Diagnosis, definitions, drugs and dilemmas

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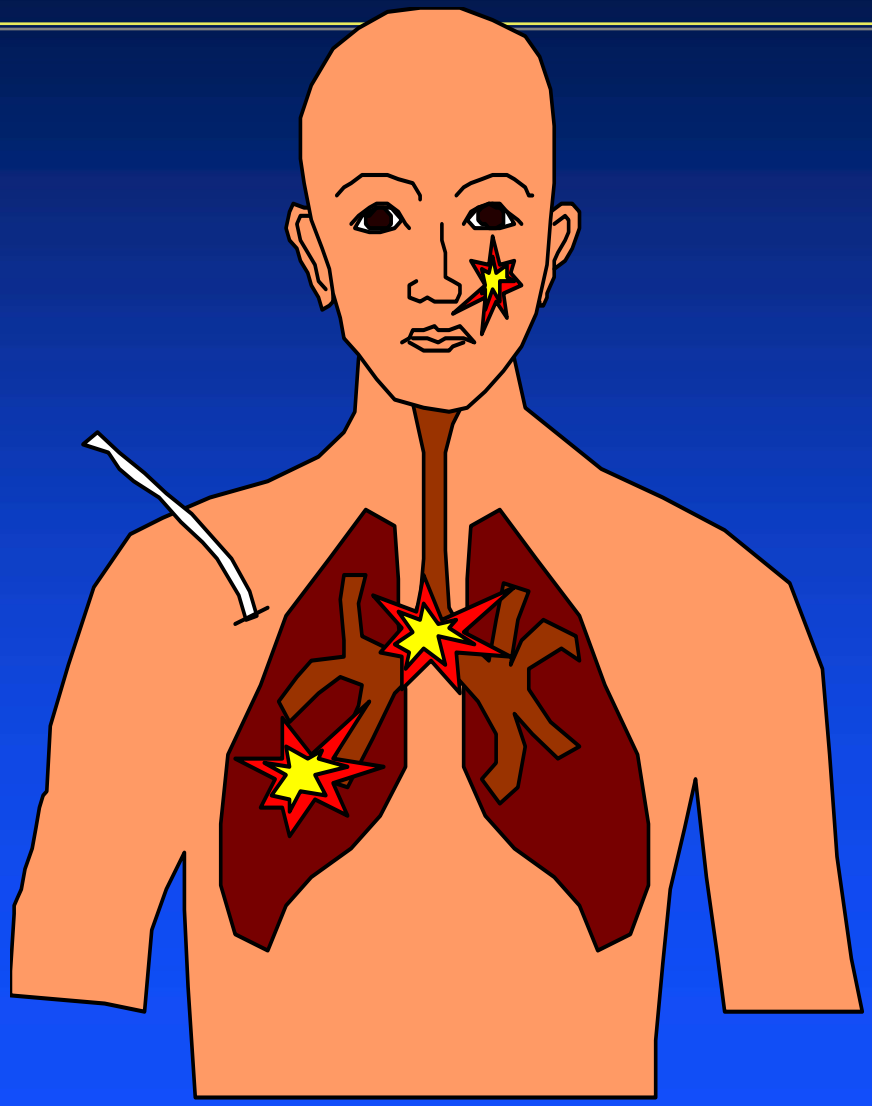
Nijmegen University Centre for Infectious Diseases
University Hospital St Radboud
Radboud University Nijmegen
The Netherlands

The main players on the fungal field

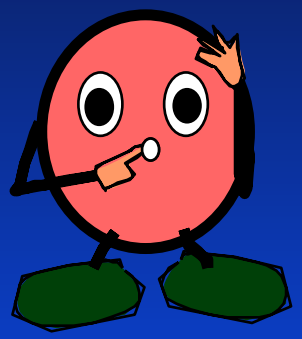
Diagnosis

Aspergillosis

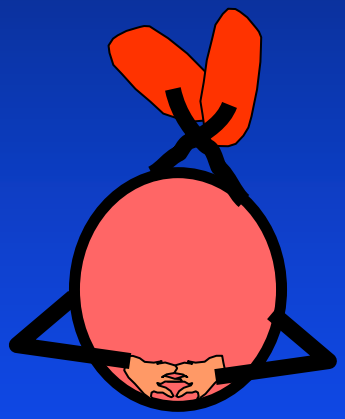


In the past ....

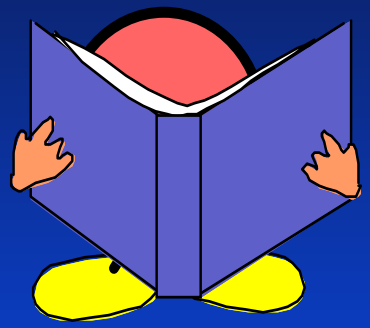
Diagnosis of aspergillosis - in the past



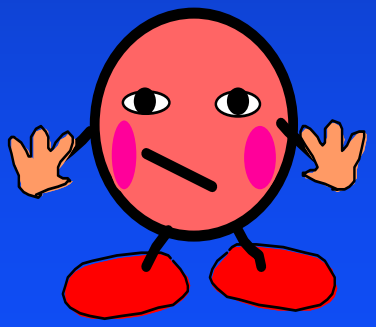
Clinician



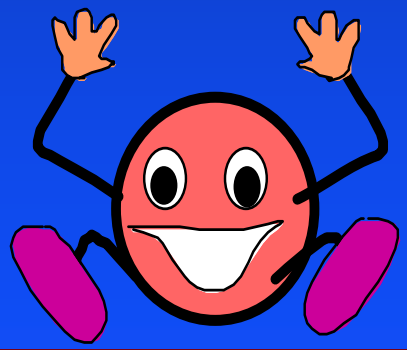
Pathologist



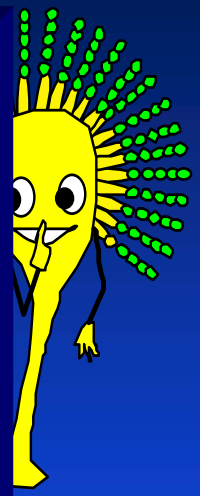
Microbiologist



Infectious Disease Physician

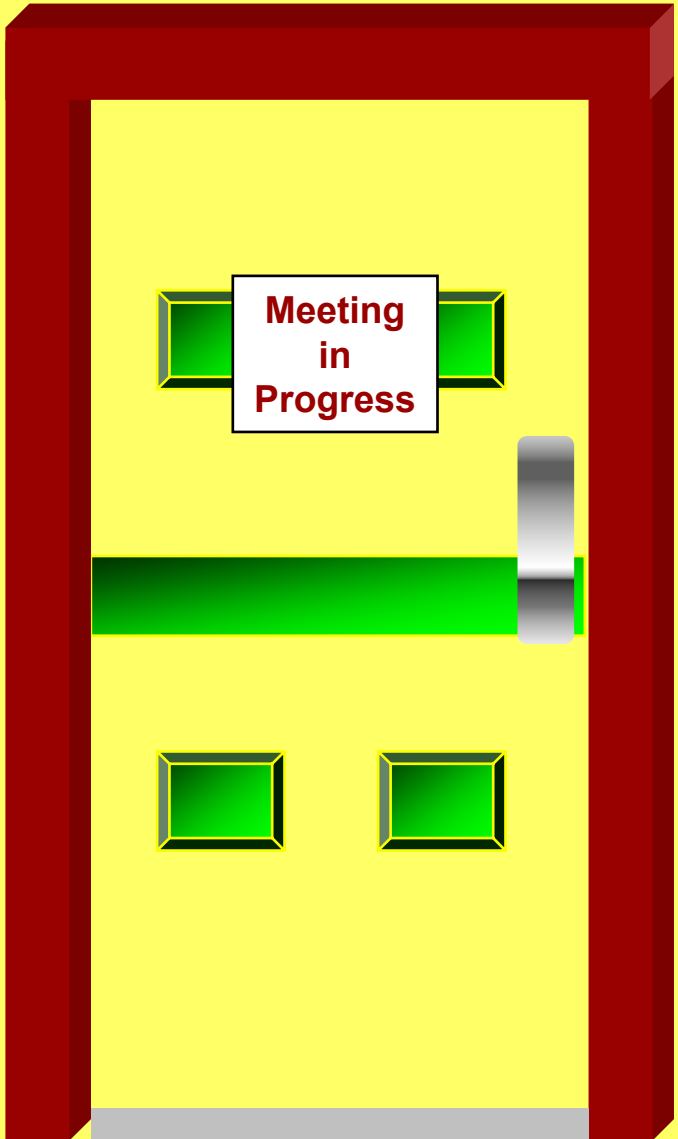


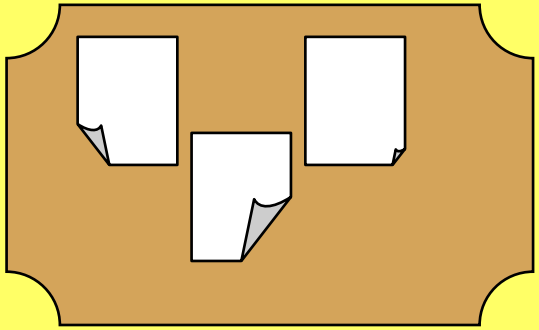
Pharmaceutical Industry



Laboratory tempo

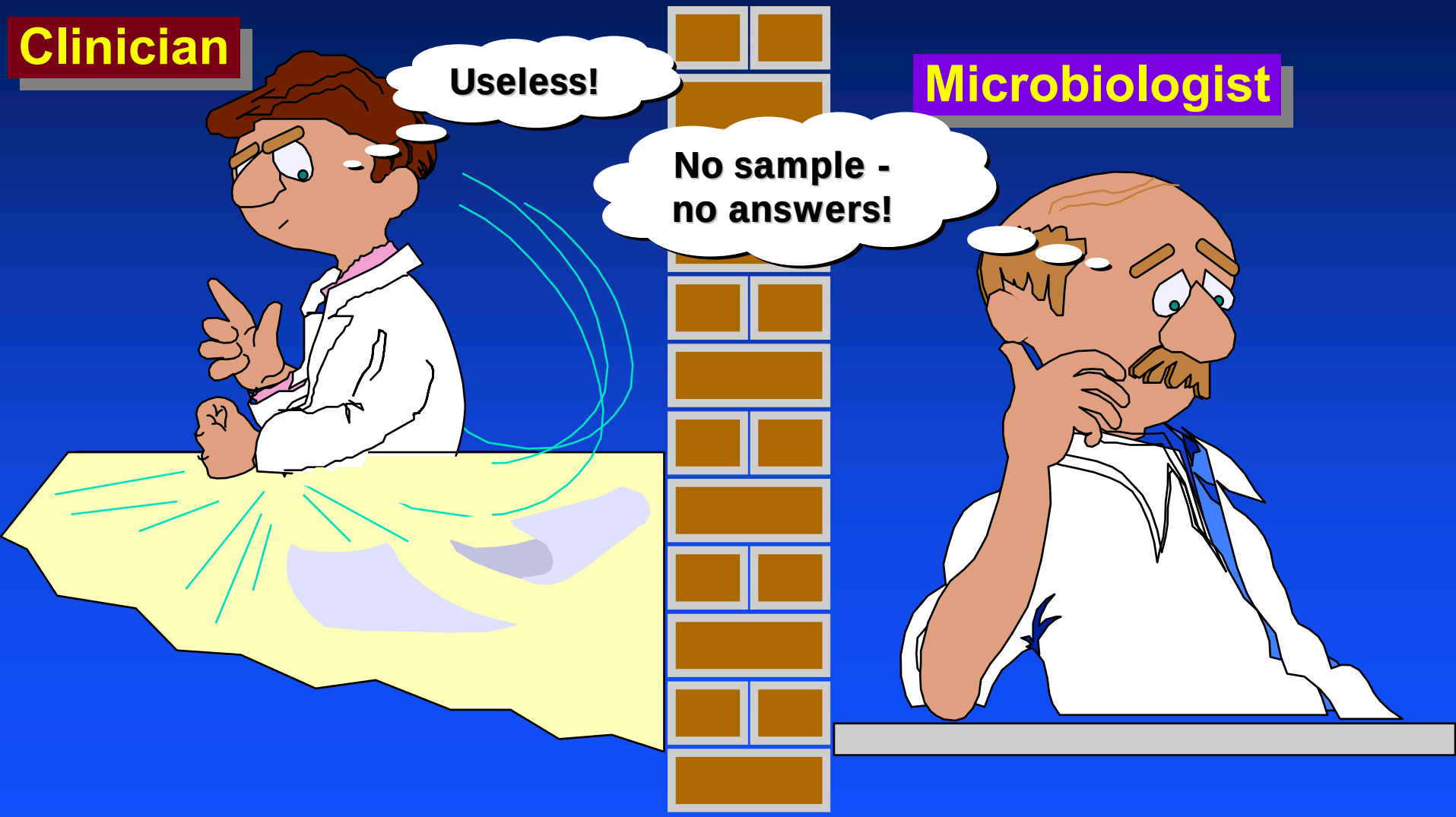
Opening hours
Mon - Fri 09:00 - 17:00
Sat 09:00 - 12:00
CLOSED on Sundays & Public Holidays





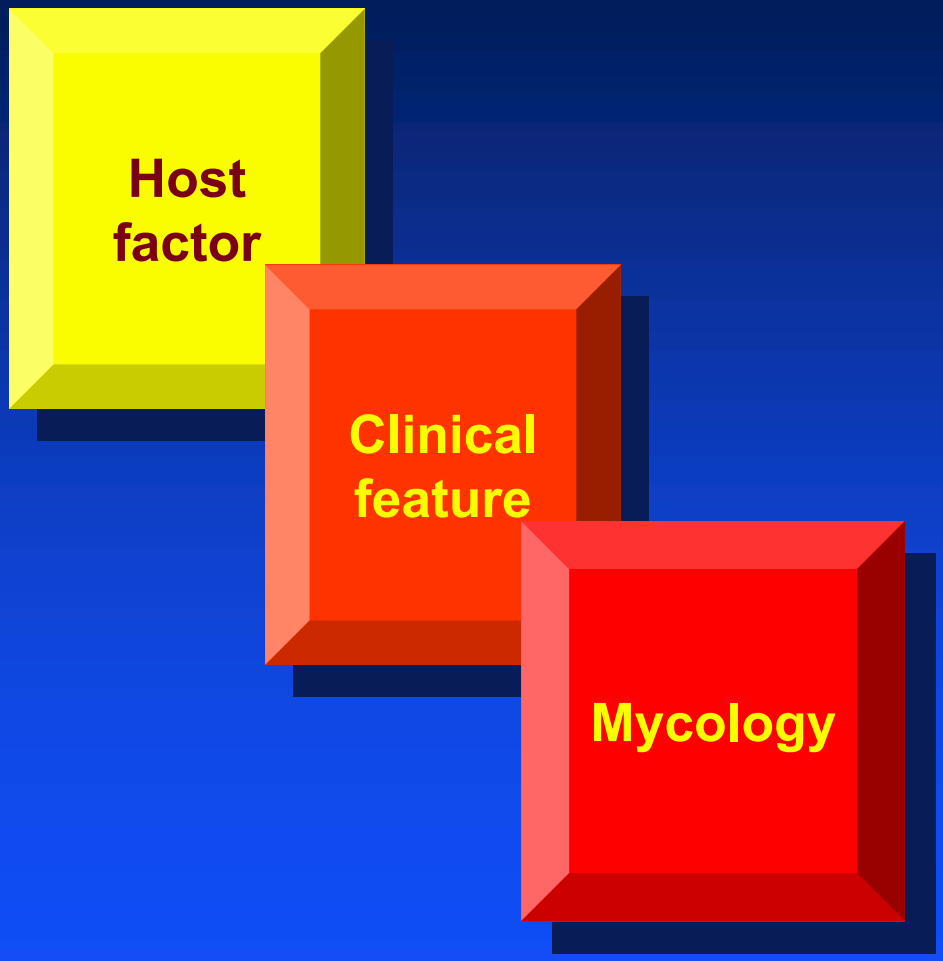
Clinicians response to laboratory diagnosis

Worlds apart



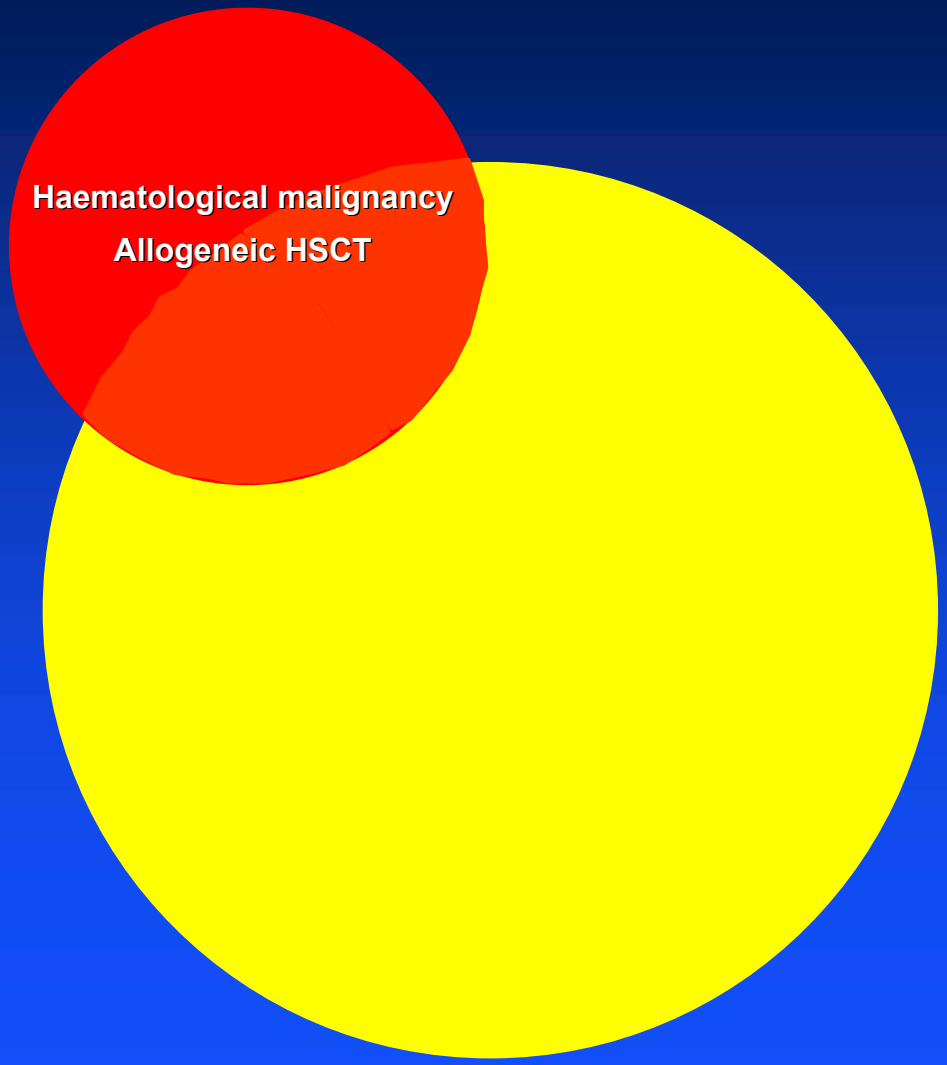
Today….

Defining invasive fungal disease



Host factors

Patients at risk of developing IFD



Invasive fungal disease

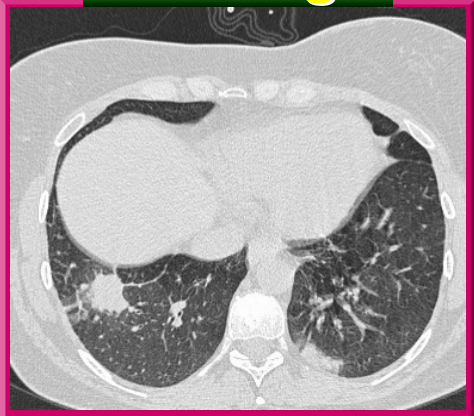
Host factor

Probability of invasive fungal disease

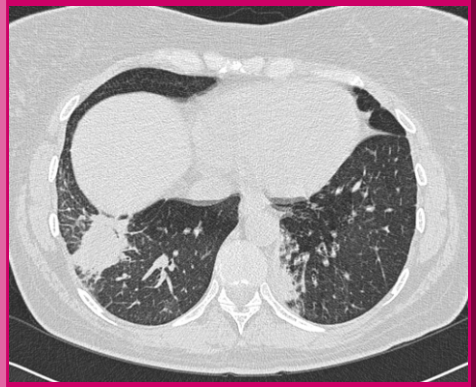
Clinical features

Specific pulmonary infiltrates on CT scan

halo sign



air crescent sign



cavity

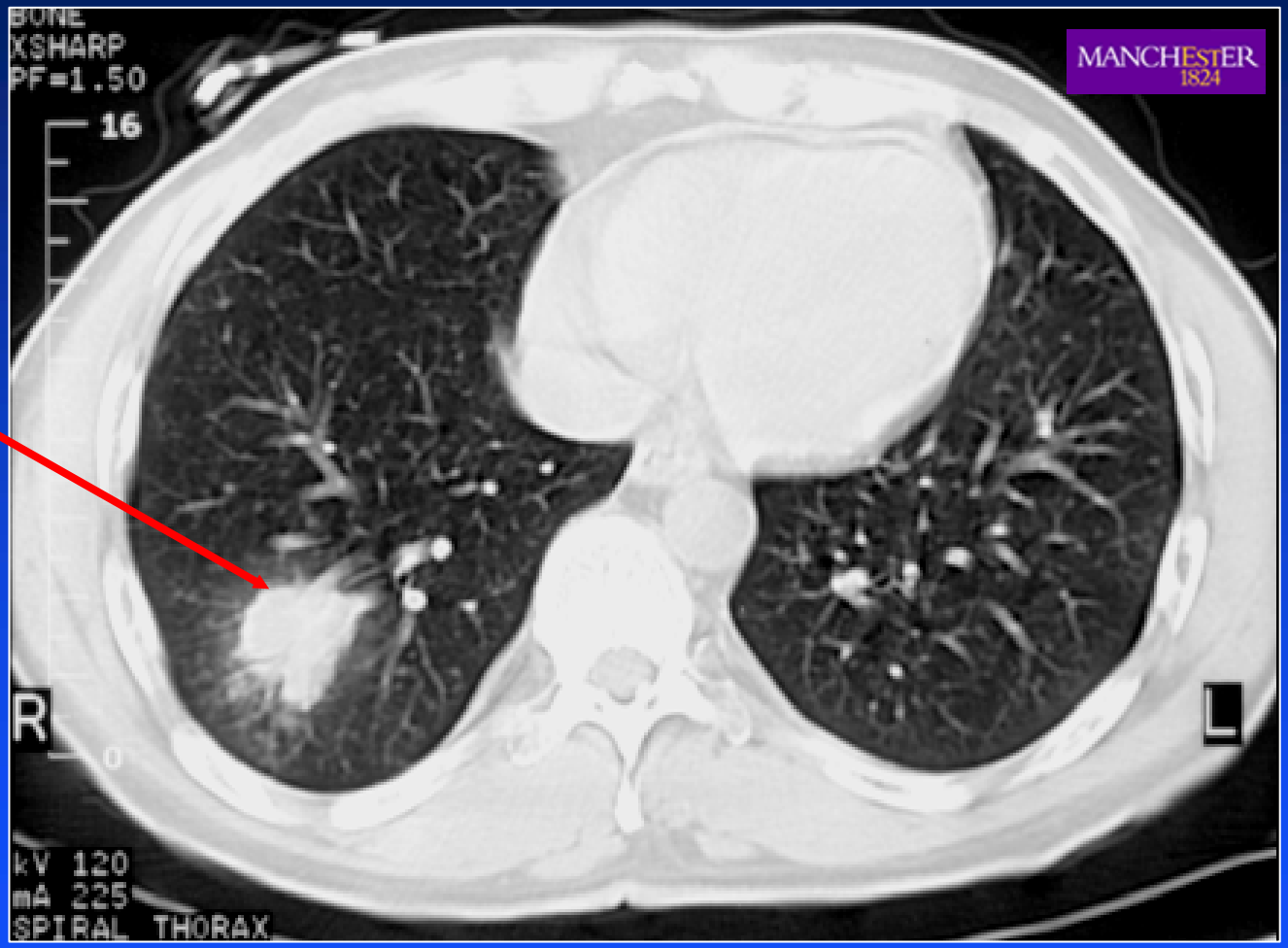
nodules

Caillot et al 2001

Unequivocal 'Halo sign' surrounding a nodule

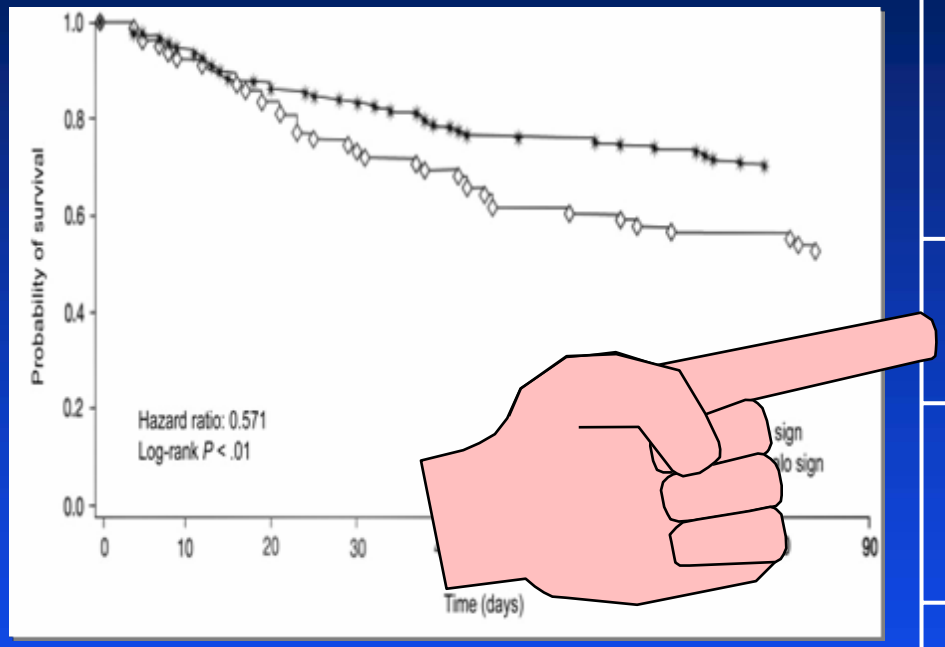
Halo

Small vessel angioinvasion



Herbrecht, Denning et al, NEJM 2002;347:408-15.

