FUNGUS:
FROM A RARITY TO A REGULAR CUSTOMER WITH SPECIFIC DEMANDS

OUTLINE OF THE PRESENTATION

- ✓Introduction
- ✓Role of a fungus in nature
- ✓Pathophysiology of fungal disease
- ✓Options and limitations of antifungals
- ✓Strategic choices
- ✓Side reflections
- ✓Final remarks

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BenQ
JVC


AP

CAUSES OF DEATH IN PATIENTS WITH MALIGNANCIES NIJMEGEN, THE NETHERLANDS

328 autopsies

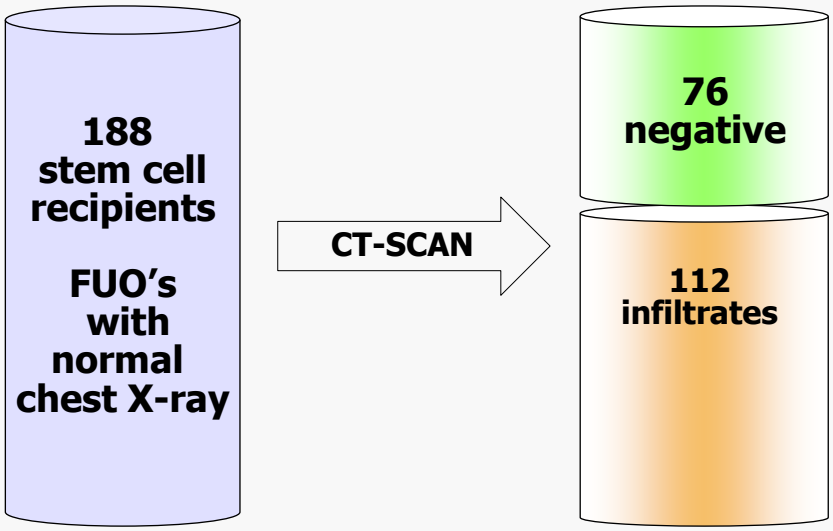
BACTERIAL INFECTION	**7%**
FUNGAL INFECTION	**36%**
MULTIFACTORIAL	**40%**
HEMORRHAGE	**17%**

DIAGNOSTIC DILEMMAS IN FUNGAL INFECTIONS

- Clinical symptoms not characteristic
- Manifestations on imaging seldom specific
- Biopsy often impossible
- Serologic tests not universally available

VALUE OF HIGH-RESOLUTION CAT SCAN IN THE DETECTION OF PULMONARY INFILTRATES

Heuser et al. J Clin Oncol 1999; 17:796-805

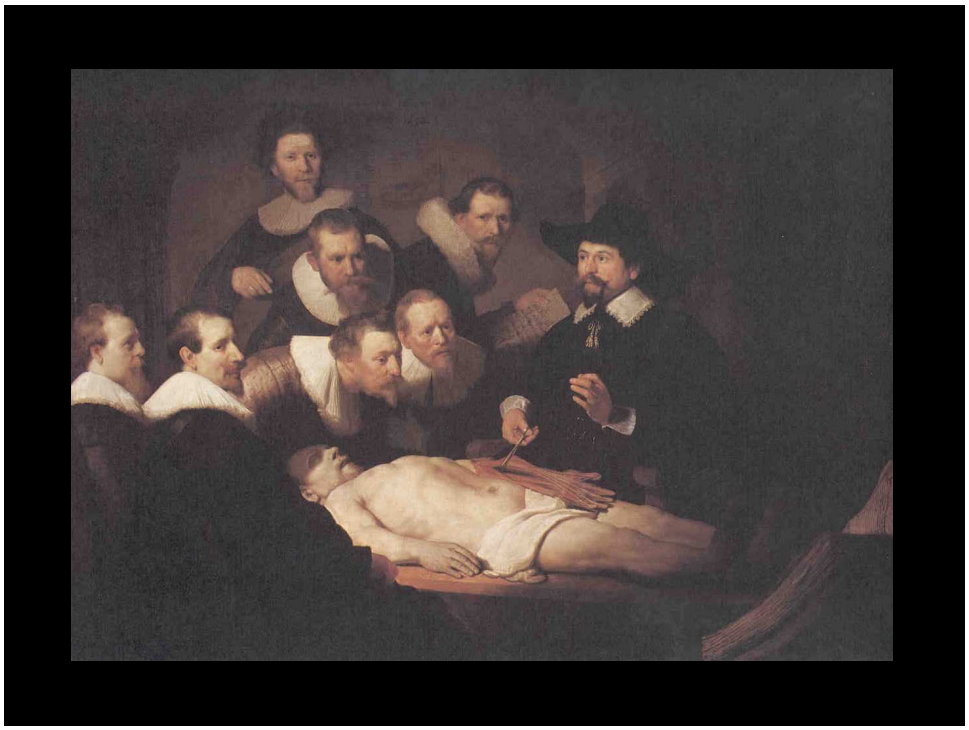


COMPARISON SEROLOGICAL TEST FOR THE DETECTION OF ASPERGILLOSIS

Kawazu et al. J Clin Microbiol 2004;42:2733-2741

149 epsiodes in 96 patients with hematological malignancy

	sensitivity	P.P.V.
Galactomannan ELISA (cut-off 0.6)	100%	55%
PCR	55%	40%
Glucan-test	55%	40%



AUTOPSY SURVEY ASPERGILLUS INFECTIONS

Bodey et al. Eur J Clin Microbiol Infect Dis 1992

TOTAL AUTOPSIES	**4,096**
FUNGAL INFECTION	**455**

	% ASPERGILLUS:
BELGIUM	**55**
CANADA	**50**
GERMANY	**46**
THE NETHERLANDS	**43**
ITALY	**29**
UNITED KINGDOM	**28**
AUSTRIA	**23**
JAPAN	**22**
OVERALL	***30%***

AUTOPSY SURVEY ASPERGILLUS INFECTIONS

Bodey et al. Eur J Clin Microbiol Infect Dis 1992

15-30% OF PATIENTS WITH

INVASIVE FUNGUS AT AUTOPSY

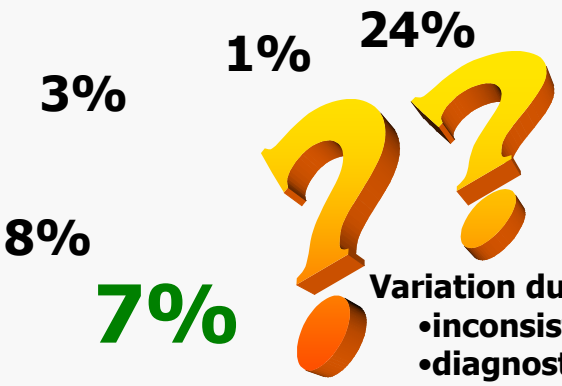
NEVER RECEIVED

ANY SYSTEMIC ANTIFUNGAL THERAPY

VALUE OF AUTOPSY AS DIAGNOSTIC TOOL FOR ASPERGILLUS INFECTIONS

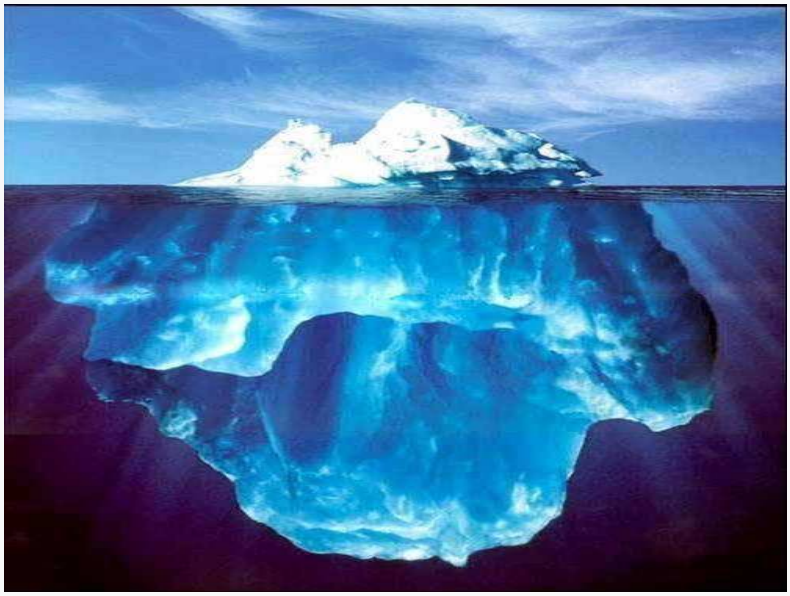
AUTOPSY RATE 1980-2010

INCIDENCE OF INVASIVE ASPERGILLOSIS



Variation due to:

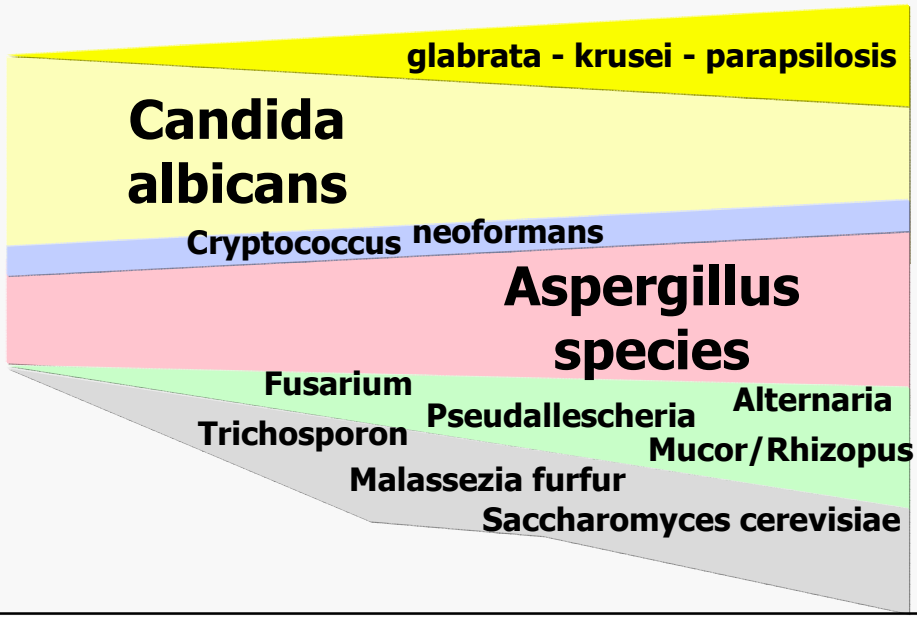
- inconsistent definitions
- diagnostic tools applied
- moment diagnostic procedures
- invasive procedures
- autopsy rate



INCREASE IN FUNGAL INFECTIONS

- higher awareness
- better diagnostic tools
- more complex interventions
- less mortality from other causes
  - -underlying disease
  - -better antibacterial therapy
- more co-morbidity
  (diabetes, higher age, COPD)

EVOLVEMENT OF THE FUNGAL ASSORTMENT



A CHANGING SPECTRUM OF FUNGAL INFECTIONS?

IMPROVEMENT OF IDENTIFICATION TECHNIQUES, INCLUDING A HIGHER AWARENESS

DIFFICULT CASES ARE BETTER REMEMBERED

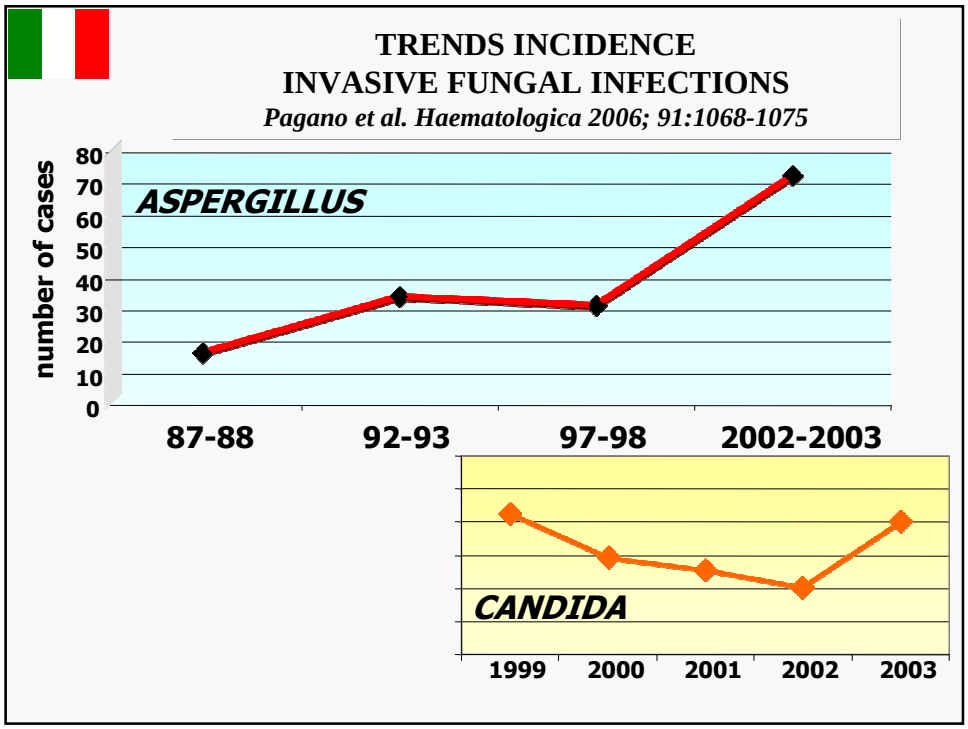
CURIOSITIES ATTRACT MORE ATTENTION, INCLUDING PUBLICATION BIAS

LITERATURE ON CANDIDAEMIA INCIDENCE TRENDS (SINCE 1990)

Courtesy of Frank Odds

Setting	Increasing	No change	Decreasing
Single- & multi-centre surveys	Asmundsdottir '02 Hsueh 2002 Macphail 2002 Poikonen 2003 Schelenz 2003 Yapar 2006	Alonso-Valle '03 Diekema 2002 Duran 2003 Ellis 2003 Hope 2002 Kibbler 2003 Luzatti 2000 Malani 2001 Marchetti 2004 Peman 2005 San Miguel 2005 Viudes 2002	Baran 2001 Boo 2005 Chakrabarti '02 Garbino 2002 Safdar 2002
ICUs	Bassetti 2006 San Miguel 2005	Boo 2005 Duran 2003	Fridkin 2006 Luzzati 2000 Roilides 2004 Swoboda 2003 Tortorano 2004 Trick 2002

Papers published since 2000



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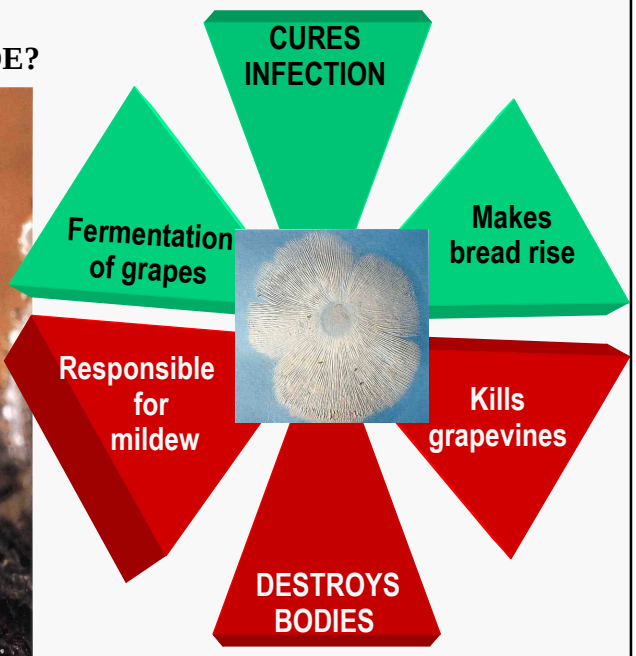
TREAT OR THREAT?

CLEANING UP NATURE….

WHEREVER BIO-DEGRADABLE MATERIAL IS PRESENT

FUNGUS as JEKYLL and HYDE?

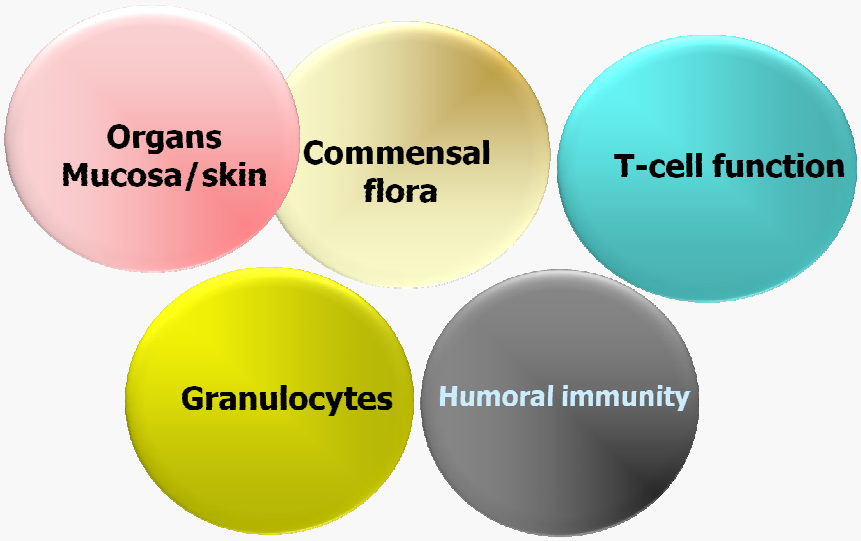


DEFENSE SYSTEMS

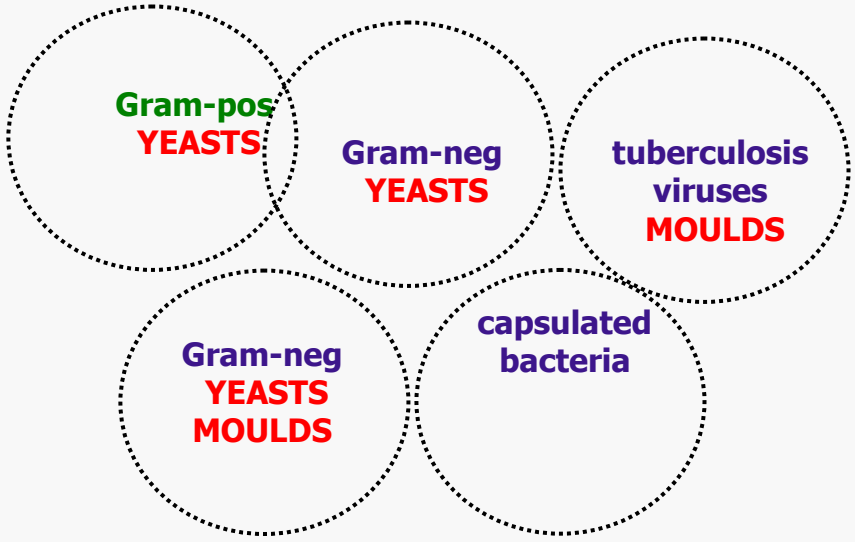
GENETIC PREDISPOSITION

- **T-cell function**
- **Humoral immunity**
- **Commensal flora**
- **Granulocytes**
- **Organ function: Mucosa / Skin -- Lung – Kidney -- Liver**

