Modeling to Assess Antifungal Treatment Strategies in High Risk Patients:

The Hematological Malignancies

Russell E. Lewis
Associate Professor
Department of Medical Sciences and Surgery
Infectious Diseases Unit, S. Orsola Malpighi Hospital
University of Bologna

Session 227: Can we predict fungal infections?
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Causes of death in leukemia patients at the start of the chemotherapy era

Parameter	1954-1959 Number (%)	1960-1963 Number (%)	*P value*
Patents	184	170	
Infections (total)	124 (67)	131 (71)	NS
S. aureus	30 (24)	6 (5)	<0.001
E. coli	27 (22)	17 (13)	NS
Klebsiella spp.	9 (7)	16 (12)	NS
P. aeruginosa	31 (25)	45 (34)	NS
Fungi	10 (8)	30 (23)	<0.001
Infection alone	45 (24)	80 (44)	<0.001
Hemorrhage alone	40 (22)	25 (14)	<0.001
Other	24 (13)	23 (12)	NS

Hersh EM et al. JAMA 1965;193:105-9.
Bodey GP. *J Antimicrob Chemother* 2009;63:Suppl. 1, i3-il3

Risk factors for fungal infection (1950s and 1960s)

- **Bodey GP. *J Chronic Dis* 1966:[1]**
  - 189 fungal infections in 161/454 patients (35%)
  - 127 infections
    - invasive candidiasis (n=73)
    - aspergillosis (n=38)
    - mucormycosis (n=6)

Risk factors:

Longer periods of neutropenia
and adrenal corticosteroids…*however*
no association with lymphocyte counts
or antibiotic consumption

[1] Bodey GP. *J Chron Dis* 1966;19:667-87.
Bodey GP. *J Antimicrob Chemother* 2009;63:Suppl. 1, i3-il3

Primary and Secondary Risk Factors For Invasive Aspergillosis

INNATE IMMUNE STATUS

Toll-like receptor polymorphism
C-type lectin receptor polymorphism
Mannose binding lectin polymorphism
Plasminogen polymorphism
Other polymorphisms?

UNDERLYING CONDITION

Neutropenia
Progressive cancer
Graft versus host disease
Anticancer chemotherapy
Corticosteroids
Anti-T-cell antibodies

PRIMARY HOST FACTOR

Hematological Malignancy Type
Allogeneic HSCT
Solid tumor
Other immune disorders

ENVIRONMENTAL FACTORS

Climate
Construction work
Place of residence
Tobacco or cannabis use
Contaminated food or spices
Pets, plotted plants and gardening
No HEPA filtration during hospitalizations

OTHER FACTORS

Diabetes
Iron overload
Trauma, burns
Renal impairment
Metabolic acidosis
Prior respiratory disease

Herbrecht et al. Ann NY Acad Sci 2012;1272:23-30.

Disease Characteristics Where Clinical Risk Models Can Be Helpful

- **Risk for disease is *complex, dynamic, multivariate***
- **Multiple diagnostic challenges or limitations**
- **Interventions have proven (survival) benefit in select populations**
- **Need for guidance in decisions regarding diagnostic and treatment**
- **Heterogeneity in clinical studies (comparisons)**
- **Need for tools to facilitate clinical trial enrollment**

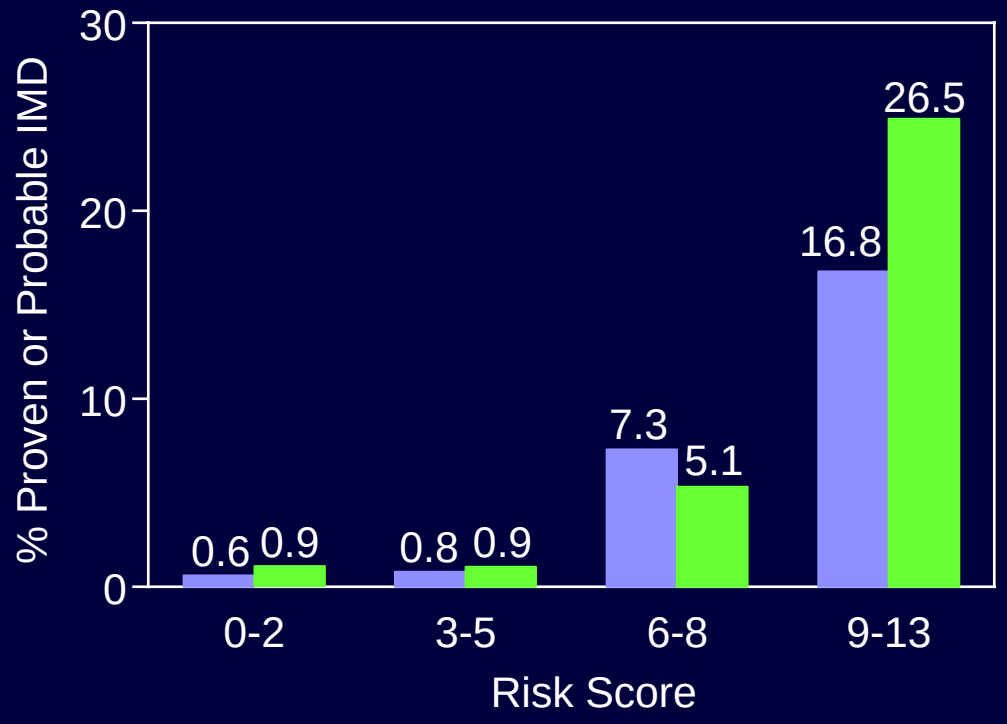
Harrell Lee & Mark. *Statistics In Medicine* 1996;15:361-87.