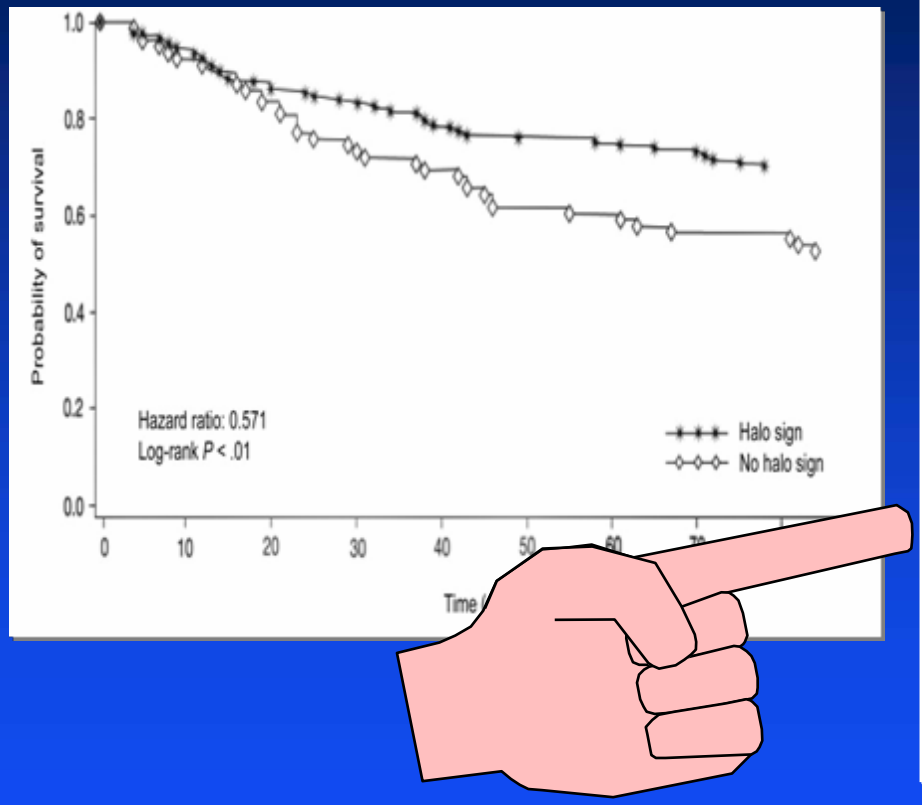
The 'Halo' Sign



Nodules in IA	Nodule	Nodule with Halo
Neutropenia	97 %	82 %
No neutropenia Hematology	96 %	49 %
Not Hematology	82 %	24 %

Greene et al. Clin Infect Dis 2007; 44: 373-9

The 'Halo' Sign



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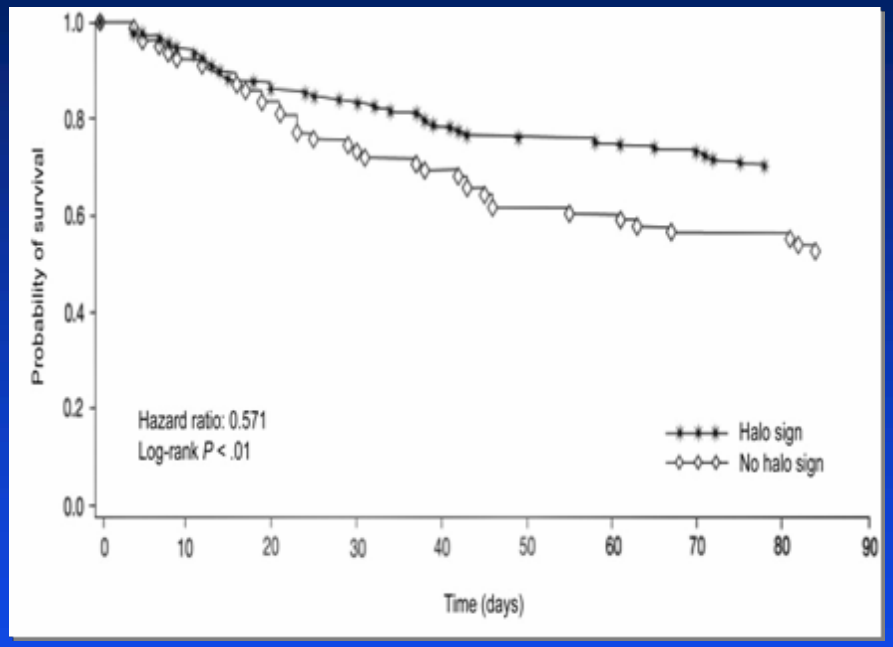

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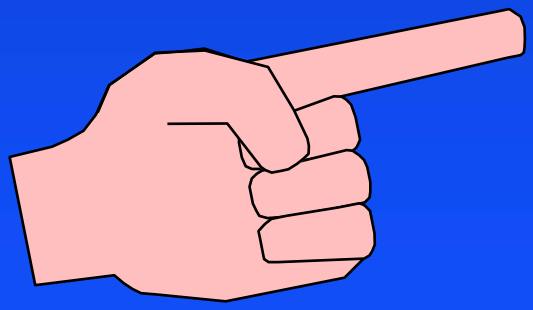

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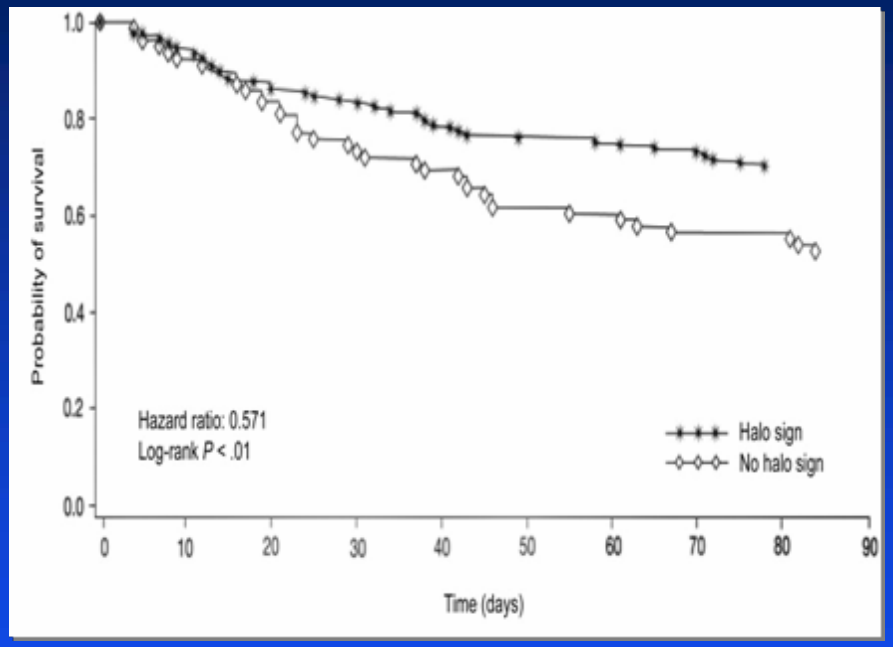

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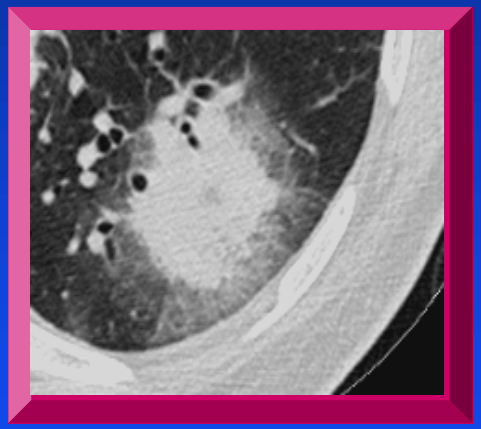
Halo sign indicates IA only in the neutropenic context

Greene et al. Clin Infect Dis 2007; 44: 373-9

Evolution of CT scan images in invasive pulmonary aspergillosis

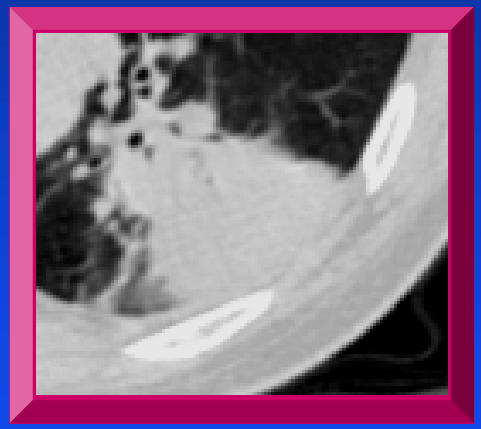
halo sign

D 0 - 5



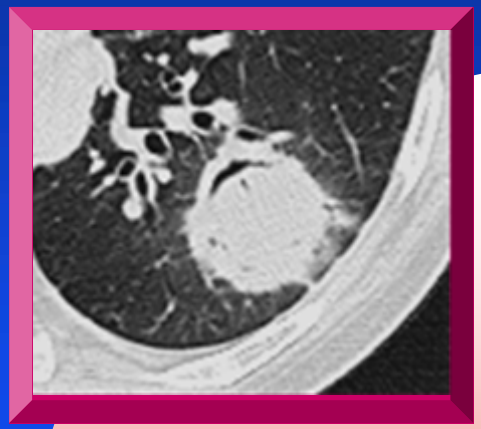
Air-space consolidation

D 5 - 10



air-crescent sign

D 10 - 20



Neutropenia

Caillot et al 2001

Invasive fungal disease

Host factor + Clinical features

Probability of invasive fungal disease

Mycology

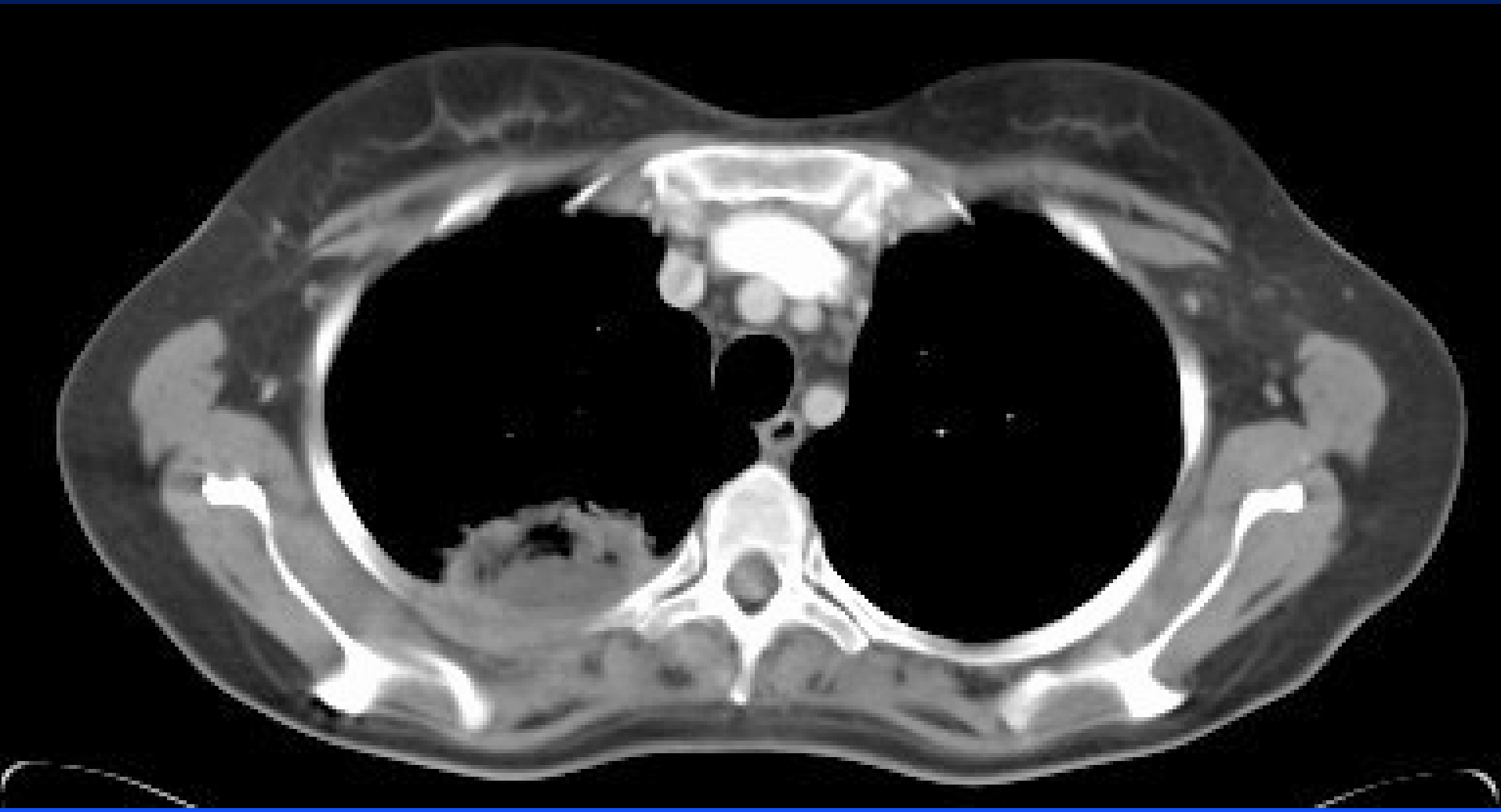
Specific diagnosis

No specimen - no specific diagnosis

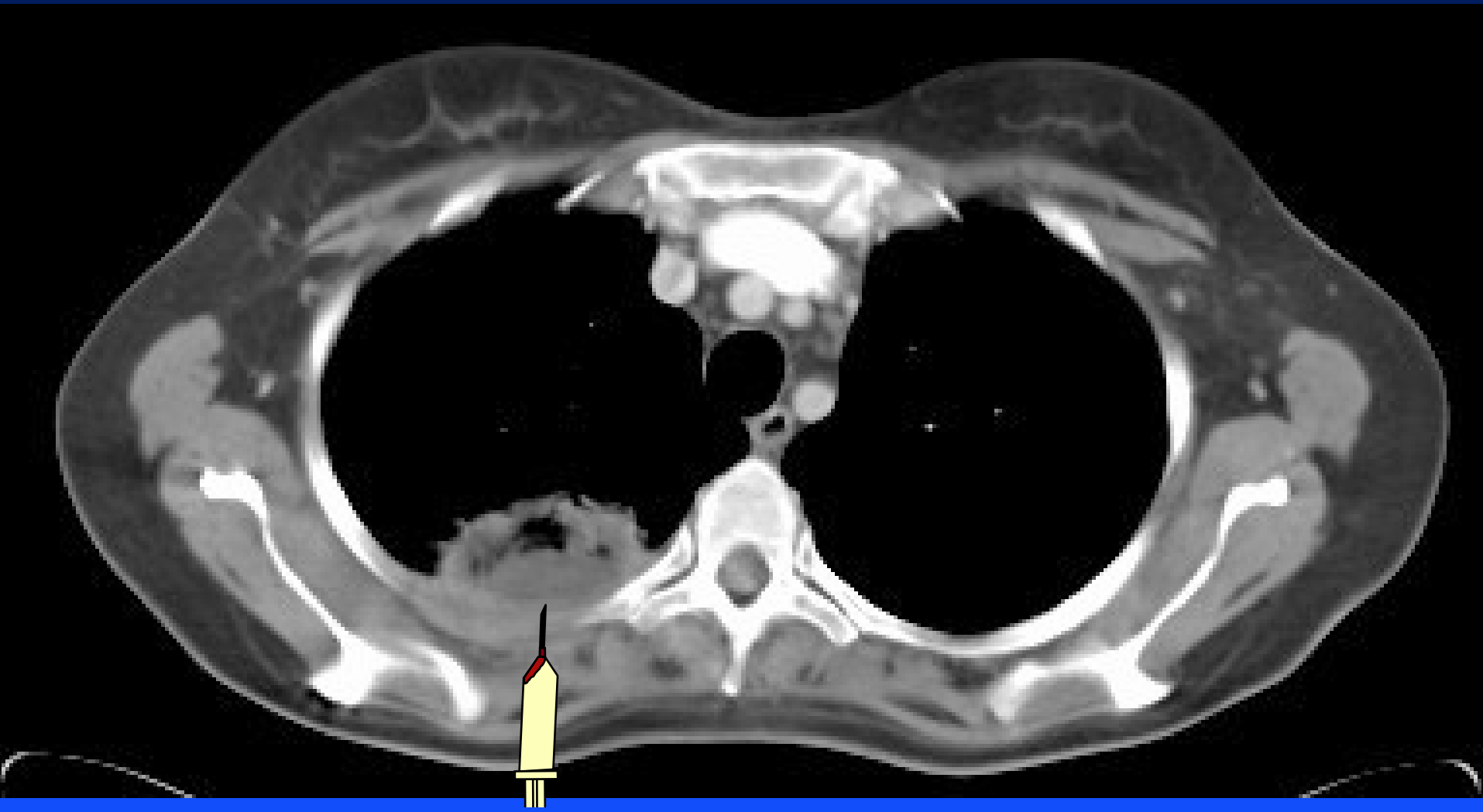
- Biopsy difficult to obtain - autopsy rarely done
- Specimens often sent EITHER for histopathology (Formalin and Fix) OR for mycology (Crush and Culture) but seldom for both
- Classical mycology techniques

UMC St Radboud

Pulmonary zygomycosis

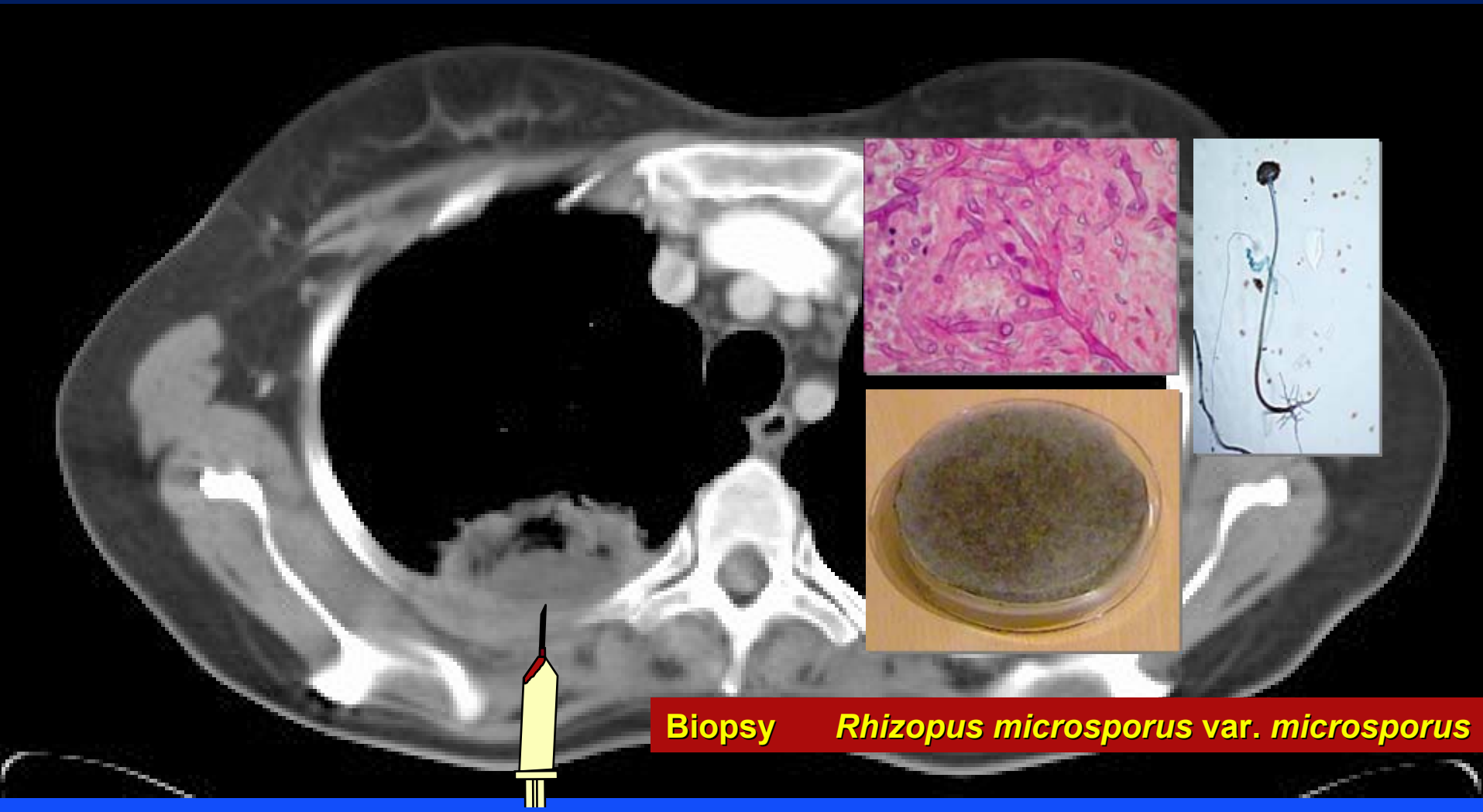


Pulmonary zygomycosis



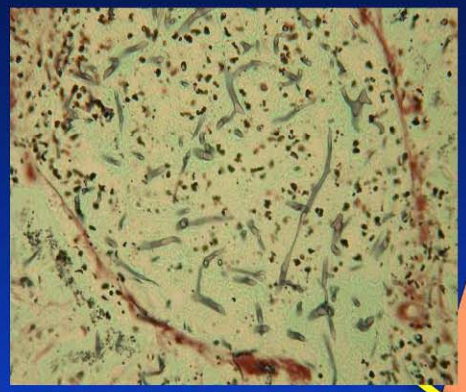
fine needle aspirate

Pulmonary zygomycosis

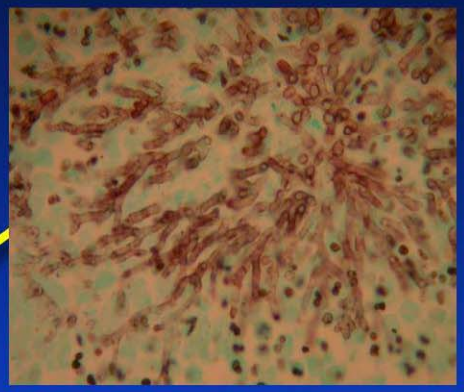


fine needle aspirate

Autopsy findings



zygomyces



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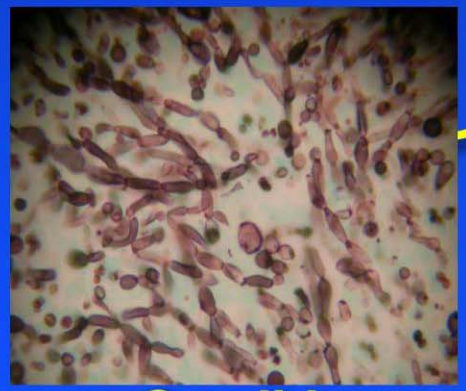
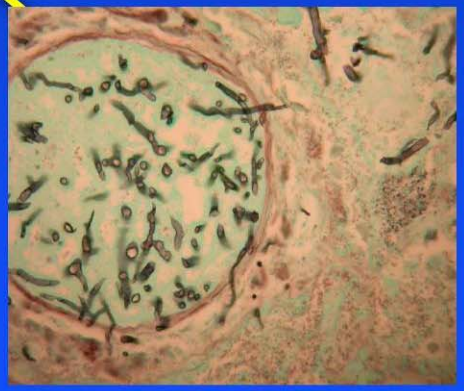
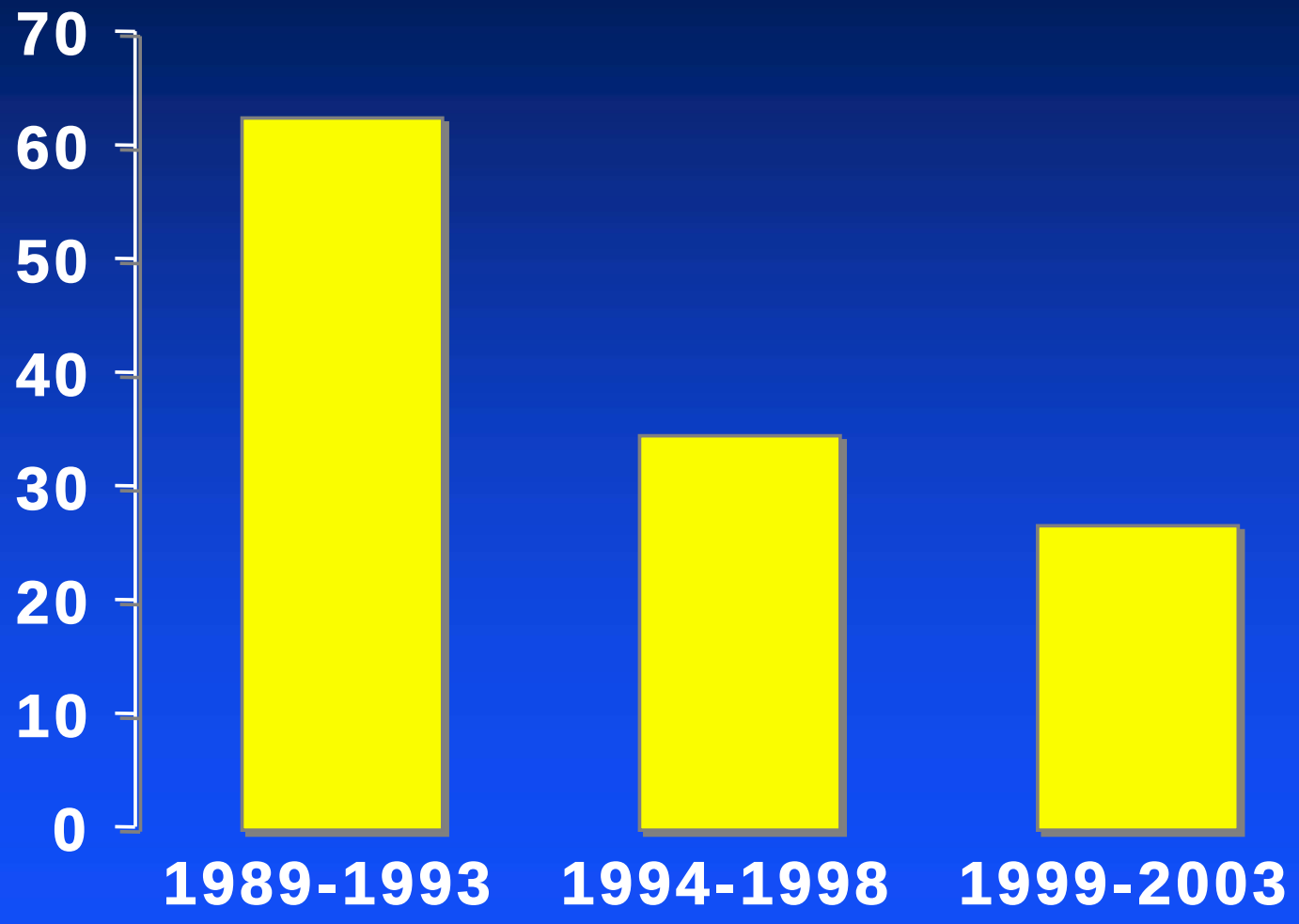


Candida



zygomyces

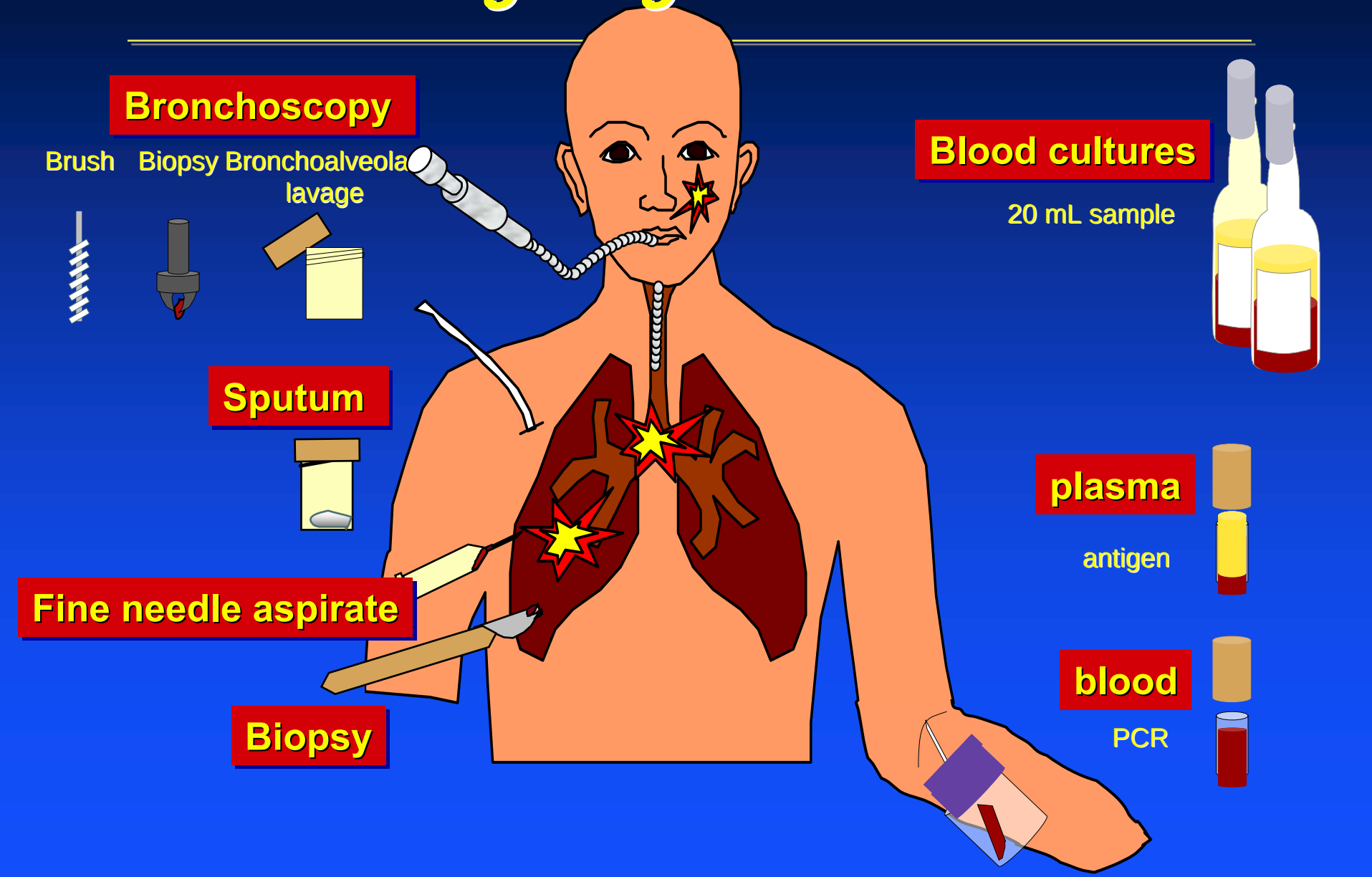
Autopsy rates at the MDACC



Chamilos 2006 Haematologica 91:986

Samples are vital...
no sample .. no results

Investigating abnormalities



Laboratory diagnosis

Specimen

tissue
- **biopsy**

body fluids
- **blood**
- **urine**
- **CSF**

body secretions
- **sputum**
- **mucous**

body surfaces
- **oral cavity**
- **wounds**
- **skin**
- **vagina**

Detection

direct
- **microscopy**
  - light
  - fluorescence
- **culture**
- **immunohistochemical staining**

indirect
- **microbial material**
  - cell wall *eg galactomannan*
  - metabolites *eg 1-3-ß-D-glucan*
  - nucleic acid *eg PCR*
  - enzyme *eg enolase*
- **serology**
  - whole cell lysates
  - specific antigens