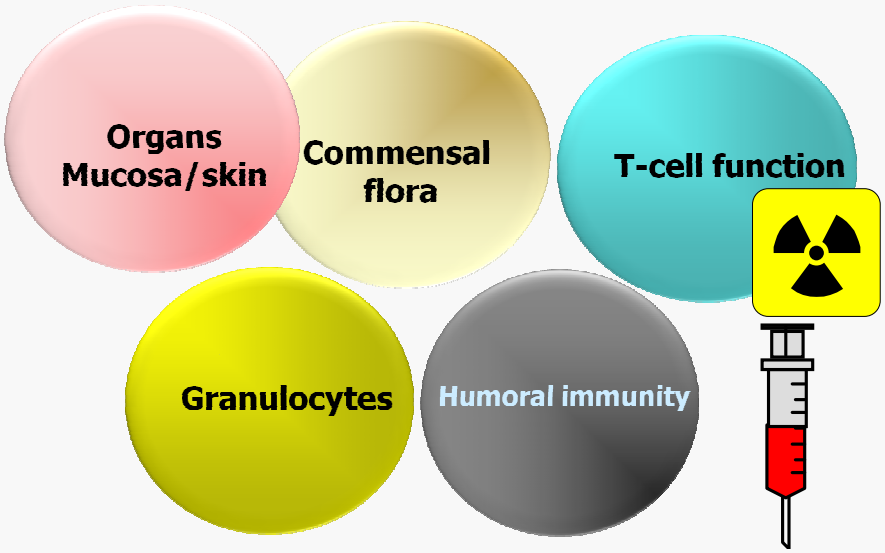
COMPONENTS OF THE IMMUNE SYSTEM AND SPECIFIC PATHOGENS



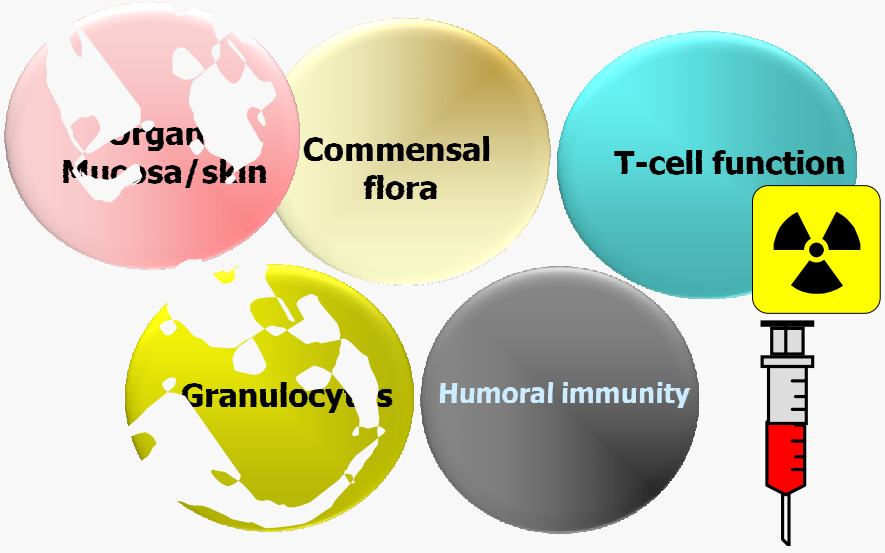
COMPONENTS OF THE IMMUNE SYSTEM AND SPECIFIC PATHOGENS



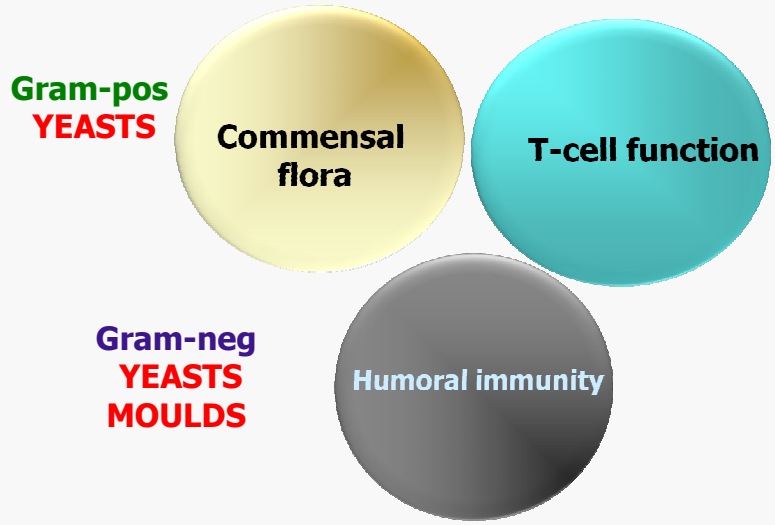
COMPONENTS OF THE IMMUNE SYSTEM AND SPECIFIC PATHOGENS



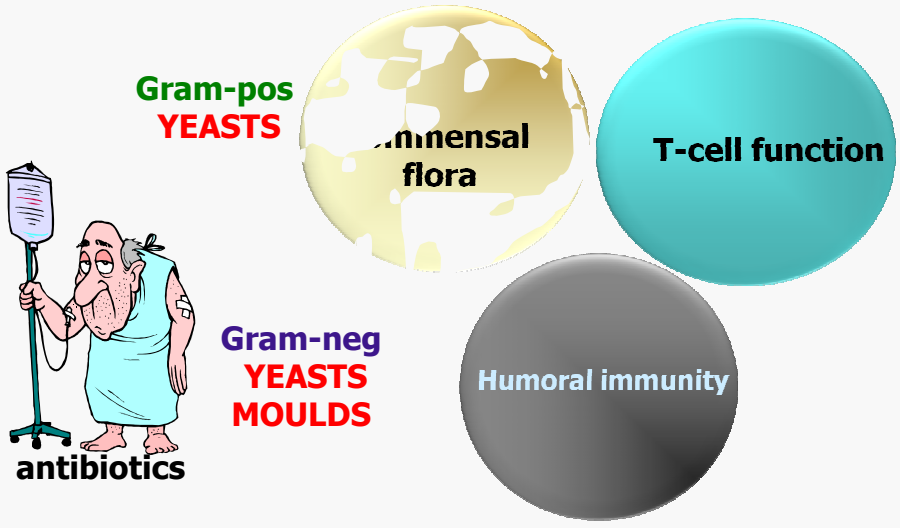
COMPONENTS OF THE IMMUNE SYSTEM AND SPECIFIC PATHOGENS



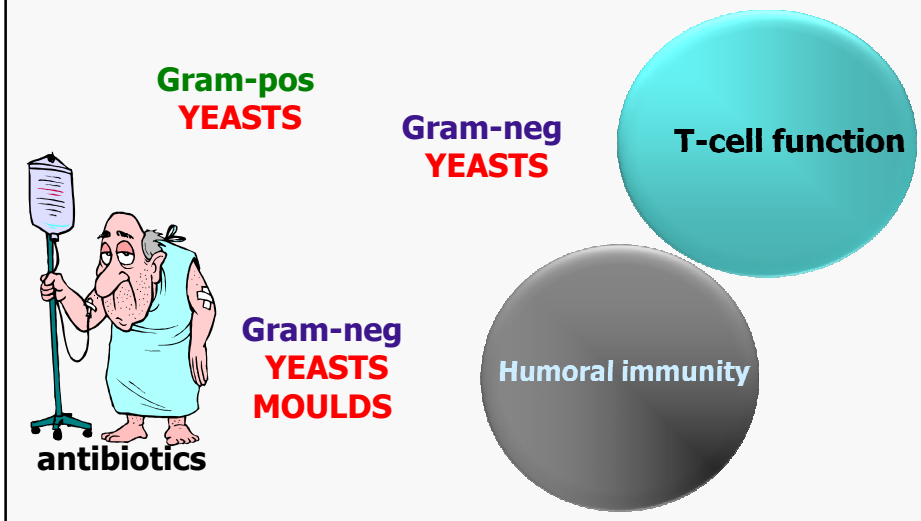
COMPONENTS OF THE IMMUNE SYSTEM AND SPECIFIC PATHOGENS



COMPONENTS OF THE IMMUNE SYSTEM AND SPECIFIC PATHOGENS



COMPONENTS OF THE IMMUNE SYSTEM AND SPECIFIC PATHOGENS



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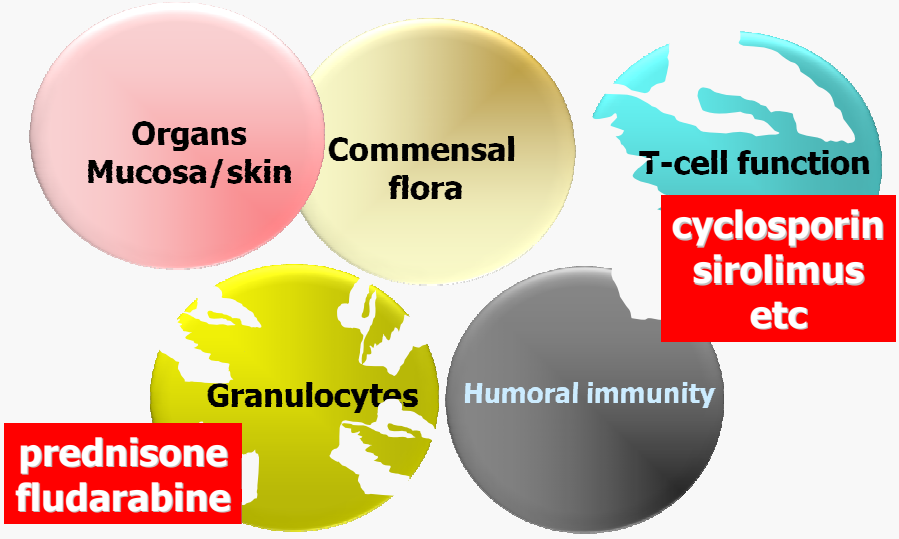

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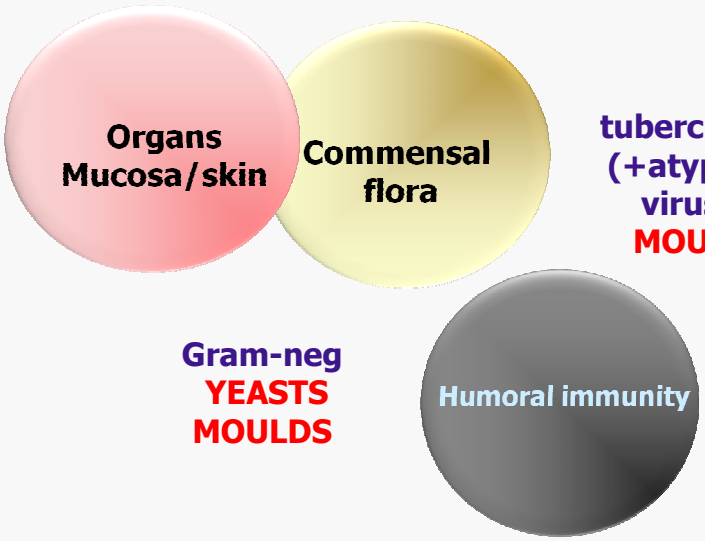

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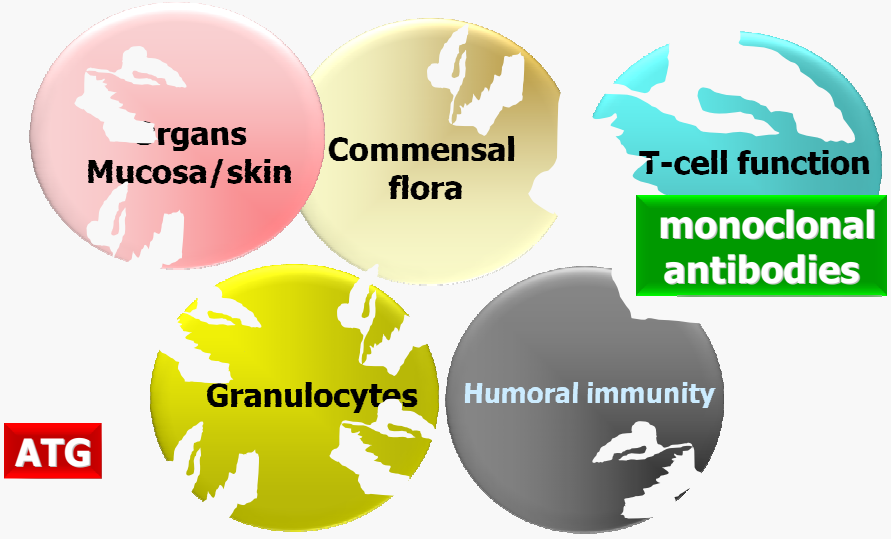

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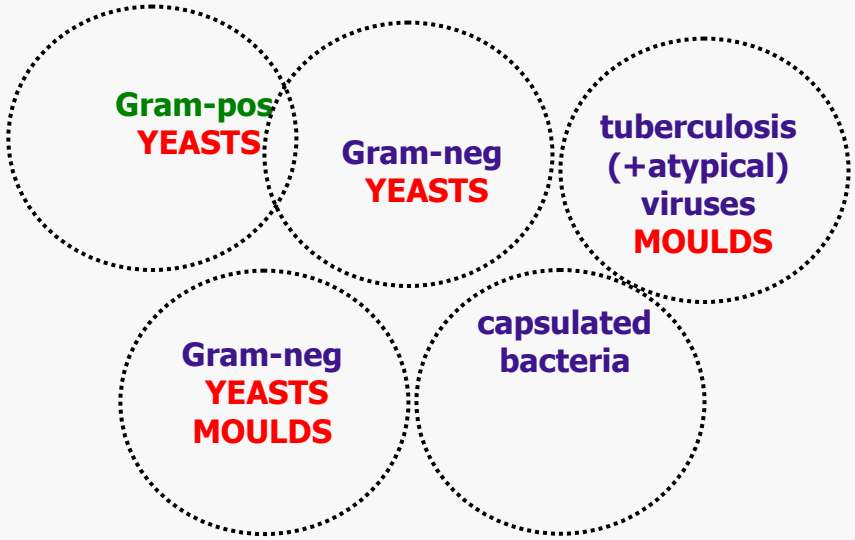
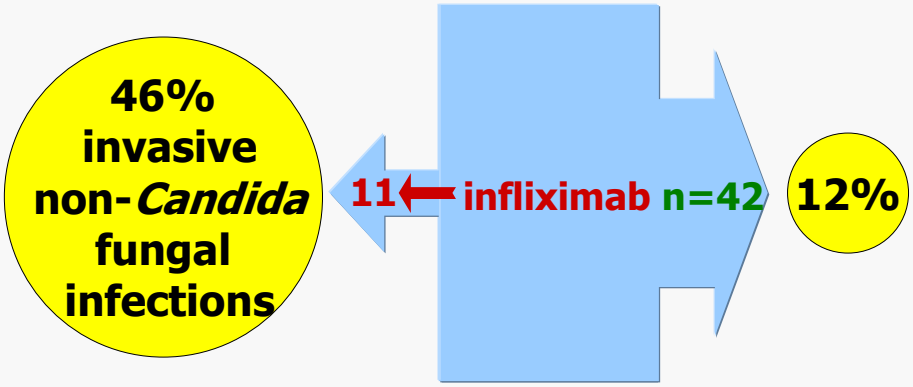


INFLIXIMAB AND FUNGAL INFECTIONS DURING STEM CELL TRANSPLANTS

Marty et al. Blood 2003; 102:2768-2776

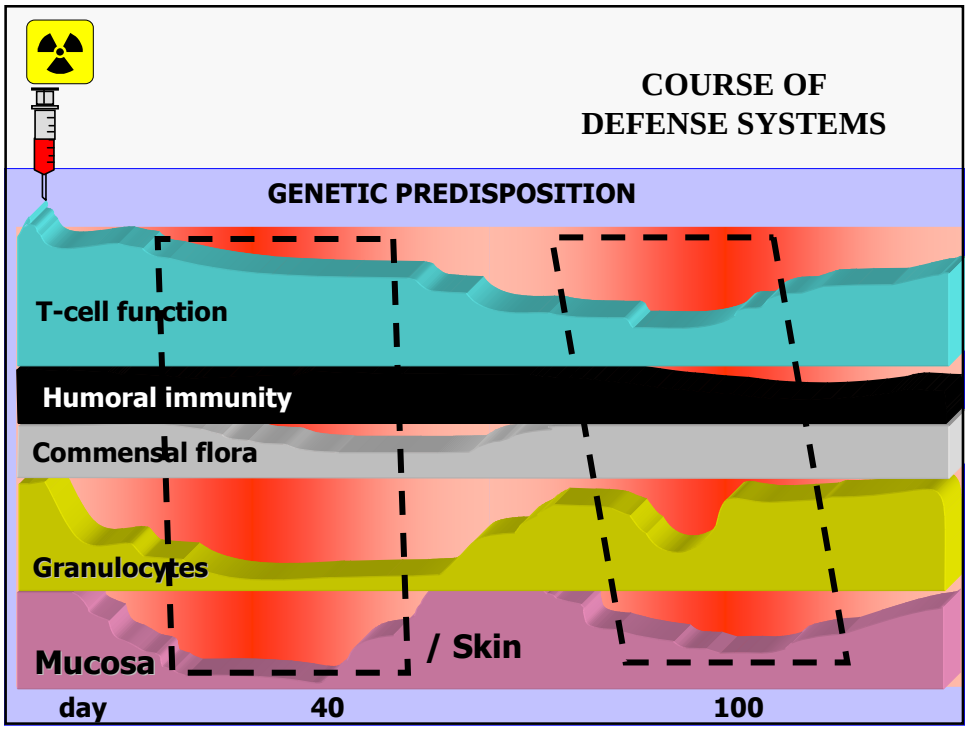
264 alloBMT → 53 (20%) severe GvHD

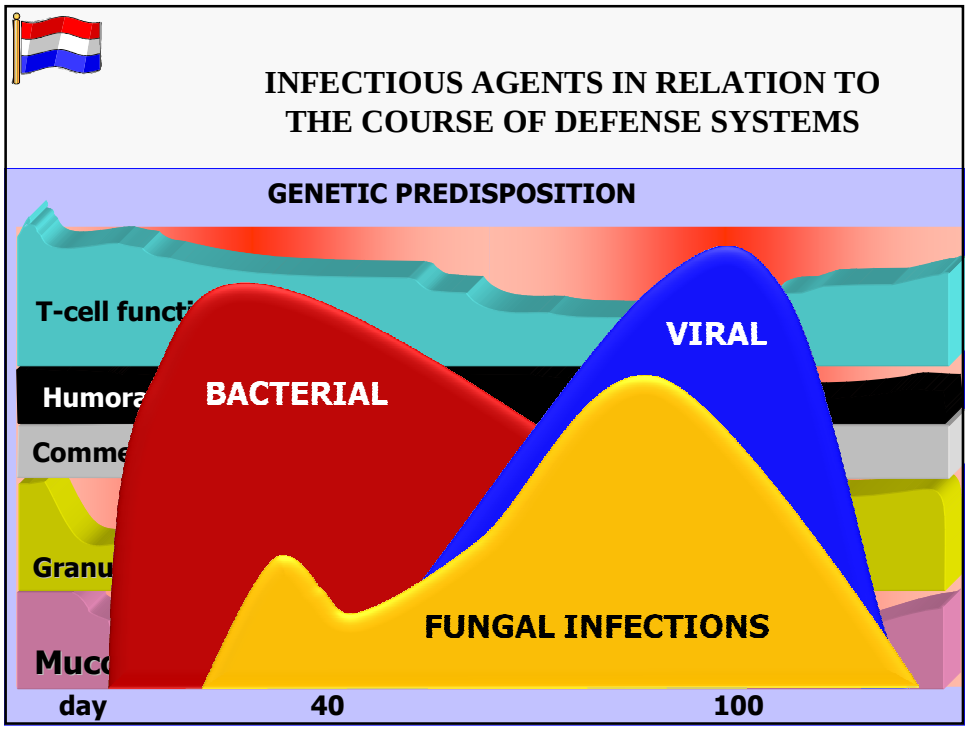


RITUXIMAB AND THE RISK FOR FUNGAL INFECTIONS

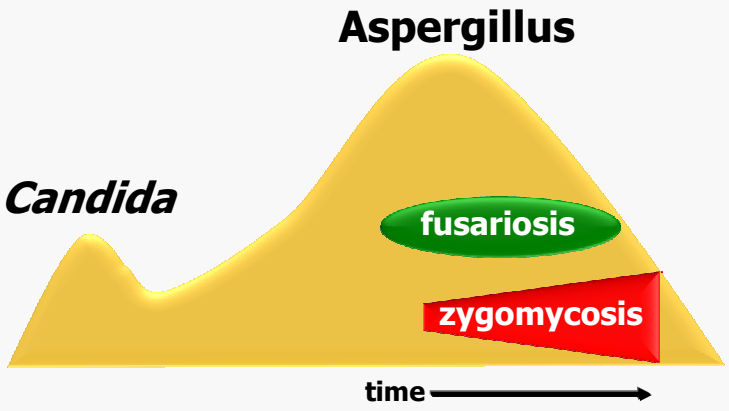
Lin P-C et et al. Ann Hematol 2007; 86:95-100

RITUXIMAB-CHOP n = 35		CHOP n = 35
56%	complete remissions	46%
78%	infections	70%
71%	bacterial	58%
3%	viral	6%
42%	fungal	17%
(40%)	*Candida* spp	(17%)
(2%)	others	-


COURSE OF
DEFENSE SYSTEMS
GENETIC PREDISPOSITION
T-cell function
Humoral immunity
Commensal flora
Granulocytes
Mucosa / Skin
day
40
100


INFECTIOUS AGENTS IN RELATION TO
THE COURSE OF DEFENSE SYSTEMS
GENETIC PREDISPOSITION
BACTERIAL
VIRAL
FUNGAL INFECTIONS
day
40
100

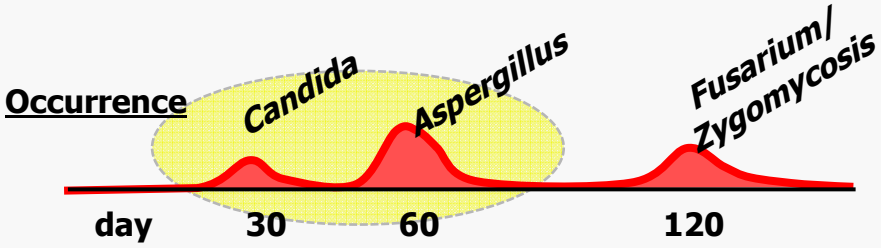
FUNGI IN RELATION TO DEFECTS IN THE DEFENSE SYSTEMS



TRANSNET 2002-2006: FUNGAL INFECTIONS IN BONE MARROW TRANSPLANT RECIPIENTS

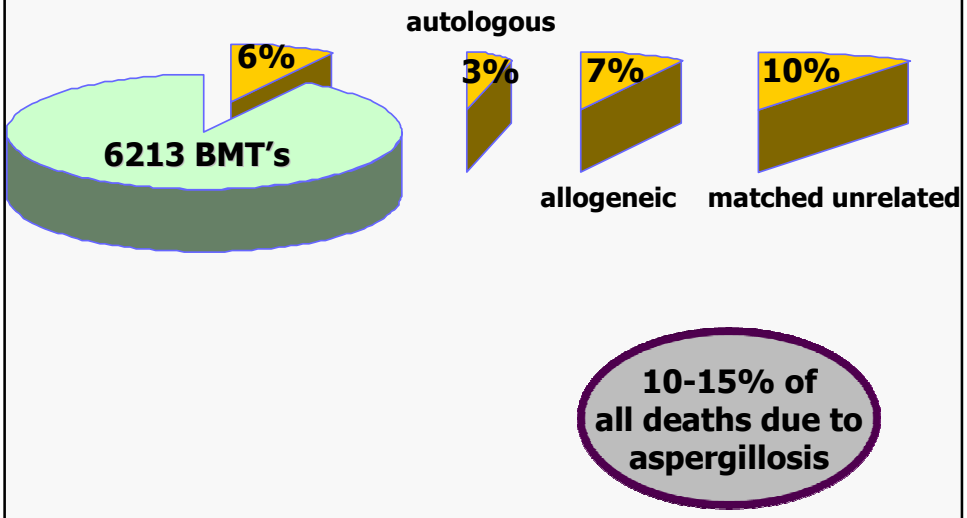
Kontoyiannis et al. Clin Infect Dis 2010;50:1091-1100

Survey 16,200 transplant recipients



ASPERGILLOSIS IN TRANSPLANT RECIPIENTS

Paterson & Singh. Medicine 1999; 78:123

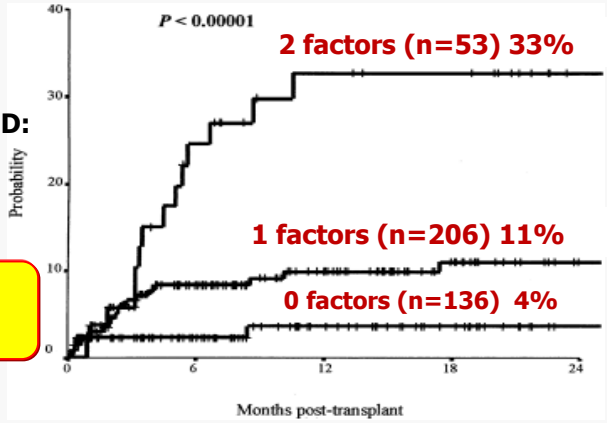


10-15% of all deaths due to aspergillosis

INVASIVE ASPERGILLOSIS IN ALLO- TRANSPLANTS

Marr et al. Blood; Martino et al. Br J Haematol; Jantunen et al. BMT

- Older age (> 40 yr)
- Status and type of UD: AA, MDS, and MM
- Neutropenia
- Acute GvHD
- Chronic GvHD
- CMV disease
- RSV infection
- Corticosteroids > 2mg/kg/day



FUNGAL INFECTIONS AMONG STEM CELL TRANSPLANT RECIPIENTS

Pagano et al. Clin Infect Dis 2007; 45: 1161-1170

1999-2003
3228 stem cell transplants

4%
invasive fungus
(74% moulds)

1249 allogeneic

8%
invasive fungus

1979 autologous

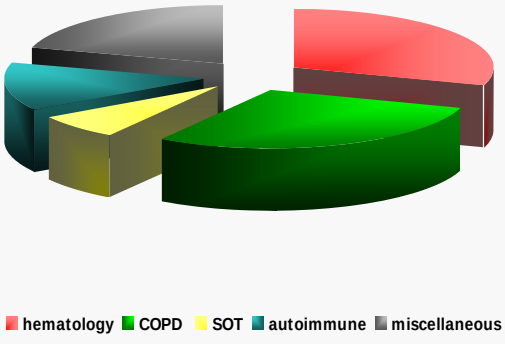
1%
invasive fungus

INCIDENCE AND FATE OF *ASPERGILLUS* INFECTIONS IN ICU UNITS

Meersseman et al. Clin Microbiol Infect 2004;10,Suppl 3:266

1850 admissions 2000-2003
6.9%

Mortality 80%



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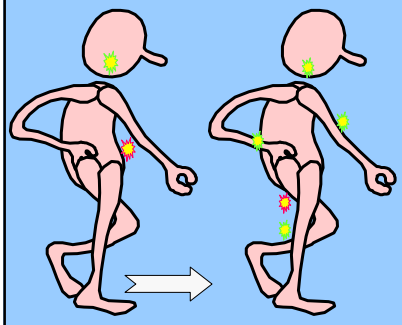
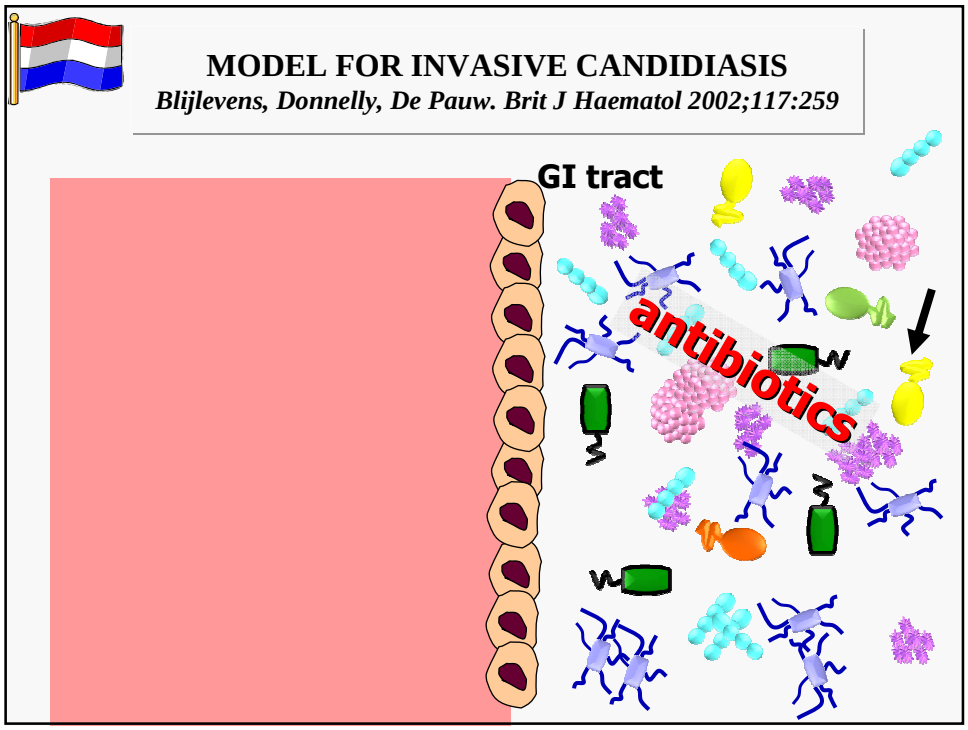
THE DIFFERENCE

