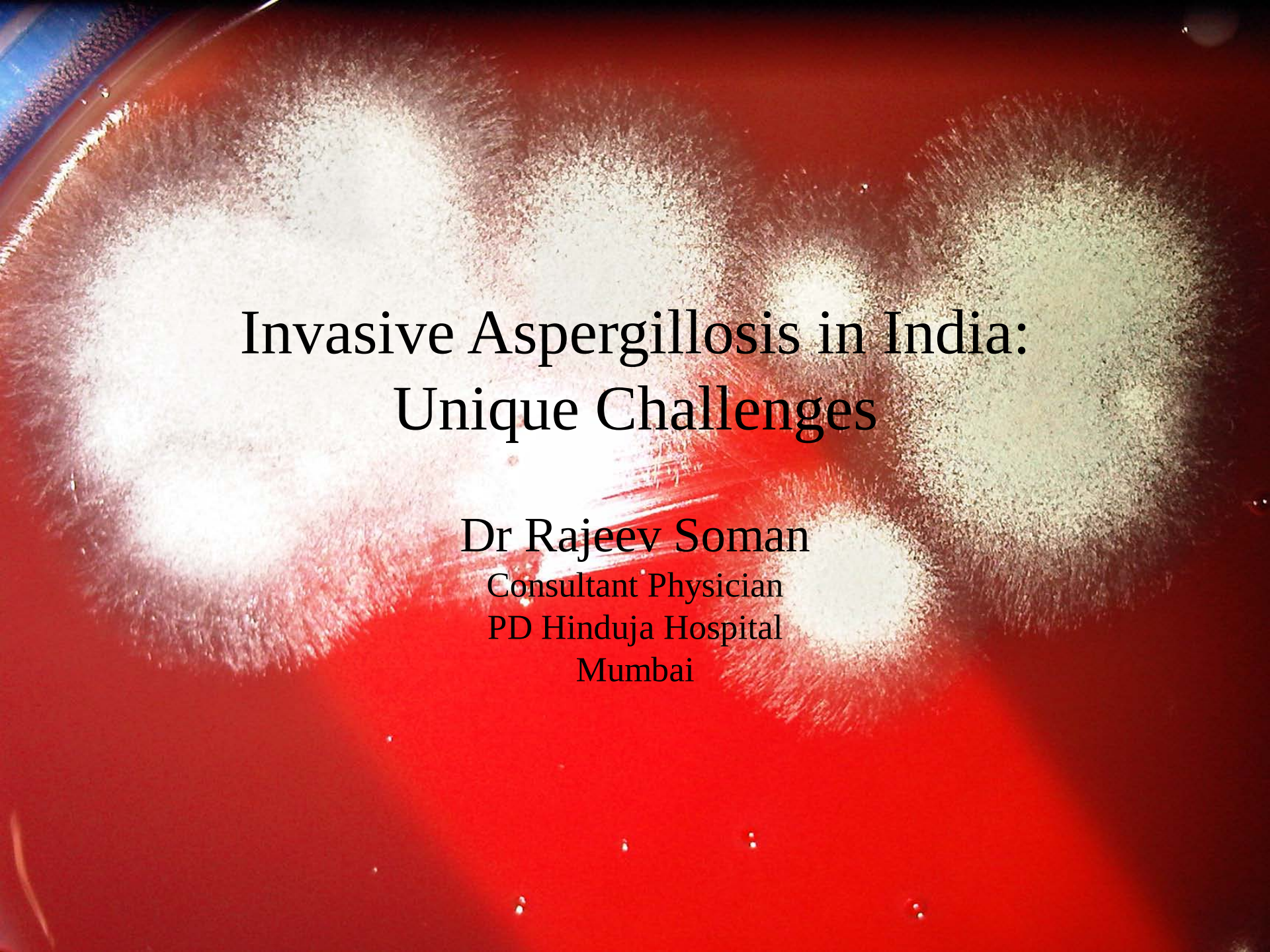

Invasive Aspergillosis in India: Unique Challenges

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Aspergillus Challenges

Capable of surviving & thriving in all the diverse environmental conditions in India

Few other infectious agents produce such a variety of infectious & allergic syndromes

