

Medical University of Graz

Broad spectrum triazoles: which drug and when?

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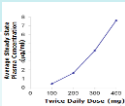
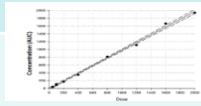
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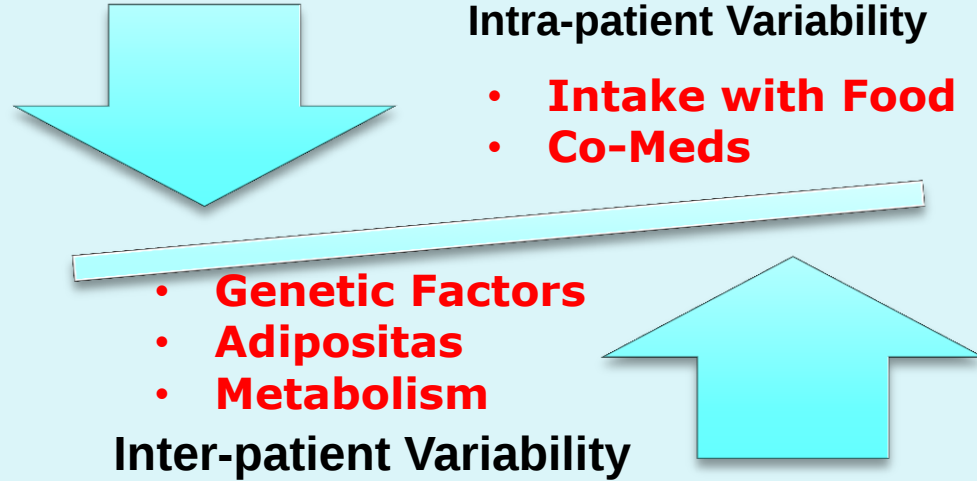
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SANTA BARBARA • SANTA CRUZ

	Voriconazole	Posaconazole	Isavuconazole
Dosage	2x6mg/kg Tag 1, 2x4mg/kg ab Tag 2	Susp: 4x200mg Tablette / iv 2x300mg (Tag 1), 1x300mg ab Tag 2	200mg 3xtgl Tag 1+2; 200mg 1xtgl Erhaltung
po/iv	po = iv (+/-; Dosage matters!)	po < iv	po = iv
Intake	Fasting state	Fatty meals (Suspension) No influence (Tablette)	No influence
Half-Life	6h	27-35h	110-115h
Oral Bioavailability	96%	Suspension: variable, no data. Tablet: 54%	98%
Linear PK	No 	Yes (Suspension, Tablet), No (iv)	Yes 
CNS Penetration	High	Low	High (Animal Model)
Renal Excretion	2%	<1%	<1%
Metabolism	CYP2C19, CYP2C9, CYP3A4	UGT	CYP3A4/5

TDM necessary?



Hoenigl AAC 2013
Hoenigl IJAA 2014
Hoenigl IJAA 2012

	Voriconazole	Posaconazole	Isavuconazole
Intrapatient Variability	high	Medium to low (tablet and iv formulation), high (suspension)	Low
Interpatient Variability	high	Medium to low (tablet and iv formulation), high (suspension)	Medium to low
Exposure-Response Relationship	yes	probably	no



■ TDM Voriconazol

Low VPCs associated with Treatment Failure & Mortality

- Dolton AAC 2012: Treatment failure associated with VPCs <1.7 mg/L
- Pascual CID 2007: Failure of therapy associated with VPCs <1 mg/L
- Neely CID 2010: Higher mortality (OR 2,6) in children with <1 mg/L
- Smith AAC 2006: Failure of therapy associated with VPCs <2.05 mg/L

Higher VPCs associated with Treatment response

- Miyakis CMI 2009: Response to therapy associated with VPCs >2.2 mg/L
- Hoenigl AAC 2012: Response to therapy associated with VPCs >1.5 mg/L

Higher VPCs associated with Toxicity

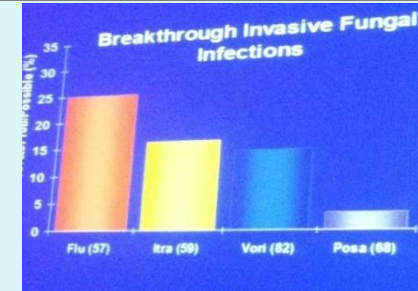
- Kim IJID 2012: only predictor for SAE VPC >5.83 mg/L
- Dolton AAC 2012: visual disturbances/hallucinations associated with VPCs > 5.0 mg/L

■ TDM Posaconazole

- **Breakthrough infections rare in those with Posaconazole Prophylaxis**

Ananda Rajah MR, Hematologica 2012

- **but those who develop Breakthrough infections have usually low PPCs**



Fungal species	Posaconazole MIC when available (mg/L)	Patient's age years/ sex	Specimen of fungal detection	Days of Posaconazole prophylaxis before breakthrough infection	Last Posaconazole plasma level before diagnosis of IMI (days before diagnosis)	Antifungal therapy after IMI diagnosis	Outcome
Aspergillus fumigatus	0.032	58/f	BAL	8	0.28 µg/mL (1)	Voriconazole	Died
Aspergillus spp.		20/m	BAL / Serum	23	<0.20 µg/mL (4)	Voriconazole	Survived
Geosmithia argillacea	0.25	52/m	BAL / Blood culture	>60	0.31 µg/mL (7)	Voriconazole, LipAmph B	Died

