Diagnostik von Pilzinfektionen - offene Fragen und Kontroversen

PEG-Tagung - Sektion “Antimykotische Chemotherapie”

Bonn, 9.3.2018

Prof. Markus Ruhnke
GLOBAL CATASTROPHE: HOW 150 PEOPLE DIE EVERY HOUR FROM FUNGAL INFECTION WHILE THE WORLD TURNS A BLIND EYE

Neglected by policy makers and most international health agencies, the launch of Global Action Fund for Fungal Infections (GAFFI), an international organisation set to highlight the plight of 300 million people worldwide will begin to reverse the unnecessary trend in death and suffering.

Fungal infections kill at least 1,350,000 patients with or following AIDS, cancer, TB and asthma as well as causing untold misery and blindness to tens of millions more worldwide. Yet its symptoms are mostly hidden and occur as a consequence of other health problems. Diagnostic tests are not available to millions to worldwide, and they need to be.

www.GAFFI.org
Estimated burden of fungal infections in Kenya

John A. Gutu1,2, Christine C. Bili3, David W. Denning1,3,4

Estimated burden of fungal infections in Germany

Markus Ruhnke,1 Andreas H. Groll,7 Peter Maysel,3 Andrew J. Ullmann,4 Werner Mendl,5 Herbert Hof,6 David W. Denning7 and The University of Manchester in association with the LIFE program

The burden of fungal disease in Spain

Klaus L. Mortensen,1 David W. Denning2

The burden of serious fungal diseases in Russia

N. Klimko,1 Y. Kozlova,1 S. Khostalidi,1 O. Shadrinova,1 Y. Borzova,1 E. Burygina,1 N. Vasilieva1 and D. W. Denning2

An estimate of the burden of serious fungal diseases in Greece

European Journal of Clinical Microbiology & Infectious Diseases
1... July 2016, Volume 35, Issue 7, pp 1115-1120

Burden of serious fungal infections in Spain

N. Blanca-Chaparro,1 C. León,1 M. Miro,4 A. Nuñez Bullón,1 C. E. Cuenca-Estrella1,2 M. Cuenca-Estrella1,2, and D. W. Denning

Fungal Diseases in Israel

Ronen Ben-Ami MD1 and David W. Denning FRCP2,3

Pilzdiagnostik in der Hämatologie

Prof. M. Ruhnke
### Table 1: Burden of fungal diseases in Germany according the selected underlying diseases.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Unknown</th>
<th>HIV/AIDS</th>
<th>Respiratory</th>
<th>Cancer/Tx</th>
<th>ICU</th>
<th>Total burden</th>
<th>Rate/100K²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fungal skin diseases</td>
<td>6,721,000</td>
<td>n.a.¹</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>6,721,000</td>
<td>8347</td>
</tr>
<tr>
<td>Oral candidosis</td>
<td>n.a.²</td>
<td>15,600</td>
<td>n.a.</td>
<td>97,965</td>
<td>n.a.</td>
<td>113,565</td>
<td>141</td>
</tr>
<tr>
<td>Oral candidiasis</td>
<td>5</td>
<td>10</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>15</td>
<td>0.02</td>
</tr>
<tr>
<td>Fungal keratitis</td>
<td>32</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>32</td>
<td>0.04</td>
</tr>
<tr>
<td>Total burden estimated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9,610,789</td>
<td></td>
</tr>
</tbody>
</table>

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**Invasive Aspergillose** N = ca. 4280

**Candidämien** N = ca. 3700

**Candida Peritonitis** N = ca. 3700

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Ruhnke et al., Mycoses, 2015, 58 (Suppl. S5), 22–28
Revised Definitions of Invasive Fungal Disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group

