*Faenza, 14 maggio 2016*

# Tante infezioni micotiche e tanti farmaci: ipotesi per la scelta di una terapia appropriata

**Pierluigi Viale** **Infectious Disease Unit** **Teaching Hospital S. Orsola – Malpighi Bologna**

**Epidemiology and outcomes of invasive fungal infections in allogeneic HSCT recipients in the era of antifungal prophylaxis: a single-centre study with focus on emerging pathogens.** *Corzo-Leon DE et al, Mycoses 2015; 58: 325–336*

**378 adult patients who received their first allogeneic HSCT** during the study period

**Proven Probable IFI** occurred in 53 patients. The **incidence was 14.0%** (95% CI 10.7–17.9%). The **median time from transplantation until first IFI was 147 days** (range = 6–2130) and 28% of patients developed their first IFI greater than 1 year after their transplant

**The incidence of invasive aspergillosis was 7.9%** (30 patients) and the median time from transplantation until diagnosis of aspergillosis was 182 days (range = 10–893)

**The incidence of invasive candidiasis was 3.4%** (13 patients) and the median time from transplantation until diagnosis of candidiasis was 107 days (range = 19–808)

**Fifteen (4.0%) patients developed an IFI other than candidiasis or aspergillosis** and the median time from transplantation was 100 days (range = 6–2130). The most common NC/NA IFI was mucormycosis, which occurred in 1.6% (n = 6) of patients.

## Incidence and risk factors of post-engraftment invasive fungal disease in adult allogeneic HSCT recipients receiving oral azoles prophylaxis

*Montesinos P et al Bone Marrow Transpl 2015; 50: 1465-72*

single-center retrospective study including 404 alloSCT adult recipients surviving 440 days who engrafted and were discharged without prior IFD.

**The 1-year Cumulative Incidence of IFD was 11%.**

The non-relapse mortality was 40% in those developing IFD and 16% in those who did not.

Age > 40 years, ⩾ 1 previous SCT, pre-engraftment neutropenia >15 days, extensive chronic GVHD and CMV reactivation were independent risk factors

## Invasive fungal diseases in patients with acute lymphoid leukemia

*Nicolato A et al, Leukemia & Lymphoma , 2016*

A retrospective study involving all patients with ALL who developed febrile neutropenia from 1987 to 2013

During the study period 350 episodes of febrile neutropenia among 153 patients with ALL were observed

31 cases of IFD, classified as proven or probable were diagnosed (8.8%).

# Lymphoproliferative disorders and IFI

Within the heterogeneous group of patients with lymphoproliferative disorders, IFI epidemiology is not well defined and antifungal prophylaxis practices vary.

## Epidemiological trends in invasive aspergillosis in France: the SAIF network (2005–2007)

*Lortholary O et al, Clin Microbiol Infect 2011; 17: 1882–1889*

A prospective hospital-based multicentre surveillance of EORTC/MSG-proven or probable invasive aspergillosis cases whatever the underlying diseases implemented in 12 French academic hospitals: 424 case-patients included, median incidence 0.271 x$10^3$ admissions (range 0.072–0.910)

| | N | % |
|---|---|---|
| Acute leukaemia | 136/393 | (34.6%) |
| Allogeneic HSCT | 84/393 (21.4) | |
| Chronic lymphoproliferative disorde | | |
| Solid organ transplantation | | |
| Solid tumours | | |
| Systemic inflammatory diseases | | |
| Chronic respiratory diseases | 9/393 | (2.3) |
| None of the above risk factors | 10/393 (2.5) | |

| | |
|---|---|
| Lymphoma | 42 (49.4) |
| Chronic lymphoid leukaemia | 26 (30.6) |
| Multiple myeloma | 13 (15.3) |
| Others | 4 (4.7) |

## The Nationwide Austrian Aspergillus Registry: a prospective data collection on epidemiology, therapy and outcome of invasive mould infections

*Perkhofer S et al, Intern J Antimicrob Ag 2010; 36: 531–536*

A prospective, observational, multicentre study was performed to assess the incidence, diagnosis, epidemiology and outcome of invasive mould infections. In total, 186 cases were recorded, corresponding to an annual incidence of 42 cases/1000 patients at risk or 2.36 cases/100 000 inhabitants

| Underlying disease | N | % |
|---|---|---|
| Acute myelogenous leukaemia | 63 | (34) |
| Acute lymphatic leukaemia | 17 | (9) |
| Chronic lymphatic leukaemia | 10 | (5) |
| Non-Hodgkin's lymphoma | 19 | (10) |
| Hodgkin's lymphoma | 2 | (1) |
| Multiple myeloma | 1 | (0.5) |
| Myelodysplastic syndrome | 15 | (8) |
| Solid tumour | 10 | (5) |
| Lung transplant recipients | 31 | (17) |
| Other | 18 | (10) |

## Epidemiology of Invasive Fungal Disease in Lymphoproliferative Disorders

*Teng JC et al, Haematologica, 2015;100: e462-6*

**retrospective cohort study at the Peter MacCallum Cancer Centre to determine the epidemiology of IFD in patients with lymphoproliferative disorders receiving cytotoxic chemotherapy according to disease type and chemotherapy exposure.**

**773 patients fulfilled inclusion criteria**

**Overall, 29 episodes IFD were identified in 29 patients, corresponding to a prevalence of 3.8% (95% CI 2.5-5.4%)**

**Patients with IFD had a mean age (range) of 62 years (18-88 years)**

**Male predominance (65%)**

**Fluconazole was administered to 287/773 (37.1%) pts**
**Mold-active antifungal prophylaxis were administered to 38/773 (4.9%) pts**

***Aspergillus* species was the most frequently identified fungal pathogen**

**30-day all-cause mortality was 31.0% (9/29).**

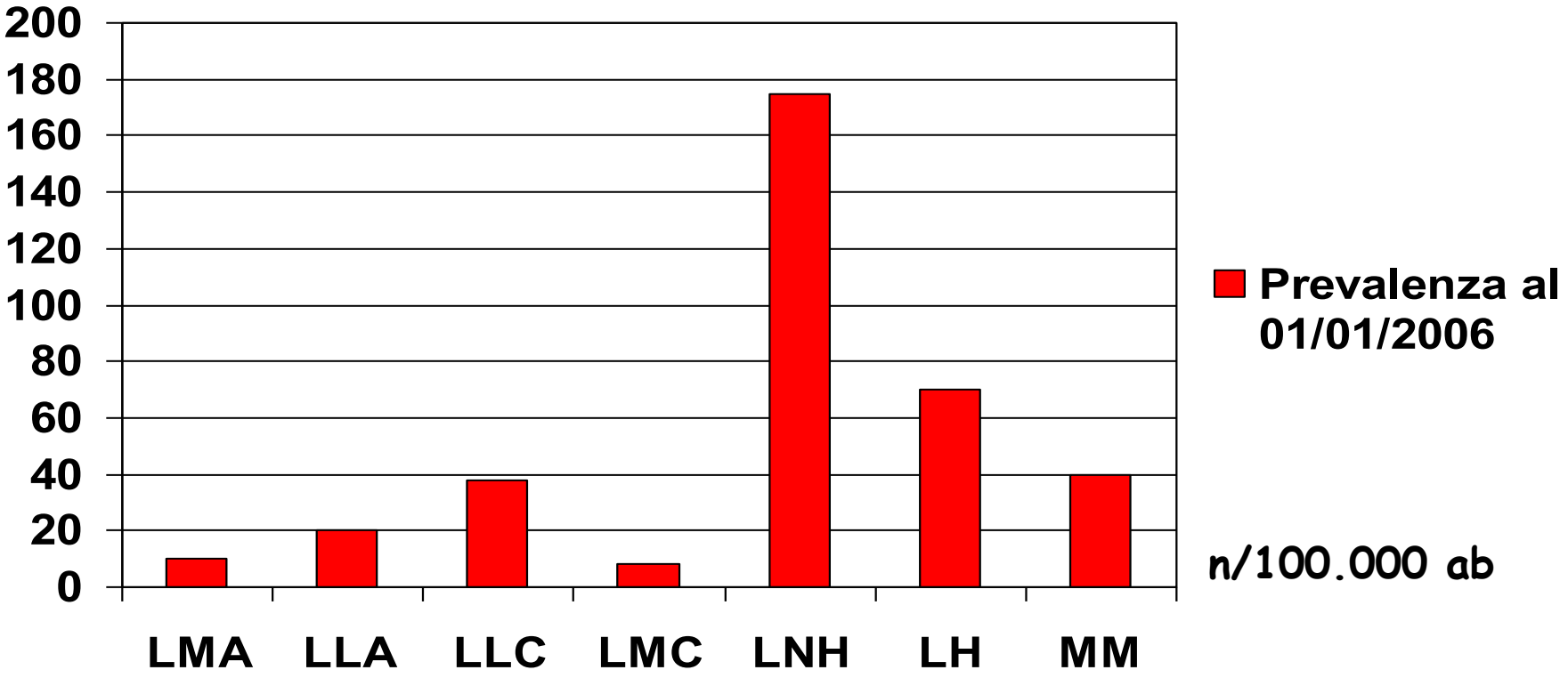
# Epidemiology of Invasive Fungal Disease in Lymphoproliferative Disorders

