Sessione 5
Sessione Congiunta AMCLI – FADOI
INFEZIONI GRAVI IN MEDICINA INTERNA: GESTIONE E NUOVI FARMACI

L'Aspergillosi invasiva nel paziente non neutropenico

Carlo Tascini

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Il sottoscritto Carlo Tascini
ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,

dichiara

che negli ultimi due anni ha avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

- *Merck*
- *Pfizer*
- *Astellas*
- *Angelini*
- *Gilead*
- *Novartis.*
- *Thermofischer*
- *Biotest*

Incidenza

Infect Dis Ther (2018) 7:17–27
https://doi.org/10.1007/s40121-017-0183-9

REVIEW

Challenges and Solution of Invasive Aspergillosis in Non-neutropenic Patients: A Review

Matteo Bassetti · Maddalena Peghin · Antonio Vena

high rates of morbidity and mortality [1]. Over the past decades, the population of patients susceptible to develop IA has expanded significantly and IA has increasingly been recognized as an emerging disease of non-neutropenic patients with an incidence varying between 0.33–5.8% [2, 3]. In addition, the classical view

Mortalità e sospetto diagnostico

Invasive aspergillosis in non-neutropenic patients is associated with bad prognosis, with mortality rates exceeding 80%, mainly due to delayed diagnosis [2, 3]. Difficulties in achieving a timely diagnosis of IA in non-neutropenic patients is related to the non-specificity of clinical presentation and to lower yields with diagnostic tests compared to neutropenic patients [2, 3].

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REVIEW

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Intermediate-risk category

Prolonged treatment with corticosteroids before admission to the ICU

Autologous bone marrow transplantation

Chronic obstructive pulmonary disease

Liver cirrhosis with a duration of stay in the ICU > 7 days

Solid-organ cancer HIV infection

Lung transplantation

Systemic diseases requiring immunosuppressive therapy

Infect Dis Ther (2018) 7:17–27
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REVIEW

Challenges and Solution of Invasive Aspergillosis in Non-neutropenic Patients: A Review

Matteo Bassetti · Maddalena Peghin · Antonio Vena

lying conditions (Table 1) [6], immunoregulatory abnormalities following critical illness can induce a state of immunoparalysis, hampering adequate host response to fungal disease in the ICU [9]. Other predisposing risk factors frequently met in ICUs include acute respiratory distress syndrome (ARDS), severe sepsis, acute renal failure, and H1N1 virus infection (especially if CS prior to ICU admission) [8]. More-

Epidemiologia IFI in ICUItaly 2006 – 2008

Tortorano AM et al Mycoses 2011

- Aspergillus
  - 6.31 / 1000 ricoveri
- Corticosteroidi
  - Rischio più comune
- Mortalità cruda maggiore rispetto a candidemia
  - 63% Vs. 46%

Table 2 Characteristics of *Aspergillus* infections in ICU patients.

Sex, male/female	34/23
Age, mean (range), years	52.08 (4–85)
SAPS-II, median (range)	47 (15–96)
SOFA, median (range)	9.42 (1–19)
Host/predisposing factors	
Corticosteroid treatment	25
Autoimmune disease	9
COPD	6
Haematological cancer	6
Solid cancer	5
Organ transplantation	4
Aspergillus species	
Aspergillus fumigatus	47
Aspergillus flavus	5
Aspergillus niger	1
Mixed infection[1]	4
Laboratory diagnosis	
Positive biopsy/autopsy	7
Positive: hyphae, culture[2], GM	17
Positive: hyphae, culture[2]	14
Repeatedly positive cultures[2]	19

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

REVIEW

R. J. Trof
A. Beishuizen
Y. J. Debets-Ossenkopp
A. R. J. Girbes
A. B. J. Groeneveld

Management of invasive pulmonary aspergillosis in non-neutropenic critically ill patients

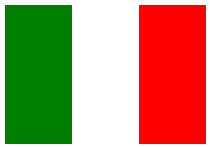
Table 1 Risk factors for IPA in non-neutropenic critically ill patients in the ICU

Risk factor	Reference
COPD in combination with prolonged corticosteroid use	[1, 24–26]
High-dose systemic corticosteroids > 3 weeks (e. g. prednisone equivalent > 20 mg/day)	[2, 31, 33]
Chronic renal failure with RRT	[8, 35]
Liver cirrhosis/acute hepatic failure	[2–4, 34]
Near-drowning	[4, 36–38]
Diabetes mellitus	[2, 3, 31, 33]

COPD, Chronic obstructive pulmonary disease; *RRT*, renal replacement therapy

Falcone et al. Inter Emerg med 24 maggio 2014

- Aspergillosi nel non-neutropenico
- Medicine 60 %
- ICU 30%
- Chirurgie 10%
- Fattori di rischio: BPCO, Cirrosi, terapia steroidea, H1N1



CURRENT OPINION

Invasive pulmonary aspergillosis complicating severe influenza: epidemiology, diagnosis and treatment

Lore Vanderbeke[a,b], *Isabel Spriet*[c,d], *Christine Breynaert*[e]
Bart J.A. Rijnders[f], *Paul E. Verweij*[g,h], *and Joost Wauters*[b,i]

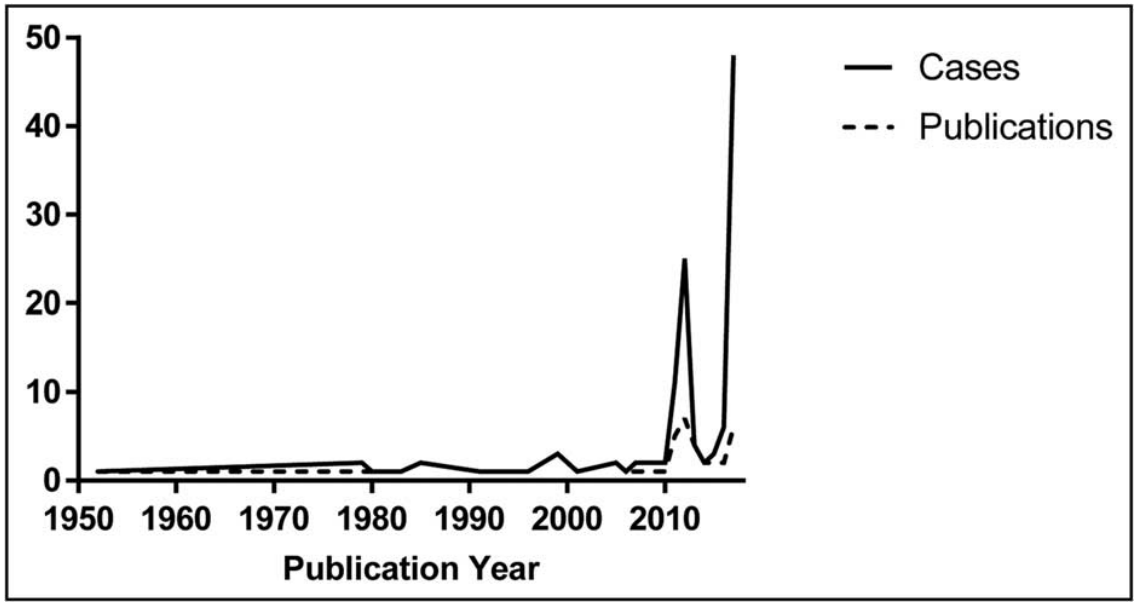


FIGURE 1. Overview of IAA cases and publications in literature over time (1952–2017 period) [5–50,51▪,52▪,53,54]. IAA, influenza-associated aspergillosis.

Table 1. Summary of 128 cases of influenza-associated aspergillosis (literature review of cases and case series [5–50,51▪,52▪,53,54])

Characteristic	Number (%) or median (IQR range)
Demographics	
Age	59 (IQR 51–63)
Male	79 (62%)
Risk factors	
Cirrhosis	6 (5%)
COPD	10 (8%)
Corticosteroids before hospitalisation	11 (9%)
Diabetes mellitus	19 (15%)
Haematological malignancy	19 (15%)
Haematological transplant	5 (4%)
Immunosuppression	32 (25%)
Neutropenia	12 (9%)
Previously healthy	36 (28%)
Solid organ malignancy	11 (9%)
Solid organ transplant	10 (8%)
Aspergillosis classification	
Proven	40 (31%)
EORTC probable	31 (24%)
AspICU putative	31 (24%)
Unclassifiable	47 (37%)
Influenza type	
Influenza A	111 (87%)
A, H1N1	65 (59%)[a]
A, H3	5 (4%)[a]
A, not specified	41 (37%)[a]
Influenza B	12 (9%)
Not specified	5 (4%)

Invasive pulmonary aspergillosis complicating severe influenza: epidemiology, diagnosis and treatment

Lore Vanderbeke[a,b], *Isabel Spriet*[c,d], *Christine Breynaert*[e]
Bart J.A. Rijnders[f], *Paul E. Verweij*[g,h], *and Joost Wauters*[b,i]

morbidity and mortality [110▪,111]. Influenza pneumonia is, however, deemed an exception, based on low-quality evidence showing an association between corticosteroids and prolonged viral shedding with increased risk of mortality [1,112–114]. The available evidence on the value of corticosteroids in patients with influenza argues against its use as long as data from a prospective randomized clinical trial are lacking. Additionally, corticosteroids were an independent risk factor for the development of IPA in ICU patients in general, but very recently also in patients admitted with influenza [4▪▪,35,115,116,117▪▪].

