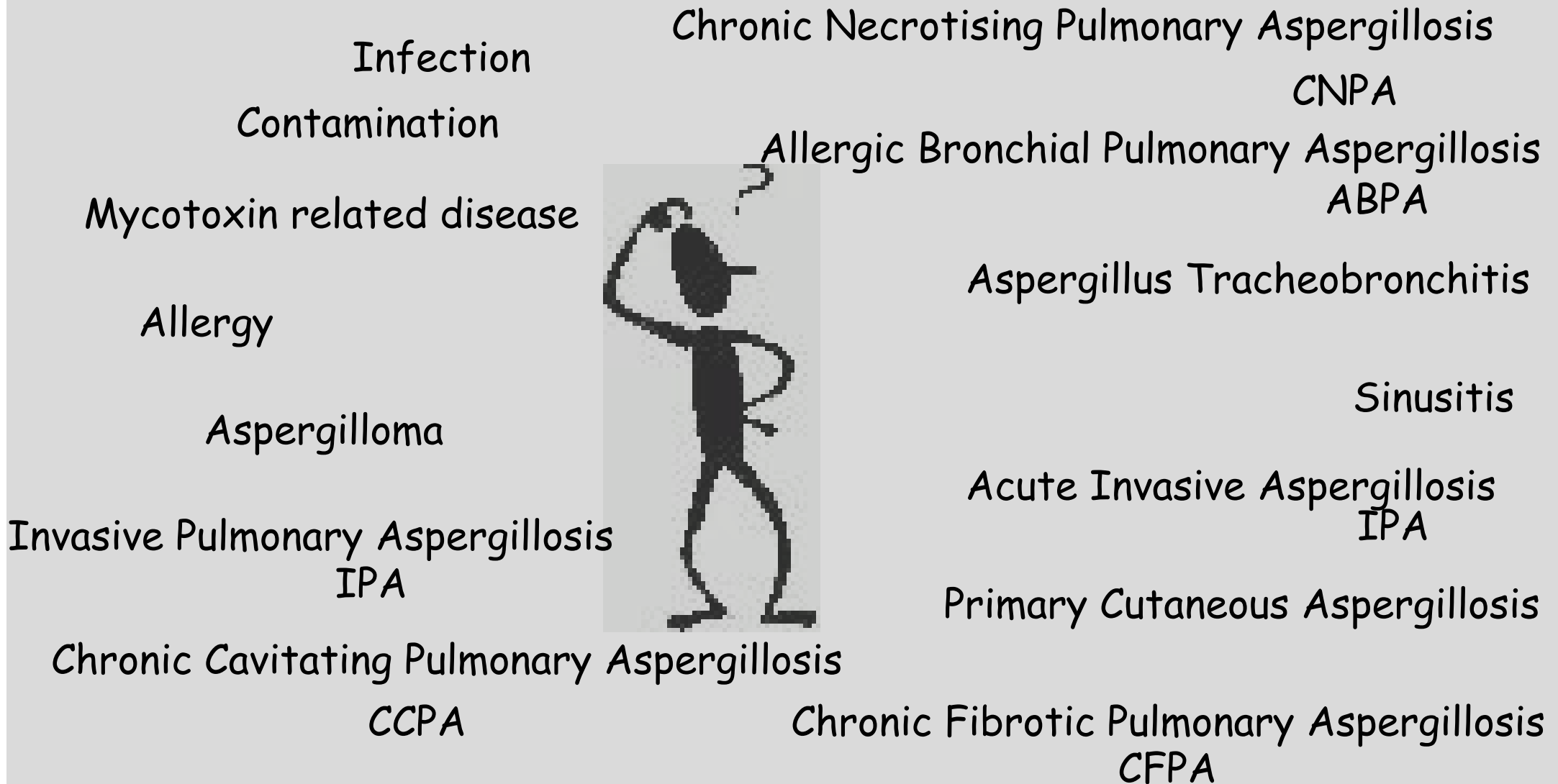


Aspergillosis: New risk groups



Maiken Cavling Arendrup
Unit of Mycology and Parasitology
Staten Serum Institut
Denmark
mad@ssi.dk

Aspergillus the Multi-artist



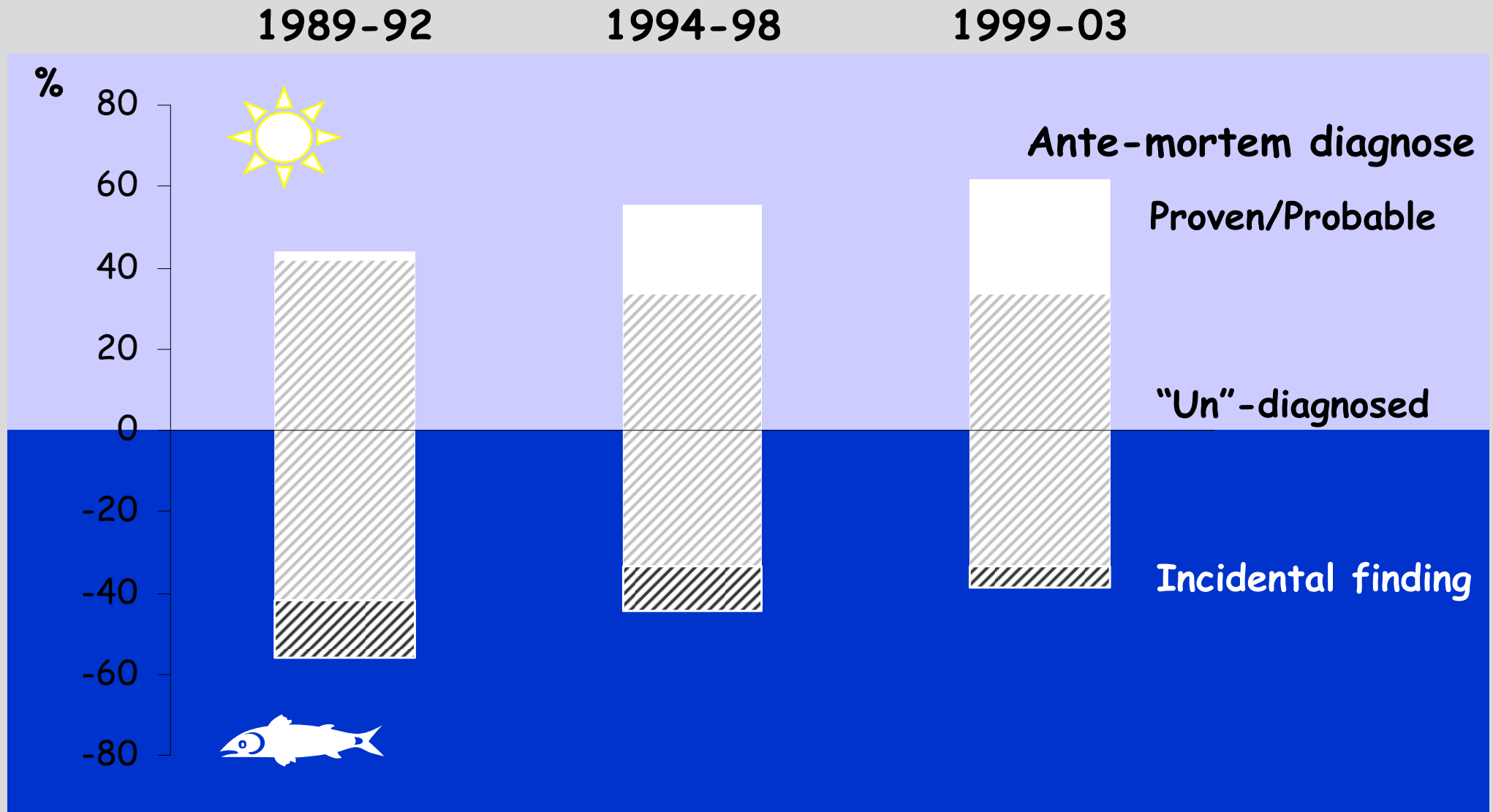
Invasive

Aspergillosis: New risk groups



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Difficult Diagnosis: Tip of the iceberg



