

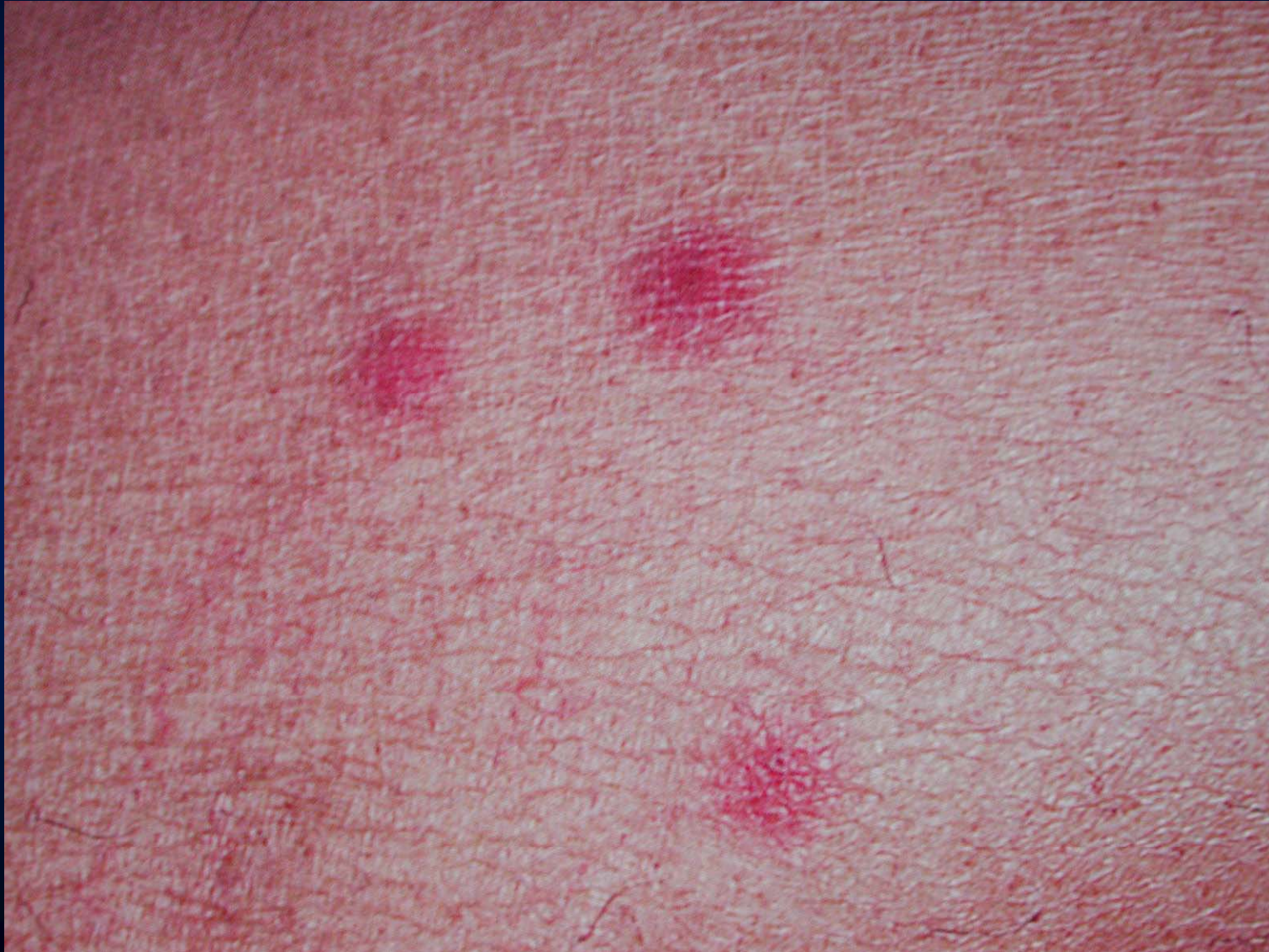
Infections fongiques au cours des hémopathies myéloïdes



Infections invasives à levures

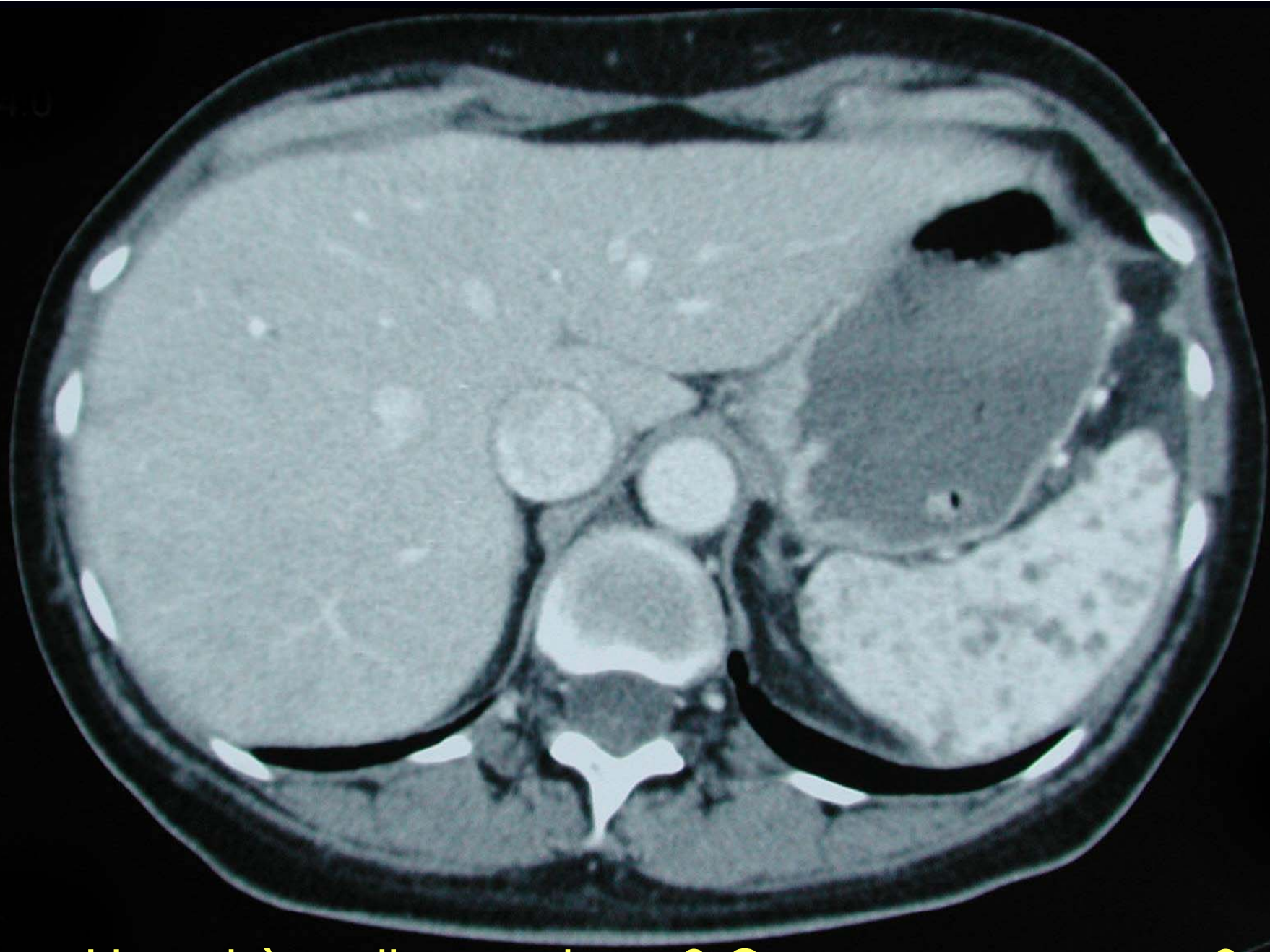
- Principalement les candidoses
 - Facteurs de risque :
 - Voie veineuse
 - Neutropénie
 - Colonisation
 - Antibiothérapie large spectre
 - Alimentation parentérale
 - Intervention chirurgicale abdominale
 - Prophylaxie possible
 - Fluconazole
 - validée lors des greffes de CSH
 - controversé lors des inductions de LAM
 - résistance de *C. glabrata* et *C. krusei*
 - Itraconazole
 - efficace mais nécessite la forme iv
 - tolérance médiocre
 - Posaconazole
 - efficace dans les inductions de LAM / MDS

Aspect typique Candidose aiguë disséminée



Cas clinique 1

- Femme de 60 ans
 - LAM, induction classique
 - Episode fébrile non documenté pendant l'aplasie
 - Fièvre prolongée en sortie d'aplasie résistante aux antibactériens et à un antifongique à spectre large; douleurs abdominales
 - Syndrome inflammatoire biologique
 - Marqueurs négatifs (mannane candidosique, galactomannane aspergillaire)
 - PCR et bêta-D-glucane non disponibles
- Hypothèse diagnostique ? Que proposez-vous ?

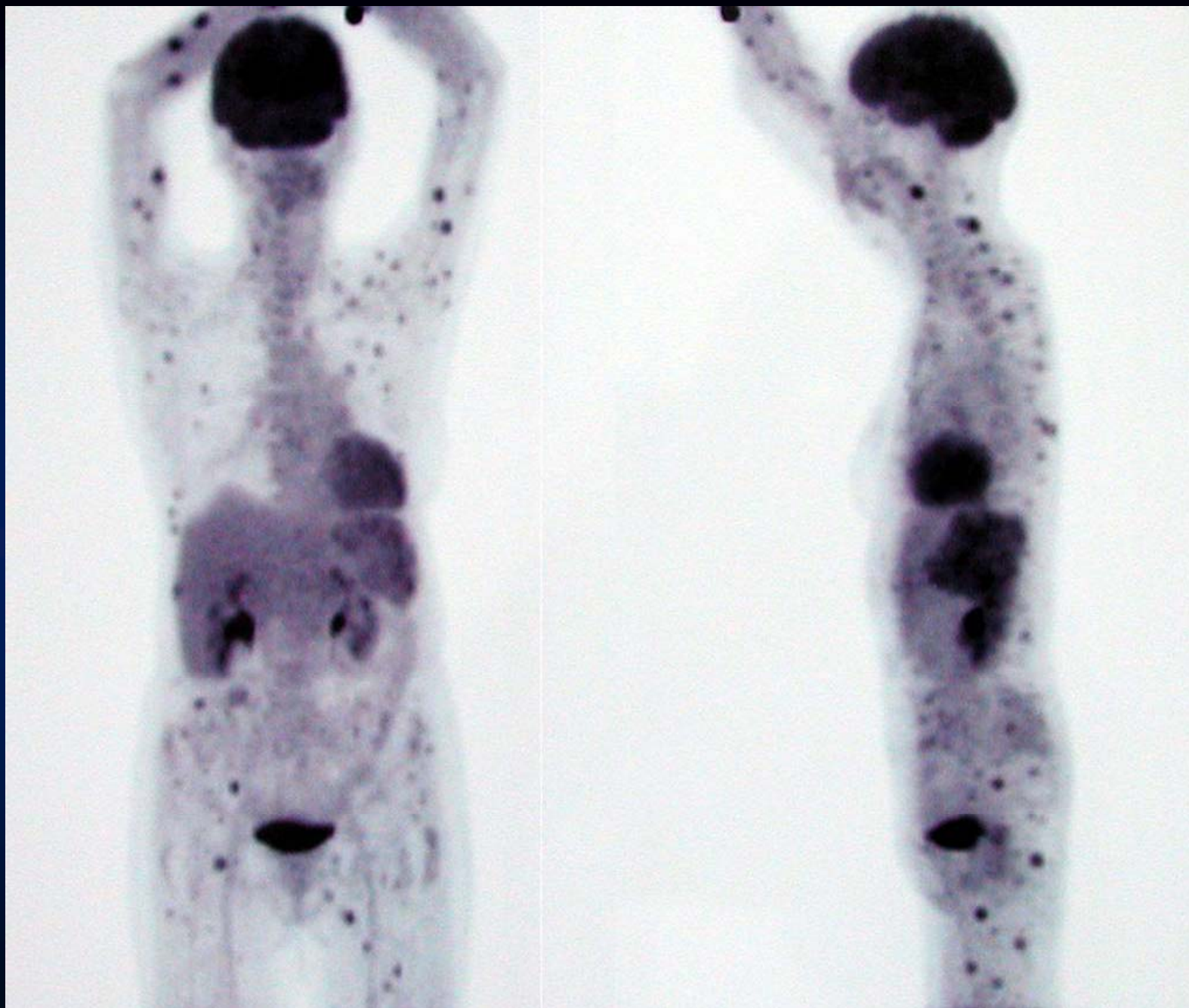


Hypothèse diagnostique ? Que proposez-vous ?

Cas clinique 1 suite

- **Biopsie hépatique**
 - **Négative en histologie**
 - **Négative en examen direct et en culture mycologique et bactériologique**
 - **Négative pour la recherche d'antigène mannane candidosique et galactomannane aspergillaire**

Hypothèse diagnostique ? Que proposez-vous ?



Cas clinique 1 2

- Femme de 60 ans
- LAM, induction classique
 - Episode fébrile non documenté pendant l'aplasie
 - Fièvre prolongée en sortie d'aplasie résistante aux antibactériens et à un antifongique à spectre large; douleurs abdominales
 - Syndrome inflammatoire biologique
 - Marqueurs négatifs (mannane candidosique, galactomannane aspergillaire)
 - PCR et bêta-D-glucane non disponibles

Hypothèse diagnostique ? Que proposez-vous ?

