# ECIL 5

## September 19-21, 2013

# Primary Antifungal Prophylaxis

Chair: **Johan Maertens** (Belgium)

Group members:

- Acute myeloïd leukemia: **Johan Maertens**, **Peter Donnelly** (The Netherlands), and **Chris Kibbler** (UK)
- Lymphoma: **Johan Maertens** and **Rafael Duarte** (Spain)
- Acute Lymphoblastic Leukemia: **Oliver Cornely** (Germany)
- Myeloma: **Per Ljungman** (Sweden) and **Catherine Cordonnier** (France)
- Myelodysplastic syndromes: **Catherine Cordonnier** and **Per Ljungman**
- Allogeneic HSCT: **Corrado Girmenia** (Italy), **Rafael Duarte** and **Patricia Ribaud** (France)
- Myeloproliferative disorders: **Zdeněk Ráčil** (Czech republic)
- Chronic lymphocytic leukemia: **Monica Slavin** (Australia)
- Clinical Pharmacy: **Roger Brüggeman** (The Netherlands)

# CDC grading system used for ECIL 1,2,3

| Quality of Evidence | Strength of Recommendation |
|---|---|
| I Evidence from ≥ 1 properly randomized, controlled trial. | A Strong evidence for efficacy and substantial clinical benefit; strongly recommended |
| II Evidence from ≥ 1 well-designed clinical trial, without randomization: from cohort or case-controlled analytic studies (preferably from > 1 center); from multiple time-series studies; or from dramatic results from uncontrolled experiments. | B Strong or moderate evidence for efficacy, but only limited clinical benefit; generally recommended |
| III Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees | C Insufficient evidence for efficacy; or efficacy does not outweigh possible adverse consequences (e.g. drug toxicity or interactions) or cost of chemoprophylaxis or alternative approaches; optional |
| | D Moderate evidence against efficacy or for adverse outcome; generally not recommended |
| | E Strong evidence against efficacy or of adverse outcome; never recommended |

Update: ECIL 5, 2013

# Primary antifungal prophylaxis:
## ECIL 3 (2009) recommendations

| Acute myeloid leukaemia patients undergoing induction chemotherapy | | |
|---|---|---|
| *Antifungal drug* | *Grading* | *Comments* |
| Fluconazole (50–400 mg/day) | **CI** | Azoles should not be used empirically in case of previous azole prophylaxis. Combined with a mould-directed diagnostic approach for centers not having HEPA-filtered rooms and/or having a high baseline incidence of mould infections |
| Itraconazole oral solution (2.5 mg/kg b.i.d.) | **CI** | May be limited by drug interactions and/or patient tolerability. Azoles should not be used empirically in case of prior azole prophylaxis. It is recommended to monitor serum drug concentrations |
| Posaconazole oral solution (200 mg t.i.d.) | **AI** | Azoles should not be used empirically in case of previous azole prophylaxis. It is recommended to monitor serum drug concentrations |
| Echinocandins IV | **Insufficient data** | |
| Polyenes IV | **CI** | Includes low doses of conventional amphotericin B and lipid formulations |
| Aerosolized liposomal amphotericin B combined with oral fluconazole | **BI** | The ECIL recommendation for aerosolized amphotericin B deoxycholate is DI |

Update: ECIL 5, 2013

# Primary antifungal prophylaxis:
## ECIL 3 (2009) recommendations

- Allogeneic hematopoietic stem cell transplantation: neutropenic phase
  - Fluconazole 400 mg qd iv/oral: AI[2,5]
  - Itraconazole 200 mg IV followed by oral solution 200 mg bid: BI[1,2,3]
  - Posaconazole oral solution 200 mg tid: no data
  - Micafungin 50 mg qd iv: CI
  - Polyene[4] iv: CI
  - Voriconazole 200 mg bid oral: provisional AI
  - Aerosolized liposomal amphotericin B plus fluconazole: BII
- Allogeneic hematopoietic stem cell transplantation: GvHD phase
  - Fluconazole 400 mg qd iv/oral: CI[2]
  - Itraconazole 200 mg IV followed by oral solution 200 mg bid: BI[1,2,3]
  - Posaconazole oral solution 200 mg tid: AI[2,3]
  - Candins iv: insufficient data
  - Polyene iv: CI
  - Voriconazole 200 mg bid oral: provisional AI
  - Aerosolized liposomal amphotericin B plus fluconazole: insufficient data

1. May be limited by drug interactions and/or patient tolerability;
2. Azoles should not be used empirically in case of prior azole prophylaxis;
3. It is recommended to monitor serum drug concentrations;
4. Includes low doses of conventional amphotericin B and lipid formulations;
5. Combined with a mould-directed diagnostic approach for centers not having HEPA-filtered rooms and/or having a high baseline incidence of mould infections

# Primary antifungal prophylaxis:
## ECIL 5 (2013): what's on the agenda?

- Implementation of the new CDC grading system (see slide #6)
- Separate recommendations for transplant and non-transplant recipients
- Include more at-risk populations (except aplastic anaemia: guidelines were recently published by EBMT- aplastic anaemia working party, *Höchsmann B et al. BMT 2013*)
- Invite a clinical pharmacist
- New group members and assigned tasks
  - Johan Maertens (B), Peter Donnelly (NL) and Chris Kibbler (GB): AML
  - Johan Maertens (B) and Rafael Duarte (SP): Lymphoma
  - Oliver Cornely (D): Acute lymphoblastic leukaemia
  - Per Ljungman (SE) and Cathérine Cordonnier (FR): Myeloma
  - Catherine Cordonnier (FR) and Per Ljungman (SE): Myelodysplastic syndromes
  - Corrado Girmenia (IT), Rafael Duarte (SP) and Patricia Ridbaud (FR): Allogeneic HSCT
  - Zdeněk Ráčil (CZ): Myeloproliferative disorders
  - Monica Slavin (Australia): Chronic lymphocytic leukaemia

# CDC Grading system used since ECIL 4

| Quality of Evidence | Strength of Recommendation |
|---|---|
| I Evidence from ≥ 1 properly randomized, controlled trial. | A Good evidence to support a recommendation for or against use |
| II Evidence from ≥ 1 well-designed clinical trial, without randomization: from cohort or case-controlled analytic studies (preferably from > 1 center); from multiple time-series studies; or from dramatic results from uncontrolled experiments. | B Moderate evidence to support a recommendation for or against use |
| III Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees | C Poor evidence to support a recommendation |

# ECIL 5

# Antifungal prophylaxis: main questions

- Who should get prophylaxis and when (what time of treatment phase)?
  - Anti-yeast or anti-mould prophylaxis, or both?
- Which drugs are best?
- Does prophylaxis reduce incidence of IFD?
- Does prophylaxis reduce all-cause (and IFD-related) mortality?
- Is prophylaxis safe and well-tolerated?
- Should resistance be taken into consideration?
- Should TDM be implemented?

