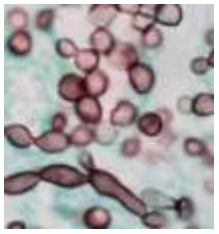
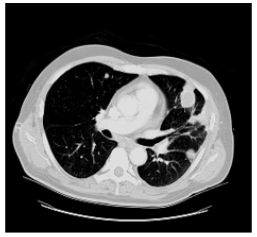
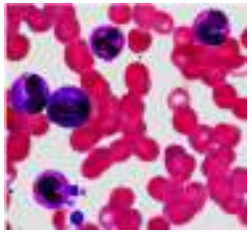


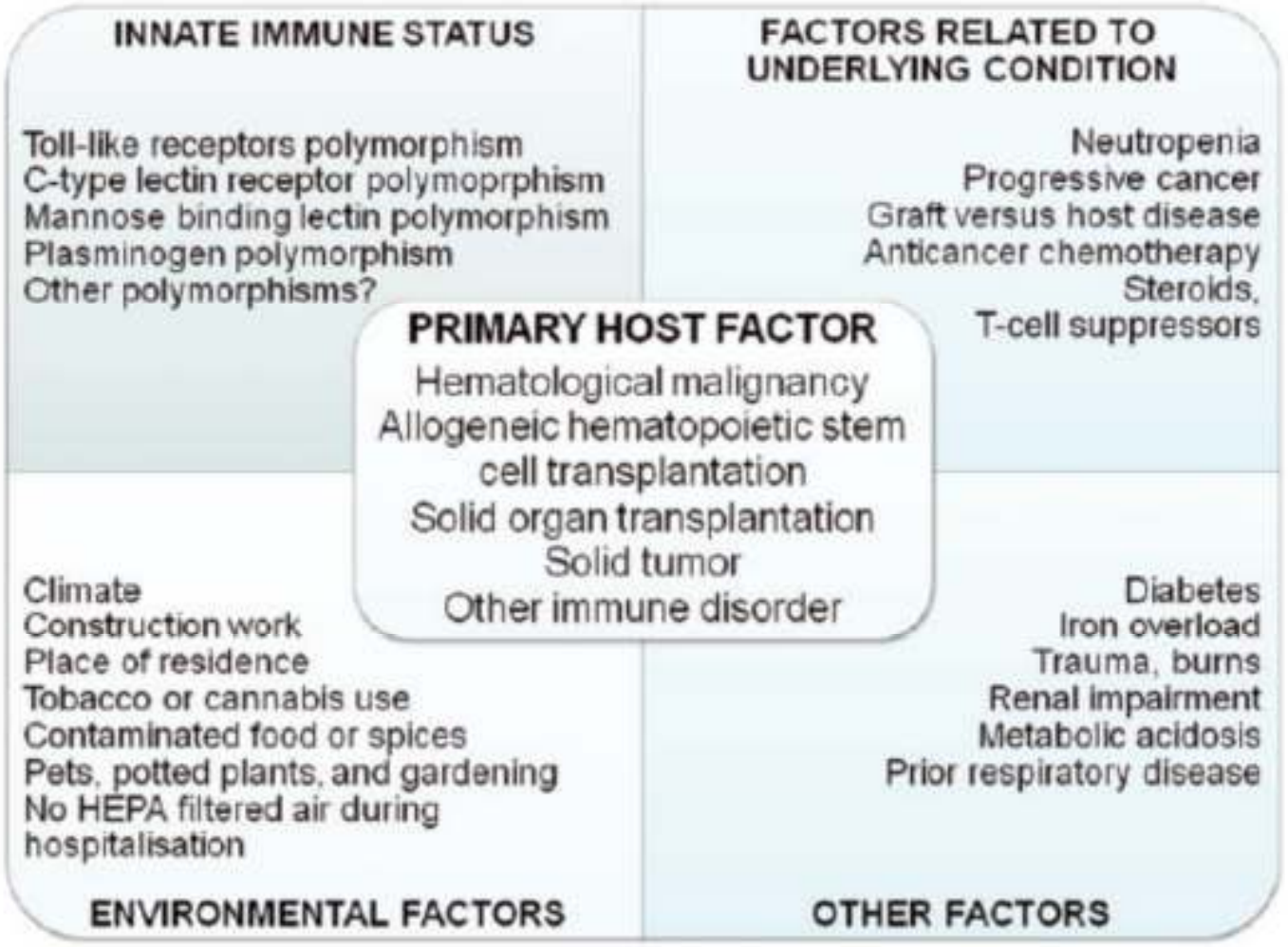

Αντιμυκητιακή προφύλαξη

Σαμπατάκου Ελένη

3ο Εκπαιδευτικό Σεμινάριο

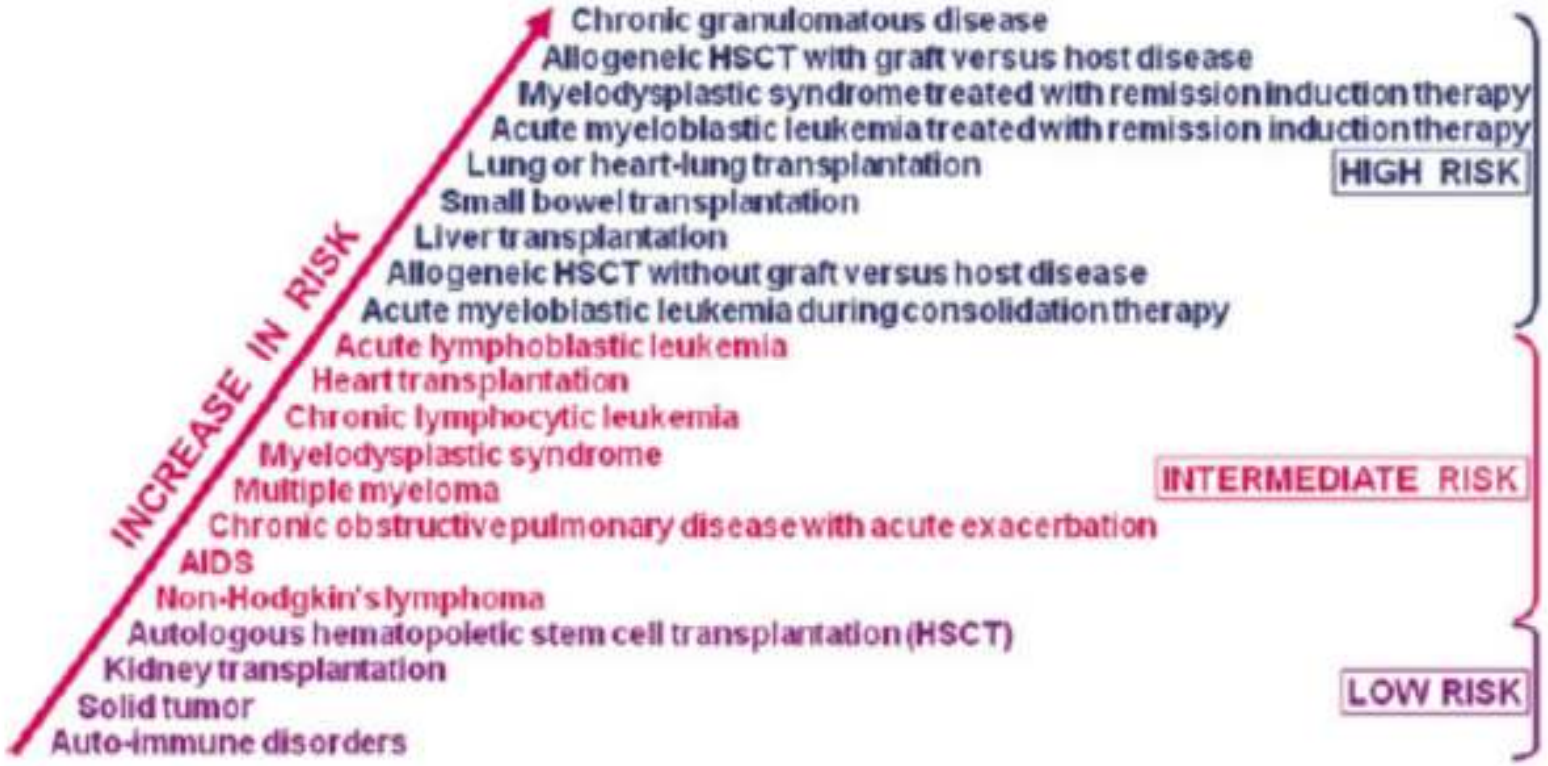
«Λοιμώξεις σε νοσοκατεσταλμένους ασθενείς»

Diagram of the various risk factors affecting the primary host condition



Herbrecht et al. Ann. N.Y. Acad. Sci. 1272 (2012) 23–30

Risk of invasive aspergillosis based on the primary host factor



Herbrecht et al. Ann. N.Y. Acad. Sci. 1272 (2012) 23–30

Εκτιμώμενη ετήσια επίπτωση συστηματικών μυκητιακών λοιμώξεων

Είδος μυκητίασης	Περιπτώσεις/έτος	Εκτιμώμενη θνητότητα (% των προσβεβλημένων)
Cryptococcosis	>1.000.000	20-70%
Candidiasis	>400.000	10-75%
Invasive Aspergillosis	>200.000	30-95%
CPA	>1.200.000	
ABPA	4.800.000	
SAFS	10.000.000	
Pneumocystis pneumonia	>400.000	20-80%
Mucormycosis	>11.000	30-90%

Identified main underlying conditions predisposing to invasive aspergillosis

Herbrecht et al. Ann. N.Y. Acad. Sci. 1272 (2012) 23–30

Underlying conditions	Incidence (%)	Identified specific patient and treatment-related risk factors
Allogeneic hematopoietic stem cells	2.7–23	Delayed neutrophil engraftment, secondary neutropenia, lymphocytopenia, monocytopenia, cord blood, T cell-depleted or CD34-selected stem cell products, unrelated or mismatched donor graft, acute or chronic graft versus host disease, corticosteroids, CMV disease, respiratory virus infections, renal failure, reduced-intensity conditioning regimen, purine analogs or monoclonal antibodies, history of invasive aspergillosis, iron overload, advanced age, donor toll-like receptor polymorphism
Autologous hematopoietic stem cells	0.5–6	Neutropenia, purine analogs or monoclonal antibodies, lymphoproliferative malignancy as indication for transplantation
Transplant Lung or heart-lung	3–26	Airways colonization, single lung transplant, cystic fibrosis as indication for transplantation, rejection and increased immunosuppression, obliterative bronchitis, lymphocytopenia, corticosteroids, CMV disease, renal dysfunction, hypogammaglobulinemia, advanced age