The Microbiome and the Lung

Lijia Cui[1,2], Alison Morris[3,4], Laurence Huang[5], James M. Beck[6,7], Homer L. Twigg III[8], Erika von Mutius[9], and Elodie Ghedin[1,10]

The Fungal Microbiome (Mycobiome) and Lung Disease

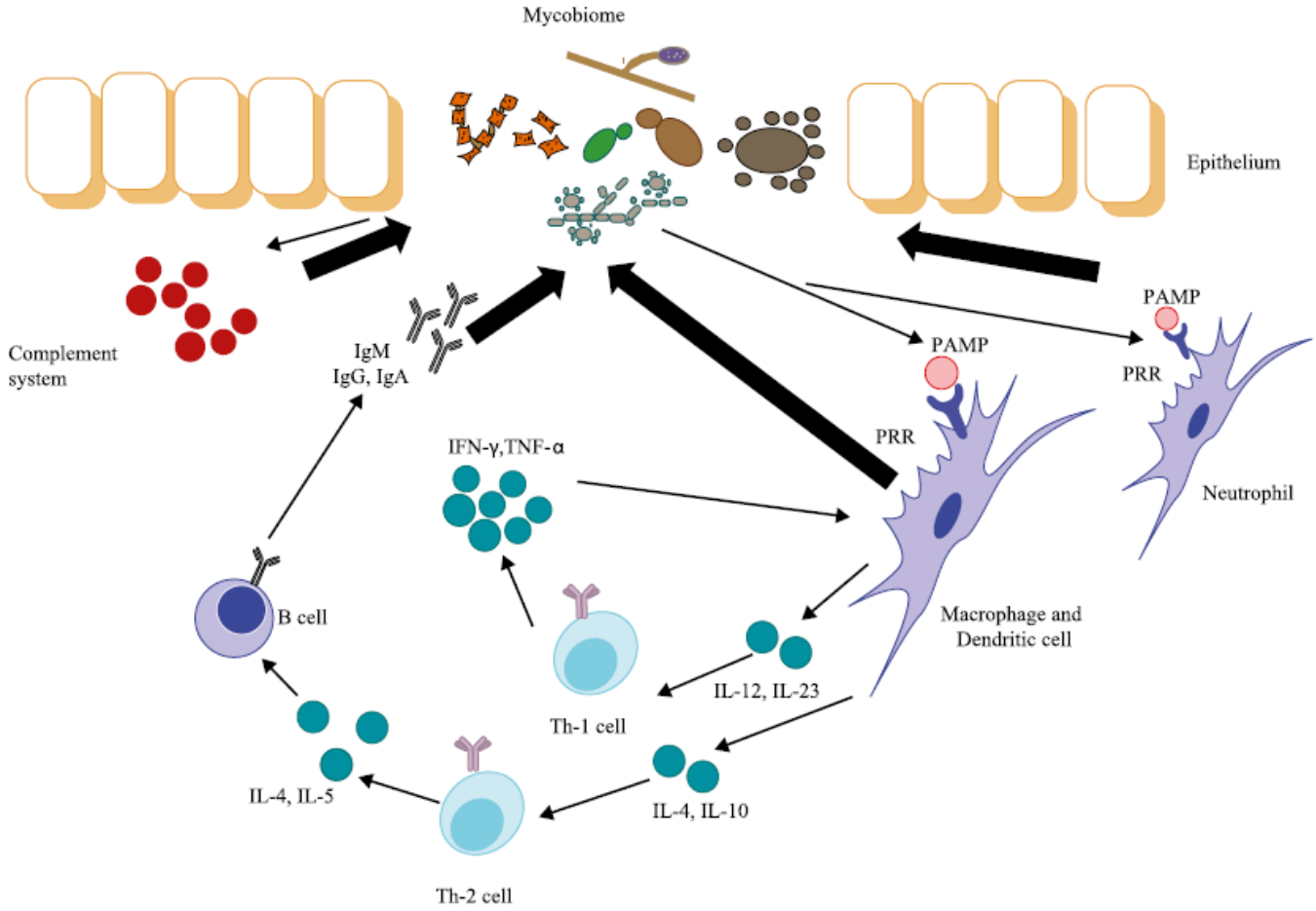


Figure 2. Interaction between the mycobiome and the immune system. The mycobiome shapes the immune response by the recognition between pathogen-associated molecular patterns (PAMPs) and pattern recognition receptors (PRRs) and the stimulation of the complement system and immune cell maturation. IFN = interferon; Ig = immunoglobulin; IL = interleukin; Th = T helper; TNF = tumor necrosis factor. Reprinted by permission from Reference 13.

Ann Am Thorac Soc Vol 11, Supplement 4, pp S227–S232, Aug 2014

ORIGINAL ARTICLE | *Clin Microbiol Infect* 2010; 16: 870–877 | MYCOLOGY

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]

1) Clinical Microbiology and Infectious Diseases Department, Hospital General Universitario Gregorio Marañón, Universidad Complutense, 2) CIBER de Enfermedades Respiratorias (CIBERES CD06/06/0058), Palma de Mallorca, 3) Pneumology Department and Clinical Epidemiology Unit, Hospital Universitario Doce de Octubre and 4) Pneumology Department, Hospital General Universitario Gregorio Marañón, Universidad Complutense, Madrid, Spain

Abstract

We describe a large series of patients with chronic obstructive pulmonary disease (COPD) and probable invasive pulmonary aspergillosis (IPA), and the risk factors and incidence of the disease in patients with isolation of *Aspergillus* from lower respiratory tract samples. From 2000 to 2007, we retrospectively studied all patients admitted with COPD and isolation of *Aspergillus* (239; 16.3/1000 admissions). Multivariate logistic regression and survival curves were used. Fifty-three patients had probable IPA (3.6 cases of IPA per 1000 COPD admissions). IPA affects at least 22.1% of patients with COPD and isolation of *Aspergillus* in culture. In 33 of the 53 patients with probable IPA, serum galactomannan was determined; in 14 (42.4%) of these, the result was positive. Five variables were independent predictors of IPA with statistical significance: admission to the intensive-care unit, chronic heart failure, antibiotic treatment received in the 3 months prior to admission, the accumulated dosage of corticosteroids equivalent to >700 mg prednisone received in the 3 months prior to admission, and the similar accumulated dosage of corticosteroids received from admission to the first clinical isolation of *Aspergillus*. Multivariate analysis gave an area under the curve of 0.925 (95% CI 0.888–0.962; p <0.001). The overall mean survival of the cohort was 64.1% (28.3% for IPA patients and 75.2% for non-IPA patients). The median number of days of survival was 48 (95% CI 33.07–62.92). However, we found statistically significant differences between patients with IPA (29 days; 95% CI 20.59–37.40) and patients without IPA (86 days; 95% CI 61.13–110.86) (log rank, p <0.001).

TABLE 3. Variables selected for prediction of invasive pulmonary aspergillosis by multivariate logistic regression analysis in patients with chronic obstructive pulmonary disease and clinical isolation of *Aspergillus* from lower respiratory tract (LRT) samples

	Wald	p	OR	95% CI Inferior	Superior
ICU admission	4.758	0.029	2.406	1.093	5.294
Chronic heart failure	3.649	0.056	2.102	0.981	4.504
Accumulated dose of corticosteroids prior to admission[a]	6.213	0.013	2.987	1.263	7.060
Accumulated dose of corticosteroids during admission[b]	13.338	0.000	4.568	2.022	10.324
Antibiotic treatment[a]	5.924	0.015	2.570	1.202	5.497
Constant	66.327	0.000	0.034		

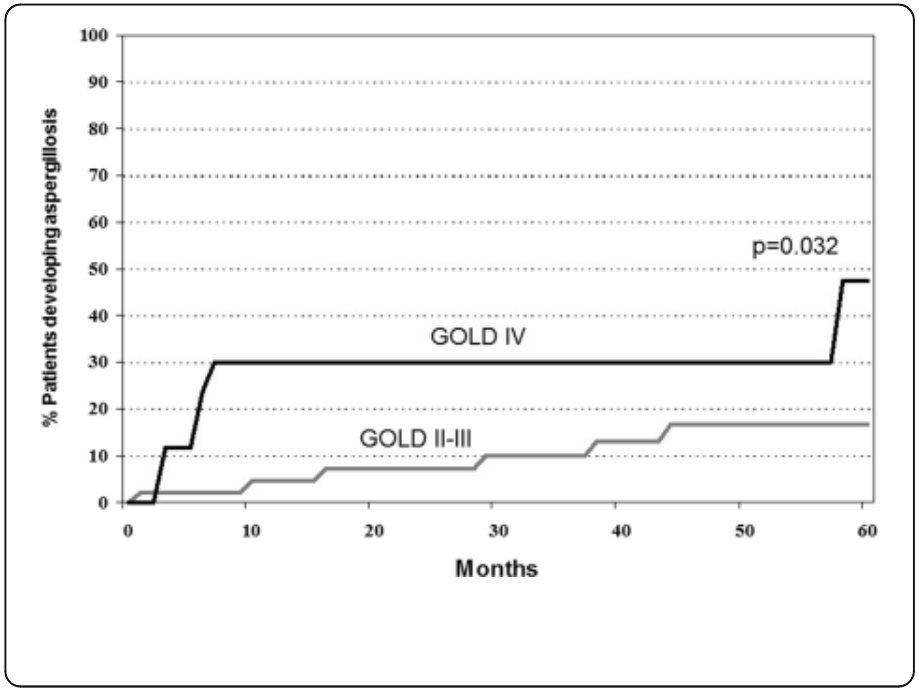
ICU, intensive-care unit.
[a]In the 3 months prior to admission.
[b]From admission to the first clinical isolation of *Aspergillus* from LRT samples.

