



# Pilzinfektionen

⇒ Epidemiologie und Risikofaktoren

⇒ Diagnostik

⇒ Effektivität von Mundschutz

⇒ Neue Antimykotika

⇒ Antimykotische Therapie



# Epidemiologie und Risikofaktoren

# Epidemiologie invasiver Pilzinfektionen: Aktuelle Fragestellungen

- Welchen Stellenwert haben Zygomycosen („Mucormykosen“)?
- Verschiebt sich das Spektrum invasiver *Candida*-Infektionen zugunsten von *non-albicans*-Species?
- Sind früher Therapiebeginn und prompte Venenkatheter-Entfernung prognostisch von signifikantem Vorteil?
- Verbreiten sich azolresistente *Aspergillus*-Species in Zeiten des breiten Einsatzes von Voriconazol und Posaconazol?

# Zygomykosen in Europa, 2005-2008

## Registerstudie

- *European Confederation of Medical Mycology* (ECMM)
- Lokale Koordinatoren in 13 Ländern
- 230 Fälle (114 gesichert, 116 wahrscheinlich)
- Mittleres Alter 50 (1-87) Jahre, 61% männlich

## Risikofaktoren

- Hämatologische Neoplasie 45%, Stammzelltransplantation 10%, Tumor 5%, Trauma 9%, Diabetes mellitus 9%, chirurgischer Eingriff 8%, Verbrennung 3%, Organtransplantation 4%; ca. 30% immunkompetent

## Hauptmanifestation

- Pulmonal 29%, Weichteile 25%, Sinus 13%, rhinocerebral 14%, zerebral 2%, disseminiert 15%, Sonstige 2%
- Bei hämatologischer Neoplasie 34% pulmonale Manifestation
- Bei pulmonaler Manifestation 52% hämatologische Neoplasie
- Diabetes mellitus assoziiert mit rhinocerebraler Manifestation

## Vorbehandlung

- Glukokortikoide 46%, andere Immunsuppression 44%, Antimykotika 48%
  - ▶ 19% Voriconazol, 17% Fluconazol, 13% Amphotericin B, 13% Caspofungin

# Zygomykosen in Europa, 2005-2008

## Häufigste Isolate

- *Rhizopus* spp. 55, *Mucor* spp. 50, *Absidia* spp. 32, *Rhizomucor* spp. 20, *Cunninghamella* 8

## Therapie

- Antimykotika 82%, chirurgische Behandlung 43%, keine antimykotische Therapie 11%
  - ▶ alleinige medikamentöse Therapie 42%, alleinige chirurgische Therapie 3%

## Antimykotische Therapie

- Amphotericin B (AmB, meist liposomal) allein 35%, Posaconazol (Posa) alleine 7,8%, AmB + Posa 21,3%, AmB + andere 8,3%, AmB + Posa + andere 3,9%, Posa + andere 0,4%

## Sterblichkeit

- Gesamt 47,7%
  - ▶ Bei rhinozerebraler Manifestation 59%
  - ▶ Bei pulmonaler Manifestation 58%
  - ▶ Bei Sinus-Manifestation 40%

## Multivariate Analyse

- Günstig: chirurgische Therapie ( $p < 0,001$ ); Behandlung mit AmB
- Ungünstig: höheres Alter ( $p = 0,037$ ); nicht-traumatisch bedingte Infektion ( $p = 0,022$ ); Glukokortikoidtherapie ( $p = 0,035$ ); Caspofungin-Vorbehandlung

# Zygomykosen in Europa, 2005-2008

## Kommentar

- Diese Studie zeigt erstmals aktuelle Daten zu Zygomykosen aus Europa, ist aber nicht repräsentativ, da die Dokumentation der Daten vom Engagement lokaler Koordinatoren abhängig war.
- Es dominieren *Rhizopus*-Spezies.
- Bei hämatonkologischen Patienten steht der pulmonale Befall im Vordergrund.
- Der Einsatz von liposomalem Amphotericin B ist Standard, die Kombination mit Posaconazol experimentell.

# ***A. fumigatus*: keine Zunahme der Triazol-Resistenz bei hämatologischen Patienten**

## **Prospektive Studie**

- Hôpital Henri Mondor, Paris
- 77 *A. fumigatus*-Isolate, prospektiv gesammelt bei 51 hämatologischen Patienten im Zeitraum 1/2006-12/2007
  - ▶ 3 gesicherte, 32 wahrscheinliche, 1 mögliche invasive Aspergillose
  - ▶ 15 ohne klinischen Hinweis auf invasive Aspergillose
- Molekulare Identifikation mittels Sequenzierung des *A. fumigatus* beta-Tubulin-Gens
- Bei Isolaten mit Itraconazol-MHK (Etest) >4 mg/l: Sequenzierung des CYP51A-Gens und Promoters
- Heterogenität der Isolate durch Genotypisierung gesichert
- 30 der 77 Isolate stammten von Patienten unter Voriconazol.

## **Ergebnisse**

- Nur 1 Isolat hatte Itraconazol-MHK >4 mg/l (16 mg/l) bei Voriconazol- und Posaconazol-MHK <0,38 mg/l
  - ▶ Der Träger dieses Isolates hatte keine Azoltherapie.
- CYP51A-Sequenzierung zeigte keine Mutation oder Tandem-Repeat-Insertion im Genpromotor.

# ***A. fumigatus*: keine Zunahme der Triazol-Resistenz bei hämatologischen Patienten**

## **Kommentar**

- In diesem großen französischen Zentrum hat sich eine Ausbreitung Triazol-resistenter Aspergillen unter dem Einsatz von Voriconazol und Posaconazol bislang nicht nachweisen lassen.
- Die Studie besticht durch aufwändige molekulargenetische Diagnostik

# Candidämie: 2019 dokumentierte Fälle aus der *PATH Alliance*

## *PATH-Alliance-Kohorte*

- Größte bislang existierende Candidämie-Patientenkohorte
- 23 Zentren in USA; Zeitraum 7/04 bis 3/08; auch Kinder eingeschlossen

## *Candida-Isolate*

● <i>C. albicans</i>	921
● <i>C. glabrata</i>	525
● <i>C. parapsilosis</i>	316
● <i>C. tropicalis</i>	163
● <i>C. krusei</i>	51
● <i>C. lusitaniae</i>	17
● <i>C. dubliniensis</i>	7
● <i>C. guilliermondii</i>	5
● Andere/nicht identifizierte	14

## *Mortalität*

- Gesamt nach 12 Wochen: 35,2%

# Candidämie: 2019 dokumentierte Fälle aus der *PATH Alliance*

## Therapeutisch eingesetzte Antimykotika

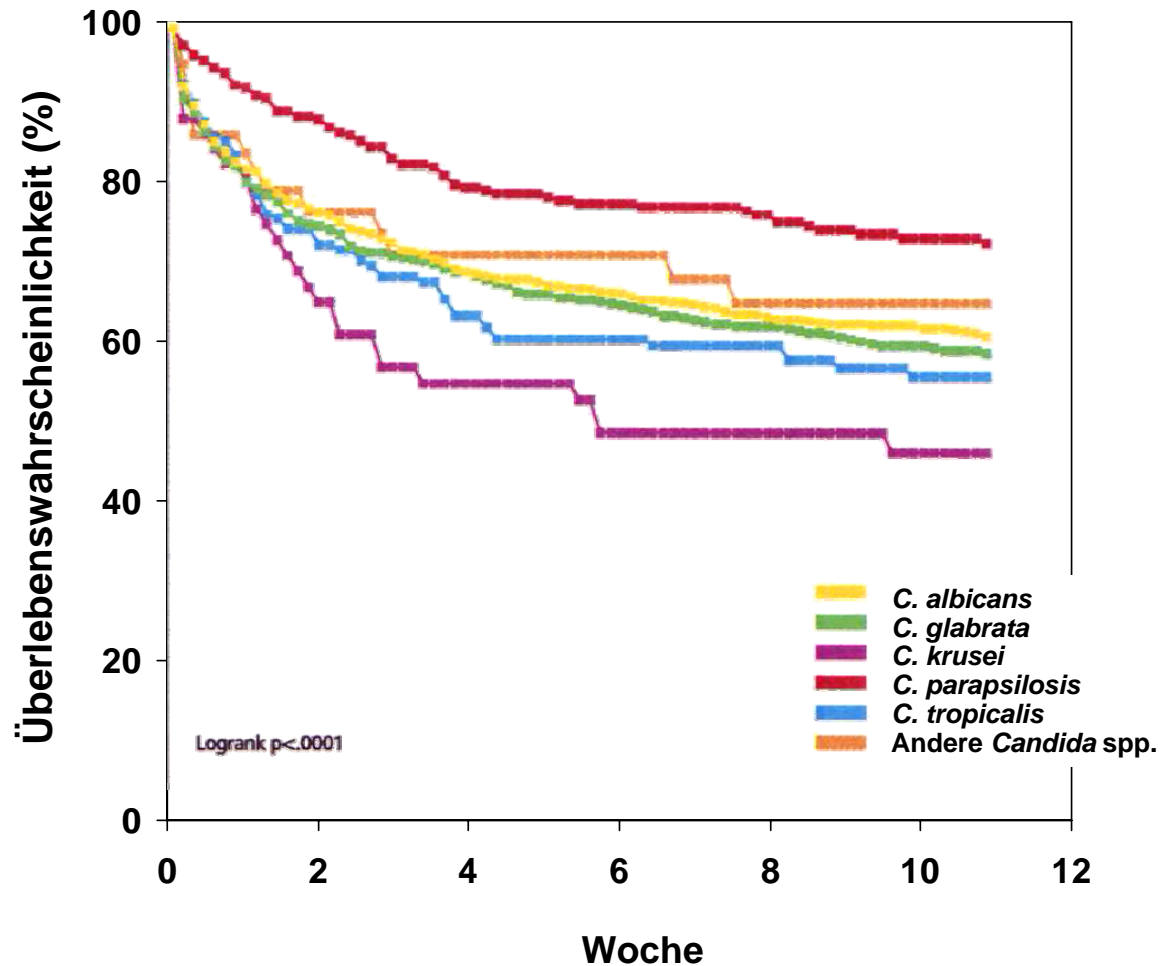
- Fluconazol 67,7%
- Caspofungin 38,1%
- Micafungin 10,8%
- Amphotericin B Lipidformulierung 10%
- Voriconazol 6,7%
- AmB-Desoxycholat 2,2%
- Verblindete Studienmedikation 1,7%
- Einige Patienten erhielten mehr als 1 Antimykotikum

