# Aspergillose en Réanimation: *nouvelles populations ?*

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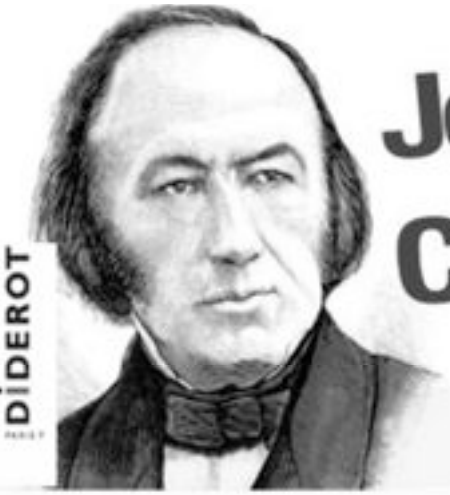
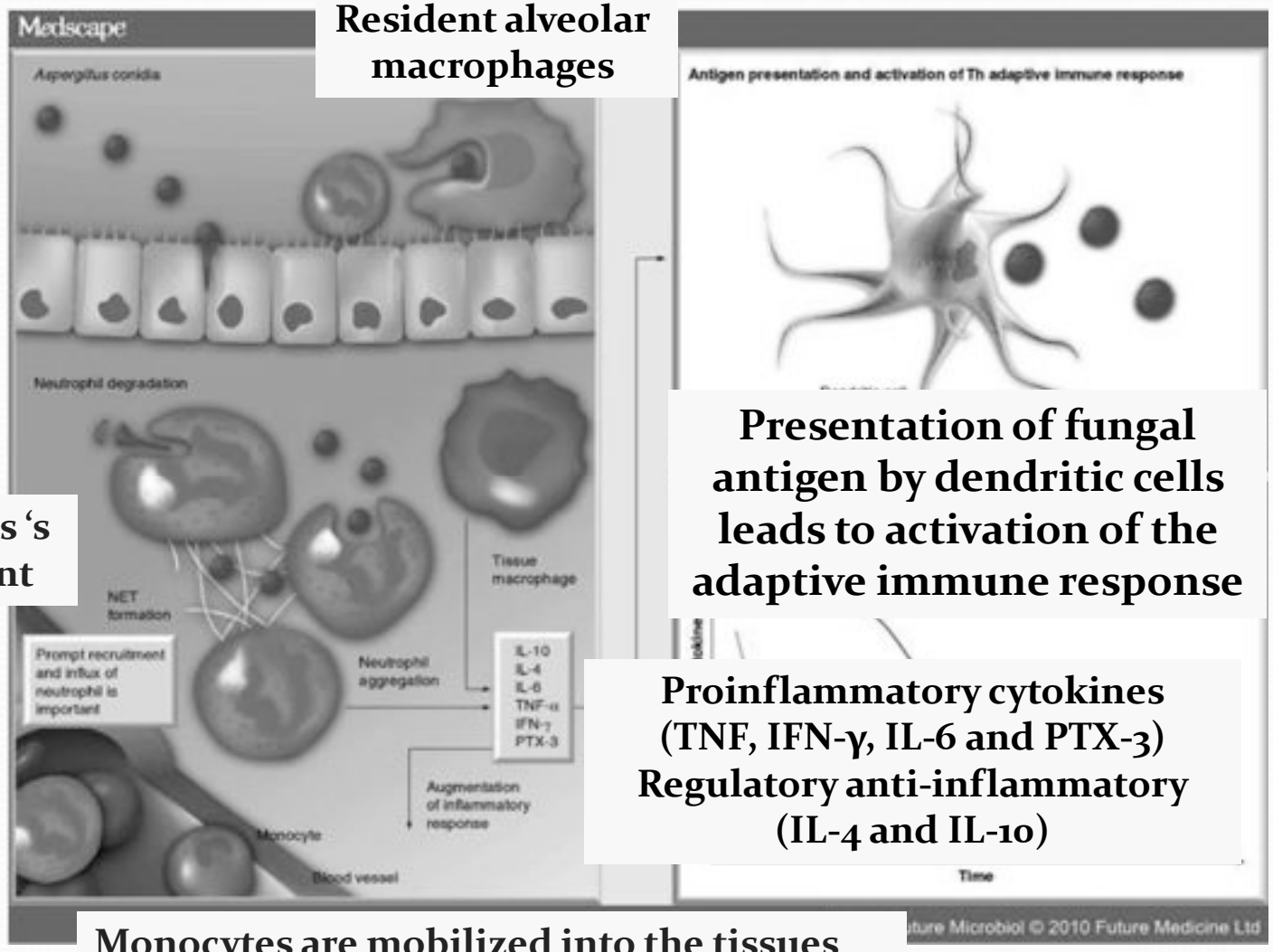


# Journée de l'Hôpital Claude Bernard

Merci de votre invitation

# Host innate immune response to *Aspergillus*

**Resident alveolar macrophages**



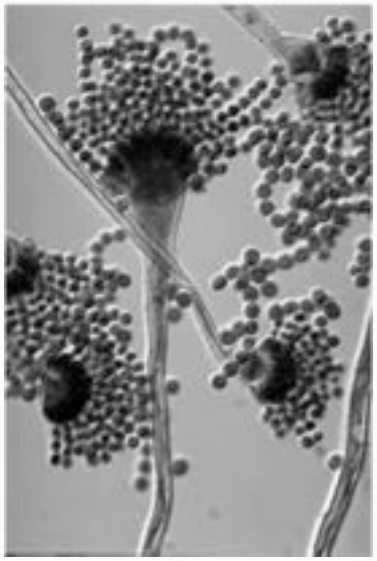

**Neutrophils 's recruitment**

**Presentation of fungal antigen by dendritic cells leads to activation of the adaptive immune response**

**Proinflammatory cytokines (TNF, IFN-γ, IL-6 and PTX-3) Regulatory anti-inflammatory (IL-4 and IL-10)**

**Monocytes are mobilized into the tissues**
**Collaboration avec macrophages tissulaires**

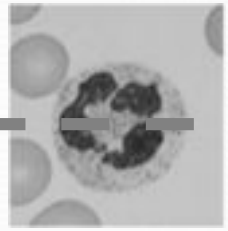
# Aspergillus dans l'arbre respiratoire

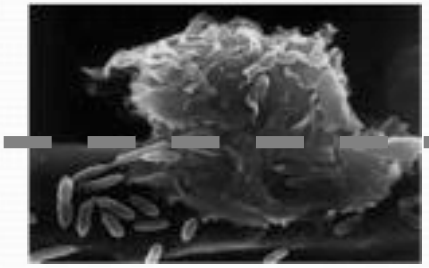


**Colonisation**

**Hypersensibilité**

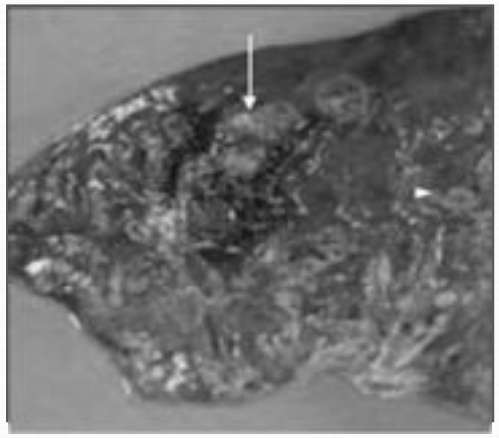
**Allergie**





**(semi)**
**(chronic)**

**ASPERGILLOSE INVASIVE**



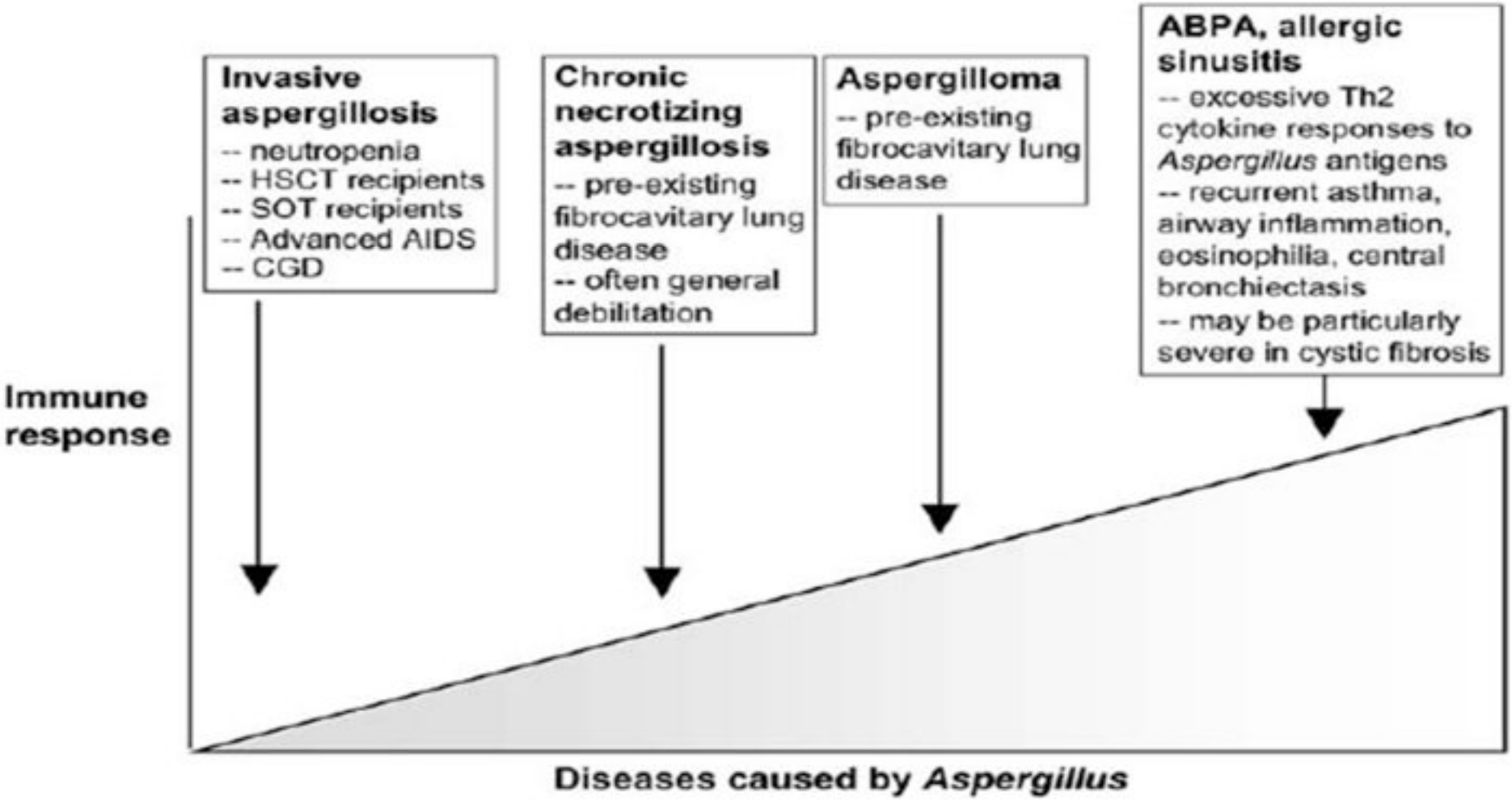
**Subaiguë**

# State of the Art

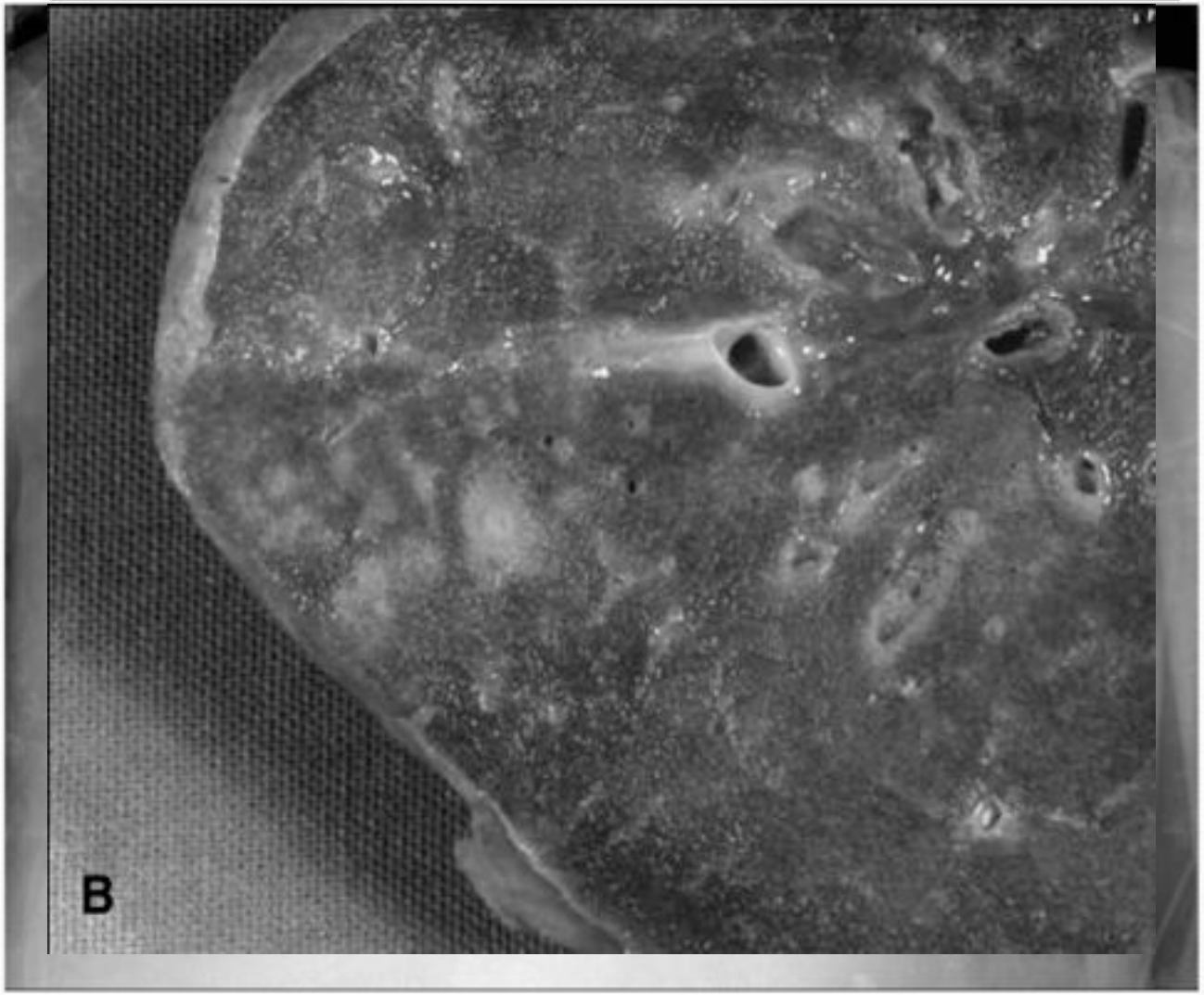
## Current Approaches to Diagnosis and Treatment of Invasive Aspergillosis

Am J Respir Crit Care Med Vol 173. pp 707–717, 2006

Brahm H. Segal and Thomas J. Walsh



# Homme de 38ans, J11 péritonite appendiculaire
# Une PAVM sans documentation bactérienne et sans guérison sous ATB probabiliste



# Aspergillose en Réanimation

1. Est-ce fréquent ?
2. **Qui est à risque ?**
3. **Pourquoi ?**
4. **Stratégie diagnostique**
5. **Qui faut il traiter?**

# Est-ce fréquent?

## Aspergillus dans des prélèvements respiratoires

- Vignette clinique
  - PAVM?
  - PDP-LBA
  - (ECBC)
  - (aspi trachéale)

## Aspergillose Pulmonaire Invasive en réanimation

- EORTC
- Algorithme spécifique
- Biopsies
- Autopsies

# International Study of the Prevalence and Outcomes of Infection in Intensive Care Units

(Reprinted) JAMA, December 2, 2009—Vol 302, No. 21

Jean-Louis Vincent, MD, PhD

**1.4%**

**Infections Gram - = 62.2%**
**Gram + = 46.8%**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Fungi | | | | | | | | |
| *Candida* | 843 (17) | 495 (18.5) | 66 (18.5) | 92 (12.8)[b] | 83 (18.2) | 26 (12.7) | 6 (11.1) | 75 (15.7) |
| *Aspergillus* | 70 (1.4) | 44 (1.6) | 1 (0.3) | 5 (0.7) | 12 (2.6) | 3 (1.5) | 0 | 5 (1) |
| Other | 50 (1) | 22 (0.8) | 5 (1.4) | 7 (1) | 10 (2.2) | 2 (1) | 0 | 4 (0.8) |

*Vincent et al. JAMA, 09*

Journal of Hospital Infection (2010) 74, 186–196

Available online at www.sciencedirect.com

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# Invasive pulmonary aspergillosis in intensive care units: is it a real problem?