■ TDM Posaconazole

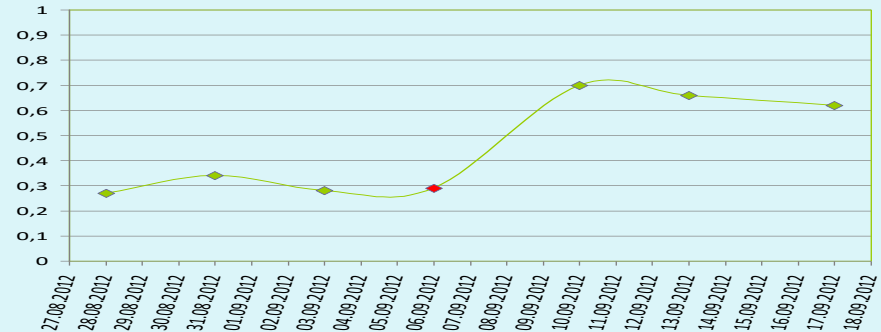
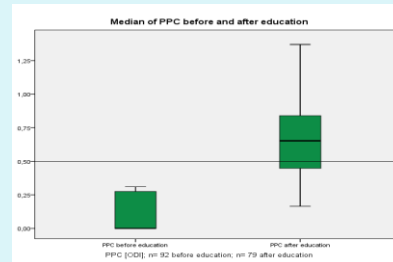
- **Posaconazole Suspension: 30% - 70% of all PPCs below target**
- **Posaconazole DRT: Generally <10% of PPCs below target**

Solution Patient Education

NOXAFIL® wird unter den folgenden Bedingungen optimal aufgenommen:

Bitte beachten Sie die Gebrauchsinformation, welche der Verpackung beiliegt.

Einnahme von NOXAFIL® gemeinsam mit
Fettthaltiger Nahrung
falls nicht möglich
Nahrung
falls nicht möglich
Nahrungsergänzungsmitteln/Sondennahrung
falls nicht möglich
Kohlensäurehaltigen Getränken (z. B. Cola)



TDM Recommendations

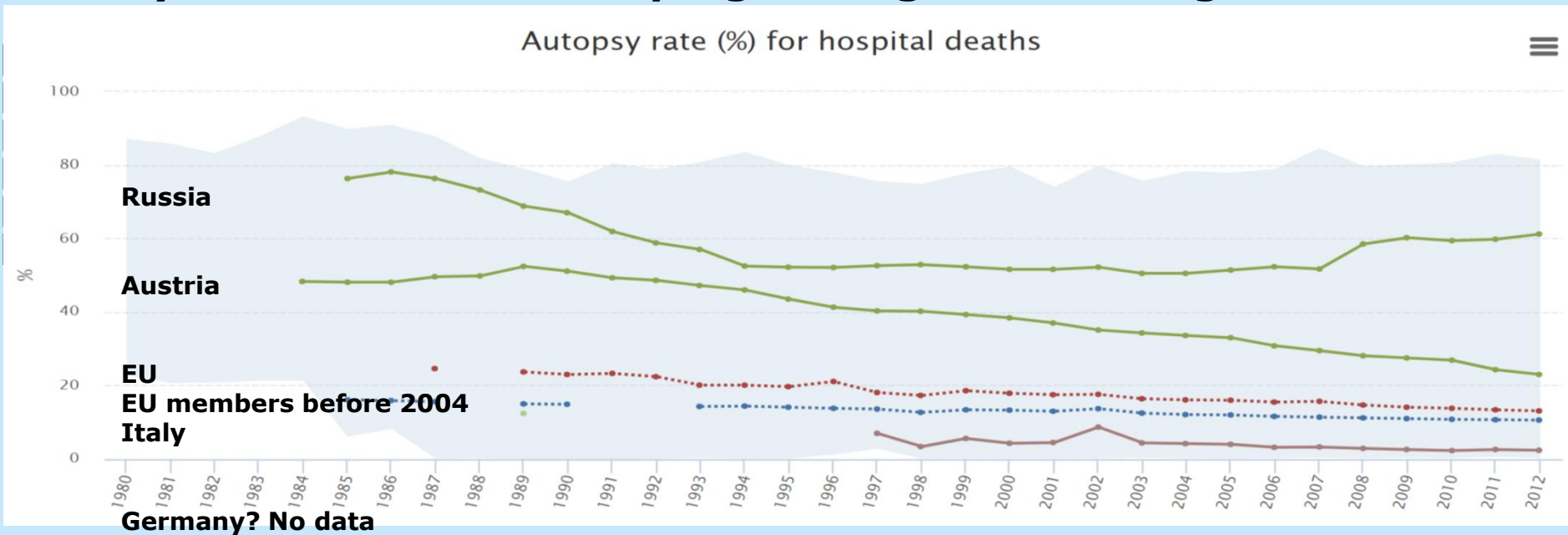
ECIL-6	Voriconazole	Posaconazole	Isavuconazole	Itraconazole
TDM Treatment	All (efficacy) All (toxicity)	All (efficacy)	TDM not routinely recommended	All (efficacy) BII (toxicity)
TDM Prophylaxis		BII (efficacy)		
Lower target concentration (Efficacy)	1-2 mg/L (>2mg/L for severe infections, higher MICs)	Prophylaxis: 0.7 mg/L Treatment: 1.0 mg/L	NA	>0.5 mg/L Prophylaxis > 1mg/L Treatment
Upper target (Toxicity)	5-6 mg/L	More studies needed	NA	HPLC <4 mg/L Bioassay <17 mg/L
TDM Timepoint	Day 2-5, repeat!	Suspension: Day 5-7 Tablet/iv: after Day 3	NA	Day 7-14
ESCMID 2017	Voriconazole	Posaconazole	Isavuconazole	Itraconazole
TDM Treatment	AI	AI	CIII	AI
TDM Prophylaxis	AI	CII	CIII	AI