Ben De Pauw, a Thomas J. Walsh, a J. Peter Donnelly, a David A. Stevens, John E. Edwards, Thierry Calandra, Peter G. Pappas, Johan Maertens, Olivier Lortholary, Carol A. Kauffman, David W. Denning, Thomas F. Patterson, Georg Maschmeyer, Jacques Bille, William E. Dismukes, Raoul Herbrecht, William W. Hope, Christopher C. Kibbler, Bart Jan Kullberg, Kieren A. Marr, Patricia Muñoz, Frank C. Odds, John R. Perfect, Angela Restrepo, Markus Ruhnke, Brahm H. Segal, Jack D. Sobel, Tania C. Sorrell, Claudio Viscoli, John R. Wingard, Theoklis Zaoutis, and John E. Bennett b

Ascioglu et al., CID (2002):34; De Pauw et al., CID (2008):46
EORTC/MSG - Definitionen
"Proven Invasive Fungal Infections/Disease"

Gesichert = proven
Histologisch: invasives Wachstum
oder
kultueller Nachweis aus primär sterilem Material
Wahrscheinlich = probable
Risikofaktor + Klinik + Mikrobiologie
Möglich = possible
Risikofaktor + Klinik oder Mikrobiologie

Histopathologie ist der „Goldstandard“

Ascioglu et al., CID (2002);34; De Pauw et al., CID (2008);46
Table 1. Patterns of invasive fungal disease in practice, based on 2008 EORTC-MSG criteria.

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiological signs and clinical symptoms</td>
<td>Persistent febrile neutropenia</td>
<td>No clinica (any new infiltrate not fulfilling the EORTC/MSG criteria)</td>
<td>Radiological signs on CT (dense, well-circumscribed lesion(s) with or without a halo sign, air-crescent sign, or cavity)</td>
<td>Not considered necessary</td>
</tr>
<tr>
<td>Mycology results</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Positive biomarker or microscopy or culture</td>
</tr>
<tr>
<td>Clinical evidence of IFD</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Mycological evidence of IFI</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Final diagnosis</td>
<td>Unclassified</td>
<td>Positive (possible) IMD</td>
<td>Probable IMD</td>
<td>Proven IMD</td>
</tr>
<tr>
<td>Management</td>
<td>Prophylaxis</td>
<td>Empirical therapy</td>
<td>Diagnostic-driven (pre-emptive) therapy</td>
<td>Targeted therapy</td>
</tr>
</tbody>
</table>
Indications and outcomes of antifungal therapy in French patients with haematological conditions or recipients of haematopoietic stem cell transplantation

**Methods**: observational prospective study, children/adults with haematological conditions or HSCT were recruited upon start of non-prophylactic systemic AF treatment in 37 French haematological facilities (2007 -2008). IFD episodes were classified according to the 2008 EORTC/MSG criteria.

**Results**: 419 patients (298 adults and 121 children): 88% haematological malignancies, 28% HSCT recipients and 68% neutropenic.

423 IFD episodes: 21% mycologically documented (59% probable/proven aspergillosis, 32% proven candidiasis and 9% probable/proven other IFD), 20% classified as possible IFD.
The 12-week mortality was 18% for probable/proven aspergillosis, 15% for proven candidiasis, 10% for probable/proven other IFD, 9% for possible IFD, 3% for febrile neutropenia, and 12% for unclassified episodes.

<table>
<thead>
<tr>
<th>Species</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Yeasts</strong></td>
<td></td>
</tr>
<tr>
<td>Candida albicans</td>
<td>14 (29)</td>
</tr>
<tr>
<td>Candida glabrata</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Candida krusei</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Candida parapsilosis</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Candida kefyr</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Candida guillermondii</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Candida lambica</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Candida tropicalis</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Candida spp.</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Candida albicans and Candida glabrata</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Candida albicans and Candida parapsilosis</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Candida albicans, Candida glabrata and Candida zeylanoides</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Rhodotorula mucilaginosa</td>
<td>1 (2)</td>
</tr>
<tr>
<td>unidentified yeast(^a)</td>
<td>2 (4)</td>
</tr>
<tr>
<td><strong>Moulds</strong></td>
<td></td>
</tr>
<tr>
<td>Aspergillus fumigatus</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Aspergillus flavus</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Fusarium solani</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Fusarium spp.</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Mucor spp.</td>
<td>2 (4)</td>
</tr>
<tr>
<td>unidentified mould(^a)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