Barberán et al. BMC Infectious Diseases (2017) 17:34
DOI 10.1186/s12879-016-2143-5

RESEARCH ARTICLE Open Access

Development of Aspergillosis in a cohort of non-neutropenic, non-transplant patients colonised by *Aspergillus* spp

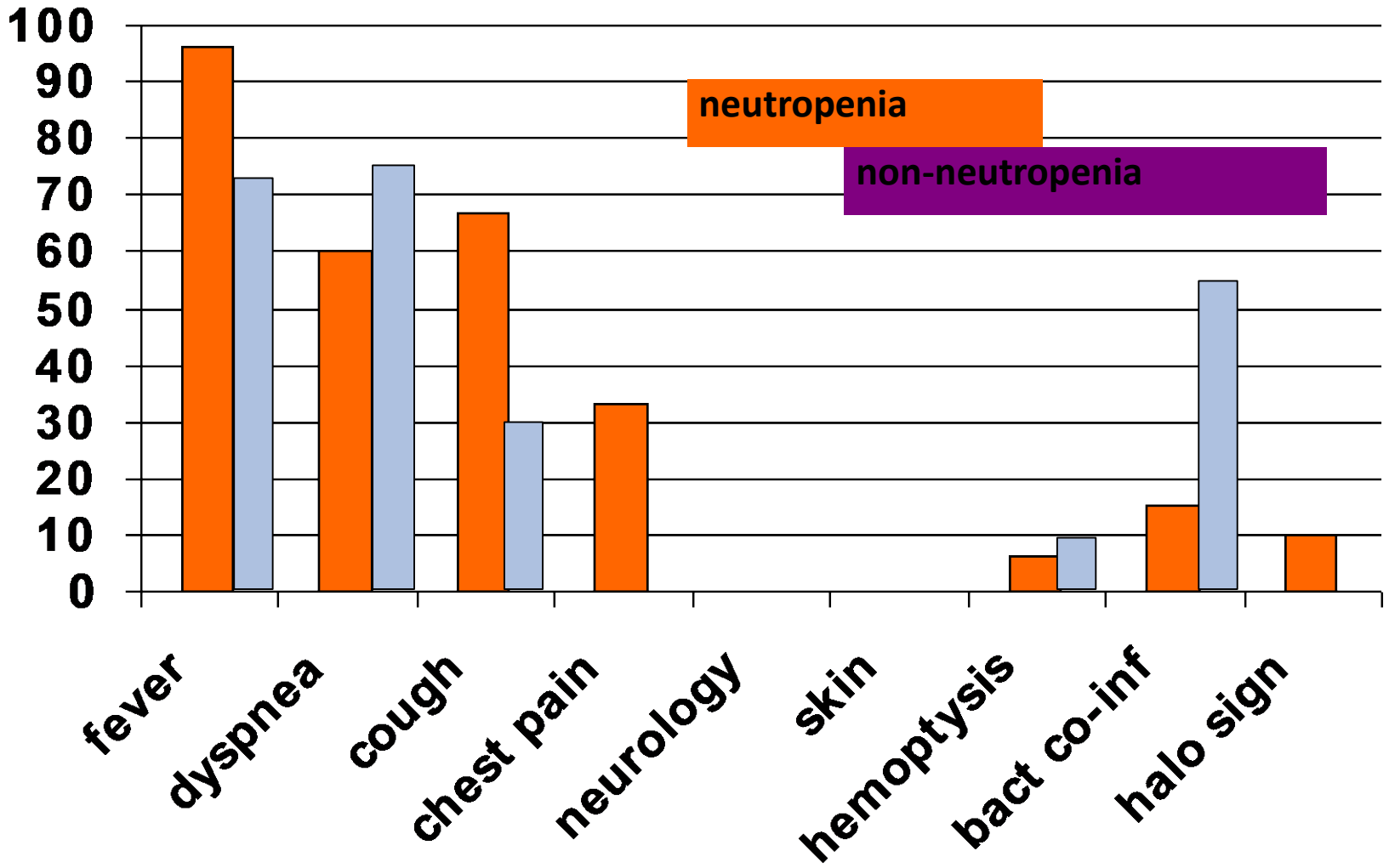
José Barberán[1*], Francisco-Javier García-Pérez[2], Victoria Villena[3], Alberto Fernández-Villar[4], Eduardo Malmierca[5], Cristina Salas[6], María-José Giménez[7], Juan-José Granizo[8], Lorenzo Aguilar[7] on behalf of the working group on Infectious Diseases from the Spanish Society of Internal Medicine



ASPERGILLOSIS IN NEUTROPENIA AND NON-NEUTROPENIA

88 cases

Cornillet et al. Clin Infect Dis 2006; 43:577-584

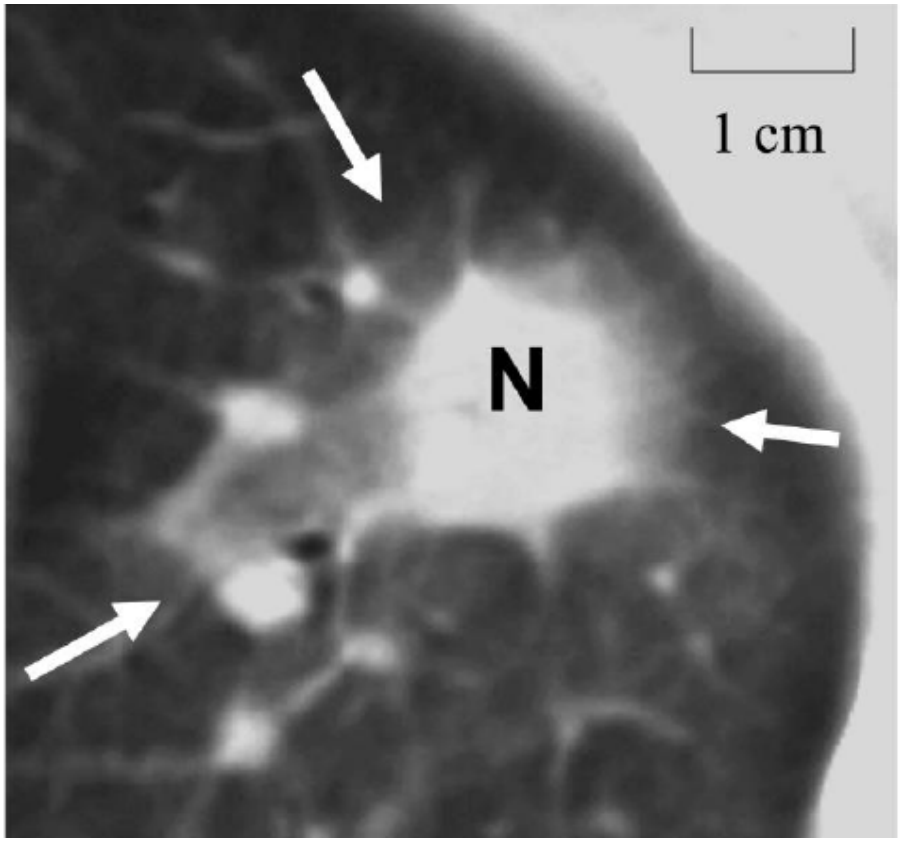


Aspergillosi: fattori di rischio classici

- Neutropenia profonda e prolungata (< 150/mmc per almeno 15 gg)
- Leucemia mieloide e mielodisplasia
- Trapianto di midollo allogenico
- GVHD
- Trapianto organo solido: Polmone>fegato etc
- HIV