Definitions I - Mycology

Culture of mould from BAL or sputum

antigen in blood, BAL. CSF

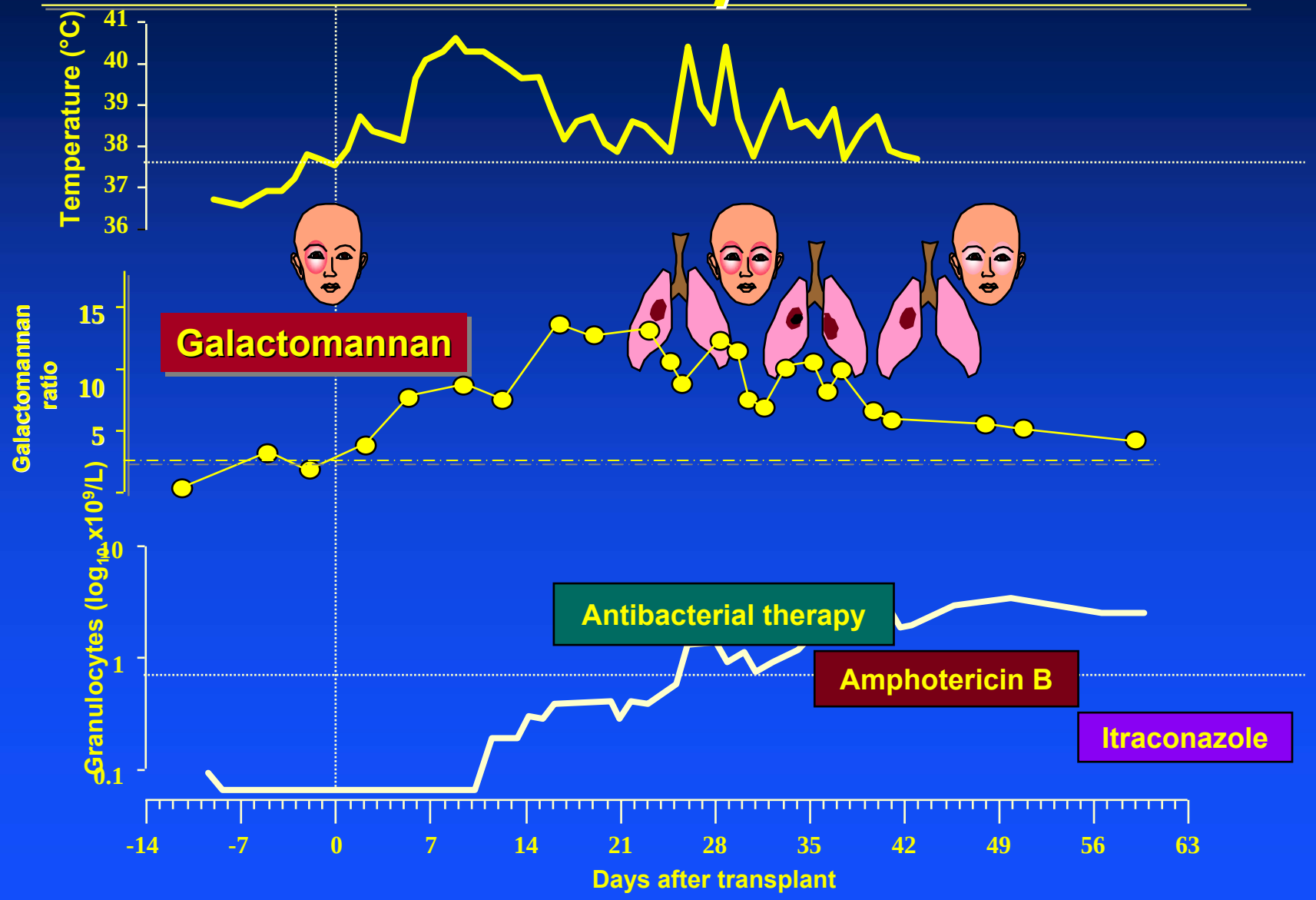
Mycology

mould seen in sinus aspirate

Mould seen in BAL

Galactomannan

Allogeneic haematopoietic stem cell transplant



Galactomannan - comparisons

Author	Year	Likelihood ratio of proven / probable IA		Diagnostic odds ratio (LR^+ / LR^-)
		LR^+	LR^-	
Bretagne	1997	4.34	-	-
Bretagne	1998	3.54	0.28	12.64
Machetti	1998	4.41	0.30	14.7
Maertens	1999	18.6	0.07	265.71
Sulahian	2001	11	0.24	45.83
Ulusakarya	2000	13.8	0.32	43.12
Herbrecht	2002	4.57	0.73	6.26
Maertens	2002	10.62	0.16	66.37
Becker	2003	2.87	0.64	4.48
Platelia PI	2003	7.36	0.21	35
Jarque	2003	22.33	0.34	65.67
Moragues	2003	25	0.96	26.04
Pinel	2003	25	0.96	26.04
Pazos	2003	44	0.12	366.66
Marr	2004	2.07	0.62	3.33
Rovira	2004	22.33	0.34	65.67
Buchheidt	2004	33	0.67	49.25
Maertens	2004	48.5	0.03	1616.66
Yoo	2005	3.90	0.17	22.94

Galactomannan - comparisons

High LR

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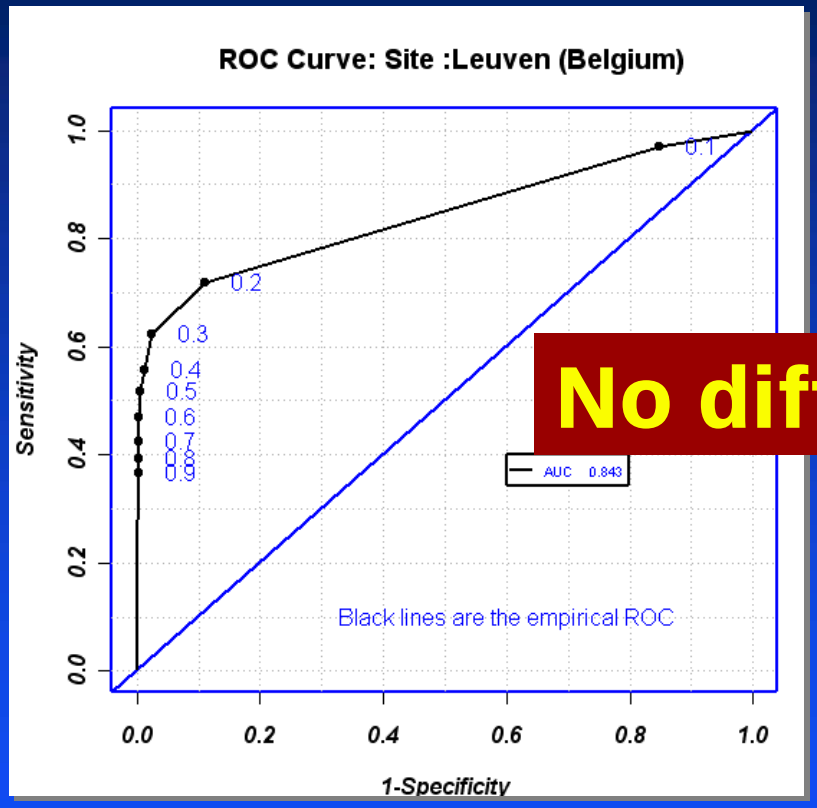
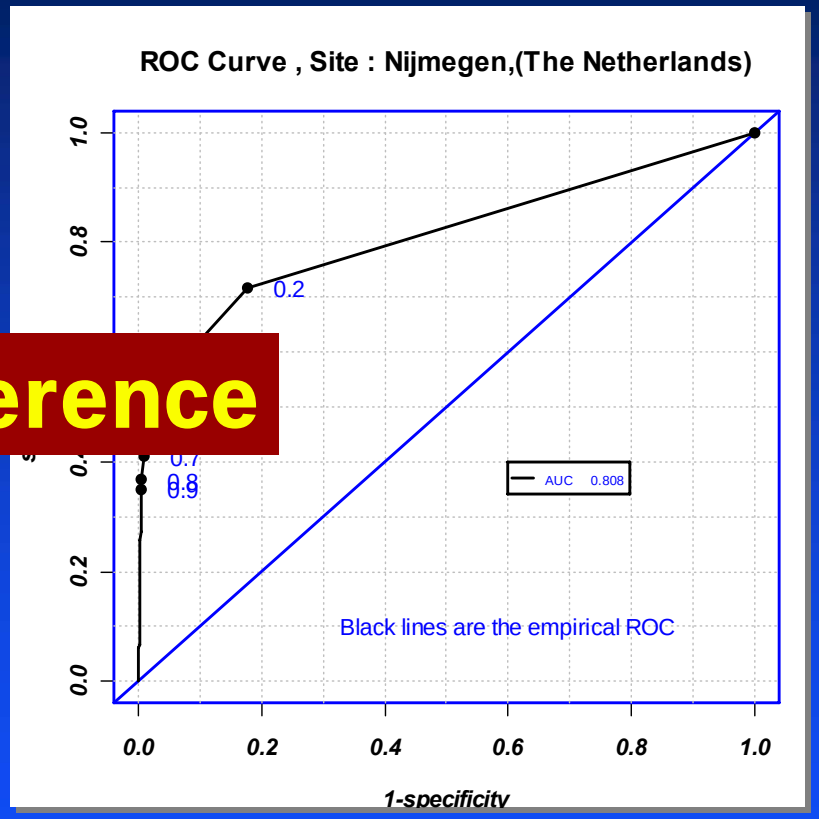
Galactomannan - impact of sampling schedule





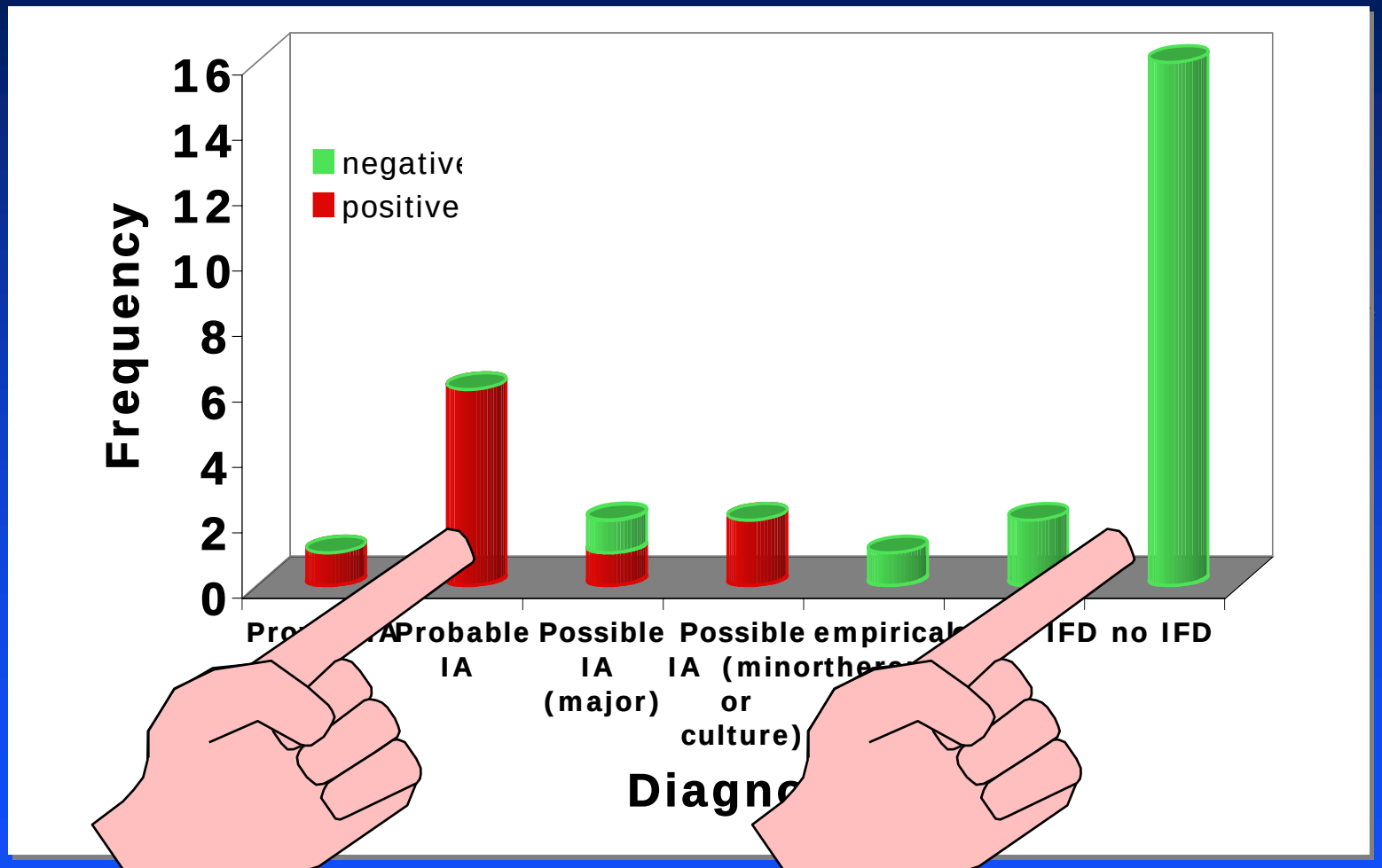
No difference

Daily sampling

Monday-Thursday sampling

Maertens et al 2007 Clin Infect Dise 44:1329

BAL - galactomannan



Becker et al 1999 Brit J Haematol. 24:1195-99

Risk groups

HSCT allogeneic

AML/MDS

GVHD ≥ grade 2

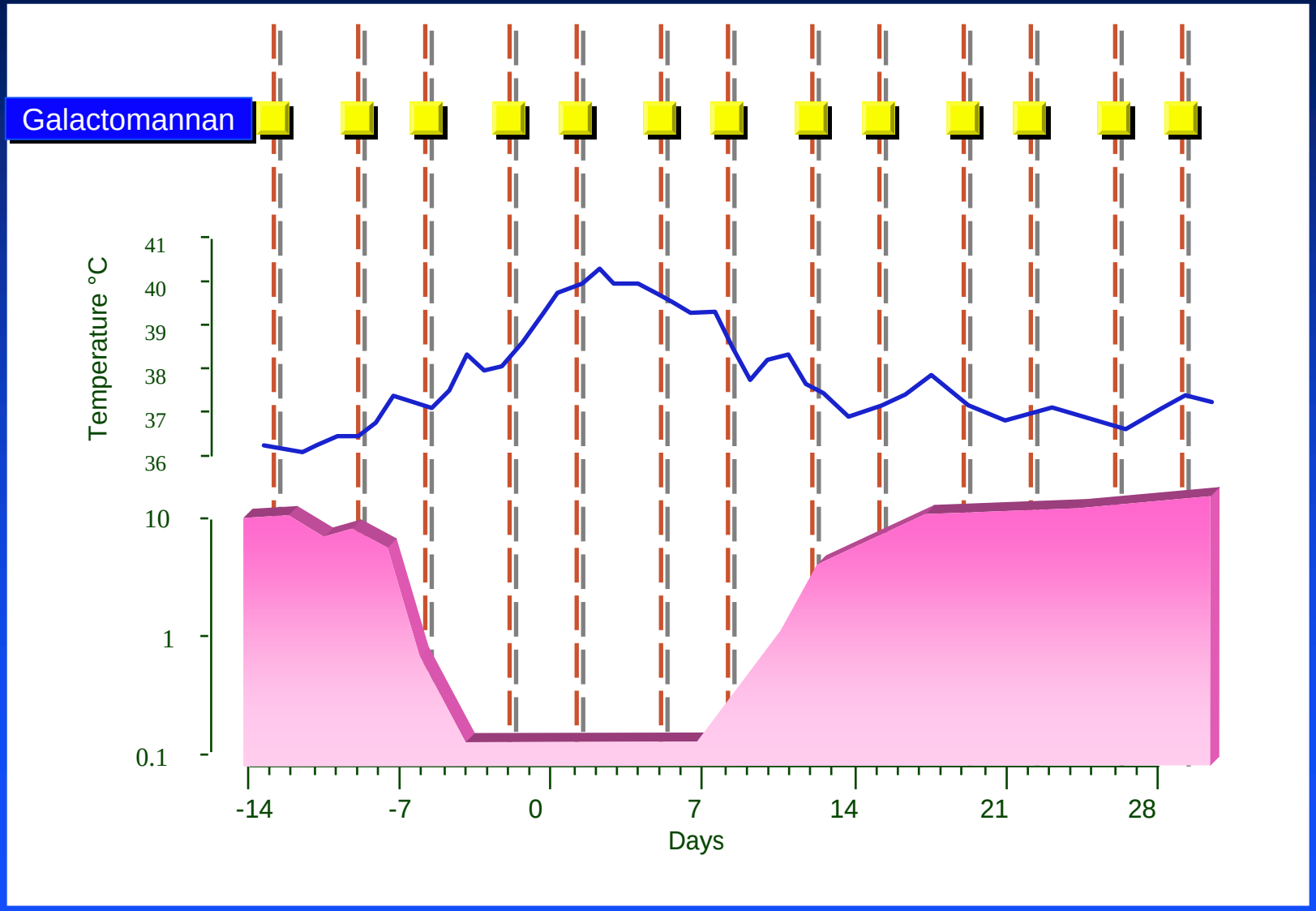
Chronic GVHD

Steroid treatment

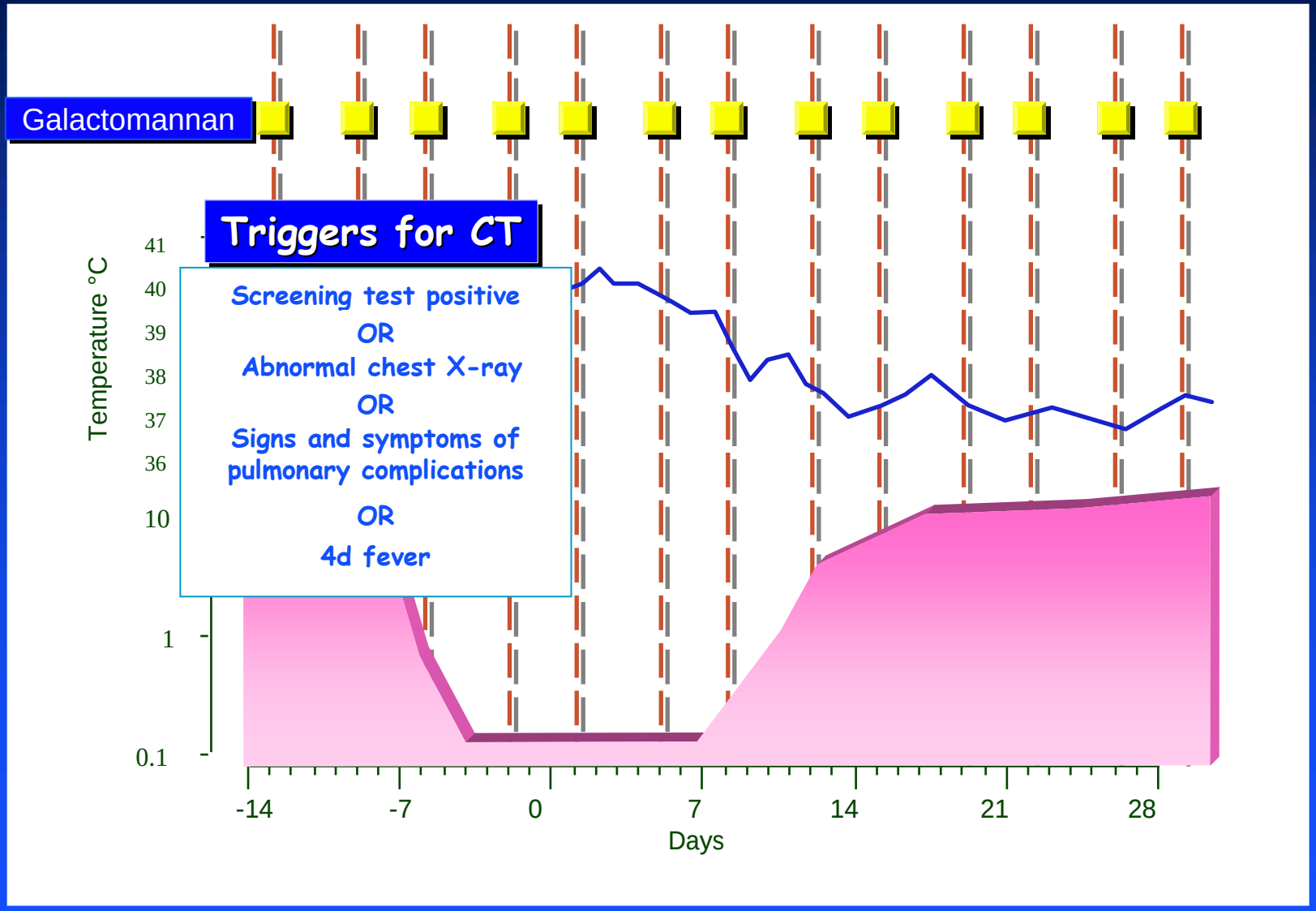
and

On haematology ward

Investigating invasive fungal disease



Investigating invasive fungal disease



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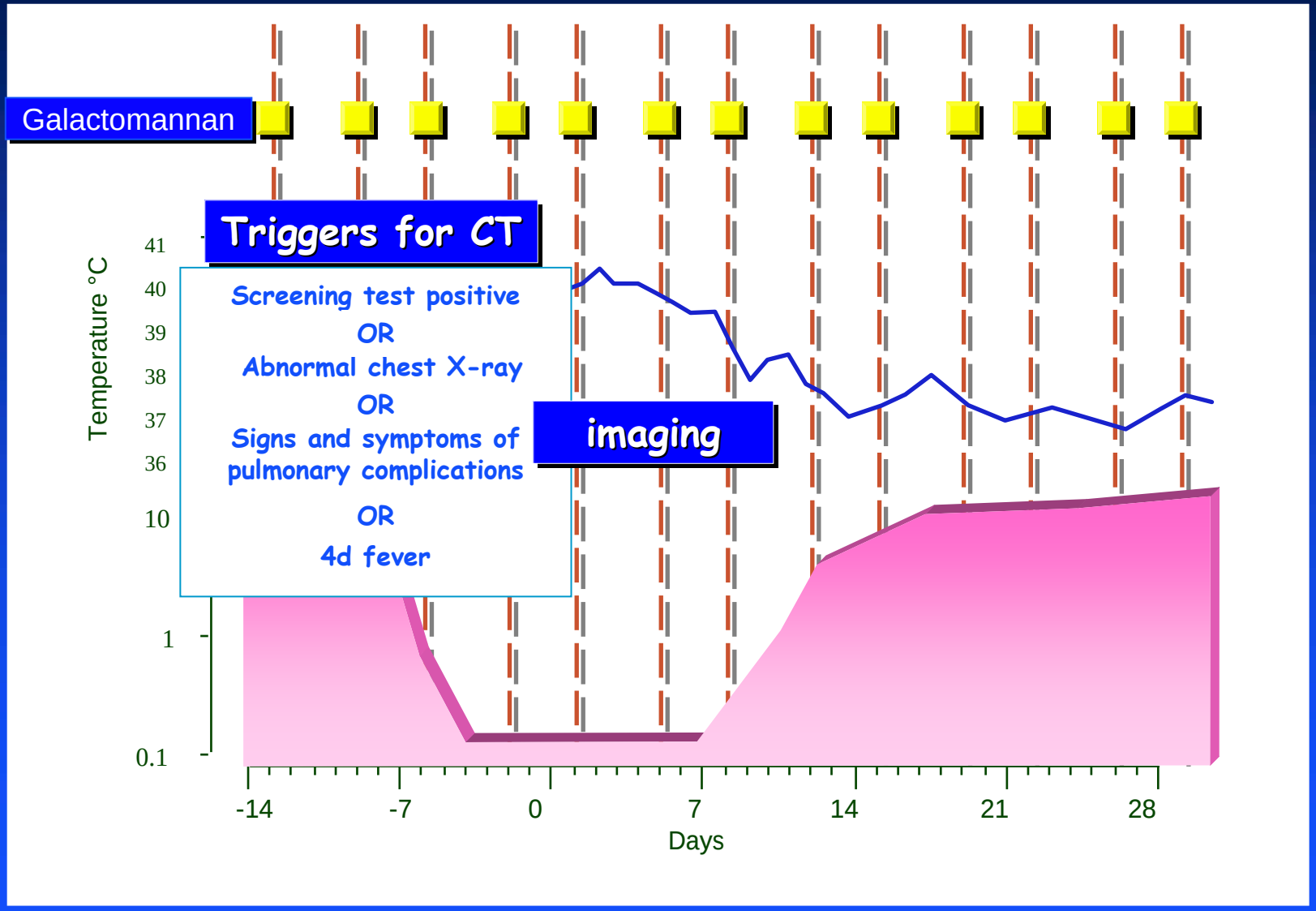