Diagnosis requires invasive &/or hi-tech procedures

Management requires pharmacological insights

Prevention needs better identification of target populations

Diagnosis

EORTC/MSG criteria are only for use in clinical studies
Failure to meet criteria does not rule out IA
Conceptual framework tempts clinicians to extend it to other patient groups & also to make treatment decisions

Proven IA
Culture from a sterile site or
Culture (to show Aspergillus) & histology (for invasion) from a non sterile site
Difficult due to inaccessibility of the lesion & the physiologic condition of the patient

Probable IPA
Susceptible host
Compatible clinico-radiologic syndrome
Mycological test

Host factors
Conventional neutropenia, immunocompromised states
Non conventional COPD, ICU, malnutrition, liver disease, contaminated IV fluids, needles, ophthalmic surgery, IVDU *Chakraborty A Med Mycol 2011;49(1):s35-47*

Radiologic features
Conventional dense nodule ± halo, cavitation, cresent
Nonspecific in non-neutropenic, overlap with TB
Availability, cost of HRCT

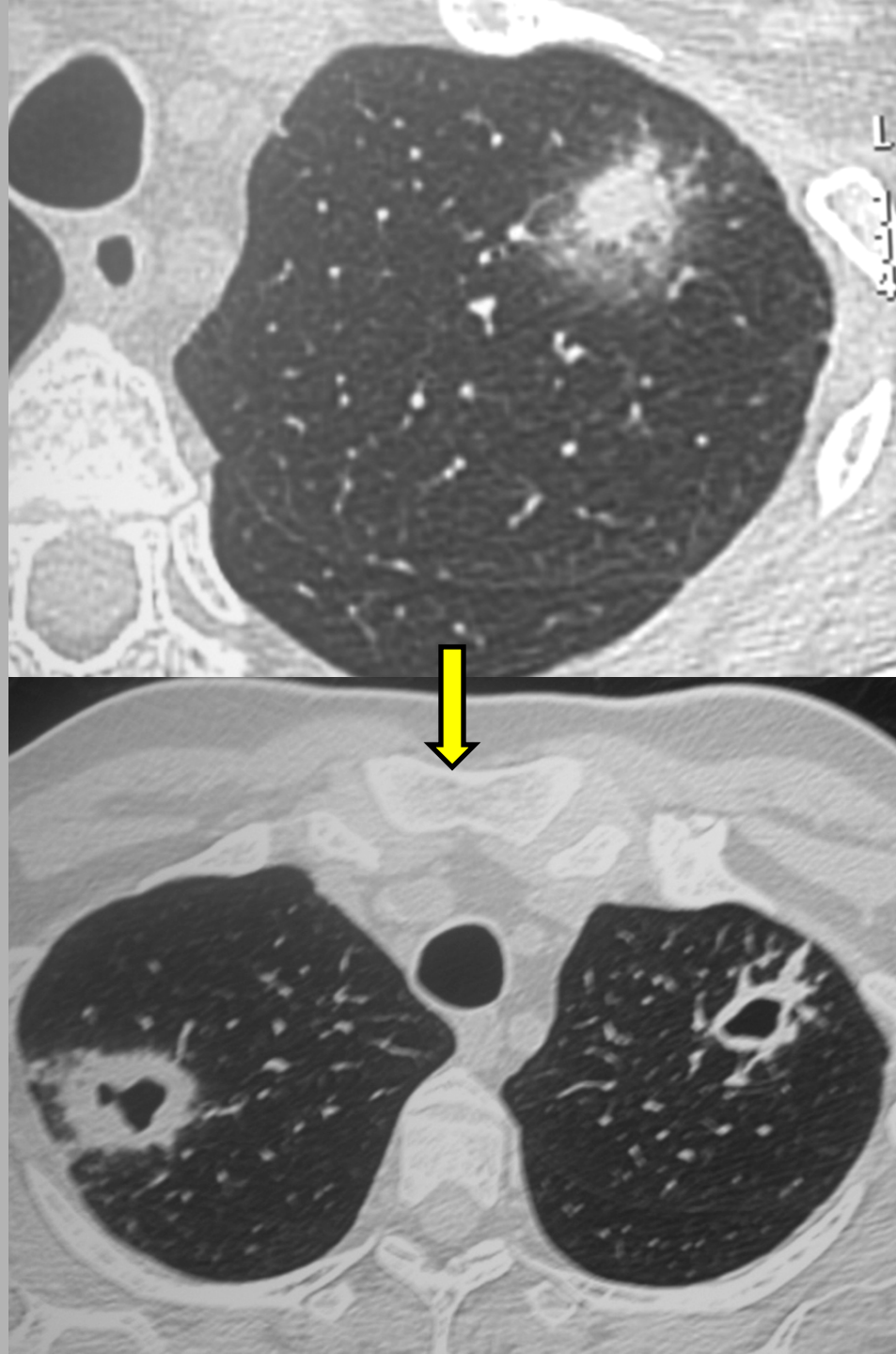
Mycological tests
Sensitivity, specificity, availability, cost

