El Paciente Oncohematológico y las Infecciones Fúngicas Invasivas

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Transparency Disclosure

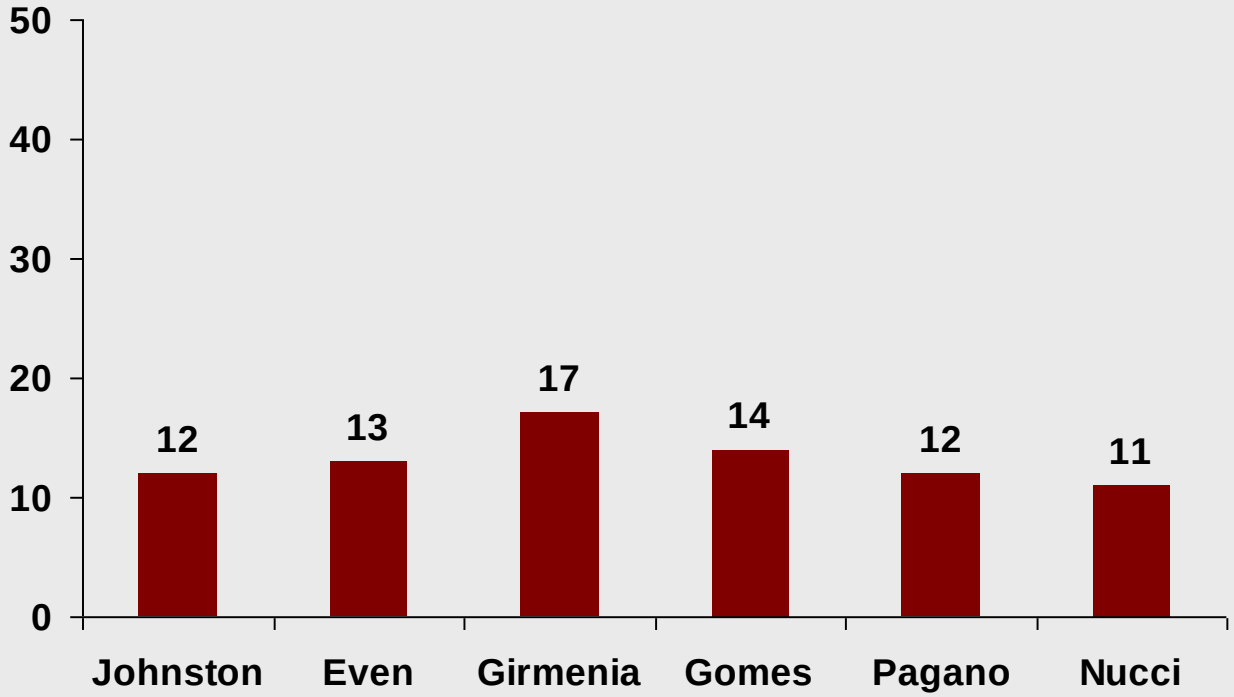
- Research grant
  - Pfizer
- Consulting
  - Pfizer, Merck, Astellas, Gilead, Basilea
- Speaker
  - Pfizer, Merck, Gilead, Astellas, United Medical, Teva

Who in the Hematology Department is at Risk for Invasive Fungal Diseases?

- High risk
  - AML, induction remission
  - ALL, relapse
  - Aplastic anemia, refractory to immunosuppression
  - Allogeneic cell transplantation
- Intermediate risk
  - ALL, induction remission
  - Autologous hematopoietic cell transplantation
  - AML, consolidation
  - Multiple myeloma, heavily pre-treated
  - Chronic lymphoid leukemia, treatment with alentuzumab
- Low risk
  - Others

Nucci & Anaissie. Blood 2014;124:3858-69

Incidence of Invasive Fungal Diseases in Patients with Acute Myeloid Leukemia



Johnston et al. Mycoses 2013;56:482-7
Even et al. Haematologica 2011;96:337-41
Girmenia et al. Leuk Research 2014;38:469-74
Gomes et al. AAC 2014;58:865-73
Pagano et al. Haematologica 2006;91:1068-75
Nucci et al. Clin Microbiol Infect 2013;19:745-51

Invasive Fungal Disease in Acute Promyelocytic Leukemia

- 103 patients from 33 centers in Italy
- ATRA + Chemotherapy (n=90) or arsenic trioxide (n=13)
- 4 proven/probable IFD (4%), all caused by molds
- 4 other cases of possible IFD
- Most cases in 1st induction
- Incidence of IFD in AML in the same cohort: 9%

Pagano et al. Br J Haematol 2015;170:434-9

Incidence of Invasive Fungal Diseases in Patients with Acute Lymphoid Leukemia

	No. patients	IFD (%)	Molds (%)	Yeasts (%)
Salzer	209	4.3	NR	NR
Afzal	447	1.1	0	1.1
Pagano	1173	6.5	4.3	2.2
Offidani	97	4.1	4.1	0
Montagna	136	3.0	1.5	1.5
Cornely	111	11.7	NR	NR

NR = not reported

Montagna et al. Int J Mol Sci 2012;13:774-87
Offidani et al. Leuk Lymphoma 2004;45:'1617-21
Pagano et al. Haematologica 2006;91:1068-75
Afzal et al. Pediatr Infect Dis J 2009;28:1064-8
Salzer et al. Pediatr Blood & Cancer 2012;59:834-9
Cornely et al. 56th ASH Meeting (Abstract 3646)

Invasive Fungal Disease in Acute Lymphoid Leukemia

350 Episodes of Febrile Neutropenia

- 31 episodes of IFD (8.8%)
  - Candidiasis (10), Aspergillosis (9), Fusariosis (5)
- Risk factors for IFD
  - Yeasts:
    - Prolonged neutropenia
  - Molds:
    - Allogeneic HCT
    - Prolonged neutropenia
    - Relapsed ALL

Nicolato et al. Leukemia & Lymphoma 2016; Mar 7:1-6

Why the Risk for IFD is Higher in AML than ALL?

- Lower probability of obtaining complete remission
- More intensive induction chemotherapy regimens
- Older age (co-morbidities)
- Poor phagocytic function of remaining neutrophils
- Antecedent myelodysplasia
  - Poor phagocytic function
  - Transfusion-related iron overload
  - Failure to obtain complete remission

Nucci & Anaissie. Blood 2014 Oct 22

Invasive Fungal Diseases in Severe Aplastic Anemia

- 78 children
  - 3 cases (4%)
    - Mucormycosis (1)
    - Aspergillosis (2)

Quarello et al. Eur J Haematol 2012;88:526-34

- 174 patients with severe aplastic anemia unresponsive to immunosuppressive therapy
  - 40 cases (23%)
    - Yeasts: 9 (Candida 8, Cryptococcus 1)
    - Molds: 31

Valdez et al. Clin Infect Dis 2011;52:726-35

Emerging Underlying Diseases in Invasive Aspergillosis

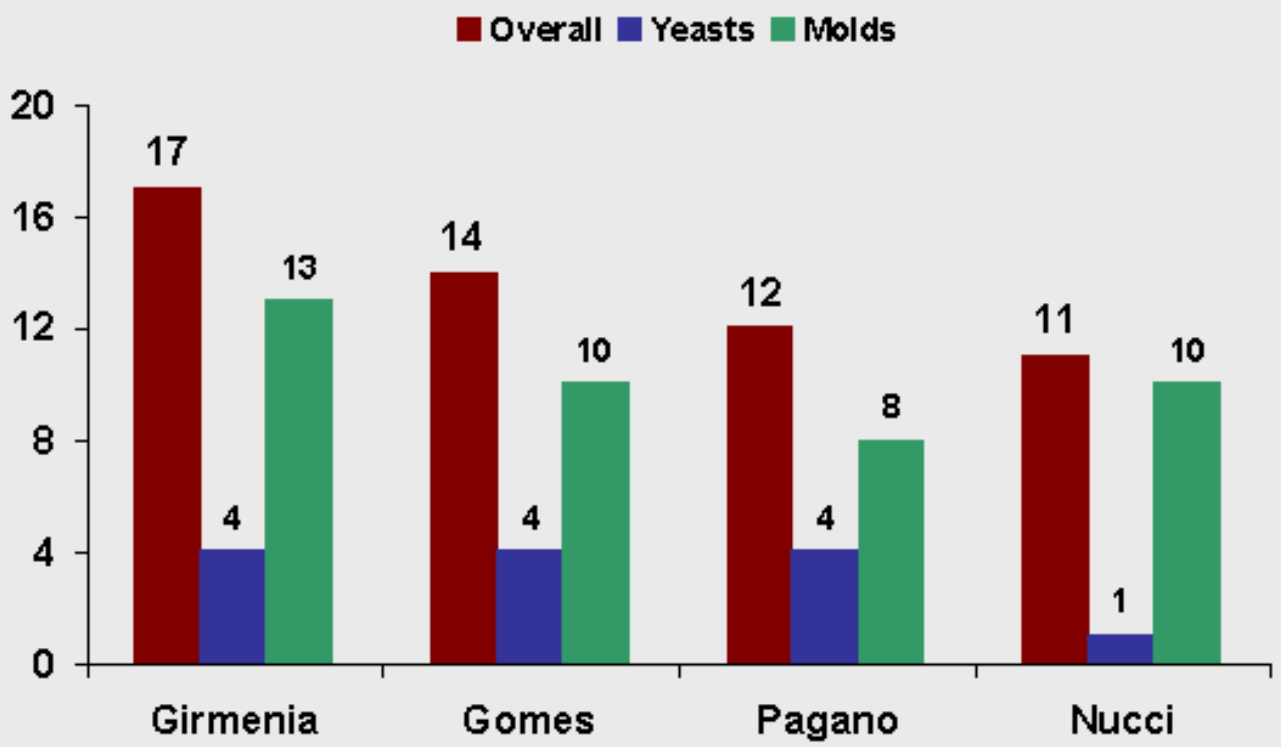
- Multiple myeloma
  - High-dose dexamethasone
  - “ALL-like” therapeutic plan
  - ↑ overall survival thanks to repeated courses of treatment regimens → cumulative immunosuppression
  - Novel agents

