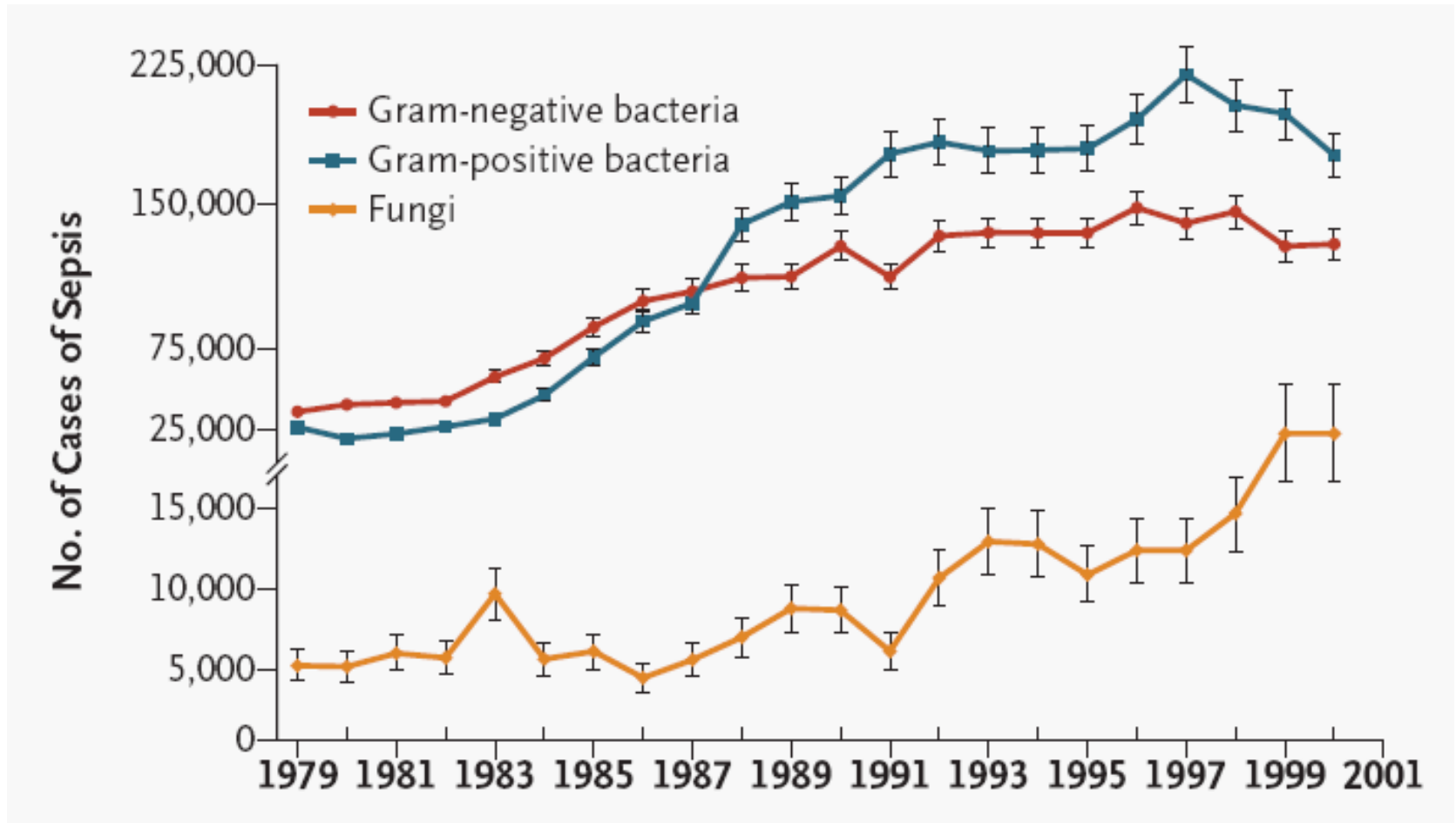


Current Options for Empiric Therapy of Febrile Neutropenia: - Role of Itraconazole

**9th Febrile Neutropenia Congress
Ankara, Turkey**

PD Dr. Ulrich Schuler
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Numbers of Cases of Sepsis in the United States, According to the Causative Organism, 1979–2000



Invasive Fungal Infection – Case-Fatality

Case-Fatality

Aspergillosis

Pulmonary Aspergillosis

50-75%

cerebral Aspergillosis

95%

Candidiasis

Candidemia

40%

Long-term influence on overall survival in Acute Leukemia
even worse due to

delays in the treatment of the underlying disease

What do we treat ?

Defining Opportunistic Invasive Fungal Infections ...:

An International Consensus

S. Ascoglu et al. (EORTC, MSG) CID 2002

„.....Three levels of probability are proposed:
“**proven,**” “**probable,**” and “**possible.**”

**The definitions are intended
for use in the context of clinical
and/or epidemiological research,
not for clinical decision making.**

UPDATED 2008, minor changes for hematology patients

What do we treat ? (2)

- **‘proven’ fungal infection**
 - histopathologic examination
 - culture from sterile compartment
(Fungemia with the **Exception of** [possibly false positive] **Molds, BAL not considered sterile**)
 - Cryptococcus (-antigen) in CSF
- **‘probable’ fungal Infection**
 - minimum 1 ‘host factor’
 - and 1 microbiological criterium
 - and** 1 clinical major or 2 minor criteria
- **‘possible’ fungal Infection**
 - at least 1 ‘host factor’
 - and 1 microbiological criterium **or**
 - 1 clinical major or 2 minor criteria

When do we treat ?

- **prophylactically**
(whom ?)
- **empirical**
possible + probable (when?)
- **preemptive**
no uniform definition:
sometimes
(a) preemptive = empirical (possible infection)
(b) preemptive = positive culture or antigen in high risk situation
without signs of Infection / fever
- **therapeutic**
(proven **+probable?**)
e.g. classical CT-course and repeated culture of Aspergillus in
sputum **+positive Antigen = „probable Infection“**

Prophylaxis ?

2002 Guidelines for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer

W.T. Hughes, CID 2002

< Use of *antibiotic* prophylaxis **is not routine** because of emerging antibiotic resistance, except TMP-SMX to prevent *PcP*. >

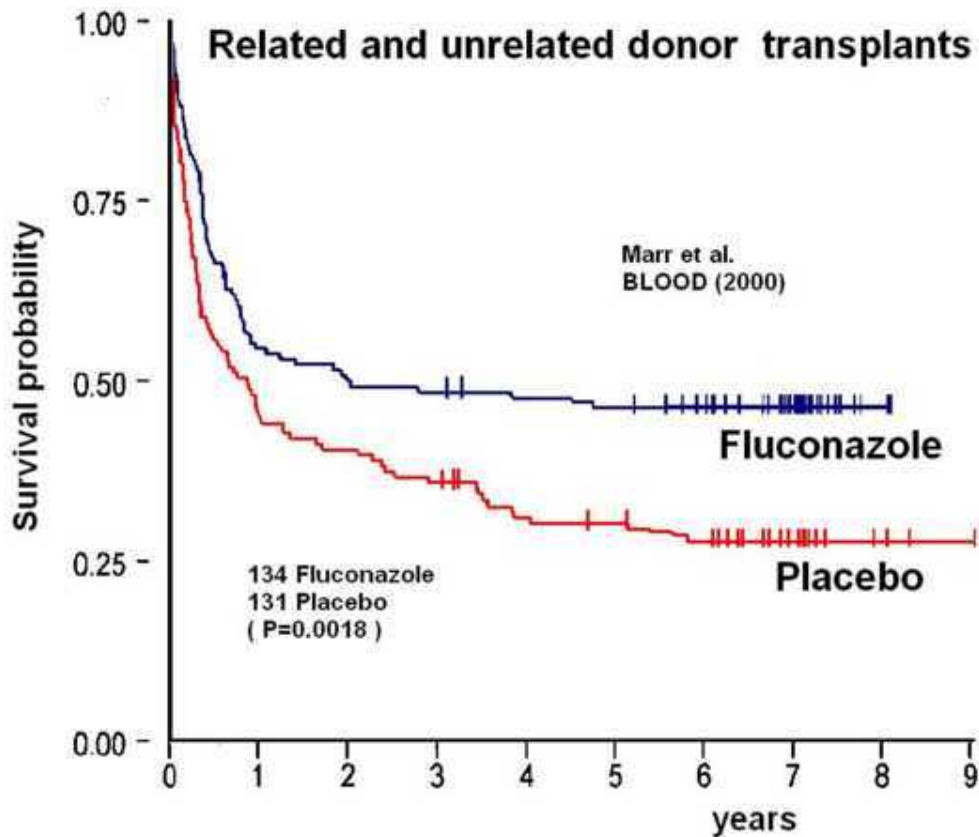
Antifungal prophylaxis with fluconazole

and antiviral prophylaxis with acyclovir or ganciclovir

are **warranted for patients undergoing allogeneic HSCT.**

For patients other than allo-SCT: „.....**may be appropriate** in institutions in which the infections are encountered frequently.“

Why fluconazole used to be standard for prophylaxis in the recommendations in allo-SCT



- K Marr et al
Blood 2000 96:2055
- **Amazing long-term results**
of a randomised study
with regard to survival (!)
-but
- difficult to accept because
not active in aspergillosis

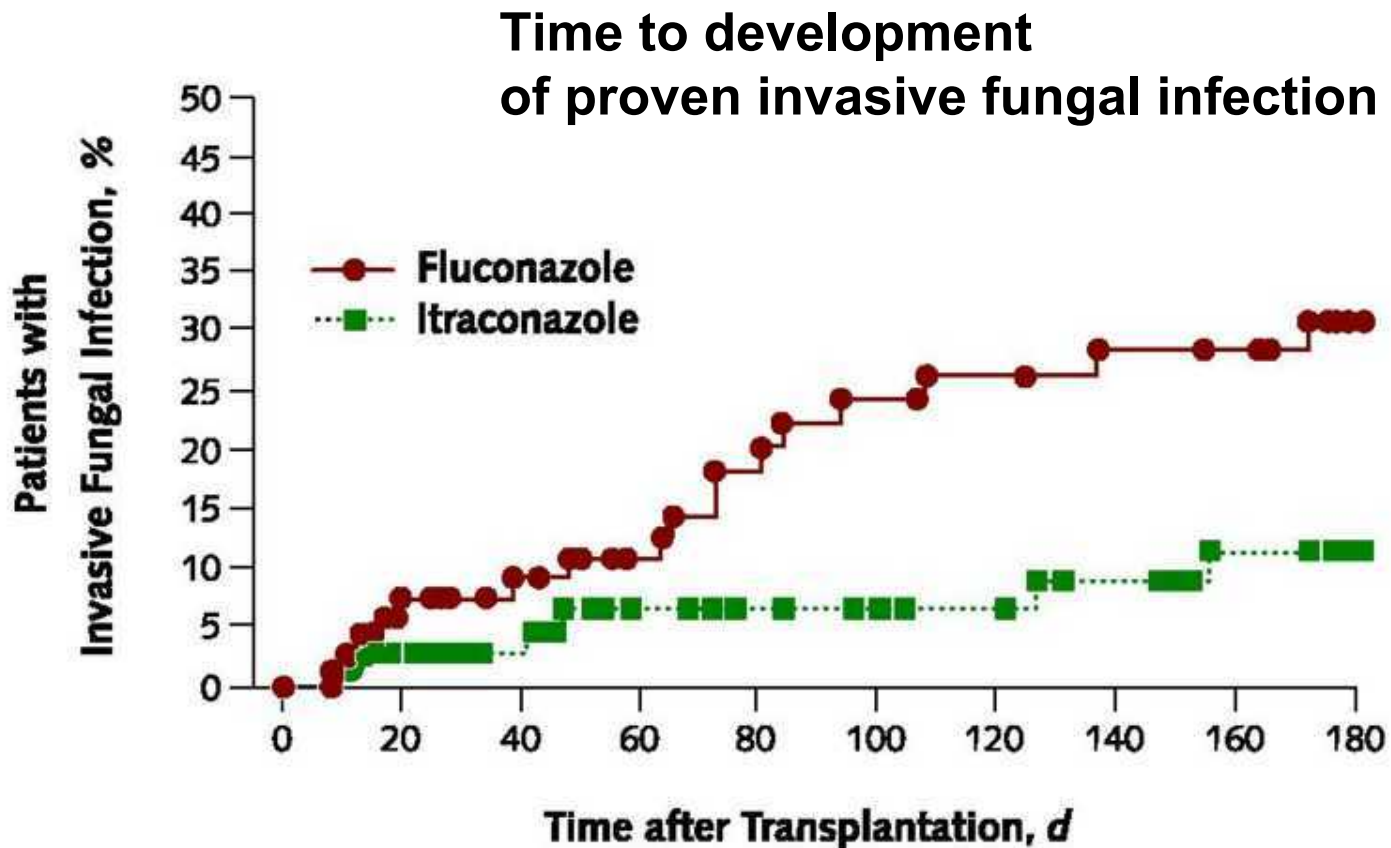
IV and Oral **ITRA** vs IV and Oral **FLUC** for Long-Term Antifungal Prophylaxis in **Allo-SCT**, - A Multicenter, Randomized Trial

