Aspergillosis

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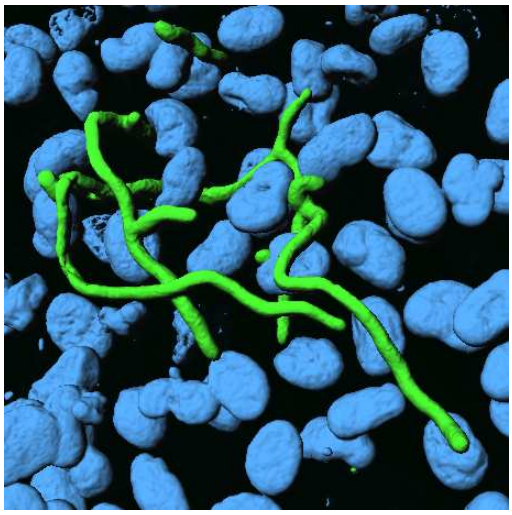
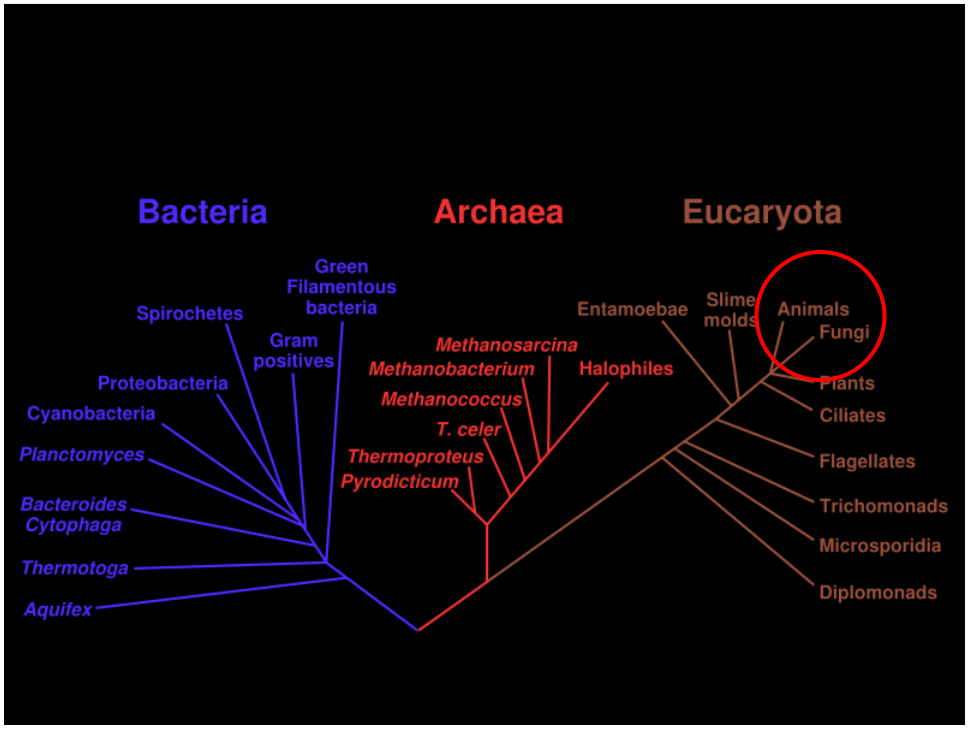
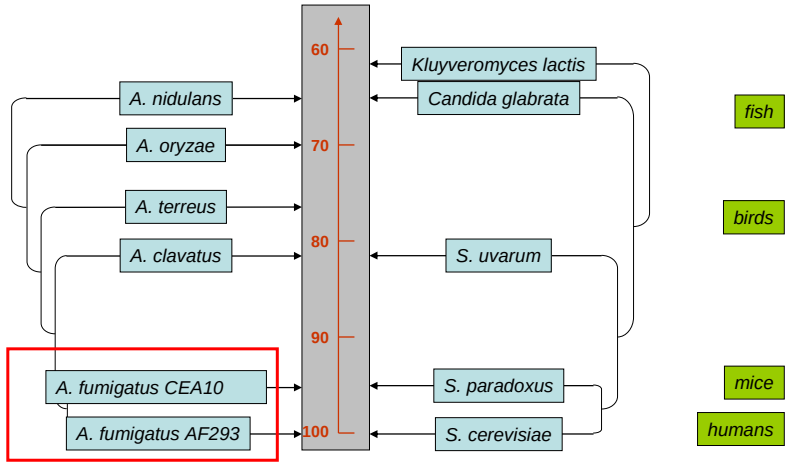