A10002731553
07/08/2008
14:07:21.88
2 IMA 57
SPI 2
SP 380.5

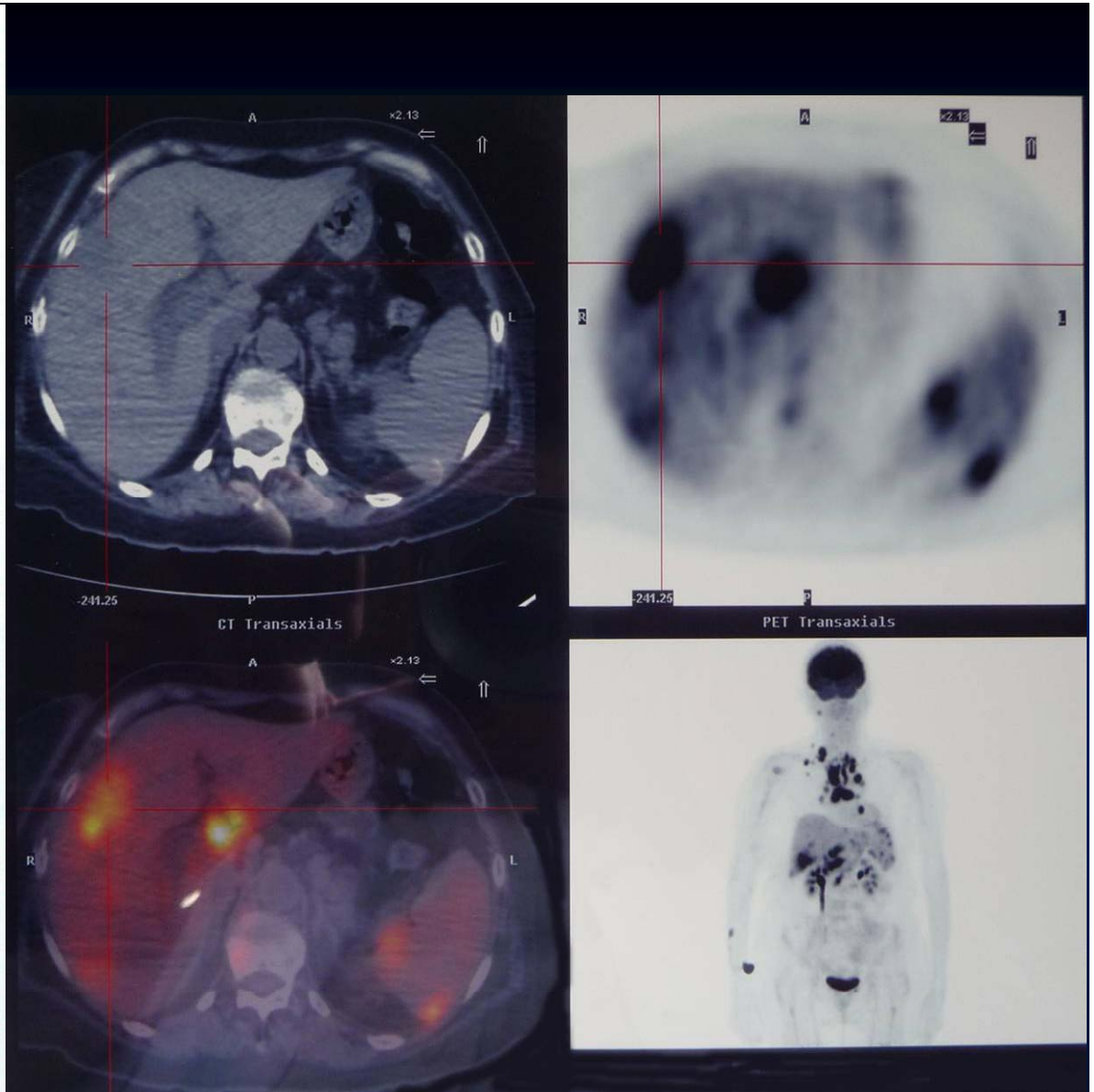
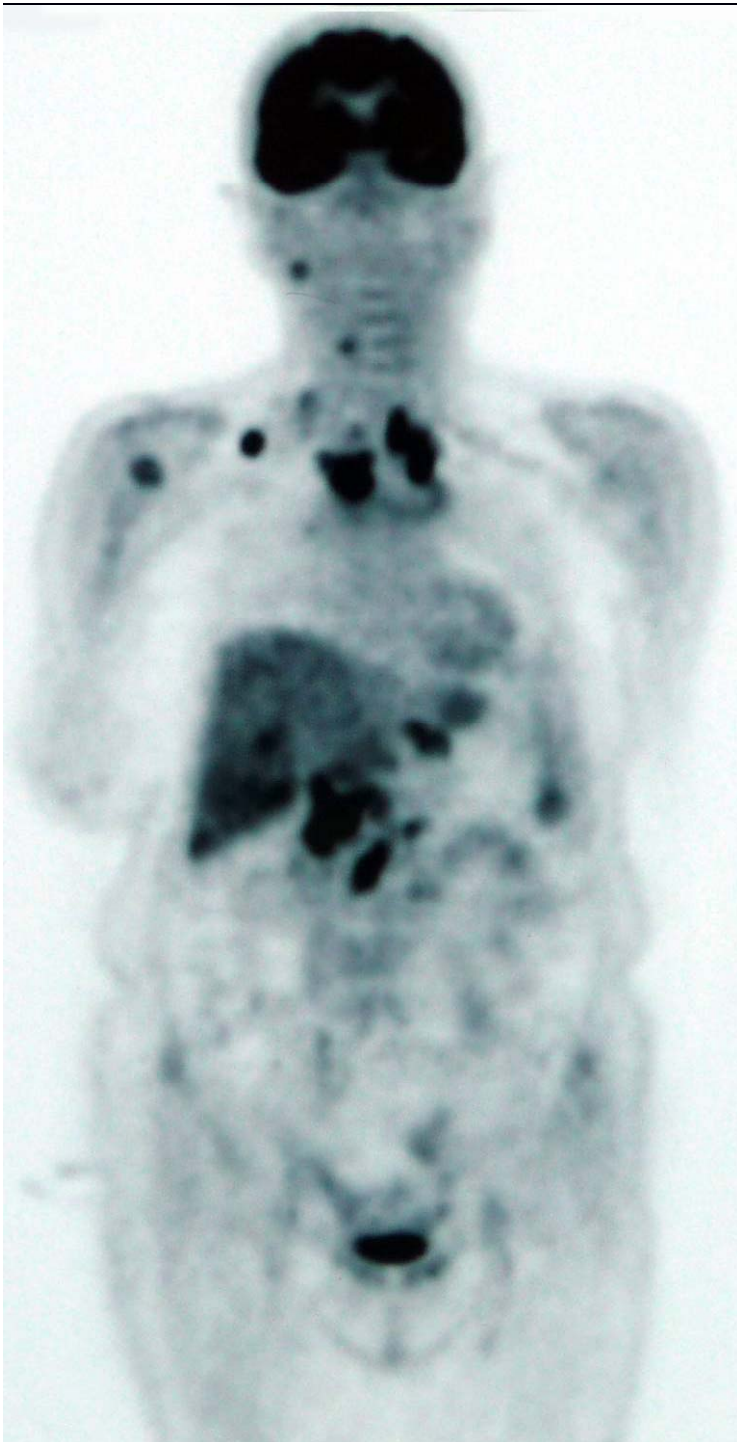
H-SP-CR #
0
1
2
S
S

R

10cm

kV 120
eff.mAs 142
TI 0.5
GT 0.0

Hypothèse diagnostique ? Que proposez-vous ?



Hypothèse diagnostique ?

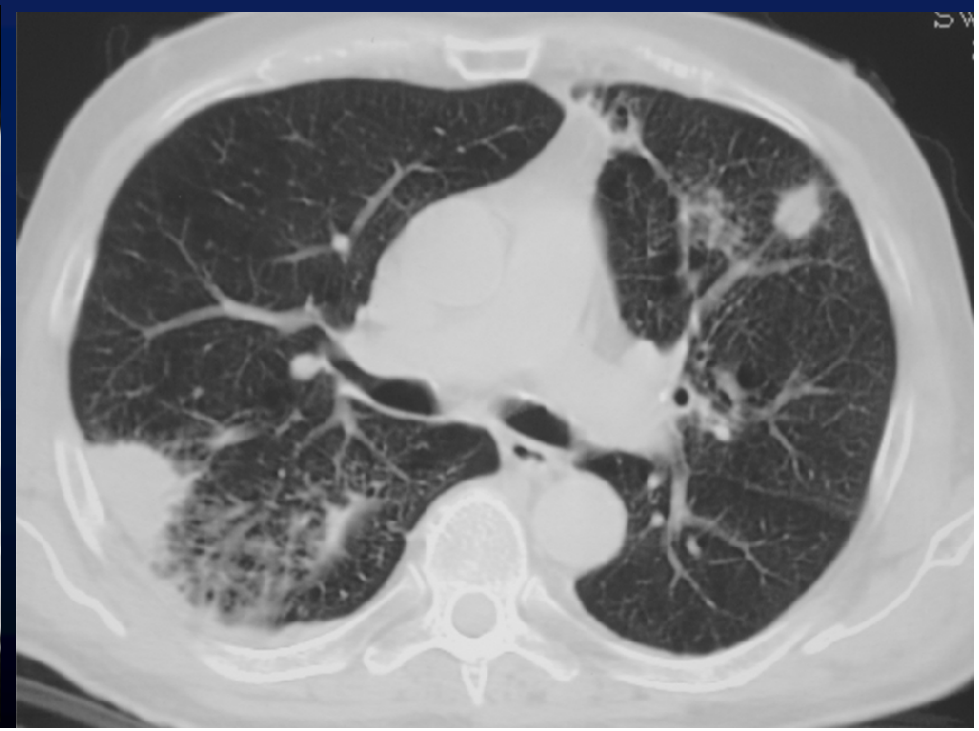
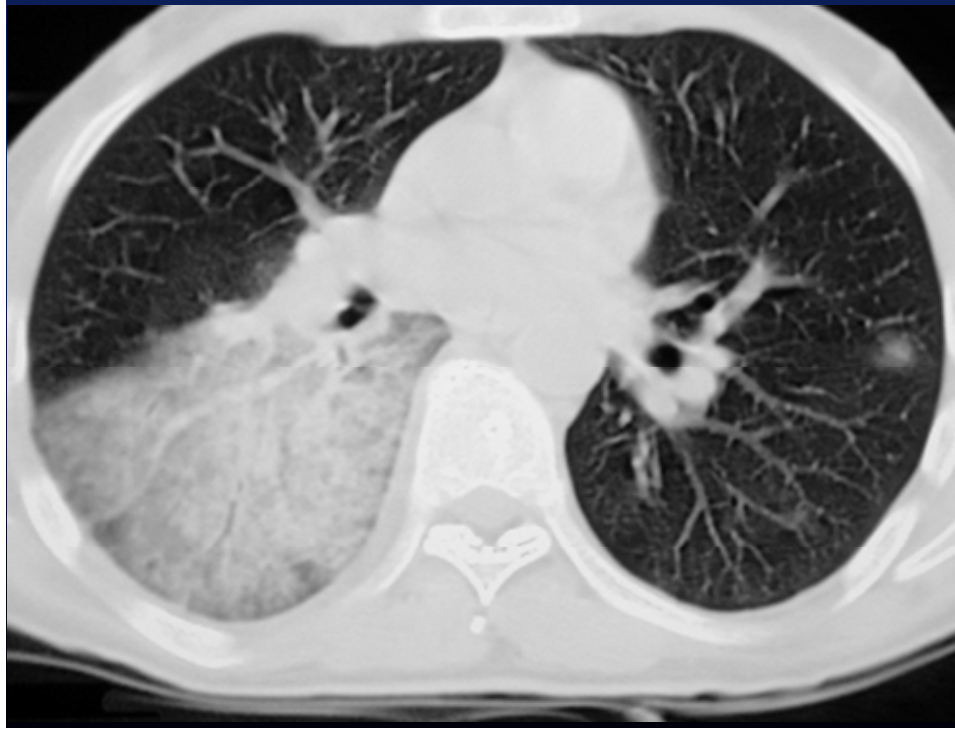
Cas clinique 2 suite

- **Biopsie hépatique**
 - **Négative en examen direct et en culture mycologique et bactériologique y compris BK**
 - **Négative pour la recherche d'antigène mannane candidosique et galactomannane aspergillaire**
 - **Granulome géantocellulaire, coloration de Ziehl négative**
 - **Apyrexie sous tuberculostatiques**

