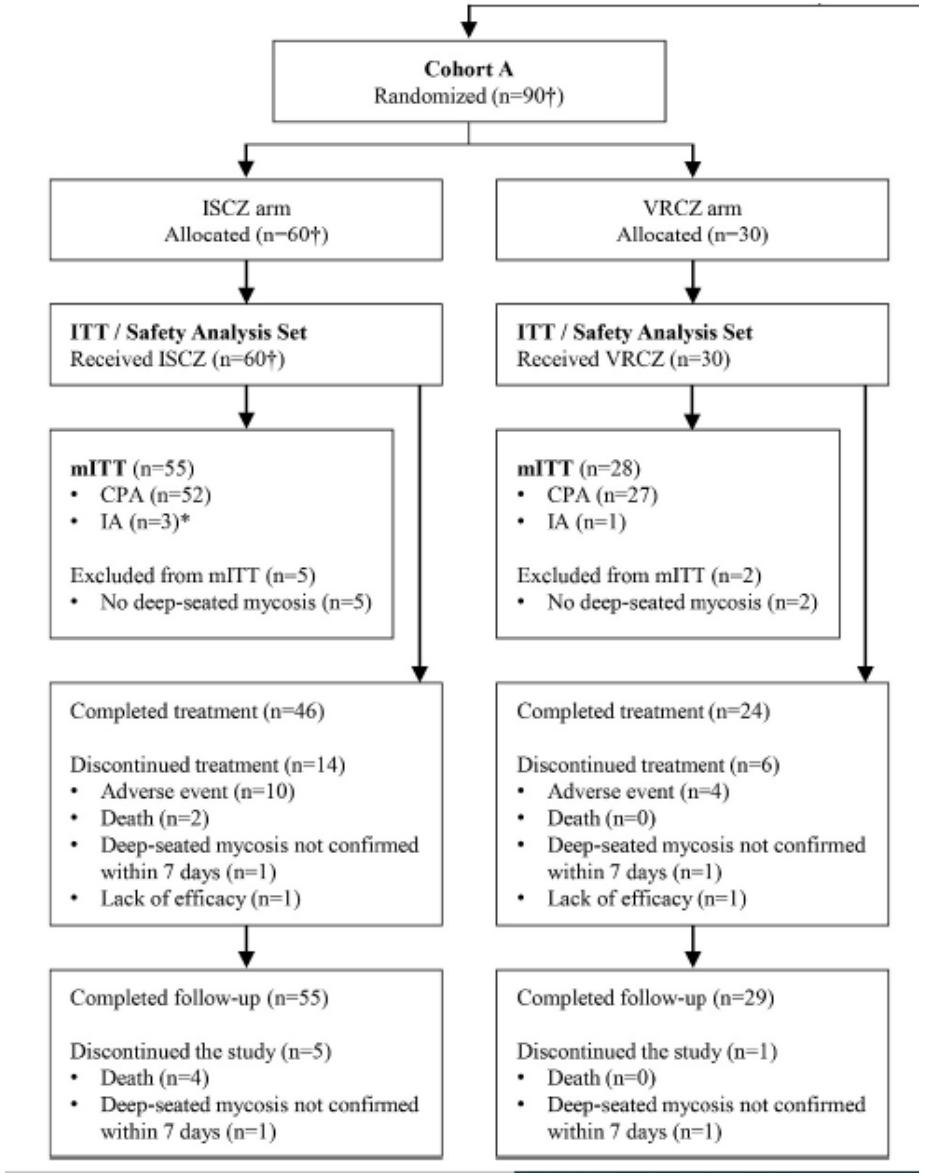
Journal of Infection and Chemotherapy

journal homepage: www.elsevier.com/locate/jic

Original Article

Efficacy and safety of isavuconazole against deep-seated mycoses: A phase 3, randomized, open-label study in Japan

Shigeru Kohno [a], Koichi Izumikawa [b,*], Takahiro Takazono [b,c], Taiga Miyazaki [d],



Journal of Infection and Chemotherapy 29 (2023) 163–170

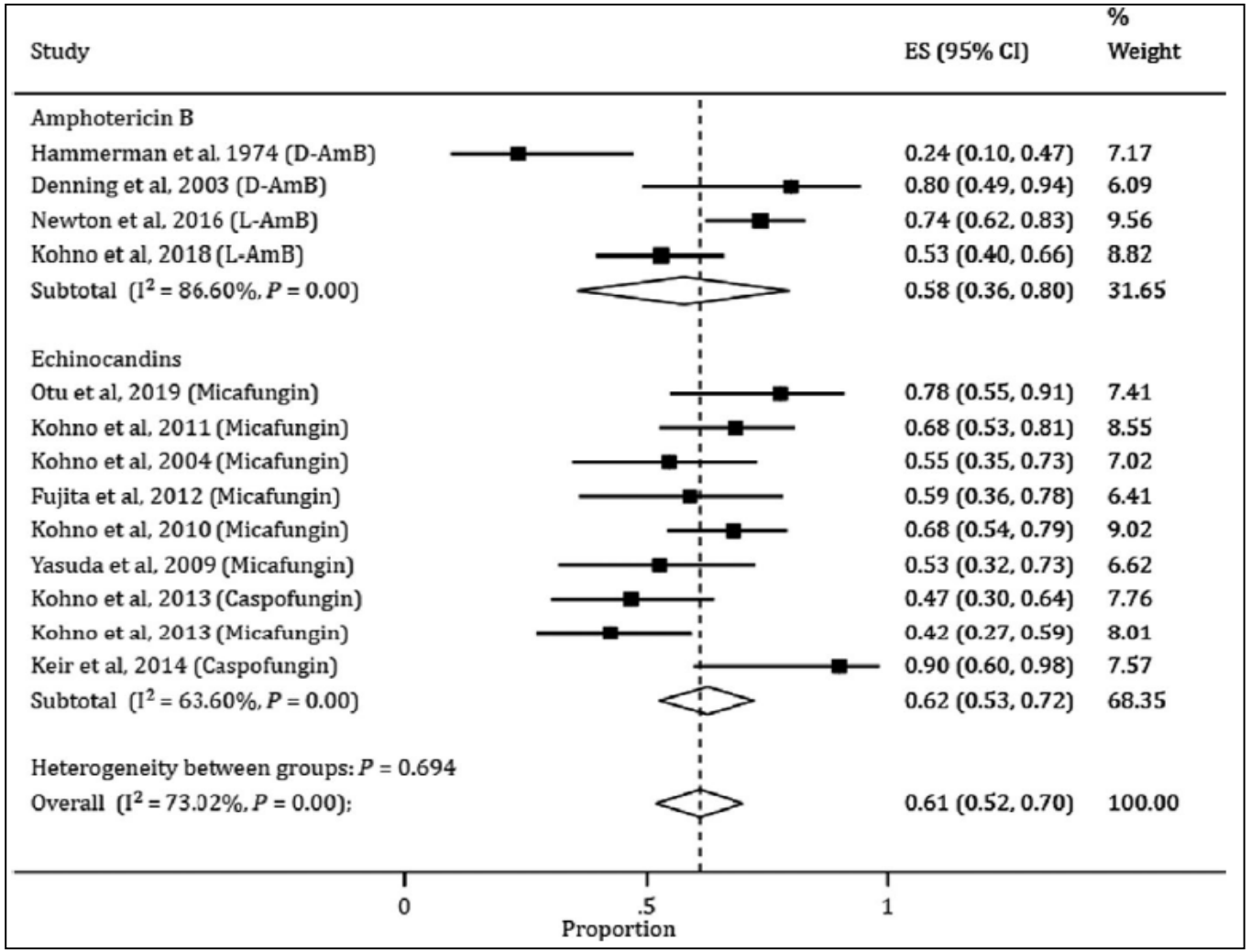
DRC-assessed response in chronic pulmonary aspergillosis (mITT set).

	Day 42		Day 84		EOT	
	ISCZ	VRCZ	ISCZ	VRCZ	ISCZ	VRCZ
	(N = 52)	(N = 27)	(N = 52)	(N = 27)	(N = 52)	(N = 27)
Overall response						
Success	41 (78.8)	17 (63.0)	44 (84.6)	20 (74.1)	43 (82.7)	21 (77.8)
95% CI (%) of Success	(65.3–88.9)	(42.4–80.6)	(71.9–93.1)	(53.7–88.9)	(69.7–91.8)	(57.7–91.4)
Improved	41 (78.8)	17 (63.0)	44 (84.6)	20 (74.1)	43 (82.7)	21 (77.8)
Failure	11 (21.2)	10 (37.0)	8 (15.4)	7 (25.9)	9 (17.3)	6 (22.2)
Stable	1 (1.9)	3 (11.1)	1 (1.9)	2 (7.4)	3 (5.8)	3 (11.1)
Progression	5 (9.6)	4 (14.8)	2 (3.8)	2 (7.4)	2 (3.8)	2 (7.4)
Unevaluable	5 (9.6)	3 (11.1)	5 (9.6)	3 (11.1)	4 (7.7)	1 (3.7)
Clinical response						
Success	36 (69.2)	15 (55.6)	38 (73.1)	17 (63.0)	37 (71.2)	18 (66.7)
95% CI (%) of Success	(54.9–81.3)	(35.3–74.5)	(59.0–84.4)	(42.4–80.6)	(56.9–82.9)	(46.0–83.5)
Radiological response						
Success	42 (80.8)	17 (63.0)	42 (80.8)	19 (70.4)	41 (78.8)	20 (74.1)
95% CI (%) of Success	(67.5–90.4)	(42.4–80.6)	(67.5–90.4)	(49.8–86.2)	(65.3–88.9)	(53.7–88.9)
Mycological response						
Success	9 (17.3)	8 (30.8)	14 (26.9)	8 (30.8)	14 (26.9)	9 (34.6)
95% CI (%) of Success	(8.2–30.3)	(14.3–51.8)	(15.6–41.0)	(14.3–51.8)	(15.6–41.0)	(17.2–55.7)

Intravenous therapy for chronic pulmonary aspergillosis: A systematic review and meta-analysis

Felix Bongomin[1] | Lucy Grace Asio[1] | Ronald Olum[2] | David W. Denning[3,4]

- 12 eligible studies. 380 patients Amphotericin B (n = 143) or an Echinocandin (n = 237)
- In a pooled analysis, overall response to IV antifungals was 61% ((95% confidence interval (CI): 52%-70%; *I*2 = 73.3%; *P* < .001),
- **Amphotericin B:** 58% (95% CI: 36%-80%; *I*2 = 86.6%; *P* < .001)
- Echinocandins: 62% (95% CI: 53%-72%; *I*2 = 63.6%; *P* < .001).