## Mortalität nach isolierter *Candida*-Spezies

- *C. parapsilosis* 23,7% versus *C. krusei* 52,9% ( $p < 0,0001$ )

# Candidämie: 2019 dokumentierte Fälle aus der *PATH Alliance*

## Überleben nach isolierter *Candida*-Spezies



# Candidämie: 648 Fälle (1998-2007)

## Monozentrische Studie

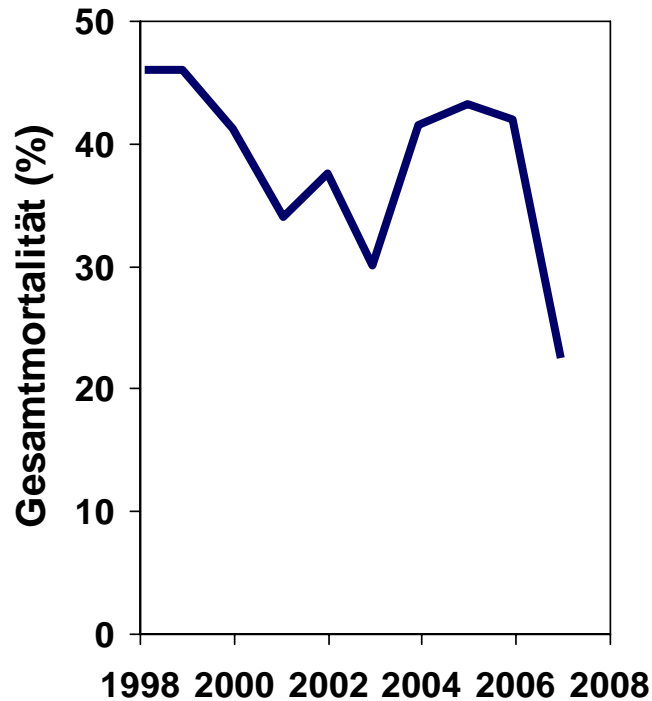
- Northwestern University Hospital
- Nur erwachsene Patienten

## Ergebnisse

- Signifikante Verschiebung des Erregerspektrums
  - ▶ **Anstieg** *C. albicans* von ca. 30% auf ca. 50% ( $p = 0,0081$ )
  - ▶ Gleichbleibender Anteil von *C. glabrata* um 22%
  - ▶ **Rückgang** von *C. krusei* und *C. tropicalis* ( $p = 0,02$  bzw.  $0,008$ )
- Rückgang der Sterblichkeit während Hospitalisierung von 47% auf 22% ( $p = 0,051$ )
  - ▶ Kein Unterschied zwischen *C. albicans* und *non-albicans*-Spezies

# Candidämie: 648 Fälle (1998-2007)

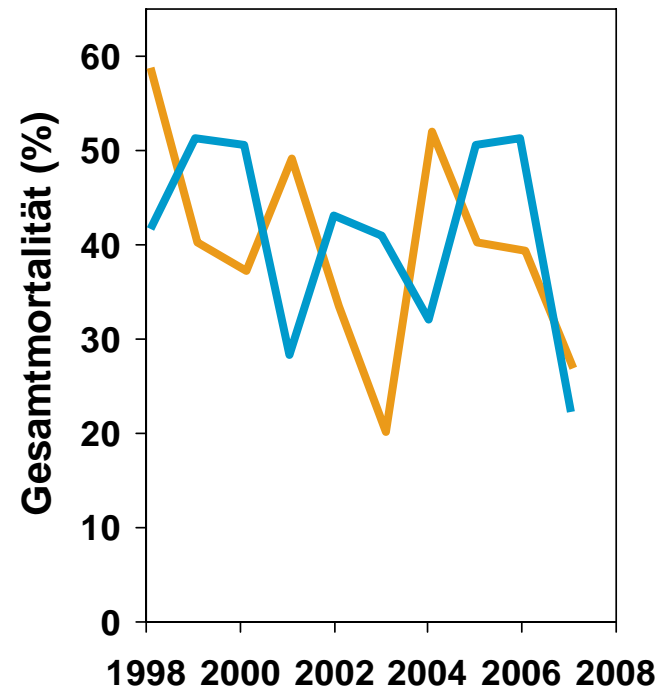
## Gesamt mortalität



## Gesamt mortalität bei

— *C. albicans*

— *non-albicans*-Spezies



# Candidämien: Epidemiologische Aspekte

## Kommentar

- *Candida albicans* bleibt die bei weitem häufigste Spezies.
- *C. glabrata* belegt mit 20-25% den zweiten Rang
- Eine zunehmende Bedeutung der *non-albicans Candida* spp. ist keineswegs generell zu beobachten.
- *C. parapsilosis* kommt vor allem bei Kindern vor und ist deshalb statistisch mit einer niedrigeren Letalität assoziiert.
- Die Verbesserung der Überlebensraten dürfte in erster Linie einer Optimierung der intensivmedizinischen Behandlung zu verdanken sein, denn die Schwere der Grunderkrankung ist der entscheidende prognostische Faktor bei der Candidämie.

# Candidämie: Bedeutung der frühzeitigen adäquaten Antimykotikatherapie

## Monozentrische Studie

- University of Kansas
- Retrospektive Analyse von 131 Candidämien (2002-2007) bei erwachsenen Patienten
  - ▶ *C. albicans* 38%, *C. glabrata* 32%

## Ergebnisse

- Sterblichkeit 29% ohne signifikante Speziesdifferenz ( $p = 0,32$ )
- Fluconazol-Resistenz bei *C. glabrata* 15%
- Adäquate antimykotische Primärtherapie nur in 65% der Fälle
  - ▶ Bei *C. albicans* häufiger als bei *C. glabrata* (72% vs. 54%)

# Candidämie: Bedeutung der frühzeitigen adäquaten Antimykotikatherapie

## Univariate Analyse

- Signifikant assoziiert mit höherer Sterblichkeit waren:
  - ▶ Intensivaufenthalt ( $p = 0,02$ ), Beatmung ( $p < 0,01$ ), Steroidbehandlung ( $p < 0,01$ ), höherer APACHE-II-Score ( $p < 0,01$ )
  - ▶ Längeres Intervall bis zur adäquaten Antimykotikatherapie ( $p = 0,04$ ; adjustiert nach Schwere der Erkrankung)
- Signifikant assoziiert mit geringerer Sterblichkeit waren:
  - ▶ Venenkatheterentfernung ( $p = 0,05$ )
- Fluconazol-Empfindlichkeit ohne Einfluss auf das Überleben

## Multivariate Analyse

- Signifikant assoziiert erhöhter Sterblichkeit während des Krankenhausaufenthaltes:
  - ▶ Höherer APACHE-II-Score und längeres Intervall bis zur adäquaten Antimykotikatherapie ( $p = 0,01$ )

# Candidämie: Bedeutung der sofortigen ZVK-Entfernung

## Retrospektive Analyse

- 107 Episoden mit 112 Kathetern
  - ▶ Getunnelt: 41
  - ▶ Nicht getunnelt: 71
  - ▶ Zeit bis zur Katheterentfernung: Median 2 Tage; Mittelwert 5 Tage
- Altersmedian 49 Jahre
- Patientencharakteristika
  - ▶ Parenterale Ernährung 75
  - ▶ Organtransplantation 26
  - ▶ Maligne Erkrankung 20
  - ▶ Neutropenie 8
  - ▶ Antimykotische Vorbehandlung 43
- *Candida*-Species
  - ▶ *C. albicans* 42
  - ▶ *C. glabrata* 44
  - ▶ *C. parapsilosis* 14
  - ▶ Andere 5