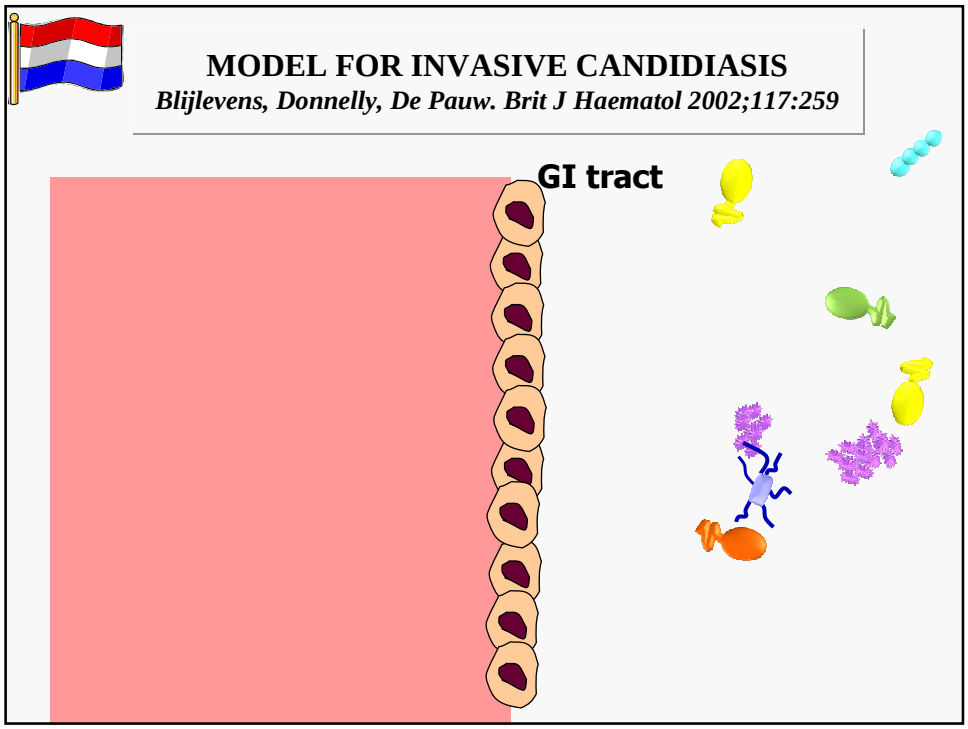
YEAST

MOULD

LIVING IN SYMBIOSIS




MODEL FOR INVASIVE CANDIDIASIS
Blijlevens, Donnelly, De Pauw. Brit J Haematol 2002;117:259
GI tract
antibiotics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GI tract

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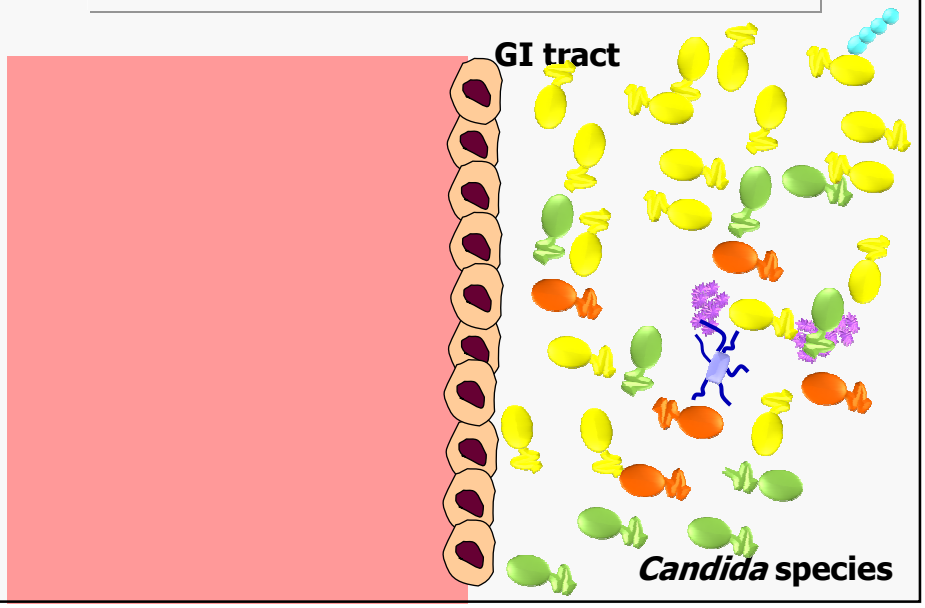
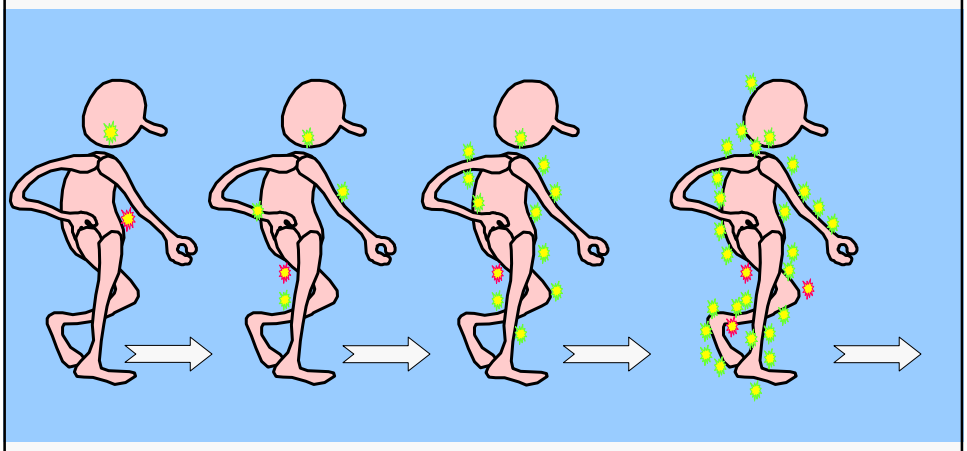


LIVING IN SYMBIOSIS



Initial situation .....increasing colonization **So what??**

RISK FACTORS FOR CANDIDA INFECTIONS

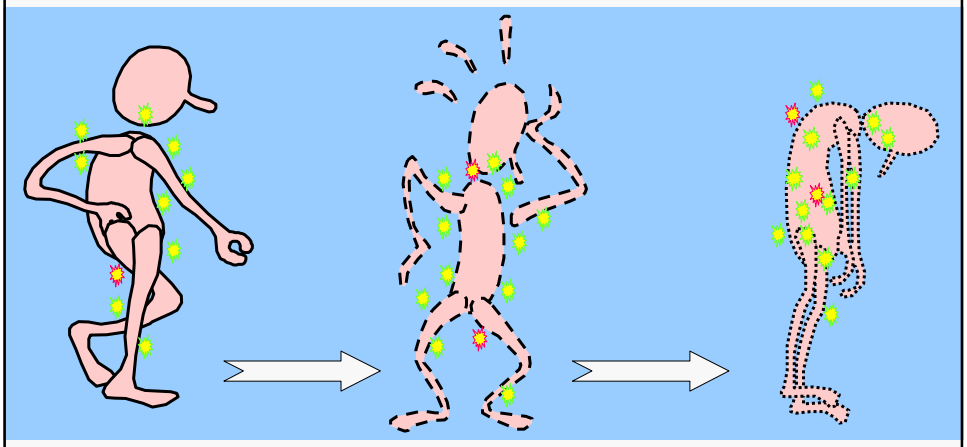
Edwards jr JE et al. Ann Intern Med 1978

I AM HERE
TO HELP YOU!!!

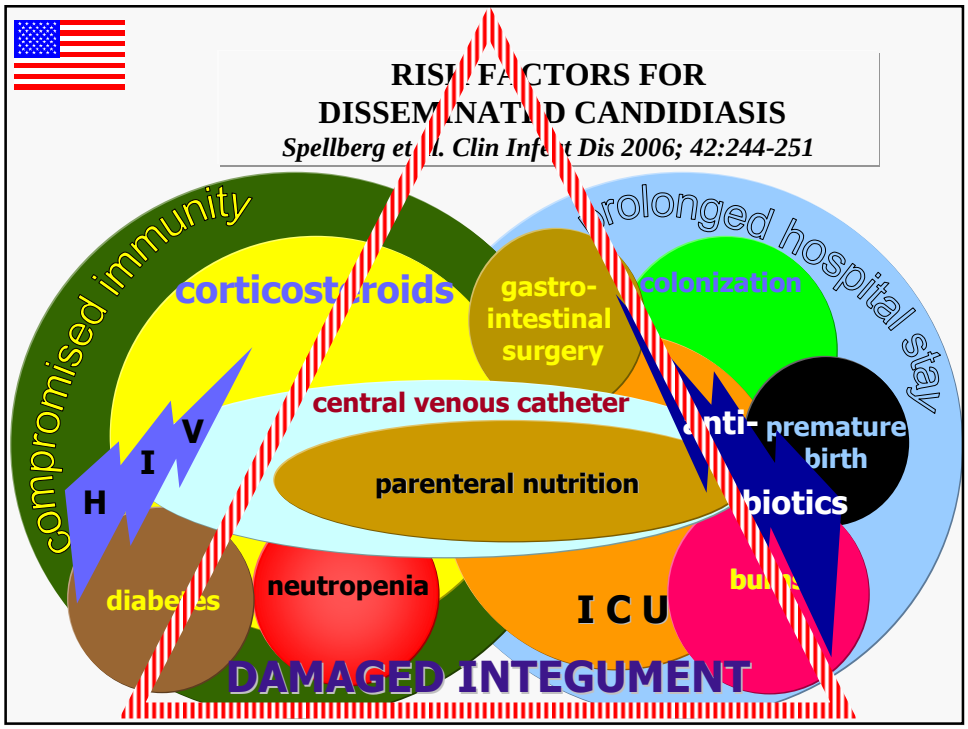
USE OF:

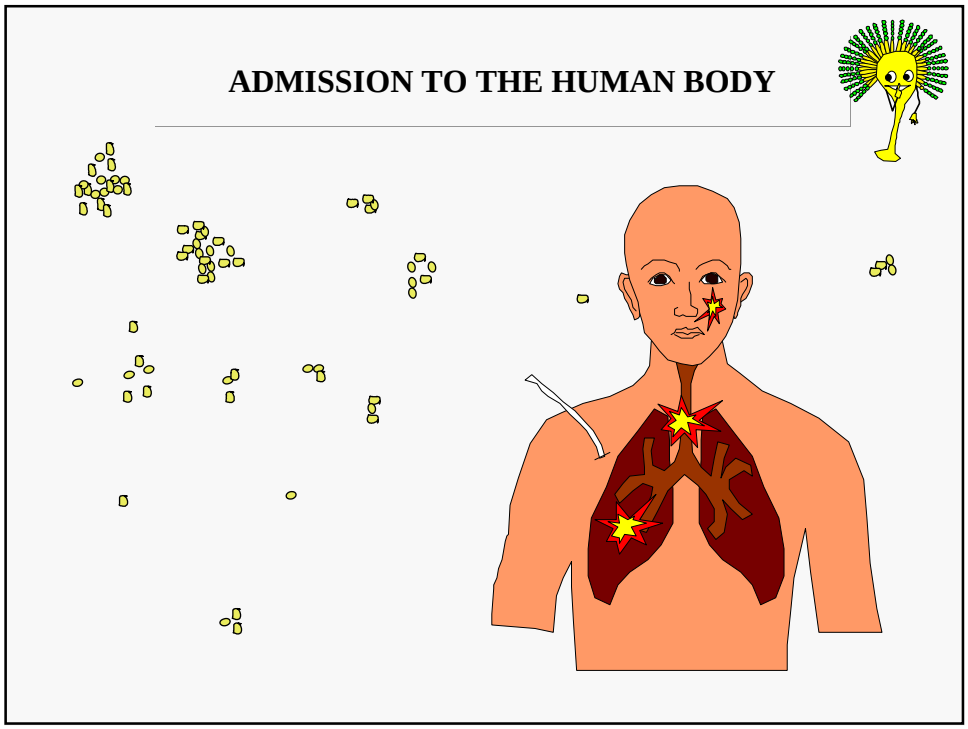
- **antibiotics**
- **immunosuppressants**
- **hyperalimentation**
- **polyethylene catheters**
- **prosthetic devices**
- **heroin**
- **abdominal surgery**

FROM COLONIZATION TO INVASION



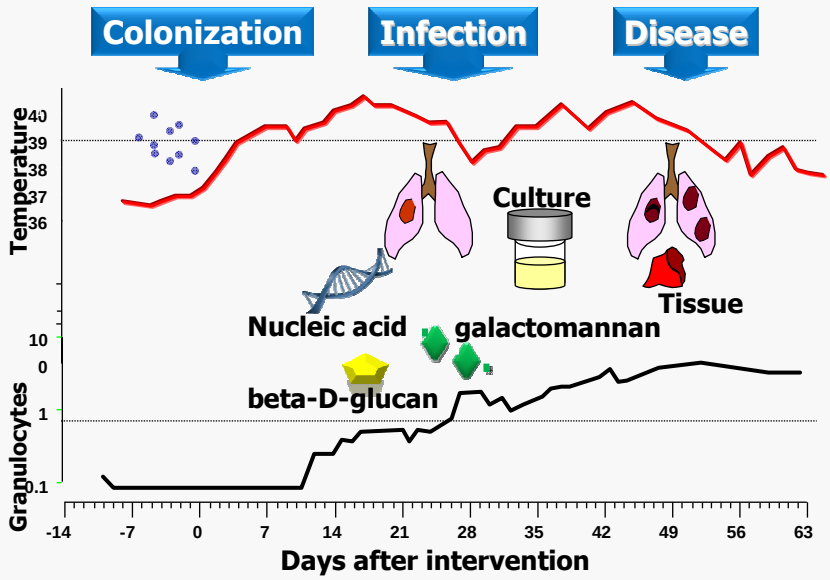
Initial situation **compromised defense** **invasion**


RISK FACTORS FOR
DISSEMINATED CANDIDIASIS
Spellberg et al. Clin Infect Dis 2006; 42:244-251
compromised immunity
corticosteroids
gastro-intestinal surgery
central venous catheter
parenteral nutrition
H
I
V
diabetes
neutropenia
ICU
DAMAGED INTEGUMENT
prolonged hospital stay
colonization
premature birth
biotics


ADMISSION TO THE HUMAN BODY

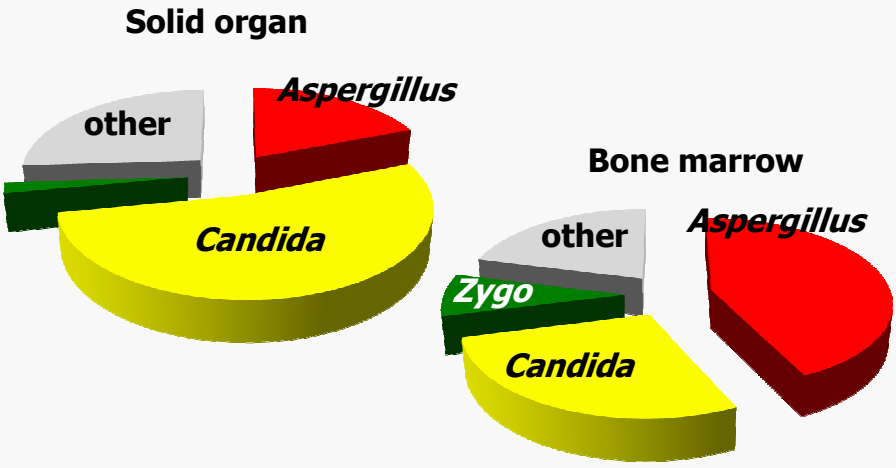
EVOLUTION OF MOULD DISEASE

Peter Donnelly & Ben dePauw



TRANSNET 2002-2006: FUNGAL INFECTIONS IN TRANSPLANT RECIPIENTS

Kontoyiannis / Pappas et al. Clin Infect Dis 2010;50:1091-1111



MORTALITY OF NOSOCOMIAL BLOODSTREAM INFECTIONS IN MALIGNANCIES

Wisplinghoff et al. Clin Infect Dis 2003; 36:1103-10

SCOPE, 1995-2001; 2652 patients

	Incidence %	Mortality %
Coag-neg staphylococci	30	33
Enterococci	14	34
Staphylococcus aureus	11	23
***Candida* species**	**9**	**45**
Escherichia coli	8	35
Klebsiella species	7	24
Enterobacter species	3	28
Pseudomonas species	5	36
Viridans streptococci	1	16

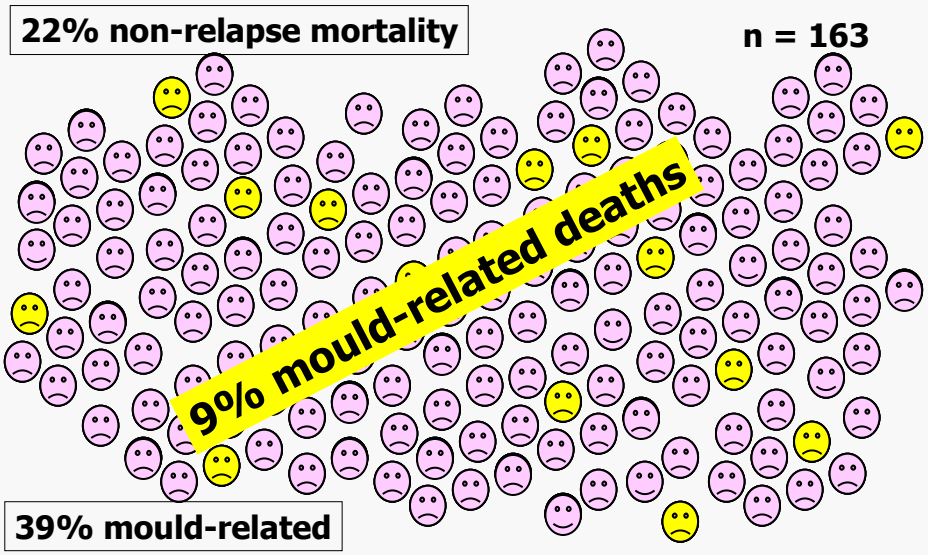
MORTALITY OF INVASIVE ASPERGILLOSIS

97%

22%

INVASIVE FUNGAL DISEASE AFTER NON-MYELOABLATIVE ALLO-BMT

Fukuda et al. Blood 2003; 102:827-833



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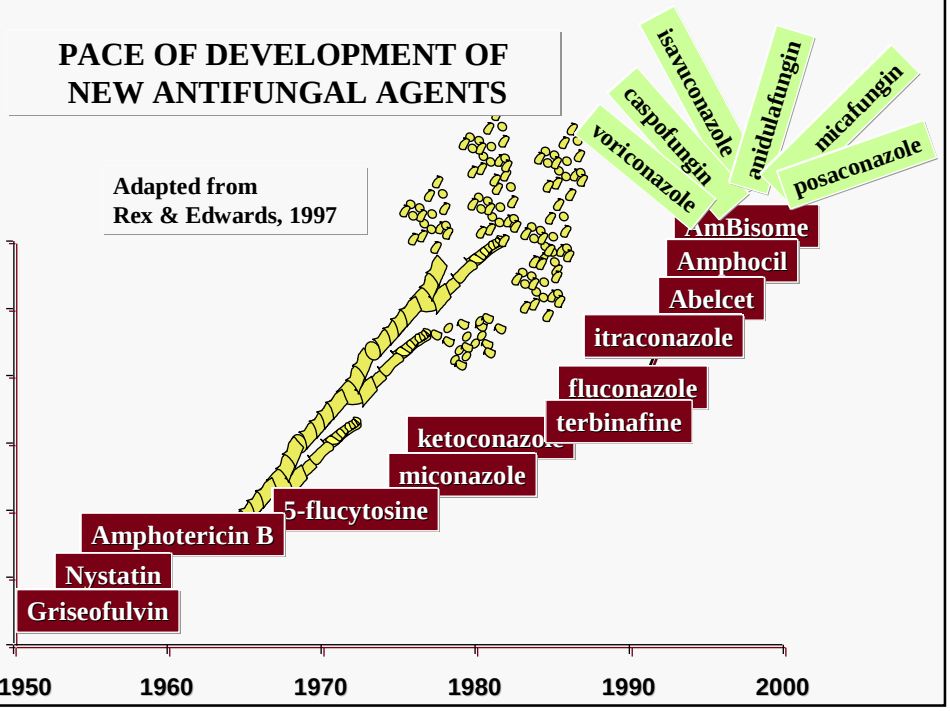
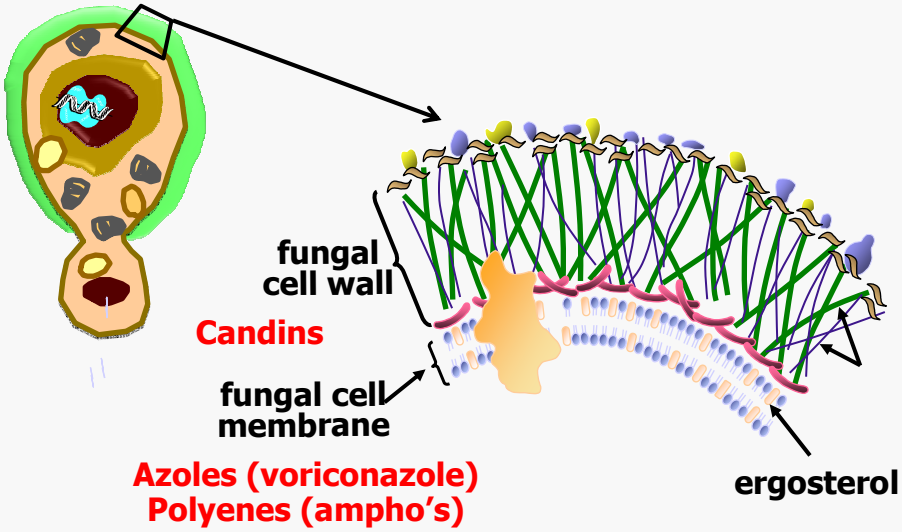
- ✓Final remarks

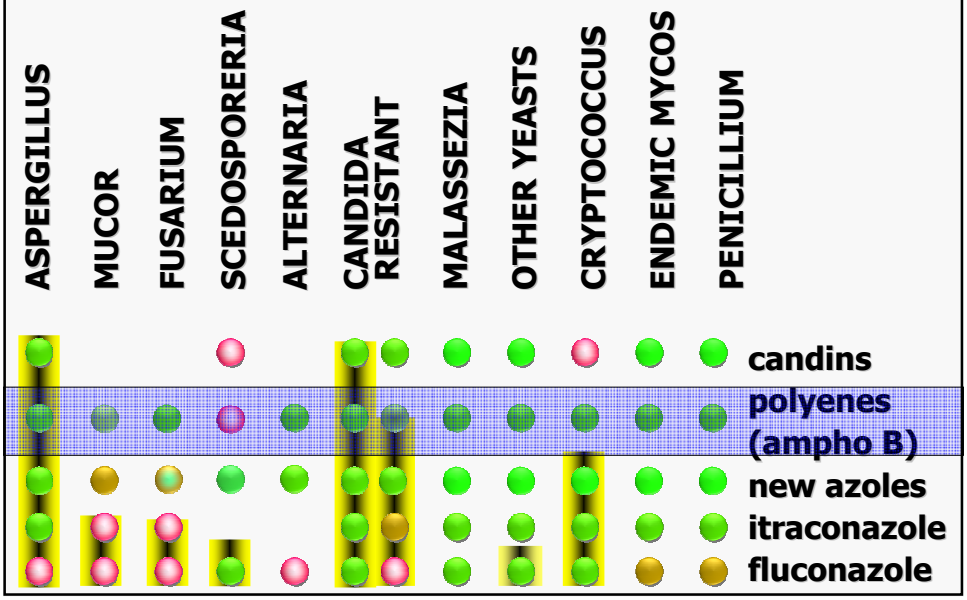
PACE OF DEVELOPMENT OF NEW ANTIFUNGAL AGENTS