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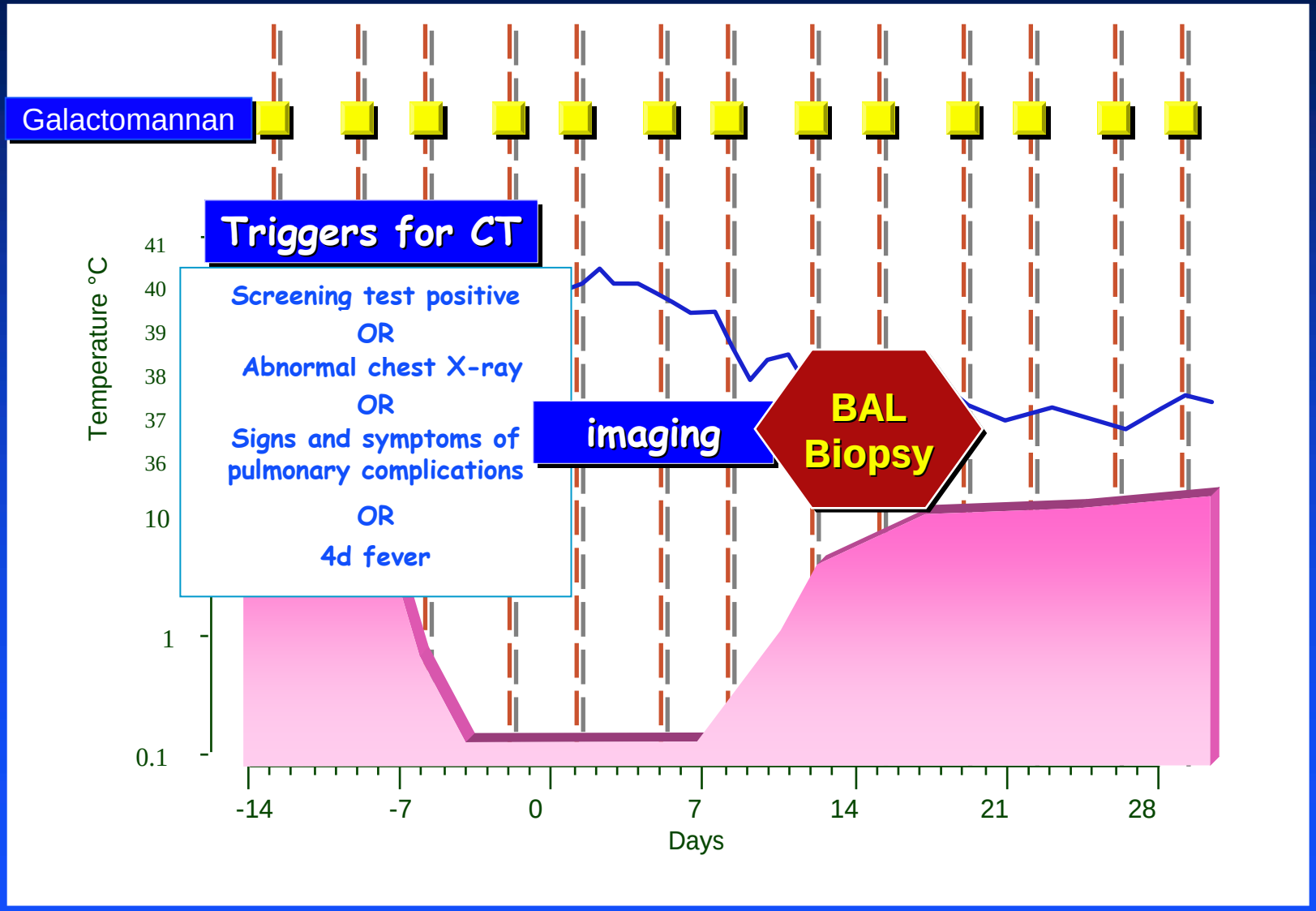

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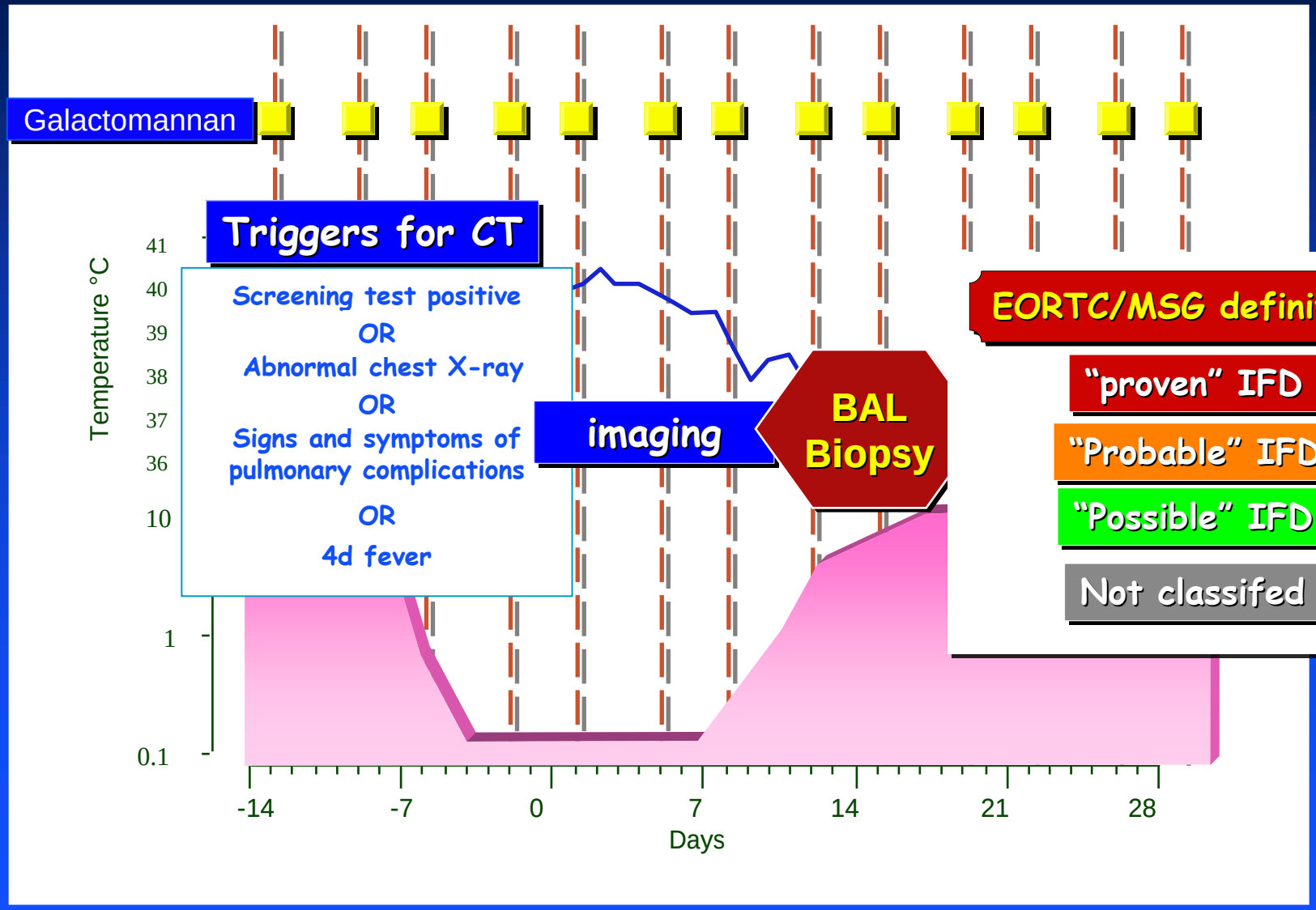
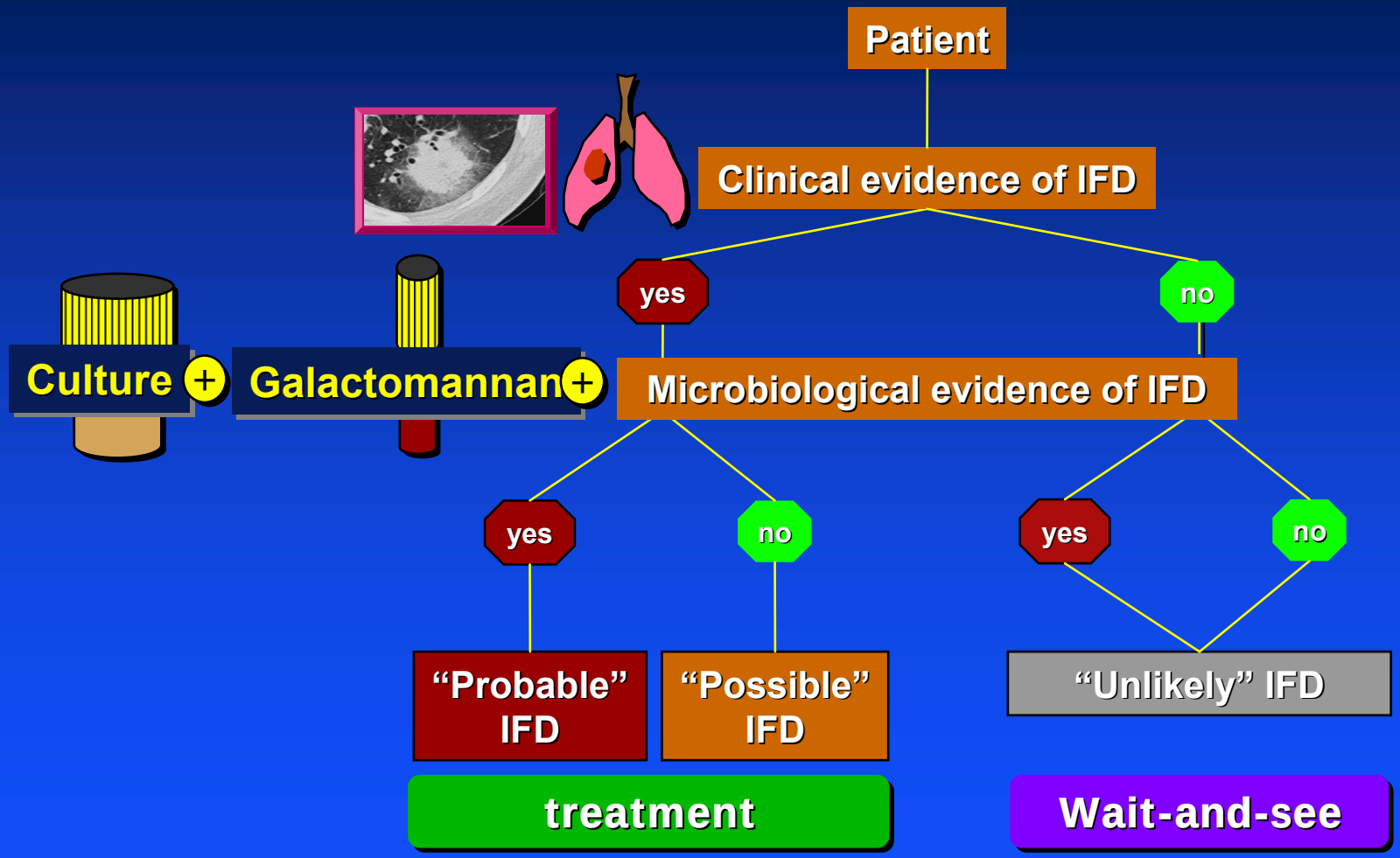
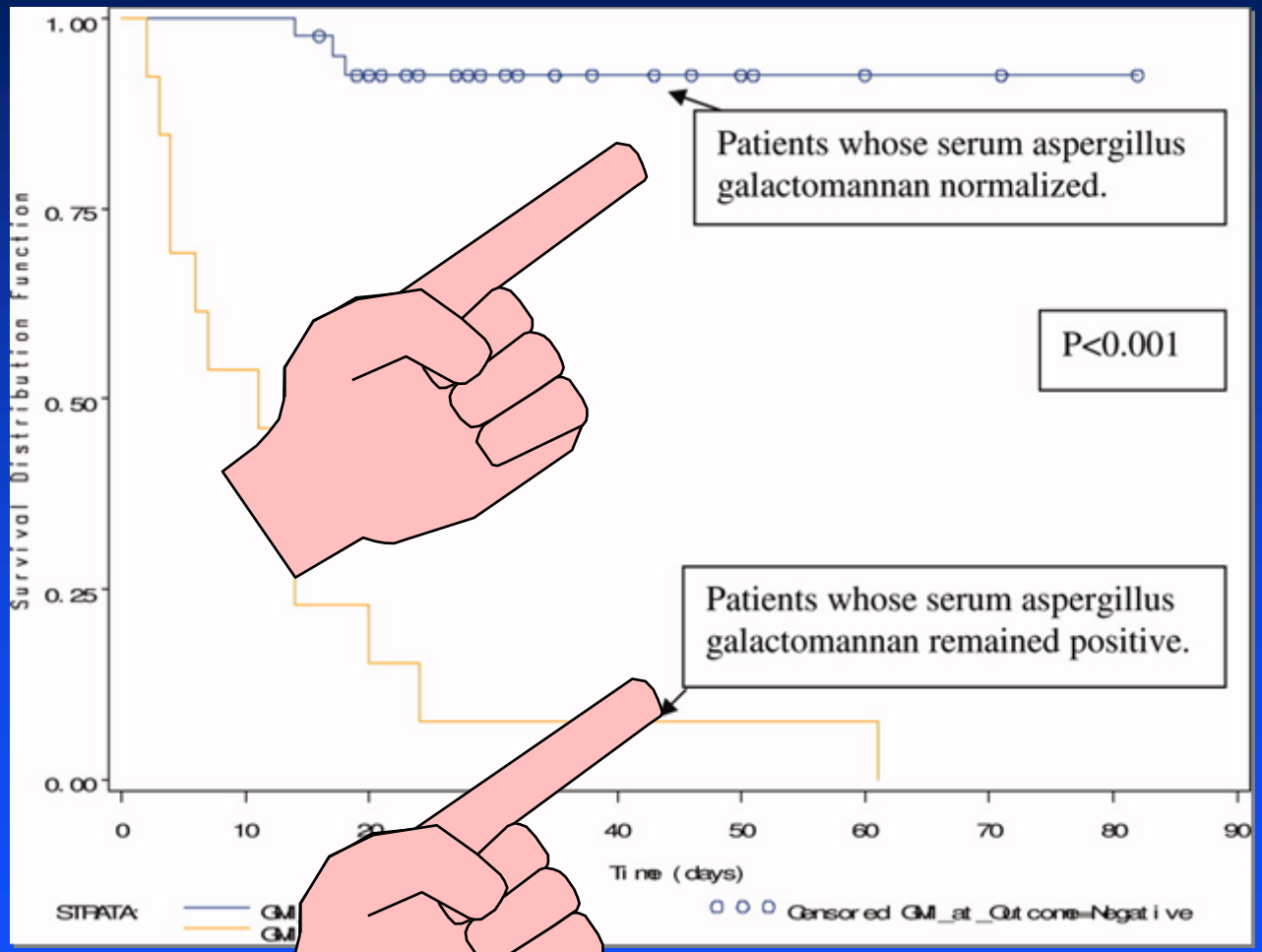


Scheme for managing high-risk patients



Survival and serum galactomannan



Woods et al 2007 Cancer 110:830

Are we screening or confirming?

(1→3)-β-D-glucan

Definitions I - Mycology

Culture of mould from tissue. aspirate BAL or sputum

antigen in blood, BAL, CSF

Mycology

mould seen in sinus aspirate

Fungi seen in tissue or sterile body fluids

Definitions II - Mycology

Culture of mould from tissue. aspirate BAL or sputum

antigen in blood, BAL, CSF

mould seen in sinus aspirate

Mycology

Beta-D-glucan in BAL, CSF or blood

Fungi seen in tissue or sterile body fluids

Definitions II - Mycology

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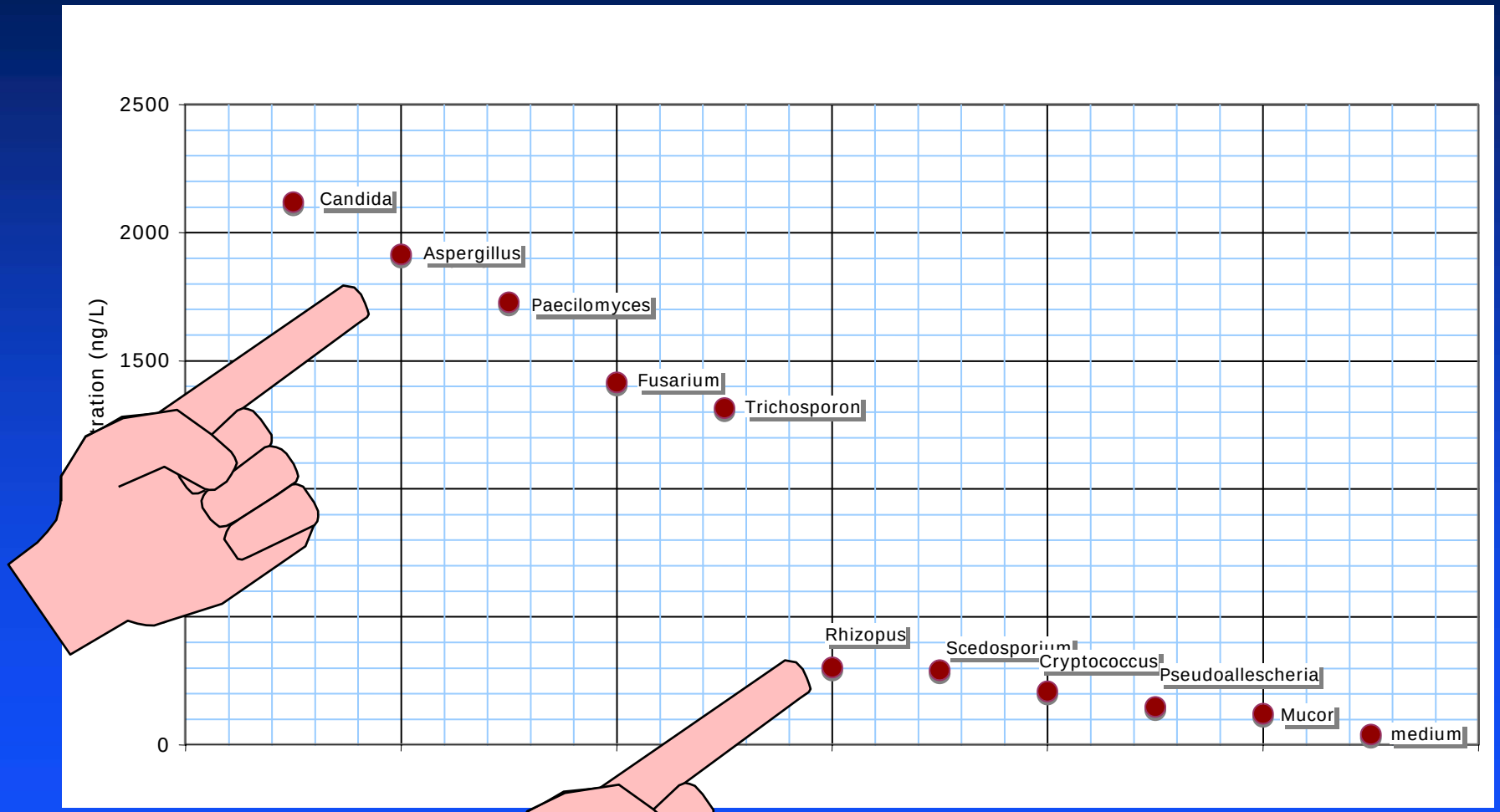
Mycology

Beta-D-glucan in BAL, CSF or blood

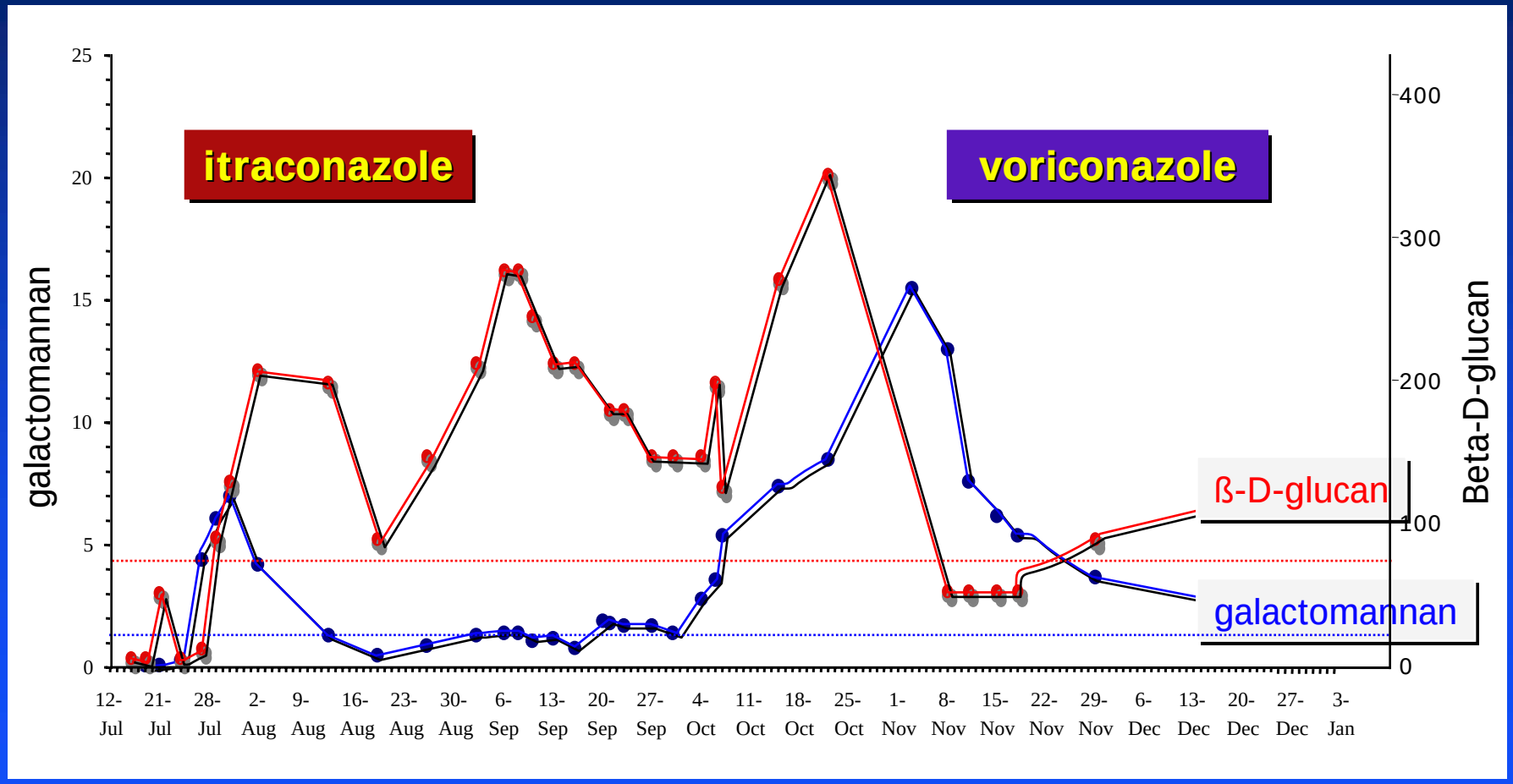
Fungi seen in tissue or sterile body fluids

BDG - different fungi ... different levels



Odabasi et al Med Mycol 2006;44:267-272

Dynmics of BDG and galactomannan



More experience needed

PCR

Definitions II - Mycology

Culture of mould from tissue. aspirate BAL or sputum

antigen in blood, BAL, CSF

mould seen in sinus aspirate

Mycology

Beta-D-glucan in BAL, CSF or blood

Fungi seen in tissue or sterile body fluids

~~PCR~~ to detect nucleic acid

Not until a PCR system is developed that has been externally validated for blood, tissue, or BAL fluid

PCR - comparisons

Author	Sensitivity (%)	Specificity (%)	Likelihood ratio of probable/proven IA for a positive PCR test	Likelihood ratio of probable/proven IA for a negative PCR test
Einsele et al 1997	100	98	50.00	<0.01
Skladny et al 1999	100	89	9.09	<0.01
Hebart et al 2000	100	65	2.86	<0.01
Hebart et al 2000	100	73	3.70	<0.01
Williamson et al 2000	81	100	100	0.19
Lass-Florl et al 2001	75	96	18.75	0.26
Buchheidt et al 2001	2	81.3	4.90	0.10
Kami et al 2001	79	92	9.88	0.23
Buchheidt et al 2004	64	63.5	1.74	0.57
Kawazu et al 2004	64	87	4.92	0.41
Jordanides et al 2005	75	70	2.50	0.36
White et al 2005	92	95	17.09	0.08

Donnelly Clin Infect Dis 2006;42:487-489

PCR - comparisons

High LR

Author	Sensitivity (%)	Specificity (%)	Likelihood ratio of probable/proven IA for a positive PCR test	Likelihood ratio of probable/proven IA for a negative PCR test
Einsele et al 1997	100	98	50.00	<0.01
Skladny et al 1999	100	89	9.09	<0.01
Hebart et al 2000	100	65	2.86	<0.01
Hebart et al 2000	100	73	3.70	<0.01
Williamson et al 2000	81	100	100	0.19
Lass-Florl et al 2001	75	96	18.75	0.26
Buchheidt et al 2001	2	81.3	4.90	0.10
Kami et al 2001	79	92	9.88	0.23
Buchheidt et al 2004	64	63.5	1.74	0.57
Kawazu et al 2004	64	87	4.92	0.41
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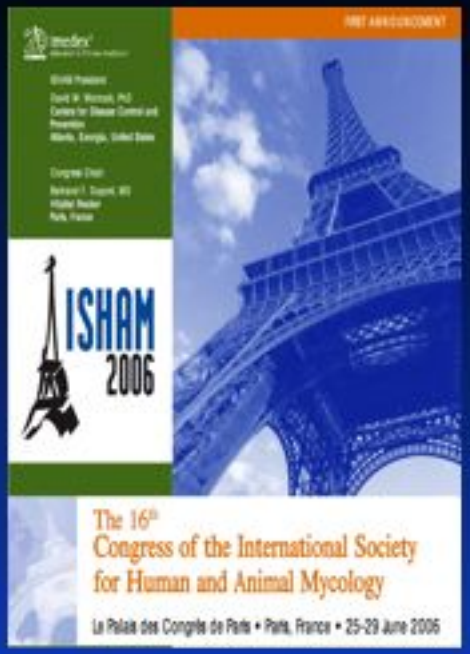
Donnelly Clin Infect Dis 2006;42:487-489



Towards a standard for PCR to diagnose aspergillosis

Sunday 25 June 2006
13:00 17:00
Level 3 Room 341
Le Palais des Congrès de Paris
Paris, France