# Candidämie: Bedeutung der sofortigen ZVK-Entfernung

## Kathetermanagement

- Komplette Entfernung 91%
- Erhaltung oder partieller Wechsel 9%

## Ergebnisse

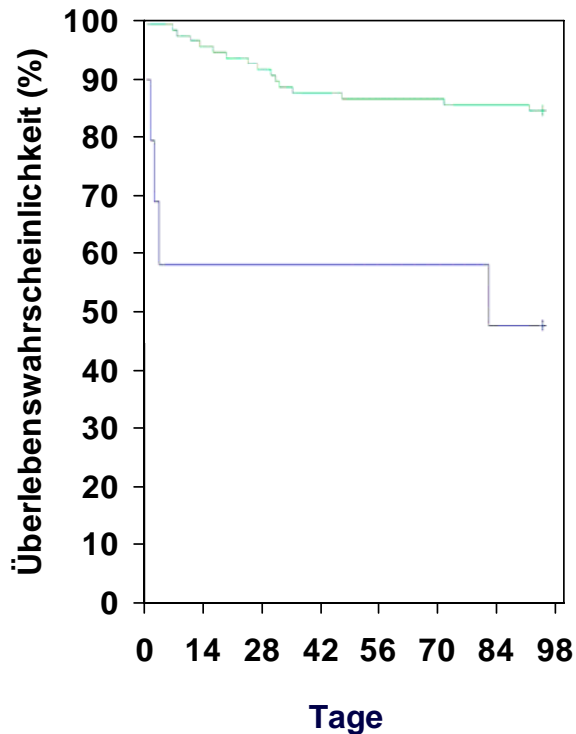
- Gesamtmortalität bis Tag 90: 17% versus 56% ( $p = 0,017$ )
- Signifikant ungünstige Einflußfaktoren:
  - ▶ Antimykotische Vorbehandlung
  - ▶ Maligne Grunderkrankung
- Kein Einfluss der *Candida*-Species

Logistische Regression: 90-Tage-Mortalität	Odds Ratio	P =
Komplette Katheterentfernung	0,10	0,017
Vorangegangene Antimykotikatherapie	3,13	0,05
Maligne Grunderkrankung	7,97	0,002

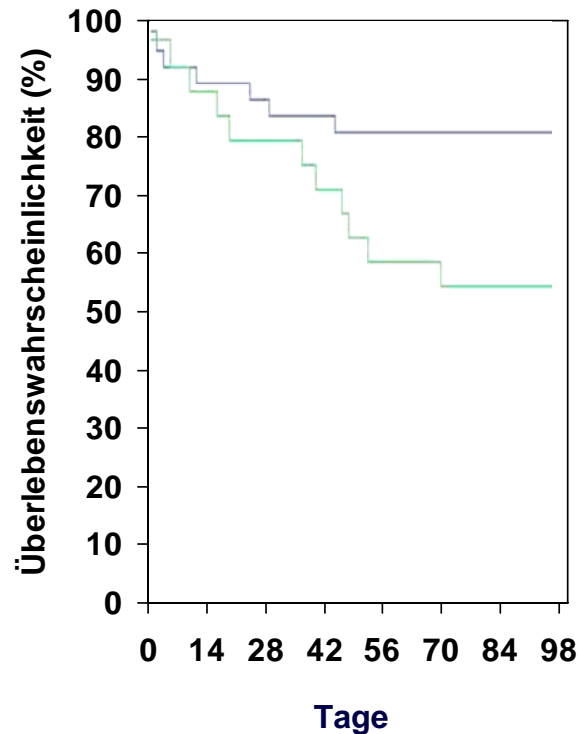
# Candidämie: Bedeutung der sofortigen ZVK-Entfernung

Zeitintervall zwischen 1. *Candida*-positiver Kultur und Tod

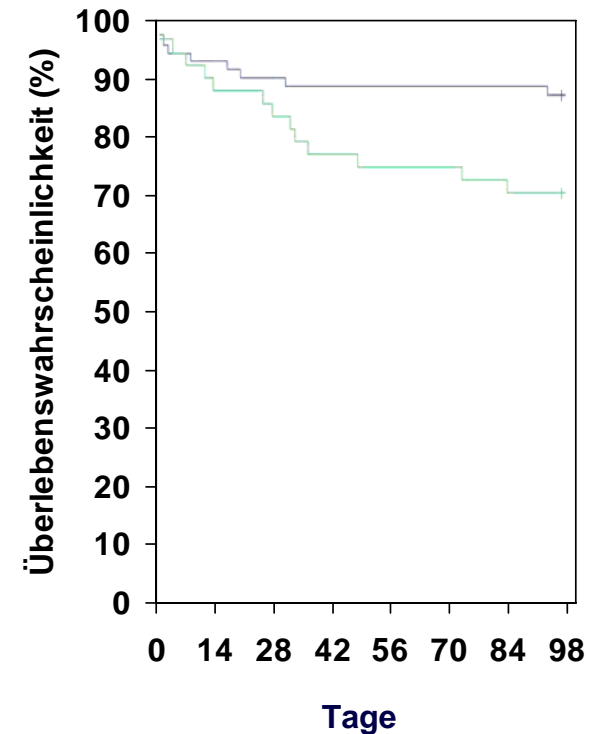
— Vollständige Katheterentfernung  
— Keine vollst. Katheterentfernung



— Malignom  
— Kein Malignom



— Antimykotikavortherapie  
— Keine Antimykotika



# Candidämien: Prognostische Faktoren

## Kommentar

- Hier bestätigt sich, dass die Schwere der Grunderkrankung für die Prognose bei Candidämie entscheidend ist.
- Durch rasche Einleitung einer adäquaten antimykotischen Therapie und prompte Entfernung des Venenkatheters lässt sich jedoch die Sterblichkeit vermindern – wie es in aktuellen Leitlinien auch empfohlen wird.



# Diagnostik

# ***Pneumocystis*-Pneumonie (PcP): PCR aus bronchoalveolärer Lavage (BAL)**

## **Prospektive Studie**

- 140 konsekutive Patienten mit Verdacht auf *Pneumocystis*-Pneumonie
  - ▶ HIV-positiv 14, hämatologische Neoplasie 102 (davon 41 Stammzelltransplantation), solider Tumor 9, Nierentransplantation 5, anderweitige immunsuppressive Therapie 10
- Vergleich PCR vs. Mikroskopie (Methenamin-Silber und Giemsa) aus Bronchoalveolärlavage
  - ▶ PCR für 3 Gene

## **Ergebnisse**

- Sensitivität und negativer prädiktiver Wert bei PCR höher
- Spezifität und positiver prädiktiver Wert bei Mikroskopie: 100%

# *Pneumocystis*-Pneumonie: PCR aus BAL

## Patienten mit/ohne PcP und Ergebnisse der PCR und Mikroskopie

	PcP +			PcP –		
	Gesamt	HIV	Non-HIV	Gesamt	HIV	Non-HIV
<b>PCR +</b>	RP = 33	RP = 7	RP = 26	FP = 6	FP = 1	FP = 5
<b>PCR –</b>	FN = 9	FN = 2	FN = 7	RN = 92	RN = 4	RN = 88
<b>Mikroskopie +</b>	RP = 6	RP = 3	RP = 3	FP = 0	FP = 0	FP = 0
<b>Mikroskopie –</b>	FN = 36	FN = 6	FN = 30	RN = 98	RN = 5	RN = 93

## Leistungsfähigkeit der Tests

		Sensitivität	Spezifität	PPV	NPV	Richtigkeit
<b>PCR</b>	Gesamt	79	93	85	91	89
	HIV	78	80	87	67	79
	Non-HIV	79	95	84	93	90
<b>Mikroskopie</b>	Gesamt	14	100	100	73	74
	HIV	33	100	100	45	57
	Non-HIV	9	100	100	75	76

PPV = positiver prädiktiver Wert; NPV = negativer prädiktiver Wert;  
 FP = falsch positiv; RP = richtig positiv; FN = falsch negativ; RN = richtig negativ

# *Pneumocystis*-Pneumonie: PCR aus BAL

## Kommentar

- Die *Pneumocystis*-PCR aus der bronchoalveolären Lavage ist deutlich sensitiver als die klassische Mikroskopie und ergänzt die Diagnostik sehr gut.
- Aber Vorsicht: eine alleinige PCR-Positivität beweist noch keine *Pneumocystis*-Pneumonie, sondern ist häufig – in Abhängigkeit von der Prätest-Wahrscheinlichkeit – falsch positiv.



# Effektivität von Mundschutz

# Dicht sitzende FFP2-Mundschutzmasken und Pilzinfektionen

## Hintergrund

- CDC-Leitlinien empfehlen das Tragen dicht sitzender FFP2- bzw. N95-Masken für Patienten mit schwerer Neutropenie oder nach allogener Stammzelltransplantation

## Erste prospektive, randomisierte Studie

- Erwachsene unter Chemotherapie wegen akuter Leukämie oder unter allogener Stammzelltransplantation
- Standardprophylaxe +/- dicht sitzende FFP2-Masken bei Verlassen des Zimmers (n = 41 vs. 39)
- Primärer Endpunkt: invasive Aspergillosen gemäß EORTC/MSG-Kriterien
- Sekundäre Endpunkte: Tolerabilität, Mortalität, therapeutische Gabe systemischer Antimykotika