Identified main underlying conditions predisposing to invasive aspergillosis

Herbrecht et al. Ann. N.Y. Acad. Sci. 1272 (2012) 23–30

Heart	0.4–15	Airways colonization, reoperation, Lymphocytopenia, corticosteroids, CMV disease, post-transplant hemodialysis, advanced age
Liver Transplant	0.7–10	Retransplantation, smoking, CMV disease, dialysis requirement, fulminant hepatic failure as indication for transplantation
Pancreas	1.1–2.9	None identified
Kidney	0.2–1	Graft failure requiring prolonged hemodialysis, lymphocytopenia, corticosteroids, sirolimus ± mycophenolate mofetil, advanced age
Small bowell	0–11	Lymphocytopenia, corticosteroids, CMV disease, renal dysfunction, advanced age

Frequency of major fungal infections in organ transplant recipients

	Incidence of invasive fungal infections*	Infections due to Aspergillus	Infections due to Candida
Renal	1.4 - 14%	0 - 10%	2.0 - 100%
Heart	5 - 21%	77 - 91%	8 - 23%
Liver	7 - 42%	9 - 34%	35 -91%
Lung and heart -lung	15 - 35%	25 - 50%	43 - 72%
Small-bowel	40 - 59%	0 - 3.6%	80 - 100%
Pancreas	18 - 38%	0 - 3%	97 - 100%

Identified main underlying conditions predisposing to invasive aspergillosis

Acute myeloid leukemia	5–24	Neutropenia, monocytopenia, purine analogs or monoclonal antibodies, advanced age, iron overload, influenza H1N1 virus infection, lack of response to induction chemotherapy
Acute lymphoblastic leukemia	3.8	Lymphocytopenia, corticosteroids, advanced age
Multiple myeloma	2–3	Neutropenia, corticosteroids, advanced age
Non-Hodgkin's lymphoma	0.8	Corticosteroids, purine analogs or monoclonal antibodies, advanced age
Hodgkin's disease	0.4	None identified
Lung cancer	2.6	Stage IV disease, corticosteroids
AIDS	0–12	<50 CD4+ cells/L, neutropenia, corticosteroids
Chronic granulomatous disease	20–40	None identified
Burns	1–7	Body surface area burn, full thickness burn, length of hospital stay, older age, inhalation injuries

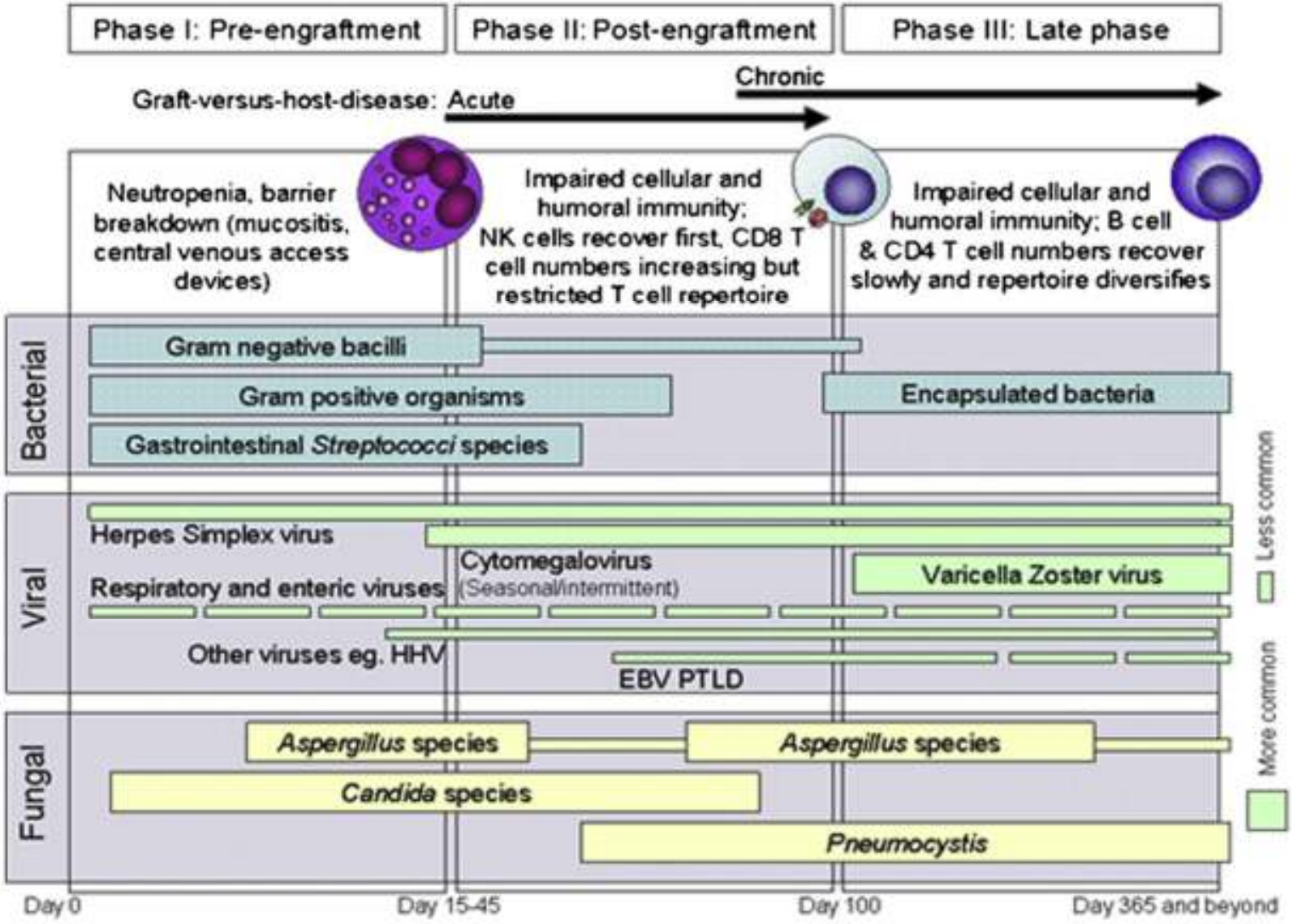
Identified main underlying conditions predisposing to invasive aspergillosis

Herbrecht et al. Ann. N.Y. Acad. Sci. 1272 (2012) 23–30

Underlying conditions	Incidence (%)	Identified specific patient and treatment-related risk factors
Chronic obstructive pulmonary disease with acute exacerbation	1.9	Systemic or inhaled corticosteroids, admission to the intensive-care unit, chronic heart failure, antibiotic treatment received in the three months prior to admission, airways colonization
Systemic lupus erythematous	0.5–2.1	Corticosteroids, other immunosuppressive drugs
Liver failure*	5.4	Multiple antibiotic use, frequent invasive procedures
Severe combined immunodeficiency	3.5	None identified

*Hepatitis B virus-related liver failure

Phases of opportunistic infections among allogeneic HCT recipients



Biol Blood Marrow Transplant. 2009 Oct;15(10):1143-238.

Blood Reviews 31 (2017) 17–29

Contents lists available at ScienceDirect

Blood Reviews

journal homepage: www.elsevier.com/locate/blre

REVIEW

Risk stratification for invasive fungal infections in patients with hematological malignancies: SEIFEM recommendations

Livio Pagano [a,*], Alessandro Busca [b], Anna Candoni [c], Chiara Cattaneo [d], Simone Cesaro [e], Rosa Fanci [f],

Risk factors for IFIs in AML according to Leukemia, Host, Treatment and Fungal Exposure

Leukemia related	Host related	Treatment related factors	Fungal exposure
Lower Probability of CR (Adverse Cytogenetic/gene mutation profiles; WBC > 50.000/μL; Secondary AML	Age >65 yrs	Expected treatment related severe and prolonged neutropenia (ANC <100/μL for >10 d)	Rooms without HEPA filtration; Building constructions or renovations/ recent house renovation
Baseline neutropenia with ANC <500/μL for>7 d; MDS-related phagocytic dysfunction.	Organ dysfunction with High comorbidity index or Poor Performance status (≥2)	Highly mucotoxic regimen	Documented Airway Colonization By Aspergillus species
Leukemia status: relapse-refractory > first induction > consolidation	Chronic obstructive pulmunary disease. Active smoking	Mucositis grade ≥3 for >7 days, especially if involving lower gut.	Prior Aspergillosis
Persistance of day 15 bone marrow blast cells	Immunity polymorphism		Multisite colonization by Candida species.
No CR by end of induction phase	Pharmacogenomics of antineoplastic drugs		Jobs with high exposure (farming, gardening, contruction work)

CR = Complete Remission; ANC = absolute Neutrophils count; WBC = White Blood cells.

Bone Marrow Transplantation (2018) 53:1304–1310
https://doi.org/10.1038/s41409-018-0161-1