*Teng JC et al, Haematologica Published Ahead of Print on July 23, 2015*

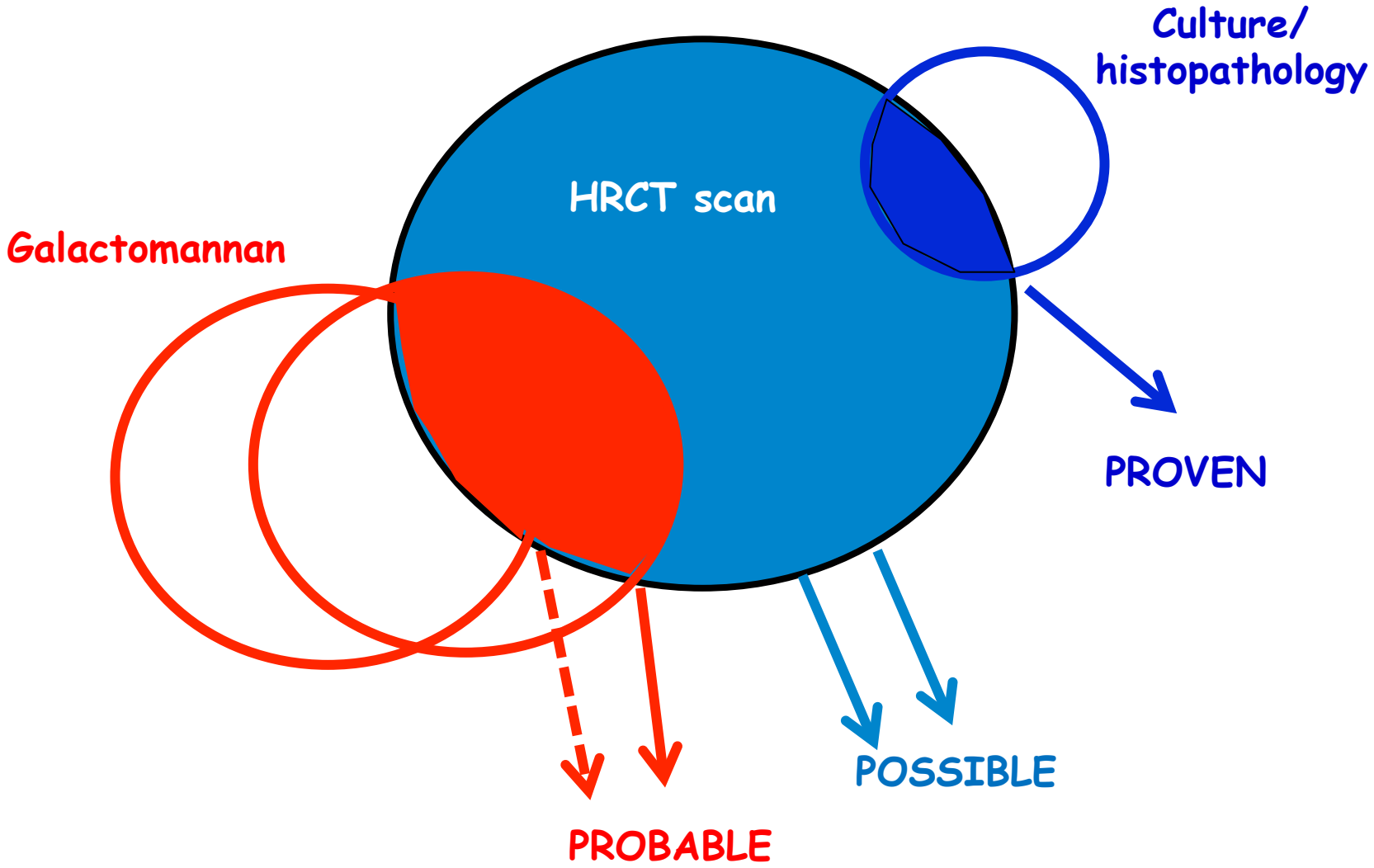
| | Haematological malignancy | | | | | | |
|---|---|---|---|---|---|---|---|
| | Precursor lymphoid neoplasms | Mature B-cell neoplasms | | | | Mature T- & NK-cell neoplasms | Hodgkin lymphoma |
| | | CLL/SLL | DLBCL | Plasma cell neoplasms | Other B-cell NHL | | |
| Total no. of patients | 17 | 51 | 186 | 251 | 175 | 37 | 56 |
| No. receiving antifungal prophylaxis | | | | | | | |
| • Fluconazole | 7 | 9 | 99 | 103 | 38 | 18 | 13 |
| • Mold-active agent | 9 | 3 | 6 | 6 | 7 | 3 | 0 |
| IFD episodes | | | | | | | |
| • *n* | 5 | 4 | 8 | 7 | 3 | 0 | 2 |
| • IFD prevalence (95% CI) | 29.4% (9.5-68.6%) | 7.8% (2.1-20.1%) | 4.3% (1.9-8.5%) | 2.8% (1.1-5.7%) | 1.7% (0.4-5.1%) | 0% | 3.6% (0.4-12.9%) |
| • IFD rate per 10,000 treatment days | 10.7 | 4.4 | 2.8 | * | 0.4 | 0 | 2.8 |

**The IFD prevalence was highest in patients with precursor lymphoid neoplasms (29.4%). This occurred despite 52.9% of patients receiving mold-active prophylaxis. This finding may be attributed to the increasing intensity of induction chemotherapy protocols for lymphoblastic lymphoma comprising high corticosteroid exposure and prolonged periods of neutropenia**