Nucci & Anaissie. Clin Infect Dis 2009;49:1211-25

- Chronic lymphocytic leukemia
  - Purine analogues
  - Monoclonal antibodies

Nedel et al. Rev Iberoam Micol 2009;26:175-83

Incidence of Mold and Yeast Fungal Diseases in Patients with Acute Myeloid Leukemia



Girmenia et al. Leuk Research 2014;38:469-74
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Pagano et al. Haematologica 2006;91:1068-75
Nucci et al. Clin Microbiol Infect 2013;19:745-51

Incidence of Invasive Fungal Diseases in Hematologic Patients in Brazil

- 700 HCT, 237 AML/MDS

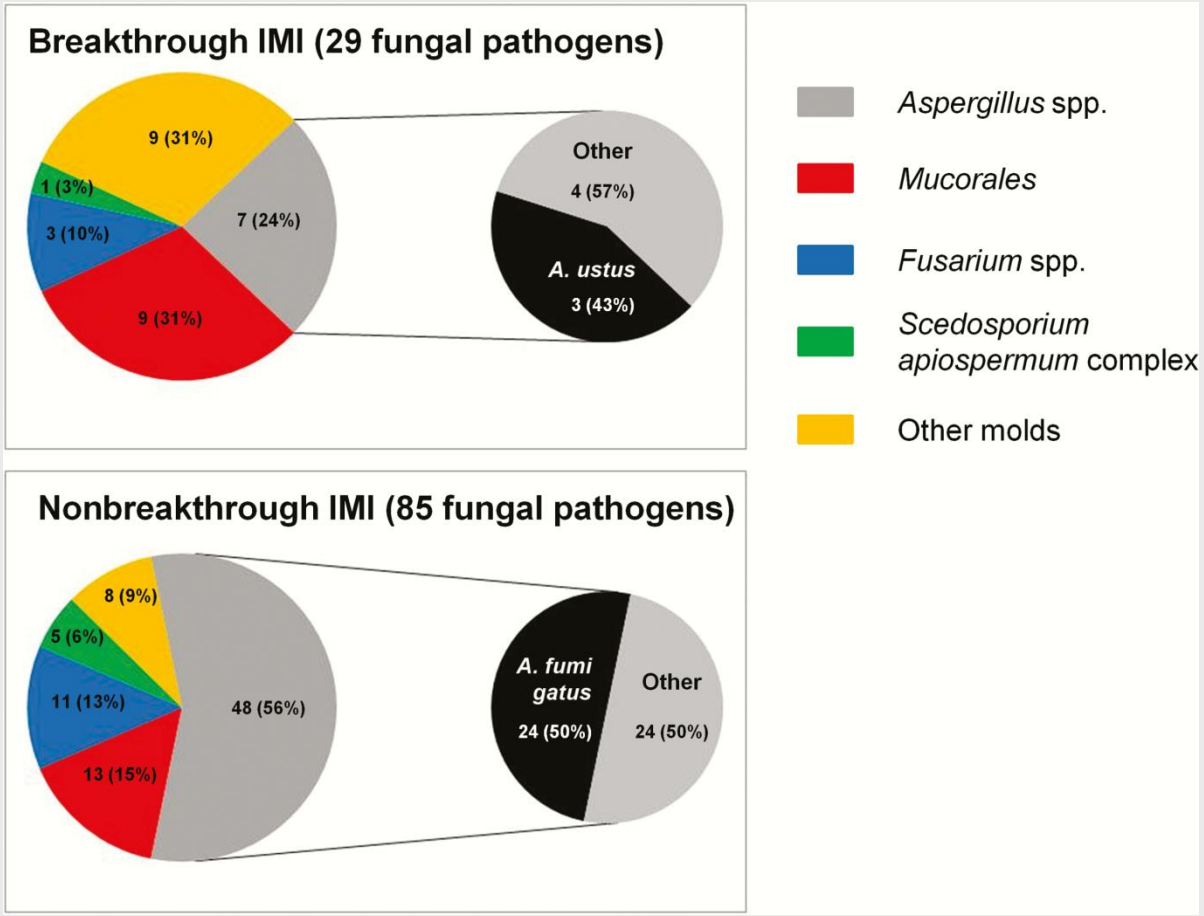
	Allogeneic HCT	Autologous HCT	AML/MDS	Total (%)
Fusariosis*	5.2 (%)	0.6 (%)	3.8 (%)	
Aspergillosis**	2.3	–	13.4	
Candidiasis	2.4	0.6	1.7	
Mucormycosis		–	–	
All IFD	11.3	1.9	18.7	8.7

HCT, haematopoietic cell transplantation; AML, acute myeloid leukaemia; MDS, myelodysplasia; IFD, invasive fungal disease.
*p 0.01; **p <0.001.

Nucci et al. Clin Microbiol Infect 2013;19:745-51

Mold Infections in Patients with or without Anti-mold Prophylaxis

- Non-Aspergillus molds
  - Breakthrough: 31%
  - Non-breakthrough: 8%
    - p=0.03
- Aspergillus ustus
  - Breakthrough: 43%
  - Non-breakthrough: 0%
    - p<0.001



Lamoth et al. Clin Infect Dis 2017;64:1619-21

When Should I Suspect Candidemia or Invasive Candidiasis

- Patients with severe mucositis without antifungal prophylaxis
  - *C. albicans*, *C. tropicalis*, *C. parapsilosis*
- Breakthrough infection in patients under prophylaxis
  - *C. glabrata*, *C. krusei*, *C. parapsilosis*
- Catheter-related candidemia
  - *C. parapsilosis*

Beyond Candidemia...
Other Yeasts in Hematologic Malignancies

- Cryptococcosis
  - Rare
  - Chronic lymphoproliferative diseases (relapsed Hodgkin's disease, CLL)
  - Purine analogues
- Trichosporonosis
  - Acute leukemia, neutropenia – 0.4%
  - Risk factors similar to invasive candidiasis

Pagano et al. Haematologica 2004;89:852-6
Girmenia et al. J Clin Microbiol 2005;43:1818-28

Invasive Fungal Diseases in Hematologic Patients
Non-Aspergillus Molds

- Fusariosis
  - AML, ALL (relapse), allogeneic HCT (pre and post-engraftment)
  - Neutropenia, receipt of corticosteroids
  - Fever, metastatic skin lesions, pneumonia, positive blood cultures
- Mucormycosis
  - Same setting, severe immunosuppression, hyperglycemia
  - Pneumonia

Nucci & Anaissie. Clin Microbiol Rev 2007;20:695-704
Petrikkos et al. Clin Infect Dis 2012;54(S1):S23-34

Are All AML Patients at the same Risk for IFD?

- 56-year-old male, admitted with a diagnosis of acute myeloid leukemia (AML)
- 65,000 WBC, normal cytogenetics, FLT3/ITD genes (+), NPM1 (-)
- Treatment plan:
  - Standard induction followed by allogeneic hematopoietic stem-cell transplantation (HSCT)

Factors Influencing the Risk of Invasive Fungal Diseases in AML (1)

- Duration of severe neutropenia
  - AML risk group (reflects the probability of achieving complete remission)
    - Age, WBC, AML cytogenetic and molecular profile, others
  - Intensity of induction chemotherapy
- Co-morbidities
  - Poor performance status, limited functional capacity, organ dysfunction especially lungs / smoking, respiratory viral disease, mucositis hyperglycemia

Nucci & Anaissie. Blood 2014;124:3858-69

Factors Influencing the Risk of Invasive Fungal Diseases in AML (2)

- Environmental exposure
  - Before admission
    - high-risk job activity (construction work, farming, gardening, florist shop employee, forestry work)
  - After admission
    - Room without HEPA filter, building construction / renovation
    - Water leakage on hospital floor
- Local epidemiology

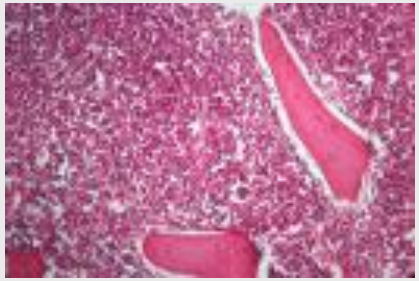
Nucci & Anaissie. Blood 2014;124:3858-69
Caira et al. Haematologica 2015;100:284=92