Goal

Achieve a standard for PCR

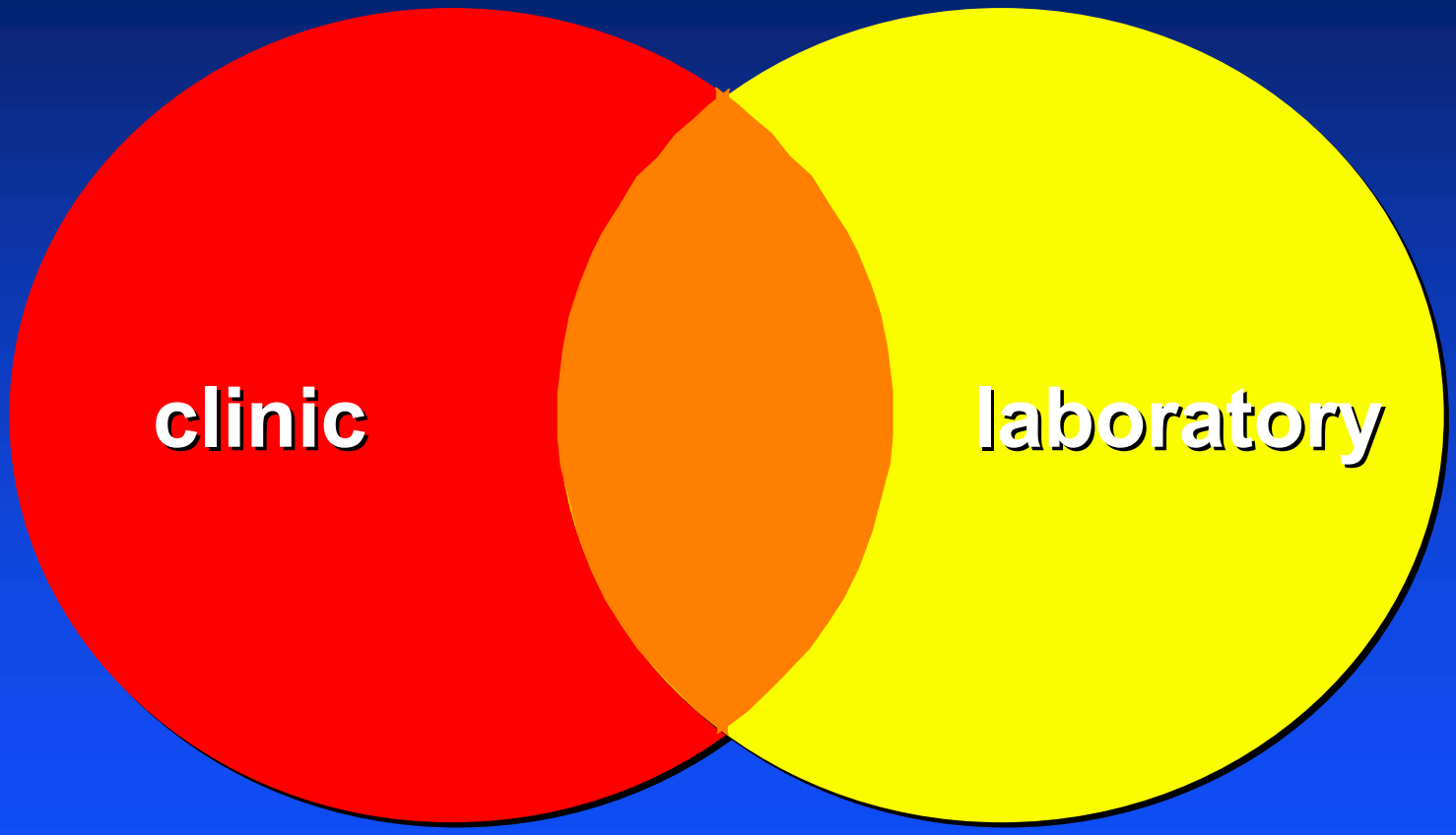
~ 2008

What do we need

clinic

laboratory

Complete cooperation



European Collaboration

EBMT

agreed

HSCT

EORTC

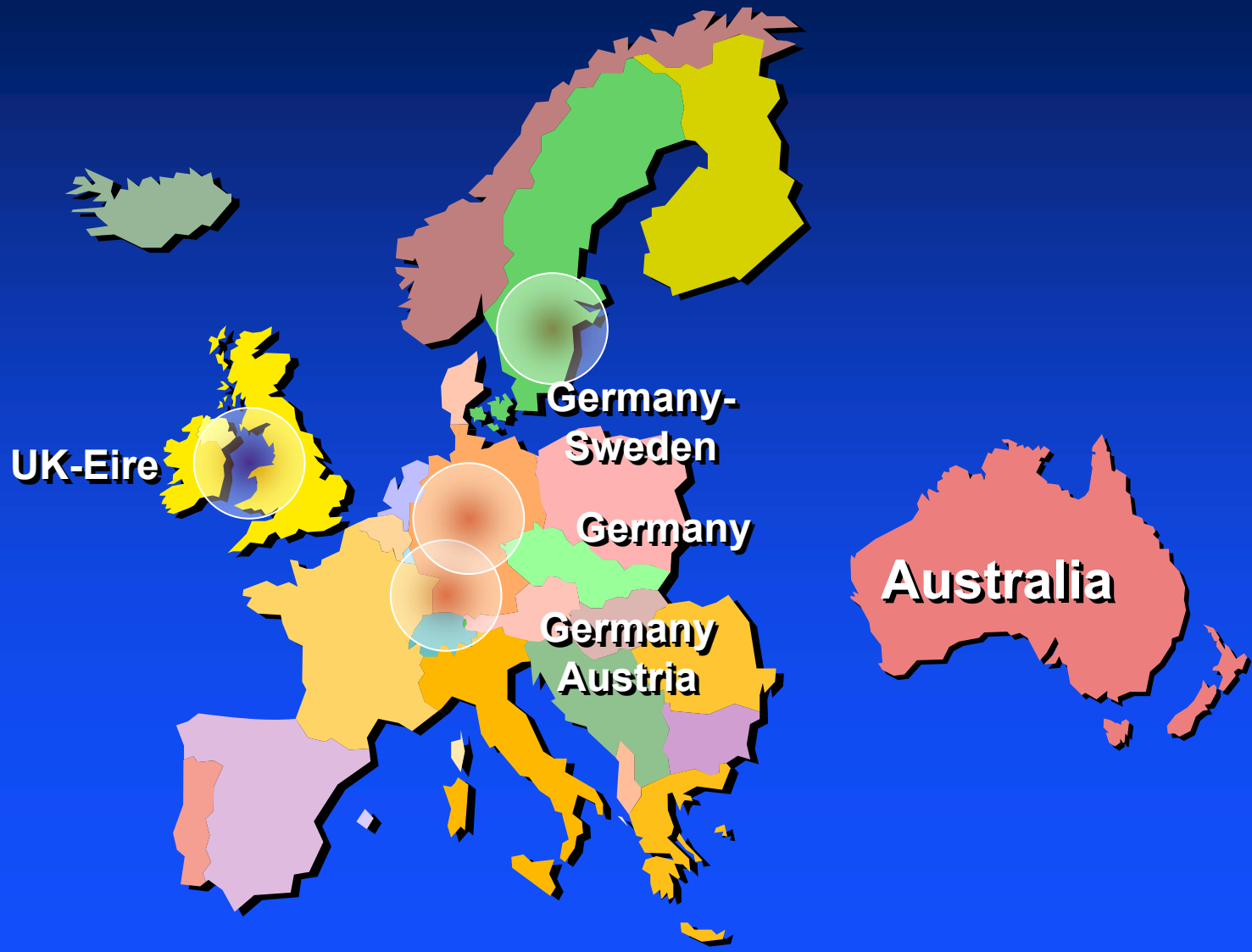
European Organisation for Research

AISBL International

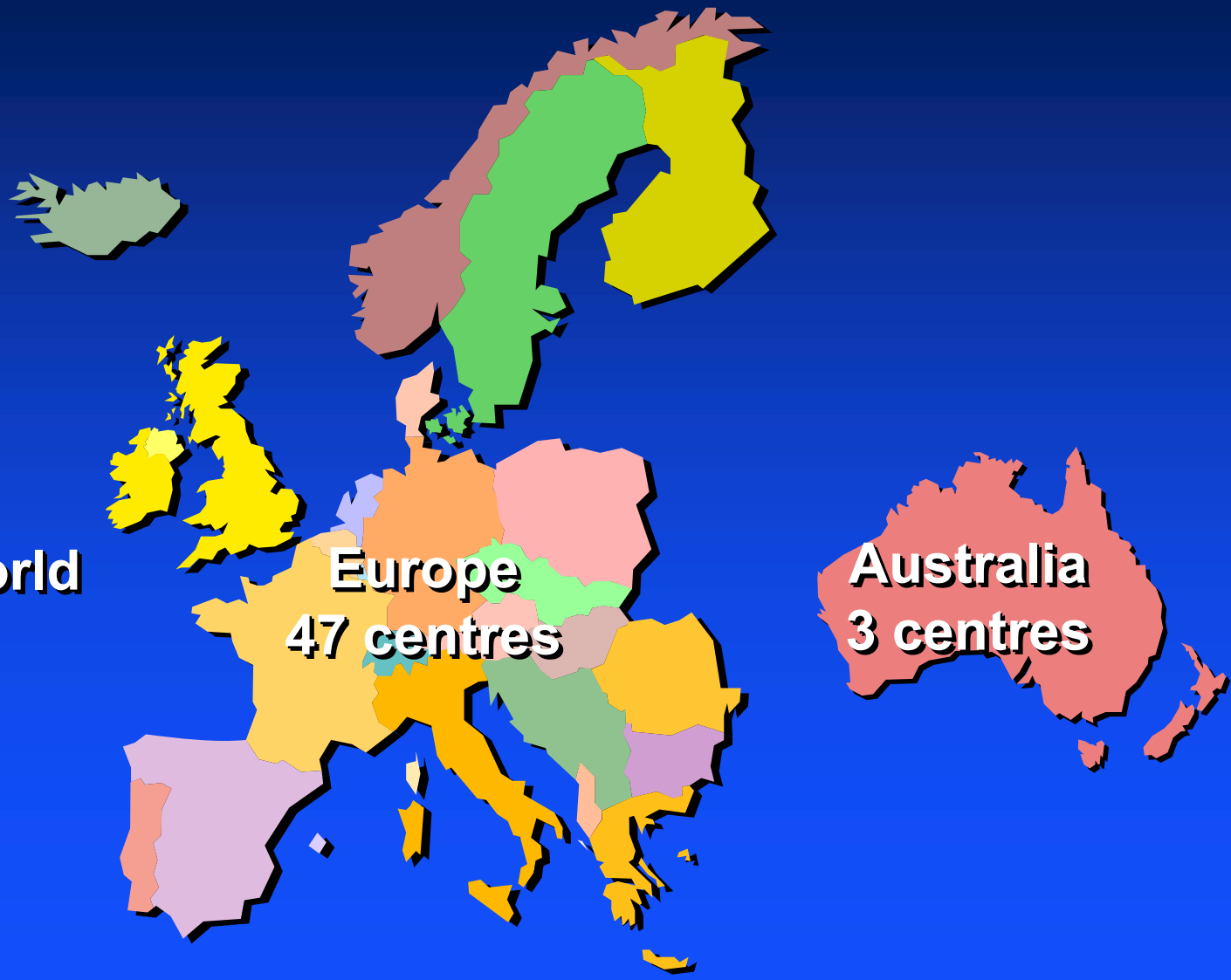
agreed

chemotherapy

Existing initiatives



Interested parties



UMC St Radboud

European Aspergillus PCR initiative

Steering committee

J Peter Donnelly

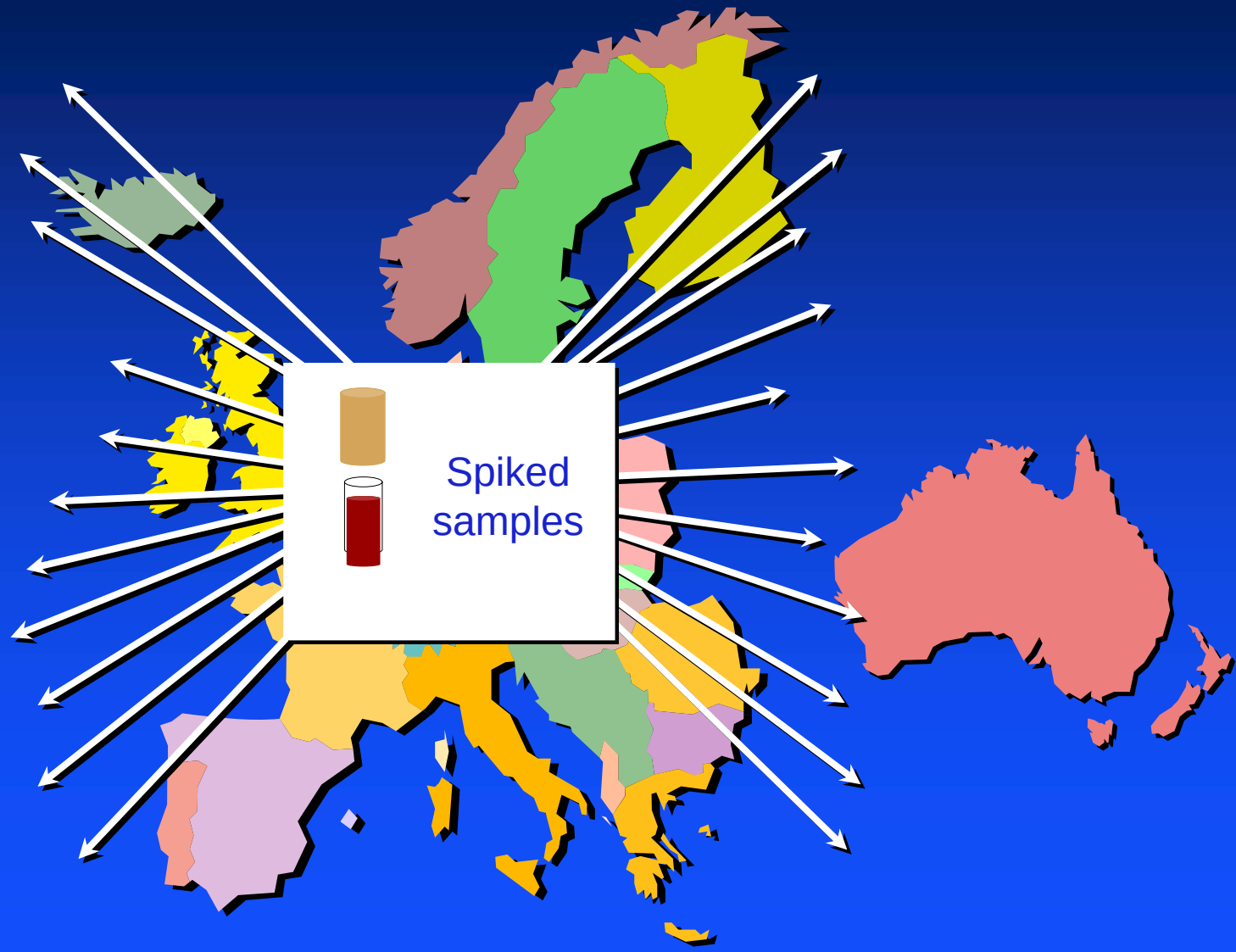
Laboratory Working party

Jurgen Loeffler

Clinical Working party

Rosemary Barnes

Laboratory studies



UMC St Radboud

European Aspergillus PCR initiative

ISHAM
INTERNATIONAL SOCIETY FOR HUMAN AND ANIMAL MYCOLOGY

WORKING GROUP
EUROPEAN ASPERGILLUS PCR INITIATIVE
EAPCRI

http://www.isham.org/Groups.html

Working Group “Towards a standard for Aspergillus PCR”

Watch this space...

Definitions

EORTC-IFICG & NIAID-MSG

Defining Opportunistic Invasive Fungal Infections in Immunocompromised Patients with Cancer and Hematopoietic Stem Cell Transplants: An International Consensus

S. Ascioglu,[1] J. H. Rex,[2] B. de Pauw,[1] J. E. Bennett,[2] J. Bille,[1] F. Crokaert,[1] D. W. Denning,[1] J. P. Donnelly,[1] J. E. Edwards,[2] Z. Erjavec,[1] D. Fiere,[1] O. Lortholary,[1] J. Maertens,[1] J. F. Meis,[1] T. F. Patterson,[2] J. Ritter,[1] D. Selleslag,[1] P. M. Shah,[1] D. A. Stevens,[2] and T. J. Walsh,[2] on behalf of the Invasive Fungal Infections Cooperative Group of the European Organization for Research and Treatment of Cancer and Mycoses Study Group of the National Institute of Allergy and Infectious Diseases

[1]European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group, Brussels; and [2]National Institute of Allergy and Infectious Diseases Mycoses Study Group, National Institutes of Health, Bethesda, Maryland

Clinical Infectious Diseases 2002;34:7–14

2002

Strengths

Who uses the EORTC/MSG definitions?

Clinical trials

MAJOR ARTICLE

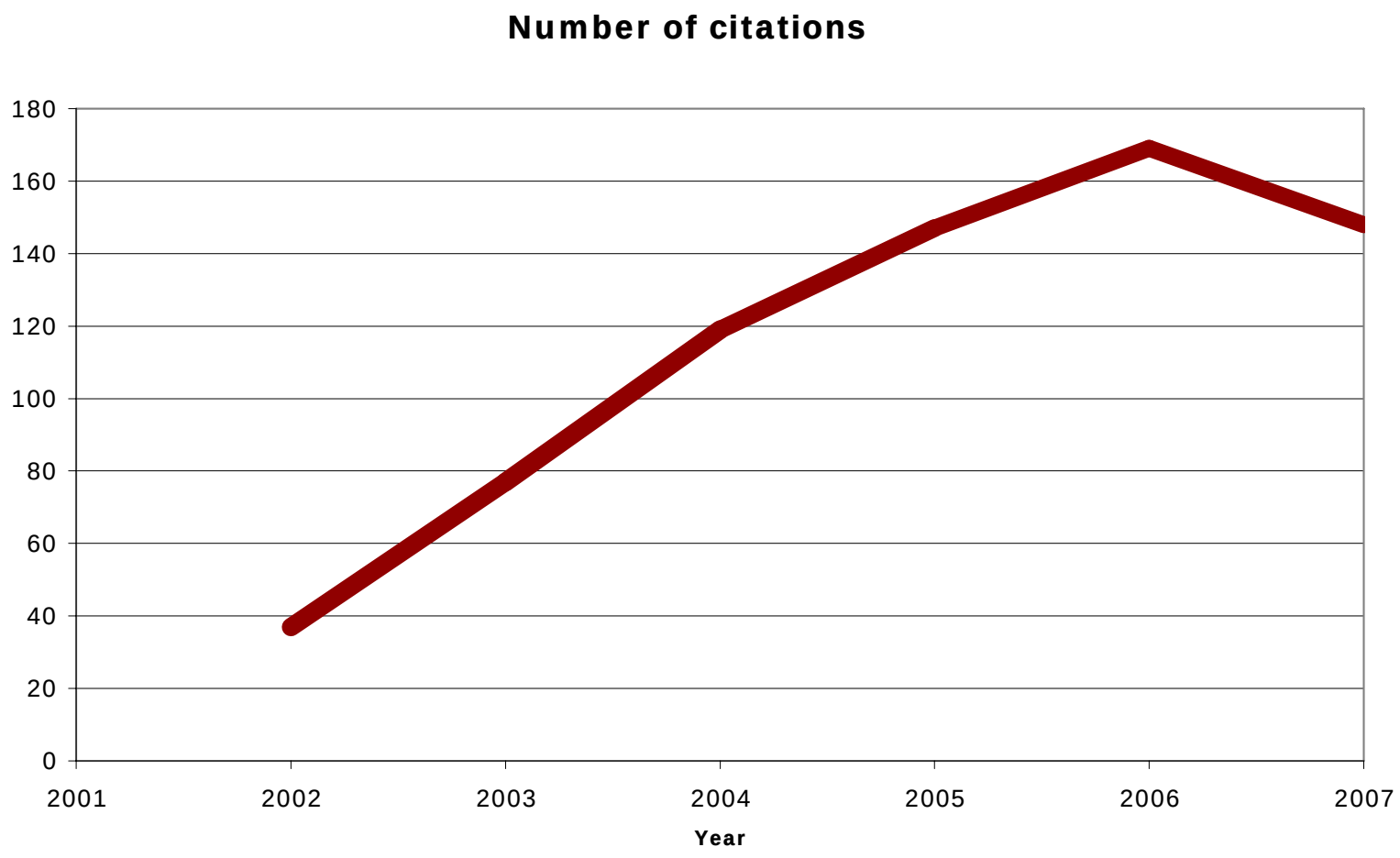
Liposomal Amphotericin B as Initial Therapy for Invasive Mold Infection: A Randor
Comparing a High–Loading Dose Reg
with Standard Dosing (AmBiLoad Tria

Diagnostic tests

MAJOR ARTICLE

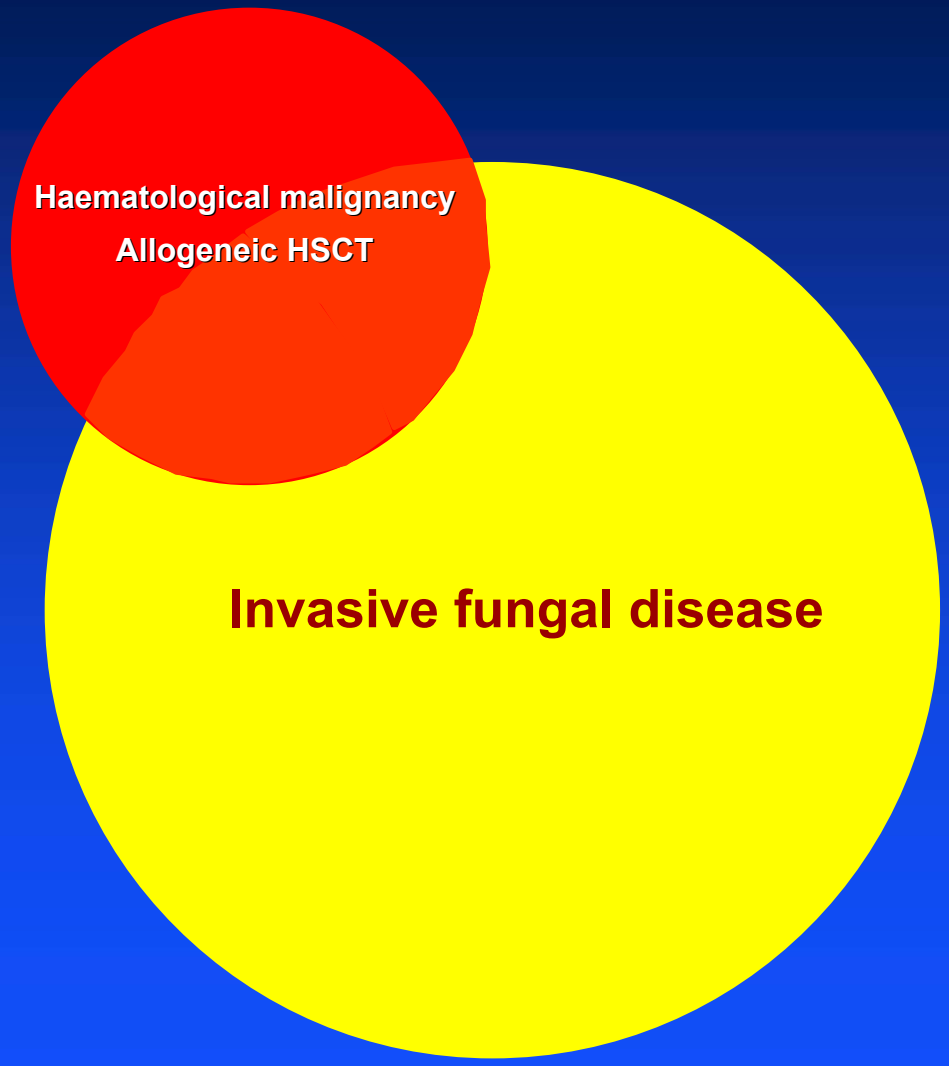
Optimization of the Cutoff Value for the *Aspergillus* Double-Sandwich Enzyme Immunoassay

Citations of the original definitions

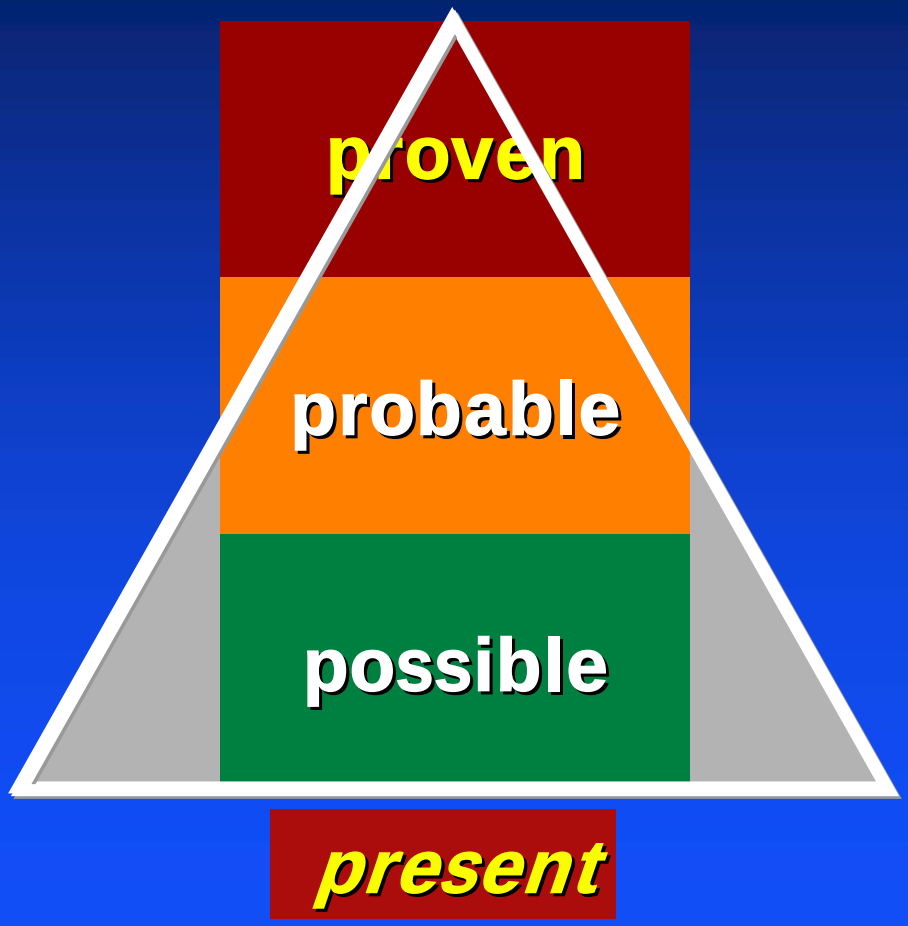


Limitations

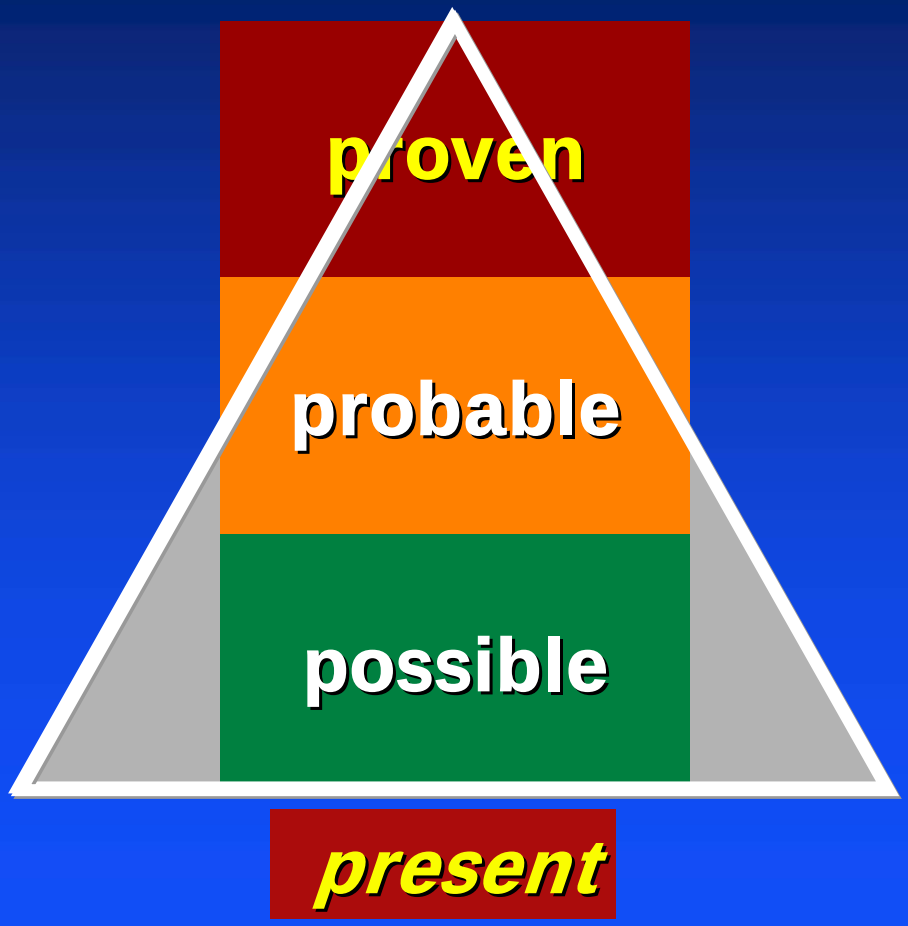
Patients at risk of developing IFD



Goal of adapting definitions



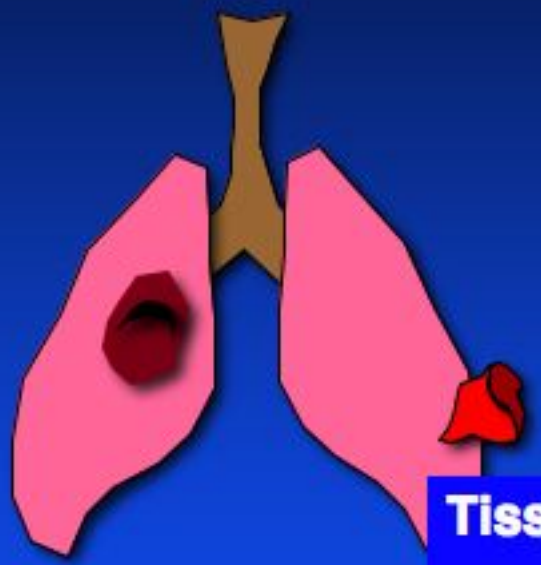
Goal of adapting definitions



Round 'em up

No change

Proven invasive fungal infective disease



Tissue

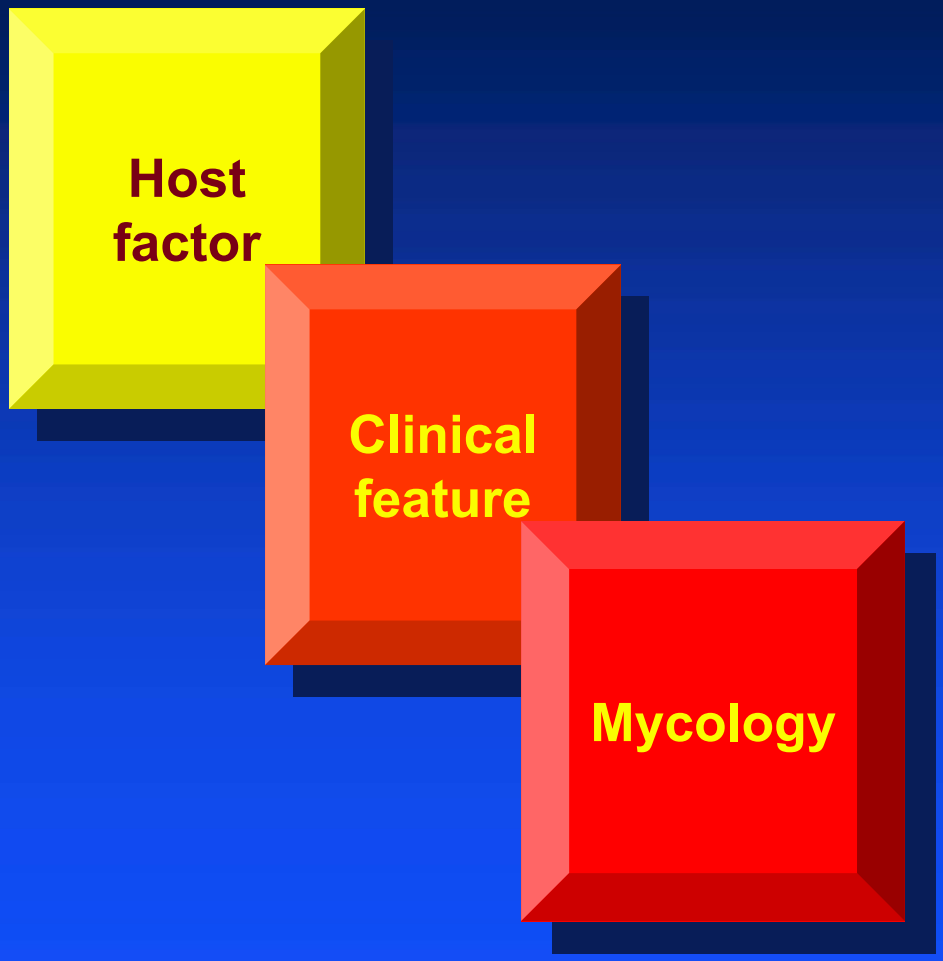
histology

Mycology

Blood culture

culture

Defining invasive fungal disease



EORTC / MSG

Definitions for invasive fungal disease

Changes

What's in a name?