## Malattie Ematologiche maligne in italia (registro AIRTUM)



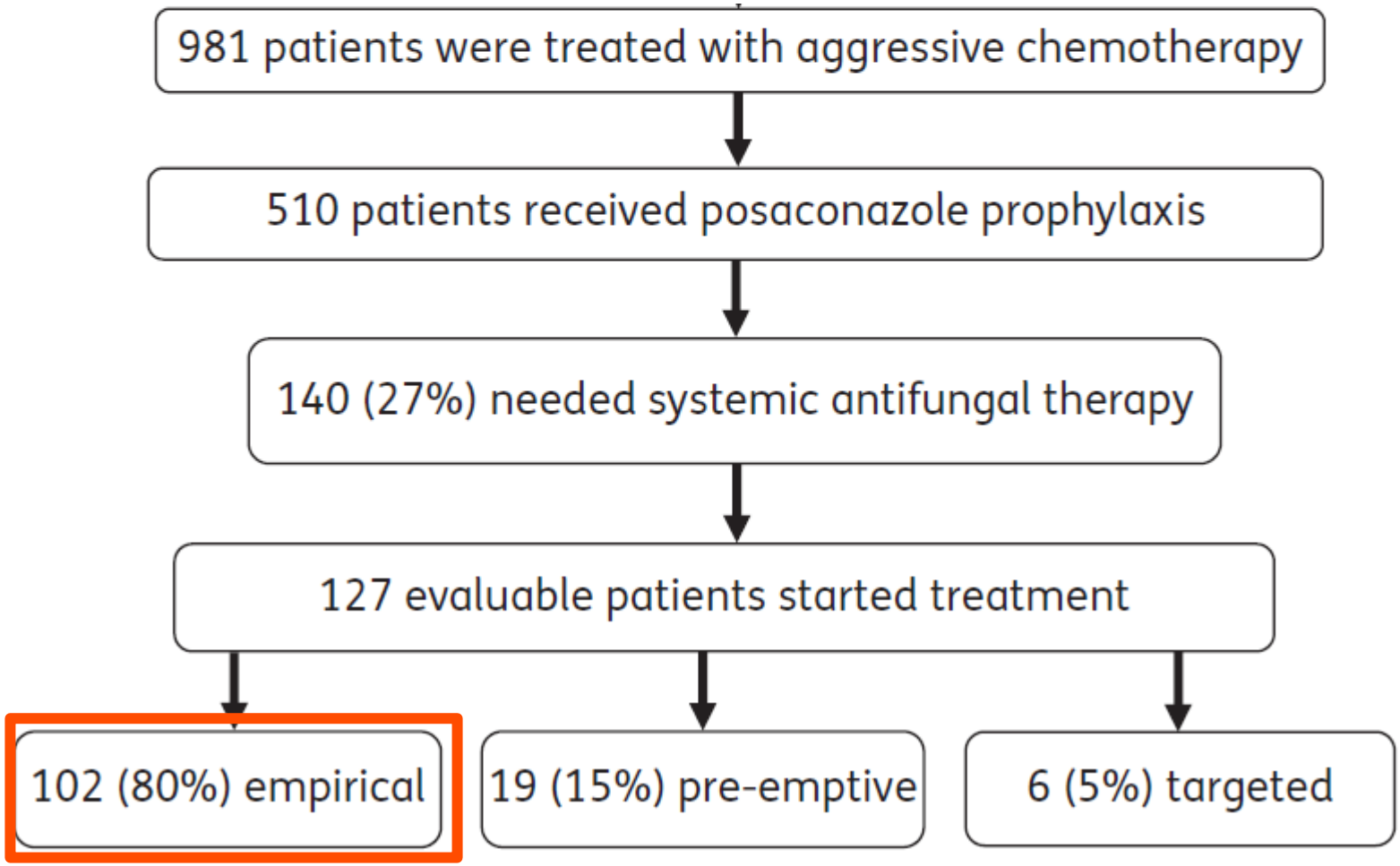

Rapporto Leucemie Acute / altro: prevalenza 1/16
incidenza 1/8




*Nivoix et al. Clin Infect Dis 2008;47:1176.85* *Kohno Clin Infect Dis 2008;47:1185-7*

**Systemic antifungal treatment after posaconazole prophylaxis: results from the SEIFEM 2010-C survey** *Pagano L et al - J Antimicrob Chemother 2014; 69: 3142-3147*

**From January 2010 to April 2012, 1192 consecutive patients with newly diagnosed AML were prospectively registered at 33 participating Italian centers**



**How do we fill the gap between probable and possible mold cases?**

Annals of Internal Medicine ORIGINAL RESEARCH

# Combination Antifungal Therapy for Invasive Aspergillosis

## A Randomized Trial

**Kieren A. Marr, MD; Haran T. Schlamm, MD; Raoul Herbrecht, MD; Scott T. Rottinghaus, MD; Eric J. Bow, MD, MSc; Oliver A. Cornely, MD; Werner J. Heinz, MD; Shyla Jagannatha, PhD; Liang Piu Koh, MBBS; Dimitrios P. Kontoyiannis, MD; Dong-Gun Lee, MD; Marcio Nucci, MD; Peter G. Pappas, MD; Monica A. Slavin, MD; Flavio Queiroz-Telles, MD, PhD; Dominik Selleslag, MD; Thomas J. Walsh, MD; John R. Wingard, MD; and Johan A. Maertens, MD, PhD**

**Background:** Invasive aspergillosis (IA) is associated with poor outcomes in patients with hematologic malignancies (HMs) and hematopoietic cell transplantation (HCT). Small studies suggest a role for combination antifungal therapy.

**Objective:** To assess the safety and efficacy of voriconazole and anidulafungin compared with voriconazole monotherapy for treatment of IA.

**Design:** Randomized, double-blind, placebo-controlled multicenter trial. (ClinicalTrials.gov: NCT00531479)

**Setting:** 93 international sites.

**Patients:** 454 patients with HM or HCT and suspected or documented IA were randomly assigned to treatment with voriconazole and anidulafungin or placebo. Primary analysis was done in the modified intention-to-treat population of 277 patients in whom IA was confirmed.

**Measurements:** The primary outcome was 6-week mortality; secondary outcomes included 12-week mortality, mortality in major subgroups, and safety measures.

**Results:** Mortality rates at 6 weeks were 19.3% (26 of 135) for combination therapy and 27.5% (39 of 142) for monotherapy (difference, −8.2 percentage points [95% CI, −19.0 to 1.5]; $P$ = 0.087). Secondary mortality outcomes favored combination therapy. Multivariable regression analysis suggested that maximum galactomannan value, Karnofsky score, and baseline platelet count had prognostic significance. Most patients (218 of 277 [78.7%]) had IA diagnosis established by radiographic findings and maximum galactomannan positivity. In a post hoc analysis of this dominant subgroup, 6-week mortality was lower in combination therapy than monotherapy (15.7% [17 of 108] vs. 27.3% [30 of 110]; difference, −11.5 percentage points [CI, −22.7 to −0.4]; $P$ = 0.037). Safety measures, including hepatotoxicity, were not different.

**Limitations:** Mortality at 6 weeks was higher than expected, and the difference in mortality was lower than expected, which reduced power to detect a treatment effect. Enrollment was restricted to patients with HM or HCT, which limited generalizability.

**Conclusion:** Compared with voriconazole monotherapy, combination therapy with anidulafungin led to higher survival in subgroups of patients with IA. Limitations in power preclude definitive conclusions about superiority.

**Primary Funding Source:** Pfizer.

*Ann Intern Med.* 2015;162:81-89. doi:10.7326/M13-2508 **www.annals.org**

For author affiliations, see end of text.

REVIEWS OF ANTI-INFECTIVE AGENTS INVITED ARTICLE

Louis D. Saravolatz, Section Editor

# Isavuconazole: A New Broad-Spectrum Triazole Antifungal Agent

**Marisa H. Miceli[1] and Carol A. Kauffman[1,2]**

[1]Division of Infectious Diseases, Department of Internal Medicine, University of Michigan Health System, and [2]Veterans Affairs Ann Arbor Healthcare System, Michigan