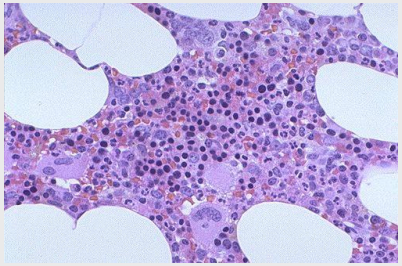
Risk Assessment in Patients with AML

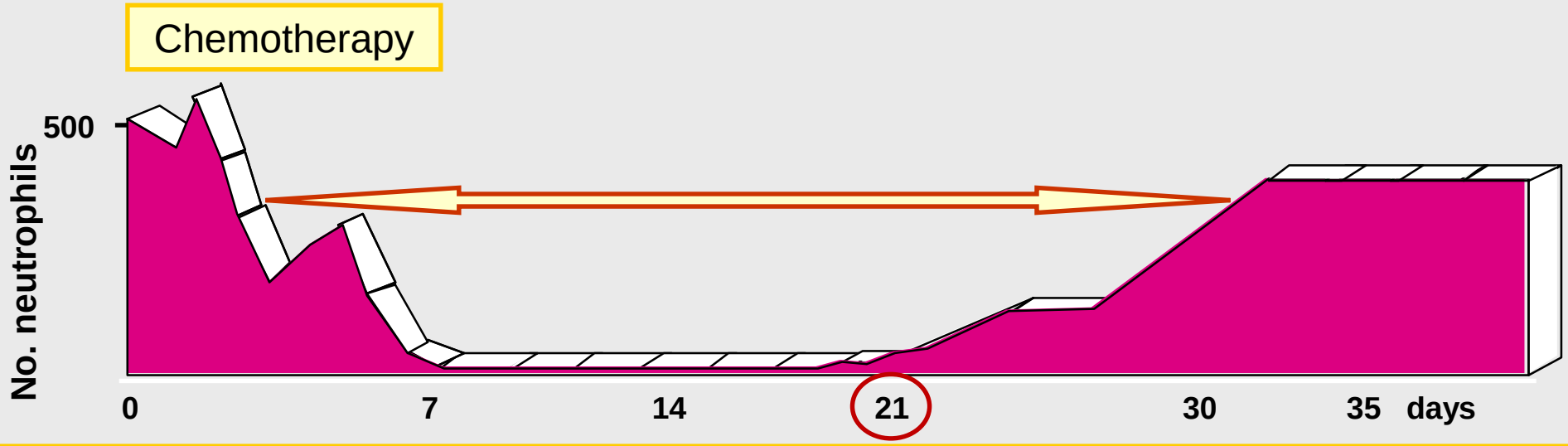
	Risk group		
	Low	**Intermediate**	**High**
Age	<40	41-59	≥60
AML	De novo		Secondary, relapsed
Cytogenetics	T(8;21), inv(16)	Normal	Other abnormalities
Gene mutation	Mutated NPM1, CEBPA	Wild NPM1,	Mutated FLT3/IDT
WBC count	<10,000/mm^3	10-50,000/mm^3	>50,000/mm^3
Room	HEPA filter		No HEPA filter
Co-mobiditles	No	Diabetes, lung disease, iron overload, respiratory viral disease	
Prior mold disease	No		Yes

Nucci & Anaissie. Blood 2014;124:3858-69

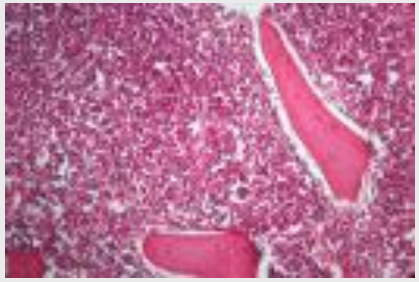
Complete Remission and Duration of Neutropenia in AML







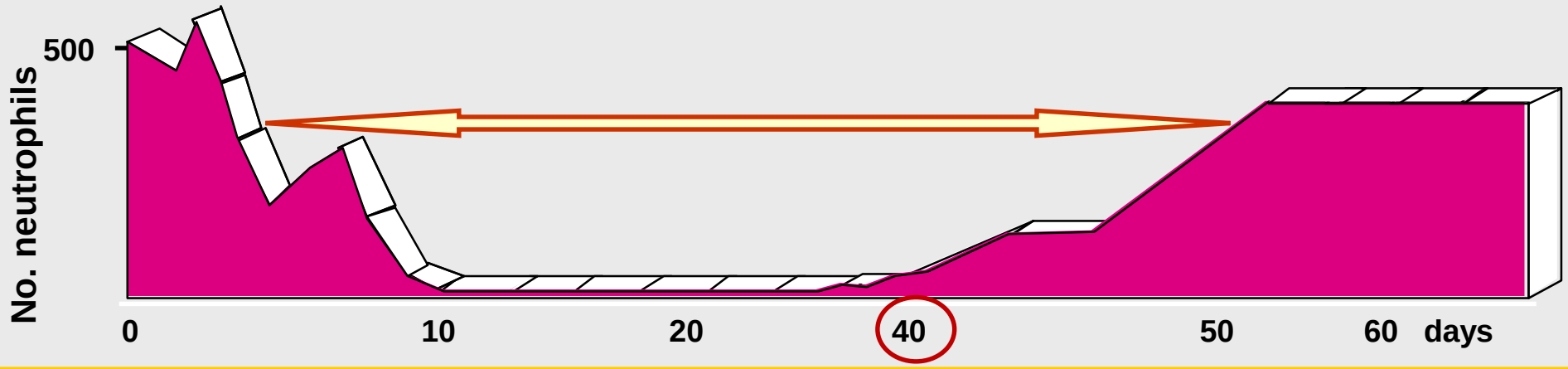
Complete Remission and Duration of Neutropenia in AML



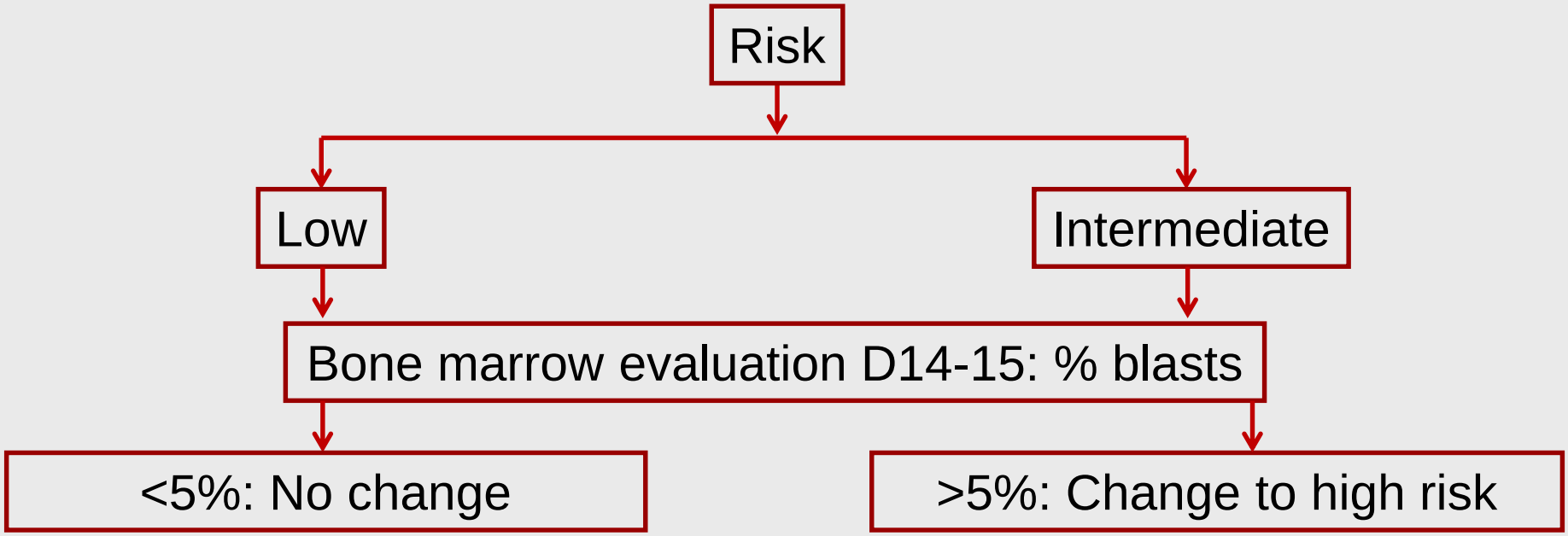
No response or partial remission

Additional chemotherapy

Chemotherapy



Dynamic Risk Assessment of Invasive Fungal Disease on AML Patients



Nucci & Anaissie. Blood 2014;124:3858-69

Most Invasive Fungal Diseases Occur in the Induction Remission Phase

- 237 patients, 26 cases of invasive fungal disease

Cohort	No. of cases	
AML/MDS	Induction	Consolidation
Aspergillosis	11	1
Candidiasis	1	1
Fusariosis	6	–
Other	6	–

92%

Nucci et al. Clin Microbiol Infect 2013;19:745-51

Why Risk Assessment of Invasive Fungal Disease is Important?
Defining Prophylactic Strategy

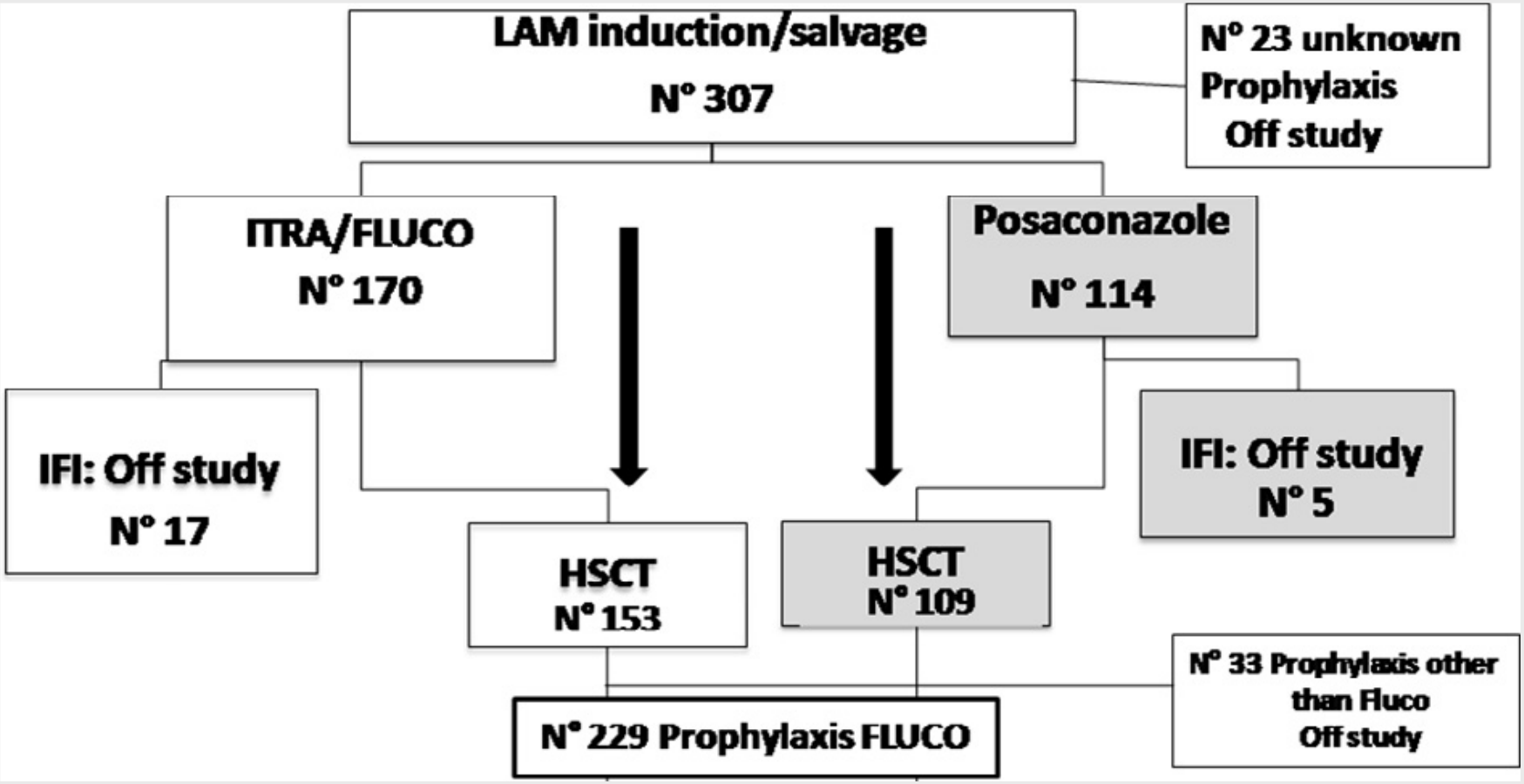
Option 1: Broad-spectrum azole for all patients → POSACONAZOLE