- **Prospective study, 2years, 2 ICUs**
- **More than 48h in the ICU**
  - **No malignancy, No steroids**
- **Surveillance cultures of LRT samples for filamentous fungi**
- **Aspergillus spp. were recovered in 4/436 patients (0.9%).**
- **Only one case of IPA in a COPD patient after coronary bypass surgery.**

**<1%**

**Basseti et al. J Hosp Infect 2010**

Research

Open Access

# Isolation of *Aspergillus* spp. from the respiratory tract in critically ill patients: risk factors, clinical presentation and outcome

José Garnacho-Montero[1], Rosario Amaya-Villar[2], Carlos Ortiz-Leyba[3], Cristóbal León[4], Francisco Álvarez-Lerma[5], Juan Nolla-Salas[6], José R Iruretagoyena[7] and Fernando Barcenilla[8]

- **Multicentre prospective study conducted over a 9-m period in 73 ICUs. Tracheal aspirate were collected weekly.**

**2%**

- **36/1756 (2%) patients had Aspergillus spp. recovered. Mortality rates were 50% in the colonization group and 80% in the invasive infection group.**

- **Treatment with steroids and COPD were significantly associated with Aspergillus spp. isolation in multivariate analysis.**

# Clinical diagnoses and autopsy findings: Discrepancies in critically ill patients*

**8 cas en 15 ans: 1%**

Eva Tejerina, MD, PhD; Andrés Esteban, MD, PhD; Pilar Fernández-Segoviano, MD, PhD; José María Rodríguez-Barbero, MD; Federico Gordo, MD, PhD; Fernando Frutos-Vivar, MD; José Aramburu, MD; Ángela Algaba, MD; Óscar Gonzalo Salcedo García, MD; José A. Lorente, MD

| Major Discrepancies | Periods of Years | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 1982–1984 | 1985–1987 | 1988–1991 | 1992–1994 | 1995–1997 | 1998–2000 | 2001–2003 | 2004–2007 |
| Pulmonary embolism | 1 | 3 | 0 | 8 | 4 | 3 | 3 | 2 |
| Pneumonia | 1 | 1 | 0 | 1 | 1 | 0 | 8 | 11 |
| Secondary peritonitis | 4 | 1 | 0 | 0 | 1 | 2 | 4 | 0 |
| Invasive aspergillosis | 0 | 0 | 1 | 2 | 1 | 2 | 2 | 0 |
| Endocarditis | 1 | 0 | 2 | 0 | 0 | 1 | 2 | 2 |
| Myocardial infarction | 3 | 3 | 1 | 0 | 0 | 0 | 1 | 0 |
| Mesenteric ischemia | 1 | 0 | 1 | 2 | 2 | 0 | 0 | 0 |
| Gastrointestinal hemorrhage | 3 | 1 | 0 | 1 | 0 | 0 | 1 | 1 |

N = 834

# Trends in the Postmortem Epidemiology of Invasive Fungal Infections at a University Hospital

***Groll et al. Jour of Infect, 96***

**Table III.** Prevalence of invasive fungal infections at autopsy.

| Fungus | No. of patients (%) | | | *P* value |
|---|---|---|---|---|
| | 1978–82 ($n$=2956) | 1983–87 ($n$=2718) | 1988–92 ($n$=2450) | |
| *Candida* | 51 (1.7) | 47 (1.7) | 31 (1.3) | 0.3110 |
| *Aspergillus* | 11 (0.4) | 32 (1.2) | 76 (3.1) | 0.0001* |
| *Cryptococcus* | — | 5 (0.2) | 3 (0.1) | 0.0790 |
| *Mucor* | 4 (0.1) | — | 1 (<0.1) | 0.1075 |
| *Asperg. + Cand.* | — | — | 6 (0.2) | 0.0010* |
| *Asperg. + Crypt.* | — | — | 1 (<0.1) | 0.3141 |
| *Unclassified* | — | 2 (<0.1) | 8 (0.3) | 0.0020* |
| Total | 66 (2.2) | 86 (3.2) | 126 (5.1) | 0.0001* |

* Increase over time significant by 3 × 2 Chi-square test.

# ARDS*

## A Clinicopathological Confrontation

*Quentin de Hemptinne, MD; Myriam Remmelink, MD, PhD; Serge Brimioulle, MD; Isabelle Salmon, MD, PhD; and Jean-Louis Vincent, MD, PhD, FCCP*

Original Research

CRITICAL CARE MEDICINE


**8/64 patients with IPA**

| Variables | Values |
|---|---|
| DAD | |
| Total | 32 (50) |
| Exudative phase | 16 (25) |
| Organized phase | 16 (25) |
| Isolated | 20 (31) |
| Associated with | 12 (19) |
| Pneumonia/bronchopneumonia | 4 |
| Pulmonary invasive aspergillosis | 4 |
| *Pneumocystis carinii (jiroveci)* pneumonia | 1 |
| Pulmonary infarct | 1 |
| Congestion | 1 |
| Lymphangioleiomyomatosis + microthrombi | 1 |

| Other pathologic diagnoses (not associated with DAD) | |
|---|---|
| Pneumonia/bronchopneumonia | 16 (25) |
| Congestion | 7 (11) |
| Pulmonary invasive aspergillosis | 4 (6) |
| Chronic nonspecific inflammatory changes | 3 |
| Pulmonary embolism | 2 |
| Alveolar hemorrhage | 2 |
| Usual interstitial pneumonia | 2 |
| *P carinii (jiroveci)* pneumonia | 1 |
| Pulmonary infarct | 1 |
| Acute pulmonary graft rejection | 1 |
| Inhalation pneumonia | 1 |
| Bronchiolitis obliterans organizing pneumonia | 1 |

# The spectrum of aspergillosis at 24 medical centers by assessing 1477 cultures that were positive for *Aspergillus sp.* in 1209 patients

J. R. Perfect,[1] G. M. Cox,[1] J. Y. Lee,[2] C. A. Kauffman,[3] L. de Repentigny,[4] S. W. Chapman,[5] V. A. Morrison,[6] P. Pappas,[2] J. W. Hiemenz,[7] D. A. Stevens,[8] and the Mycoses Study Group[a]

| Underlying disease or characteristic | No. (%) of patients ($n$ = 1209) | Underlying disease or characteristic | No. (%) of patients ($n$ = 1209) |
|---|---|---|---|
| Pulmonary disorder | 477 (40) | Malnutrition | 99 (8) |
| Corticosteroid use | 381 (32) | Neutropenia | 61 (5) |
| Diabetes mellitus | 151 (12) | Allogeneic transplant | 39 (3) |
| HIV infection | 138 (11) | Graft-vs.-host disease | 34 (3) |
| Cystic fibrosis | 127 (11) | Trauma | 24 (2) |
| Surgery | 126 (10) | Connective tissue disease | 28 (2) |
| Solid-organ cancer | 124 (10) | Autologous transplant | 14 (1) |
| Hematologic cancer | 106 (9) | Chronic granulomatous disease | 2 (<1) |
| Solid-organ transplant | 100 (8) | None | 92 (8) |

# Aspergillose en Réanimation

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# Qui est à risque d'aspergillose invasive?

- **Choc septique, défaillances multiviscérales**
- **Stéroïdes**

- **BPCO (et maladies structurelles pulmonaires)**
- **Cirrhoses**

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- **Et □**

# Aspergillosis

Brahm H. Segal, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2009;360:1870-84.

## Host Defense against Aspergillus

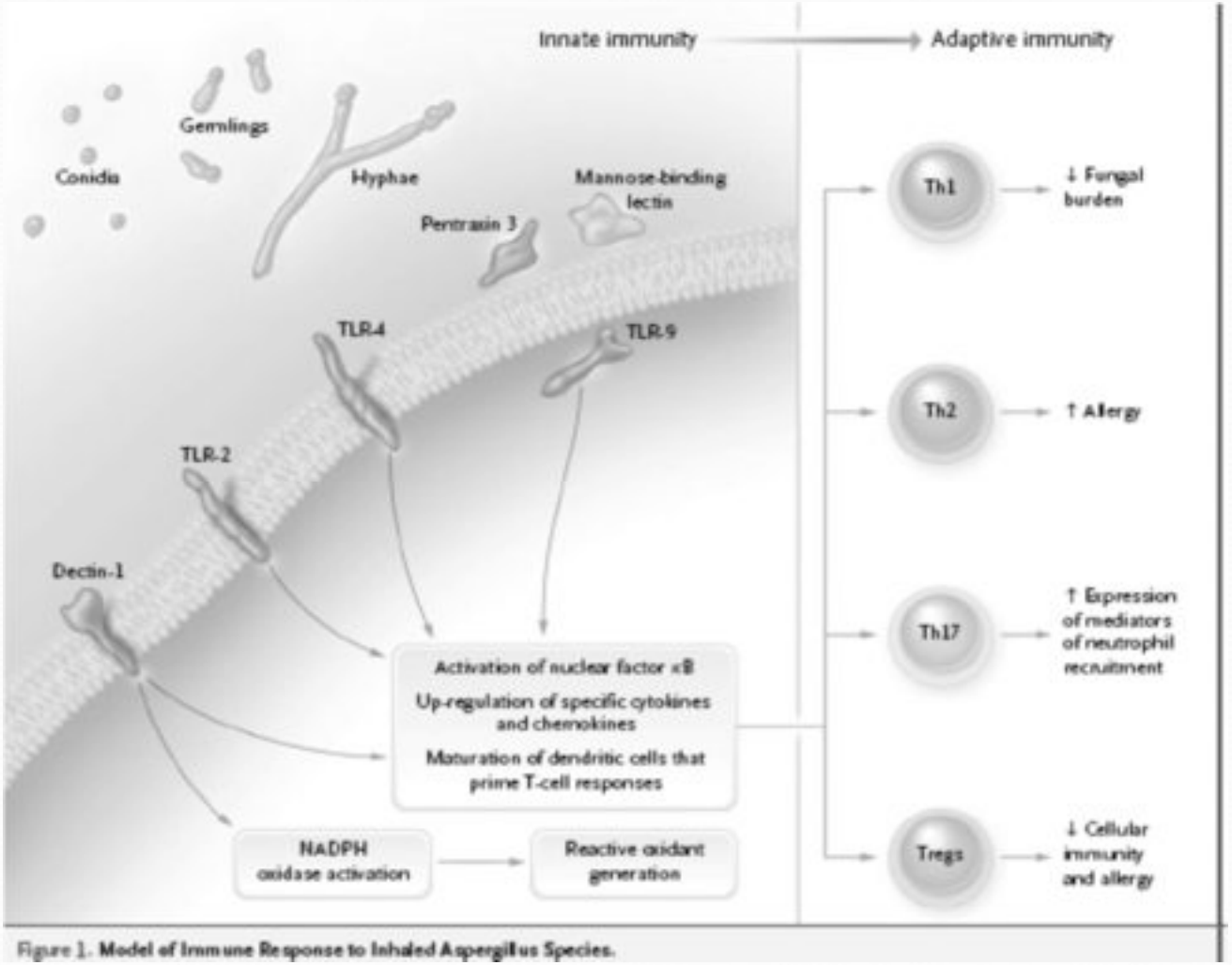



Figure 1. **Model of Immune Response to Inhaled Aspergillus Species.**

JAMA, December 21, 2011—Vol 306, No. 23

# Immunosuppression in Patients Who Die of Sepsis and Multiple Organ Failure

**Analyse des tissus pulm, et spléniques pour étude de l'immunité innée et adaptative chez 40 pts décédant de sepsis (29 témoins).**

Jonathan S. Boomer, PhD
Kathleen To, MD
Kathy C. Chang, PhD
Osamu Takasu, MD
Dale F. Osborne, BS
Andrew H. Walton, MS
Traci L. Bricker, BS
Stephen D. Jarman II, BSN, RN
Daniel Kreisel, MD, PhD
Alexander S. Krupnick, MD
Anil Srivastava, MD
Paul E. Swanson, MD
Jonathan M. Green, MD
Richard S. Hotchkiss, MD

- **Diminution de sécrétion par les splénocytes de TNFα, IFNγ, IL6 et IL10**
- **Taux ≈10% des témoins, ajustés sur âge, durée du sepsis et stéroïdes.**
- **Augm. de la sécrétion d'inhibiteurs des Rc et ligands, et des cell. suppressives (FAX).**
- **En immunohistochimie, déplétion CD4, CD8 et HLA-DR dans la rate et de l'expression des ligands pour les Rc sur les cell. épithéliales pulmon.**