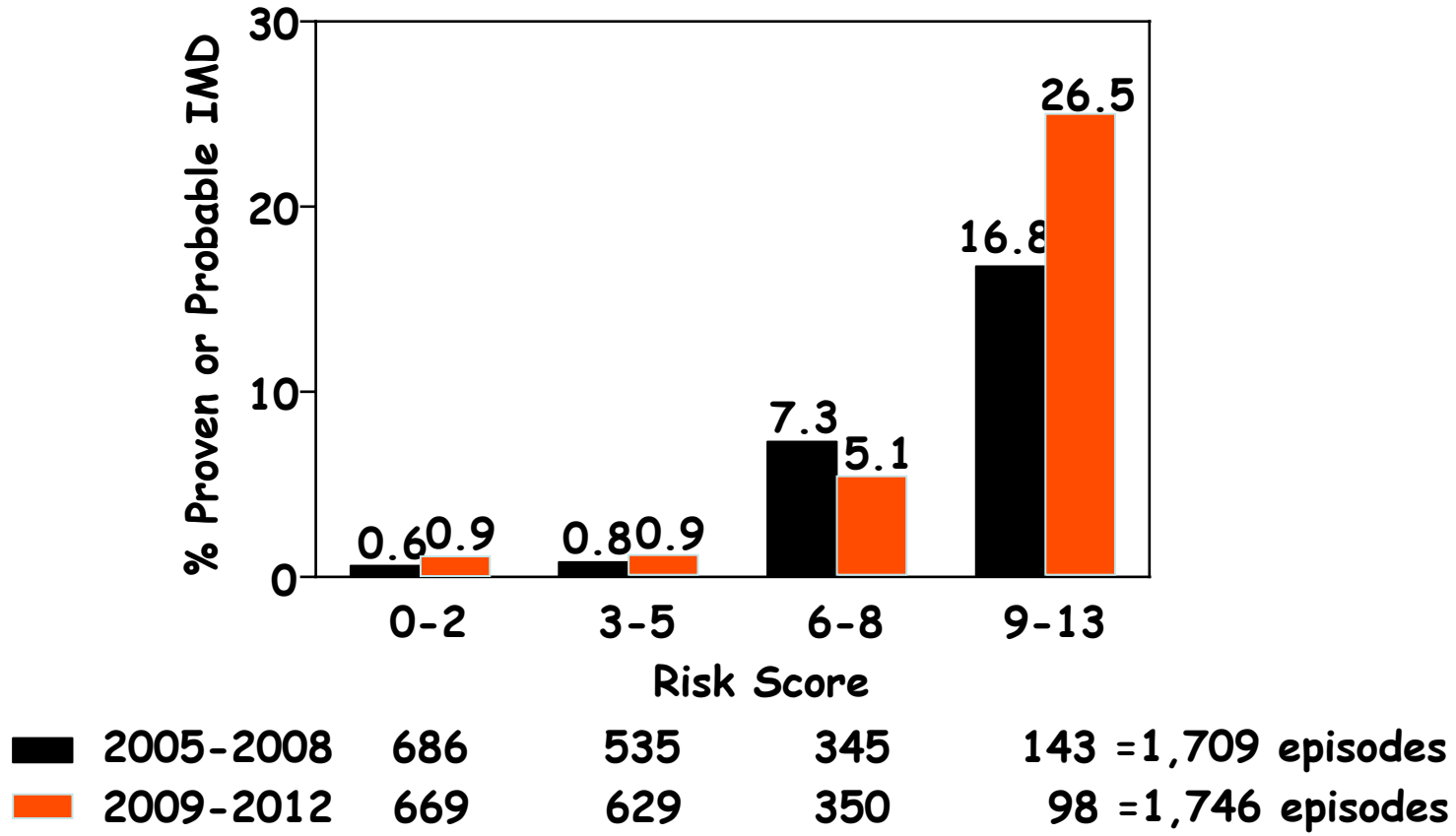
**Isavuconazole is a new extended-spectrum triazole with activity against yeasts, molds, and dimorphic fungi. It is approved for the treatment of invasive aspergillosis and mucormycosis. Advantages of this triazole include the availability of a water-soluble intravenous formulation, excellent bioavailability of the oral formulation, and predictable pharmacokinetics in adults. A randomized, double-blind comparison clinical trial for treatment of invasive aspergillosis found that the efficacy of isavuconazole was noninferior to that of voriconazole. An open-label trial that studied primary as well as salvage therapy of invasive mucormycosis showed efficacy with isavuconazole that was similar to that reported for amphotericin B and posaconazole. In patients in these studies, as well as in normal volunteers, isavuconazole was well tolerated, appeared to have few serious adverse effects, and had fewer drug–drug interactions than those noted with voriconazole. As clinical experience increases, the role of this new triazole in the treatment of invasive fungal infections will be better defined.**

**Clinical Infectious Diseases® 2015;61(10):1558–65**

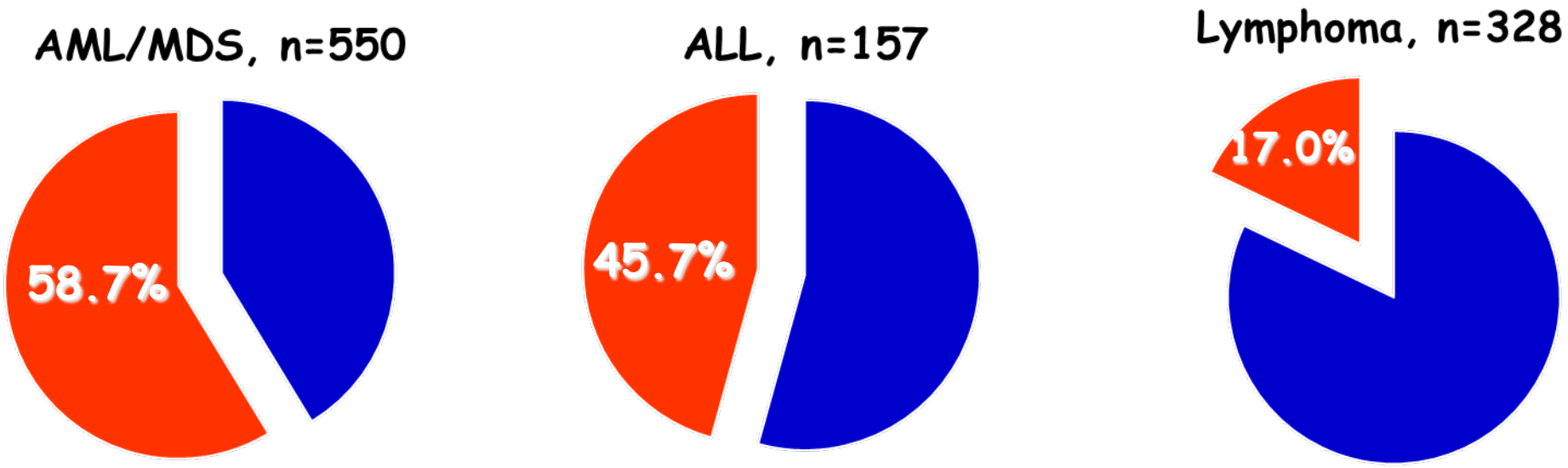
## A Risk Prediction Score for Invasive Mold Disease in Patients with Hematological Malignancies

*Stanzani M et al, PLoS One. 2013 Sep 26;8(9):e75531*

**Proven of Probable IMD by Quartile of Risk Score**



# Frequency of BoScores ≥ 6 in Non-Transplanted Hematology Populations



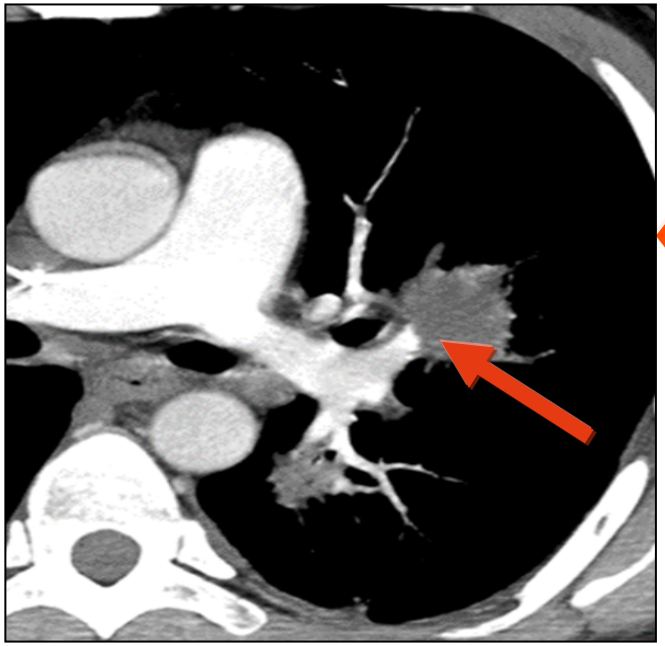
**The strategy for the diagnosis of invasive pulmonary aspergillosis should depend on both the underlying condition and the leukocyte count of patients with hematologic malignancies.** *Bergeron A et al, Blood 2012;119:1831-1837*