Knowledge of risk groups

✓ Prevent infection

- Prophylaxis: identify patients who may benefit

✓ Improve outcome

- Earlier diagnosis
 - Microscopy & culture
 - CT scans
 - Galactomannan/ β -Glucan/PCR
- Earlier treatment
 - Pre-emptive therapy
 - Therapy

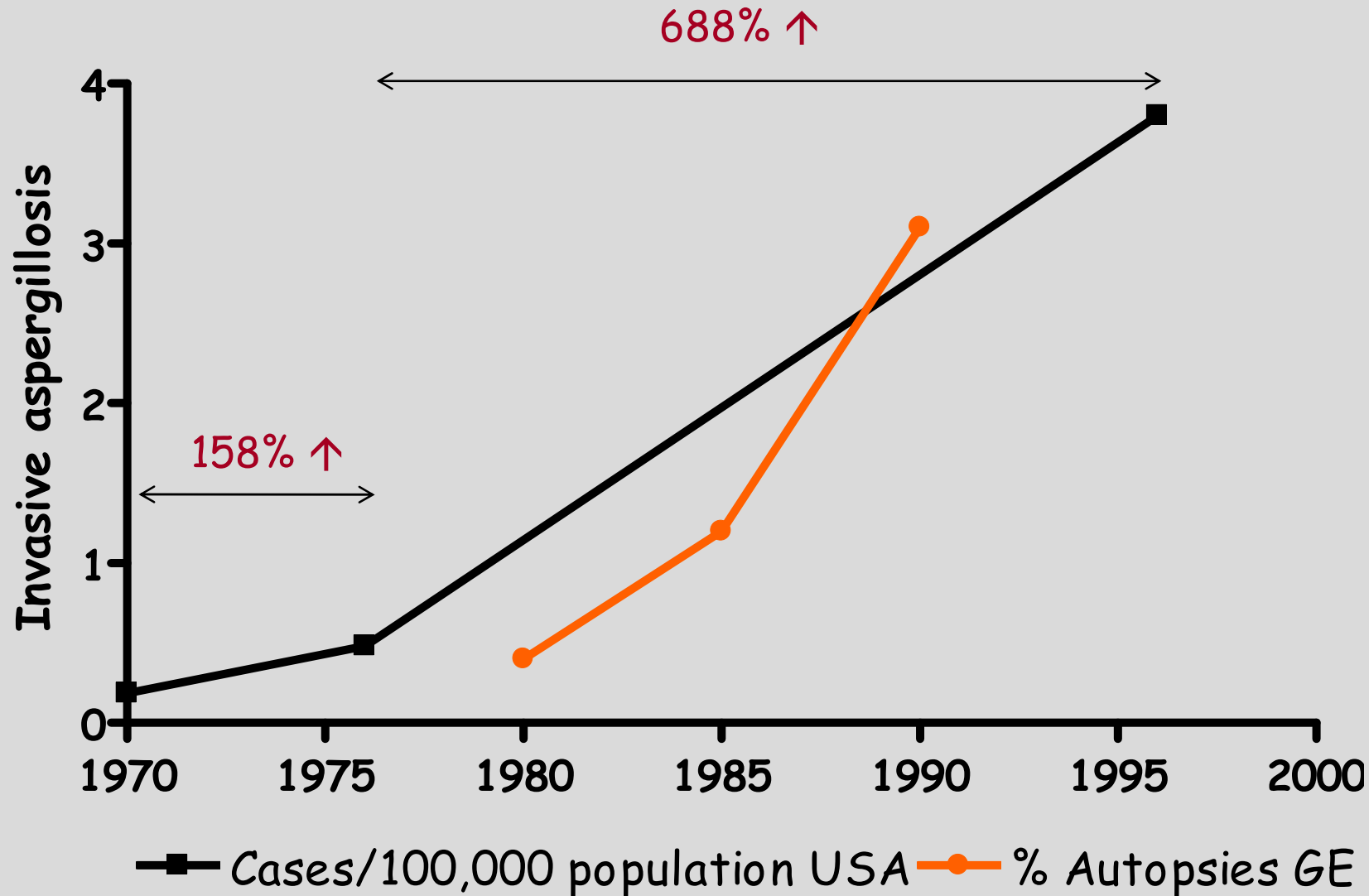


Overall 58%

Agenda

- Long Term Epidemiology
- Recent Hospital and ICU surveys
- New Trends in recognised Risk Groups
 - Haematological population
 - SOT
- Host Genetics as Risk factors
- Heavy Exposure as only Risk factor
- Conclusion

