

# Risk Factors for the Development of Invasive Fungal Infections

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# Classical Risk Factors

- Neutropenia
- Mucositis
- Immunosuppressive drugs
- Graft vs host disease
- Iron overload
- Various environmental factors

# Risk Categories of Immunocompromised Patients for IFIs

## Low to intermediate risk

Underlying disease	Reported incidence (%)
Auto HSCT	0.5-6
ALL	3,8
Hodgkin's lymphoma	0,4
Non-Hodgkin's lymphoma	0,8
Multiple myeloma	2-3
Lung cancer	2,6
Kidney tx	0,2-1
Pancreas tx	1.1-2.9
SLE	0,5-2,1
COPD	1,9

Pagano L, et al. J Antimicrob Chemother 2011;66(suppl.1):i5  
Herbrecht R, et al. Ann NY Acad Sci 2012;1272:23

# Risk Categories of Compromised Patients for IFI

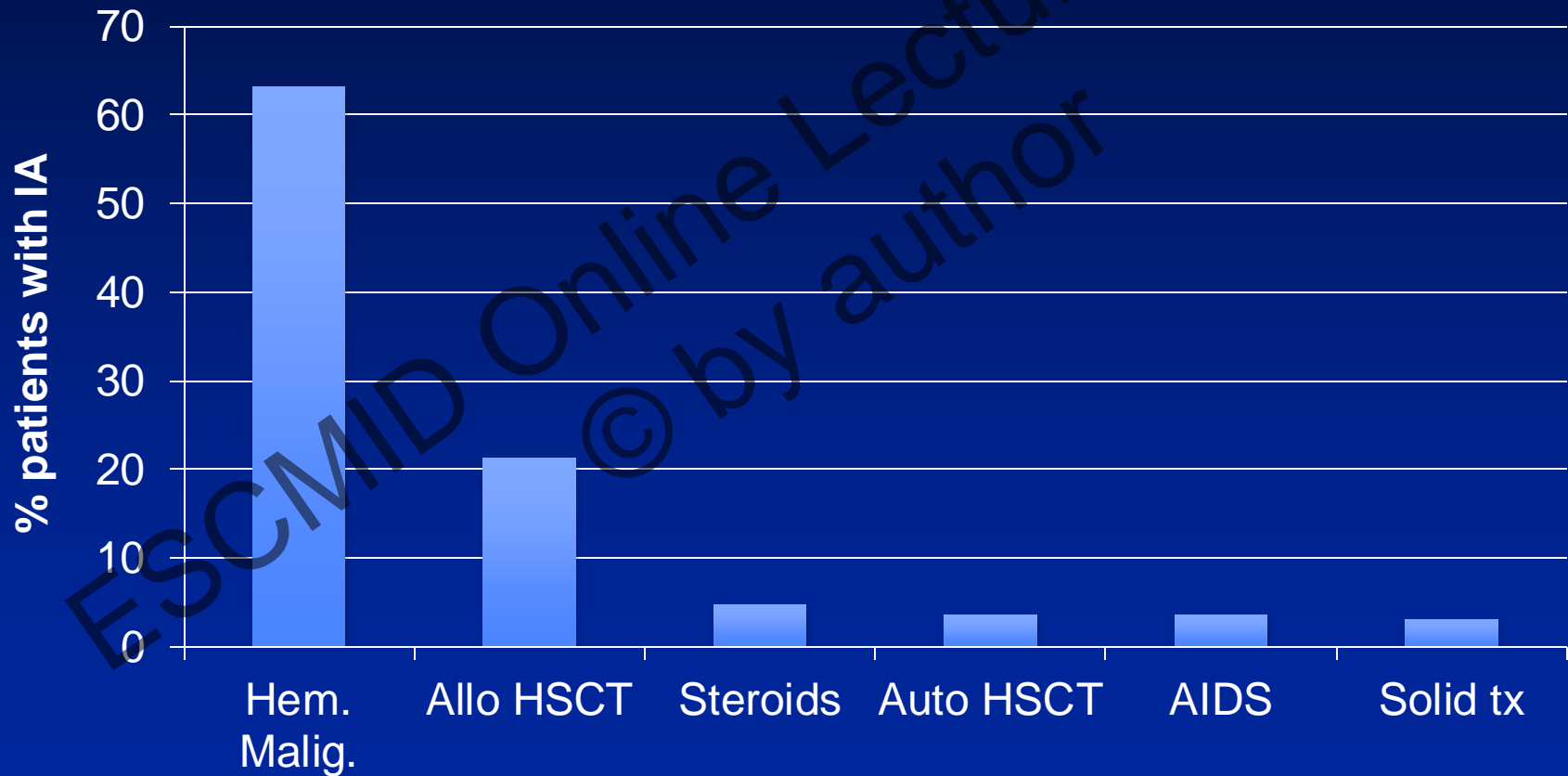
## High risk

Underlying disease	Reported incidence (%)
Allogeneic HSCT	2.7-23
Chronic granulomatous dis.	20-40
AML	5-24
Lung or heart-lung tx	3-26
Heart tx	0,4-15
Liver tx	0,7-10
AIDS	0-12
Burns	1-7