Invasive **F**ungal **I**nfection

2002

What's in a name?

Invasive **F**ungal **I**nfection

↓

Invasive **F**ungal **D**isease

2007

Definitions - Host factors

neutropenia

3 weeks corticosteroids

<36°C or 38°C and
- prior mycosis
- AIDS
- Immunosuppressive drugs
- 10 days neutropenia

4 days unexplained fever despite broad spectrum antibiotics

Graft versus Host Disease

Host factor

2002

Definitions - Host factors

Host factor

- neutropenia
- 3 weeks corticosteroids
- Allogeneic HSCT recipient
- Treatment with other recognized T-cell immune suppressants
- Inherited severe immunodeficiency

2007

Definitions - Clinical features

MAJOR

≥ 1

Lower respiratory tract infection

Halo sign
Air-crescent sign
cavity

Chronic disseminated candidiasis

Bull's eye lesions in liver or spleen

Clinical feature

Sinonasal infection

Radiological evidence

CNS infection

Radiological evidence

Disseminated fungal infection

Unexplained papular or nodular skin lesions
Chorioretinitis
phthalmitis

2002

Definitions - Clinical features

MINOR

≥ 2

Lower respiratory tract infection

Cough, chest pain, haemoptysis, dyspnoea
Physical finding of pleural rub
Any new infiltrate not fulfilling major criterion

CNS infection

CSF
- No pathogens
- no malignant cells
- abnormal biochemistry
- abnormal cell count

Focal neurological
- seizures
- hemiparesis
- cranial nerve palsy

Mental changes
Meningeal irritation

Clinical feature

Sinonasal infection

Nasal discharge. stuffiness
Nose ulceration. eschar or epistaxis
Periorbital swelling
Maxillary tenderness
Black necrotic lesions or perforatic[illegible]ard-palate

2002

Definitions - Clinical features

Lower respiratory tract IFD

Chronic disseminated candidiasis

Sinonasal IFD

Clinical feature

CNS IFD

No more major and no more minor

2007

Definitions - Clinical features

Lower respiratory tract IFD

A) the presence of one of the following "specific" imaging signs on CT:-

- Dense well circumscribed lesions(s) with or without a halo sign
- Wedge-shaped infiltrate
- Air crescent sign
- Cavity

2007

Definitions - Mycology

Culture of mould from tissue. aspirate BAL or sputum

antigen in blood, BAL, CSF

Mycology

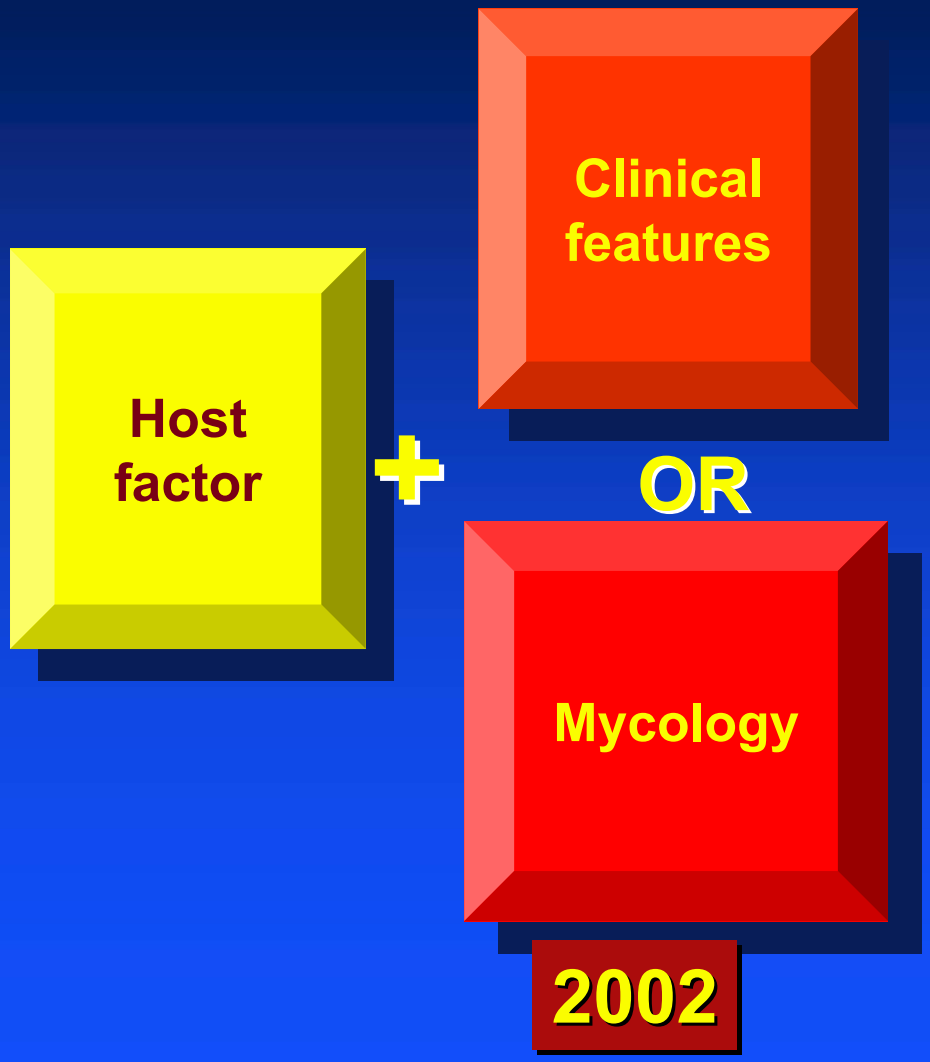
mould seen in sinus aspirate

eta-D-glucan in BAL, CSF or blood

Fungi seen in tissue or sterile body fluids

2007

Definitions I - Possible invasive fungal disease



Definitions II - invasive fungal disease

Host factor + Clinical features

possible

2007

Definitions II - invasive fungal disease

Host factor + Clinical features + Mycology

probable

2007

From: Clinical Infectious Diseases <cid-reviews@press.uchicago.edu
Date: 20 Feb 2008 10:21:42 -0500
To: <p.donnelly@usa.net
Subject: CID MS 52430R1

Dear Dr. Donnelly:

We are pleased to inform you that your manuscript MS 52430R1, entitled "Revised definitions of the EORTC/MSG Consensus Group for invasive Fungal diseases.," was accepted for publication in Clinical Infectious Diseases and will be sent to our publisher, the University of Chicago Press (UCP).

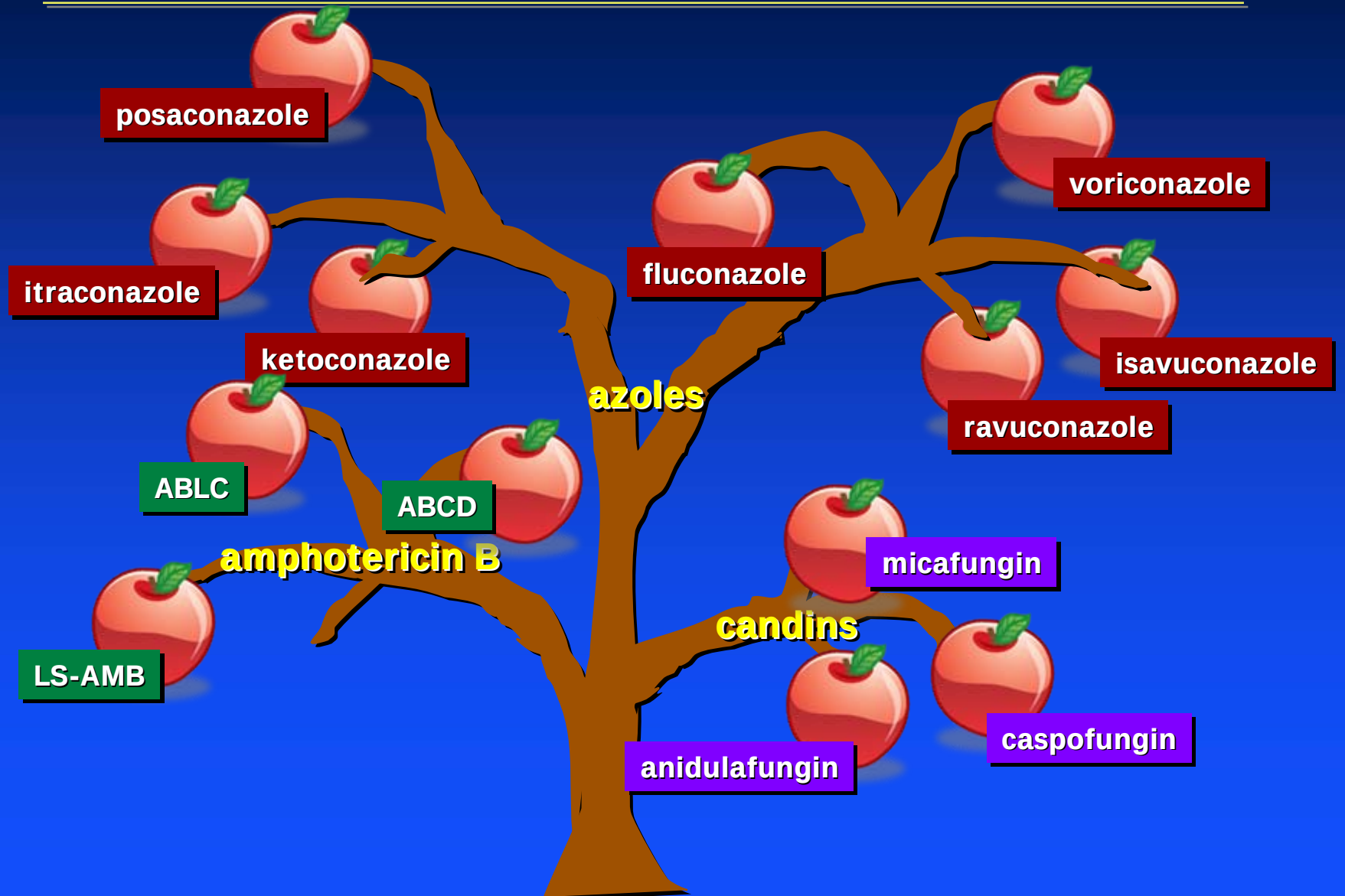
Thank you for submitting your manuscript to Clinical Infectious Diseases.

Sincerely,

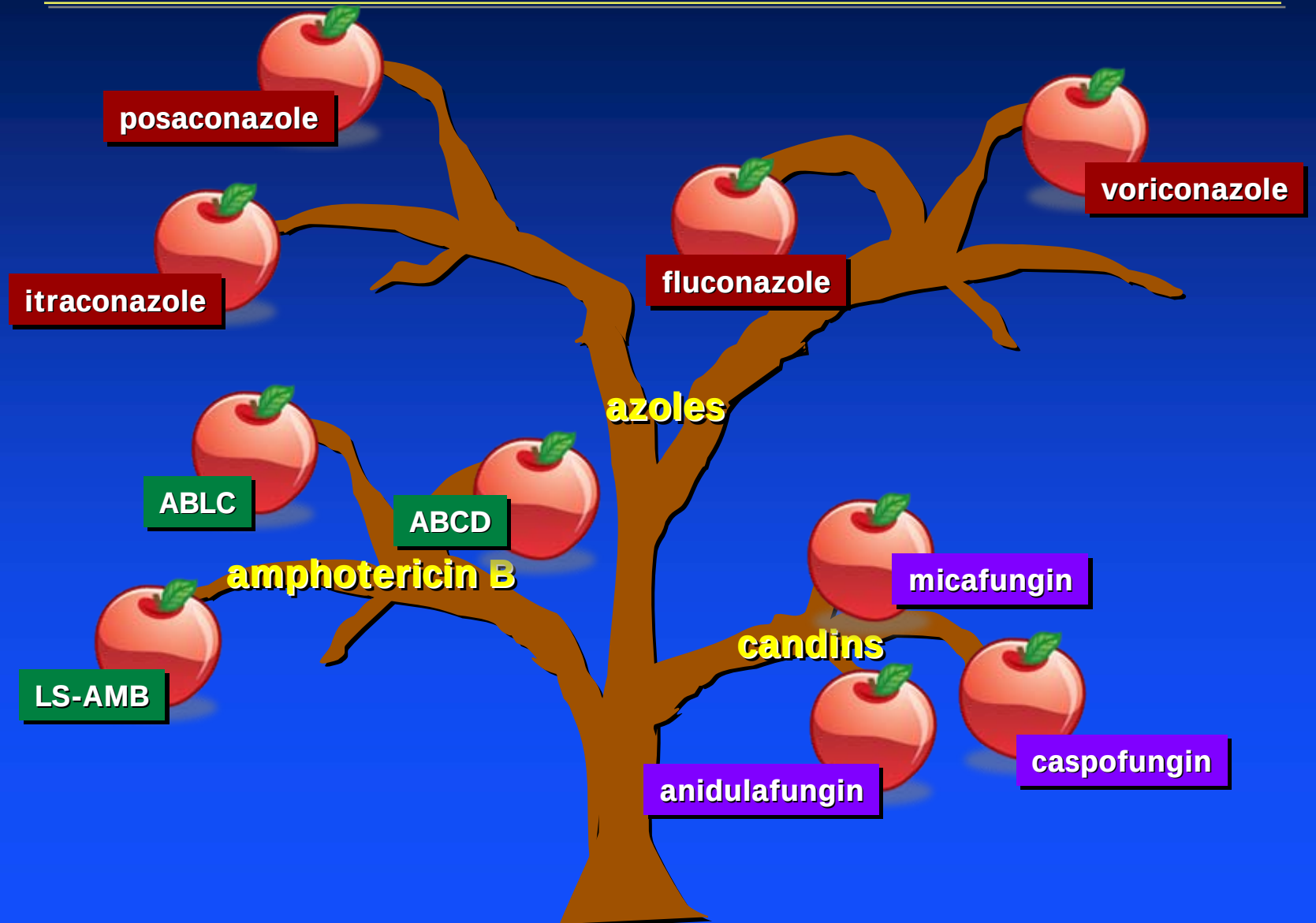
Sherwood L. Gorbach, M.D., Editor
Clinical Infectious Diseases
Tufts University School of Medicine
200 Harrison Ave.
Boston MA 02111-1800
Tel: 617-636-2780
Fax: 617-636-4060
Email: cid1@press.uchicago.edu