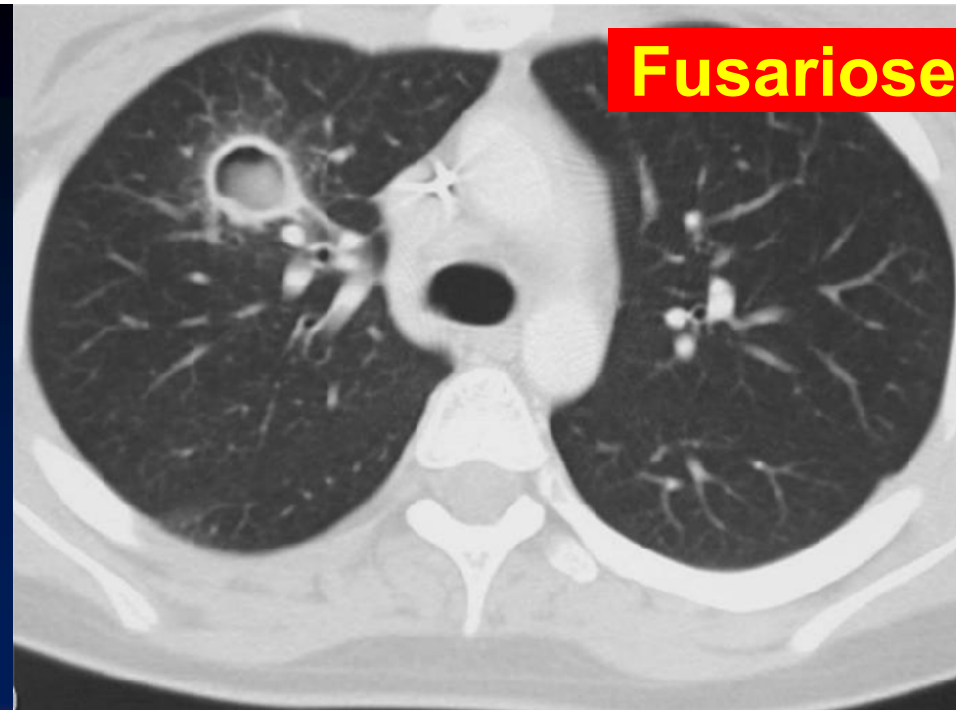
Fusariose

Aspergillose

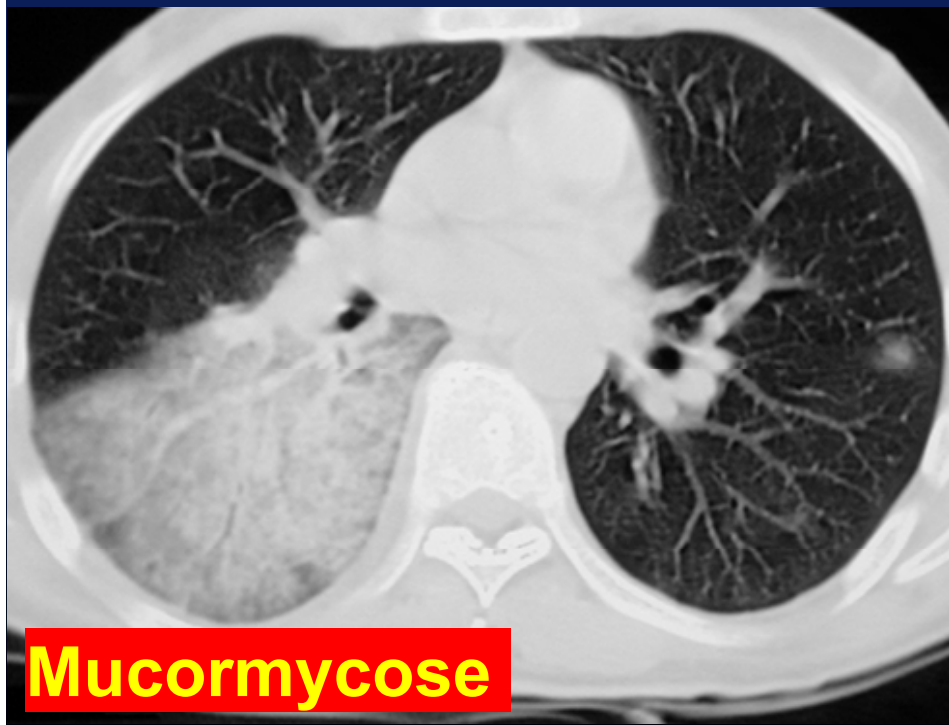
**Mucormycose
(Zygomycose)**



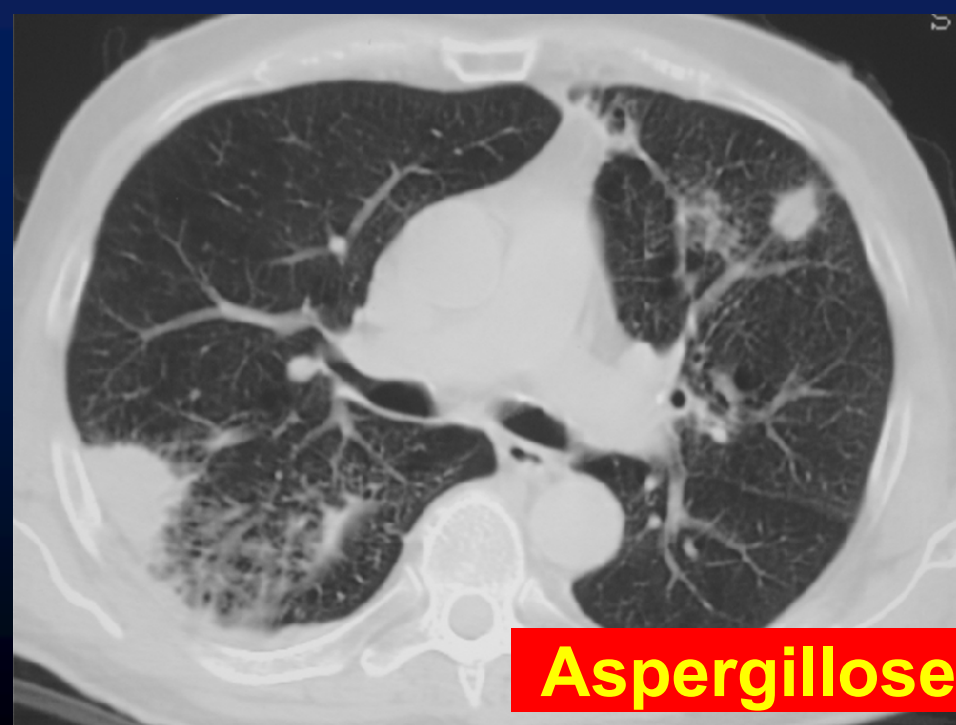
Fusariose



Mucormycoze



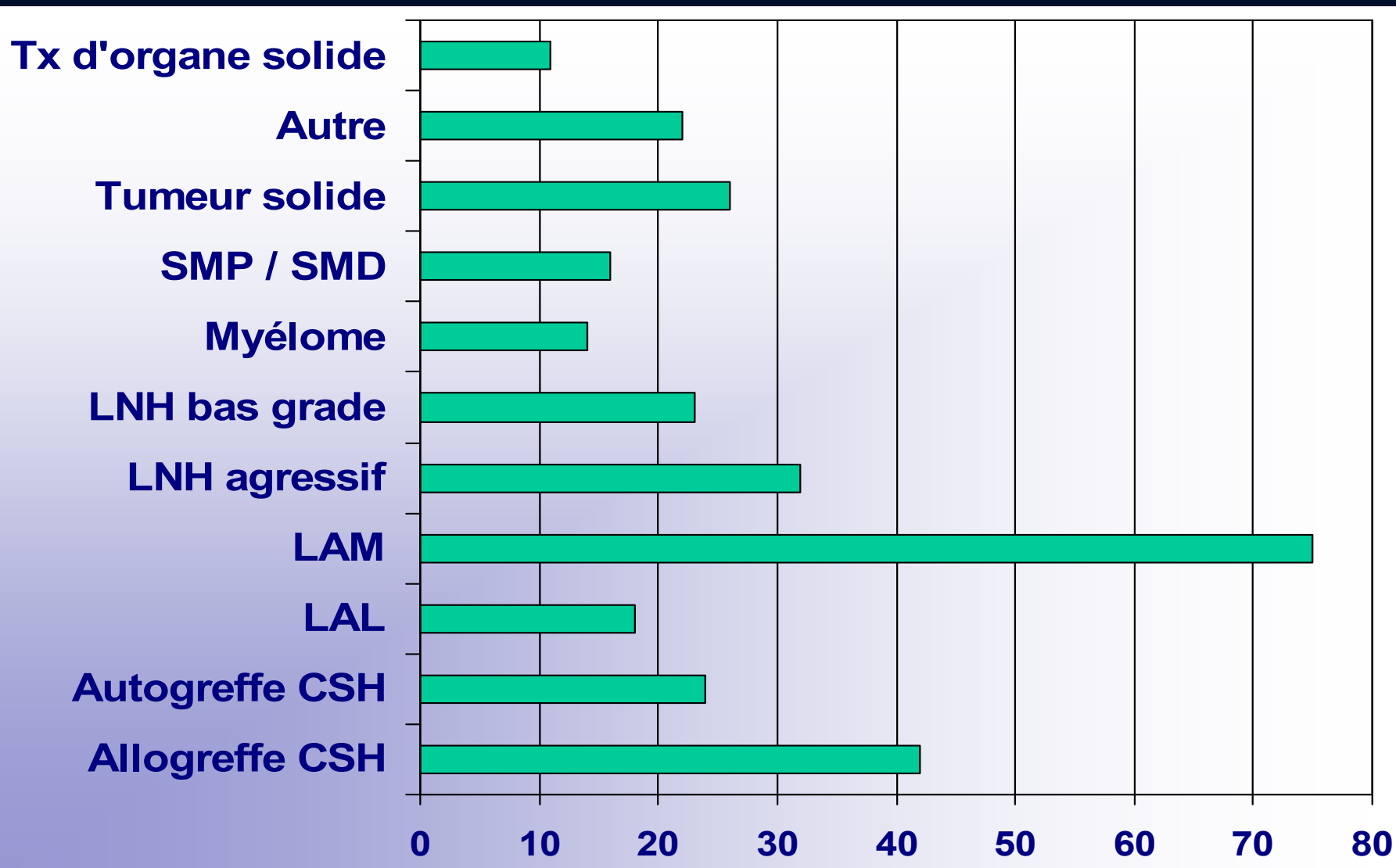
Aspergillose



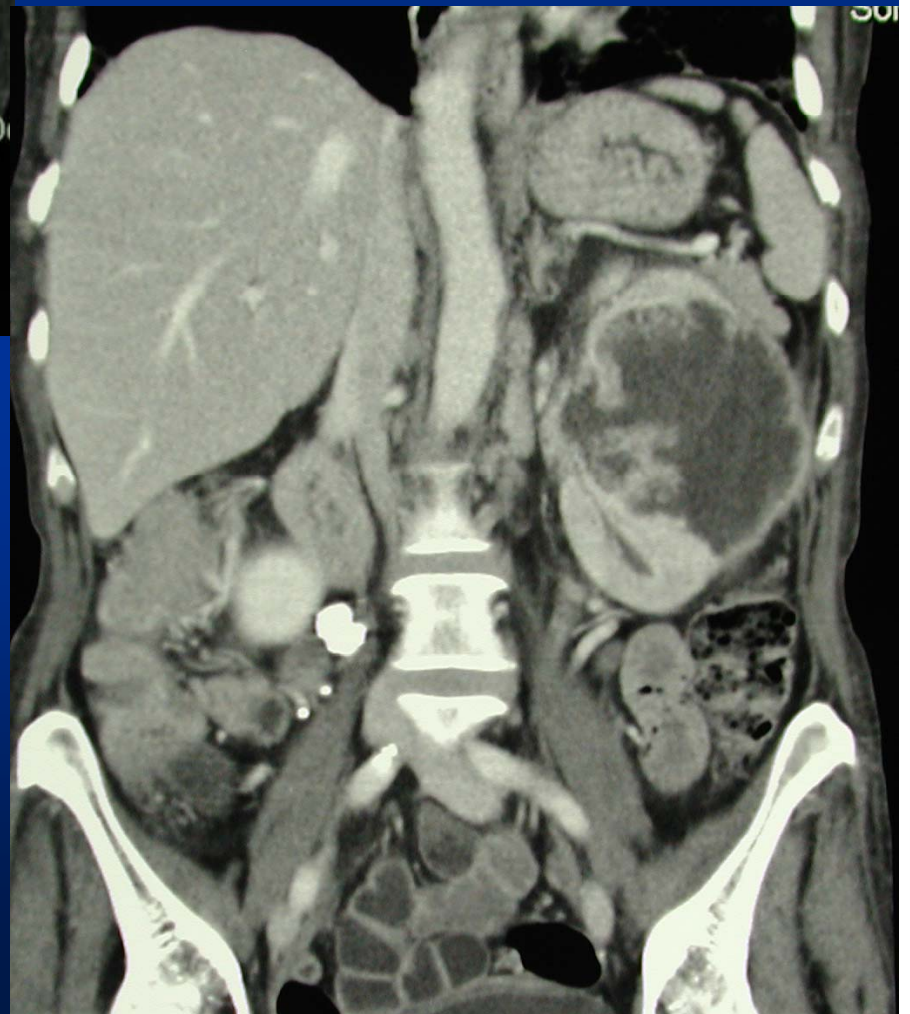
DIAGNOSTIC DES ASPERGILLOSES INVASIVES

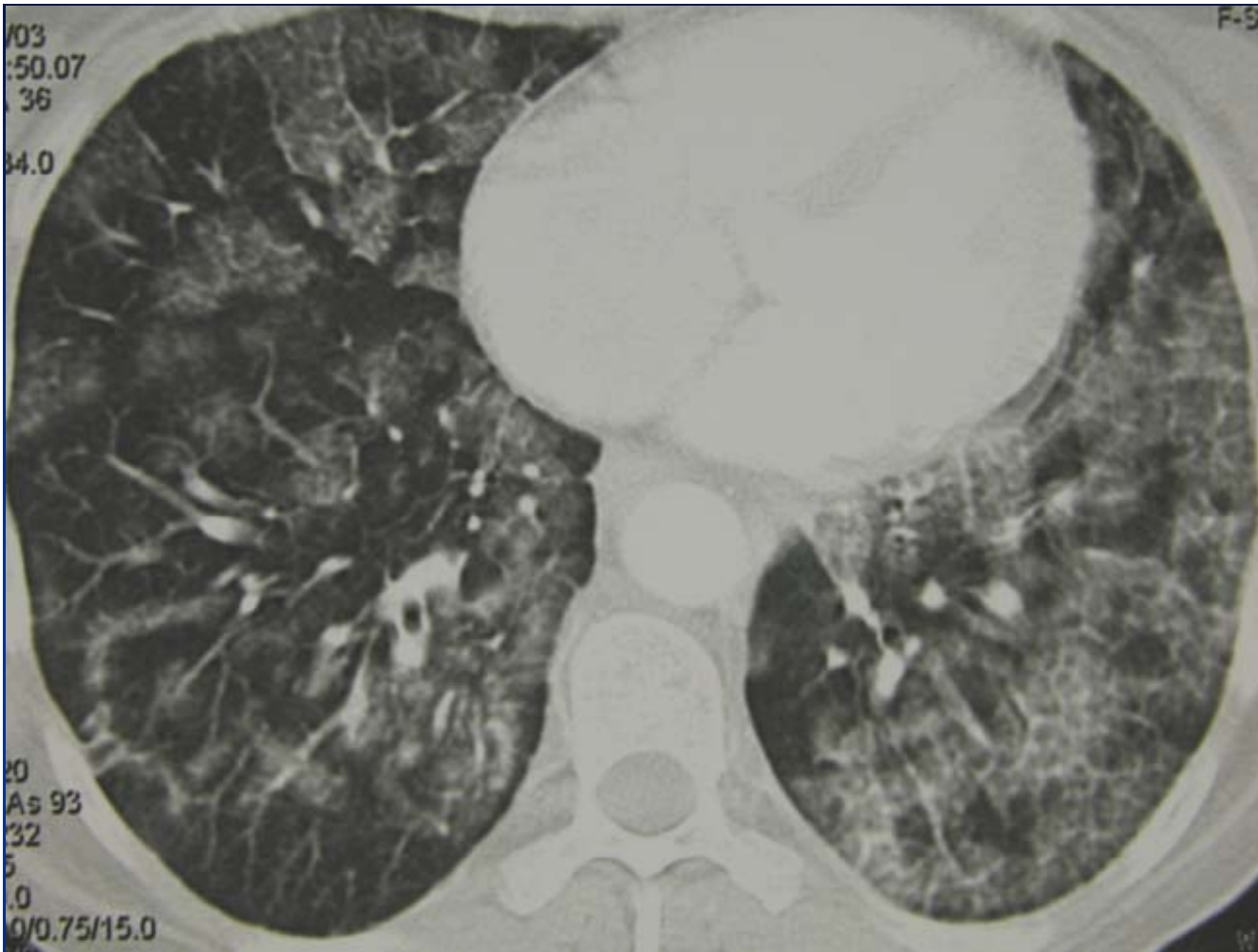
Aspergilloses invasives en onco-hématologie

Pathologie sous-jacente (série de 303 cas)



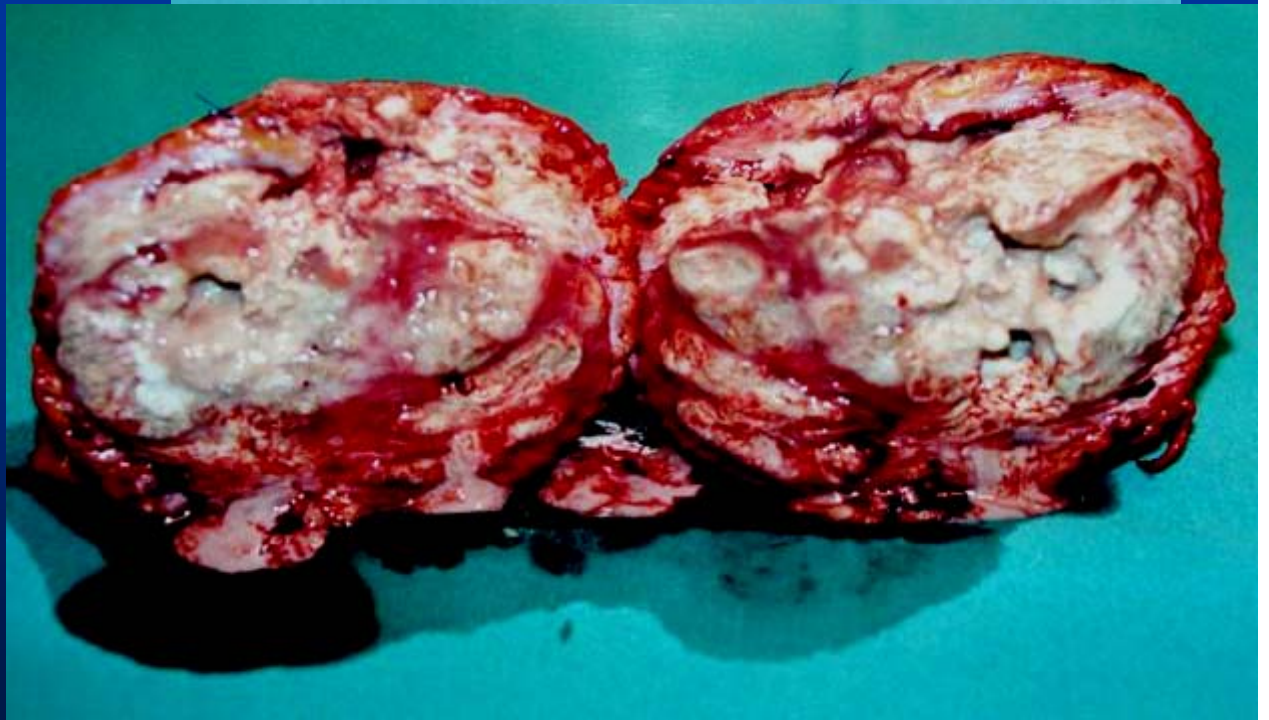
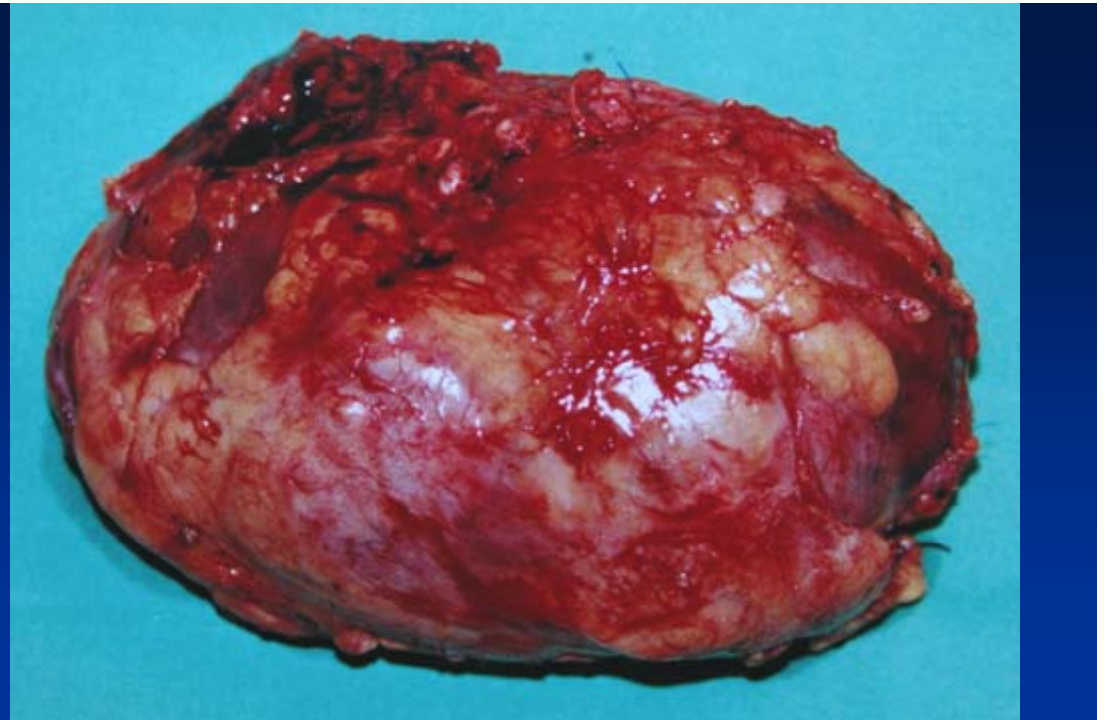
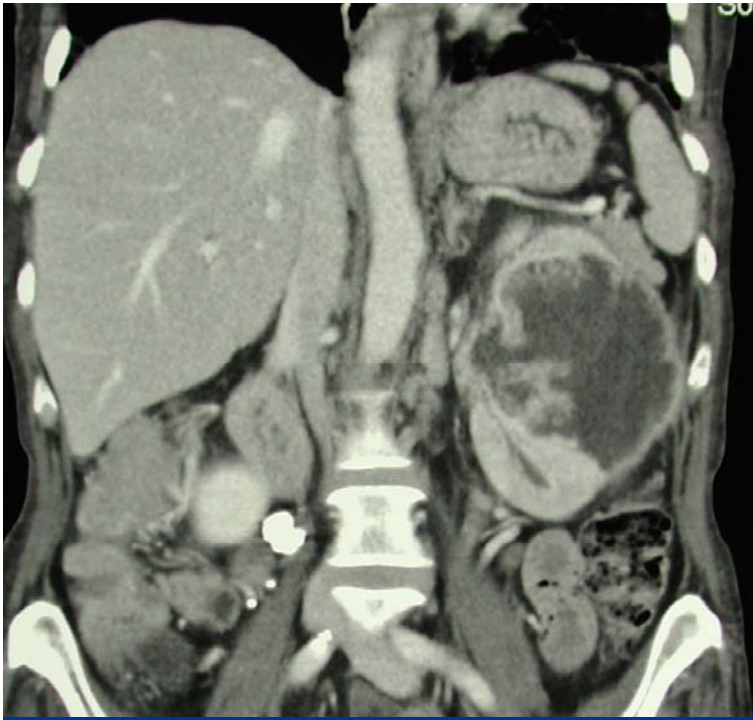
(Nivoix et al., ICAAC, 2006)