Winston et al. (2003), Ann Intern Med. 138:705

- **Itra** (IV 2d 2x200mg continued orally with 400 mg) vs. oral **Fluconazole** (400 mg)
- proven invasive fungal infections
9% Itra-, 25% Flu-Arm (until d180 after SCT, P = 0.01).
- multivariate analysis:
Itra associated with **reduced rate of fungal infections** (yeasts + molds, OR 0.3 [CI, 0.1 to 0.8]; P = 0.02).
- Itra inferior in GI-side effects (24% vs. 9%; p= 0.02)
- No difference in mortality,
trend for fewer fungal deaths in ITRA-arm (9% vs. 18%, p = 0.13)

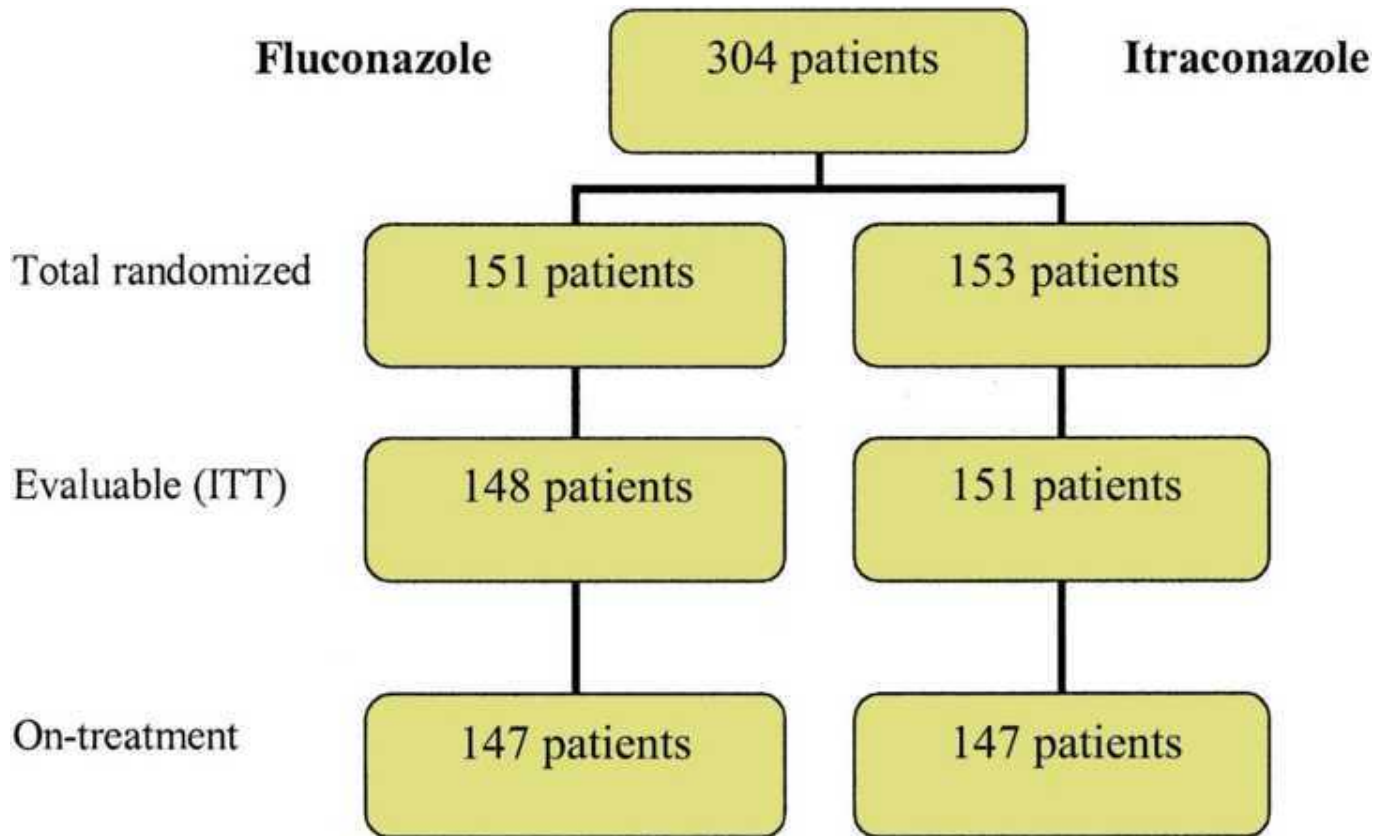
IV and Oral ITRA vs IV and Oral FLUC for Long-Term Antifungal Prophylaxis in Allo-SCT, - A Multicenter, Randomized Trial

Winston et al. (2003), Ann Intern Med. 138:705



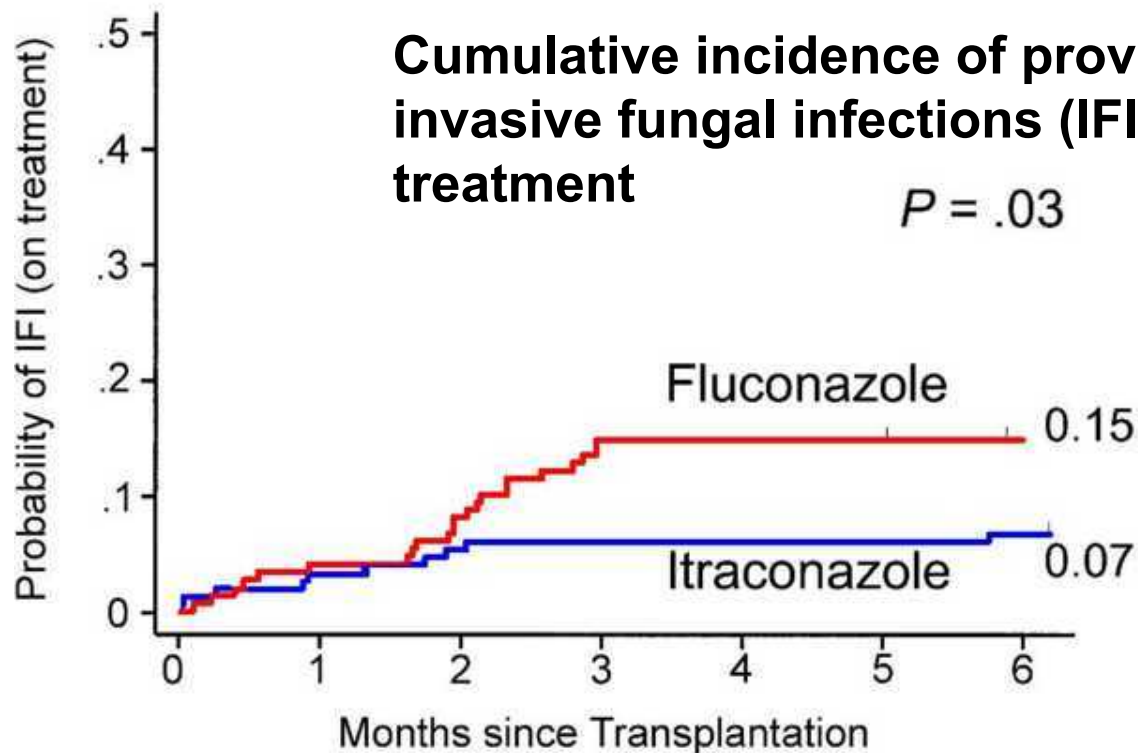
Comparison fluconazole versus itraconazole for prophylaxis in allo-SCT

K.Marr et al Blood 2004 103:1527



Comparison fluconazole versus itraconazole for prophylaxis in allo-SCT

K.Marr et al Blood 2004 103:1527



Patients on SD and at risk (N):

Flu:	147	136	123	97	53	29	1
Itra:	147	109	83	71	42	29	1

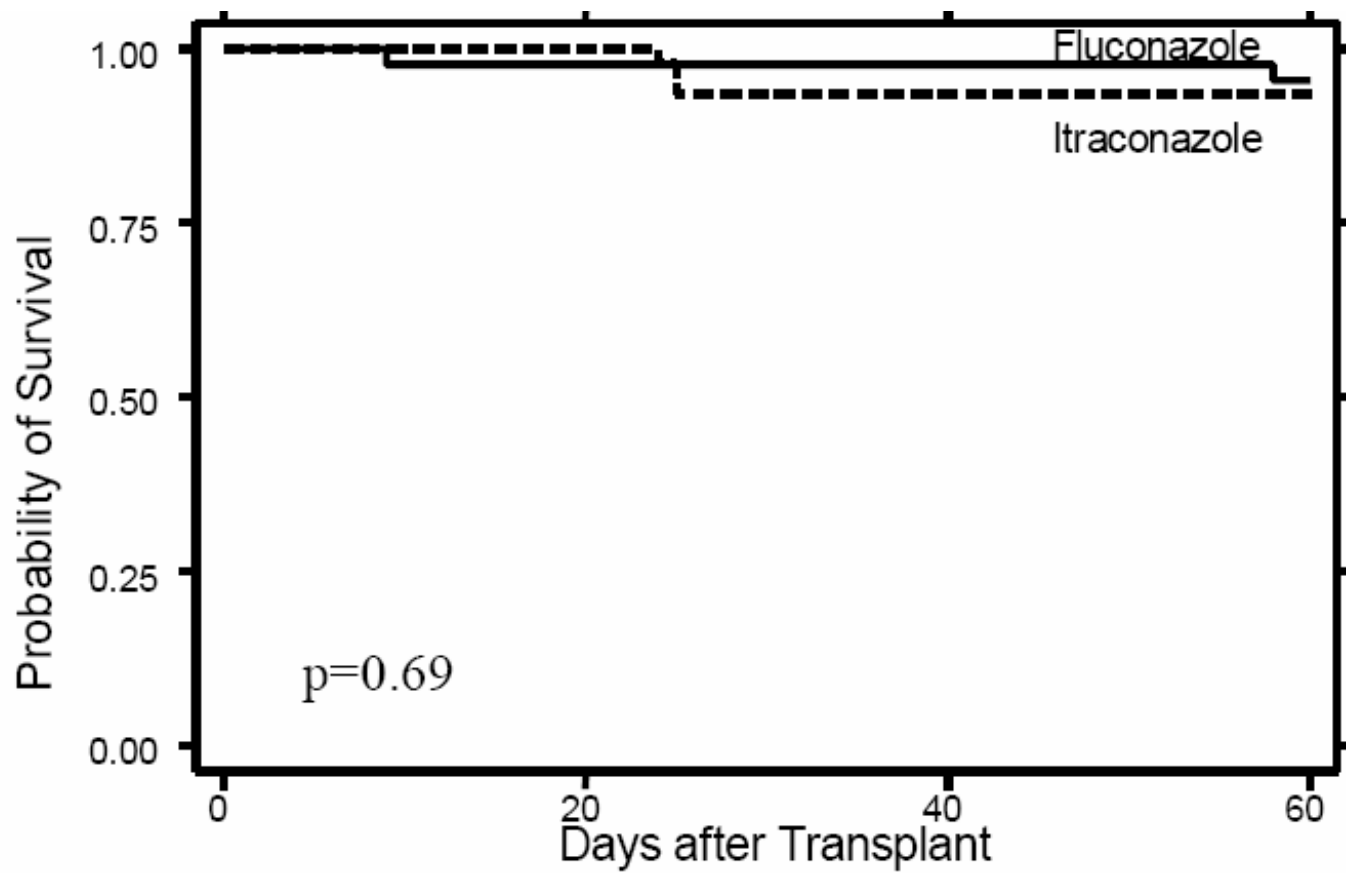
but ...