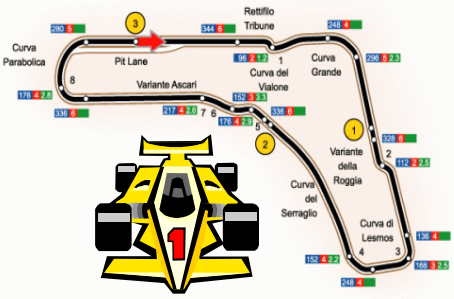


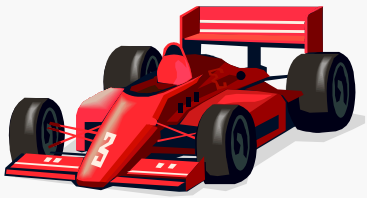
MECHANISMS OF ACTION



ACTIVITY ANTIFUNGALS

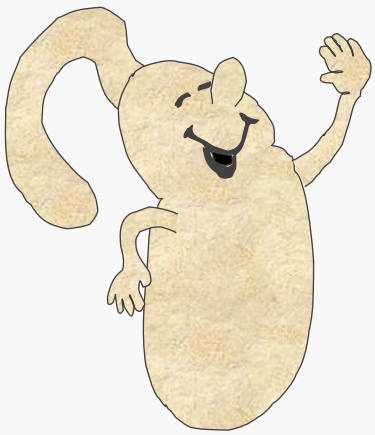




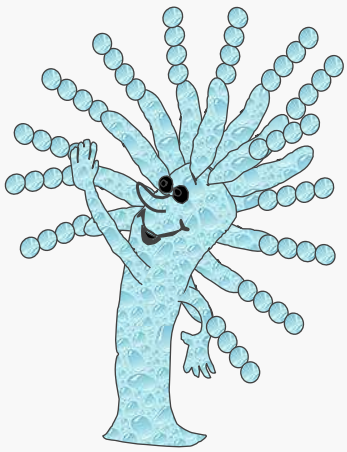


EFFICACY
versus
EFFICIENCY

WELCOME TO MYCOLOGY

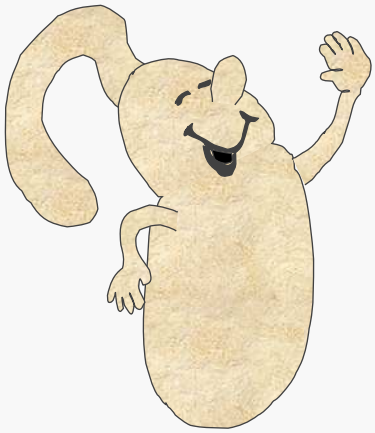


YEAST



MOULD

WELCOME TO MYCOLOGY



YEAST

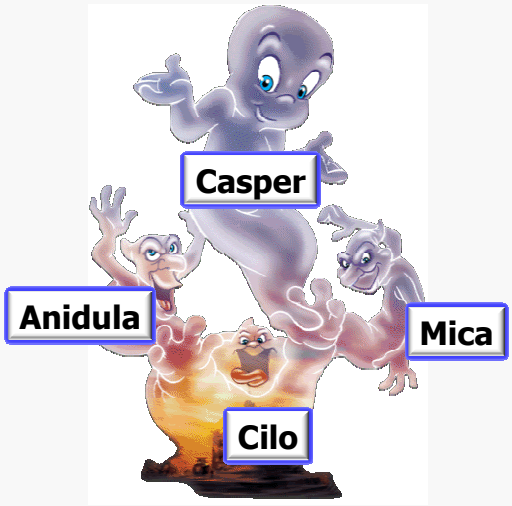
COMPARISON OF RESULTS FROM CLINICAL TRIALS ON CANDIDEMIA

	response	mortality
Fluconazole 400 mg/day	72%	39%
Amphotericin B	79%	40%
	62%	40%
	71%	34%

COMPARISON OF RESULTS FROM CLINICAL TRIALS ON CANDIDEMIA

	response	mortality
Fluconazole 400 mg/day	72%	39%
Amphotericin B	79%	40%
	62%	40%
	71%	34%
Voriconazole	65%	36%

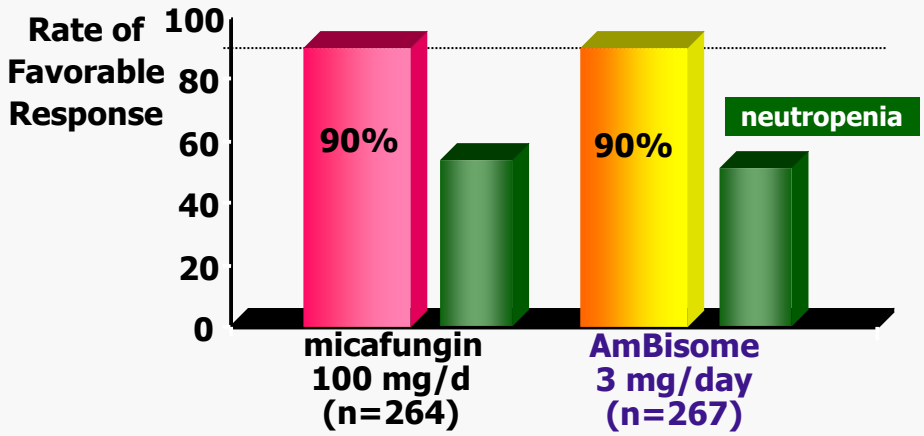
THE FUNGINS



MICAFUNGIN *vs* AMBISOME FOR CANDIDEMIA AND INVASIVE CANDIDOSIS

Kuse et al. Lancet 2007; 369:1519-1527

Double-blind comparison, n = 541



MICAFUNGIN *vs* AMBISOME FOR CANDIDEMIA AND INVASIVE CANDIDOSIS

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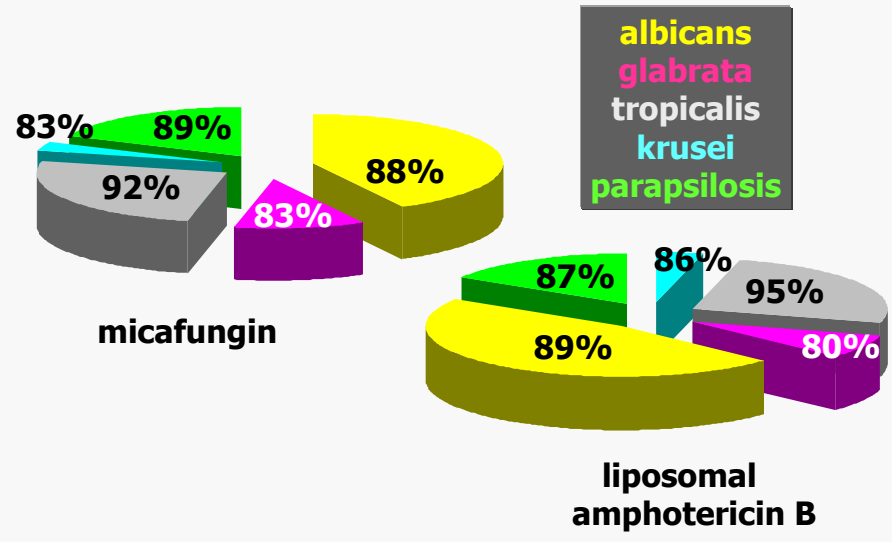
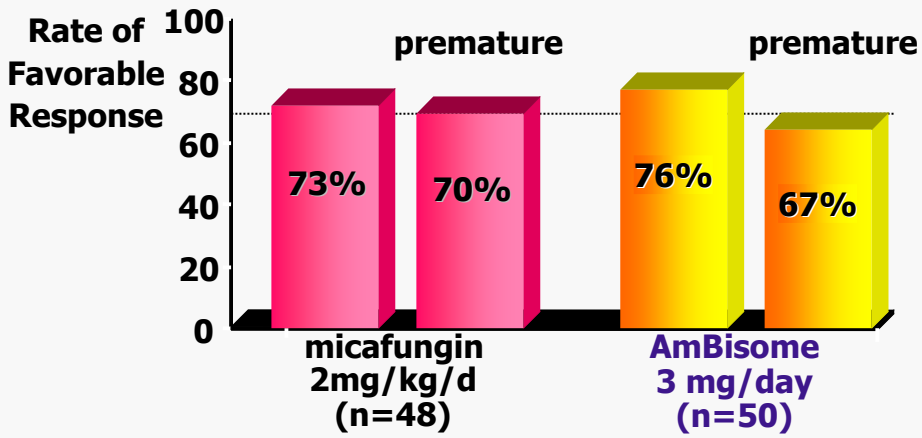


MICAFUNGIN versus AMBISOME IN CHILDREN WITH INVASIVE CANDIDOSIS

Queiroz-Telles et al. Pediatr Infect Dis J 2008;27:820-827

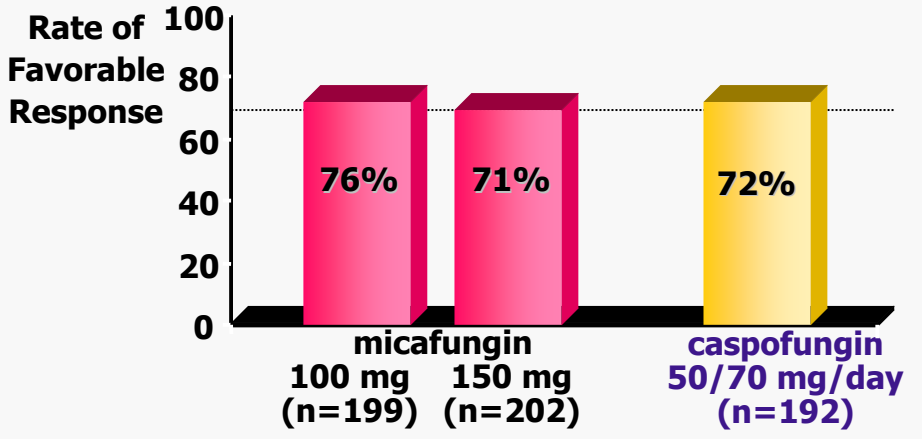
Double-blind comparison, n = 98



MICAFUNGIN versus CASPOFUNGIN FOR CANDIDEMIA AND INVASIVE CANDIDOSIS

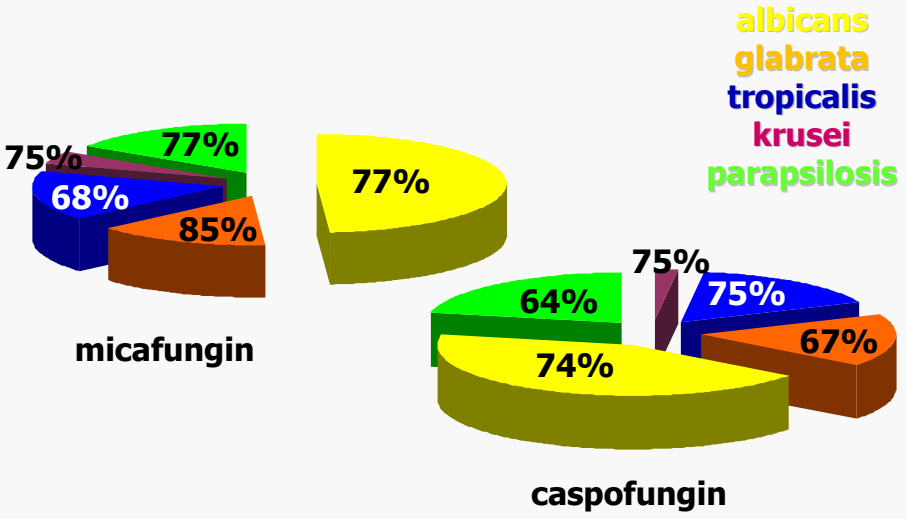
Pappas et al. Clin Infect Dis 2007; 45:883-893

Double-blind comparison, n = 593



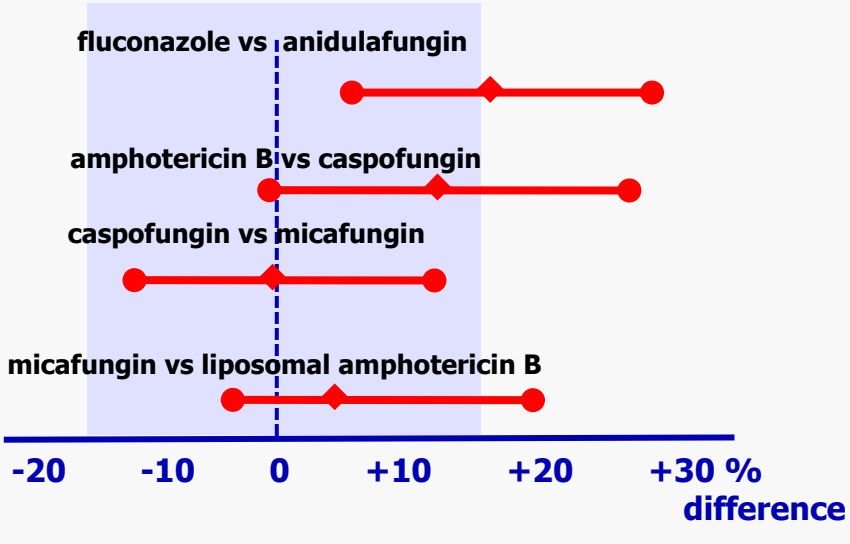
MICAFUNGIN versus CASPOFUNGIN FOR CANDIDIASIS – OUTCOME PER SPECIES

Pappas et al. Clin Infect Dis 2007; 45:883-893



ECHINOCANDINS FOR INVASIVE CANDIDIASIS

Glöckner et al. Mycoses 2009; 52:476-486



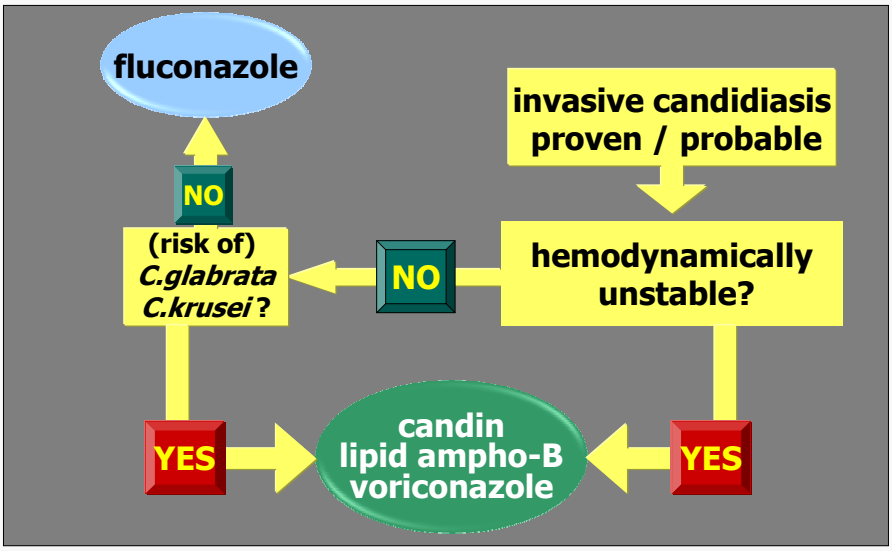
COMPARISON OF RESULTS FROM CLINICAL TRIALS ON CANDIDEMIA

	response	mortality
Fluconazole 400 mg/day	72%	39%
Amphotericin B	79%	40%
	62%	40%
	71%	34%
Micafungin	74%	
Caspofungin	74%	30%
Anidulafungin	76%	23%
Voriconazole	65%	36%

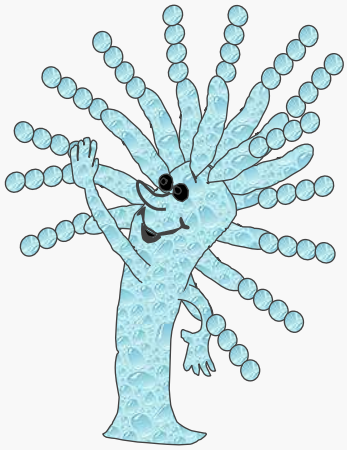
STRATEGY FOR THE TREATMENT OF DISSEMINATED CANDIDIASIS

IDSA

Pappas et al. Clin Infect Dis 2009; 48:503-535



WELCOME TO MYCOLOGY



MOULD

Peter Donnelly & Ben de Pauw

PROPHYLAXIS	EMPIRICAL THERAPY	THERAPY

POSA CONAZOLE

CASPO FUNGIN - LIPOSOMAL AMPHO B

VORI-CONAZOLE

ANTI-ASPERGILLUS DRUGS

INDICATION NOT RELEVANT !!!

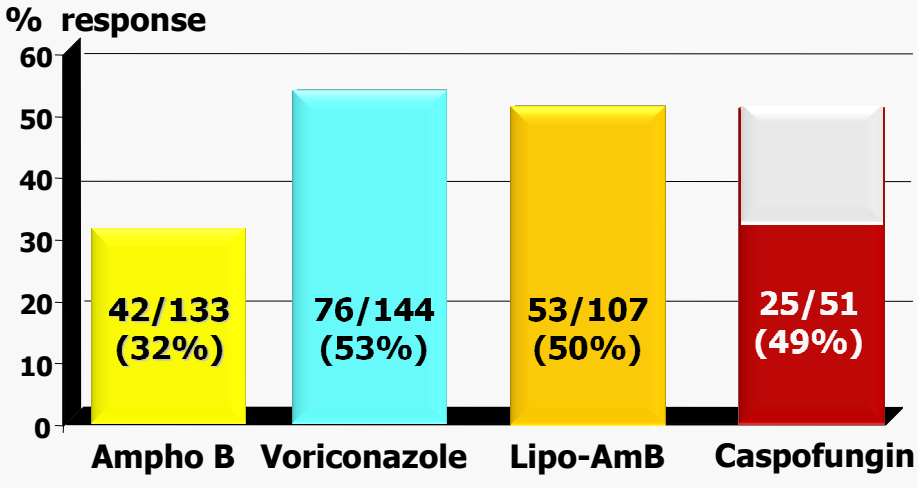
Selection criteria:

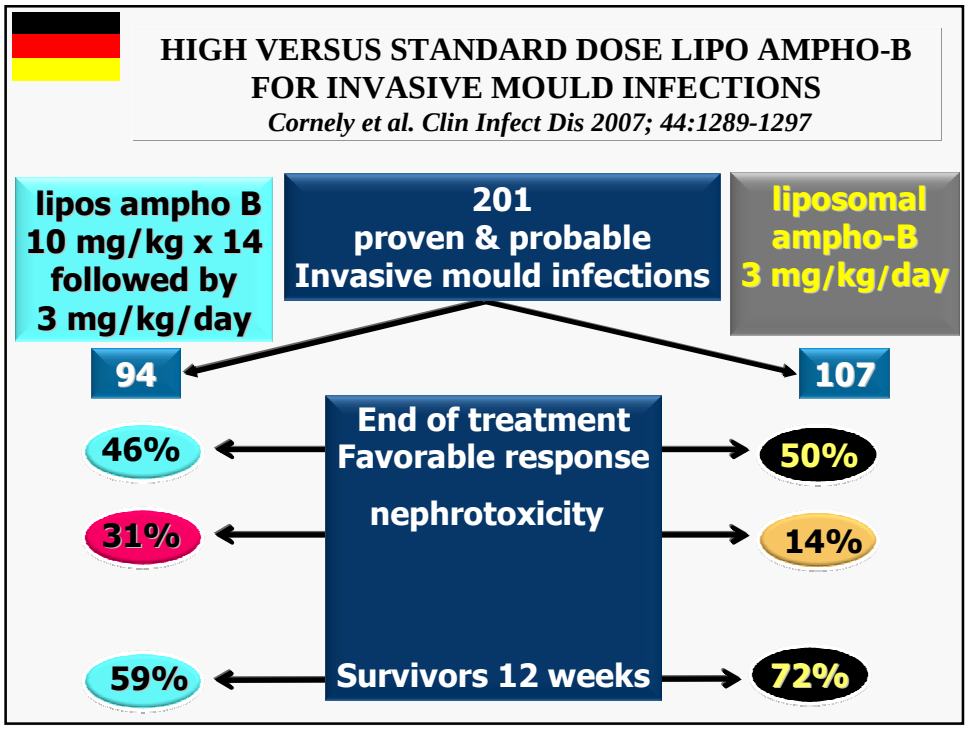
- **Established efficacy in proven disease**
- **Safety and compatibility / interaction**

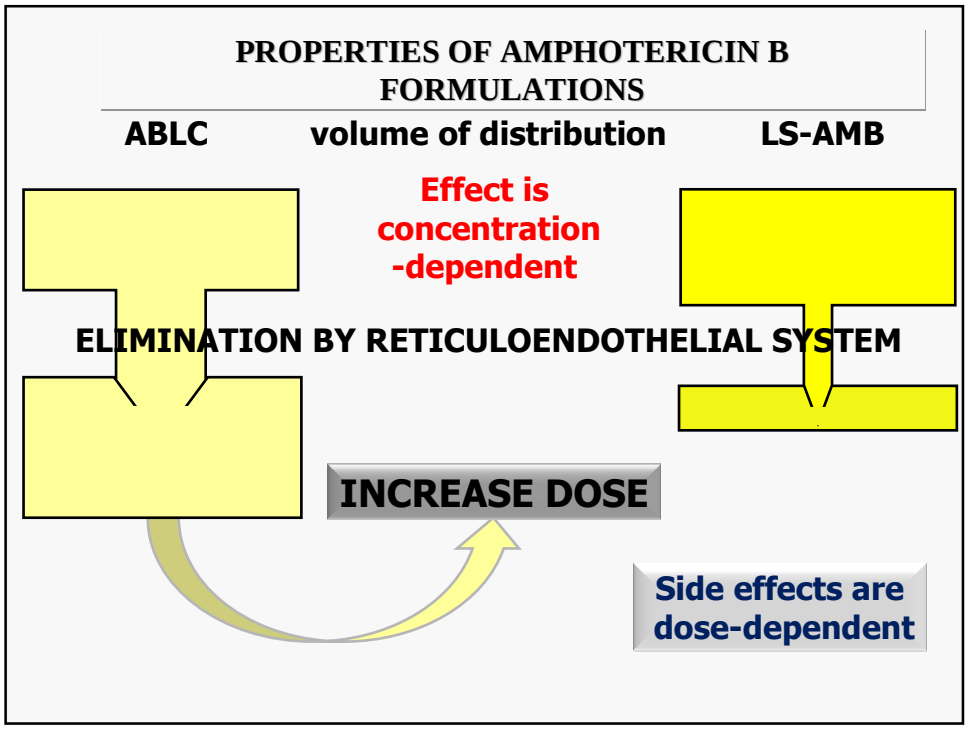
EORTC IFICG

RESULTS FIRST LINE TREATMENT OF INVASIVE ASPERGILLOSIS

Herbrecht et al N Engl J Med 2002; 347:408-415
Cornely et al. Clin Infect Dis 2007; 44:1289-1297
Viscoli et al. J Antimicrob Chemother 2009; 64:1274-1281



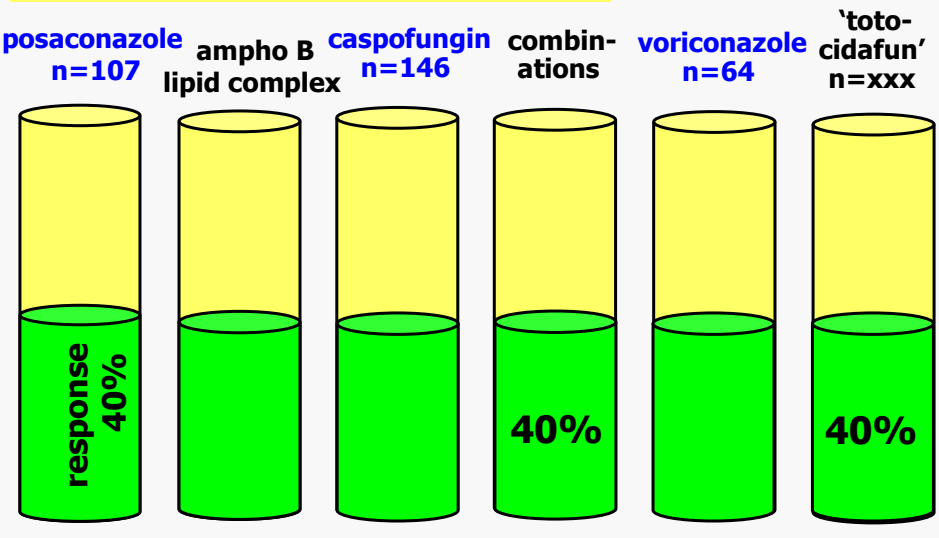

HIGH VERSUS STANDARD DOSE LIPO AMPHO-B FOR INVASIVE MOULD INFECTIONS
Cornely et al. Clin Infect Dis 2007; 44:1289-1297
lipos ampho B 10 mg/kg x 14 followed by 3 mg/kg/day
201 proven & probable Invasive mould infections
liposomal ampho-B 3 mg/kg/day
94
107
End of treatment Favorable response
46%
50%
nephrotoxicity
31%
14%
Survivors 12 weeks
59%
72%