CASE REPORT

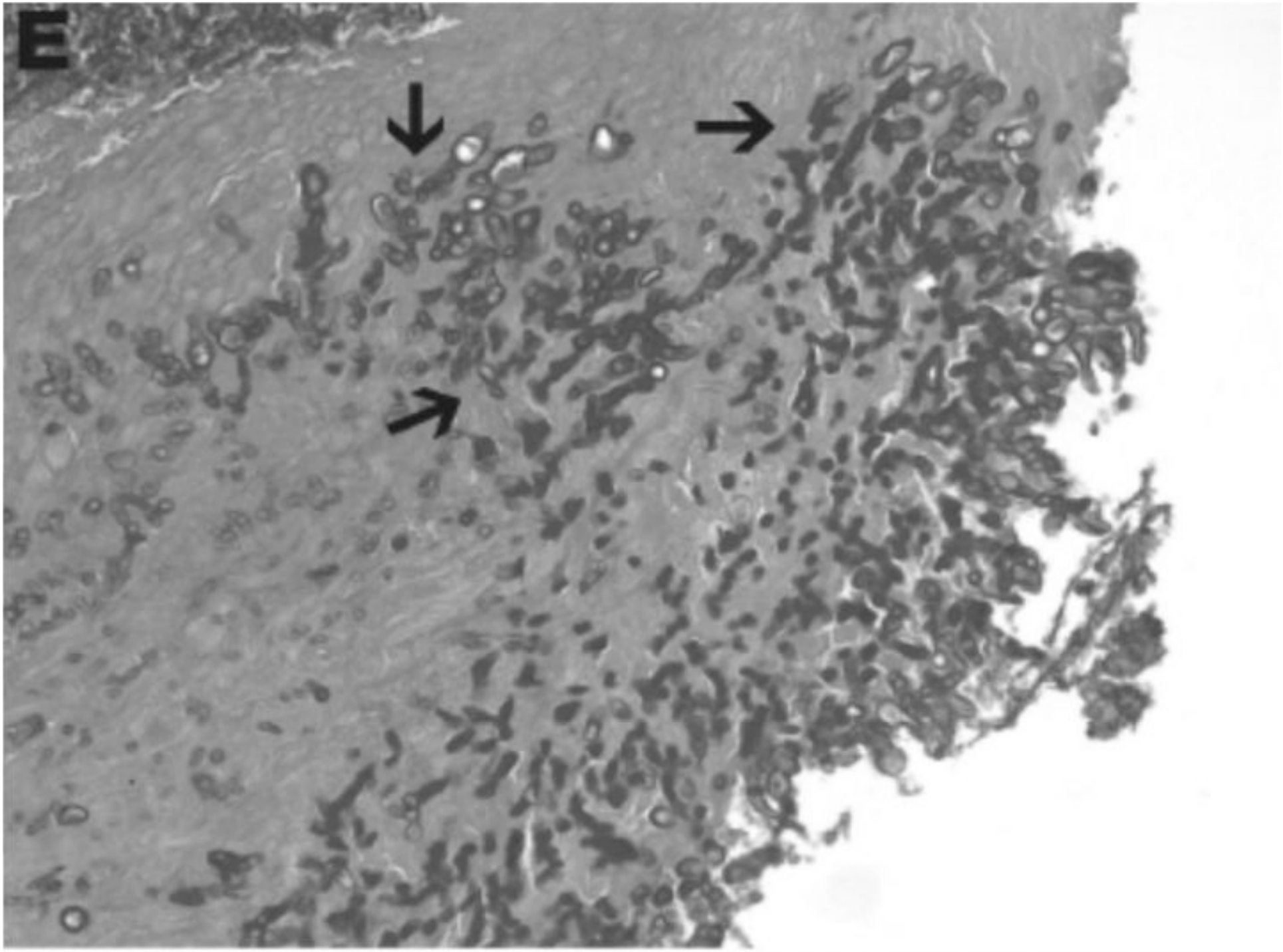
*Respirology* (2005) **10**, 116–119

# Invasive pulmonary aspergillosis associated with influenza B

NOBUCHIKA HASEJIMA,[1] KUNIO YAMATO,[1] SHINJI TAKEZAWA,[1] HIROAKI KOBAYASHI[1] AND CHIKABUMI KADOYAMA[2]

**Table 1** Cases of invasive pulmonary aspergillosis associated with influenza

| Case No. (Year reported) | Age (Sex) | Underlying disease | Type of influenza | Method of IPA diagnosis | Therapy for IPA | Outcome | Reporter (reference) |
|---|---|---|---|---|---|---|---|
| 1 (1957) | 51 (F) | (–) | NM | autopsy | (–) | died | Abbott (3) |
| 2 (1979) | 59 (F) | (–) | A | sputum/biopsy | (–) | died | Fisher (4) |
| 3 (1979) | 47 (F) | (–) | A | sputum | (–) | died | Fisher (4) |
| 4 (1982) | 69 (F) | (–) | A | TA | AMPH, 5-FC, Econazole | survived | McLeod (5) |
| 5 (1983) | 42 (M) | DM, HT | A | BW/autopsy | AMPH | died | Horn (6) |
| 6 (1985) | 72 (M) | (–) | A | BA/autopsy | AMPH | died | Urban (7) |
| 7 (1985) | 28 (F) | (–) | A | sputum/biopsy | AMPH | died | Lewis (8) |
| 8 (1990) | 49 (M) | alcoholism | A | sputum/BAL/ serology | AMPH, 5-FC | died | Kobayashi (9) |
| 9 (1991) | 61 (M) | (–) | A | TA/autopsy | AMPH | died | Havenden (10) |
| 10 (1996) | 58 (M) | (–) | A | TA | AMPH | survived | Alba (11) |
| 11 (1999) | 83 (F) | (–) | A | sputum/autopsy | ITCZ/AMPH | died | Funahiki (12) |
| 12 (1999) | 89 (F) | (–) | A | BA/necropsy | ITCZ | died | Vandenbos (13) |
| 13 (2001) | 55 (M) | pneumoconiosis | A | sputum/autopsy | FLCZ | died | Matsushima (14) |
| 14 (2004) | 63 (F) | (–) | B | sputum/serology | AMPH, ITCZ | survived | This case |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Research

Open Access

# Clinical relevance of *Aspergillus* isolation from respiratory tract samples in critically ill patients

Koenraad H Vandewoude[1,2], Stijn I Blot[1,2], Pieter Depuydt[1], Dominique Benoit[1], Werner Temmerman[1], Francis Colardyn[1] and Dirk Vogelaers[3]

*Critical Care* 2006, **10**:R31

## Chronic respiratory diseases, Steroids ...

**Underlying diseases in intensive care unit patients with respiratory tract samples positive for *Aspergillus* spp.**

| Underlying condition | Associated with invasive aspergillosis[a] | Associated with *Aspergillus* colonisation |
|---|---|---|
| Chronic obstructive pulmonary disease | 29 (4) | 25 |
| Requiring chronic systemic corticosteroid use | 21 (3) | 12 |
| Requiring inhalation corticosteroids | 24 (3) | 16 |
| Asthma | 2 | 1 |
| Liver cirrhosis | 3 (2) | 2 |
| Malnutrition | 3 | - |
| Diabetes mellitus | 8 (1) | 9 |
| Alcoholism | 5 (2) | 3 |
| Chronic heart failure | 6 | 5 |
| Chronic renal failure – dialysis dependent | 3 (1) | 2 |
| Lung fibrosis | 2 | 1 |
| Active Cytomegalovirus disease | 3 | 1 |
| Active tuberculosis | - | 1 |
| Absence of known underlying disease | 14 (5) | 27 |

# Invasive Aspergillosis in Critically Ill Patients without Malignancy

Wouter Meersseman, Stefaan J. Vandecasteele, Alexander Wilmer, Eric Verbeken, Willy E. Peetermans, and Eric Van Wijngaerden

**90% received steroids in the ICU**

TABLE 2. CLINICAL CHARACTERISTICS OF PATIENTS WITHOUT HEMATOLOGICAL MALIGNANCY WITH PROVEN OR PROBABLE IA

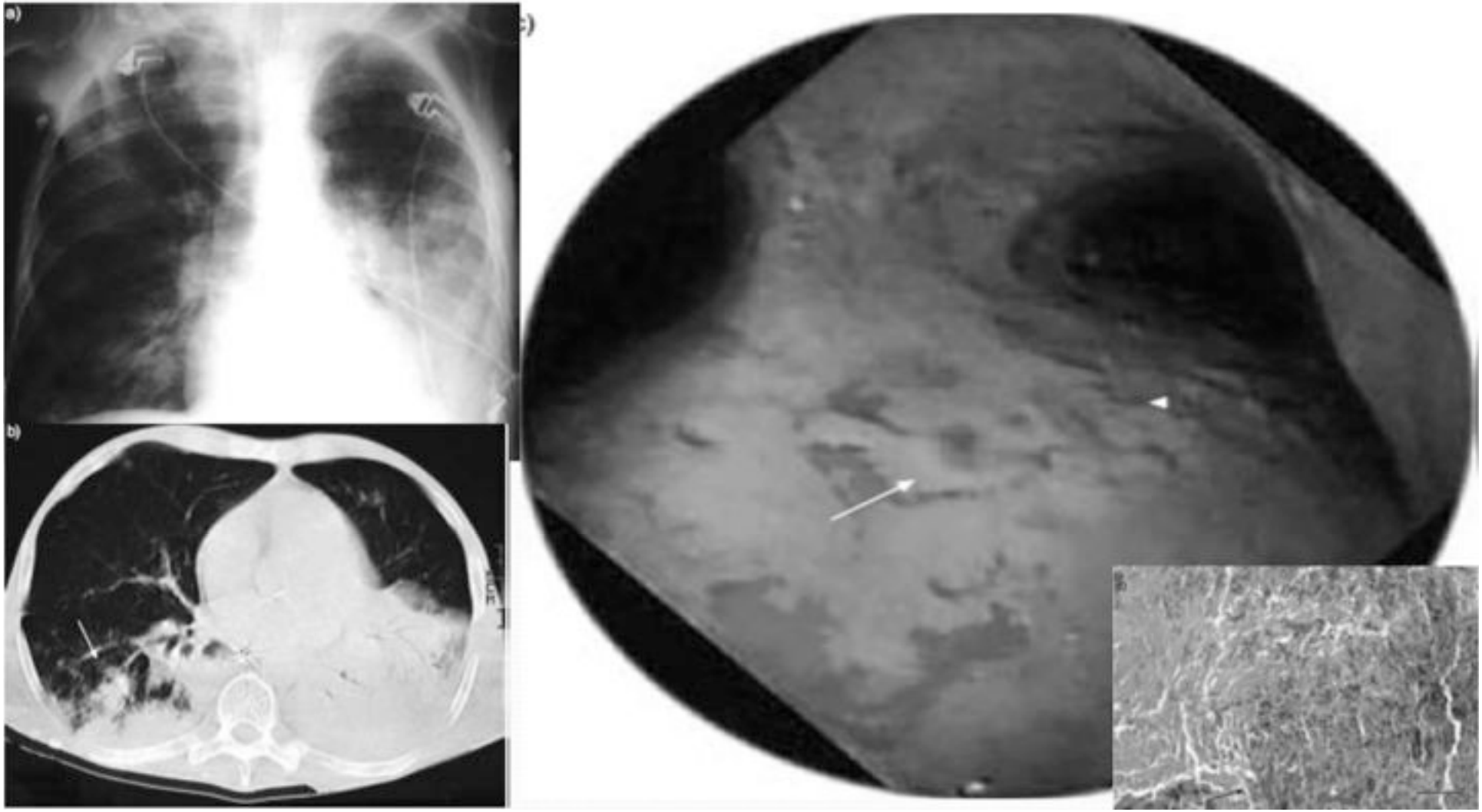
| | All (*n* = 67) | COPD (*n* = 33) | Systemic Disease (*n* = 14) | Liver Cirrhosis (*n* = 3) | Solid Organ Transplants (*n* = 9) | Other (*n* = 8) |
|---|---|---|---|---|---|---|
| Age, yr, mean | 65 | 69 | 60 | 55 | 51 | 73 |
| SAPS II, mean | 52 | 49 | 50 | 64 | 47 | 66 |
| Predicted mortality, % | 48 | 43 | 44 | 71 | 40 | 73 |
| Observed mortality, % | 91 | 85 | 93 | 100 | 100 | 100 |
| Length of stay, d | 21 | 23 | 18 | 13 | 22 | 14 |
| Culture positive* | 56/67 | 31/33 | 10/14 | 1/3 | 6/9 | 8/8 |
| Asp Ag** Positive* | 27/51 | 12/25 | 7/11 | 0/0 | 4/9 | 4/6 |
| Autopsy positive* | 27/41 | 12/19 | 6/9 | 3/3 | 3/6 | 3/4 |

**5 patient with no other immune suppression, than Age (95yo), cirrhosis or multiple organ failure**

# Invasive pulmonary aspergillosis in patients with chronic obstructive pulmonary disease

**P. Bulpa*, A. Dive* and Y. Sibille#**

Eur Respir J 2007; 30: 782–800



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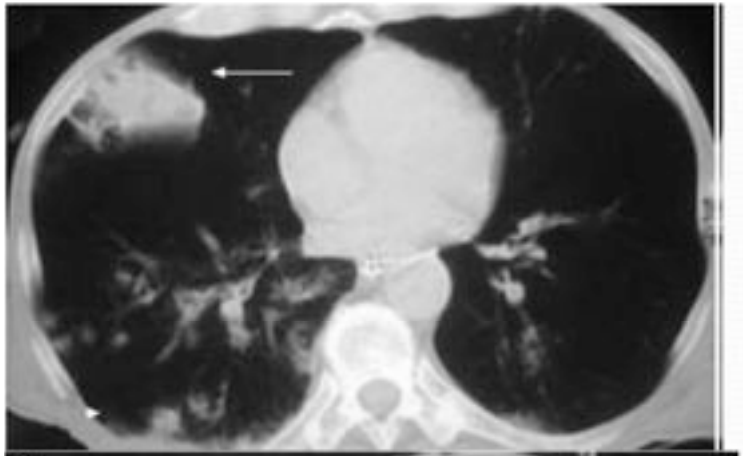

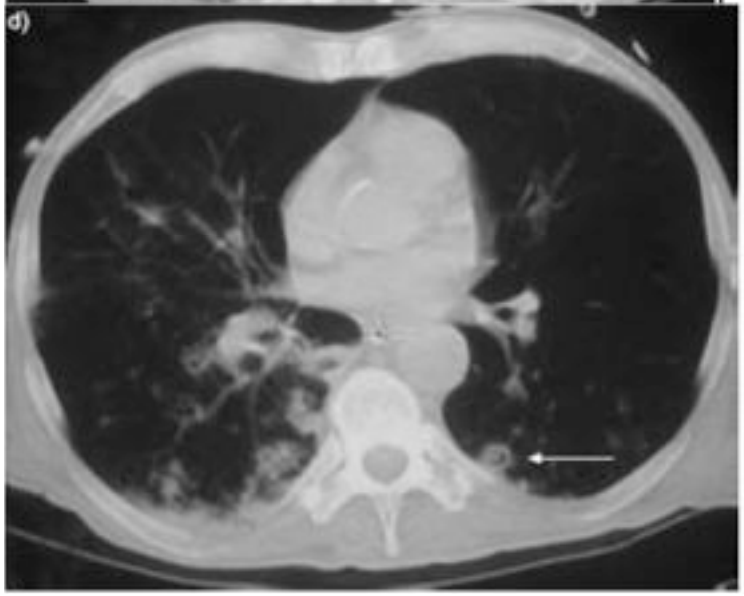


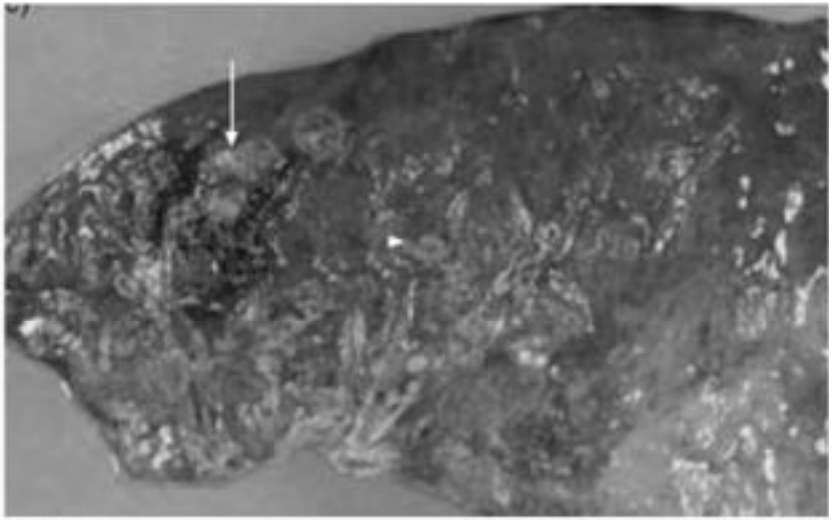

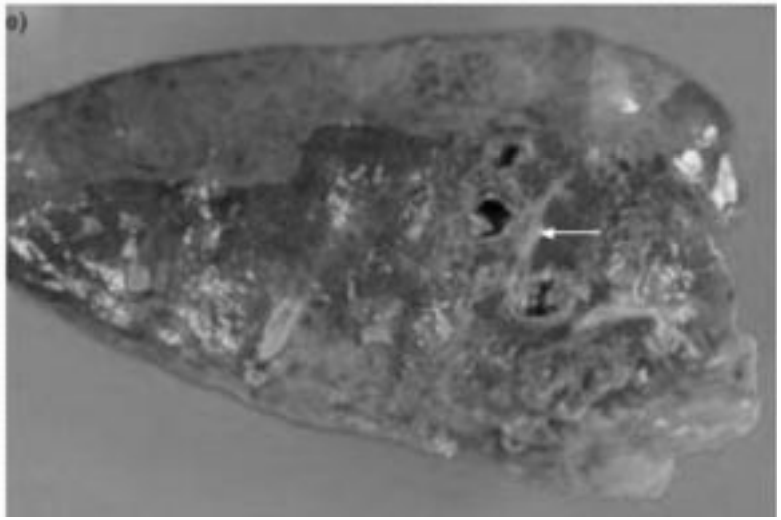

ORIGINAL ARTICLE 10.1111/j.1469-0691.2009.03015.x

Clin Microbiol Infect. 2009 Nov 10

# Pulmonary aspergillosis in patients with chronic obstructive pulmonary disease: incidence, risk factors, and outcome

J. Guinea[1,2], M. Torres-Narbona[1], P. Gijón[1], P. Muñoz[1,2], F. Pozo[2,3], T. Peláez[1,2], J. de Miguel[4] and E. Bouza[1,2]