Comparison fluconazole versus itraconazole for prophylaxis in allo-SCT

K.Marr et al Blood 2004 103:1527

...liver toxicities in the first cohort of patients.

Therefore itraconazole **only after conditioning ...**



ITRA vs Caspofungin Prophylaxis in AML/MDS Induction Chemo

- Gloria Mattiuzzi et al, (2006) AAC 50:143
M.D. Anderson Cancer Center.
- prophylactic ITRA i.v. → oral
2x200mg i.v./1h for 2 days
followed by 200mg i.v./day

vs. CASPO 50mg/day
- randomised study, 192/200 patients evaluable
- invasive infections 5 ITRA / 6 CASPO
- → conclusion : comparable

Antifungal Prophylaxis in SCT (3)

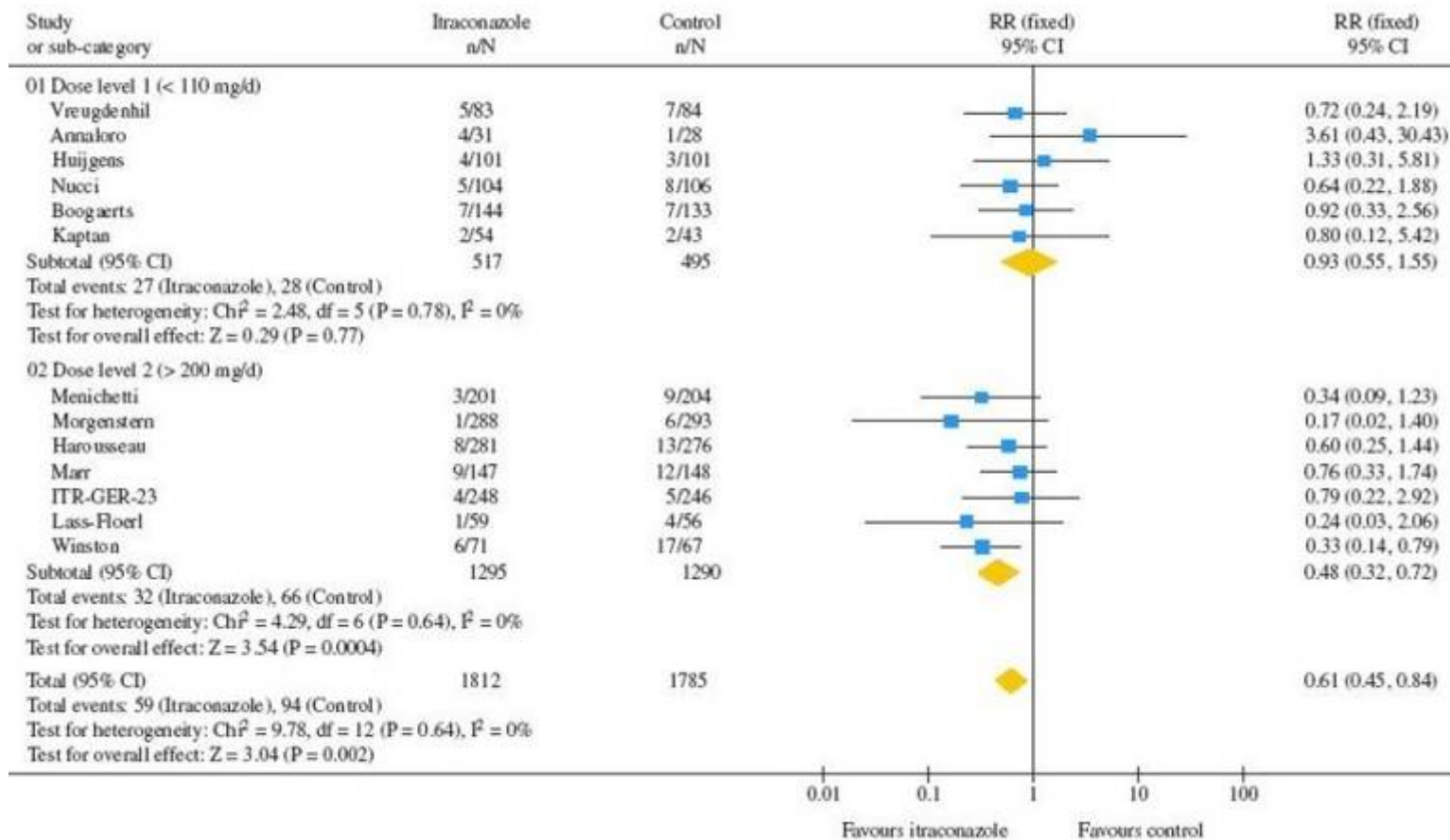
- **Micafungin**
van Burik CID 2004 39:1407
RCT, #=882, **SCT-patients**,
Micafungin (50 mg or 1 mg/kg with < 50 kg KG)
vs **FLU 400 mg**
until end of neutropenia (or maximum of 42 days)
- **Micafungin** -arm :
higher success rate (80.0% vs. 73.5%, p=0.025)
favorable trend in Aspergillus-Rate (1 vs. 7 Pt., p=0.07)
lower rate of empirical therapy (15.1 vs. 21.4 % p=0.018)
- No differences in side effects

Meta-Analyses Prophylaxis: Incidence of IFI in relation to expected absorbed dose

Glasmacher et al. (2005) JAC (Sup.1):23

<110 mg/d

>200 mg/d

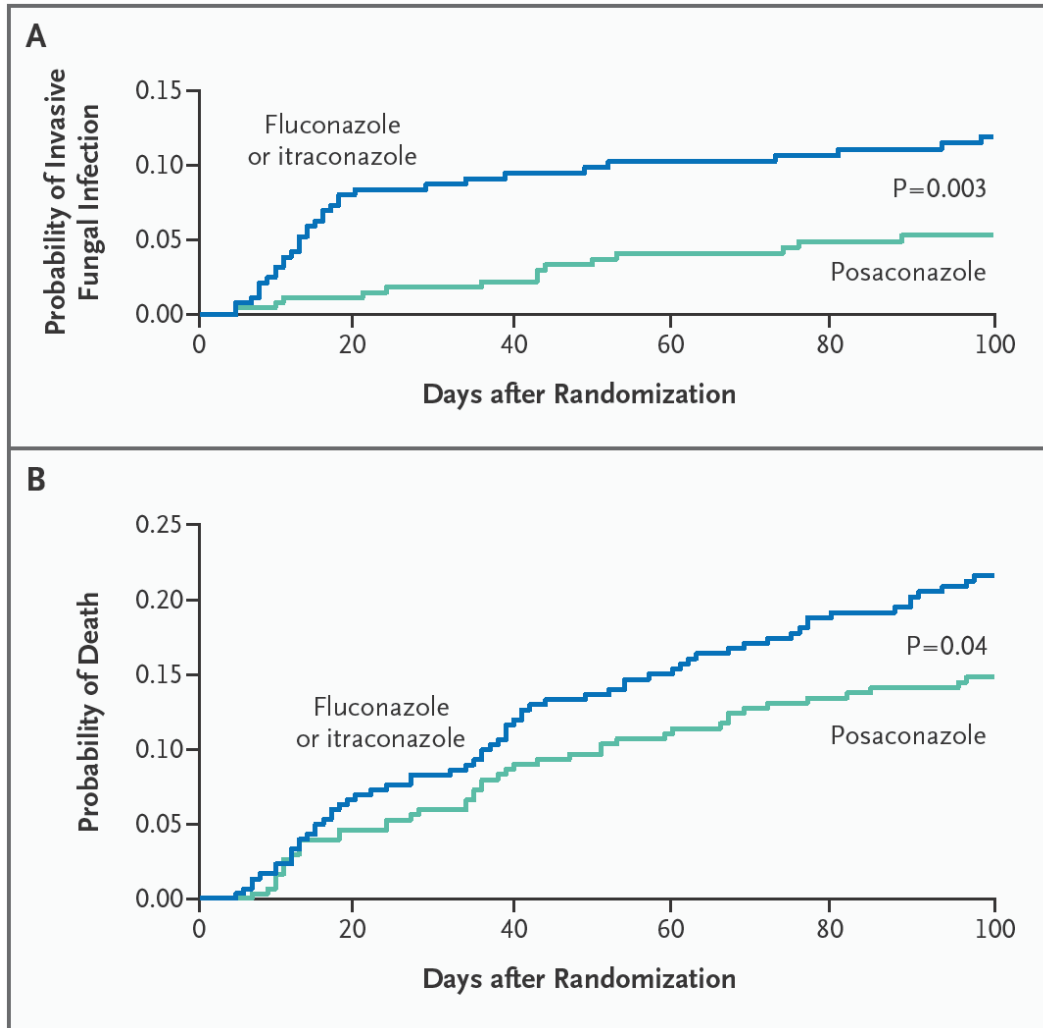


Assumptions: Bioavailability 22% for capsules, 55% for oral solution

More recent developments...

- Two RCTs evaluating **posaconazole** in prophylaxis
N Engl J Med 2007;356
 - (a) Cornely et al. (AML/MDS induction, **open label**)
(b) Ulmann et al. (GVHD-Patients after SCT, **blinded**)
- 3x200 mg **posaconazole** as oral suspension versus
 - (a) AML/MDS: 400 mg Fluconazole
or 2x200 mg ITRA suspension
 - (b) GVHD 400 mg Fluconazole
- Results:
 - fewer IA in both studies
 - improved survival by day 100 in AML-Study (p=0.035)
 - no difference in OS in GVHD-Study

Posaconazole prophylaxis in AML



- Cornely et al. N Engl J Med 2007;356
- Open-label RCT
- More than one cycle of chemo allowed per patient while on study
- No information about censoring
- Independent confirmation desirable

IDSA-Guidelines 2008: Summary of recommendations

-Prophylaxis

Condition	Therapy		Comments
	Primary	Alternative	
Prophylaxis against invasive aspergillosis	POSA (200 mg every 8h)	ITRA (200 mg every 12 h IV for 2 days, then 200 mg every 24 h IV) or ITRA (200 mg PO every 12 h); MICA (50 mg/day)	Efficacy of POSA prophylaxis demonstrated in high-risk patients (patients with GVHD and neutropenic patients with AML and MDS)

Itraconazole Prophylaxis for Fungal Infections after Liver Transplantation

	ITRA	Placebo	FLU	p=
Winston et al. 2002				
patients	97		91	
dose	2x200 mg		400 mg	
proven infection	9%		4%	n.s.
Sharpe et al. 2003				
patients	33	38		
dose	5 mg/kg followed by 2.5 mg/kg	x		
infection resulting in Amphotericin treatment	4%	24%		p=0.04
deaths	1	6		n.s.