SA 61 M DM LRKT recipient
Tac MMF Prednisolone
3m later cough followed by fever, hemoptysis after 2 w

Dense nodule, halo sign +ve
BAL GM not available
BAL Aspergillus PCR +ve
Later on crescent like sign
Treated with Voriconazole

BAL TB MGIT culture turned +ve after 6 w

Looked like Possible IPA
Turned out to be TB



Does a firm alternative diagnosis
(in a case of Possible IPA)
lead to a
rejected diagnosis of IPA?

NP 55 M LRKT recipient
7 y post transplant AZA PSN
Fever, cough,
Looked like miliary TB
Turned out IPA & Nocardiosis

Sample	BRONCHIAL ALVEOLAR LAVAGE
GRAM STAIN(PRIMARY)	
Pus Cells	OCCASIONAL
Yeast	OCCASIONAL
Fungal Filaments	VERY OCCASIONAL
Culture Fungus	
Culture Fungus	ASPERGILLUS FUMIGATUS *

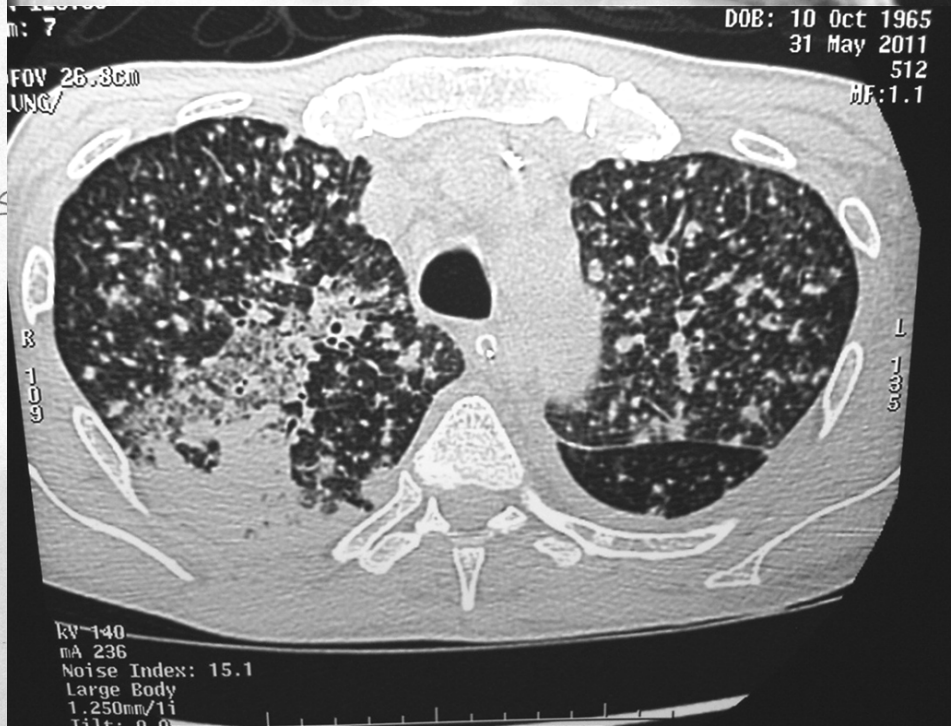
ASPERGILLUS GALACTOMANNAN

Test	Result	Units
ASPERGILLUS GALACTOMANNAN		
Patients value	0.70	
Results	POSITIVE *	

Comments : Test Method : Immunoenzymatic sandwich microplate assay.