# Problems encountered

- Most studies date from the late 1980s and early 1990s when standards of study design and conduct were less strict, there were no biomarkers available and no agreed definitions of invasive fungal disease
- Primary aims of studies differ widely
- Very few well-executed, prospective, blinded, controlled trials with an adequate numbers of patients to ensure sufficient power
- Different drug doses and routes of administration
- Only invasive fungal diseases that are proven and probable are considered as an endpoint
- The impact of HEPA filtration remains unknown

# Acute Myelogenous Leukaemia (AML) and Myelodysplastic syndromes (MDS) undergoing AML-like chemotherapy

# Risk factors for invasive fungal disease in AML and MDS undergoing AML-like chemotherapy

- Advanced age
- Genetic susceptibility
- Pre-admission factors (see next slide)
- Neutropenia - depth and duration
- Monocytopenia
- Purine analogue (e.g. fludarabine)
- Iron overload
- Lack of HEPA filtration

# Pre-admission predisposing factors (multivariate analysis)

| VARIABLE | MOULD CASES | | | YEAST CASES | | |
|---|---|---|---|---|---|---|
| | OR | P value | CI 95% | OR | P value | CI 95% |
| PRE-HOSPITAL | | | | | | |
| 1. PERFORMANCE STATUS ≥2 * | 2.69 | 0.002 | 1.44-5.00 | --- | --- | --- |
| 2. HOUSE RENOVATION | 3.93 | <0.0010 | 1.83-8.40 | --- | --- | --- |
| 3. HIGHER BODY WEIGHT | 0.31 | .007 | 0.13-0.72 | --- | --- | --- |
| 4. HIGHLY EXPOSING JOB | 3.14 | 0.006 | 1.38-7.17 | --- | --- | --- |
| 5. Chronic Obstructive Pulmonary Disease | 3.54 | 0.022 | 1.19-10.5 | --- | --- | --- |

* According to WHO

SEIFEM 2010-A data presented by Caira M et al. ICAAC 2013

# Preventative measures

- Avoid construction/renovation activities as well as heavily contaminated items (such as potted plants, soil, pepper, …)
- Protective isolation with HEPA-filtration to prevent exposure
- Mould-active prophylaxis to prevent disease

# Predominantly AML and MDS receiving AML-like chemotherapy: selection of the studies

- For randomized studies that used a fluconazole arm, only those studies that used fluconazole 400 mg/d were included.
- We included studies using itraconazole oral solution 400 mg/d or intravenous 200 mg/d
- All studies using an amphotericin B arm in any form were already evaluated during previous ECIL meetings and no changes have been made as there is no standard dose, route of administration or frequency
- There are few properly designed studies with echinocandins
- Studies with less than 200 patients are underpowered to answer the relevant questions and (although published) are not included in the analysis (as agreed upon during ECIL 3)
- No meta-analysis of studies involving only AML/MDS
- See also slide deck ECIL 1, 2 and 3

# Multicenter studies of prophylaxis in AML

| First author | Patients | Total participants |
|---|---|---|
| Winston 1993 | acute leukaemia. | 255 |
| Menichetti 1999 | 1) acute leukaemia or other HM<br>2) autologous HSCT | 405 |
| Rotstein 1999 | 1) acute leukaemia<br>2) autologous HSCT | 304 |
| Harousseau 2000 | 1) acute leukaemia<br>2) MDS<br>3) autologous HSCT<br>4) blast crisis CML<br>5) lymphoma or myeloma | 557 |
| Glasmacher 2006 | 1) acute leukaemia<br>2) autologous HSCT<br>3) blast crisis of CML<br>4) lymphoma or myeloma | 494 |
| Cornely 2007 | 1) AML<br>2) MDS receiving AML-like therapy | 602 |

# Studies of prophylaxis in AML

| First author | Control | Experimental |
|---|---|---|
| Winston 1993 | placebo | Fluconazole oral 400 mg q24h or IV 200 mg q12h |
| Menichetti 1999 | placebo | Itraconazole oral solution 2.5 mg/kg q12h |
| Rotstein 1999 | placebo | Fluconazole oral 400 mg q24h |
| Harousseau 2000 | placebo plus 2g/day oral amphotericin B | Itraconazole oral solution 2.5 mg/kg q12h plus placebo capsules |
| Glasmacher 2006 | fluconazole 400 mg q24h | Itraconazole oral solution 2.5 mg/kg q12h |
| Cornely 2007 | fluconazole 400 mg q24h or itraconazole oral solution 200 mg q12h | Posaconazole oral suspension 200 mg q8h |

# Studies of prophylaxis in AML - IFD

| First author | Control participants | % IFD | Experimental participants | % IFD | Absolute risk reduction |
|---|---|---|---|---|---|
| Winston 1993 | 132 | 8 | 123 | 4 | 0.04 |
| Menichetti 1999 | 204 | 4 | 201 | 2 | 0.02 |
| Rotstein 1999 | 151 | 21 | 153 | 6 | 0.15 |
| Harousseau 2000 | 276 | 5 | 281 | 3 | 0.02 |
| Glasmacher 2006 | 246 | 2 | 248 | 2 | 0.00 |
| Cornely 2007 | 298 | 8 | 304 | 2 | 0.06 |

# Studies of prophylaxis in AML -Mortality

| First author | Control participants | % mortality | Experimental participants | % mortality | Absolute risk reduction |
|---|---|---|---|---|---|
| Winston 1993 | 132 | 0.03 | 123 | 0.01 | 0.02 |
| Menichetti 1999 | 204 | 0.09 | 201 | 0.07 | 0.01 |
| Rotstein 1999 | 151 | 0.10 | 153 | 0.10 | 0.00 |
| Harousseau 2000 | 276 | 0.08 | 281 | 0.06 | 0.02 |
| Glasmacher 2006 | 246 | 0.03 | 248 | 0.02 | 0.01 |
| Cornely 2007 | 298 | 0.22 | 304 | 0.16 | 0.06 |

# Posaconazole in AML and MDS undergoing AML-like chemotherapy

**Incidence of proven and probable invasive fungal infections during the treatment period**

| | Fluconazole | | Posaconazole | | Itraconazole | | Posaconazole | |
|---|---|---|---|---|---|---|---|---|
| **IFD** | 19 | (7.9%) | 4 | (1.7%) | 6 | (10.3%) | 3 | (4.6%) |
| **None** | 221 | | 235 | | 52 | | 62 | |
| **Total** | 240 | | 239 | | 58 | | 65 | |
| | $\Delta$= 6.2% (2.4 -10.1%)<br>$p$ = 0.001 | | | | $\Delta$= 5.7% (2.9 – 21.%)<br>$p$ = 0.22 | | | |

Cornely et al. N Engl J Med 2007;356:348-59 *Supplementary Appendix*

# Proposed changes to the ECIL 3 recommendations

- Set a threshold for the incidence of invasive mould disease to 8% (as documented by the PIMDA audit[1])
- BII recommendation for voriconazole: no specific study in AML/MDS but results inferred from data during neutropenic pre-engraftment phase in allo-BMT recipients
- Change the way doses are reported from the Latin to the “q” system; for example q6h, q8h, q12h, q24h