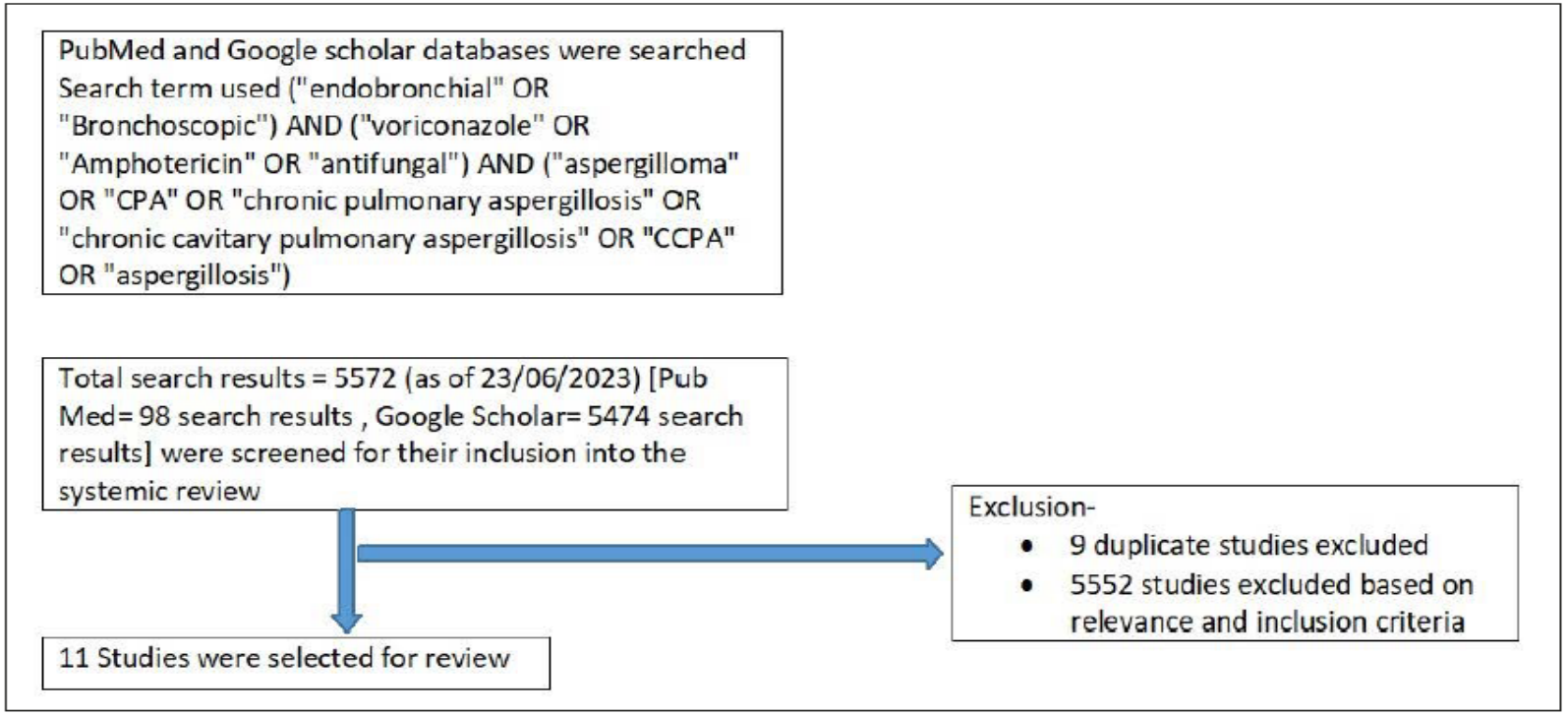
Bongomin F et al, Mycoses 2020;63:921

Le Infezioni in Medicina, n. 4, 575-582, 2023
doi: 10.53854/liim-3104-17

CASE REPORTS

Clinical utility of intrabronchial antifungal instillation in a complicated case of chronic pulmonary aspergillosis: case report and systematic review of literature

Sreyas Sharma, Rohit Kumar, Pranav Ish, Mahendran AJ, Neeraj Kumar Gupta, Nitesh Gupta, Manu Madan
Department of Pulmonary, Critical Care and Sleep Medicine, VMMC and Safdarjung Hospital, New Delhi, India



9.	Mohan A et al., 2017 [20]; [Case series]	Aspergilloma -82	Procedure performed under local anaesthesia - 4 sessions at weekly intervals	Voriconazole (400 mg dissolved in 20 ml 0.9% normal saline)	(Voriconazole)	I. Clinical II. Radiological	Clinical - significant resolution of hemoptysis was seen in 30.5% patients after first session, and in 68.3% patients after the second session of voriconazole instillation. Median hemoptysis-free period was 12 months. Radiologic- follow-up CT showed reduction in aspergilloma size in 54% patients.Transient postprocedure cough seen is 46.3%
11.	Hadda V et al., 2022 [22]; [Randopmized controlled trial]	Aspergilloma -60	Procedure performed under local anesthesia (lignocaine) - 4 sessions	Voriconazole (400 mg)	Itraconazole 100 mg BD or Voriconazole 200 mg BD	I. Clinical II. Radiological	VAS Score: At 3 months follow-up, significant decrease in hemoptysis was seen more in the intervention group (86.7% vs 36.7%; p value of <0.0001). Reduction in cough severity and size of the aspergilloma Transient tachypnea (30.4%), post-procedure cough (27.9%), bronchospasm (10%), and mild hemoptysis (2.9%) seen

Chronic Pulmonary Aspergillosis and Ambisome Aerosol With Itraconazole

- Compares the therapeutic (clinical and radiological) efficacy of a six-month treatment by itraconazole and nebulised Ambisome® (liposomal amphotericin B = LAmB) versus treatment by itraconazole alone, in non - or mildly - immunocompromised patients affected by Chronic Pulmonary Aspergillosis (single aspergilloma excluded).

• Control arm: Itraconazole 200 mg x 2/day associated with inactive nebulised treatment twice a week during 24 weeks.

• Experimental arm: Itraconazole 200 mg x 2/day associated with nebulised LAmB, at 25 mg twice a week during 24 weeks.

Outcome

Composite efficacy criterion defined by the association of clinical improvement/stability and radiological improvement evaluated at 6 months

•Clinical Trial NCT03656081

Duration of therapy for CPA

TABLE 9 Duration of therapy for chronic pulmonary aspergillosis (CPA)

Population	Intention	Intervention	SoR	QoE	Ref.	Comment
CPA patients on antifungal therapy	Control of infection, arrest of pulmonary fibrosis, prevention of haemoptysis, improved quality of life	06 months of antifungal therapy	B	II	[15, 30, 31, 59, 83, 89, 96]	Optimal duration of therapy in CPA is unknown, indefinite suppressive therapy may be appropriate in selected patients
		Long-term antifungal therapy, depending on status and drug tolerance	C	III	[15, 30, 89, 59]	
SAIA/CNPA	Cure	6 months	B	II	[15, 30]	Longer durations may be necessary in those with continuing immunosuppression

SoR: strength of recommendation; QoE: quality of evidence; SAIA: subacute invasive aspergillosis; CNPA: chronic necrotising pulmonary aspergillosis.

Denning et al, Eur Resp J 2016;47:45

Efficacy of 12-months oral itraconazole versus 6-months oral itraconazole to prevent relapses of chronic pulmonary aspergillosis: an open-label, randomised controlled trial in India

Inderpaul S Sehgal, Sahajal Dhooria, Valliappan Muthu, Kuruswamy T Prasad, Ashutosh N Aggarwal, Arunaloke Chakrabarti, Hansraj Choudhary, Mandeep Garg, Ritesh Agarwal

- 164 cases, 81 patients (6-month group) and 83 patients (12-month group).
- **Relapse was significantly lower in the 12-month group, 31 (38%) had a relapse in the 6-month group compared with 8 (10%) in the 12-month group, with an absolute risk reduction of 0.29 [95% CI 0·16–0·40].**
- The mean time to first relapse was 23 months in the 12-month group, which is significantly longer than the mean of 18 months in the 6-month group ($p<0.0001$).
- There were 16 deaths in total, eight in each group.

Sehgal et al. Lancet Infect Dis. 2022 April 13

Efficacy of 12-months oral itraconazole versus 6-months oral itraconazole to prevent relapses of chronic pulmonary aspergillosis: an open-label, randomised controlled trial in India

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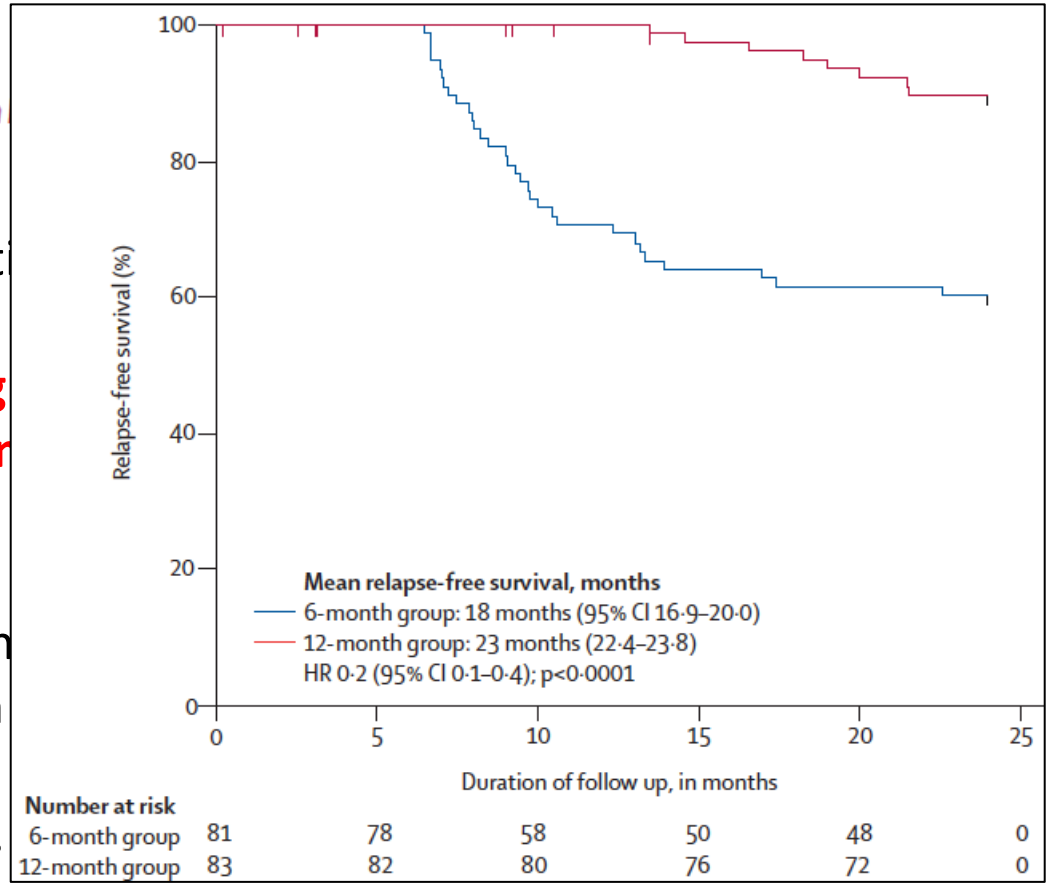