Loading Dose Concept

Patients: N=17

2 days

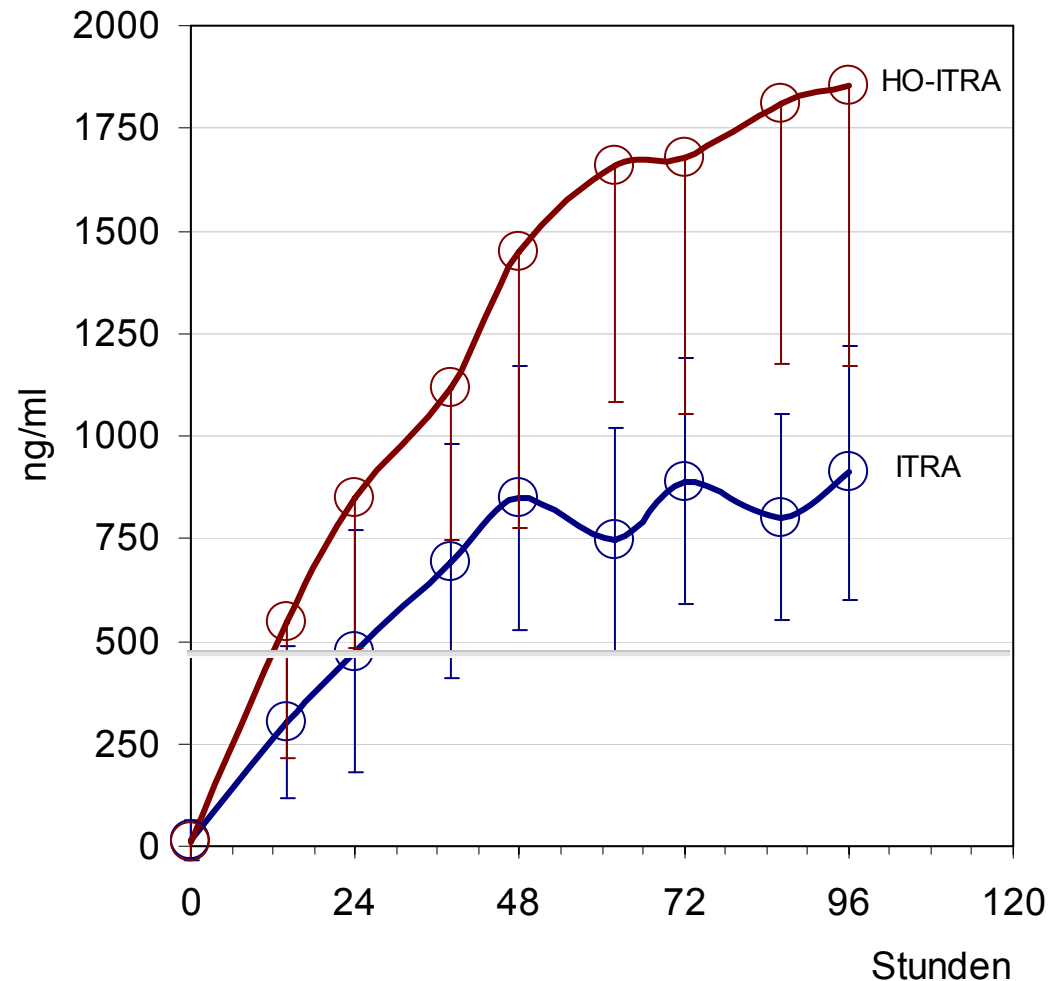
4x200 mg **oral** solution,

then 2x200 mg

15 min earlier ~12 mg
metoclopramide

samples at

0, 14, 24, 38, 48, 62, 72,
86, 96 h, trough levels





Dresden

Empirical Therapy, yes or no?

2002 Guidelines for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer

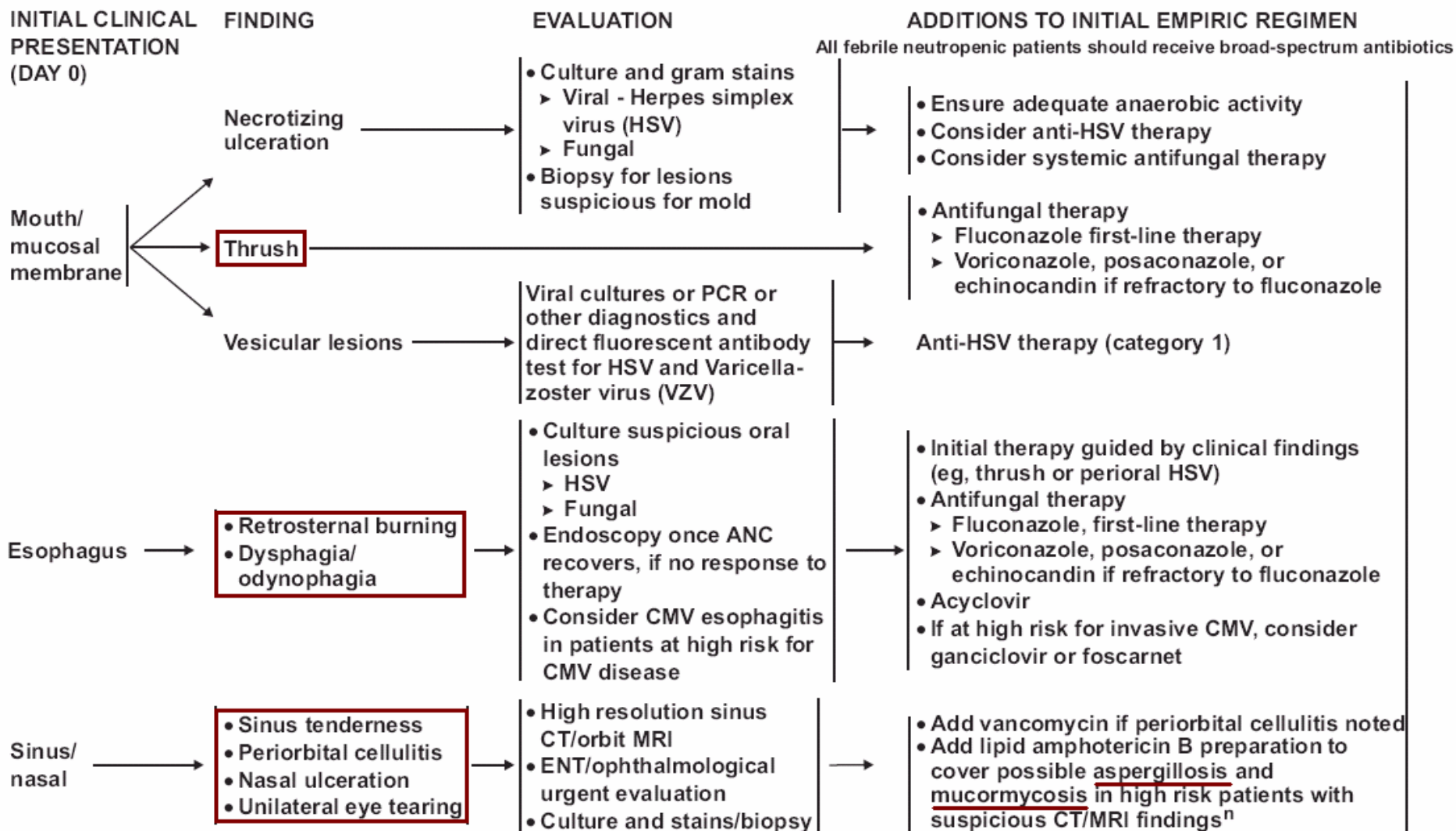
W.T. Hughes, CID 2002

If the patient is febrile after **5 days**, consider adding an antifungal drug, with or without a change in antibiotic regimen.

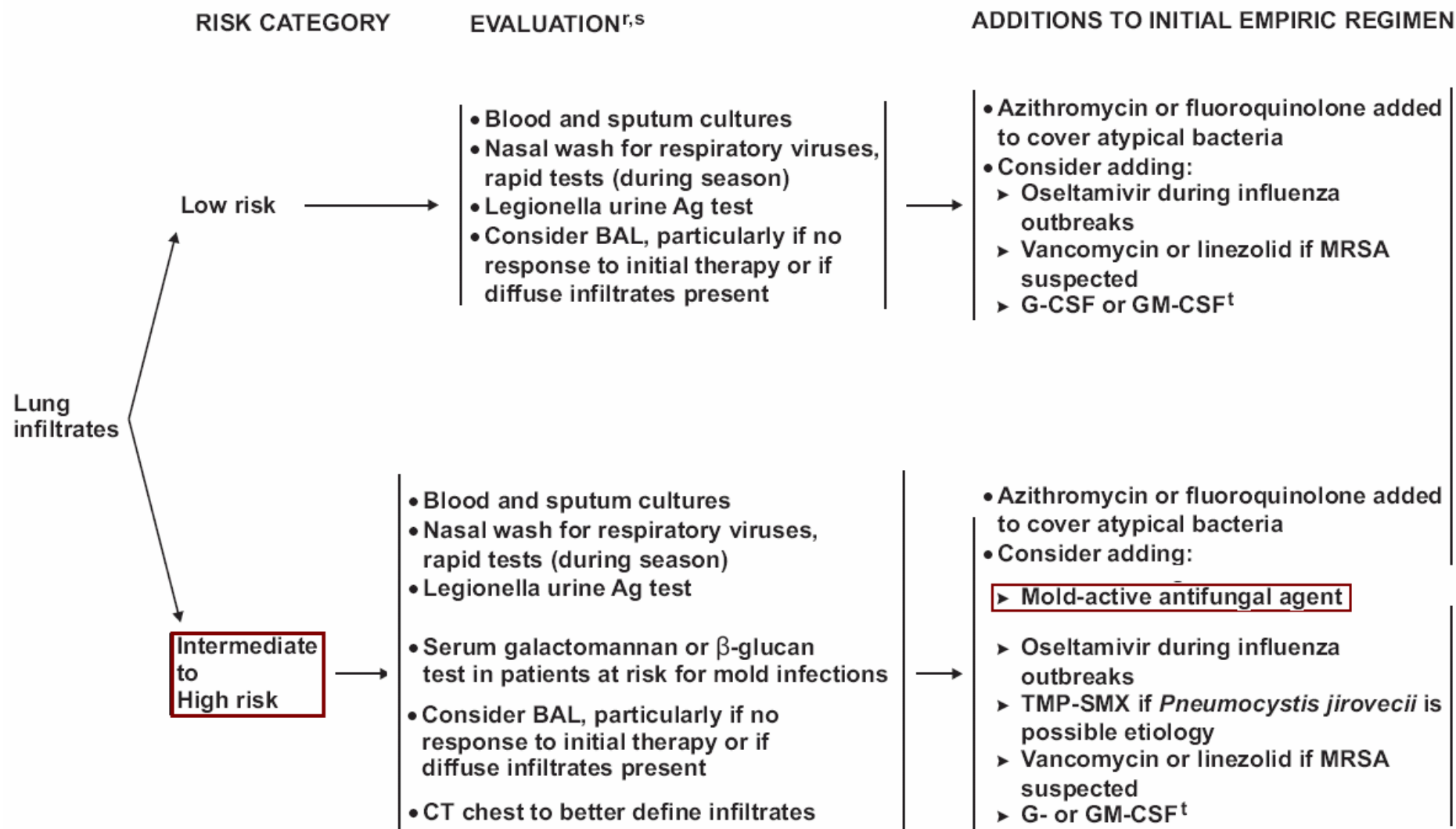
2008 NCCN Guidelines „Prevention and Treatment of Cancer Related Infections“ www.nccn.org

...In addition, the availability of newer broad spectrum antifungal agents with a good safety profile raise the possibility of using mold-active prophylaxis in patients at high risk for invasive fungal infections **without the need to empirically modify antifungal therapy** solely on persistent neutropenic fever of unknown etiology. Algorithms that include chest CT scans and laboratory surrogates for invasive fungal infections are discussed.

