Invasive Aspergillosis in Acute Leukaemias

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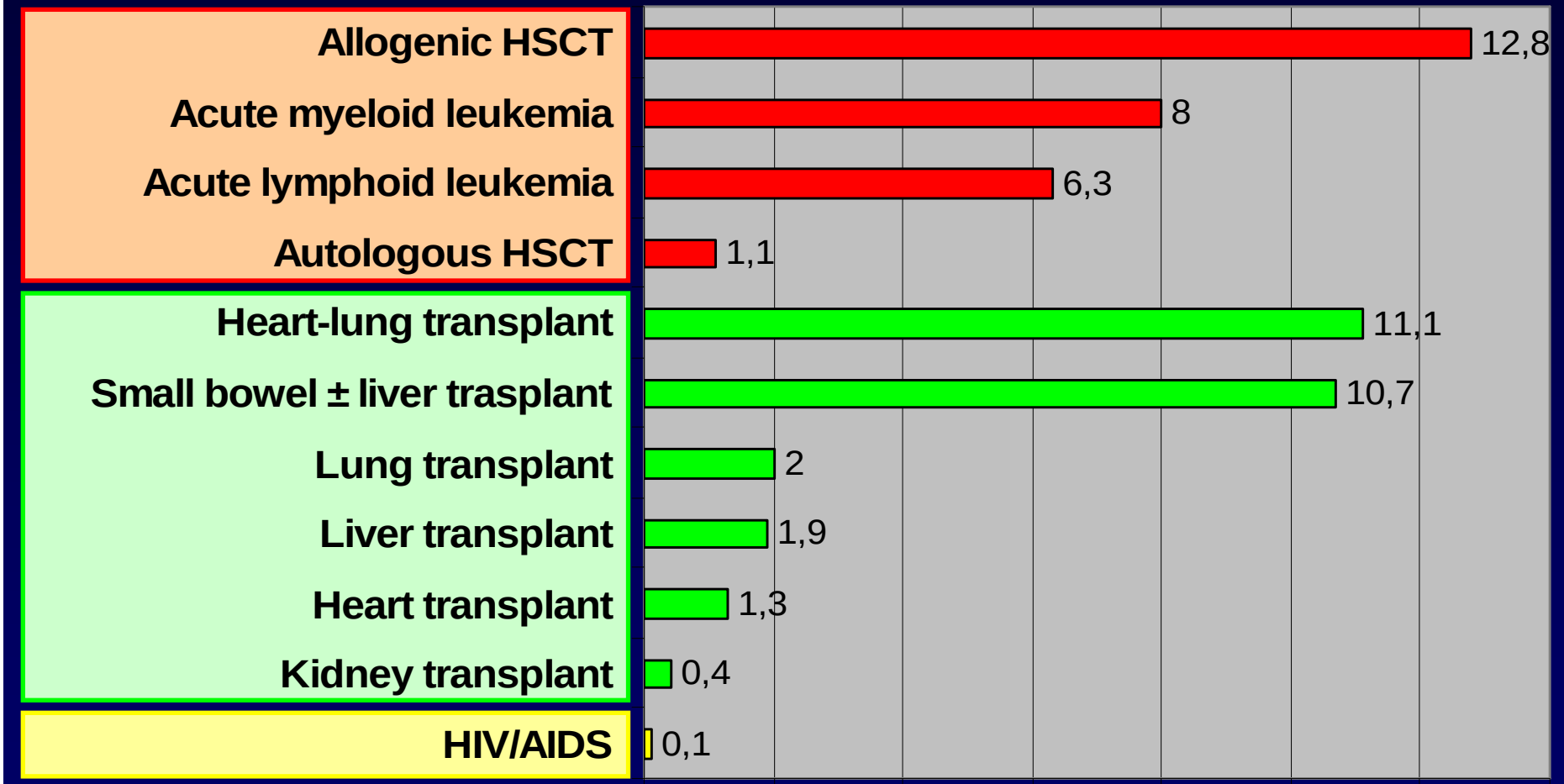
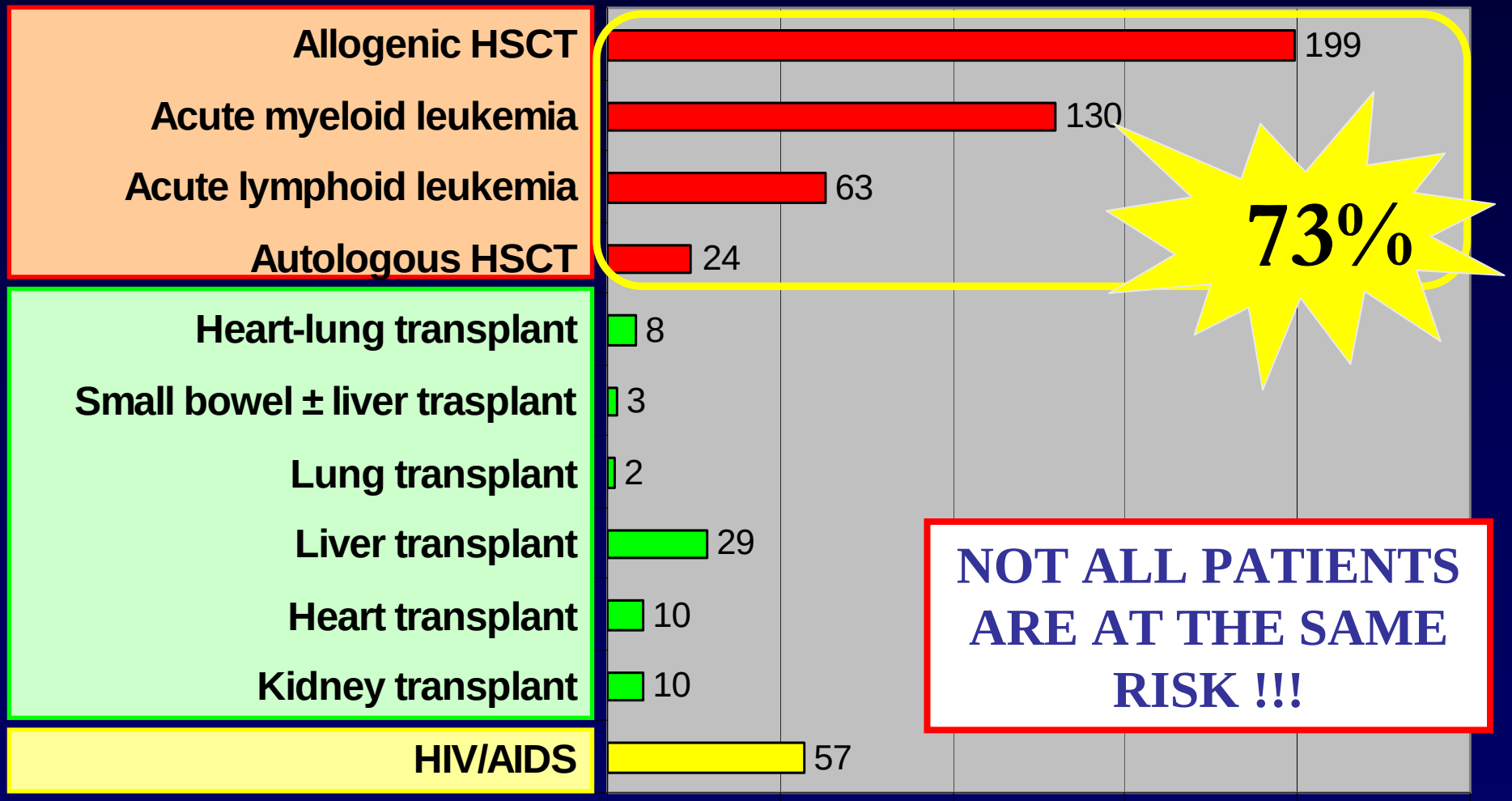
ROME, February 4th, 2010

INVASIVE ASPERGILLOSIS IN VARIOUS CATEGORIES



Cornet et al, J Hosp Infect 2002

INVASIVE ASPERGILLOSIS IN VARIOUS CATEGORIES



Cornet et al, J Hosp Infect 2002

SEIFEM-2004 Study

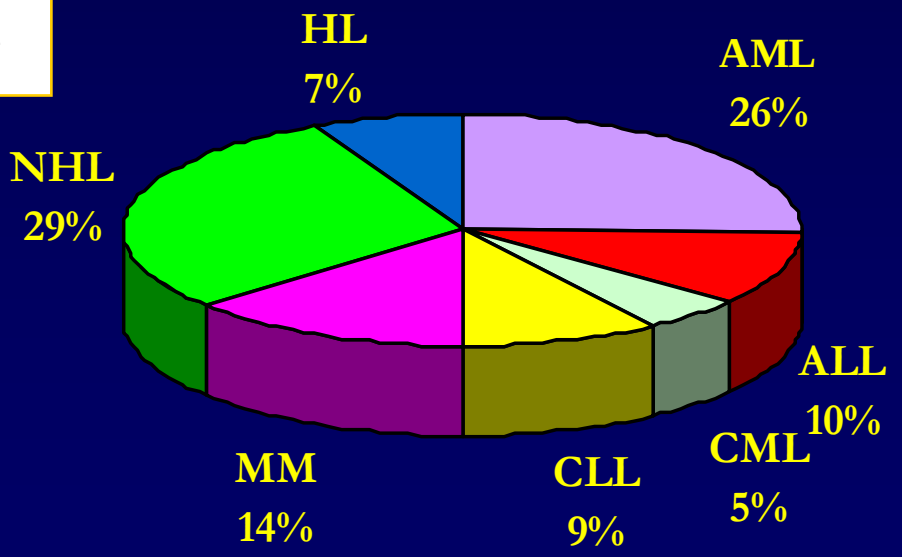
(1999-2003)

SEIFEM 2004

1. S.Martino Hosp.-Genova
2. Reggio Calabria Hosp.
3. Reggio Emilia Hosp.
4. Niguarda Hosp.-Milano
5. Bari Univ.
6. Udine Univ.
7. S.Giovanni Hosp- Rome
8. Firenze Univ.
9. Parma Univ.
10. Ancona Univ.
11. Federico Ii Univ.-Napoli
12. S.Matteo Hosp.-Pavia
13. Cuneo Hosp.
14. Palermo Univ.
15. S.Giovanni Rotondo Hosp.
16. Catholic Univ.- Rome
17. La Sapienza Univ.-Rome
18. Perugia Univ