Sehgal et al. Lancet Infect Dis. 2022 April 13

Journal of Fungi

MDPI

Article

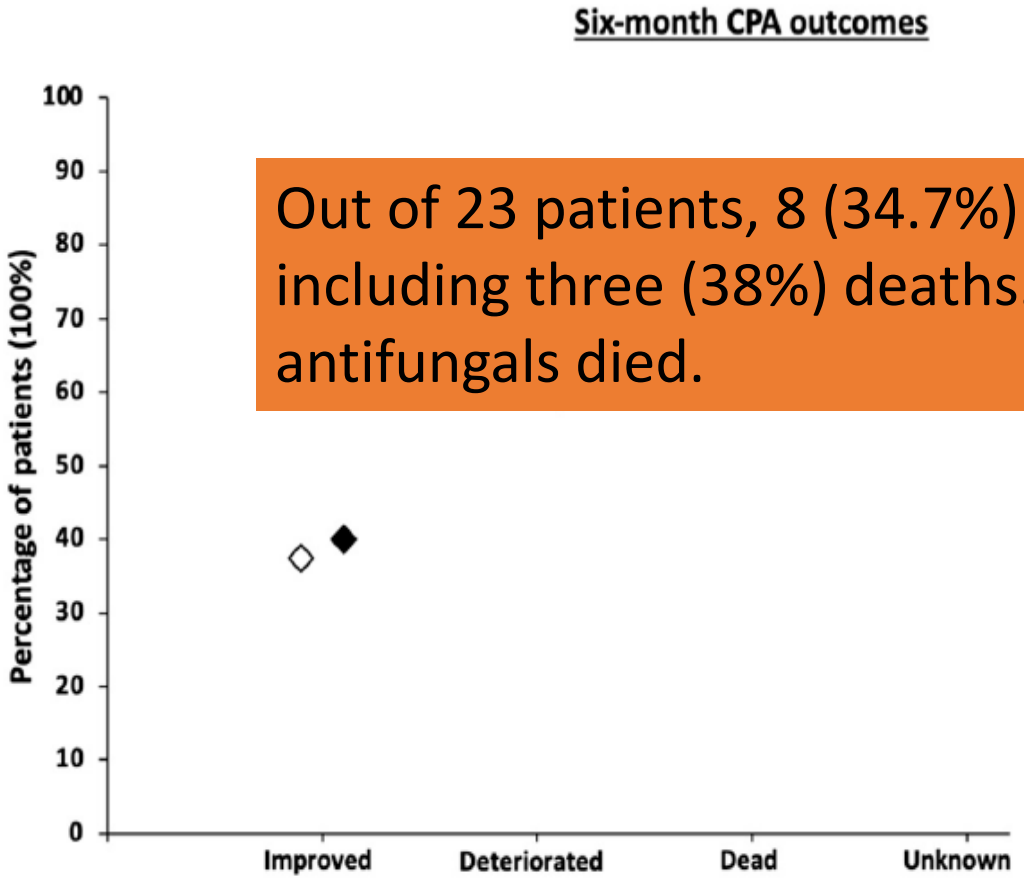
Chronic Pulmonary Aspergillosis: Burden, Clinical Characteristics and Treatment Outcomes at a Large Australian Tertiary Hospital

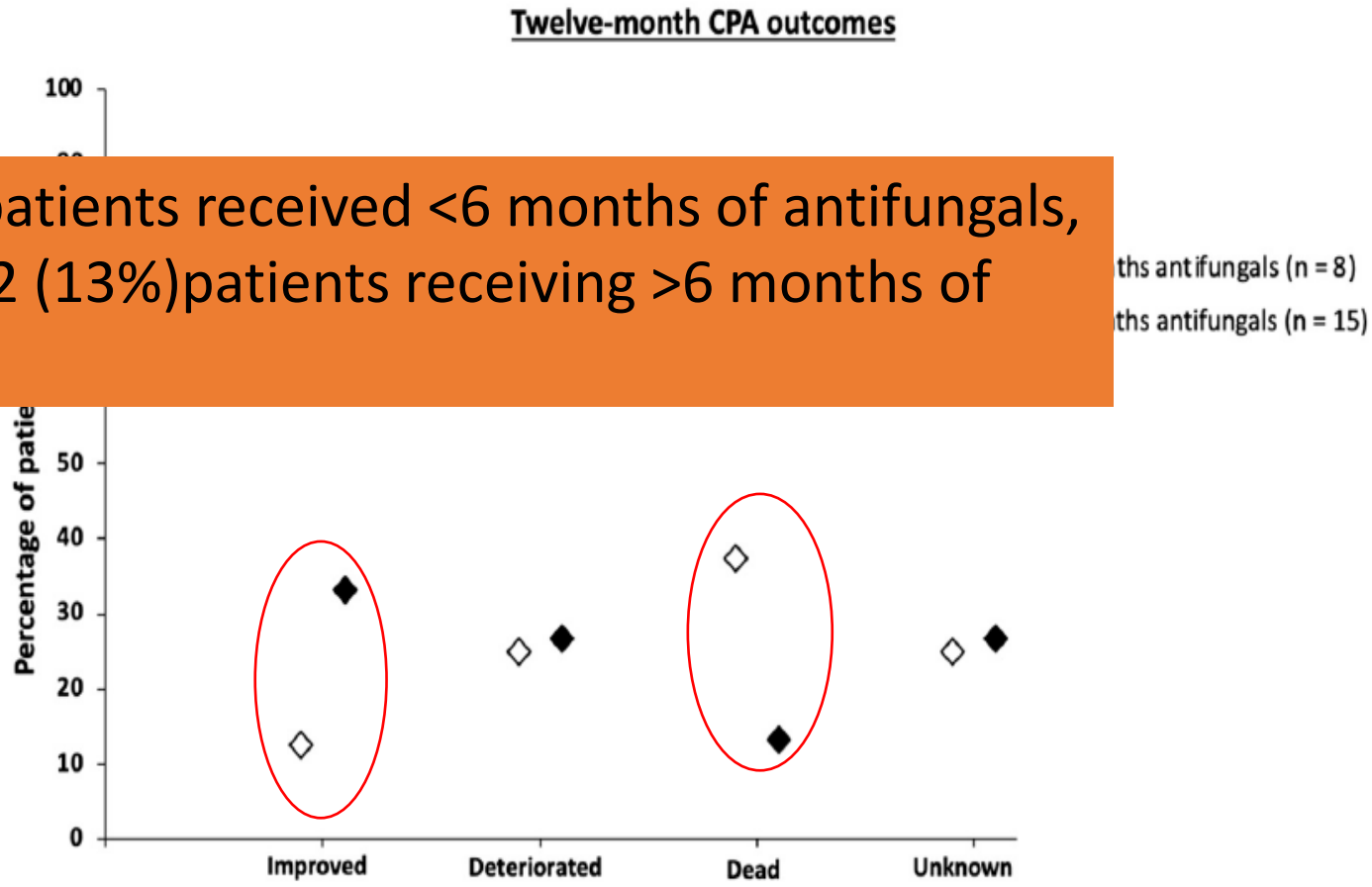
Olivier Despois [1], Sharon C-A. Chen [1,2], Nicole Gilroy [1,2], Michael Jones [3], Peter Wu [4] and Justin Beardsley [1,5,*]

	Total (n = 28)	CCPA (n = 17)	SA (n = 4)	CNPA/SAIA (n = 3)	CFPA (n = 3)	AN (n = 1)
Median age (years), (IQR)	60 (57–66)	60 (58–65)	52 (38–68)	72 (50–74)	59 (58–59)	60 (NA)
Gender, n (%)						
Male	17 (60.7%)	12 (66.7%)	0	2 (66.7%)	2 (100%)	1 (100%)

J Fungi (Basel). 2022 Feb; 8(2): 110.

Treatment outcomes for CPA patients at six- and twelve-months post-diagnosis





Out of 23 patients, 8 (34.7%) patients received <6 months of antifungals, including three (38%) deaths. 2 (13%)patients receiving >6 months of antifungals died.

J Fungi (Basel). 2022 Feb; 8(2): 110.