Epidemiology

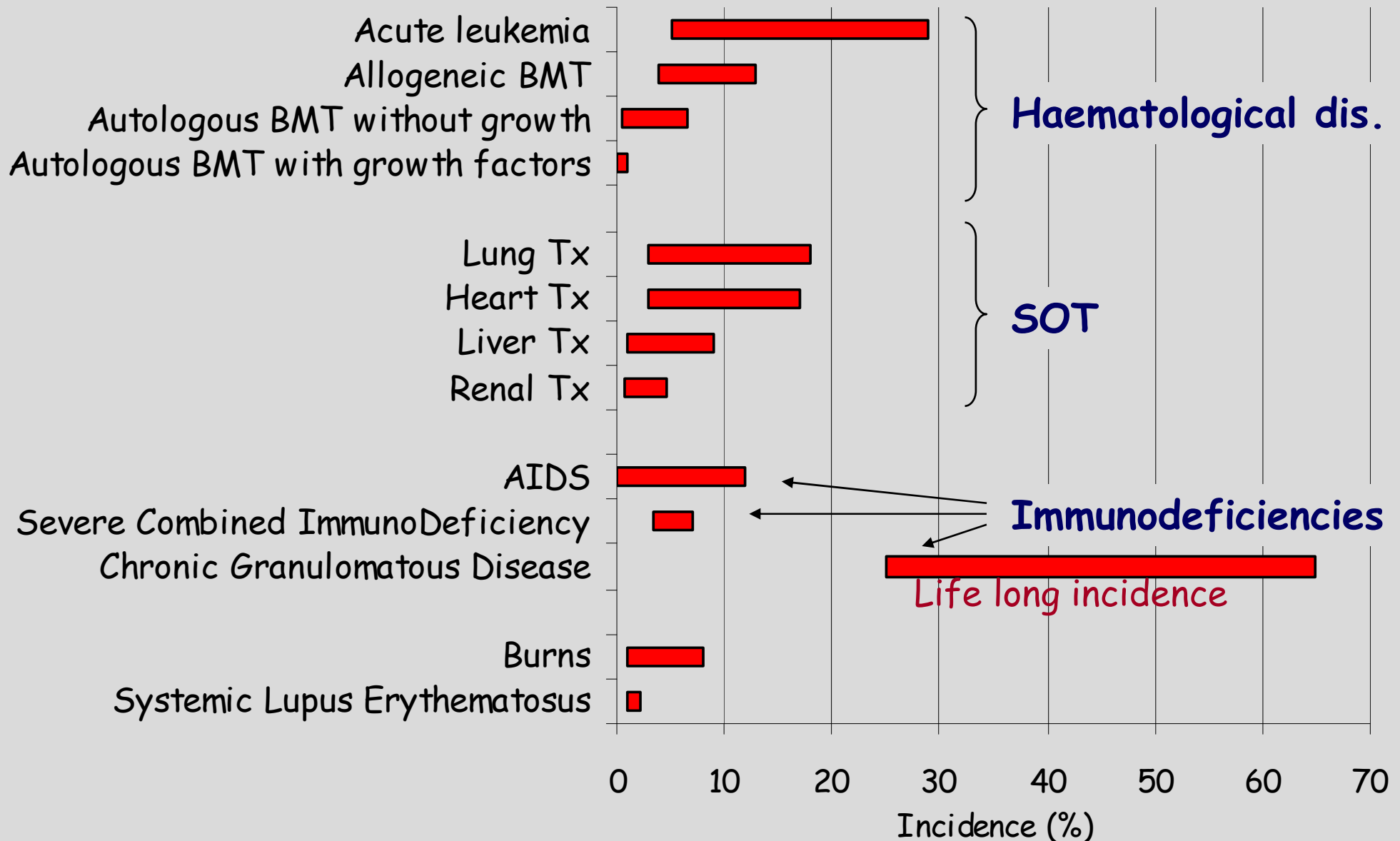


Incidence rates 80'ties

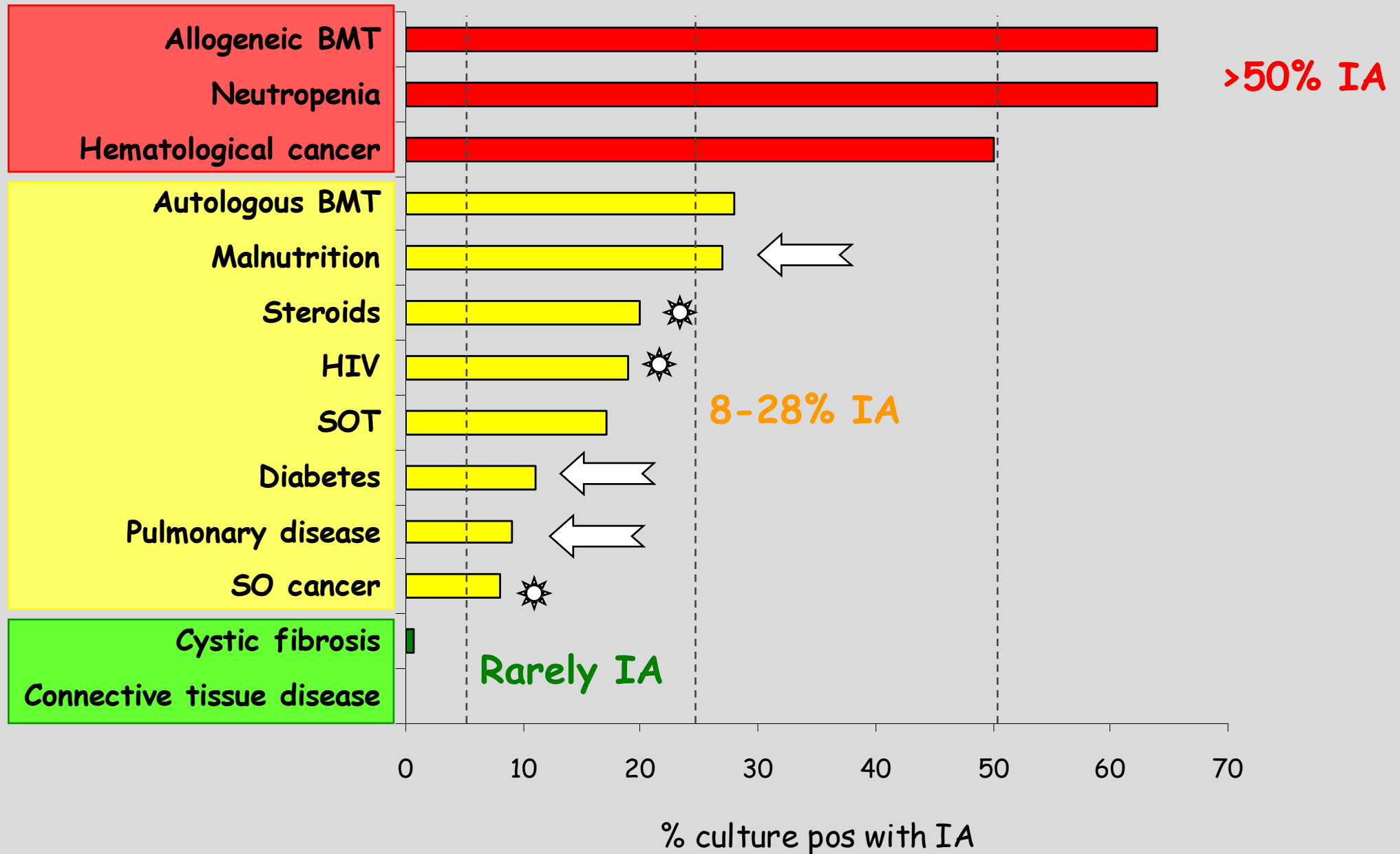
32 IA in 2315 autopsies (1.4%) in UK 1980-89

■ 16	Haematological	11.4%	} ~ 90%
	BMT	25%	
■ 13	SOT	11.6%	
	Liver	16.9%	
	Kidney	2.4%	
■ 3	Other cases		
	Major surgery, pulmonary disease, steroids for RA		