11,802 patients

538 IFIs



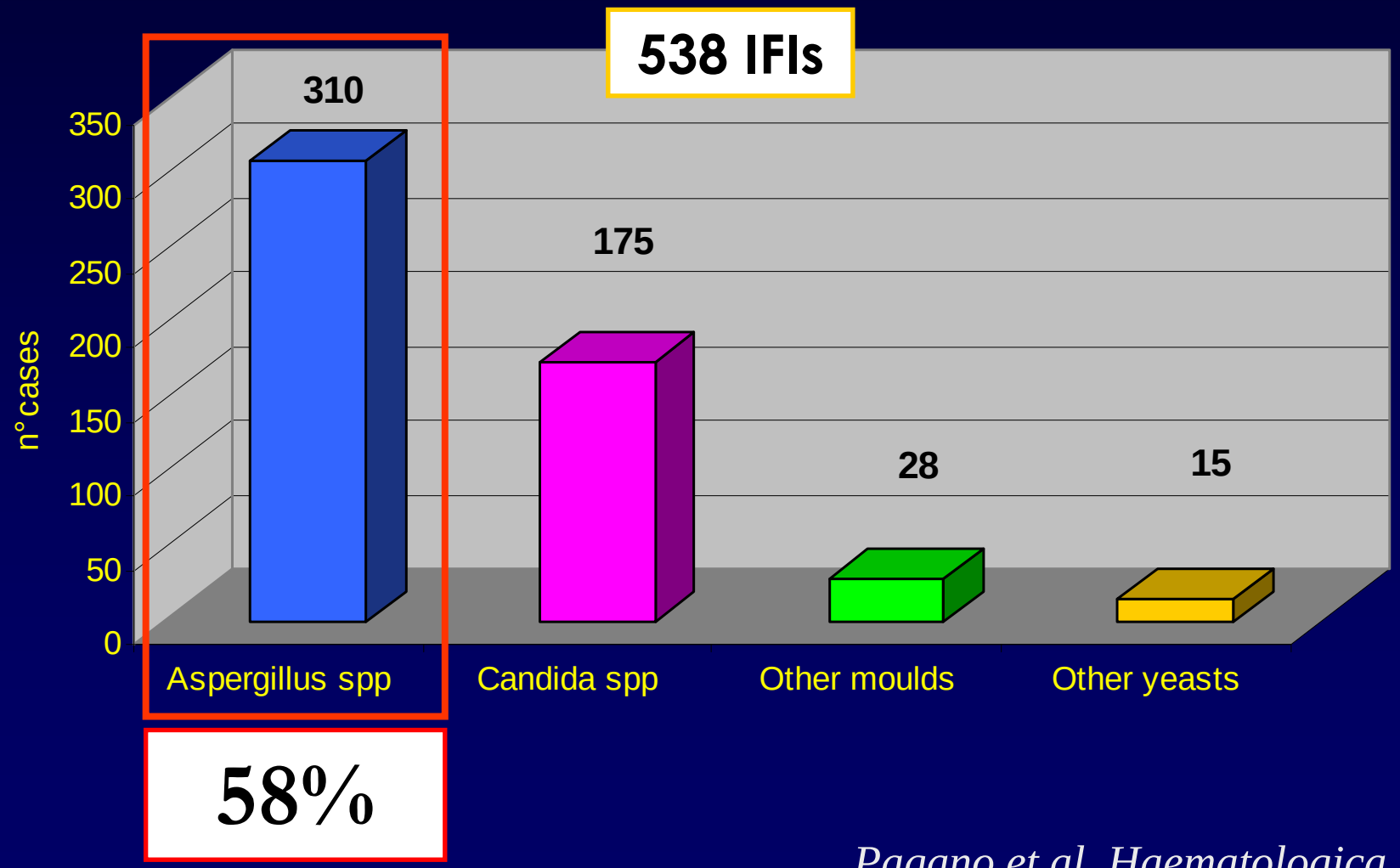
Underlying diseases

18 Haematology Divisions

Pagano et al, Haematologica 2006

SEIFEM 2004

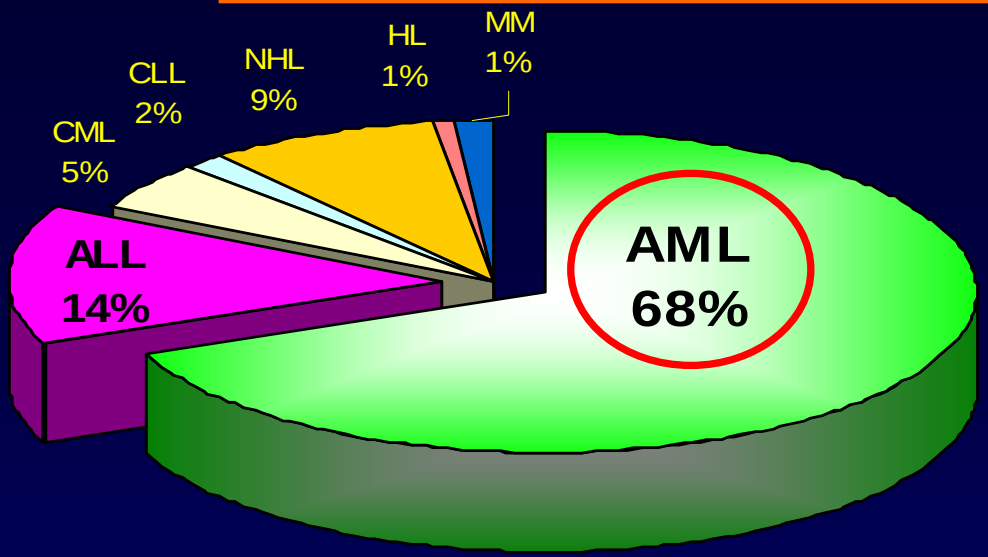
INVASIVE FUNGAL INFECTIONS



Pagano et al, Haematologica 2006

SEIFEM 2004

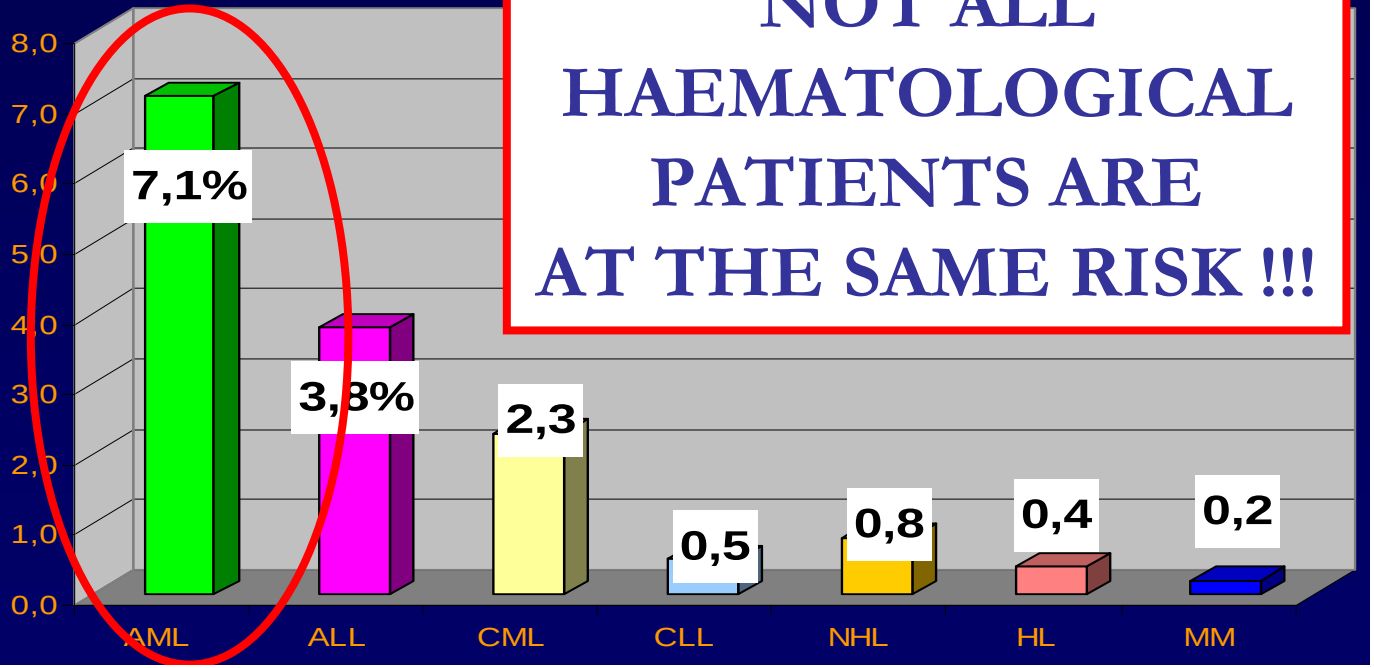
INVASIVE ASPERGILLOSIS



AML:

EPISODES 213/310
INCIDENCE 7,1%

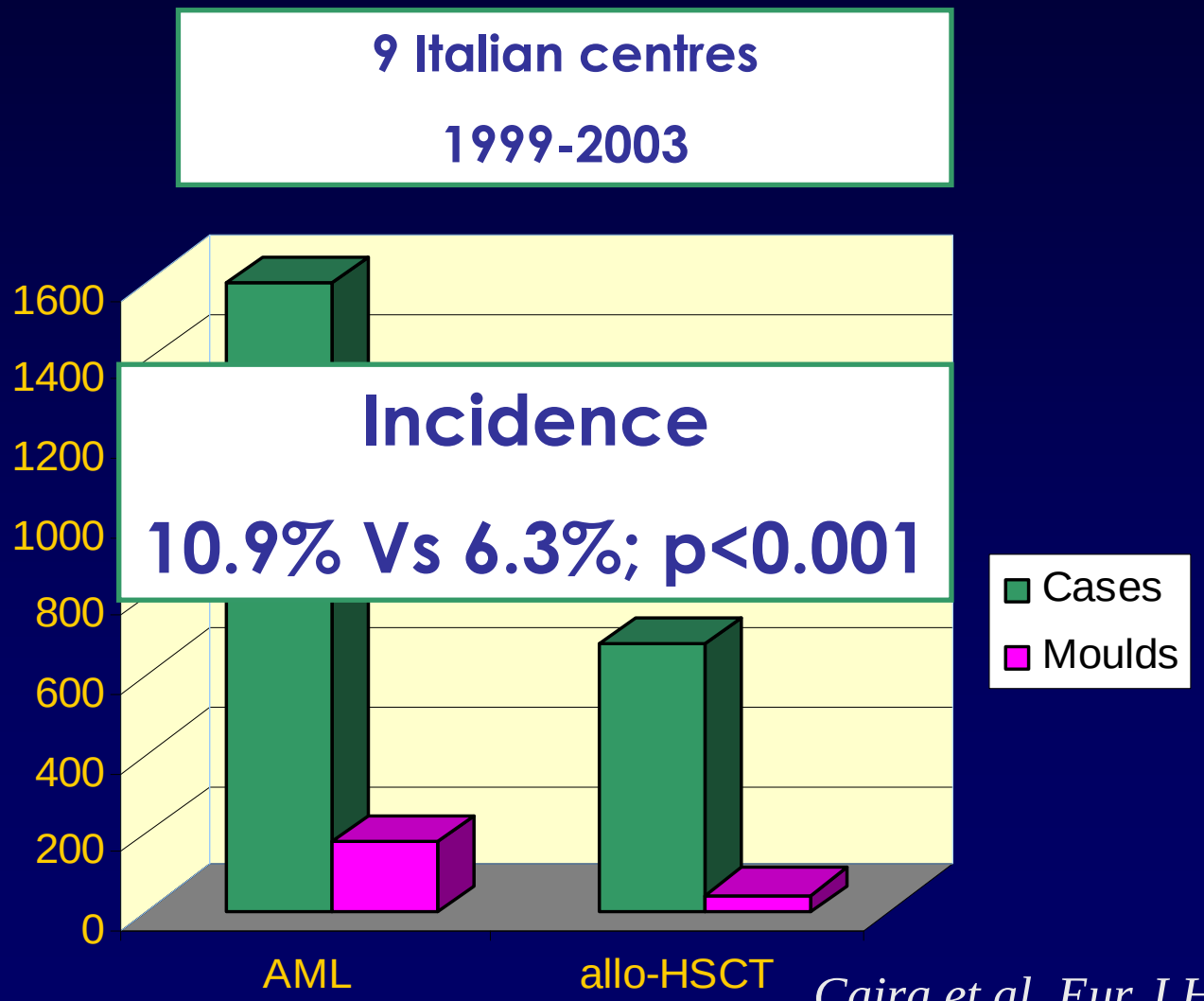
NOT ALL HAEMATOLOGICAL PATIENTS ARE AT THE SAME RISK !!!