Duration of therapy for CPA

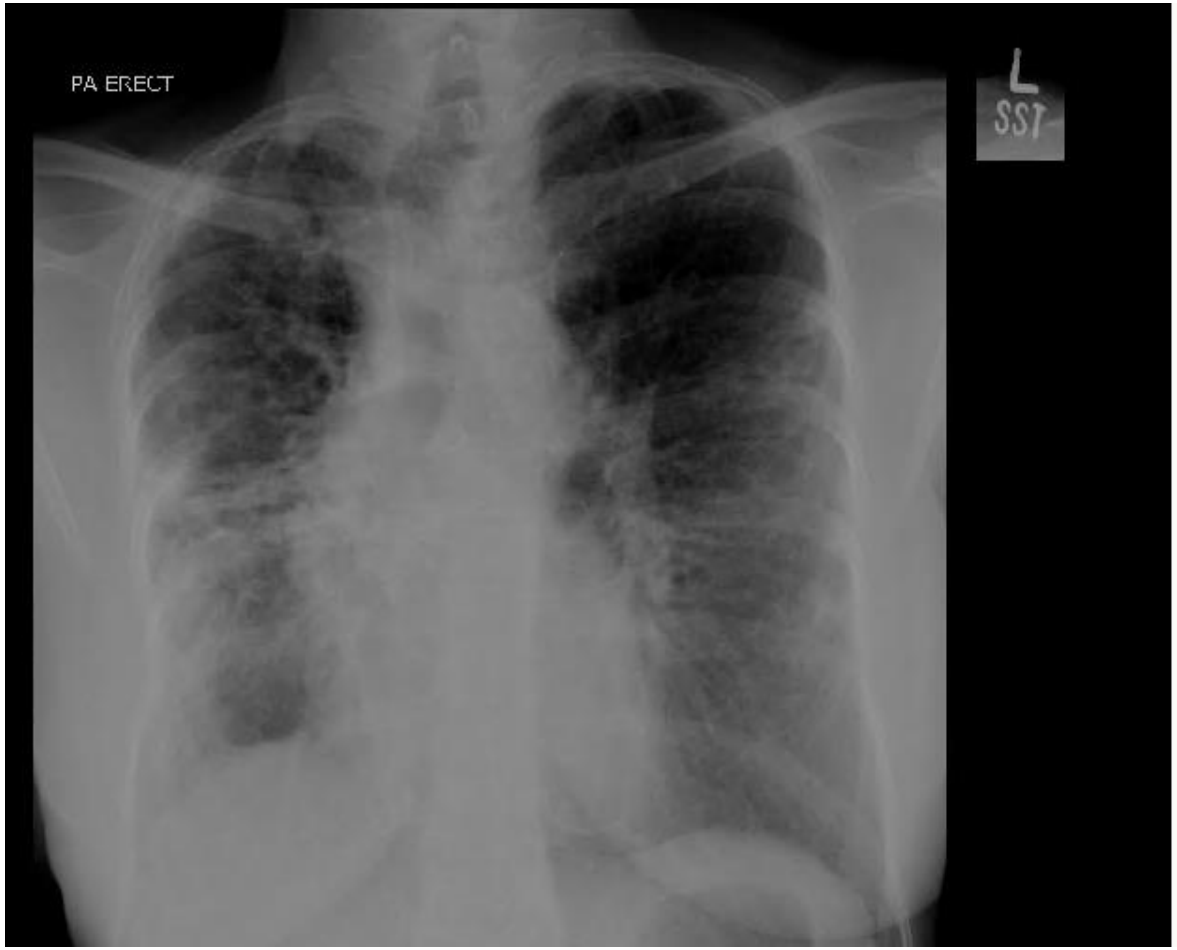
TABLE 9 Duration of therapy for chronic pulmonary aspergillosis (CPA)

Population	Intention	Intervention	SoR	QoE	Ref.	Comment
CPA patients on antifungal therapy	Control of infection, arrest of pulmonary fibrosis, prevention of haemoptysis, improved quality of life	12 months of antifungal therapy	A	I	[15, 30, 31, 59, 83, 89, 96]	Optimal duration of therapy in CPA is unknown, indefinite suppressive therapy may be appropriate in selected patients
		Long-term antifungal therapy, depending on status and drug tolerance	C	III	[15, 30, 89, 59]	
SAIA/CNPA	Cure	6 months	B	II	[15, 30]	Longer durations may be necessary in those with continuing immunosuppression

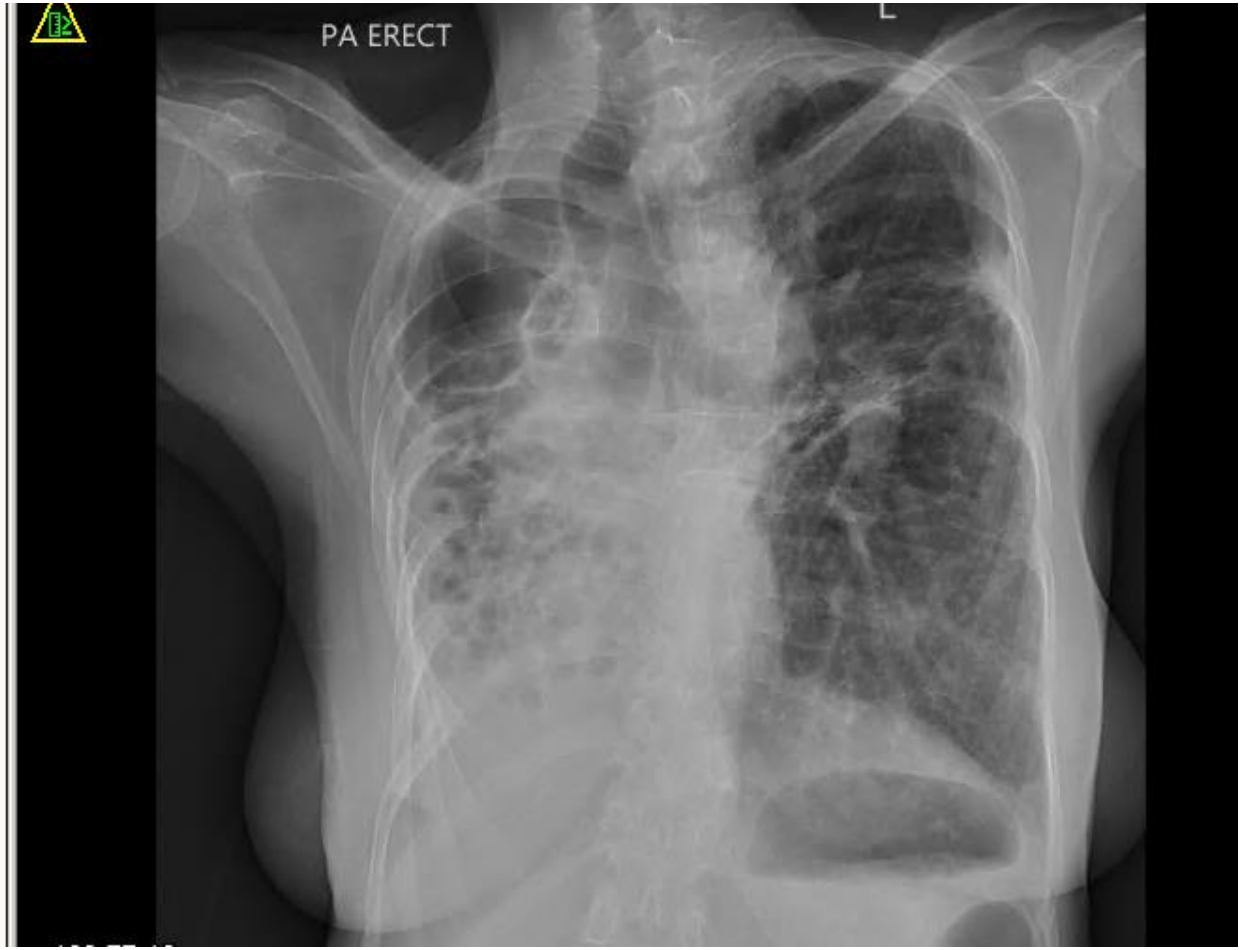
SoR: strength of recommendation; QoE: quality of evidence; SAIA: subacute invasive aspergillosis; CNPA: chronic necrotising pulmonary aspergillosis.

Denning et al, Eur Resp J 2016;47:45

42-years female with CPA –Disease Progress even after 18 months of treatment



2019



2023

Risk factors for relapse of chronic pulmonary aspergillosis after discontinuation of antifungal therapy

Felix Bongomin [a,b], Akaninyene Otu [a,c,*], Chris Harris [a], Philip Foden [d], Chris Kosmidis [a], David W. Denning [a]

102 patients who discontinued therapy – retrospective analysis

Relapse was defined as a deterioration in any two of the following:

- clinical, radiological, serological, or sputum microbiological markers of CPA activity.

The median duration of continuous triazole therapy before discontinuation of therapy was 19 months (range: 1–106)

The clinical decision of the treating physician to re-institute antifungal therapy was used as a surrogate marker of relapse.

Bongomin F et al, Clin Infect Pract 2020;5:100015

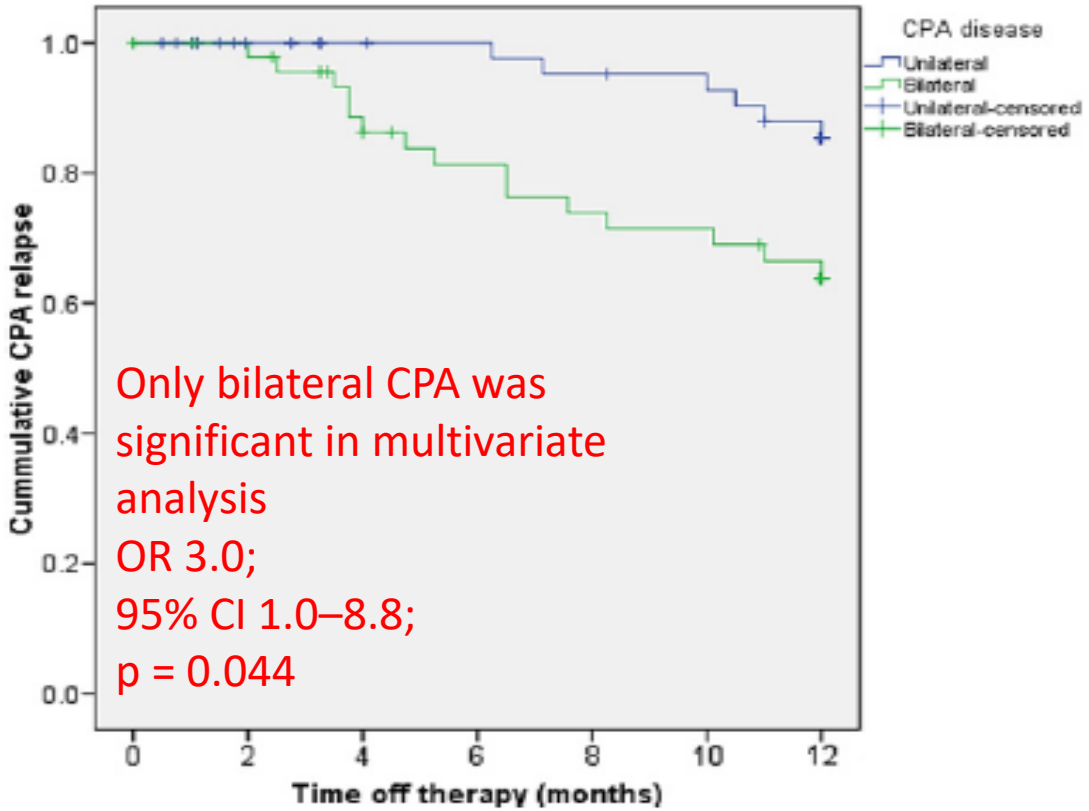
Risk factors for relapse of chronic pulmonary aspergillosis after discontinuation of antifungal therapy

Felix Bongomin [a,b], Akaninyene Otu [a,c,*], Chris Harris [a], Philip Foden [d], Chris Kosmidis [a], David W. Denning [a]

102 patients who discontinued therapy – retrospective analysis

Table 2
Univariate analysis for risk factors for relapse of chronic pulmonary aspergillosis.