Incidence in the 90'ties



Risk factors: PP positive culture



Trend during 80 and 90'ties

- Haematological malignancies
SOT, AIDS, SCID, CGD

} "Old" risk groups

- HIV

- Steroids

- Solid organ cancer

} Emerging risk groups
during the 90'ties

- Malnutrition

- Pulmonary disease

- Diabetes

} "New" risk groups

Recent Hospital and ICU surveys

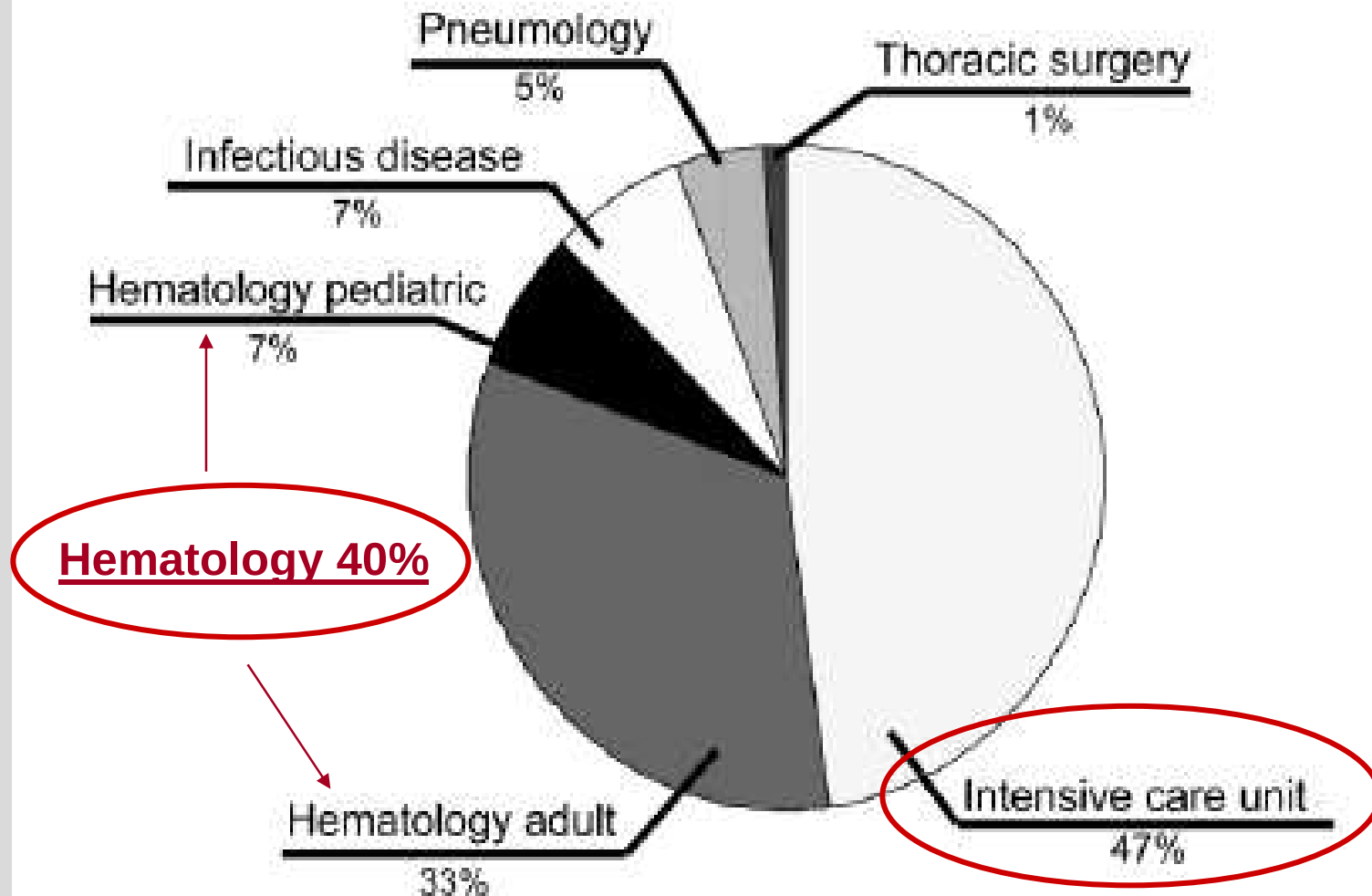
■ Publications recent 3 years →

– Renne, France	88 cases	1998-2004	Hospital
– Grenoble, France	74 cases	2000-2002	Hospital
– Leuven, Belgium	107 cases	2000-2003	MICU
– Gent, Belgium	83 cases	1997-2003	ICU
– 5 centres, Spain	20 cases	1998-1999	ICU

■ 372 cases (~300 from 2000-2004)

Invasive Aspergillosis (France)

Department at the time of diagnosis



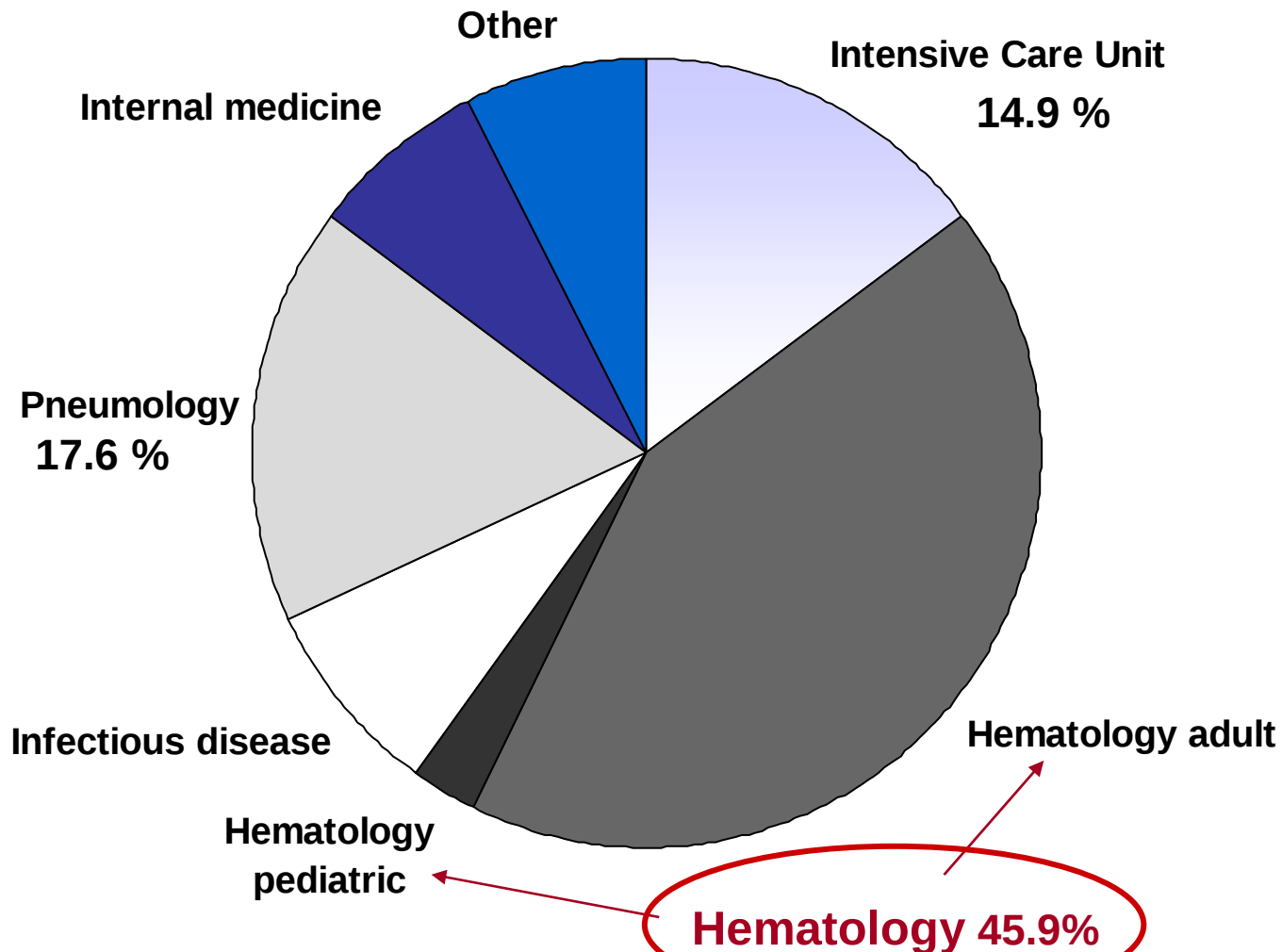
88 Cases

1998-2004

Rennes
Teaching
Hospital

Invasive Aspergillosis (France)

