

# ASH 2006

## Pilzinfektionen in der Hämatologie

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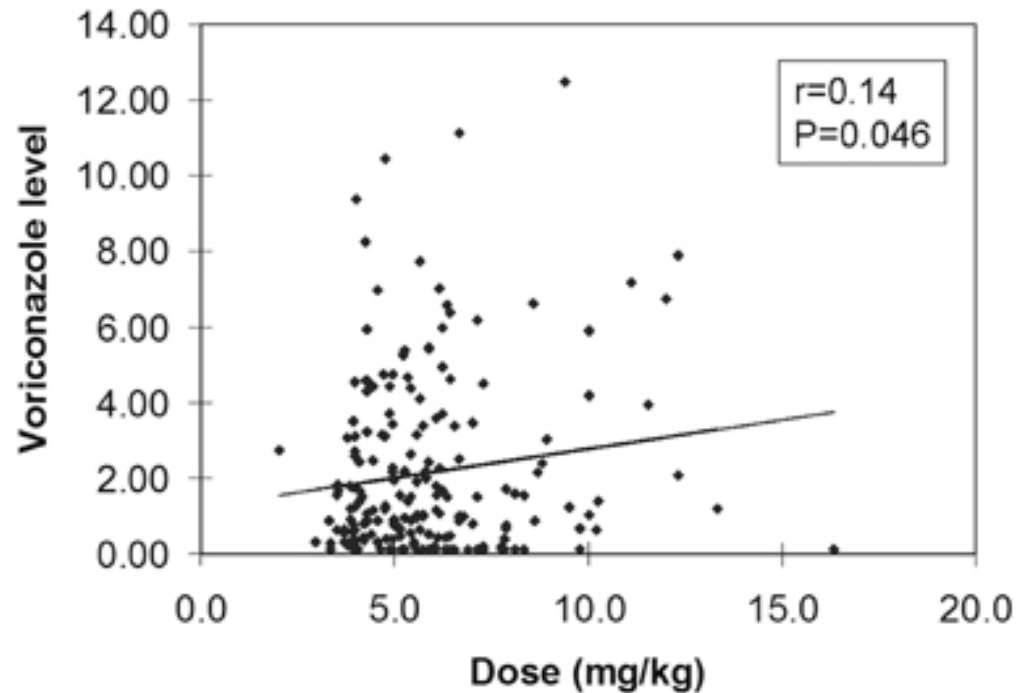
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# Monitoring von Voriconazol Plasmaspiegeln

- Voriconazol erreicht zuverlässig hohe Plasmaspiegel
- Regelmäßige Kontrollen der Plasmaspiegel von Voriconazol gelten als nicht notwendig
- Voriconazolspiegel von  $<0,5 \mu\text{g/ml}$  wurden mit höherem Versagen der Therapie beschrieben
- Co-Medikamente nach Stammzelltransplantation werden häufig ebenfalls über CYP450 System metabolisiert
- Homozygote CYP450 Träger zeigen einen extensiven Metabolismus und signifikant niedrigere Voriconazolspiegel
- Unizentrische Studie: prüft retrospektiv die Korrelation von Voriconazolspiegeln und Tagesdosis von Voriconazol

# Monitoring von Voriconazol Plasmaspiegeln



- Keine eindeutige Korrelation zwischen Dosis und Plasmaspiegeln bei 87 Patienten und 201 Spiegelmessungen nach  $\geq 5$  Tagen Voriconazol

# Monitoring von Voriconazol Plasmaspiegeln

Voriconazol Spiegel in µg/ml	N=	Dosis (mg)	Dosis (mg/kg)	P (Dose in mg/kg; verglichen mit der >5.0µg/ml Gruppe)
<0.2 (undetectable)	30 (15%)	400 (200-800)	5.6 (3.5-11.5)	0.008
0.2-0.5	25 (12%)	400 (400-800)	6.2 (3.8-10.2)	0.18
>0.5 to 2.0	70 (35%)	400 (400-800)	5.2 (3.7-13.3)	0.062
>2.0 to 5.0	53 (26%)	400 (400-800)	4.9 (2.0-9.8)	0.0008
>5.0	23 (11%)	400 (400-800)	6.9 (3.4-16.3)	

## Zusammenfassung und Kommentar:

hoch variable Plasmaspiegel, Patienten wiesen aber sehr unterschiedliche Komedikationen auf

27% der Spiegel befanden sich unterhalb von 0,5 µg/ml

Plasmaspiegel nicht systematisch gemessen (1-5 Messungen, Median 2)

Eine sichere Dosis und Plasmaspiegelbeziehung fand sich nicht unterhalb von 5,0 µg/ml

Praktischer Bezug: Neue Studien sollten Drug-Monitoring prüfen

Durchbruchinfektionen bei Prophylaxe mit Voriconazol (z.B. HSCT + GvHD mit Diarrhoe) ?

Kann ein Drug-Monitoring Versagen bei der p.o. Behandlung verhindern?

## #594 Monitoring Plasma Voriconazole Levels May Be Essential To Avoid Subtherapeutic Levels.

*S. Trifilio, G. Pennick, J. Pi, J. Zook, M. Golf, K. Kaniecki, J. Mehta. Northwestern Memorial Hospital, Chicago; UT Health Sciences Center, San Antonio; Northwestern University, Chicago*

There are limited data on the effects of drug levels on therapeutic success in fungal infections. Low itraconazole trough levels have been associated with breakthrough fungal infections (Glasmacher et al. *Mycoses* 1999;42:443-51). Low voriconazole levels have been associated with a higher failure rate in patients with confirmed fungal infections (Smith et al. *Antimicrob Agents Chemother* 2006;50:1570-2). Success rate in patients with mean voriconazole plasma levels <0.5 µg/mL was 46% compared to 56% with mean plasma levels >0.5 µg/mL ([www.fda.gov/ohrms/dockets/ac/01/briefing/3792b2\\_02\\_FDA-voriconazole.htm](http://www.fda.gov/ohrms/dockets/ac/01/briefing/3792b2_02_FDA-voriconazole.htm)). The period after HSCT is characterized by the use of multiple drugs that can affect the liver cytochrome P450 system. The CYP450 isoenzyme 2C19 plays a significant role in voriconazole metabolism, and exhibits significant genetic polymorphism. Homozygous extensive metabolizers have a significantly lower exposure to voriconazole than heterozygous extensive metabolizers and poor metabolizers. Steady-state plasma trough voriconazole levels were measured after at least 5 days of therapy in 87 patients with hematologic malignancies on 201 separate occasions (1-5 levels per patient; median 2). Most patients had undergone allogeneic HSCT. Drug levels were monitored using HPLC (Pennick et al. *Antimicrob Agents Chemother* 2003;47:2348-50). The daily voriconazole dose (divided into 2) was 200 mg (n=4), 400 mg (n=151), 500 mg (n=20), 600 mg (n=18), and 800 mg (n=8); corresponding to 2.0-16.3 mg/kg (median 5.4). The voriconazole levels were <0.2-12.5 µg/mL (median 1.2). In keeping with the non-linear pharmacokinetic profile of the drug, a strong correlation was not seen between the dose and levels (figure). The table below shows the relationship between levels and dose. While the amount of drug administered in mg/kg was significantly higher when the levels were >5.0 µg/mL, there was no consistent relationship between dose and level below that threshold.

Voriconazole level	n	Dose (mg)	Dose (mg/kg)	P (Dose in mg/kg; compared to the >5.0 level group)
<0.2 (undetectable)	30 (15%)	400 (200-800)	5.6 (3.5-11.5)	0.008
0.2-0.5	25 (12%)	400 (400-800)	6.2 (3.8-10.2)	0.18
>0.5 to 2.0	70 (35%)	400 (400-800)	5.2 (3.7-13.3)	0.062
>2.0 to 5.0	53 (26%)	400 (400-800)	4.9 (2.0-9.8)	0.0008
>5.0	3 (11%)	400 (400-800)	6.9 (3.4-16.3)	

These data show that in adult patients getting standard doses of voriconazole orally, the drug levels are highly variable. Based on the data on the FDA files, 27% of these levels would be associated with a lower likelihood of response. Based on the data of Smith et al, 65% of these levels would be associated with a higher likelihood of failure. We suggest that future voriconazole studies should incorporate prospective therapeutic drug monitoring, and that pending further clarification, consideration should be given to checking levels in patients receiving the drug for confirmed, life-threatening fungal infections.