## Ergebnisse

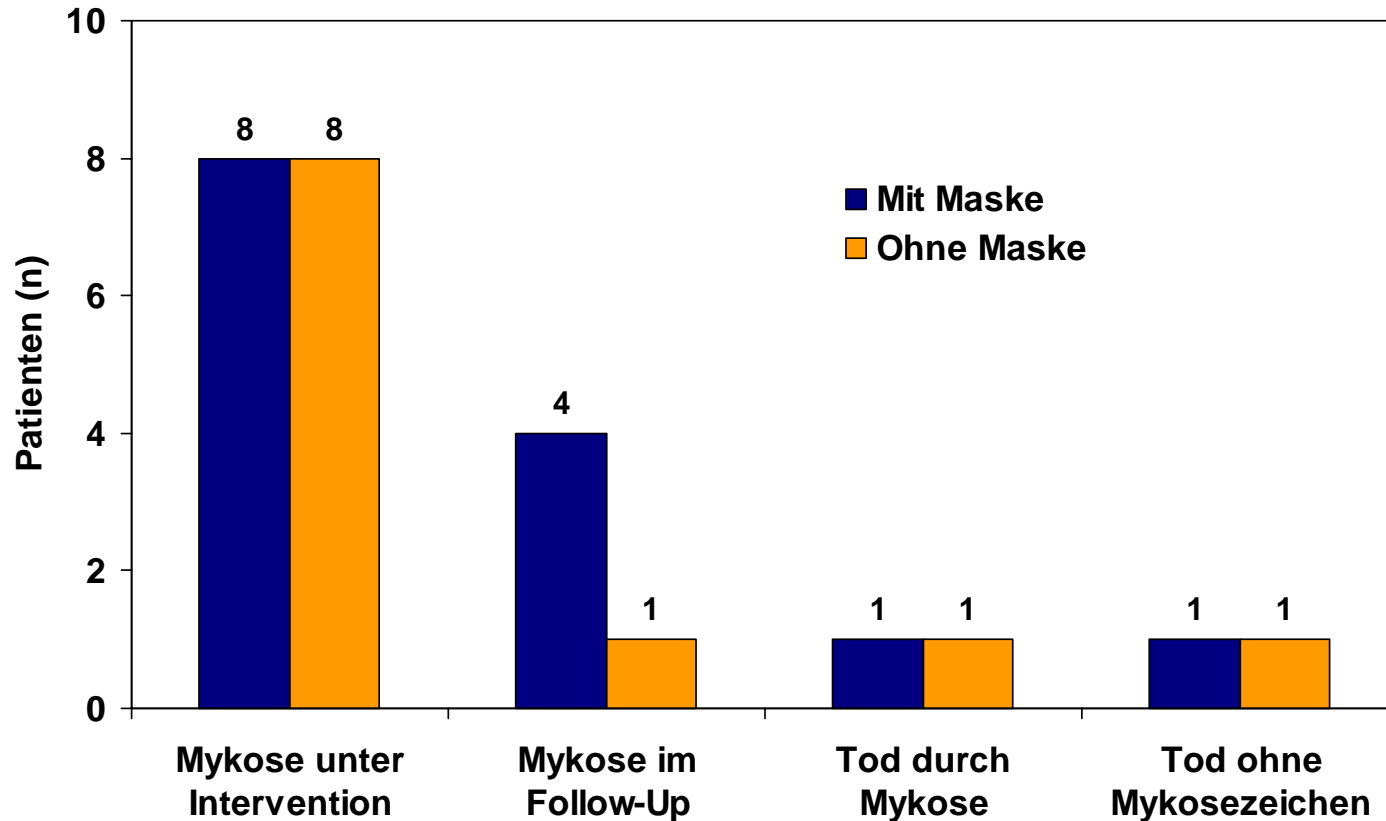
- In beiden Gruppen je 8 invasive Pilzinfektionen
- Kein erkennbarer Effekt der Mundschutzmasken

# Dicht sitzende FFP2-Mundschutzmasken und Pilzinfektionen

Maske	Art der Infektion	Diagnostische Befunde
Ja	Wahrscheinliche IA	Klinisch + radiologisch
Ja	IC	Nicht näher spezifiziert
Ja	Wahrscheinliche IA	Klinisch + radiologisch
Ja	Mögliche IA	Klinisch + radiologisch
Ja	Dokumentierte Mykose*	Klinisch + radiologisch + kulturell (BAL)
Ja	Gesicherte Aspergillose	Klinisch + radiologisch + kulturell + serologisch + histologisch (Autopsie)
Ja	Wahrscheinliche Mykose*	Klinisch + radiologisch + Follow-Up
Ja	Mögliche IA	Klinisch + radiologisch
Nein	Wahrscheinliche IA + IC	Klinisch + radiologisch + serologisch
Nein	IC	Nicht näher spezifiziert
Nein	Mögliche IA	Klinisch + radiologisch
Nein	Mögliche IA	Klinisch + radiologisch
Nein	Mögliche IA	Klinisch + radiologisch
Nein	Mögliche IA	Klinisch + radiologisch
Nein	Wahrscheinliche IA	Klinisch + radiologisch
Nein	Gesicherte Aspergillose	Klinisch + radiologisch + histologisch

IA = Invasive Aspergillose; IC = Invasive *Candida*-Infektion; \* nicht IC und IA

# Dicht sitzende FFP2-Mundschutzmasken und Pilzinfektionen



# Dicht sitzende FFP2-Mundschutzmasken und Pilzinfektionen

## Kommentar

- Ein Nutzen der weit verbreitete Verwendung von FFP2-Mundschutzmasken lässt sich mit dem Ergebnis dieser bislang einzigen randomisierten Studie nicht untermauern.
- Eine größere Zahl eingeschlossener Patienten hätte die Aussagekraft dieser Studie zweifellos noch erhöht.



# Neue Antimykotika

# Isavuconazol

## Hintergrund

- Oral und parenteral verfügbares Azolantimykotikum
- Gute Wirksamkeit und Verträglichkeit bei Soor-Ösophagitis
- Wirkspektrum in vitro
  - ▶ *Candida*, *Aspergillus*, Zygomyceten u.a.
- Verträglichkeit
  - ▶ Keine relevanten Nebenwirkungen

## Pharmakokinetik bei Erwachsenen

- Probanden
  - ▶ Die Exposition bei oraler Gabe ist unabhängig von der Nahrungsaufnahme
- Patienten
  - ▶ Zur Prophylaxe in der Neutropenie wurden folgende Dosierungen evaluiert
    - ▶ Standard: Tag 1: 400/200/200 mg, Tag 2: 200/200 mg, Tag 3-27: 200 mg
    - ▶ Dosisverdopplung: Tag 1: 800/400/400 mg, Tag 2: 400/400 mg, Tag 3-27: 400 mg
  - ▶ Die Talspiegel liegen über den MHK-Werten der meisten bisher getesteten Isolate.

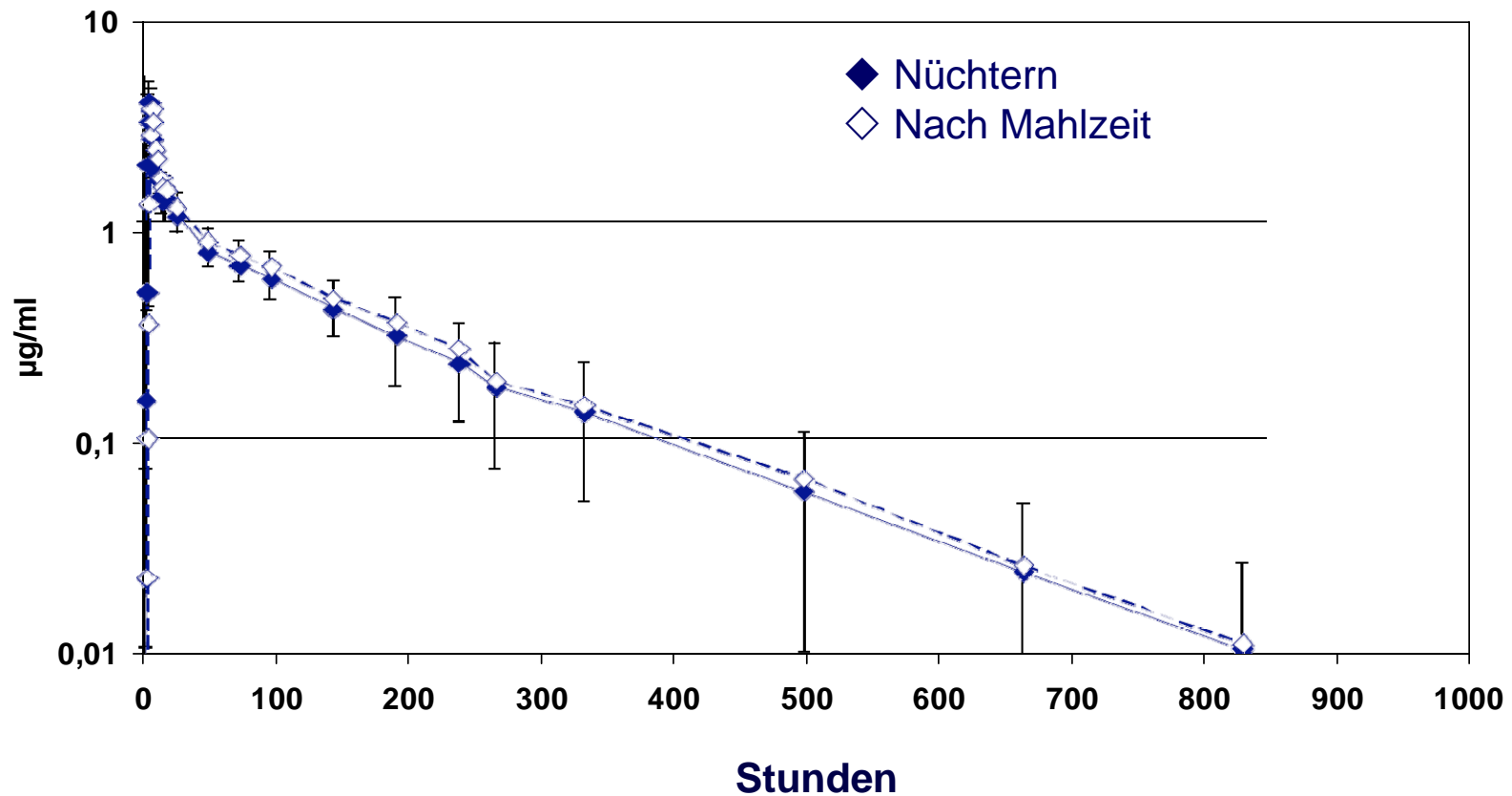
➔ Perkhofer M-1526

➔ Schmidt-Hoffmann A-007

➔ Schmidt-Hoffmann A-008

⤴ Übersicht

# Verlauf der Serumkonzentration nach Einnahme von 1 x 400 mg Isavuconazol



# Isavuconazol – Pharmakokinetik bei Patienten mit Neutropenie

Behandlungsschema	Standarddosis	Doppelte Dosis
Studientag	7	7
n =	8	10
$C_{\max}$ (µg/ml)	3,44 ± 0,71	6,47 ± 1,56
AUC (µg/ml)	58,0 ± 22,0	109 ± 13,3