Bologna (BoSCORE) Development and Validation

- **Review of literature, consensus opinion of multidisciplinary group**
  - Needs for clinical score, all hematology patients
  - Which variables need to examined (n=17 candidate)
- **Retrospective analysis (2005-2008)**
  - 840 patients: 1,709 admissions
  - Multivariate risk score: proven or probable mold
- **Prospective analysis (2009-2012)**
  - 855 patients: 1,746 admissions
  - Score calculated on admission, patients followed 90 days for development of invasive mold disease

Stanzani et al. *PloS One* 2013

BoSCORE Calibration

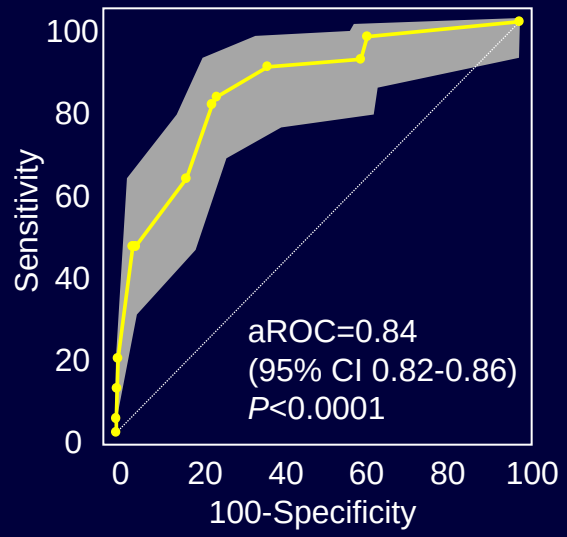


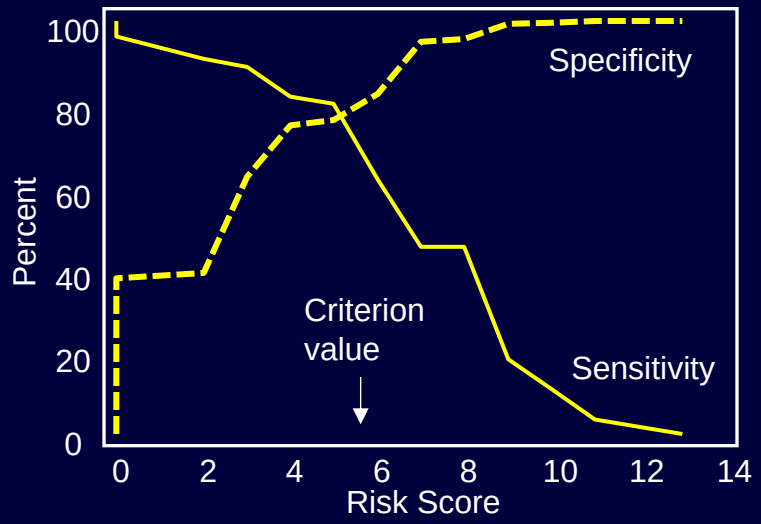
BoSCORE	Points
Neutropenia > 10 days	4
Previous mold infection	4
Uncontrolled malig.	3
Lymphopenia *or* lymph. dysfunct.	2

	0-2	3-5	6-8	9-13	
2005-2008	686	535	345	143	=1,709 admissions
2009-2012	669	629	350	98	=1,746 admissions

Stanzani et al. *PloS One* 2013

BoSCORE Discrimination (2009-2012)





- **Sensitivity 0.80 (0.67-0.89)**
- **Specificity 0.77 (0.74-0.78)**
- **+LR 3.3 (2.9-3.9); - LR 0.26 (0.20-0.40)**
- **Pos. PV 0.10 (0.07-0.13)**
- **Neg. PV 0.99 (0.98-1.0)**

Invasive mold disease prevalence 3.2%

Typical aROC for clinical risk scores between 0.6-0.85.
Royston et al. BMJ 2009;338:1373-77.

Risk score cut-off >6 across various hematology subpopulations

Group	Median risk score	Anti-mold prophy	IMD Prev.	aROC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
All patients n=1,746	3	20%	3.2%	0.84 (0.82-0.86)	0.80 (0.67-0.89)	0.76 (0.74-0.78)	0.10 (0.07-0.13)	0.99 (0.99-1.0)
Acute myeloid leukemia (remission-induction), n=131[a]	7	57%	6.1%	0.64 (0.55-0.72)	0.88 (0.47-0.99)	0.24 (0.17-0.33)	0.07 (0.03-0.14)	0.97 (0.83-0.99)
Acute myeloid leukemia (consolidation/salvage), n=284[b]	4	46%	1.4%	0.80 (0.75-0.85)	0.75 (0.19-0.99)	0.71 (0.65-0.76)	0.04 (0.007-.10)	0.99 (0.97-1.0)
Lymphoma, n=390[b]	3	7.2%	1.5%	0.99 (0.97-1.0)	1.0 (0.54-1.0)	0.94 (0.91-0.96)	0.20 (0.08-0.39)	0.99 (0.99-1.0)
Allogeneic HSCT, n=227	5	13%	10.6%	0.72 (0.65-0.77)	0.88 (0.68-0.97)	0.33 (0.26-0.39)	0.13 (0.8-0.20)	0.96 (0.88-0.99)