Abstract #594 appears in *Blood*, Volume 108, issue 11, November 16, 2006

**Keywords:** Voriconazole|Pharmacokinetic|Fungal infection

# Voriconazol und Lebertoxizität

- CYP 450, insbesondere Isoenzym 2C19 für Metabolismus von Voriconazol wichtig, ein genetischer Polymorphismus ist bekannt. Schlechte Metabolisierer könnten erhöhte Vori-Plasmaspiegel aufweisen
- Beziehung zwischen Voriconazolspiegel und Leberfunktion retrospektiv bei 87 Patienten untersucht (s.auch # 594)
- Multivariat war eine Korrelation nachweisbar zwischen dem Voriconazolspiegel und der
  - GPT (p=0.0005)
  - GOT (p=0.003)
  - AP (p=0.027)
- Keine Korrelation bestand zur täglichen Voriconazoldosis

# Voriconazol und Lebertoxizität

- Lebertoxizität mit hohen Spiegeln von Voriconazol verbunden
- Conclusion: Spiegelmessungen bei gestörter Leberfunktion
- Kommentar
  - Studie retrospektiv, keine systematisches Abnahmeprotokoll für Spiegelmessungen
  - Kein Bezug zu den Komedikationen hergestellt
  - Heterogene Gruppe von Patienten
  - Klärung des Bezugs von Voriconazolspiegeln und Lebertoxizität über prospektive Studien notwendig

**Abstract 2950 Voriconazole Therapeutic Drug Monitoring: Relationship between Drug Levels and Liver Function Tests. Session Type: Poster Session, Board #179-III**

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Voriconazole is increasingly being used after HSCT. The hepatic cytochrome P450 isoenzyme 2C19 plays a significant role in voriconazole metabolism. As CYP2C19 exhibits significant genetic polymorphism, some patients metabolize voriconazole poorly resulting in increased plasma drug levels. However, the clinical significance of this is unknown. There is some evidence that toxicity rates are higher in patients with higher voriconazole levels (Boyd et al. Clin Infect Dis 2004;39:1241-1244). In a preliminary study of 41 voriconazole levels in 25 patients, we had found that voriconazole levels correlated with aspartate aminotransferase (AST) and alkaline phosphatase (AP) levels (Trifilio et al. Bone Marrow Transplant 2005;35:509-513). It was unclear if the abnormal liver function was the cause or the result of higher voriconazole levels. To further elucidate this relationship, we analyzed data on 171 steady-state plasma trough levels performed after at least 5 days of voriconazole therapy in 87 patients with hematologic malignancies. There were 1-5 levels per patient (median 2). Most patients had undergone allogeneic hematopoietic stem cell transplantation. Drug levels were monitored using HPLC (Pennick et al. Antimicrob Agents Chemother 2003;47:2348-2350). Of the 201 samples assayed, 30 were below the detection limit of the assay (0.2 g/mL), and were excluded. The daily voriconazole dose (divided into 2) was 200 mg (n=3), 400 mg (n=129), 500 mg (n=18), 600 mg (n=15), or 800 mg (n=6); corresponding to 2.0-13.3 mg/kg (median 5.3). The voriconazole levels were 0.2-12.5 g/mL (median 1.7). The table shows the correlation between voriconazole levels, and weight, dose and biochemical parameters individually.

Parameter	Median (range)	r	P
Dose (mg)	400 (200-800)	0.19	0.013
Weight (kg)	80 (39-135)	0.18	0.018
Dose (mg/kg)	5.3 (2.0-13.3)	0.23	0.002
ALT (IU/L)	25 (4-608)	0.10	0.25
AST (IU/L)	25 (6-524)	0.14	0.11
AP (IU/L)	95 (27-920)	0.27	0.002
Bilirubin (mg/dL)	1.1 (0.1-17.3)	0.01	0.89
Albumin (g/dL)	2.4 (0.8-3.9)	0.28	0.001
Creatinine (mg/dL)	1.1 (0.2-10.1)	0.01	0.92

However, in multivariate regression analysis, the parameters found to correlate significantly with voriconazole levels were ALT (P=0.0005), AST (P=0.003), and AP (P=0.027). The relationship with albumin was of borderline significance (P=0.062). Importantly, the daily dose of voriconazole in mg or in mg/kg was not predictive of drug levels. This larger data set confirms our previous observation that there is a significant relationship between elevated liver function tests and higher voriconazole levels. However, because of the relatively high frequency of abnormal liver function tests in such groups of patients, the cause-effect relationship still remains uncertain. These data suggest that pending further clarification, voriconazole levels may need to be monitored in patients with significantly abnormal liver function tests.

Abstract #2950 appears in Blood, Volume 108, issue 11, November 16, 2006

**Keywords:** Voriconazole|Liver|Fungal infection

# Voriconazolspiegel und Durchbruchinfektionen

- 71 Patienten mit Voriconazol Prophylaxe  $\geq 7$  Tage
  - 35 matched sibling donor, 27 matched unrelated donor (MUD) (submyeloablativ), 7 MUD myeloablativ
  - Voriconazol 2x200 mg/d p.o. mit Beginn zum Zeitpunkt der Steroidgabe zur Therapie einer GvHD (n=54)
  - Voriconazol 2x200 mg/d p.o. ab Tag 1 nach SCT wenn in der Vorgeschichte eine IA bestanden hatte (n=17)
- Prophylaxedauer Median 117 Tage (bis 1 Mo nach Ende der Immunsuppression oder Nachweis einer IFI)
- 54 Patienten hatten zunächst Itraconazol als Prophylaxe
- Voriconazolspiegel ab Tag 5 der Behandlung

# Voriconazolspiegel und Durchbruchinfektionen

- Mediane Voriconazolspiegel 1,04 µg/ml (0,2 - 6,97 µg/ml)
- 10/71 Patienten bewiesene invasive Mykosen
  - 6 IFI mit Candida (pos. BAL+ radiologisches Infiltrat, 1 x Blut)
  - 4 Fälle von Zygomycosen ( 1 Mucor, 2 Rhizopus, 1 Cunninghamella)
- Bei den 6 Fällen von IF durch Candida Plasmaspiegel <2µg/ml
- Es waren keine invasiven Aspergillosen in der retrospektiven Analyse nachweisbar
- Durchbruchinfektionen mit sensiblen Candidaspezies wurden nur bei niedrigen Spiegel von Voriconazol beobachtet
- Autoren fordern Drug Monitoring für Voriconazol

# Plasmaspiegel von Voriconazol

- Beobachtungen der Arbeitsgruppe sind wichtig
- Prophylaxe von Voriconazol bisher off-label
- Systematische Daten zur Resorption bei Diarrhoe und GvHD?
- Metabolismus und Komedikationen nach SCT?
- Versager mit niedrigen, Lebertoxizität mit hohen Spiegel in Verbindung gebracht
- Trifilio Abstract 594, 2849 und 2950 beziehen sich auf die gleiche Patientengruppe, retrospektive Analysen, systematisches Protokoll fehlend
- Prospektive Studie mit Spiegelbestimmung sinnvoll

**Abstract 2849 Breakthrough Fungal Infections after Allogeneic Hematopoietic Stem Cell Transplantation in Patients on Prophylactic Voriconazole. Session Type: Poster Session, Board #78-III**

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Voriconazole is a triazole anti-fungal agent with excellent activity against *Aspergillus* spp. We use liquid itraconazole 200 mg PO twice daily from day 0 to a month beyond discontinuation of all immunosuppression as standard anti-fungal prophylaxis after allogeneic HSCT in patients with no prior history of aspergillosis. This is changed to PO voriconazole 200 mg twice daily if corticosteroid therapy is started for GVHD. Voriconazole is continued even after steroid therapy is discontinued. Patients with a past history of aspergillosis get voriconazole from day 0. 71 allograft recipients who received voriconazole, and in whom complete clinical, microbiologic, and pharmacokinetic data were available were studied to determine the efficacy of voriconazole in preventing invasive fungal infections (IFI). 17 patients had not received itraconazole previously. The remainder had received itraconazole for 1-161 days (median 14). The length of voriconazole therapy was 6-956 days (median 133). The total number of patient-days on voriconazole was 13805 (38 years). A total of 10 IFIs were seen in patients on voriconazole: *Candida glabrata* (n=5), *Candida krusei* (n=1), *Cunninghamella* (n=1), *Rhizopus* (n=2), and *Mucor* (n=1). The figure below shows the actuarial probability of IFI - 18% at 1 year.