NCCN 2008



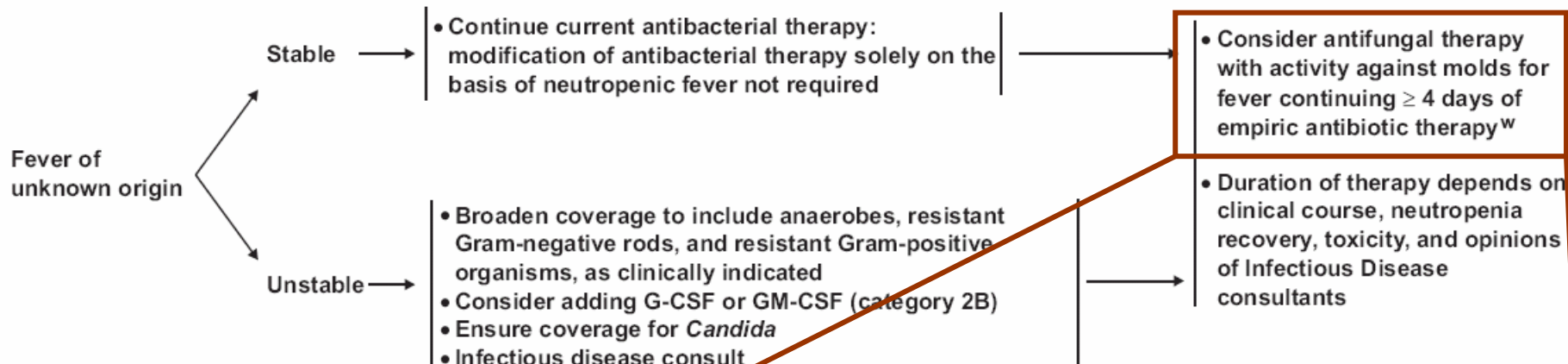
NCCN 2008



NCCN 2008

FOLLOW-UP THERAPY FOR NONRESPONDING PATIENTS

SUGGESTED DURATION OF THERAPY



^W The timing to add empirical antifungal therapy (EAFT) varies The panel recommends adding EAFT after 4 d unless patient is receiving prophylaxis directed against molds.

- Consider antifungal therapy with activity against molds for fever continuing ≥ 4 days of empiric antibiotic therapy^W

Studies in empirical indication

Agent 1	Success	Agent 2	Success	Author	Note
cAMB	49%	lipAMB	50%	Walsh 1999	
cAMB	38%	ITRA	47%	Boogaerts 2001	
lipAMB	30.6%	VORI	26%	Walsh 2002	No empiric indication for VORI
lipAMB	33.7%	Caspo	33.9%	Walsh 2004	

IV and oral ITRA versus iv **AMB** as **Empirical** Therapy for Persistent Fever in Neutropenic Patients with Cancer . .

Boogaerts et al. *Ann Intern Med.* 2001;135:412-422

- 384 patients
 - in 10 countries 1/96 until 12/97
 - mostly hematological diseases
 - neutropenic ($<0.5 \times 10^9$ ANC/l)
 - FUO ($>38^\circ\text{C}$)
 - 3-7 days of antibiotic treatment
- comparison of
 - **IV ITRA** (7 - 14 days)
followed by ITRA oral solution
 - **IV Ampho B** (28 days)

IV and oral ITRA versus iv AMB as Empirical Therapy for Persistent Fever(demographics).

Characteristic	Itraconazole Group (n=192)	Amphotericin B Group (n=192)
Men/women, <i>n/n</i>	119/73	110/82
Median age (range), <i>y</i>	46.5 (18–80)*	50 (18–81)*
Underlying diagnoses , <i>n (%)</i>		
ALL	15 (8)	11 (6)
AML	107 (56)	108 (56)
Lymphoma/ Myeloma	49 (26) / 9 (5)	36 (19) / 16 (8)
Other	12 (6)	21 (11)
Status of underlying disease, <i>n</i>		
Induction of remission	104	103
Relapse/Refractory	53/12	53/11
Autol. transplant recipient, <i>n (%)</i>	68 (35)	76 (39)
Time since last chemo (range), <i>d</i>	13 (4–376)	14 (0–60)
Duration of neutropenia before study entry (range), <i>d</i>	7 (2–34)	7 (5–39)
Duration of neutropenia during study (range), <i>d</i>	10 (0–35)	8 (0–29)

IV and oral **ITRA** versus iv **AMB** as **Empirical** Therapy for Persistent Fever in Neutropenic Patients with Cancer . .

Results	ITRA	AMB
overall Response	47%	38%
defervescence	73%	70%
breakthrough-infection	5/179	5/181
„composite endpoint“	53%	46%

Composite Endpoint

- *Walsh TJ et al. N Engl J Med*
1999;340:764 and 2002;346:225 and 2004;351:1391
- Success defined as **all** of:
 - Survival for ≥ 7 days after discontinuation of study medication
 - No breakthrough fungal infection for up to 7 days after discontinuation of study medication
 - Defervescence* during** neutropenia
 - Not discontinued from study medication because of toxicity or lack of efficacy
 - Baseline infections: global response assessed as complete or partial at end of therapy

*definition ? 2004: temperature (oral, axillary?) below 38°C for at least 48 hours,

**logical? What, if neutropenia resolves before fever?

IV and oral ITRA versus iv AMB as Empirical Therapy for Persistent Fever in Neutropenic Patients with Cancer (side effects)

	Itraconazole	AmphoB	
	N (%)	N (%)	
Drug related adverse events	9 (5)	103 (54)*	p=0.001
AE leading to treatment withdrawal	36 (19)	73 (38)*	p=0.001
Severe adverse event	37 (19)	65 (34)*	p=0.001
Infusion-related toxicity			
Fever	12 (6)	20 (10)	
Chills or rigors	19 (10)†	77 (40)†	p<0.001
Nausea	46 (24)	45 (23)	
Vomiting	37 (19)	40 (21)	
Dyspnea	17 (9)	21 (11)	
Tachycardia	6 (3)	12 (6)	
Hypotension	13 (7)	21 (11)	

IV and oral ITRA versus iv AMB as Empirical Therapy for Persistent Fever in Neutropenic Patients with Cancer (side effects)

	Itraconazole	AmphoB	
Metabolic toxicity	N (%)	N (%)	
Nephrotoxicity	10 (5)	46 (24)	p<0.001
Hypokalemia	34 (18)	59 (31)	p=0.004
Hypomagnesemia	14 (7)	17 (9)	
Bilirubinemia	19 (10)	9 (5)	p<0.001
Increased ALAT	5 (3)	3 (2)	
Increased ASAT	4 (2)	1 (1)	
Increased γ -GT	4 (2)	3 (2)	
Premedication to support study drug administration			
Analgetics	8 (4)	82 (43)	p<0.001
Antihistamines	6 (3)	69 (36)	p<0.001
Corticosteroids	1 (0.5)	50 (26)	p<0.001

VORI compared with LAMB for Empirical Therapy in Patients with Neutropenia and Persistent Fever

T. J. Walsh 2002

	Voriconazole	L-AMB	
severe infusion-related reactions			p<0.01
chest pain	0.2%	4%	
back pain	0%	3%	
flank pain	0.2%	2%	
dyspnea	0.7%	8.8%	
anaphylactoid reactions	0	1.6%	
nephrotoxicity			
SCr>1.5xbaseline	10.4%	19.0%	p<0.001
SCr>2.0x baseline	7.0%	7.6%	
hepatotoxicity			
bilirubin >3xbaseline)	40 (10%)	46 (12%),	
transient visual changes	21.9%	0.7%	p<0.001
hallucinations	4.3%	0.5%	p<0.001

Small confirmatory study for the Boogaerts study (1)

- Open, randomised, parallel group
- 3 Strata:
 - allo SCT patients
 - febrile patients with lung-infiltrates (CT not IFI specific)
 - other FUO patients
- randomisation ITR i.v. or AMB i.v.,
cross-over in cases of poor tolerability / efficacy,
(comparison of strategies „ITRA first“ vs „AMB first“)
- centers: 24 hospitals in Germany

German confirmatory empiric study (2)

	Itraconazole (n = 81)	Amphotericin B (n = 81)
Gender (female), %	29.6	32.1 ^a
Age, median (range), years	55.0 (18–73)	50.0 ^b (18–76)
Underlying diagnosis, patients, %		
Acute lymphatic leukaemia	7.4	14.8
Acute myeloid leukaemia	51.9	53.1
Chronic myeloid leukaemia	12.3	4.9
Lymphoma	17.3	16.0
Myeloma	1.2	2.5
Other	9.9	8.6
Treatment of haematological disease, patients, %		
Total	70.4	71.6
Chemotherapy	29.6	28.4
Allogeneic SCT	14.8	16.0
Autologous SCT	2.5	2.5
PBSCT	23.5	23.5
Stratum, patients, n (%)		
1: Allogeneic SCT	26 (32.1)	24 (29.6)
2: FUO with lung infiltrates	22 (27.2)	33 (40.7)
3: FUO	33 (40.7)	24 (29.6)

German confirmatory empiric study (3)

- response criteria

- Failure
 - documented deep fungal infection or highly suggestive CT, ...
 - death due to fungal infection
 - persistent fever on day 28
 - deterioration of signs and symptoms potentially attributable to deep fungal infection ...
 - empirical antifungal regimen changed by investigator
 - discontinuation of study medication due to poor tolerance ...
- Unevaluable
 - treatment duration < 3 days, except when due to poor tolerance
 - death not due to fungal infection
 - microbiologically documented bacterial or viral infection alone responsible for the fever
- Response
 - not being classified into the failure or unevaluable category
 - patients who have received 10 days of study medication and remained afebrile for at least 2 consecutive days (< 38 °C)

German confirmatory empiric study (4)

	Itraconazole	Amphotericin B	P value
Discontinued treatment due to any adverse event, %	22.2	56.8	< 0.0001
Average treatment period, days	14.5	9.3	< 0.0001
Response rate, %	61.7	42	< 0.0001
Success rate, %	70.4	49.3	< 0.0001
Composite endpoint (according to Walsh [5]), %	55.1	26.6	0.0002
Fungal infections			
Baseline	4	2	n.s.
Breakthrough ^a	6	6	n.s.

^a1 in each group based on CT scans only.

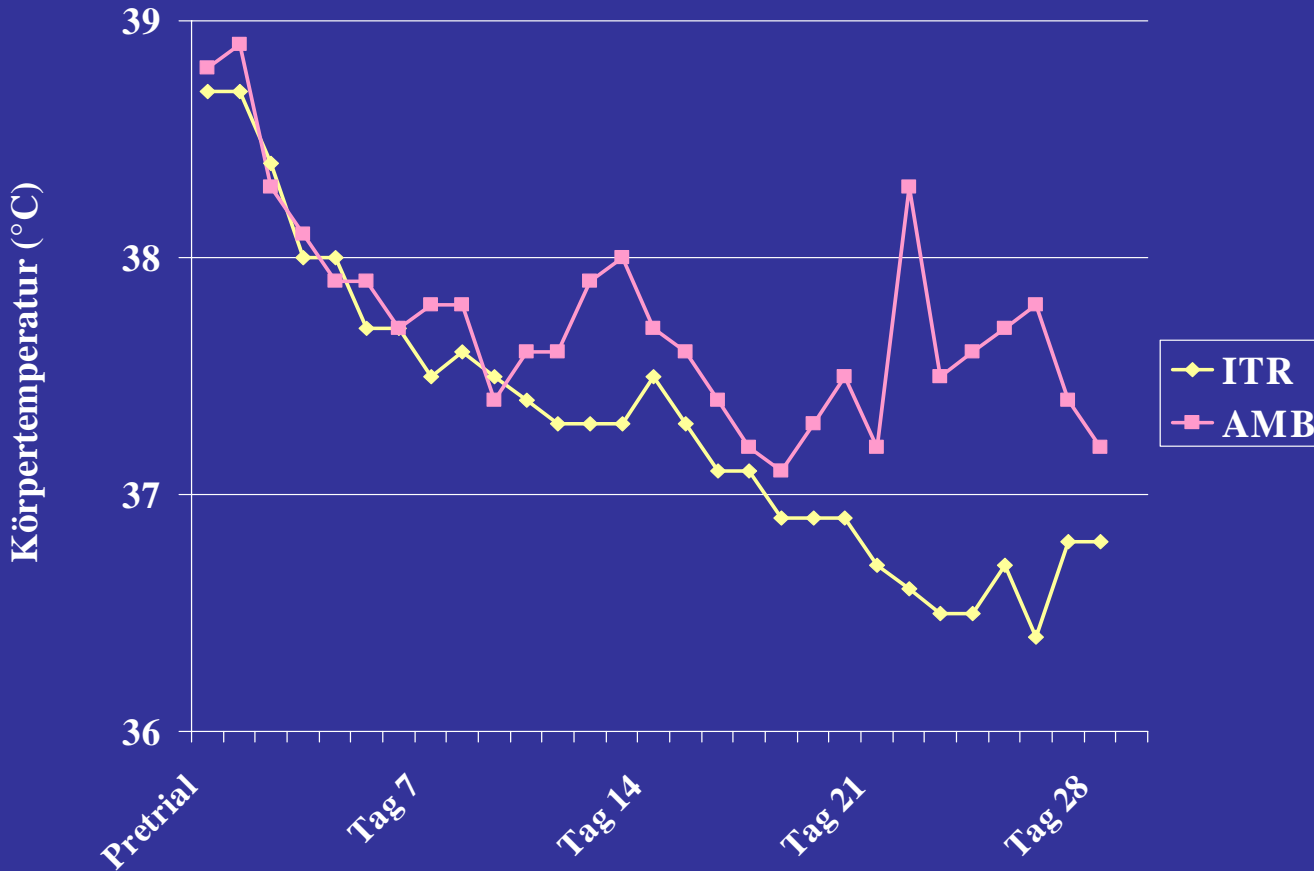
n.s. = Not significant.