- **239 severe COPD patient with Aspergillus isolated from the LRT.**
- **16.3/1000 admissions.**
- **53 (22.1%) patients had probable IPA**
  - **42.4% positive serum galactomannan**
- **Independent predictors of IPA were:**
  - **ICU admission,**
  - **chronic heart failure,**
  - **Antibiotics received in the last 3 months**
  - **Steroids**
- **Survival was 64.1% (IPA 28.3% vs. 75.2%).**

# Aspergillosis

Brahm H. Segal, M.D.

N Engl J Med 2009;360:1870-84.

The NEW ENGLAND JOURNAL of MEDICINE

Table 1. **Predisposing Host Factors and Clinical and Histologic Features Associated with Invasive Pulmonary Aspergillosis.***

| Population of Patients | Predisposing Host Factors | Clinical and Histologic Features |
|---|---|---|
| Acute leukemia, myelodysplastic syndrome, aplastic anemia, and other causes of marrow failure | Neutropenia from chemotherapy or underlying hematologic disease | Hyphal angioinvasion with vascular thrombosis and tissue infarction; scant inflammatory response; possible evolution to cavitation |
| Allogeneic hematopoietic stem-cell transplantation after neutrophil recovery | Immunosuppression for GVHD (e.g., the use of corticosteroids, T-cell depletion, inhibition of tumor necrosis factor $\alpha$) | Inflammatory fungal pneumonia and angioinvasion with coagulative necrosis, which are classically associated with neutropenia[32-34] |
| Solid-organ transplantation | Immunosuppression to prevent allograft rejection | Acute inflammatory pneumonia, chronic necrotizing aspergillosis; tracheobronchitis affecting the anastomotic site and causing dehiscence in lung-transplant recipients |
| Advanced AIDS | CD4+ T-cell count usually <100 per cubic millimeter; other immunocompromising conditions (e.g., neutropenia) | Acute to slowly progressive necrotizing pneumonia; variable histologic findings: neutrophilic infiltrates, vascular invasion, walled-off abscesses, and cavitation[35] |
| Chronic granulomatous disease | Defective NADPH oxidase | Acute to slowly progressive pneumonia; pyogranulomatous inflammation without hyphal vascular invasion or coagulative necrosis; "mulch pneumonitis," an acute hypersensitivity response to a large, aerosolized exposure[36] |
| Preexisting structural lung disease (e.g., emphysema, previous cavitary tuberculosis) | Coexisting conditions (e.g., diabetes and malnutrition) and the use of inhaled and systemic corticosteroids | Chronic necrotizing pulmonary aspergillosis; slowly progressive invasive fungal pneumonia with inflammatory necrosis[37] |

# Aspergillose en Réanimation

1. Est-ce fréquent ?
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3. Pourquoi ?
4. Stratégie diagnostique
5. Qui faut il traiter?

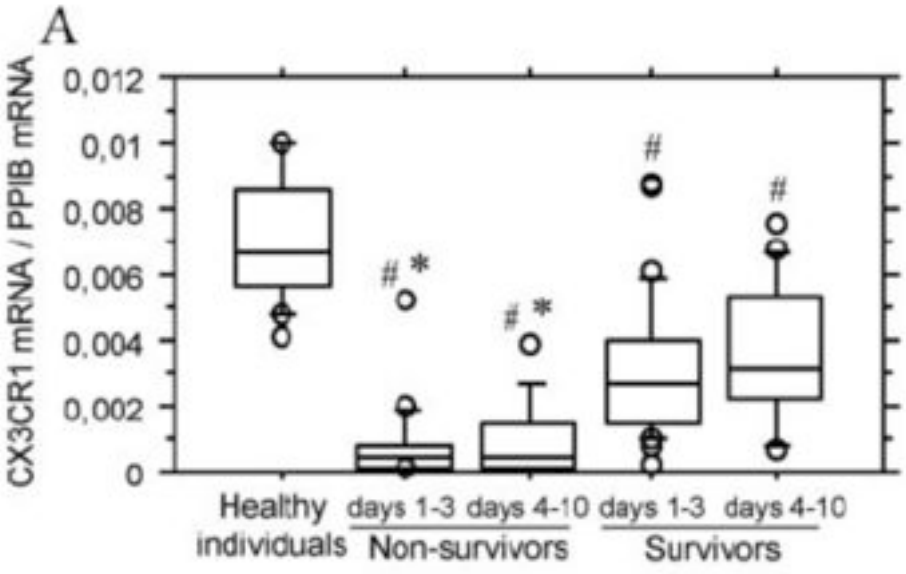
# Decreased Expression of the Fractalkine Receptor CX3CR1 on Circulating Monocytes as New Feature of Sepsis-Induced Immunosuppression

*The Journal of Immunology*, 2008, 180: 6421–6429.

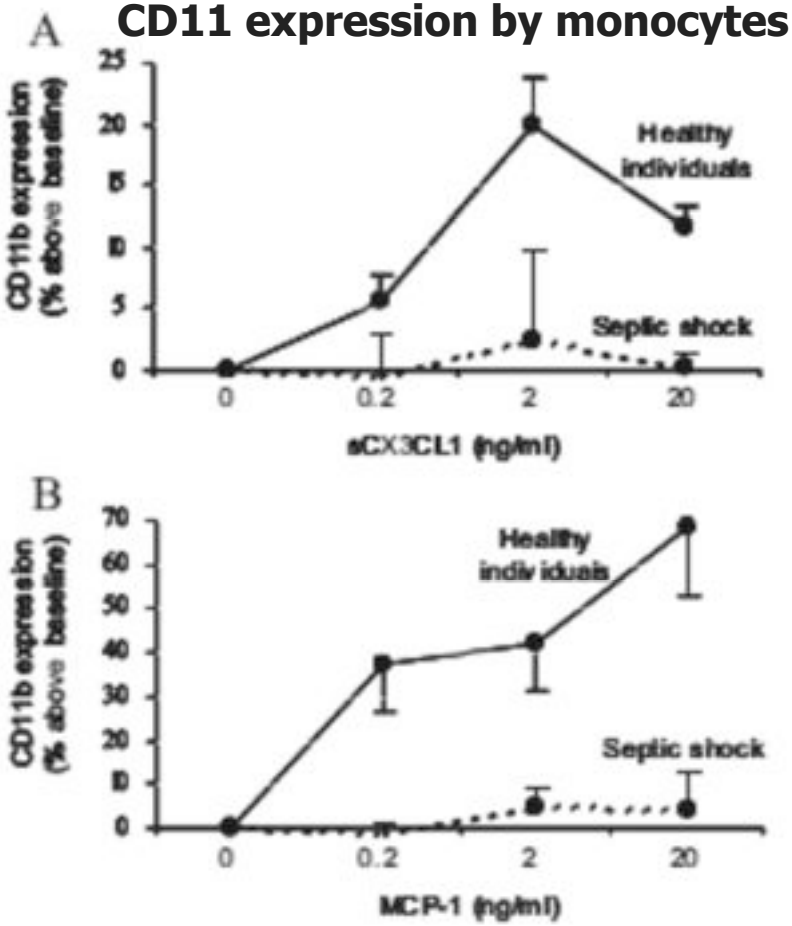
The Journal of Immunology

Alexandre Pachot,* Marie-Angélique Cazalis,* Fabienne Venet,‡ Fanny Turrel,* Caroline Faudot,* Nicolas Voirin,† Jennifer Diasparra,* Naïck Bourgoin,* Françoise Poitevin,‡ Bruno Mougin,* Alain Lepape,§ and Guillaume Monneret[1†]

**Decreased expression of CX3CR1 mRNA in circulating cells from septic shock patients. Quantitative real-time PCR in whole blood from 47 septic shock patients (17 nonsurvivors) and 21 healthy individuals.**




**CD11 expression by monocytes**

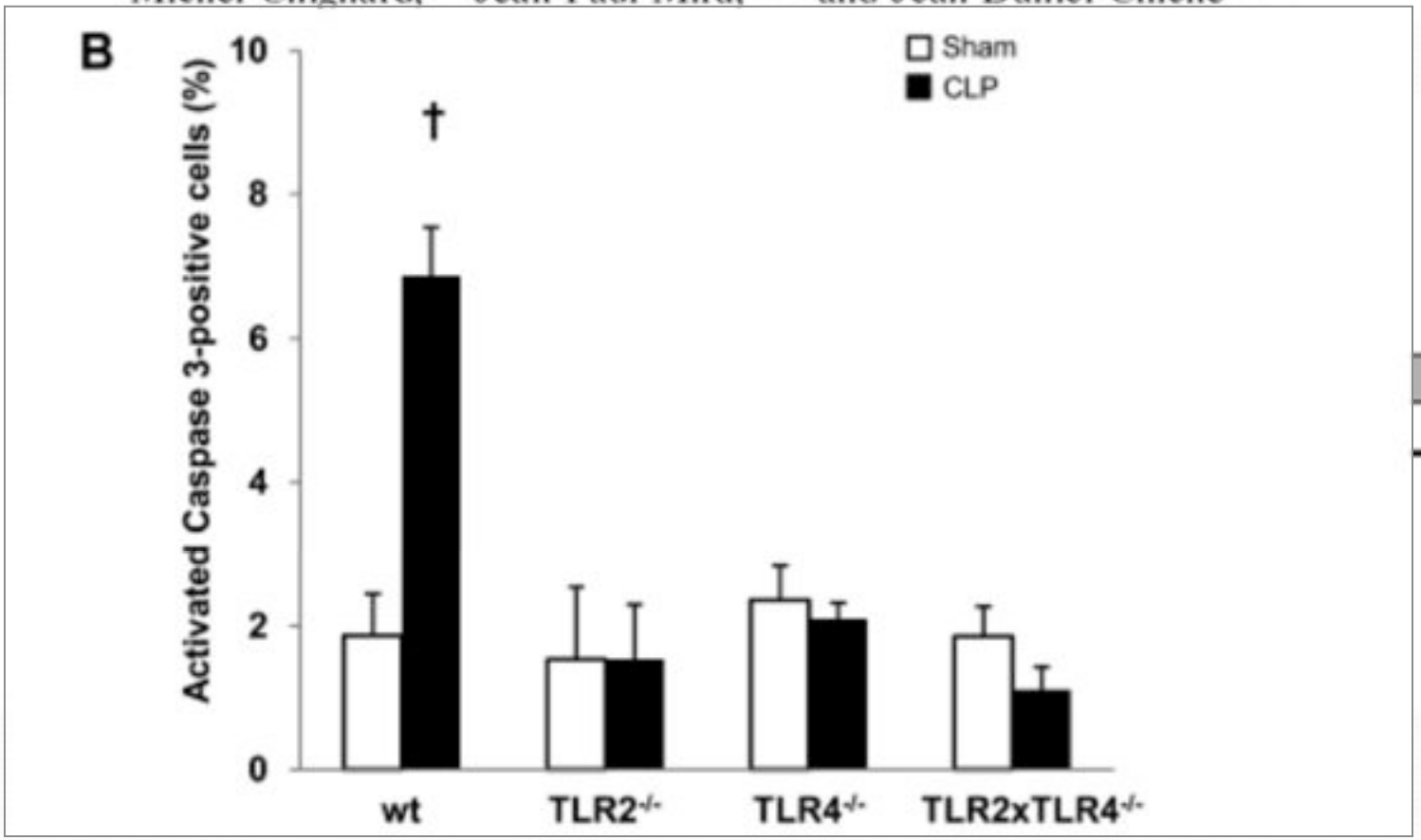


INFECTION AND IMMUNITY, Dec. 2009, p. 5651–5658 Vol. 77, No. 12
0019-9567/09/$12.00 doi:10.1128/IAI.00238-09


# Toll-Like Receptors 2 and 4 Contribute to Sepsis-Induced Depletion of Spleen Dendritic Cells[▽]

Frédéric Pène,[1,2,3] Emilie Courtine,[1,2] Fatah Ouaaz,[1,2] Benjamin Zuber,[1,2,3] Bertrand Sauneuf,[1,2] Gonzalo Sirgo,[1,2]† Christophe Rousseau,[1,2] Julie Toubiana,[1,2] Viviane Balloy,[4,5] Michel Chignard,[4,5] Jean-Paul Mira,[1,2,3] and Jean-Daniel Chiche[1,2,3]*

A



**SHOCK,** Vol. 18, No. 6, pp. 487–494, 2002

# EARLY CIRCULATING LYMPHOCYTE APOPTOSIS IN HUMAN SEPTIC SHOCK IS ASSOCIATED WITH POOR OUTCOME

**Yves Le Tulzo, Céline Pangault, Arnaud Gacouin, Valérie Guilloux, Olivier Tribut, Laurence Amiot, Pierre Tattevin, Rémi Thomas, Renée Fauchet, and Bernard Drénou**