It is noteworthy that while 4 cases of zygomycosis were seen, no case of *Aspergillus* infection was seen. The figure below shows the actuarial probability of zygomycosis - 7% at 1 year.

Zygomycetes are generally not susceptible to voriconazole, and thus breakthrough infections are not surprising. However, *C. glabrata* and *C. krusei* are often susceptible to voriconazole with MICs of <2 g/mL (Spellberg et al. Clin Infect Dis 2006;42:244-251). In that context, it is interesting that plasma steady-state trough voriconazole levels around the time the infection occurred were <0.2, <0.2, 0.33, 0.55, 0.63, and 1.78 g/mL in the 6 candidiasis cases. Excluding the 4 zygomycosis cases, all 6 candidiasis cases were seen amongst the 43 patients with voriconazole levels of 2 g/mL and none amongst the 24 with levels of >2 g/mL (P=0.061; Fishers exact test). This observation is in keeping with a recent report that showed correlation between voriconazole levels and therapeutic success in aspergillosis (Smith et al. Antimicrob Agents Chemother 2006;50:1570-1572). We conclude that (1) voriconazole is extremely effective at preventing aspergillus infections, (2) zygomycosis is a concern in voriconazole-treated patients although the incidence appears low, and (3) therapeutic drug monitoring with dose adjustment may be indicated in patients on voriconazole to avoid breakthrough infections with fungi that are otherwise susceptible to the drug.

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**Keywords:** Fungal infection|Voriconazole|Hematopoietic cell transplantation

## **Granulozytentransfusionen zur Therapie oder als Prophylaxe von schweren Infektionen bei neutropenen Patienten**

- randomisierte multizentrische Studie, 74 Pat (79 Episoden)
- Granulozytentransfusion (GT) vs keine GT
- Einschluß bei ANC  $\leq 200$ , klinischen Zeichen einer schweren Infektion durch Bakterien oder Pilze (kein Schock)
- 23/74 Patienten hatten Infektionen bei Randomisation
  - davon 17 Pilzinfektionen, 4 bakterielle Infekte
- Mediane Zahl der GT            3 (Range 1-11)
- Mediane Tage mit GT            6(1-27)
- Mediane ANC/kg/Konz        6,6 (2 -16)

## **Granulozytentransfusionen zur Therapie oder als Prophylaxe von schweren Infektionen bei neutropenen Patienten**

	GT (n=40)	keine GT (n=39)
Todesfälle insgesamt	18	18
Überleben an Tag 28	80%	80%
Tod nach 100 Tagen	11	9
Tod durch Infektion	5	3

Kein Unterschied zwischen beiden Armen

Kein Effekt von GT auf den Infektionsausgang nachweisbar

Allerdings einzelne Pat im Arm ohne GT hatten doch GT erhalten

**Abstract 2934 Granulocyte Transfusions for Treatment or Prophylaxis of Severe Infections in Immunocompromized Neutropenic Patients A Randomized Clinical Trial. Session Type: Poster Session, Board #163-III**

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Background: Despite availability of potent anti-bacterial, anti-mycotic drugs and hematopoietic growth factors invasive bacterial or fungal infections remain a severe threat to neutropenic patients after chemotherapy or hematopoietic stem cell transplantation (HSCT). Granulocyte transfusions (GT) from granulocyte colony stimulating factor (G-CSF)-stimulated donors have been shown to increase the leukocyte count prior to expected hematopoietic regeneration, resulting in a shorter period of neutropenia and thus offer a therapeutic option for the control of severe infections. However, published studies rely on clinical observations of individual cases as no statistical comparison with control groups could have been established. The aim of this study was to define the clinical benefit and the leukocyte increment / duration of neutropenia after randomized administration of leukocyte transfusions in immunocompromized neutropenic patients. Patients and methods: Between 1999 and 2005 80 patients with underlying hematological diseases with or without allogeneic or autologous HSCT were randomized to receive either G-CSF, anti-infective treatment according to local standards with or without therapeutic or prophylactic application of GT from G-CSF-stimulated volunteer donors. The mean age was 47 years (range, 14 62 y). Indications were either fever in neutropenia and pulmonary infiltrates or soft tissue infiltration (*therapeutic*) or the history of invasive fungal infection during episodes of neutropenia following earlier chemotherapy courses and anticipated neutropenia of > 10 days (*prophylactic*). Results: 10 centers participated in the trial, however only five centers recruited patients (n=80) for randomization during the study period. This corresponds to 50% of the expected sample size of 160 patients, hence results are statistically insignificant. Patient characteristics were comparable within the randomized cohorts (underlying disease, stage of disease, indication for GT, length of neutropenia). No significant difference in the clinical outcome was found between patients who received either therapeutic or prophylactic GT from G-CSF stimulated donors or no GT. The probability of survival on day 28 was 85% in both groups. Furthermore, no difference in the incidence and causes of death could be identified within the compared cohorts. Conclusion: The high percentage of infection clearance and survival in patients with severe infections in both groups contrasts with published results and own experiences. We speculate whether this is due a bias in including predominantly patients into the randomized study who presented with relatively favourable prognostic factors, as in the observation period numerous GT were performed in the participating centers without randomization. Most likely, existing clinical evidence for the benefit of this therapeutic measure was sufficient in many cases to exclude patients in serious conditions from randomization. Although well designed, a randomized trial may not always provide the expected results.

Abstract #2934 appears in Blood, Volume 108, issue 11, November 16, 2006

**Keywords:** Invasive aspergillosis|Engraftment|Leukocytes

# Späte Infektionen nach allogener Stammzelltransplantation

- Bekannt: hohe Rate Pilzinfektionen (IFI) in ersten 6 Mo
- Studie: Unizentr. 196 Patienten Infektionen (>1 Jahr nach SCT)
- Unklar ist das Risiko für IFI nach > 6 Monaten:
  - 3 Risikofaktoren: CMV-Status vor SCT, chron. extens. GvHD
- Medianes Follow-up 7,9 Jahre
- 30/196 späte bakterielle Infektionen (kumulat. Inzidenz 15%)
- 8/196 Patienten wiesen invasive Mykosen auf
  - 6 invasive Aspergillose, 2 Candida Sepsis
  - 4 Pneumocystis jurevei
- Die kumulative Inzidenz über 8 Jahre für IFI betrug 3,6%

**#2848 Risk Factors for Late Infections after Allogeneic Hematopoietic Stem Cell Transplantation from a Matched Related Donor. Session Type: Poster Session, Board #77-III**

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After allogeneic hematopoietic stem cell transplantation (HSCT), late infections represent a major cause of morbidity and mortality but little has been previously reported. In a retrospective cohort study, late infections incidence was determined in 196 long-term survivors after matched related HSCT. Only patients transplanted for aplastic anemia, chronic myeloid leukemia (CML) and acute myeloblastic leukemia (AML) were included in this study. Median follow-up was 8 years. Among 30 patients who died beyond the first year, 9 patients died from graft-versus-host disease (GVHD) and 10 from infections. Bacterial late severe infections occurred in 30 patients, yielding an 8-year cumulative incidence of 15%. Late invasive fungal infection occurred in 8 patients corresponding to a cumulative incidence of 3.6%. Most viral infections were hepatitis C and VZV and overall late viral infection incidence was 35%. We identified 3 risk factors for bacterial infections in multiple analysis: CMV status (positive recipient and negative donor), irradiation based conditioning regimen and extensive chronic GVHD within the first year. Extensive chronic GVHD was the only risk factor of non-HCV viral infection in patients transplanted for AML or CML. Thus, late life threatening infections may occur in nearly a fourth of late survivors even after matched related transplantation and are associated not only with chronic GVHD but also with irradiation and to CMV status prior to transplantation.