Success rate =
Response/(Response+Failure)

Schuler et al.
Onkologie 2007;30:185

Temperature

- first treatment



IDSA-Guidelines 2008: Summary of recommendations

- empiric therapy

Condition	Therapy		Comments
	Primary	Alternative	
Empirical and preemptive antifungal therapy	For empirical antifungal therapy, L-AMB (3 mg/kg/day IV), CASPO (70 mg day1 IV and 50 mg/day IV thereafter), ITRA (200 mg every day IV or 200mg BID), VORI (6 mg/kg IV every 12h for 1 day, followed by 3mg/kg IV every 12 h; oral dose is 200 mg every 12 h)		... Preemptive therapy is a logical extension of empirical antifungal therapy in defining a high-risk population with evidence of invasive fungal infection (e.g., pulmonary infiltrate or positive galactomannan assay result)



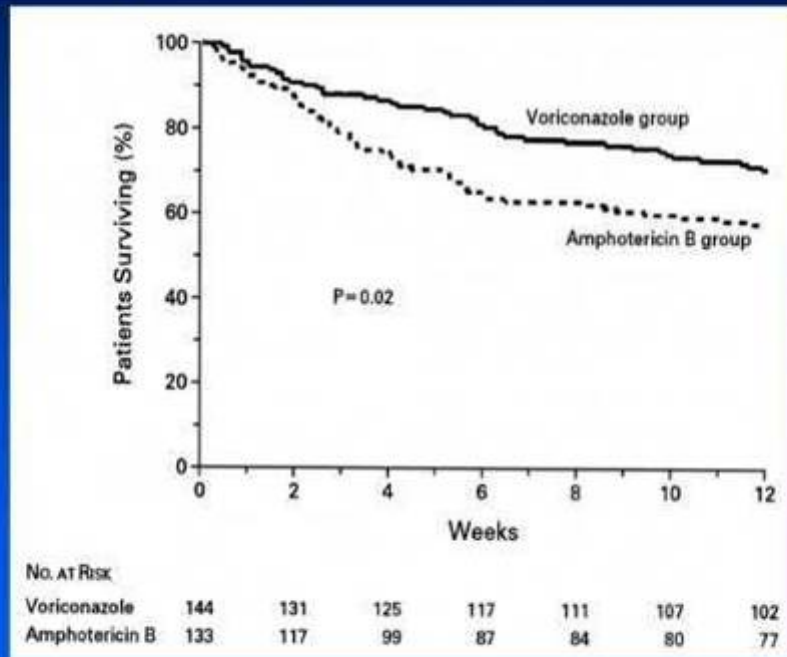
Moritzburg

residence of

Electoral
August the Strong
of Saxony and
King of Poland
(1694-1733)

..everybody kows this slide

Randomized Comparison of Voriconazole vs AmB for Primary Therapy of Invasive Aspergillosis



Herbrecht R et al (EORTC IFICG), N Engl J Med 2002;347:408-15

Why is L-AMB \geq D-AMB \geq Vori in the Walsh studies (EAFT) but Vori \gg D-AMB in the „therapeutic“ Herbrecht et al. study ?

... it is not a positive selection for VORI

TABLE 2. SITE OF THE INFECTION, DEGREE OF CERTAINTY, AND EVIDENCE SUPPORTING BASE-LINE DIAGNOSIS IN THE MODIFIED INTENTION-TO-TREAT POPULATION.

VARIABLE	VORICONAZOLE GROUP (N= 144)	AMPHOTERICIN B GROUP (N= 133)
	no. (%)	
Site of the infection		
Lung only	123 (85.4)	117 (88.0)
Sinus	8 (5.6)	7 (5.3)
Cerebral*	5 (3.5)	5 (3.8)
Disseminated†	4 (2.8)	1 (0.8)
Other	4 (2.8)	3 (2.3)
Level of certainty of the diagnosis of aspergillosis		
Definite‡	67 (46.5)	41 (30.8)
Probable	77 (53.5)	92 (69.2)
Initial evidence of aspergillosis§		
Positive finding on microscopy	56 (38.9)	46 (34.6)
Positive culture	84 (58.3)	65 (48.9)
Positive histologic examination	35 (24.3)	22 (16.5)
Halo or air-crescent sign only	46 (31.9)	49 (36.8)

*Category includes those with other organ involvement.

†Category excludes those with cerebral involvement.

‡There were significantly more definite cases in the voriconazole group

- But „definite“ in this study is not „proven“ in the EORTC-criteria
- Some of the „probable“ patients might have ended as „empiric“ in other studies
- “...radiologic evidence of new pulmonary lesions
(*..not necessarily halo..*)
...in a patient
...who had a neutropenic hematologic condition with
.... a sputum culture that was positive for aspergillus
(*.....not from a sterile site...*)

IDSA-Guidelines 2008: Summary of recommendations

- Invasive pulmonary aspergillosis

		Therapy		
Condition	Primary	Alternative		Comments
IPA	VORI (6 mg/kg IV every 12 h for 1 day, followed by 4 mg/kg IV every 12 h; oral dosage is 200 mg every 12 h)	L-AMB (3–5 mg/kg/day IV), ABL C (5 mg/ kg/day IV), CASPO (70 mg d1 IV +50 mg/day IV thereafter), MICA (IV 100–150 mg/day; dose not established), POSA (200 mg QID initially, then 400 mg BID PO after stabilization), ITRA (dosage depends upon formulation)		Primary combination not routinely recommended limited clinical experience is reported with anidulafungin;

Treatment of invasive aspergillosis: Analysis of **Compassionate Use Itraconazole** Therapy for Invasive Aspergillosis by the NIAID* Mycosis Study Group Criteria

Stevens & Lee, Arch Intern Med (1997)

Site of Aspergillosis	Complete Response	Improved	Unchanged	Worsened	Total	CR+PR
Pulmonary	21 (23)	34 (38)	13 (14)	22 (24)	90	(61)
Bone	5 (29)	6 (35)	2 (12)	4 (24)	17	(64)
Sinus	1 (08)	3 (25)	3 (25)	5 (42)	12	(33)
Skin	3 (27)	5 (45)	1 (09)	2 (18)	11	(72)
CNS	0	3 (38)	2 (25)	3 (38)	8	(38)
other	7 (28)	9 (36)	3 (12)	6 (24)	25	(64)
Overall	34 (27)	45 (36)	20 (16)	26 (21)	125	(63)

* National Institute of Allergy and Infectious Diseases

Analysis of **Compassionate Use Itraconazole: Therapy** for Invasive Aspergillosis by the NIAID* Mycosis Study Group Criteria

Stevens & Lee, Arch Intern Med (1997)

Underlying Disease Group	Complete Response	Improved	Unchanged	Worsened	Total	CR+PR
Hematological dyscrasia Neutropenia	20 (35)	12 (21)	5 (09)	20 (35)	57	(56)
Solid organ transplantation	6 (38)	4 (25)	1 (06)	5 (31)	16	(63)
Solid tumor	2 (17)	7 (58)	2 (17)	1 (08)	12	(75)

* National Institute of Allergy and Infectious Diseases

Invasive Aspergillosis	itraconazole	Voriconazole	conv Amph B	Caspofungine
Caillot et al, CID 2001, 33; 83-00.	Total response %48			
	Complete response %25	Partial response %23		
Denning et al, CID 2002, 34; 563-71.			%48	
			%14 %34	
Herbrecht et al, NEJM, 2002, 347			%53	%32
			%21 %32	%17 %15
Stevens et al, Arch Inc Med, 1997; 157, 1857.	Total response % 63			
	Complete response %27	Partial response %36		
Viscoli et al, JAC, 2009 64, 1274–1281.				%33
				%2 %31

Summary

- Itraconazole is a valuable drug in the increasing armamentarium of antifungals
- Both the **oral solution** and the **i.v. formulation** can provide **adequate serum levels** of itraconazole and hydroxyitraconazole even in critically ill patients
- Current IDSA-Guidelines list itraconazole as a **possible primary choice for empiric therapy** and as an **alternative in prophylaxis and therapy of definite IPA**
- In most health care systems the price of itraconazole compares favorably to other antifungals
- Due to changes in prophylaxis and new approaches to diagnosis, concepts of diagnosis and empiric therapy are under constant reevaluation

A scenic view of the Sächsische Schweiz (Saxon Switzerland) in Germany. The image shows dramatic rock formations, including a prominent, tall, narrow rock spire in the center. The foreground is dominated by a large, dark rock formation. The background features a misty lake and distant hills under a clear blue sky. The text "Thank you !" is overlaid on the right side of the image.

Thank you !

Sächsische Schweiz

Discussion slides

Aspergillus-Antigen

- Most data:
Aspergillus galactomannan antigen testing
using the Platelia ELISA
- cut-off used to determine positivity:
the ratio between
a weak positive control and the test specimen
- Initially value of 1.5 suggested,
now lowered to 0,5-1.0 [**0.5 FDA-approved**]
- Others: single value of 0.7 or above
 or multiple values of 0.5 or greater
- [In the end: arbitrary decision affecting both sensitivity
and specificity]

Mode of Action of Antifungals

Mechanism of Echinocandins
e.g. Caspofungin:
Inhibition of β -(1,3)-glucan synthase

β -(1,6)-glucan

cellwall

phospholipid bilayer
of the
cell-membrane

combination=
structural
weakening
in 2 levels !