Department at the time of diagnosis



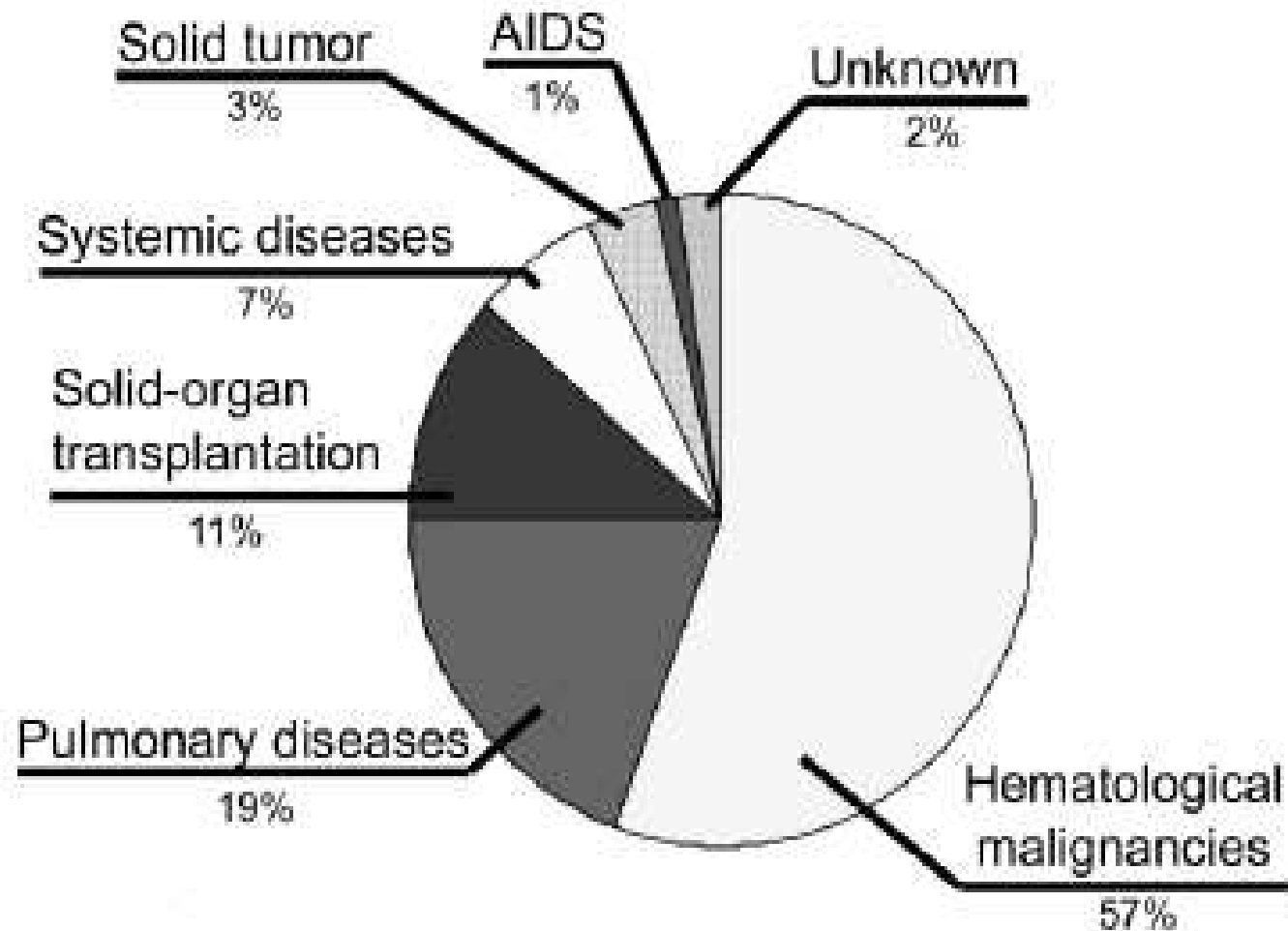
74 Cases

2000-2002

Grenoble
University
Hospital

Invasive Aspergillosis (France)

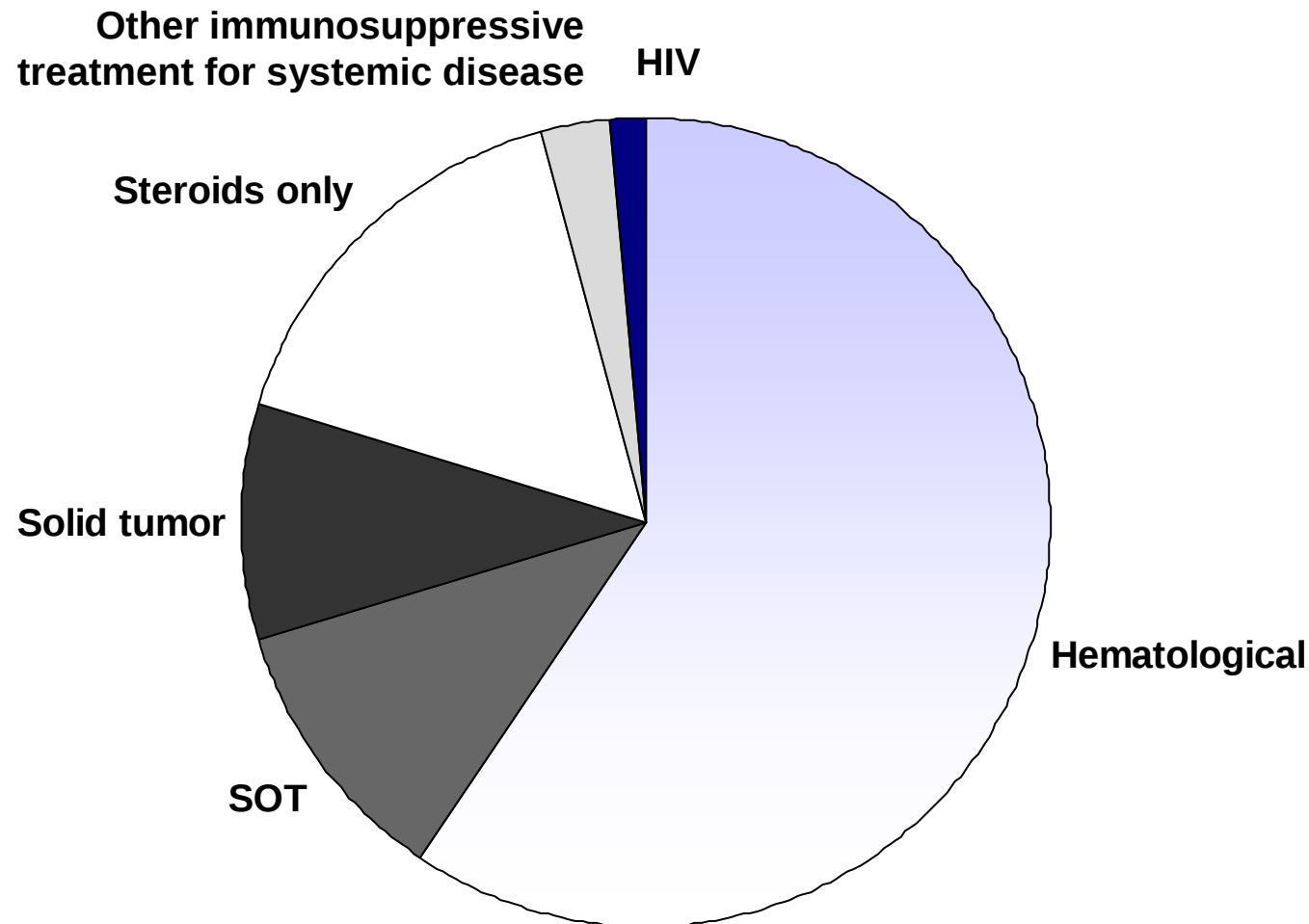
Underlying Disease



88 Cases
1998-2004
Rennes
Teaching
Hospital

Invasive Aspergillosis (France)

Underlying disease



74 Cases

2000-2002

Grenoble
University
Hospital

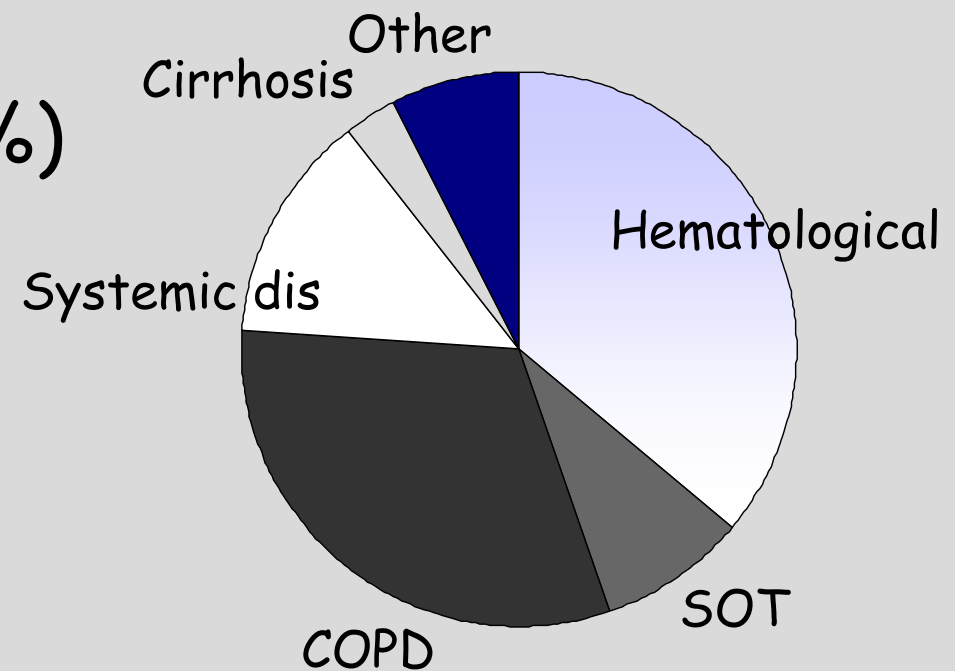
Medical ICU (Belgium)