Autopsy Rates in Europe

Big Difference between countries. Overall Trend: DECREASE!



Many cases of Invasive Aspergillosis get never diagnosed



https://gateway.euro.who.int/en/visualizations/line-charts/hfa_544-autopsy-rate-for-hospital-deaths

RCTs on Antifungal Prophylaxis

	AML/MDS induction Cornely NEJM 2007 (n=602)		Allo-SCT with GVHD Ullmann NEJM 2007 (n=600)		Allo-SCT Wingard Blood 2011 (n=600)		Allo-SCT Marks Br J Haematol 2011 (n=489)	
	Posa (n=304)	Flu/Itra (n=298)	Posa (n=301)	Flu (n=299)	Vori (n=305)	Flu (n=295)	Vori (n=234)	Itra (n=255)
Invasive Aspergillosis	0.7% (n=2)	6.7% (n=20)	1.0% (n=3)	5.7% (n=17)	3.0% (n=9)	5.8% (n=17)	0.4% (n=1)	2.1% (n=5)
Total Invasive Fungal infections (IFI)	2.3% (n=7)	8.3% (n=25)	2.3% (n=7)	7.4% (n=22)	7.3% (n=22)	11.2% (n=33)	1.3% (n=3)	2.1% (n=5)
Reductions in IFIs	72%		69%		35%		38%	
IFI related Death / Fungal free survival	2%	5%	3%	8%	78%	75%	-	-
Death all cause	16%	22%	25%	28%	81%	80%	82%	81%

Red = significant difference

Guidelines: Acute (Myeloid) Leukemia & Prolonged Neutropenia

	Posaconazole Tablet/OS 	Voriconazole	Itraconazole	Fluconazole	Micafungin / Caspofingin
ECIL 5 AML	AI	BII	BI	BI	CII
ESCMID 2017	AI	CII	DII	-#	CII
IDSA 2016*	AI	AII	AII	-	CIII

* During prolonged neutropenia for those who are at high risk for IA (both AML and HSCT without GvHD)

BI if given together with nebulized liposomal Amphotericin B

Maertens et al., ECIL 5

Ullmann et al., ESCMID, CMI submitted

Patterson et al., CID 2016;63(4)

Guidelines: Allogeneic HSCT until Engraftment

	Posaconazole Tablet/OS 	Voriconazole	Itraconazole	Fluconazole	Micafungin / Caspofingin
ECIL 5 HSCT Pre-engraftment low risk	BII	BI	BI	AI	BI (Micafungin)
ECIL 5 HSCT Pre- engraftment High risk	BII	BI	BI	AIII against \$	CI
ESCMID 2017	BII	CI	DI	-#	CI
IDSA 2016*	AI	AII	AII	-	CIII

*During prolonged neutropenia for those who are at high risk for IA (both AML and HSCT without GvHD)

BI if given together with nebulized liposomal Amphotericin B

\$ BIII if given together with nebulized liposomal Amphotericin B

Guidelines: GVHD

	Posaconazole Tablet/OS 	Voriconazole	Itraconazole	Fluconazole	Micafungin
ECIL 5	AI	BI	BI	AIII against	CII
ESCMID 2017	AI	CII	CII	-	CIII
IDSA 2016	AI	AII	AI	-	-

Maertens et al., ECIL 5

Ullmann et al., ESCMID, CMI submitted

Patterson et al., CID 2016;63(4)

Golden Raspberry for the rest?

Posaconazole
Tablet/OS



Voriconazole

Itraconazole

Fluconazole

Micafungin

BI

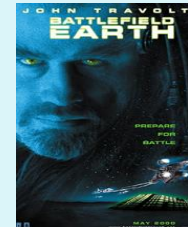
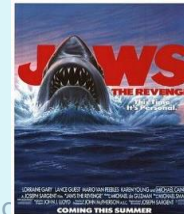
CII

All

CII

CIII

-



When would alternative Prophylaxis options make sense?