Protéïnose
alvéolaire





Patients characteristics

- Severe neutropenia 187 / 303 (62%)
- Progression of cancer 199 / 270 (74%)
- Steroids treatment 140 / 303 (46%)
- Concomitant non-infectious respiratory disease 80 / 303 (26%)
- Diabetes mellitus 55 / 303 (18%)
- Severe renal impairment 48 / 303 (16%)

(Nivoix et al., ICAAC, 2006)

Autres facteurs de risque ?

Mannose-binding lectin (MBL) deficiency- a risk factor for invasive aspergillosis in immunocompromised pts

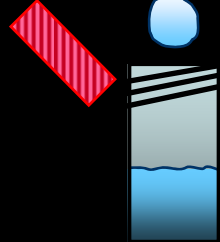
- MBL deficiency occurs in 10-15% of the population and has been identified as a susceptibility factor in animal models of aspergillosis.
- Calcium-dependent serum protein binds to carbohydrates on the surface of a viruses, bacteria, fungi, protozoa where it can activate the complement system or act directly as an opsonin.
- 65 patients with probable or proven invasive aspergillosis
- 79 immunocompromised controls with fever not due to aspergillosis.
- Deficiency in 65% of IA compared to 33% in controls (p=0.0002)

T. Harrison et al., submitted ASH 2008

Invasive aspergillosis: diagnostic procedures

Bronchoscopy

Broncho -
alveolar
lavage



Biopsy



Sputum

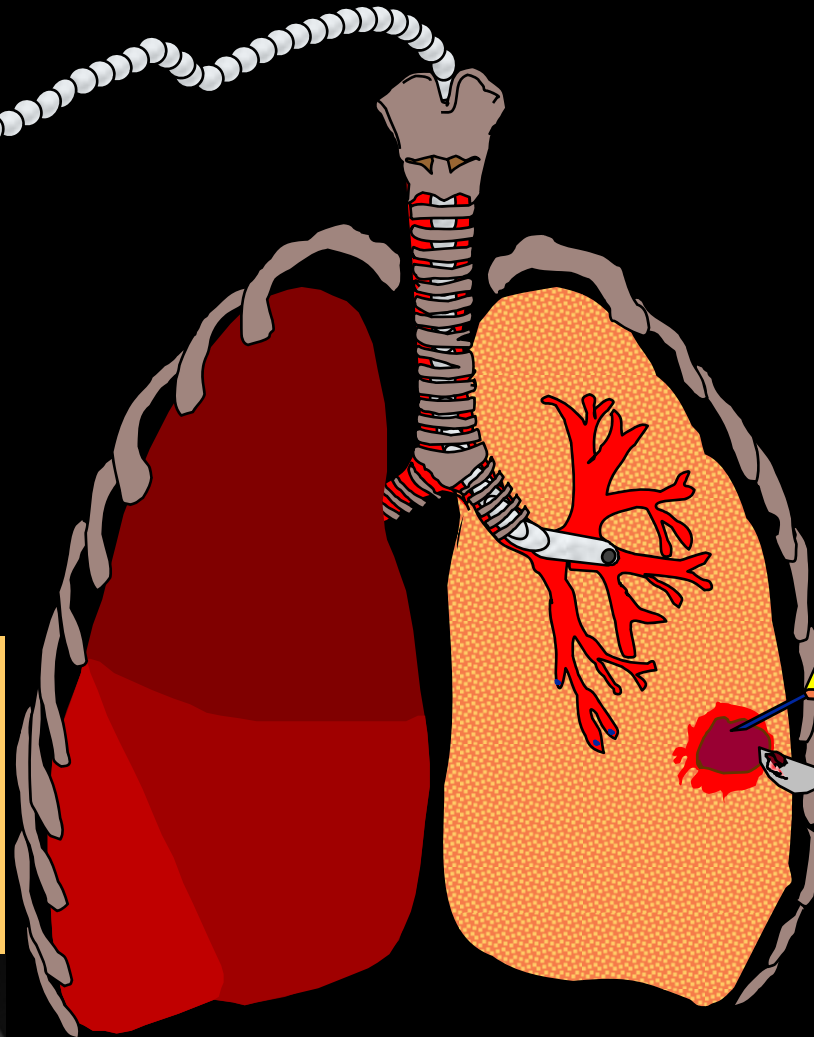
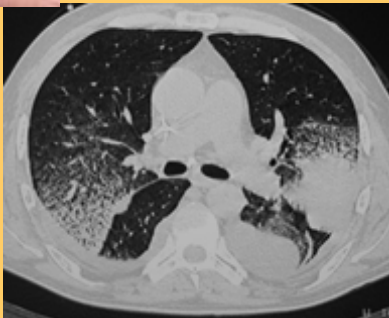


Fine
needle
aspirate

Open lung
biopsy

Antigen,
PCR
 β -glucan

CT-scan



PROPHYLAXIE

Prophylaxie

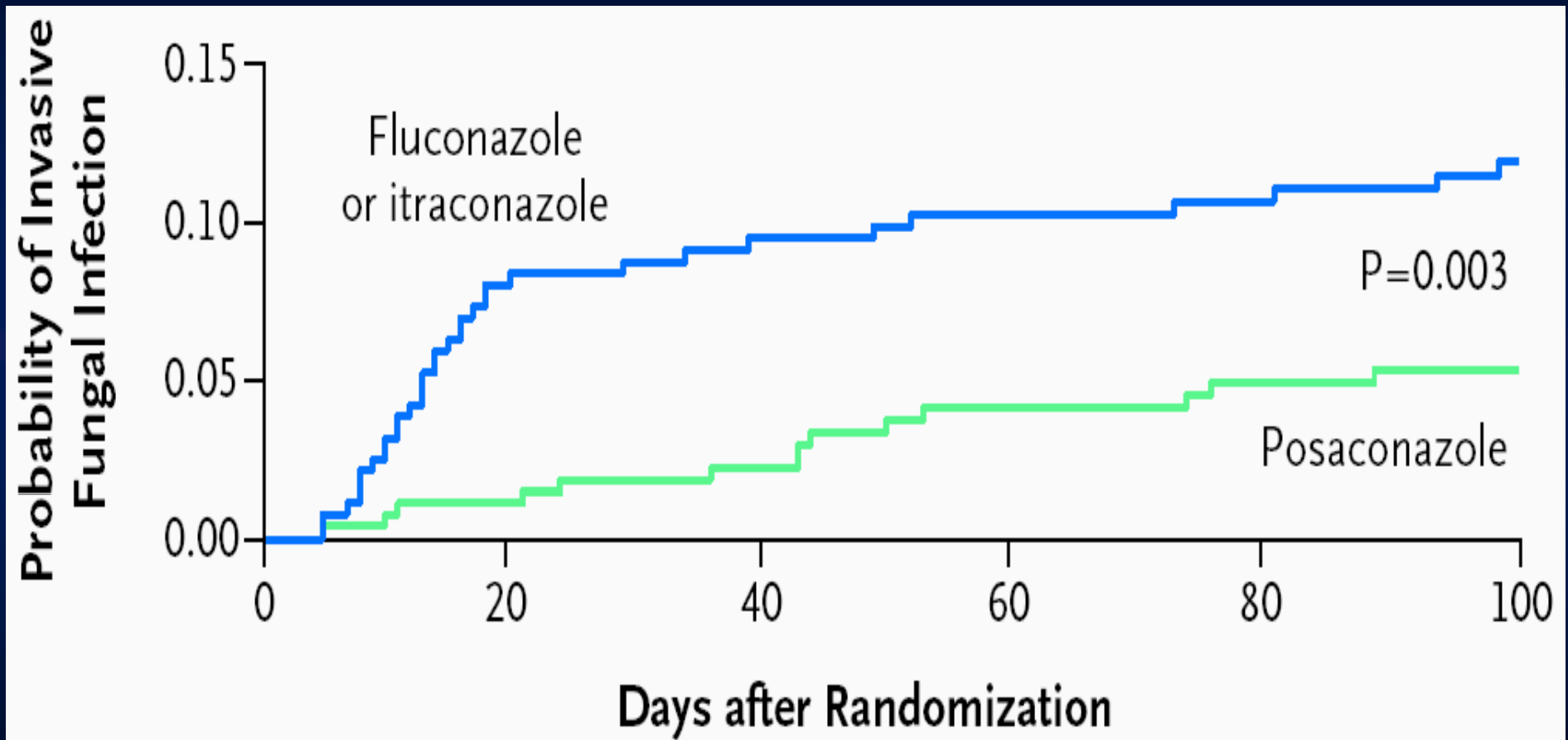
- **Amphotéricine B et ses formulations lipidiques** : pas de données convaincantes
- **Itraconazole** : efficacité avec les formulations iv et suspension buvable si taux sériques > 500 ng/ml (controverses) ; interactions médicamenteuses dont certains cytostatiques (Marr et al., Blood, 2004)
- **Micafungine** : tendance à la réduction des aspergilloses comparativement au fluconazole (p=0.07) (van Burik et al., Clin Infect Dis, 2004) ; AMM aux US pour la prévention des candidoses chez les greffés de CSH

Prophylaxie

- **Voriconazole:** une étude chez les allogreffés (versus fluconazole), moins d'aspergilloses mais pas de bénéfice en "fungal free survival" (Wingard et al., ASH 2007)
- **Posaconazole:**
 - deux belles études de prophylaxie
 - Allogreffés (Ullmann et al, NEJM, 2007)
 - Leucémies aiguës et myélodysplasies en traitement d'induction (Cornely et al., NEJM, 2007)

Leucémies aiguës / myélodysplasies

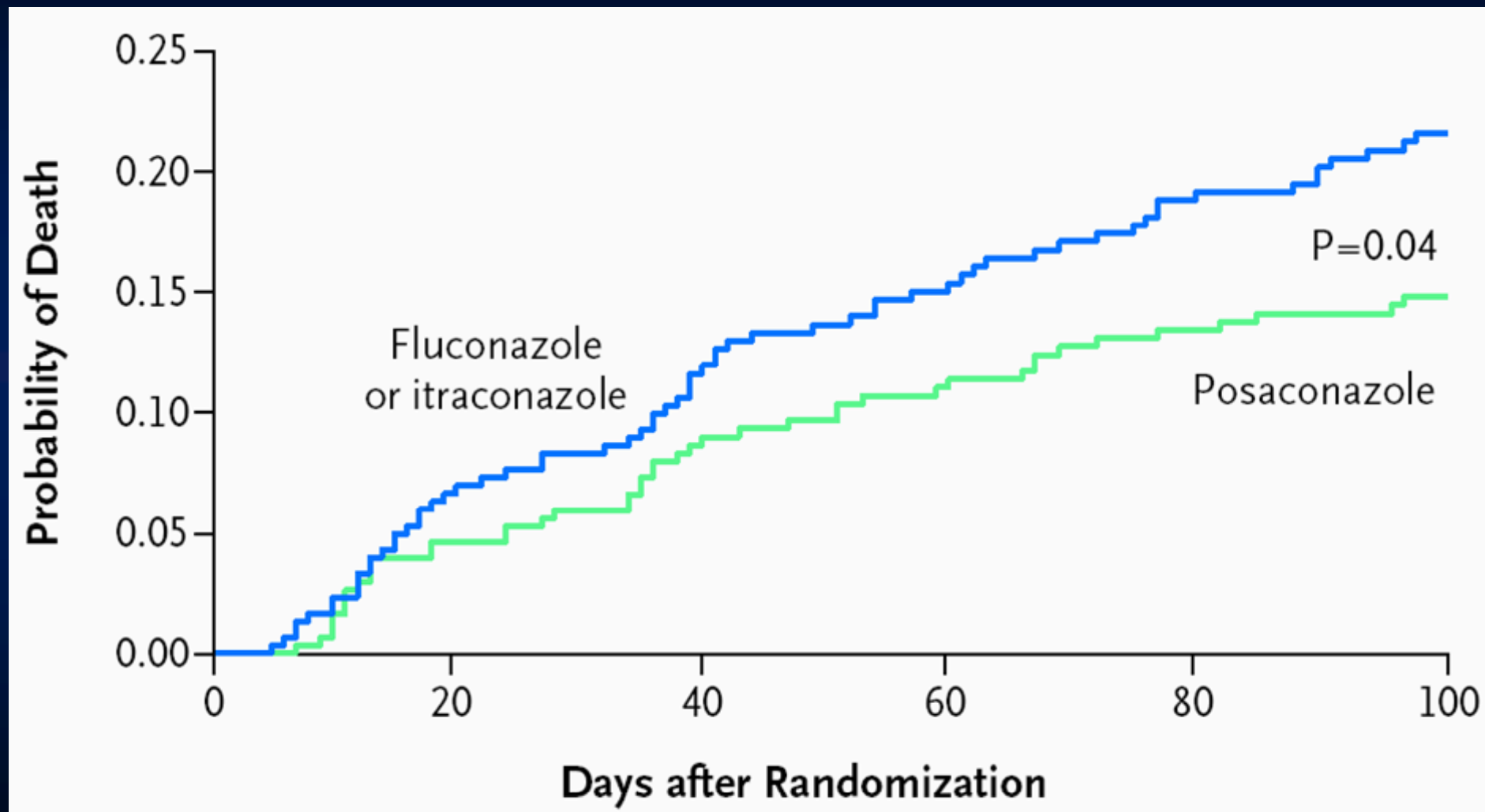
Probabilité d'infection fongique



Cornely et al., NEJM, 2007)