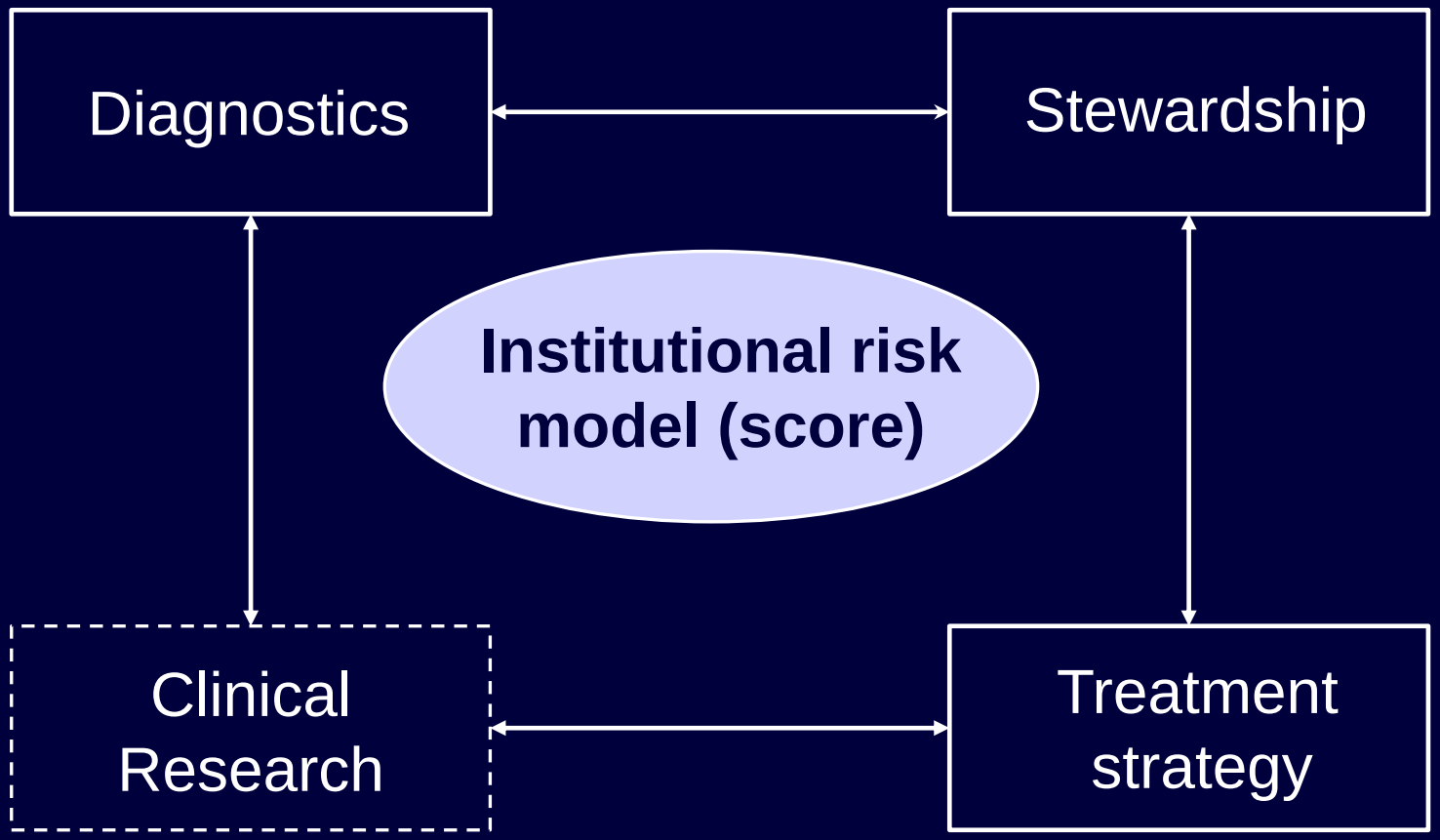
[a] Only first admission for remission-induction chemotherapy was considered

[b] Excludes patients who received allogeneic or autologous HSCT

Note: Risk score performance for autologous HSCT is not shown in the table because only 1 case of IMD was documented in 344 admissions

Consistently high NPV

Managing Invasive Fungal Disease



Importance of Pretest Assessment of Disease Probability

Clinician assessment of pretest probability of disease in the patient

- “High” pretest probability → Positive test clinically important
- “Low” pretest probability → Positive test ignored, or will trigger confirmation with other testing…

Problematic if test has frequent false positive results

Maertens et al. Mycoses 2007;50:Suppl1. 2-17.

Serum galactomannan-based early detection of invasive aspergillosis in hematology patients receiving effective-anti-mold prophylaxis

- Patients (n=262) AML induction chemotherapy or allogeneic HSCT
- Posaconazole primary antifungal prophylaxis
- Biweekly galactomannan screening
- All patients, IMD prevalence 1.9% (5/262)
  - False-positive tests 13.8%
  - Prompted additional testing
  - PPV 12%

Useless test

- Clinical suspicion (persistent fever, CT findings) IMD prevalence 55.5% (4/9)
  - PPV 89.6%