Halo sign: intorno al nodulo

- DD: *P. aeruginosa* e zigomiceti

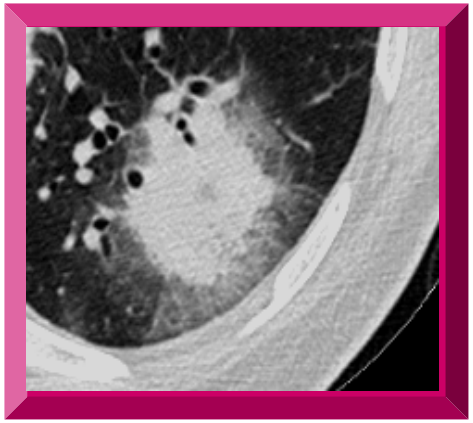


Non-neutropenici: 5-24% dei casi solamente

Evolution of CT scan images in IPA

halo sign

D 0 - 5



Air-space consolidation

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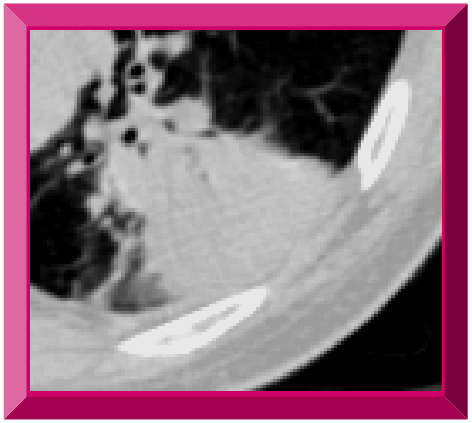

air-crescent sign

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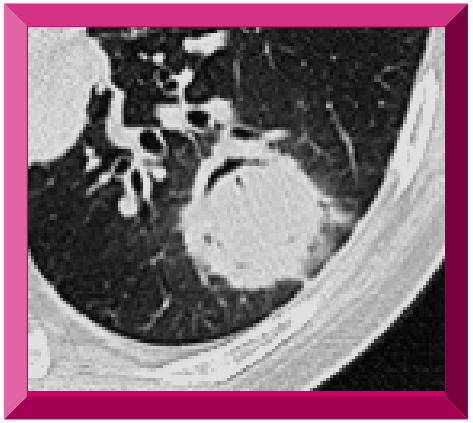
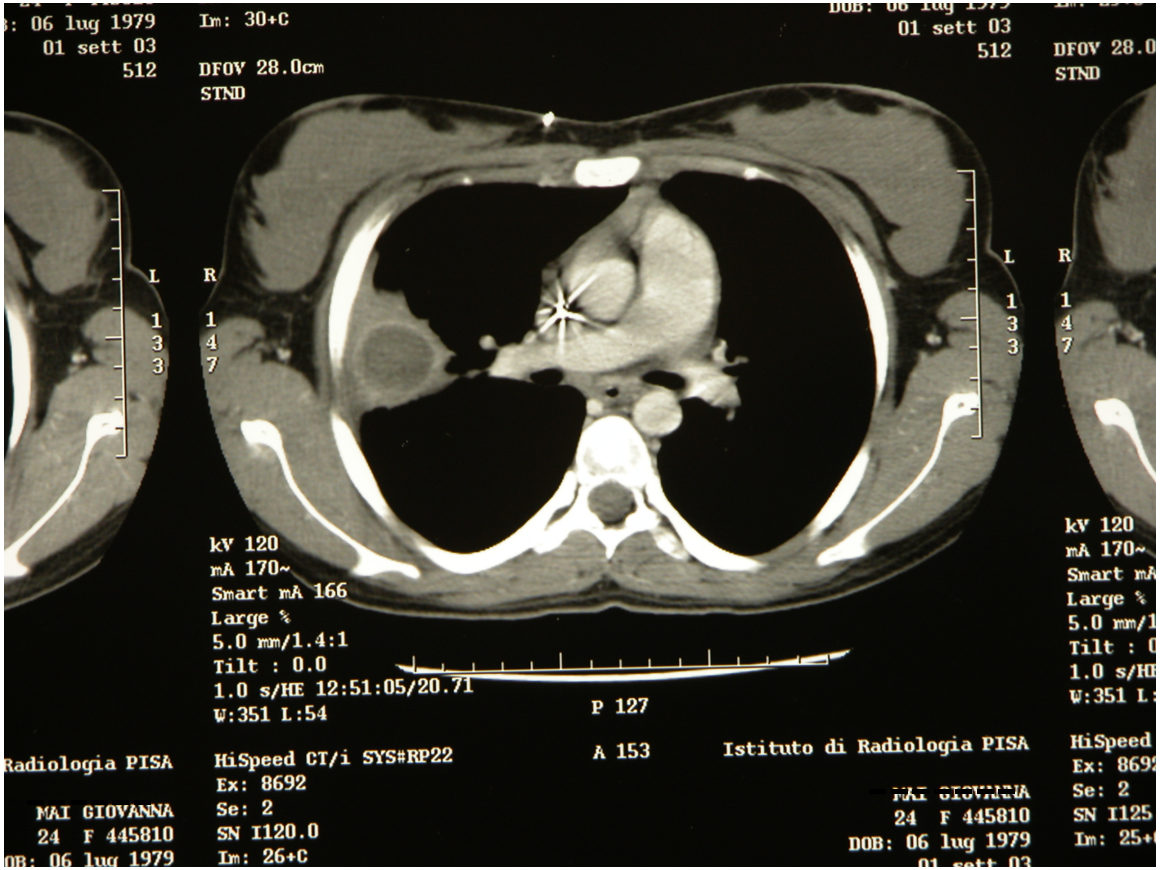


Neutropenia

Caillot et al. 2001

TAC torace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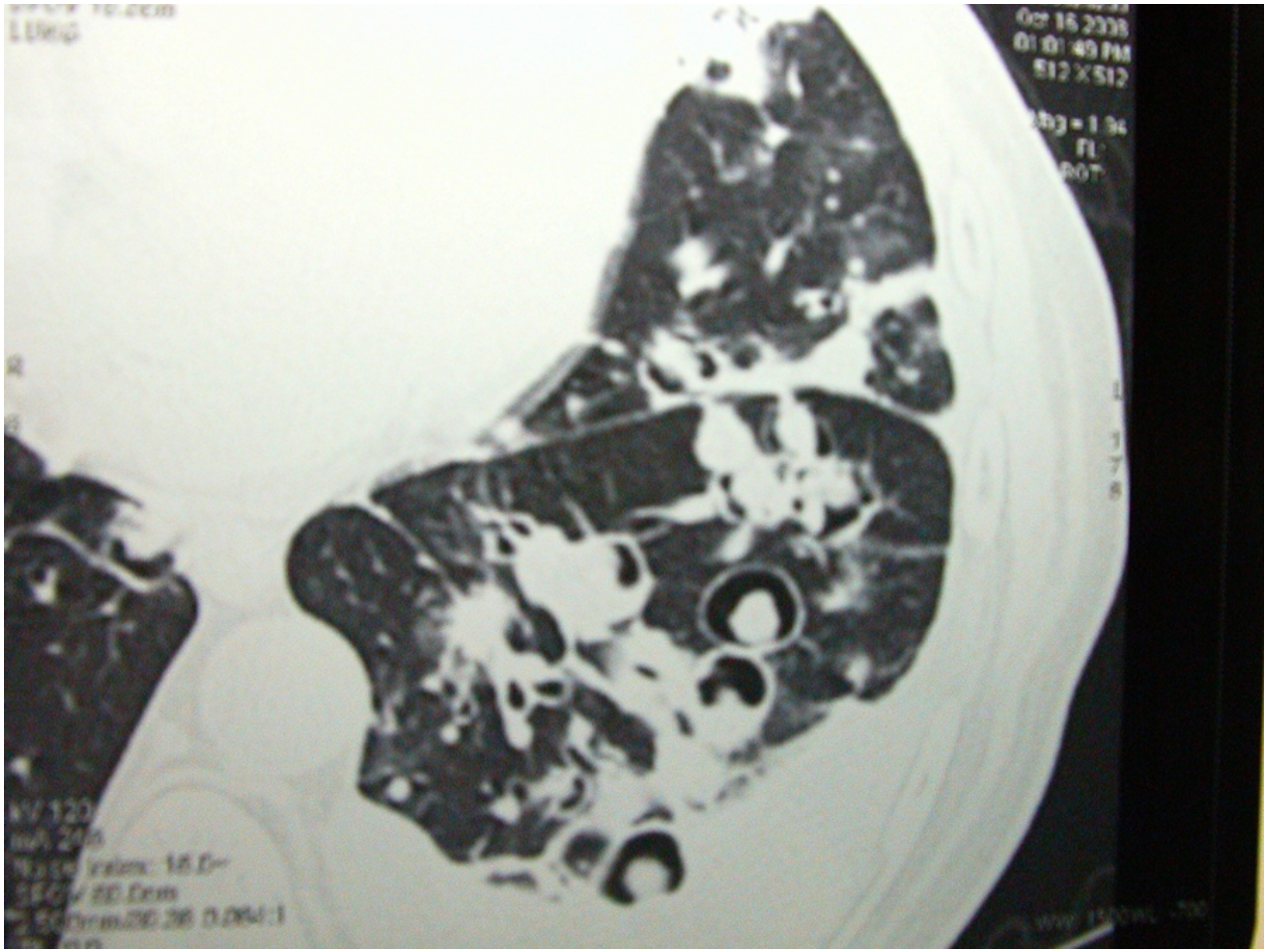