[1] A European period-prevalence study to estimate the rate of invasive pulmonary mould disease (PIMDA study) Donnelly et al Poster P0028a ECCMID 2014, Barcelona, Spain

# Recommendations (2013)

Update: ECIL 5, 2013

## Acute myeloid leukaemia patients undergoing intensive chemotherapy

| *Antifungal drug* | *Grading* | *Comments* |
|---|---|---|
| Fluconazole (400 mg q24) | **BI** | Only recommended if the incidence of mould infections is low. Fluconazole may be part of an integrated care strategy together with a mould-directed diagnostic approach. |
| Itraconazole oral solution (2.5 mg/kg q12h.) | **BI** | Recommended if baseline incidence of mould infections is high. May be limited by drug interactions or patient tolerability. It is recommended to monitor serum drug concentrations. |
| Posaconazole (oral solution 200 mg q8h *or* tablet 300 mg q24h following a loading dose of 300 mg q12h on day 1) | **AI** | Recommended if baseline incidence of mould infections is high. Given the increased absorption of the tablet, it is likely that need for therapeutic drug monitoring will become restricted to specific populations (e.g. severe mucositis or GvHD). |
| Voriconazole (200 mg q12h) | **BII** | Recommended if baseline incidence of mould infections is high. It is recommended to monitor serum drug concentrations. |

Azoles should not be used empirically in case of prior mould-active azole prophylaxis.

# Recommendations (2013)

## Acute leukaemia patients undergoing induction chemotherapy

| *Antifungal drug* | *Grading* | *Comments* |
|---|---|---|
| Echinocandins IV | **CII** | Insufficient data on efficacy and tolerability |
| Amphotericin B liposomal IV | **CII** | Insufficient data on dose, frequency and duration as well as on efficacy and tolerability |
| Amphotericin B lipid associated IV | **CII** | Insufficient data on dose, frequency and duration as well as on efficacy and tolerability |
| Aerosolized liposomal amphotericin B | **BI** | Only when combined with oral fluconazole |
| Amphotericin B desoxycholate IV | **AII-against** | |
| Aerosolized amphotericin B deoxycholate | **AI-against** | |

# Multiple myeloma

# IFD in multiple myeloma

No recent, prospective study to specifically address this question in myeloma

Myeloma patients do have several potential risk factors for IFI such as:

- Most myeloma patients are treated with high doses of corticosteroids
- Poor marrow function is common in heavily treated patients
- High dose chemotherapy and autologous HSCT is incorporated in treatment strategies in recently diagnosed younger patients with multiple myeloma

*Nucci and Anaissie. CID 2009*

# Incidence of IFD in multiple myeloma

In a large study of patients with different types of haematological malignancies, the incidence of IFI caused by yeasts was 0.2% and by moulds 0.3% among 1616 patients with multiple myeloma *(Pagano 2004).*

Among 395 patients with multiple myeloma undergoing autologous HSCT, 3 (0.8%) developed IFI *(Jantunen 2004).*

Similar rates have been found also in other studies *(Gil 2009; Kurosawa 2012)*.

Four of 538 (0.7%) patients having undergone autologous HSCT were reported to have died from IFI *(Jantunen 2006).*

# Incidence of IFD in myeloma

| Reference | Study Design | Study period | Type of IFD | Total no. of patients with IFD | No. (%) myeloma patients |
|---|---|---|---|---|---|
| *Lortholary* 2011 | Prospective registry of IFD | 2005-2007 | Proven and probable invasive aspergillosis | 393 | 0 (%) |
| *Skiada* 2011 | Prospective registry of IFD | 2005-2007 | Proven and probable zygomycosis | 230 | Not reported |
| *Herbrecht* 2012 | Prospective registry of haematology patients receiving antifungals | 2007-2008 | All | 419 | 0 (%) |

# Recommendations for antifungal prophylaxis in myeloma patients

1) Although few data are available, the risk of IFD in multiple myeloma patients including patients having undergone autologous HSCT is < 1%. Based on this low risk, primary antifungal prophylaxis is not recommended

2) Prophylaxis against oral and/or esophageal candida infections with fluconazole can be considered (BIII).

# Myelodysplastic Syndromes (MDS)

excluding MDS treated with AML-like chemotherapy

# IFD in MDS

No recent, prospective study that specifically address this question in MDS patients not treated with AML-like chemotherapy.
Patients with transformed MDS (secondary AML and MDS with high blast counts) are usually treated with the same chemotherapy regimens as *de novo AML* patients

Patients with MDS have multiple spontaneous or acquired risk factors of infection, at least*:

- neutropenia
- functional neutrophil impairment
- impaired antibody production
- T-cell, NK-cell, impairments
- Iron overload due to transfusion

** Toma et al. Haematologica 2012*

# MDS as the underlying disease in large recent, European series of IFD

| Ref. | Study design | Study period | Type of IFD | Total no. of patients with IFD | No. (%) MDS patients | Compared no. (%) of AML patients in the same series |
|---|---|---|---|---|---|---|
| Lortholary 2011 | Prospective registry of IFD | 2005-2007 | Proven and probable invasive aspergillosis | 393 | 9 (2.3%) | 90 (23%) |
| Skiada 2011 | Prospective registry of IFD | 2005-2007 | Proven and probable zygomycosis | 230 | 6 (2.6%) ( 6% of the haematology population) | 49 (21.3%) (48% of the haematology population) |
| Herbrecht 2012 | Prospective registry of haematology patients receiving antifungals | 2007-2008 | All | 419 | 17 (4%) | 191 (46%) |

# Incidence of IFD in large prospective series on MDS treated with novel agents

Hypomethylating agents or lenalidomide may transiently induce or increase neutropenia. However, their impact on the risk of IFD is poorly assessed but seems very low.

IFD is not mentioned as a complication in MDS patients treated with 5-azacytidine (*Silverman 2002, Silverman 2006, Fenaux 2009, Musto 2010, Garcia-Manero 2011)* , or with lenalidomide (*List 2006, Raza 2008, Ades 2009, Fenaux 2011, Lebras 2011*) IFD is mentioned in only one study with decitabine in 95 high-risk MDS patients, with an incidence of 5.2% (*Kantarjian 2007*).