**55 pts with IA enrolled**

## Association between lung CT scan pattern and leukocyte count

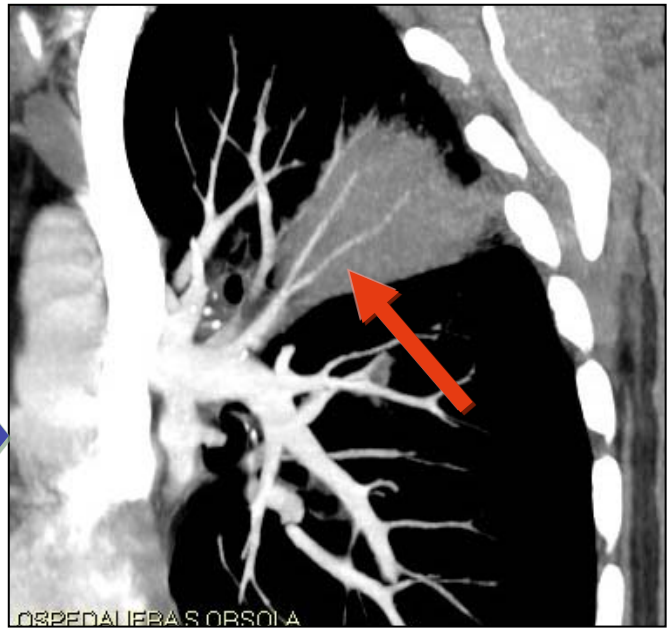
| | Leukocyte count < 100/mm3 (n 27) | Leukocyte count > 100/mm3 (n 28) | |
|---|---|---|---|
| Angioinvasive disease (n 140) | 13 | 1 | .001 |
| At least 1 airway-invasive sign (n 22) | 4 | 18 | .001 |
| Airway-invasive disease (n 15) | 2 | 13 | .005 |