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# Primary Host Factors Predisposing to IA\*

\*Data from voriconazole and Ambiload trials, n=478



Adapted from Herbrecht R, et al. Ann NY Acad Sci 2012;1272:23

# Real Life Situations Differ from Trial Settings...

- **22% of 195-patient cohort would not be eligible for voriconazole and Ambiload trials**
  - Decreased renal function
  - Need for mechanical ventilation
  - Short life expectancy
  - Lack of host factors defined by EORTC/MSG criteria

# Risk Factors Affecting Primary Host Condition

## Innate Immune Status

Toll-like receptors PM  
C-type lectin receptor PM  
Plasminogen PM  
Other polymorphisms

## Environmental Factors

Climate  
Construction work  
Place of residence  
Tobacco or cannabis use  
Pets, potted plants  
No HEPA-filtered air

## Primary Host Factors

Hematological cancer  
Allo HSCT  
SOT  
Solid tumor  
Other immunodeficiency

## Underlying Conditions

Neutropenia  
Uncontrolled cancer  
GVHD  
Chemotherapy  
Steroids  
T-cell suppressors

## Other factors

Diabetes  
Iron overload  
Trauma, burns  
Renal impairment  
Metabolic acidosis  
Prior resp. disease

# Biological Characteristics of Leukemia and Type of Chemotherapy vs IFIs

- Lower risk due to less toxic chemotherapy
  - Promyelocytic leukemia
    - All-trans retinoic acid
  - Ph (+) ALL
    - Tyrosine kinase inhibitors
- Induction vs maintenance vs refractory chemotherapy
- Type of HSCT
  - Related vs unrelated vs partially related match
  - Cord blood vs peripheral vs marrow harvested



# Type of Therapeutics vs IFIs

- **Purine analogues (e.g. fludarabine)**
  - Long-lasting T-cell abnormalities
- **Steroids**
  - Inhibit PNL chemotaxis, oxidative burst
  - Suppress non-oxidatives processes in mono/macrophages and lysosomal activity

# Environmental Risk factors

- ↑ incidence of IA in dry seasons with high temperature
- Personal habits and life style
  - Colonisation at admission
  - AML patients with
    - Cigarette smoking
    - Live in countryside
    - Exposed to high concentrations of fungal spores

# Other Environmental Risk Factors

- **Construction in hospital leading contamination of the air**
  - Even in remote sites from patient's ward
- **Malfunction of ventilation systems**
- **Absence of HEPA-filtered rooms**
- **Potted plants, flowers and carpets**
- **Water supplies**