β -(1,3)-glucan

Mechanism of Azols

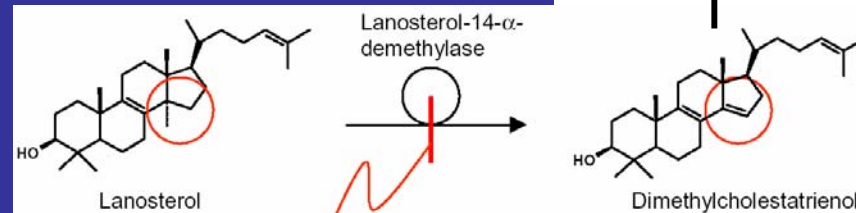
e.g. Itraconazole, Fluconazole,
Voriconazole:

Change of sterole-composition
of membrane (less ergosterol, *different*
steroles

Accumulation of *intermediates of*
synthesis in the cell

„Polyen-Channels“

Ergosterole



Price comparison of present systemic antifungals in the market

Product	Company	Formulation	Posology	Price	7 day tx cost /patient
SPORANOX (Itrakonazole)	Janssen Cilag	IV 200mg & Oral	First 2 days 2x200mg loading	215,93 TL	1.943,37 TL
			After loading 1x200 mg	98,07 TL	98,07 TL
AMBISOME (Lip-Amf-B)	ERKİM /GILEAD	IV 50 mg	Every day 3mg/Kg/day	305,46 TL	8.552,88 TL
ABELCET (Lipid Complex)	ONKO KOÇSEL	IV 100 mg	Every day IV 5 mg/kg/day	209,08 TL	4.390,68 TL
CANCIDAS (Caspofungine)	MSD	IV 50 mg	First day 70 mg loading Every day IV 50 mg	701.20 TL	5.114,19 TL
VFEND (Voriconazole)	PFIZER	Oral 200 mg & IV 200 mg	First day 6 mg loading	989,73 TL	494,86 TL
			Every day 2x4mg	578,92	6.182,88 TL
FUNGIZONE (C-Amf-B)	BMS	IV 50 mg	IV 50 mg	16,14 TL	112,98 TL

Drug Monitoring

Voriconazole Therapeutic Drug Monitoring in Patients with Invasive Mycoses Improves Efficacy and Safety Outcomes

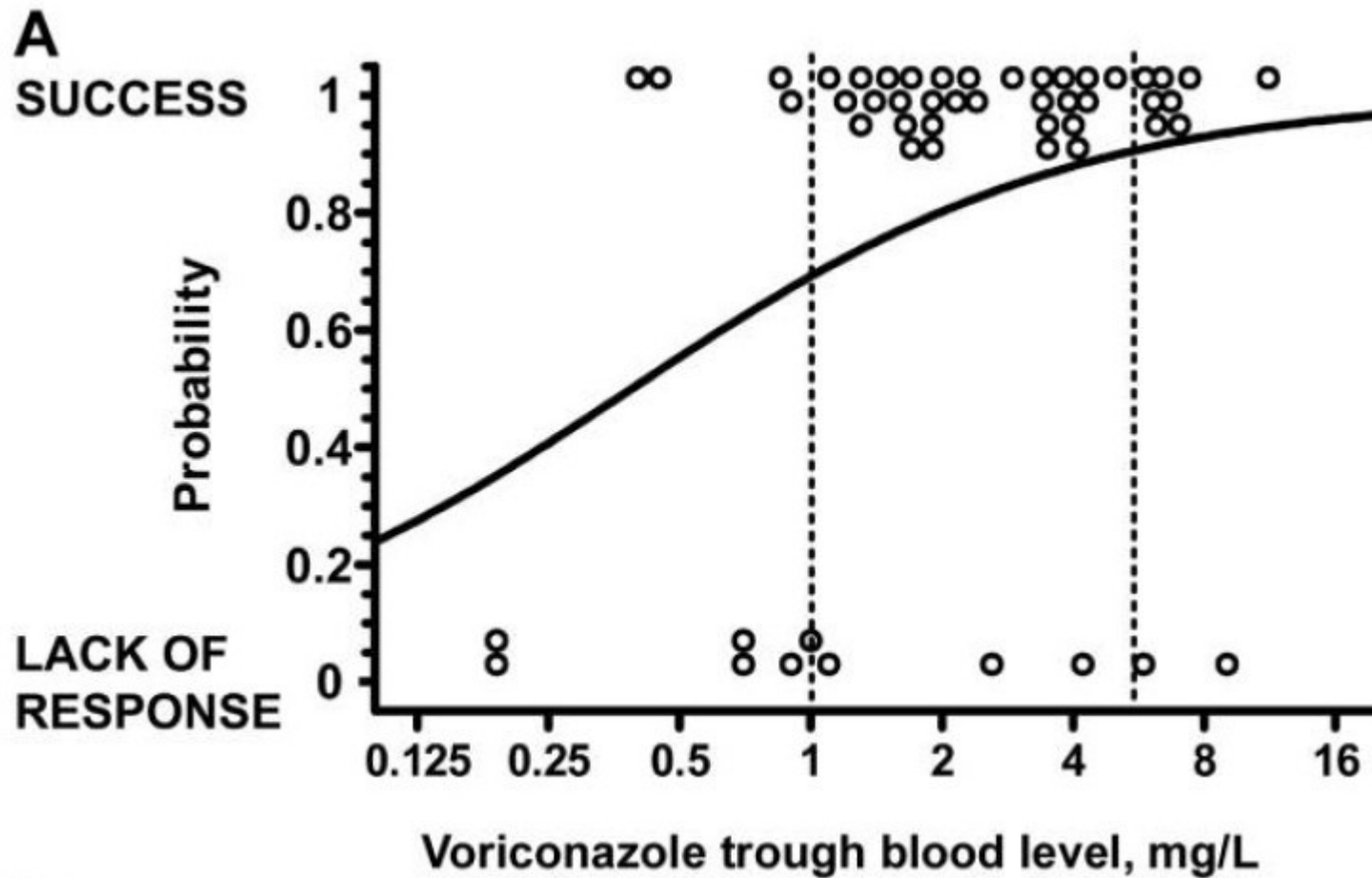
Andres Pascual,¹ Thierry Calandra,¹ Saskia Bolay,¹ Thierry Buclin,² Jacques Bille,³ and Oscar Marchetti¹

¹Infectious Diseases Service, ²Division of Clinical Pharmacology, and ³Institute of Microbiology, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland

Outcome

Variable	Voriconazole trough blood level		P
	≤1 mg/L (n = 13)	>1 mg/L (n = 39)	
Route of voriconazole administration			.05
Intravenous	4 (31)	24 (61)	
Oral	9 (69)	15 (39)	
Voriconazole dosage, median mg/kg/day (range)			
Overall	7 (2.5–9)	8 (2–11)	NS
Intravenous	7.5 (7–8)	8 (6–11)	NS
Oral	6 (2.5–9)	7 (2–11)	NS
Response to antifungal therapy			
Interval between start of voriconazole therapy and assessment, median days (range)	21 (10–120)	17.5 (10–180)	NS
Treatment success			
Overall	7 (54) ^a	34 (88)	.02
Complete response	5	27	
Partial response	2	7	
Lack of response			
Persistence	3 (23)	0 (0)	
Progression	3 (23)	4 (10)	
Breakthrough IFI	0 (0)	1 (2)	

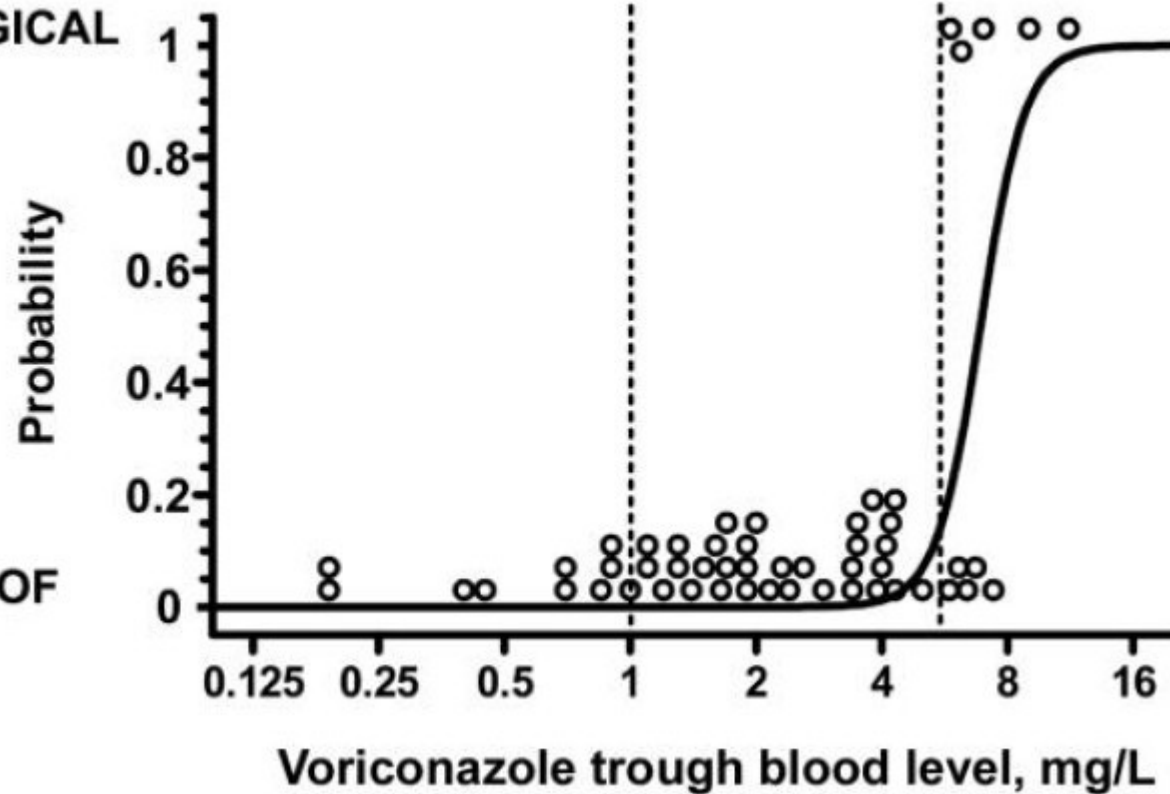
Outcome



Outcome

B

NEUROLOGICAL
TOXICITY



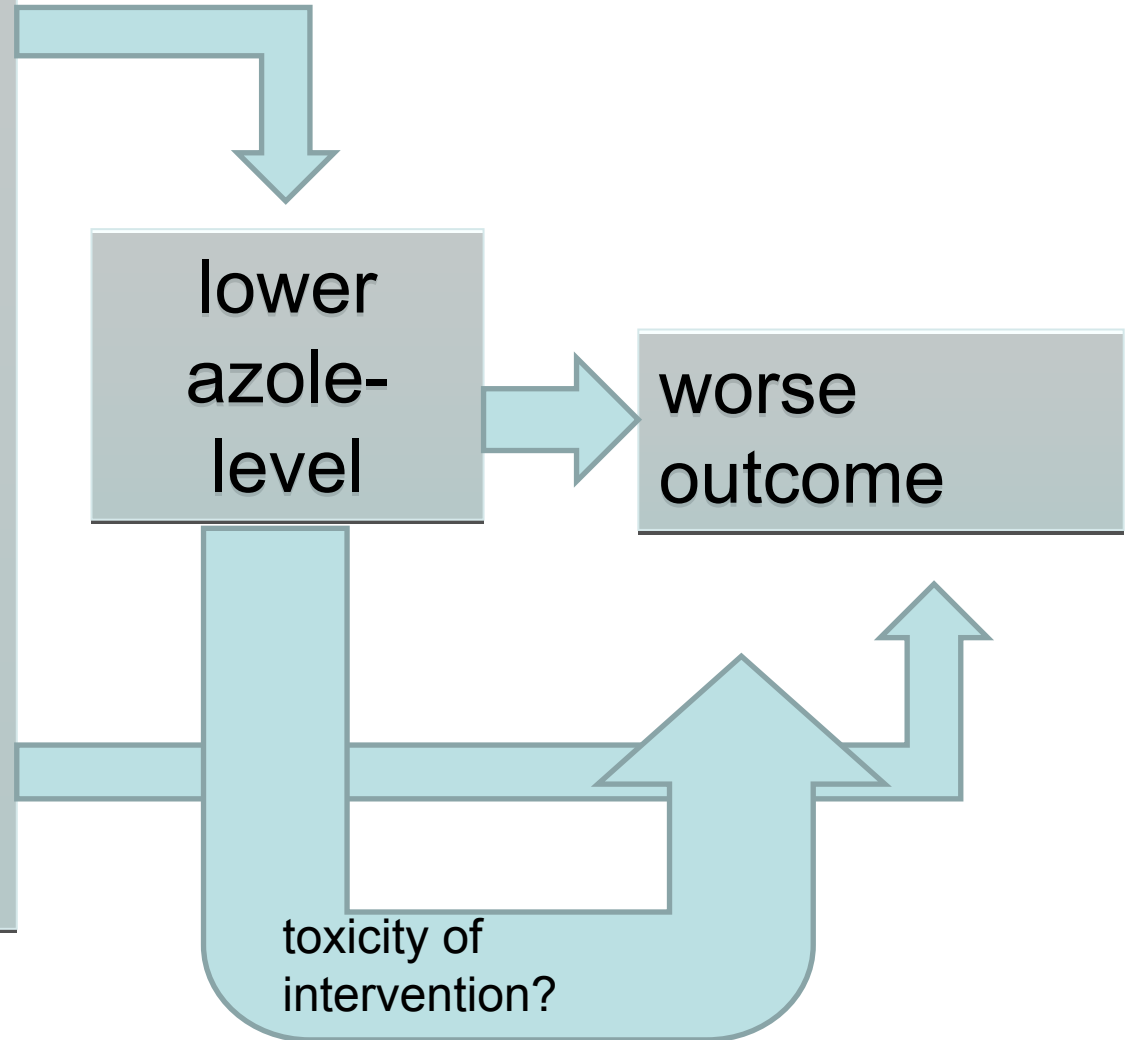
ABSENCE OF
TOXICITY

What would be an AI-Level recommendation for TDM?