Confirmatory test

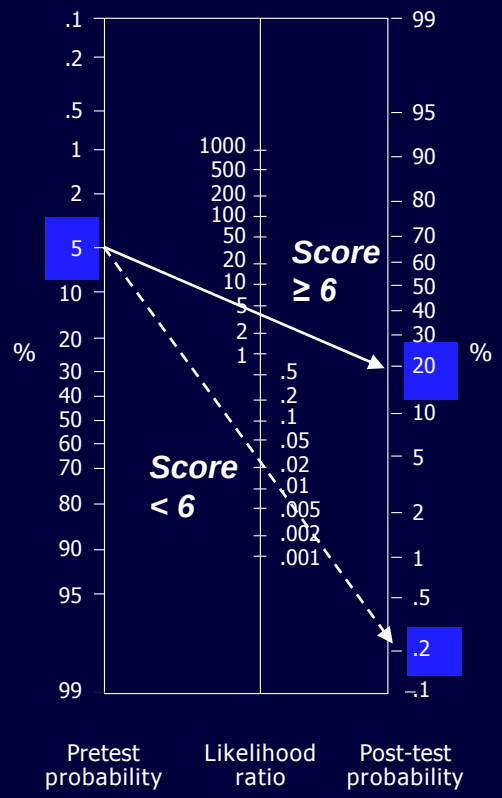
Single test >0.7, or two samples > 0.5

Duarte et al. Clin Infect Dis. Adv. Access Published, August 27, 2014

A Risk Score Can Help Estimate Pre-Diagnostic Probability of Disease

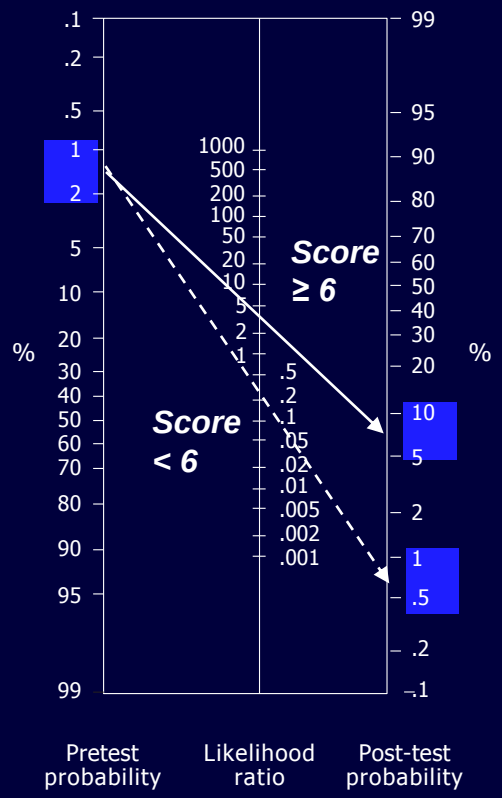
Higher primary risk group
(5% risk of IMD)

+LR 3.3; - LR -0.26



Lower primary risk group
(1-2% risk of IMD)

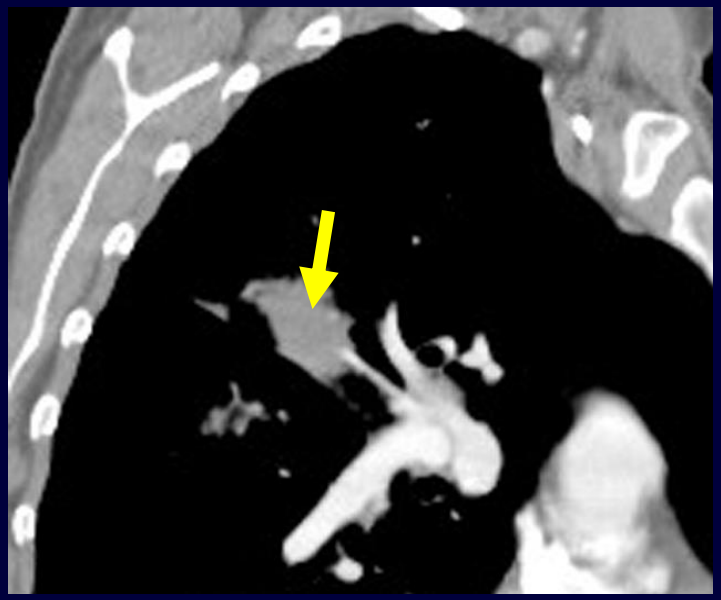
+LR 3.3; - LR -0.26



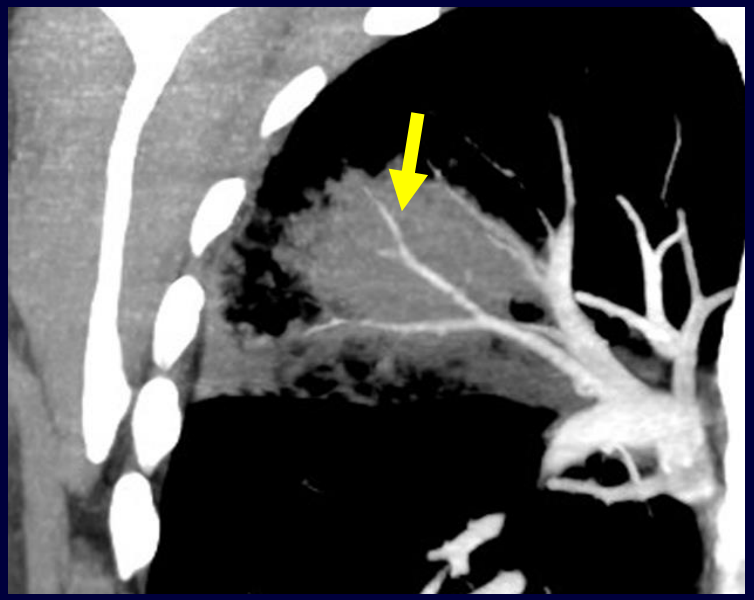
"As a general rule of thumb, a diagnostic test usually provides valuable information if the pretest probability exceeds 10%"

Maertens et al. Mycoses 2007;50:Suppl1. 2-17.