Aspergillus fumigatus genomic sequence now known



Aspergillosis is a spectrum of disease

- Angioinvasive
- Non-angioinvasive

- ABPA
- Extrinsic allergic alveolitis
- Asthma with fungal sensitisation
- Allergic Aspergillus sinusitis

Invasive Disease	Chronic Pulmonary Aspergillosis	Allergic Disease
Significant impairment of systemic immunity	Subtle immunological defects	Dysregulated immunity

Hope *et al* Medical Mycology

Invasive aspergillosis: there have been major advances for clinical care

- A vastly improved understanding of molecular biology
- Dramatically improved understanding of immunology
- Improved diagnostics
  - Galactomannan and 1,3 β-D-glucan
- New drugs & drug classes
  - Voriconazole probably drug of choice
  - Newer triazoles- posaconazole
  - Echinocandins
  - Know that 3 mg/kg liposomal amphotericin B is same as 10 mg/kg
- Improved understanding of:
  - Therapeutic ranges and use of TDM
  - Potential advantages and disadvantages of combinations

Invasive pulmonary aspergillosis in non classical settings

Classical risk groups for invasive aspergillosis

- Prolonged and profound neutropenia
  - AML 8%
  - ALL
  - MDS
- High dose corticosteroids
- CGD 25-40%
- Allogeneic HSCT 11-15%
- Lung Transplant 6-13%
- Heart Transplant 11%
- Small Bowel Transplant 11%
- Others (e.g. neonates, IVDU, near drowning, HIV/AIDS)

Invasive Aspergillosis in Critically Ill Patients without Malignancy

Wouter Meersseman, Stefaan J. Vandecasteele, Alexander Wilmer, Eric Verbeken, Willy E. Peetermans, and Eric Van Wijngaerden

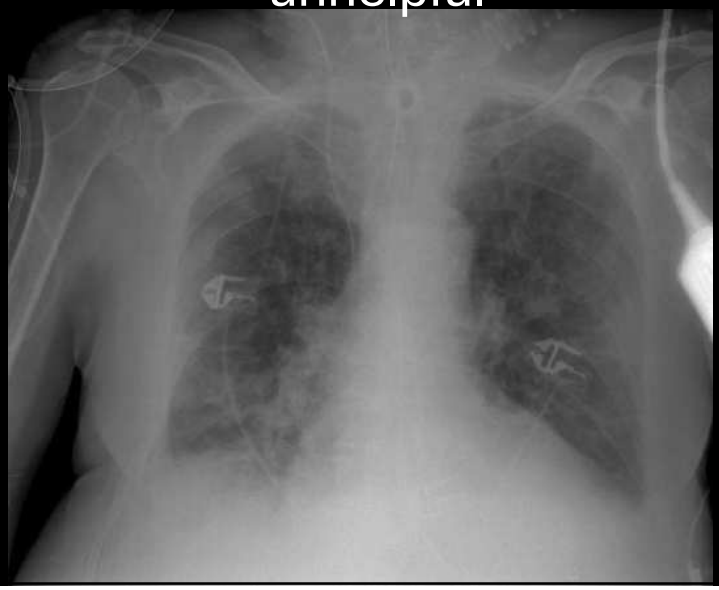
Medical Intensive Care Unit and Infectious Diseases Unit, Department of General Internal Medicine; and Department of Pathology, University Hospital, Leuven, Belgium