- Randomisation of TDM-based Intervention (or Randomisation TDM yes/no)
- Prophylaxis:
 - o Estimate of necessary cases at an IA-Rate of 2% without TDM with posaconazole?
?will 1000 patients per arm be sufficient?
- Therapie?
 - o Evidence: (a) „Failure“ \leftrightarrow drug level ▼
(b) Intervention \leftrightarrow Outcome ▲ ?

What could be sources of bias?

- GI-comorbidity (oral route)
- medication for other comorbidity
- increased metabolism
- non-compliance
- genetics
-



Interaktionspotential

	FLUC	ITRA	VORI	POSA
Metabolisierung [Metabolit]	sehr gering (CYP)	CYP3A4, [OH-ITRA aktiv]	CYP2C19, CYP3A4, (CYP2C9), [N-Oxid inaktiv]	Glucoronidierung (Uridindiphosphat- glucoronosyl- transferase, [inaktiv])
Interaktions- potential	CYP2C9, CYP2C19, CYP3A4	CYP3A4, pH- Wert-Erhöhung	CYP2C9, CYP2C19, CYP3A4	Pgp-, UGT- Beeinflussung, pH- Wert-Erhöhung, Nahrung
Relevanz IA- Potential für Dosierung Azol	-	CYP3A4 Induktoren (-), Antacida (-)	CYP3A4 Induktoren (-), Omeprazol (+), CYP2C19 poor and extensive metabolizers, Phenytoin (-)	z.B. Ciclosporin (+), Rifampicin (-), Antacida (-)

Patients

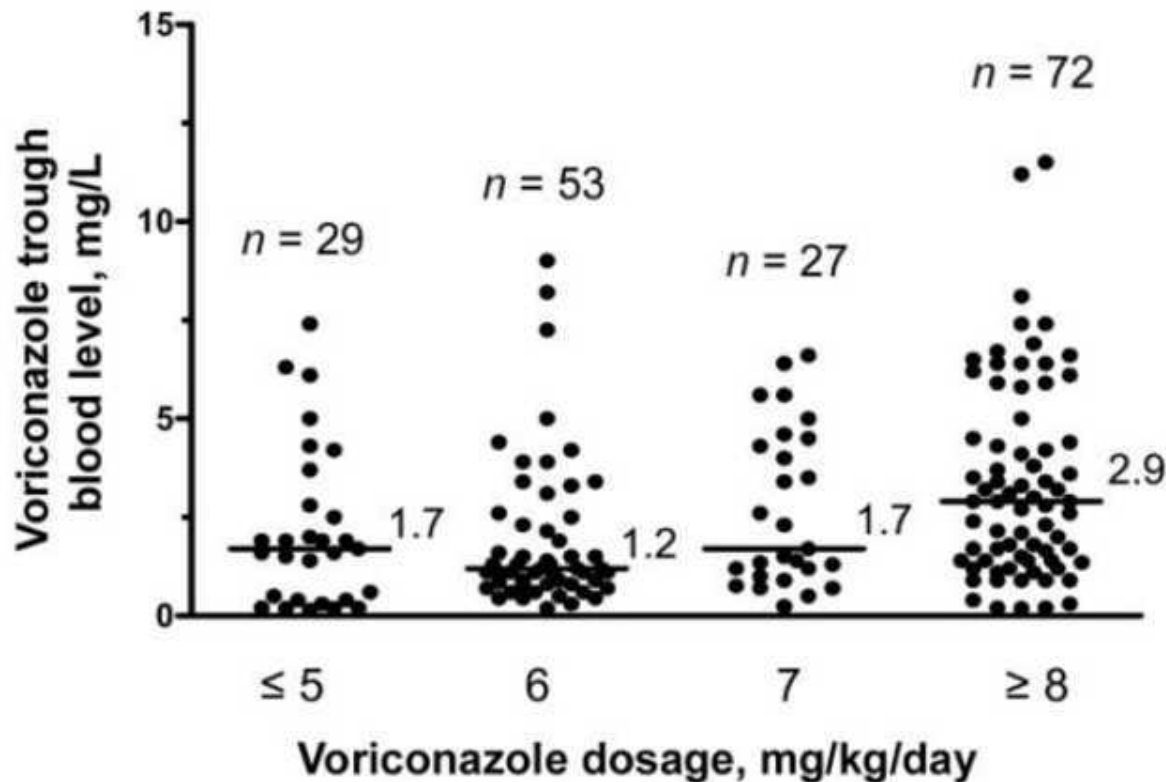
N=52

Underlying condition

Hematological malignancy, neutropenia <0.5 g/L	32 (61)
Solid-organ transplantation	3 (6)
Abdominal surgery	3 (6)
Chronic liver disease	3 (6)
Other condition ^a	7 (13)
None	4 (8)

Fungal infection

Proven or probable invasive aspergillosis ^b	26 (50)
Lung	19 (36)
Sinus ^c	3 (6)
Disseminated ^d	3 (6)
Intra-abdominal	1 (2)
Proven or probable invasive candidiasis ^e	8 (15)
Bloodstream	3 (6)
Hepatosplenic	4 (7)
Bone	1 (2)
Other proven invasive fungal infection (<i>Pseudallescheria boydii</i> and <i>Paecilomyces</i> species): bone	2 (4)



N=52

Figure 1. Relationship between voriconazole dosage and voriconazole trough blood level. Each point represents a single blood level measurement. Numbers of measurements for each daily dose are reported. Horizontal bars represent median values (the numerical values are reported on the right of the horizontal bar for each group). Voriconazole dosages have been rounded to the nearest unit.

Die 6 Patienten mit „lack of response“

	Underlying disease	IFI	When <1 mg/l	Outcome Dose ▲
1	Acute Leukemia	Probable IA	24	CR
2	Crohn´s diseas	Proven IA	20	CR
3	AIDS	Proven IA	14	CR
4	Hodgkin	Probable Hepatosplenic Candidiasis	34	CR
5	Alcoholic liver cirrhosis	Proven Sinus Aspergillosis	13	CR
6	?	Proven Sinus Aspergillosis	22	CR

CYP2C19 Genotyp als Ursache der Variabilität?

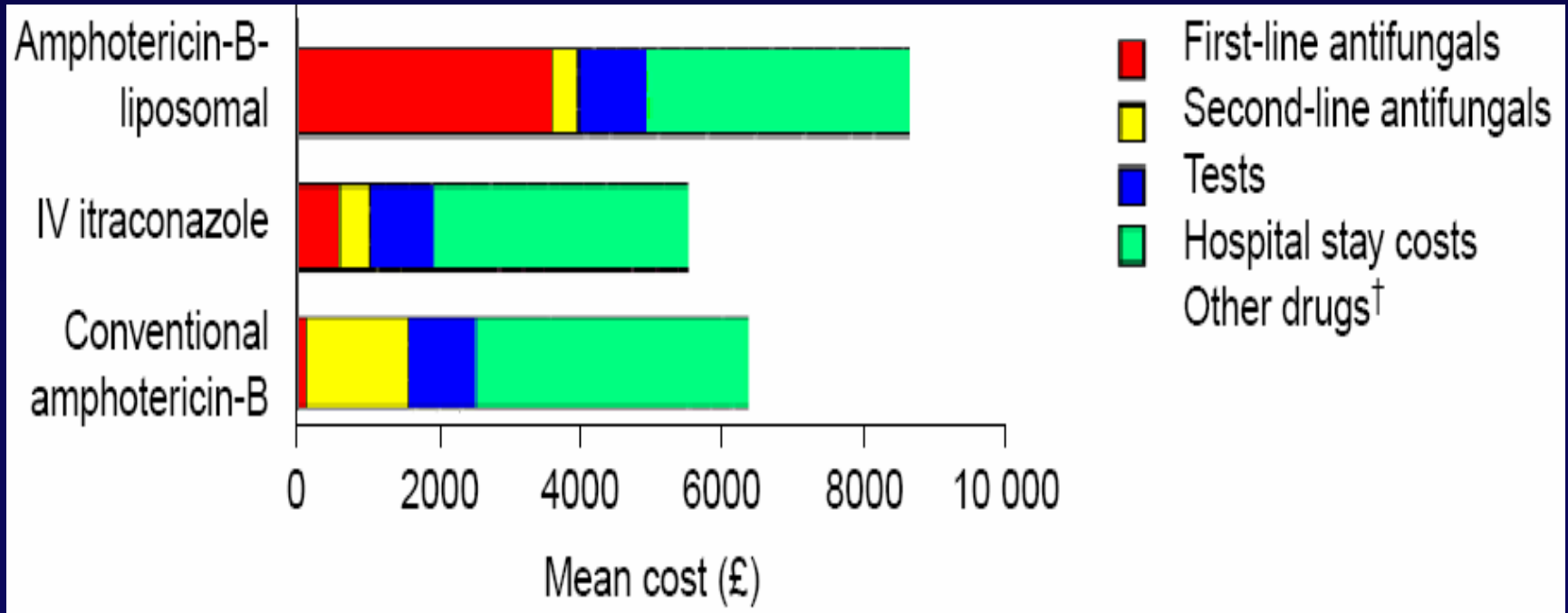
mean values

Parameter	Cyp2C19 *1/ *17; *2/*17 (n=10)	Cyp2C19 *1/ *1 (n=9)	Cyp2C19 *1/ *2 (n=11)	Cyp2C19 *2/ *2 (n=5)
C_{max} (µg/ml)	2,16	3,10	2,84	3,13
T_{1/2} (h)	6,96	7,23	8,25	14,28
AUC (h×µg/ ml)	13,27	16,44	25,66	45,73
Cl (ml/min)	526,9	465,5	319,2	162,9

Mod. from Weiss J. et al. (J Clin Pharmacol 2009; 49: 196-204)

Caucasians: 2-5% PM, 26-28% heterozygous EM, 70-73% homozygous EM (10% ultrarapid metabolizers)? Andes et al. AAC 2009; 53: 24-34

Sporanox IV provides a cost-effective treatment on empirical treatment



IV itrakonazol < konv AmfB < AmfB liposomal
 5500 £ < 6200 £ < 9000 £

¹ van Gool et al. The Cost of Treating Systemic Fungal Infections, Drugs, 2001; 61 Suppl 1:49-56.

What about prophylaxis? Allogenic BMT Patients **Itra vs Fluc**

200 mg IV / oral itraconazole vs 400 mg IV / oral fluconazole

	Itraconazole	Fluconazole	
Invazive Fungal Infection (IFI)	% 9	% 32	*
Superficial fungal infections	% 4	% 3	
GIS side effects	% 24	% 9	*
General Mortality	% 45	% 42	
IFI related mortality	% 9	% 18	



pathways through the `antifungal jungle`

dangers
of the jungle:

- suboptimal
therapy
- delayed
chemotherapy
- budget-
limits

-.....