\(^a\)Diagnosis by microscopy on biopsy material, no culture growth.
Leitlinie “Diagnostik von Mykosen” der AG Infektionen der DGHO (AGIHO)

<table>
<thead>
<tr>
<th>General recommendations</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>The highest level of evidence for the presence of IFI should be obtained before initiating systemic antifungal therapy</td>
<td>A</td>
</tr>
<tr>
<td>Most signs and symptoms related to IFI are unpecific and require further diagnostic procedures</td>
<td>A</td>
</tr>
<tr>
<td>A combination of various methods with regular screenings is mandatory for early diagnosis of IFD, as well as for monitoring response to antifungal treatment</td>
<td>A</td>
</tr>
</tbody>
</table>

Strength of Recommendation = \textit{SoR} \\
Quality of Evidence = \textit{QoE} \\
→ Allows strong recommendations in the absence of highest quality of evidence.

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient with fever</td>
<td>Diagnose fungaemia</td>
<td>Take blood cultures</td>
<td>A</td>
<td>II</td>
<td>Acme WJFD 2002</td>
<td></td>
</tr>
</tbody>
</table>

ECMM guideline Mucormycosis, Cornely et al.
Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

**Objectives** To determine whether parachutes are effective in preventing major trauma related to gravitational challenge.

**Design** Systematic review of randomised controlled trials.

**Data sources:** Medline, Web of Science, Embase, and the Cochrane Library databases; appropriate internet sites and citation lists.

**Study selection:** Studies showing the effects of using a parachute during free fall.

**Main outcome measure** Death or major trauma, defined as an injury severity score > 15.

**Results** We were unable to identify any randomised controlled trials of parachute intervention.

**Conclusions** As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials. Advocates of evidence based medicine have criticised the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence based medicine organised and participated in a double blind, randomised, placebo controlled, crossover trial of the parachute.

*BMJ 2003; 327 doi: [https://doi.org/10.1136/bmj.327.7429.1459](https://doi.org/10.1136/bmj.327.7429.1459)*
Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Analysis And Comment  »  Controversy

Parachute approach to evidence based medicine

BMJ 2006; 333  doi: https://doi.org/10.1136/bmj.333.7570.701 (Published 28 September 2006)
Cite this as: BMJ 2006;333:701

Waiting for the results of randomised trials of public health interventions can cost hundreds of lives, especially in poor countries with great need and potential to benefit. If the science is good, we should act before the trials are done

In 2003 Smith and Pell published an entertaining but profound article titled: “Parachute use to prevent death and major trauma due to gravitational challenge.”¹ They used the lack of randomised controlled trials in testing parachutes to show that situations still exist where such trials are unnecessary. We argue that the parachute approach, where policies are set based on good science but without randomised trials, is often more suitable in resource poor settings. We use the examples of oral rehydration therapy, male circumcision to prevent HIV infection, and misoprostol for postpartum haemorrhage to show how an overemphasis on randomised controlled trials in poor settings poses important ethical and logistic problems and may incur avoidable deaths.

BMJ 2006; 333 doi: https://doi.org/10.1136/bmj.333.7570.701
Diagnostik von Mykosen
AGIHO - Leitlinie 2018

Was hat sich seit 2012 geändert?

- Mikroskopie
- Kultur (Erregernamen, Namensänderungen)
  - Resistenztestung von Aspergillus spp. und Resistenzentwicklung gegen Azole (u.a. molekulare Resistenztestung)
- Antigen - / Antikörper
  - Daten zur kombinierten Diagnostik/Screening der IA mit Galactomannan + PCR +/−β-D-Glucan
- Neue Testsysteme (LFD = „laminar flow device“)
- Molekulare Diagnostik
  - Mehr Daten zur molekularen Diagnostik (neue Verfahren, z.B. „microarrays“)
  - Kommerzielle PCR-Teste eingeführt
Diagnostik von Mykosen
AGIHO - Leitlinie 2016