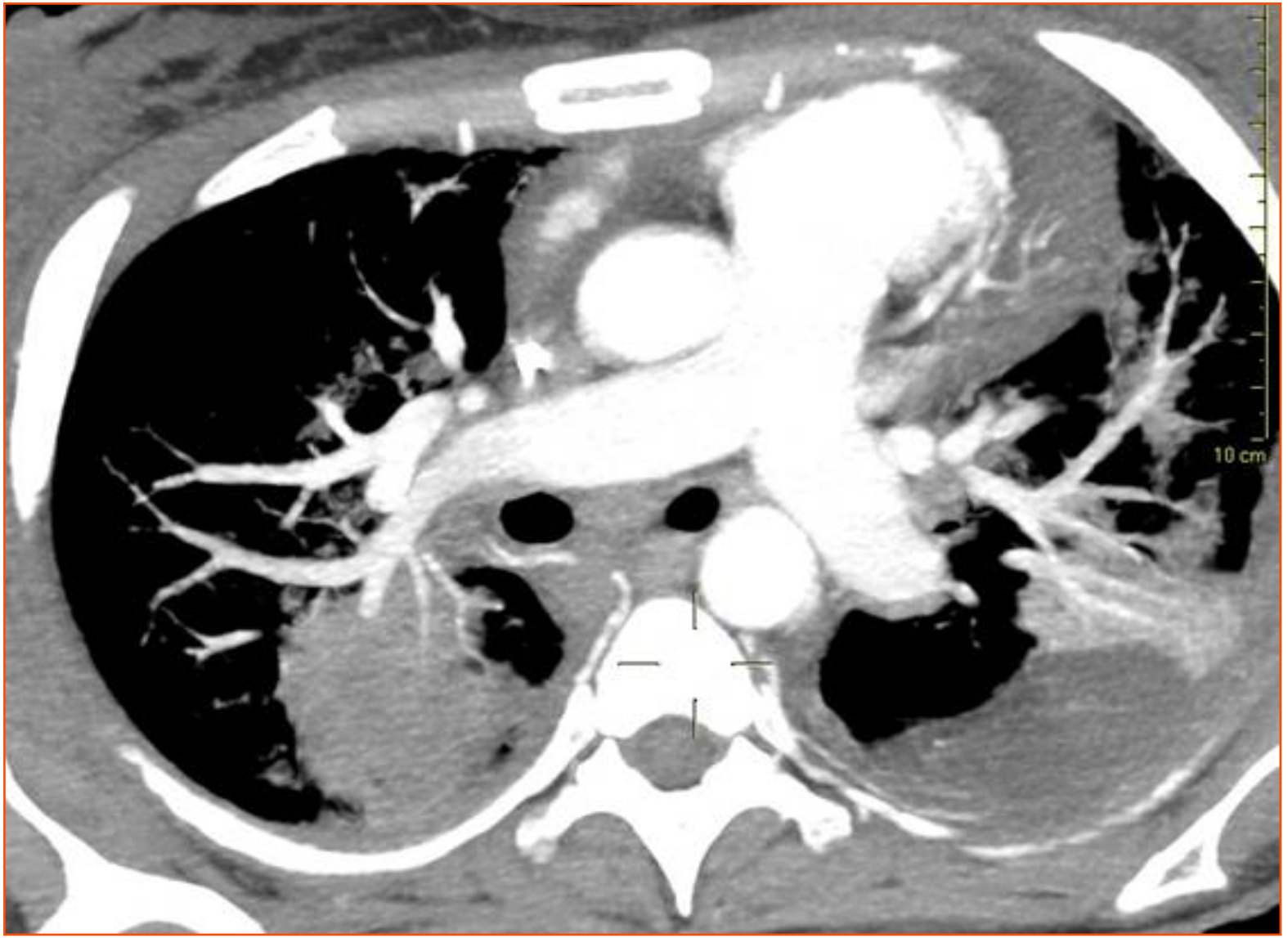
# ANGIOINVASIVITY FINDINGS



PRESENT

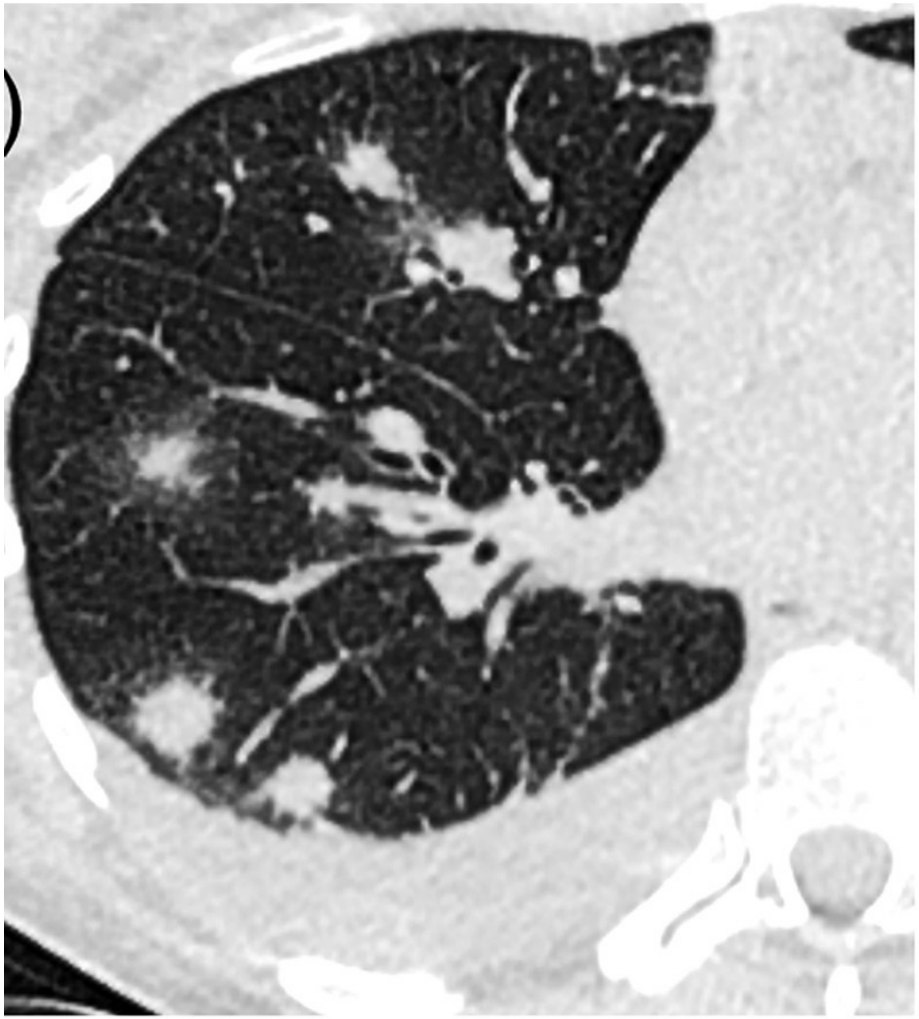
ABSENT

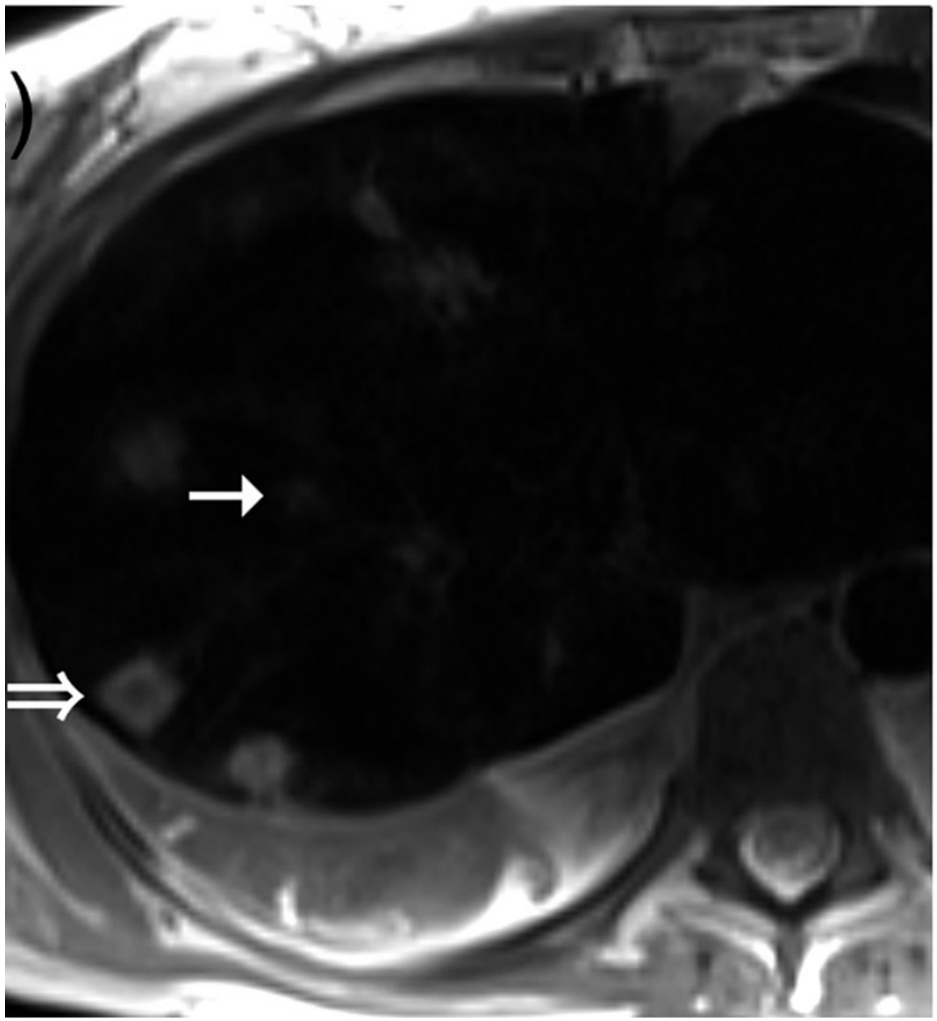



10 cm

**Can MRI be an alternative to CT in immunocompromised patients with suspected fungal infections? Feasibility of a speed optimized examination protocol at 3Tesla.**

*Nagela NS et al, Eur J Radiology 85 2016; 85: 857–863*





## Galactomannan detection for invasive aspergillosis in immunocompromised patients

*Leeflang MGM et al, Cochrane Database of Systematic Reviews 2015, Issue 12*

**54 studies were analyzed (50 in the meta-analyses), containing 5660 patients, of whom 586 had proven or probable invasive aspergillosis.**

**When using an optical density index (ODI) of 0.5 as a cut-off value, the sensitivity of the test was 82% (73% to 90%) and the specificity was 81% (72% to 90%).**

**Using the test at a cut-off value of 0.5 OD in a population of 100 patients with a disease prevalence of 9% two patients who have invasive aspergillosis would be missed (sensitivity 82%, 18% false negatives), and 17 patients would be treated unnecessarily or referred unnecessarily for further testing (specificity 81%, 19% false negatives).**

**Direct comparison of galactomannan performance in concurrent serum and bronchoalveolar lavage samples in immunocompromised patients at risk for invasive pulmonary aspergillosis.** *Boch T et al, Mycoses 2016; 59: 80–85*

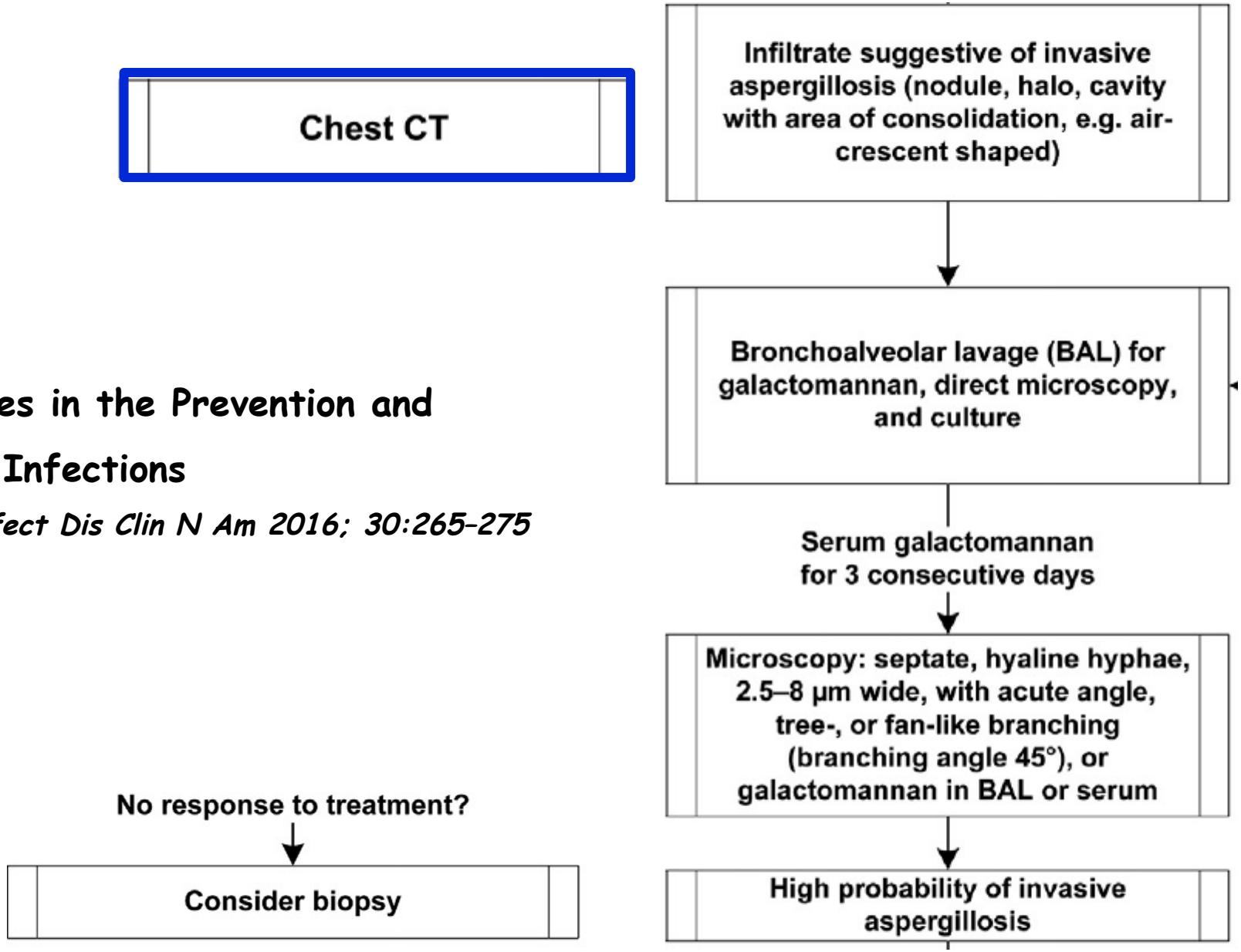
Twenty-six proven/probable patients and eight patients with no IPA according to the EORTC/MSG 2008 criteria were included in this study.