CT Pulmonary Angiography (CTPA) Can Differentiate Mold vs. Bacterial Pneumonia



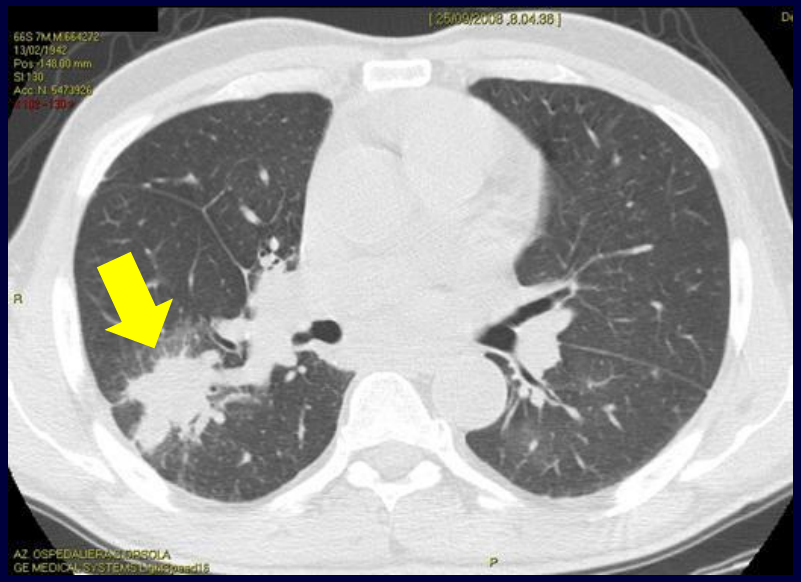
CTPA positive, proven mold disease

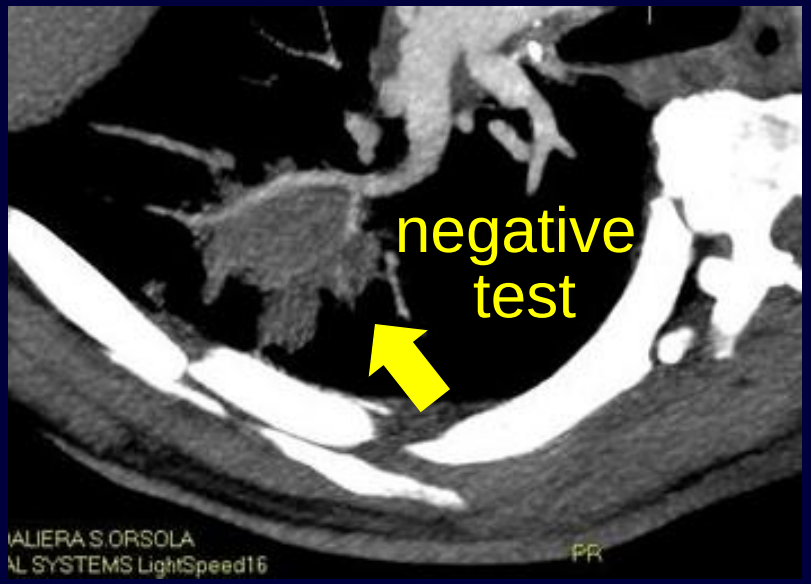


CTPA negative, bacterial PNA

Stanzani et al. Clin Infect Dis 2012;54(5):610-6.

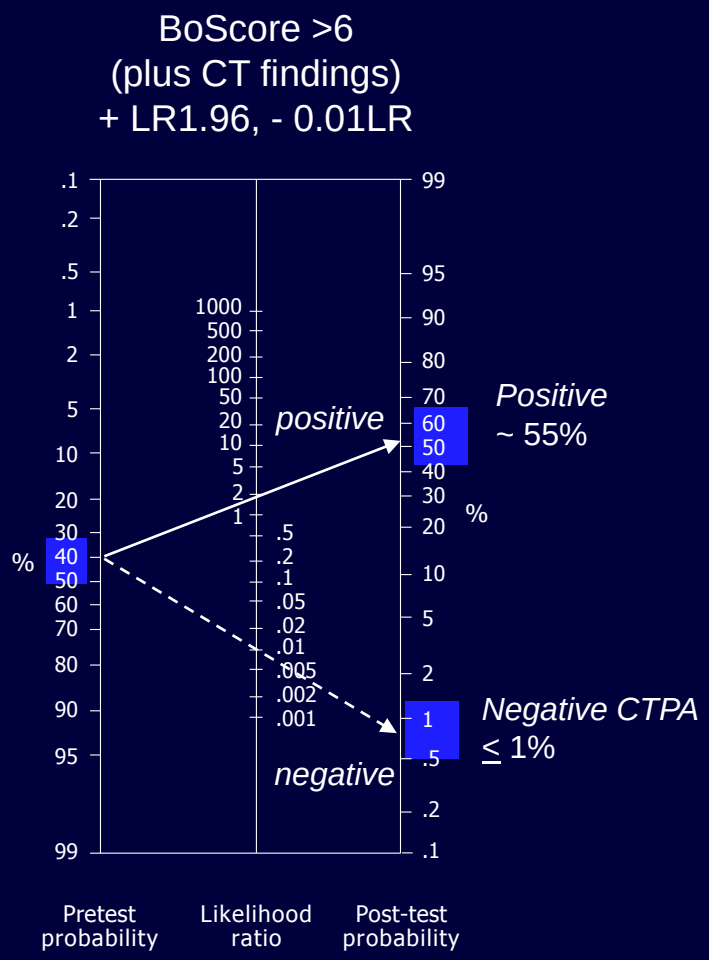
CT Pulmonary Angiography (CTPA) Can Differentiate Mold vs. Malignancy