Pagano et al, Haematologica 2006

SEIFEM 2004

ASPERGILLOSIS IN AML *versus* ALLOGENIC-HSCT

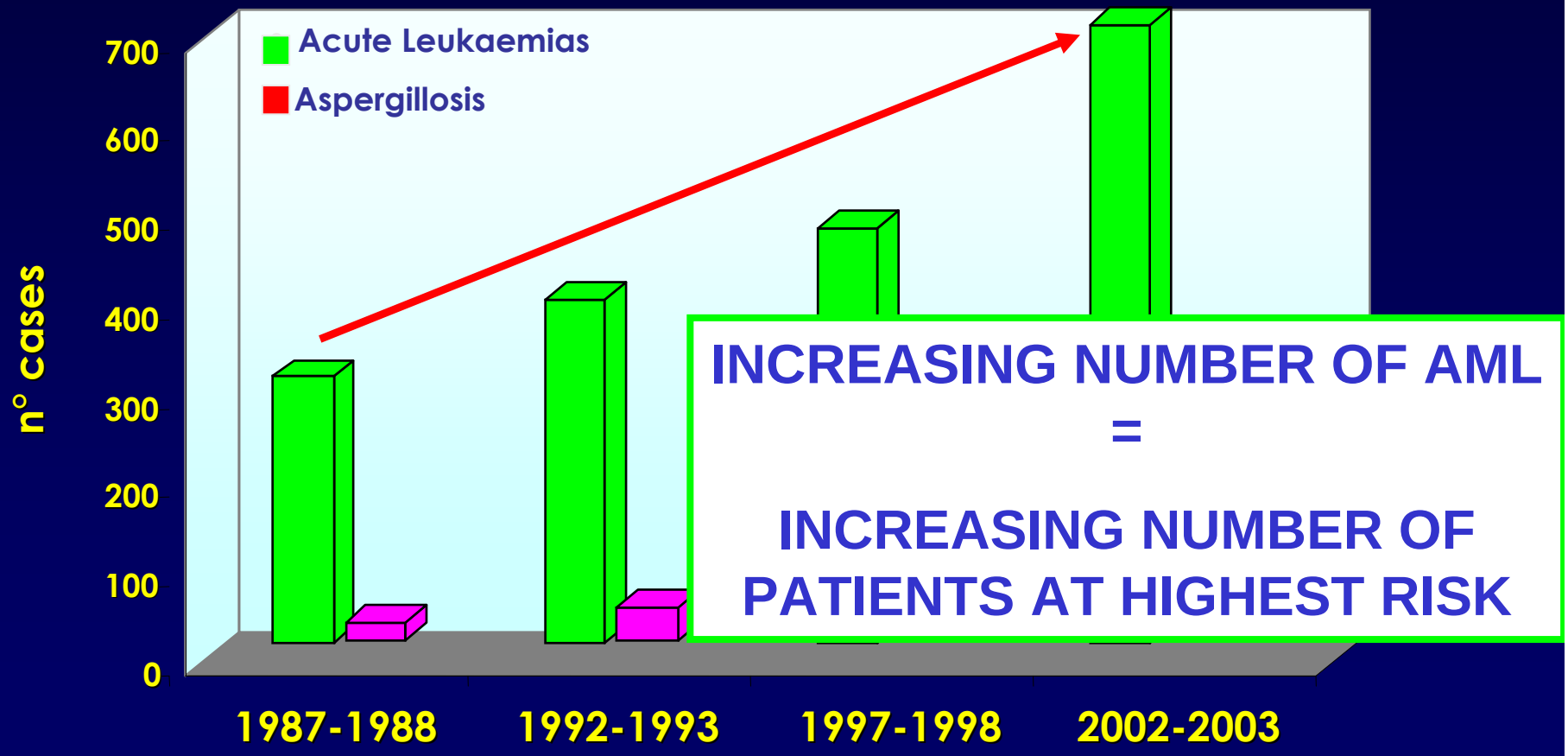


Caira et al, Eur J Haematol 2008

SEIFEM 2004

ACUTE LEUKAEMIA and ASPERGILLOSIS OVER THE YEARS

6 HAEMATOLOGICAL INSTITUTIONS



Pagano et al, Haematologica 2006

MANAGEMENT OF HIGH RISK PATIENTS

- ANTI-MOLD PROPHYLAXIS
- INTENSIVE DIAGNOSTIC WORK-UP

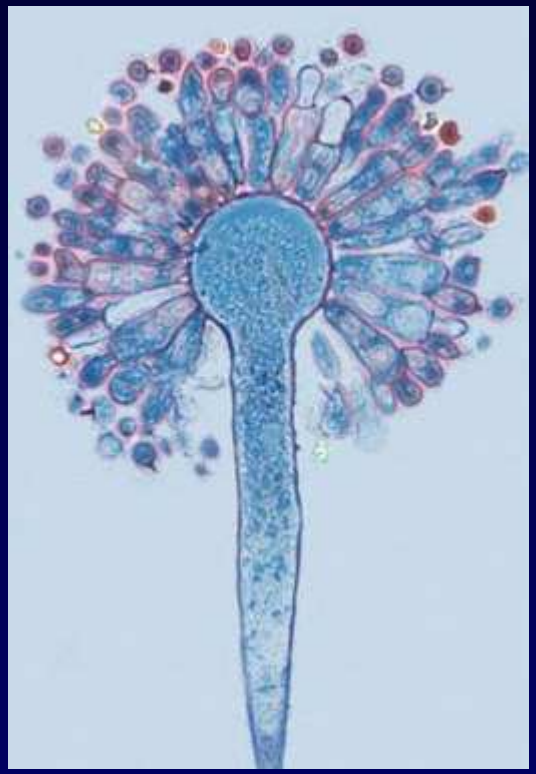
In 2010

Is it really necessary in all AML PATIENTS ???