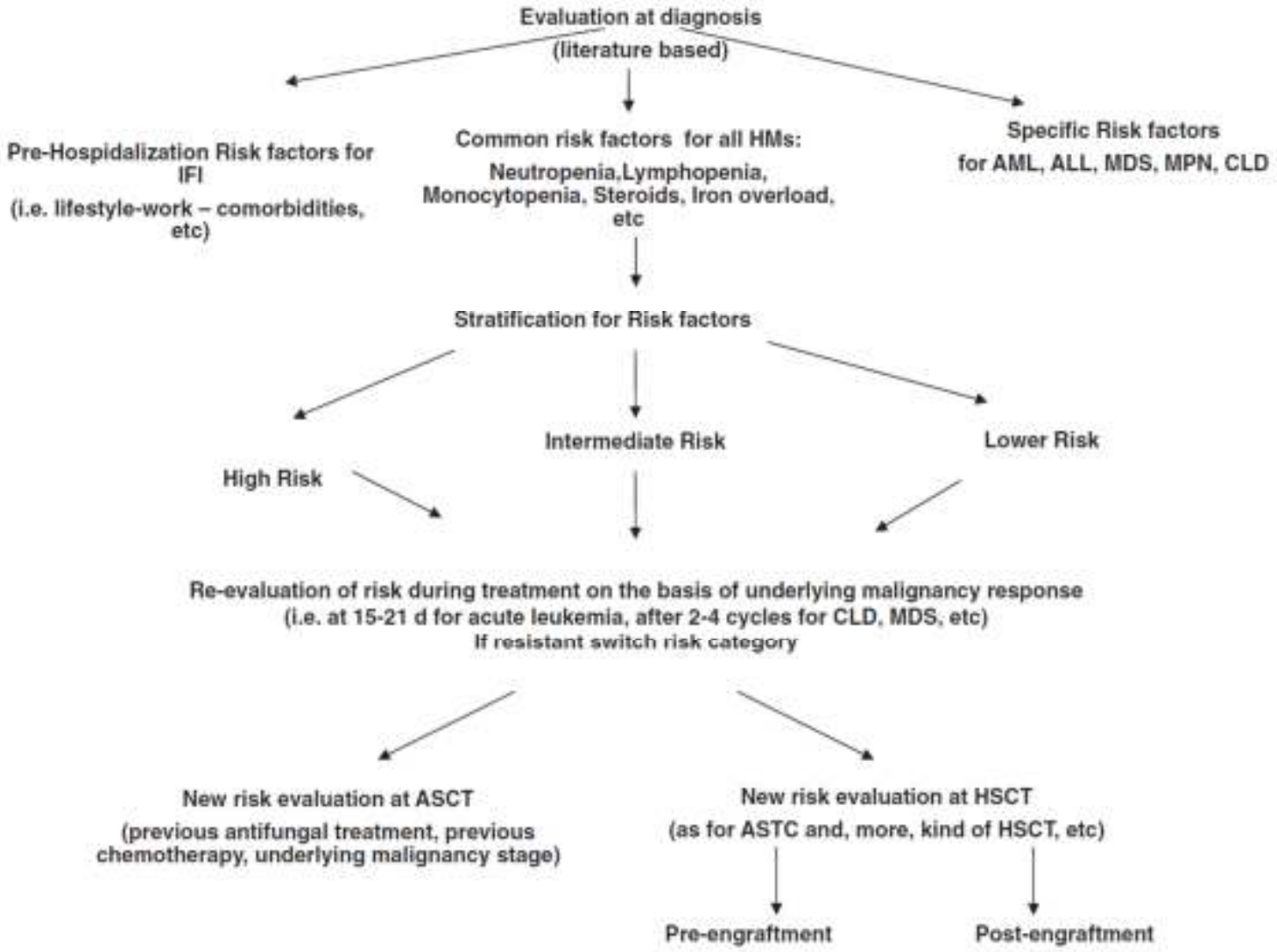
ARTICLE

Hematopoietic cell transplantation comorbidity index and risk of developing invasive fungal infections after allografting

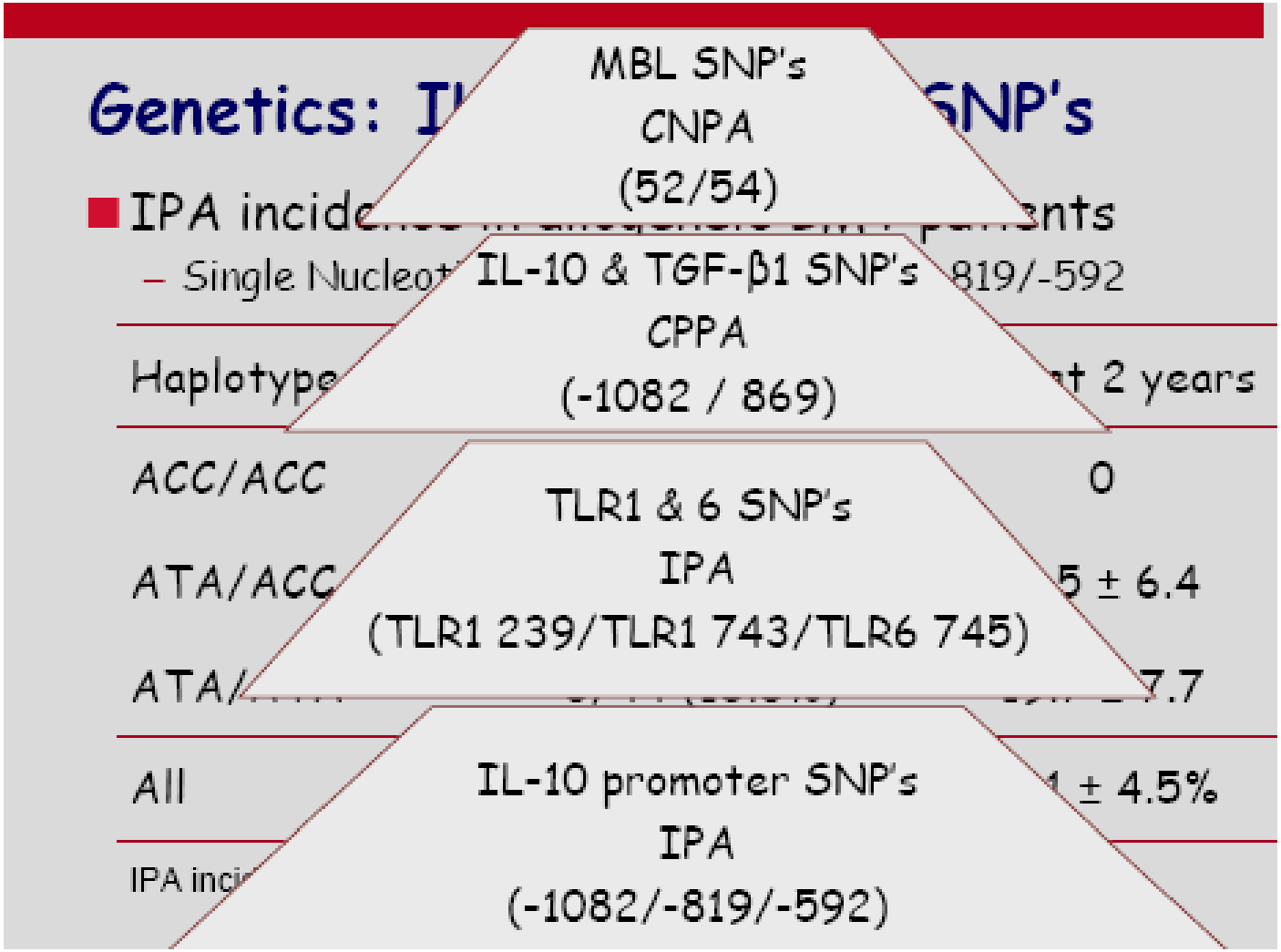
Alessandro Busca[1] · Roberto Passera[2] · Enrico Maffini[1,3] · Moreno Festuccia[1,3] · Lucia Brunello[1,3] · Chiara Maria Dellacasa[1] · Semra Aydin[4] · Chiara Frairia[4] · Sara Manetta[1,4] · Sara Butera[1,3] · Giorgia Iovino[1,3] · Luisa Giaccone[1,3] · Mohamed Sorror[5] · Rainer Storb[5] · Francesco Giuseppe De Rosa[6] · Benedetto Bruno[1,3]

Possible dynamic risk stratification.

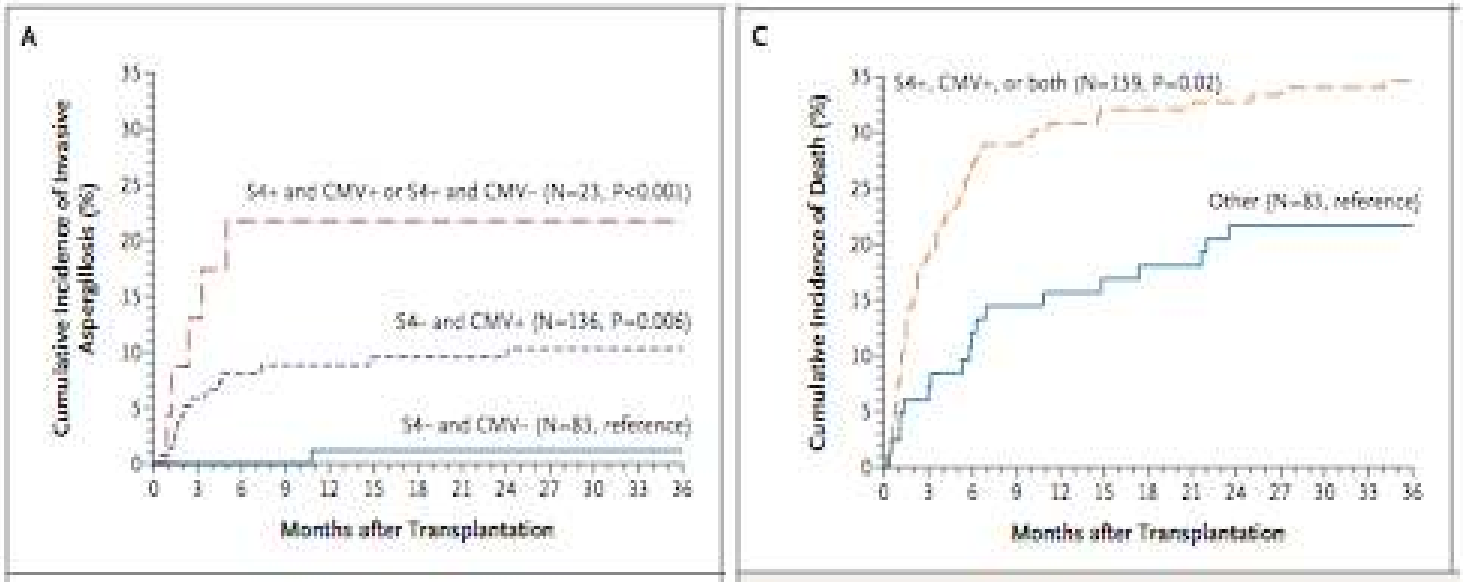
L. Pagano et al. / Blood Reviews 31 (2017) 17–29



Genetic stratification of risk of IFIs



The future :
Predictive markers for *Aspergillus* infection?



Bochud PY et al, NEJM 2008

- TLR4 haplotypes in unrelated donors are associated with an increased risk of IA among recipients of allogeneic hematopoietic-cell transplants

- Polymorphisms in genes encoding IL-1, IL-10, TNF r2,

Seo, BMT 2005; Kesh Ann N Y Acad Sci 2005; Sainz Immunol lett 2007;
Sainz Human Immunol 2007; Vaid Clin Chem Lab Med 2007; Sainz J Clin Immunol 2008

Προφύλαξη σε ποιούς ασθενείς ?
Ποιο αντιμυκητιακό?
Χρόνος έναρξης και για πόσο?
Πως μπορούμε να κάνουμε διαβάθμιση του κινδύνου?
Νέοι παράγοντες κινδύνου για συστηματικές μυκητιάσεις ή προγνωστικοί παράγοντες επιβίωσης?
Εκτίμηση κινδύνου/οφέλους?