Parameter	Total (n = 102)	Non-relapse (n = 81)	Relapse (n = 21)	p-Value
Bilateral CPA disease	48 (51)	33 (69)	15 (31)	**0.01****
Unilateral CPA disease	54 (49)	48 (89)	6 (11)	
No aspergilloma	26 (31)	24 (92)	2 (8)	**0.06***
Aspergilloma	76 (69)	57 (75)	19 (25)	
Single aspergilloma	33 (43)	27 (82)	6 (18)	0.23
Multiple aspergilloma	43 (57)	30 (70)	13 (30)	
Duration of therapy before discontinuation, median (range) (months)	19 (1–106)	21.3 (1–106)	15.8 (2–90)	0.35
Therapy prior to discontinuation				
Itraconazole	8 (8)	8 (100)	0 (0)	0.28
Voriconazole	61 (60)	47 (77)	14 (23)	
Posaconazole	31 (30)	25 (81)	6 (19)	
Isavuconazole	2 (2)	1 (50)	1 (50)	
Reason for discontinuation of therapy				
Adverse events	71 (70)	53 (75)	18 (25)	0.48
Triazole resistance	20 (20)	18 (90)	2 (10)	
Adverse events and triazole resistance	5 (5)	4 (80)	1 (20)	
Clinical failure	5 (5)	5 (100)	0 (0)	
Clinical stability	1 (1)	1 (100)	0 (0)	



Only bilateral CPA was significant in multivariate analysis
OR 3.0;
95% CI 1.0–8.8;
p = 0.044

Bongomin F et al, Clin Infect Pract 2020;5:100015

Predictors of mortality in chronic pulmonary aspergillosis

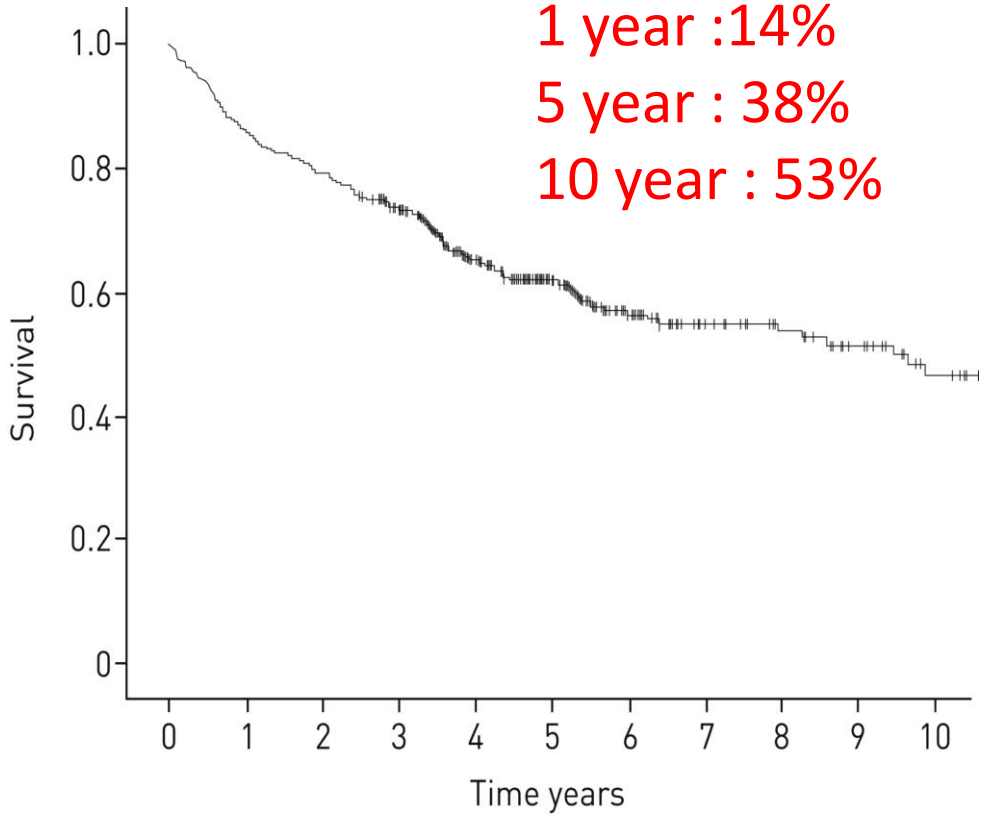
David Lowes[1,3], Khaled Al-Shair[1,3], Pippa J. Newton[1], Julie Morris[2],

387 patients

1 year :14%

5 year : 38%

10 year : 53%

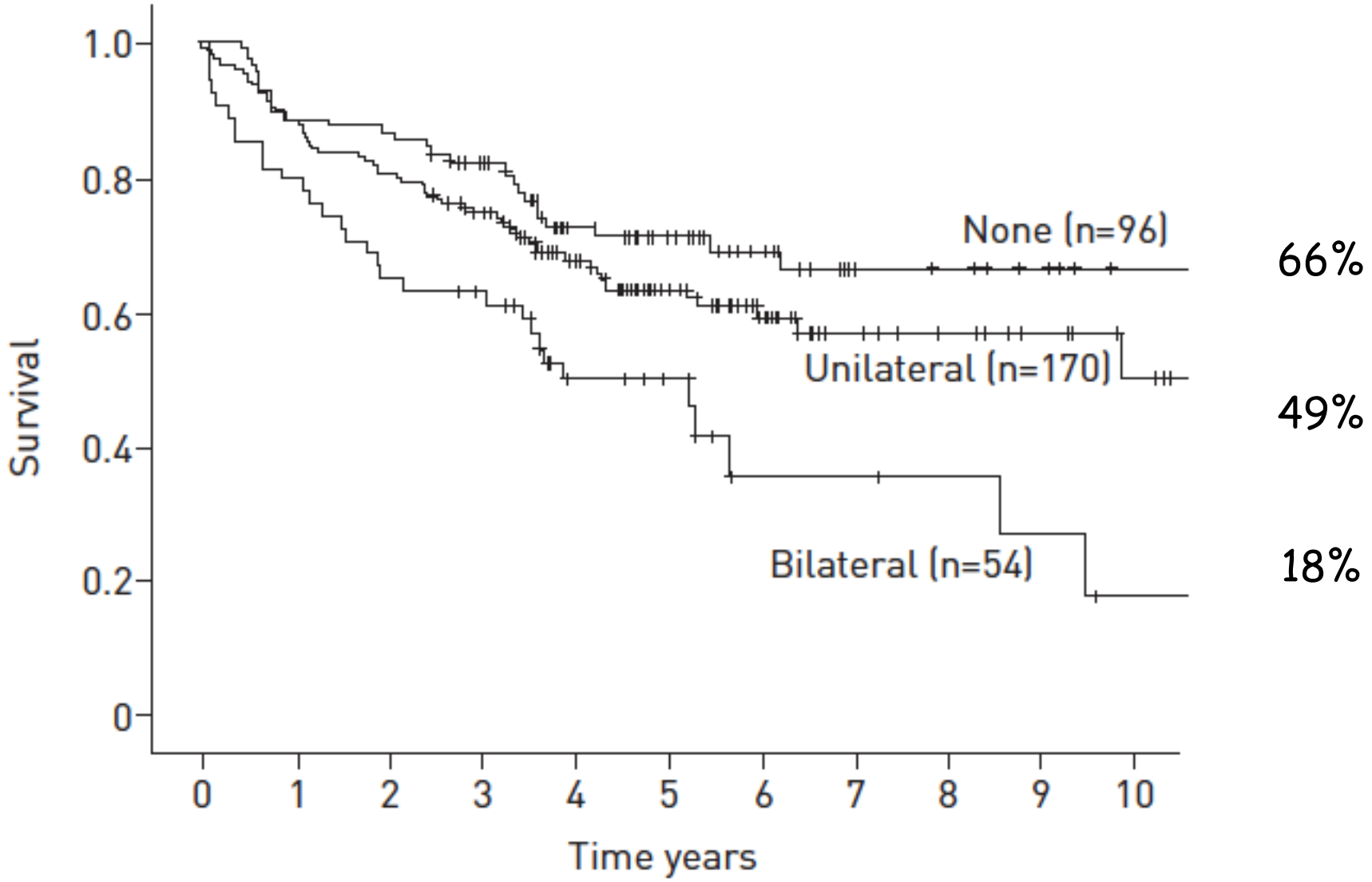


Independent predictors of mortality

- previous NTM disease (HR 2.07, 95% CI 1.22–3.52; p=0.007)
- previous COPD (1.57, 1.05–2.36; p=0.029)
- age (1.05, 1.03–1.07; p<0.001)
- SGRQ activity score (1.02, 1.01–1.03) per unit increase, p<0.001)
- Albumin (0.92, 0.87–0.96 per $g \cdot L^{-1}$; p<0.001)