# Isavuconazol

## Kommentar

- Mit Isavuconazol steht möglicherweise ein weiteres gut verträgliches Azol zur Verfügung.
- Derzeit werden Studien durchgeführt zu den Indikationen invasive Candidiasis/Candidämie, invasive Aspergillose, seltene Mykosen.
- Vorteile der Substanz sind die orale und parenterale Darreichungsform, die gute Verträglichkeit und das breite Wirkspektrum.
- Es stehen die Ergebnisse der Phase-III-Studien aus, die entscheidend für die abschliessende Bewertung der Substanz sind.

➔ Schmidt-Hoffmann A-008

➔ Cornely M-2137

➔ Perkhofer M-1526

➔ Schmidt-Hoffmann A-007

⬆ Übersicht

# FG3409

## Hintergrund

- FG3409 ist ein Antimykotikum aus einer neuen Substanzklasse.

## Methode

- Vergleich der MHK-Werte von FG3409, Voriconazol und Posaconazol
- *In vitro*-Aktivität gegen 163 klinische Pilzisolat:
  - ▶ *Aspergillus* spp., *Scedosporium prolificans*, *Fusarium solani*, *F. oxysporum*, *Scopulariopsis brevicaulis*, *Paecilomyces variotii*, seltene Erreger

MHK	FG3409	POSA	VORI
MHK <sub>50</sub> für alle Isolate	0,125	0,06	0,5
MHK <sub>90</sub> für alle Isolate	>32	8	>8
MHK <sub>90</sub> (ohne primär resistente Isolate)	2 (= MHK <sub>100</sub> )	1	2

# FG3409 - Kommentar

## Kommentar

- FG3409 ist eine vielversprechende Substanz.
- Da entscheidende Eigenschaften aber unbekannt bzw. unpubliziert sind, ist die Einschätzung vorläufig.
- *Candida* spp. wurden nicht getestet, da FG3409 hier vollständig unwirksam ist.
- Bei den Zygomyzeten bestehen wahrscheinlich ebenfalls Lücken im Wirkspektrum.
- Zukünftige Indikationen zeichnen sich noch nicht deutlich ab.



# Antimykotische Therapie

# Randomisierter Vergleich von Caspofungin (CAS), liposomalem Ampho B (L-AmB) und der Kombination

## Hintergrund

- In vielen Krankenhäusern werden vor allem bei Aspergillosen Kombinationstherapien durchgeführt.
- Zur Kombinationstherapie liegen keine Daten aus randomisierten Studien vor.

## Methodik

- Untersuchung von Sicherheit und Verträglichkeit
- 55 allogene Stammzelltransplantationspatienten mit Antibiotika-refraktärem Fieber

## Therapiearme

- L-AmB 3 mg/kg/d versus CAS 50 mg/d (Tag 1: 70 mg) versus Kombination

# Randomisierter Vergleich von Caspofungin, liposomalem Ampho B und der Kombination

Endpunkt	L-AmB	CAS	CAS + L-AmB	P-Wert
Studienabbrüche wg. Grad III/IV-Toxizität	2/20	1/18	0/17	n.s.
Hypokaliämie	7/20	8/18	15/17	(p < 0,05)
<b>Therapieerfolg</b> (= kein Abbruch wegen Toxizität, keine invasive Mykose, Überleben bis Tag 14 nach Ende der Studientherapie)	15/20	14/18	16/17	n.s.

# Antimykotische Kombinationstherapie – Kommentar

## Kommentar

- Erstmals liegen Ergebnisse zu einer antimykotischen Kombinationstherapie im randomisierten Vergleich zur Standard-Monotherapie vor.
- Liposomales Amphotericin B, Caspofungin und die Kombination waren – bis auf eine höhere Hypokaliämierate unter CAS + LAMB – gleich gut verträglich. Diese Nebenwirkung kann leicht beherrscht werden.
- Nach dieser Verträglichkeitsstudie und Tiermodellstudien, die teils nicht erfolgreich waren, besteht immer noch der dringende Bedarf nach einer Effektivitätsstudie bei Patienten mit invasiven Mykosen.
- Derzeit wird Voriconazol gegen Voriconazol + Anidulafungin in einer weltweiten Studie zur invasiven Aspergillose randomisiert geprüft.
- In der klinischen Routine ist eine Kombinationstherapie sehr selten gerechtfertigt.

# Caspofungin bei invasiver Aspergillose nach allogener Stammzelltransplantation

## Hintergrund

- Daten zur Erstlinientherapie invasiver Aspergillosen liegen nur für neutropenische Patienten vor.

## Methodik

- Einarmige Untersuchung von Sicherheit und Verträglichkeit
- N = 24 Patienten mit allogener Stammzelltransplantation

## Therapie

- Caspofungin 50 mg/d (Tag 1: 70 mg)

# Caspofungin bei invasiver Aspergillose nach allogener Stammzelltransplantation

## Ergebnisse

<b>Ansprechen bei Ende der Caspofungin-Therapie</b>	10/24 (42%)
<b>Ansprechen nach 84 Tagen</b>	7/23 (30%)
<b>Gesamtsterblichkeit nach 84 Tagen</b>	12/24 (50%)
<b>Therapieabbruch wegen Nebenwirkungen</b>	0 (0%)

## Zum Vergleich

- In früheren Studien lagen die Ansprechraten sowohl mit Voriconazol als auch mit liposomalem Amphotericin B bei ~50%.

# Antimykotische Kombinationstherapie

## Kommentar

- Erstmals liegen Daten zur Erstlinientherapie der invasiven Aspergillose mit Caspofungin bei allogenen stammzelltransplantierten Patienten vor.
- Die Ansprechrate liegt in der erwarteten Größenordnung.
- Einarmige Studien helfen nicht in der Weiterentwicklung der Therapie gegen die invasive Aspergillose.
- Ein randomisierter Vergleich zwischen Caspofungin und der Referenzsubstanz Voriconazol steht weiterhin aus.



# Abstracts

# A-007

## Pharmacokinetics of Isavuconazole in Liver Impairment Preliminary Data

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**Background:** Isavuconazole is an extended-spectrum azole administered orally or intravenously as a water-soluble pro-drug (WSA). Isavuconazole is currently under investigation in phase 3 studies in patients with systemic candidiasis, aspergillosis or invasive fungal infection with rare moulds. Isavuconazole is slowly eliminated by CYP-mediated clearance. Therefore, we investigated the PK of isavuconazole in subjects with hepatic impairment.

**Methods:** Healthy volunteers and patients with mild and moderate liver impairment received a single 2-h i.v. dose of BAL8557 equivalent to 100 mg BAL4815. This resulted in three groups (n=8) matched for age, gender, body weight and BMI. Pharmacokinetic parameters were derived using WinNonlin 5.1. ANOVA was used to assess the statistical significance of differences in isavuconazole pharmacokinetics.

**Results:** Average Child-Pugh score of 5.3 and 7.4 were measured in patients with mild and moderate hepatic impairment, respectively. Liver disease compared to healthy resulted in a significant decrease of the systemic clearance (CL) of isavuconazole accompanied by approximately a two-fold increase in the half-life and the AUC ( $p < 0.05$ ).  $C_{\max}$  was slightly decreased in patients corresponding to a modest increase of  $V_{SS}$  ( $p > 0.05$ ).

**Conclusion:** Administration of isavuconazole to patients with mild or moderate hepatic impairment will require a dose adjustment compared to normal patients.

Subjects/ parameters	$C_{\max}$ ( $\mu\text{g}/\text{mL}$ )	$\text{AUC}_{0-\infty}$ ( $\mu\text{g}\cdot\text{h}/\text{mL}$ )	CL (L/h)	$T_{1/2}$ (h)	$V_{SS}$ (L)
Healthy volunteers	$1.09 \pm 0.193$	$39.4 \pm 12.0$	$2.72 \pm 0.750$	$123 \pm 38.8$	$422 \pm 96.3$
Mild hepatic impairment	$0.977 \pm 0.371$	$71.9 \pm 55.5$	$1.93 \pm 0.920$	$224 \pm 147$	$492 \pm 111$
Moderate hepatic impairment	$0.838 \pm 0.137$	$101 \pm 52.3$	$1.43 \pm 1.23$	$302 \pm 131$	$471 \pm 121$

# A-008

## No Relevant Food Effect in Man on Isavuconazole Oral Pharmacokinetics: Preliminary Data

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**Background:** Isavuconazole is an extended-spectrum azole administered orally or intravenously as a water-soluble pro-drug (WSA). Isavuconazole is currently under investigation in phase 3 studies. The PK/PD drivers are AUC/MIC and trough/MIC for *Candida* spp and *Aspergillus* spp, respectively. Preclinical evidence suggested a food effect on the PK of Isavuconazole when administered as WSA, therefore, we investigated the effect of food on the oral pharmacokinetics of Isavuconazole in man.