ZIEHL NIELSON STAIN (AFB)	
Acid Fast Bacilli	NOT SEEN
Culture Aerobes	NOCARDIA SPECIES *

* GRAM STAIN : GRAM POSITIVE BRANCHING FILAMENTS SUGGESTIVE OF NOCARDIA SEEN.
MODIFIED ZNCF STAIN : ACID FAST BRANCHING FILAMENTS SUGGESTIVE OF NOCARDIA SEEN.



Radiologic criteria from EORTC MSG
Do not apply well to non neutropenic hosts
CT in IPA in SOT recipients Bilateral nodules 74%, consolidation 46%, halo 29%, cavitation 29%, air crescent 3% *Alexander BD M IDSA 2009 abstract#406*

Have been commented on as being nonspecific, transient, observer dependent, not quantifiable, may worsen with treatment & derived from old studies before recent serologic tests & preventive therapy
It is proposed that Probable IPA should be diagnosed without pre-specified radiologic criteria & greater weight should be given to mycological test results *Nucci M CID 2010;51:1273-80*

Mycological tests also have limitations

Smear, culture has suboptimal sensitivity & specificity
PPV varies from 17-72%, > 2 colonies has a high PPV
PCR can be false +ve due to conidia colonizing the airways

GM is released from growing hyphae, may provide a better evidence of actual infection
Maertens J Aspergillosis: from Diagnosis to Prevention 2010
Needs to be performed on site, 3/w, cost constraints
Neofytos D Editorial CID 2010;51:1281-3

False +ve Pip tazo, especially generic (but less likely with BAL GM), lab contamination, rare pathogens (Penicillium)
False –ve In non-neutropenic, with mould active prophylaxis, with Aspergillus tracheobronchitis

In neutropenic GM (index) BAL 100% (1) serum 90% (0.5)

In non neutropenic GM BAL 94.7% serum 36.8%

Maertens J CID 2010;50:1071-2

Due to lesser number of hyphae, smaller zone of infarction & more WBC in peripheral blood

More likely +ve in patients with hemoptysis 52% vs 9%

Park SY CID 2011;52:e149

OD >0.5 serum, >1 BAL *Maertens J CID 2010;50:1071-2*

Dynamic cut off 2 values > 0.5 or 1 of > 0.8

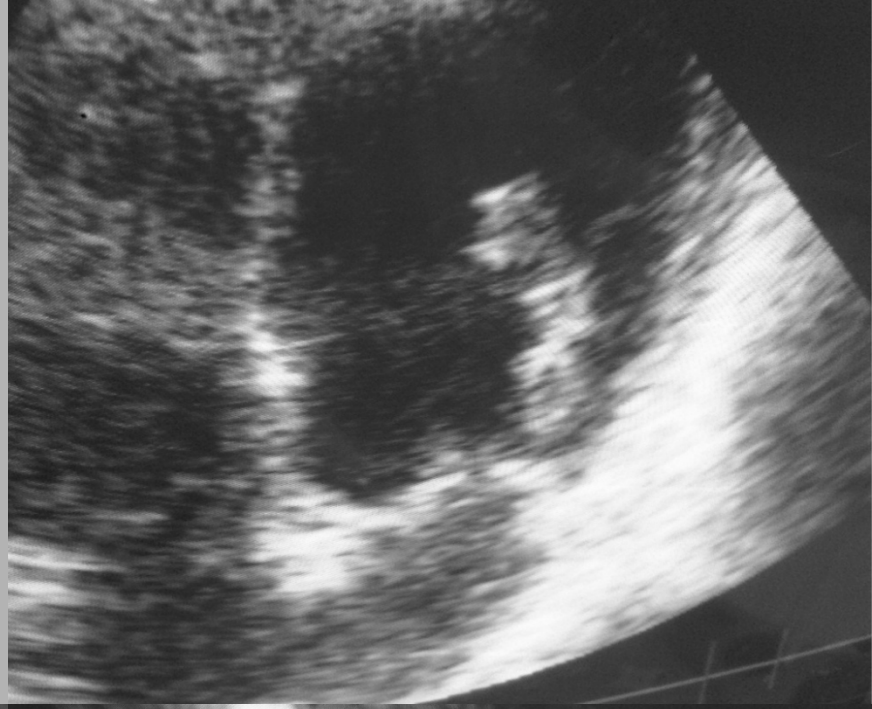
Maertens J Br J Haematol 2004;126:852-60