Lowes et al, Eur Resp J 2017 49: 1601062

Aspergilloma and survival



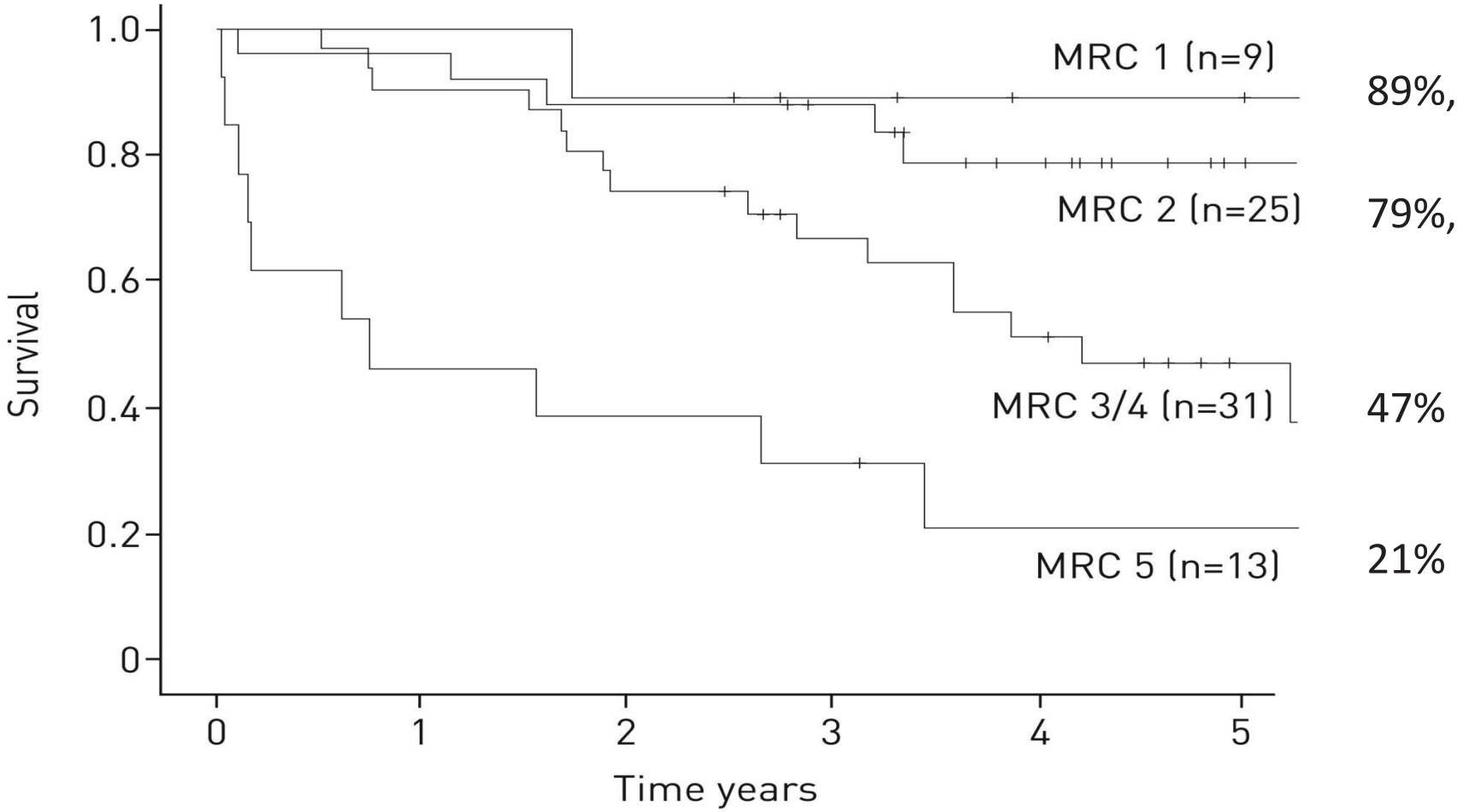
66%

49%

18%

Lowes et al, Eur Resp J 2017 49: 1601062

Dyspnea score and survival



Lowes et al, Eur Resp J 2017 49: 1601062

ORIGINAL ARTICLE

mycoses WILEY

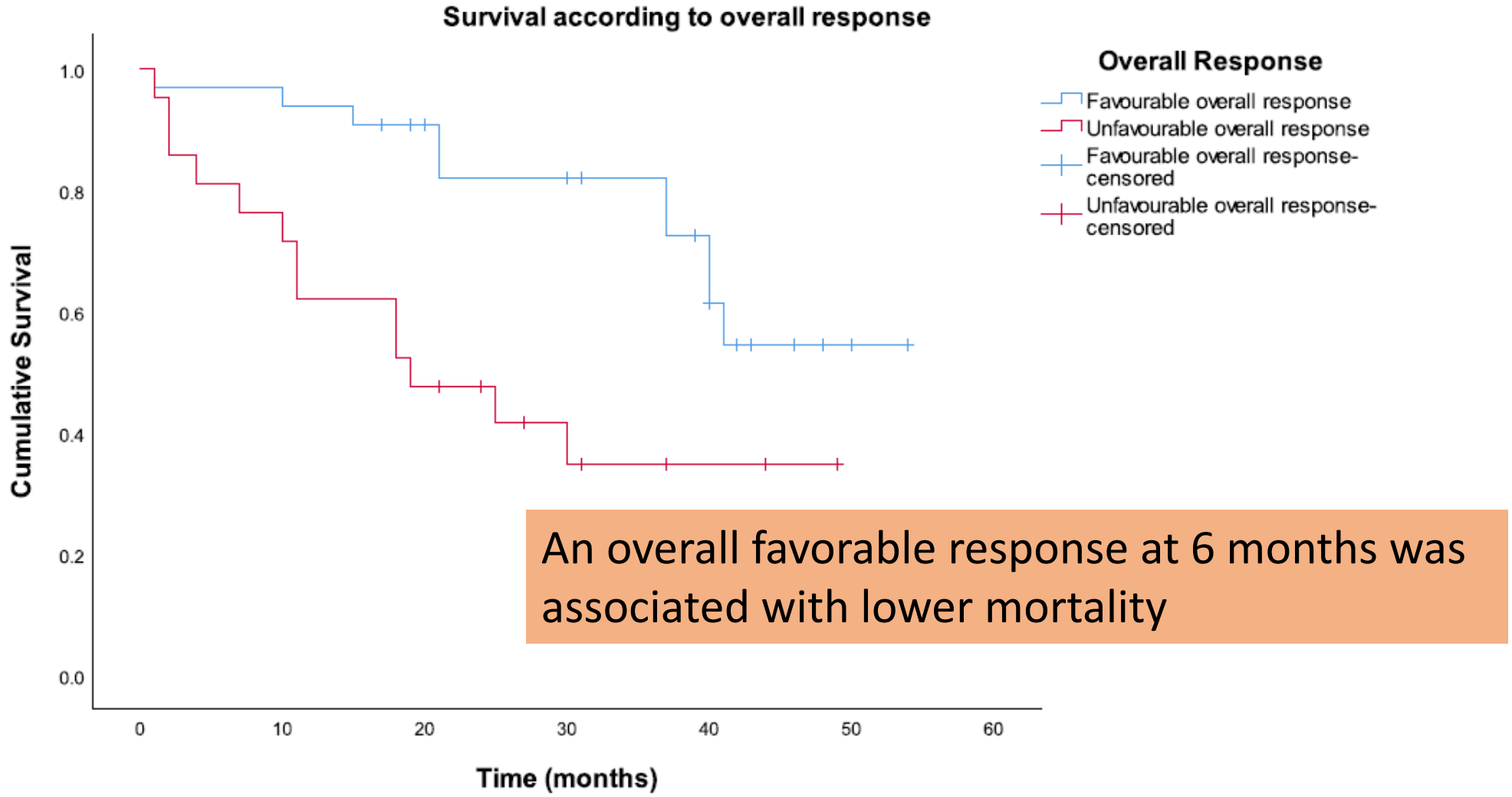
Predictive factors for treatment response and mortality in chronic pulmonary aspergillosis

Chris Kosmidis[1,2] | Holly Smith[2] | Guy Mollett[2] | Chris Harris[2] | Suha Akili[2] | Rohit Bazaz[1,2]

- 59 patients were included with a mean age of 61 years.
- In total 24 (41%) patients died during follow up. (Mean follow up time was 35.6 (SD 15.5) months.
- On univariate analysis, high CRP, low albumin, and high Aspergillus IgG were associated with higher mortality

Conclusion: mortality in CPA is driven mainly by the chronic fungal infection itself rather than the underlying disease

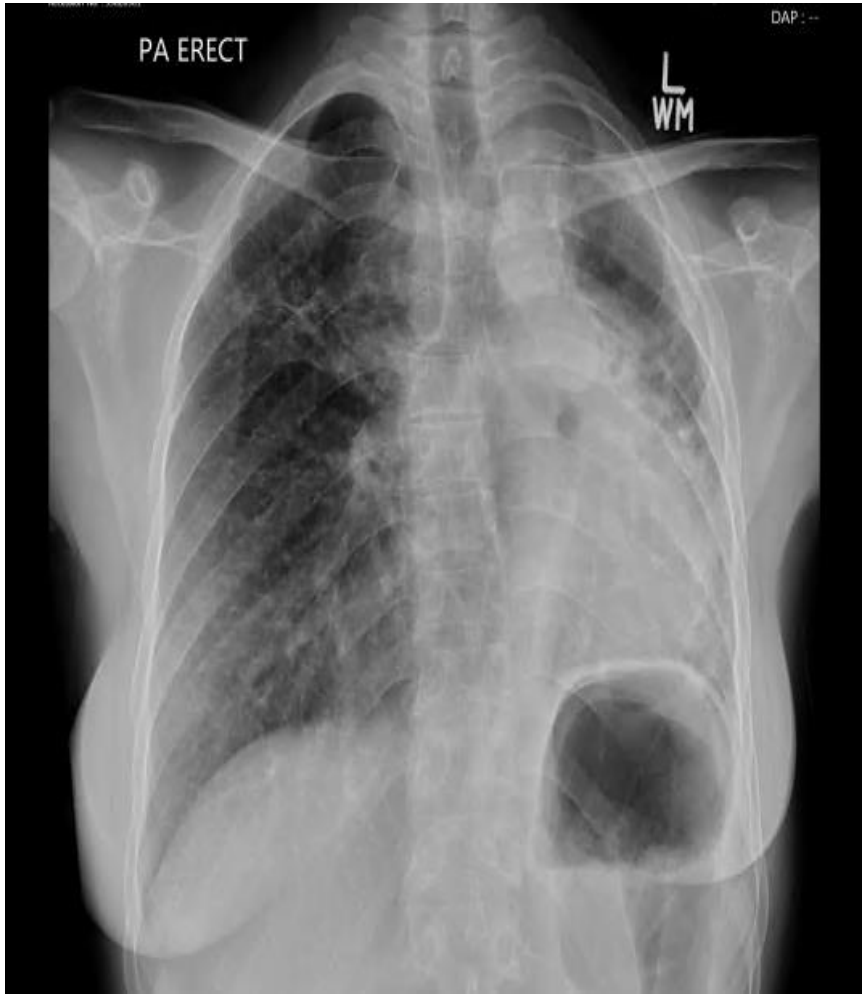
Kosmid C et al. Mycoses. 2023;66:960–968



F I G U R E 1 Kaplan–Meier curve of survival according to overall response (favourable response defined as: clinically better/stable and radiologically better/stable).

