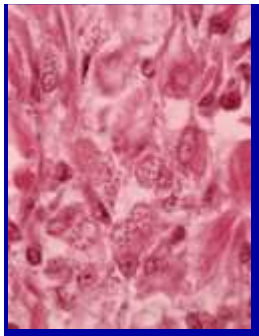

Fungal infections in the returning immunosuppressed traveler from the tropics: lessons from three cases

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Oslo May 21st, 2014

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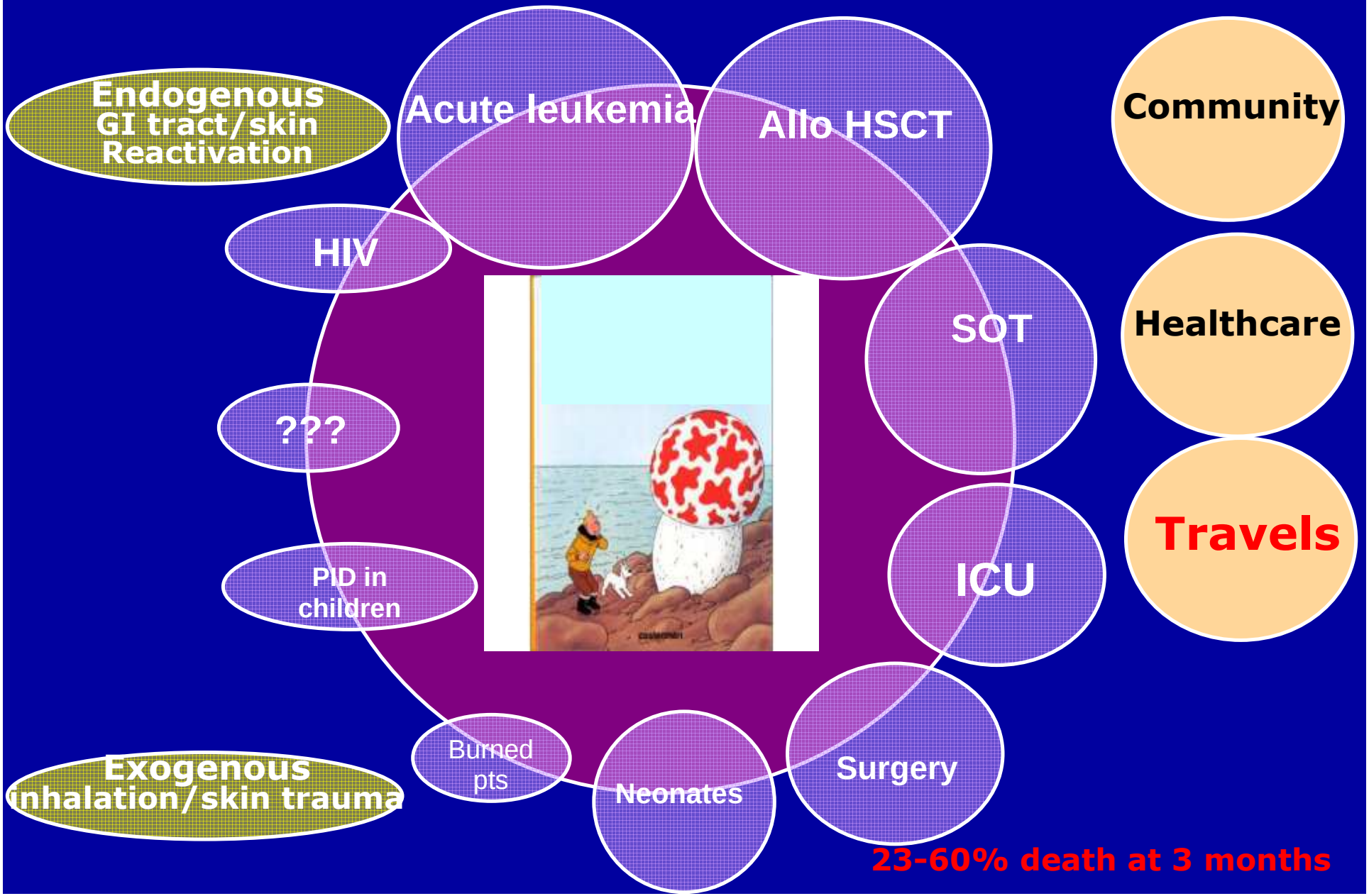
Institut Pasteur