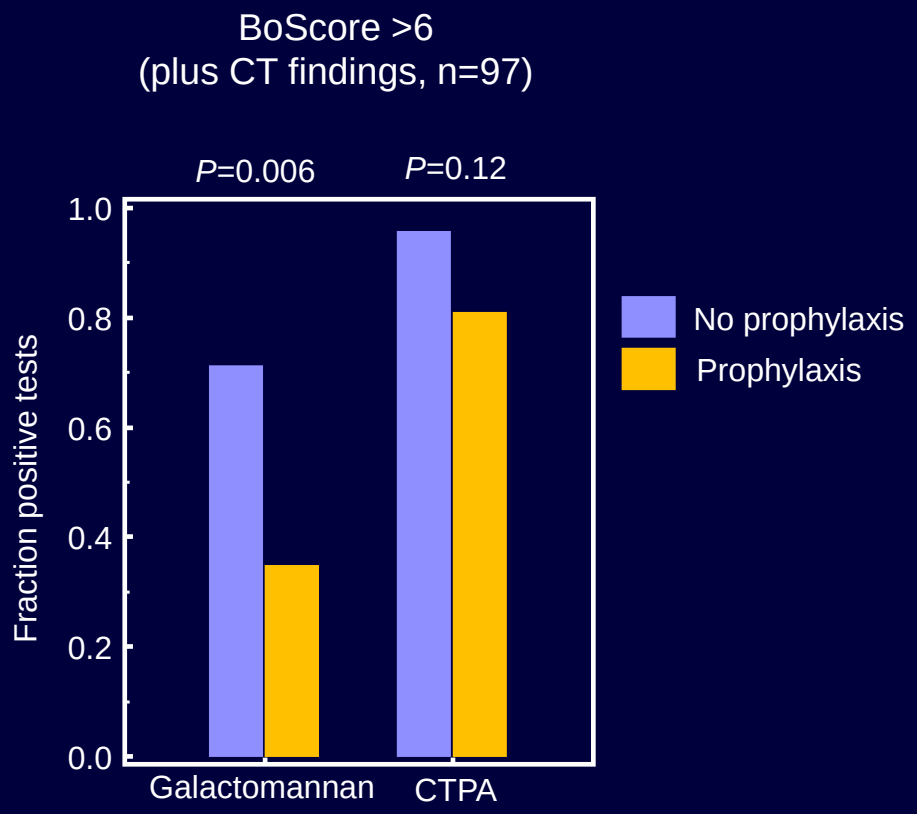




Lymphoma relapse in lung of extensively-treated patient presenting with fever

Role for CTPA in De-escalating Antifungal Therapy in High-Risk Hematology Patients





Sassi et al. *Submitted*

The Case for Antifungal Stewardship

Restraining empiric antifungal use relies on improved diagnostics…but clinical confidence in de-escalation is hampered by suboptimal diagnostic performance of current tests.

Harnessing the excellent negative predictive value of non-culture based tests [galactomannan, *Aspergillus* PCR, computer tomography] may be the most appropriate means of using them by ***excluding invasive aspergillosis***

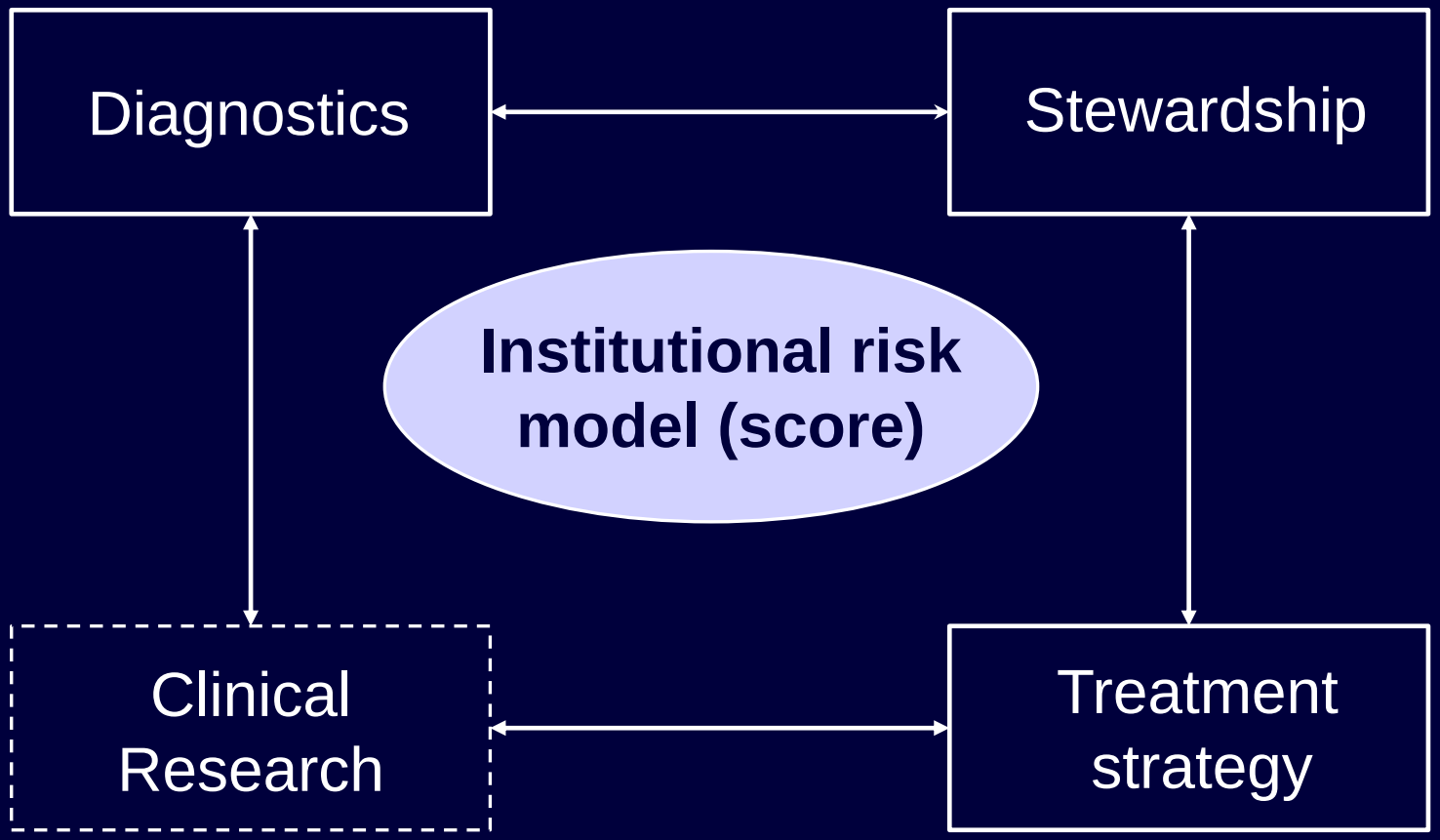
Ananda-Rajah, Salvin & Thursky. Curr Opinion Infect Dis 2012;25:107-115.