Abstract #2848 appears in Blood, Volume 108, issue 11, November 16, 2006

**Keywords:** Hematopoietic cell transplantation|Infection|Graft-versus-host disease (GVHD)

## **1,3-Beta-D-Glucan (BGL) bei Patienten mit AML und hohem Risiko für invasive Pilzinfektionen (IFI)**

- BGL ist ein Bestandteil der Zellwand von Pilzen
- Studie prüft BGL als serologischer Marker bei HR-Patienten mit AML
- BGL-Bestimmung 2x/Wo bei 95 Patienten (80 AML/15 ALL)
- 190 Eps mit Neutropenie (median 22 Tage) mit 337 febrilen Episoden
- 62 Pilzinfektionen davon 30 proven/probable IFI
- 15 Invasive Aspergillosen davon 5 proven IA
- 17 Invasive Candidainfektionen davon 4 proven
- 4 PcP Infektionen
- BGL wies eine Spezifität von 95% und Sensitivität von 63% auf
- Die optimale Wert für BGL-Test: 2 Proben >7pg/ml bei einem positiven prediktiven Wert (PPV) von 79% und negat. Wert (NPV) von 90,7%
- Konstant hohe BGL Werte >50 pg/ml bei therapierefraktären Patienten

**Abstract 2924 Monitoring of 1,3-Beta-D-Glucan (BGL) Antigenemia in Neutropenic Patients with Acute Leukemia at High Risk for Invasive Fungal Infections (IFI). Session Type: Poster Session, Board #153-III**

*Laurence Senn, James O. Robinson, Sabine Schmidt, Marlies Knaup, Nobuo Asahi, Shinji Satomura, Shuuji Matsuura, Jacques Bille, Bertrand Duvoisin, Thierry Calandra, Oscar Marchetti (Intr. by Michel A Duchosal) Infectious Diseases Service, CHUV, Lausanne, Switzerland; Radiodiagnostic Service, CHUV, Lausanne, Switzerland; Wako, Osaka, Japan*

Invasive candidiasis (IC) and aspergillosis (IA), the most frequent IFI in leukemic patients, are associated with high morbidity and mortality. As early diagnosis of IFI is difficult, empirical antifungal therapy is recommended in persistently febrile neutropenic patients. This standard of care results in a broad use of antifungals. New non-invasive diagnostic tests such as circulating BGL, a fungal cell wall component, are thus needed to optimize management of patients with IFI. The objective of the current study was to evaluate the utility of monitoring BGL antigenemia in neutropenic patients at high risk for IFI. We conducted a prospective study of 189 episodes of neutropenia (median duration 22 days, range 7-113) following induction (n=107) or consolidation chemotherapy (n=82) in 99 consecutive patients with acute leukemia (85 AML, 14 ALL). Blood was collected 2x weekly before onset of fever and daily thereafter until resolution of fever. BGL was measured by colorimetric assay (Wako, Japan). Two cut-off values (5 or 11 pg/ml) were studied. A positive result was defined by 2 consecutive samples with BGL higher than the cut-off value. A median of 2 (0-4) febrile episodes occurred per neutropenic episode. Among 320 febrile episodes, 31 IFI were diagnosed according to EORTC-MSG criteria: 17 IC (4 proven, 13 probable) and 14 IA (5 proven, 9 probable). A median of 15 samples (4-47) per episode of neutropenia were analyzed over a median period of 34 days (19-121). The diagnostic performance of BGL was evaluated in patients with proven or probable IFI compared with febrile patients without IFI (Table). In patients with IC, the median time between onset of fever as first sign of IFI and BGL positivity ( $\geq 5$ ) was 0 (3 to 17 days) as compared with 16 (0 to 51 days) until diagnosis of infection using conventional microbiological and imaging techniques ( $p=0.03$ ). In IA patients, it was 3 (9 to 14 days) vs. 7 (1 to 21 days) ( $p=0.07$ ). In IC and IA, median peak BGL (21 [6-111] and 15 [7-51] pg/ml) occurred on day 13 (1 to 41) and on day 7 (3 to 20) after fever onset, respectively. Median time to initiation of antifungal therapy after fever onset was similar in IC (2.5, range: 1 to 10 days) and IA (5, range: 0 to 10 days). BGL antigenemia decreased or cleared in patients responding to therapy (n=19) and continued to increase (peak 111 and 66 pg/ml) in 2 cases of IC, in whom therapy failed. BGL was negative ( $< 5$  pg/ml) in 100/102 episodes of bacteremia. In conclusion, monitoring of 1,3-beta-D-glucan antigenemia provides a new tool for early diagnosis and follow-up of IFI in neutropenic patients with acute leukemia.

**Diagnostic Performance of BGL**

BGL Cut-off (pg/ml)	2 x 5	2 x 5	2 x 5	2 x 11	2 x 11	2 x 11
Type of proven/probable IFI	IC	IA	All IFI	IC	IA	All IFI
Sensitivity %	65	93	76	35	43	38
Specificity %	89	89	89	99	99	99
PPV %	48	52	65	86	86	92
NPV %	94	99	93	91	93	86
Positive Likelihood Ratio	5.9	8.5	6.9	35	43	38
Negative Likelihood Ratio	0.4	0.1	0.3	0.7	0.6	0.6

Abstract #2924 appears in Blood, Volume 108, issue 11, November 16, 2006

**Keywords:** Diagnosis|Aspergillus|Adult

# Empirische oder pre-emptive antimykotische Therapie: Eine ökonomische Analyse

- Empirische Gabe von Antimykotika ist Standard bei antibiotikarefraktärem Fieber in der Neutropenie
- multizentrische, offene randomisierte Studie untersucht Kosteneffektivität von Antimykotika, 293 Patienten mit hämatologischen Malignomen, ANC  $<500/\mu\text{l}$   $\geq 10$  d, GM 2x/Wo
- empirische vs pre-emptive Polyen-Therapie (AFT)
  - empirische AFT: bei persistierendem oder rekurrentem Fieber
  - pre-emptive AFT: nur bei Pneumonie, schwerer Mukositis, septischem Schock, Sinusitis, Aspergillus-Kolonisation oder pos. GM-Test

# Empirische oder pre-emptive antimykotische Therapie: Eine ökonomische Analyse

Vergleich der mittleren Medikationskosten, Antimykotischen Therapiekosten, und Verhältnis von IFI zwischen den Armen mit pre-emptiver Therapie und empirischer Therapie (€)

		Pre-empt. Strategie	Empirische Strategie	p
Overall (n=293)	Medication costs	3595 (7444), n=143	3745 (4768), n=150	ns
	Antifungal therapy costs	2218 (6969), n=143	2337(4093), n=150	ns
	Proportion of IFI	9.1% (13/143)	2.7% (4/150)	<0.02
Induction (n=151)	Medication costs	5714 (9843), n=73	4793 (5330), n=78	ns
	Antifungal therapy costs	3974 (9360, n=73	3353 (4876), n=78	ns
	Proportion of IFI	16.4% (12/73)	3.9% (3/78)	<0.01
Consolidation or ASCT (n=142)	Medication costs	1387(1807), n=70	2610 (3795), n=72	<0.02
	Antifungal therapy costs	386 (1367), n=70	1237 (2649), n=72	<0.02
	Proportion of IFI	1.4% (1/70)	1.4% (1/72)	ns

# Empirische oder pre-emptive antimykotische Therapie: Eine ökonomische Analyse

- Gleiche Kosten bei empirischer oder pre-emptiver Therapie
- Kosten der empirischen Therapie in der Induktionstherapie sogar etwas günstiger als bei pre-emptiver Therapie
- Ursache ist die hohe Rate an Pilzinfektionen bei den Patienten mit hohem Risiko während der Induktion von Leukämien
- Bei Konsolidationstherapie oder autologer SCT ist die pre-emptive Strategie kosteneffektiver bedingt durch das hier insgesamt geringere Risiko an invasiven Pilzinfektionen
- Kosteneffektivität hängt entscheidend vom Risikoprofil für IFI ab (Erkrankung und lokaler Epidemiologie)

**#2021 Empirical Versus Pre-Emptive Antifungal Therapy in High-Risk Febrile Neutropenic Patients: An Economic Analysis. Session Type: Poster Session, Board #199-II**

*Michael Schwarzingger, Celine Beauchamp, Sebastien Maury, Cecile Pautas, Anne Vekhoff, Hassan Farhat, Felipe Suarez, François Hemery, Mathieu Kuentz, Patrick Maison, Catherine Cordonnier (Intr. by catherine cordonnier). Medical Economics Department, IGR, Villejuif; Hematology, Informatics, and URC, Henri Mondor Hospital, Creteil; Hotel Dieu Hospital; Andre Mignot Hospital; Necker Hospital, Paris, France*