Risk factors for IFI



Tropical mycoses : background (1)

- Not present in Europe (except histoplasmosis in Northern Italy) …

may change in the future!

- Found in tropical areas ; « exotic or endemic mycoses»

- Contamination may occur after inhalation
  - – Acute (primary) infection = pulmonary
- Contamination after inoculation (skin effraction / vegetal)
  - -Cutaneous/subcutaneous mycoses

Tropical mycoses : background (2)

- No interhuman transmission (except solid organ transplantation)
- Occurring in healthy travellers, expatriates, migrants
- Frequency and severity increased during cellular immune deficiencies (AIDS < 100 CD4/mm^3, SOT, anti-TNF-α,…)

Imported Mycoses in Europe

- Dimorphic fungi +++
  - *Histoplasma capsulatum* var. *capsulatum/duboisii*
  - *Coccidioides immitis/posadasii; Blastomyces dermatitidis*
  - *Penicillium marneffei/Paracoccidioides brasiliensis*
  - *Sporothrix schenckii*
- Cryptococcosis : *C. gattii* (serotypes B/C)
- Phaeohyphomycoses (*C. bantiana*, *Rhinocladiella*)
- Entomophthoromycoses
  - Conidiobolosis
  - Basidiobolosis
- Chromomycosis
- Fungal mycetoma
- Rhinosporidiosis
- Lobo’s disease
- Anthropophilic dermatophytes

South-East Asian HIV-infected patient(s) in Paris

What is your diagnosis ?

Infection due to…

- 1. *Cryptococcus neoformans*
- 2. *Aspergillus fumigatus*
- 3. *Histoplasma capsulatum var. capsulatum*
- 4. *Sporothrix schenckii*
- 5. *Penicillium marneffei*

Infection due to…

- 1. *Cryptococcus neoformans*
- 2. *Aspergillus fumigatus*
- 3. *Histoplasma capsulatum var. capsulatum*
- 4. *Sporothrix schenckii*
- 5. *Penicillium marneffei*

Infection due to *P. marneffei*…

- 1. becomes prevalent in South China & India
- 2. is limited to the skin
- 3. is correlated with the presence of birds
- 4. may be associated with positive galactomannan test
- 5. can be treated by fluconazole or an echinocandin

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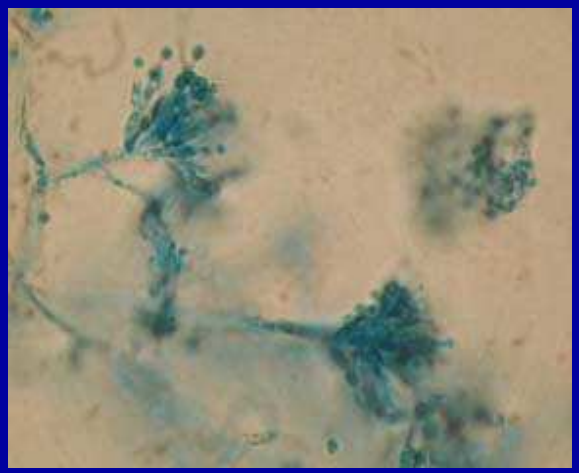
Infection due to *Penicillium marneffei*