Drugs

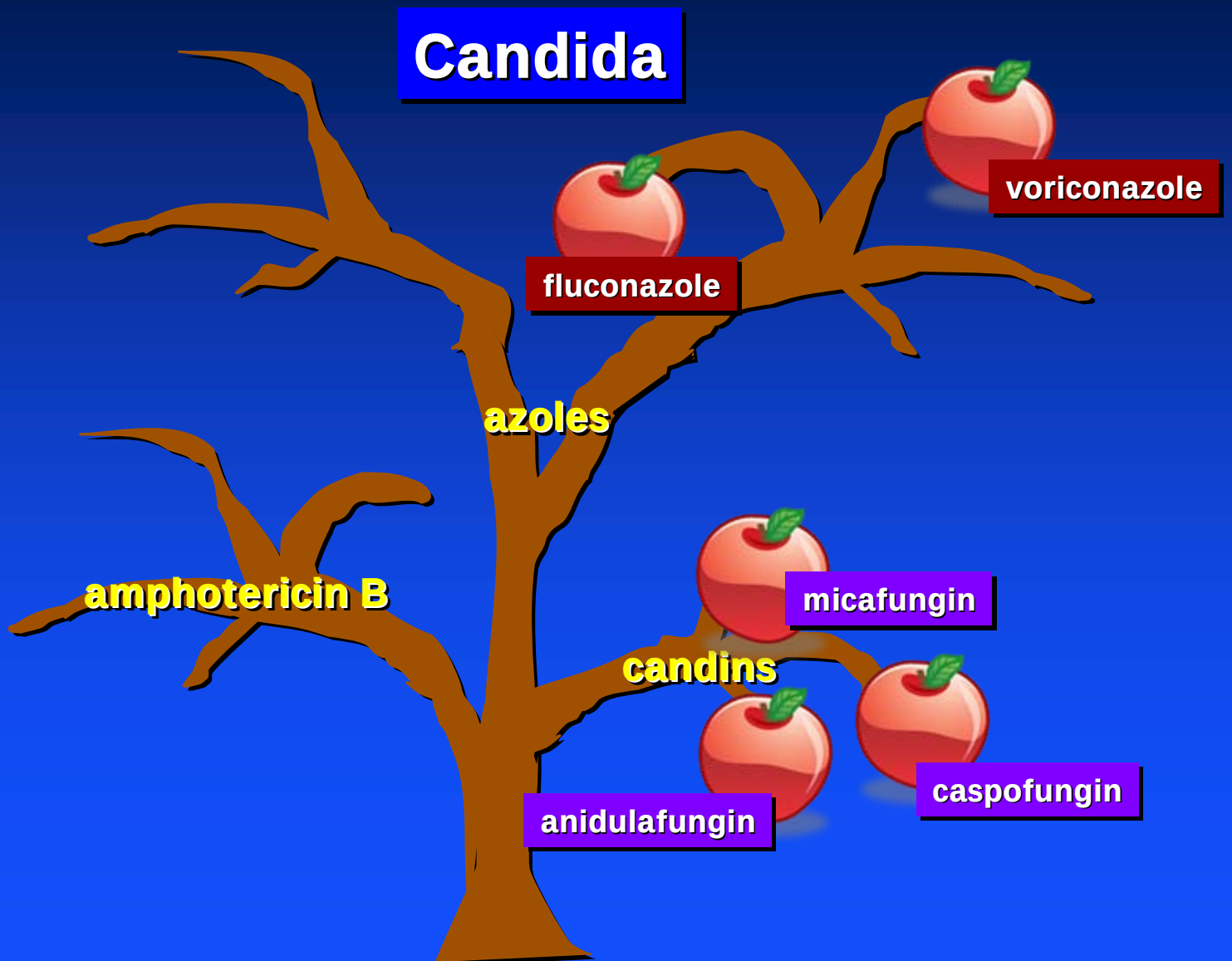
Fruits of the antifungal tree



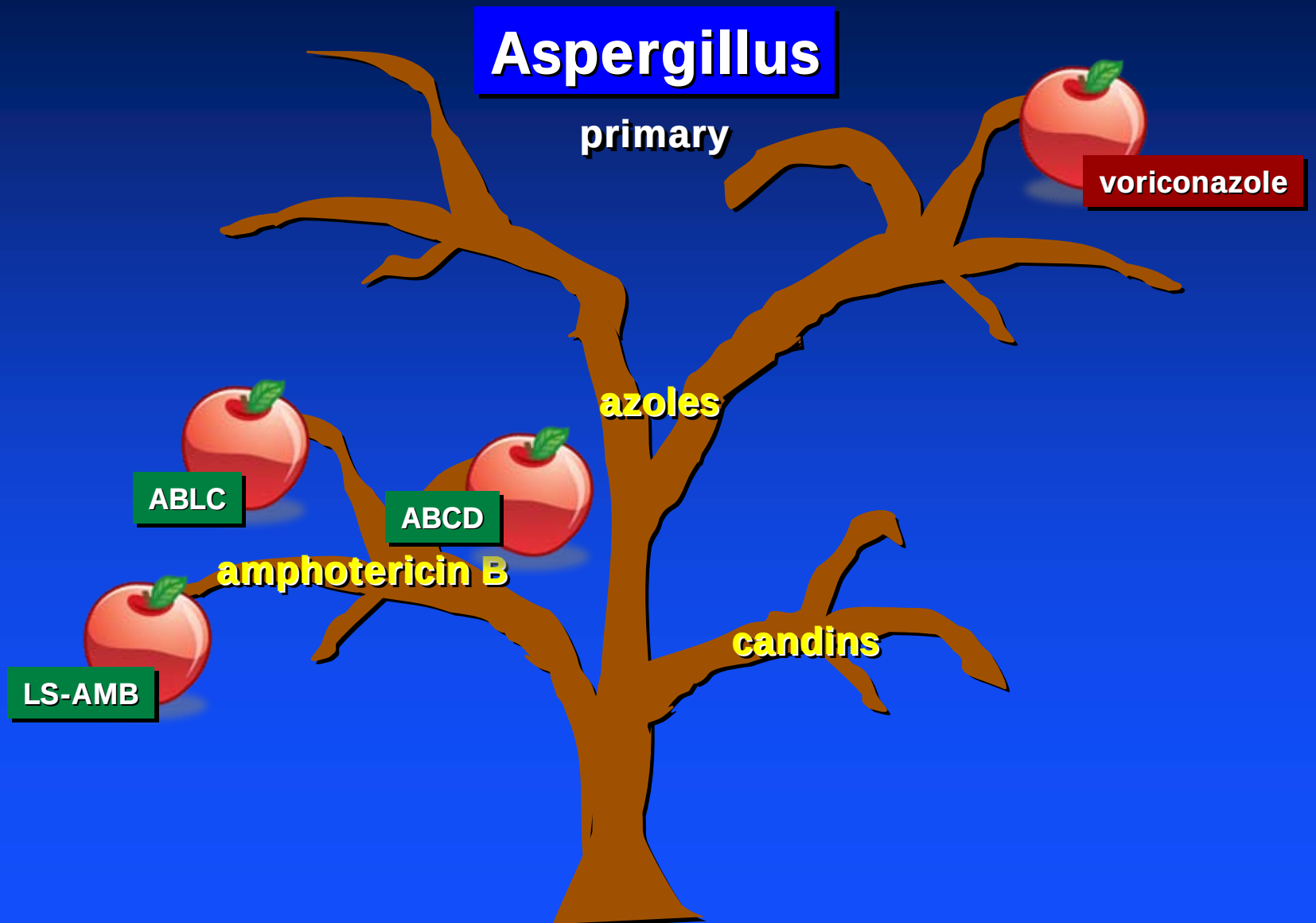
Fruits of the antifungal tree



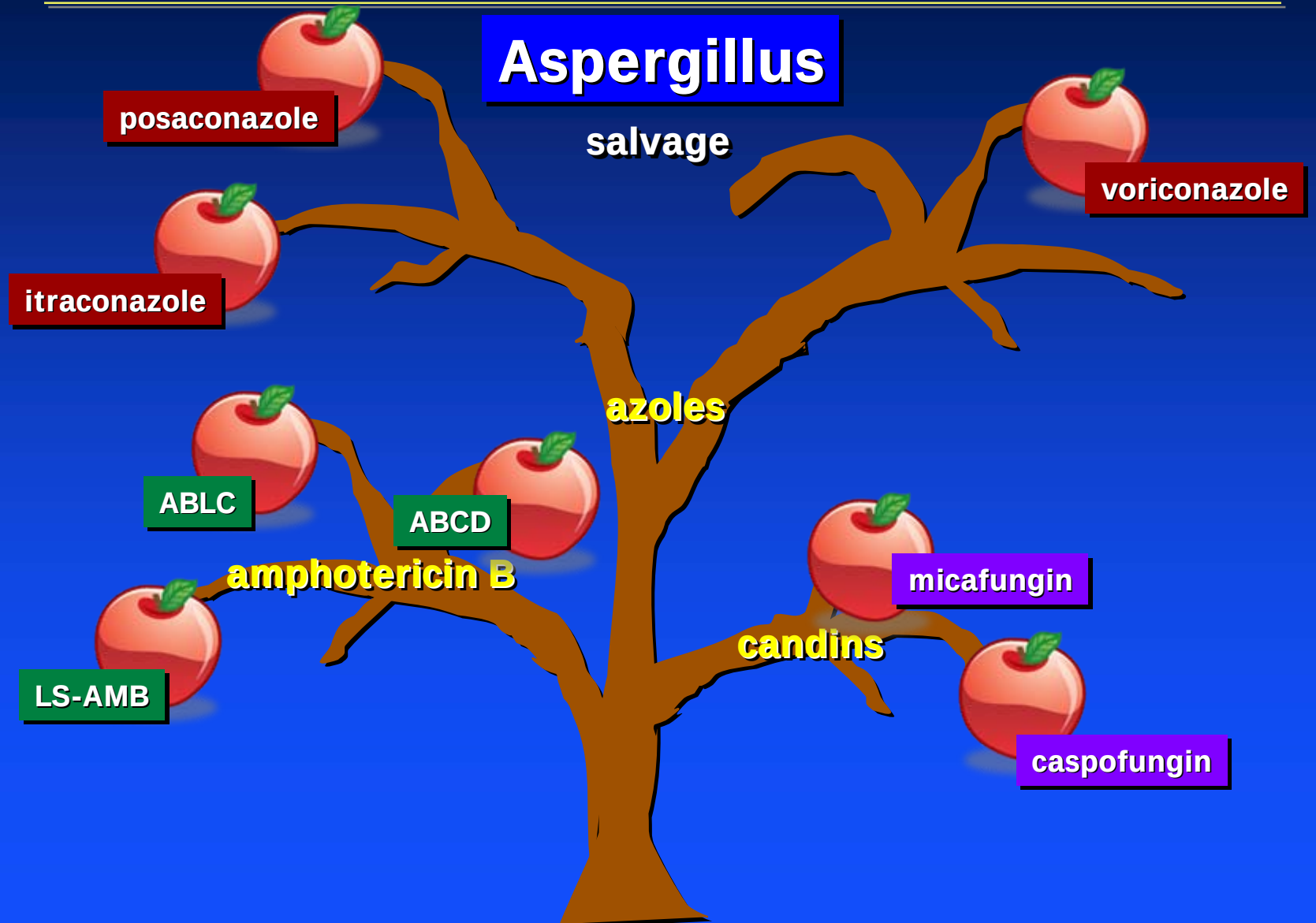
Fruits of the antifungal tree



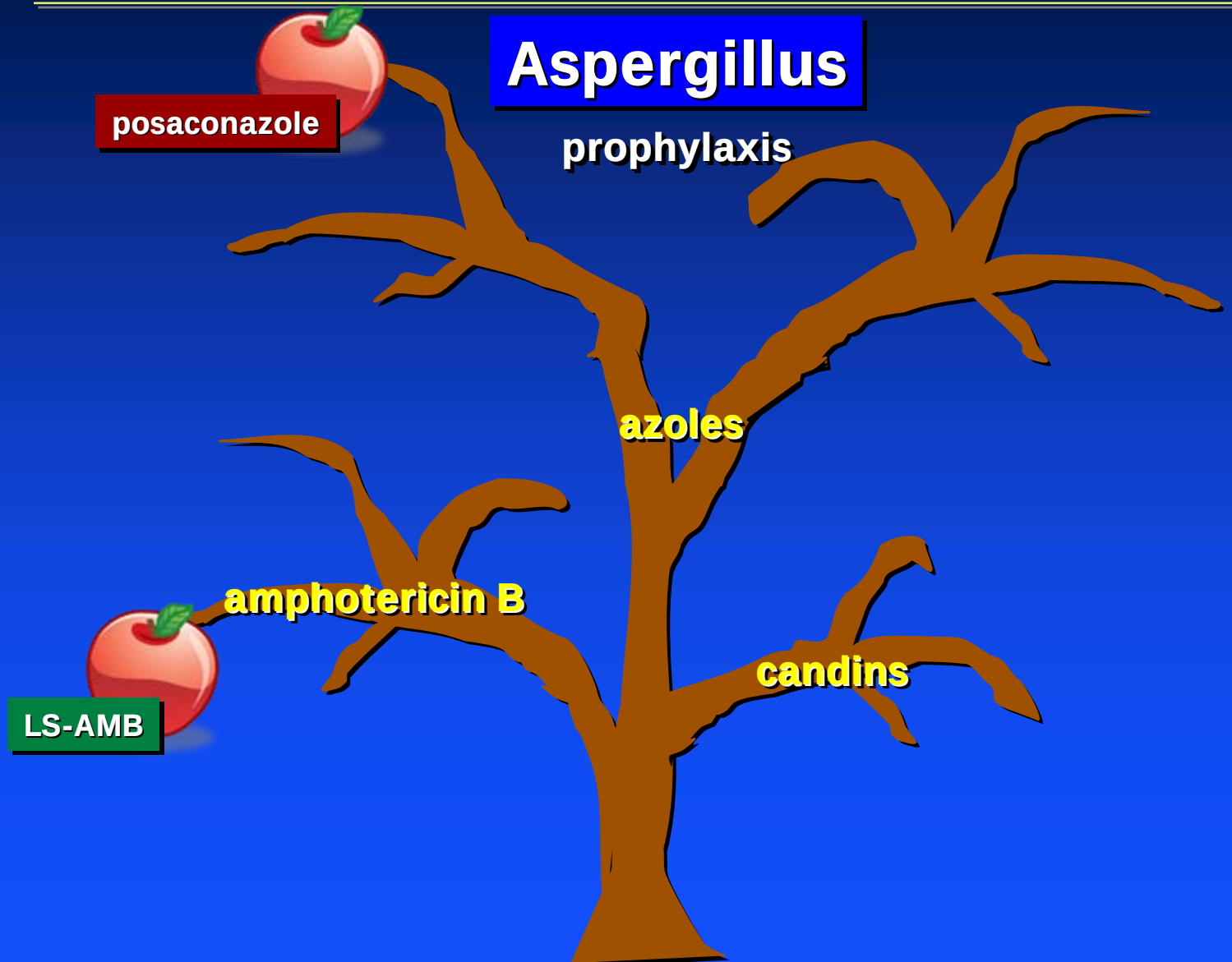
Fruits of the antifungal tree



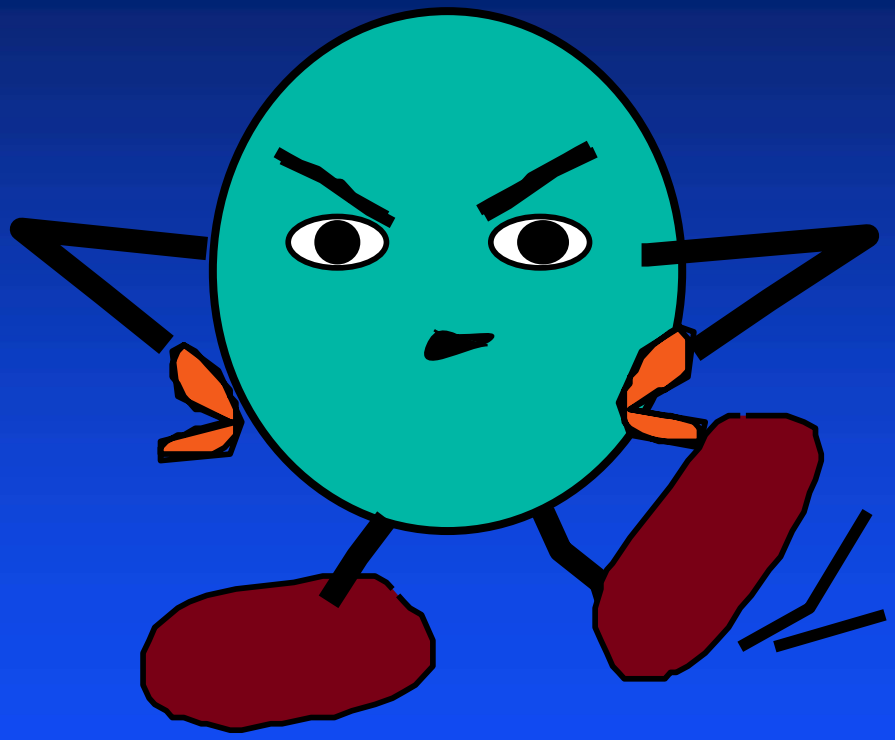
Fruits of the antifungal tree



Fruits of the antifungal tree



So don’t waste them

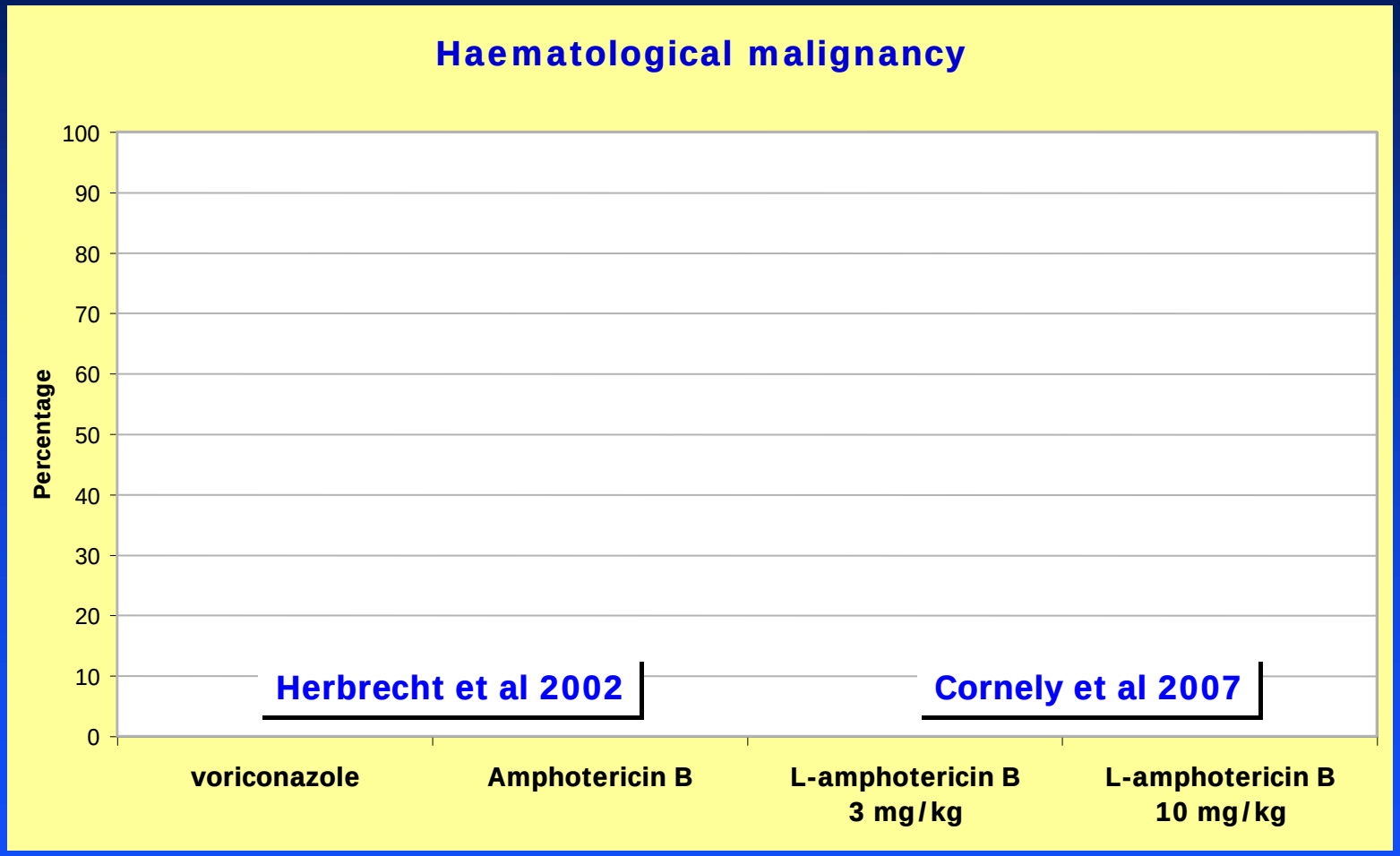


Dilemmas

Dilemma 1

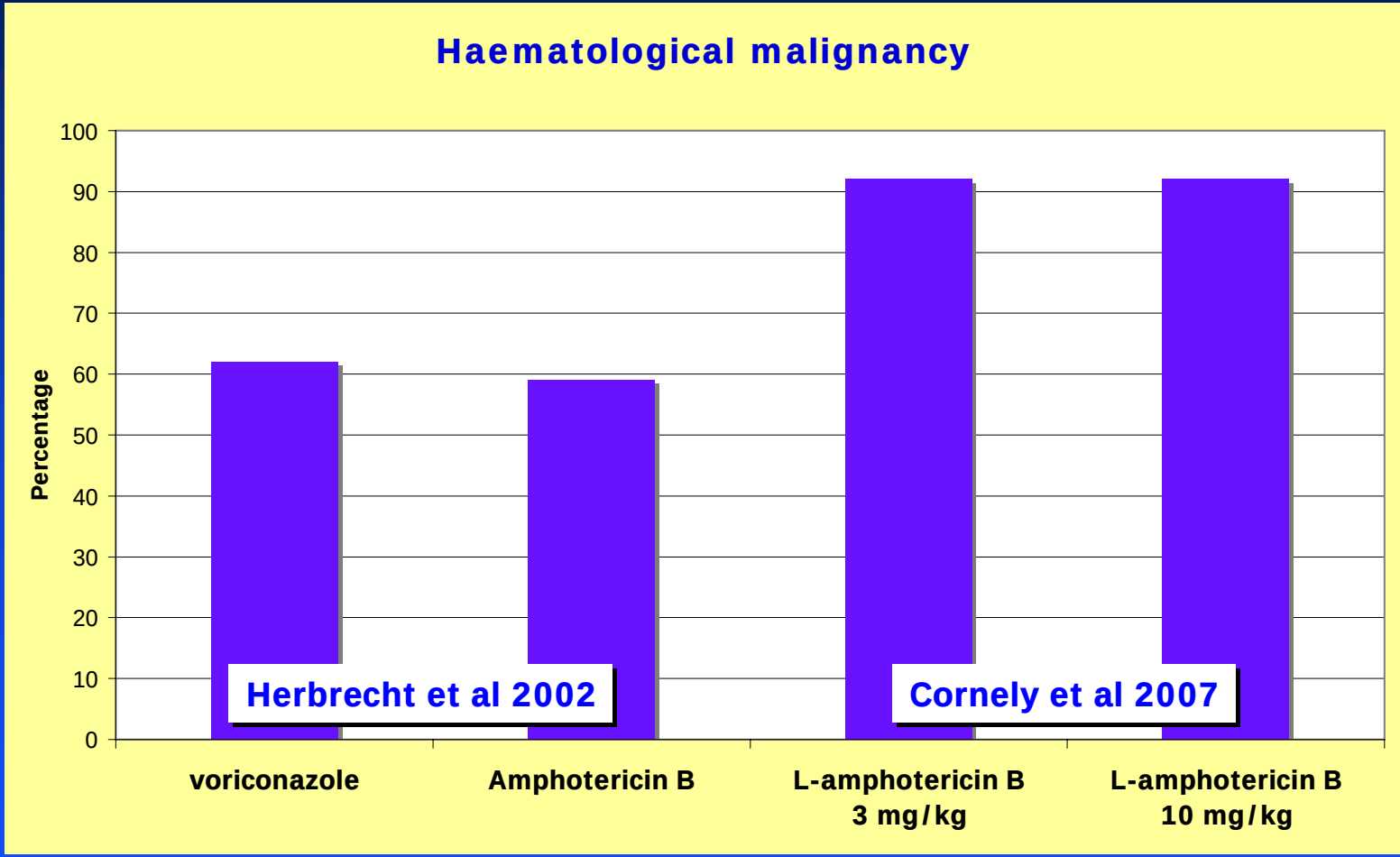
Voriconazole or liposomal amphotericin B for first-line therapy of invasive aspergillosis