Empirical (E) antifungal therapy (ATF) is a standard of care in neutropenic patients with persistent or recurrent fever. However, the safety and cost-effectiveness of the E strategy are challenged by the development of better diagnostic methods and more effective therapies for invasive fungal infection (IFI). An economic analysis was conducted alongside a multicenter open-label randomized non-inferiority trial showing that a pre-emptive (PE) strategy based on clinical symptoms and GM Ag did not reduce the overall survival of prolonged neutropenic patients when compared to a E strategy (details provided in abstract 551005). Objective: The objective of the study was to compare hospital costs between the PE strategy and E strategy. Patients: 293 adult patients with hematologic malignancies and an expected neutropenia (<500 PMN) of  $\geq 10$  days following chemotherapy were randomized between E or PE strategy with polyens. All were screened 2/w for GM Ag. E patients were given ATFs in case of persistent or recurrent fever, whatever the accompanying symptoms, while PE patients were given ATFs only in case of pneumonia, severe mucositis, septic shock, sinusitis, or skin lesions evocative of filamentous infection, aspergillus colonization, or positive GM Ag. Methods: The economic analysis was conducted from the hospital perspective (€2005). Total medication costs were computed from individual records during hospital stay. Results: Overall, mean medication costs did not differ significantly between the PE and E groups (see Table). In patients in induction phase (n=151), mean medication costs were higher in the PE group than the E group (+921€ [95%CI, -1602 to +3444]) as explained by the significantly higher proportion of IFI in the PE group (16.4% vs. 3.9%, p<0.01) and the significantly higher medication costs in case of IFI (+4224€ [95%CI, +1200 to +7244]). In patients in consolidation phase (n=51) or autologous stem cell transplant (ASCT) (n=91), mean medication costs were significantly lower in the PE group than the E group (-1224€ [95%CI, -233 to -2215]) as explained by the significantly lower proportion of patients receiving ATF in the PE group (31% vs. 50%, p<0.03). Conclusion: Cost comparison between E and PE strategy showed opposite results in induction or consolidation/ASCT phases. This finding is mainly explained by different risks of developing IFI according to the therapeutic phase. (*Grants: PRC 2002 AOR02028*).

Abstract #2021 appears in Blood, Volume 108, issue 11, November 16, 2006

**Keywords:** Febrile neutropenia|Cost analysis|Fungal infection

# Kosteneffektivität einer niedrig-dosierten Prophylaxe mit liposomalem AmB

- Analyse der Prophylaxe-Studie (ASH 2005, #1310) mit niedrig dosiertem liposomalem AmB anhand der Akten

	Arm A (lAmB)	Arm B (Kontrollarm)
	n=56 Pat	n=44 Pat
Kosten Prophylaxe	360 Euro	0 Euro
Kosten Antibiotika	210 Euro	670 Euro
Antimykotische Therapie	360 Euro	2170 Euro
Antimikrobielle Therapie (insgesamt pro Aufenthalt)	1200 Euro	2840 Euro

# Kosteneffektivität einer niedrig-dosierten Prophylaxe mit liposomalem AmB

- Kosteneffektivität ist im Zeitalter der DRGs bedeutsam
- Antimykotika (AF) zeigen Kostenvariabilität - bedeutsam Arm B!
- Verkürzung der KH-Aufenthaltsdauer ist aus ökonomischen Gesichtspunkten bei akuten Leukämien sinnvoll
- KH-Aufenthaltsdauer unter antimykotischer Prophylaxe ist u.U. unter DRG-Gesichtspunkten wichtiger als Kosten der AF selbst
- DRG-System entlohnt die Aufwendungen der Prophylaxe nicht, führt aber im Einzelfall zu geringerem Schweregrad und damit geringerem Erlös
- Unklar warum mit einer antimykotischen Prophylaxe bei Patienten mit hohem Risiko Antibiotika eingespart werden

**#3324 Low Dose Liposomal Amphotericin B (L-AmB) as Prophylaxis of Invasive Fungal Infections (IFI) in Neutropenic Patients (pts): Is It Cost Effective? Session Type: Poster Session, Board #553-III**

*Olaf Penack, Peter Martus, Eckhard Thiel, Igor W. Blau. Department of Hematology, Oncology and Transfusion Medicine, Charité Campus Benjamin Franklin, Berlin, Germany; Department of Biostatistics and Clinical Epidemiology, Charité Campus Benjamin Franklin, Berlin, Germany*

Background In a recently reported randomized trial (ASH meeting 2005, oral presentation #1310) low-dose intravenous L-AmB reduced the incidence of IFI (20.2% vs. 4.6%,  $p < 0.001$ ) in high risk pts with hematological malignancies and prolonged neutropenia. The purpose of the current study was to compare the pharmacoeconomics of L-AmB prophylaxis vs. no systemic antifungal prophylaxis. Methods: Records of all randomized pts with acute leukemia were reviewed for dosage and duration of antimycotic and antibiotic treatment during hospital stay. Based on this data and current drug prices the mean costs of antimicrobial treatment (AT) per hospital stay were calculated. Results Pt. characteristics: Randomized pts 132; eligible pts 100; arm A: 56 (L-AmB prophylaxis); arm B: 44 (no prophylaxis). Baseline characteristics were balanced for age (mean 55.8 years), underlying disease (81 AML, 19 ALL) and duration of neutropenia (mean 18.5 days). Endpoints: The costs for antifungal treatment (excluding prophylaxis) were 360 Euro in arm A vs. 2170 Euro in arm B ( $p < 0.001$ ). Expenditures for antifungal prophylaxis accounted for 630 Euro in arm A vs. 0 Euro in arm B. The costs of antibiotic treatment were lower in arm A compared to arm B (210 Euro vs. 670 Euro,  $p < 0.001$ ). The total costs for AT (including antifungal prophylaxis) per hospital stay were 1200 Euro in arm A vs. 2840 Euro in arm B ( $p = 0.071$ ). Conclusion: Our results suggest that antifungal prophylaxis with low dose L-AmB in high risk patients with hematologic malignancies has the potential to reduce the incidence of IFI and may be a cost-saving strategy.

Abstract #3324 appears in Blood, Volume 108, issue 11, November 16, 2006

**Keywords:** Prophylaxis|Fungal infection|Amphotericin

# Effektivität und Sicherheit von Micafungin bei Pilzinfektionen in der Hämatologie

- prospektive Studie von 2003-05 an 87 japanischen Zentren
- Einschluss: 186 hämatologische Pat, 91 Pat mit SCT, davon auswertbar für Effektivität und Sicherheit 196 (134/62)
- Einschlusskriterien bei hämatologischen Patienten
  - proven, probable und possible IFI
  - Fieber unklarer Ursache refraktär auf Antibiotika
- Kombinierte Kriterien für das Ansprechen aus
  - klinischen Symptomen
  - mykologischen Befunden
  - Bildgebung (Röntgen, CT, Ultraschall)
  - Serologie