- Southeast Asia, South China and Northeast and South India
- Bamboo rats (Rhizomys/Cannomys)
- Several imported cases in Europe (France, Italy and Greece)
  - Late stage AIDS
  - Skin lesions (71%)
  - Anemia (78%)/pancytopenia
  - Culture + :
    blood 76%, skin 90%, bone marrow 100%
  - Aspergillus galactomannan +



Supparatpinyo et al Lancet 1994, Michael Mycoses 2005; Filiotou Am J Med Sci & Antinori JTM & Clyti Presse Med 2006

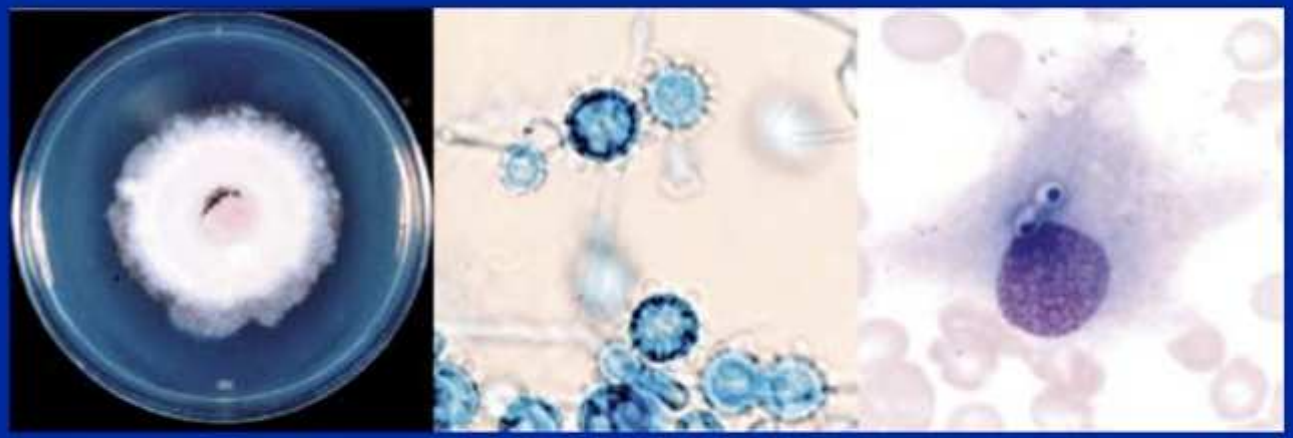
Infection due to *Penicillium marneffei:* recent data in AIDS

- 27% increase during rainy months [Le CID 2011]
- Identical genotypes between humans and rats [Cao, EID 2011]
- 11.5% of mucocutaneous lesions in Chinese HIV+ pts (Guangxi) [Han, J Eur Acad Dermatol Venereol 2012]
    - Influence of HAART and CD4 cell count
- 16.5% of ALL positive BC in HCM city in 2005 [Nga TVT, Tr Roy Soc Trop Med 2012]
- Prognosis [Vietnam, 1996-2009, Le, CID 2011]
    - Injection drug use, shorter history, no fever/skin lesions, respiratory difficulty, higher lymphocyte and lower platelet counts
- Occurrence of IRIS [Sudjarituk, BMC Infect Dis 2012]

Therapeutic proposal for *Penicillium marneffei* infection

- 20% deaths. No randomized trial for 1st line therapy
- Susceptible to Ket, Itra, FC, AmB and newer azoles but less to FCZ [Supparatpinyo AAC 1993, Imwidthaya Mycopathologia 2001, Pfaller AAC 2002]
- More clinical failure with FCZ (64%) compared to Amb/Itra (≤ 25%) [Supparatpinyo AAC 1993]
- Induction phase : AmB B 2 wks then Itra 400 mg/d 10 wks : effective in 97% [Sirisanthana CID 1998]
- Maintenance phase : Itra 200 mg/d : no relapse vs 57% in placebo [Supparatpinyo, NEJM 1998]
- Primary prophylaxis : Itra 200 mg/d if CD4 count <100 cells/µL [Chariyalertsak, CID 2002]