Εμπύρετος ουδετεροπενία, HSCT

Όταν η ανασφάλεια και ο φόβος κυριαρχούν….

Clinical Therapeutics/Volume 36, Number 2, 2014

Systemic Antifungal Prophylaxis After Hematopoietic Stem Cell Transplantation: A Meta-Analysis

Panayiotis D. Ziakas, MD, PhD[1,2]; Irene S. Kourbeti, MD, PhD[1,2]; and Eleftherios Mylonakis, MD, PhD, FIDSA[1,2]

- **20** studies including **4823** patients receiving HSCT. Overall, the risk for IFI while on prophylaxis was **5.1%.**
- The risk of IFI, systemic candidiasis and the need for empiric antifungal treatment was significantly reduced in patients receiving fluconazole compared with patients receiving placebo.
- Itraconazole was more effective than fluconazole for the prevention of aspergillosis at the expense of more frequent withdrawals. Micafungin was marginally more effective than fluconazole for the prevention of mold infections and IA and reducing the need for empiric antifungal therapy.
- Voriconazole showed marginally significant effects compared with fluconazole regarding IA and the need for empiric treatment.

ELSEVIER

Newer Antifungal Agents for Fungal Infection Prevention During Hematopoietic Cell Transplantation: A Meta-Analysis

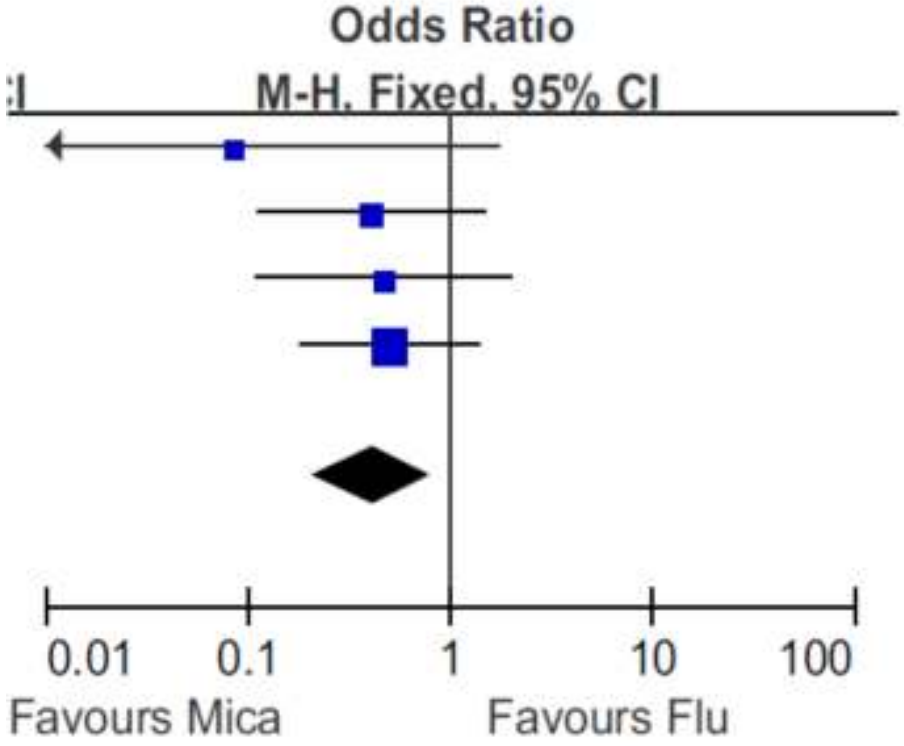
S.-X. Xu, J.-L. Shen, X.-F. Tang, and B. Feng

Transplantation Proceedings, 45, 407–414 (2013)

17 studies including 5122 patients.

The new mold-active agents, **posaconazole, voriconazole, and micafungin** have reduced the incidence of IFI compared to fluconazole and itraconazole;

in addition, posaconazole and voriconazole have reduced transplant-related mortality significantly.



Bow et al. BMC Infectious Diseases (2015) 15:128
DOI 10.1186/s12879-015-0855-6

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Systematic review and mixed treatment comparison meta-analysis of randomized clinical trials of primary oral antifungal prophylaxis in allogeneic hematopoietic cell transplant recipients

Eric J Bow[1*], David J Vanness[2], Monica Slavin[3], Catherine Cordonnier[4], Oliver A Cornely[5], David I Marks[6],

- Five eligible RCTs, randomizing 2147 patients in total, were included.
- Randomized controlled trials (RCTs) of fluconazole, itraconazole, posaconazole, and voriconazole for primary antifungal prophylaxis
- **posaconazole, voriconazole reduced the risk of proven/probable IFI compared to fluconazole and itraconazole.**
- **Conclusion**: As expected, mould-active azoles prevented IFIs, particularly invasive aspergillosis, more effectively than fluconazole in alloHCT recipients. The paucity of comparative efficacy data suggests that other factors such as long-term tolerability, availability of intravenous formulations, local IFI epidemiology, and drug costs may need to form the basis for selection among the mould-active azoles

Οξεία μυελογενής λευχαιμία –συστηματικές μυκητιάσεις

- Πρόσφατη διαπίστωση ότι η ύπαρξη παραγόντων κινδύνου από την εισαγωγή, όπως ΧΑΠ, επαγγελματική έκθεση, ενασχόληση με χώρους με φορτίο μυκήτων, απουσία θαλάμων HEPA, λοίμωξη με H1N1, μη ανταπόκριση σε θεραπεία "induction" αυξάνει τον κίνδυνο για συστηματικές μυκητιάσεις (1,2).
- Επιπρόσθετοι παράγοντες κινδύνου: μεγάλη ηλικία, πτωχή πρόγνωση ύφεσης νόσου για λόγους κυτταρογενετικής, υποτροπή κακοήθειας, παρουσία πολλαπλών baseline συννοσηροτήτων ή κακό " performance status".
- Επιδημιολογική αλλαγή παγκόσμια με επικράτηση υφομυκήτων με την εισαγωγή της προφύλαξης με φλουκαναζόλη από τις αρχές του 1990. Ο *Aspergillus* είναι ο κυρίαρχος μύκητας στην Ευρώπη με επίπτωση της διηθητικής Ασπεργίλλωσης σε ΟΜΛ σε ποσοστό 5% - 24%, ενώ η καντινταιμία σε 2% (3).
- Λόγω των ποσοστών συστήνονται μέτρα πρόληψης. Εκτός της αποφυγής των έργων οικοδομικών ανακατασκευών και φυτών, χώματος, πιπεριού και θαλάμων με HEPA, η πρωτογενής προφύλαξη συστήνεται και θεωρείται εδραιωμένη πρακτική σε πολλά Ευρωπαϊκά αιματολογικά κέντρα.
- Αν και η συγχορήγηση ανθρακυκλινών (doxorubicin, daunorubicin and idarubicin) και αζολών δεν αντενδείκνυται, οι αζόλες αναστέλλουν τους "efflux transporters" και μπορούν να μεταβάλλουν την κινητική των ανθρακυκλινών (4). Συστήνεται μία περίοδος "washout" 24 ωρών πριν τη χορήγηση προφύλαξης με αζόλη.

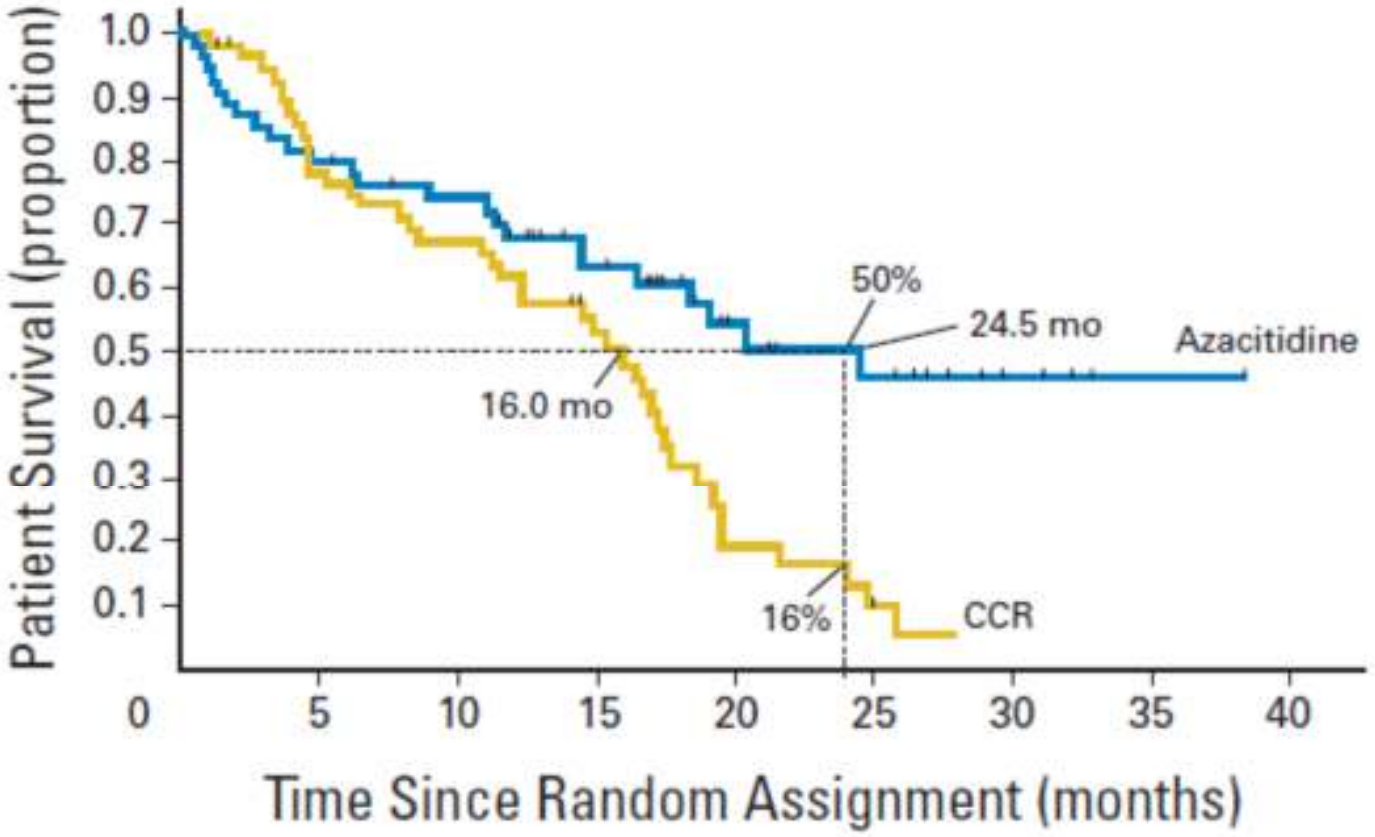
1. Caira M, et al. Haematologica 2015; 100: 284–92.
2. Herbrecht R, et al. Ann N Y Acad Sci 2012; 1272:23–30.
3. Cornely OA, et al. Clin Infect Dis 2015; 61: 324–31.
4. Lempers VJ, et al. Antimicrob Agents Chemother 2016; 60: 3372–9.