PROPERTIES OF AMPHOTERICIN B FORMULATIONS
ABLC
volume of distribution
LS-AMB
Effect is concentration -dependent
ELIMINATION BY RETICULOENDOTHELIAL SYSTEM
INCREASE DOSE
Side effects are dose-dependent

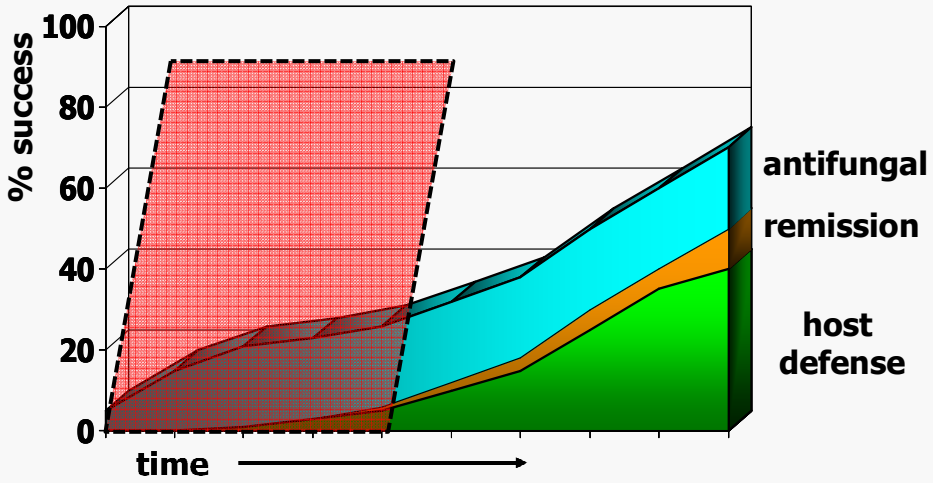
ABELCET - POSACONAZOLE
TRIALS FIRST LINE TREATMENT ASPERGILLOSIS

SALVAGE FOR INVASIVE ASPERGILLOSIS

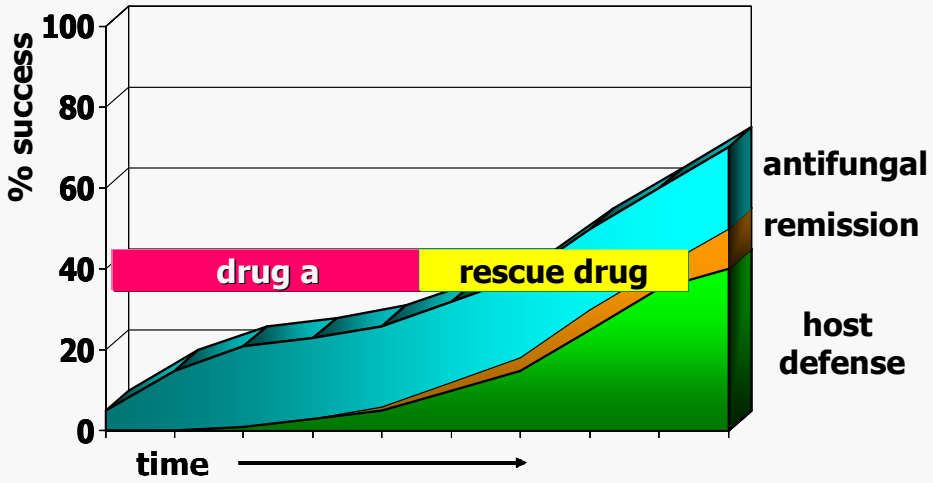
Refractory / intolerant amphotericin B



EVOLUTION OF ELEMENTS DETERMINING SUCCESS OR FAILURE

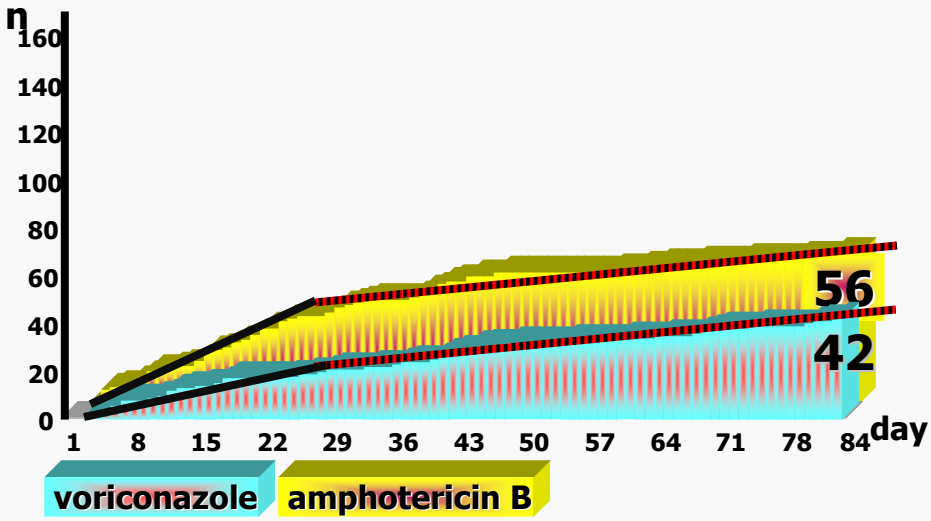


CONSIDERATIONS ON THE EXPLORATION OF 'RESCUE' THERAPY



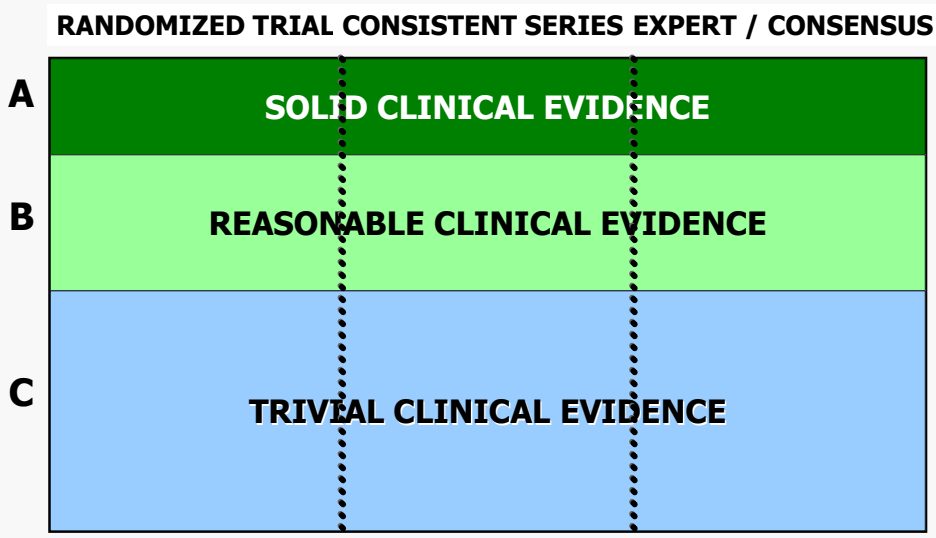
VORICONAZOLE VERSUS AMPHOTERICIN B FOR INVASIVE ASPERGILLOSIS: MORTALITY OVER TIME

Herbrecht et al N Engl J Med 2002; 347:408-15

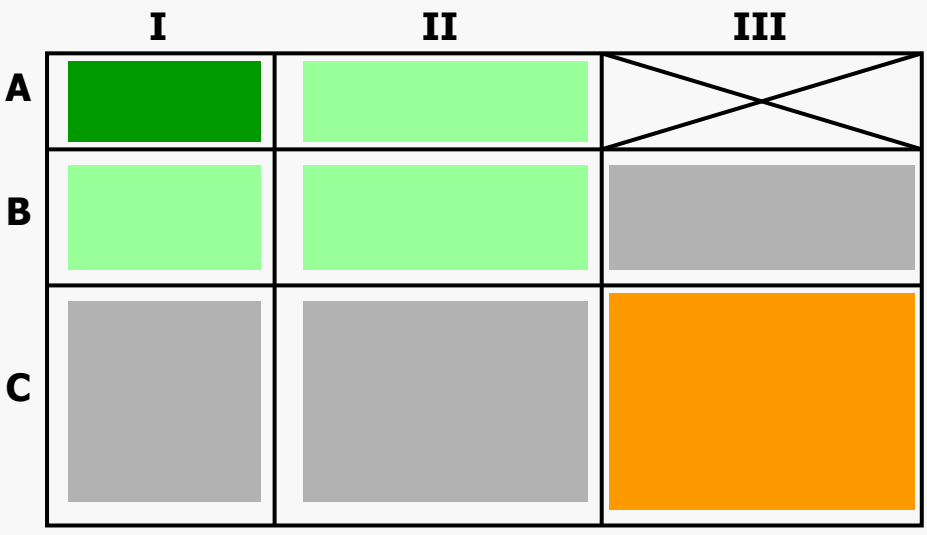


HAPPY WITH GUIDELINES?

RECOMMENDATIONS



RECOMMENDATIONS



GUIDELINES ON ANTI-ASPERGILLUS DRUGS

DRUGS:	USA:	UK:	ECIL:	AUS:	ITA:
➢ Desoxy AmB	D	D	D	AII	D
➢ LS-AMB	AI	AI	BI	BI	AI
➢ ABLC	-	-	BII	BII	-
➢ ABCD	-	-	D	BIII	-
➢ Itraconazole	-	-	CIII	-	-
➢ Voriconazole	AI	AI	AI	AI	AI
➢ Posaconazole	-	-	-	-	-
➢ Caspofungin	-	AI	CII	BII	-

GUIDELINES ON ANTI-ASPERGILLUS DRUGS

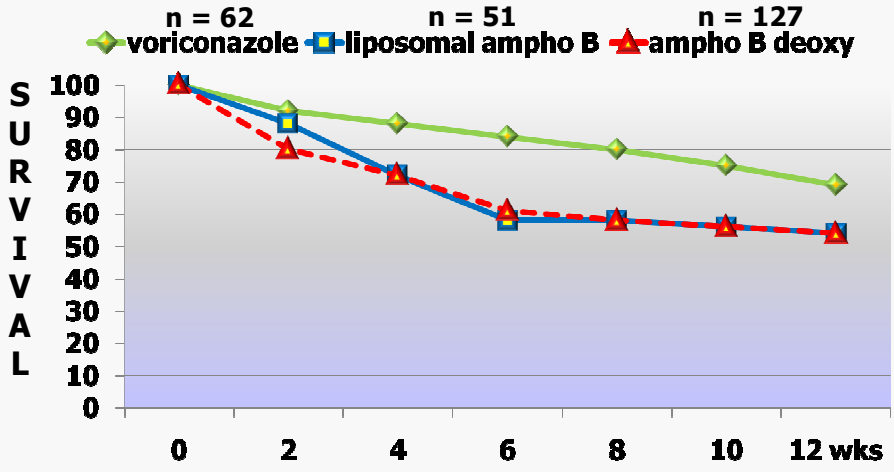
DRUGS:	USA:	UK:	ECIL:	AUS:	ITA:	MINE:
➢ Desoxy AmB	D	D	D	AII	D	D
➢ LS-AMB	AI	AI	BI	BI	AI	AII
➢ ABLC	-	-	BII	BII	-	D/BII
➢ ABCD	-	-	D	BIII	-	D
➢ Itraconazole	-	-	CIII	-	-	BII
➢ Voriconazole	AI	AI	AI	AI	AI	AI
➢ Posaconazole	-	-	-	-	-	D
➢ Caspofungin	-	AI	CII	BII	-	BII

WE ARE HERE FROM THE GOVERNMENT TO HELP YOU…

OUTCOME OF ASPERGILLOSIS IN RELATION TO INITIAL ANTIFUNGAL THERAPY

Nivoix, Y et al. Clin Infect Dis 2008; 47:1176-1184

n = 289

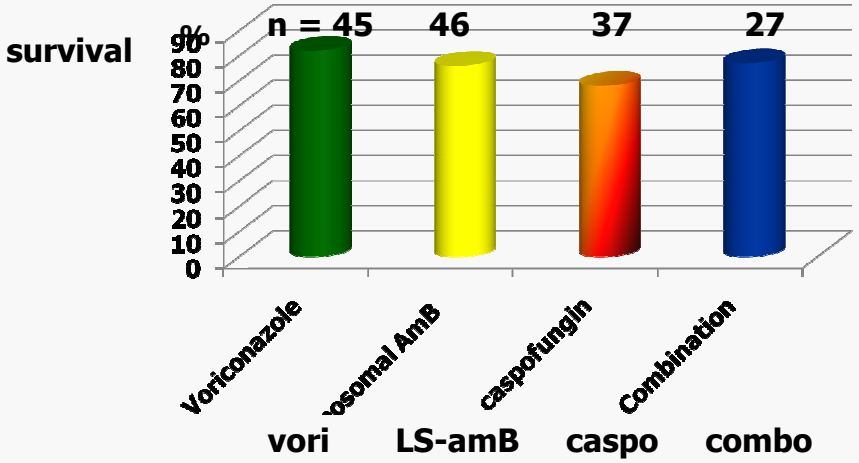


OUTCOME OF THERAPY FOR ASPERGILLOSIS ARISING DURING AML IN DAILY PRACTICE

Pagano et al. SEIFEM 2008

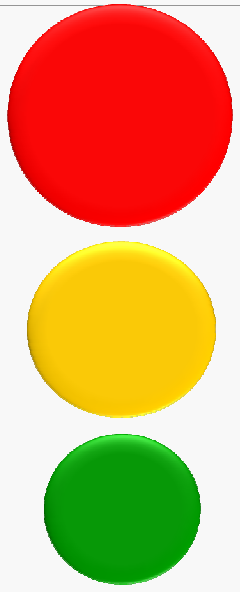
140 probable/proven cases

First line therapy



EORTC IFICG

LIMITS TO VORICONAZOLE: INTERACTIONS AND ADVERSE EVENTS



Visual effects

Hallucinations

Liver toxicity

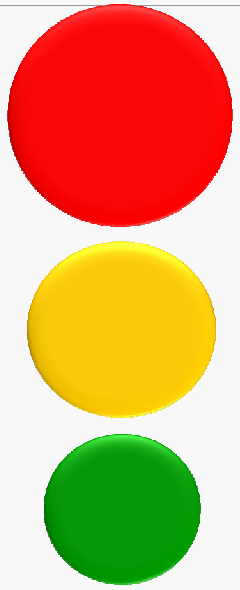
Nausea

Allergy

EORTC
IFICG

LIMITS TO VORICONAZOLE: INTERACTIONS AND ADVERSE EVENTS

-warfarin
-cyclosporin
-tacrolimus
-sulphonureas
-statins
-benzodiazepines
-vinca alkaloids
-sirolimus
-rifabutin
-rifampicin
-terfenadine



Visual effects

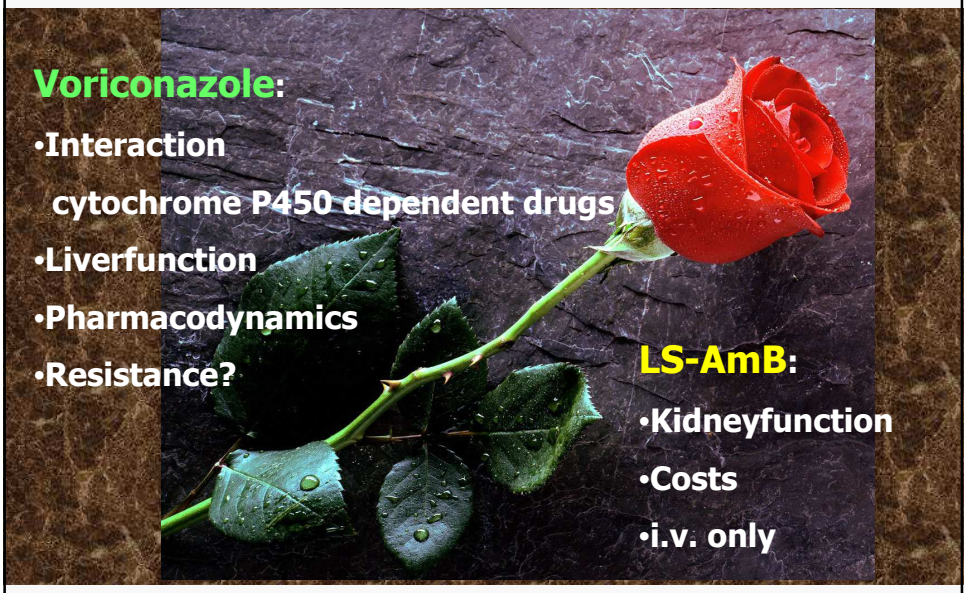
Hallucinations

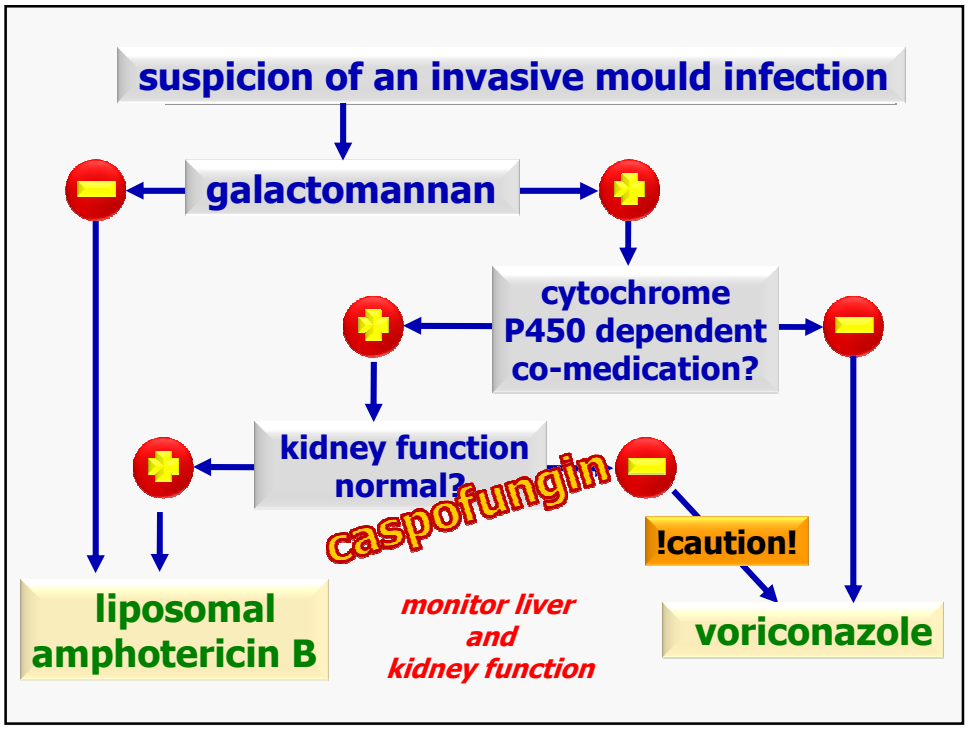
Liver toxicity

Nausea

Allergy

LIMITS TO THE USE OF PREFERRED DRUGS INTERACTIONS AND ADVERSE EVENTS





OUTLINE OF THE PRESENTATION

- ✓Introduction
- ✓Role of a fungus in nature
- ✓Pathophysiology of fungal disease
- ✓Options and limitations of antifungals
- ✓Strategic choices
- ✓Side reflections
- ✓Final remarks

OUTLINE OF THE PRESENTATION

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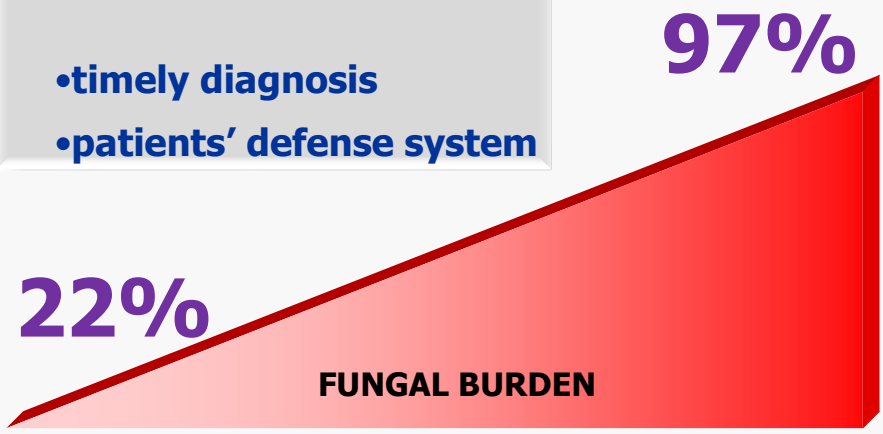
- ✓**Strategic choices**
- ✓Side reflections
- ✓Final remarks

MORTALITY IN RELATION TO THE FUNGAL BURDEN

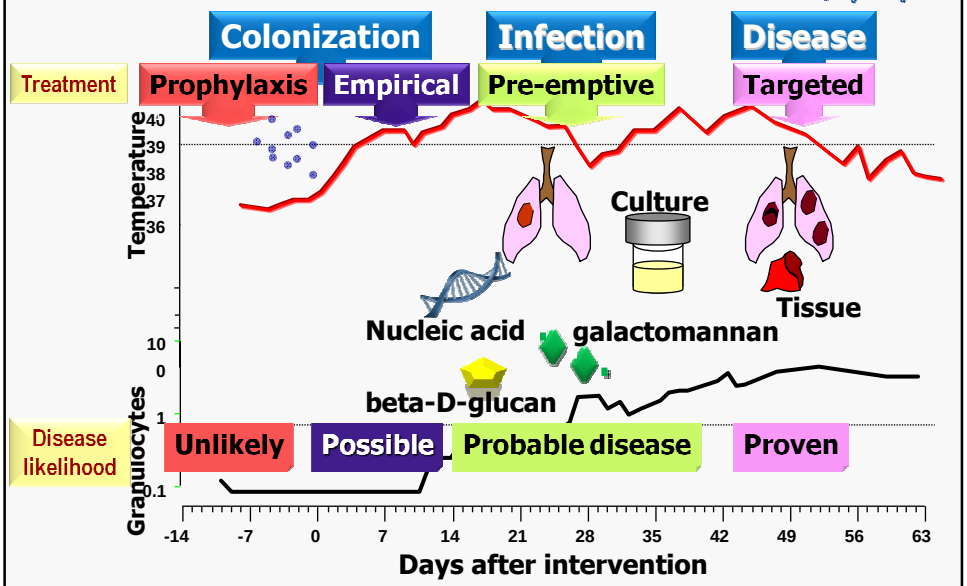
Variation due to:

- **timely diagnosis**
- **patients' defense system**



THERAPEUTIC STRATEGIES

Peter Donnelly & Ben dePauw



PATTERNS OF INVASIVE FUNGAL DISEASE

Donnelly 2010

Radiological signs & clinical symptoms
Mycology results
Proof of IFD
Proof of IFI

PATTERNS OF INVASIVE FUNGAL DISEASE

Donnelly 2010

Radiological signs & clinical symptoms	No
Mycology results	Negative
Proof of IFD	No
Proof of IFI	No

PATTERNS OF INVASIVE FUNGAL DISEASE

Donnelly 2010

Radiological signs & clinical symptoms	No	Persistent febrile neutropenia
Mycology results	Negative	Negative
Proof of IFD	No	No
Proof of IFI	No	No

PATTERNS OF INVASIVE FUNGAL DISEASE

Donnelly 2010

Radiological signs & clinical symptoms	No	Persistent febrile neutropenia	No
Mycology results	Negative	Negative	Positive bio-marker
Proof of IFD	No	No	No
Proof of IFI	No	No	Yes

PATTERNS OF INVASIVE FUNGAL DISEASE

Donnelly 2010

Radiological signs & clinical symptoms	No	Persistent febrile neutropenia	No	Clinical symptoms
Mycology results	Negative	Negative	Positive bio-marker	Negative
Proof of IFD	No	No	No	No
Proof of IFI	No	No	Yes	No

PATTERNS OF INVASIVE FUNGAL DISEASE

Donnelly 2010

Radiological signs & clinical symptoms	No	Persistent febrile neutropenia	No	Clinical symptoms	Radio-logical signs
Mycology results	Negative	Negative	Positive bio-marker	Negative	Negative
Proof of IFD	No	No	No	No	Yes
Proof of IFI	No	No	Yes	No	No