Patients with MDS are at high-risk of IFD after allogeneic HSCT (*Marr CID 2002*), especially if neutropenic just before transplant (*Scott 2008)* or in case of iron overload (*Maertens 1999, Altes 2004, Kontoyiannis 2007, Busca 2010).*

# Recommendations: MDS

1) **Patients with MDS (not treated with AML-like chemotherapy), with a risk of IFD <5% and a projected risk period of long duration (exposing them to the risk of antifungal resistance):**

- Primary antifungal prophylaxis is not recommended
- Prospective epidemiological study on IFI is encouraged, especially in prospective therapeutic trials

2) **Patients with MDS transformed to AML or patients receiving AML-like induction therapy should receive primary antifungal prophylaxis similar to *de novo* AML patients .**

   The recommendations are those of AML patients

3) **Patients with MDS should be regarded as a high-risk population for IFD after allogeneic HSCT and should especially be considered for antifungal prophylaxis**

# Myeloproliferative Diseases (MPD)

# IFD in MPD patients (I)

Update: ECIL 5, 2013

| Study | Type of study | Type of IFD | TIme | Results | Comments |
|---|---|---|---|---|---|
| ***Campo* 2010** | Group of IFD | Invasive fusariosis | 1998-2009 | Chronic leukaemias / lymphoma 7/44 (16%) | - CML rate not specified in this subgroup;<br>- no data about therapy |
| ***Pagano* 2010** | Epidemiology | All IFDs | 1999-2003 | Incidence of IFD in CML (auto- and allo-HSCT excluded) - 2.5% (IA - 4.5%, IZ 0, fusarium 0, IC 0.5%); incidence in MPD not specified | - no data about phase of disease in CML (chronic phase vs. Blast crisis, or end stage in pre-TKI era);<br>- no data about therapy of CML (INF, chemotherapy, hydroxyurea, low dose ARAC);<br>- majority of patients in pre-TKI era |
| ***Lewis* 2013** | Group of IFD | All IFDs | 1989-2008 | Defined unusual subgroup "CML/lymphoma"? (not CLL or NHL) - 1989-1993 - 25 CML/lymphoma patients from 145 pts. with IFD in autopsy; 1994-1998 -4/86; 1998-2003 5/81; 2004-2008 7/59 | - unusual subgroup CML/lymphoma;<br>- No data about phase of CML (CP vs. BC)<br>- no data about therapy (approx. 30-50% allo HSCT) |

# IFD in MPD patients (II)

Update: ECIL 5, 2013

| Study | Type of study | Type of IFD | Time | Results | Comments |
|---|---|---|---|---|---|
| ***Racil* 2013** | Group of IFD | IA | 2005-2009 | CML+MPD/176 (2,3%) | - no data about phase of disease (CP vs. BC vs. Progression);<br>- no data about therapy (HSCT vs. INF vs. TKI) |
| ***Steinbach* 2012** | Group of IFD | IA | 2004-2008 | CML 16/464 (3.5%), MPD- no information | - no data about phase of disease (CP vs. BC vs. Progression);<br>- no data about therapy (HSCT vs. INF vs. TKI) |
| ***Nicole* 2011** | Group of IFD | IA | 2004-2009 | CML 0/127 | - no data about phase of disease (CP vs. BC vs. Progression);<br>- no data about therapy (HSCT vs. INF vs. TKI) |

# Recommendations for MPD patients

- There is no increased risk of IFD in patients with chronic phase CML treated with TKIs or conventionally treated patients with MPD. No antifungal prophylaxis recommended

- Patients undergoing intensive therapy for blast phase of CML or undergoing allogeneic HSCT should be managed based on guidelines for patients undergoing induction for acute leukaemia or undergoing allogeneic HSCT

- TKI-inhibitors and azoles: drug interactions should be taken into account

# Acute Lymphoblastic Leukaemia (ALL)

# Recommendations: ALL patients

- SEIFEM-2004 study* collected information on 1,173 ALL patients and reported an incidence rate of invasive fungal disease of 6.5%, with invasive aspergillosis being the most prevalent IFD.
- No randomized clinical trials on antifungal prophylaxis in ALL
- Drug-drug interactions: mould-active azoles such as itraconazole, voriconazole and posaconazole should be avoided in patients treated with vincristine because of the risk of increased neurotoxicity.
- In the absence of convincing efficacy AND toxicity data, fluconazole prophylaxis may be considered (C-III) pending results of the recently completed AmbiGuard trial.

*Pagano et al. Clin Infect Dis 2007*

# Chronic Lymphocytic Leukaemia (CLL)

Update: ECIL 5, 2013

# CLL and IFD

| Author | Registry | Data base | CLL cases/total (%) |
|---|---|---|---|
| Pagano 2013 | Treatment zygomycosis | SEIFEM & Fungiscope | 0 |
| Skiada 2011 | Zygomycosis in Europe | ECMM | Not described |
| Nosari 2011 | IFD in haematology | Haema e-chart | 2/147 |
| Steinbach 2012 | Invasive aspergillosis | Path Alliance | 33/960 (7%) |
| Pagano 2006 | Haemological admissions | SEIFEM-2004 | 6/1104 (0.5%) |
| Pagano 2012 | Fever in haematologic malignancies | Haema e-chart | 2/172 |
| Lortholary 2011 | Invasive aspergillosis proven/probable | SAIF | Chronic lymphoprolif. 424; (21.6%) |
| Molteni 2005 | CLL and febrile neutropenia | Single center | 10/379<br>2% proven IFI |

# CLL and newer chemotherapy regimens

Update: ECIL 5, 2013

| Author | Population (n) | Regimen | IFI | Prophylaxis | Comment |
|---|---|---|---|---|---|
| Dearden 2011 | Mixed (369) | IV vs oral Fludarabine | Not described | - | |
| Tam 2006 | Mixed (77) | FCR | 0 | - | |
| Hallek 2101 | Naïve (817) | FC vs FCR | 4 (<1%) | - | |
| Pettit 2012 | TP-53 del (39) | Alemtuzumab and methyl prednisone | Candida 2<br>Suspected IPA 1 | Itraconazole | Infection ↑in >60 yrs |
| Fischer 2012 | Naive (117) | BR | 0 | - | Grade 3 and 4 infection: 7.7% |
| Elter 2012 | High risk Relapse/refractory (57) | FC+ alemtuzumab | 0 | - | TRM 9%<br>50% SAE mainly infection |

# CLL and new chemotherapy regimens

Update: ECIL 5, 2013

| Author | Population | regimen | IFI | prophy | comment |
|---|---|---|---|---|---|
| Tam 2007 | Fludarabine/ Alemtuzumab refractory /bulky (99) | varied | 1 fungal sinusitis | Not described, possibly | Rai stage predicts infection |
| Strati 2013 | Cytopenic at 3 mths post FCR first-line (72) | FCR | 1 IA (1/24 cytopenic at 9 mths) | No comment | Only signif ↑: cytopenia at 9 mths |
| Badoux 2013 | Relapsed/ refractory (59) | Lenalidomide + R | 0 | None mandated | 73% neutropenia |
| Byrd 2013 | Relapsed/ refractory (85) | Ibrutinib | 0 | none | Low rate mild neutropenia |
| Thursky 2005 | Early alemtuzumab trials in pre-treated pts | Alemtuzumab | 11/222 (5%) IA (7), IC (2), zygo (1), crypto (1) | none | Heavily pre-treated, advanced age risks |

# Recommendations: CLL

- In general: no antifungal prophylaxis needed
- Consider in individuals with prolonged neutropenia (>6 months), elderly, advanced and unresponsive disease