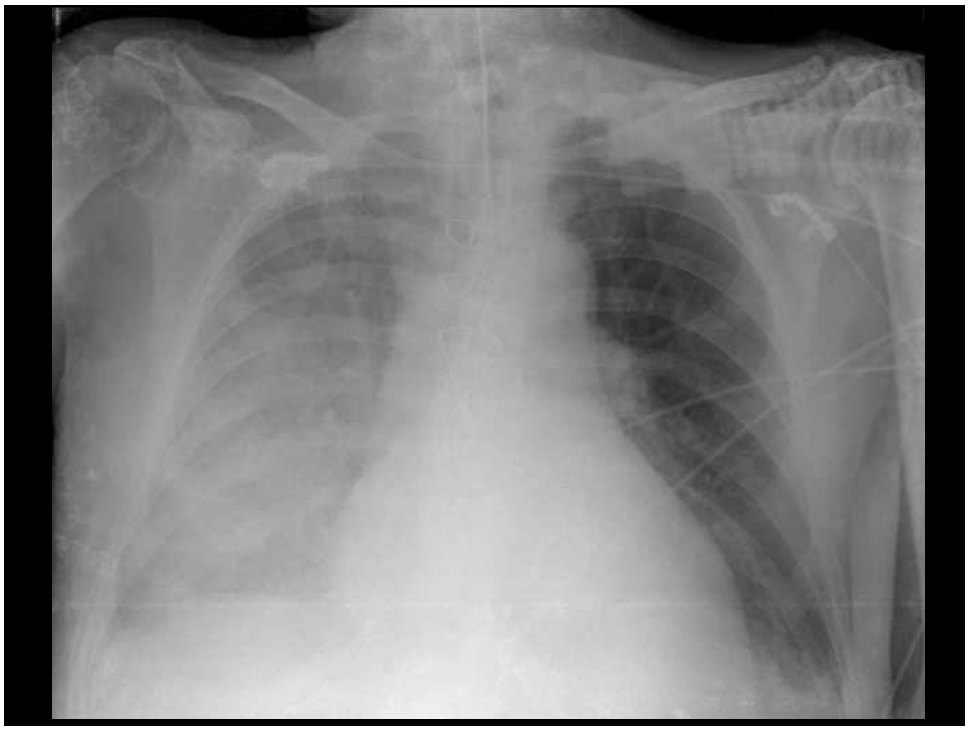
- 127 of 1850 (6.9%) consecutive medical ICU admissions with IA or colonisation (micro/histol).
- 89/127 (70%) did not have haematological malignancy
- 67/89 proven/probable IA, 33 of 67 (50%) COPD
- Predicted mortality = 48%, actual 80%

First hurdle for ICU: standard diagnostic tests have problems

- Sensitivity of cultures in BAL probably low
  - ~50% in neutropenic patients
- The prevalence in non-classical groups is relatively low, which has immediate implications for the PPV of diagnostic tests
- Specificity potentially compromised by patients receiving piperacillin/tazobactam

2nd Hurdle: Radiology completely unhelpful





What is a reasonable practical approach to this problem?

- Getting serial data helpful
- High-level input required from the microbiology lab, because interpretation is always difficult
- I order a CT on all patients looking for nodules
- If there is clinical and radiological disease/deterioration and established microbiological diagnosis, then difficult to withhold therapy
- I tend to start with voriconazole,
  - Other triazoles, polyenes and echinocandins may be reasonable choices depending on the context

Other manifestations of pulmonary aspergillosis

Chronic pulmonary aspergillosis

So, what is chronic pulmonary aspergillosis?

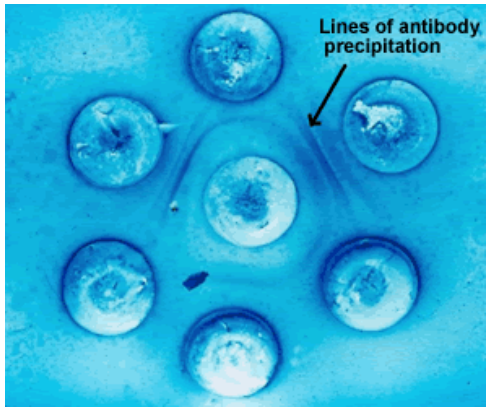
A progressive syndrome characterized by:

1. Chronic respiratory symptoms
2. Disease arising within the context of *pre-existing* structural lung disease
3. The clinical course is very slow (months-years)
4. Positive *Aspergillus* serology (IgG, IgE)

Hope *et al* Medical Mycology 2005

Aspergillus serology is a cornerstone of the diagnosis

- Patients invariably have positive *Aspergillus* precipitins
- Many have mildly elevated total IgE and *Aspergillus* specific IgE
- IgE levels not as high as ABPA



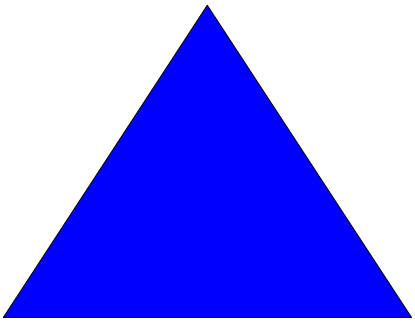
Denning *et al*, Clin Infect Dis 2003; 37:S265

Patients with CPA are generally terribly symptomatic…and do poorly

- In the majority, there are chronic debilitating symptoms
- Symptoms include:
  - Weight loss
  - Cough ± haemoptysis
  - Weakness, lethargy
  - Shortness of breath
- Accurate mortality figures not available since introduction of triazoles