■ 3-year retrospective study

- 1850 admissions (💀 28%)

■ 105 Proven/probable (5.7%)

- 37 hæmatological dis
- 1 seminoma
- 67 no malignant dis (64%)



Aspergillosis attributable mortality

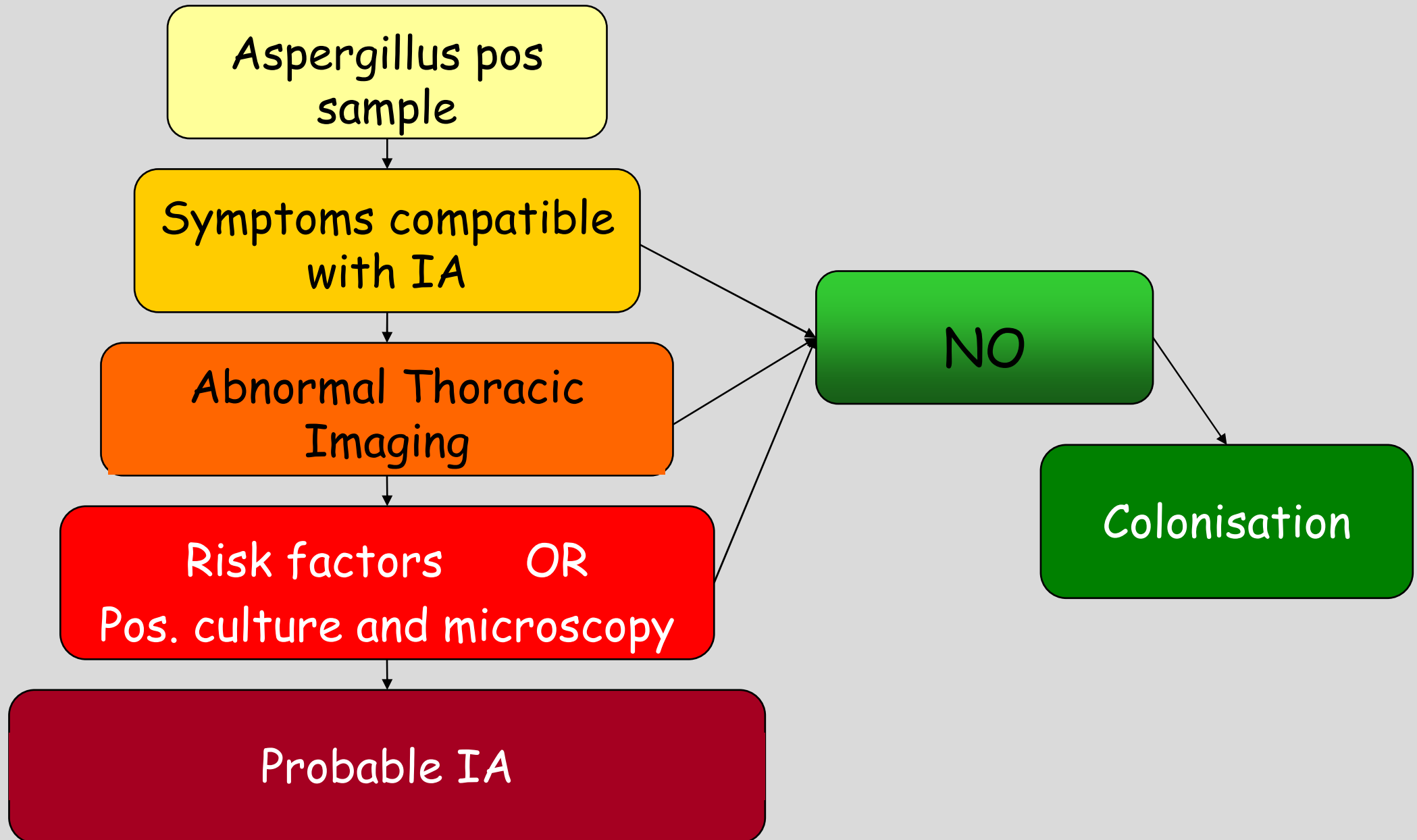


■ No malignant underlying disease (89)

– 30 Proven, 37 Probable, 2 Possible, 20 Colonisation

	Proven/probable IA					Coloni- sation
	COPD (33)	Syst. dis (14)	Cirrhosis (3)	SOT (9)	Others (8)	All (20)
SAPS	49	50	64	47	66	54
Predict. ☠	43%	44%	71%	40%	73%	51%
Observ. ☠	85%	93%	100%	100%	100%	50%

Interpretation of pos. culture in ICU



Recent Epidemiological studies



	Grenoble 74 cases	Rennes 88 cases	Gent 83 cases	Spain 20 cases	Leuven 107 cases
ICU	15%	47%	100%	100%	100%
Mortality	46%	72%	77%	80%	93%
Proven	8%	14%	20%	NI	52%
Probable	49%	59%	80%	NI	46%
Possible	43%	27%	0%	NI	2%
Haematol	60%	57%	40%	NI	36%
SOT	11%	11%	10%	NI	8%
Pulm/sys- temic	30%	26%	44%	58%	46%

Characteristics: non-neutropenic Pts

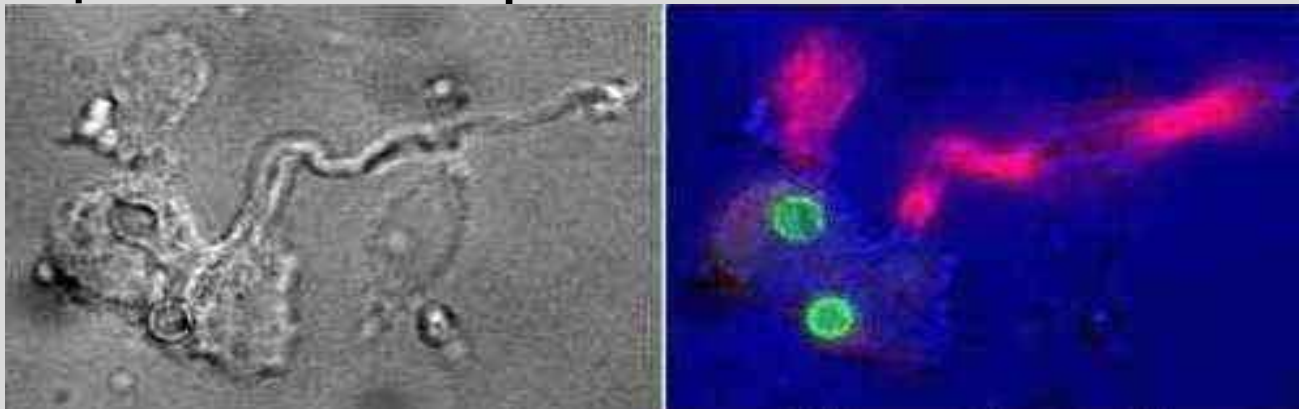
Variable	Neutropenic	Non-neutropenic
Recovery	16 (31%)	3 (8%)
Fever	50 (96%)	25 (69%)
Cough	35 (67%)	10 (28%)
Chest pain	17 (33%)	4 (11%)
Halo/air crescent	82%	5%
+ Bacterial infect.	8 (15%)	20 (56%)

Outcome IA in COPD

Author	Publ. year	No. Pts	No. deaths
Cornillet	2006	17	15
Ader	2005	13	13
Meersseman	2004	33	28
Kisteman	2002	2	2
Rello	1998	24	24
Pittet	1996	2	2
Total		91	84 (92%)

COPD and *Aspergillus*

- Impaired architecture of the lung tissue
- Steroids act *Aspergillus* enhancing in two ways
 1. ↓ Mφs and neutrophil function



<http://www.pasteur.fr/recherche/unites/aspergillus/research2.htm>

2. ↑ Growth rate *Aspergillus fumigatus* and *flavus*
 - 44% growth increase 10^{-6} M Hydrocortisone