Leucémies aiguës / Myélodysplasies

Décès toutes causes confondues



Cornely et al., NEJM, 2007)

British Society for Medical Mycology proposed standards of care for patients with invasive fungal infections

David W Denning, Christopher C Kibbler, and Rosemary A Barnes on behalf of the British Society for Medical Mycology

THE LANCET Infectious Diseases Vol 3 April 2003

Treatment options of invasive fungal infections in adults

Ursula Flückiger^{a}, Oscar Marchetti^{b*}, Jacques Bille^c, Philippe Eggimann^d, Stefan Zimmerli^e,
Alexander Imhoff^f, Jorge Garbino^g, Christian Rueff^f, Didier Pittet^b, Martin Tüüber^e, Michel Glauser^b,
Thierry Calandra^b for the Fungal Infection Network of Switzerland (FUNGINOS)*

Ann Hematol (2003) 82 (Suppl 2):S133-S140
DOI 10.1007/s00277-003-0767-1

**Angelika Böhme · Markus Ruhnke · Dieter Buchheidt ·
Meinolf Karthaus · Hermann Einsele · Stefan Guth ·
Gudrun Heussel · Claus-Peter Heussel ·
Christian Junghanss · Winfried K. Kern ·
Thomas Kubin · Georg Maschmeyer · Orhan Sezer ·
Gerda Silling · Thomas Südhoff · Hubert Szelényi† ·
Andrew J. Ullmann**

Treatment of fungal infections in hematology and oncology

**Guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society
of Hematology and Oncology (DGHO)**

Internal Medicine Journal 2004; 34: 192–200

REVIEW

Guidelines for the use of antifungal agents in the treatment of invasive *Candida* and mould infections

M. A. SLAVIN,^{1,3,5} J. SZER,² A. P. GRIGG,² A. W. ROBERTS,² J. F. SEYMOUR,³ J. SASADEUSZ,¹ K. THURSKY,^{1,3} S. C. CHEN,⁴ C. O. MORRISSEY,⁵ C. H. HEATH⁶ and T. SORRELL⁴

DOCUMENTO DE CONSENSO

Recomendaciones para el tratamiento de la infección por *Aspergillus* spp.

Joan Gavaldà e Isabel Ruiz por parte de los Grupos de Estudio de Micología Médica (MICOMED) y de Infección en el Trasplante (GESITRA) de la Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC)

Enferm Infecc Microbiol Clin 2003;21(10):571-8

Jpn. J. Med. Mycol.
Vol. 45, 209—215, 2004
ISSN 0916—4804

総 説

好中球減少患者における診療指針

吉 田 稔

帝京大学医学部附属溝口病院第4内科

organisée conjointement par

la SFAR, la SPILF et la SRLF

Prise en charge des candidoses et aspergilloses invasives de l'adulte

avec la participation de la Société Française d'Hématologie,
de la Société Française de Mycologie Médicale
et de la Société Française de Greffe de Moelle

Treatment of Aspergillosis: Clinical Practice Guidelines of the Infectious Diseases Society of America

Thomas J. Walsh,^{1,a} Elias J. Anaissie,² David W. Denning,¹³ Raoul Herbrecht,¹⁴ Dimitrios P. Kontoyiannis,³ Kieren A. Marr,⁵ Vicki A. Morrison,^{6,7} Brahm H Segal,⁸ William J. Steinbach,⁹ David A. Stevens,^{10,11} Jo-Anne van Burik,⁷ John R. Wingard,¹² and Thomas F. Patterson^{4,a}

Clinical Infectious Diseases 2008;46:327–60

Guidelines for Treatment of Candidiasis

Peter G. Pappas,¹ John H. Rex,² Jack D. Sobel,³ Scott G. Filler,⁴ William E. Dismukes,¹ Thomas J. Walsh,⁵ and John E. Edwards⁴

Clinical Infectious Diseases 2004;38:161–89



**1st
European
Conference on
Infection in
Leukemia**

Antifungal therapy

Ursula Flückiger, Patricia Ribaud, Anne Thiebaut,
Bertrand Gachot, Raoul Herbrecht

Sept. 30th / Oct. 1st 2005 Juan-les-Pins - France



IDSA grading system

Strength of recommendation

- A Good evidence to support a recommendation for use
- B Moderate evidence to support a recommendation for use
- C Poor evidence to support a recommendation

Quality of evidence

- I Evidence from ≥ 1 properly randomized, controlled trial
- II Evidence from ≥ 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments
- III Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

IDSA Guidelines 2008

Primary Therapy of Invasive Aspergillosis

Products		Rating
Voriconazole	Preferred therapy Voriconazole is recommended for the primary treatment of invasive aspergillosis in most patients	A-I
	Oral therapy can be maximized by using a dose of 4 mg/kg rounded up to convenient pill sizes	B-III
	For seriously ill patients, the parenteral formulation is recommended	A-III
	Caution is advised when using the IV formulation in patients with renal impairment	C-III

IDSA Guidelines 2008

Primary Therapy of Invasive Aspergillosis

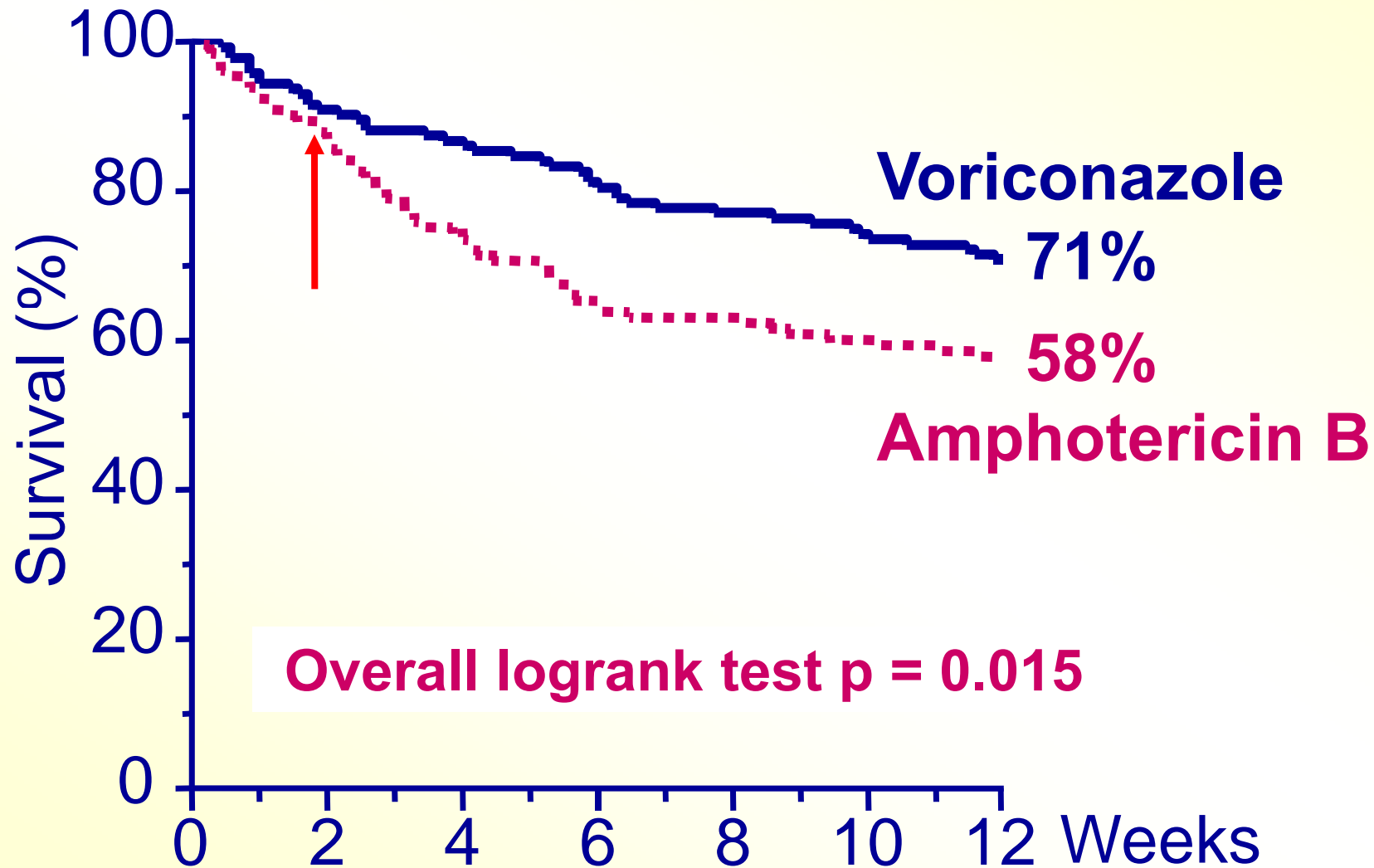
Products		Rating
Triazoles	The committee recommends that determination of a plasma drug level, in conjunction with other measures of clinical assessment, may be another factor in evaluating reasons for therapeutic failure attributable to suboptimal drug exposures or for toxicity attributable to the drug	B-III

IDSA Guidelines 2008

Primary Therapy of Invasive Aspergillosis

Products		Rating
Liposomal amphotericin B	Alternative A randomized trial comparing two dosages of liposomal amphotericin B showed similar efficacy in both arms, suggesting that liposomal therapy could be considered as alternative primary therapy in some patients	A-I

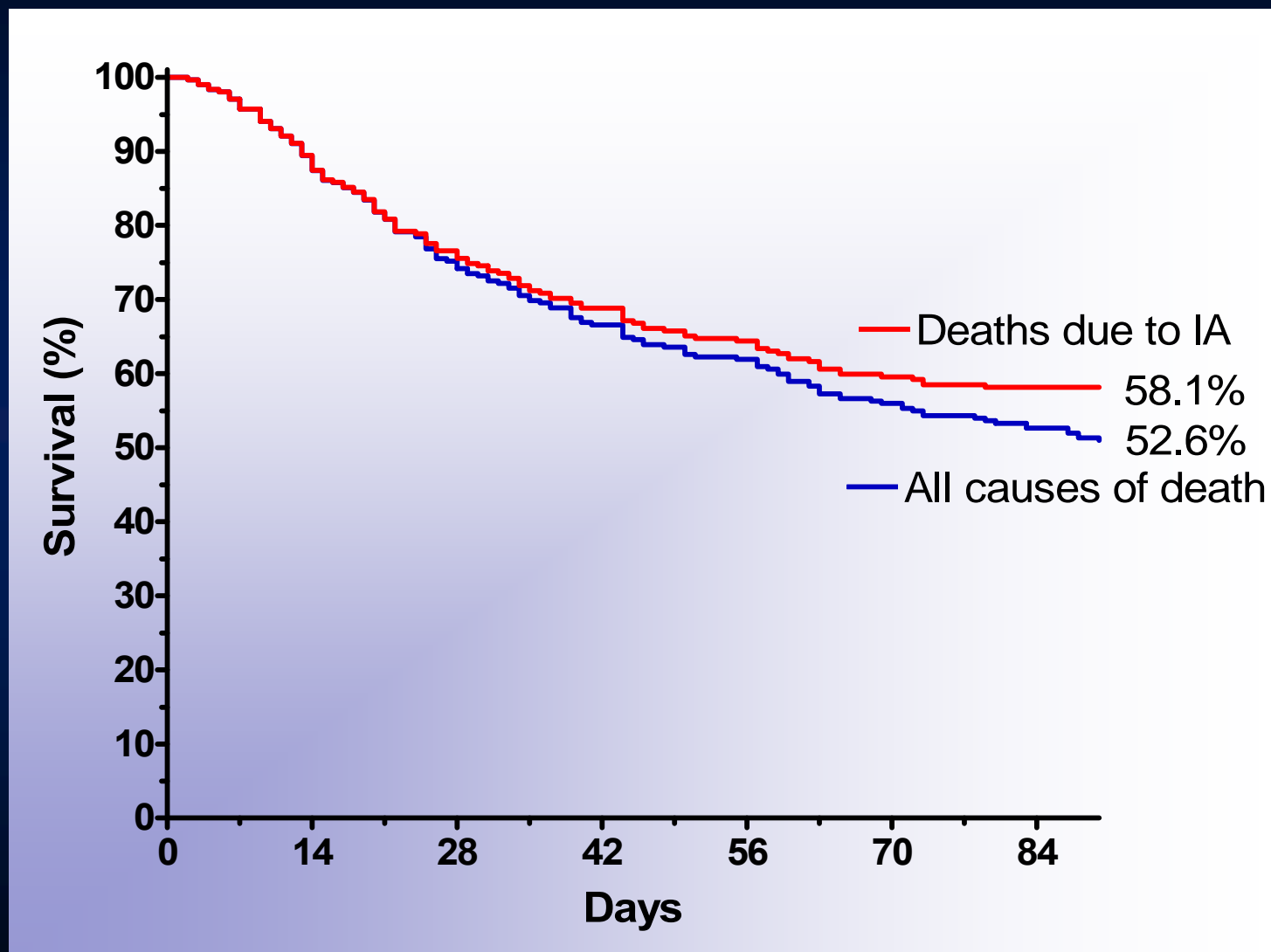
Overall survival (277 patients)



(Herbrecht et al., N Engl J Med 2002, 347: 408 - 415)