Pathogenesis

Structural Lung Disease



Generalized immunological defects

Diabetes, alcohol, corticosteroids

Localized immunological defects

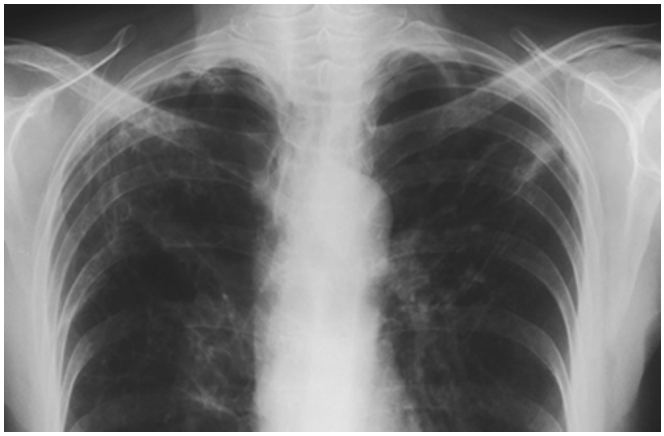
Surfactant, MBL

Disease within context of *pre-existing* structural lung disease

- Tuberculosis especially common
- Atypical mycobacteria
- Sarcoidosis
- Recurrent pneumothorax
- Prior pulmonary surgery
- ABPA