Ng. Microbiol. 1994

M. Cavling Arendrup

"New risk groups"

Recent Hospital and ICU surveys

	Risk of IA
■ ICU stay and <i>Aspergillus</i> +	47%-83%
Risk group profile	% of asp cases
■ ↑ COPD	31%-44%
■ ↑ Steroids as only RF	16%
■ ↓ HIV/AIDS	<2%

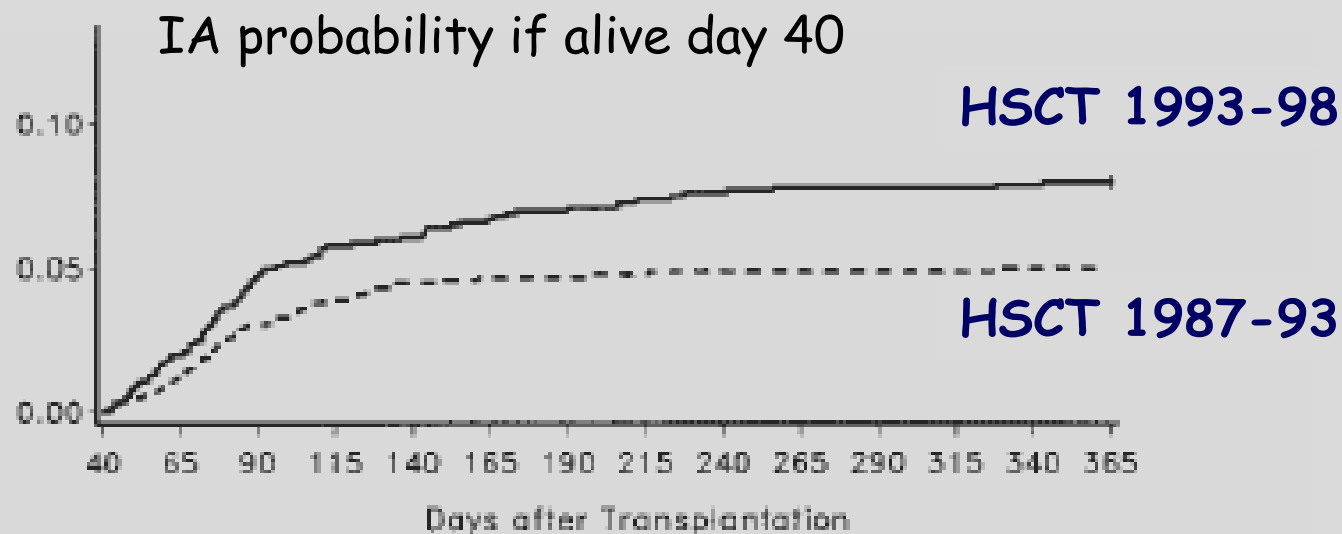
Hematologic subpopulations

	Incidence		
	Cornet 18 hosp FR	Marr Seattle USA	Pagano 18 wards IT
AML	8.0%		7.0%
ALL	6.3%		3.8%
Allo-HSCT	12.8%	11.1%	
- Mismatched unrelated		10.5%	
- Matched related		7.3%	
Auto-HSCT	1.1%		
- Bone marrow stem cell	6.0%		
- Peripheral stem cell	1.6%		

Timing of onset has changed!

DESIGN. 1682 Myeloablative HSCT. 187 Proven/probable IA

	Early ≤ 40 d	Late 41-180 d	Very late >180 d
1987-93	39%	56%	4%
1993-98	30%	53%	17%



Risk factors IA in Myeloablative HSCT

Early ≤40 d	Late 41-180 d	Very Late >180 d
CMV disease	CMV disease Respiratory virus ✗	CMV disease
Old age	Old age	
	GvHD 2-4	GvHD
Cord blood ✗	T-cell depleted CD34 selected	MisMatched/ Unrelated PBSC ✗
Aplastic anemia Myelodysplastic Syndrome	Multiple Myeloma Prednisone ≥2 mg/kg/d	
	Neu-/lymphopenia ✗	Neutropenia

SOT: Change in time of onset

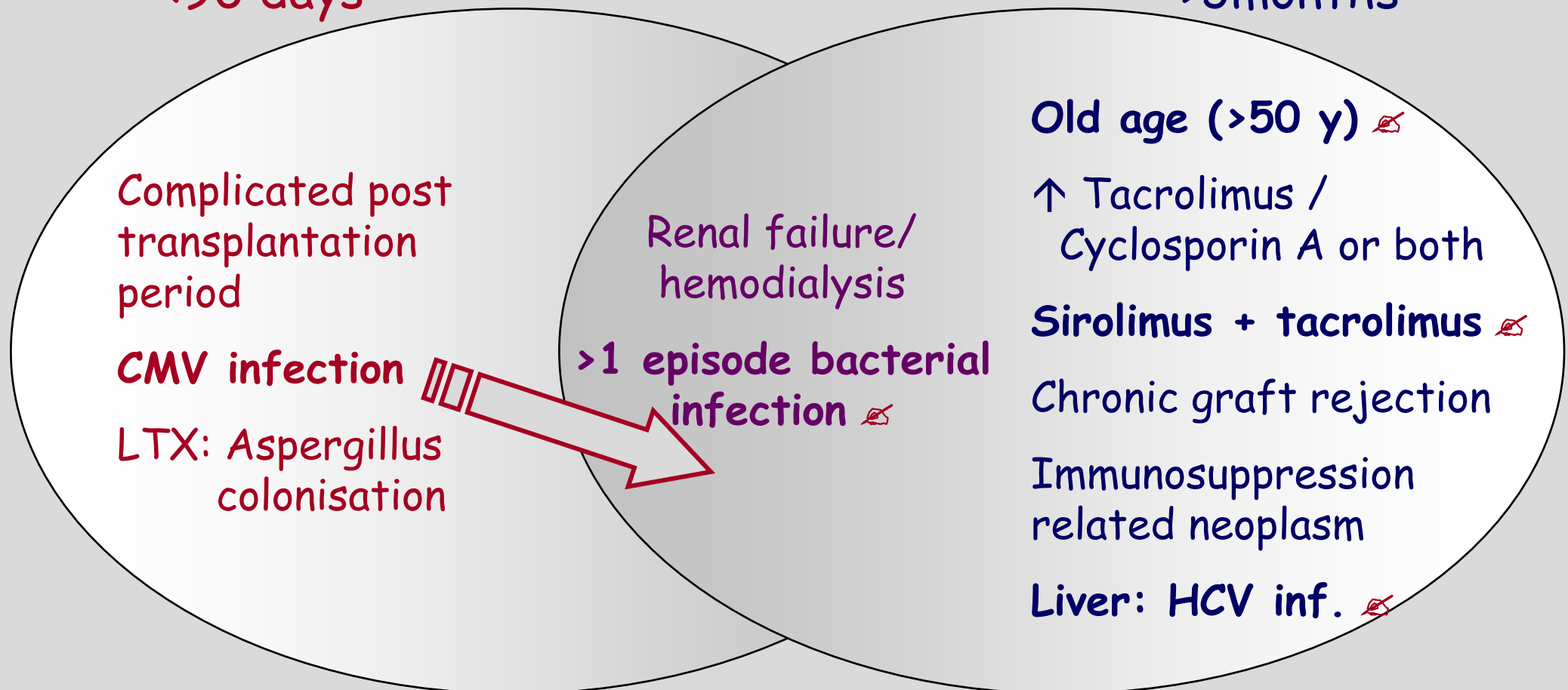
	Inci- dence	0-30 days	31-90 days	3-6 months	6-12 months	>1 year
1990- 1995	1.06	58%	19%	4%	8%	12%
1990- 2001	2.0	34%	21%	19%	14%	13%
1998- 2001	1.18	25%	25%	10%	15%	25%
1994- 2000	5.6	← 38% →		← 62% →		
2003- 2005?	NI	20%	30%	8%	15%	28%