Kosmid C et al. Mycoses. 2023;66:960–968

34 yrs. Female with refractory CPA



P2074

Open-Label Study to Evaluate the Efficacy and Safety of SCY-078 (Ibrexafungerp) in Patients with Fungal Diseases that are Refractory to or Intolerant of Standard Antifungal Treatment (FURI)

Dr. Syed Faisal Mahmood(site PI)[1], Dr. David Anguelo[2], Dr. Michelle Middle[2], Dr. Nkichie Azie[2], Dr. Joveria Farooqi[1], Dr. Muhammad Irfan[1], Dr. Nosheen Iqbal[1], Dr. Ali Zuberi[1], Dr. Aliya Begum[1], Dr. Shazia Abrar[1], Dr. Ammara Muzammil[1]
[1]Aga Khan University, Karachi, Pakistan. [2]Scynexis, New Jersey, USA

Introduction

- Ibrexafengerp is a novel antifungal
- Glucan synthase inhibitor (GSI)
- Member of a new class of triterpenoid antifungal agents
  - Oral
  - Broad Spectrum (yeasts and molds)
  - Very good safety profile
  - Low resistance noted

Objectives

- Efficacy and safety of Ibrexafungerp in the treatment of relapsed, are refractory to or intolerant to treatment fungal infections
- Include
- Candidemia and Candidiasis
  - Chronic Pulmonary Aspergillosis (CPA)
  - Invasive Pulmonary Aspergillosis (IPA)
  - Allergic Bronchopulmonary Aspergillosis (ABPA)
  - Esophageal Candidiasis
  - Oropharyngeal Candidiasis
  - Vulvovaginal Candidiasis (VVC)
  - Disseminated fungal infections

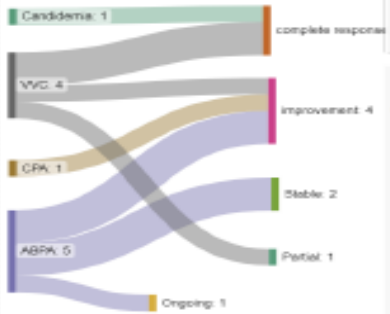
Study Site

- Multicenter, open-label, non-comparator, single-arm study.
  - 34 sites
  - Participating countries are US, UK, Austria, Germany, Netherlands, Canada and Pakistan.
  - In Pakistan, AKUH is the only study site.

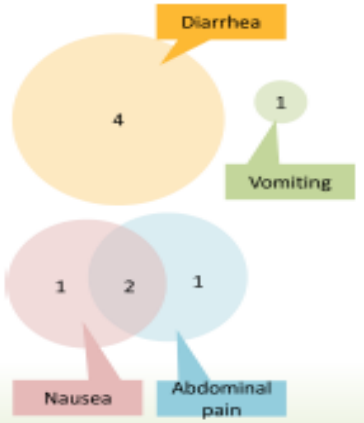
Enrollment (Nov'2021-Sept'2022)

Pre-screened	Screened	Enrolled
233	19	11

Enrollment by site and outcomes



Adverse effects



Inclusion and exclusion criteria

- Inclusion
  - Adults
  - Documented refractory, relapsed fungal infection or intolerant to treatment
- Exclusion
  - CNS disease
  - Elevated LFTs
  - Unstable patients

Results

- To date 11 patients have been enrolled from this site
  - 1 candidemia
  - 1 CPA
  - 5 ABPA
  - 4 VVC
- Overall
  - 7 patients showed complete response or significant improvement
  - 2 patients showed stable response
  - 1 patient showed a partial response
  - No failures
- No serious side effects
  - GI disturbance most common in 9 participants

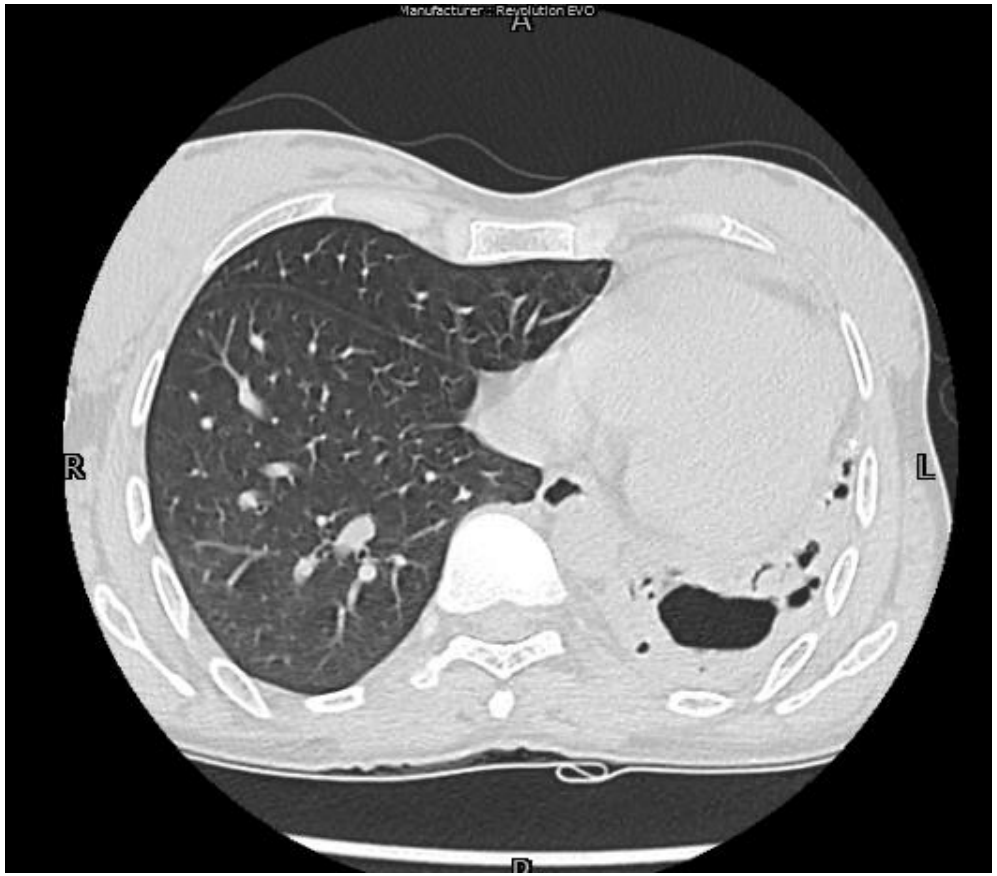
Conclusion

Ibrexafungerp has the potential to be a viable option for treating refractory serious fungal infections Further data is awaited to define its role in fungal therapeutic

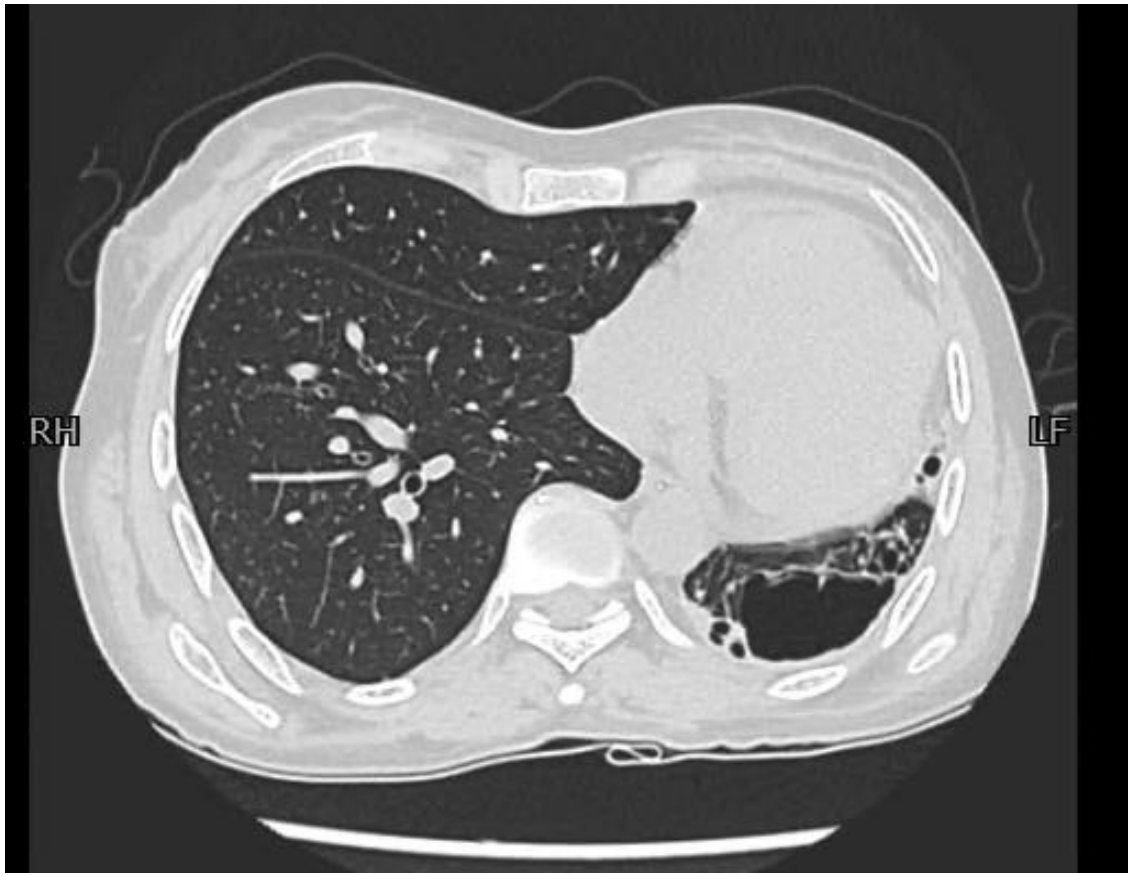
33rd ECCMID EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES
Copenhagen, Denmark
15–18 April 2023