- Bildgebung
  - Dünnschicht-CT Thorax statt HR-CT
  - „reversed halo sign“ bei Zygomykosen
- Endoskopie
- Gewebediagnostik
- Allgemeine Vorgehensweisen
  - „integrated pathways“
  - „clinical driven“ vs. „diagnostic driven“
- Diagnostischer Algorithmus unter Antimykotika-Prophylaxe
Challenges and Pitfalls of Morphologic Identification of Fungal Infections in Histologic and Cytologic Specimens

A Ten-Year Retrospective Review at a Single Institution

Ankur R. Sangoi, MD,¹ William M. Rogers, MD,¹ Teri A. Longacre, MD,¹ Jose G. Montoya, MD,² Ellen Jo Baron, PhD,¹ and Niaz Banaei, MD¹

- Of the 47 of 338 positive mold and yeast cultures with concurrent surgical pathology evaluation without known history of a fungal infection,
- 37 (79%) were correctly identified based on morphologic features in histologic and/or cytologic specimens.
- The 10 discrepant diagnoses (21%) included misidentification of septate and nonseptate hyphal organisms and yeast forms.
- Errors resulted from morphologic mimics, use of inappropriate terminology, and incomplete knowledge in mycology. The accuracy did not correlate with preceding antifungal therapy or use of special stains and was not operator-dependent.
Diagnostic Accuracy of Histopathologic and Cytopathologic Examination of Aspergillus Species

Akeesha A. Shah, MD, and Kevin C. Hazen, PhD*

Diagnostic accuracy was defined as the percentage of cases with culture proven Aspergillus spp divided by the number of cases diagnosed as Aspergillus spp on HCE that had growth on fungal culture. 90 surgical/cytology cases with concurrent fungal culture were reviewed, 58 of which grew a fungal organism. Of these, 45 grew an Aspergillus spp, whereas 13 grew an organism other than Aspergillus spp (9 with common (Scedosporium, Fusarium, and Paecilomyces spp) and uncommon mimickers (Trichosporon loubieri), resulting in a diagnostic accuracy of 78%.

The low diagnostic accuracy indicates that several fungal organisms can morphologically mimic Aspergillus spp and can only be distinguished by fungal culture and DNA sequencing.
Wie nennen wir die Erreger?
### Nomenklatur von Pilzen

**Aspergillus Spezies**

<table>
<thead>
<tr>
<th>Teleomorph = geschlechtliche (perfekte) Vermehrung</th>
<th>Anamorph = ungeschlechtliche (imperfekte) Vermehrung</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eurotium amstelodami</td>
<td>Aspergillus glaucus</td>
</tr>
<tr>
<td>Emericella nidulans</td>
<td>Aspergillus nidulans</td>
</tr>
<tr>
<td>Fennellia terrei</td>
<td>Aspergillus terreus</td>
</tr>
<tr>
<td>Hemicarpenteles clavati</td>
<td>Aspergillus clavatus</td>
</tr>
<tr>
<td>Neosartorya fumigata</td>
<td>Aspergillus fumigatus</td>
</tr>
<tr>
<td>Neosartorya fischeri</td>
<td>Aspergillus fischerianus</td>
</tr>
<tr>
<td>Petromyces flavi</td>
<td>Aspergillus flavus</td>
</tr>
<tr>
<td>Petromyces nigri</td>
<td>Aspergillus niger</td>
</tr>
</tbody>
</table>

= no sex!
This amendment has a potentially profound effect on clinical mycology, because with this fundamental change all established fungal names and many disease names are jeopardised. Additionally, many well known, clinically important species, such as Aspergillus fumigatus, Coccidioides immitis, Exophiala jeaneslmei, and Sporothrix schenckii, have been found to consist of several molecular siblings. Molecular diversity leads to an enormous increase in potentially relevant fungi and to changes of
Most members of this new cryptic species were recovered as colonizing isolates from immunocompetent patient populations, had decreased in vitro susceptibilities to the antifungal drug amphotericin B, and were morphologically similar to but genetically distinct from *Aspergillus terreus* isolates...
Kommt man ohne die molekulare Diagnostik und Erregeridentifizierung heute noch aus?
Taxonomy of Fungi Causing Mucormycosis and Entomophthoramycosis (Zygomycosis) and Nomenclature of the Disease: Molecular Mycologic Perspectives