The clinical course is slow & progressive

1999



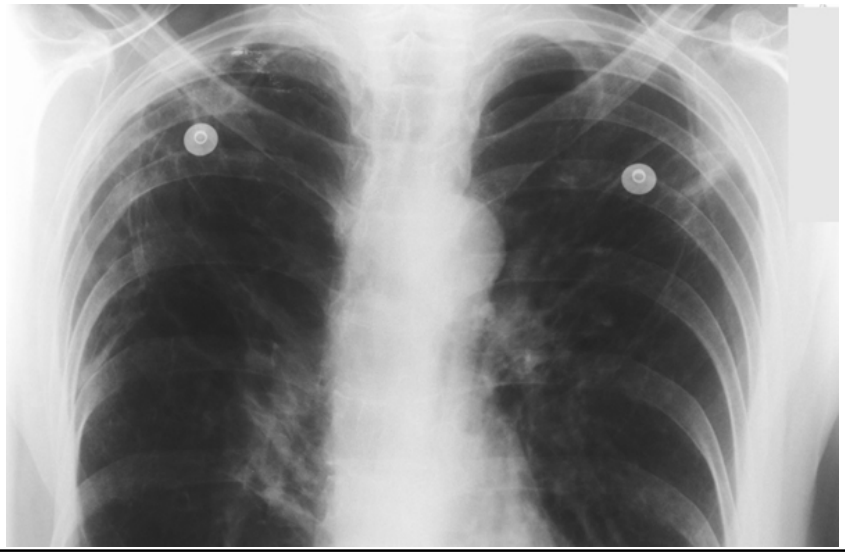
Smoker

Emphysema

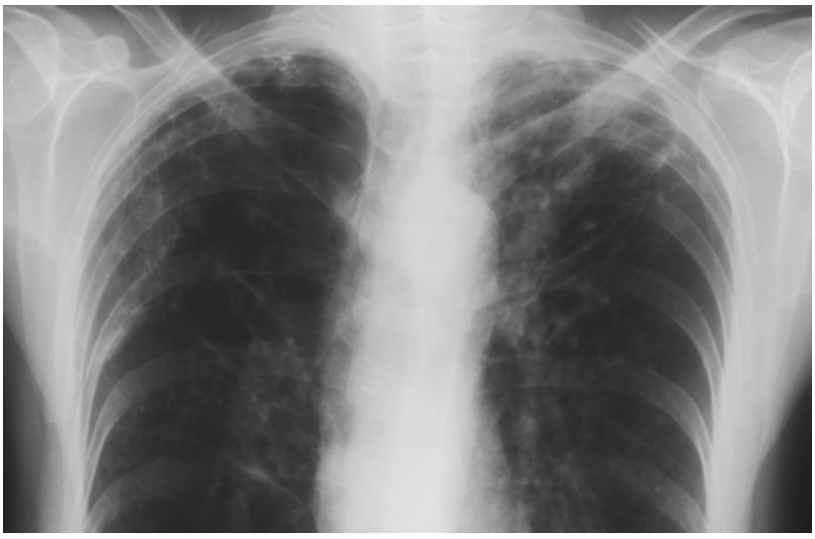
PNX

MTB

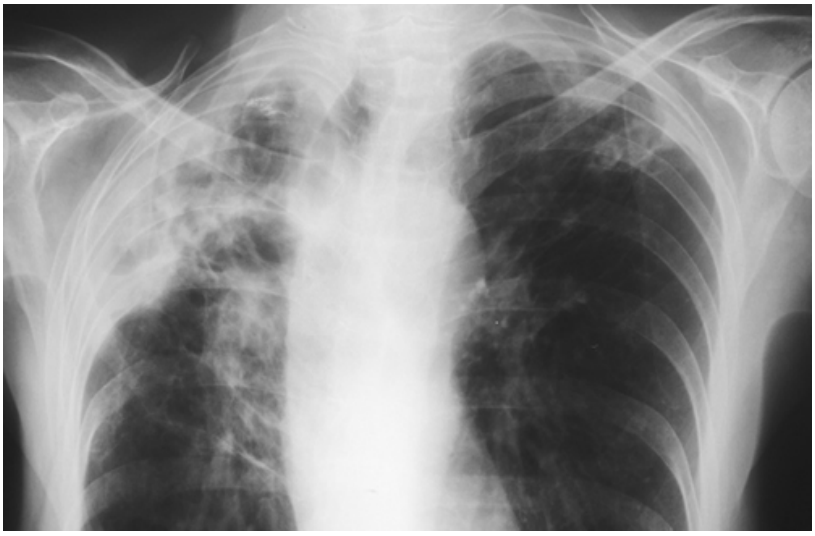
2000



2002

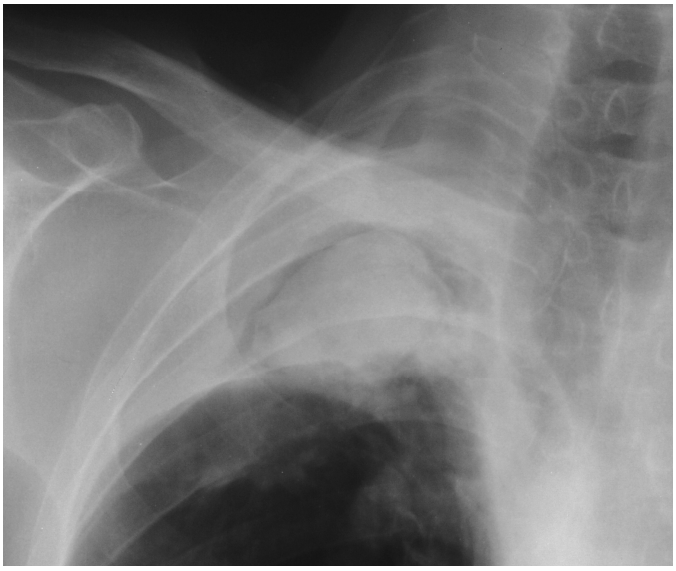


2003



What is the spectrum of chronic pulmonary aspergillosis?