Option 2: Risk stratification →
- LOW or INTERMEDIATE: FLUCONAZOLE + ACTIVE MONITORING (*)
- HIGH: POSACONAZOLE

* Serial (2-3x/wk) serum galactomannan and chest and sinus CT scan

Nucci & Anaissie. Blood 2014;124:3858-69

Antifungal Prophylaxis During Induction Chemotherapy Impacts the Risk for IDF during Transplant



Busca et al. BBMT 2016;22:2214-9

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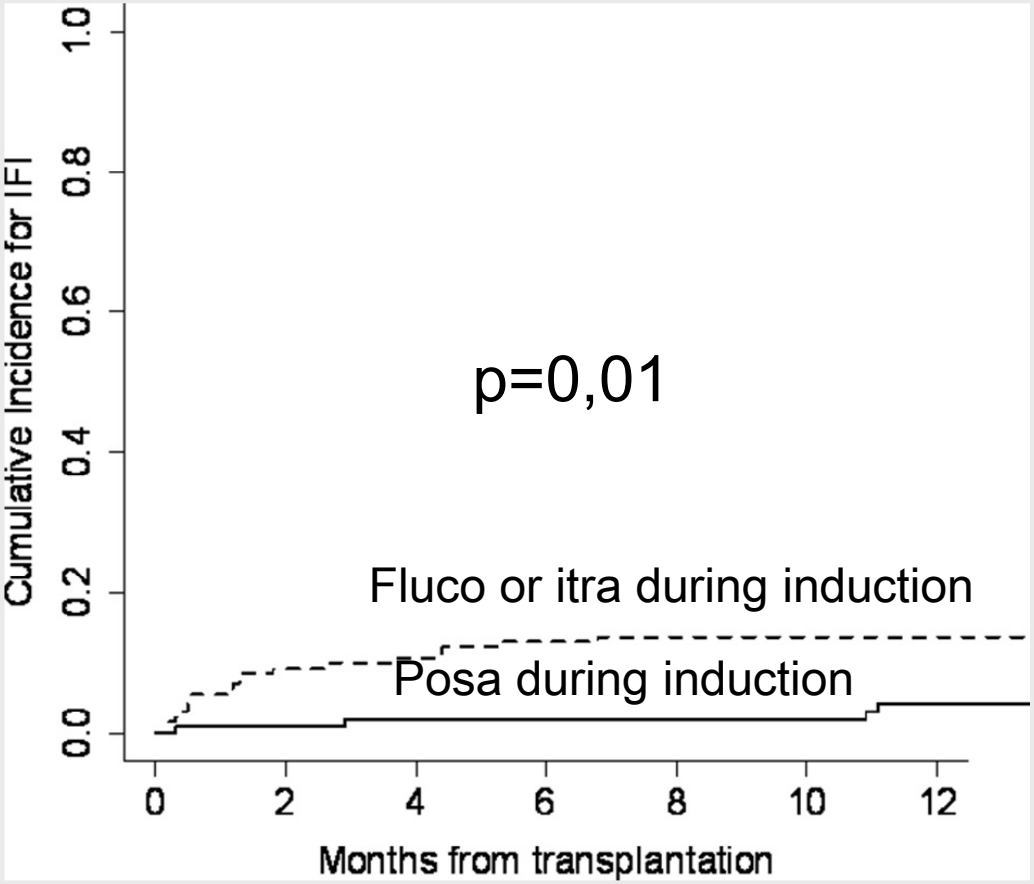


- Risk factors for IFD
  - Unrelated donor
  - Haploidentical transplant
  - Reduced intensity conditioning
  - Prophylaxis with itra or fluco during induction (OR 3.72)

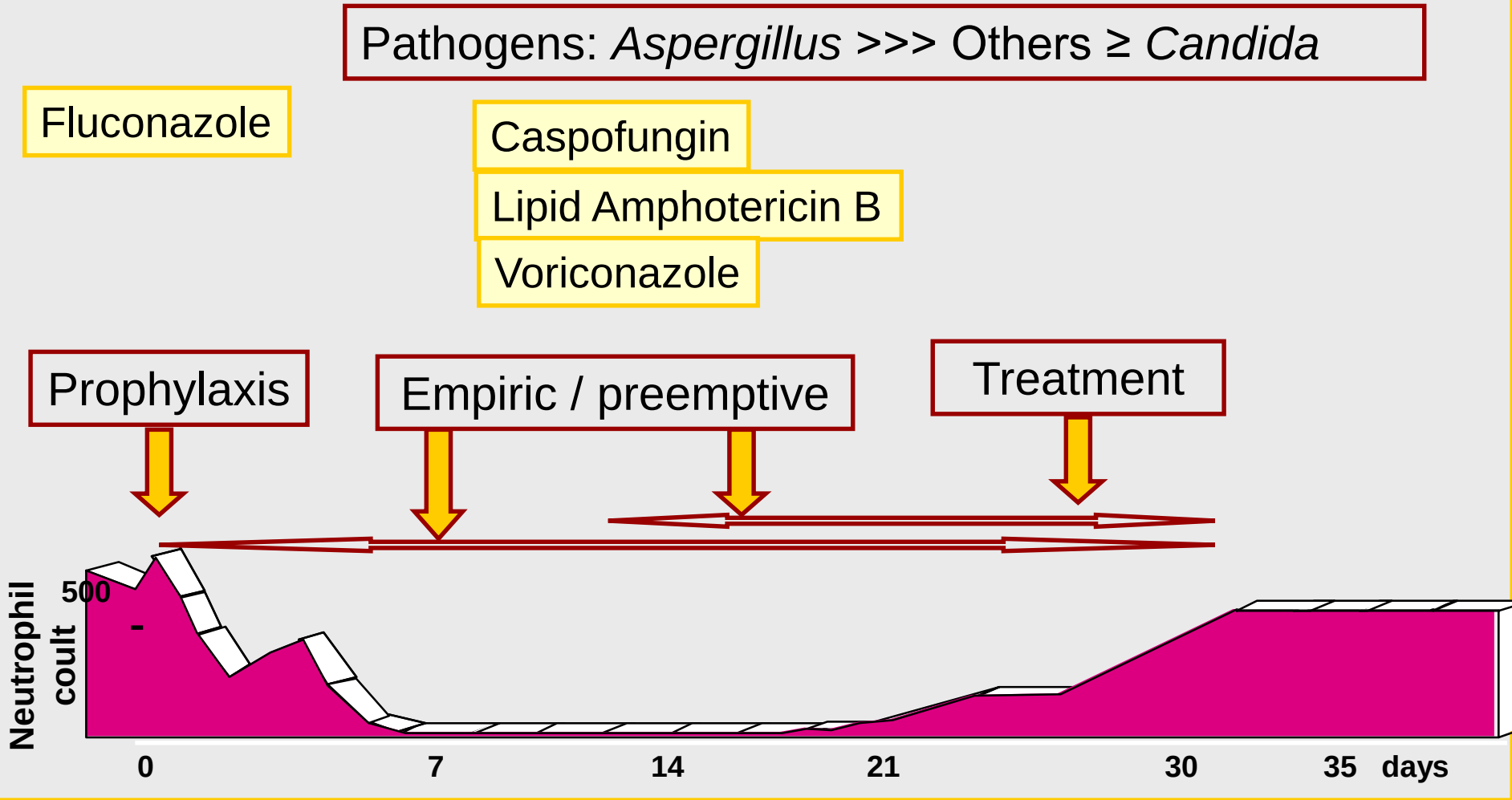
Busca et al. BBMT 2016;22:2214-9

“Side Effects” of Posaconazole Prophylaxis

- Limits the choice of subsequent antifungal agents in empirc / preemptive therapy
- Changes strategy for monitoring with images and galactomannan