Voriconazole:

- Cheaper alternative in hospitalized patients in settings that do regular TDM (iv>po).
- Alternative in prophylaxis in Allo SCT before engraftment
- Good option for **prophylaxis in Lung TX** patients (AIII according to ESCMID 2018)

Isavuconazole:

- No studies, but should work

Itraconazole:

- Alternative for low ressource settings/low risk patients



BAL LFD, BAL Culture & Antifungals

Retrospective analysis 63 cases with probable/proven IPA

Test	Under mould active AF	Without mould active AF
BAL LFD	56% (14/25)	86% (36/42)
BAL Culture	14%	31%

GM cut-off 0.5:

Sensitivity without AF 95%
Sensitivity with AF 71%

GM cut-off 1.0:

Sensitivity without AF 81%
Sensitivity with AF 52%

Eigl, Prattes, Buchheidt, Hoenigl et al.
Int J Antimicrob Agents Chemotherapy 2015
Heldt, Hoenigl. Curr Fung Infect Report 2017

Mould active AF also reduce sensitivity of **Aspergillus PCR** from:

- Blood samples
 - Springer CMI 2015: European PCR initiative Blood PCR in patients with AF specificity 52%, sensitivity 50%
- BAL samples
 - Reinwald, JAC 2012

All diagnostic lab tests for IA have REDUCED SENSITIVITY UNDER MOULD ACTIVE AF!!

- Blood samples more affected than BAL samples!

SOLUTION: BIOMARKER/TEST COMBINATIONS!!

- GM +/- PCR +/- LFD from BALF +/- Blood
 - +/- BAL culture +/- Blood BDG +/- Cytokines
- Markedly increased sensitivity, specificity mostly unchanged

REFS FOR BIOMARKER COMBINATIONS : Buchheidt, BOCH et al. CMI 2016; Hoenigl , Buchheidt et al JCM 2014; 52(6):2039-45; Eigl, Hoenigl, Boch et al. Med Mycol 2017; White et al JCM 2013; Reinwald et al Eur J Hematol 2012; Torrelli et al. JCM 2011



Novel Biomarkers for Combination



FIGURE 1 Results with the new *Aspergillus*-specific lateral-flow device test ranging (from the left to the right) from negative (-) to weak positive (+), moderate positive (++) and strong positive (+++)

Hoenigl et al
Mycoses 2017

DOI: 10.1111/myc.12704

Heldt et al
Mycoses 2017

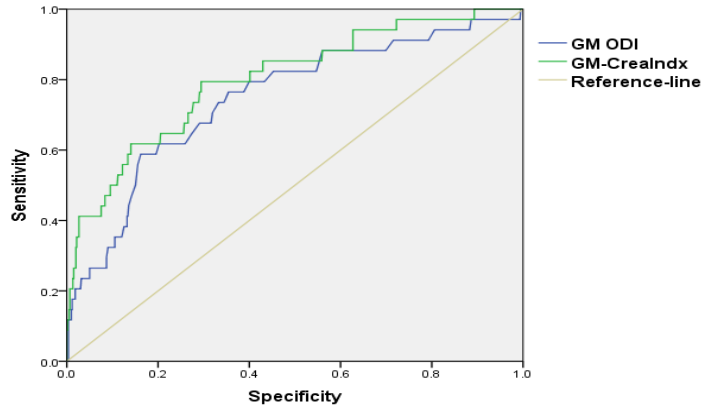
Goncalves et al
*Frontiers
Microbiol* 2017

New *Aspergillus* specific LFD from BALF

IL-8 (and IL-6) from Serum and BALF

Cytokine	Cut-off (pg/mL)	Sensitivity	Specificity
<i>Serum</i>			
IL-6	>15	90	60
	>200	60	90
IL-8	>88	60	85
	>360	50	95
IL-10	>6.75	60	90
<i>BALF</i>			
IL-6	>56	100	65
IL-8	710	90	70