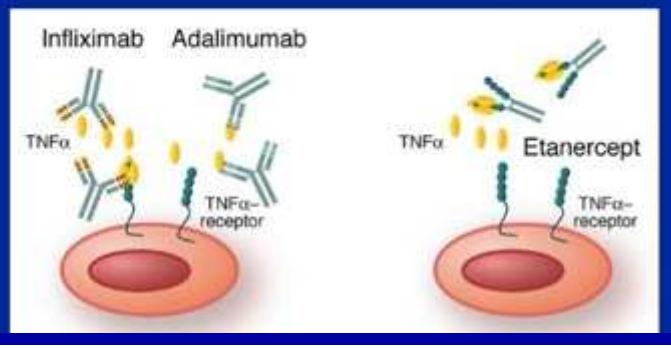
An anti-TNF-treated woman who traveled to South America



A 58-yrs-old female with rheumatoid arthritis receiving oral prednisone and adalimumab who traveled to Cuba (2002) and Brazil (2003):

- developped mitral endocarditis with leg arterial embolism in 2005
- mitral valve direct examination (small yeasts) and culture : ???

- Valvular prosthesis + amphotericin B
- Death (2.5 mo, valve thrombosis)



Infection due to…

- 1. *Trichosporon asahii*
- 2. *Candida kefyr*
- 3. *Histoplasma capsulatum* var. *capsulatum*
- 4. *Paracoccidioides brasiliensis*
- 5. *Coccidioides immitis*

Infection due to…

- 1. *Trichosporon asahii*
- 2. *Candida kefyr*
- 3. *Histoplasma capsulatum* var. *capsulatum*
- 4. *Paracoccidioides brasiliensis*
- 5. *Coccidioides immitis*

Infection due to *H. capsulatum* var. *capsulatum*

- 1. can be acquired during an hotel stay
- 2. acute infection is often asymptomatic
- 3. may reveal a latent immune deficiency
- 4. may be associated with positive galactomannan test in SOT patients
- 5. preferred Rx is L-Amb if disseminated