A tale of two studies



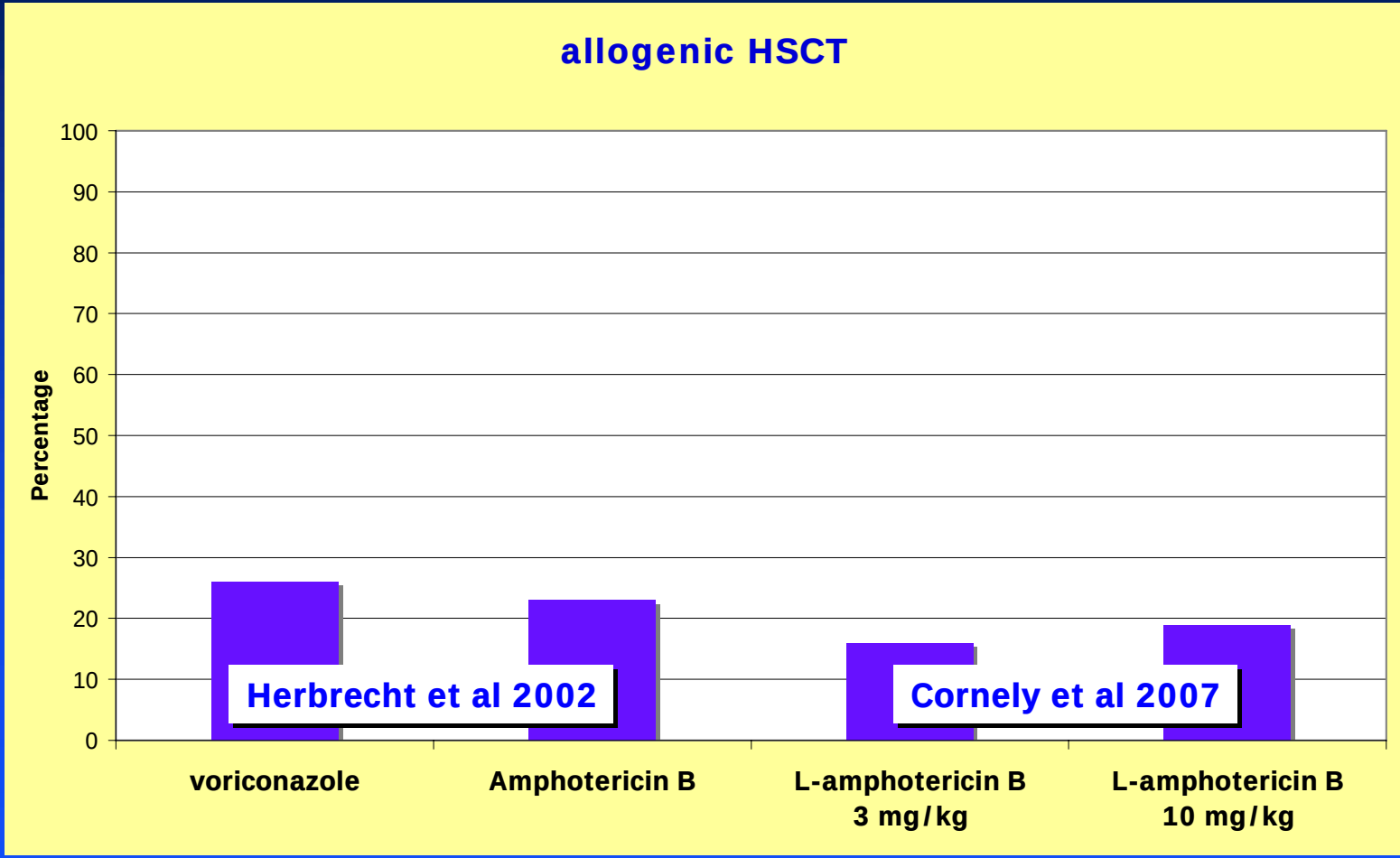
Denning 2007 Clin Infect Dis 45:1106

A tale of two studies



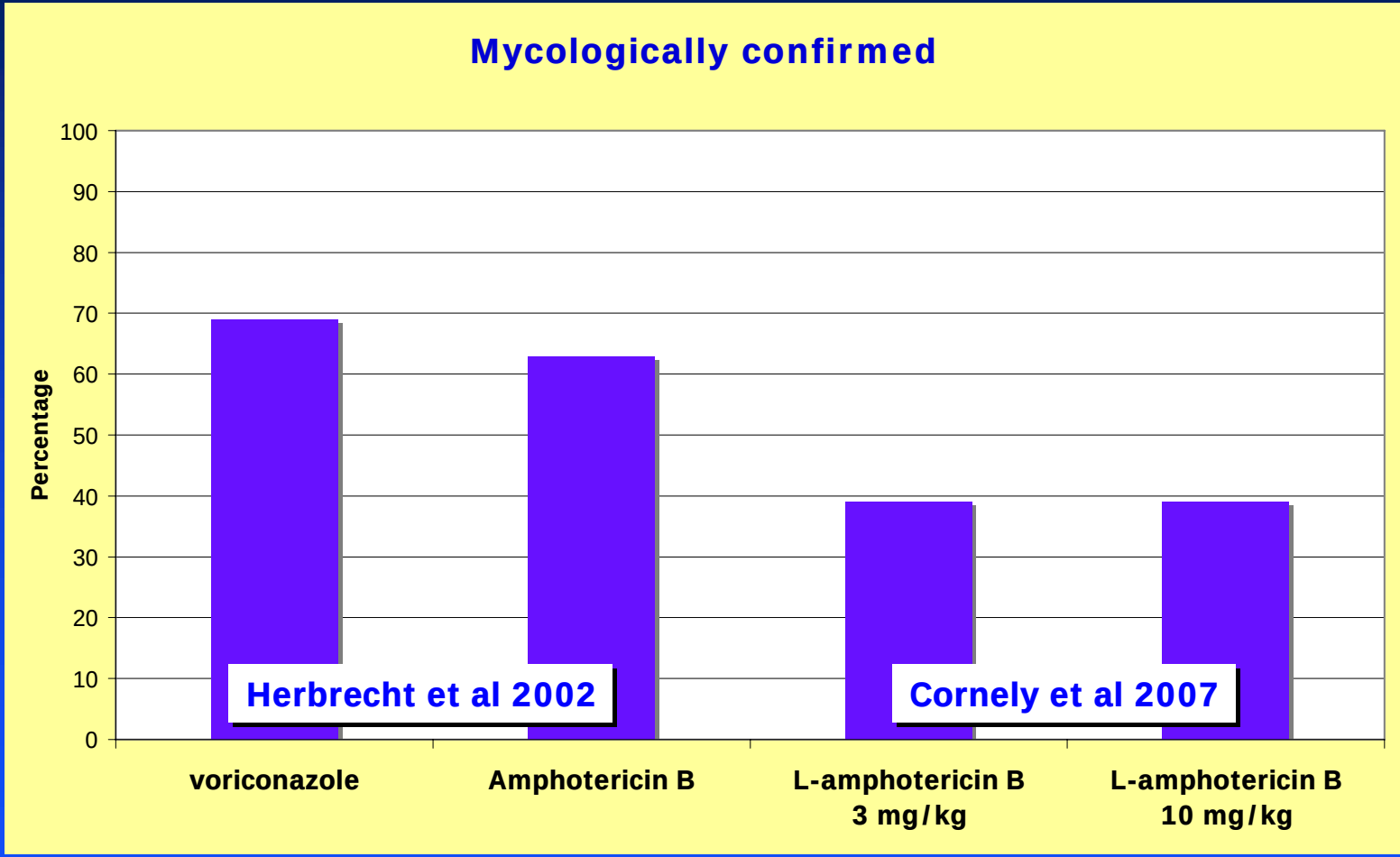
Denning 2007 Clin Infect Dis 45:1106

A tale of two studies



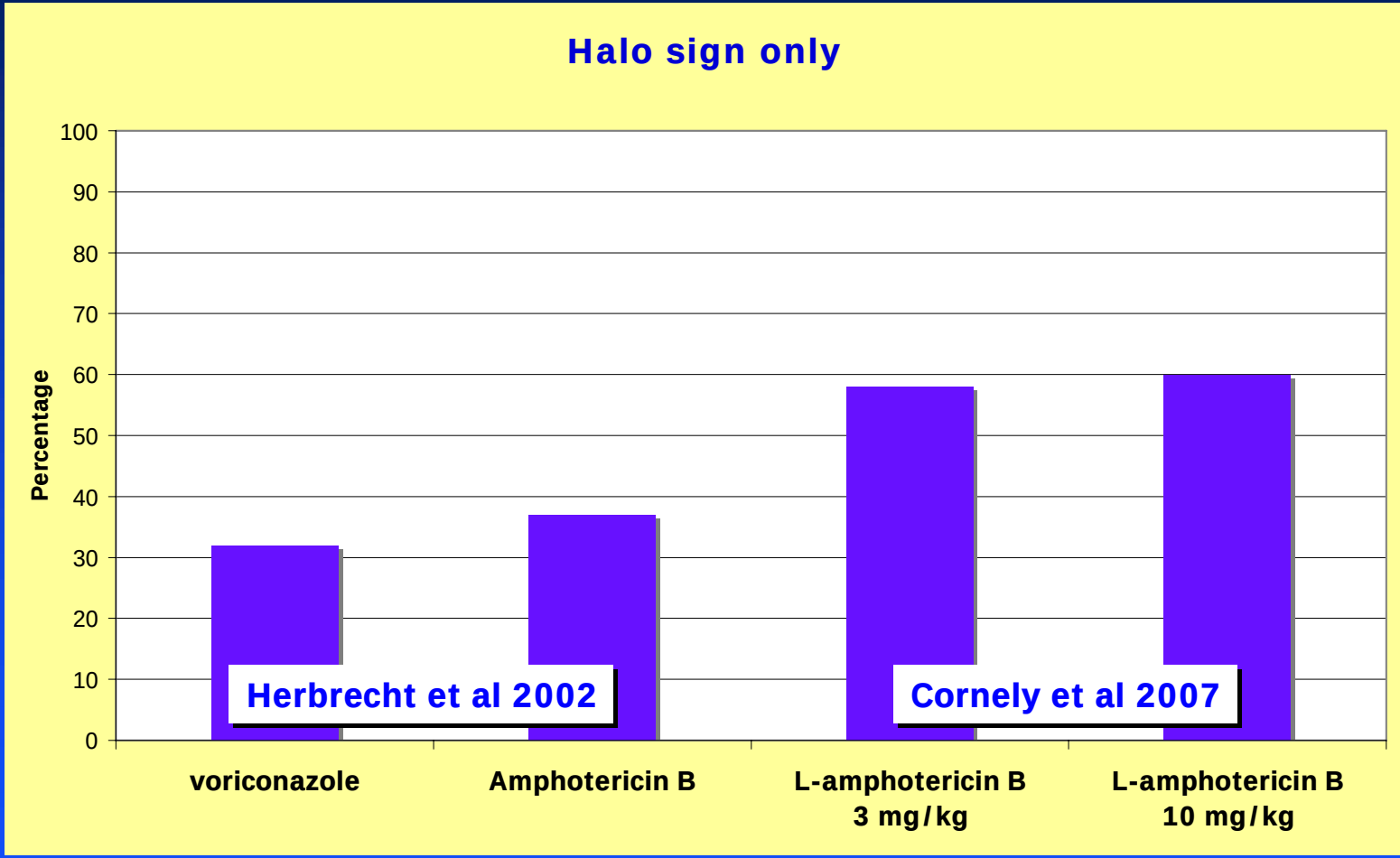
Denning 2007 Clin Infect Dis 45:1106

A tale of two studies



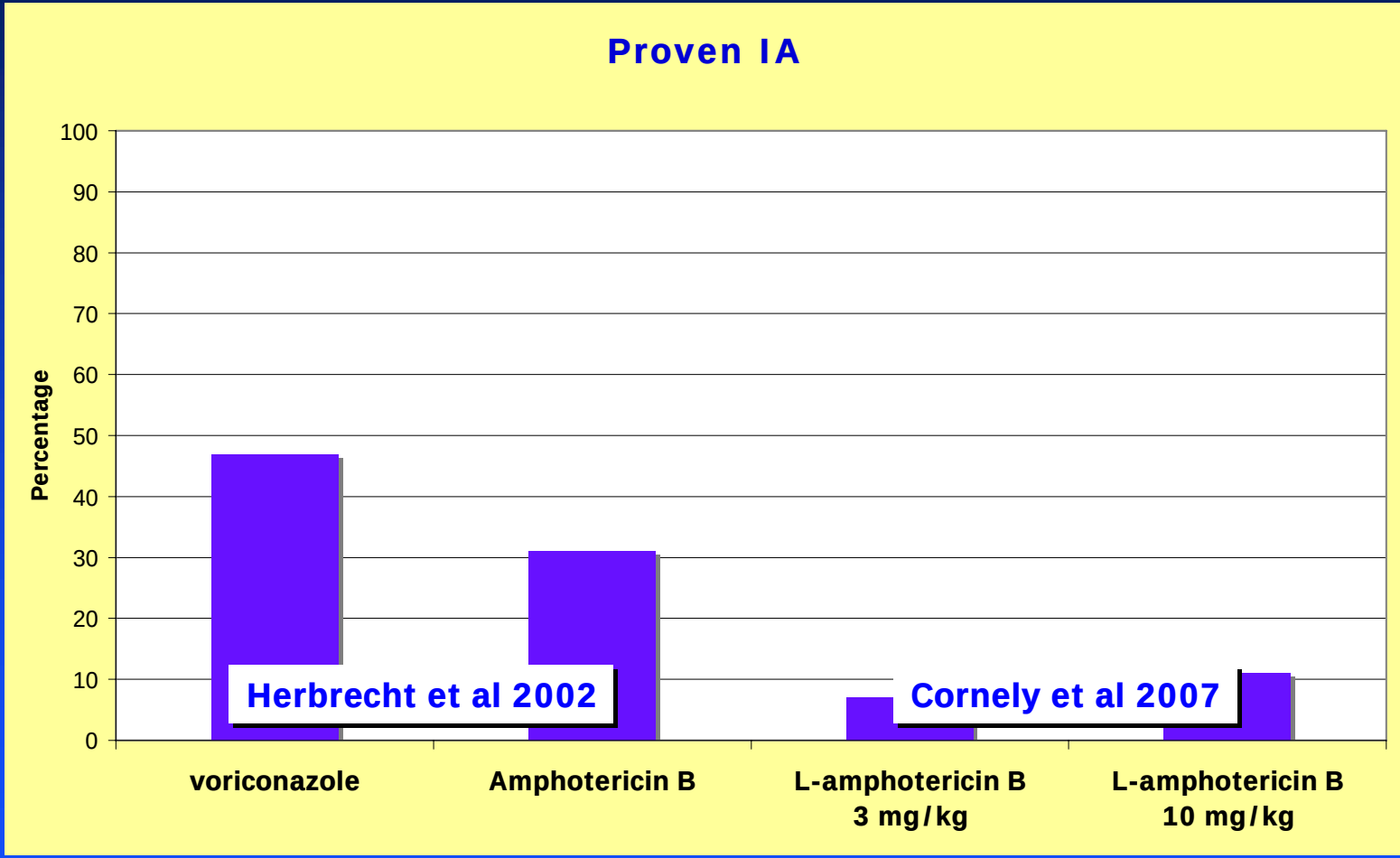
Denning 2007 Clin Infect Dis 45:1106

A tale of two studies



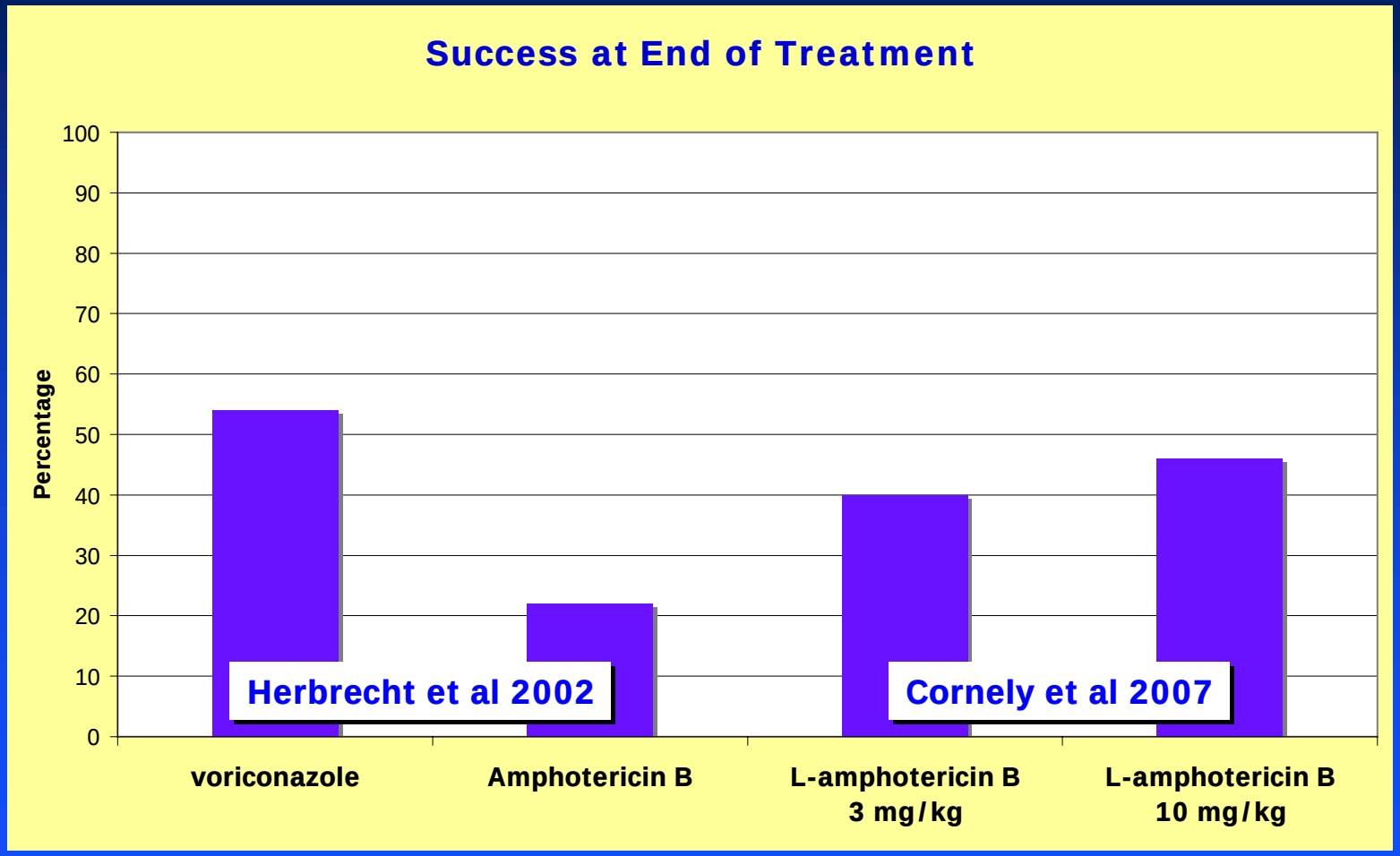
Denning 2007 Clin Infect Dis 45:1106

A tale of two studies



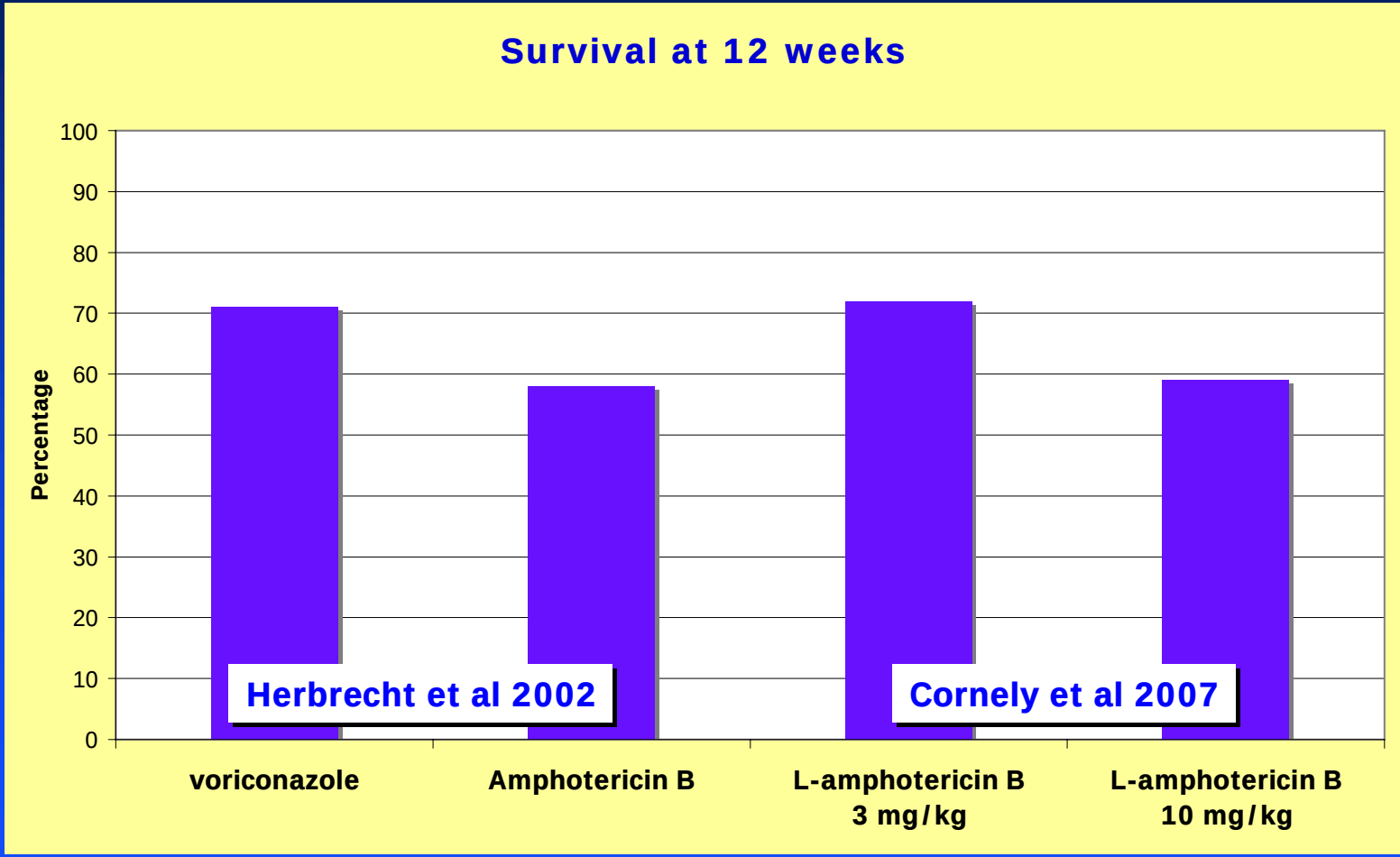
Denning 2007 Clin Infect Dis 45:1106

A tale of two studies



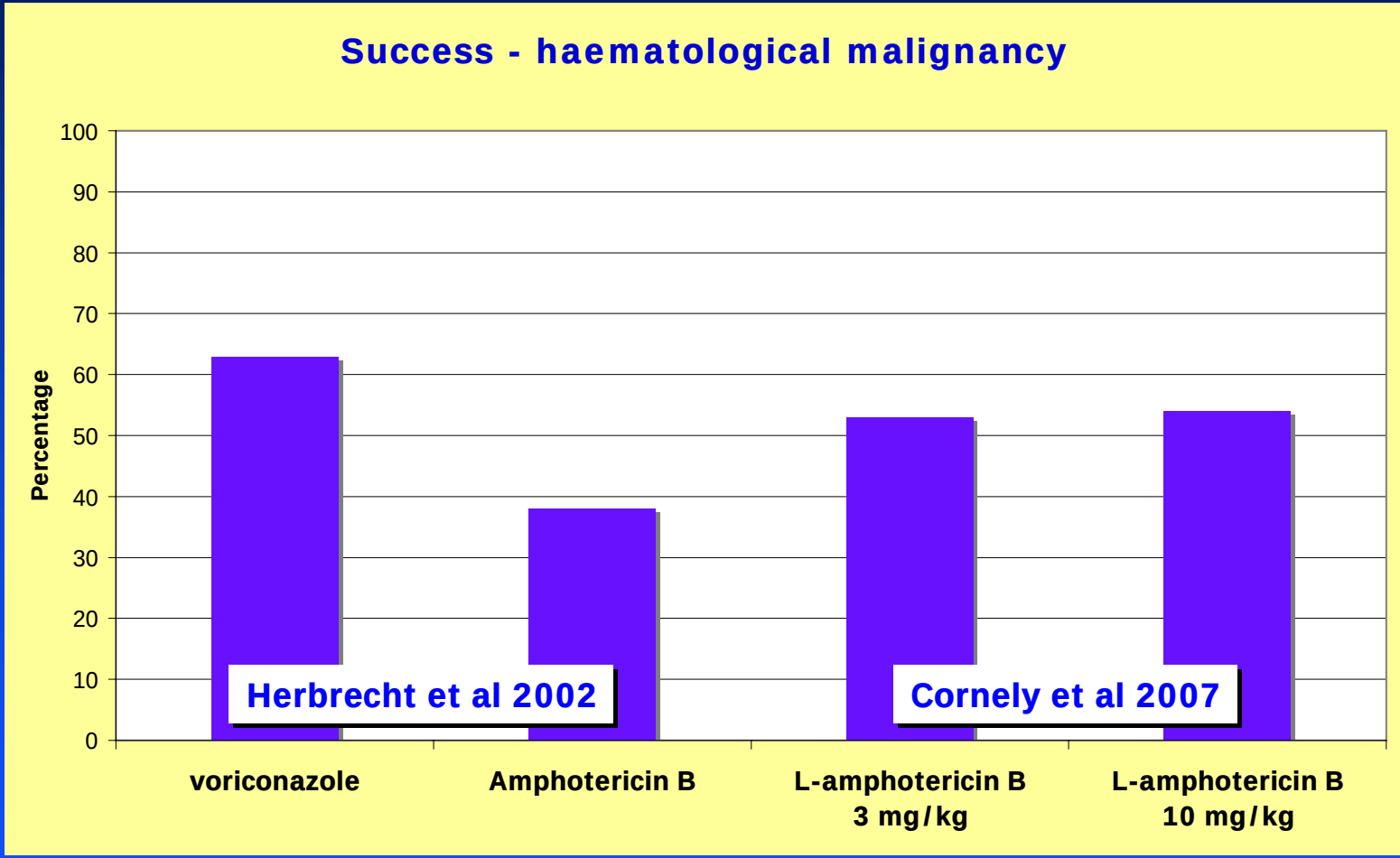
Denning 2007 Clin Infect Dis 45:1106

A tale of two studies



Denning 2007 Clin Infect Dis 45:1106

A tale of two studies



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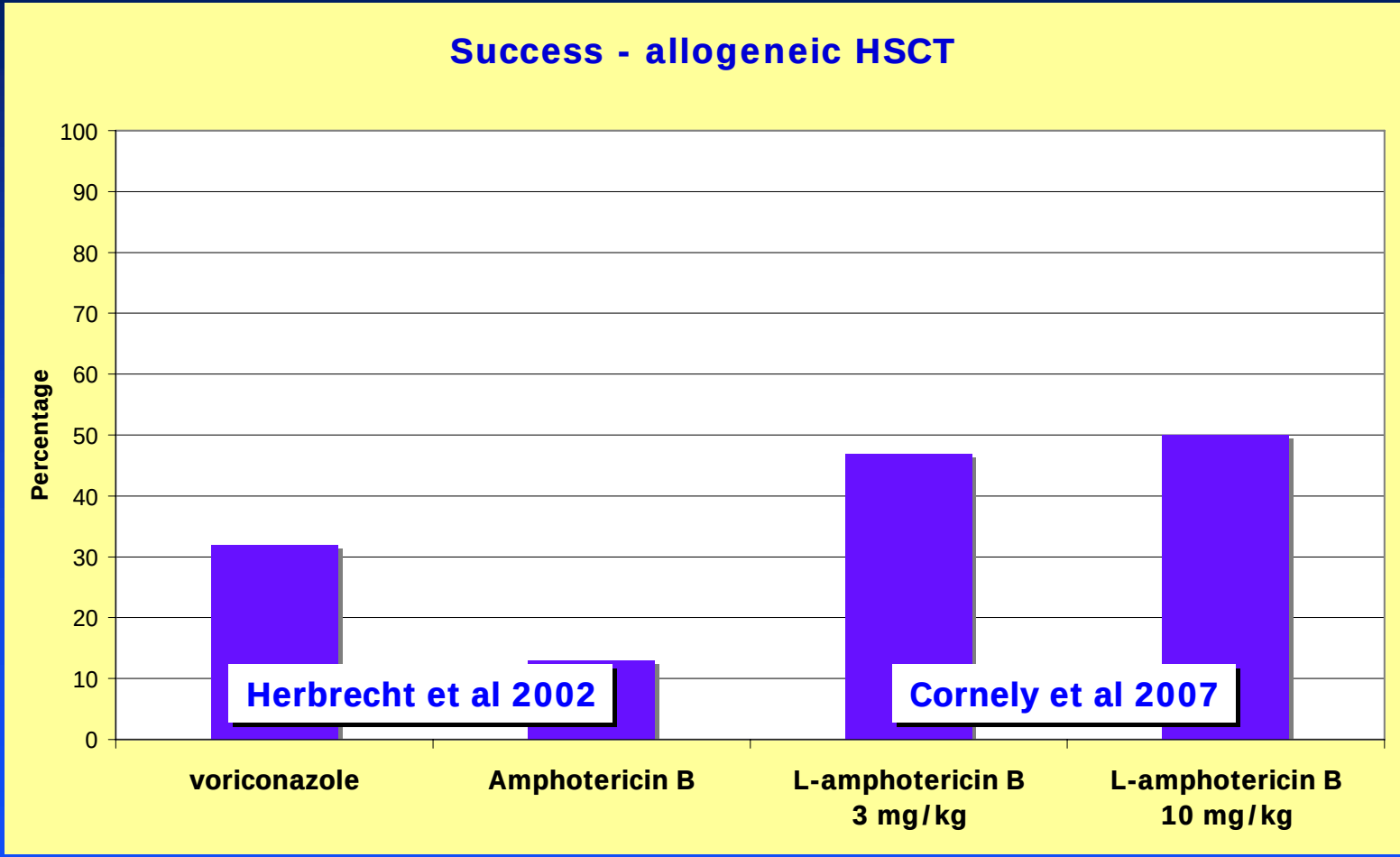
A tale of two studies



Denning 2007 Clin Infect Dis 45:1106

Is liposomal amphotericin B a better choice for neutropenic HSCT recipients?

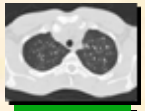
Dilemma 2

Salvage therapy

Bridging the gap .....

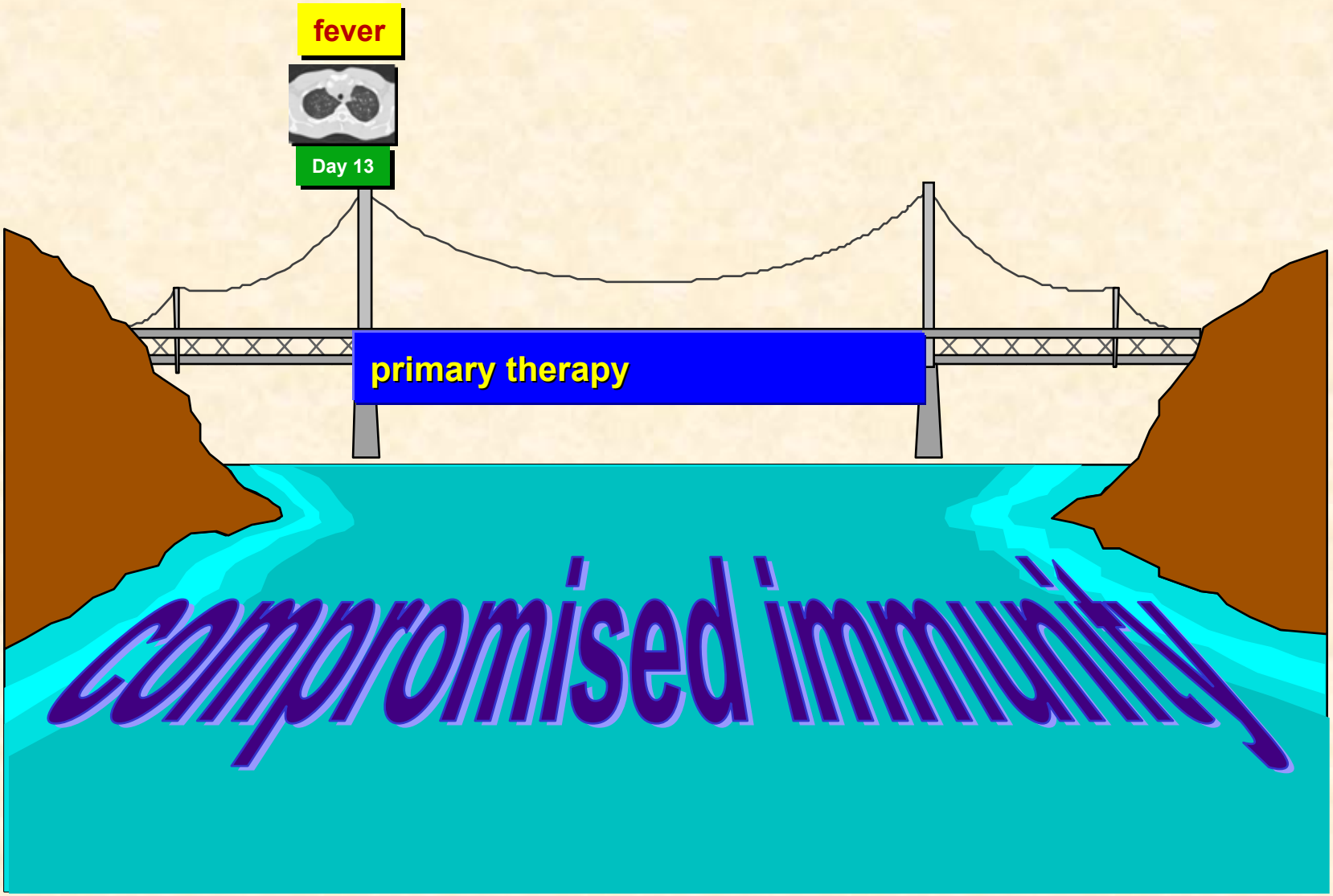
Bridging the gap .....

fever

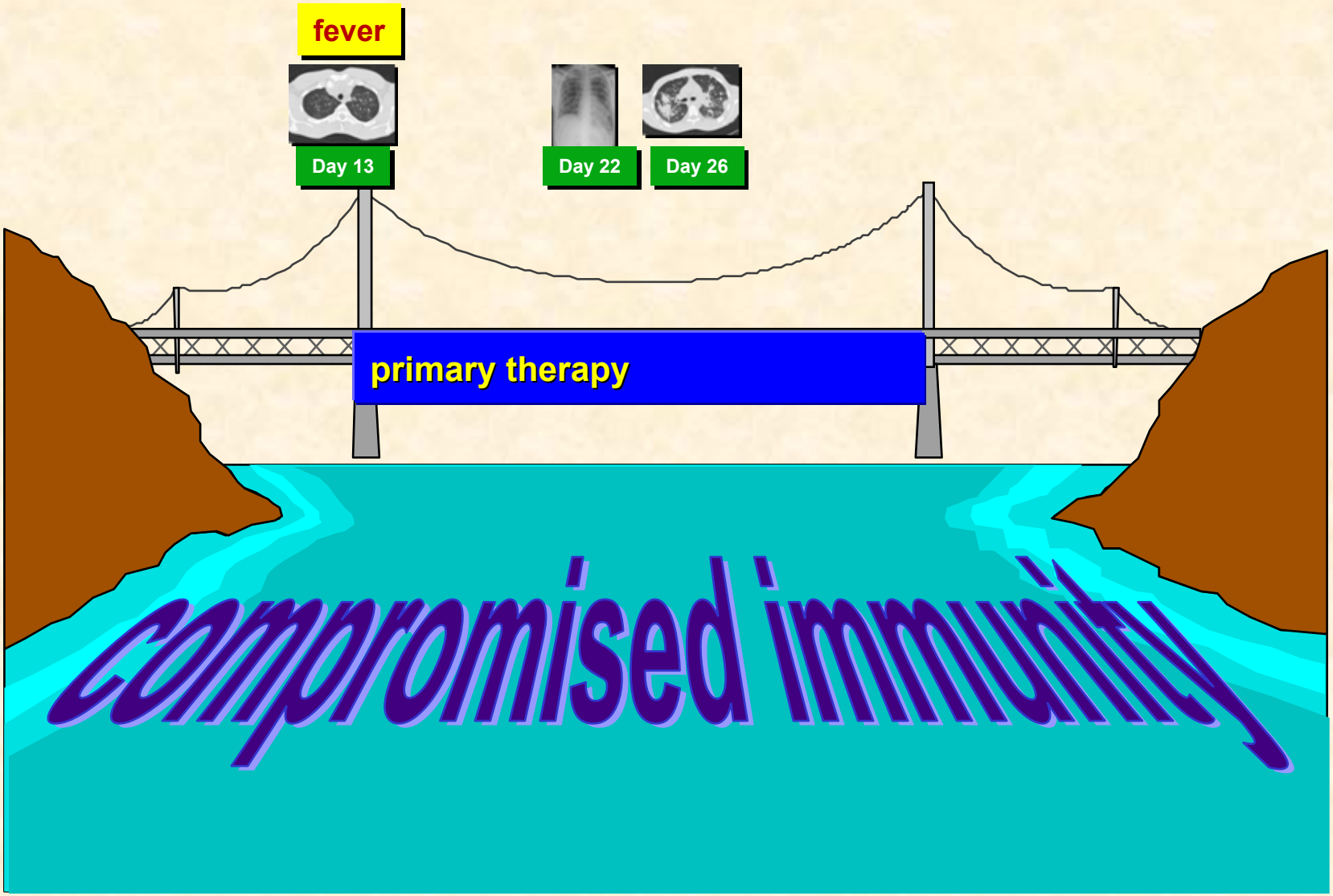


Day 13

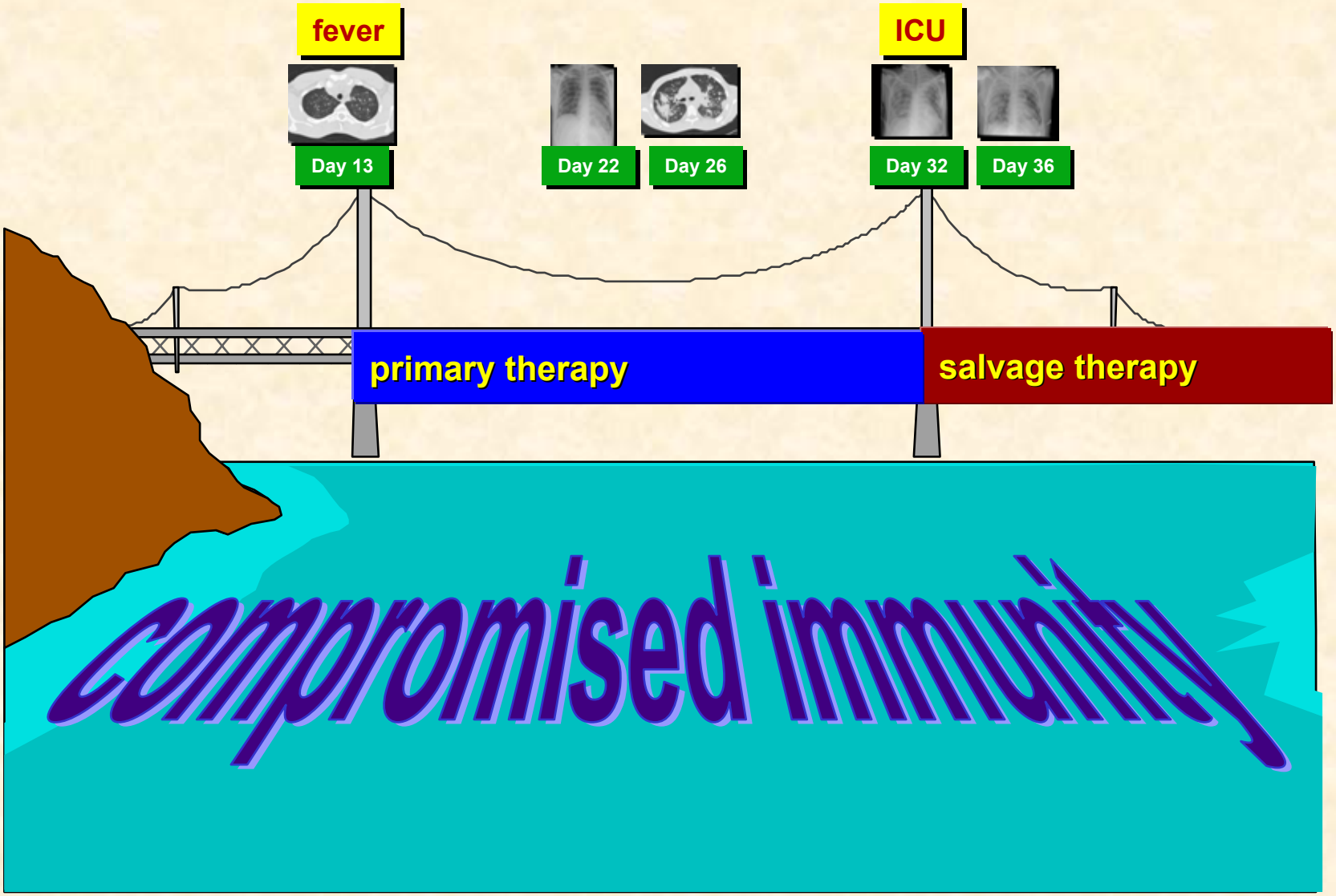
Bridging the gap .....



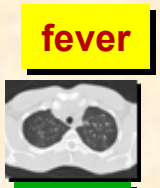
Bridging the gap .....



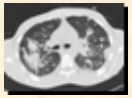
Bridging the gap .....



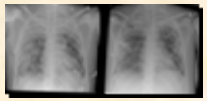
Bridging the gap .....


fever
Day 13

Day 22


Day 26

ICU
Day 32


Day 36 Day 39

†
Day 45

Conclusions

Diagnosis	improving but a still a way to go
Definitions	revisions should help
Drugs	make the most of what we have
Dilemmas	we will face more of them