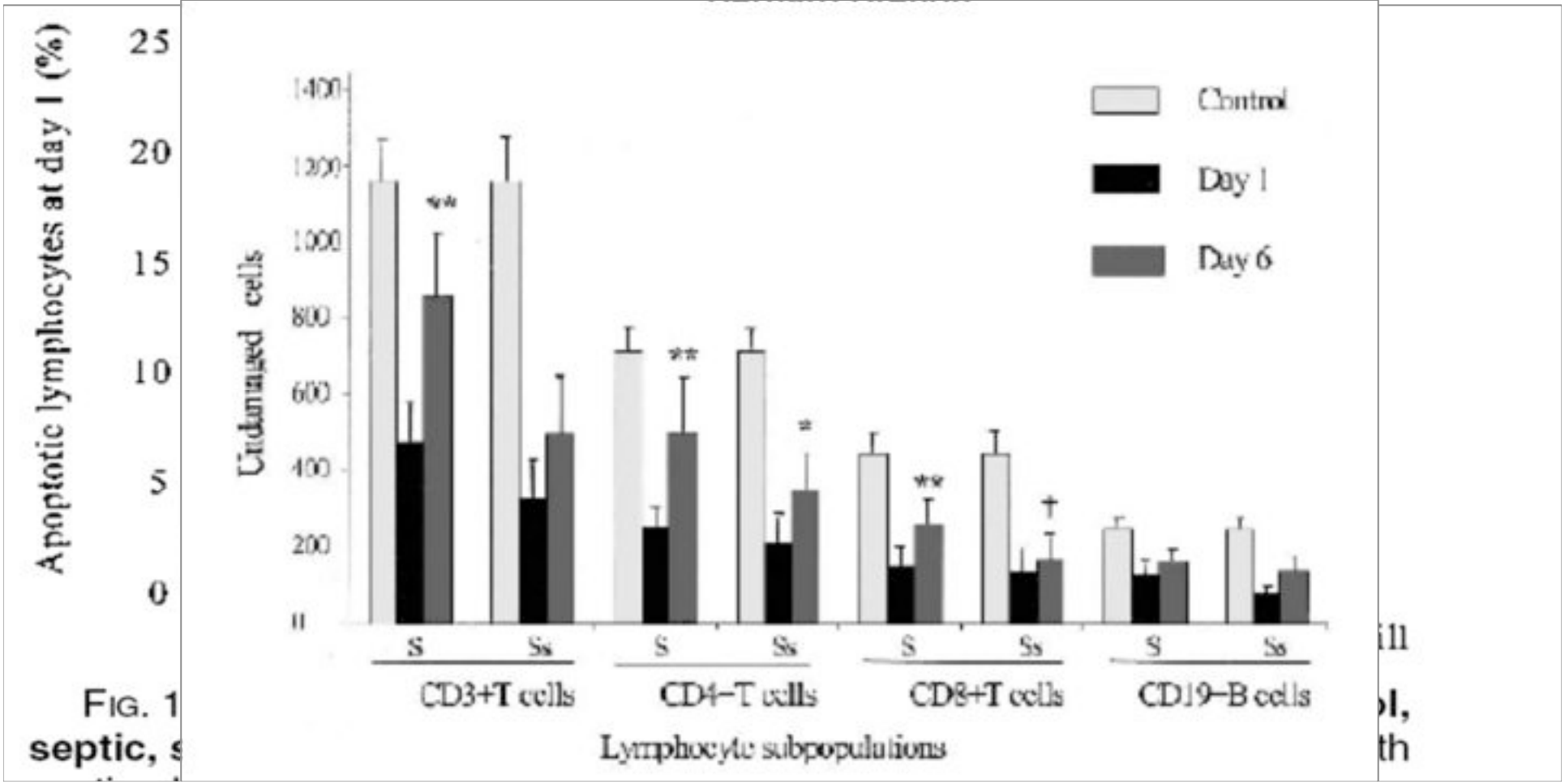



FIG. 1

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Review

Michail S Lionakis and Dimitrios P Kontoyiannis

# Glucocorticoids and invasive fungal infections

Lancet 2003; 362: 1828–38

**Effects on host**

Lymphocytes
- Reversible lymphopenia, CD4 depletion (>50% reduction)[10,11]
- Decreased proliferation and migration of lymphocytes[5,11–13,26]
- Impaired delayed-type hypersensitivity[14,27]
- Impaired natural killer cell cytotoxicity[15]
- Decreased lymphokine production (interleukin-2, TNFα, interleukin-12, interferon γ)[9,28–30]
- Th1/Th2 dysregulation of T-helper cells[9,28–30] (decreased Th1 and increased Th2 cytokine production)
- Impaired phagocyte effector cell function and cellular immune response[5,9–13,28]

Neutrophils
- Impaired phagocytosis, degranulation, and oxidative burst[12,16]
- Reduced cytokine production[16]
- Impaired formation of nitric oxide[22,26]
- Defective adherence to endothelium, extravasation, chemotaxis[16,18–21]
- Inhibition of apoptosis[31]

Monocytes/macrophages
- Reversible monocytopenia (>40% reduction)[25]
- Impaired phagocytosis and oxidative killing[12,17,25,34,35]
- Decreased chemotaxis and migration to sites of inflammation[11,17,25,34,35]
- Impaired formation of nitric oxide[22,26]
- Impaired maturation of monocytes to macrophages[11,17,25,34,35]
- Inhibition of pro-inflammatory cytokine production (interleukin-1, interleukin-6, TNFα)[23,24,30,37,38,80]

Other immune effector cells
- Decreased counts for alveolar dendritic cells, central nervous system microglial cells, and Langerhans' epidermal cells[39–41]
- Impaired antigen-presenting capacity of dendritic and Langerhans' cells (decreased expression of MHC II on their surface)[38,40]
- Defective microglial cell-killing capacity (impaired nitric oxide formation)[41]

Other effects
- Inhibition of prostaglandin production[2]
- Inhibition of host's inflammatory response[2]
- Attenuation of clinical (ie, fever) and radiological signs of infection[2,45]
- Potential delay of diagnosis[2,45]

**Effects on fungi**

*Aspergillus* species
- In vitro increased growth rates of *A fumigatus* and *A flavus*[67]

*Candida* species
- Increased colonisation rates of the oral mucosa and gastrointestinal tract of mice by *Candida albicans* and increased bloodstream translocation from the gastrointestinal tract[62,81]
- Increased adherence capacity to mucosal cells[81]

*Microbiology* (1994), **140**, 2475–2479 Printed in Great Britain

# Hydrocortisone-enhanced growth of *Aspergillus* spp.: implications for pathogenesis

Tony T. C. Ng,[1,3]† Geoffrey D. Robson[2] and David W. Denning[1,3]

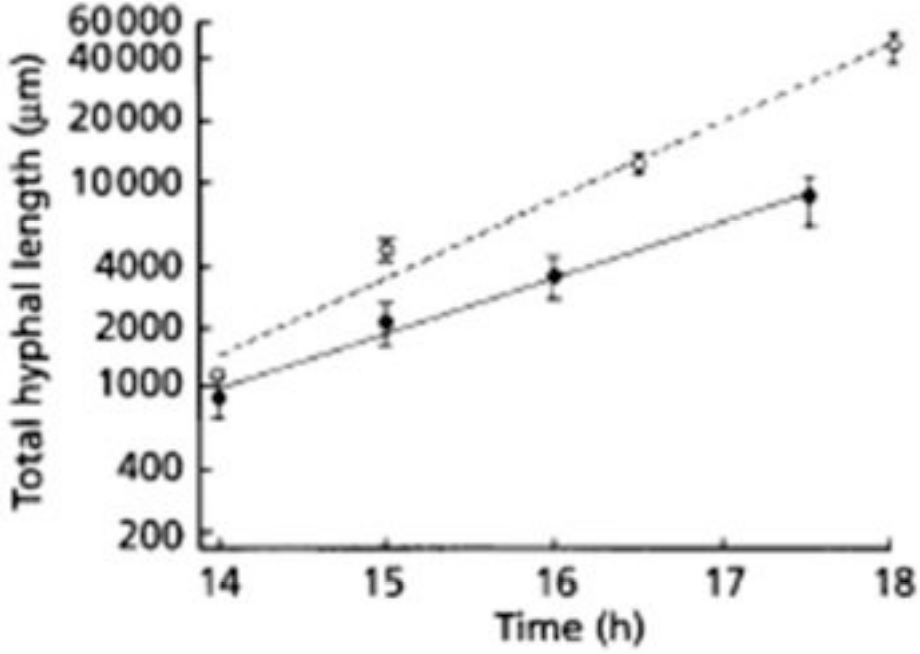



***Fig. 1.*** Increase in total hyphal length (µm) with time (h) in germlings of isolate AF-6 grown at 37 °C with (○) or without (●) $10^{-6}$ M hydrocortisone. At each time point the mean ± SEM of five replicate germlings was plotted.

# Pulmonary Infiltrates in Patients Receiving Long-term Glucocorticoid Treatment*

*Carlos Agustí, MD, PhD; Ana Rañó, MD, PhD; Xavier Filella, MD, PhD; Juliá González, MD, PhD; Asunción Moreno, MD, PhD; Antoni Xaubet, MD, PhD; and Antoni Torres, MD, PhD, FCCP*

**Table 2—*Etiology of Pulmonary Infiltrates and Associated Mortality****

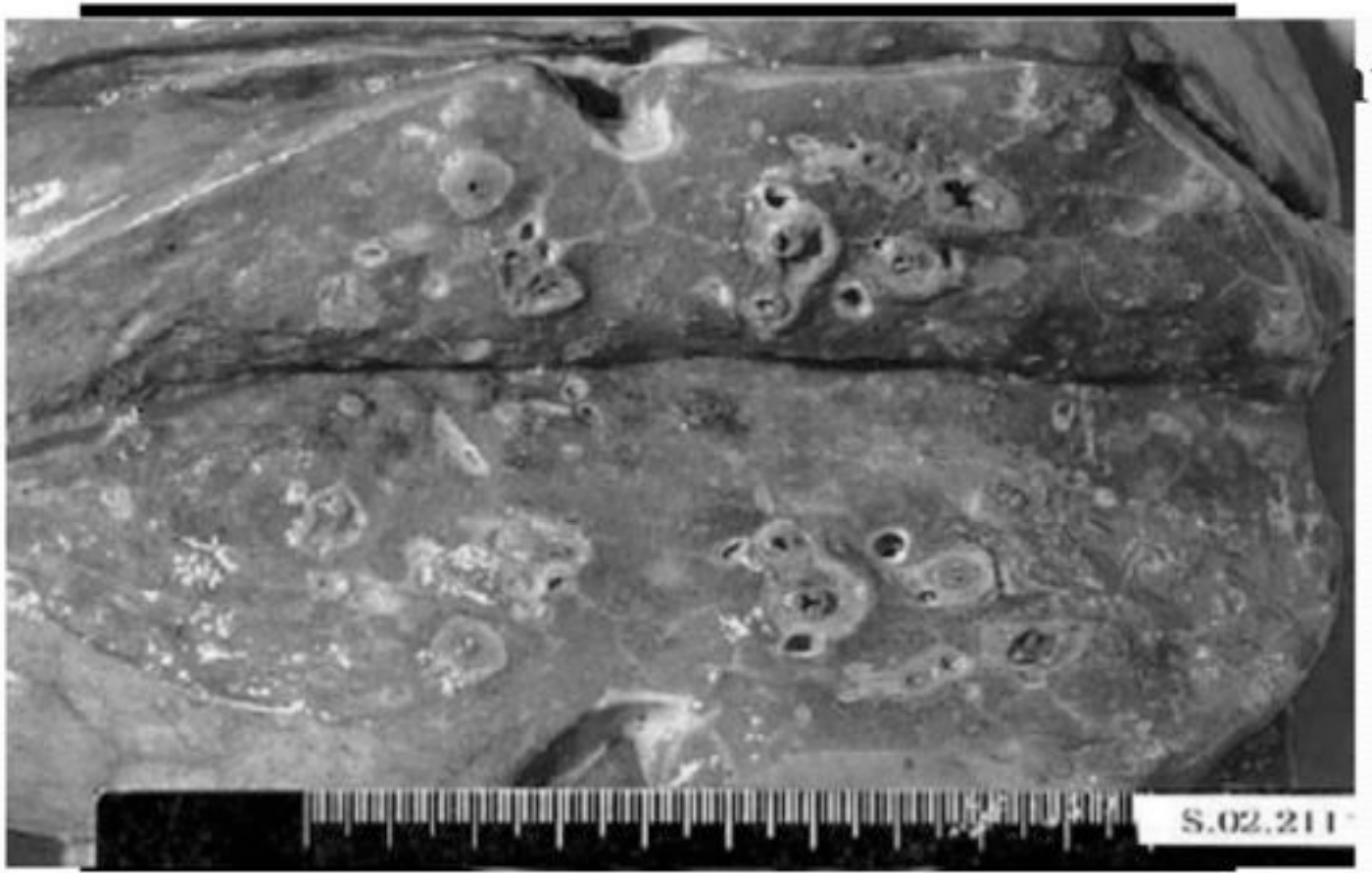
| Variables | Pulmonary Comorbidity: No | Pulmonary Comorbidity: Yes | No./Total Patients (%) |
|---|---|---|---|
| Bacterial | | | |
| *Staphylococcus aureus* oxacillin sensitive | 1 | 1 | |
| MRSA | 1 | 2 | |
| *Enterococcus faecalis* | | 1 | |
| *Gemella morbillorum* | | 1 | 4/10 (40) |
| *P aeruginosa* | | 1 | |
| *Legionella pneumophila* | 1 | | |
| *N asteroides* | | 1 | |
| Fungal | | | |
| *Aspergillus fumigatus* | 1 | 5 | |
| *Candida albicans* | 1 | 1 | 6/9 (67) |
| *Candida tropicalis* | | 1 | |
| Polymicrobial | | | |
| *P aeruginosa* plus *A fumigatus* | 1 | | |
| *Escherichia coli* plus *Aspergillus niger* plus MRSA | | 1 | 2/3 (67) |
| *P aeruginosa* plus *Stenotrophomona maltophilia* plus *A fumigatus* | | 1 | |
| Viral | | | |
| Varicella zoster virus | | 1 | |
| Influenza A virus | 1 | | |
| Other infections | | | |
| *P carinii* | 2 | | 2/4 (50) |
| *M tuberculosis* | 2 | | |
| Noninfectious | | | |

Intensive Care Med (2003) 29:2068–2071
DOI 10.1007/s00134-003-1778-z

BRIEF REPORT

Koen J. Hartemink
Marinus A. Paul
Jan Jaap Spijkstra
Armand R. J. Girbes
Kees H. Polderman

# Immunoparalysis as a cause for invasive aspergillosis?



# Aspergillose en Réanimation

1. Est-ce fréquent ?
2. Qui est à risque ?
3. Pourquoi ?
4. Stratégie diagnostique
5. Qui faut il traiter?

# A Clinical Algorithm to Diagnose Invasive Pulmonary Aspergillosis in Critically Ill Patients

Stijn I. Blot[1], Fabio Silvio Taccone[2], Anne-Marie Van den Abeele[3], Pierre Bulpa[4], Wouter Meersseman[5], Nele Brusselaers[1], George Dimopoulos[6], José A. Paiva[7], Benoit Misset[8], Jordi Rello[9], Koenraad Vandewoude[1], Dirk Vogelaers[1], and the *Asp*ICU Study Investigators*

## EORTC/MSG

- Proven IPA

  **Microscopic analysis or culture on sterile material**

- Probable IPA (all 3 criteria)
  - **1. Host factors**
  - **2. Clinical features**
  - **3. Mycological criteria (one of the following)**
    - **Direct test (cytology, direct microscopy, or culture)**
    - **Indirect tests galactomannan antigen detected in plasma, serum, or BAL fluid**
- Possible IPA