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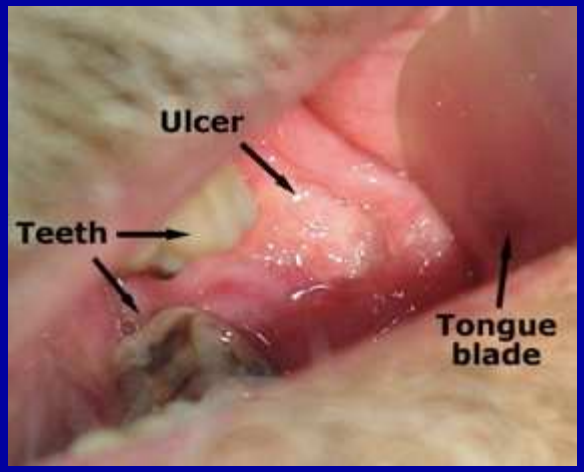
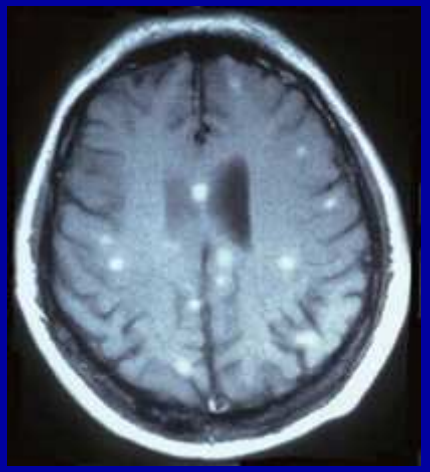
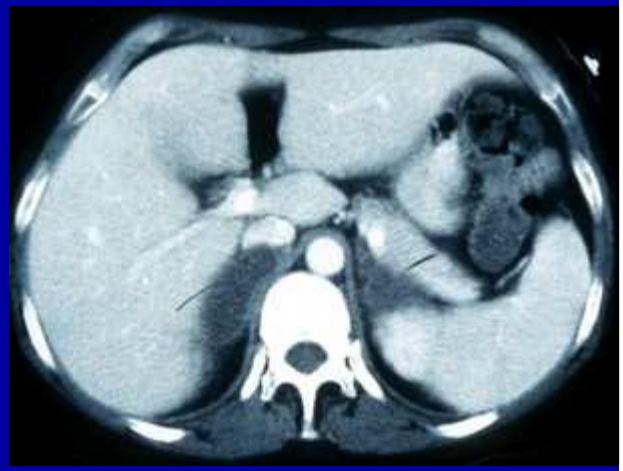
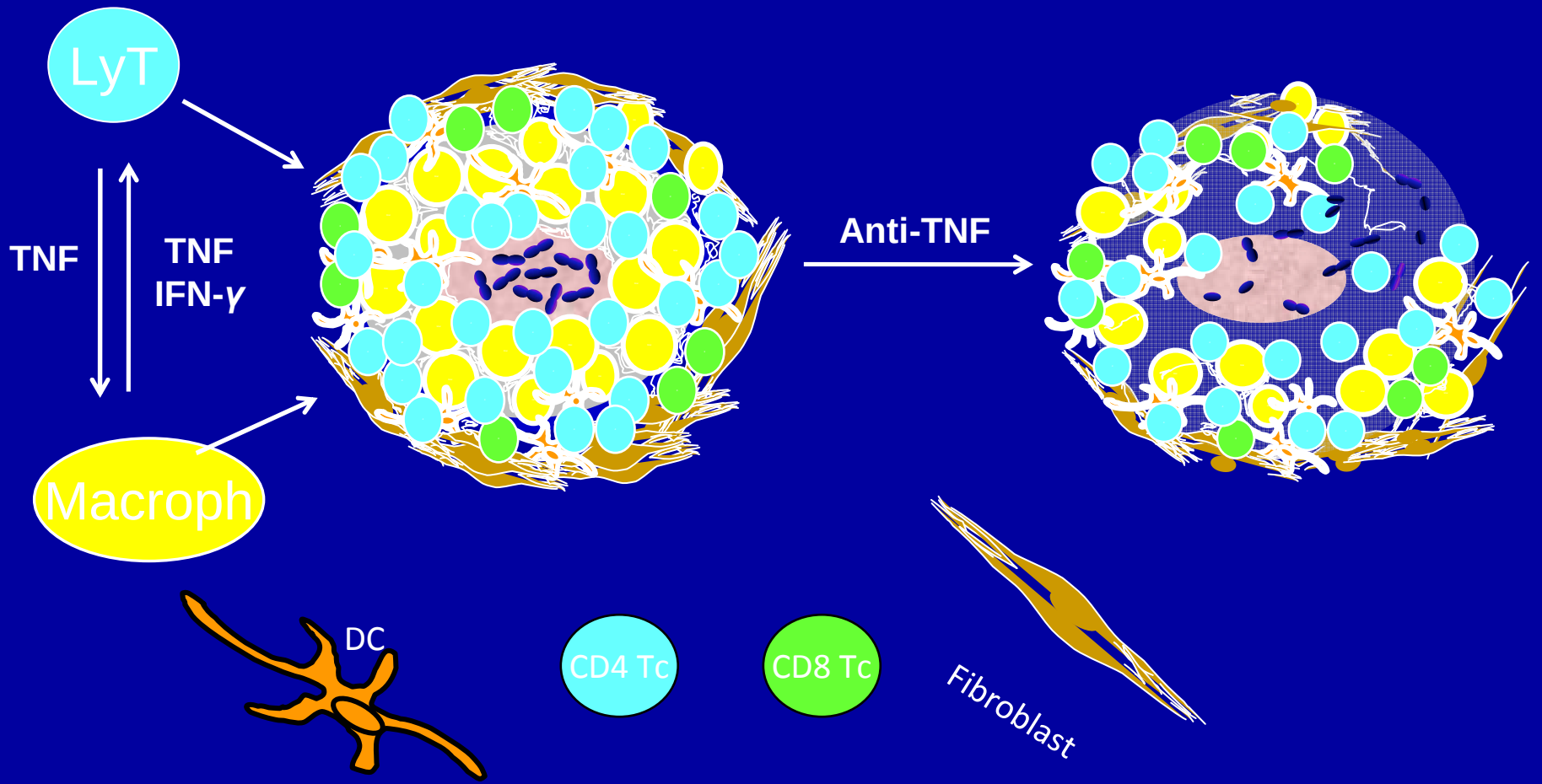
Histoplasmosis in anti-TNF-treated patients