# Lymphoma

# IFD in lymphoma patients

Update: ECIL 5, 2013

| | | |
|---|---|---|
| **Jantunen 2004** | IFD in autologous SCT recipients:<br>Retrospective study among adult autologous HSCT recipients (95% peripheral blood SC) using the original EORTC/MSG definitions<br>N = 1188 | 0.8% for proven and probable aspergillosis<br>0.3% for candidaemia |
| **Pagano 2006** | IFD in patients with haematological malignancies:<br>Retrospective, multicenter cohort study.<br>N = 11802, including 844 Hodgkin and 3457 non-Hodgkin lymphoma | 4.6% in patients receiving chemotherapy alone<br>0.7 % in patients with Hodgkin's lymphoma<br>1.6% in patients with non-Hodgkin's lymphoma (9 cases of mould infection and 12 cases of yeast infection) |
| **Chamilos 2006** | Autopsy-proven IFD in patients with haematological malignancies<br>N = 314 cases (out of 1017 autopsies) | 11% of patients with autopsy-proven IFD had underlying non-Hodgkin's lymphoma |

Update: ECIL 5, 2013

# IFD in lymphoma patients

| | | |
|---|---|---|
| **Kume 2011** | Autopsy-proven IFD | In 1989, lymphoma represented 8.5% of the underlying diseases (compared to 26.1% for leukaemia and MDS)<br>In 2007, lymphoma represented 8.3% of the underlying diseases (compared to 18.8% for leukaemia and MDS) |
| **Lortholary 2011** | Invasive aspergillosis: prospective, hospital-based, multicenter surveillance of EORTC/MSG proven and probable cases<br>N = 424 | 21.6 % had a chronic LPD (lymphoma in 50% of cases) as underlying risk host factor (acute leukaemia 34.6% and allogeneic HSCT 21.4%).<br><br>35% of haematology-associated cases of IA occurred in patients with chronic LPD, with 67% occurring during second-line therapies<br><br>The incidence was 0.8% in autologous transplants. |

# IFD in lymphoma patients

Update: ECIL 5, 2013

| | | |
|---|---|---|
| **Kurosawa 2012** | EORTC/MSG proven and probable cases of IFD<br>Retrospective study in patients undergoing cytotoxic chemotherapy or transplantation (excluding CLL and CML)<br>N = 2821 | The incidence was<br>0.8% in patients receiving chemotherapy alone<br>1.1 % in patients with Hodgkin's lymphoma<br>0.3% in patients with non-Hodgkin's lymphoma (/ 1373 pts)<br>0.4% in autologous transplants.<br>All cases in LPD were caused by Aspergillus species |
| **Des Champs-Bro 2011** | Retrospective, monocentric and descriptive only<br>N = 192 out of 1130 (16.9%) surveyed patients received antifungals (including prophylaxis) | 7% of the patients receiving antifungals had underlying lymphoma. |
| **Nosari 2012** | IFD in patients with haematologic disorders.<br>Prospective (3/2007-3/2009) survey using EORTC-MSG criteria in haematology patients receiving cytoreductive therapy<br>N = 147 patients with IFD (including 72 possible cases) | 8 patients (5.4%) had underlying non-Hodgkin's lymphoma |

# Antifungal prophylaxis in lymphoma patients

1) The risk of IFD in lymphoma patients, including patients having undergone autologous HSCT, is < 2%. Based on this low risk, primary antifungal prophylaxis is not recommended

2) Prophylaxis against oral and/or esophageal candida infections with fluconazole can be considered (BIII).

# Allogeneic HSC Transplantation

# Recommendations on protected isolation

- *Guidelines for preventing infectious complications among **hematopoietic cell transplant** recipients: a global perspective*.
  - Tomblyn M et al. Biology of Blood and Marrow Transplantation 2009; 15: 1143-1238.
  - Yokoe et al. Bone Marrow Transplant 2009; 44(8): 495-507.

# Risk factors for IFD in allogeneic HSCT

| High risk-conditions during engraftment | High-risk conditions after engraftment * |
|---|---|
| Active acute leukaemia at transplant | Grade III-IV Acute graft-versus-host disease (GVHD) |
| Cord-blood transplant | Grade II acute GVHD in transplant from alternative donors, or unresponsive to standard steroid therapy |
| Multiple factors: alternative donor, iron overload, early CMV infection, acute GVHD | Secondary neutropenia |
| Prior fungal infection (secondary prophylaxis) | Multiple factors: alternative donor, early CMV infection, steroid therapy for more than 1 week. |

- Chronic GVHD is not by definition a high risk condition unless it is associated to other risk factors

Girmenia C et al. Biol Blood Marrow Transplant. 2014. [Epub ahead of print]

# General requirements

- All centers should know their local incidence and epidemiology of invasive fungal disease. Of note: environmental exposure to moulds may be altered by construction activity
- Centers should have an institutional protocol for diagnosing invasive fungal disease
- Mould-active azoles should not be used for treatment following failing prophylaxis with voriconazole or posaconazole

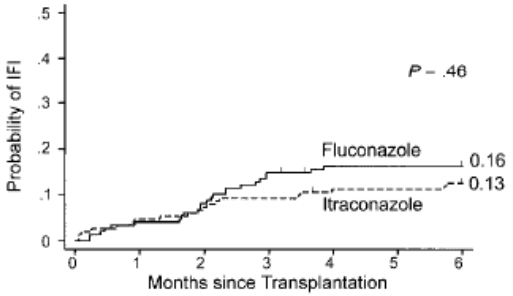
# Prospective, controlled studies on primary antifungal prophylaxis in allogeneic HSCT over the last 10 years

Update: ECIL 5, 2013

| | |
|---|---|
| Itraconazole versus fluconazole<br>Marr KA et al. Blood 2004 | **Until 180 days after allo SCT, or until 4 weeks after discontinuation of GvHD therapy** |
| Micafungin versus fluconazole<br>Van Burik et al. Clin Infect Dis 2004 | **Allogeneic and autologous HSCT only pre-engraftment** |
| Posaconazole versus fluconazole<br>Ullmann A et al. NEJM 2007 | **Allogeneic HSCT only during GvHD** |
| Voriconazole versus fluconazole<br>Wingard JR et al. Blood 2010 | **Allogeneic HSCT until 100 days or until 180 days if GvHD** |
| Voriconazole versus itraconazole<br>Marks D et al. Br J Haematol 2011 | **Allogeneic HSCT until 100 days or until 180 days if GvHD** |

Update: ECIL 5, 2013

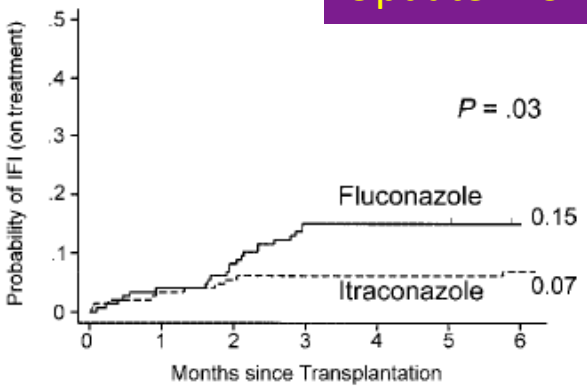
# Itraconazole (n=151) versus fluconazole (n=148)
# Marr KA et al. Blood 2004




Patients at risk (N)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Flu: | 148 | 139 | 127 | 106 | 97 | 92 | 85 |
| Itra: | 151 | 136 | 120 | 109 | 99 | 97 | 90 |

**Figure 2. Cumulative incidence of proven or probable invasive fungal infections according to antifungal prophylaxis.** The probability of infection among all patients is shown. The number of patients at risk (alive) at each interval in the fluconazole (flu) arm and itraconazole (itra) arm is indicated. The *P* value shown was calculated from tests comparing the incidences at 6 months.