Computed Tomographic Pulmonary Angiography for Diagnosis of Invasive Mold Diseases in Patients With Hematological Malignancies

Marta Stanzani,[1] Giuseppe Battista,[2] Claudia Sassi,[2] Russell E. Lewis,[3,4] Giulia Tolomelli,[1] Cristina Clissa,[1] Rayka Femia,[2] Alberto Bazzocchi,[2] Fabio Tumietto,[5] Pierluigi Viale,[5] Simone Ambretti,[6] Michele Baccarani,[1] and Nicola Vianelli[1]

Nel neutropenico:
forme angio-invasive

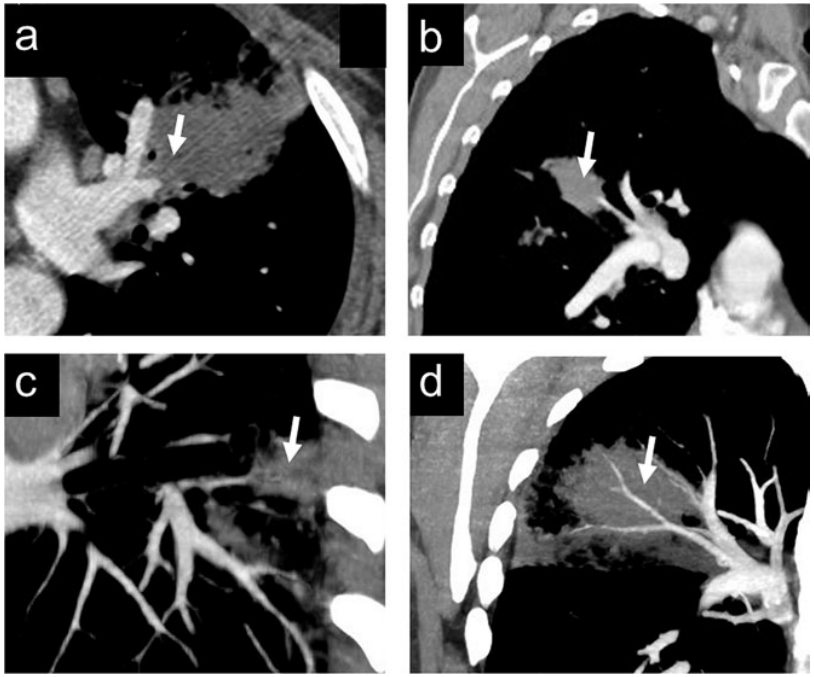
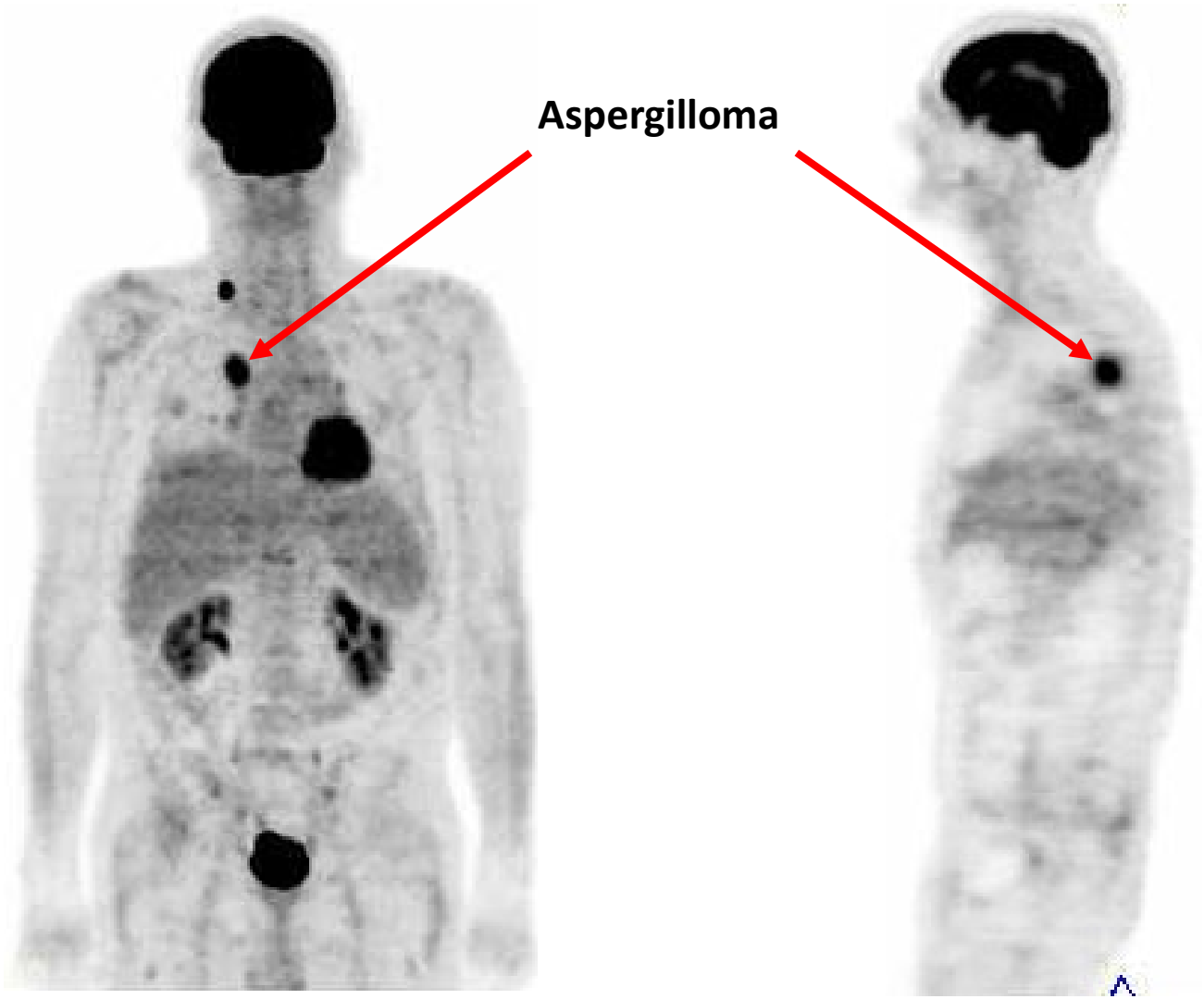


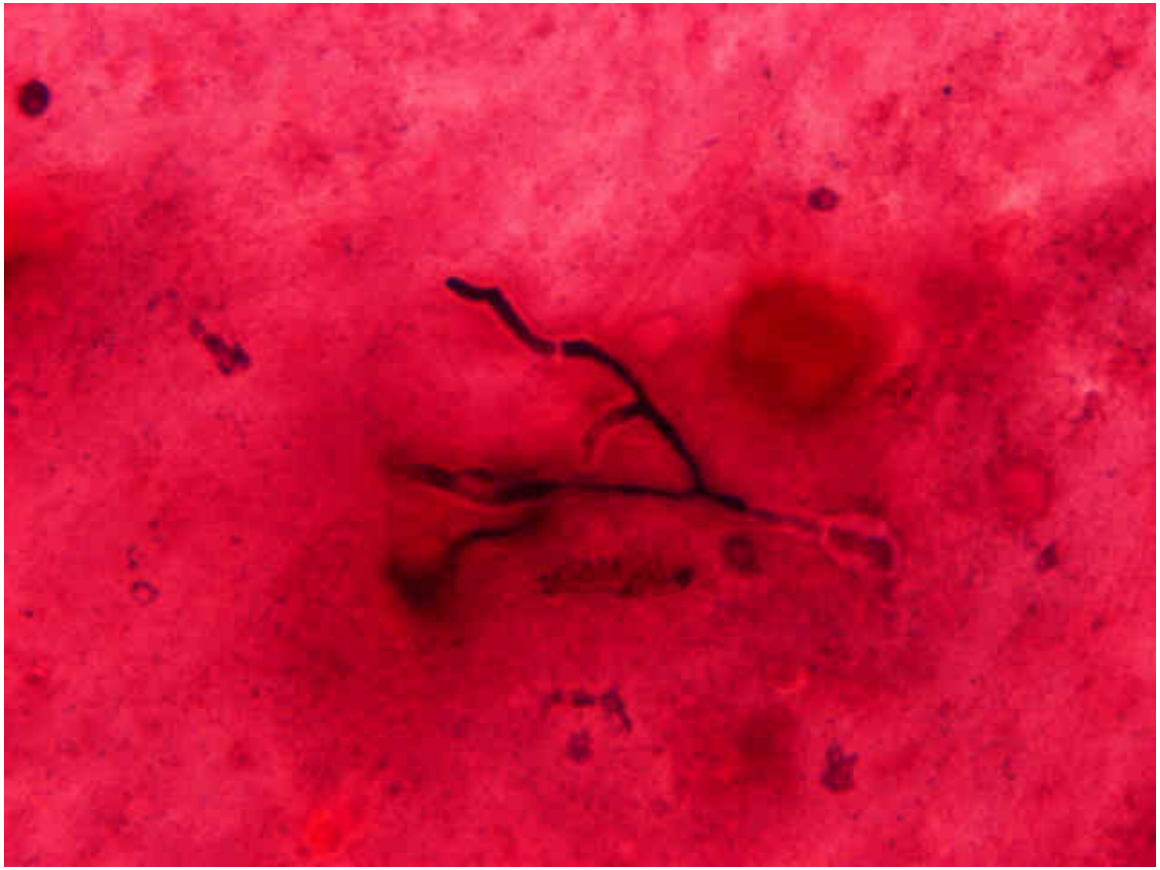
Figure 1. *A, B,* Representative high-resolution computed tomographic (HRCT) findings for patients with positive CT pulmonary angiographic (CTPA) findings and proven invasive mold disease. *C,* False-positive CTPA findings for a patient with *Staphylococcus aureus* pneumonia with septic emboli. *D,* Negative CTPA findings for a patient with bacterial pneumonia. Arrows indicate areas of vessel interruption (*A–C*) or lack of vessel interruption (*D*).