GM/Crea Index from Urine



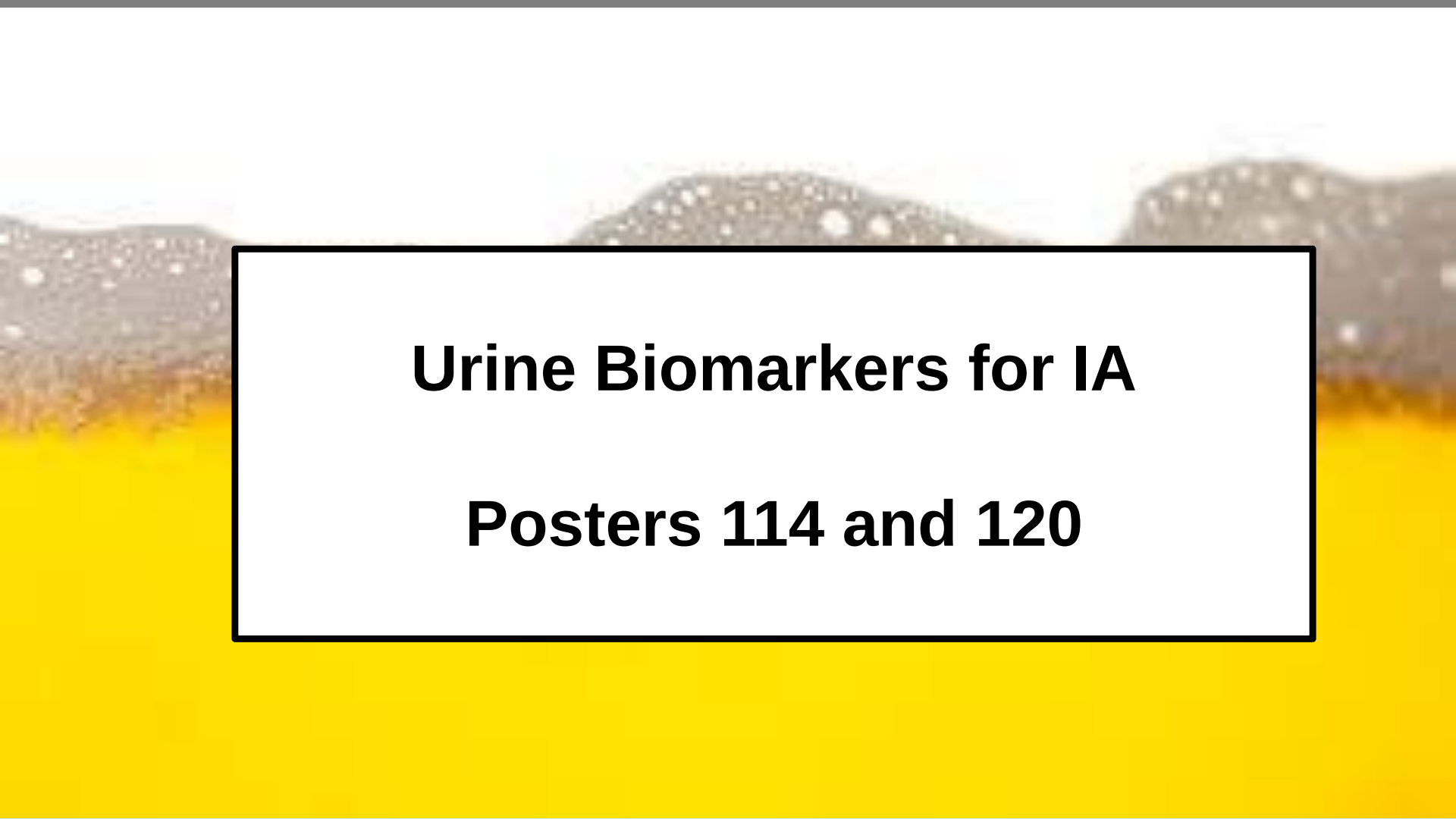
Reischies et al *JCM* 2015

TAFC/Crea Index from Urine

	Sensitivity	Specificity	PLR	NLR
Per Patient				
TAFC/crea (95% CI)	0.86 (0.49 – 0.97)	0.88 (0.64 – 0.97)	6.86 (1.81 – 25.96)	0.16 (0.03 – 1.01)
Per Sample				
TAFC/crea (95% CI)	0.81 (0.60 – 0.92)	0.90 (0.71 – 0.97)	8.5 (2.2 – 32.3)	0.21 (0.09 – 0.51)

Prattes, Haas et al *TIMM* 2017

Martin Hoenigl



Urine Biomarkers for IA

Posters 114 and 120

Triazoles for Treatment of Aspergillosis

NNT to Avoid Organ Toxicity by Replacing Voriconazole with Isavuconazole

Liver

NNT = 14

Eye

NNT = 9

Skin toxicity

NNT = 11

Targeted Treatment of Invasive (Pulmonary) Aspergillosis in Hematological Malignancy Patients

	Isavuconazole	Voriconazole	Itraconazole	Liposomal Amphotericin B
ECIL 6	AI	AI	CIII	BI
ESCMID 2017	AI - AII	AI - AII	CII - CIII	BII
IDSA 2016	AII	AI	-	AII

Salvage Treatment for IA: Switch to another Drug Class

	Liposomal Amphotericin B	Voriconazole	Itraconazole	Posaconazole
ECIL 6	BII	BII	CIII	BII
ESCMID 2017	BII	AII	CII	BII

Frederic Tissot et al. Haematologica 2017;102:433-444

Ullmann et al., ESCMID, CMI submitted

Patterson et al., CID 2016;63(4)

Targeted Treatment of Invasive (Pulmonary) Aspergillosis in Hematological Malignancy Patients

	Isavuconazole	Voriconazole	Itraconazole	Liposomal Amphotericin B
ECIL 6	AI	AI	CIII	BI
ESCMID 2017	IA in other patients (i.e. without Hematological Malignancy) 1st line: Voriconazole AIII (ESCMID 2018)			BII
IDSA 2016				AII
Sa				Class
				ole
ECIL 6				BII
ESCMID 2017				BII

Frederic Tissot et al. *Haematologica* 2017;102:433-444

Ullmann et al., *ESCMID*, CMI submitted

Patterson et al., *CID* 2016;63(4)