# Effektivität und Sicherheit von Micafungin bei Pilzinfektionen in der Hämatologie

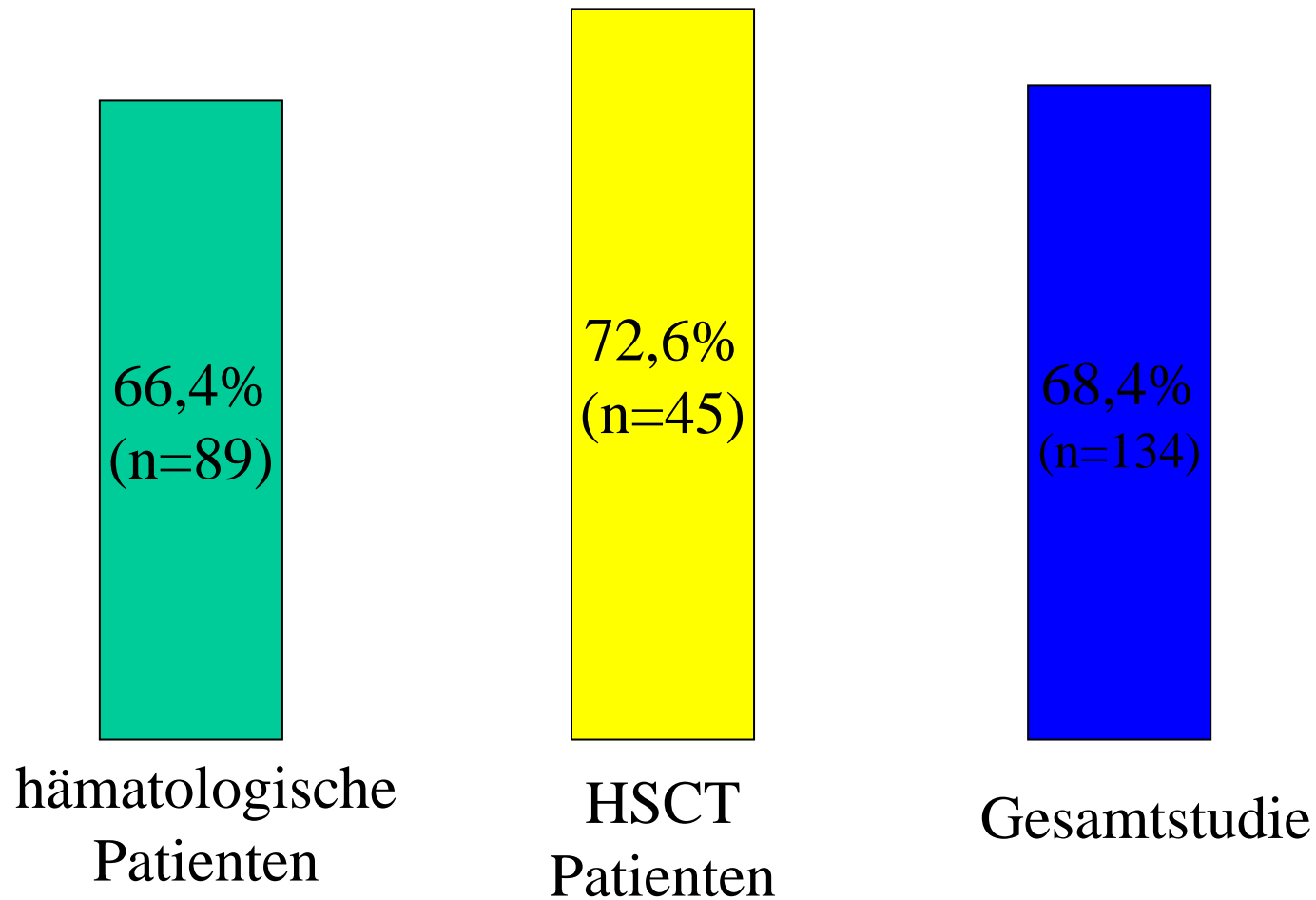
Patienten	Hämatologie (134)	SCT (62)
Männer/Frauen	80/54	38/24
Mittleres Alter (J)	62,0	45,7
Alter <39/40-59/>60	18/33/83	18/36/8
Dosis Micafungin (mg)	161,8 (SD 69)	190,3 (SD 73)
Micafungin 100/150/300 mg	33/76/25	5/37/20
Mittlere Therapiedauer (T)	21,4 (SD 15)	22,6 (SD 16)
Therapie <14/15-28/>29 T	61/42/31	26/18/18

# Sicherheit von Micafungin bei Pilzinfektionen in der Hämatologie

Sicherheit von Micafungin: NW bei 30.1% beobachtet, häufigste:

Leberfunktionsstörungen	64
Hyperbilirubinämie	10
ALP Erhöhung	7
LDH Erhöhung	12
Nierenfunktionsstörungen	10
Andere Nebenwirkungen	
Hyponatriämie	2
Hypokaliämie	3

# Effektivität von Micafungin bei Pilzinfektionen in der Hämatologie



**Abstract 2933 Efficacy and Safety of Micafungin, an Echinocandin Antifungal Agent on Systemic Fungal Infections in Patients with Hematological Disorders. Session Type: Poster Session, Board #162-III**

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Background and Purpose: Severe infections in patients (pts) with hematological disorders (HD) are mostly the result of a compromised immune system by the underlying disease itself including neutropenia aggravated by chemotherapy and conditioning treatment for hematopoietic stem cell transplantation (HSCT). Systemic fungal infections (SFIs) particularly are often encountered in this field associated with morbidity and mortality. It is deemed crucial to initiate an early introduction of antifungal therapy by using criteria for an early diagnosis. Micafungin (MCFG) that was launched in Japan in 2002 and approved in another 3 countries is shown to be safe and efficacious for SFIs. Since there are few clinical reports on the effects of MCFG in a large number of patients, a multicenter study (87 institutions) was initiated to see its efficacy and safety.

Methods: The study was conducted from Apr. 03 to Mar. 05 on pts diagnosed with HD, who met any of the following criteria: pts 1) who are found to have a causative fungus identified by mycological or pathological testing (proven), 2) with a SFI defined by clinical symptoms/findings and serological testing or diagnostic imaging (probable/possible), or 3) with a suspected SFI identified by unexplained persistent fever (an axillary temperature higher than 37.5 C) and clinical symptoms/findings (refractory to antibacterial treatment). Efficacy was evaluated by the degree of improvement in clinical symptoms/findings, mycological findings, imaging study findings such as chest X-ray or CT, and fungal serological tests. The overall effects were rated as either effective or ineffective, based on an algorithm combining these indices.

Results: A total of 277 pts were registered to the central office and 276 were evaluable for safety assessment. Eighty-one pts were not evaluable for efficacy due to a violation of entry criteria, etc. Thus 196 pts were assessed for clinical efficacy by the steering committee (118 males and 78 females, the mean age: 56.8). There were 62 pts with HSCT and 134 with chemotherapy in whom 67 had acute leukemia. The mean dosage and duration of MCFG were 170.8mg per day and 21.8days, respectively. Overall clinical effects were achieved in 134 out of 196 pts (68.4%). Clinical response was seen in 72.6% (45/62) for those with HSCT and 66.4% (89/134) for those of chemotherapy and particularly 68.7% (46/67) of the pts with chemotherapy for acute leukemia, respectively. The success rates were 87.5% (7/8) for pts with proven SFIs like candidemia, 44.7% (17/38) for probable SFIs, 62.9% (39/62) for possible SFIs, and 80.7% (71/88) for those who failed to respond to antibacterial treatment. The success rate for 13 pts with persistent fever on antibacterials and neutrophil counts below 500/L before and after MCFG treatment was 69.2%. The incidence of adverse events related to MCFG was 30.1% (83/276), and the most common one was elevation of liver transaminase levels.

Conclusions: MCFG demonstrated excellent clinical efficacy and safety when used to treat possible to proven SFIs in pts with HD, indicating its usefulness as a novel therapeutic drug for both empirical and targeted therapy for deep-seeded fungal infection.

Abstract #2933 appears in Blood, Volume 108, issue 11, November 16, 2006

**Keywords:** Fungal infection|Clinical outcome|Febrile neutropenia

# Langzeitinfektionen nach allogener SCT mit reduzierter Konditionierung (RIC)

- Langzeitkomplikationen nach allo SCT mit RIC wenig untersucht
- unizentrische Daten von 159 konsekutiven Pat. med. Follow-up 19 Mo, 120 Pat.(75%) wiesen wenigstens 1 Infektionsepisode nach >6Mo auf
- 144 dokumentierte Infektionen
  - 48 Bakterien (33%), davon 19 gram-positiv, 26 gram-negativ, 2 andere
  - 78 virale Infektionen (54%); davon CMV (25), HSV (27), VZV (22)
  - 18 Pilzinfektionen (13%)
- Pilzinfektionen (n=18)
  - 8 invasive Aspergillosen
  - 6 *Candida albicans*, 2 *Candida glabrata*
- Risikofaktoren für späte Infektionskomplikationen (multivariate Analyse)
  - KM > PBSCT p=0.005
  - extensive cGvHD > limitierte p=0.0003

**Abstract 2850 Long Term Infectious Complications Following Reduced Intensity Conditioning (RIC) Allogeneic HLA-Identical Sibling Transplantation (allo-SCT). Session Type: Poster Session, Board #79-III**

*Anne Etienne, Mohamad Mohty, Catherine Faucher, Sabine Furst, Jean El-Cheikh, Christine Zandotti, Pierre Berger, Norbert Vey, Anne-Marie Stoppa, Reda Bouabdallah, Patrice Viens, Jean-Albert Gastaut, Didier Blaise Hematology Dpt, Institut Paoli-Calmettes, Marseille, France; Virology Dpt, Hopital de la Timone, Marseille, France; Oncology Dpt, Institut Paoli-Calmettes, Marseille, France*