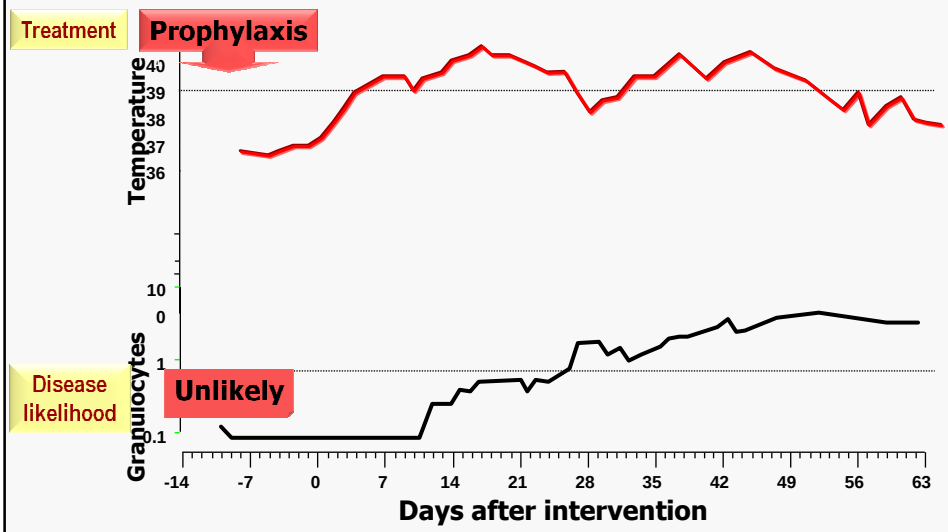
PATTERNS OF INVASIVE FUNGAL DISEASE

Donnelly 2010

Radiological signs & clinical symptoms	No	Persistent febrile neutropenia	No	Clinical symptoms	Radio-logical signs	Radio-logical signs and/or symptoms
Mycology results	Negative	Negative	Positive bio-marker	Negative	Negative	Positive Biomarker or microscopy or culture
Proof of IFD	No	No	No	No	Yes	Yes
Proof of IFI	No	No	Yes	No	No	Yes

THERAPEUTIC STRATEGIES

Peter Donnelly & Ben dePauw



PATTERNS OF INVASIVE FUNGAL DISEASE

Donnelly 2010

	Prophylaxis					
Radiologic signs & clinical symptoms	No	Persistent febrile neutropenia	No	Clinical symptoms	Radio-logical signs	Radio-logical signs and/or symptoms
Mycology results	Negative	Negative	Positive bio-marker	Negative	Negative	Positive Biomarker or microscopy or culture
Proof of IF	No	No	No	No	Yes	Yes
Proof of IF	No	No	Yes	No	No	Yes

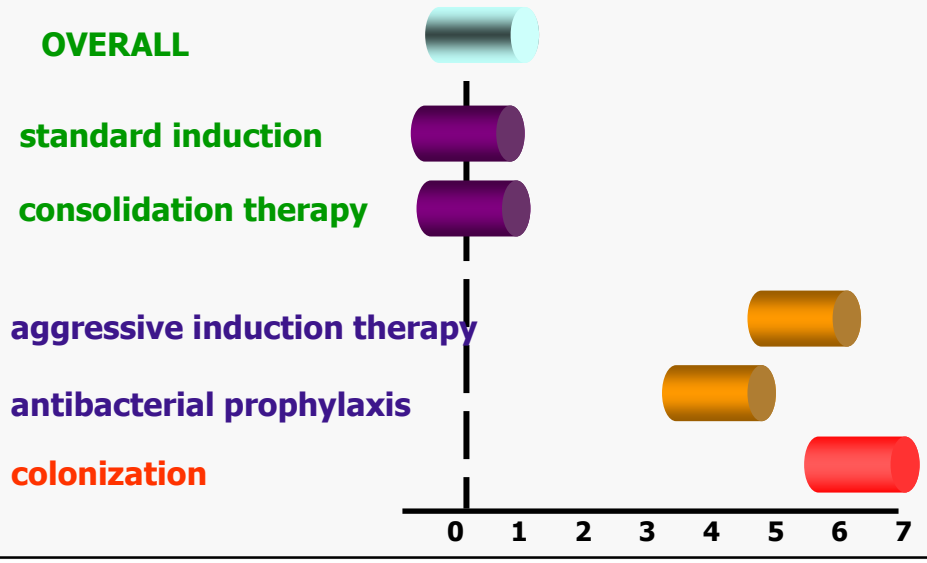
PROPHYLAXIS WITH FLUCONAZOLE IN BONE MARROW TRANSPLANTATION

Goodman et al. N Engl J Med 1992; 326: 845

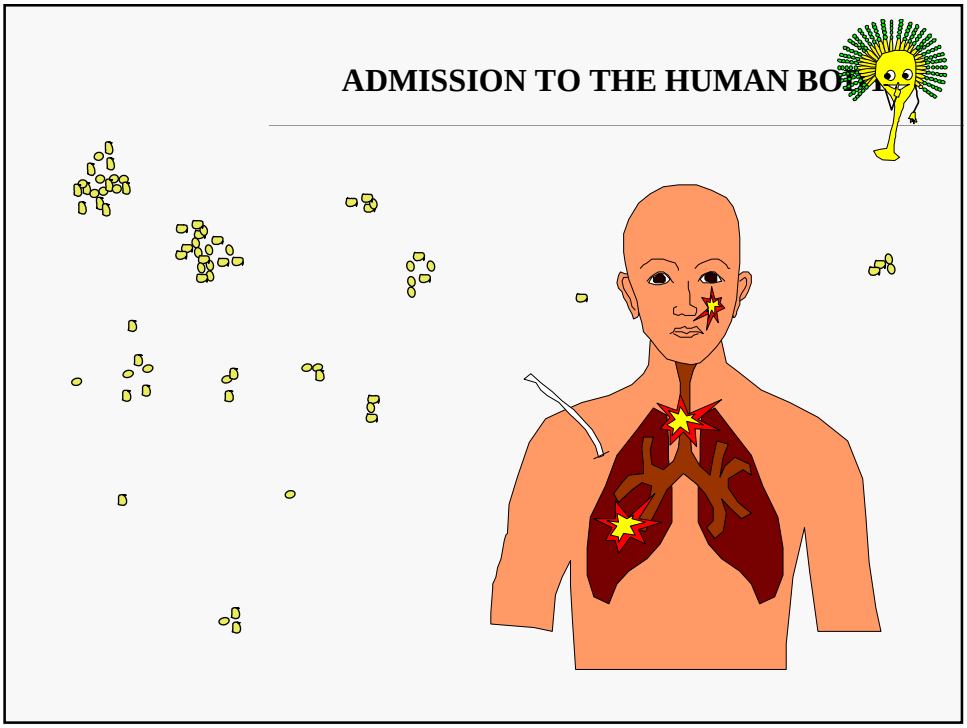
	FLUCONAZOLE n = 179	PLACEBO n = 177
INVASIVE FUNGUS	3%	16%
CANDIDIASIS	0%	10%
SUPERFICIAL	8%	33%
FATAL FUNGUS	1%	6%

GROUPS BENEFITTING FROM FLUCONAZOLE PROPHYLAXIS IN NEUTROPENIA

Rotstein et al. Clin Infect Dis 1999;28:331

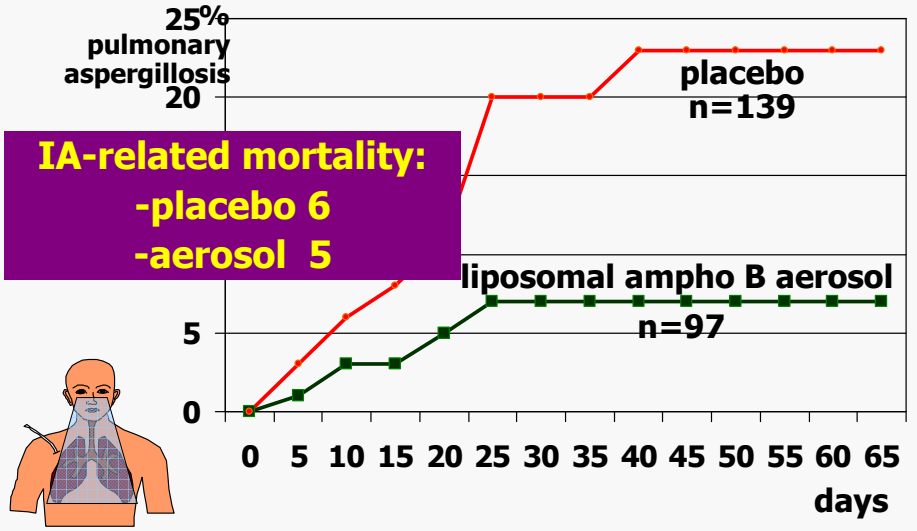


ADMISSION TO THE HUMAN BO



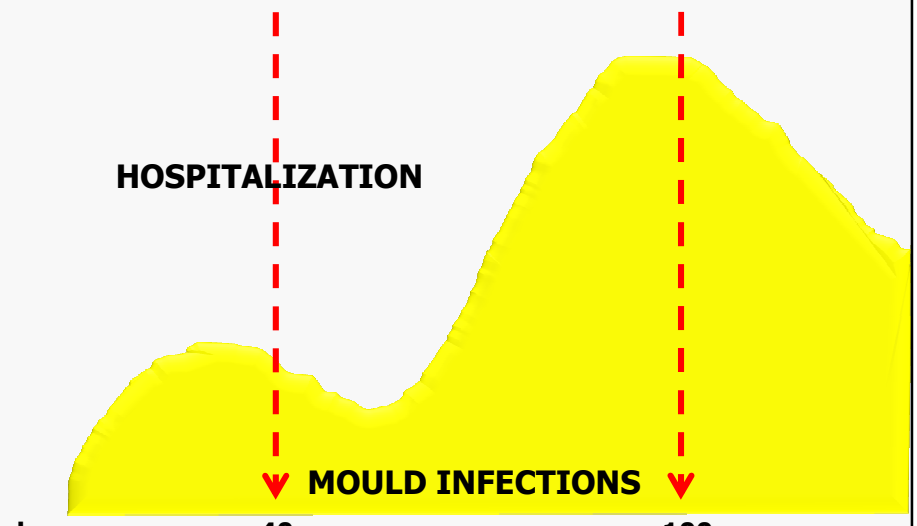
AEROSOLISED LIPOSOMAL AMPHO-B TO PREVENT INVASIVE ASPERGILLOSIS

Rijnders et al. Clin Infect Dis 2008; 46:1409-1411



IA-related mortality:
-placebo 6
-aerosol 5

OCCURRENCE INVASIVE MOULDS AFTER BONE MARROW TRANSPLANT



POSACONAZOLE vs FLU AS PROPHYLAXIS IN ALLO STEM CELL TRANSPLANTATION

Ullmann et al. N Engl J Med 2007; 356:335-347

allo HSCT, double-blind 16 weeks

	FLUCONAZOLE 400 mg/day iv/po n = 299	POSACONAZOLE 200 mg/day tid n = 301
INVASIVE FUNGUS	7%	2%
ASPERGILLOSIS	6%	1%
FATAL FUNGUS	4%	1%
OVERALL MORTALITY	28%	25%
ADVERSE EVENTS	38%	36%

POSACONAZOLE vs AZOLES AS PROPHYLAXIS IN MYELOID MALIGNANCIES

Cornely et al. N Engl J Med 2007; 356:348-359

Randomized; NOT BLINDED AML, MDS 12 weeks

	AZOLES 400 mg/day iv/po n = 298	POSACONAZOLE 200 mg/day tid n = 304
INVASIVE FUNGUS	8%	2%
ASPERGILLOSIS	7%	1%
FATAL FUNGUS	5%	2%
OVERALL MORTALITY	22%	16%
ADVERSE EVENTS	2%	6%

POSACONAZOLE ASPERGILLOSIS PROPHYLAXIS STUDIES

Cornely et al - Ullmann et al. N Engl J Med 2007

	COMPARATOR	POSACONAZOLE
CORNELY		
FATAL FUNGUS	5%	2%
ULLMANN		
FATAL FUNGUS	4%	1%

INADEQUATE DIAGNOSTICS FOR FATAL ASPERGILLOSIS

- **NO AUTOPSIES!!**

TRIAL BIAS 'OVERALL' MORTALITY?

- **DIFFERENCE IN NON-BLINDED STUDY ONLY!**

VORICONAZOLE vs FLUCONAZOLE AS PROPHYLAXIS IN BONE MARROW TRANSPLANTS

Wingard et al. Blood 2010; 116:5111-5118

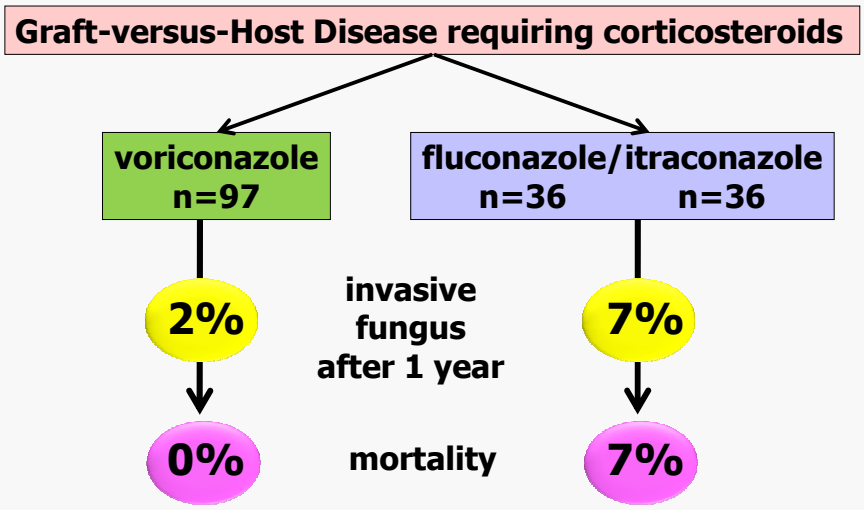
Double-blind, randomized, high-risk 180 days, others 100

	FLUCONAZOLE 400 mg/day n = 295	VORICONAZOLE 200 mg/day tid n = 305
INVASIVE FUNGUS	11%	7%
ASPERGILLOSIS	5%	2%
FATAL FUNGUS	NA	NA
OVERALL MORTALITY	25%	22%

VORICONAZOLE AS PROPHYLAXIS IN CORTICOSTEROID-TREATED GVHD

Gregis et al. Bone Marrow Transpl 2010;45: 662-667

Retrospective analysis



PATTERNS OF INVASIVE FUNGAL DISEASE

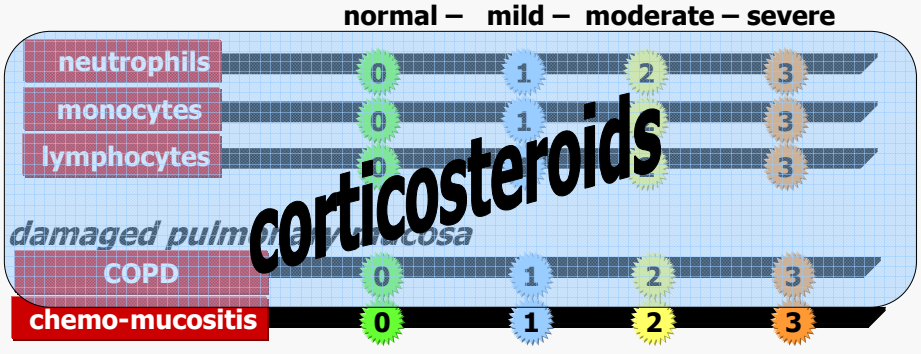
Donnelly 2010

	Prophylaxis					
Radiological signs & clinical symptoms	High risk of IFD	Persistent febrile neutropenia	No	Clinical symptoms	Radio-logical signs	Radio-logical signs and/or symptoms
Mycology results	Negative	Negative	Positive bio-marker	Negative	Negative	Positive Biomarker or microscopy or culture
Proof of IFD	No	No	No	No	Yes	Yes
Proof of IFI	No	No	Yes	No	No	Yes

RATING THE NEED FOR *ASPERGILLUS* PROPHYLAXIS

impaired function immunocompetent cells

normal – mild – moderate – severe

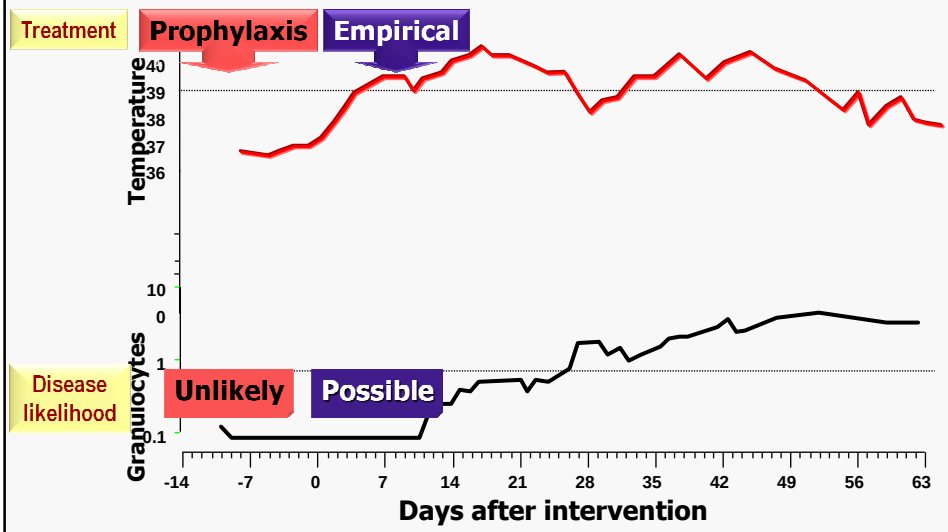


high exposure

- building activity
- agricultural
- green waste bins

THERAPEUTIC STRATEGIES

Peter Donnelly & Ben dePauw



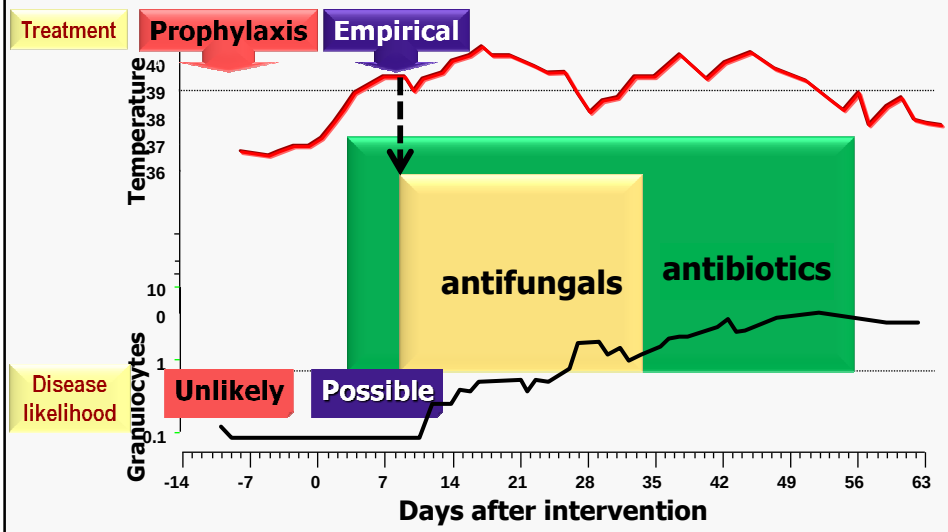
PATTERNS OF INVASIVE FUNGAL DISEASE

Donnelly 2010

		Empirical				
Radiological signs & clinical symptoms	No	Persistent febrile neutropenia	No	Clinical symptoms	Radio-logical signs	Radio-logical signs and/or symptoms
Mycology results	Negativ	Negative	ositive bio-arker	Negative	Negative	Positive Biomarker or microscopy or culture
Proof of IFD	No	No	No	No	Yes	Yes
Proof of IFI	No	No	Yes	No	No	Yes

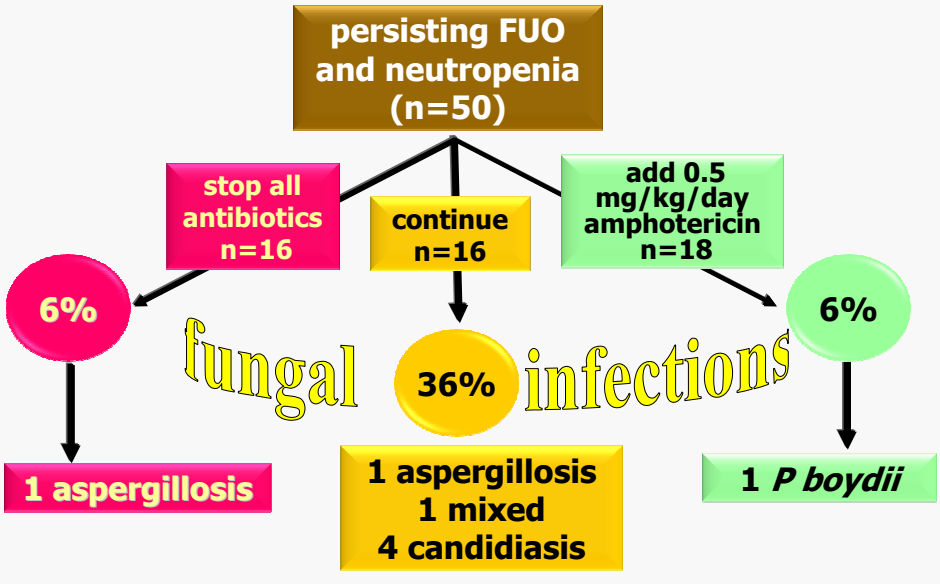
THERAPEUTIC STRATEGIES

Peter Donnelly & Ben dePauw

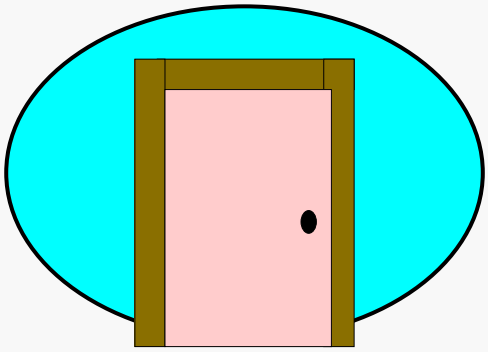


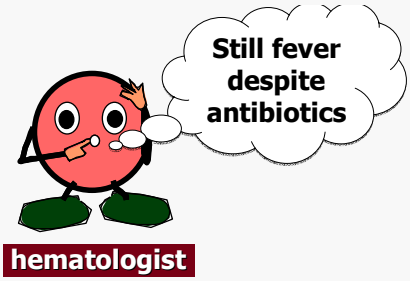
THE BASIS FOR EMPIRIC ANTIFUNGAL THERAPY IN FEBRILE NEUTROPENICS

Pizzo et al. Am J Med 1982; 72:101-110

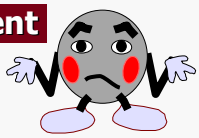


LABORATORY OR PHARMACY ?



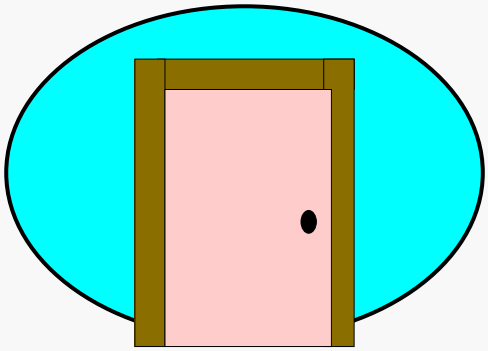


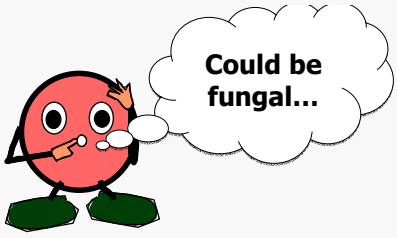
patient



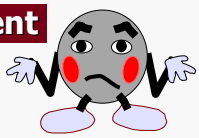
hematologist

LABORATORY OR PHARMACY ?