A VERY SIMPLE EQUATION

HOST

+



ASPERGILLUS

+

ENTRANCE

=

ASPERGILLOSIS

…BUT A COMPLEX VARIABLE

Genetic pattern

Underlying disease

Exposure

Therapies and consequences

Age and performance status

HOST

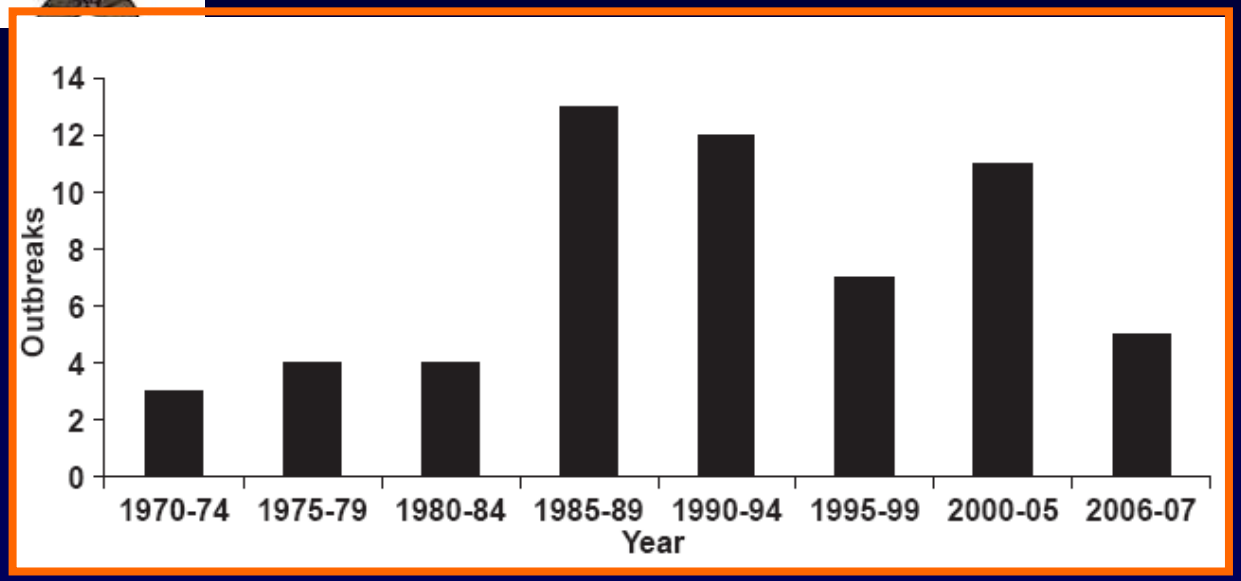
GENETIC PATTERN

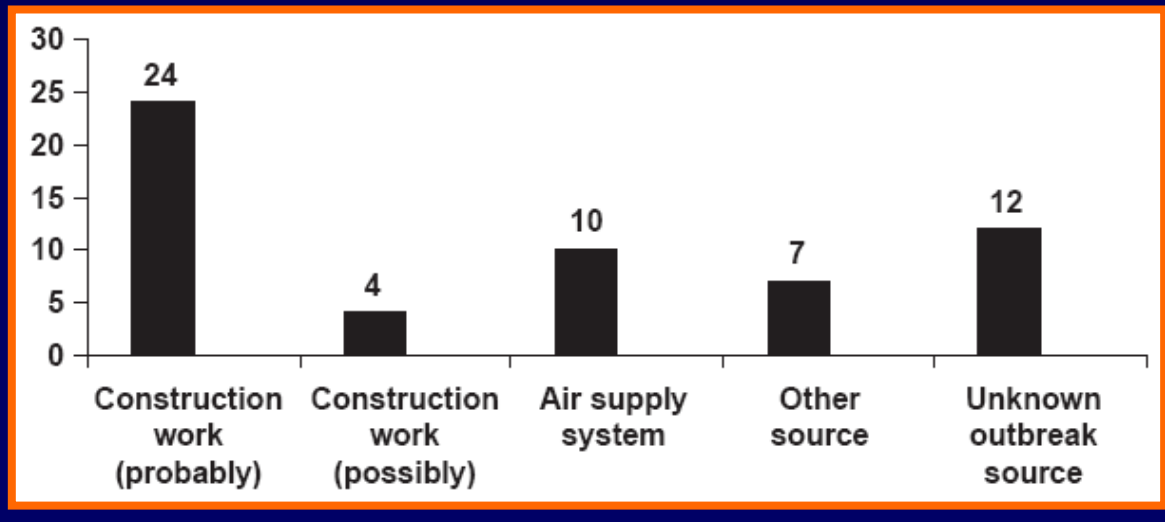
GENETICAL FACTORS	MECHANISM
DEFECTIVE OXIDANT PRODUCTION	NADPH-oxidase activity within PMN aggregates prevents hyphal proliferation and tissue invasion.
SNPs IN IL-10 GENE PROMOTER	High IL-10 level = impaired citokines production
TNFα RECEPTOR 2 PROMOTER	Low TNF-α level = impaired control of infection
SNPs IN TLR-4	Impaired immune signal at time of infection. Impaired production of inflammatory cytokines
POLIMORFISM IN TLR-1 e TLR-6	
POLIMORFISM IN THE PLASMINOGEN GENE	Impaired immune signal at time of infection

Modified from Erjavec et al, Clin Microbiol Infect 2009

Exposure:

HOSPITAL-DEPENDENT





Weber et al, Med Mycol 2009

Exposure:

HOSPITAL-INDEPENDENT

- 234 patients, admitted in different departments at Innsbruck Medical University (118 with HM)

A subgroup analysis showed that AML patients are more at risk for IMI when:

- **smoking cigarettes (P< 0.05),**
- **living in the countryside (P<0.05),**
- **having two or more fungus exposures (P<0.05)**

Lass-Florl et al, 19th ECCMID, Helsinki 2009

PHASE OF AML TREATMENT

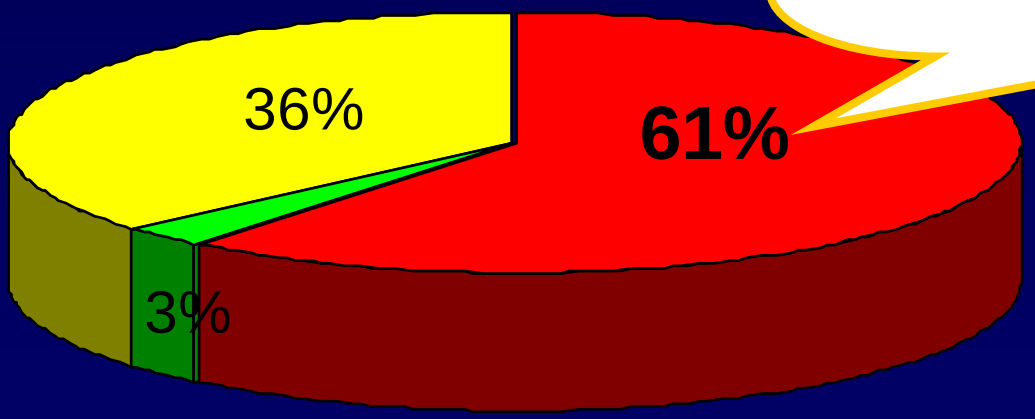
The risk of IA is not constant over all the phases of AML treatment

391 patients

COLONIZATION ???

001

140 AML patients



Pagano et al, Haematologica 2009

"ACUTE LEUKAEMIA" SPECIFIC EPIDEMIOLOGICAL ISSUES

- Ageing and the increasing number of AML patients

"AGE" AS A KEY RISK FACTOR

CHILDREN ≠ ADULTS

- Greater ability to tolerate intensive treatments
- Less exposures

CHILDREN *vs* ADULTS

	Years	Cases	Population	%
ADULT				
Pagano et al, Haematologica 2006	1999-2003	213	3012 AML	7.1
		44	1173 ALL	3.7
Pagano et al, Clin Infect Dis 2007	1999-2003	79	1249 allo-HSCT	6.3
		7	1979 auto-HSCT	0.4
Cornet et al, J Hosp Infect 2002	1994-1997	130	AML	8
		63	ALL	6.3
		150	1175 allo-HSCT	12.8
		24	2115 auto-HSCT	1.1
PEDIATRICS				
Zaoutis et al, Pediatrics 2006	2000	173	4692 AML	3.7
		171	26926 ALL	0.6
		101	2219 allo-HSCT	4.5
		3	822 auto-HSCT	0.3

"AGE" AS A KEY RISK FACTOR

CHILDREN ≠ ADULTS

- Greater ability to tolerate intensive treatments
- Less exposures

YOUNGER ADULTS ≠ OLDER ADULTS

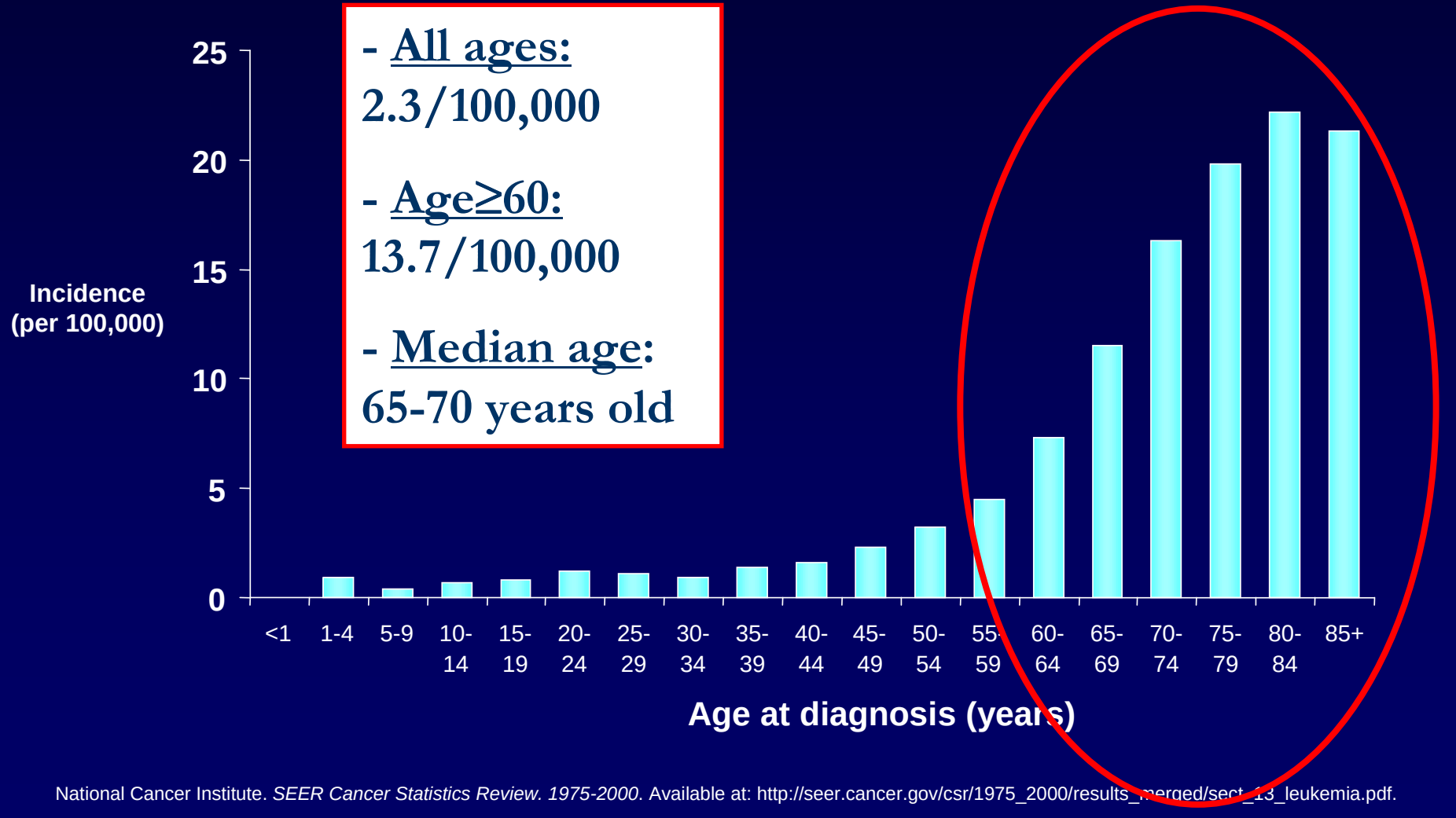
- Greater ability to tolerate intensive treatments
- Less comorbidities