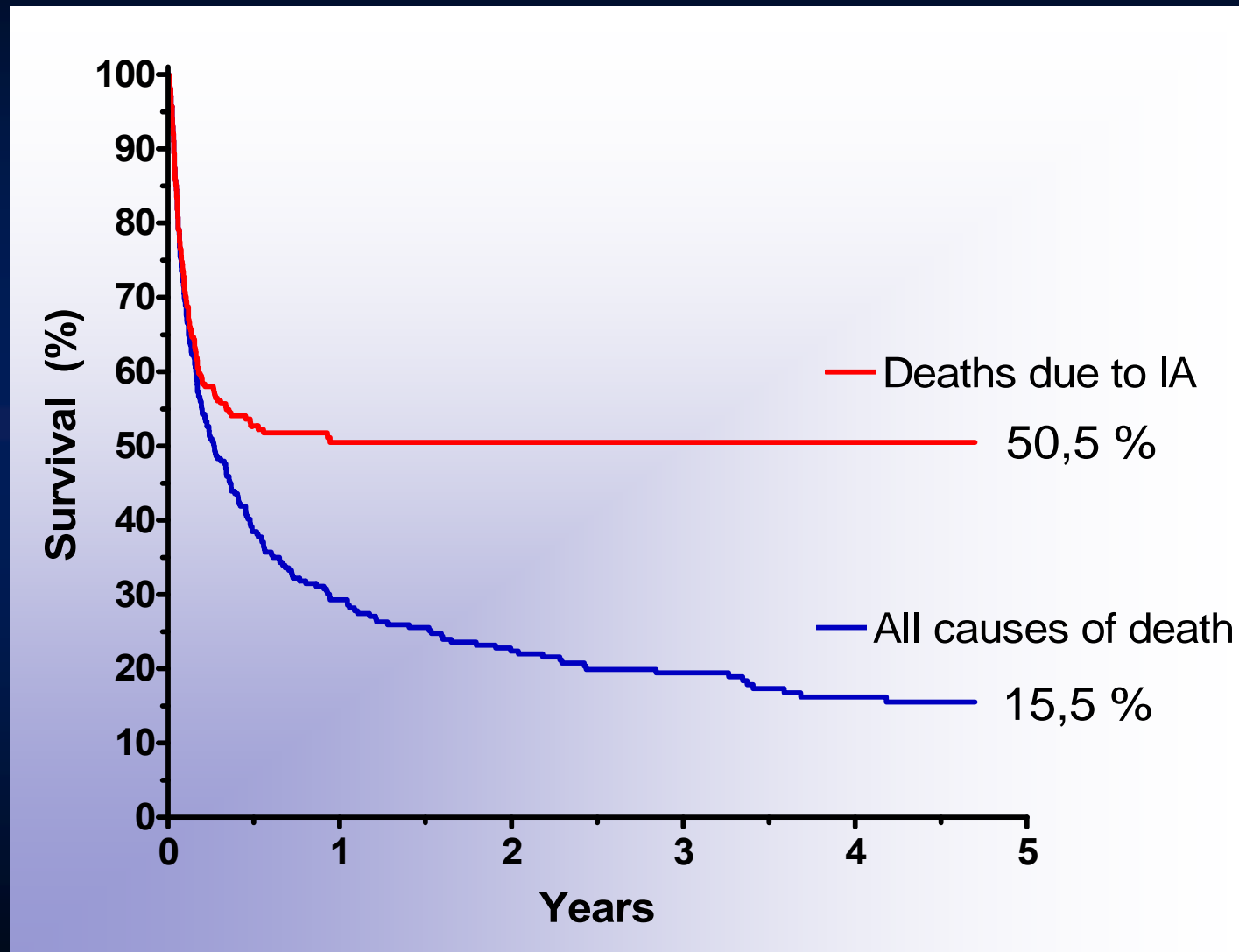
LES ASPERGILLOSES DANS LA VRAIE VIE

Overall and specific survival (censored at 12 weeks; 303 patients)



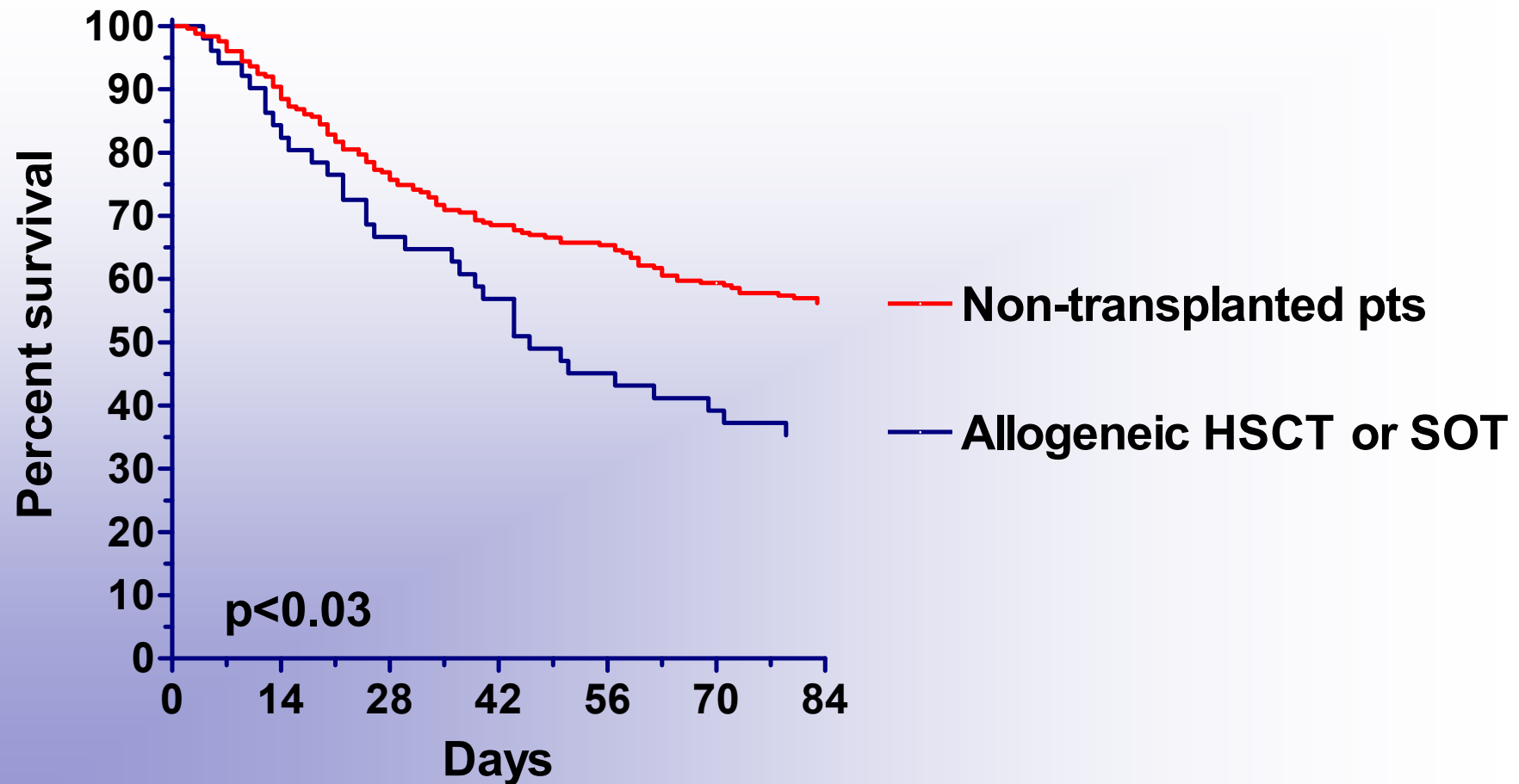
(Nivoix et al., ICAAC, 2006)

Overall and specific long term survival in 303 patients



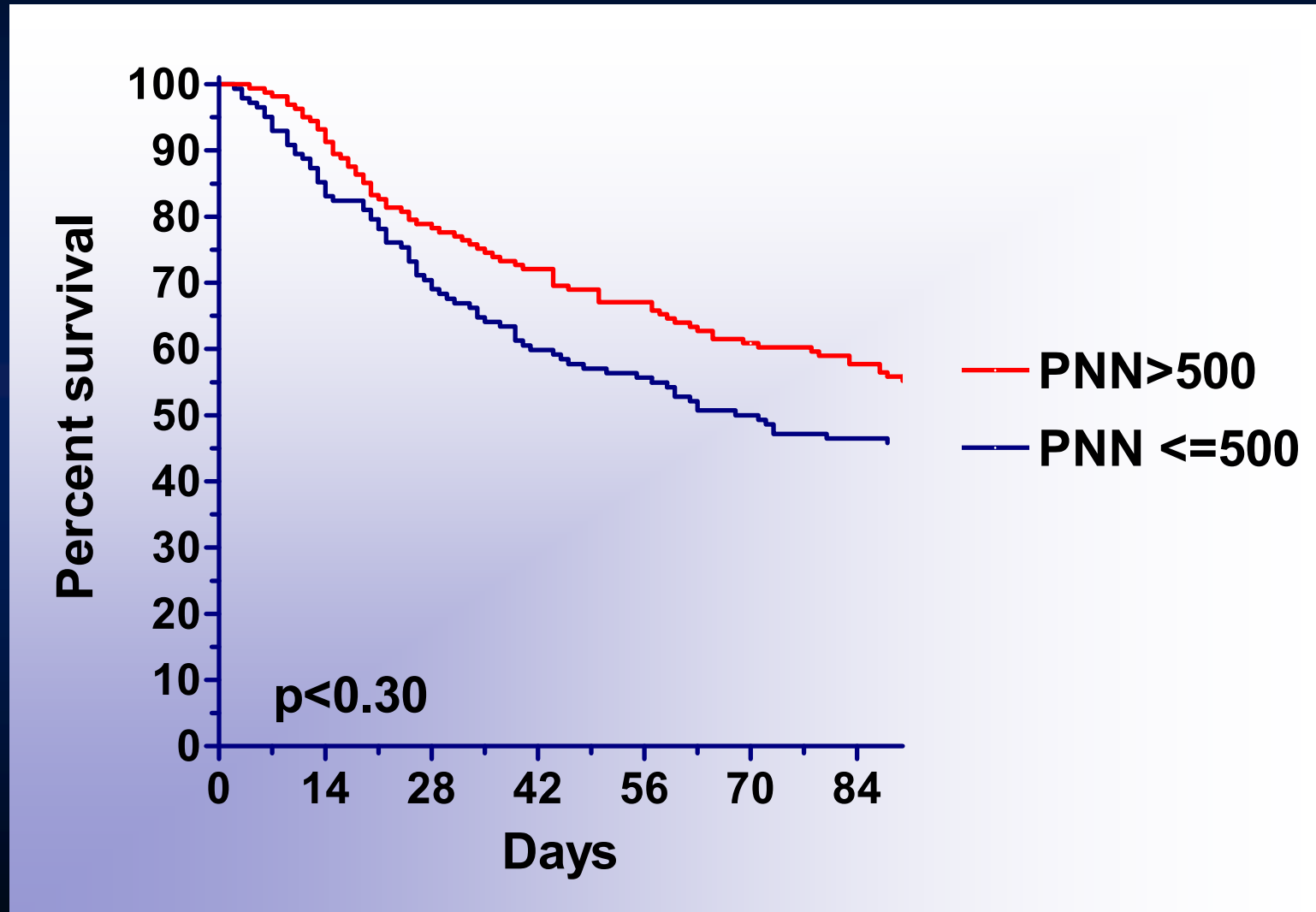
(Nivoix et al., ICAAC, 2006)

12-week overall survival according to underlying condition



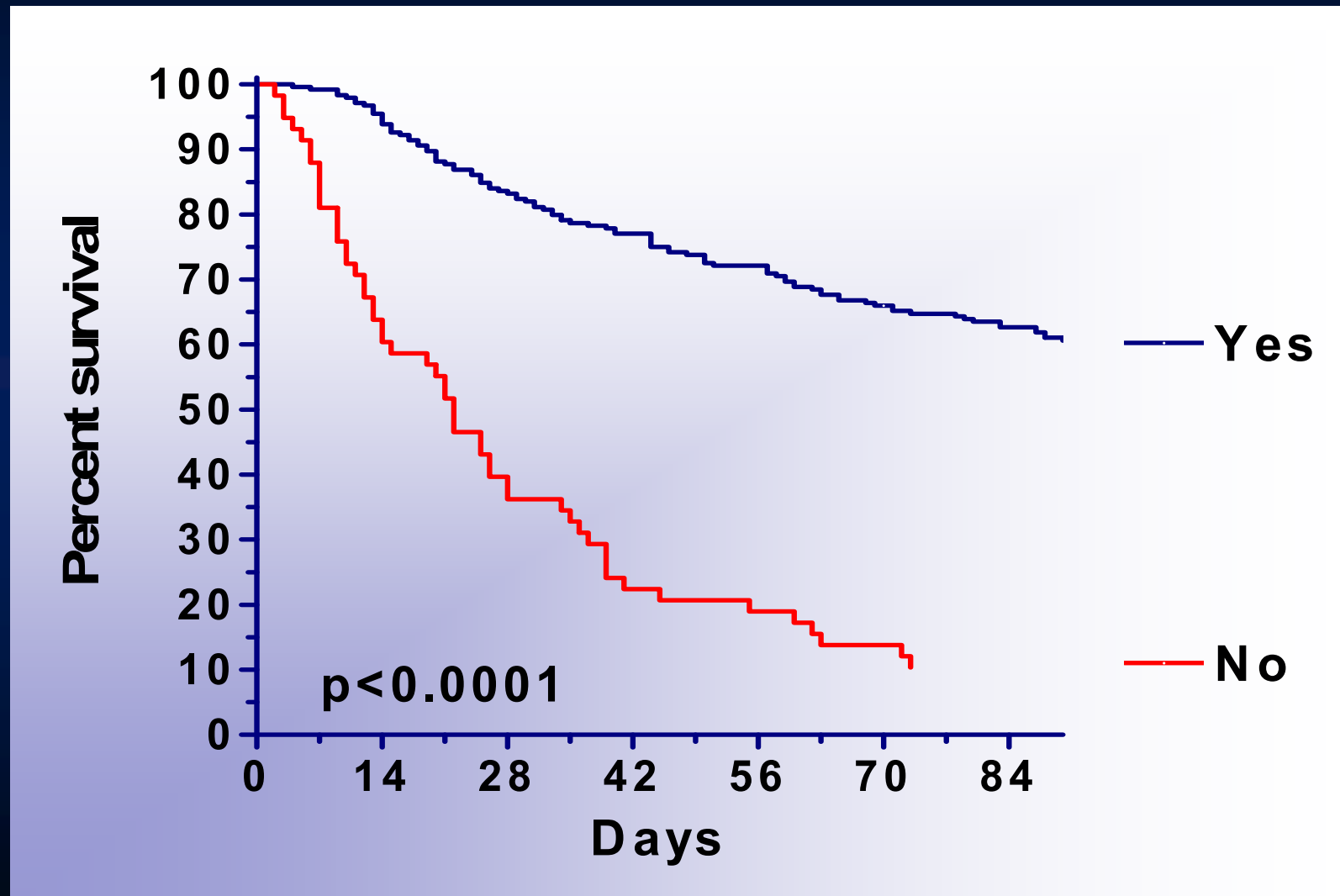
(Nivoix et al., ASH, 2006)

12-week overall survival according to baseline neutrophil count



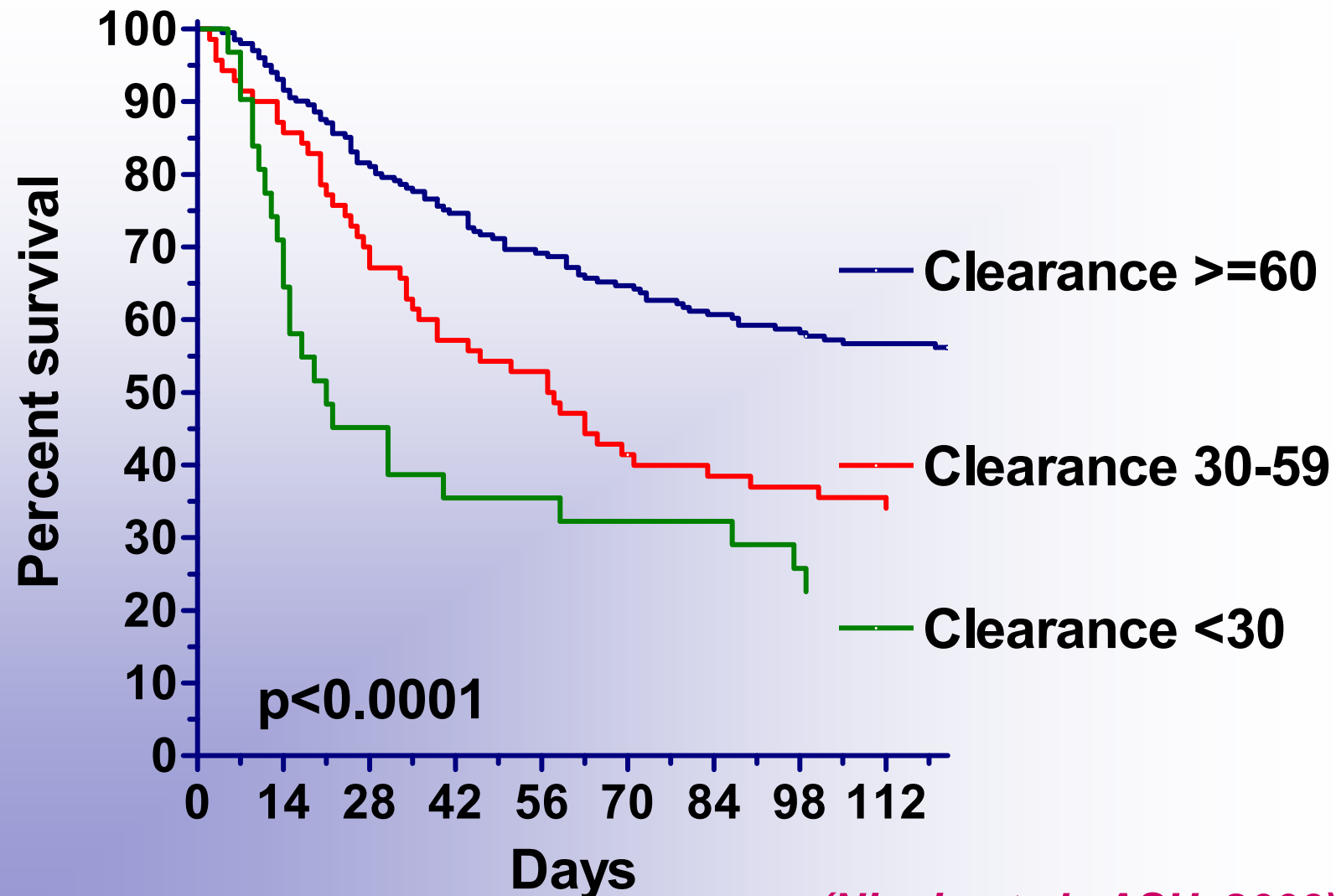
(Nivoix et al., ASH, 2006)

