Top 3 Papers in Aspergillosis for Clinical Sciences

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School of Medicine
Section of Infectious Diseases
Ankara, Turkey

Topics to be Covered

- Diagnosis
- Assessment of treatment response
- Azole resistance

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1. RT-qPCR detection of Aspergillus fumigatus RNA **in vitro** and in a murine model of invasive **aspergillosis** utilizing the PAXgene(®) and Tempus™ RNA stabilization systems.
   Morton CO, de Luca A, Romani L, Rogers TR.
   Med Mycol. 2012 Jan 23. [Epub ahead of print]
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2. Immunoproteomics based identification of thioredoxin reductase GliT and novel Aspergillus fumigatus antigens for serologic **diagnosis** of invasive **aspergillosis**.
   Shi LN, Li FQ, Huang M, Lu JF, Kong XX, Wang SQ, Shao HF.
   BMC Microbiol. 2012 Jan 18;12(1):11. [Epub ahead of print]
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3. Pictorial essay: Allergic bronchopulmonary **aspergillosis**.
   Agarwal R, Khan A, Garg M, Aggarwal AN, Gupta D.
   Indian J Radiol Imaging. 2011 Oct;21(4):242-52.
   PMID: 22223932 [PubMed - in process] **Free PMC Article**
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4. Invasive mycoses: diagnostic challenges.
   Ostrosky-Zeichner L.
   Am J Med. 2012 Jan;125(1 Suppl):S14-24.
   PMID: 22196205 [PubMed - in process]
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5. The effects of the Influence of pretreating serum samples on the performance of a latex agglutination test for

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1. Global burden of chronic pulmonary **aspergillosis** as a sequel to pulmonary tuberculosis.
Denning DW, Pleuvry A, Cole DC.
Bull World Health Organ. 2011 Dec 1;89(12):864-72. Epub 2011 Sep 27.
PMID: 22271943 [PubMed - in process]

2. Prophylactic efficacy of single dose pulmonary administration of amphotericin B inhalation powder in a guinea pig model of invasive pulmonary **aspergillosis**.
Kirkpatrick WR, Najvar LK, Vallor AC, Wiederhold NP, Bocanegra R, Pfeiffer J, Perkins K, Kugler AR, Sweeney TD, Patterson TF.
J Antimicrob Chemother. 2012 Jan 11. [Epub ahead of print]
PMID: 22240402 [PubMed - as supplied by publisher]
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3. Fatal subarachnoid hemorrhage caused by Aspergillus arteritis without angiographic abnormalities.
Miki Y, Tomiyama M, Haga R, Nishijima H, Suzuki C, Nishijima M, Midorikawa H, Sannohe S, Kurotaki H, Wakabayashi K, Baba M.
Neuropathology. 2012 Jan 12. doi: 10.1111/j.1440-1789.2011.01289.x. [Epub ahead of print]
PMID: 22239342 [PubMed - as supplied by publisher]
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4. Breakthrough invasive mould infections in patients treated with caspofungin.
Phai Pang KA, Godet C, Fekkar A, Scholler J, Nivoix Y, Letscher-Bru V, Massias L, Kauffmann-Lacroix C, Elsendoorn A, Uzunov M, Datry A, Herbrecht R.
J Infect. 2011 Dec 29. [Epub ahead of print]
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1. High Prevalence of **Azole**-Resistant Aspergillus fumigatus in Adults with Cystic Fibrosis Exposed to Itraconazole.
Burgel PR, Baixench MT, Amsellem M, Audureau E, Chapron J, Kanaan R, Honoré I, Dupouy-Camet J, Dusser D, Klaassen CH, Meis JF, Hubert D, Paugam A.
Antimicrob Agents Chemother. 2012 Feb;56(2):869-74. Epub 2011 Nov 28.
PMID: 22123701 [PubMed - in process]
Related citations