AML IS PRIMARILY A DISEASE OF OLDER ADULTS

- All ages:
2.3/100,000

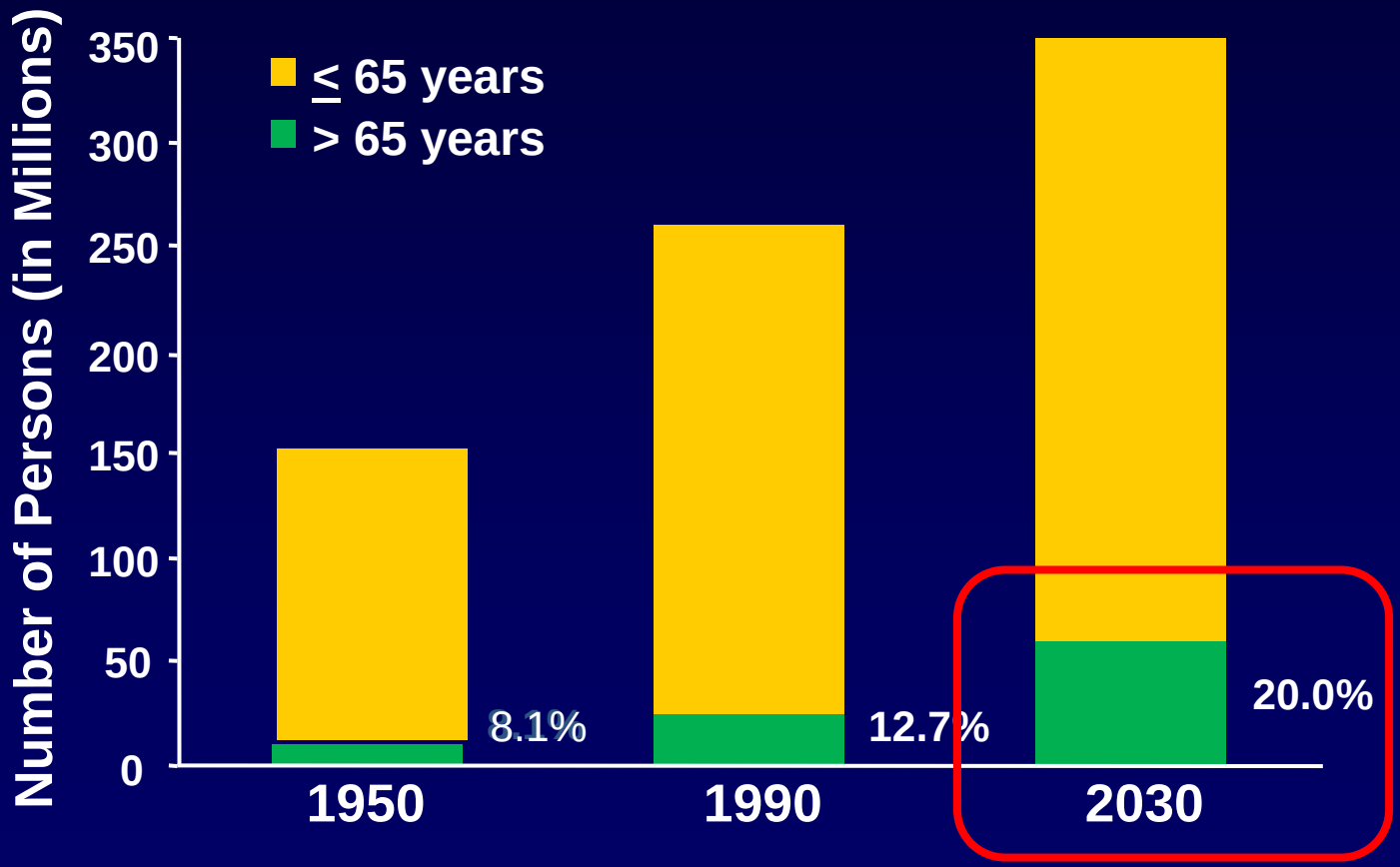
- Age≥60:
13.7/100,000

- Median age:
65-70 years old



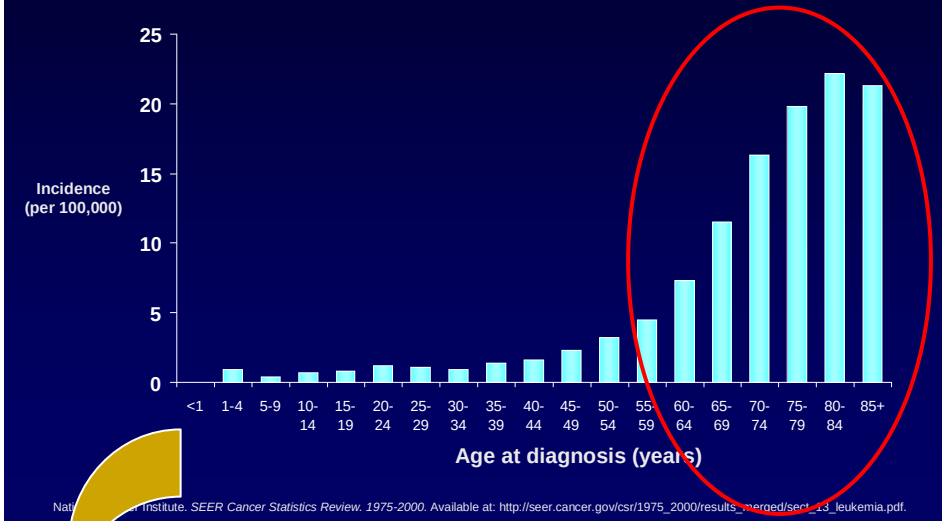
National Cancer Institute. *SEER Cancer Statistics Review. 1975-2000*. Available at: http://seer.cancer.gov/csr/1975_2000/results_merged/sect_13_leukemia.pdf.

AGEING OF POPULATION



US Bureau of the Census. 1996.

AML IS PRIMARILY A DISEASE OF OLDER ADULTS



Nati… Institute. *SEER Cancer Statistics Review. 1975-2000.* Available at: http://seer.cancer.gov/csr/1975_2000/results_merged/sect_13_leukemia.pdf.

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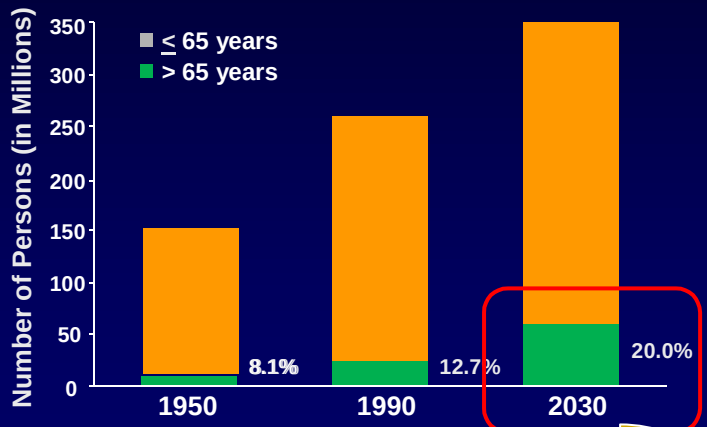
AGEING OF POPULATION



US Bureau … 1996.

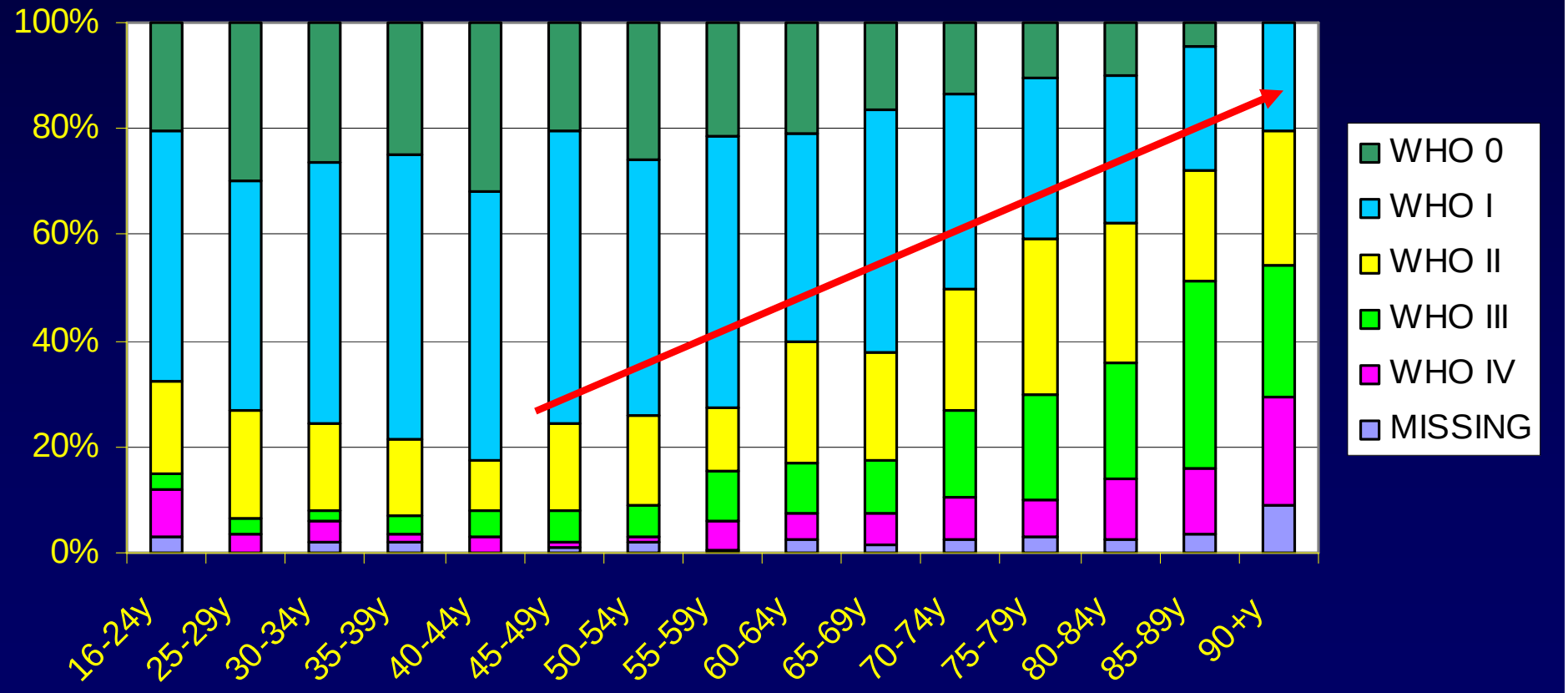
THE ABSOLUTE NUMBER OF INVASIVE ASPERGILLOSIS IN AML IS INCREASING!!!