Overall survival in patients receiving azacitidine (n 55) or conventional care regimens (CCR; n 58)

Fenaux et al. J Clin Oncol 2010;28:562-569

Reduced GI toxicity, less severe neutropenia=fewer fungal infections?

Antifungal prophylaxis needed?



No. of patients at risk									
Azacitidine	55	43	38	26	15	10	4	1	0
CCR	58	43	36	22	6	3	0	0	0

mycoses
Diagnosis, Therapy and Prophylaxis of Fungal Diseases

Original article

Invasive fungal infections in AML/MDS patients treated with azacitidine: a risk worth considering antifungal prophylaxis?

Helena Pomares, Montserrat Arnan, Isabel Sánchez-Ortega, Anna Sureda and Rafael F. Duarte

Department of Haematology, Catalan Institute of Oncology – Hospital Duran i Reynals, Biomedical Research Institute of Bellvitge (IDIBELL), Barcelona, Spain

- Retrospective analysis. Incidence of IFI according to EORTC-MSG criteria in **121** consecutive AML/MDS patients receiving **948** azacitidine courses (median 5, range 1–43) between June 2007 and June 2015. **Four cases of IFI** (two possible, one probable aspergillosis and one proven candidemia) occurred in this series.
- The **incidence rate of proven/probable IFI** was **0.21%** per treatment cycle and **1.6% per patient** treated for the whole series, and 0.73% per treatment cycle and 4.1% per patient treated in those with severe neutropenia. Two patients died from IFI, leading to an IFI-attributable mortality rate of 1.65% per patient and 0.21% per treatment cycle.
- **The numbers needed to treat with prophylaxis** to prevent one case of IFI are 238 azacitidine cycles or **30 patients** throughout their whole treatment course, and 137 azacitidine cycles or 24 patients among those with severe neutropenia.
- **AML/MDS patients treated with azacitidine**, including those with severe prolonged neutropenia, have **a very low risk of IFI which does not justify the use of antifungal prophylaxis.**

Bone Marrow Transplantation (2013) 48, 168–173

www.nature.com/bmt

REVIEW

Supportive care in severe and very severe aplastic anemia

B Höchsmann[1], A Moicean[2], A Risitano[3], P Ljungman[4] and H Schrezenmeier[1] for the EBMT Working Party on Aplastic Anemia

- **In our opinion, prophylactic antifungals should be used in general for patients with very severe AA.**
- **Voriconazole or posaconazole appear to be more effective than fluconazole, as they have activity against *Aspergillus* and also some other mold species.**
- **Antifungal prophylaxis should also be considered during the first months after antithymocyte globulin (ATG) therapy and after SCT as long as neutropenia and/or lymphopenia is present**.

Robenshtok E, et al. Antifungal prophylaxis in cancer patients after chemotherapy or hematopoietic stem-cell transplantation: systematic review and meta-analysis. J Clin Oncol 2007; 25: 5471–5489.

ΟΛΛ

- ΄Εχει αναφερθεί ποσοστό συστηματικών μυκητιάσεων στο 6.5% στην αναδρομική μελέτη SEIFEM-2004 με 1173 ενήλικες ασθενείς υπό θεραπεία για ΟΛΛ, με τη διηθητική ασπεργίλλωση και καντιντίαση να είναι οι συχνότερες* (1)
- ΟΛΛ Philadelphia+ που λαμβάνουν αναστολείς της τυροσινικής κινάσης (imatinib, dasatinib, nilotinib, and bosutinib), ως μέρος της θεραπείας γαίνεται να έχουν χαμηλό κίνδυνο για διηθητικές μυκητιάσεις (3–5%)
- Δεν υπάρχει αποδεδειγμένο standard of care
- Το European Working Group for Adult ALL (EWALL) τοποθετείται ενάντια στη χορήγηση νεοτέρων αζολών, λόγω της δυνητικής νευροτοξικότητας σε συνδυασμό με Vinca αλκαλοειδή.
- Απουσία δεδομένων αποτελεσματικότητας και ασφάλειας, προσεκτική χρήση προφύλαξης με fluconazole για ζυμομύκητες μπορεί να συσταθεί (C-III).

**Pagano L, et al. Haematologica 2006; 91: 1068–75.*

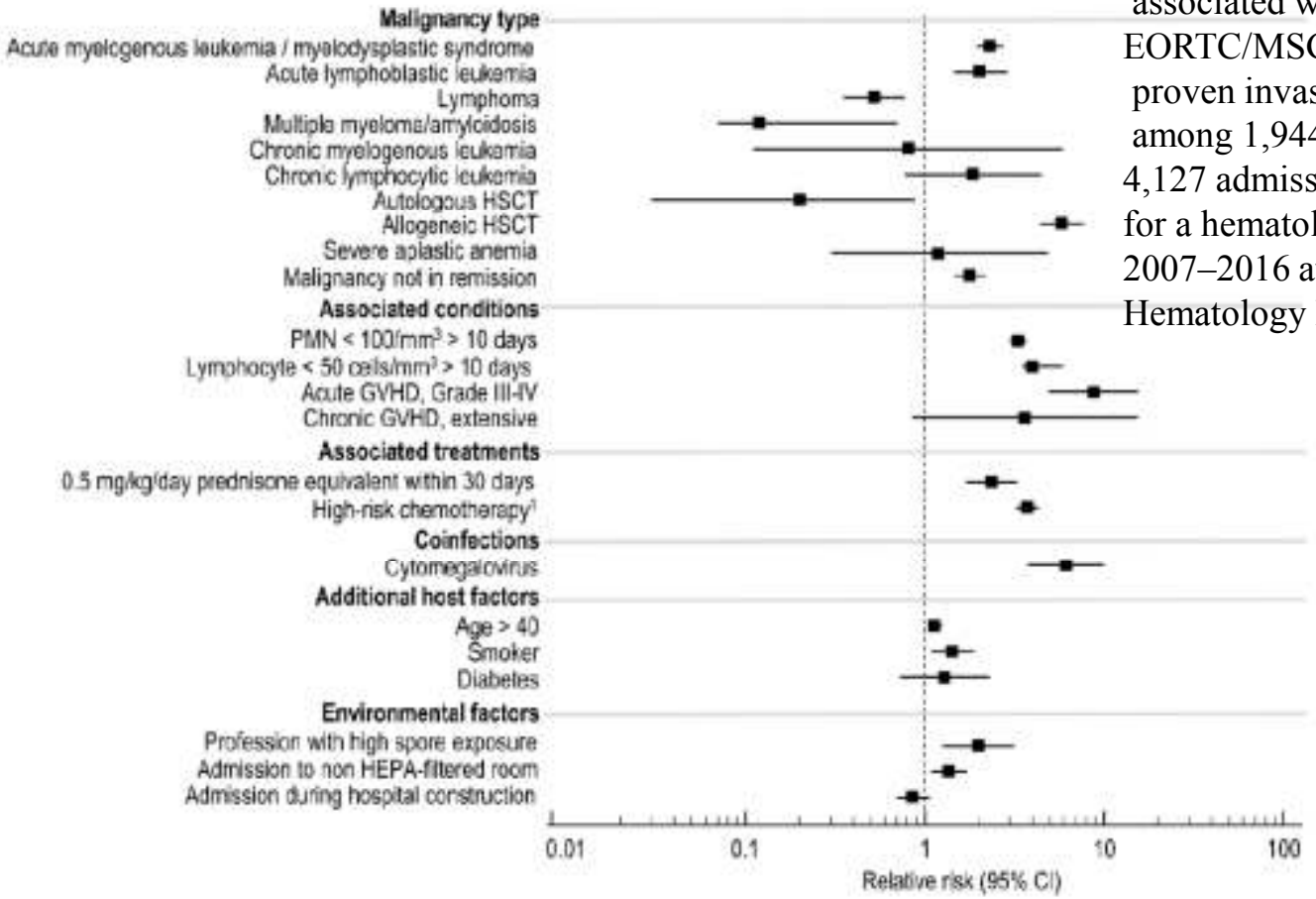
Journal of *Fungi*

MDPI

Review

Development and Applications of Prognostic Risk Models in the Management of Invasive Mold Disease

Marta Stanzani [1] and Russell E. Lewis [2,*]



Risk factors in univariate analysis associated with the development of EORTC/MSG defined probable or proven invasive mold disease (n = 133) among 1,944 adult inpatients (n = 4,127 admissions) undergoing treatment for a hematological malignancy from 2007–2016 at the Seràgnoli Hematology Institute in Bologna, Italy.