2. Isolation of multiple-triazole-resistant Aspergillus fumigatus strains carrying the TR/L98H mutations in the cyp51A gene in India.
Chowdhary A, Kathuria S, Randhawa HS, Gaur SN, Klaassen CH, Meis JF.
J Antimicrob Chemother. 2012 Feb;67(2):362-6. Epub 2011 Oct 25.
PMID: 22028200 [PubMed - in process]
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3. Clinical implications of **azole resistance** in Aspergillus fumigatus, The Netherlands, 2007-2009.
van der Linden JW, Snelders E, Kampinga GA, Rijnders BJ, Mattsson E, Debets-Ossenkopp YJ, Kuijper EJ, Van Tiel FH, Melchers WJ, Verweij PE.
Emerg Infect Dis. 2011 Oct;17(10):1846-54.
PMID: 22000354 [PubMed - in process] **Free Article**
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4. **Azole** antifungal **resistance** today: focus on Aspergillus.
Bowyer P, Moore CB, Rautemaa R, Denning DW, Richardson MD.
Curr Infect Dis Rep. 2011 Dec;13(6):485-91.
PMID: 21931980 [PubMed]
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blood

Prepublished online October 18, 2011;
doi:10.1182/blood-2011-04-351601

The strategy for the diagnosis of invasive pulmonary aspergillosis should depend on both the underlying condition and the leucocyte count of patients with hematological malignancies

Anne Bergeron, Raphaël Porcher, Annie Sulahian, Cédric de Bazelaire, Karine Chagnon, Emmanuel Raffoux, Anne Vekhoff, Muriel Cornet, Françoise Isnard, Benoit Brethon, Claire Lacroix, Jean Louis Poirot, Claire Bouges, Francis Derouin, Abdellatif Tazi and Patricia Ribaud

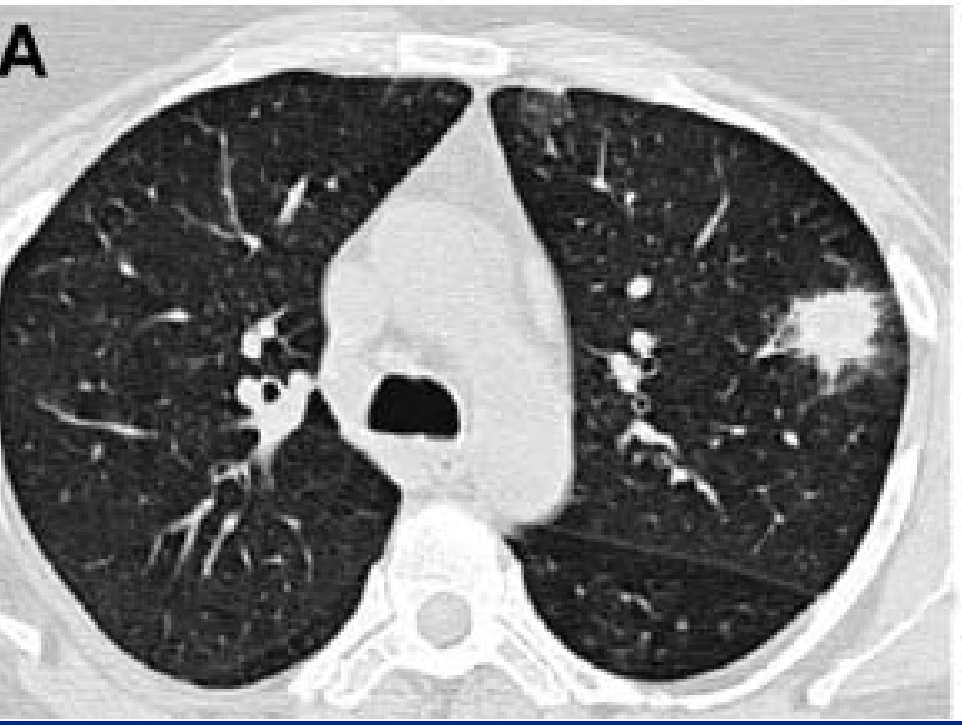
- **Diagnostic yield of BAL in immunocompromised 40-60%**
  - **Associated w underlying hematologic condition and neutropenia**
- **Host immunosupression may influence**
  - **Radiologic presentation**
  - **Prognosis**