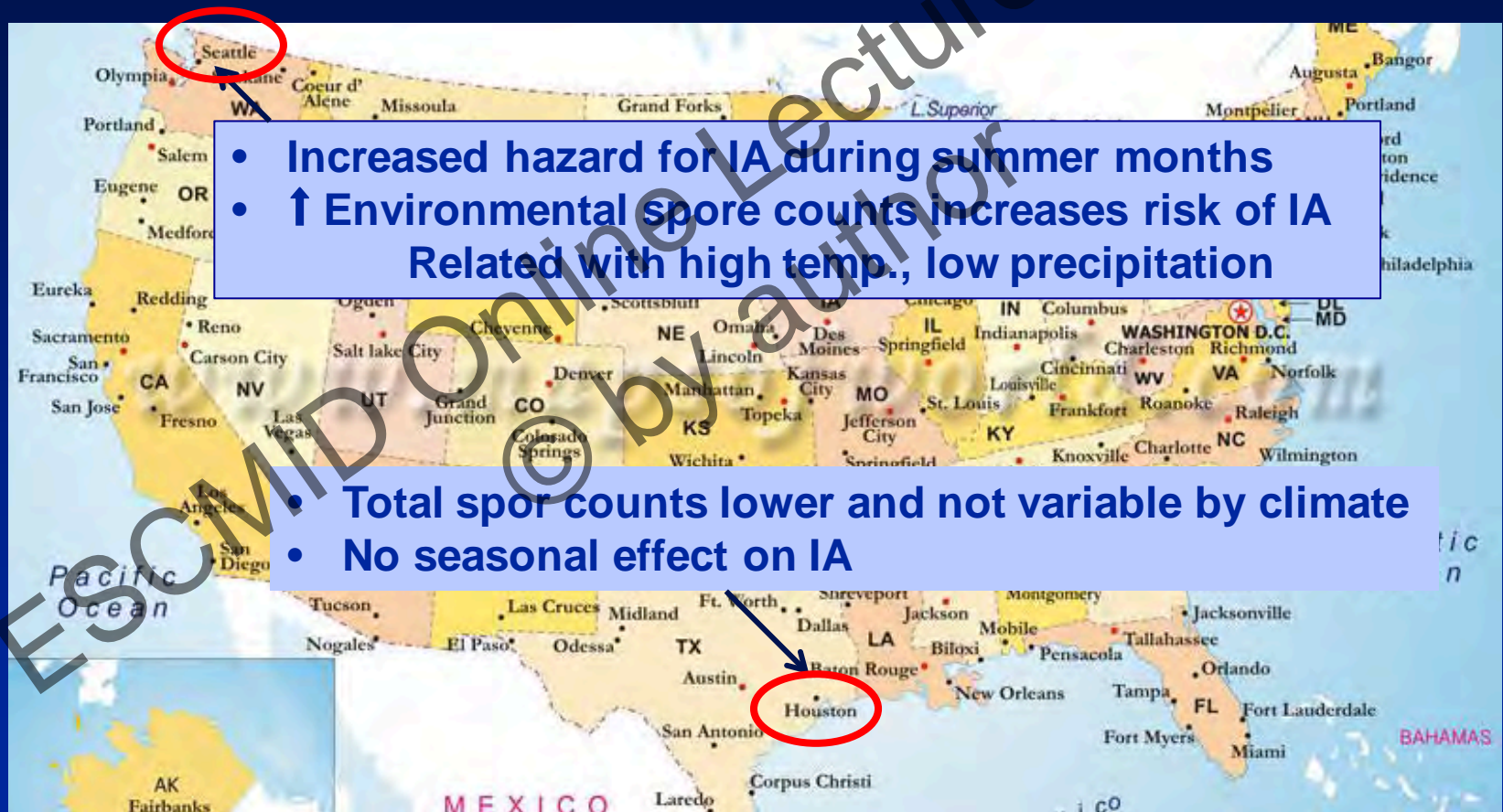
# **Spatio-temporal and Healthcare Trends of IFI, US Data**

- **372 hospital discharge data, 1996-2006**
  - HIV
  - Hematological malignancy
  - Transplant patients
- **Case-fatality proportion, 11.7%**
- **Independent predictors for IFI, apart from other well-know risk factors**

# Risks Identified for IFIs in US

- Most IFIs occurred in mid-west and south of US
- Highest risk in autumn
- Transfer from another healthcare facility
- Mortality was least for the young, regardless of area and season

# Comparative Geoclimatic Influences on IA in HSCT



# Unanswered Questions for Management of IFIs

- Which patients will benefit most:
  - Antifungal prophylaxis
  - Empirical therapy
  - Diagnostic driven strategies
- Is a tailored diagnostic, prophylactic and therapeutic approach plausible?



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# Genetic Risk Factors

- Increased risk for IFIs in hematology patients related with
  - Decreased serum levels of mannose-binding lectin
  - SNPs in pattern-recognition receptors increase risk for IFIs
    - TLR4
    - Dectin-1
  - SNPs in genes encoding cytokines, chemokines and their receptors

# SNPs in Cytokine And Chemokine Genes

- **Risk for IAs increased in presence of**
  - SNPs in promotor region of IL-10 gene
  - ATA haplotype: ↑ IL-10
- **Decreased risk**
  - ACC haplotype: ↓ IL-10
- **Major flaw in the study**
  - The impact of donor genotype was not considered
    - Influence by donor immune cells might have contributed to IL-10 production

## Other SNPs

- 84 SNPs in 18 genes coding different PRRs, chemokines and cytokines
  - ↑ IAs
    - IL-10 promoter SNP
    - IFN $\gamma$  promoter SNP
    - Chemokine ligand-10 (CXCL10) SNP
      - Strong association
  - Again no mention of donor genotype
- No statistical significance

# Most Common Limitations in Genetic Association Studies

- Small sample size
- Low incidence of IAs
- Heterogeneity of cohorts studied
- Failure to include nongenetic factors
- No consideration of donor genotype
- Inconsistent definitions of outcome
- Not adjusting for multiple comparisons

# Cytokine Gene Polymorphisms and Outcome in Invasive Candidiasis

- 338 candidemia patients and 351 noninfected controls
  - Genotyped for SNPs in 6 cytokine genes and 1 receptor gene (IL12RB1)
- No SNPs associated with ↑ candidemia
- Persistent candidemia (13%) associated with SNPs in genes
  - IL10 and IL12B which resulted in ↓ production of proinflammatory cytokines

# Iron Overload

- Usually in heavily transfused patients
  - AML patients
  - HSCT recipients
- Iron is essential for growth and virulence for moulds
- High levels of free iron
  - Damage mucosa
  - Impair cellular antifungal protection