## Diagnostic performance of BAL GM and serum GM for proven/probable and no IPA

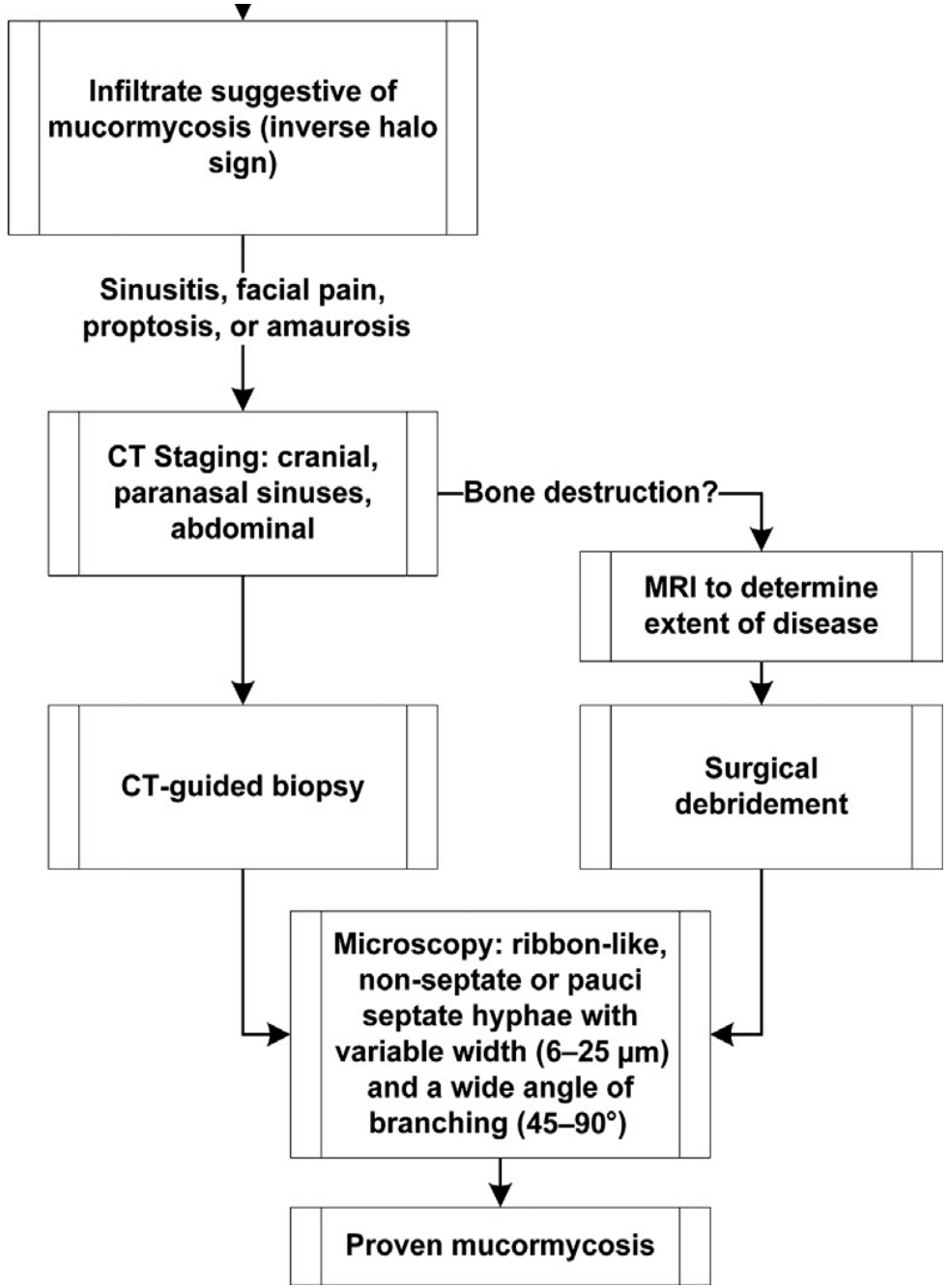
| Test | Sens % | Spec % | PPV % | NPV % | DOR | 95% CI |
|---|---|---|---|---|---|---|
| BAL GM | 85 | 88 | 96 | 64 | 38.5 | 3.7-404.2 |
| Serum GM | 23 | 88 | 88 | 26 | 2.1 | 0.2-20.7 |