Patients on SD and at risk (N):

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

**Figure 3. Cumulative incidence of proven or probable IFI while on-treatment.** Probability of infections that occurred in patients while receiving or within 2 weeks of discontinuation of study drugs (SD) is shown. The number of patients at risk (alive and on SD) at each interval is indicated. The *P* value shown was calculated from tests comparing the incidences at 6 months.

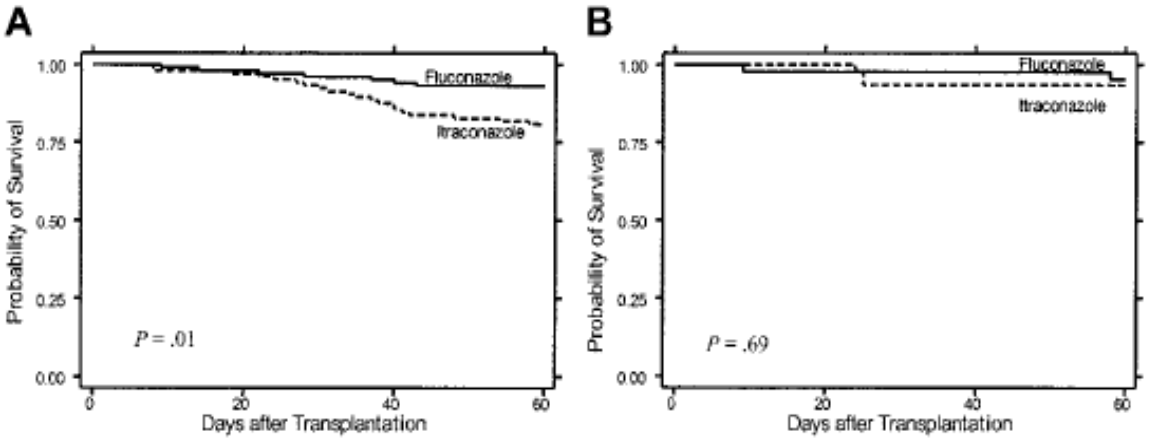
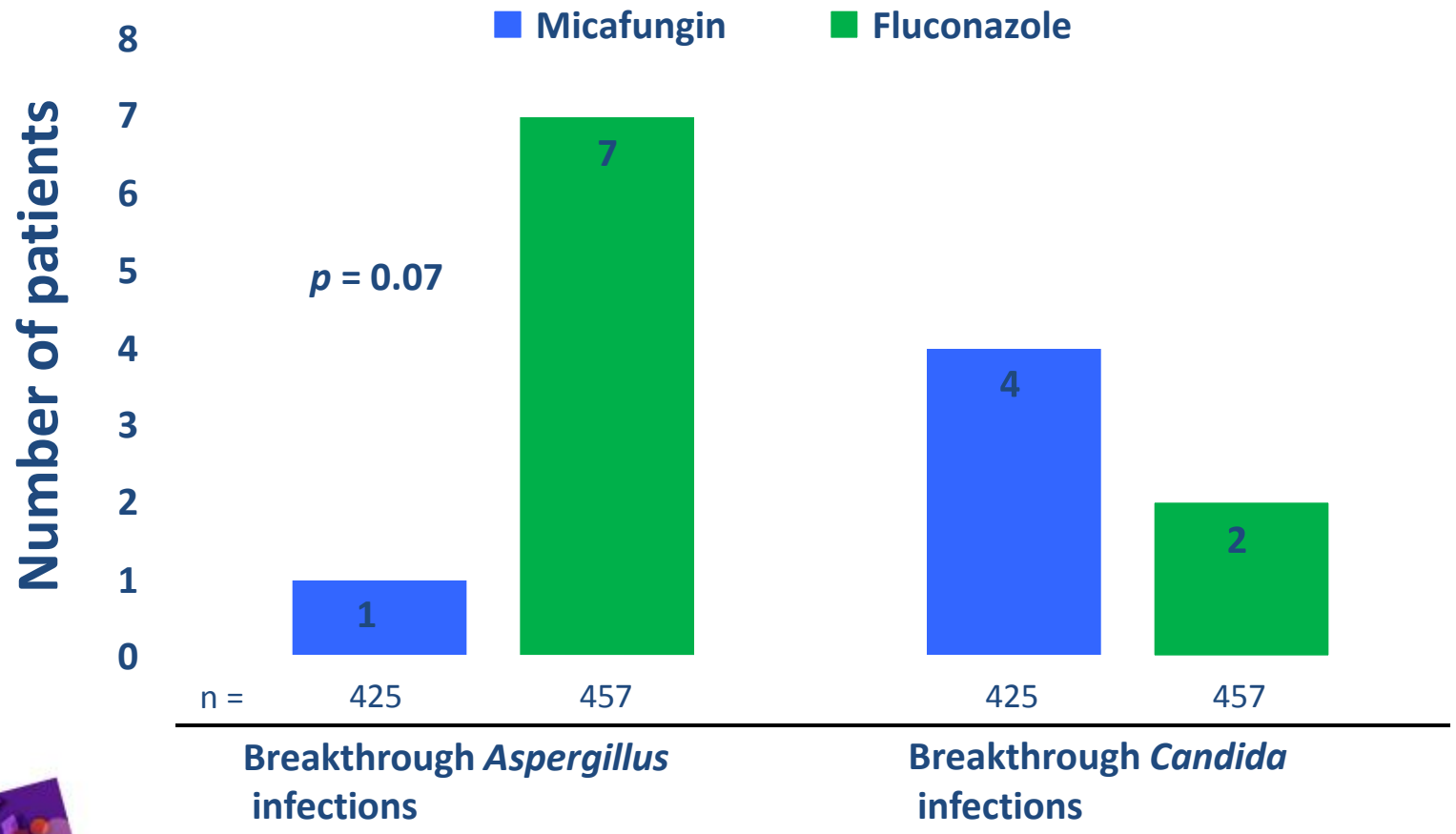



**Figure 4. Survival early after transplantation.** The probability of survival is shown among (A) 209 patients enrolled before the protocol amendment and (B) 90 patients enrolled after the protocol amendment. The *P* value shown was calculated from log-rank tests comparing the curves.

Itraconazole provided better protection against invasive mould infections (IMI) (fluconazole 12% versus itraconazole 5%, *P 0.03),* but *similar protection against* candidiasis (3% versus 2%, *P 0.69).* No difference in overall or fungal-free survival. Itraconazole appears to prevent IMI in the subset of patients who tolerate the drug, but toxicities and tolerability limit its usefulness as prophylaxis.