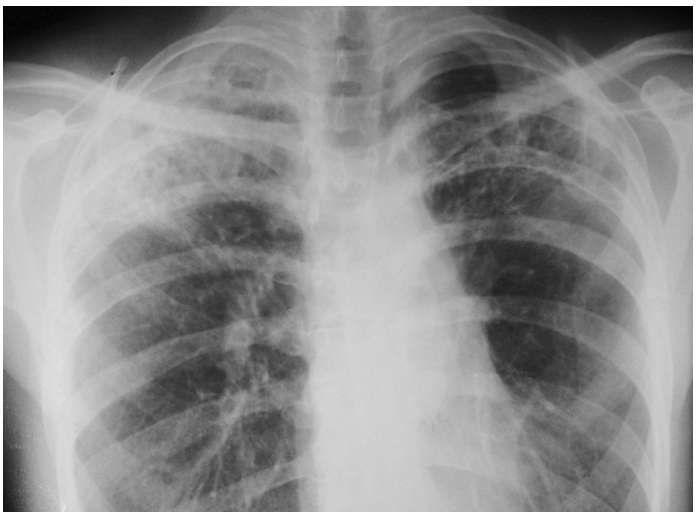
Simple (single) aspergilloma



Cough
Tiredness
Haemoptysis

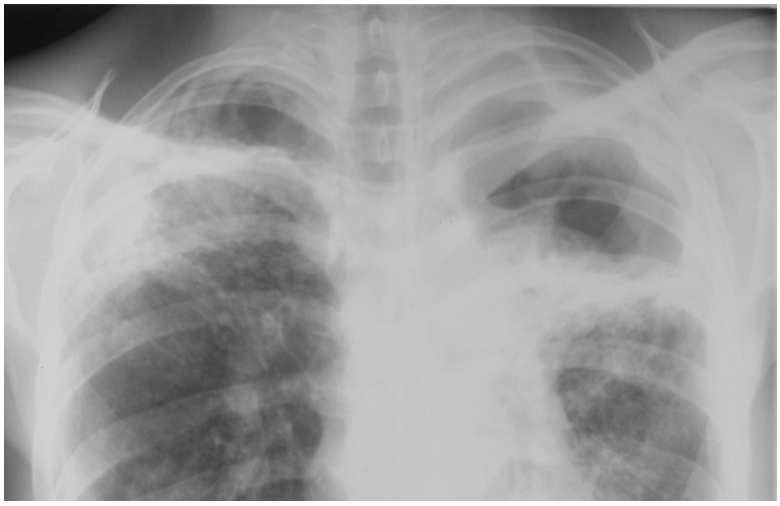
Chronic Cavitary Pulmonary Aspergillosis:

Progressive pulmonary cavitation is the key



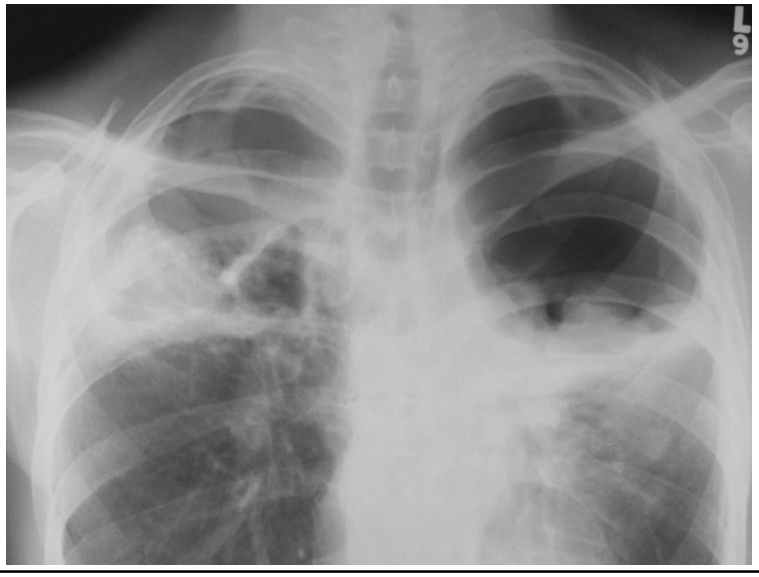
Patient JA
Jan 2001

Chronic Cavitary Pulmonary Aspergillosis



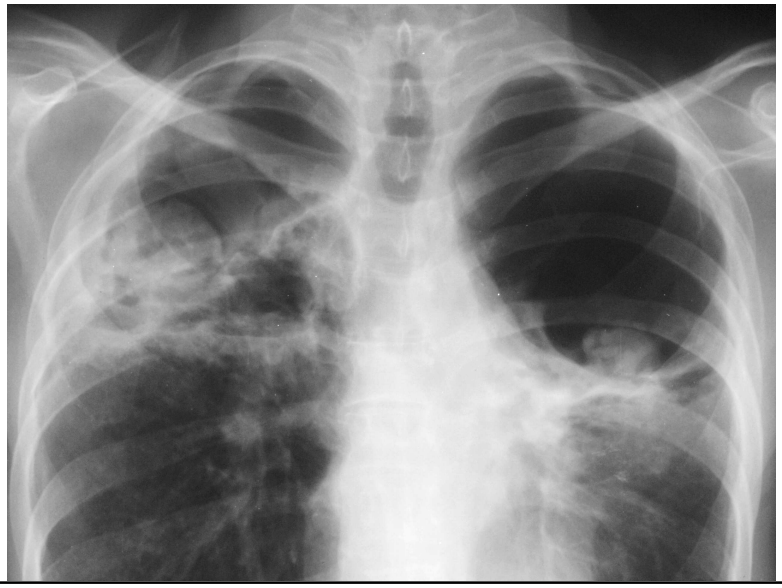
Patient JA
Feb 2002

Chronic Cavitary Pulmonary Aspergillosis



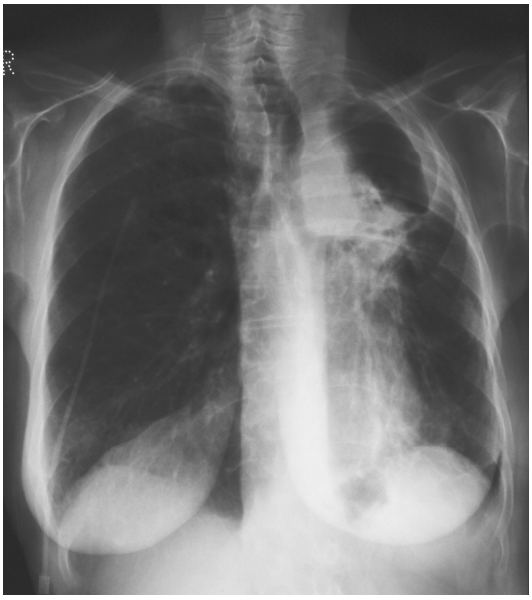
Patient JA
April 2003

Chronic Cavitary Pulmonary Aspergillosis



Patient JA
July 2003

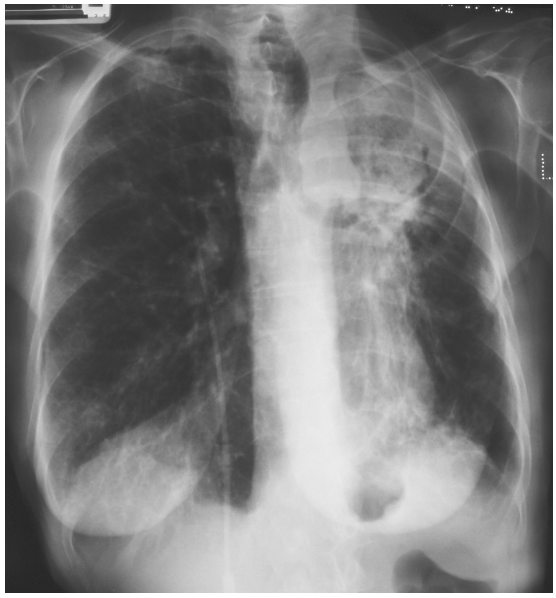
Chronic fibrosing pulmonary aspergillosis



Patient JP
June 1999

Denning DW et al, Clin Infect Dis 2003; 37(Suppl 3):S265-80

Chronic Fibrosing Pulmonary Aspergillosis

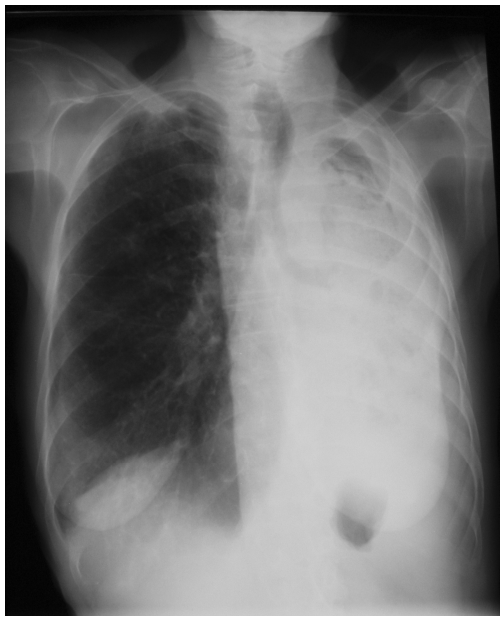


Patient JP
July 2001,

untreated

Denning DW et al, Clin Infect Dis 2003; 37(Suppl 3):S265-80.

Chronic Fibrosing Pulmonary Aspergillosis



Patient JP
April 2002,

Untreated

Denning DW et al, Clin Infect Dis 2003; 37(Suppl 3):S265-80.

What therapeutic options are available?

- Triazoles: the mainstay of therapy
  - Itraconazole
  - Voriconazole
  - Posaconazole

  } Therapeutic Drug Monitoring required
- Polyenes
  - Induction, not maintenance (in general)
- Echinocandins
  - Their role is completely unclear, but probably limited

Adjunctive modalities

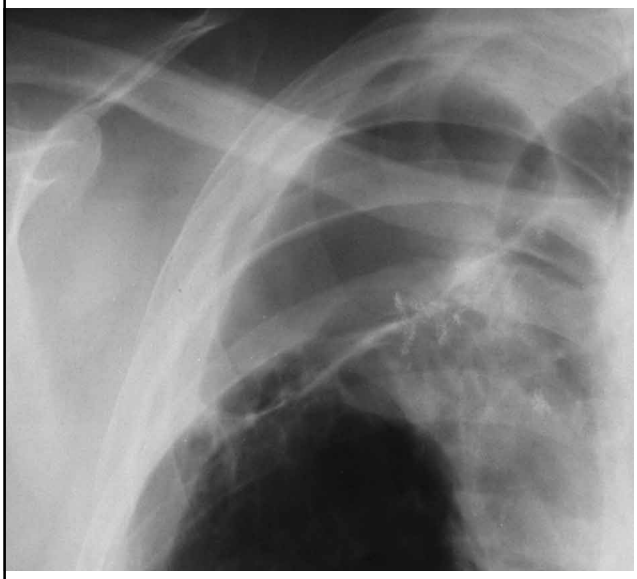
- Intra-cavitary instillation of amphotericin B
  - Often successful but only temporarily so
- Surgery
  - Accessible lesion(s)
  - Adequate respiratory reserve
  - Risk of pleural seeding/bronchopleural fistula
- Bronchial artery embolisation & tranexamic acid for recurrent haemoptysis
- Gamma interferon in selected cases