•Clinical Trial NCT03059992

34 yrs. female with refractory CPA- Ibrexafungerp for 6 month

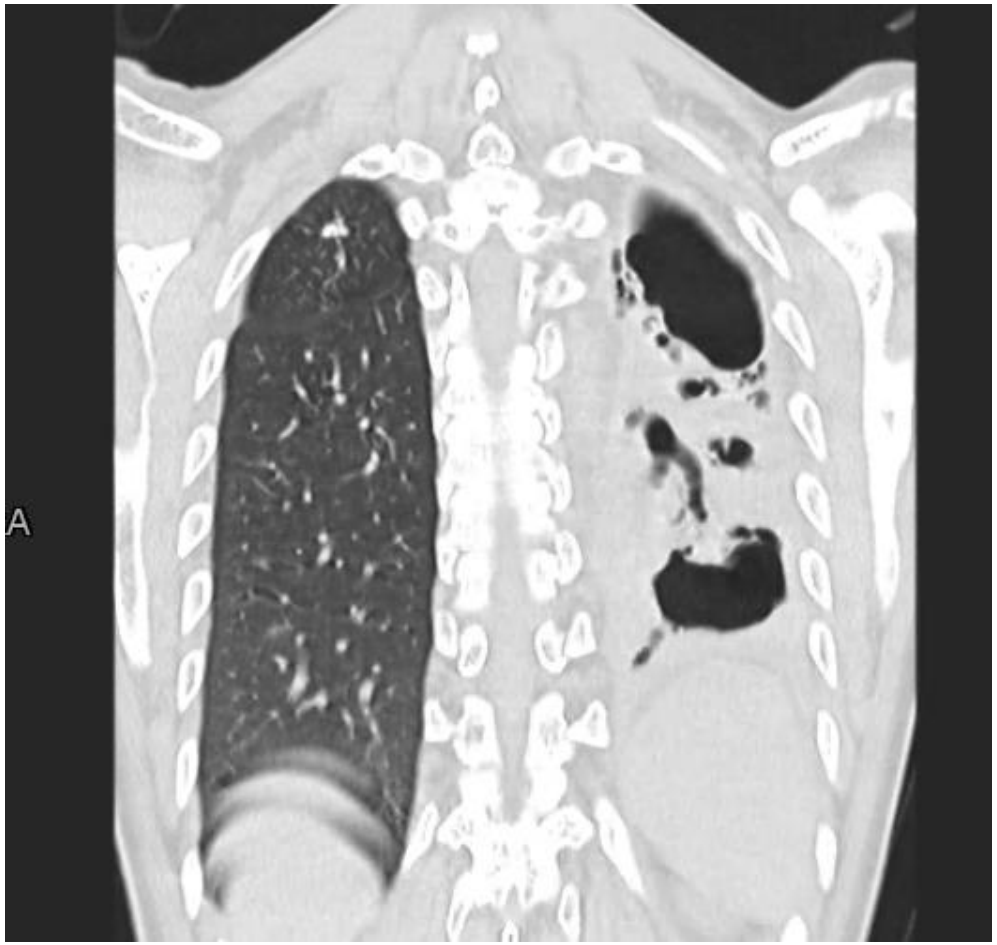


Feb 2022

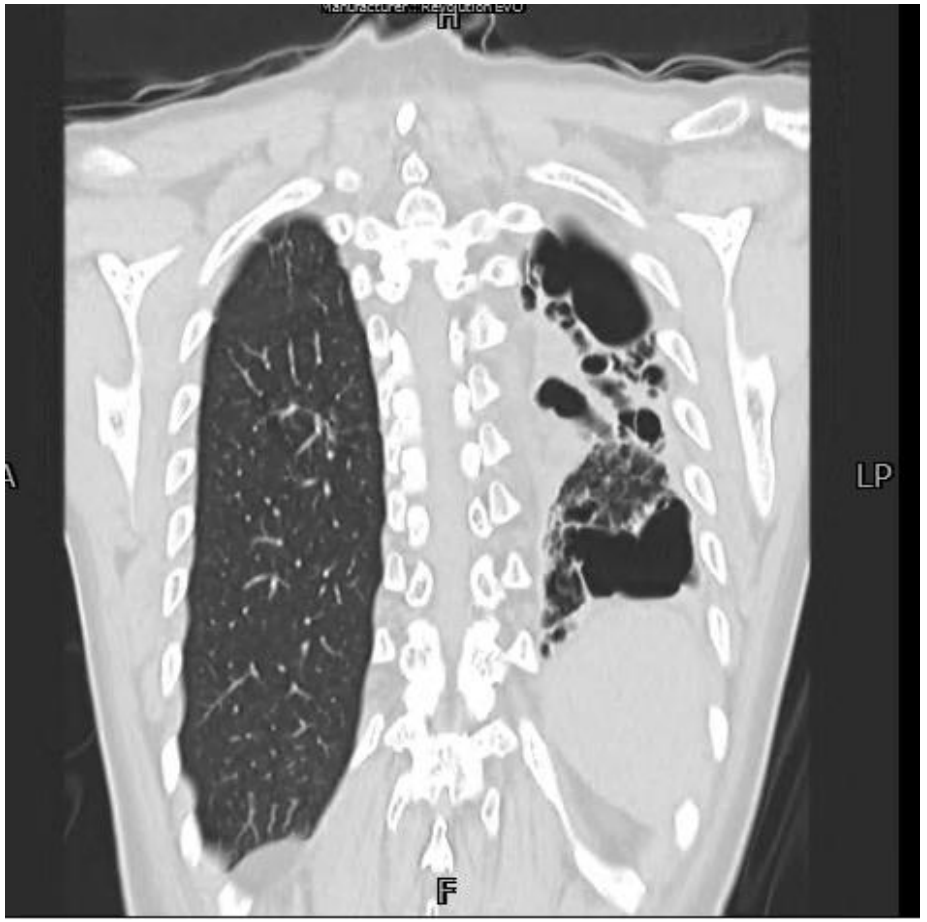


Sept 2022

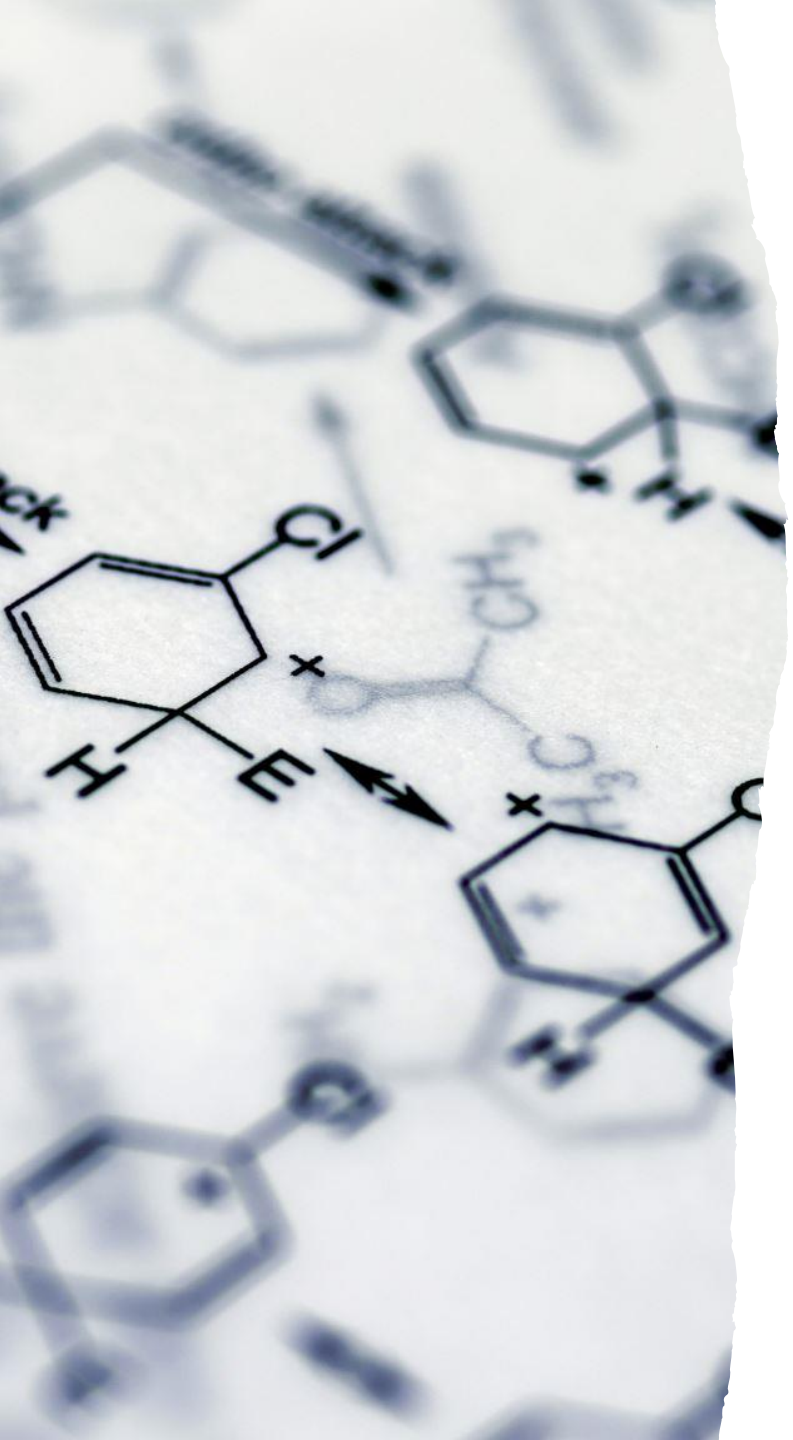
34 yrs. female with refractory CPA- Ibrexafungerp for 6 month



Feb 2022



Sept 2022



Novel Antifungal Therapies

- A number of novel antifungal agents (e.g., Fosmanogepix, olorofim , ibrexafungerp, nikkomycin Z, rezafungin, opelconazole) are in various stages of development

- Their role, if any, in the treatment of chronic pulmonary aspergillosis is yet to be established

Summary

- Many potential CPA patients exist specially in countries with high TB prevalence
- At times it may remain silent but can be lethal and usually associated with high morbidity and mortality
- Diagnostic mainstay; advanced imaging and *Aspergillus* serology, are not readily available in many low resource settings
- Itraconazole & voriconazole remains the initial treatment of choice
- Limited data on posaconazole and isavuconazole- comparable results with better tolerance

Summary

- 12 months treatment is associated with better outcome
- Favourable response at 6 month is associated with lower mortality
- Novel antifungals are in pipeline, but their role is yet to be established
- Lack of awareness among pulmonologists/physicians/ microbiologists and TB control program in LMICs
- Access to readily available diagnostics, in addition to algorithms that easily identify patients with CPA, will improve patient care and outcomes
- Clinical research - to address key questions and provide additional information on the most beneficial therapeutic options


THANK YOU!