Micafungin 50 mg/day (n=425) versus fluconazole (n=457)
Van Burik et al. Clin Infect Dis 2004




Overall incidence of IFDs: 1.2 % in the micafungin group and 2 % in the fluconazole group

Micafungin (n=425) versus fluconazole (n=457)
Van Burik et al. Clin Infect Dis 2004

**Table 1. Demographic and clinical characteristics of study subjects.**

| Characteristic | Micafungin group | Fluconazole group[a] | *P* |
|---|---|---|---|
| Transplant type | | | |
| Syngeneic or autologous | 203/425 (47.8) | 201/457 (44.0) | |
| Allogeneic, by mortality risk | 220/425 (51.8) | 256/457 (56.0) | |
| High | 127/425 (29.9) | 152/457 (33.3) | |
| Low | 94/425 (22.1) | 104/457 (22.8) | |

## Comments

- Population at low risk for IFD
- Very low incidence of IFDs
- No work-up for diagnosing IFD pre-defined in the study

Posaconazole (n=301) versus fluconazole (n=299)
Ullmann A et al. NEJM 2007

## Primary endpoint

- Incidence of proven + probable IFDs from randomization to day 112

## Results

- All IFDs: Posaconazole: 5.3% vs Flucoconazole 9% (p=0.07)
  - IFD on treatment: Posaconazole 2.4% vs Fluconazole 7.6% (p=0.004)
  - IA: Posaconazole 2.3% vs Fluconazole 7% (p=0.006)
  - No difference observed in patients with chronic (limited or extensive) GvHD

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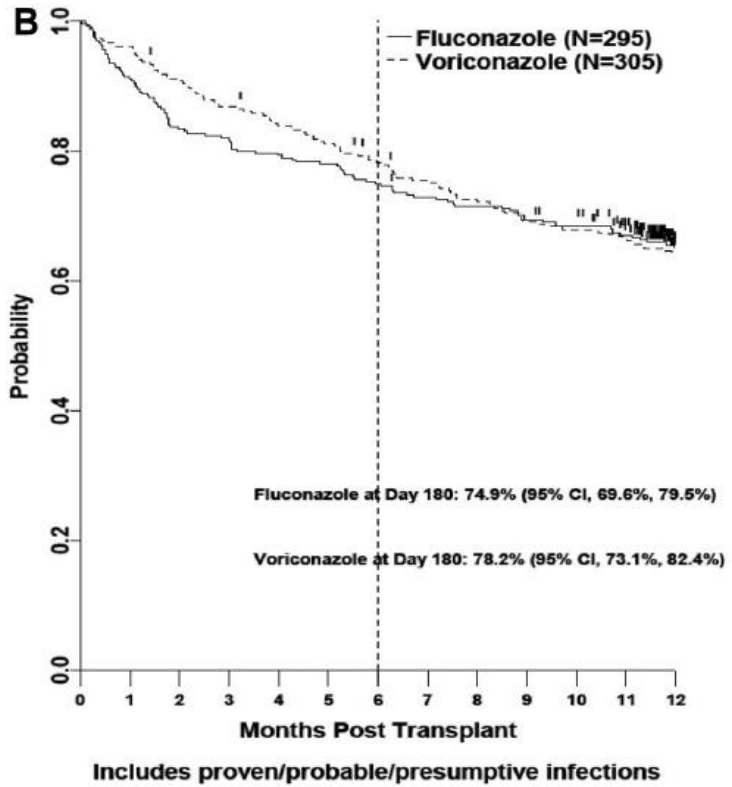
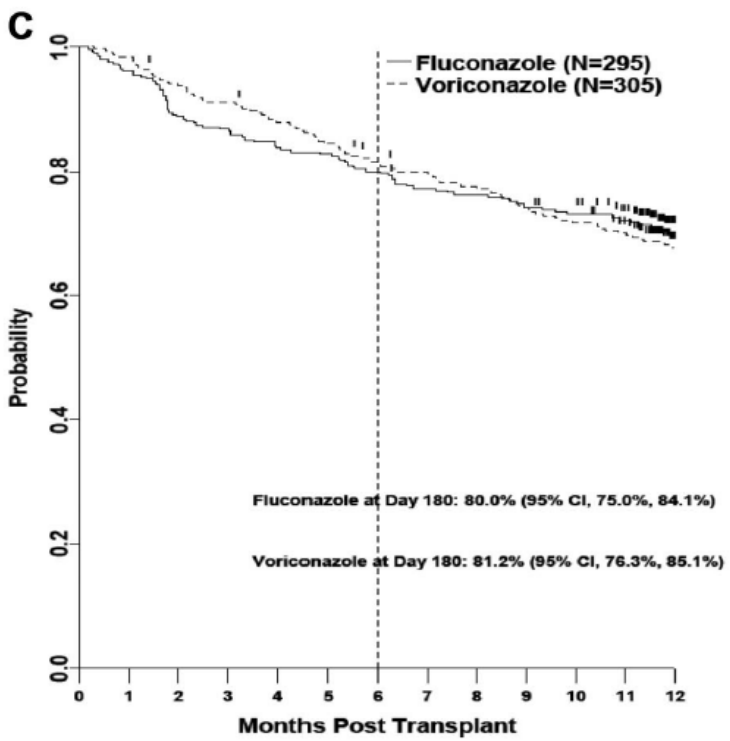
# Voriconazole (n=305) versus fluconazole (n=295)
# Wingard JR et al. Blood 2010

## Fungal free survival




## Overall survival




- IFIs:(180 d) Voriconazole 7.3% vs fluconazole 11.2%(p=0.12)
- IFIs: (12 m) Voriconazole 12.7% vs fluconazole 13.7% (p=0.56)
- IA (180 d): Voriconazole 9 cases vs fluconazole 17 cases (p=0.09)
- Empiric therapy: Voriconazole 24% vs fluconazole 30% (p=0.11)
- Toxicity: similar in the two arms

Voriconazole versus fluconazole
Wingard JR et al. Blood 2010

**Multivariate analysis of risk factors**

- Poorer Fungal Free Survival: age > 18, AML, severe acute GVHD
- The only factor associated with more IFDs was HCT for AML.
- In AML patients: fewer IFDs in the voriconazole group (8.5% vs. 21%; *P* .04) and improved FFS (78% vs. 61%; *P*= .04), but no difference in OS (81% vs. 72%; *P*= .32).

**Voriconazole prophylaxis and the risk of IFD after allogeneic HCT.**

**Corrado Girmenia et al. E-letter April 22, 2011.**

90% of patients had a standard risk disease status, over half of the transplants were matched related, the HLA match was 6/6 in 96% of cases, half of the patients did not develop acute or chronic GVHD and the incidence of disease relapse/progression was only about 10%.

One would be interested to evaluate voriconazole's performance in a higher risk population.