Assessing response to therapy: a global assessment required

- Symptoms usually improve first (weight increases, better energy levels)
- Inflammatory markers fall
- Serological markers improve
- Peri-cavitary infiltrates decrease

- Response to therapy is slow!

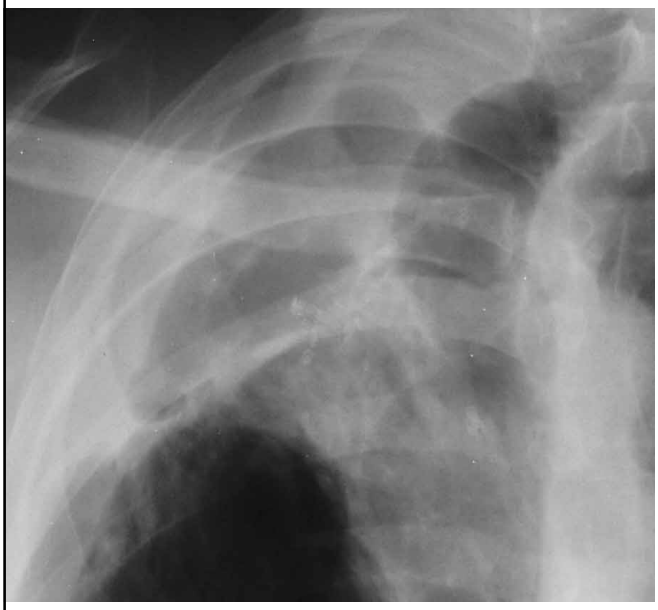
Chronic cavitary pulmonary aspergillosis



June 2002

•Asymptomatic
•Normal infl. markers
•Low titre precipitins
•Long-term itra

Chronic cavitary pulmonary aspergillosis - relapse



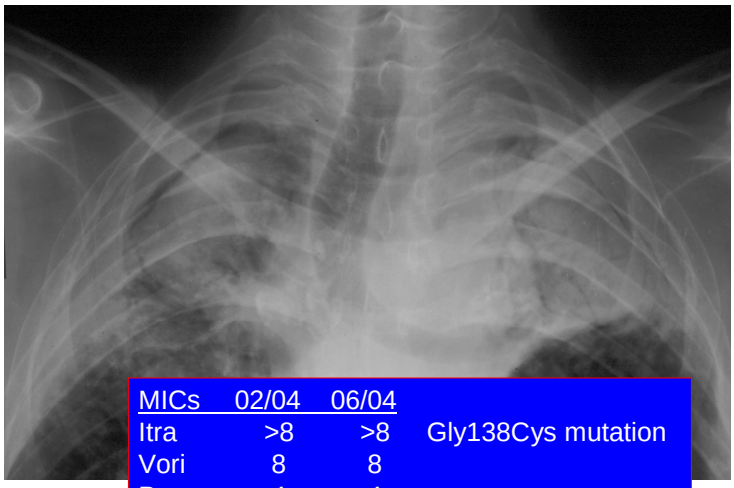
•new cough,
•weight loss,
• ↑CRP/ESR
• ↑Aspergillus precipitins

Itraconazole restarted

The likely cause of triazole failure

1. Inadequate treatment time
2. Non-compliance
3. Suboptimal pharmacokinetics
4. Suboptimal penetration of triazole into the cavity
5. An additional diagnosis (e.g. atypical mycobacterial infection, cancer)
6. Triazole resistance

Chronic fibrosing pulmonary aspergillosis, with bilateral aspergillomas and azole resistance



MICs	02/04	06/04	
Itra	>8	>8	Gly138Cys mutation
Vori	8	8	
Posa	4	4	

Patient SM
June 2004

After treatment with itraconazole and voriconazole

Howard et al, Int J Antimicrob Ag. 2006

Conclusions

- There have been significant advances in the management of invasive aspergillosis
- Infection in non-classical risk groups now increasingly recognised
- Much more work needs to be done in ICU
- Beware of patients with cavitary disease and think of *Aspergillus*!