MULTIPLE MYELOMA PATIENT WITH FDG-PET SCAN DISPLAYING *ASPERGILLUS* INFECTION

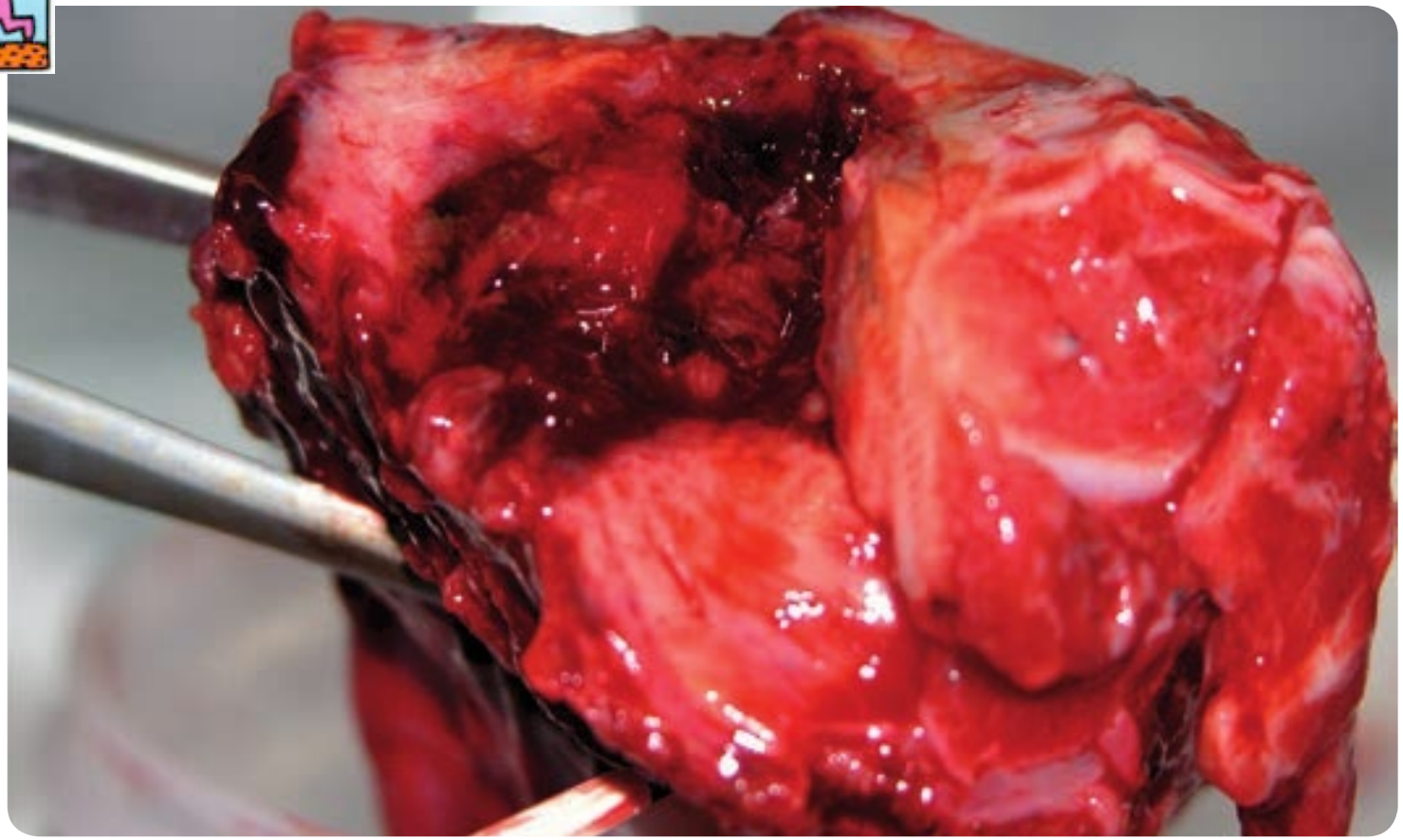
Anaissie et al, Little Rock



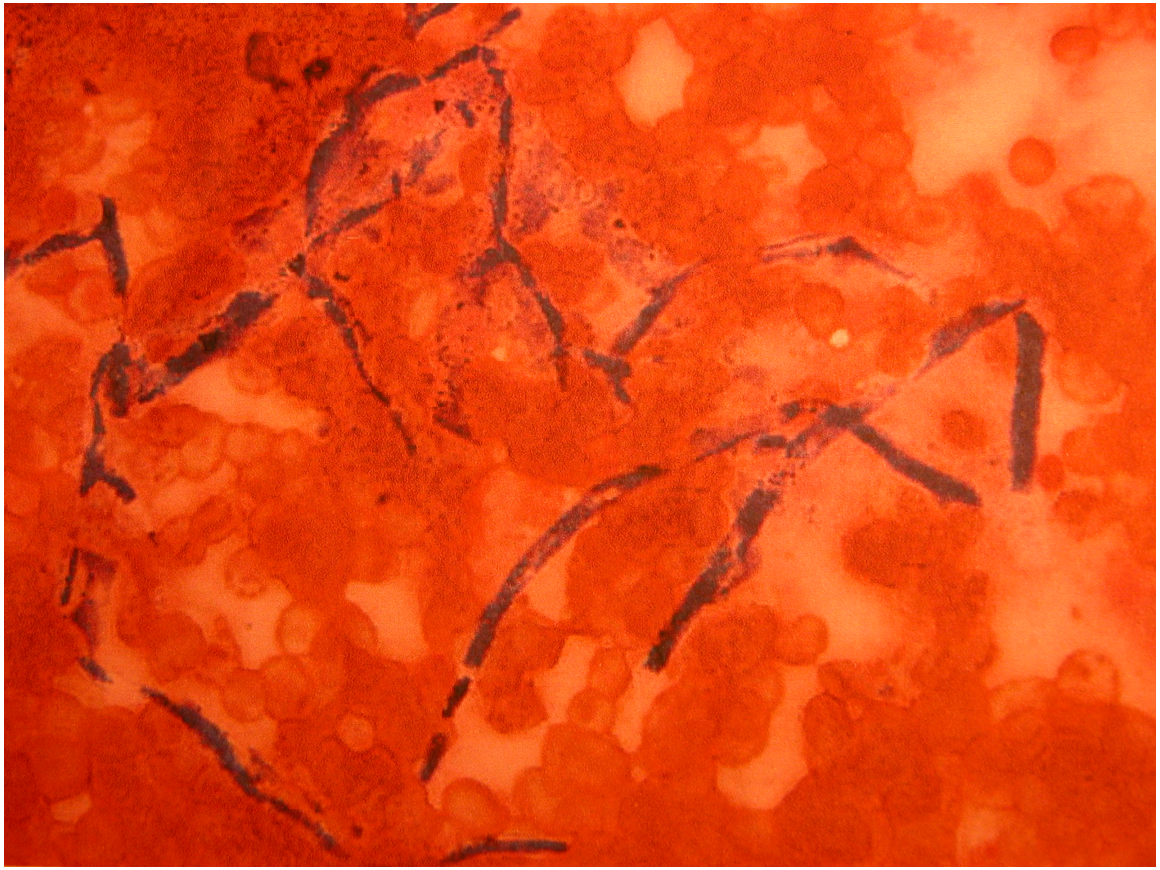
Gram da BAL:
ife ad angolo acuto



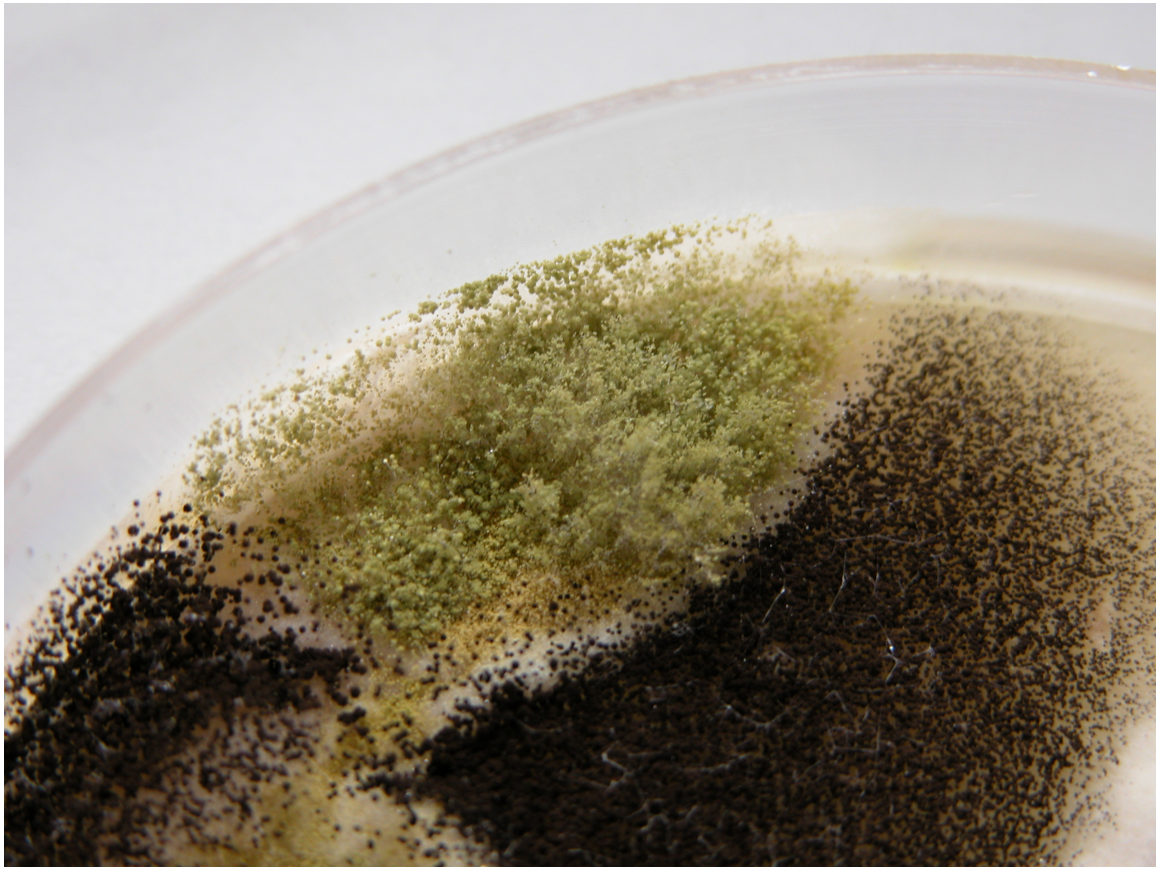
Aspergillosi polmonare



Gram dell'agoaspirato di lesione polmonare

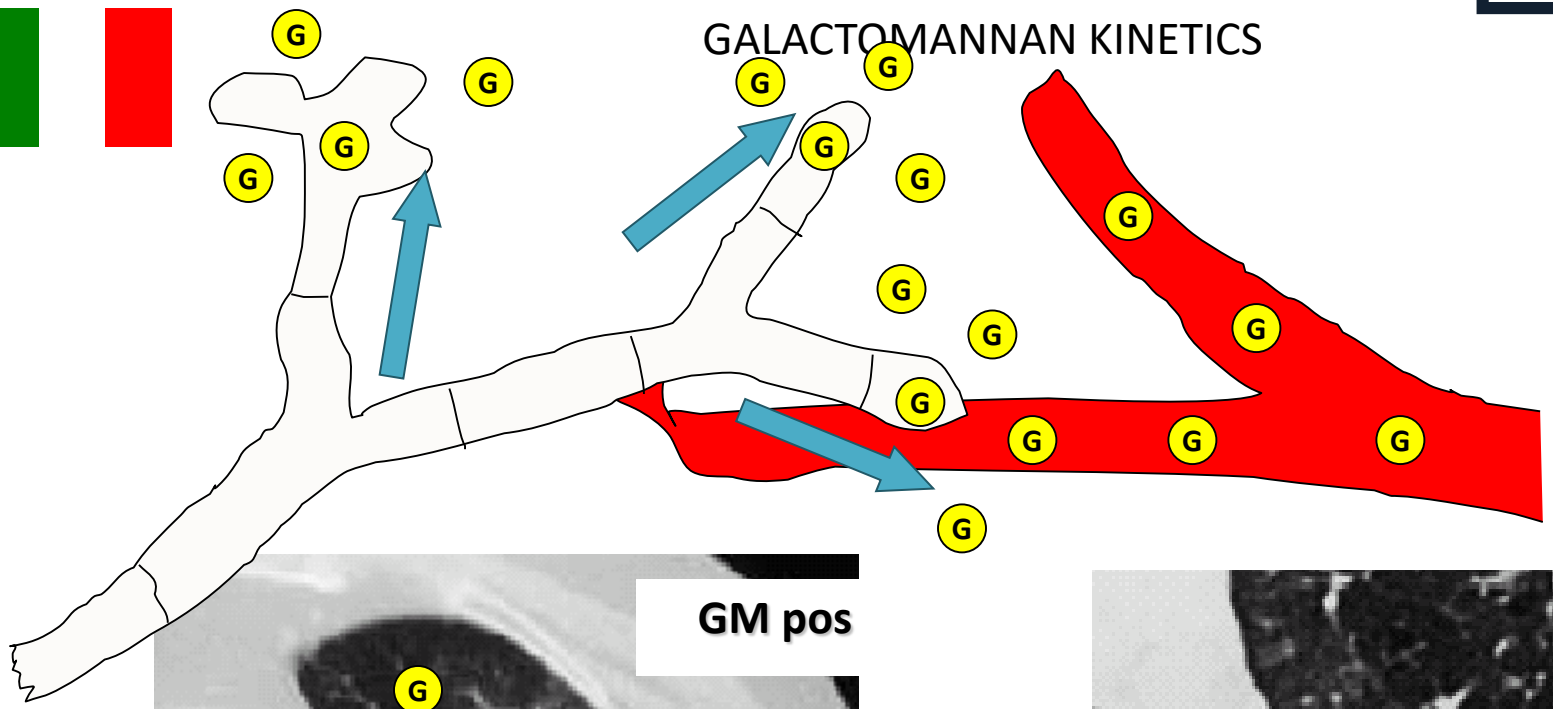


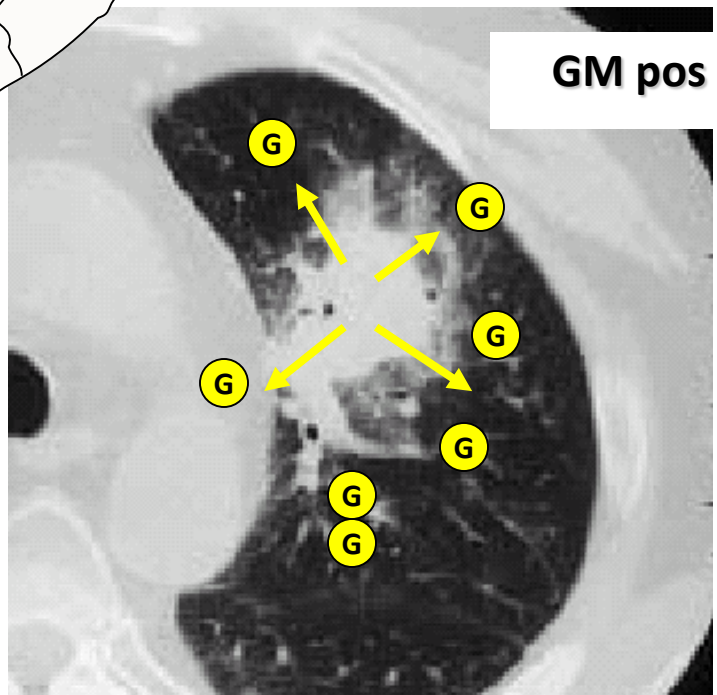
Coltura dell’agoaspirato polmonare: doppia popolazione

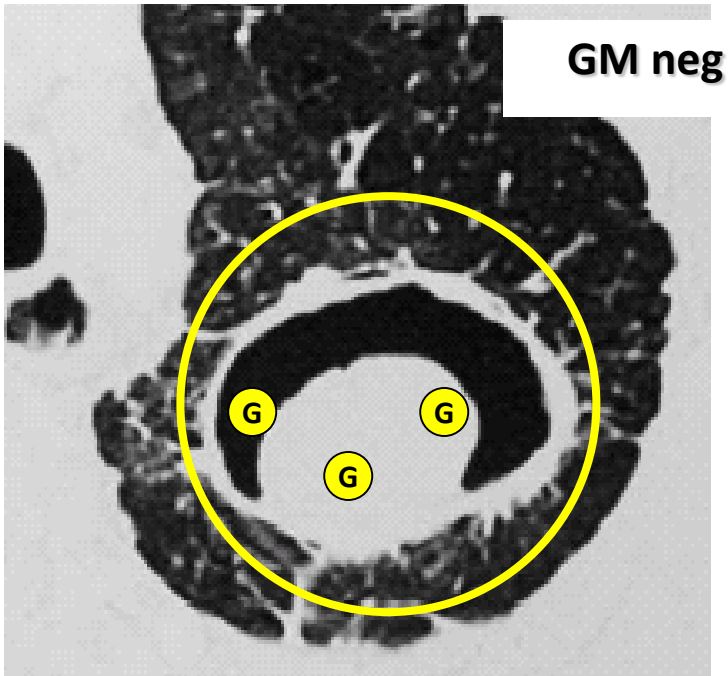


Courtesy of
Corrado Girmenia

GALACTOMANNAN KINETICS







Terapia: voriconazolo

Other series studying non-neutropenic patients, with proven or probable invasive pulmonary aspergillosis, confirmed a favorable response rate with voriconazole [64, 65]. Particularly remarkable is one study of pulmonary and disseminated IA, including 103 non-neutropenic patients, in which receiving voriconazole treatment was found to be the only factor associated with a reduced risk of death [1].