# How does Iron Impair Cellular Protection Against Fungi

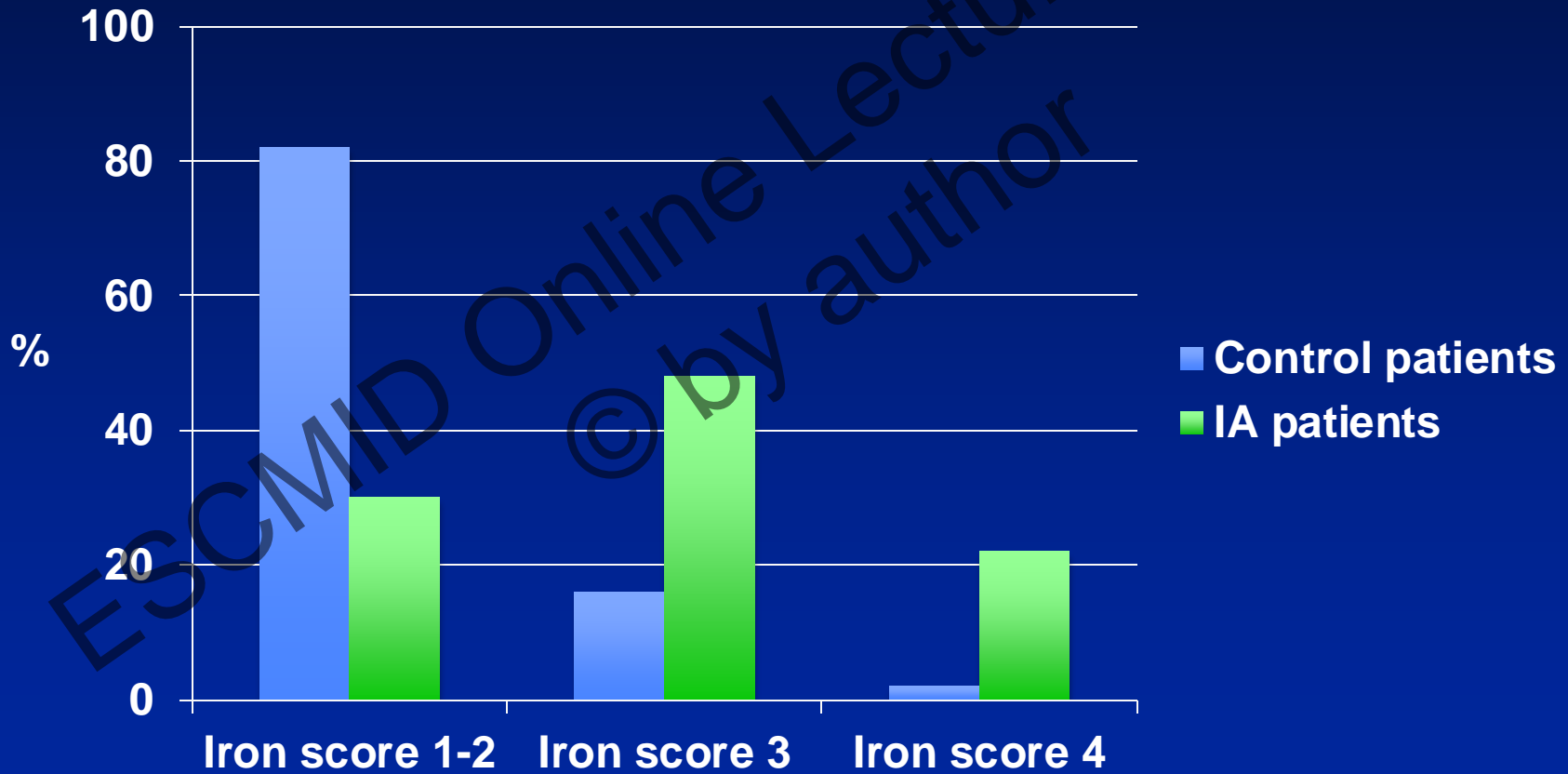
- Inhibition
  - Interferon-g
  - Tumor necrosis factor
  - IL-12
  - Nitric oxide formation
- Impairment of functions
  - Macrophage
  - Neutrophil
  - T-cells

# Increased Bone Marrow Iron Stores as a Risk Factor for IAs

- 33 hospitalized patients with hematological malignancies and IA
- 33 high-risk patients without IA
- Bone marrow slides reviewed retrospectively
- Both groups were matched
  - Demographics,
  - Clinical characteristics
- Iron load in biopsy specimens was scored between 0-4



# Distribution of Patients According to Iron Stores Scores



# Conclusions

- Many cofactors are related with occurrence and outcome of IFDs
- In addition to well-defined factors
  - Genetic predisposition
  - Iron overload
  - Newly defined environmental factors should require further analysis

**Thank you....**

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