## Alternative clinical algorithm

- Proven IPA
  - **Idem EORTC/MSG criteria**
- Putative invasive pulmonary aspergillosis (all 4 criteria)
- **1. Aspergillus-positive LRT**
- **2. Compatible signs and symptoms**
  - **Fever persistent, Pleuritic chest pain, Pleuritic rub, dyspnea, hemoptysis,**
- **3. Abnormal medical imaging**
- **4. Either 4a or 4b**
  - **4a. Host risk or 4b. Semiquantitative Aspergillus-positive culture of BAL**
- Aspergillus colonization

# Comparison of Epidemiological, Clinical, and Biological Features of Invasive Aspergillosis in Neutropenic and Nonneutropenic Patients:

| Characteristic | Neutropenic patients ($n$ = 52) | Nonneutropenic patients ($n$ = 36) | All patients ($n$ = 88) | $P$ |
|---|---|---|---|---|
| Outcome | | | | |
| Death | 31 (60) | 32 (89) | 63 (71.5) | |
| Recovery | 16 (31) | 3 (8) | 19 (21.5) | .007[a] |
| Unknown | 5 (9) | 1 (3) | 6 (7) | |
| Sensitivity of test, *n/N* (%) | | | | |
| BAL fluid examination[c] | 24/41 (58) | 22/26 (85) | 46/67 (69) | .025[a] |
| *Aspergillus* GM antigenemia test | 7/11 (64) | 15/23 (65) | 22/34 (65) | 1 |
| Antibody serologic test | 1/16 (6.25) | 10/21 (48) | 11/37 (30) | .01[a] |
| Thoracic CT sign, *n/N* (%) | | | | |
| Segmental areas of consolidation | 26/42 (62) | 9/24 (37.5) | 35/66 (53) | .056 |
| Nodules | 18/42 (43) | 11/24 (46) | 29/66 (44) | .81 |
| Cavitated nodules | 8/42 (19) | 6/24 (25) | 14/66 (21) | .57 |
| Ground-glass attenuation | 15/42 (36) | 5/24 (21) | 20/66 (30) | .21 |
| Pleural effusion | 16/42 (38) | 8/24 (33) | 24/66 (36) | .7 |
| Halo sign | 4/42 (9.5) | 0/24 (0) | 4/66 (6) | .29 |
| Air crescent sign | 1/42 (2.5) | 0/24 (0) | 1/66 (1.5) | 1 |
| Bell sign | 3/42 (7) | 1/24 (4) | 4/66 (6) | 1 |
| Aspergillosis cavity | 6/42 (14) | 2/24 (8) | 8/66 (12) | .7 |

Clinical Infectious Diseases 2007; 45:205–16

# Invasive Aspergillosis in the Intensive Care Unit

Wouter Meersseman,[1] Katrien Lagrou,[2] Johan Maertens,[3] and Eric Van Wijngaerden[1]

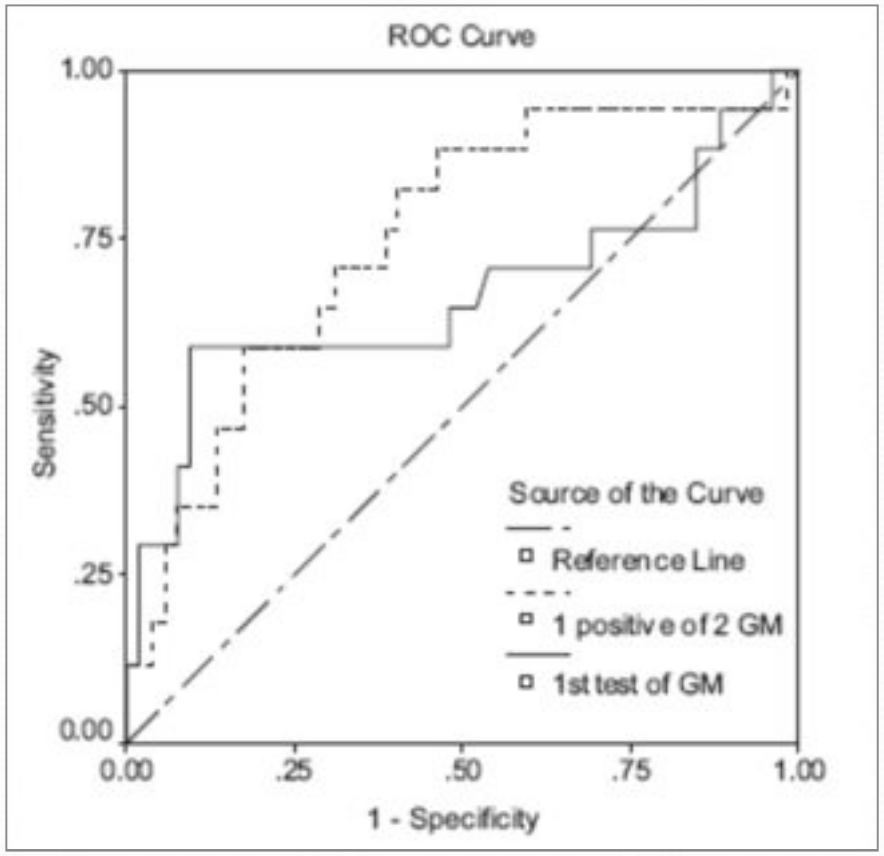
| Diagnostic tool | Characteristic finding | No. of patients [reference] | Applicable in the ICU | Comments |
|---|---|---|---|---|
| CT halo | Halo sign | 25 proven cases [53] | No | Not specific for *Aspergillus* species (also other molds) |
| CT crescent | Crescent sign | 25 proven cases [53] | No | CT often not feasible in a patient with a high fraction of inspired oxygen |
| Histopathologic evidence HistoPat | Acutely branching (45°), septated hyphae mainly in lung tissue | 129 (56 proven) [10];* 100 (15 proven) [5]* | Yes | Biopsies often not feasible in patients with thrombocytopenia or a high fraction of inspired oxygen |
| Culture Culture | Growth on Sabouraud agar | 172 (17 proven) [12];* 36 (5 proven) [11];* (24 centers) [55]; 260 (31 proven) [30] | Moderate | Isolation of the species takes several days; 50% of cases are missed on the basis of culture and microscopy findings; discrimination of colonization versus invasive disease is difficult; positive predictive value increases with increased immunosuppression |
| Direct microscopy | PAS, Grocott stain, calcofluor visualization of hyphal elements (not only *Aspergillus* species), rapid test | 172 (17 proven) [12];* 36 (5 proven) [11];* (24 centers) [55]; 260 (31 proven) [30] | Moderate | Same as above |
| GM | Polysaccharide released by the fungus in the event of invasiveness (threshold, 0.5–1.5 ng/mL) | [56] | eval | In the nonneutropenic, critically ill patient, bronchoalveolar fluid may perform better than serum |
| PCR | DNA material of *Aspergillus fumigatus* | [57] | eval | In the nonneutropenic, critically ill patient, bronchoalveolar fluid may perform better than blood |
| β-(1,3)d-Glucan | Fungal cell wall component | 61 [58] | eval | Not specific for *Aspergillus* species; also present in yeasts and bacteria; may be useful as a negative predictor of fungal infection |

*Medical Mycology* Month 2010, **Early Online**, 1–7

**90 COPD patients. GM D1/D4.**

# Value of consecutive galactomannan determinations for the diagnosis and prognosis of invasive pulmonary aspergillosis in critically ill chronic obstructive pulmonary disease

HANGYONG HE*,†, LIN DING*,†, SHUO CHANG*, FANG LI† & QINGYUAN ZHAN*




**Prevalence of IPA = 21.1%**

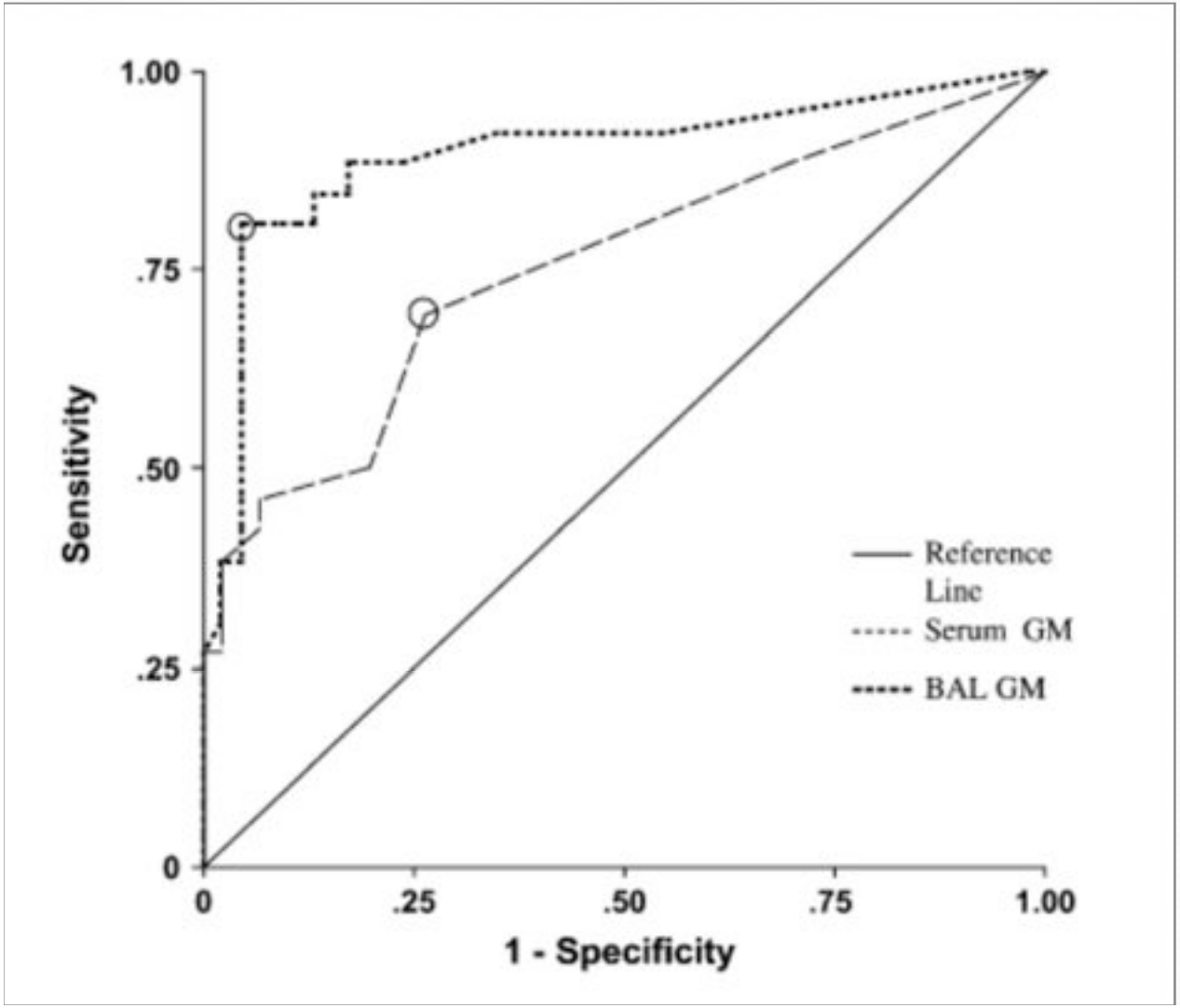
**AUC**
**0.662 (0.483 – 0.842) for a first positive result,**

**0.749 (0.612 – 0.886) for at least one positive GM**

# Galactomannan in Bronchoalveolar Lavage Fluid

## A Tool for Diagnosing Aspergillosis in Intensive Care Unit Patients

Wouter Meersseman[1], Katrien Lagrou[2], Johan Maertens[3], Alexander Wilmer[1], Greet Hermans[1], Steven Vanderschueren[1], Isabel Spriet[4], Eric Verbeken[5], and Eric Van Wijngaerden[1]




**Se**

**Serum GM 42%**

**BAL GM 88%**

## A prospective comparison of GM in BAL fluid for the diagnosis of pulmonary invasive aspergillosis

- **AUC for GM in BAL was 0.98 (0.94-1.00), whilst for GM and BG in serum were 0.85 (0.74-0.96) and 0.815 (0.66-0.96), respectively.**
- **In 2 IA cases, GM in serum remained negative, whereas GM in BAL was positive.**
- **In patients with IA, GM(90%) and BG(80%) appeared a mean of 4.3 days (1-10 days) before Aspergillus was cultured.**

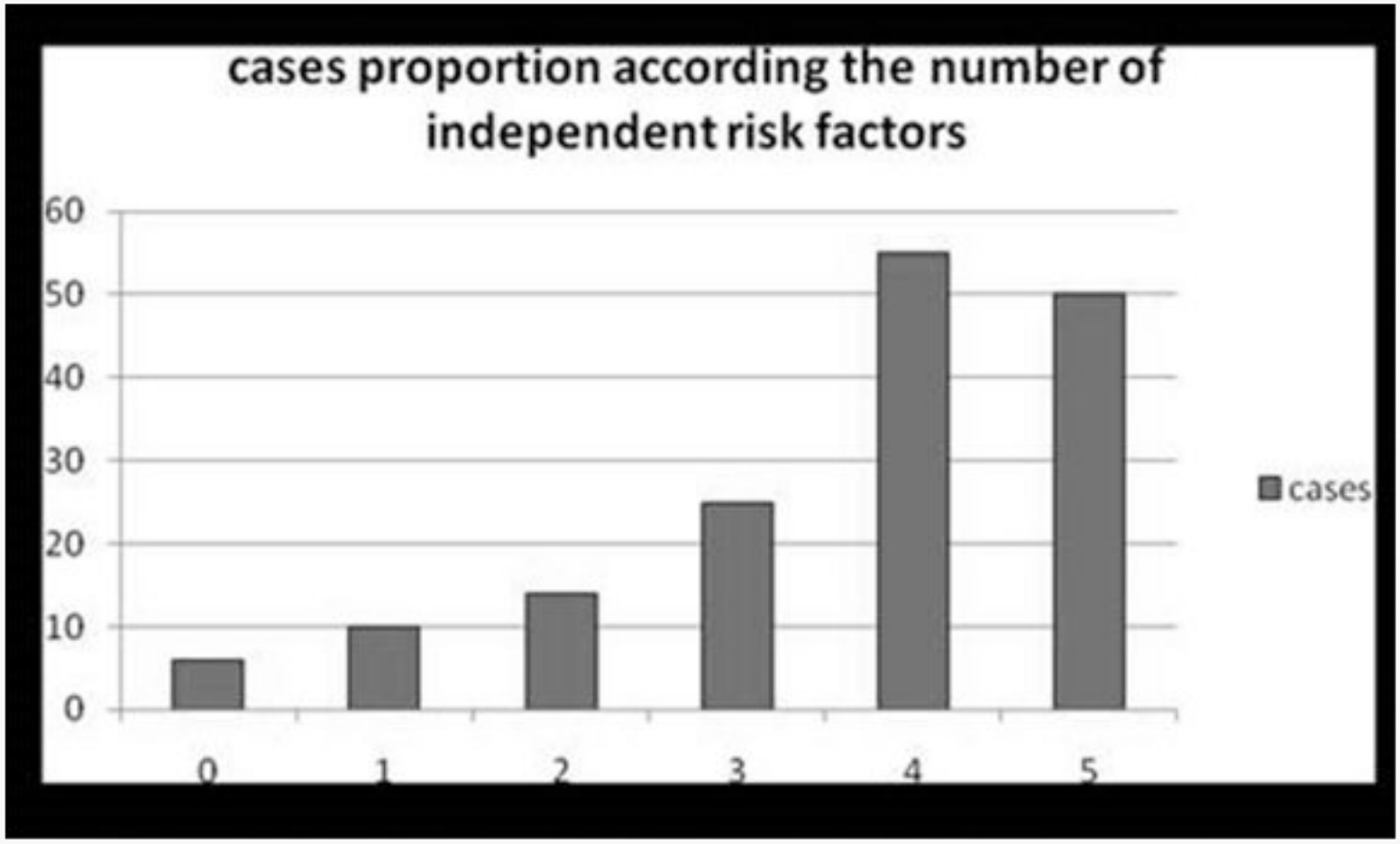
Acosta J et al. Clin Microbiol Infect. 2010 Sep 3.