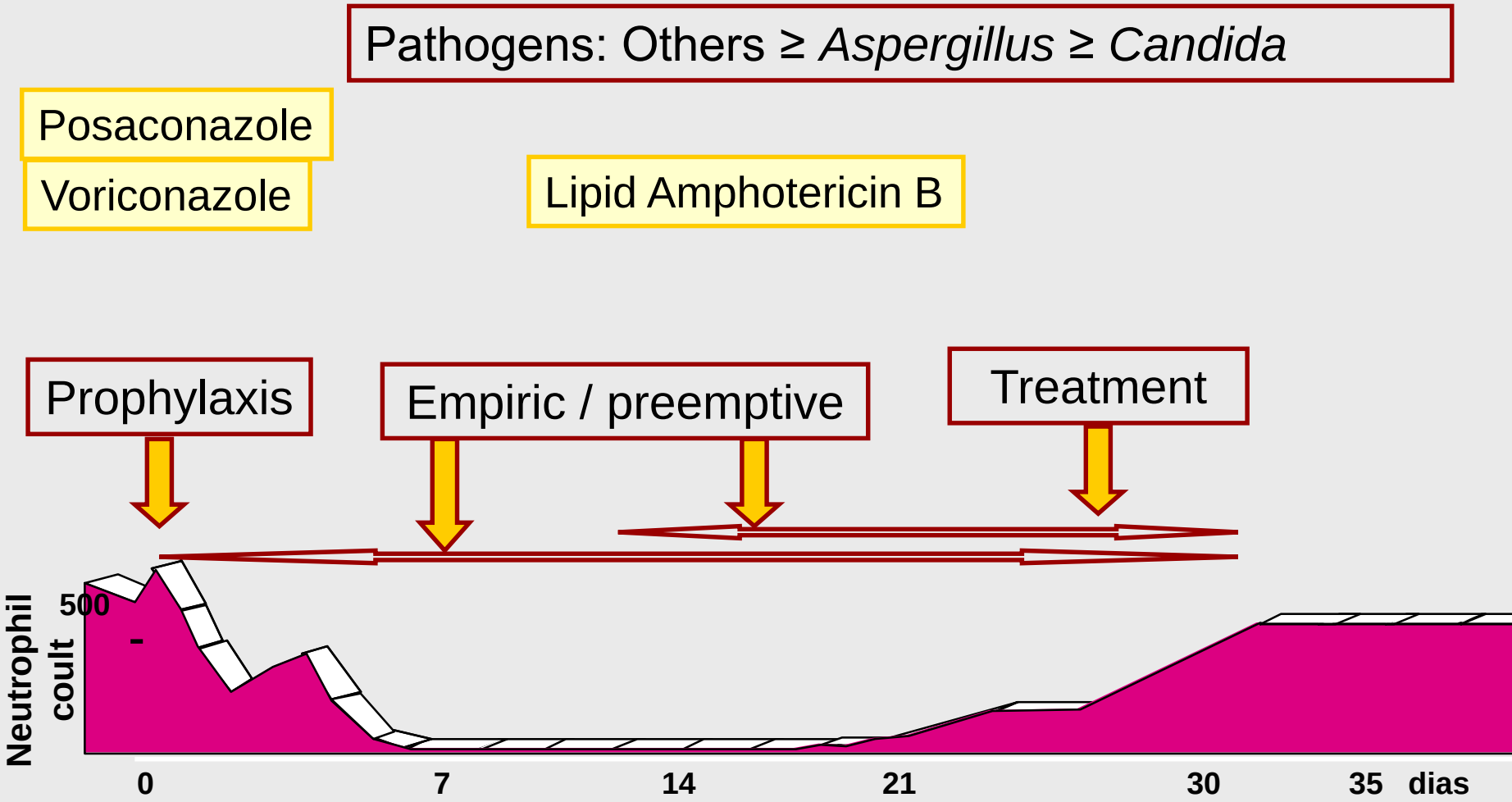
Effect of Prophylaxis on the Choice of Empiric or Preemptive Antifungal Therapy

Fluconazole



Effect of Prophylaxis on the Choice of Empiric or Preemptive Antifungal Therapy

Posaconazole (or voriconazole)



Prophylaxis with Posaconazole in AML

What if I need additional antifungal therapy?

- 981 AML patients receiving induction chemo, 33 Italian centers, 28 months
- 510 received posaconazole
  - 140 (27%) received another antifungal during induction
    - Empiric: 80%, preemptive 15%, treatment of IFD 5%
      - Antifungal agents used as empiric or preemptive therapy:
        - Lipid formulation of amphotericin B in 70%

Pagano et al. J Antimicrob Chemother 2014;69:3142-7

Use of Non-prophylactic Antifungal Agents in Febrile Neutropenia

- Empiric therapy
  - Antifungal started if unexplained persistent or recurrent FEVER
    - PROBLEMS: overuse of antifungals, no commitment with diagnosis, many patients with IDF do not have fever
- Preemptive (or diagnostic-driven) therapy
  - Antifungal started ONLY of a marker of IFD appears (e.g. positive galactomannan)
    - PROBLEMS: needs lab and multidisciplinary approach

Monitoring Strategy for Diagnostic Driven Antifungal Therapy
1. All patients, entire period at risk

- Start monitoring a the beginning of the period at risk (e.g. neutropenia)
- Serum galactomanann 2-3x/week, results in “real time” (on the same day)
- CT scan (thorax and sinuses) IF:
  - Positive biomarker
  - Persistent or recurrent fever
  - Any clinical manifestation suspicious of IFD

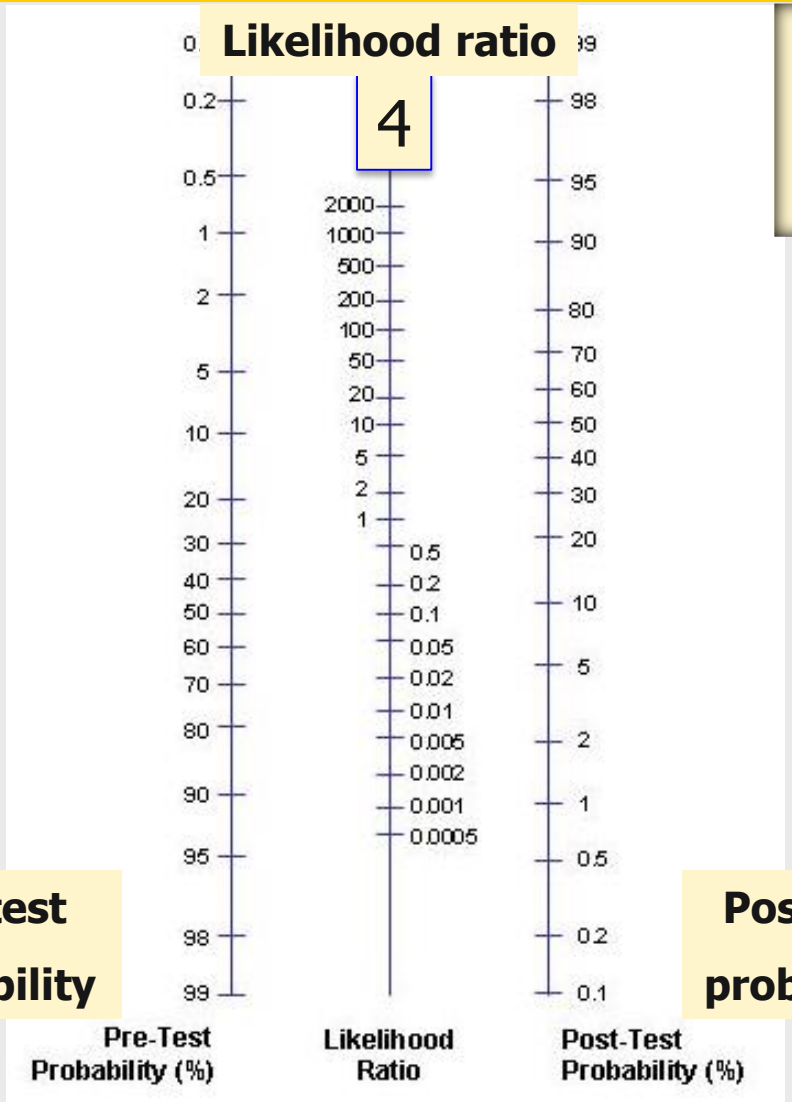
Maertens et al. Clin Infect Dis 2005;41:1242-50

Monitoring Strategy for Diagnostic Driven Antifungal Therapy
2. On clinical demand

- Intensive workup trigered by clinical findings
  - Sart monitoring IF
    - Persistent or recurrent fever
    - Any clinical manifestation suspicious of IFD
  - Galactomannan for 3 consecutive days
  - CT scan (thorax and sinuses)
  - Additional tests as needed

Girmenia et al. J Clin Oncol 2010;28:667-24

Post-test probability of Invasive Fungal Disease in Patients with or without Anti-mold Prophylaxis