Anti-TNF→ granuloma suppression



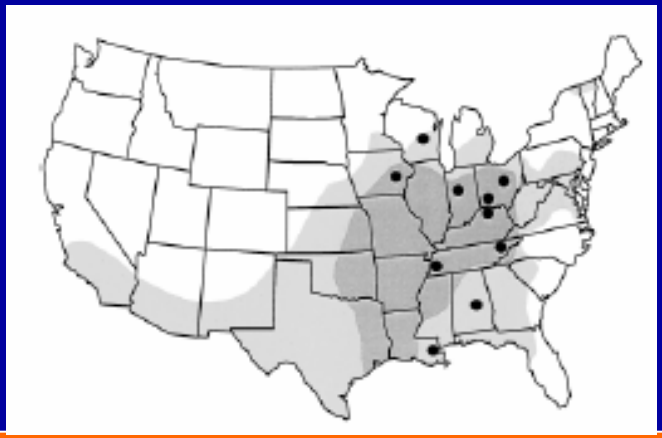
Anti TNF & *Histoplasma capsulatum*

10 cases; 9 infliximab

1 wk-6 mo after initiation

9 in ICU, 1 death

Lee, Arthritis Rheum 2002



Increased number of cases in USA (240 cases reported to FDA)

3 x more frequent than TB in anti-TNF-α living in endemic areas

Most frequent IFI; mortality = 20%

Infliximab (x7) > Etanercept

Pneumonia/dissemination (70-80%)

Hage et al. CID 2010

IRIS = 42% cases in Indianapolis

Screening not useful (Ag/Ab)

Anti-TNF may be restarted if ATF ≥ 1 year without relapse

How preventing histoplasmosis when starting an anti-TNF-α drug

Before starting TNF blocker, tell your doctor about

1. Possible exposure to *Histoplasma* via the following sites (activities):
   - Old buildings (demolition, remodeling, cleaning)
   - Chicken coops (demolition, cleaning, fertilizer)
   - Bird roosts (excavation, camping, cutting wood)
   - Wood piles (transporting or burning wood)
   - Caves (spelunking)
2. Recent travel to an area of endemicity[1]
3. Past diagnosis of histoplasmosis
4. Pneumonia in past 2 years
5. Any symptoms in past 3 months[2]

During TNF blocker therapy,

1. Avoid exposure to *Histoplasma*
2. Tell your doctor about possible exposure and recent travel[1]
3. Tell your doctor about any new symptoms
4. Don't put off contacting your doctor

Hage et al. CID 2010

Clinical Practice Guidelines for the Management of Patients with Histoplasmosis: 2007 Update by the Infectious Diseases Society of America

L. Joseph Wheat,[1] Alison G. Freifeld,[3] Martin B. Kleiman,[2] John W. Baddley,[4,5] David S. McKinsey,[6] James E. Loyd,[7] and Carol A. Kauffman[8]