# Outcomerea (Asparagus) ARDS, sepsis, steroids ...

| Characteristic | Odds Ratio | Confidence interval | P value |
|---|---|---|---|
| **Age greater than 70 years** | 2.18 | [1.06-4.47] | P=0.03* |
| **ARDS** | 2.35 | [1.13-4.86] | P=0.02* |
| **Stress Dose Steroids** | 9.80 | [3.91-24.60] | P<0.01* |
| **Long Term Steroids** | 6.30 | [1.85-21.39] | P<0.01* |
| **Maximal SOFA score *in the 10 days before positive sample*** | 1.13 | [1.03-1.25] | P=0.01* |
| **Bacterial infection** | 2.69 | [1.34-5.36] | P<0.01* |

**Lugosi et al. Submmited**

# ARDS d'origine septique qui a reçu des stéroïdes



# *Inconnues*

1. **Réalité de l'immunocompétence?**
2. **Le délai avant Aspergillus+ est de deux semaines: nouvelles études?**
   - **Uniquement ARDS ou MOF?**
3. **Les patients sont ils décédés avec une API ou d'une API?**
4. **Prophylaxie? Traitement précoce?**
5. **Immunomodulation?**


# Merci de votre attention

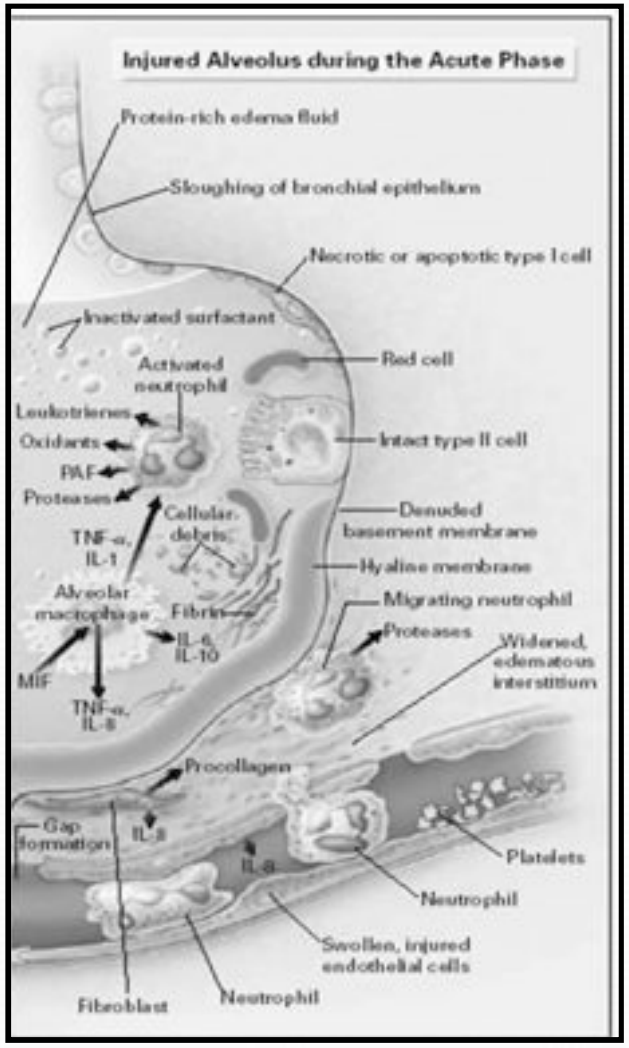
# SDRA et aspergillose

**Dans une étude observationnelle cas-témoin appariés, le SDRA apparaissait comme un facteur de risque d'avoir un prélèvement positif à aspergillus**

**OR= 2,36 [1,14-4,89] (p=0,02)**

***Vandewoude et al. Crit Care, 06***

# SDRA et aspergillose




**Parallèlement à la réponse pro inflammatoire, apparition d'une réponse anti inflammatoire (IL-10, TNFr, IL-1ra,…)**

- **Désactivation monocytaire sous ventilation mécanique**

***Copland et la, AJRCCM, 03***

- **Déséquilibre dans la répartition des Lymphocytes T effecteurs en faveur des Th2/Th3** ***PLötz et al, Crit Care Med, 04***
- **Augmentation des cytokines anti inflammatoire (IL-10, TNFα-r1, IL-1ra)**
- **Le ratio pro/anti inflammatoire est en faveur des cytokines anti inflammatoires dans les 1er jours du SDRA puis S'équilibre vers le 7e jour.**

***Park et al, AJRCCM, 01***

# Etude prospective multicentrique dans l'ARDS

- **Patients ventilés > J7 et sous antibiotiques**
- **Surveillance bi-hebdomadaire aspirations, galactomannane et clinique**
- **Si +, TDM-HR, LBA et sinus**
- **Malades classés en API, colonisation**
- **Discussions thérapeutiques**

# Invasive aspergillosis: a life-threatening complication of short-term steroid treatment.

- **A 78-year-old man with COPD developed an IPA after short-term (less than 1 week) intravenous steroid therapy.**

- **The diagnosis was established by recovering *Aspergillus fumigatus* from a bronchoalveolar lavage and was confirmed by autopsy, with the additional finding of an aspergilloma.**

**Conesa D, Rello J, Vallés J, Mariscal D, Ferreres JC. Ann Pharmacother. 1995 Dec;29(12):1235-7.**

# The Impact of Culture Isolation of *Aspergillus* Species: A Hospital-Based Survey of Aspergillosis

Clinical Infectious Diseases 2001;33:1824–33

J. R. Perfect,[1] G. M. Cox,[1] J. Y. Lee,[2] C. A. Kauffman,[3] L. de Repentigny,[4] S. W. Chapman,[5] V. A. Morrison,[6] P. Pappas,[2] J. W. Hiemenz,[7] D. A. Stevens,[8] and the Mycoses Study Group[a]

- **Risk for invasive aspergillosis**
- **High**
  - **AlloBMT, neutropenia, hematological malignancy**
- **Intermediate**
  - **autoBMT, Malnutrition,**
  - **Sepsis, Steroids,**
  - **COPD, underlying pulmonary disease, Diabetes**
  - **HIV, SOT, Solid tumor**
- **Low**
  - **CF, Connective tissue disorder**

BMC Gastroenterology

BioMed Central

Case report

Open Access

**Invasive pulmonary aspergillosis in patients with decompensated cirrhosis: case series**

Hélène Prodanovic[1], Christophe Cracco[1], Julien Massard[2], Camille Barrault[3], Dominique Thabut[2], Alexandre Duguet[1], Annick Datry[4], Jean-Philippe Derenne[1], Thierry Poynard[2] and Thomas Similowski*[1]

- **Three cases of IPA in cirrhotic patients**
- **All were treated by steroids**
- **All died (all on voriconazole)**

Intensive Care Med (2001) 27: 59–67
DOI 10.1007/s001340000768

ORIGINAL

Pierre A. Bulpa
Alain M. Dive
Maria-Grazia Garrino
Monique A. Delos
Manuel R. Gonzalez
Patrick A. Evrard
Youri Glupczynski
Etienne J. Installé

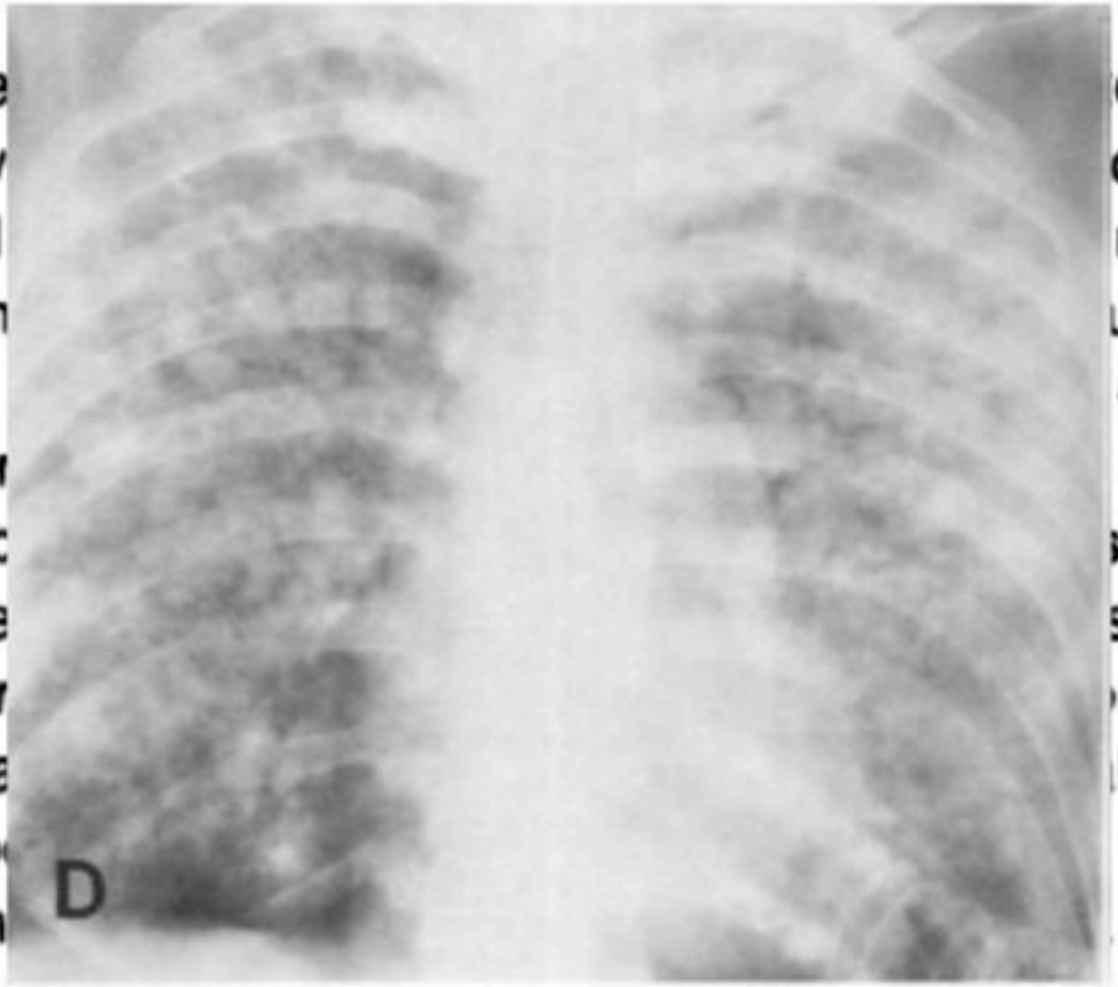
# Chronic obstructive pulmonary disease patients with invasive pulmonary aspergillosis: benefits of intensive care?

| Patient no. | Source of *Aspergillus fumigatus* isolation | Histological confirmation | Probability of diagnosis[a] | Treatment: mean AmBd (mg/kg per day) |
|---|---|---|---|---|
| 1 | ETA | Yes | Confirmed (H) | 1.3 + itra, 4 days |
| 2 | Sputum + ETA | Yes | Confirmed (H) | 0.8 + itra, 6 days |
| 3 | Sputum + ETA | Yes | Confirmed (H + A) | 1 + itra + GM-CSF, 23 days |
| 4 | ETA | Yes | Confirmed (H + A) | 1.3 + itra, 3 days |
| 5 | Sputum + ETA | No | Probable | 0.55, 3 days |
| 6 | Sputum + ETA | Yes | Confirmed (H) | 0.9, 25 days |
| 7 | Sputum + ETA | No | Probable | 0.73 + itra, 14 days |
| 8 | ETA | Yes | Confirmed (A) | 0.7, 5 days |
| 9 | ETA | No | Probable | 0.8, 2 days |
| 10 | Sputum + ETA | No | Probable | 0.57 + itra + GM-CSF, 17 days |
| 11 | ETA | No | Probable | 0.56, 4 days |
| 12 | Sputum + ETA | No | Probable | 0.83, 5 days |
| 13 | ETA + BAL | No | Probable | 0.7 + itra, 12 days |
| 14 | Sputum + ETA | Yes | Confirmed (A) | 0.74, 7 days |
| 15 | Sputum + ETA + BAL | No | Probable | 0.71, 10 days |
| 16 | Sputum + ETA | No | Probable | 0.9, 16 days |

# Miliary Aspergillosis Associated with Alcoholism

JEFFREY BLUM,[1] JAMES C. REED,[1] SALVATORIE V. PIZZO,[2] AND WILLIAM M. THOMPSON[1]

*Am J Roentgenol* 131:707–709, October 1978


The patie er admission. Autopsy rev of both lungs. The pleural nodules measuring 3 mn ungs revealed similar tan diffusely and uniformly i vessels were unremarkab strated a necrotizing pne s containing a mass of thi nstrated both by routine a lly, this is the typical app liver showed passive con

# Aspergillus in COPD patients

| Study | Year | Number of Patients | Outcome | Aspergillus Isolation | Steroid Treatment | Diagnosis confirmation |
|---|---|---|---|---|---|---|
| Tankanow et al | 1988 | 1 | NS | SP | YES | Autopsy |
| Wiest et al | 1989 | 3 | NS | SP,PSB,BAL | YES | Autopsy |
| Palmer et al | 1991 | 1 | NS | BA | YES | Autopsy |
| Thommi et al | 1991 | 2 | NS | BAL,PSB, LB | YES | Autopsy |
| Rodriguez et al | 1992 | 5 | NS | SP,LB | YES | Autopsy |
| Crean et al | 1992 | 1 | NS | PSB | YES | Autopsy |
| Conesa et al | 1995 | 1 | NS | BAL | YES | CT-scan and Autopsy |
| Pittet et al | 1996 | 2 | NS | BAL, BA | YES | CT-scan and Autopsy |
| Rello et al | 1998 | 8 | NS | BAL,PSB, BSP | YES | CT-scan and Autopsy |
| Franquet et al | 2003 | 9 | NS | LB | YES | CT-scan and Autopsy |
| Dimopoulos et al | 2002 | 5 | NS | BAL, SP | YES | Autopsy |

**Miguel Gallego, Sabadell**

Intensive Care Med (2003) 29:1981–1988
DOI 10.1007/s00134-003-2008-4

ORIGINAL

# A 7-year study of severe hospital-acquired pneumonia requiring ICU admission

Jordi Vallés
Eduard Mesalles
Dolors Mariscal
Ma del Mar Fernández
Rocío Peña
José Luis Jiménez
Jordi Rello