Journal of *Fungi*

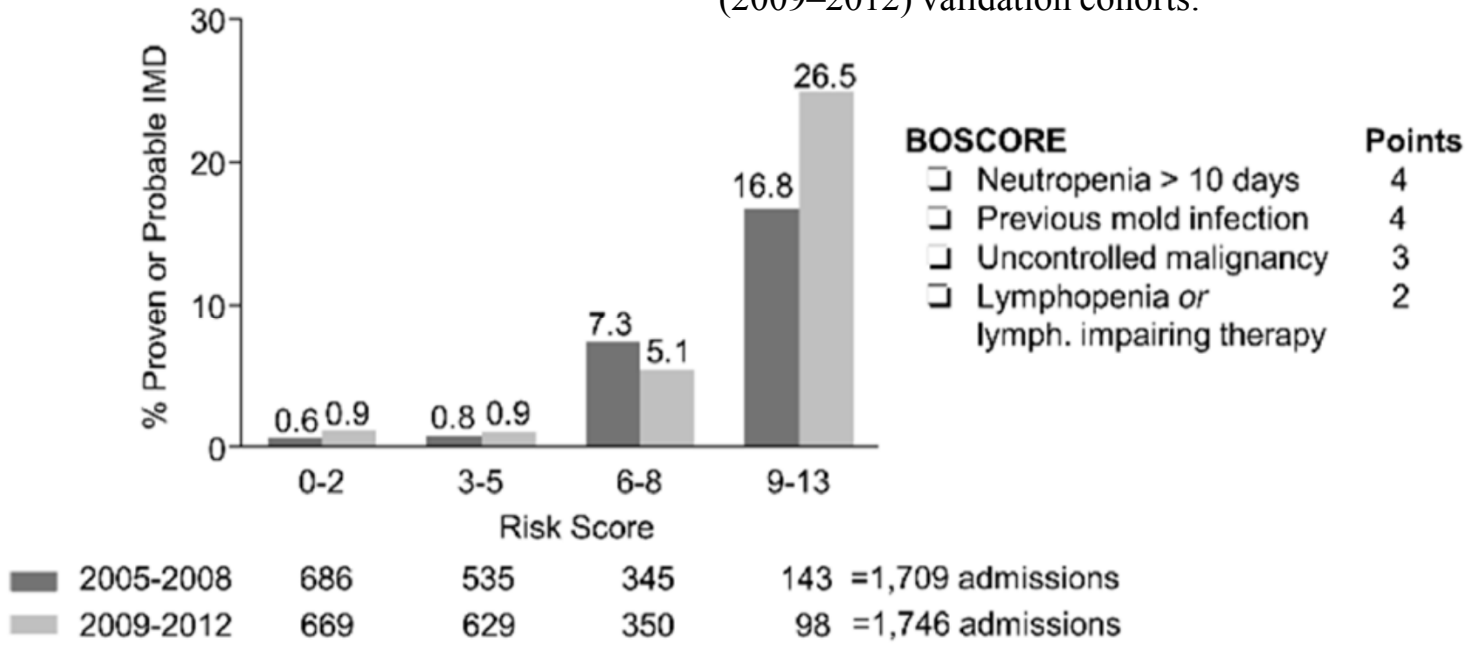
MDPI

Review

Development and Applications of Prognostic Risk Models in the Management of Invasive Mold Disease

Marta Stanzani [1] and Russell E. Lewis [2,*]

BOSCORE distribution observed 90-day cumulative incidence of IMD in the retrospective (2005–2008) development and prospective (2009–2012) validation cohorts.



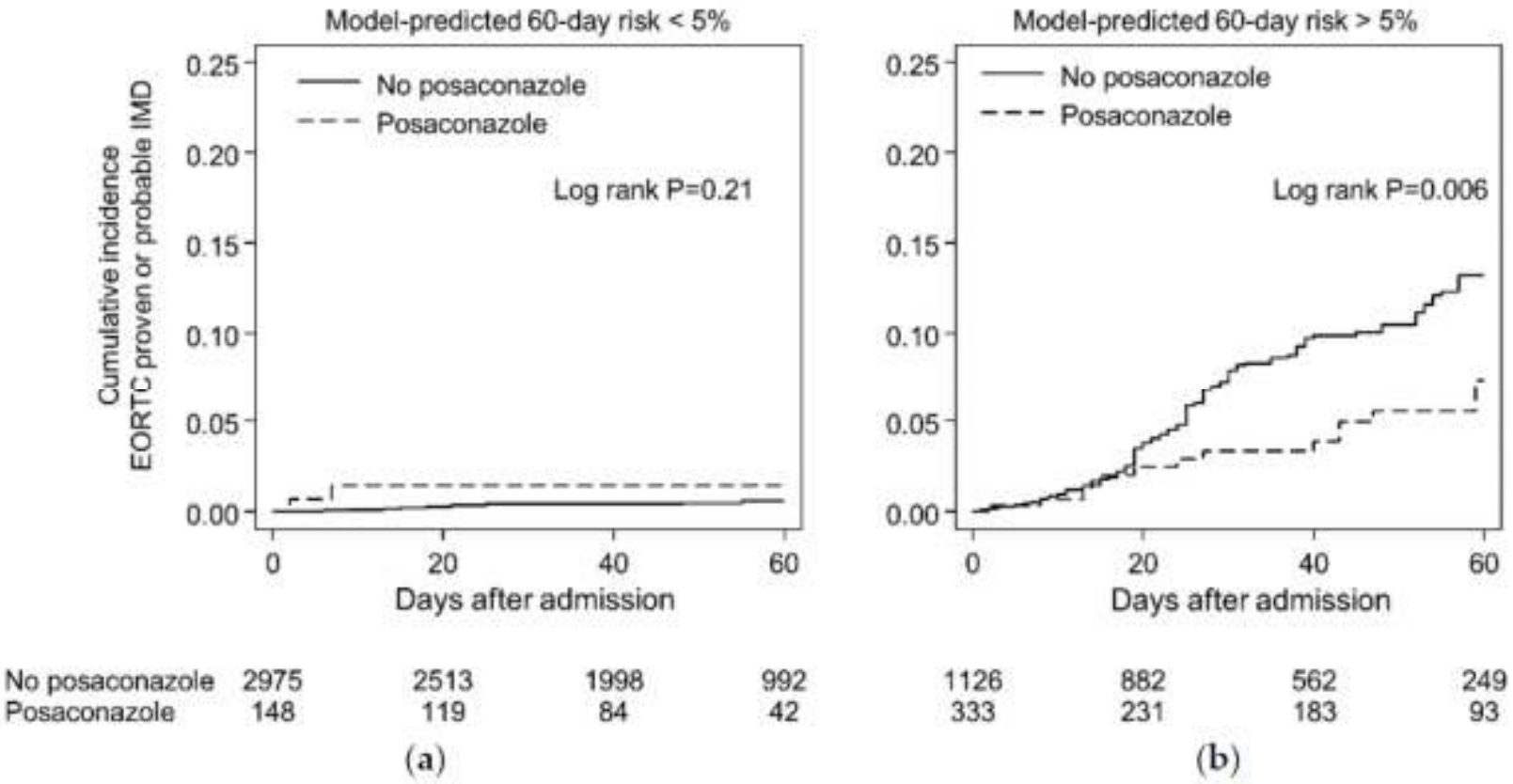
Smartphone-assisted prognostic model assessments of lower-risk (**a**) and higher-risk (**b**) nonneutropenic patient.

M Stanzani and R E. Lewis. Fungi 2018, 4, 141

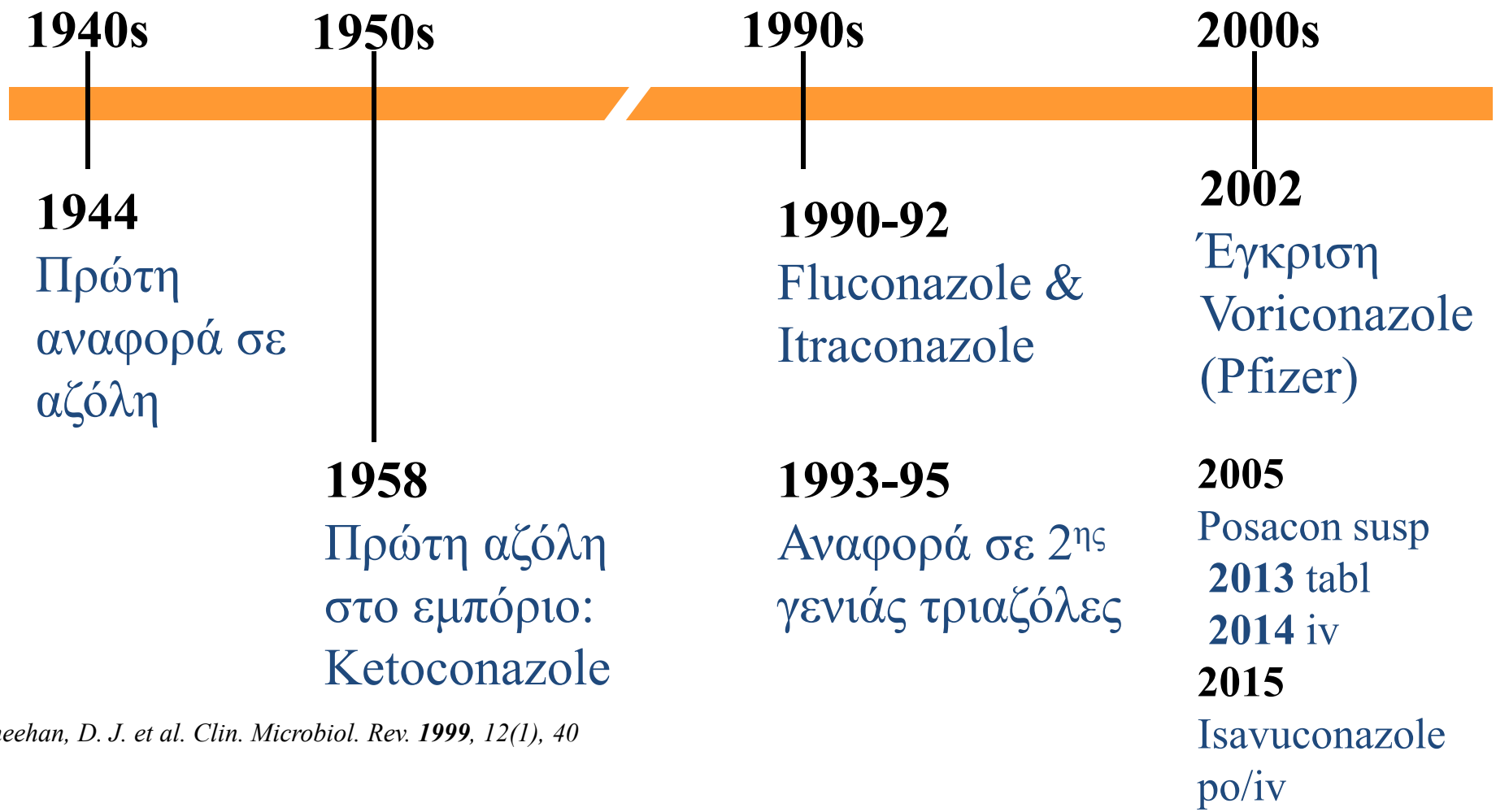
(a) (b)

Impact of posaconazole prophylaxis on the 60-day cumulative incidence of IMD in patients with model predicted risk of IMD < 5% (**a**) and > 5%