A

Kingdom FUNGI

<table>
<thead>
<tr>
<th>Phylum</th>
<th>Subphyla</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZYGOMYCOTA</td>
<td>Subphylum</td>
</tr>
<tr>
<td>CHYTRIDIOMYCOTA</td>
<td>Mucoromycotina, Entomophthoramycotina, Kickxellomycotina, Zoopagomycotina</td>
</tr>
<tr>
<td>ASCOMYCOTA</td>
<td></td>
</tr>
<tr>
<td>BASIDIOMYCOTA</td>
<td></td>
</tr>
</tbody>
</table>

B

Kingdom FUNGI

Subkingdom DIKARYA

<table>
<thead>
<tr>
<th>Phylum</th>
<th>Subphyla</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHYTRIDIOMYCOTA</td>
<td>Subphylum</td>
</tr>
<tr>
<td>NEOCLIMASTIGOMYCOTA</td>
<td></td>
</tr>
<tr>
<td>BLASTOCADIOMYCOTA</td>
<td></td>
</tr>
<tr>
<td>GLOMEROMYCOTA</td>
<td></td>
</tr>
<tr>
<td>ASCOMYCOTA</td>
<td></td>
</tr>
<tr>
<td>BASIDIOMYCOTA</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. Old (A) and a proposed new (B) classification schemes of the kingdom Fungi.
Six of 8 (75%) of those with ABPA and 12 of 24 (50%) with CPA had resistance markers present, some without prior triazole treatment...
...From a total of 527 samples, 17 (3.2%) showed elevated MIC<sub>0</sub> values ...for at least one of the three substances (itraconazole, voriconazole, and posaconazole) tested. The highest prevalence of resistant isolates was observed in cystic fibrosis patients (5.2%). Among resistant isolates, the TR/L98H mutation in cyp51A was the most prevalent, but isolates with the G54W and M220I substitutions and the novel F219C substitution were also found...
Methods: Between January 2009 and September 2016, 233 specimens, consisting of fresh and formalin-fixed, paraffin-embedded tissues and sterile body fluids with known diagnosis of IFD based on reference method results (n = 117), and specimens with negative fungal culture, but with microscopic and ancillary findings indicative of IFD (n = 116), were included. PCR amplicons from the internal transcribed spacer 2 and the D2 region of 28S ribosomal RNA gene were sequenced and fungi identified.

Results: Sensitivity and specificity of fungal sequencing in specimens with known diagnosis were 96.6% and 98.2%, respectively.

In patients with suspected IFD, the diagnostic yield of fungal sequencing was 62.9% (73/116) overall and 71.3% (57/80) in patients classified with proven IFD (EORTC/MSG criteria). Samples obtained by open biopsy had a significantly higher diagnostic yield (71.5%) compared with core-needle biopsy (50%) and fine needle aspiration...
Die Realität in der Hämatologie: „integrated pathways“?
„clinical driven“ vs. „diagnostic driven“
Diagnostischer Algorithmus unter Antimykotika-Prophylaxe
Algorithmus zur “diagnostic driven” Behandlung der invasiven Aspergillose

Diagnostisch gesteuerte Therapie
  - screening-Test *
  - CT kurzfristig mögl.
  - Broncho kurzfristig mögl.

* etabliert und Ergebnisse am gleichen/nächsten Tag verfügbar
  z.B. BAL; Calcoflour, GM, PCR, Biopsie etc.

CT
- Invasive Aspergillose Verächtig Screening POSITIV
- Auffällig Screening NEGATIV
- Unspezifisch Screening NEGATIV
- Normal Screening POSITIV
- Normal Screening NEGATIV

IA
- wahrscheinlich
- Möglich Andere Ursachen?
- Unklare Befundsituation
- Falschpositiver Test oder Extrapul. IA?