"*ACUTE LEUKAEMIA*" SPECIFIC EPIDEMIOLOGICAL ISSUES

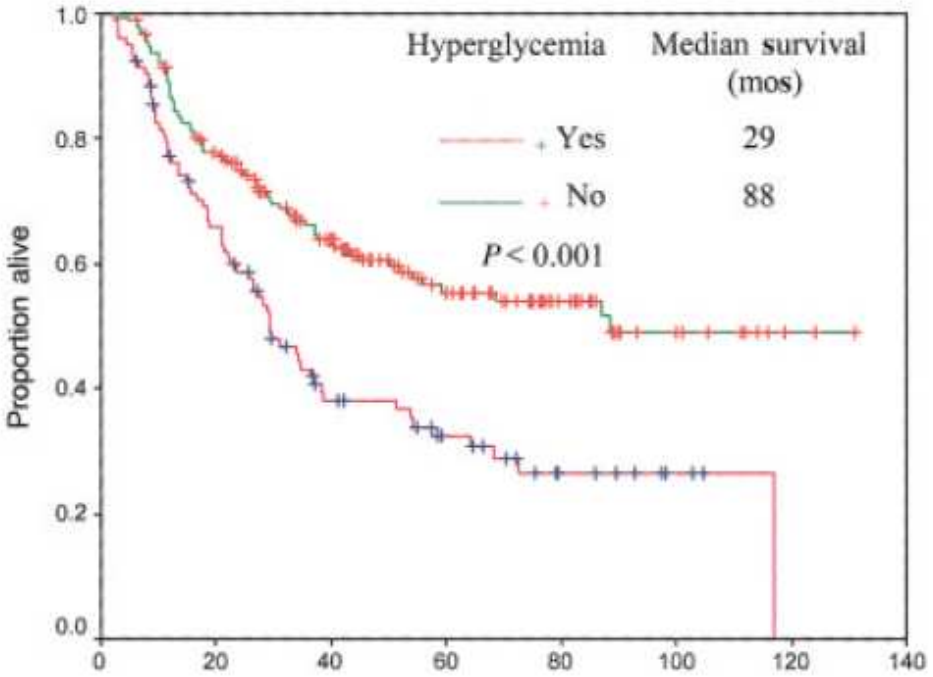
- Ageing and the increasing number of AML patients
- Comorbidities and performance status

PERFORMANCE STATUS

PS at 1st diagnosis in 2,696 AL patients from the Swedish Adult Acute Leukemia Registry



Juliusson et al, Blood 2009,113(18)

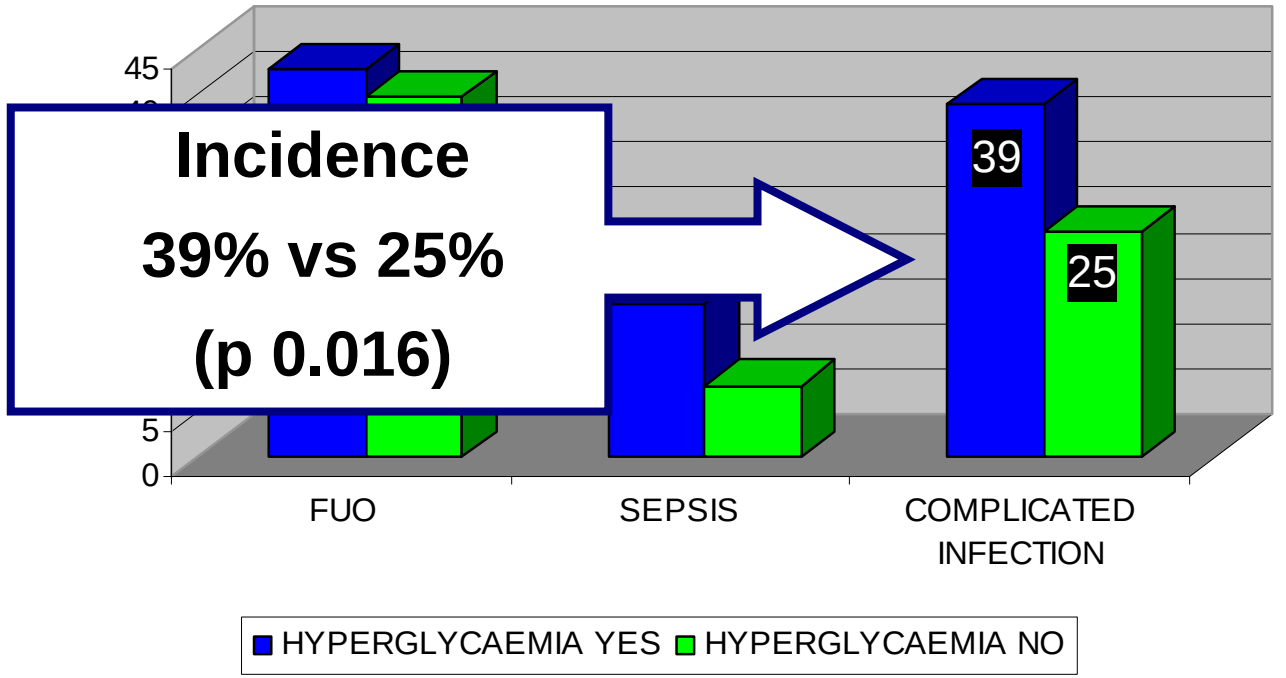


Including sepsis, pneumonia or fungal

Incidence

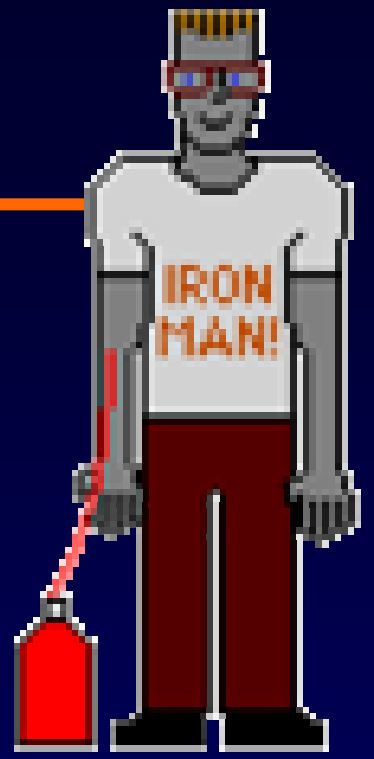
39% vs 25%

(p 0.016)



Weiser et al, Cancer 2004

IRON OVERLOAD



Leukaemic patients = HEAVELY TRANSFUSED

↓

IRON OVERLOAD =

high availability of free iron

Fi acts as a free radical catalyser

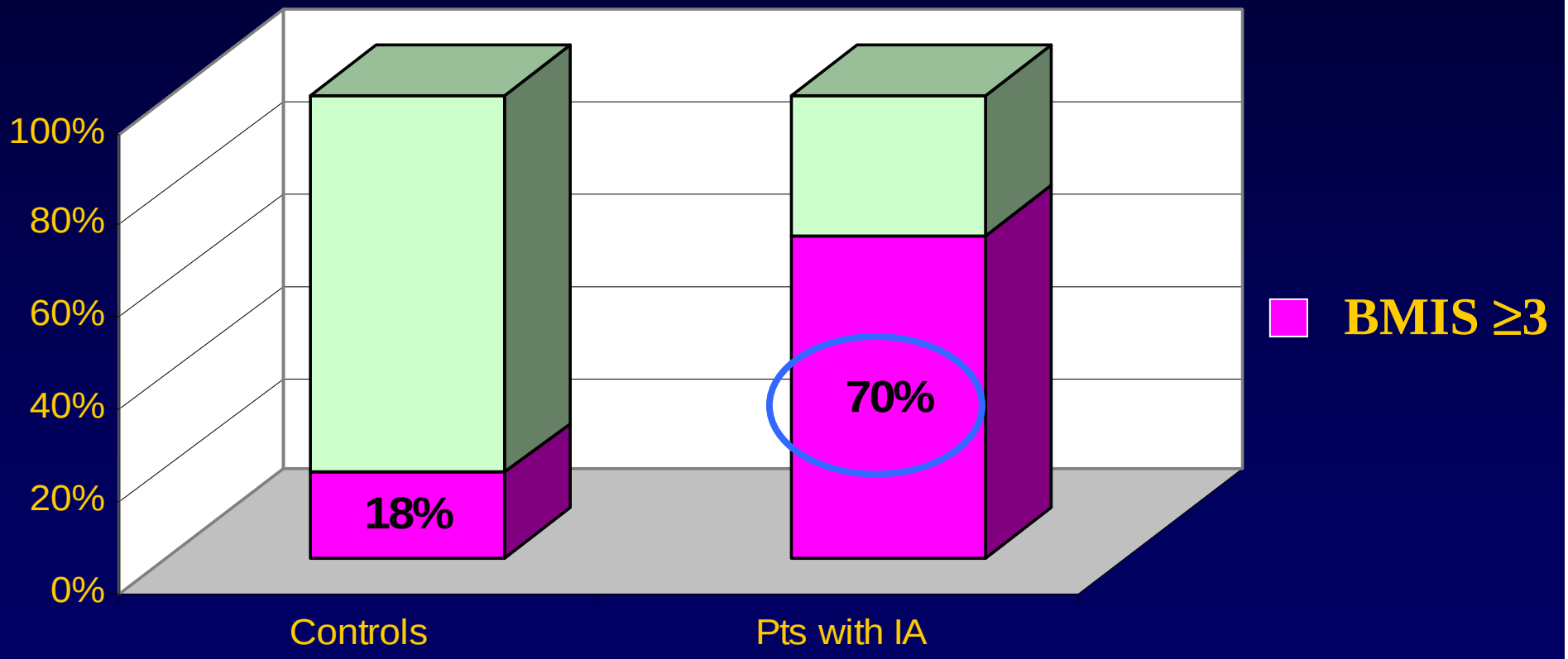
↓

MUCOSITIS

FI has negative effect on antimicrobial functions of neutrophils, monocytes, NK and macrophages

FI is used by fungi to promote their growth

IRON OVERLOAD IN INVASIVE ASPERGILLOSIS



p-value <0.0001

Kontoyiannis et al, Cancer 2007

"*ACUTE LEUKAEMIA*" SPECIFIC EPIDEMIOLOGICAL ISSUES

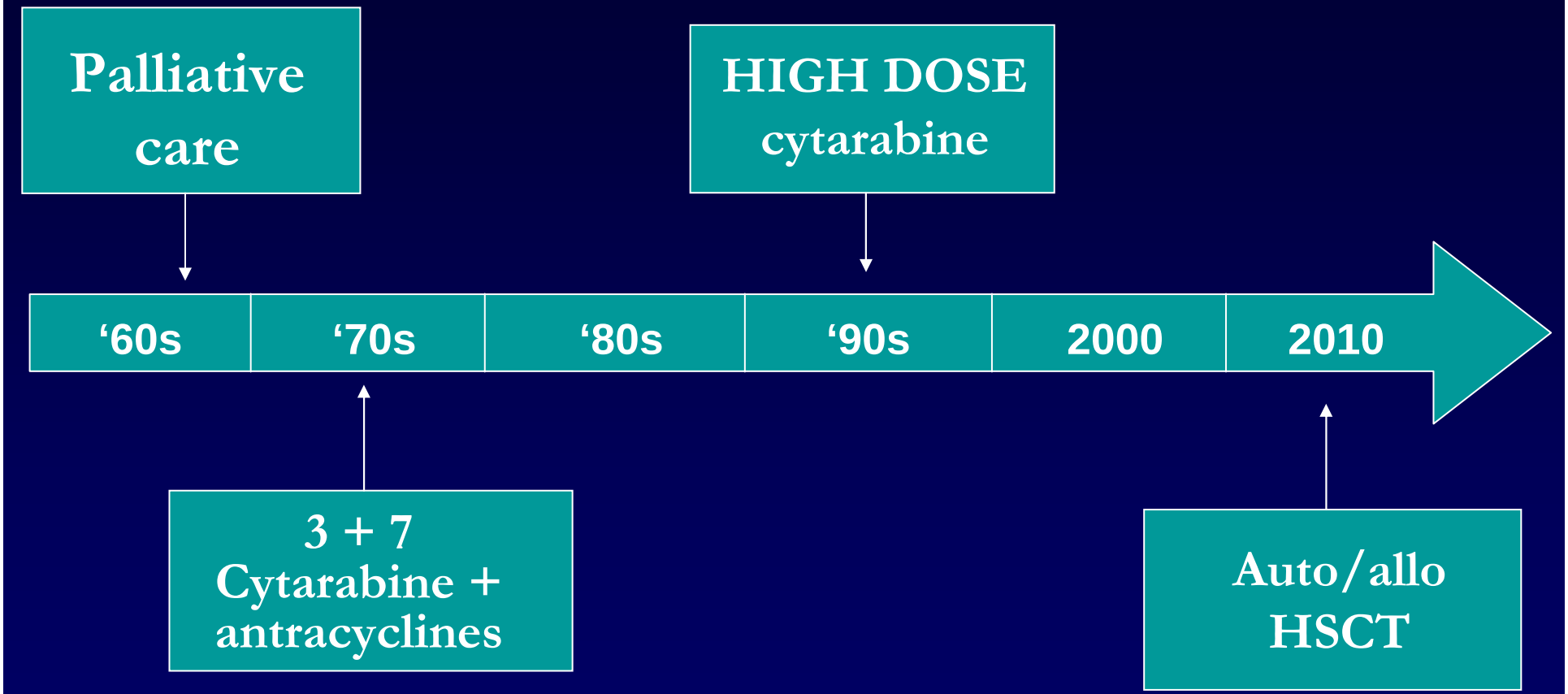
- Ageing and the increasing number of AML patients
- Comorbidities and performance status
- Changes in leukaemia treatment strategy

WHAT ARE THE MAJOR DETERMINANT FACTORS IN TREATMENT DECISIONS ???