CNS Aspergillosis & Endophthalmitis

CNS Aspergillosis

Hoenigl, Krause. Curr Pharmaceutical Design 2012

Voriconazole 1st line

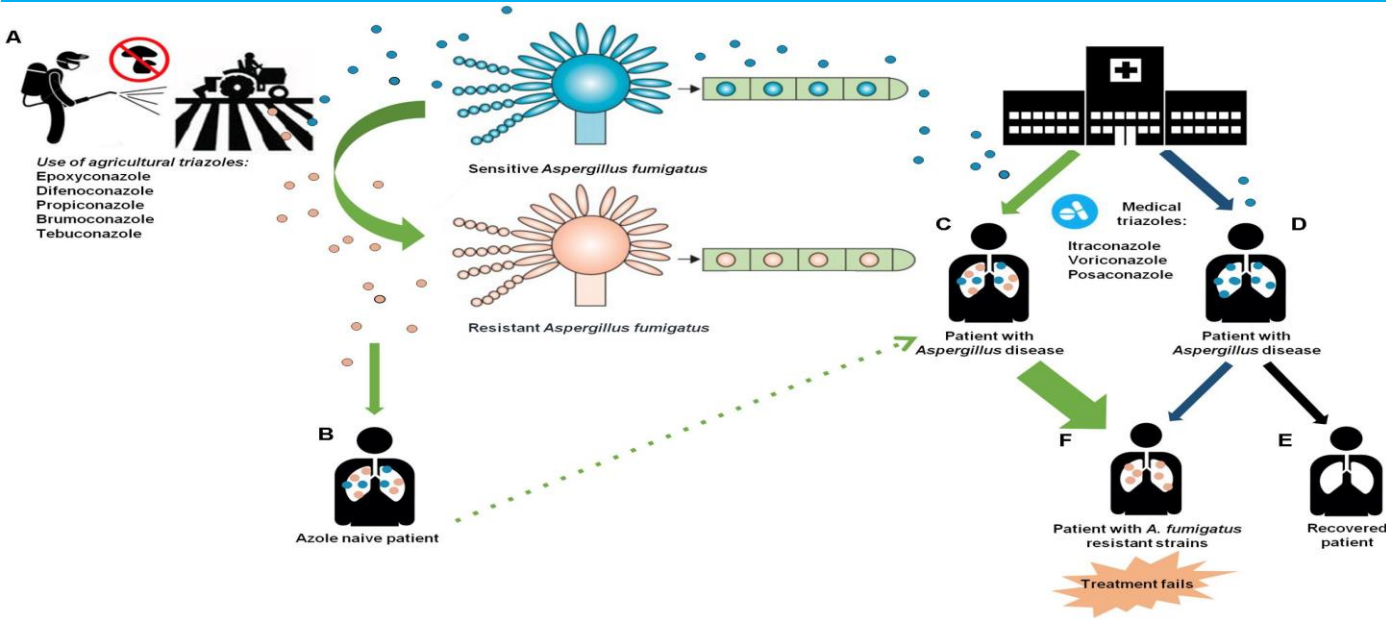
AII recommendations in ESCMID 2017 and IDSA 2016

Salvage: Ambisome and Isavuconazole (Good CNS penetration in Animal Models)

Aspergillus Endophthalmitis

Systemic Voriconazole + intravitreal Vori / Ampho B (IDSA AIII)

Aspergillus Azole Resistance



Berger et al
Frontier Microbiol
2017



Treatment of Mucormycosis

Chamilos et al. CID 2008

- **Hit early and hard when mucormycosis is suspected**
- **Do not think only of Aspergillus**

Triazoles for Treatment of Mucormycosis

Survival: Isavuconazole versus Amphotericin B Regimens Matched Control Comparison

*Marty F, et al. VITAL-FungiScope. Lancet Infect Dis
2016; 16: 828–37*



www.fungiscope.net



Targeted Treatment for Mucormycosis

	Isavuconazole	Liposomal Amphotericin B	Posaconazole
ECIL 6	?	BII	CIII (for 1 st line) BII (for salvage)
ESCMID 2013	-	All	BII (for 1 st line) All (for salvage)

Initial use of combination treatment does not impact survival of 106 patients with haematologic malignancies and mucormycosis: a propensity score analysis

A. Kyvernitakis ^{1, 2}, H.A. Torres ¹, Y. Jiang ¹, G. Chamilos ³, R.E. Lewis ⁴, D.P. Kontoyiannis ^{1, *}

Update of Guidelines currently in Progress!

Frederic Tissot et al. Haematologica 2017;102:433-444

Cornely et al CMI 2013

Other Fungal Infections: Fusarium

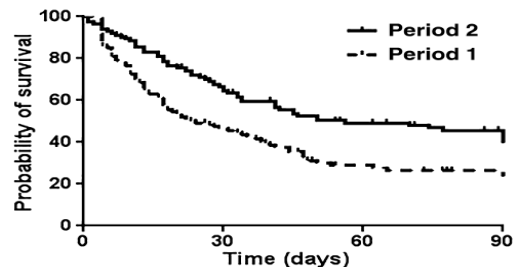


FIG. 1. Probability of 90-day survival of 233 patients with invasive fusariosis in period 1 (1985–2000) and period 2 (2001–2011).

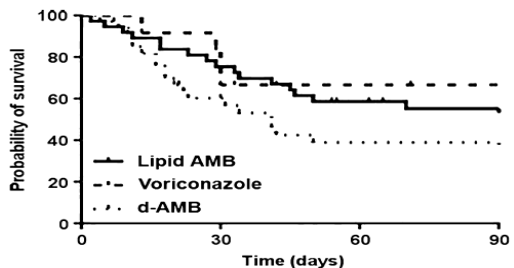


FIG. 2. Probability of 90-day survival of 83 patients with invasive fusariosis in period 2 treated with deoxycholate amphotericin B (d-AMB), voriconazole, or a lipid formulation of amphotericin B (Lipid AMB).