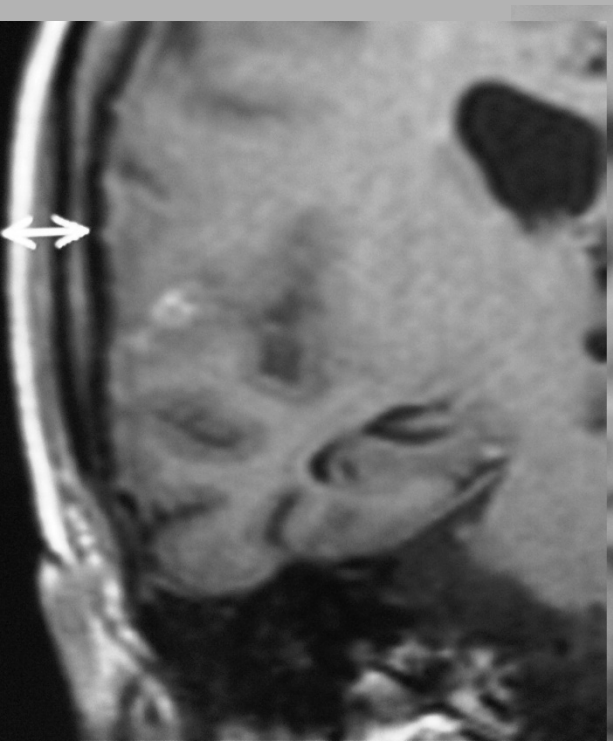
Different thresholds for different patients, samples & purposes such as screening or supporting the diagnosis

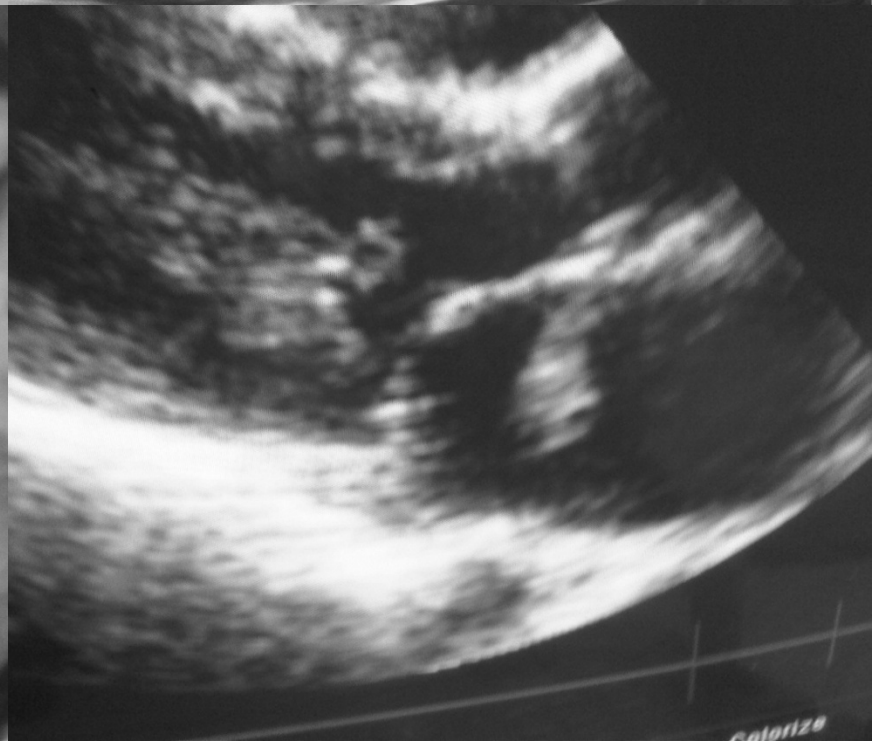
Donnelly JP CID 2010;50:1070-1

Management

JM 55 F SLE on PSN AZA
Presented elsewhere with dyspnea, no fever
4 blood cultures –ve
thought to be LSE or myxoma
Severe headache thought to be tuberculomas started ATT