IA ausgeschlossen

Agrawal et al; JAC (2011)
Consensus guidelines for the use of empiric and diagnostic-driven antifungal treatment strategies in haematological malignancy, 2014

Surveillance-driven diagnostic antifungal treatment strategy

Twice-weekly testing of serum with GM-ELISA and whole blood with Aspergillus PCR

Perform HRCT scan of chest for any of the following:
- At time-point of first (+) GM-ELISA or PCR result. Continue with GM-ELISA and PCR testing while awaiting HRCT results
- If GM-ELISA and PCR testing produces consistently negative results but patient has refractory fevers (+/– neutropenia)
- Clinical signs/symptoms of IFD

Commence antifungal therapy if any of the following is fulfilled:
- 2 consecutively (+) GM-ELISA or PCR results
- >2 intermittently (+) GM-ELISA or PCR results in a 2-week period
- Single positive GM-ELISA or PCR and any lesion on HRCT scan of chest
- Characteristic lesion on HRCT scan of chest only

Antifungal therapy should not be given and investigations for other infections should be implemented for any of the following:
- Single positive GM-ELISA or PCR result alone
- Non-characteristic lesion on HRCT scan of chest only
- All test results are negative

Morrissey et al; Internal Medicine (2014)
Overview on diagnostic procedures recommended in patients at risk for IFD before, during or after granulocytopenia (<500 cells/μL) with or without fever

**Fever ≥ 38.5°C or IFD suspected**

- **yes**
  - **high-risk for IFD?**
    - **yes**
      - Extensive examination for IFD
        - **yes**
          - Daily physical examination
            - Microscopy + mycological culture of all samples (e.g. BC)
            - HR-CT lungs
          - Galactomannan (GM) (+/- β-D-Glucan) +/- fungal (Aspergillus) PCR twice weekly
          - BAL if pulmonary infiltrate
            - (Crypto-Ag in CSF if LP indicated)
        - **optional**
          - Ultrasound/CT/MRI of all suspected areas
          - Organ biopsy from suspected areas if clinically feasible
    - **no**
      - Persistent fever >72 hrs?
        - **yes**
          - Routine screening for IFD
            - **yes**
              - Galactomannan (GM) (+/- β-D-Glucan) +/- fungal (Aspergillus) PCR twice weekly
            - BAL if pulmonary infiltrate
              - (Crypto-Ag in CSF if LP indicated)
        - **recommended**
          - Screening only if clinically indicated
      - **no**
        - **no**
Diagnostic algorithm for IFD in high-risk patients under mould active prophylaxis

Patients under mould-active prophylaxis with clinical signs* and or positive biomarkers ** suggestive for IFD

CT chest negative

Biomarkers positive

Excludes focus outside the lungs (e.g. sinusitis, CNS, liver, GI tract)

Biomarkers negative

Continue prophylaxis, consider TDM; actively exclude alternative focus

CT chest positive

Biomarkers positive

Start targeted antifungal treatment (consider change of antifungal class)

Biomarkers negative

Discontinue prophylaxis and / or consider TDM; Start targeted antifungal treatment (consider change of antifungal class)

CT negative

Biomarkers positive

Exclude focus outside the lungs (e.g. sinusitis, CNS, liver, GI tract)

Biomarkers negative

Continue prophylaxis, consider TDM; actively exclude alternative focus

Mandatory diagnostic procedures: CT (lungs), mycological cultures/microscopy;
* clinical signs suggestive for IFD (e.g. lung infiltrate, brain abscess, liver/spleen lesions)
** Biomarkers (e.g. GM, β-d-Glucan, PCR)
Zusammenfassung

- „laufende“ Veränderung von Erregernamen macht den Biologen glücklich, aber nicht den Kliniker!
- „aggressive Diagnostik“ (Biopsie) ist für die Wahl und Dauer der antimykotischen Therapie wichtig!
- Erregerdiagnostik geht nicht mehr ohne molekularbiologische Methoden!
- Diagnostisch/therapeutische Algorithmen haben insbes. bei Schimmelpilzmykosen eine hohe Bedeutung („diagnostic-driven“ bzw. „pre-emptive therapy“ – aufgrund von Mängeln div. diagnostischer Methoden)!