**Methods:** In an open-label, randomized, 2-way cross-over study, 26 healthy male subjects received orally 400 mg Isavuconazole as WSA in the fed or fasted state. Serial blood samples for PK were collected and analyzed by a specific LC-MS/MS method. Pharmacokinetic parameters were derived using WinNonLin 5.1 and the scheduled sampling times. The 90% confidence intervals of the geometric mean ratios were estimated.

**Results:** While a delayed T<sub>max</sub> and decreased C<sub>max</sub> of Isavuconazole were observed in presence of food, there was no effect on the AUCs, T<sub>1/2</sub> nor on the C<sub>24h</sub>-values. This indicates that in presence of food the rate of absorption was delayed but its extent was unaffected.

**Conclusions:** The PK/PD drivers: trough levels and daily AUC, are unaffected by fasted or fed state. Therefore, the slightly delayed absorption in presence of food is considered not clinically relevant contrary to other azoles that exhibit a clinically relevant food effect.

# A-021a

## Efficacy of the Combination of Voriconazole and Anidulafungin in Experimental Invasive Pulmonary Aspergillosis in Neutropenic Rats

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**Background:** Voriconazole (VOR) is used to treat patients with invasive pulmonary aspergillosis (IPA). In advanced stage of IPA, VOR is not always fully effective or tolerated. Here we investigated whether a combination of VOR and anidulafungin (ANI) improves therapeutic outcome in transiently neutropenic rats with advanced IPA.

**Methods:** To compensate for the faster metabolism of VOR and the occurrence of autoinduction of the metabolism in rats compared to humans, rats received VOR doses that gradually increased from 7.5 to 17.5 mg/kg q12h intraperitoneally (ip) to obtain drug exposure comparable to the clinical situation. Doses of ANI were 20 mg/kg ip on day 1 and 5 mg/kg q24h on the subsequent days. Target for the area under the plasma concentration time curve were 30 µg/ml.h (AUC<sub>12h</sub> VOR) and 120 µg/ml.h (AUC<sub>24h</sub> ANI). The therapeutic efficacy of VOR was assessed after administration for a 10-day period started at 16h (early infection), 24h or 72h (advanced infection) after fungal inoculation. Combination of ANI and VOR was applied in advanced stage of IPA (treatment start 72h). Efficacy parameters were rat survival, and quantitative fungal burden in lung and serum in terms of the galactomannan (GM) concentration.

**Results:** AUC values of VOR and of ANI ranged from 88-128% and 64-164% of the target value, respectively. VOR showed excellent efficacy in early IPA (100% survival), but moderate efficacy in advanced IPA (50% survival). Surviving animals exhibited a decrease of serum GM concentration. Monotherapy with ANI in advanced IPA resulted in only 22% survival; decreases in serum GM concentrations were not observed. Addition of ANI to VOR did not result in a significant increase in therapeutic efficacy in advanced IPA (67% survival and a decrease in GM concentration in serum).

**Conclusions:** VOR and ANI as monotherapy show therapeutic efficacy in advanced stage IPA. Combining both agents does not significantly improve therapeutic outcome.

# D-1088

## PCR-Based Detection of *Pneumocystis jirovecii* in Broncho-Alveolar Lavage (BAL) Fluid for Diagnosis of Pneumocystis Pneumonia (PCP)

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**Background:** *P. jirovecii* causes PCP, an opportunistic infection in the immunocompromised patient. Since *P. jirovecii* cannot be cultured, the standard method for diagnosis of PCP is cytological staining of BAL fluid or tissue stains, both characterized by a relative low sensitivity, especially in non HIV infected patients. Recent studies have confirmed that PCR has greater sensitivity for detection of *P. jirovecii*.

**Methods:** We developed a PCR-based detection system for *P. jirovecii*, based on the amplification of three different genes. The first being the mtLSUrRNA coding for the mitochondrial large subunit (23S) rRNA gene. The second gene MSG coding for the major surface glycoprotein, which exists in more than 100 copies in the *P. jirovecii* genome, therefore increasing the sensitivity of the assay, and the third being the T1-T2 region of the large subunit ribosomal rRNA gene. We have evaluated the performance of this test for the diagnosis of PCP during three years period (1/2005-1/2008).

**Results:** 140 consecutive patients underwent bronchoscopy with BAL for suspected PCP. 14 were HIV infected and 126 were non-HIV immunocompromised patients. 42 patients received eventually the diagnosis of PCP, of them 9 were HIV infected and 33 were non-HIV immunocompromised patients. PCR correctly diagnosed 33/42 (sensitivity 79%) patients with PCP comparing to 6/42 (sensitivity 14%) diagnosed by cytological stains, and increased the diagnostic yield 5.6 fold. PCR was significantly more sensitive for diagnosis of PCP in HIV infected patients compared to direct smear (78% vs. 30%), and even more so in non-HIV immunocompromised patients (79% vs. 9%). Specificity however was 100% for direct smear in HIV infected patients, non-HIV immunocompromised patients and in the total cohort, as compared to 80%, 95% and 93% respectively.

**Conclusions:** In summary our data confirm the usefulness of *P. jirovecii* PCR based detection for PCP diagnosis in HIV and immunocompromised patients.

# K-1390

## Trends in Species Distribution and Associated Mortality of Candidemia

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**Background:** *Candida* species are the fourth leading cause of nosocomial bloodstream infections (BSI) in the United States, and are associated with a high mortality rate. Recently, there have been reports that non-*albicans* *Candida* species are increasing in prevalence presumably related to selective pressure exerted by widespread use of azole antifungal agents. The objective of our study was to determine the trends in species distribution and associated mortality in patients with candidemia at Northwestern Memorial Hospital.

**Methods:** Microbiologic data of all adult patients hospitalized with candidemia from January 1998 to December 2007 were reviewed retrospectively. Patients infected with multiple *Candida* species or who had recurrent episodes of candidemia over the study period were excluded. Medical records were reviewed for outcome at hospital discharge (dead vs. alive). We conducted trend analyses on 648 patients infected with a single *Candida* species over the study period.

**Results:** The trend analyses showed that the proportion of patients infected with *Candida albicans* increased significantly from 1998 to 2007 ( $p=0.008$ ) while patients infected with *C. krusei* or *C. tropicalis* decreased significantly over time ( $p= 0.021$  and  $0.008$  respectively). Other *Candida* species (*C. dubliniensis*, *C. guilliermondii*, *C. lusitaniae* and *C. pseudoparapsilosis*) were rarely isolated (2.6%) and remained stable over the 10 years of this study. The crude mortality rate was 38% and the proportion of patients that died decreased over time ( $p=0.051$ ).

**Conclusions:** There was a significant increase in BSI caused by *C. albicans* over this 10-year period and a significant reduction in both *C. krusei* and *C. tropicalis*. In addition, despite advances in antifungal therapy, mortality in patients with candidemia remains high.

# K-4101

## Well-Fitting Masks for Prevention of Invasive Aspergillosis (IA) in High-Risk Neutropenic Patients

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**Background:** The problem of inhalation of *Aspergillus* spores outside rooms with highly effective air filtration (HEPA) has not been resolved as yet. Well-fitting masks (N95 in the USA or FFP2 in Germany) are used in industrial and healthcare settings to protect from inhaling particles of 0.3-0.5 µm size. To investigate the efficacy and tolerability of well-fitting FFP2 masks in high-risk patients (pts), we conducted a prospective, randomized multicenter study comparing standard hospital hygiene procedures with or without wearing FFP2 masks.

**Methods:** Adult pts undergoing chemotherapy for acute leukemia or allogeneic hematopoietic stem cell transplantation (aHSCT) were randomized to receive standard prophylaxis with or without wearing a well-fitting FFP2 mask outside their rooms. Primary endpoint was IA according to EORTC/MSG criteria. Secondary endpoints were tolerability, mortality and administration of systemic antifungals.

**Results:** Recruitment was stopped after 80 pts, when a significant benefit from posaconazole prophylaxis was reported. 41 pts were randomized to wearing masks and 39 to the control group. 76% of pts were treated in laminar airflow and/or HEPA filtered rooms, 84% received oral polyens, and 6 aHSCT recipients were given fluconazole. Duration of neutropenia was similar in both treatment groups. Invasive fungal infections were diagnosed in 16 pts with no difference between study arms. One patient in each arm died from proven IA. There was no significant difference in the use of systemic antifungals. Of pts in the mask group, 65% described the comfort as acceptable, 26% as unpleasant, and 9% as intolerable.

**Conclusions:** This first randomized clinical study on the use of well-fitting masks failed to show a benefit with respect to the incidence of or mortality due to IA.

# M-1178

## *In Vitro* Activity of FG3409 Compared to Posaconazole and Voriconazole Against a Panel of 163 Clinical Fungi

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**Background:** Despite advances in antifungal therapy, certain fungi are resistant to all available antifungal agents. As a result, there is an urgent need for new agents with activity against such resistant fungi. FG3409 is the first of a novel class of antifungal agent. Here we compared the spectrum and potency of FG3409 with posaconazole (POSA) and voriconazole (VORI) against a range of clinical fungi, including aspergilli, agents of hyalohyphomycosis, phaeohyphomycosis, dermatomycosis and the endemic mycoses.