1. Garcia-Vidal C, Peghin M, Cervera C, et al. Causes of death in a contemporary cohort of patients with invasive aspergillosis. PLoS One. 2015;10:e0120370.

Terapia: isavuconazolo

16. Maertens JA, Raad II, Marr KA, et al. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by *Aspergillus* and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial. Lancet. 2016;387:760–9.

solubility. Compared to voriconazole, isavuconazole also has the advantages of linear and predictable pharmacokinetics which is likely to obviate the need for therapeutic drug monitoring and fewer CYP enzyme-mediated drug interactions [66]. A large randomized, double-blind trial has demonstrated non-inferiority or isavuconazole versus voriconazole in terms of all-cause mortality when used as primary treatment for invasive fungal disease caused by *Aspergillus* species or other filamentous fungi, with a superior safety profile [16].

Terapia: amfotericina B

Another alternative for primary therapy is represented by amphotericin B that was historically considered the mainstay of treatment for IA before the introduction of voriconazole. Development of lipid formulations improved the poor tolerability associated with the deoxycholate formulation, but the optimal dosage remains unconfirmed [67].

67. Cornely OA, Maertens J, Bresnik M, et al. Liposomal amphotericin B as initial therapy for invasive mold infection: a randomized trial comparing a high-loading dose regimen with standard dosing (AmBiLoad trial). Clin Infect Dis. 2007;44:1289–97.

Durata della terapia

- 6-12 settimane
- Utilizzare galattomannano per stabilire la durata della malattia?
- PET TAC?

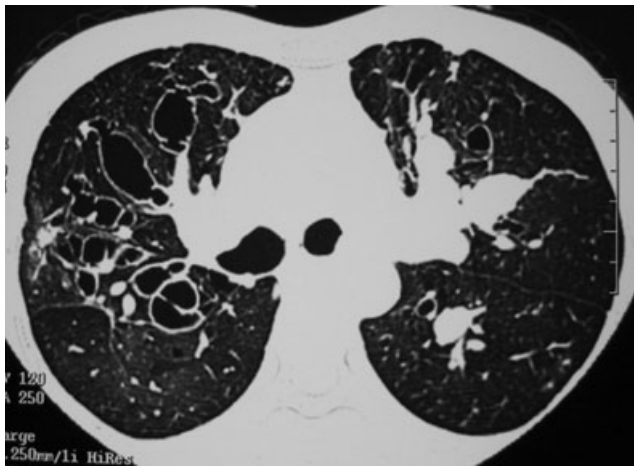
ABPA

- Asma scarsamente controllata
- Infiltrati polmonari
- Bronchiectasie

- Risposta Th2 ad antigeni aspergillari con produzione di IgE

ABPA: diagnosi

- Skin test
- IgE totali > 1000 IU/ml
- IgE specifiche
- Bronchiectasie centrali con tappi di muco ed addensamenti



doi: 10.1111/cea.12141
Clinical & Experimental Allergy, **43**, 850–873

OPINIONS IN ALLERGY

Allergic bronchopulmonary aspergillosis: review of literature and proposal of new diagnostic and classification criteria

R. Agarwal[1], A. Chakrabarti[2], A. Shah[3], D. Gupta[4], J. F. Meis[5,6], R. Guleria[7], R. Moss[8], D. W. Denning[9] and For the ABPA complicating asthma ISHAM working group*

Table 4. Newly proposed diagnostic criteria for allergic bronchopulmonary aspergillosis

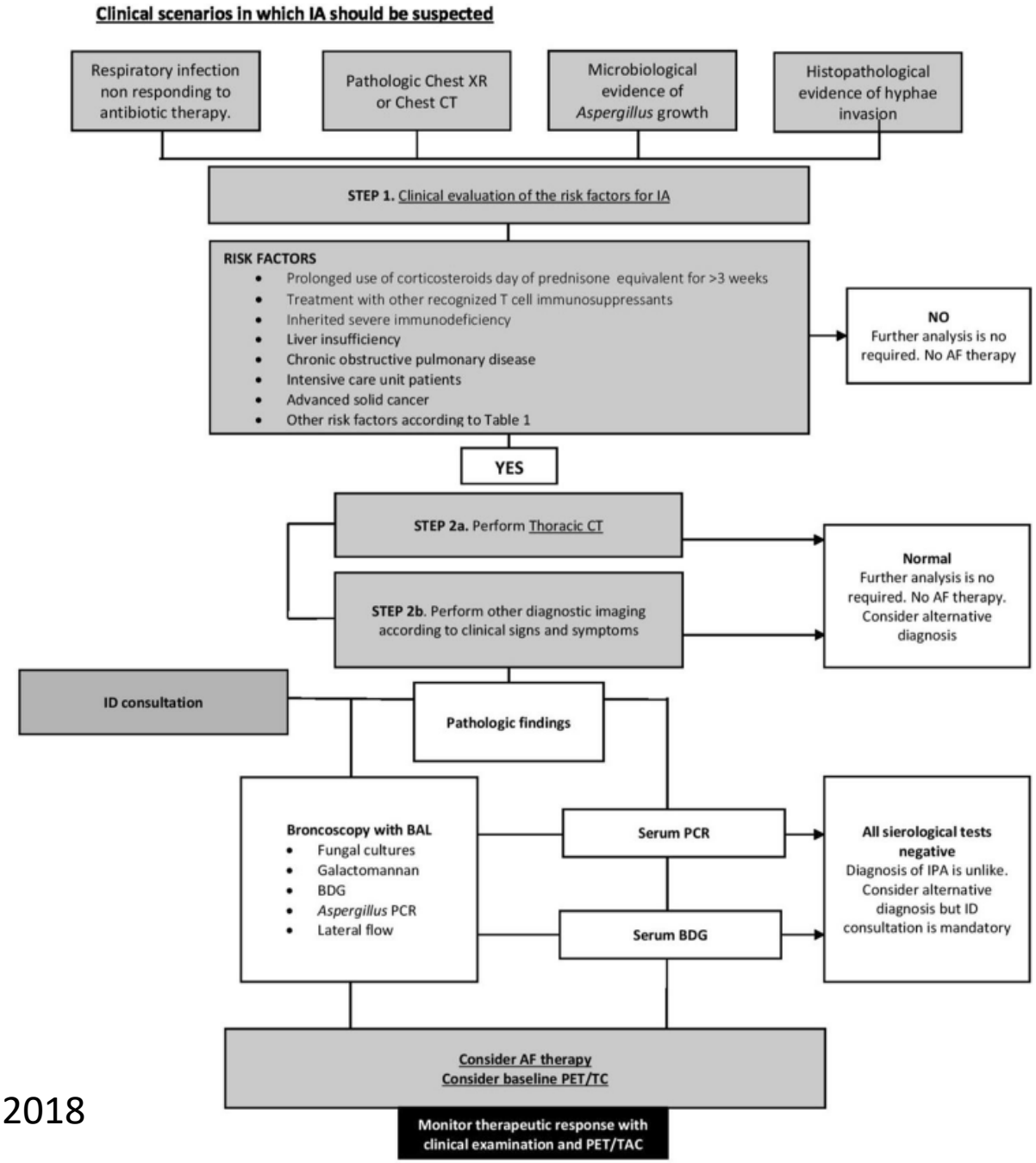
Predisposing conditions
Bronchial asthma, cystic fibrosis
Obligatory criteria (both should be present)
Type I *Aspergillus* skin test positive (immediate cutaneous hypersensitivity to *Aspergillus* antigen) or elevated IgE levels against *Aspergillus fumigatus*
Elevated total IgE levels (> 1000 IU/mL)*
Other criteria (at least two of three)
Presence of precipitating or IgG antibodies against *A. fumigatus* in serum
Radiographic pulmonary opacities consistent with ABPA†
Total eosinophil count > 500 cells/μL in steroid naïve patients (may be historical)

ABPA: terapia

- Steroidi sistemici e aerosol
- Itraconazolo

Conclusioni

- Fattori di rischio per il paziente non neutropenico
- Radiologia compatibile
- Sospetto clinico
- Inizio terapia empirica
- Conferma microbiologica



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