Antifungal Usage Patterns
(n=100 hematology patients with CT suspicion)

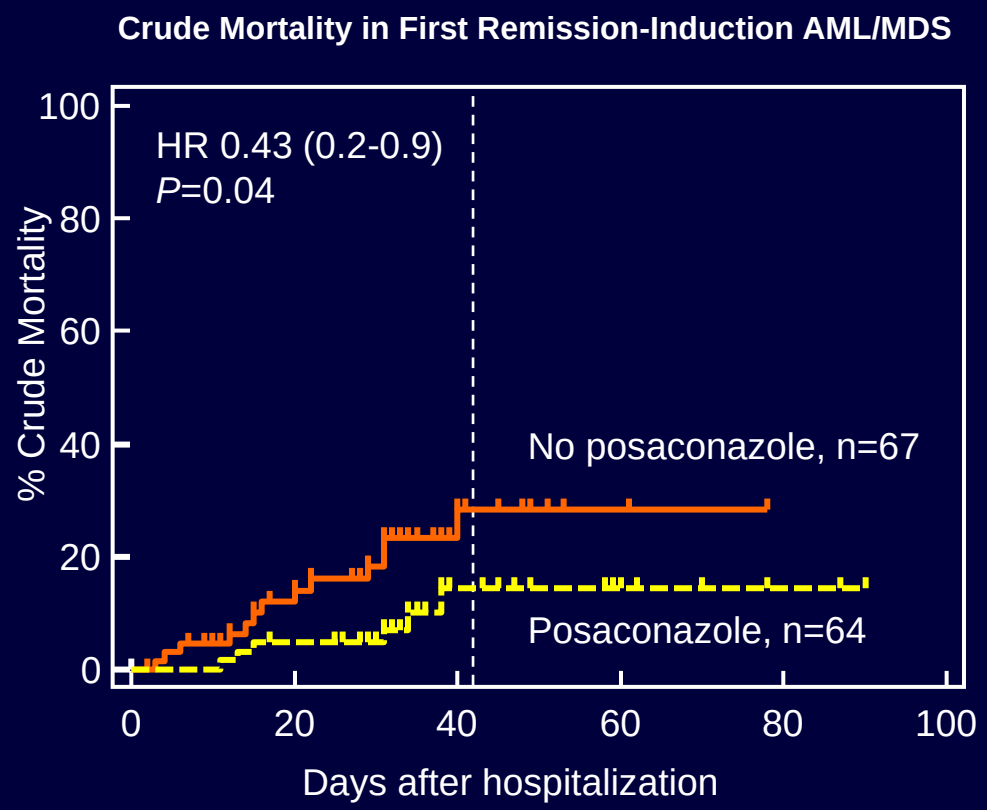
Characteristic	CTPA positive, n=67	CTPA negative, n=33	*P value* [a]
Mold infection risk score (Boscore) -median (IQR)	7 (6-8)	7 (5-8)	0.22
Intravenous antifungal therapy- no. (%)			0.001
Liposomal amphotericin B	30 (45)	8 (24)	
Voriconazole	10 (15)	1 (3)	
Caspofungin	2 (3)	2 (6)	
Itraconazole	2 (3)	2 (6)	
Combination therapy	13 (19)	2 (6)	
Median duration of therapy, -days (IQR)	16 (12-20)	5 (3-7)	<0.001
Oral antifungal therapy-no. (%)			<0.0001
Voriconazole	28 (42)	3 (9)	
Posconazole	11 (16)	3 (9)	
Itraconazole	1 (1)	3 (9)	
Median duration of therapy, -days (IQR)	14 (0-42)	0 (0-19)	0.03

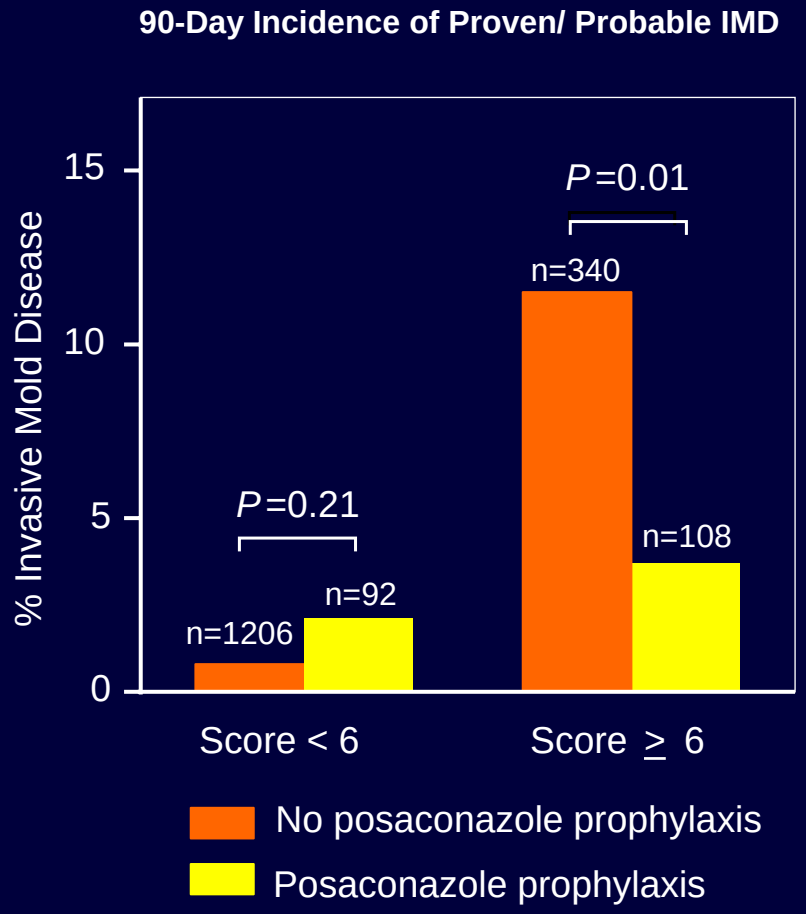
[a] *P* values determined by Mann-Whitney U test or Pearson Chi-square test