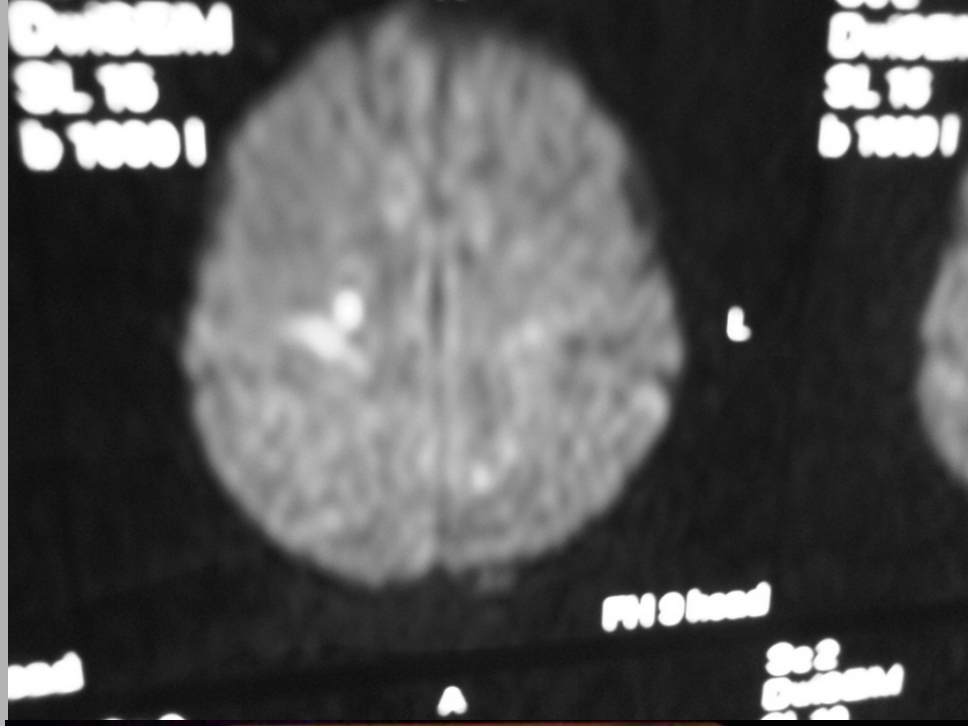


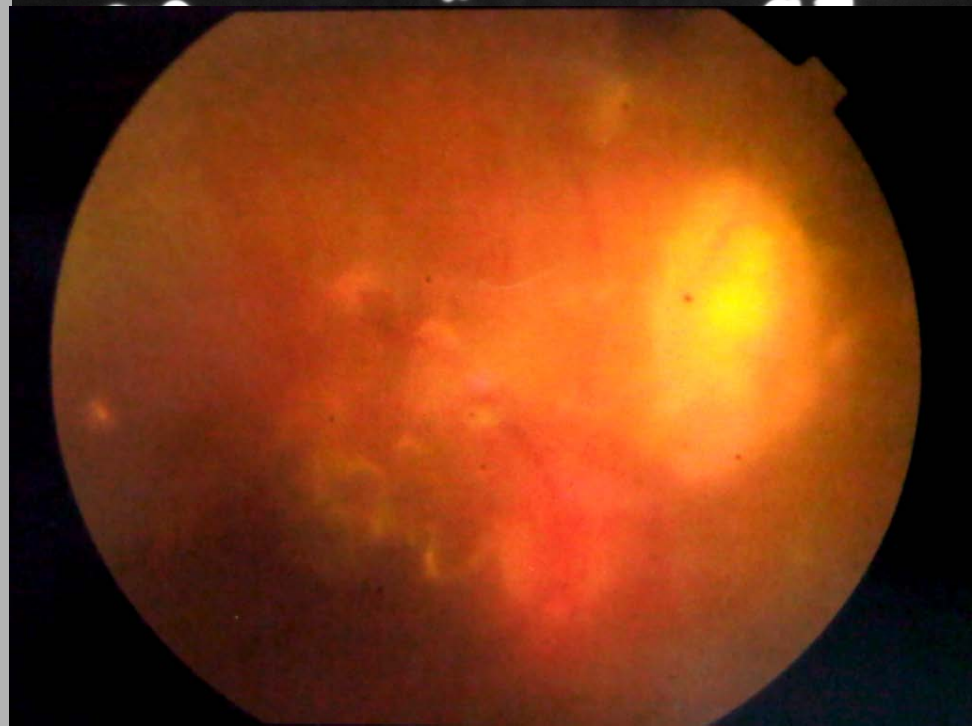


Presented to PDHNH 7 d later with sudden blindness

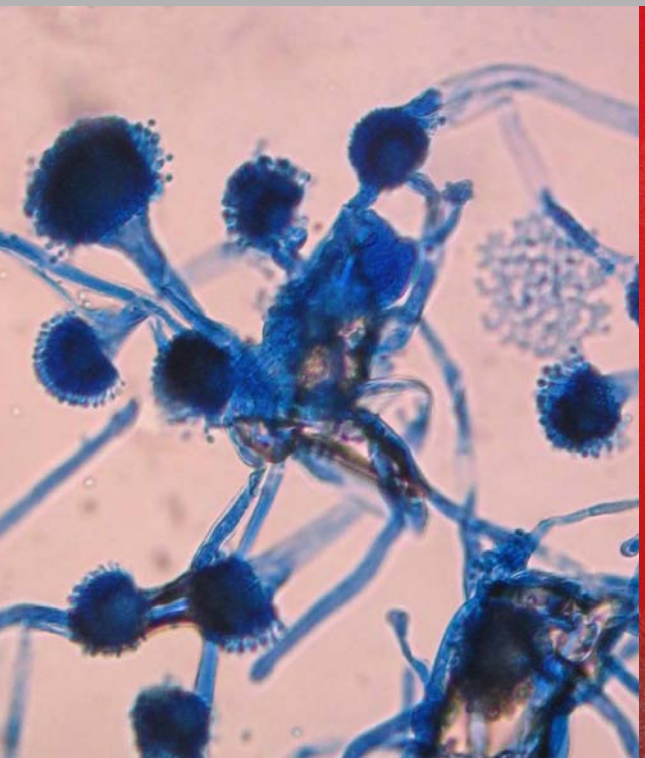
History revealed headache was of sudden onset
Diffusion weighted image showed infarct pattern

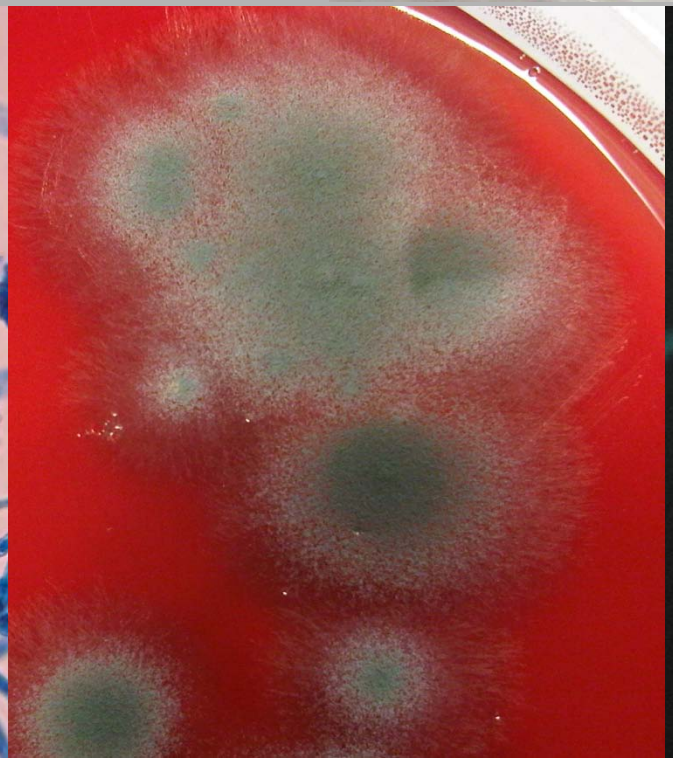
Vitrectomy L eye
string of pearls appearance & necrotic retina
Suspected Aspergillus IE & emboli
ATT was withdrawn
Voriconazole started





At surgery, large vegetations, papillary muscle abscess, vegetations en plaque on the LV free wall, MVR done
High dose Voriconazole maintained & Caspofungin added





Voriconazole drug of choice, clinical experience, cidal for Aspergillus, ocular & CNS penetration
But was on Rifampin for 7 d which reduces Voriconazole levels by 95%, TDM not available