In the setting of RIC for allo-SCT, long term outcomes are still poorly defined. Of note, the epidemiology of long term transplant-related infections is still sparse. This prospective report describes infectious complications occurring beyond 6 months after allo-SCT, in 159 consecutive patients who received a RIC allo-SCT from an HLA-identical sibling. Patients characteristics are as follow: median age was 50 (range, 18-68) years. 68 patients (43%) had a myeloid malignancy, whereas 66 patients (41%) had a lymphoid malignancy. The remaining 25 patients (16%) were treated for metastatic non-hematological malignancies. The majority of patients (n=126, 79%) had an advanced disease with high risk features precluding the use of myeloablative allo-SCT. 24 patients (15%) received donor bone marrow (BM), while the remaining 135 patients (85%) received PBSCs. In addition to fludarabine and busulfan, the RIC regimen included high dose ATG in 20 patients (13%) and low dose ATG in 95 (60%). 24 patients (15%) received fludarabine, busulfan and TLI, while the remaining 24 patients (15%) received fludarabine and low dose TBI. With a median follow-up of 19 (range, 6-90) months, 120 patients (75%) experienced at least one infectious episode (total number of episodes, 366) beyond the first six months after allo-SCT developing at a median of 8 (range, 6-34) months. In all, 212 infectious episodes (58%) required hospitalization (7% in the intensive care unit) for a median duration of 10 (1-91) days. 144 episodes (39%) could be documented (bacterial, n=48; viral, n=78; fungal, n=18). Microbiologically documented infections were distributed as follow: gram negative bacteria (18%), other bacteria (15%), CMV positive antigenemia (17%), HSV (19%), VZV (15%), other viruses (3%), aspergillus (6%), candida species (6%), other (1%). 76% of patients with an infection were under systemic immunosuppressive therapy for chronic GVHD at time of infection. Moreover, 85 patients (71%) experienced more than one infectious episode (median, 2; range, 1-12). In multivariate analysis, active or prior history of extensive chronic GVHD and the use of a BM graft were the strongest factors significantly associated with an increased risk of long term infections (P=0.0003; RR=2.04; 95% CI, 1.4-3.0; and P=0.005; RR=2; 95% CI, 1.2-3.2 respectively), highlighting the raising concern about the deleterious impact of severe chronic GVHD occurring after RIC allo-SCT, but also the protective effect of donor origin immunity based on graft origin and content. In this series of patients surviving at least 6 months after RIC allo-SCT, the overall long term transplant-related mortality was 11% (n=18), of whom 12 deaths were attributed to chronic GVHD and its complications including infections, and 5 deaths solely attributed to infections. In all, these results suggest that, despite reduction in early toxicity associated with the use of RIC regimens, long term debilitating chronic GVHD and its corollary of continuous immunosuppression and subsequent infections are still a matter of concern. Prospective efforts to develop optimal antimicrobial preventive strategies are needed to further improve the safety of the procedure and the overall benefits of RIC preparative regimens before allo-SCT.

Abstract #2850 appears in Blood, Volume 108, issue 11, November 16, 2006

**Keywords:** Transplant-related mortality|Toxicity|Immune reconstitution

# Prognostische Faktoren für das Überleben von Patienten mit Aspergillose (IA)

- Retrospektive monozentrische Analyse von 299 konsekutiven Fällen bei erwachsenen Patienten mit IA von 1997 bis 2006
  - 41 allo SCT
  - 24 auto SCT
  - 10 solid Organ Tx
  - 91 akute Leukämien, 67 andere hämatologische Malignome
  - 35 solide Tumore, 21 nicht maligne Erkrankungen
  - Verteilung der IA: 258 invasive pulmonale Aspergillosen
    - 12 andere Infektionen (Einzelorgan) zumeist Sinus
    - 19 Fälle disseminierte invasive Aspergillose
  - Gesamtüberleben 52,3% nach 3 Monaten (95% CI: 46,5-57,9%)
  - Infekt. Überleben 59,5% nach 3 Monaten (95% CI: 53,6-65,0)

# Prognostische Faktoren für das Überleben von Patienten mit Aspergillose (IA)

## Prädiktoren für 3 Mo-Überleben

Referenz	Vergleich	HR	95% CI	p =
allo SCT oder SOT	Hämatol. NPL	1,78	1,12-2,84	0,0391
Progression	keine	4,54	2,68-7,67	<0,0001
bekannte Lungenerkrankung	keine	1,76	1,18-2,62	0,006
Steroiddosis 0,2 mg/kg	<0,2 mg/kg	2,33	1,50-3,63	<0,001
Krea-Clearance 30-59ml/min	60ml/min	1,65	1,06-2,55	<0,001
	<30ml/min	2,51	1,56-4,03	0,006
Monozyten >100/ $\mu$ l	<100/ $\mu$ l	0,59	0,41-0,85	0,004
Disseminierte Infektion	Lunge allein	3,2	1,72-5,93	0,001
Pleuerguß	kein Erguß	1,77	1,19-2,63	0,005
Possible IA	probable/proven	0,51	0,34-0,78	0,002

**Abstract 2852 Prognostic Factors for Survival in Invasive Aspergillosis in Adult Oncohematological Patients. Session Type: Poster Session, Board #81-III**

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Despite recent progresses in treatment, invasive aspergillosis (IA) is still associated with high treatment failure and elevated death rates. Prognostic factors have not yet been identified in a large population of oncohematological patients (pts) developing IA. We reviewed all cases of possible, probable or definite IA according to the EORTC/MSG criteria occurring in adult oncohematological pts since January 1997. Two hundred and ninety nine pts received at least one dose of anti-aspergillus therapy and were analyzed for prognosis factors. Demographic, clinical, radiological, biological and mycological variables available at time of start of antifungal therapy were analyzed for their effects on 3-month specific survival (pts dying of another cause were censored at time of death) and 3-month overall survival. All variables with a p-value less than 0.2 in univariate analysis were introduced into a multivariate Cox regression model, allowing for interactions. The analysis was stratified by the type of first line therapy to produce a consistent analysis of the other variables. Underlying condition included allogeneic hematopoietic stem cell transplantation (HSCT) (n=41), autologous HSCT (n=24), solid organ transplantation (SOT) (n=10), acute leukemia (n=91), other hematological malignancy (n=67), solid tumor (n=35) or non-malignant disease (n=21). Infection was localized to the lung in 258 pts, to another single organ, mostly sinuses, in 12 pts and was disseminated in 19 cases. Overall and specific survival rates at 3 months were 52.3% (95% CI: 46.5-57.9%) and 59.5% (95% CI: 53.6-65.0%) respectively. Prognostic factors for 3-month overall survival are shown in table 1. Prognosis factors for 3-month specific survival were the same, with the following exceptions: monocyte count was no more significant (p=0.57), baseline neutrophil count (< vs. 500 L) and radiological aspects (single vs. multiple vs. diffuse lesions) became significant with p-values at 0.003 and 0.048 respectively. Our study identified several risk factors for death in oncohematological pts with IA. These factors should help to early identify pts who would benefit from more aggressive antifungal therapeutic strategies.