This consideration is even more valid when looking at the results among patients with AML

Voriconazole (n=234) versus itraconazole (n=255)
Marks D et al. Br J Haematol 2011; 155: 318-327

- Primary endpoint
  - Ability to tolerate study drug for at least 100 d (max 14 d interruption)
  - Survival without IFI to day 180
- Success:
  - Voriconazole 48.7% vs. Itraconazole 33.2% (95% CI, 7.7–25.1; P = 0.0002)
- Patients who completed > 100 d off study drug prophylaxis
  - Voriconazole 53.6% vs. Itraconazole 39.0%, (95% CI of difference, 5.6–23.5; P < 0.01)
- Survival at 180 d
  - Voriconazole 81.9% vs. Itraconazole 80.9%
- Proven-probable IFIs
  - Voriconazole 1.3% vs. Itraconazole 2.1% (95% CI for difference, 3.1 to 1.6; P = 0.54)

"The main driver for this difference was that significantly more voriconazole patients were able to tolerate at least 100 d of study drug with minimal interruption"

Update: ECIL 5, 2013

# Recommendations for allogeneic HSCT recipients (2013)

| Antifungal prophylaxis* | Pre-engraftment Low risk for moulds | Pre-engraftment High risk for moulds | GvHD |
|---|---|---|---|
| Fluconazole | A-I | A-III - against | A-III against |
| Itraconazole | B-I | B-I | B-I |
| Voriconazole | B-I | B-I | B-I |
| Posaconazole OS/Tablet | B-II | B-II | A-I |
| Micafungin | B-I | C-I | C-II |
| Caspofungin /anidulafungin | No data | No data | No data |
| Liposomal Amphotericin B | C-II | C-II | C-II |
| Aerosolized amphotericin B plus fluconazole | C-III | B-II | No data |

*For doses & need for Therapeutic Drug Monitoring: please refer to slides 21 and 22

# Therapeutic drug monitoring (TDM) of mould-active prophylaxis with triazoles

# Voriconazole TDM

| Population | Intention | Intervention | Reference | Comment |
|---|---|---|---|---|
| All patients receiving voriconazole for prophylaxis to prevent invasive aspergillosis | Improve efficacy | Measure plasma trough concentration on D2/3 of therapy or soon after | Park 2012, Racil 2012 Pascual 2008 & 2012, Troke 2011, Smith 2006, Dolton 2012, Ueda 2009, Kim 2011 Mitsani 2012, Pieper 2012, Trifilio 2007 Driscoll 2012, | Target range of 1-5 ug/ml. Need for repeat determinations should be determined by clinical status, or change in concomitant medications. Most papers did not include prophylaxis |
| Patients receiving voriconazole prophylaxis at risk for altered PK or in populations with reduced knowledge on PK | Improve efficacy, Reduce toxicity | As above | Michael 2011, Riscoll 2011, Han 2011 | As above. Target range of 1-5 ug/ml (including children, impaired liver function, populations with high incidence of slow/ultrarapid metabolizers) |
| Suspected breakthrough infection during voriconazole prophylaxis | Guide choice of directed therapy | Measure plasma trough concentration | Expert opinion | Inadequate voriconazole exposure may suggest preserved activity of voriconazole for treatment |
| Patients with plasma voriconazole trough concentrations below the target range | Improve efficacy | Increase dose by 25-100 % (beware of non-linear PK in adults) | Park 2012, Pascual 2008, Bartelink 2012, Smith 2006 | Repeat measurements should be performed 3 days after intervention |
| Patients with plasma voriconazole concentrations exceeding the target range with AE suspected to be related | Reduce toxicity and treatment discontinuation | Mild-moderate AE: reduce dose by 25-50% Severe AE: hold 1-2 doses then reduce the dose by 50% | Park 2012, Park 2008 | As above |
| Patients with plasma voriconazole concentrations exceeding the target range ***without*** suspected related AE | Reduce toxicity and treatment discontinuation | Consider reducing dose | Park 2012, Gorski 2011 | As above |

# Posaconazole TDM

| Population | Intention | Intervention | Reference | Comment |
|---|---|---|---|---|
| All patients receiving posaconazole for prophylaxis to prevent invasive aspergillosis | Improve efficacy | Measure plasma trough concentration on D5 of therapy or soon after | Jang 2010, Cornely 2011 Conte 2009 Campoli 2011, Campoli 2013 Dolton 2012 | Target concentration >700ng/mL. Need for repeat determinations should be determined by clinical status or change in concomitant medications; high tissue concentrations in the face of low plasma concentrations may still offer protection |
| Patients receiving posaconazole receiving concomitant medications with potential interaction (such as PPIs) | Improve efficacy | As above | Walravens 2011, Roussos 2009, Heinz 2012, Hohmann 2010, Krishna 2007, Lahner 2009 | As above |
| Patients with fasting condition or unable to take posaconazole with food | Improve efficacy | As above | Krishna 2009, Courtney 2004, Kohl 2009, Cornely 2012 | As above; Switch to IV or new solid oral formulation. Earlier sampling is possible but steady state is not reached |
| Patients with diarrhea or enhanced GI motility (e.g. gastrointestinal GvHD) | Improve efficacy | As above | | As above; Switch to IV or new solid oral formulation. |
| Patients receiving posaconazole at risk for altered PK , e.g. children | Improve efficacy | As above | Döring 2012, Welzen 2011 | As above |
| Patients receiving posaconazole suspension with plasma trough concentrations below <700 | Improve efficacy | Switch to tablet or IV formulation | Krishna 2012, Krishna 2012, Courtney 2003, Sansone-Parsons 2006, Krishna 2009 | As above; If IV or new solid oral not available: change dose to 200mg po qid Administer dose with a high fat meal or nutritional supplement Discontinue antacid therapies |
| Suspected breakthrough infection during posaconazole prophylaxis | Guide choice of directed therapy | Measure plasma trough concentration directly | Expert opinion | Inadequate posaconazole exposure may support use of voriconazole for treatment |

# Itraconazole TDM

| Population | Intention | Intervention | Reference | Comment |
|---|---|---|---|---|
| All patients receiving itraconazole treatment for IA | Improve efficacy | Measure plasma trough concentration on D5 of therapy or soon after | Denning 1989, Denning 1994; Glasmacher 1999, Lestner 2009 | Target concentration >500 ng/ml; (or > 1000 ng/ml for ITZ + hITZ) Need for repeat determinations should be determined by clinical status, or change in concomitant medications; |
| All patients receiving itraconazole for prophylaxis to prevent IA | Improve efficacy | As above | Glasmacher 2003 | As above |
| Patients receiving itraconazole | Reduce toxicity | As above | Lestner 2009 | Toxicity was associated with concentrations >17.1 mg/L by itraconazole bioassay. Translation to analytical technique complicated |
| Patients receiving itraconazole for prophylaxis who are at risk for altered PK including concomitant medications such as PPIs | Improve efficacy | As above | Glasmacher 2003, Brett 2013 | As above |
| Patients receiving itraconazole tablets with plasma trough concentrations below <500 | Improve efficacy | Change to oral solution or IV formulation | | Repeat measurement should be performed 5 days post intervention |
| Patients receiving itraconazole capsules with plasma trough concentrations below <500 | Improve efficacy | Switch to IV or oral solution. Stop interacting drug (such as PPI) If not possible coadminister capsule with acidic beverage | Lange 1997, Jaruratanasirikul 1998 | As above |