1. **PATIENT'S AGE and LIFE EXPECTANCY**
2. **PATIENT'S COMORBODITIES and TREATMENT TOLERANCE**
3. **HAEMATOLOGIST'S ATTITUDE TO INTENSIVE TREATMENT !!!**

Ferrara F, The Lancet Oncology 2004

STRATEGIES IN AML OVER THE YEARS

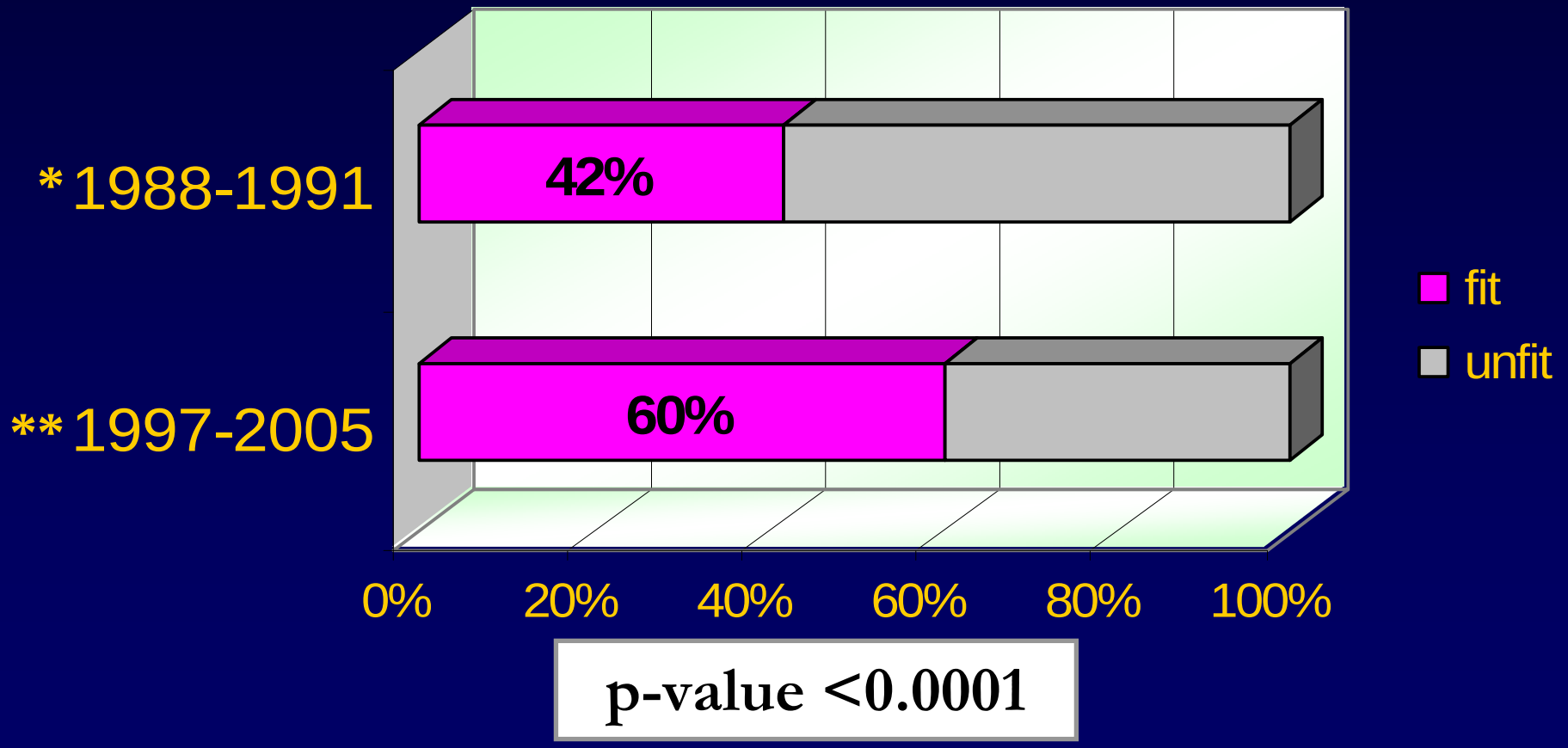


EVEN IN OLDER PATIENTS !!!

Supportive care, side effects control

INTENSIVE TREATMENTS IN OLDER PATIENTS

Patients 55+ reported *FIT* for intensive chemotherapy



** Tailor et al, Leukemia 1995, 9(2); ** Juliusson et al, Blood 2009,113(18)*

Allogeneic and autologous transplantation for haematological diseases solid tumours and immune disorders: current practice in Europe in 1998

Goldman et al, BMT1998

1998

Patient age

The age of an individual patient remains one of the most important determinants of outcome following both allogeneic and autologous HSCT procedures. As a broad generalisation it seems reasonable to recommend limits of 65 years for autograft procedures, of 60 years for allograft procedures using HLA-identical sibling donors and of 45 years for unrelated donor transplants. There will always be cases

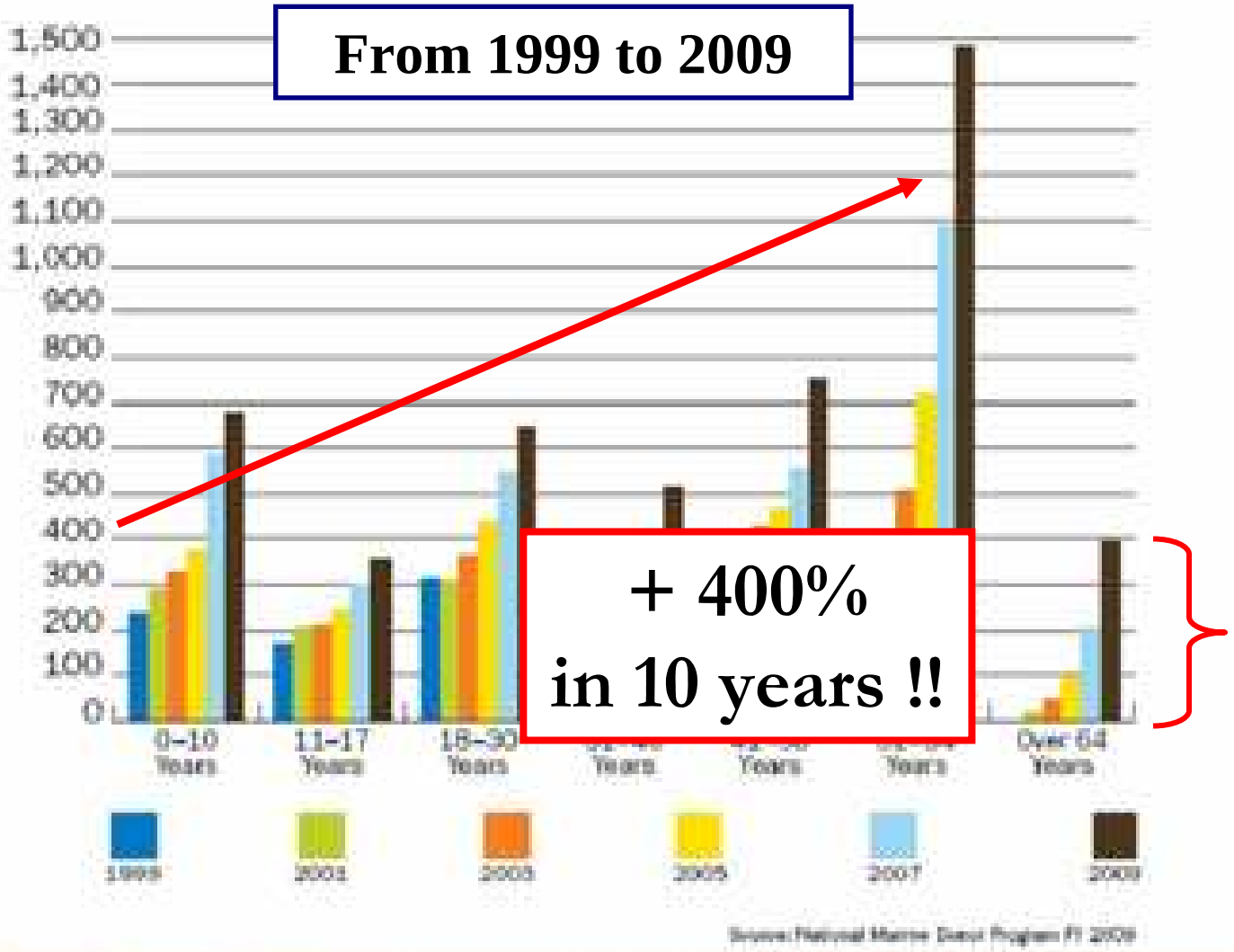
Allogeneic and autologous transplantation for haematological diseases, solid tumours and immune disorders: definitions and current practice in Europe

Ljungman et al, BMT2006

2006

HSCT in children gives better results than in adults. Age cannot be seen as a single risk factor but must be taken together with other factors in the decision-making regarding HSCT. It should, however, be recognised that biological rather than chronological age is the more important determining factor for outcome. As in previous