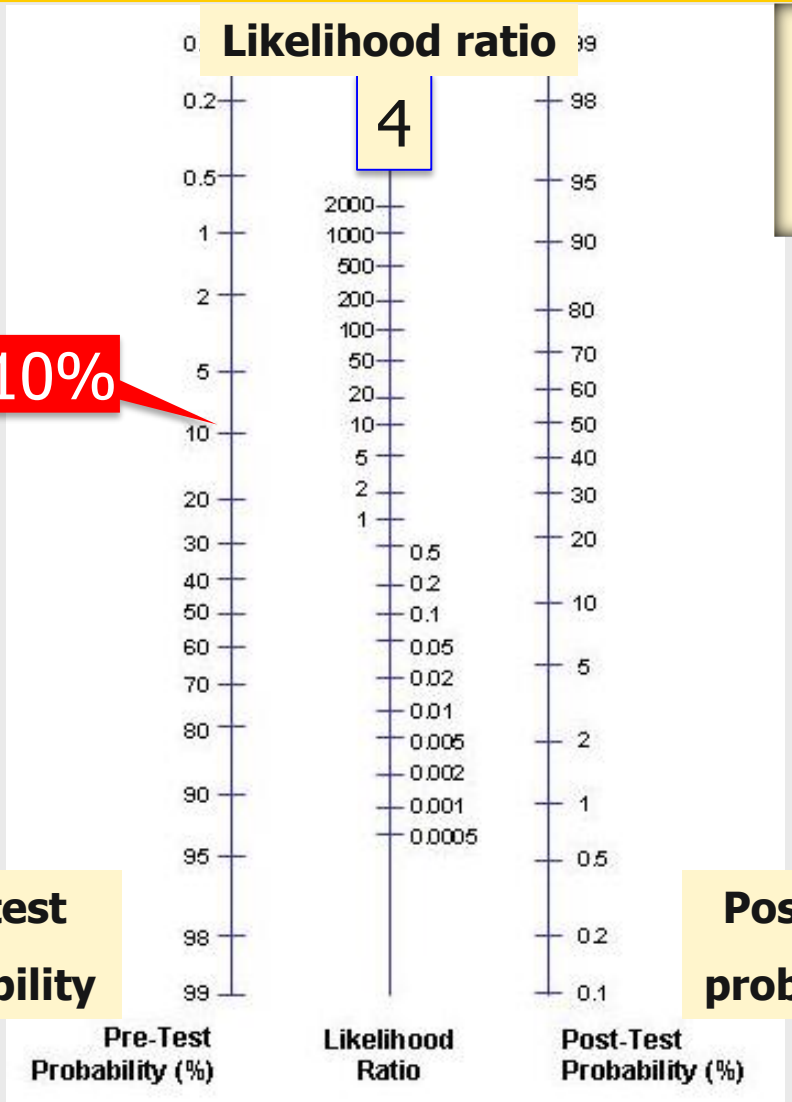


Galactomannan

Sensitivity = 0.78

Specificity = 0.81

Post-test probability
No Anti-mold Prophylaxis



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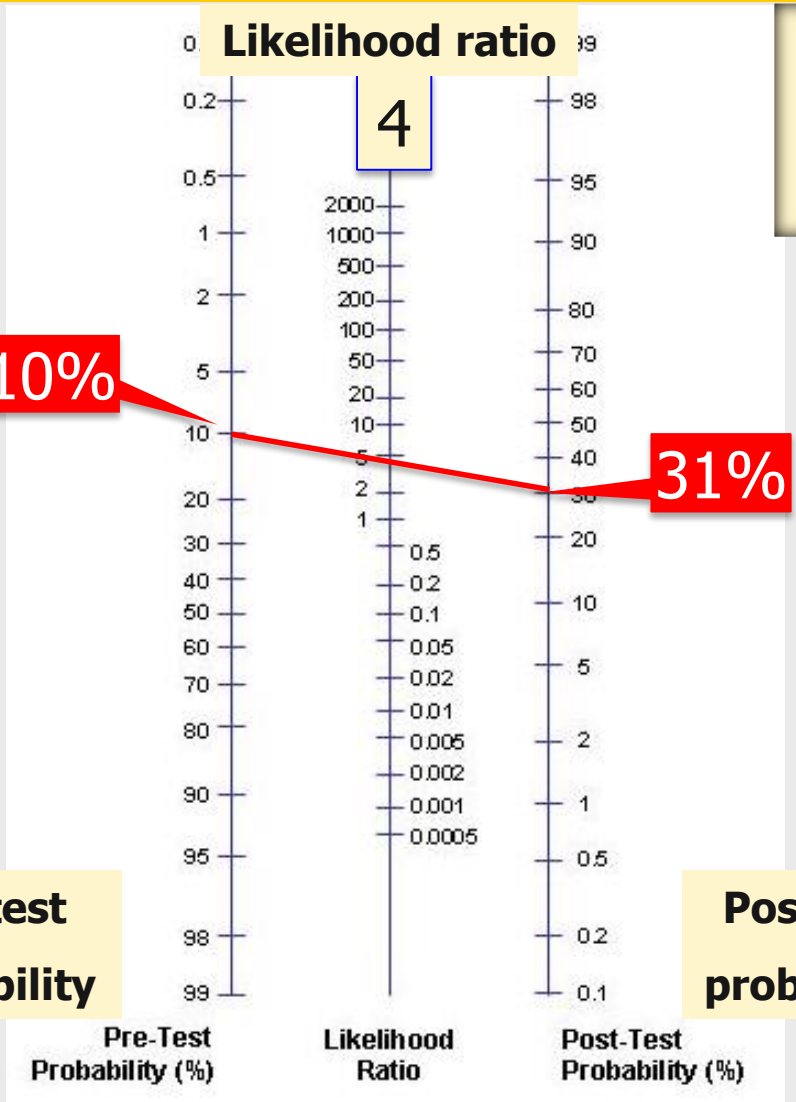


Galactomannan

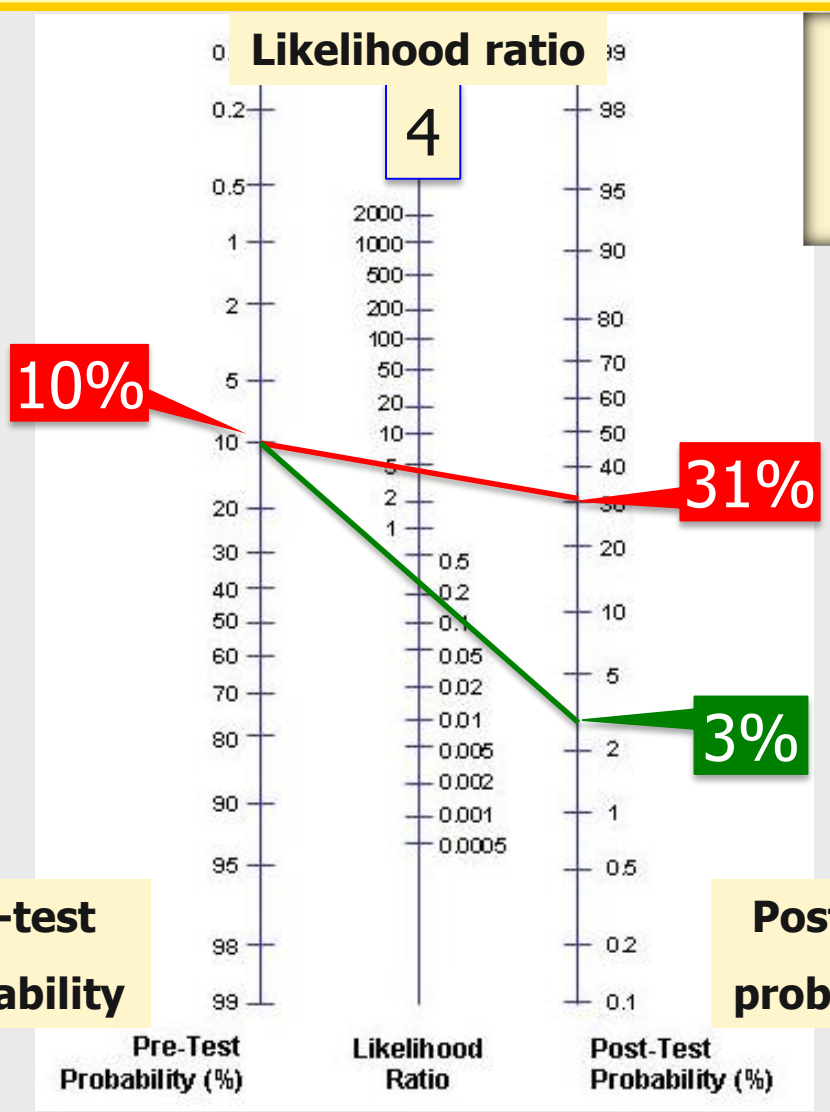
Sensitivity = 0.78

Specificity = 0.81

Proportion of patients with IA that test positive

PPV

Post-test probability
No Anti-mold Prophylaxis



Galactomannan

Sensitivity = 0.78

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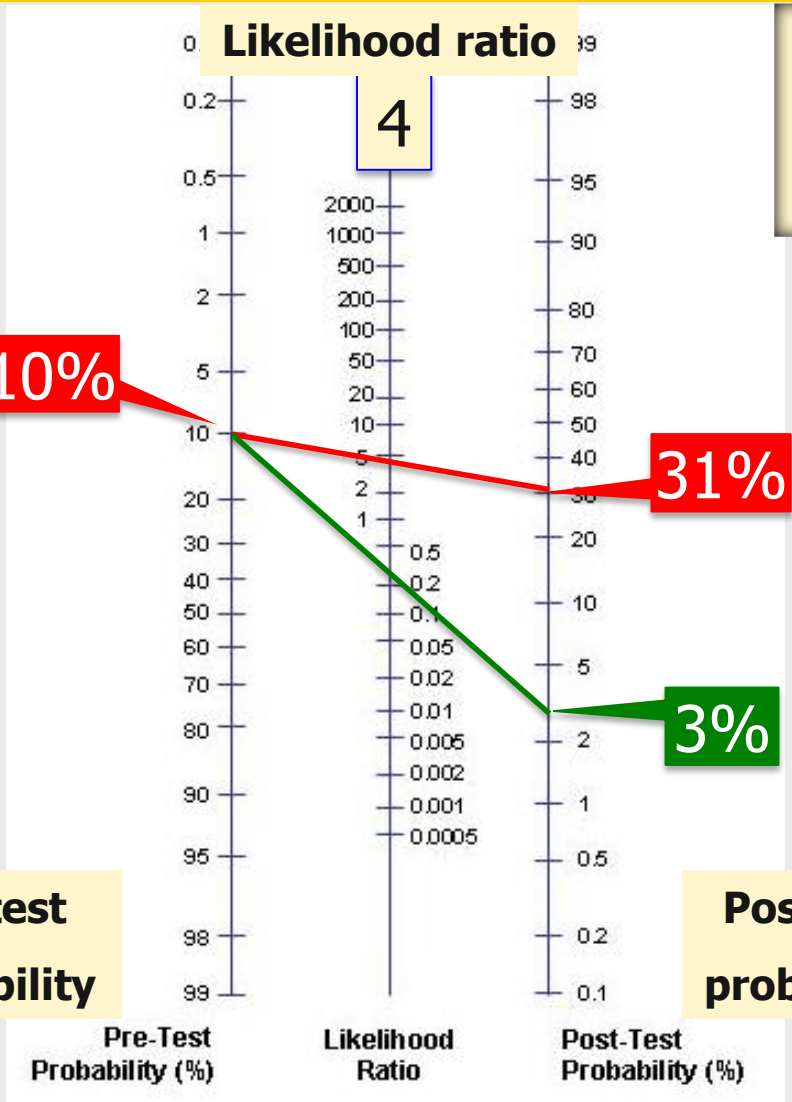
Proportion of patients with IA that test positive