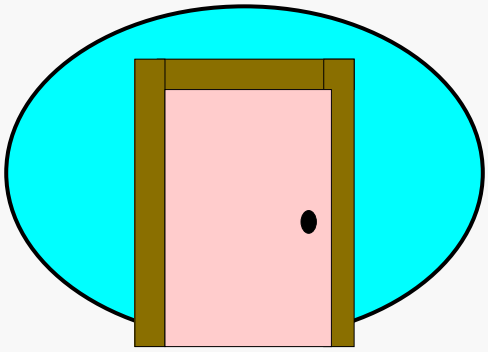


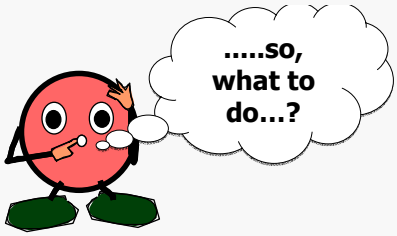
patient



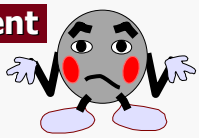
hematologist

LABORATORY OR PHARMACY ?



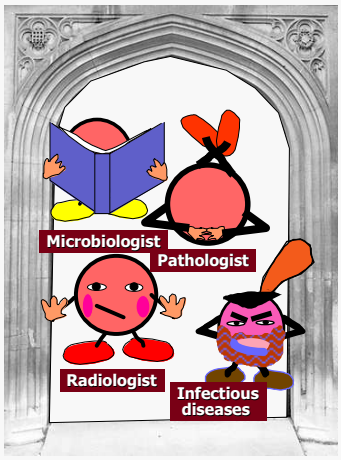


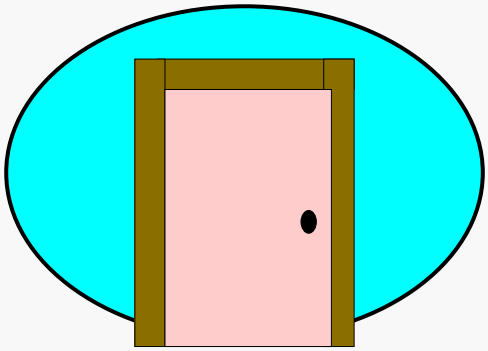
patient

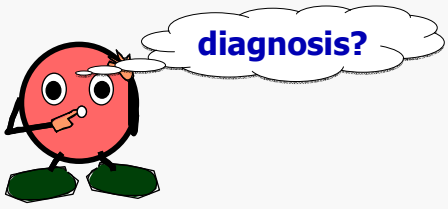


hematologist

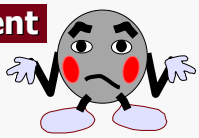
LABORATORY OR PHARMACY ?







patient



hematologist

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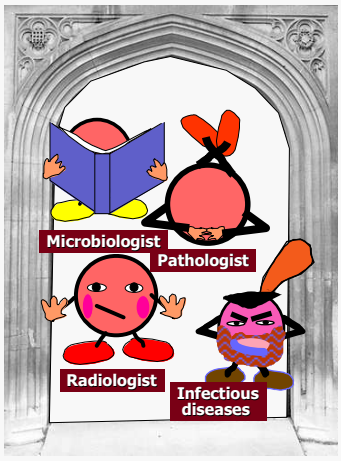
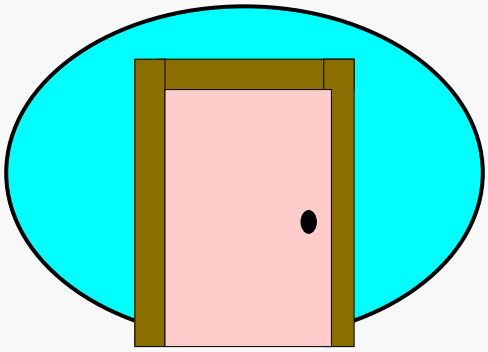
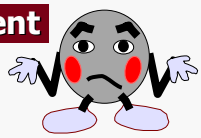




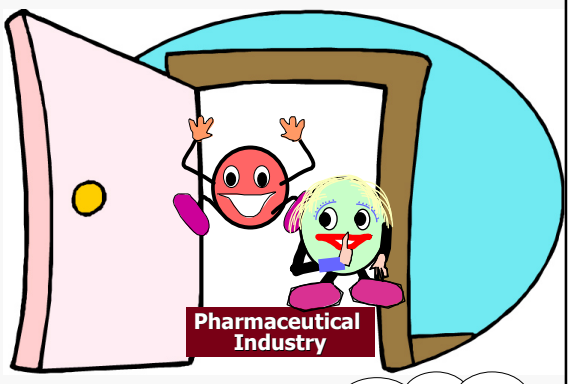
...or empirical antifungals? ??

patient



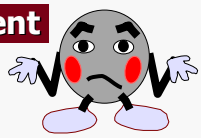
hematologist

LABORATORY OR PHARMACY ?



..or empirical antifungals? ??

patient

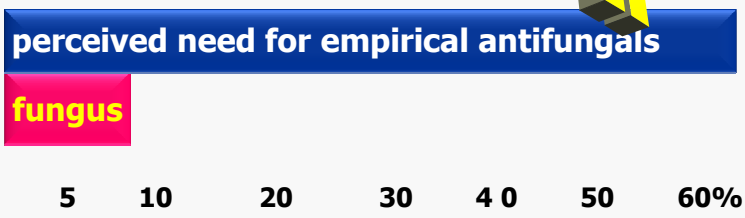


hematologist

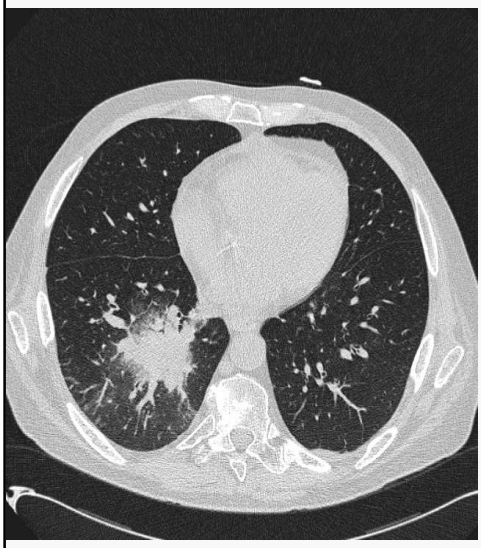
PERCEIVED NEED FOR PARENTERAL AMPHOTERICIN-B AFTER [illegible]LAXIS IN NEUTROPENIC PATIENTS

FEAR FACTOR

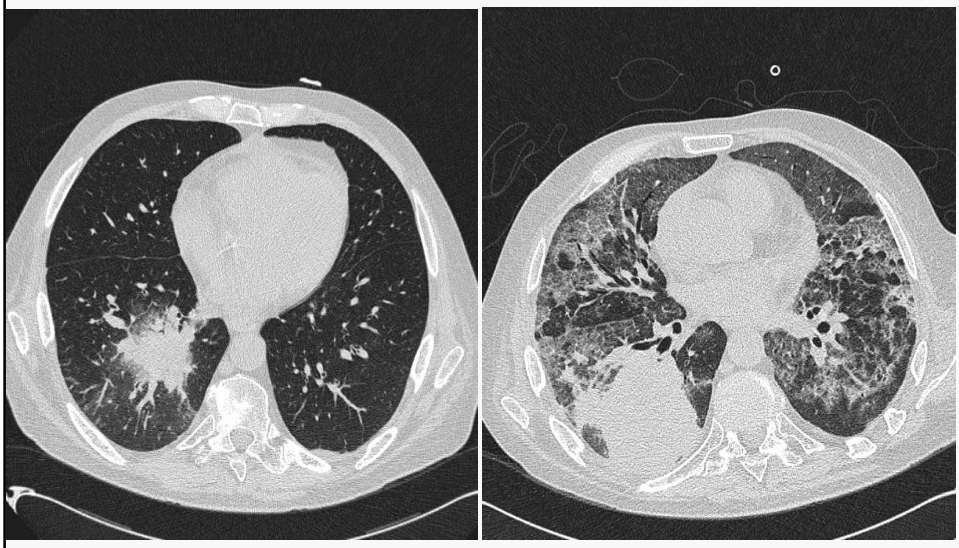
>90% no disease



FUNGAL INFILTRATE



ONE WEEK LATER….



PATTERNS OF INVASIVE FUNGAL DISEASE

Donnelly 2010

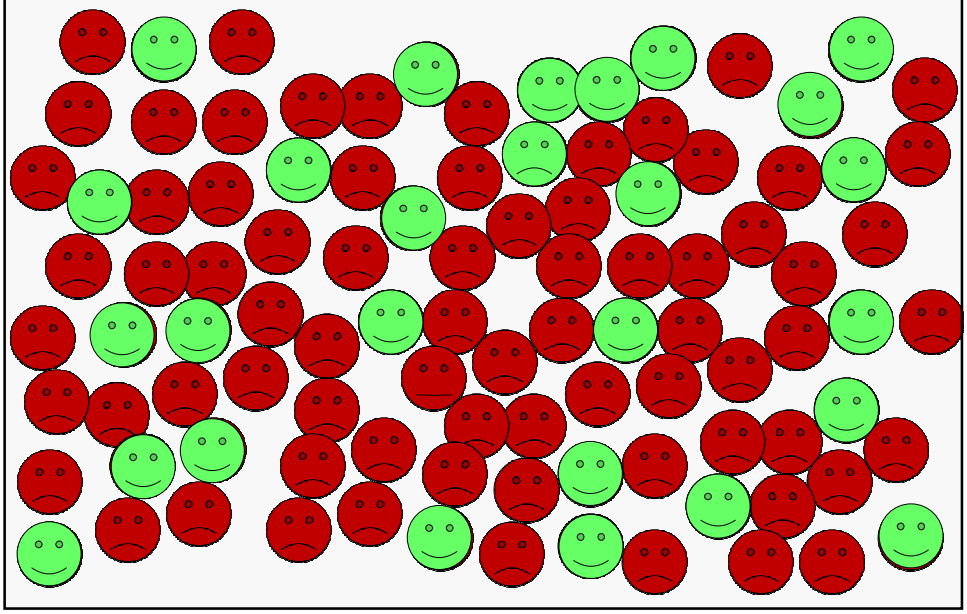
		Empirical				
Radiological signs & clinical symptoms	No	Persistent febrile neutropenia	No	Clinical symptoms	Radio-logical signs	Radio-logical signs and/or symptoms
Mycology results	Negative	Unable to exclude IFD	Positive bio-marker	Negative	Negative	Positive Biomarker or microscopy or culture
Proof of IFD	No	Short course to buy time to diagnose	No	No	Yes	Yes
Proof of IFI	No		Yes	No	No	Yes

EMPIRICAL THERAPY

- Prolonged, profound neutropenia
- Persisting fever of uncertain origin refractory to broad-spectrum antibiotic treatment
- Invasive fungal disease cannot be ruled out

High-risk, febrile but no evidence of IFD

INCIDENCE AND INTENTION

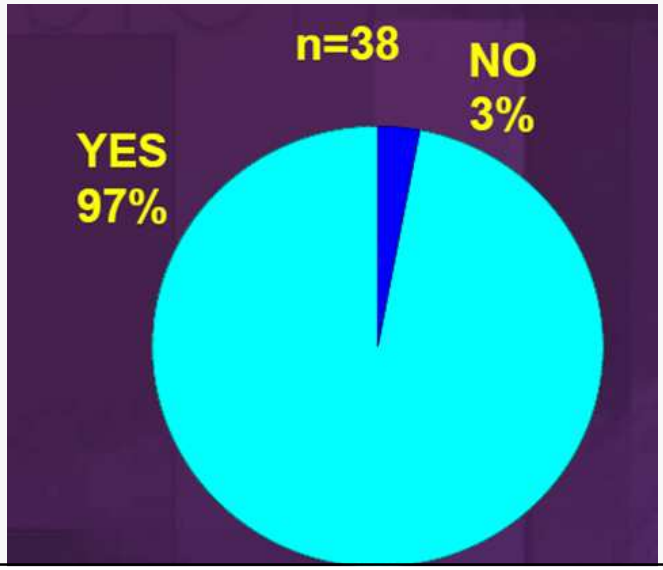


Indication for Empirical Antifungal Therapy in Persistently Febrile Neutropenic Patients

B II

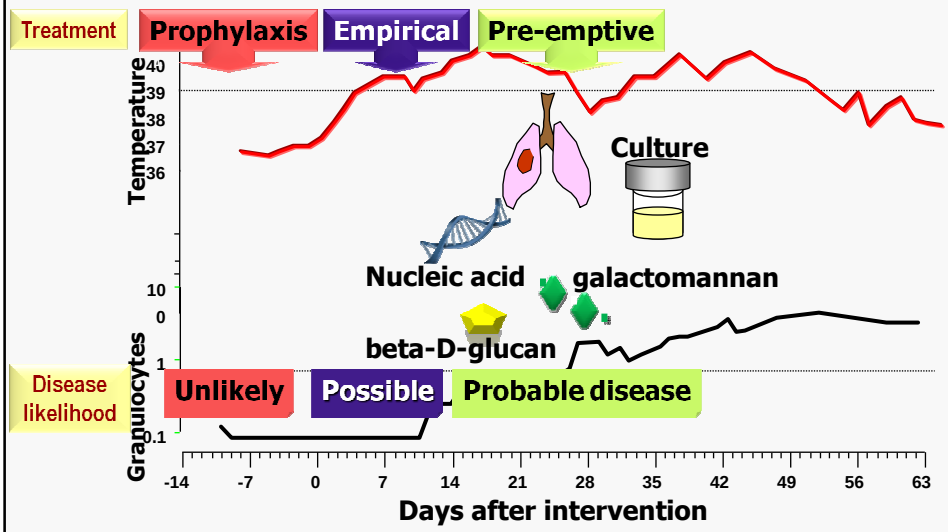
1st European Conference on Infection in Leukemia

DO YOU USE EMPIRICAL ANTIFUNGAL THERAPY? (ECIL MEETING 2008)



THERAPEUTIC STRATEGIES

Peter Donnelly & Ben dePauw



PATTERNS OF INVASIVE FUNGAL DISEASE

Donnelly 2010

			Pre-emptive			
Radiological signs & clinical symptoms	No	Persistent febrile neutropenia	No	Clinical symptoms	Radio-logical signs	Radio-logical signs and/or symptoms
Mycology results	Negative	Negative	Positive bio-marker	Negative	Negative	Positive biomarker or microscopy or culture
Proof of IFD	No	No	No	No	Yes	Yes
Proof of IFI	No	No	Yes	No	No	Yes

AWAY FROM EMPIRISM?

HIGH RESOLUTION CT SCAN

GALACTOMANNAN

β-D-GLUCAN

PCR

TRADITIONAL DIAGNOSIS

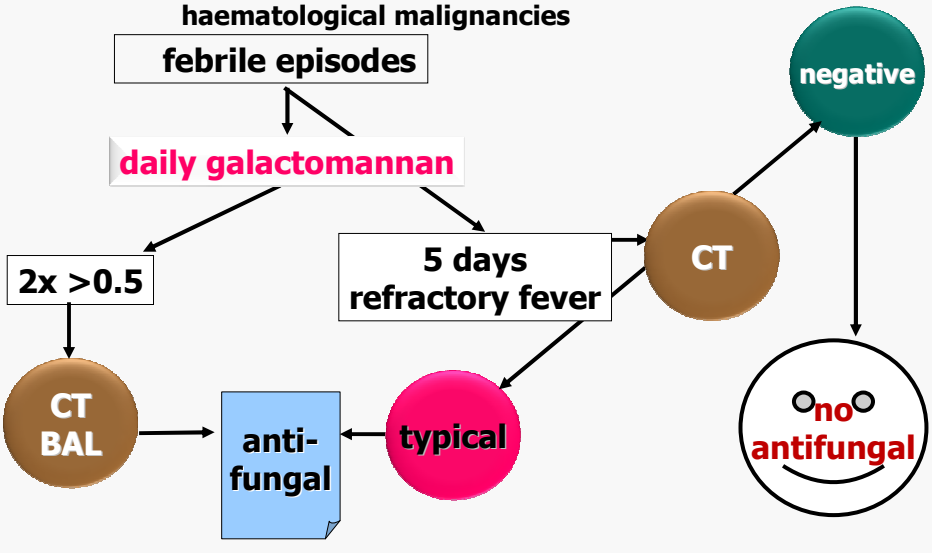
NEW TOOLS

22%

FUNGAL BURDEN

GALACTOMANAN AND CT-SCAN-GUIDED EARLY TREATMENT OF INVASIVE ASPERGILLOSIS

Maertens et al. Clin Infect Dis 2005;41:1242-1250



PRE-EMPTIVE MANAGEMENT OF INVASIVE ASPERGILLOSIS: MORTALITY

Maertens et al. Clin Infect Dis 2005;41:1242-1250

88 patients

'EMPIRIC' ANTIFUNGALS USE 16%

100% autopsy rate

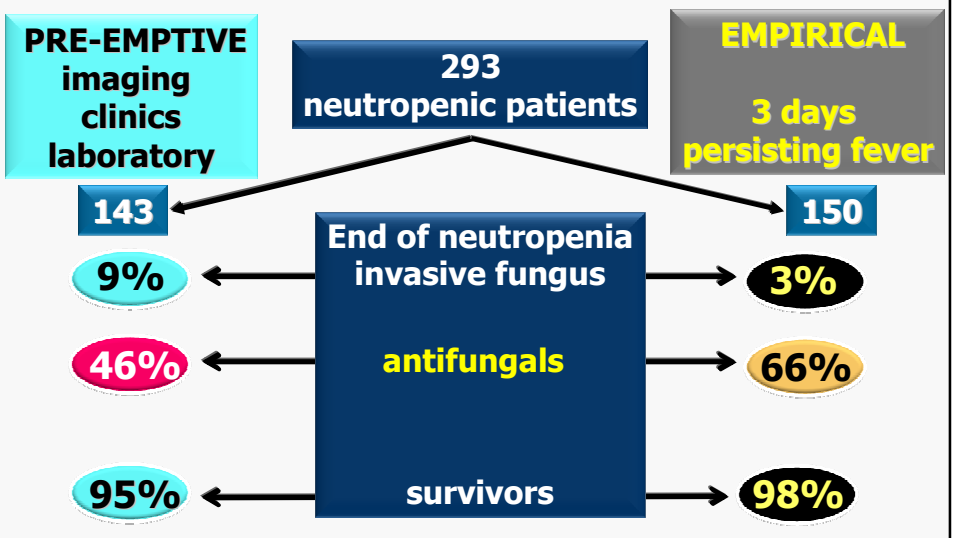
fungal mortality 8%

Fungal mortality

Walsh I	7%
Walsh II	8%
Walsh III	8%
Boogaerts	11%

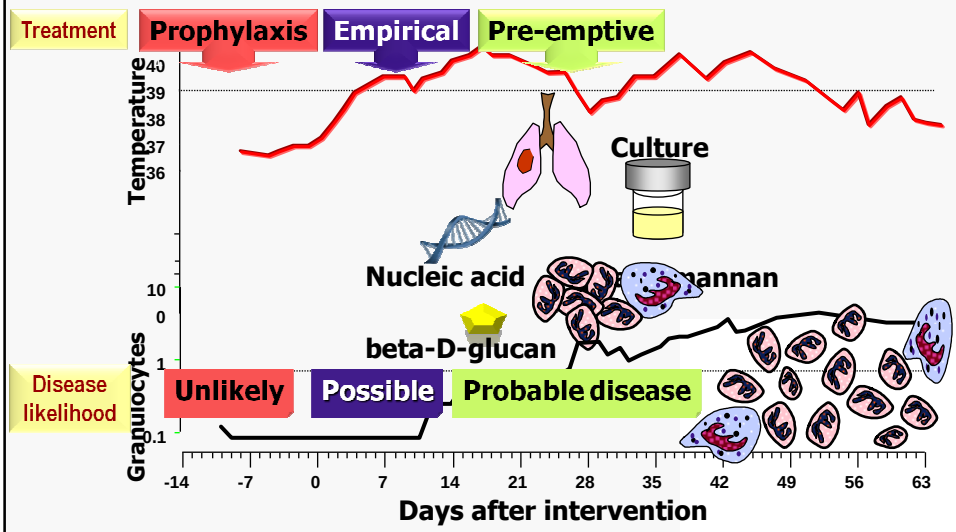
EMPIRICAL OR PRE-EMPTIVE?

Cordonnier et al. Clin Infect Dis 2009; 48:1042-1051



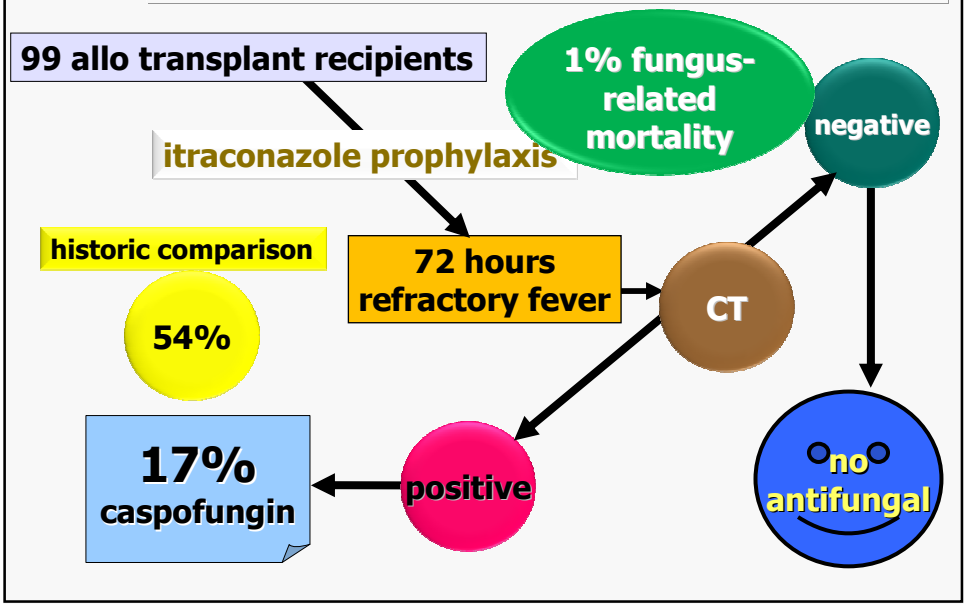
..BUT IN PATIENTS WITH GRANULOCYTES

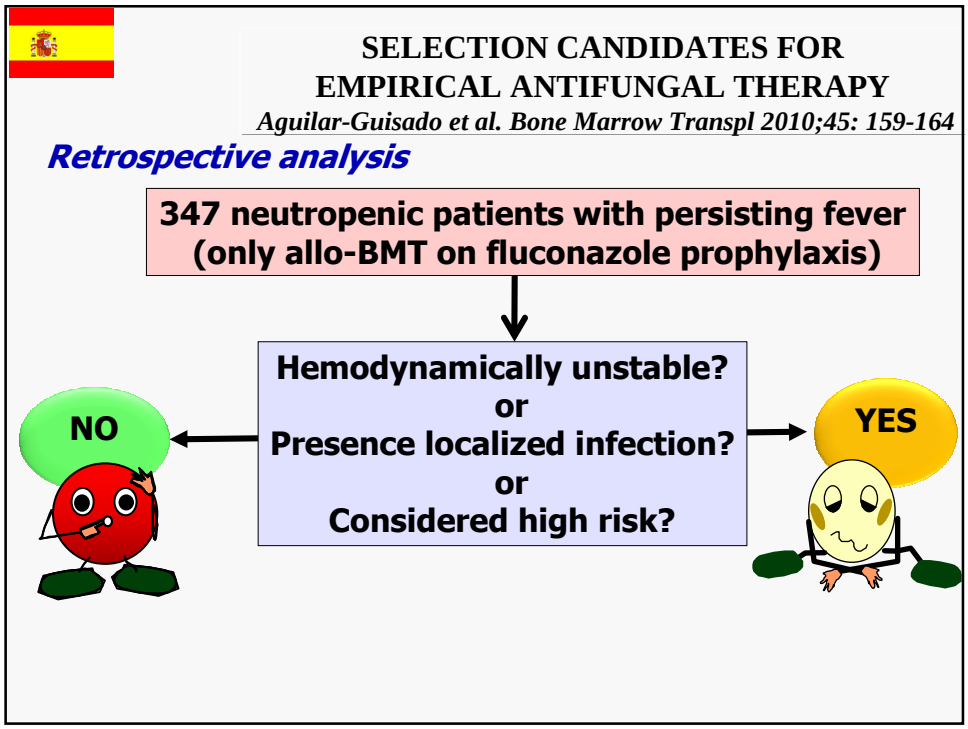
Peter Donnelly & Ben dePauw

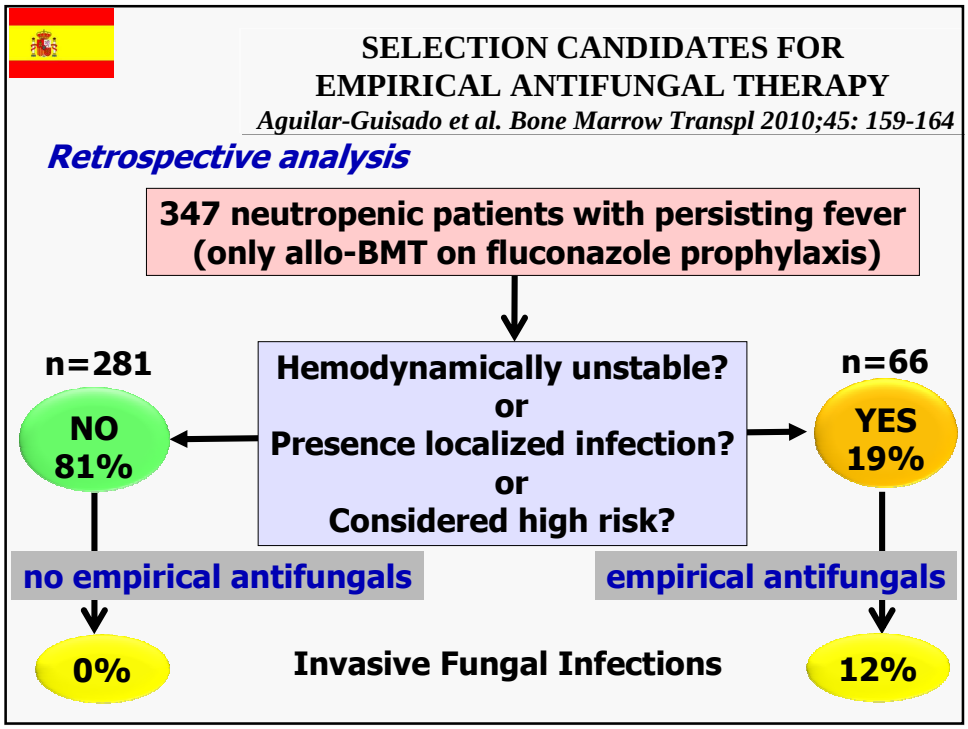


PRE-EMPTIVE MANAGEMENT OF INVASIVE MYCOSES IN TRANSPLANT RECIPIENTS

Dignan et al. Bone Marrow Transpl 2009;44:51-56




SELECTION CANDIDATES FOR
EMPIRICAL ANTIFUNGAL THERAPY
Aguilar-Guisado et al. Bone Marrow Transpl 2010;45: 159-164
Retrospective analysis
347 neutropenic patients with persisting fever
(only allo-BMT on fluconazole prophylaxis)
Hemodynamically unstable?
or
Presence localized infection?
or
Considered high risk?
NO
YES