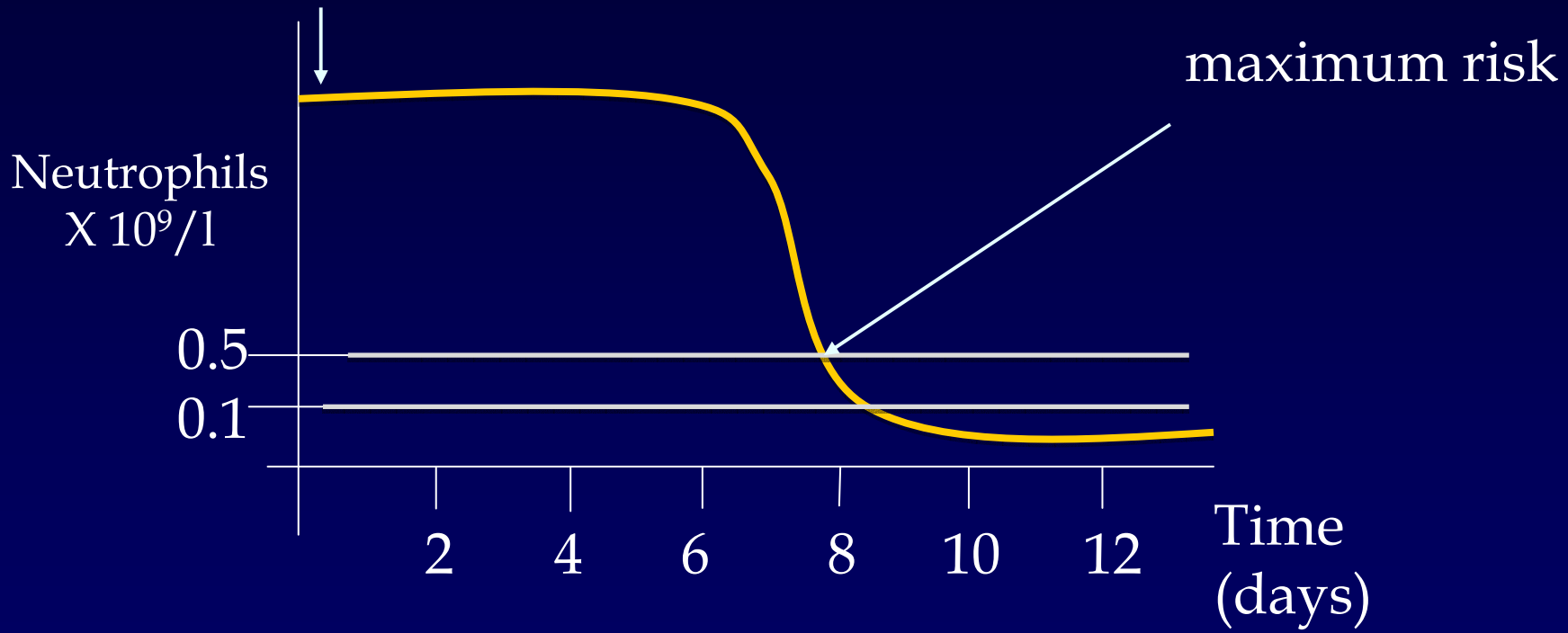
NMDP Transplants by Recipient Age



"*ACUTE LEUKAEMIA*" SPECIFIC EPIDEMIOLOGICAL ISSUES

- Ageing and the increasing number of AML patients
- Comorbidities and performance status
- Changes in leukemia treatment strategy
- Neutropenia and myelodisplasia

NEUTROPENIA: A COMMON RISK FACTOR IN AML



- <0.5 x 10^9/l: risk of infection
- <0.1 x 10^9/l: high risk of IFI

Modified from Bodey et al, Ann intern Med 1966

NEUTROPENIA IN SEIFEM-2008 Study

140 Invasive Aspergillosis in patients with Acute Myeloid Leukaemia :

21 Centres

Age	57 (14/79)
M/F	1.8/1
Neutropenia at onset of AI	130 (93%)
Neutropenia severity	
❖ Mild/moderate	7 (5%)
❖ Severe	123 (95%)
Mean duration of neutropenia	
❖ <10 days	40 (31%)
❖ ≥10 days	90 (69%)

Pagano et al, Haematologica 2009

NEUTROPHIL IMPAIRMENTS IN AML

IT MAY RESULT FROM MULTIPLE COMPONENTS:

1. **Chemotherapy**
2. **Bone marrow infiltration by blast cells**

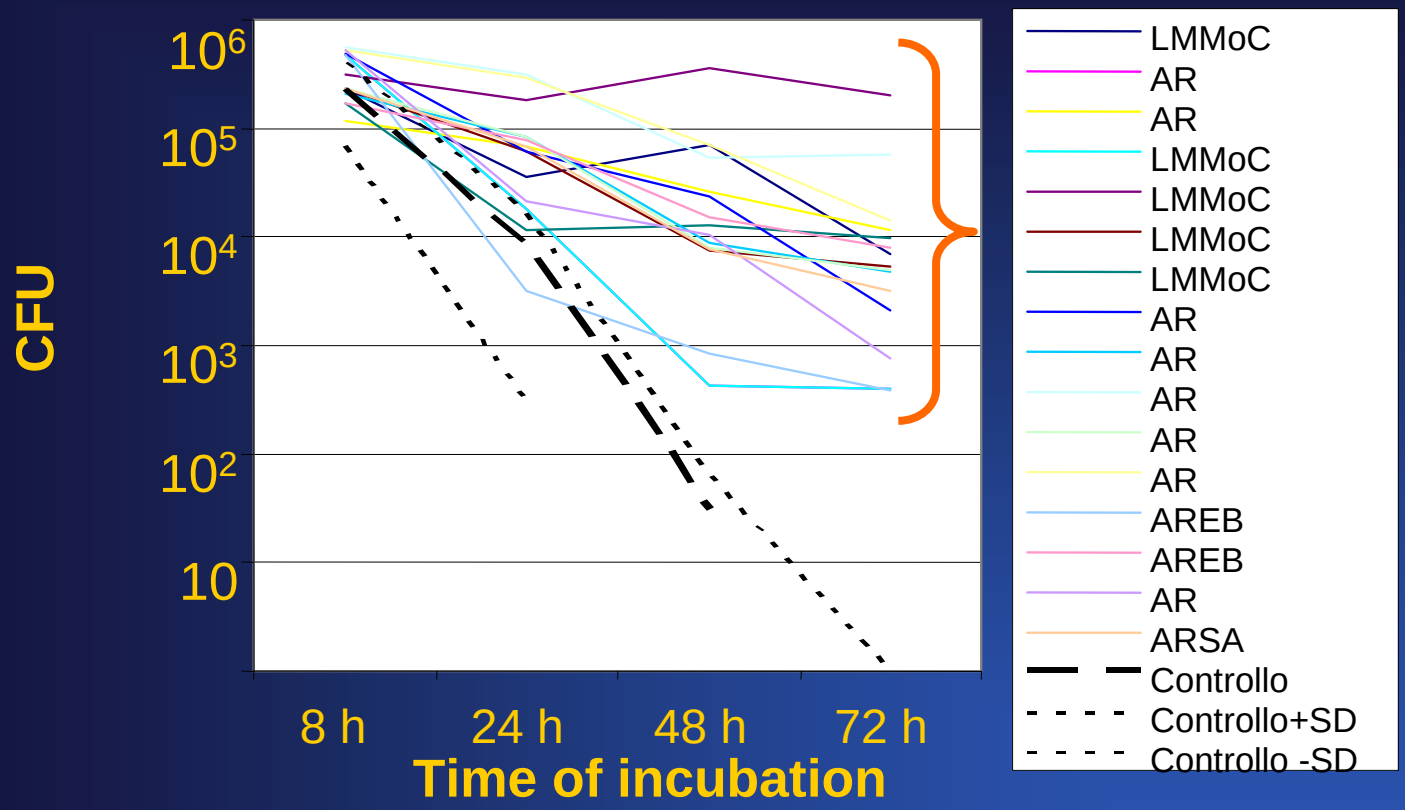
→ **↓ NUMBER of PMNs**

3. **Myelodysplasia** → **↓ FUNCTION of PMNs**

AML with *myelodysplasia-related* changes
(WHO-2008 classification)

Vardiman et al, Blood 2009

MYELODYSPLASIA



Dysplastic vs normal PMN:

↓ fungicidal activity against yeasts

↑ susceptibility to infections in myelodysplasia

Fianchi et al, P388, 42nd Congress of the SIE, Milan 2009

"*ACUTE LEUKAEMIA*" SPECIFIC EPIDEMIOLOGICAL ISSUES

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- Changes in leukaemia treatment strategy
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NOT ALL ACUTE LEUKAEMIA PATIENTS ARE AT THE SAME RISK !!!!

2010 ITALIAN PROJECTS IN ACUTE LEUKAEMIAS

SEIFEM 2010

SEIFEM-2010 study:

PROSPECTIVE SURVEY ON *PRE-HOSPITAL RISK FACTORS* FOR INVASIVE ASPERGILLOSIS IN *NEWLY* DIAGNOSED AML

TARGET: 1000 patients in 32 ACTIVE CENTRES

Hema E-Chart

Continuous Surveillance of Invasive Fungal Infection: A Realistic Goal for the Near Future

Pagano et al, Clin Infect Dis 2009

HEMA e-CHART

Prospective Multicentral Registry of Febrile Events in Haematology

IN 17 CENTRES THE REGISTRY OF ALL NEWLY DIAGNOSED HAEMATOLOGICAL MALIGNANCIES

→ INCIDENCE RATES !!!

- Patient Registry
- Disease
  - *Clinical values (i.e. body temperature, neutrophiles, etc.)*
  - *Type of Disease*
  - *Type of Therapy (I line, II line, etc.)*
  - *Pharmaceutical Therapy*
    - Antibiotics
    - Antiviral
    - Anti neoplastic
    - Corticosteroid
    - Immunoglobulin
    - Cytokine
  - *Anti-fungal name*
  - *Dosage*
  - *Administration form*
- Outcome
  - *Complete recovered /Partially recovered*
  - *Clinical evaluation of the treatment*
- Investigator Comments
  - *Tolerability*
  - *Safety*
- Monitoring of the interaction with other therapies

ADVANTAGES:

- **PROSPECTIVE**
- **MULTICENTRAL**
- **ON-LINE**
- ***COMPLETE INFORMATION !!!***

CONCLUSIONS - I

- Invasive aspergillosis remains the most crucial infectious complication in haematological patients
- Patients suffering from Acute Myeloid Leukaemia continue to be at the highest risk
- In western countries the number of IA in AML is expected to increase, particularly in older patients

CONCLUSIONS - II

- In HIGH RISK categories we are moving towards a spreading of prophylaxis measures and towards an intensive diagnostic approach
- Patients with AML should be better categorized in order to target human and economic resources
- More innovative epidemiological tools are now available to search for novel factors for IA risk stratification