Risk Factors SOT

Early Invasive Aspergillosis
<90 days

×

Late Invasive Aspergillosis
>3months

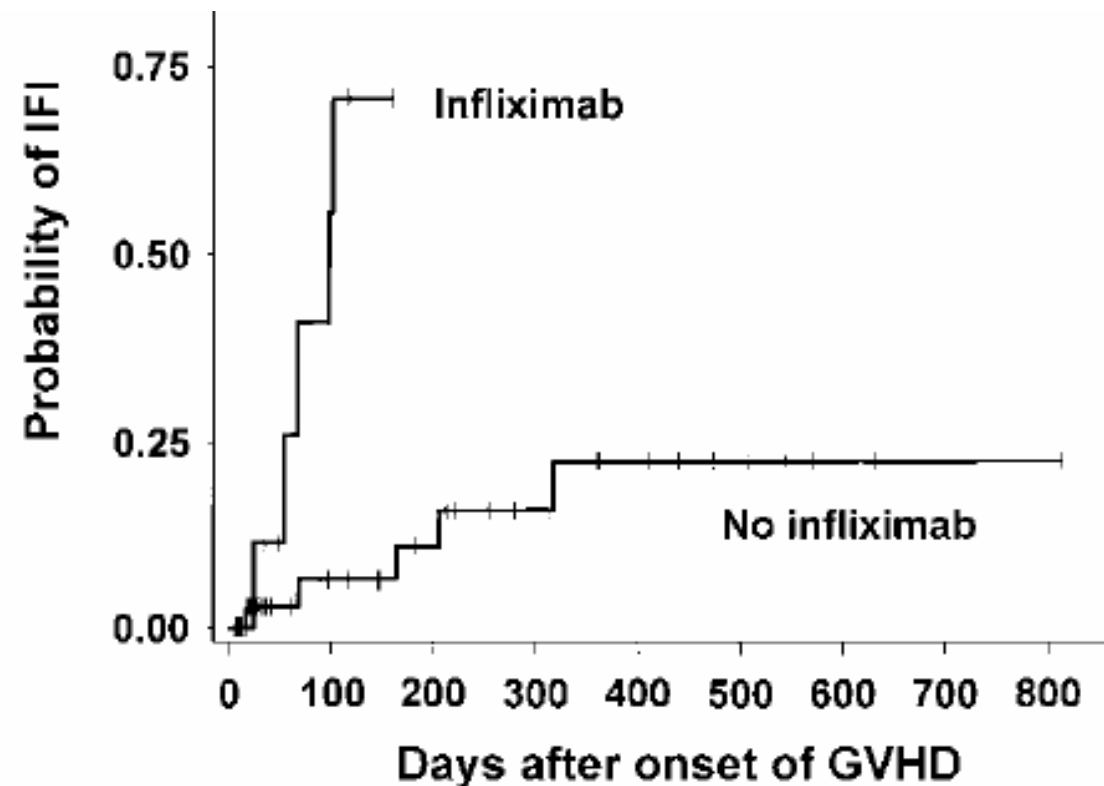


High risk medication: Infliximab

HR Adjusted

13.6 Infliximab ~~✗~~
(anti TNF- α)

264 allo-HCT, 16 IA, 53 GvHD, 11 infliximab



8.05 Non-myeloablative allogeneic HSCT (15% IMI)

3.46 Severe GvHD

New Risk Groups transplantation

- Infliximab use in GvHD (RR>13)
- ↑Late onset ~ surviving patients are at risk!!
- CMV also for late and very late onset

HSCT

- Cord blood
- Non-Myeloablative
- Respiratory virus
- Lymphopenia

SOT

- HCV virus
- Aspergillus colonisation
- >1 bacterial infections
- Old age

Genetics: IL

MBL SNP's
CNPA
(52/54)

SNP's

■ IPA incidence in allogeneic stem cell patients

- Single Nucleotide IL-10 & TGF- β 1 SNP's -819/-592

Haplotype CPPA at 2 years
(-1082 / 869)

ACC/ACC

TLR1 & 6 SNP's

0

ATA/ACC

IPA

5 $\pm$ 6.4

(TLR1 239/TLR1 743/TLR6 745)

ATA/

7.7

All

IL-10 promoter SNP's
IPA

1 $\pm$ 4.5%

IPA incidence

(-1082/-819/-592)

Heavy Exposure as sole risk factor

- 33-year old man
- Truck load bark chippings (BC) in December
- Fever a few days after working with the BC

- A week later he distributed the rest of the BC
 - Wet, slightly steaming and with mouldy spots

- Airway irritation → Fever, cough
 - Penicillin 7 days, followed by azithromycin

- Admitted to hospital Jan 6

Heavy Exposure as sole risk factor

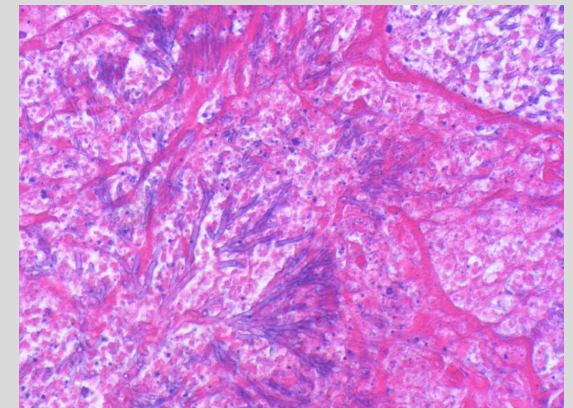
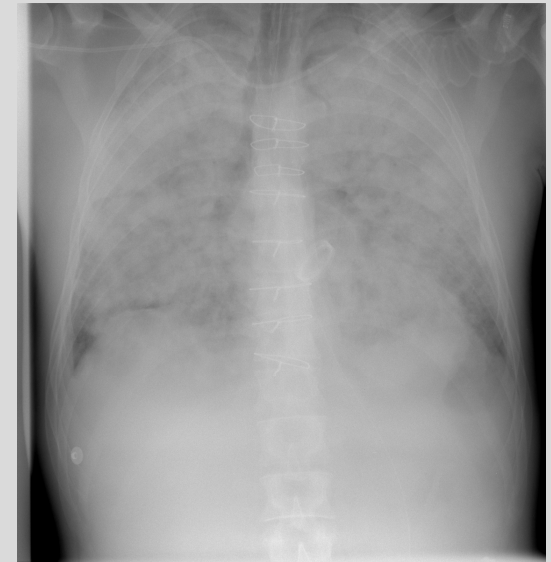
- Dry cough, fever 39°C, dyspnoea
- CRP: 780nM
- BAL: lymphocytes
- Culture/PCR/Ag neg
- Pos Asp Ab titre 18



- Tentative diagnosis
 - Atypical pneumonia and allergic alveolitis
- Treatment:
 - Clarithromycin and prednisolone 50-75 mg/day

Heavy Exposure as sole risk factor

- Re-admitted February 19
 - Fever 40°, tachypnoea, cough
 - CRP 3300 leukocyte count 10×10^9
 - BAL& biopsy: *A. fumigatus*
 - Ambisome 150mg/day
-
- Died February 28th
 - Autopsy: Disseminated Aspergillosis
-
- Serum Jan 5th: Asp Galactomannan 5.1



In conclusion

1. Recent Hospital and ICU surveys

- ↑ ICU patients
- ↑ Steroids & COPD
- ↑ Malnutrition, Diabetes and systemic/respiratory diseases

2. New trends in recognised Risk Groups

- Haematologic: later onset, high risk treatments
- SOT: later onset, age, bacterial infections, viral infections, high risk treatments, colonisation

3. Host dependent Risk factors

- Genetic influence Asp susceptibility

4. Heavy exposure as only risk factor

Thanks to

- David Denning, Manchester, UK
For being a highly qualified
"sparring partner" during the final
preparation
- ICAAC organising committee
for the invitation
- To You
for your attention