Managing Invasive Fungal Disease



Impact of Posaconazole Prophylaxis

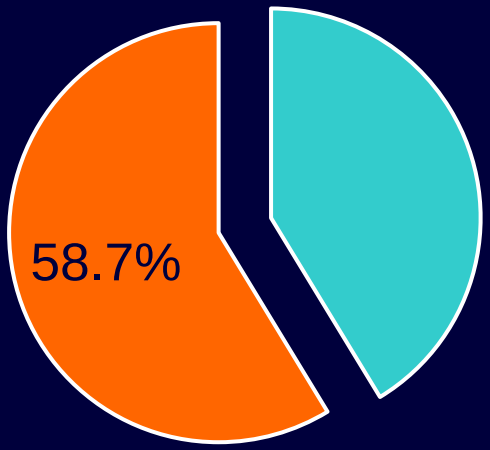




Stanzani et al. *PloS One* 2013

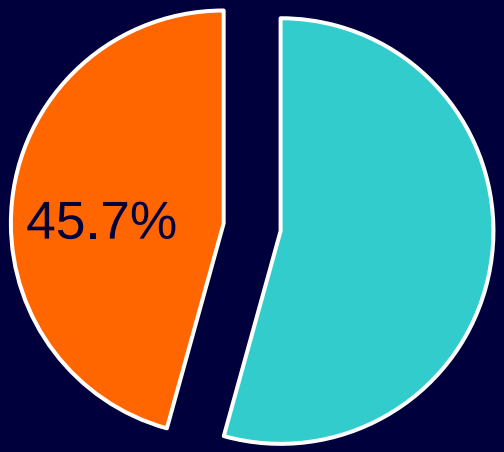
Frequency of BoSCORES ≥ 6 in Non-Transplanted Hematology Populations

AML/MDS, n=550



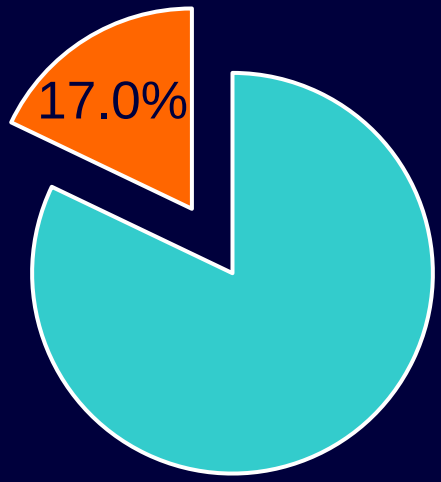
28% prophylaxis
[Median score=7]
IMI prev. 8.9%

ALL, n=157



16% prophylaxis
[Median score=7]
IMI prev. 16.3%

Lymphoma, n=328

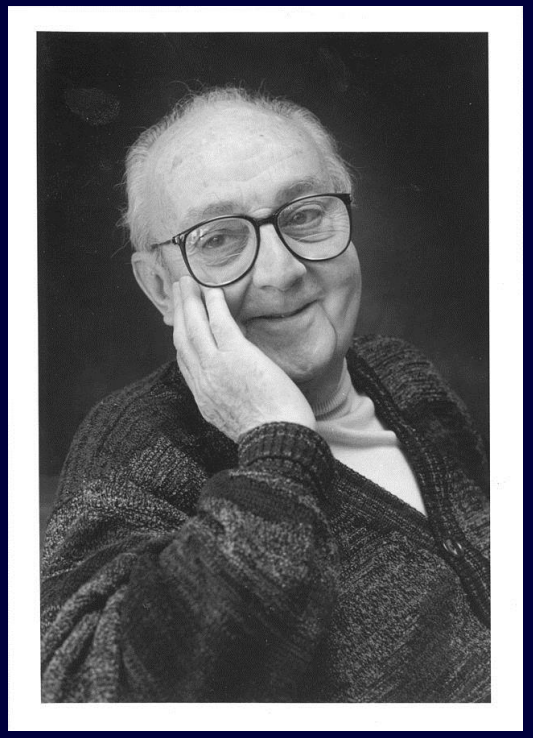


3.5% prophylaxis
[Median score=7]
IMI prev.18.6%

Population-based versus risk-score approach: improved opportunities for mortality reduction?

“Essentially, all models are wrong, but some are useful”

“…the *practical question* is how wrong do they have to be to *not be useful*?”



George EP Box
(1919-2013)

Can We Predict Invasive Mold Disease in Hematology Patients?

- **No, but we can reliably stratify lower risk vs. higher risk patients**
  - Population-based approach (primary disease) and classic risk factors
  - Institutional risk model (score)
- **Risk stratification is essential for effective [targeted] use of diagnostics → antifungal treatments →stewardship**
- **Caveats:**
  - Risk models (scores) are not fine wine, they do not age well!
  - Do not replace clinical judgment!

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