SELECTION CANDIDATES FOR
EMPIRICAL ANTIFUNGAL THERAPY
Aguilar-Guisado et al. Bone Marrow Transpl 2010;45: 159-164
Retrospective analysis
347 neutropenic patients with persisting fever
(only allo-BMT on fluconazole prophylaxis)
n=281
Hemodynamically unstable?
or
Presence localized infection?
or
Considered high risk?
n=66
NO
81%
YES
19%
no empirical antifungals
empirical antifungals
0%
Invasive Fungal Infections
12%

PATTERNS OF INVASIVE FUNGAL DISEASE

Donnelly 2010

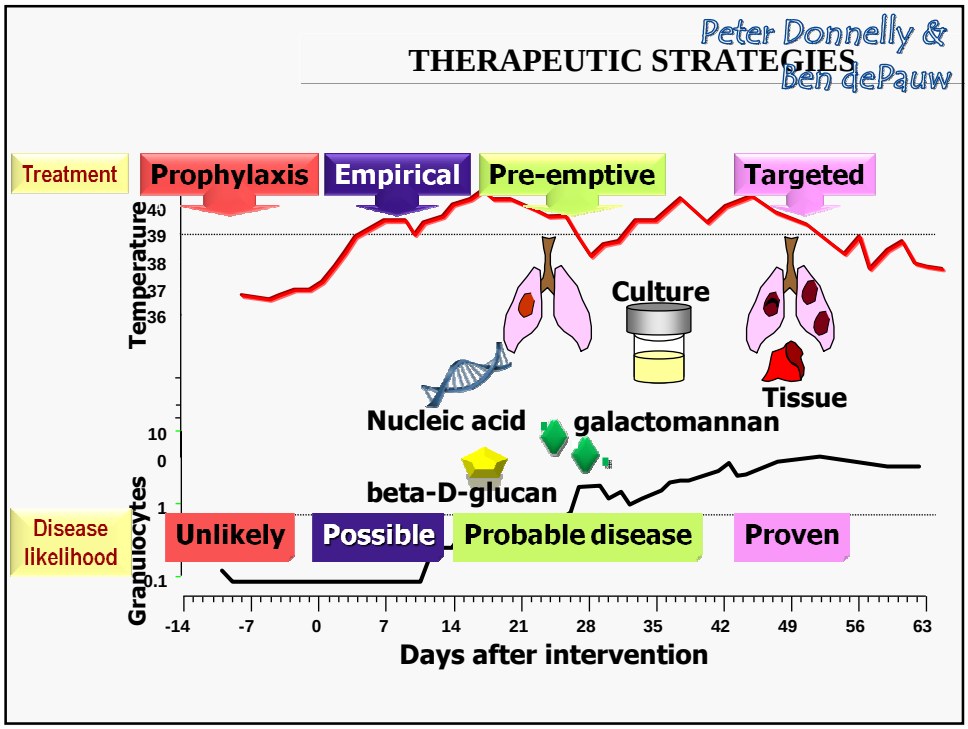
			Pre-emptive			
Radiological signs & clinical symptoms	No	Persistent febrile neutropenia	No	Clinical symptoms	Radio-logical signs	Radio-logical signs and/or symptoms
Mycology results	Negative	Negative	Positive bio-marker	Negative	Negative	Positive Biomarker or microscopy or culture
Proof of IFD	No	No	Some evidence of IFD			Yes
Proof of IFI	No	No				Yes

AIM OF A PRE-EMPTIVE STRATEGY

include all patients likely to have invasive fungal disease and treat them with the most effective drug

exclude all patients unlikely to have invasive fungal disease and adopt a **WAIT-and-SEE** policy


Diagnosis
or
therapy??


Peter Donnelly &
Ben dePauw
THERAPEUTIC STRATEGIES
Treatment
Prophylaxis
Empirical
Pre-emptive
Targeted
Temperature
40
39
38
37
36
Culture
Tissue
Nucleic acid
galactomannan
beta-D-glucan
10
0
1
0.1
Granulocytes
Disease likelihood
Unlikely
Possible
Probable disease
Proven
-14
-7
0
7
14
21
28
35
42
49
56
63
Days after intervention

PATTERNS OF INVASIVE FUNGAL DISEASE

Donnelly 2010

	Prophylaxis	Empirical	Pre-emptive			Directed
Radiological signs & clinical symptoms	High risk of IFD	Persistent febrile neutropenia	No	Clinical symptoms	Radio-logical signs	Radio-logical signs and/or symptoms
Mycology results	Negative	Unable to exclude IFD	Positive bio-marker	Negative	Negative	Positive Biomarker or microscopy or culture
Proof of IFD	No	No	Some evidence of IFD			Yes
Proof of IFI	No	No				Yes
						IFD

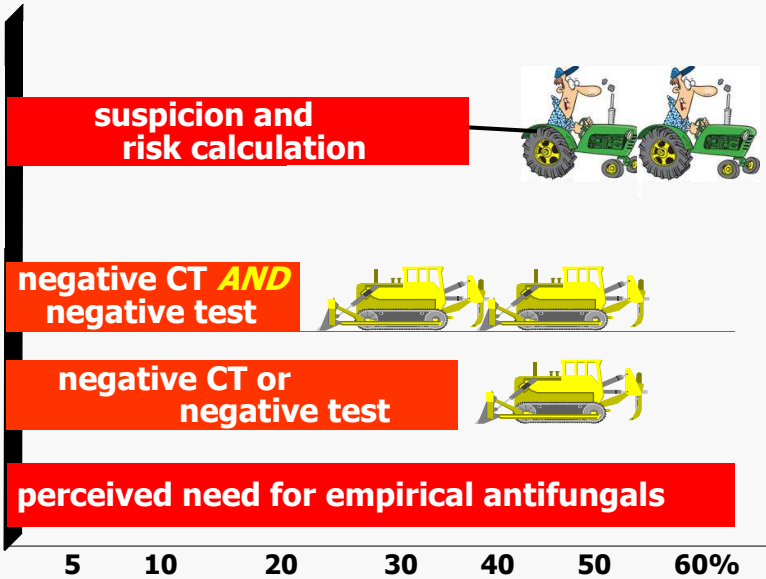
CRUCIAL ELEMENTS IN AVOIDANCE OF DISASTERS

- Knowledge on behavior of the offender

AN EYE FOR RISK FACTORS

- Early recognition
- Early treatment

MAIN FACTORS THAT DETERMINE THE USE OF ANTIFUNGALS



OUTLINE OF THE PRESENTATION

- ✓Introduction
- ✓Role of a fungus in nature
- ✓Pathophysiology of fungal disease
- ✓Options and limitations of antifungals
- ✓Strategic choices
- ✓Side reflections
- ✓Final remarks

OUTLINE OF THE PRESENTATION

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- ✓Strategic choices
- ✓Side reflections
- ✓Final remarks

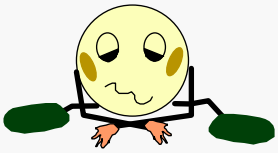
REASONS FOR FAILING ANTIFUNGAL THERAPY

-PRAGMATIC CAUSES

- •Correct diagnosis
- •Strategic reasons (too late!)

-FUNDAMENTAL CAUSES

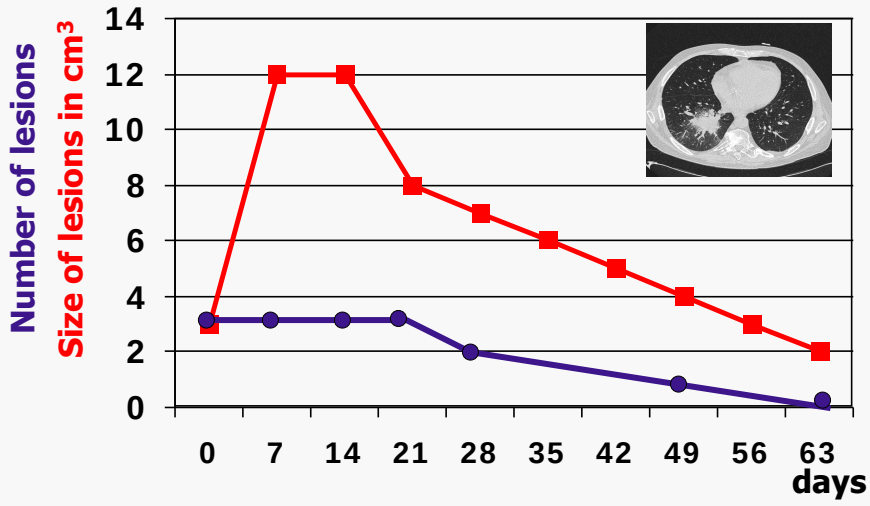
- •Drug resistance
- •Immunodeficiency



40-50% failures

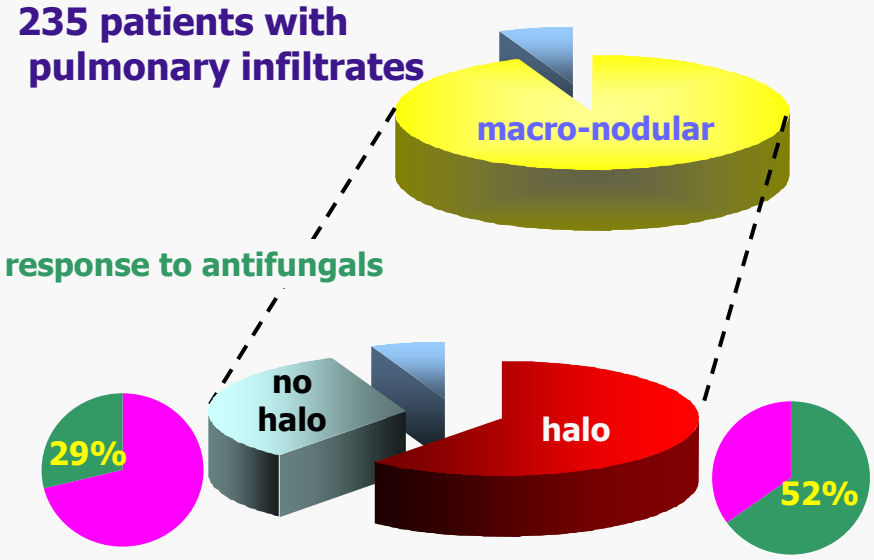
EVOLUTION OF CT-LESIONS DUE TO PULMONARY ASPERGILLOSIS

Brodoefel et al. Am J Radiol 2006; 187:404-413.



RADIOLOGIC PATTERN PULMONARY ASPERGILLOSIS IN RELATION TO OUTCOME

Greene R et al. Clin Infect Dis 2007; 44:373-379



FUNGAL INFECTIONS AMONG STEM CELL TRANSPLANT RECIPIENTS

Pagano et al. Clin Infect Dis 2007; 45: 1161-1170

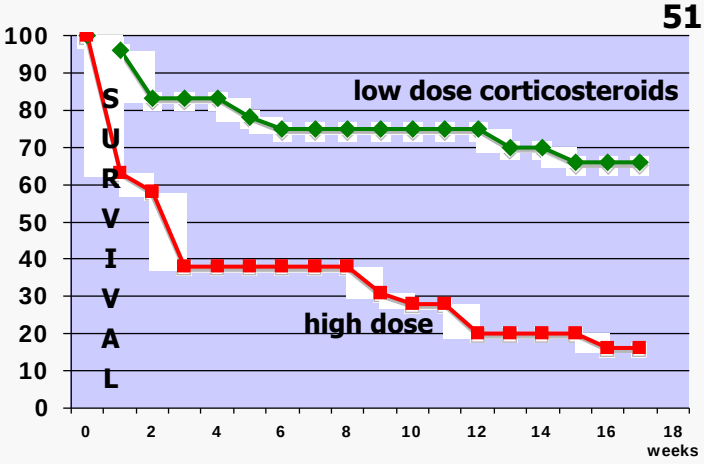
1999-2003
3228 stem cell transplants

4% invasive fungus (74% moulds)

1249 allogeneic	1979 autologous
8% invasive fungus	1% invasive fungus
Attributable mortality 72%	Attributable mortality 35%

CORTICOSTEROIDS AND SURVIVAL OF ASPERGILLOSIS IN HSCT

Cordonnier et al. Clin Infect Dis 2006;42:955-963



51 patients with aspergillosis

41 allo HSCT
10 auto

OUTLINE OF THE PRESENTATION

- ✓**Introduction**
- ✓**Role of a fungus in nature**
- ✓**Pathophysiology of fungal disease**
- ✓**Options and limitations of antifungals**
- ✓**Strategic choices**
- ✓**Side reflections**
- ✓**Final remarks**

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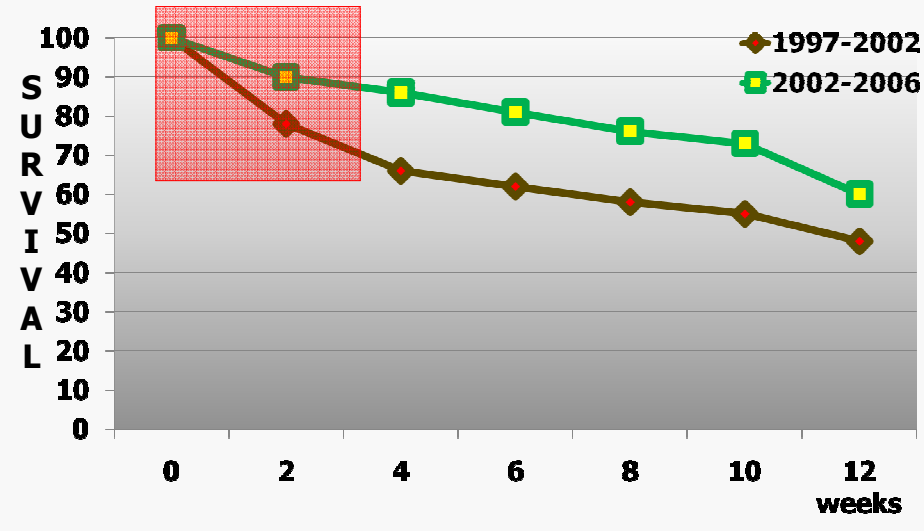
OUTCOME OF ASPERGILLOSIS IN PATIENTS TREATED FOR A MALIGNANCY

Nivoix, Y et al. Clin Infect Dis 2008; 47:1176-1184

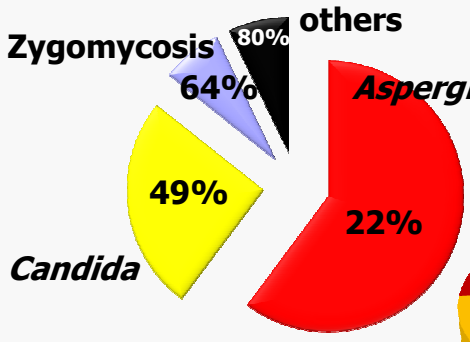
n = 289



OUTCOME OF INVASIVE FUNGAL DISEASE IN TRANSPLANT RECIPIENTS 2004-2007

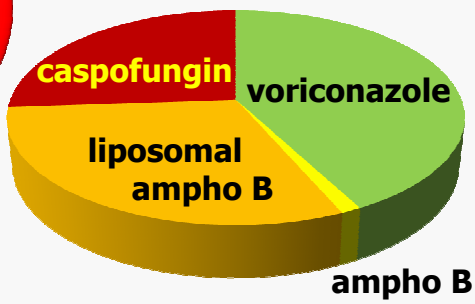
Neofytos et al. Clin Infect Dis 2009; 48:265-273

250 infections in 16 centers for BMT in the USA

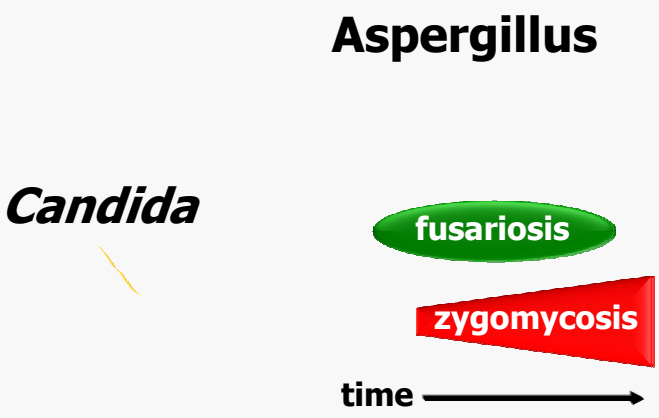


6 weeks mortality
(overall 47%)

use of antifungals



POSSIBLE EFFECT OF MORE EFFECTIVE ANTI-CANDIDA AND ASPERGILLUS THERAPY

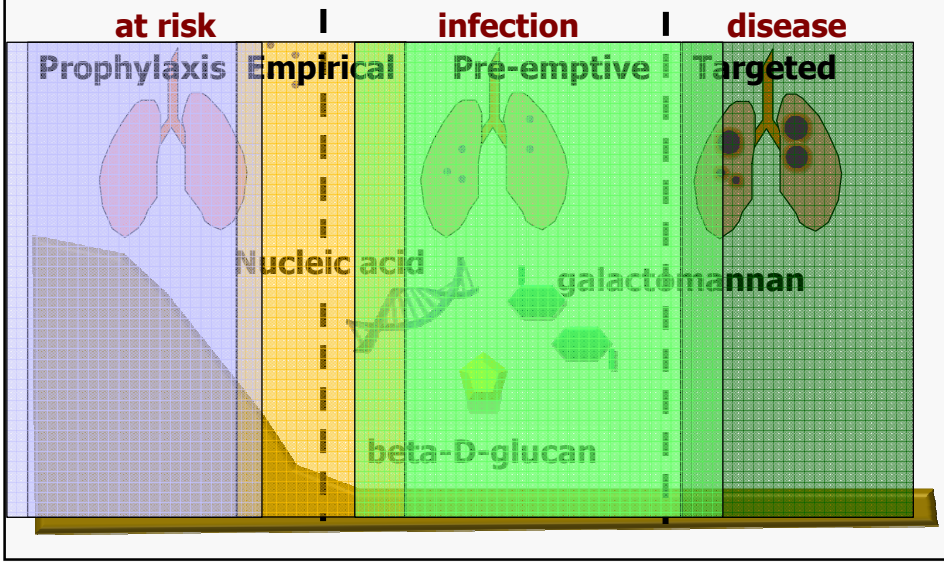


STOPPING ANTIFUNGAL THERAPY

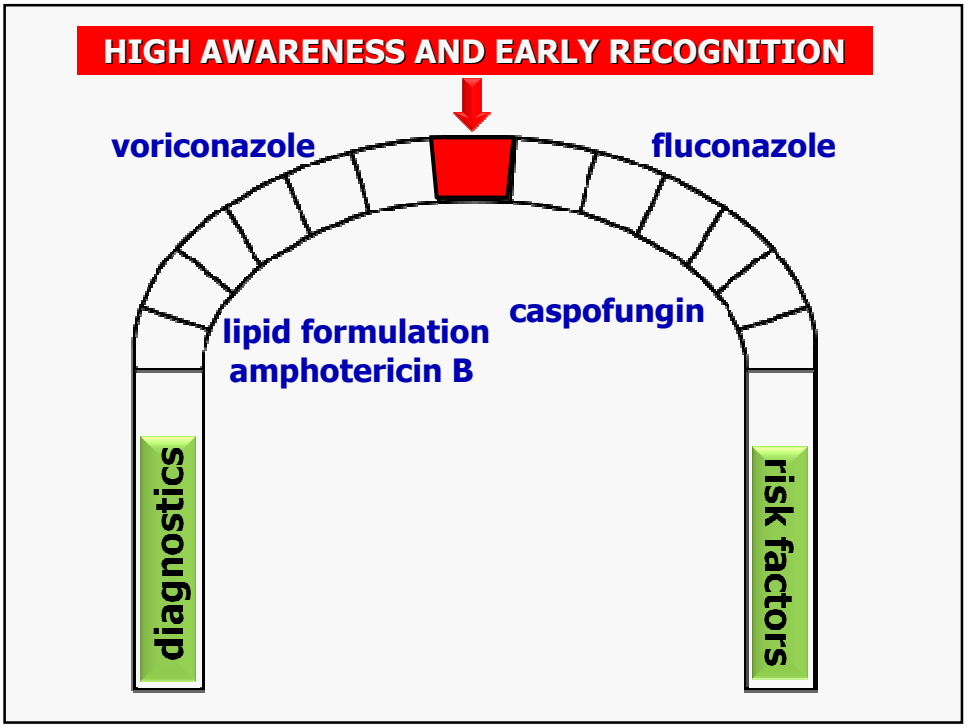
- **Empirical indication**
  - ➢ At defervescence
- **Incipient infection**
  - ➢ At disappearance of symptoms and recovery of the immune system
  - Watchful follow-up
- **Established infection**
  - ➢ At objective response and recovery of the immune system
  - ➢ Resume treatment at recurrence or new episode of immune deficiency

STRATEGIES AGAINST INVASIVE FUNGAL DISEASE

Donnelly 2010



BUILDING AN ANTIFUNGAL STRATEGY



CONCLUSIONS

THERE ARE MANY EFFECTIVE ANTI-CANDIDA AGENTS

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VORICONAZOLE AND LIPOSOMAL AMPHO B ARE DRUGS OF CHOICE AGAINST INVASIVE ASPERGILLOSIS

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TREATMENT OF INVASIVE FUNGAL DISEASE BECOMES MORE DIAGNOSTIC-DRIVEN

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