**In ICU patients with Hospital acquired pneumonia Aspergillus is recovered in 17% of the samples**

| Micro-organisms | Overall | | | Hospital | | | | Diagnostic technique (no.positive samples) |
|---|---|---|---|---|---|---|---|---|
| | Episodes | | Fatal | HS | | HGTP | | |
| | *n* | | | | | | | |
| Gram-negative | | | | | | | | |
| *P. aeruginosa* | 18 | | | | | | | B (11), S (8), Pl (3), B (3) |
| *L. pneumophila* | 9 | | | | | | | R (6), PB (6), UAg (1) |
| *S. marcescens* | 2 | | | | | | | B (1), S (1) |
| *H. influenzae* | 2 | | | | | | | B (2) |
| *A. baumannii* | 1 | | | | | | | B (1), B (1) |
| *C. freundii* | 1 | | | | | | | B (1), S (1) |
| *E. cloacae* | 1 | | | | | | | B (1) |
| *E. coli* | 1 | 1 | 1 | 1 | 2 | – | – | B (1) |
| *K. pneumoniae* | 1 | 1 | 1 | – | – | 1 | 3 | S (1) |
| *P. mirabilis* | 1 | 1 | 1 | 1 | 2 | – | – | PB (1) |
| Gram-positive | | | | | | | | |
| *S. pneumoniae* | 11 | 15 | 3 | 6 | 13 | 5 | 17 | PB (5), S (3), B (3), Pl (1) |
| *S. aureus* | 9 | 12 | 6 | 7[a] | 15.5[a] | 2[a] | 7[a] | PB (6), S (4), B (3), Pl (1) |
| *S. viridans* | 2 | 3 | 1 | 1 | 2 | 1 | 3 | PB (1), S (1) |
| Fungi | | | | | | | | |
| *Aspergillus* spp. | 13 | 17 | 10 | 11** | 24** | 2** | 7** | PB (5), H (8)[b] |
| *P. carinii* | 1 | 1 | 1 | – | – | 1 | 3 | PB (1) |
| Virus | | | | | | | | |
| Ccytomegalovirus | 2 | 3 | 1 | – | – | 2 | 7 | BAg (2) |

Intensive
DOI 10.1

George
Michael
Jacques
Isabelle
Jean-Lo

**Table 3** Major discrepancies (Class I/II) in relation to the fundamental disease

| Patient | Fundamental disease | Autopsy diagnosis | Comment / Possible treatment/Interventions |
|---|---|---|---|
| 1 | AIDS, coma | Disseminated aspergillosis | Death occurred on the 5th ICU admission. High suspicion of fungal infection. Culture negative. Involved organs: brain, lungs, kidneys, liver. Empirical antifungal therapy given |
| 2 | Pneumonia, ARDS, Sepsis, arrhythmia, arterial hypertension, alcoholism | Mesenteric infarction | Patient receiving anticoagulation. Sudden deterioration and death |
| 3 | Pneumonia, septic shock, diabetes mellitus, lymphoma | Pulmonary embolism | Patient receiving low molecular weight heparin. Sudden death |
| 4 | Cirrhosis, hepatopulmonary syndrome, | Nosocomial pneumonia | Second VAP episode. No detected pathogen. Empirical |
| | **COPS, SEPSIS, Invasive Aspergillosis** | | |
| 6 | Pulmonary embolism, thrombosis of | Nosocomial pneumonia | Empiric antibiotic therapy. Microabscesses of the lungs. |
| | **SEPSIS, Invasive Aspergillosis** | | |
| | | | urine antigen (+). Empirical antifungal therapy |
| 8 | Myocardial infarction, atrial fibrillation, VAP, sepsis | Mesenteric infarction | Sudden deterioration and death. Receiving anticoagulation |
| | **Lung Tx, Invasive Aspergillosis** | | |
| | **Lung Tx, Invasive Aspergillosis** | | |
| 13 | Ischemic heart disease, pulmonary | Pulmonary embolism | Appropriate anticoagulant therapy. Diagnosis not con- |
| | **Crohn Disease, Invasive Aspergillosis** | | |
| | | | considered |
| 15 | Pneumonia, diabetes mellitus, alcoholism, hepatitis C | Systemic candidiasis | Positive sputum cultures (+) for *Candida albicans*. Blood cultures (–). Empirical antifungal therapy |
| 16 | Septic shock, pneumonia, COPD, diabetes mellitus, pulmonary hypertension | Myocardial infarction | No specific ECG signs. Trop test (+). No elevated cardiac enzymes |
| 17 | MRSA pneumonia, septic shock, MOF | Endocarditis | Transesophageal ultrasonography not diagnostic, blood cultures negative. Appropriate therapy was given. High suspicion but no confirmed pre mortem diagnosis |
| 18 | Trauma, septic shock, MOF | Pulmonary embolism | The diagnosis was considered possible. Treatment was given |
| 19 | Pneumonia, COPD, right heart failure, pulmonary hypertension | Pulmonary embolism | The diagnosis was considered possible. Treatment was given |

# Invasive aspergillosis in critically ill patients: attributable mortality and excesses in length of ICU stay and ventilator dependence☆

Journal of Hospital Infection (2004) 56, 269-276

K.H. Vandewoude[a,*], S.I. Blot[a,1], D. Benoit[a], F. Colardyn[a], D. Vogelaers[b]

| Underlying condition/principal diagnosis | Number of patients |
|---|---|
| Haematological malignancies: | |
| With associated neutropenia | 6 |
| With previous bone marrow transplantation | 3 |
| Myelodysplastic syndrome | 2 |
| Immunosuppressive therapy: | |
| In case of liver transplant | 3 |
| In case of renal transplant and associated myelodysplastic syndrome | 1 |
| Polymyalgia rheumatica with neutropenia and septic shock | 1 |
| Aplastic anaemia due to thiamazol | 1 |
| Chronic obstructive pulmonary disease: | |
| Requiring chronic oral glucocorticoid use | 5 |
| Requiring inhalation steroids only | 2 |
| Liver cirrhosis | 3 |
| Severe bacterial infection | 3 |
| Miscellaneous: | |
| Near drowning with acute respiratory distress syndrome (ARDS) | 1 |
| Polytrauma with ARDS | 1 |
| Extensive burns with ARDS | 1 |
| Bacterial pneumonia with ARDS | 1 |
| Malnutrition | 1 |
| Fulminant liver failure | 1 |
| Viral pneumonia with myocarditis | 1 |

**20 patients !!**

Intensive Care Med (2007) 33:1694–1703
DOI 10.1007/s00134-007-0791-z

REVIEW

R. J. Trof
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# Management of invasive pulmonary aspergillosis in non-neutropenic critically ill patients

## Risk factors for IPA in non-neutropenic critically ill patients in the ICU

| Risk factor |
|---|
| COPD in combination with prolonged corticosteroid use |
| High-dose systemic corticosteroids > 3 weeks (e. g. prednisone equivalent > 20 mg/day) |
| Chronic renal failure with RRT |
| Liver cirrhosis/acute hepatic failure |
| Near-drowning |
| Diabetes mellitus |

**Incidence 0.3-6%, Mortality > 80%**
**Increased mortality in colonized patients**

# Pulmonary aspergillosis in patients with COPD

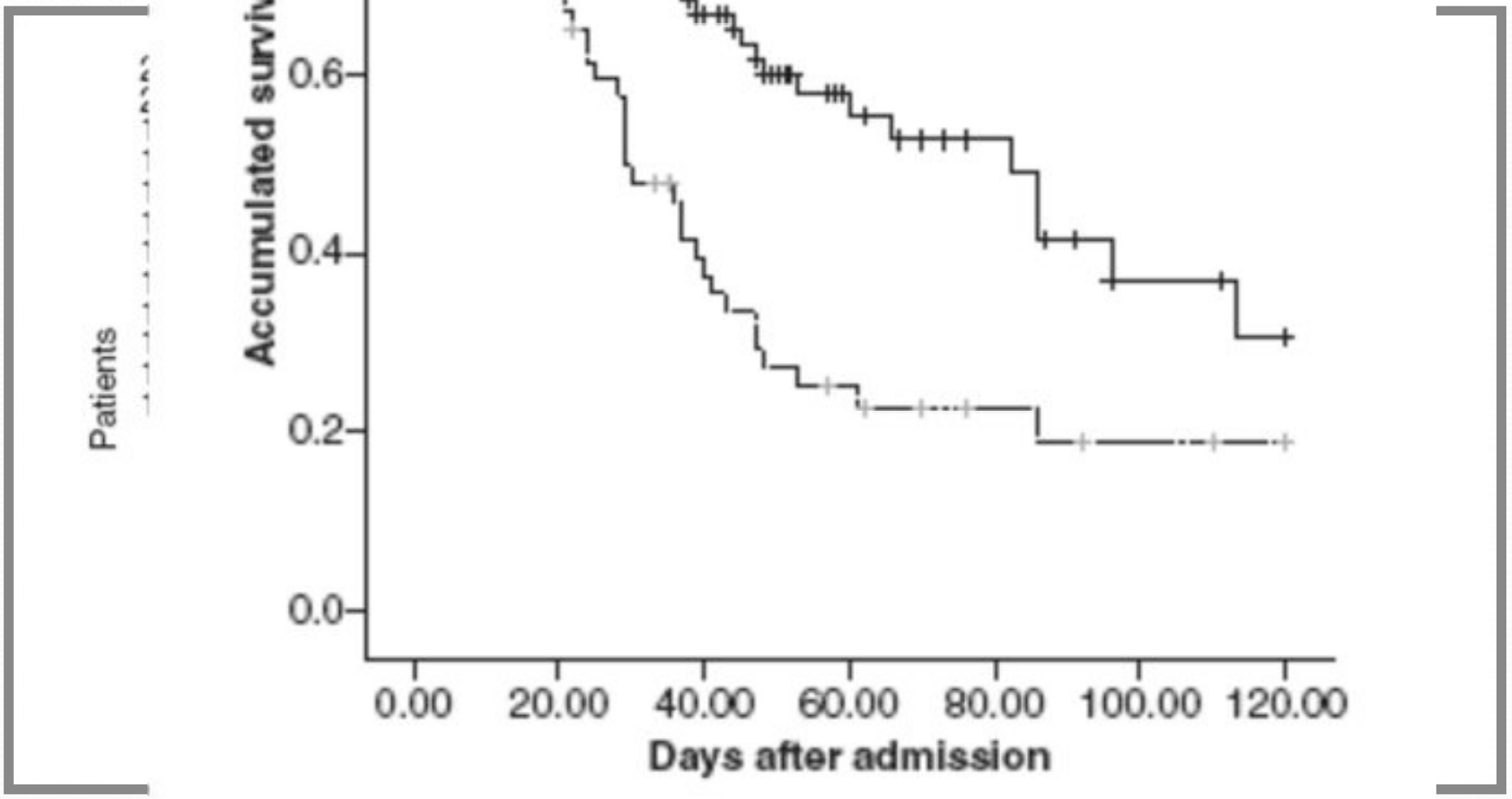
- **IPA affects at least 22.1% of patients with COPD and isolation of Aspergillus in culture.**
- **Serum galactomannan : 42.4% positivity**
- **Five variables were independent predictors of IPA (AUC 0.92 (0.88-0.96)**
  - **admission to the intensive-care unit,**
  - **chronic heart failure,**
  - **antibiotic treatment (in the 3 months),**
  - **the accumulated dosage of steroids equivalent to >700 mg prednisone received in the 3 months**
  - **accumulated dosage of steroids received from admission to the first clinical isolation of Aspergillus.**

**Guinea J, et al. Clin Microbiol Infect. 2010 Jul;16:870-7**

ORIGINAL

Pulmona
disease:

J. Guinea[1,2], M



EDITORIAL *Clin Microbiol Infect* 2005; 11: 427–429

# Invasive pulmonary aspergillosis in chronic obstructive pulmonary disease: an emerging fungal pathogen

*F. Ader[1], S. Nseir[2], R. Le Berre[3], S. Leroy[4], I. Tillie-Leblond[4], C. H. Marquette[4] and A. Durocher[2]*

| Patient no. | Source of *Aspergillus fumigatus* isolation | Chest CT scan | Number of serum GM detections | Steroid mean dose (mg/kg/day) | Treatment |
|---|---|---|---|---|---|
| 1 | Sputum + ETA | Yes | 0 | 0.9 | AmBd |
| 2 | ETA + BAL | Yes | 0 | 0.9 | Itraconazole |
| 3 | ETA + BAL | No | 2 | 1.6 | Voriconazole |
| 4 | ETA | No | 0 | 1.4 | Ambd |
| 5 | ETA | No | 0 | 1.2 | No antifungal treatment |
| 6 | ETA + BAL | No | 0 | 0.8 | No antifungal treatment |
| 7 | ETA + BAL | No | 0 | 1.9 | No antifungal treatment |
| 8 | ETA + BAL | Yes | 1 | 0.8 | AmBd |
| 9 | ETA + BAL | No | 0 | 1.2 | Ambd |
| 10 | ETA | No | 0 | 1.6 | Ambd |
| 11 | ETA + BAL | No | 1 | 0.7 | Ambd |
| 12 | ETA | No | 0 | 1.1 | Ambd |
| 13 | ETA + BAL | Yes | 3 | 1.1 | Ambd |

*Thorax* 1991;46:15–20



# Corticosteroid treatment as a risk factor for invasive aspergillosis in patients with lung disease

Lucy B Palmer, Harly E Greenberg, Mark J Schiff

| *Patient No* | *1* | *2* | *3* | *4* | *5* | *6** |
|---|---|---|---|---|---|---|
| Age, sex | 75, F | 76, M | 30, M | 63, M | 74, M | 74, M |
| Underlying disease | Idiopathic pulmonary fibrosis | Lung cancer, non-small cell CNS metastases | Sarcoidosis | Lung cancer, small cell | Lung cancer, non-small cell; radiation pneumonitis | Chronic obstructive lung disease |
| Steroid dose, duration of treatment | Prednisone: 40 mg/d × 6 wk | Dexamethasone: 16 mg/d × 4 mo | Prednisone: 20–40 mg/d × 3 y | Dexamethasone: 24 mg/d tapered to 8 mg/d × 1 mo | Prednisone: 30 mg/d × 3 wk | Prednisone: 10–30 mg/d |
| Amphotericin treatment | + | + | + | | | + |
| Sputum or lavage fluid culture | BAL: *Aspergillus fumigatus* | BAL: *A fumigatus* | BAL, sputum: *Aspergillus* sp | Sputum: *Aspergillus* sp | Sputum: *Aspergillus* sp | Sputum: *Aspergillus* sp |
| White blood count ( × $10^9$/l) | 18·3 | 14·9 | 35·0 | 6·8 | 19·5 | 33·6 |
| Chest radiograph | Diffuse infiltrates | RML infiltrate | RUL cavity RUL, LLL infiltrates | RUL, LUL infiltrates | RUL cavity, air-fluid level; RUL, LLL infiltrates | RUL infiltrate |
| Necropsy, lung histology, culture | Necrotising pneumonitis with *Aspergillus* | — | Mycetoma with *Aspergillus*; fungal culture negative *Pseudomonas aeruginosa* | Necrotising pneumonitis with *Aspergillus* | Necrotising pneumonitis with *Aspergillus* | Necrotising pneumonitis with *Aspergillus* |