12-week overall survival according to recovery of neutropenia



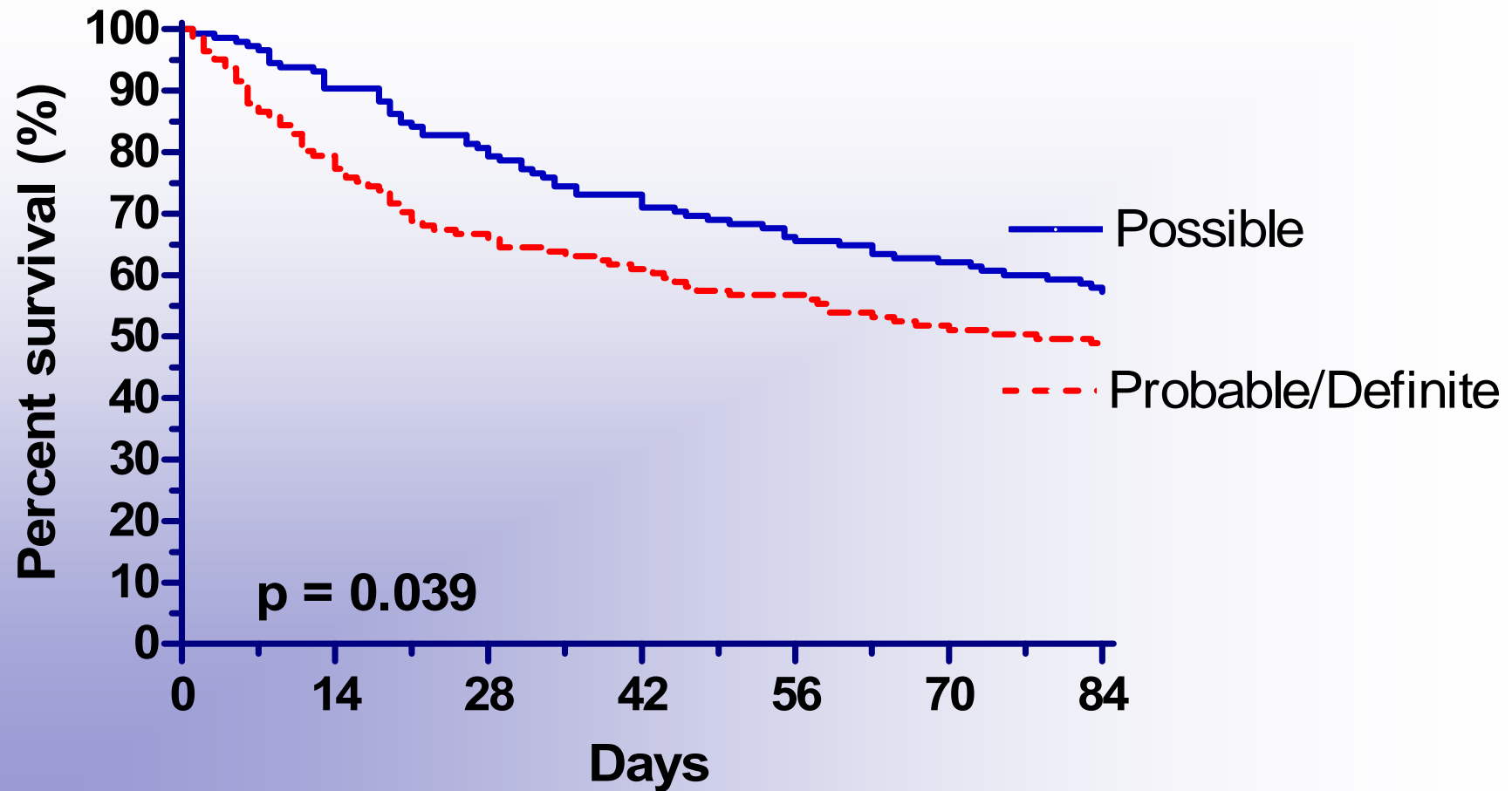
(Nivoix et al., ASH, 2006)

12-week overall survival according to baseline renal function



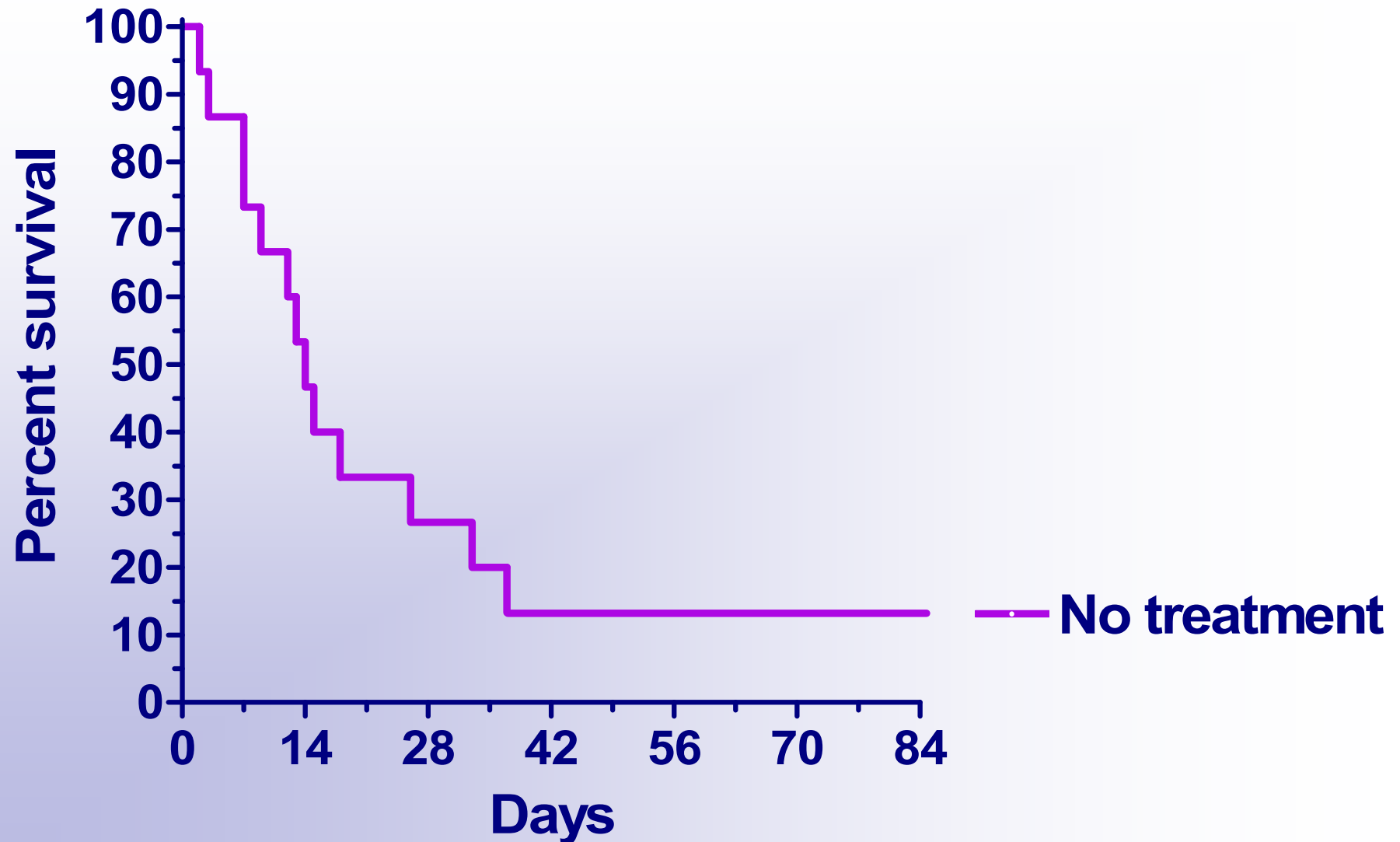
(Nivoix et al., ASH, 2006)

12-week overall survival according to level of certainty at onset of therapy

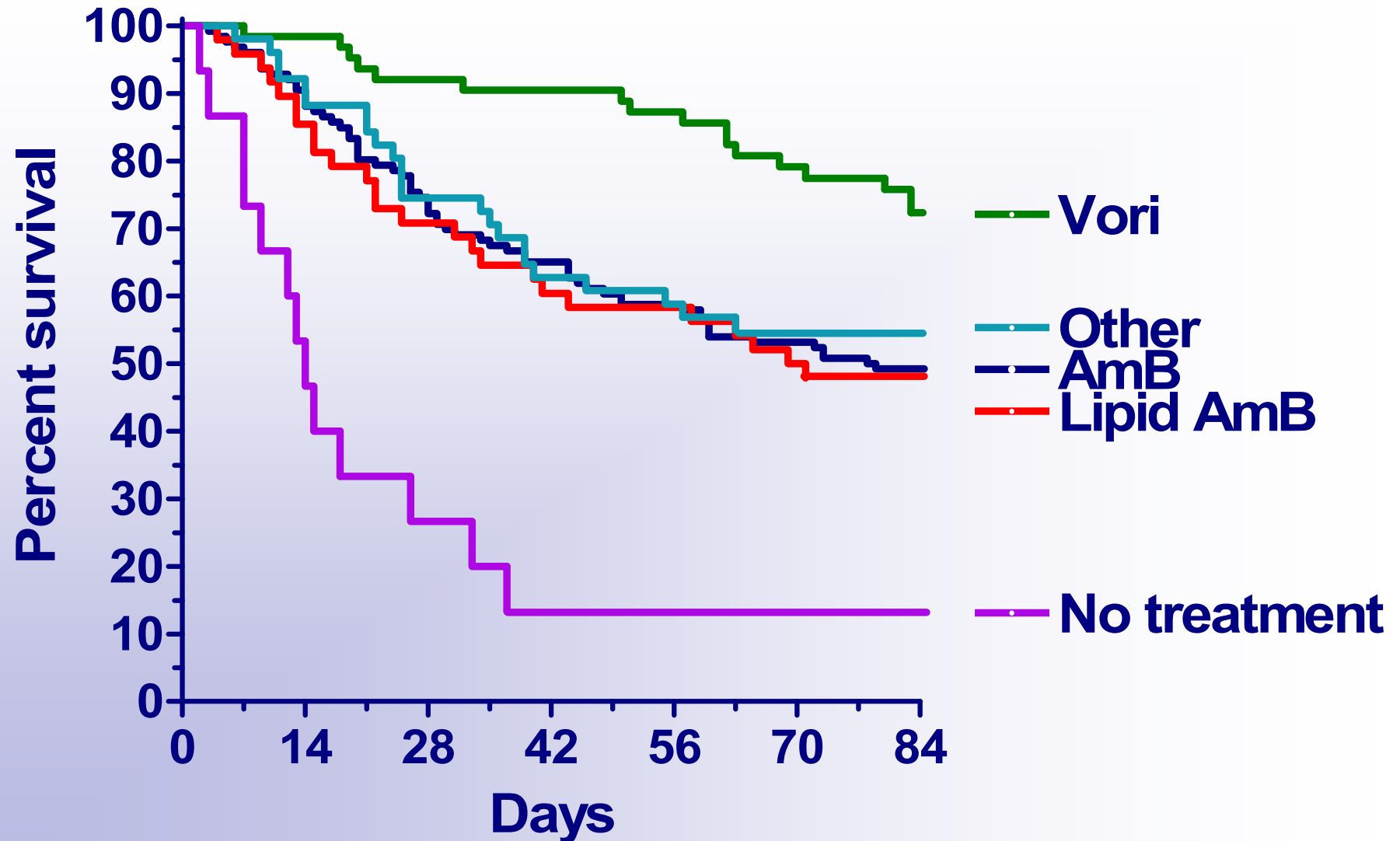


(Nivoix et al., ASH, 2006)

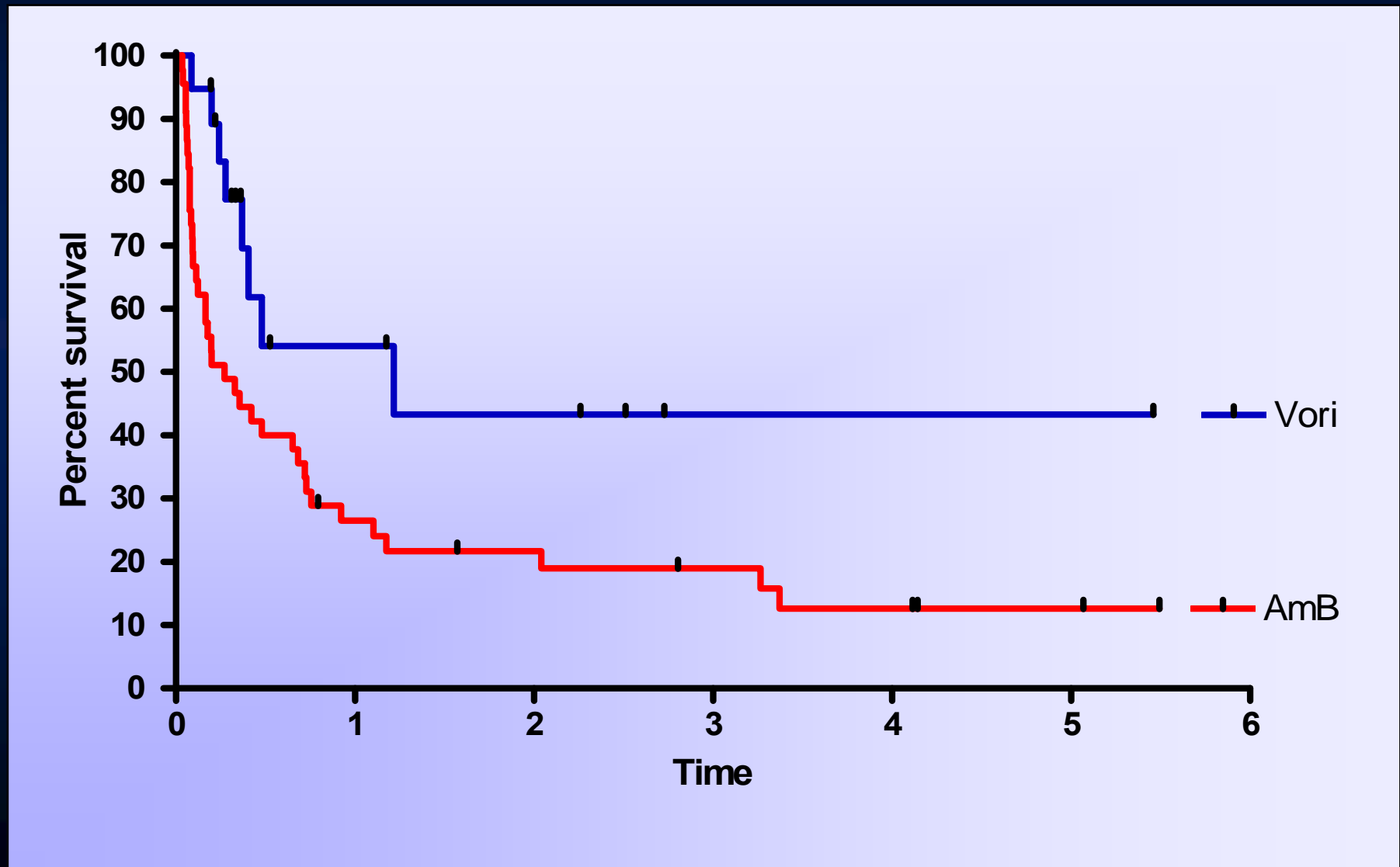
12-week survival according to 1st line therapy (303 patients)