M Stanzani and R E. Lewis. Fungi 2018, 4, 141



Ιστορικοί σταθμοί στην ιστορία των αζολών



Sheehan, D. J. et al. Clin. Microbiol. Rev. ***1999****, 12(1), 40*

Prospective, controlled studies on primary antifungal prophylaxis in allogeneic HSCT over the last 10 years

Update: ECIL 5, 2013

Itraconazole versus fluconazole Marr KA et al. Blood 2004	Until 180 days after allo SCT, or until 4 weeks after discontinuation of GvHD therapy
Micafungin versus fluconazole Van Burik et al. Clin Infect Dis 2004	Allogeneic and autologous HSCT only pre-engraftment
Posaconazole versus fluconazole Ullmann A et al. NEJM 2007	Allogeneic HSCT only during GvHD
Voriconazole versus fluconazole Wingard JR et al. Blood 2010	Allogeneic HSCT until 100 days or until 180 days if GvHD
Voriconazole versus itraconazole Marks D et al. Br J Haematol 2011	Allogeneic HSCT until 100 days or until 180 days if GvHD

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Posaconazole vs. Fluconazole or Itraconazole Prophylaxis in Patients with Neutropenia

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 25, 2007 VOL. 356 NO. 4

Posaconazole or Fluconazole for Prophylaxis in Severe Graft-versus-Host Disease

Andrew J. Ullmann, M.D., Jeffrey H. Lipton, M.D., David H. Vesole, M.D., Ph.D., Pranatharthi Chandrasekar, M.D., Amelia Langston, M.D., Stefano R. Tarantolo, M.D., Hildegard Greinix, M.D., Wellington Morais de Azevedo, M.D., Ph.D., Vijay Reddy, M.D., Navdeep Boparai, M.S., Lisa Pedicone, Ph.D., Hernando Patino, M.D., and Simon Durrant, M.D.*

bjh research paper

Voriconazole versus itraconazole for antifungal prophylaxis following allogeneic haematopoietic stem-cell transplantation

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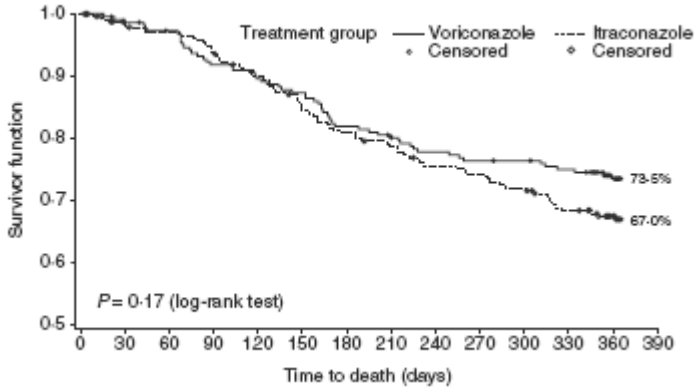
Summary

Antifungal prophylaxis for allogeneic haematopoietic stem-cell transplant (alloHCT) recipients should prevent invasive mould and yeast infections (IFIs) and be well tolerated. This prospective, randomized, open-label, multicentre study compared the efficacy and safety of voriconazole (234 patients) versus itraconazole (255 patients) in alloHCT recipients. The



Prospective study
234 pts vori, 255 itra
No difference in IFIs rate
Vori better tolerated

British Journal of Haematology 2011


GUIDELINES


GUIDELINES

NCCN National Comprehensive Cancer Network®

NCCN

Prevention and Treatment of Cancer-Related Infections, Version 2.2016

Clinical Practice Guidelines in Oncology

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Overview

There is an increased risk of infection in patients with cancer that results in higher morbidity and

National Comprehensive Cancer Network®

Prevention and Treatment of Cancer-Related Infections, Version 2.2016

OVERALL INFECTION RISK IN PATIENTS WITH CANCER[a]	DISEASE/THERAPY EXAMPLES	FEVER & NEUTROPENIA RISK (See FEV-2*)	ANTIMICROBIAL PROPHYLAXIS [d,e,f,g,h,i]
Low	• Standard chemotherapy regimens for most solid tumors • Anticipated neutropenia less than 7 d	Incidence low	• Bacterial - None • Fungal - None • Viral - None unless prior HSV episode
Intermediate	• Autologous HCT • Lymphoma[c] • Multiple myeloma[c] • CLL[c] • Purine analog therapy (ie, fludarabine, clofarabine, nelarabine, cladribine) • Anticipated neutropenia 7–10 d	Incidence usually high, significant variability may exist	• Bacterial - Consider fluoroquinolone prophylaxis • Fungal - Consider prophylaxis during neutropenia and for anticipated mucositis (See INF-2); consider PCP prophylaxis (See INF-6*) • Viral - During neutropenia and longer depending on risk (See INF-3, INF-4, INF-5)
High[b]	• Allogeneic HCT including cord blood • Acute leukemia ▸ Induction ▸ Consolidation • Alemtuzumab therapy • GVHD treated with high-dose steroids (>20 mg daily) • Anticipated neutropenia greater than 10 d	Incidence usually high, significant variability may exist	• Bacterial - Consider fluoroquinolone prophylaxis • Fungal - Consider prophylaxis during neutropenia (See INF-2); consider PCP prophylaxis (See INF-6*) • Viral - During neutropenia and longer depending on risk (See INF-3, INF-4, INF-5)

Prevention and Treatment of Cancer-Related Infections, Version 2.2016

OVERALL INFECTION RISK IN PATIENTS WITH CANCER[a]	DISEASE/THERAPY EXAMPLES	ANTIFUNGAL PROPHYLAXIS[f,l]	DURATION
INTERMEDIATE TO HIGH	ALL	Consider: • Fluconazole[m] or Micafungin • Amphotericin B products[n] (category 2B)	Until resolution of neutropenia
	MDS (neutropenic) AML (neutropenic)	Consider: • Posaconazole[m] (category 1) • Voriconazole[m], Fluconazole[m], Micafungin, or Amphotericin B products[n] (all category 2B)	
	Autologous HCT with mucositis[i]	Consider: • Fluconazole[m] or Micafungin (both category 1)	
	Autologous HCT without mucositis	Consider no prophylaxis (category 2B)	
	Allogeneic HCT (neutropenic) See Antipneumocystis Prophylaxis (INF-6*)	Consider: • Fluconazole[m] or Micafungin (both category 1) • Voriconazole[m], Posaconazole[m], or Amphotericin B product[n] (all category 2B)	Continue during neutropenia and for at least 75 d after transplant
	Significant GVHD[h] See Antipneumocystis Prophylaxis (INF-6*)	Consider: • Posaconazole[m] (category 1) • Voriconazole[m], Echinocandin, Amphotericin B products[n] (all category 2B)	Until resolution of significant GVHD

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Journal of Antimicrobial Chemotherapy

European guidelines for primary antifungal prophylaxis in adult haematology patients: summary of the updated recommendations from the European Conference on Infections in Leukaemia

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- The guidelines were extended to provide recommendations for other haematological diseases besides AML and recipients of an allogeneic HSCT).
- Posaconazole remains the drug of choice when the incidence of invasive mould diseases exceeds 8%.
- For patients undergoing remission-induction chemotherapy for AML and myelodysplastic syndrome (MDS), fluconazole can still offer an alternative/part of an integrated care strategy that includes screening with biomarkers and imaging.
- Similarly, aerosolized liposomal amphotericin B combined with fluconazole can be considered for patients at high risk of invasive mould diseases but other formulations of the polyene are discouraged.
- Fluconazole is still recommended as primary prophylaxis for patients at low risk of invasive mould diseases during the pre-engraftment phase of allogeneic HSCT whereas only a moderate recommendation could be made for itraconazole, posaconazole and voriconazole for patients at high risk.
- Posaconazole is strongly recommended for preventing invasive mould disease post-engraftment but only when graft-versus-host disease (GvHD) was accompanied by other risk factors such as its severity, use of an alternative donor or when unresponsive to standard corticosteroid therapy.
- The need for primary prophylaxis for other patient groups was less clear and should be defined by the estimated risk of invasive fungal disease (IFD).

ECIL Recommendations on primary antifungal prophylaxis (JAC 2018) in adult patients with AML/MDS undergoing intensive remission-induction chemotherapy

Antifungal AGENT	Grading	Comments
Fluconazole 400mg q24	**BI**	Only recommended if the incidence of mould is low. Fluconazole may be part of an integrated care strategy together with a mould-directed diagnostic approach
Itraconazole oral solution 2.5mg/Kg q12h	**BI**	Recommended if baseline incidence of mould infections is high May be limited by drug–drug interactions or patient tolerability. It is recommended to monitor serum drug concentrations
Posaconazole oral sol 200mg q8h tb 300mg q24h loading dose 300mg q12h	**AI**	Recommended if baseline incidence of mould infection is high Given the increased absorption of tablets, it is likely that the need for therapeutic drug monitoring will become restricted to specific populations (e.g. severe mucositis)

ECIL Recommendations on primary antifungal prophylaxis (JAC 2018) in adult patients with AML/MDS undergoing intensive remission-induction chemotherapy		
Antifungal agent	**Grading**	**Comments**
All Echinocandins	**CII**	Insufficient data on efficacy and tolerability
Liposomal Amphotericin B	**CII**	Insufficient data on efficacy and tolerability
Lipid associated Amphotericin B	**CII**	Insufficient data on dose, frequency and duration as well as on efficacy and tolerability
Aerosolized liposomal Amphotericin B(10 mg twice weekly)	**BI**	Only when combined with oral fluconazole
Amphotericin B deoxycholate	**AII against**	
Aerosolized amphotericin B deoxycholate	**AII against**	

Recommendations for allogeneic HSCT recipients (2013)

Update: ECIL 5, 2013

Antifungal prophylaxis*	Pre-engraftment Low risk for moulds	Pre-engraftment High risk for moulds	GvHD
Fluconazole	A-I	A-III - against	A-III against
Itraconazole	B-I	B-I	B-I
Voriconazole	B-I	B-I	B-I
Posaconazole OS/Tablet	B-II	B-II	A-I
Micafungin	B-I	C-I	C-II
Caspofungin /anidulafungin	No data	No data	No data
Liposomal Amphotericin B	C-II	C-II	C-II
Aerosolized amphotericin B plus fluconazole	C-III	B-II	No data

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Diagnosis and management of *Aspergillus* diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline

A.J. Ullmann [1, 62, 63], J.M. Aguado [2, 62, 63], S. Arikan-Akdagli [3, 62, 63], D.W. Denning [4, 5, 6, 63],