PPV

Proportion of patients without IA that test positive

Post-test probability
No Anti-mold Prophylaxis



Galactomannan

Sensitivity = 0.78

Specificity = 0.81

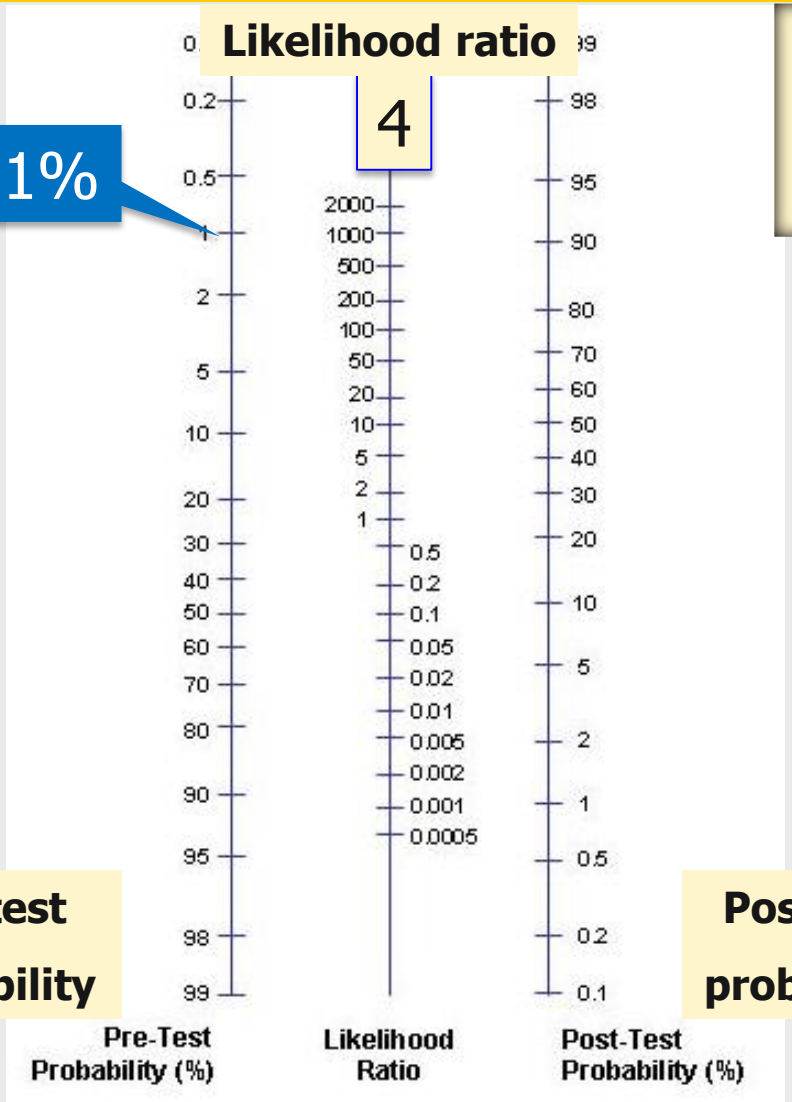
Proportion of patients with IA that test positive