12-week survival according to 1st line therapy (303 patients)



Long term survival in AML patients with an invasive aspergillosis



Most frequent primary site of zygomycosis according to underlying condition (Roden et al., Clin Infect Dis, 2005)



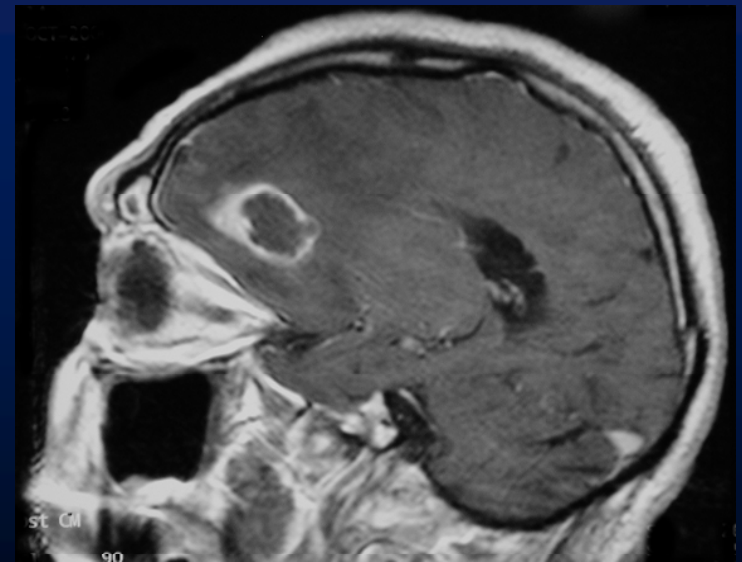
Sinus
Diabetes, Deferoxamine



Skin
No underlying condition



Lungs
HSCT or solid organ Tx
Malignancies, Deferoxamine



Brain
IV drug abuse



Febrile neutropenia



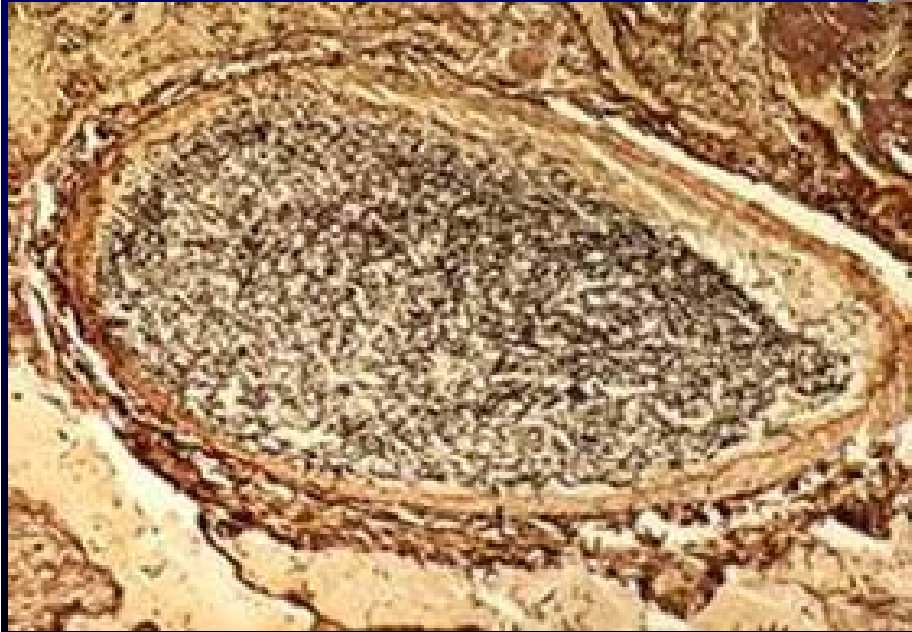
3 days later



7 days later

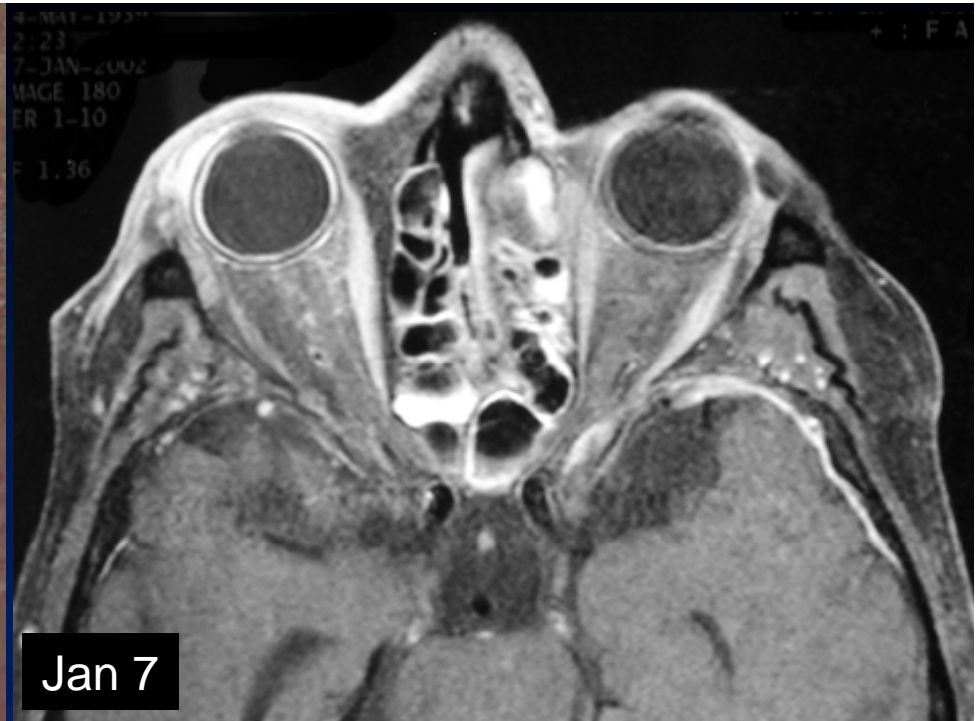
Day 3 after onset of fever







Jan 9



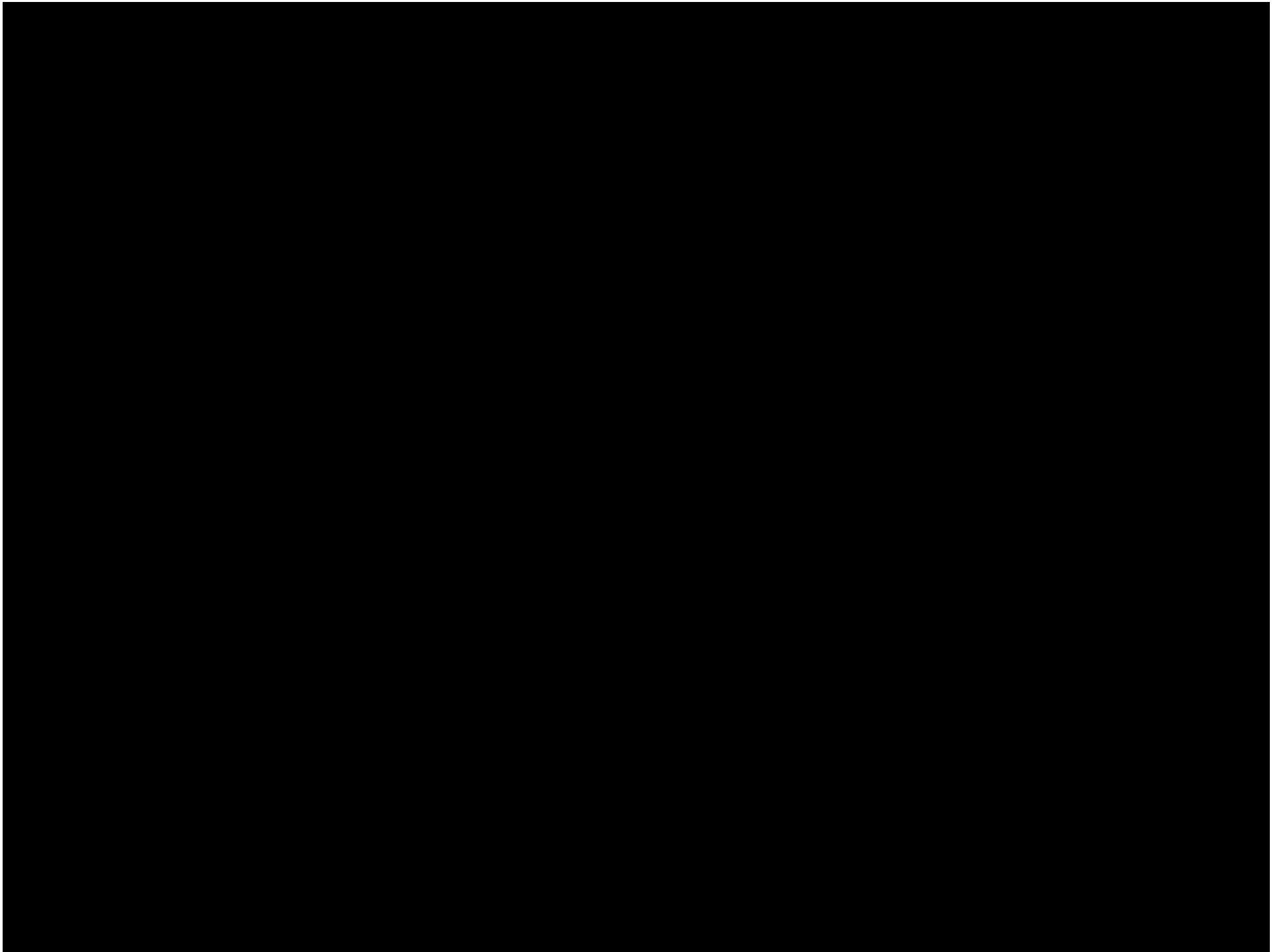
Jan 7



Jan 7

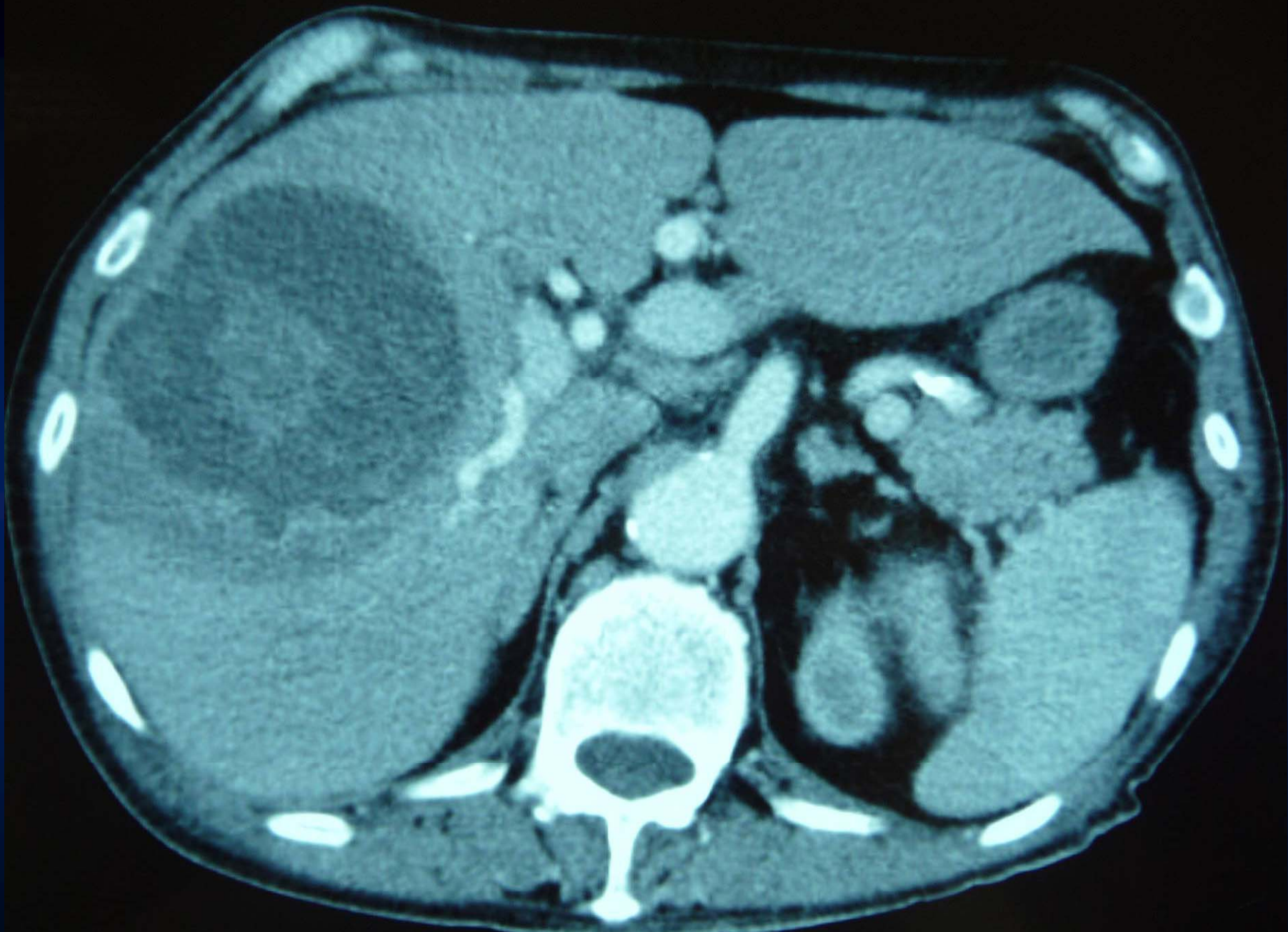


**Disseminated
Fusarium infection
in a leukemic
patient**



Cas clinique 3

- **Homme 84 ans**
- **MDS, IPSS intermédiaire 1**
- **Admis pour douleurs abdominales et fièvre**
- **Syndrome inflammatoire**
- **Bilan microbiologique négatif sauf galactomannane aspergillaire sérique positif**



Hypothèse diagnostique ? Que proposez-vous ?

- **Ponction de l'abcès :**
 - *Aspergillus fumigatus* en culture
 - Antigène galactomannane aspergillaire positif sur le liquide de ponction

Porte d'entrée ?
Quel traitement proposez-vous ?



- Drainage de l'abcès
- Voriconazole iv
 - Taux sériques élevés (> 6000 ng/mL)
 - Taux > 4000 ng/ml dans le liquide de drainage
 - Evolution favorable pour l'instant (réduction de 75 % en 30 jours mais culture toujours positive)