## Contemporary Strategies in the Prevention and Management of Fungal Infections

*Koehler P & Cornely AO, Infect Dis Clin N Am 2016; 30:265–275*



Chest CT

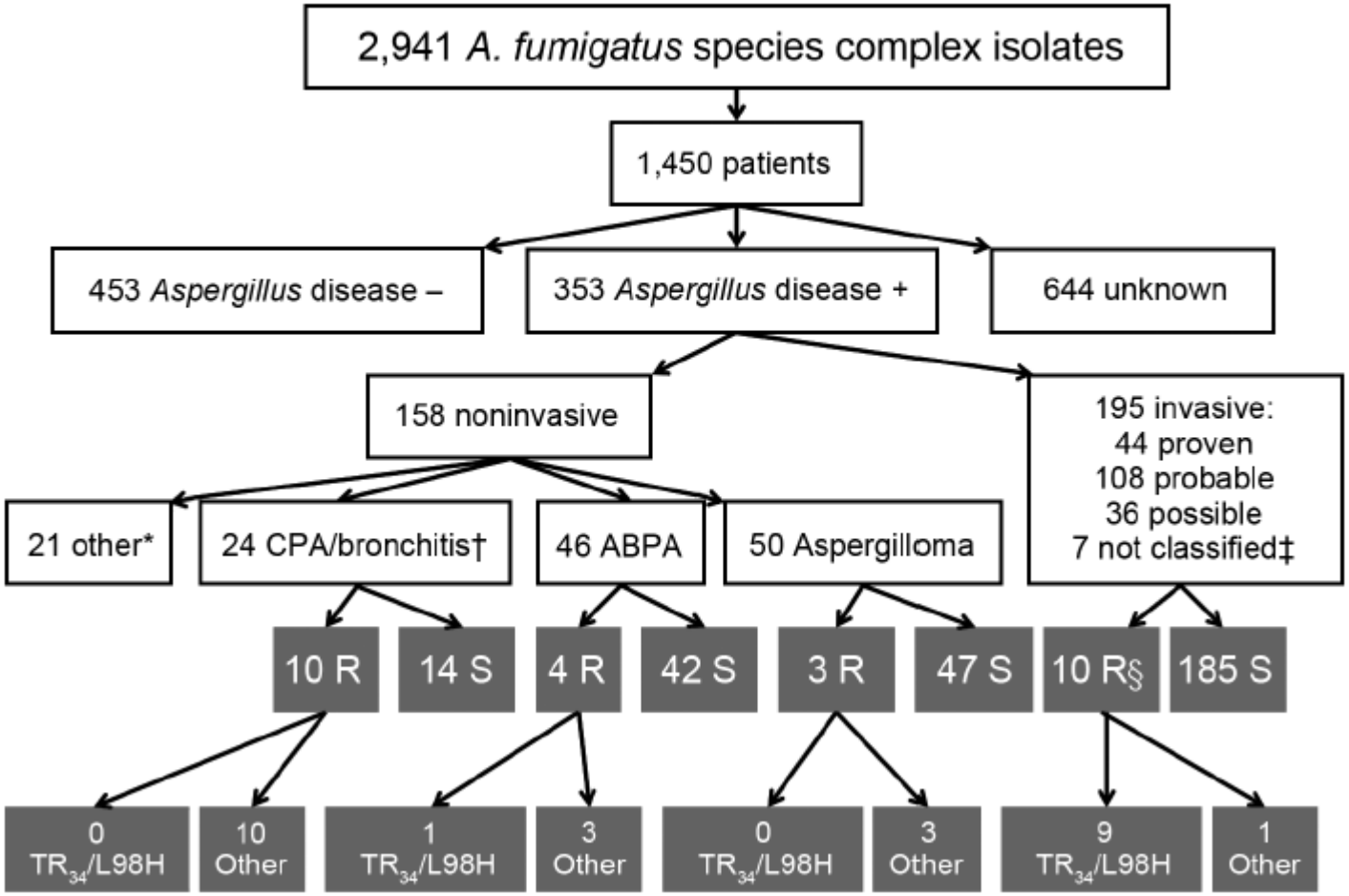



**Contemporary Strategies in the Prevention and Management of Fungal Infections**

*Koehler P & Cornely AO, Infect Dis Clin N Am 2016; 30:2*

## Prospective Multicenter International Surveillance of Azole Resistance in *Aspergillus fumigatus*

*van der Linden JWM et al, Emerg Infect Dis, 2015;21: 1041-44*




**Azole-resistant *A. fumigatus* was more frequently found (3.2% prevalence) than previously acknowledged, causing resistant invasive and noninvasive aspergillosis and severely compromising clinical use of azoles.**

## Antifungal Th immunity: growing up in family

*Borghi M et al, Front Immunol 2014;5:506*

**Evidence is accumulating to support the exciting concept that the interaction between different biomes and between the host and the mycobiome are critical in the pathogenesis of fungal infections and other human diseases.**

**Not only is the host affecting the mycobiome composition and variations, by means of genotype, physiology, immune system, and lifestyle, but also the fungal microbiota may contribute to the balance of inflammation and tolerance at local mucosal surfaces and at distal sites**

**The local Th environment may contribute to the diversity of the mycobiome at different body sites.**

**Challenging existing paradigms with new perspectives from the crosstalk between fungi, the immune system, and the microbiota will eventually lead toward the development of multi- pronged therapeutic approaches for mucosal and systemic fungal diseases.**

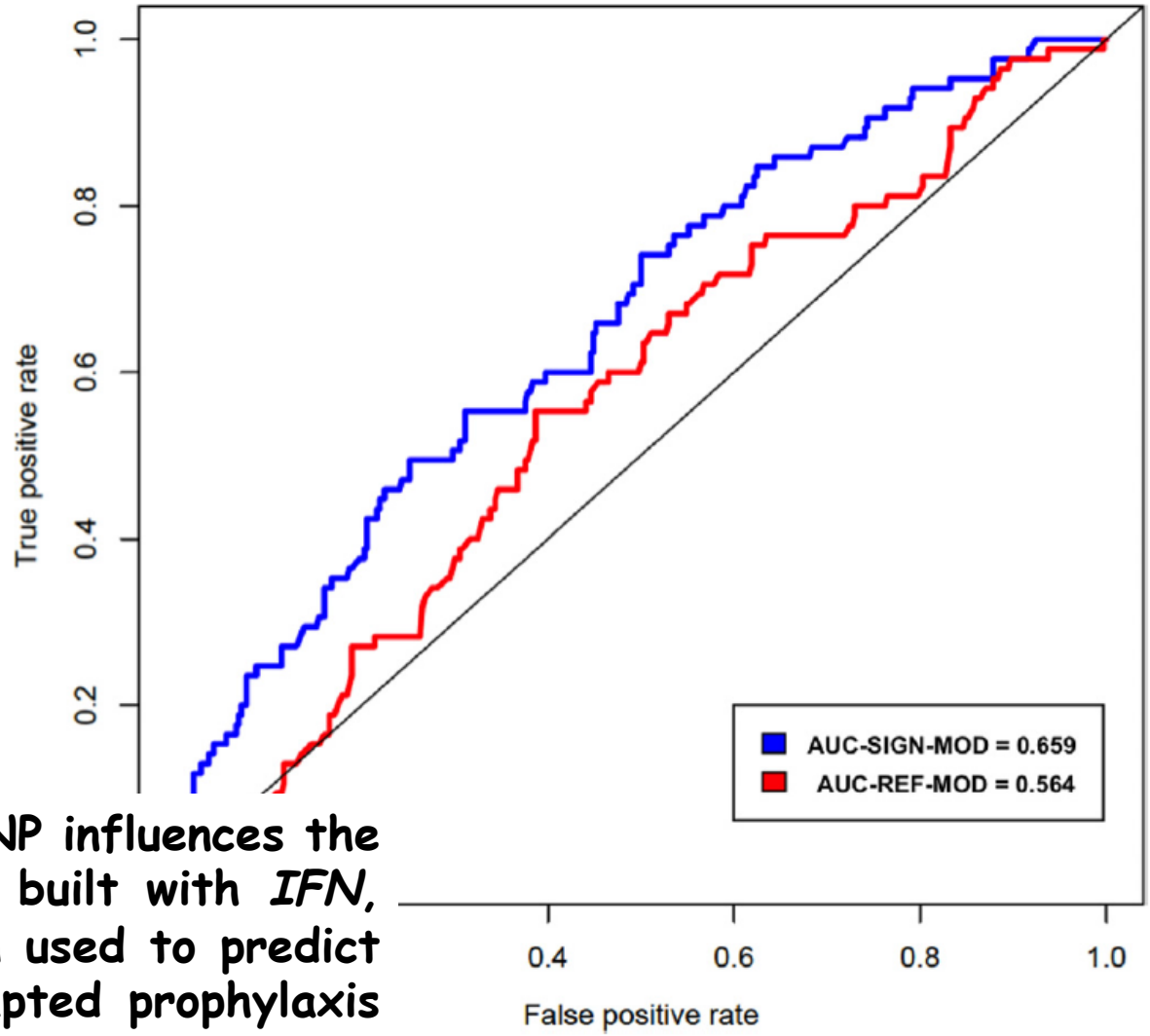
## Polymorphisms in Host Immunity-Modulating Genes and Risk of Invasive Aspergillosis: Results from the AspBIOmics Consortium

*Lupiañez CB et al, Infect Immun 2016; 84:643– 657.*

ROC curve analysis for each model

Model BLUE
demographic and clinical variables
+
immune-modulating single-nucleotide polymorphisms

RED Model
demographic and clinical variables only




These findings suggest that the *IFN* SNP influences the risk of IA and that predictive models built with *IFN*, *IL8*, *IL12p70*, and *VEGFA* variants can used to predict disease risk and to implement risk-adapted prophylaxis or diagnostic strategies.

# Lymphoproliferative disorders and IFI

Within the heterogeneous group of patients with lymphoproliferative disorders, IFI epidemiology is not well defined and antifungal prophylaxis practices vary.

The anti-infective management of these patients is significant variable because the Unit of admission can significantly vary.