- Patients known to be at high risk for IA **may receive** primary prophylaxis, especially patients with profound and prolonged neutropenia or with active graft-versus-host disease (GvHD)
- In patients treated for haematological diseases, prolonged severe neutropenia is the most important risk factor for the development of IA. T-cell-depleted grafts, glucocorticosteroids and other immune suppressive drugs have been identified as further **risk factors for IA in the later course** after haematopoietic stem cell transplantation (HSCT), even in non-neutropenic patients. In fact, **up to two-thirds of patients with IA diagnosed after allogeneic HSCT are not neutropenic**, and the med time of diagnosis of IA after allogeneic HSCT is **82 days** (range, 3-6542 days)

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SPECIAL ISSUE: TRANSPLANT INFECTIOUS DISEASES

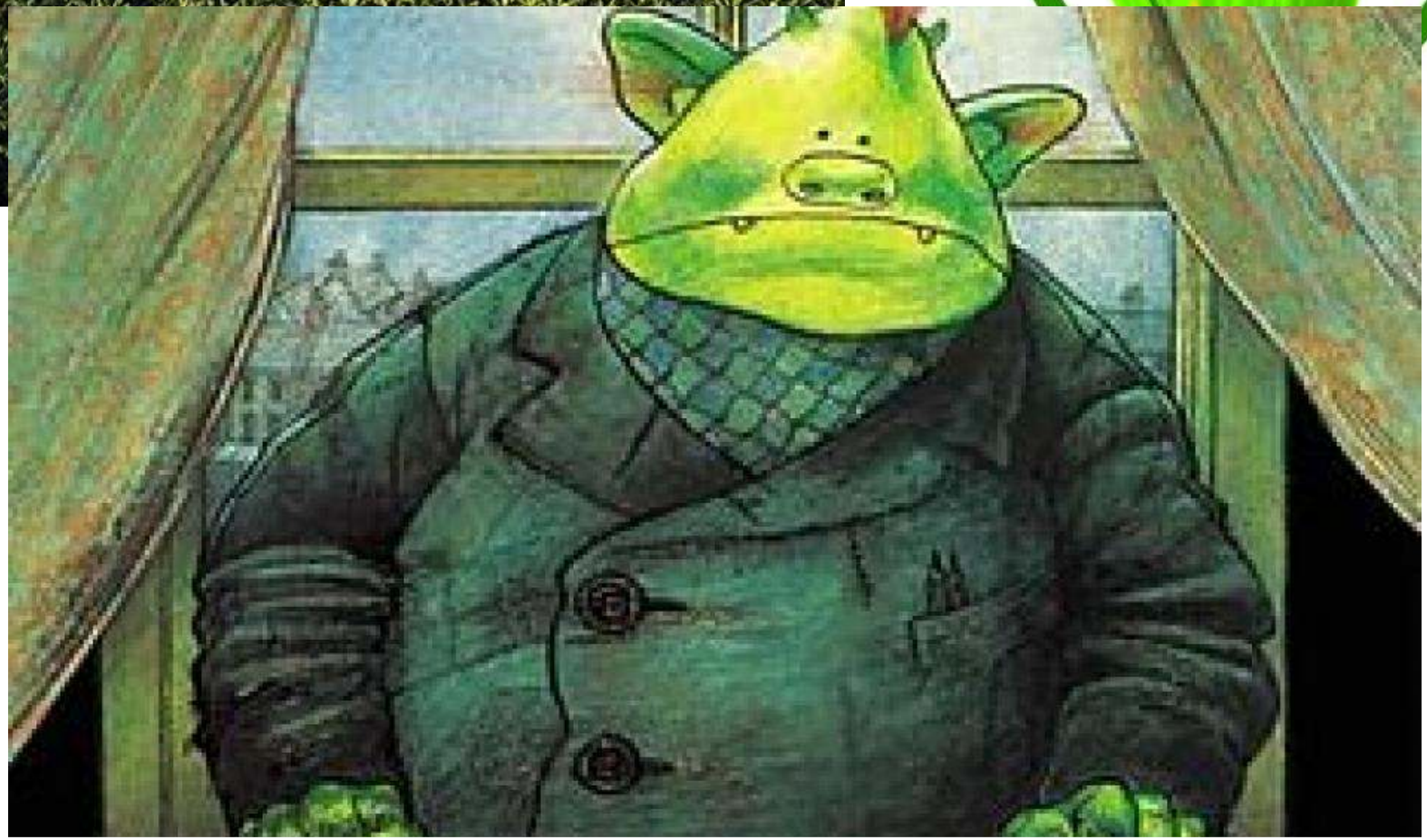
Clinical TRANSPLANTATION WILEY

Invasive Aspergillosis in solid-organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

Shahid Husain[1] | Jose F. Camargo[2] on behalf of the AST Infectious Diseases Community of Practice

Παγκόσμια κατανομή *A. fumigatus* sp ανθεκτικών σε αζόλες

Fungicide Futures



“Swabs of bulbs imported from the Netherlands and bought from a garden centre in Dublin found that the majority were cultured resistant to Voriconazole”

PressReader - Irish Examiner

New antifungal agents in late stage of development

Agent	Phase	Class	Mechanism of action	Advantage	Disadvantage	Potential use
Azoles						
Isavuconazole	Phase IV	Azole	Inhibition of lanosterol 14α-demethylase	• Oral and IV formulation • Improved safety profile • Reduction in DDIs	• Price compared to other azoles	Invasive mould disease (for example: invasive aspergillosis, mucormycosis)
Glucan synthesis inhibitors						
Rezafungin (CD101)	Phase III	GSI	Inhibition of β-1,3-glucan synthesis	• Improved stability • Long half-life = > front-loaded administration • Safety profile • Minimal interaction with CYP450 enzymes	• No oral formulation	Broad antifungal spectrum, also activity against *Candida auris* and PJP.
SCY-078 (MK-3118)	Phase III	GSI (novel subclass)	Inhibition of β-1,3-glucan synthesis	• Oral and IV formulation • Activity against resistant strains		• *Candida* and *Aspergillus* spp. • *Scedosporium prolificans* • *Candida auris*
Polyenes						
Coch-AmB	Phase II	Polyenes	Pore formation by binding to ergosterol	• Broad spectrum • Minimal DDIs • Oral administration		Broad spectrum (*Candida* spp., *Aspergillus* spp., . . .)
Orotomides						
Olorofim	Phase III	Orotomides	Inhibition of dihydroorotate dehydrogenase	• Oral and IV formulation • No evidence of cross-resistance • Activity against *Lomentospora prolificans*	• DDIs • Little or no activity against *Candida* spp., *Mucorales* spp. and *Cryptococcus neoformans*	• *Aspergillus* spp. • *Scedosporium* spp. (including *Lomentospora prolificans*)

Phase III Studies for Rezafungin

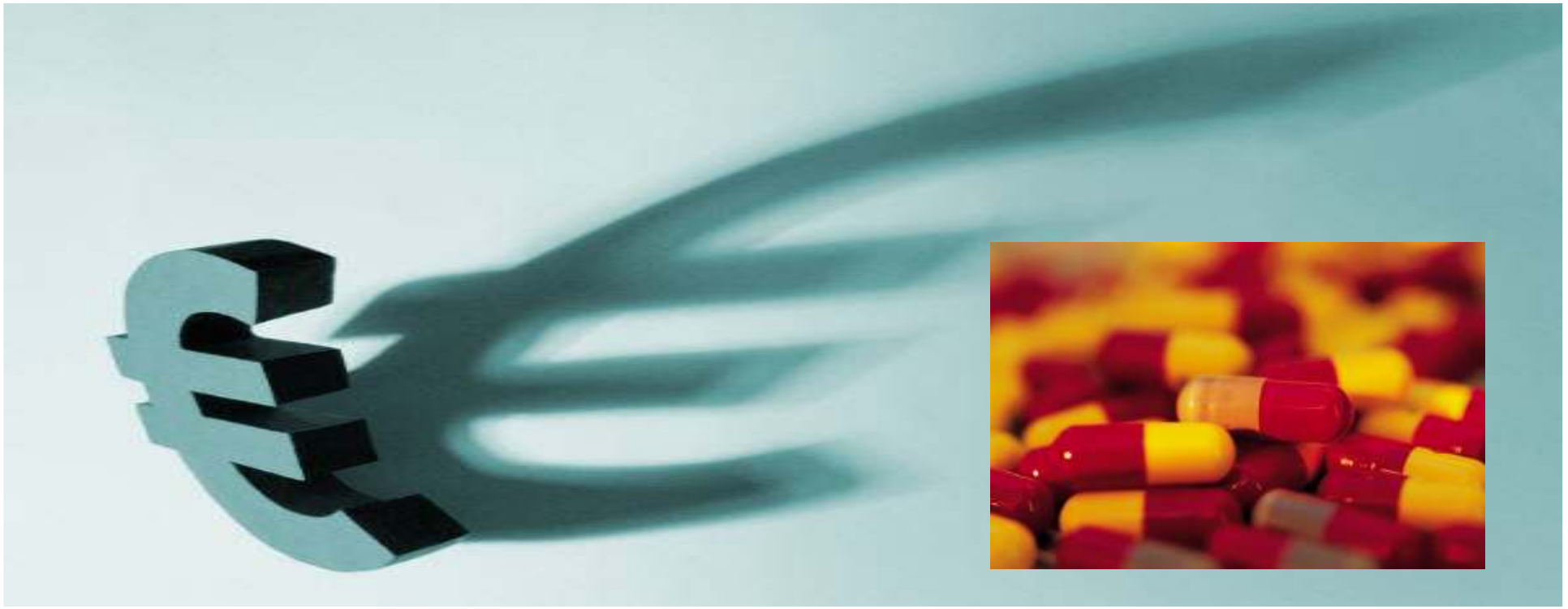
Treatment Phase 3

A Phase 3, Multicenter, **R**andomized, Double-blind Study of the **E**fficacy and **S**afety of **Re**zafungin for Injection versus Intravenous Caspofungin Followed By Optional **O**ral Fluconazole Step-down in the **T**reatment of Subjects with Candidemia and/or Invasive Candidiasis

Prophylaxis Phase 3

A Phase 3, Multicenter, Randomized, Double-blind, Study of the **E**fficacy and **S**afety of **Re**zafungin for Injection Versus the Standard Antimicrobial Regimen to **P**revent Invasive Fungal Infections in Adults Undergoing Allogeneic Hematopoietic Stem **C**ell **T**ransplantation

Antifungal Prophylaxis



Cost-Benefit Assessment


Stewardship
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