Voriconazole 1st Line (AII)

TABLE 5. Summary of recommendations for treatment of *Fusarium* infection

Population	Intention	SoR	QoE	Comment	References
Immunocompromised patients	First-line treatment Voriconazole	A	III,r	Therapeutic drug monitoring required Response rate was associated with underlying condition and infection site	[23,24,60,196,197]
	Liposomal amphotericin B	B	III,r	Fungi may be resistant to amphotericin B	[4,198,199]
	Amphotericin B lipid complex	C	III	Limited case reports	[200]
	Amphotericin B deoxycholate	D	III,u	Fungi often resistant to amphotericin B Breakthrough infections may occur	[4,198,199]
	Any echinocandin	D	III	Excessive toxicity	[21]
	Any combination therapy	C	III	Intrinsically resistant Limited reports	[23,24,63–65,67,68,196]
	Salvage treatment Posaconazole	A	II	Combination not better than voriconazole alone	[23,61]
	Voriconazole	A	III	Overall success rate 50% Breakthrough infections Therapeutic drug monitoring required Substantial efficacy Therapeutic drug monitoring required	[62]

QoE, quality of evidence; SoR, strength of recommendation.

Other Fungal Infections: *Scedosporium*

Scedosporium apiospermum complex

TABLE 8. Summary of recommendations for treatment of *Scedosporium* spp. infections

Population	Intention	SoR	QoE	Comment	References
Immunocompromised patients	First-line treatment				
	Voriconazole	A	IIr,t	Therapeutic drug monitoring required Success in 66%	[6,87,96,224–228]
	Itraconazole	D	III	Only one case, failed	[229]
	Any combination	C	III	Unclear whether combination is more effective than either drug alone	[6,196,225,230–233]
	Liposomal amphotericin B	D	III	Variable activity	[96,225]
	Amphotericin B deoxycholate	C	III	<i>S. apiospermum</i> may be resistant Excessive toxicity	[225]
Near drowning victims Cystic fibrosis patients	Posaconazole	C	III	Only case reports	[234]
	Voriconazole	A	II	Good penetration into central nervous system	[89,235–239]
	Voriconazole	B	III	Therapeutic drug monitoring	[227,240,241]
	Any combination of antifungals	C	III	Case reports	[242,243]

Voriconazole 1st Line

Isavuconazole: need more data (only 3 patients in SECURE)

Lomentospora prolificans

TABLE 9. Summary of recommendations for treatment of *Scedosporium prolificans* infection

Population	Intention	SoR	QoE	Comment	References
Immunocompromised patients Lung infections	Voriconazole	A	II _{r,t}	40% survival Therapeutic drug monitoring	[96,260,261]
	Voriconazole plus terbinafine	B	III	Case reports, 50% survival	[68,91,131,133,262–269]
	Itraconazole	C	III	Case reports, 15% survival	[97,129,263,270]
	Amphotericin B deoxycholate	D	III	Case reports, 4% survival	[118,271–276]
	Any combination	C	III	Case reports only	[86,119,130,277–281]
	Fluconazole	D	III	Case reports	[98,263,275]
	Voriconazole or Posaconazole plus terbinafine (plus granulocyte colony-stimulating factor)	B	III	Case reports	[68,131,269]
Dissemination	Voriconazole	B	II		[261]
	Voriconazole plus terbinafine or posaconazole	B	III	Review of case series	[68,261,267,282]
Skin and subcutaneous infections	Surgery	A	III		[119,283]
Skin and subcutaneous infections	Voriconazole	B	II	91% success rate	[261]
Cerebral abscess	Surgery plus antifungals	A	III	Improved outcome with voriconazole- itraconazole failed	[251,284]
Osteomyelitis/septic arthritis	Voriconazole	B	III	Extensive surgical debridement enhances recovery rates; one case even without antifungals	[261,285]
	Fluconazole	D	III		[275]
	Combination of voriconazole and terbinafine or caspofungin	B	III		[111,132,286]
	Surgery	A	III		[111,119,251,275,282,285,286]

QoE, quality of evidence; SoR, strength of recommendation.

Voriconazole often high MICs

**Combination Treatment:
Broad Spectrum
Azole plus
Terbinafine**

Role of Itraconazole?

- **(among) 1st line for ABPA and CPA**
- **1st line for Chromoblastomycoses**
- **1st line for Mycetoma**
- **1st line for Histoplasmosis**
- **(among) 1st line for Talaromyces marneffe**

New Formulation: SUBA itraconazole in Capsules:

- **173% bioavailability and 21% less interpatient variability compared to conventional capsules**
- **Also more rapid attainment of therapeutic levels with less interpatient variability compared to liquid formulation**

4th Class Broadspectrum Azoles?