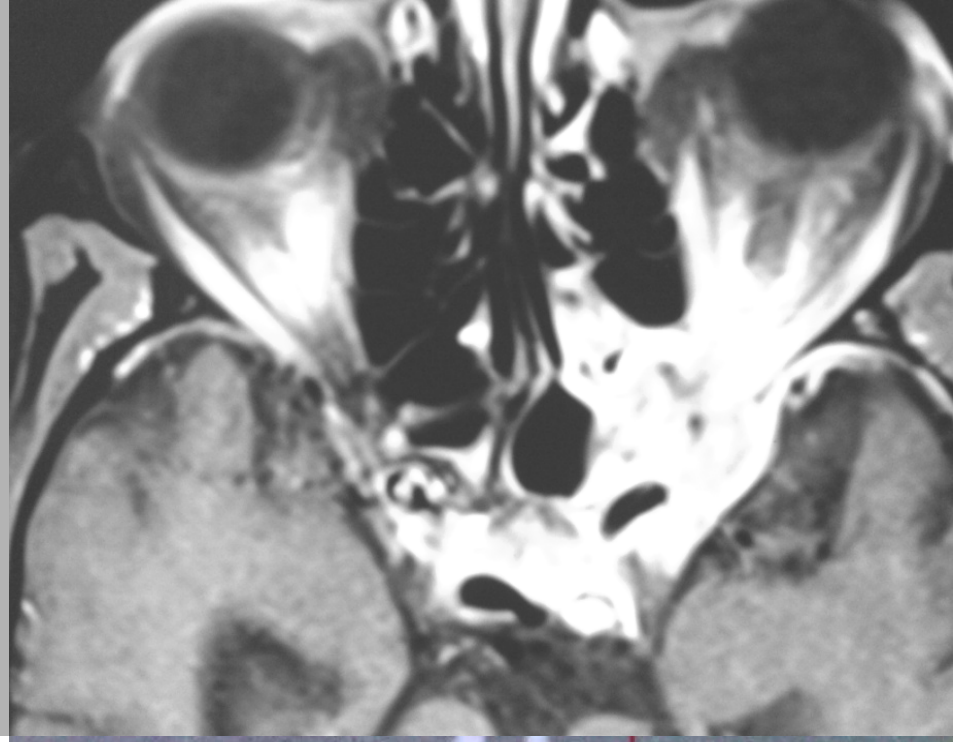
AmB inferior results compared to Voriconazole but some uncertainty exists
Echinocandins not clearly cidal, no ocular & CNS penetration

Potential benefit of combination may be best realized in patients who are at the highest risk of adverse outcome
Singh N Am J Transplantation 2009;9(4):s180-91

Surgery & immunomodulation are important

Dr AK 68 M
Granulomatous invasive fungal rhino sinusitis (FRS)
Long duration > 3m
dense fibrotic reaction, scanty hyphae

Chakraborty A
Laryngoscope 2009;119:1809-18



Tab Akurit 4· 3tab-9am

Zocon (150) 0—1—0
2pm

Tab. Grisceowin (250) 1—0

Tab Wyscolone (10) 1—1

Tab. Blong 1—0·

Aspergillus keratitis

Agriculture & outdoor workers exposed to dust, vegetable matter, injury due to tree branches, swish of a cow’s tail

Ocular procedures

Scrapings for smear, culture

Local & systemic antifungal therapy
Surgery

The drugs for IA have important limitations related to GI absorption, interactions, penetration into various body sites & ADR

They are available in this country ahead of adequate diagnostics & knowledge about their use
There is a wide range in the cost & possibly also of biological activity of products available from various pharmaceutical companies

This has led to inappropriate use, therapeutic failures & an enhanced need for TDM

The prolonged duration of treatment poses further practical difficulties

Prevention

High risk groups who demonstrably benefit
Profound, prolonged neutropenia, lung transplant & some liver transplant recipients
Aerosolized L AmB, Voriconazole, Posaconazole

Warm, dry weather allows greater dispersal of the hydrophobic spores
Targeted prophylaxis at times of high spore circulation & in the presence of severe immunosuppression
Viscoli C CID 2010;50:1598-600

Asepsis & infection control both in the hospital & in community medicine

Conclusion

More awareness about IA as a disease

Unique epidemiology

Better diagnostics

Expertise in management

Targeted preventive strategies

Resource limitation