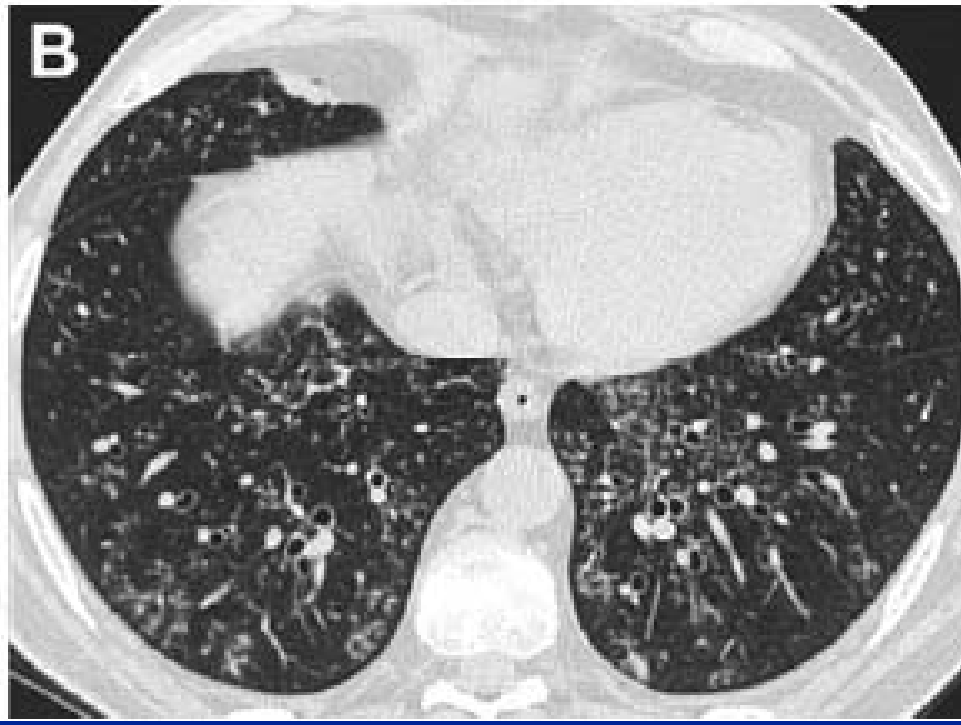
What was Done?

- Question
  - Could mycological diagnosis for IPA be adapted based on patient characteristics?
- 55 patients, prospectively evaluated
  - Acute leukemia (AL), no HSCT, 22
  - Non AL
    - » Allo HSCT, 23
    - » Another hematologic disorder, 10

Evaluation

- Baseline HRCT scan
  - Angio-invasive (nodule w a halo sign)
  - Airway invasive (centrilobuler micronodules, tree-in-bud w a halo)
- FOB with BAL performed within 24 h of CT
- GMI, positive $\geq$0.5 in serum and BAL





Angi

Airway-invasive

Table 2: Lung CT scan features at the diagnosis of invasive pulmonary aspergillosis according to patient groups.

Signs	**Allogenic HSCT** N=23	**Acute leukemia** N=22	**Others#** N=10
Angio-invasive†	3 (13%)	10 (45%)	1 (10%)
Airway-invasive¶	10 (44%)	3 (14%)	2 (20%)
Both angio- and airway-invasive	3 (13%)	2 (9%)	2 (20%)
No angio- nor airway-invasive§	7 (30%)	7 (32%)	5 (50%)

Table 3: Association between lung CT scan pattern and leucocyte count.