**Methods:** Testing methods are outlined in CLSI document M38-A2. All organisms were tested in microdilution format except dimorphic fungi and some species requiring extended incubation which were tested by macrobroth method. MIC ranges were 0.06-32µg/ml (FG3409) and 0.015-8µg/ml (POSA/VORI). POSA and VORI endpoints were determined as the lowest concentration giving 100% growth inhibition, 50 and 100% growth reduction endpoints were determined for FG3409.

**Results:** The FG3409 MIC<sub>50/90</sub> for all fungi was 0.125/>32µg/ml using both endpoints. The MIC<sub>50/90</sub> for POSA and VORI were 0.06/8µg/ml and 0.5/>8µg/ml respectively. FG3409 was inactive against 37 isolates. After eliminating data for these fungi, the MIC<sub>90</sub> fell to 0.5/2 (50/100%) µg/ml showing that FG3409 is highly active against species that do not display outright resistance. When the same criteria were applied to POSA and VORI, the MIC<sub>90</sub> fell to 1 and 2µg/ml respectively, showing that FG3409 compared favorably to both drugs. FG3409 had excellent activity against aspergilli, the endemic mycoses and dermatophytes, and in addition was active against *Scedosporium prolificans*, *Fusarium solani*, *F. oxysporum*, *Scopulariopsis brevicaulis* and *Paecilomyces variotii* which were resistant to VORI and in some cases POSA.

**Conclusions:** FG3409 has potent activity against a broad range of fungi including some azole-resistant species and is an excellent candidate for further development.

# M-1526

## The In Vitro Activity of Isavuconazole against Conidia and Hyphae of *Aspergillus* Species and Zygomycetes

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**Background:** Isavuconazole (ISAV) is a promising broad-spectrum triazole in late-stage clinical development for the treatment of invasive fungal infections. The aim of this study was to address the in vitro activity of ISAV against a wide range of non-*A. fumigatus* species and zygomycetes.

**Methods:** Susceptibility testing was performed according to the methods of the Antifungal Susceptibility Testing Subcommittee of the European Committee on Antimicrobial Susceptibility Testing. In addition, the minimal fungicidal concentrations (MFC) were performed and for a subset of fungi we evaluated the activity of ISAV against hyphae of the various fungi. For comparison of hyphal MICs, the metabolic activity of drug-treated hyphae was determined by their ability to reduce the tetrazolium compound 3-(4,5-dimethyl-2-thiazol)-2,5-diphenyl-2H-tetrazolium bromide (MTT). Voriconazole (VOR) and posaconazole (POS) served as control.

**Results:** Minimum inhibitory concentration (MIC) and MFCs of 132 clinically relevant fungi such as *A. fumigatus* (n=32), *Aspergillus flavus* (n=16), *Aspergillus terreus* (n=35), *Aspergillus niger* (n=13), *Rhizomucor* spp. (n=9), *Absidia* spp. (n=8), *Rhizopus* spp. (n=7), *Cunninghamella* spp. (n=3), and *Mucor* spp. (n=9) were investigated. The average geometric means (GMs) of MICs for ISAV against *A. fumigatus*, *A. flavus*, *A. terreus* and *A. niger* were 0.63, 0.76, 0.68 and 2.36, respectively. MFCs were within two dilutions of the MIC (range 1 - >8 µg/ml) for the various *Aspergillus* tested. Not all zygomycetes were susceptible to ISA and MICs ranged to up to > 8 µg/ml. The hyphal MICs were in the range as for conidia. Comparison of the visually determined endpoints with the results of the MTT method revealed agreement in 87%.

**Conclusions:** In conclusion, ISAV demonstrated impressive antifungal activity against hyphae and conidia of *Aspergillus* spp. and EUCAST methodology resulted in similar MIC ranges as with the CLSI reference method. The antifungal activity of ISAV is somewhat broader than for VOR.

# M-1530

## No Evidence of Azole Resistant *Fumigati* Section Species Strains from Patients Treated for Hematological Malignancies in the Voriconazole Era

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**Background:** An increase of invasive aspergillosis (IA) due to azole resistant *Aspergillus fumigatus* isolates has been reported in the 10 last years. Misidentification by morphotyping with resistant *Fumigati* section species, such as *A. lentulus*, or selection of azole resistant isolates due to azole therapies could explain this trend. Therefore, we checked the phenotypic identification of *A. fumigatus* isolates from hematological patients by using molecular methods and we determined their azole minimal inhibitory concentration (MIC) to itraconazole (ITZ).

**Methods:** Seventy-seven *A. fumigatus* morphotype isolates were prospectively collected from 51 patients treated for hematological malignancies from January 2006 through December 2007 (3 proven, 32 probable, 1 possible and 15 without IA). Molecular identification was performed by sequencing *A. fumigatus*  $\beta$ -tubulin gene. ITZ MIC was determined using Etest®. Isolates with ITZ MICs > 4 mg/L were sequenced for up to residue 300 of CYP51A gene and its promoter.

**Results:** All isolates were identified as *A. fumigatus* upon the sequence of the  $\beta$ -tubulin gene. Genotyping using 4 microsatellites markers confirmed the heterogeneity of the contaminating/infecting isolates. All but one had ITZ MICs ranged from 0.25 to 2 mg/L, although 30 of 77 isolates had grown from patients treated with voriconazole. Only one isolate had ITZ MIC > 4 mg/L (16 mg/L) whereas voriconazole and posaconazole MIC were < 0.38 mg/L. The patient was not given azole therapy. CYP51A sequencing showed no mutation or tandem repeat insertion in the promoter of the gene.

**Conclusions:** In our hematological population, there is no evidence of emergence of resistant *Fumigati* section species strains. High ITZ MIC is rare, below 2%.

# M-1845

## Zygomycosis in Europe: A Prospective, Epidemiologic Study

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**Background:** Zygomycosis has emerged as an important mould infection with a high mortality. The aim of this study was to analyze its epidemiology in Europe.

**Methods:** In each country, a national co-ordinator prospectively collected zygomycosis cases recorded on specially provided case report forms that were centrally evaluated by the study co-ordinator. The study started in Jan 2005 and lasted 3 yrs. Statistical analysis was performed with SPSS v.12.

**Results:** Thirteen countries enrolled 212 patients. Mean age was 50 yrs (range 1-87) and male gender 61%. Most common underlying conditions were hematological malignancies (53%), trauma (15%) and diabetes mellitus (10%). The main sites of infection were rhinocerebral (29%), pulmonary (27%), soft tissue (24%) and disseminated (17%). The isolated fungi were *Rhizopus* spp. (32%), *Mucor* spp. (31%), *Absidia* spp. (20%), and others (17%). 51% of patients received only amphotericin B formulations, 6.3% only posaconazole and 31.6% received both. Mortality was 47.8%. On multivariate analysis, factors influencing outcome were surgical treatment (p<0.001), age (p=0.037), non-trauma related infection (p=0.022) and previous use of corticosteroids (p=0.035).

**Conclusions:** 1. The main clinical presentations were rhinocerebral, pulmonary and soft tissue infections, while *Mucor* and *Rhizopus* spp. were isolated at similar rates. 2. Outcome is dismal in half cases and is significantly better when trauma is the predisposing factor or when surgical treatment is applied.

# M-2127a

## Review of 2019 Patients with Candidemia through the PATH Alliance Registry

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**Background:** We assessed the epidemiology and mortality of 2019 patients (pts) with candidemia (1 episode with 1 *Candida* spp). Data was collected by the multicenter, observational PATH Alliance Registry from 2004-2008.

**Methods:** Chi-square or Fisher's exact tests were used to assess the associations between *Candida* spp and demographics, risk factors and therapy; 12-week survival outcomes across spp were compared using the log-rank test.

**Results:** Among the 2019 pts, *C. albicans* (45.6%) was the most common, followed by *C. glabrata* (26.0%), *C. parapsilosis* (15.7%), *C. tropicalis* (8.1%), *C. krusei* (2.5%), *C. lusitaniae* (0.8%), *C. dubliniensis* (0.4%), *C. guilliermondii* (0.3%), and other/unknown spp. (0.7%). Pts with *C. parapsilosis* were less likely to be neutropenic (5.1%,  $P < 0.0001$ ) and receive corticosteroids (33.5%,  $P = 0.0002$ ) or other immunosuppressants (7.9%;  $P = 0.002$ ). *C. krusei* candidemia was associated with prior use of antifungal agents (70.6%), hematologic malignancy (52.9%) or SCT (17.7%), neutropenia (45.1%; all,  $P < 0.0001$ ), and corticosteroids (60.8%;  $P = 0.0002$ ). Fluconazole (67.7%) and the echinocandins (48.9%) were most commonly used. The overall, crude 12-week mortality was 35.2%, with *C. parapsilosis* and *C. krusei* candidemia having the lowest (23.7%) and highest mortality (52.9%), respectively ( $P < 0.0001$ ).

**Conclusions:** This is the largest contemporary cohort of pts with candidemia ever reported. Collectively, non-*albicans* *Candida* spp were the most common cause. Mortality remains high in pts with candidemia, with significant differences observed among the *Candida* spp. The PATH Alliance Registry can be used to analyze large numbers of pts with invasive fungal infections.

# M-2132a

## Impact of Intravascular Catheter Removal on *Candida* Bloodstream Infection Mortality

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**Background:** *Candida* species bloodstream infection (CBSI) is the fourth leading cause of nosocomial bloodstream infection. Intravascular catheters are significant risk factors for CBSI. The objective of this study is to evaluate the impact of intravascular catheter removal on the CBSI mortality rates.