Table 1. Three-month overall survival after stratification on treatment

Predictor	Reference category	Hazard ratio	95% CI	p-value
<b>Host factor</b>				
AlloHSCT or SOT	Hematological malignancy	1.78	1.12-2.84	0.0391
	Other	1.52	0.86-2.68	
Progression of underlying disease	No	4.54	2.68-7.67	<0.001
Prior non-infectious respiratory disease	Absence	1.76	1.18-2.62	0.006
Steroids dose 0.2 mg/kg	<0.2 mg/kg	2.33	1.50-3.63	<0.001
Creatinine clearance	30-59 mL/min 60 mL/min	1.65	1.06-2.55	<0.001
	<30 mL/min	2.51	1.56-4.03	
Monocytes >100/L	100/L	0.59	0.41-0.85	0.004
Site of infection	Disseminated Lung only	3.20	1.72-5.93	0.001
	Other single organ		NA	
Pleural effusion	Absence	1.77	1.19-2.63	0.005
Possible IA	Probable or definite	0.51	0.34-0.78	0.002

Abstract #2852 appears in Blood, Volume 108, issue 11, November 16, 2006

# Lungenresektionen bei invasiver pulmonaler Aspergillose

- Retrospektive Analyse von Lungenresektionen bei invasiver pulmonaler Aspergillose
- Monozentrische Kohortenstudie (37 Pat) über 7 Jahre
- Lungenresektion erfolgte nach Ende der Aplasie
- 22 Männer, 15 Frauen: AML (26) , ALL (7), Lymphome (2), multiples Myelom (2)
- Medianes Alter 49,2 Jahre (15-74 Jahre)
- Diagnosesicherheit gemäß EORTC-Kriterien vor OP
  - 18 Fälle possible IA
  - 18 Fälle probable IA
  - 1 Fall proven IA

# Lungenresektion bei invasiver pulmonaler Aspergillose (IPA)

- Chir. Therapie: 1 Pneumon-, 6 Bilob-, 18 Lobektomien, 8 Wedge-Resektionen und 4 Lobektomien + Wedge-Resektion
  - Med. KH-Aufenthalt 13 Tage, keine perioperative Letalität
  - Komplikationen in 6 Fällen: 3 prolongierte Drainage, 1 Phrenicusverletzung, 1 größere Blutung, 1 Pneumopathie
  - bei allen 32 Patienten wurde die Diagnose IPA post-op bestätigt
  - 26/32 Patienten erhielten nachfolgend intensive Chemotherapie
  - 15 Patienten erhielten SCT (10 allogene/ 5 autologe SCT)
  - alle 32 Patienten wurden weitergehend antimykotisch therapiert
  - Rückfälle der IPA in 2/32 Fällen, 1 Todesfall dissemin. cerebrale IA
- Überleben nach 8,3 Jahren 40,5% (Todesursachen Relaps)
- Lungenresektionen Teil interdisziplinärer Therapie bei IPA

**Abstract 2857 Lung Resection for Invasive Pulmonary Aspergillosis in Neutropenic Patients with Hematologic Malignancies: Long Term Results in Thirty Two Cases. Session Type: Poster Session, Board #86-III**

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Invasive pulmonary aspergillosis (IPA) is a major cause of morbidity and mortality in neutropenic patients. Despite adequate medical treatments, such as amphotericin B or voriconazole, the prognosis of IPA remains poor. Nevertheless, recent studies suggest that the outcome of IPA is improving due to early diagnosis (CT scan, antigenemia), use of new antifungal agents (Azols and Echinocandins), and possibly in some cases to early surgical resection. We here report a retrospective one center study of 32 cases of IPA treated by surgical treatment from 1988 to 2005.

Between 1988 and December 2005, thirty-seven consecutive patients underwent lung resection for suspected IPA. They were 22 men and 15 women, with a median age of 49.2 years (15 - 74). The underlying diseases were AML, ALL, aggressive lymphoma and myeloma in 26, 7, 2 and 2 cases, respectively. Surgery was planned after hematologic recovery from the last course of chemotherapy during which IPA was diagnosed, either possible in 18 cases, probable in 18 cases or proven in 1 case (Ascioglu, CID 2002). Surgery consisted in 1 pneumectomy, 6 bilobectomies, 18 lobectomies, 8 wedge resections and 4 lobectomies with wedge resections. No perioperative deaths occurred and the median duration of post surgical hospitalisation was 13 days. Six patients presented surgery related complications: three patients required prolonged pleural drainage, one had a section of the phrenic nerve, one presented a major bleeding and last patient had a pneumopathy. The diagnosis of definite IPA was confirmed in 32 cases. Immediately after surgery, 26 of the 32 patients were able to receive subsequent intensive chemotherapy courses, including 15 stem cell transplant (SCT), either auto (5) or allogenic (10). In all cases, patients subsequently received parenteral antifungal therapy. During these new intensive chemotherapy courses, recurrent aspergillosis was observed in only 2 cases, inducing 1 death from brain localization. Overall, with a median follow-up of 8.3 years (1-18), 40.5% of the patients are alive and the main cause of mortality was relapse, but not IPA .

In conclusion, early surgical resection together with antifungal therapy allows definite diagnosis of IPA, prevents from IPA recurrence and early death due to hemotysis, with very few peri-operative complications. All the more, it allows subsequent high-dose chemotherapy to treat the underlying hematologic disease. Surgery might be a treatment of choice to a define group of patient.

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**Keywords:** Invasive pulmonary aspergillosis|Surgery|Bone marrow transplant

# Galactomannan (GM) als Surrogatmarker für das Ansprechen einer antimykotischen Therapie

- Evaluation des GM als Surrogatmarker für den Ausgang von Infektionen durch *Aspergillus* spp in der Hämatologie
- Klinische Zeichen und positiver GM-Test (>0,5 OD)
- Monozentrische Studie bei 30 Patienten mit positivem GM-Test und Zeichen einer Aspergillose
- Aspergillosen nach autologer SCT (11), allogener SCT (1), oder nach konventioneller Chemotherapie (18).
- Verlauf des GM-Tests wurde in Bezug zum objektiven Infektionsausgang (Tod) gesetzt

# Galactomannan (GM) als Surrogatmarker für das Ansprechen einer antimykotischen Therapie

- 25 Patienten wiesen eine Neutropenie  $<1000/\mu\text{l}$  auf
- Persistierend erhöhte GM-Spiegel waren bei Neutropenie mit tödlichem Ausgang bei 5/5 Infektionen verbunden
- 20/20 Pat. mit rückläufigem GM bei Neutropenie überlebten
- 1/1 nicht neutropenen Pat mit dauerhaft hohem GM starb
- 4/4 nicht neutropenen Pat mit abfallendem GM überlebten
- Schlußfolgerung: Der klinische Infektionsverlauf korreliert sehr gut mit dem GM-Test
- GM erscheint als Surrogatmarker für das Ansprechen von IA verwertbar zu sein
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**Abstract 2861 Validation of Serum Aspergillus Galactomannan Index as a Surrogate Endpoint for Outcome of Invasive Aspergillosis: Clinical and Research Implications. Session Type: Poster Session, Board #90-III**

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Background: Assessing clinical outcome of aspergillosis with conventional clinical and laboratory criteria is difficult. A composite global outcome response (clinical, radiologic, pathologic and microbiologic criteria) is frequently used but suffers from poor sensitivity and specificity, and has not been standardized or validated. A reliable, quantitative, non-invasive, and easy to measure laboratory test that can substitute for this composite endpoint, i.e. serve as a surrogate endpoint for aspergillosis outcome is highly desirable. Galactomannan (GM) is an Aspergillus-specific polysaccharide released during aspergillosis and detected by the serum GM test. The test which is reported as an index of optical density (OD) is an accepted diagnostic marker for aspergillosis and preliminary data suggest a correlation between GM index (GMI) and outcome.

Purpose: To evaluate serum GMI as a surrogate endpoint for outcome of invasive aspergillosis in patients with hematological cancer.

Patients and Methods: patients at risk for aspergillosis (11/03-2/06) underwent GMI screening during periods at risk. The clinical and laboratory findings of patients with 2 (+) GMI (OD 0.5) were reviewed. To validate GMI as a surrogate endpoint for aspergillosis, a kappa correlation concordance coefficient test between GMI and an objective clinical outcome of aspergillosis (death) was applied. The correlation is considered perfect when kappa is 1.0; excellent when 0.75.

Results: 30 patients had GMI (+) aspergillosis of the respiratory tract [myeloma 92%; median age: 59 years (27-75); 15 males]. Aspergillosis developed following stem cell transplantation [autologous (11), allogeneic (1)], or after conventional chemotherapy (18). Among 25 neutropenic patients (<1000/ml), persistent GMI elevation was associated with death (5/5 patients) while return to negative values predicted survival (20/20 patients). Among 5 non-neutropenic patients, 1 with persistently elevated GMI died compared to no death among the remaining 4 whose GMI became negative. Overall, the GMI correlated with clinical outcome in all 30 patients with a perfect 1.0 kappa correlation concordance coefficient.

Conclusion: we have validated GMI as an excellent surrogate endpoint for the outcome of invasive aspergillosis among patients with hematological cancer. This FDA-approved test is reproducible, quantitative, non-invasive, easy to measure and widely available. These findings have important implications for patient care and for the design of clinical trials of mould-active antifungal agents.

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**Keywords:** Invasive aspergillosis|Outcome measurement|Supportive care