	Leucocyte count < 100/mm^3 n=27	Leucocyte count > 100/mm^3 n=28	P
Angio-invasive disease* n=14	13	1	0.001
At least one airway-invasive sign n=22	4	18	0.001
Airway-invasive disease† n=15	2	13	0.005

* at least one nodule with halo sign and no sign of airway-invasive disease, † centrilobular micronodules and/or tree in bud without any nodule with halo sign

Other Findings

- Presence of aspergillus in respiratory samples
  - More frequent in non-AL patients (82%) than AL (25%), p=.0003
  - In patients with WBC counts >100/mm^3, p=.002
- In logistic regression, they are independent factors
  - OR 7,14 and 6.97, respectively

Summary

- Different mycological diagnostic strategy may be applied to those with
  - AL and WBC <100/mm^3
  - Non-AL (with HSCT)
    - BAL

MAJOR ARTICLE

Earlier Response Assessment in Invasive Aspergillosis Based on the Kinetics of Serum *Aspergillus* Galactomannan: Proposal for a New Definition

Simone A. Nouér,[1,3] Marcio Nucci,[2,3] Naveen Sanath Kumar,[3] Monica Grazziutti,[3] Bart Barlogie,[3] and Elias Anaissie[3]

[1]Department of Preventive Medicine, [2]Department of Internal Medicine, Universidade Federal do Rio de Janeiro, Brazil; and [3]Myeloma Institute for Research and Therapy, University of Arkansas for Medical Sciences, Little Rock

- **Whether kinetics of serum Aspergillus galactomannan-index (GMI)**
  - **Compare favorably with EORTC/MSD definitions**
  - **Allow earlier and more objective response assesment**

Clin Infect Dis 2011;53:671

What was Done?

- 115 cancer patients between 2003-2010 in Arkansas
  - X 3 weekly serum galactomannan
  - Fluconazole given as prophylaxis
  - No empirical therapy
- Cases classified
  - Proven
  - Probable
    - » Probable w prespecified radiological findings (PSRF)
  - Possible cases excluded

What was Found?

- Patients w invasive aspergillosis
  - 5 proven (4%)
  - 73 probable (64%)
  - 37 probable w PSRF (32%)
- Infection site
  - Lungs only, 84
  - Lungs and sinuses, 23
  - Sinuses, 8

EORTC/MSG Criteria
Responses to Antifungal Therapy in Invasive Mold Disease

- **Complete response at 6 weeks**
  - Survival and resolution of all signs and symptoms
  - Resolution of radiological lesions
  - Documented clearance of infected sites that are accessible to repeated sampling
- **Partial response**
  - Survival and improvement of S&S
  - >25% reduction in radiology
  - Clearence of infected sites

Segal B, et al. Clin Infect Dis 2008;47:674

GMI-based Response

- **Success**
  - **Survival**
  - **Repeatedly negative serum GMI ≥2weeks after the 1st negative**
  - **Absence of new extrapulmonary lesions**
- **Failure**
  - **Persistently positive GMI**
  - **Death during 14 d period**

Outcome

- Normalization GMI in 91 patients (79%)
  - Median 8 days after 1st (+) GMI
  - 7 days after start of tx
- 79 patients survived at 6 weeks (69%)

Success after start of therapy n, (%)

Criteria	Week3	Week 4	Week 5	Week 6	After Week 6
EORTC/MSG	NA	NA	NA	73 (63)	73 (63)
GMI-based	44 (38)	65 (56)	72 (63)	76 (66)	83 (72)
Agreement, %	-	-	-	85	91

Discordant 10 Cases

- 9 died with uncontrollable cancer
- 1 classified as failure (stable disease EORTC/MSG)
  - Alive for 3 years w/o relapse of IA
- Agreement was 100% for those who failed

Summary

- GMI-based response criteria
  - Compare favorably to EORTC/MSG
  - Allow a much earlier assessment of response
    - » All failures w EORTC/IDG determined at a later time point

MAJOR ARTICLE

High-frequency Triazole Resistance Found In Nonculturable *Aspergillus fumigatus* from Lungs of Patients with Chronic Fungal Disease

David W. Denning,[1,2,3] Steven Park,[4] Cornelia Lass-Florl,[5] Marcin G. Fraczek,[2,3] Marie Kirwan,[1,2] Robin Gore,[2] Jaclyn Smith,[2] Ahmed Bueid,[2] Caroline B. Moore,[3] Paul Bowyer,[2] and David S. Perlin[2,4]