**Methods:** A retrospective study of all patients with at least one positive blood culture for *Candida* species from Jan, 2004 through July, 2005 was conducted. Demographics, risk factors, antifungal therapy, type and timing of vascular devices removal, and outcomes were reviewed. Cox proportional hazards regression was used for the time-to-event analyses.

**Results:** A total of 107 episodes of candidemia were recorded from 84 patients: solid organ transplant (N=26); cancer (N=20); TPN (N=75); neutropenia (N=8); previous antifungal therapy/prophylaxis (AF) (N=43); and intravascular catheters (N=105). Distribution of *Candida* species showed *C. albicans* (N=42), *C. glabrata* (N=44), *C. parapsilosis* (N=14), others (N=5). Complete removal (CR) of vascular catheter was performed in 96 cases (91%) vs. partial exchange or retained (PR) catheter in 9 cases (9%). Death at ninety days was 16/96 (17%) in CR group vs. 5/9 (56%) in PR group (OR 0.10 [95% CI 0.02, 0.66; p=0.017]), representing a 90% risk reduction with CR by multivariate analysis. AF in last 30 days before candidemia was significantly related to shorter time to death: 71.4 days vs 81.3 days in non-AF group (p=0.029). Cancer as an underlying disease was associated with more rapid time to death (58.2 days) than in non-cancer group (81.7 days) (p=0.001). These risk factors remained statistically significant after adjusting by the multivariate model.

**Conclusions:** Complete removal (CR) of intravascular catheter in patients with candidemia is strongly associated with mortality reduction, compared with catheter retention or partial exchange. CR remains an independent protective factor after adjusting for neutropenia, cancer, solid organ transplant, and AF.

# M-2134a

## **Candida Bloodstream Infection: Time to Initiation of Appropriate Antifungal Therapy and Association with Outcome**

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**Background:** *Candida* Bloodstream Infection (CBSI) is associated with significant mortality. The effect of timing of appropriate antifungal therapy (AF) on outcome has not been clearly established. This study incorporates antifungal susceptibility testing in determining appropriate therapy and the impact of delayed therapy on outcome.

**Methods:** Patients at the University of Kansas with *Candida spp.* blood isolates from March 2002 through May 2007 were identified. Demographic, clinical and laboratory data were collected. AF susceptibility testing was performed on all isolates

**Results:** There were 131 episodes of primary CBSI among adult patients for which complete data was available. *C. albicans* (38%) and *C. glabrata* (32%) accounted for the majority of isolates. Overall hospital mortality was 29%. Mortality did not differ significantly by species ( $p = 0.32$ ). Fluconazole resistance was highest among *C. glabrata* isolates (15%). Appropriate therapy was given in 65% of cases. Patients with *C. albicans* isolates received appropriate therapy more frequently than patients with *C. glabrata* (72% vs 54%). In univariate analysis, ICU stay ( $p = 0.02$ ), mechanical ventilation ( $p = <0.01$ ), steroid use ( $p = p < 0.01$ ) and APACHE II score ( $p = <0.01$ ) were significantly associated with mortality. Catheter removal ( $p = 0.05$ ) was associated with increased survival. Fluconazole susceptibility and receipt of appropriate therapy were not associated with survival. Timing of appropriate AF therapy was significantly associated with survival ( $p = 0.04$ ) after adjusting for severity of illness. In multivariate analysis, APACHE II score and timing of appropriate AF therapy ( $p = 0.01$ ) remained independently associated with hospital mortality.

**Conclusions:** Mortality from CBSI remains high (29%). Initial AF therapy is frequently inappropriate (35%) based on sensitivity testing. Severity of illness at onset of CBSI remains an important predictor of mortality.

# M-2137

## Pharmacokinetics, Safety and Tolerability Results of a Dose Escalation Study of Isavuconazole in Neutropenic Patients

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**Background:** Isavuconazole (BAL8557) is an IV and oral broad-spectrum azole antifungal that showed favorable tolerability and efficacy in esophageal candidiasis. Objective of this study was the assessment of increasing doses targeted for prophylaxis of invasive aspergillosis.

**Methods:** In an open-label, multi-center, sequential group trial, patients after chemotherapy for acute myeloid leukemia received 400 and 200 mg of IV isavuconazole on day 1, followed by 200mg bid on day 2, then qd as maintenance treatment. In a second cohort, dosages were doubled. Serial blood samples were taken on day 7, trough levels were monitored on days 2, 3, 5, 7, 14, 21 and EOT. Plasma levels were determined using a validated LC-MS/MS method.

**Results:** The first cohort consisted of 11 patients, the second cohort had 12 patients. PK data from of cohorts were in the range predicted from PK in healthy volunteers. Within 2 to 3 days, the loading dose regimen approached steady-state and there was a dose proportional increase of trough levels approaching steady state. None of the pre-defined criteria were met for preventing progression to the second cohort with doubling of each dosing. Treatment was generally well tolerated, no QTC prolongation, no safety signal with regard to AEs or laboratory was noted.

**Conclusion:** Isavuconazole was well tolerated in neutropenic patients at the given dosages including the dose regimen currently used in phase III for primary treatment of invasive fungal disease. After doubling the dose, PK remained dose proportional.

	Day 1 (mg per dose)	Day 2	Day 3-27	Trough level (µg/mL) day 7	
				Range	Mean and SD
First cohort	400 / 200 / 200	200 / 200	200	1.37 to 2.87	2.06 ± 0.735 (n=5)
Second cohort	800 / 400 / 400	400 / 400	400	2.38 to 5.12	4.06 ± 1.02 (n=6)

# M-2167

## Caspofungin (C) as First-Line Therapy of Invasive Aspergillosis (IA) in Allogeneic Hematopoietic Stem Cell Transplant (HSCT) Recipients: a Study of the EORTC Infectious Diseases Group

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**Background:** C at standard dose was evaluated as 1st-line monotherapy of probable/proven (strict EORTC/MSG criteria) IA in allogeneic HSCT pts.

**Methods:** Pts with possible IA were included if upgraded to probable/proven based on tests performed within 48 h after registration. Diagnosis and efficacy were assessed by a Data Review Board. The primary efficacy endpoint was complete (CR) or partial response (PR) at the end of C treatment (EOT). Other endpoints included response and survival at day 84, and safety. Thirty seven evaluable pts were needed to test the null hypothesis of a true response rate (RR)  $\leq$  13% with a power of 95% in case of a true RR of  $\geq$  33%, using a significance level of 10%. Trial had to be stopped prematurely because of low accrual.

**Results:** 42 patients were enrolled; 24 were eligible. Median age was 50 y (range: 19-65). Transplant was unrelated in 16 pts; acute/chronic GVHD was present in 10 and 7 pts, respectively. 12 pts were neutropenic ( $<500/\mu\text{L}$ ), 12 received steroids and 12 a calcineurin inhibitor. 9 pts had a +ve culture and 22 had +ve antigen in BAL or serum. Median duration of C treatment was 24 d (range: 2 -85). At EOT, 10 of 24 (42%) pts had a favorable (CR + PR) outcome (95% CI 22%-63%), while 1 (4%) and 12 (50%) had stable and worsening disease, respectively, allowing to reject the null hypothesis of a true RR  $\leq$  13%. At d 84, 7 out of 23 assessable pts (30%) had CR or PR. Survival rate at d 84 was 48%. None of the pts had a drug-related serious adverse event or discontinued treatment because of toxicity.

**Conclusions:** C was effective as first-line therapy of IA in allogeneic HSCT pts.

# M-2178

## Randomized Comparison of Safety, Tolerance and Pharmacokinetics of Caspofungin, Liposomal Amphotericin B and the Combination of Both in Allogeneic Hematopoietic Stem Cell Recipients (CASLAMB Trial)

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**Background:** The combination of liposomal amphotericin B (LAMB) and caspofungin (CAS) holds promise to improve the outcome of invasive aspergillosis. Little is known, however, about the safety and pharmacokinetics of this combination in patients.

**Methods:** The safety, tolerance and pharmacokinetics of the combination of LAMB and CAS were investigated in a risk-stratified, randomized, multicenter phase II trial in 55 adult allogeneic hematopoietic stem cell recipients (aHSCT) with granulocytopenia and refractory fever. Patients received either LAMB (3mg/kg/d), CAS (50mg/d; d1:70mg) or the combination of both (CASLAMB) until defervescence and granulocyte recovery. Safety, tolerance, development of fungal infections and survival were assessed through day 14 post end of therapy (EOT). PK plasma sampling was performed on days 1 and 4.

**Results:** All 3 regimens were well tolerated. Premature study drug discontinuations due to grade III/IV AEs occurred in 2/20, 1/18 and 0/17 pts. randomized to LAMB, CAS and CASLAMB, respectively. AEs not leading to study drug discontinuation were frequent but similar across cohorts except for a higher frequency of hypokalemia in CASLAMB ( $p < 0.05$ ). Drug exposures were similar for pts. receiving combination as compared to monotherapy. Treatment success (no discontinuation for toxicity, absence of proven/probable invasive fungal infection and survival through day 14 post EOT) was observed in 15/20, 14/18 and 16/17 pts. receiving LAMB, CAS and CASLAMB.

**Conclusion:** CASLAMB combination therapy in immunocompromised aHSCT patients was as safe as monotherapy with CAS or LAMB and had similar plasma pharmacokinetics, lending support to further investigations in pts. with invasive aspergillosis.