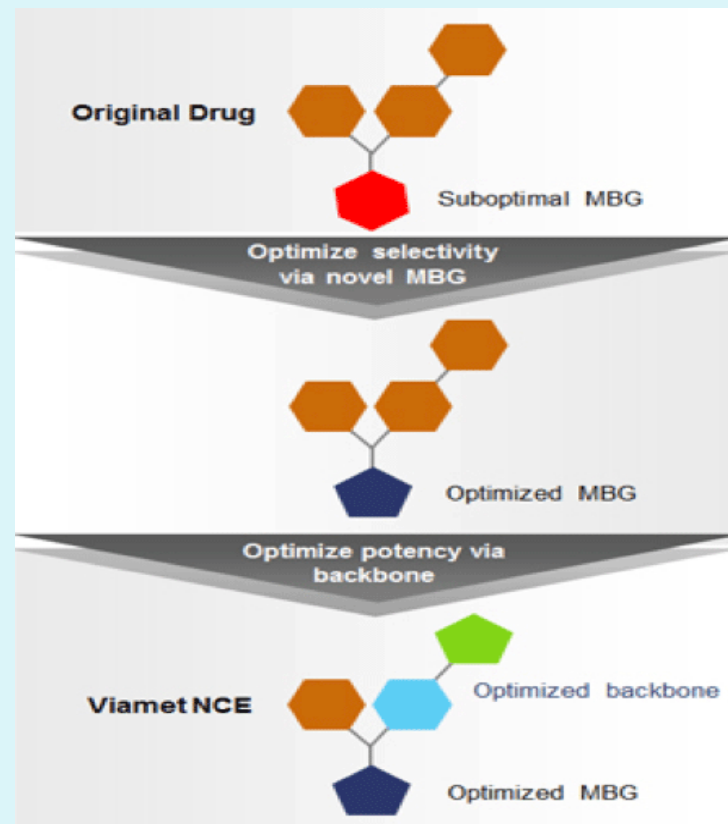
'Achilles heel' of current triazoles:
negative side effects through drug-drug
interactions



New chemistry approach: **Manipulation
of the metal-binding group** of the
standard azole compounds

**Reduced interactions with
cytochrome P450** and less drug- drug
interactions

Also chemical optimization of the
active antifungal backbone of
triazoles to increase half-lives



New Broad-spectrum Azoles?

Viamet Antifungal Franchise



VT-1161: phase II clinical trials for onychomycosis¹⁰⁶ and vaginal candidiasis (NCT02267356 and NCT02267382), and a very potent anti-cryptococcal compound

VT-1129: which has outstanding efficacy in vitro and in animal models for Crypto Meningitis

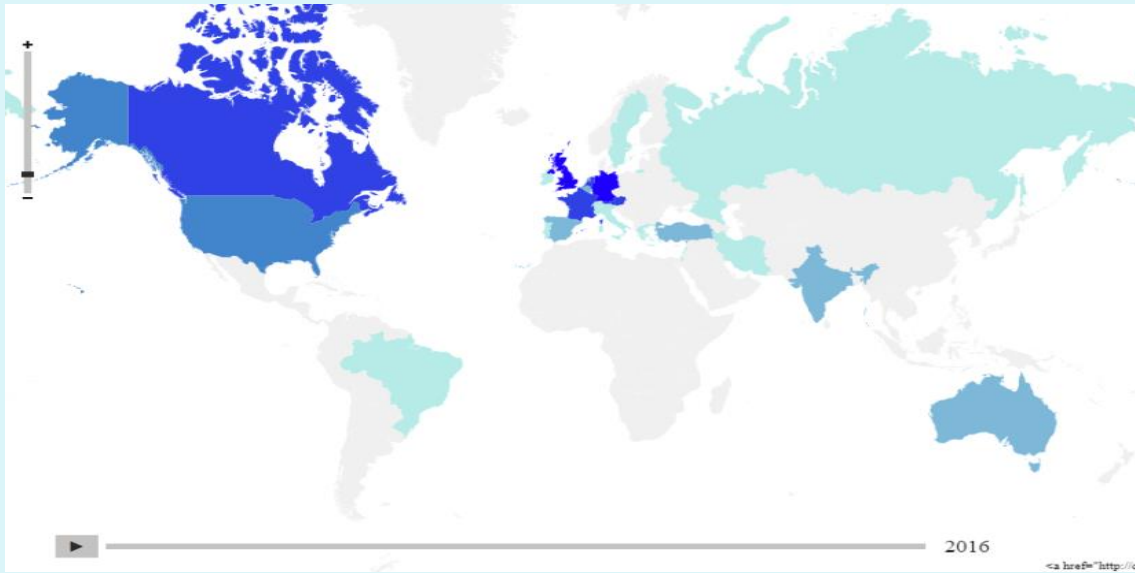
VT-1598, potent azole, with activity against endemic mycosis and cryptococcosis.

Take home messages

- **Posaconazole Prophylaxis is AI recommendation in patients at high risk for IA and has favorable PK/PD (Posa Tablet!)**
- **Voriconazole (iv) has its primary role in treatment of Invasive Aspergillosis but not in prophylaxis**
- **Isavuconazole is an excellent alternative choice for primary treatment of invasive aspergillosis**
 - **Fewer Adverse Events**
- **Liposomal Amphotericin B 1st line for Mucormycosis**
 - **Guidelines need to be updated regarding the role of isavuconazole**

Thank You For Your Attention!

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