[1]National Aspergillosis Centre, [2]School of Translational Medicine, University of Manchester, Manchester, UK, [3]Mycology Reference Centre, Manchester Academic Health Science Centre, University Hospital of South Manchester, Manchester, UK, [4]Public Health Research Institute, New Jersey Medical School-UMDNJ, Newark, New Jersey, and [5]Department für Hygiene, Mikrobiologie und Sozalmedizin, Medizinische Universität Innsbruck, Innsbruck, Austria

- **Patients are affected or at risk of diseases with *Aspergillus* spp.**
  - **Invasive PA in immunocompromised**
  - **3 million with chronic pulmonary aspergillosis**
  - **3 million with ABPA**
  - **10 million with severe astma w fungal sensitization**
- **Daily 100s of conidia exposure**

Clin Infect Dis 2011;52:1123

Resistance to Azoles

- Described worldwide
- Several mutations to CYP51A gene, most frequent culprit
  - Encodes azole target protein, lanosterol 14-∝demethylase
- Extensive use of azoles in agriculture
- Emergence of resistance during treatment

What was Done?

- Fungal load was detected with RT-PCT
  - In sputum from ABPA and CPA patients
  - In BAL from normal volunteers and IPA patients
- In a subset of PCR (+), culture (-) samples
  - CYP51A gene was amplified to detect single point mutations

What was Found?

- 11 healthy volunteers
  - All culture negative
  - 4 (36,3%) had detectable DNA
- 22 culture and microscopy confirmed IPA patients
  - 21 (95%) had DNA
- 42 patients with CPA
  - 7 (16.7%) culture-positive
  - 30 (71.4%) had DNA
- 19 patients with ABPA
  - All culture negative
  - 15 (78.9%) had DNA

Direct Detection of Azole Resistance

- 29 sputum samples
  - 25 from ABPA and CPA patients (PCR+, Cul-)
  - 4 from ABPA (PCR+, Cul+)
- 4 samples had M220 mutations
  - 2 with upstream 34 bp TR and L98H
- 27 (93%) had L98H mutation
  - 16 also had TR
    - » Combination provides R to itra and vori
- Overall azole resistance documented in
  - 16/19 (55%) sputum samples
  - 2/4 (50%) isolates

Table 2.
Interrelationship Between Azole Therapy, Sampling Time, and Frequency of Azole Resistance Marker Detected

Azole treatment experience	Number of patients with azole resistance marker/total tested (%)				
	Sample collected on azole therapy				Totals
	Itra	Vori	Posa	None	
Azole naive	–	–	–	2/3 (67)	2/3 (67)
Itra only	2/5 (40)[a]	–	–	2/2 (100)[a]	4/7 (57)
Posa only	–	–	1/4 (25)[a]	0/1 (0)	1/4 (25)
Itra + vori	1/1 (100)	2/4 (50)	-	2/2 (100)	5/7 (71)
Itra + Posa	–	–	1/2 (50)	–	1/3 (33)
Itra + vori + posa	–	–	3/5 (60)[a]	–	3/5 (40)
Totals	3/6 (50)	2/4 (50)	5/11 (45)	6/8 (75)	16/29 (55)

NOTE. Itra indicates itraconazole; vori, voriconazole; posa, posaconazole.

[a] M220 mutation (n = 4).

Resistance and Therapeutic Outcome

- 2/3 patients with no prior azole exposure
  - L98H and TR detected
  - Both culture negative
  - One treated w itra and died
  - The other w posa and survived
- All w M220 failed to tx
- 14 with L98H and TR only
  - 3 unevaluable
  - 6 failed to itra or vori
  - 5 stabilized/improved on posa, itra or vori

Summary

- Detection of azole resistance in clinical samples with PCR
  - Identifies a high rate of resistance
    - » w/o prior exposure to azoles
    - » despite adequate plasma drug concentrations
  - May optimize treatment