PPV

Proportion of patients without IA that test positive

NPV = 97%

Post-test Probability
Anti-mold Prophylaxis

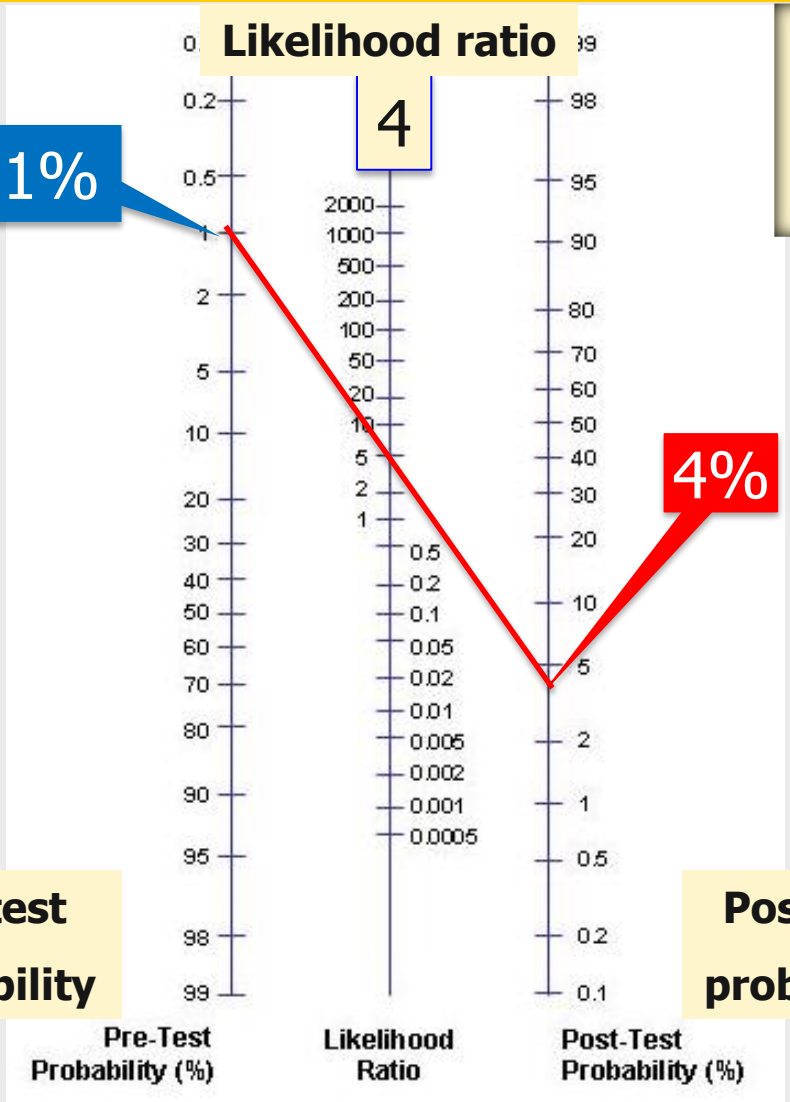


Galactomannan

Sensitivity = 0.78

Specificity = 0.81

Post-test Probability
Anti-mold Prophylaxis



Pre-test probability

Post-test probability

Galactomannan

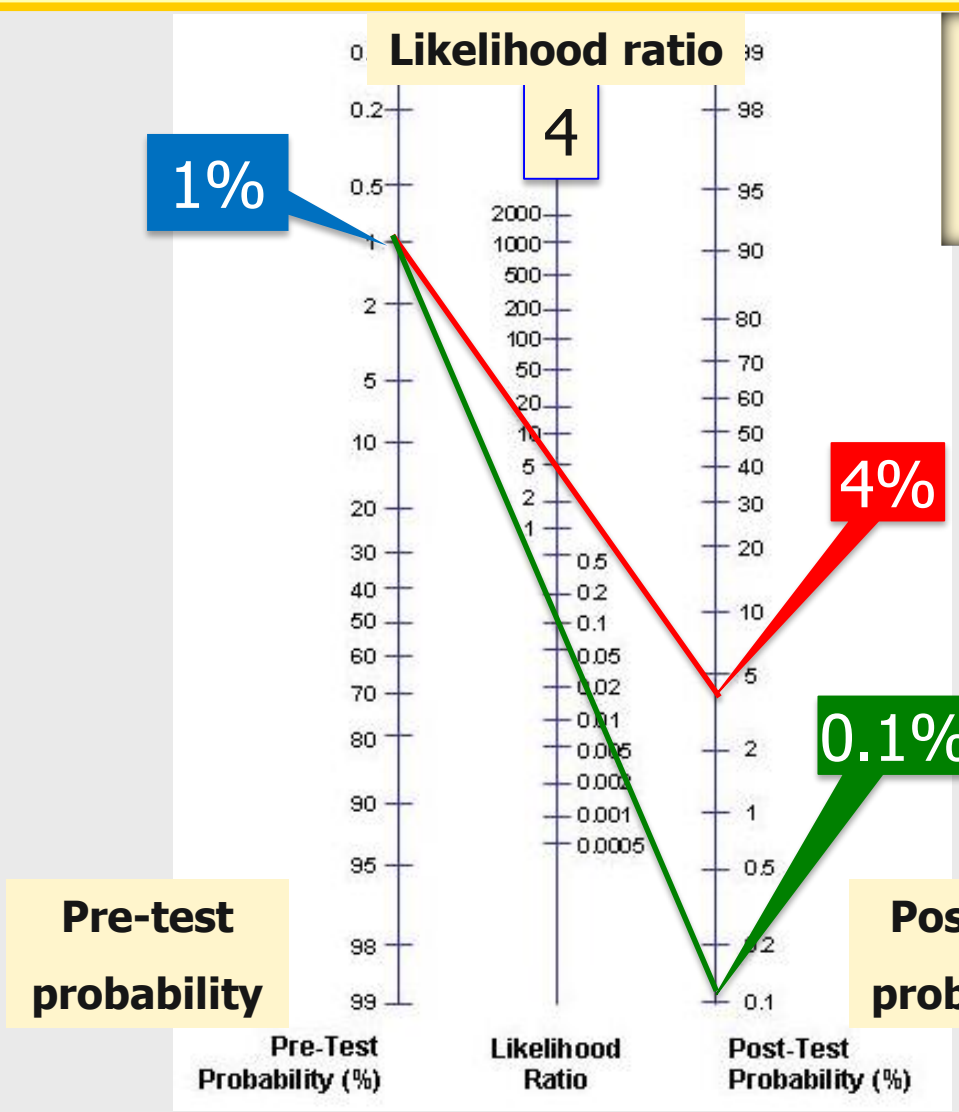
Sensitivity = 0.78

Specificity = 0.81

Proportion of patients with IA that test positive

PPV

Post-test Probability
Anti-mold Prophylaxis



Galactomannan

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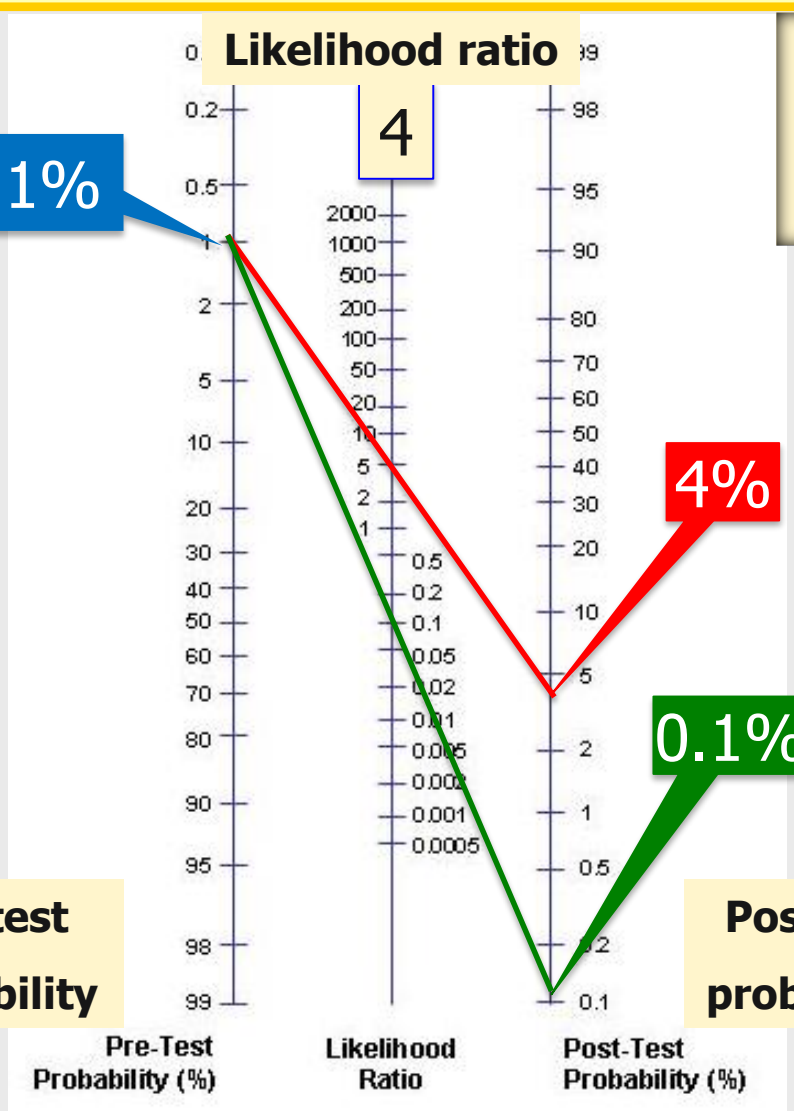
Specificity = 0.81

Proportion of patients with IA that test positive

PPV

Proportion of patients without IA that test positive

Post-test Probability
Anti-mold Prophylaxis



Galactomannan

Sensitivity = 0.78

Specificity = 0.81

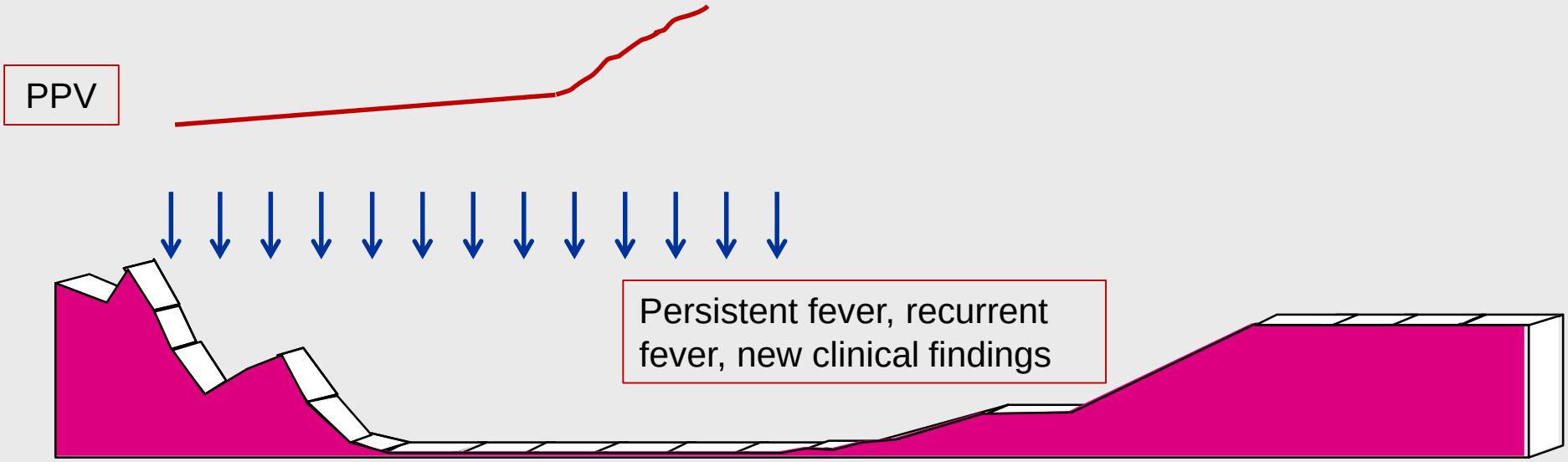
Proportion of patients with IA that test positive

PPV

Proportion of patients without IA that test positive

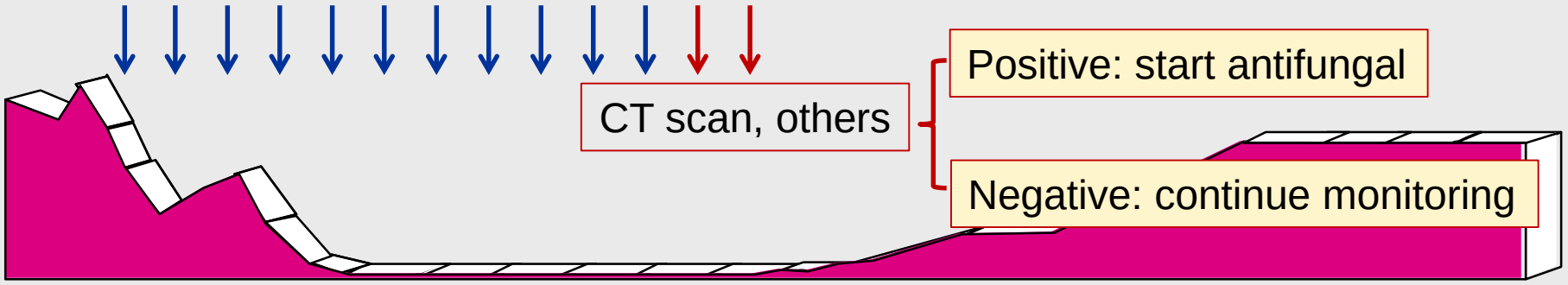
NPV = 99.9%

Active Monitoring in Patients Receiving Anti-mold Prophylaxis



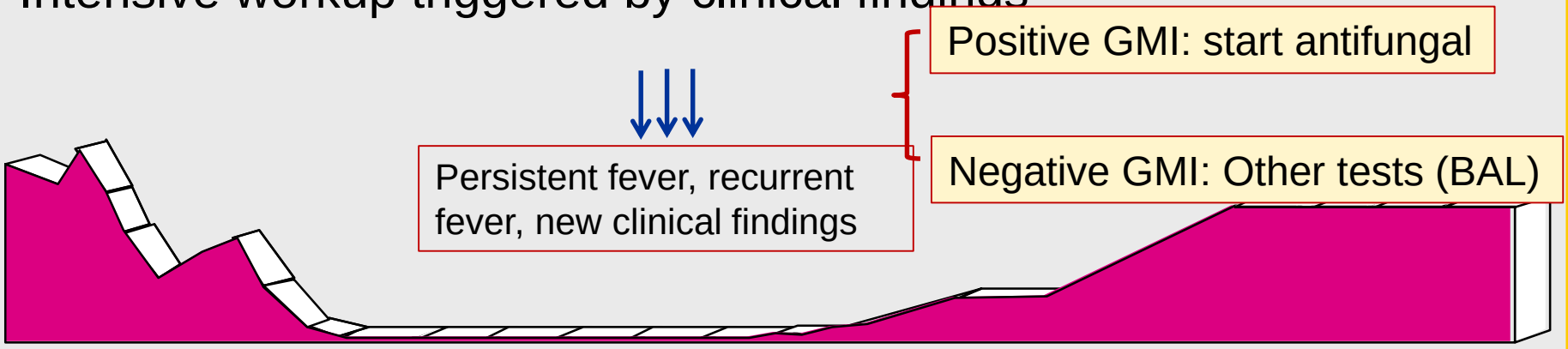
Strategies of Diagnostic-Driven Antifungal Therapy

- Active monitoring of ALL patients



Maertens et al. Clin Infect Dis 2005;41:1242-50

- Intensive workup triggered by clinical findings



Girmenia et al. J Clin Oncol 2010;28:667-24

Invasive Fungal Diseases in Hematologic Patients

- Mostly acute myeloid leukemia and acute lymphoid leukemia in relapse
- Mostly mold infections (aspergillosis >> fusariosis >> mucormycosis)
- Bedside risk assessment is a key determinant of the choice of strategies for monitoring, preventing, diagnosing and treating IFD