Clinical Infectious Diseases 2007; 45:807–25

Indications of antifungal therapy during histoplasmosis

- Definite indication, proven or probable efficacy
  - Acute diffuse pulmonary infection, moderately severe symptoms, or severe symptoms
  - Chronic cavitary pulmonary infection
  - Progressive disseminated infection
  - CNS infection
- Uncertain indication, unknown efficacy
  - Acute focal pulmonary infection, asymptomatic case, or mild symptoms that persist for >1 month
  - Mediastinal lymphadenitis
  - Mediastinal granuloma
  - Inflammatory syndromes, treated with corticosteroids
- Not recommended, unknown efficacy or ineffective
  - Mediastinal fibrosis
  - Pulmonary nodule
  - Broncholithiasis
  - Presumed ocular histoplasmosis syndrome

Treatment of disseminated histoplasmosis in immunosuppressed pts

25. For moderately severe to severe disease, liposomal amphotericin B (3.0 mg/kg daily) is recommended for 1–2 weeks, followed by oral itraconazole (200 mg 3 times daily for 3 days and then 200 mg twice daily for a total of at least 12 months) (A-I).

26. Substitution of another lipid formulation at a dosage of 5.0 mg/kg daily may be preferred in some patients because of cost or tolerability (A-III).

27. The deoxycholate formulation of amphotericin B (0.7–1.0 mg/kg daily) is an alternative to a lipid formulation in patients who are at a low risk for nephrotoxicity (A-III).

28. For mild-to-moderate disease, itraconazole (200 mg 3 times daily for 3 days and then twice daily for at least 12 months) is recommended (A-II).

29. Lifelong suppressive therapy with itraconazole (200 mg daily) may be required in immunosuppressed patients if immunosuppression cannot be reversed (A-II) and in patients

The donor might have traveled into an endemic area... [Martin-Davila Clin Microbiol Rev 2008]

- 50 yrs-old man, underwent a single-LTx for severe idiopathic fibrosis
- Acute rejection episodes treated with steroids
- Itraconazole administered for > 12 mo for suspected IA
- Uneventful until month 35 post-transplant where a graft dysfunction occurred : culture of bronchial aspirate grew : ***???***

- Acquisition of *C. immitis* attributed to a transmission from the donor graft :
  - (1) recipient never traveled outside France/donor travelled to Arizona
  - (2) his anti-*C. immitis* antibodies were positive at the time of death
  - (3) recipient anti-*C. immitis* antibodies negative pre-transplantation
  - (4) X administrations of itraconazole may explain delayed diagnosis

Infection due to *C. immitis*

- 1. may be acquired in Oslo
- 2. may be acquired in Arizona
- 3. is a major public health issue in the USA
- 4. is associated with dissemination in black people and pregnant women
- 5. acute infection is often symptomatic

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Infection due to *C. immitis*

- 1. can be reactivated with T Ly targeting biotherapies
- 2. its culture should be manipulated in P3 facility
- 3. is contagious from humans to humans
- 4. is susceptible to various triazoles
- 5. should be treated lifelong if CNS disease

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Posttransplantation coccidioidomycosis acquired from donor allograft

Type of Tx (ref)	Time of disease Presentation post-Tx	Serologic results	Diagnosis	Involved organs	Antifungal treatment	Outcome, Follow-up
Liver Tx (3)	Day 13	Donor positive (pre-Tx)	BAL and blood cultures Autopsies of recipient and donor	disseminated	FCZ, AmB	Died (day 17)
Kidney Tx (3)*	Day 17	Donor positive (pre-Tx)	BAL and blood cultures Autopsies of recipient and donor	disseminated	FCZ	Died (day 19)
Lung Tx (4)	Day 6	Recipient negative (pre-Tx)	Bronchial washings Autopsy of donor	lung	FCZ	Alive, (12 months) Lifelong FCZ therapy
Lung Tx (5)	Day 21	NA	Autopsy of recipient	disseminated	none	Died (1 month)

Brugière, Transplantation 2009

Therapeutic recommendation during SOT-associated coccidioidomycosis

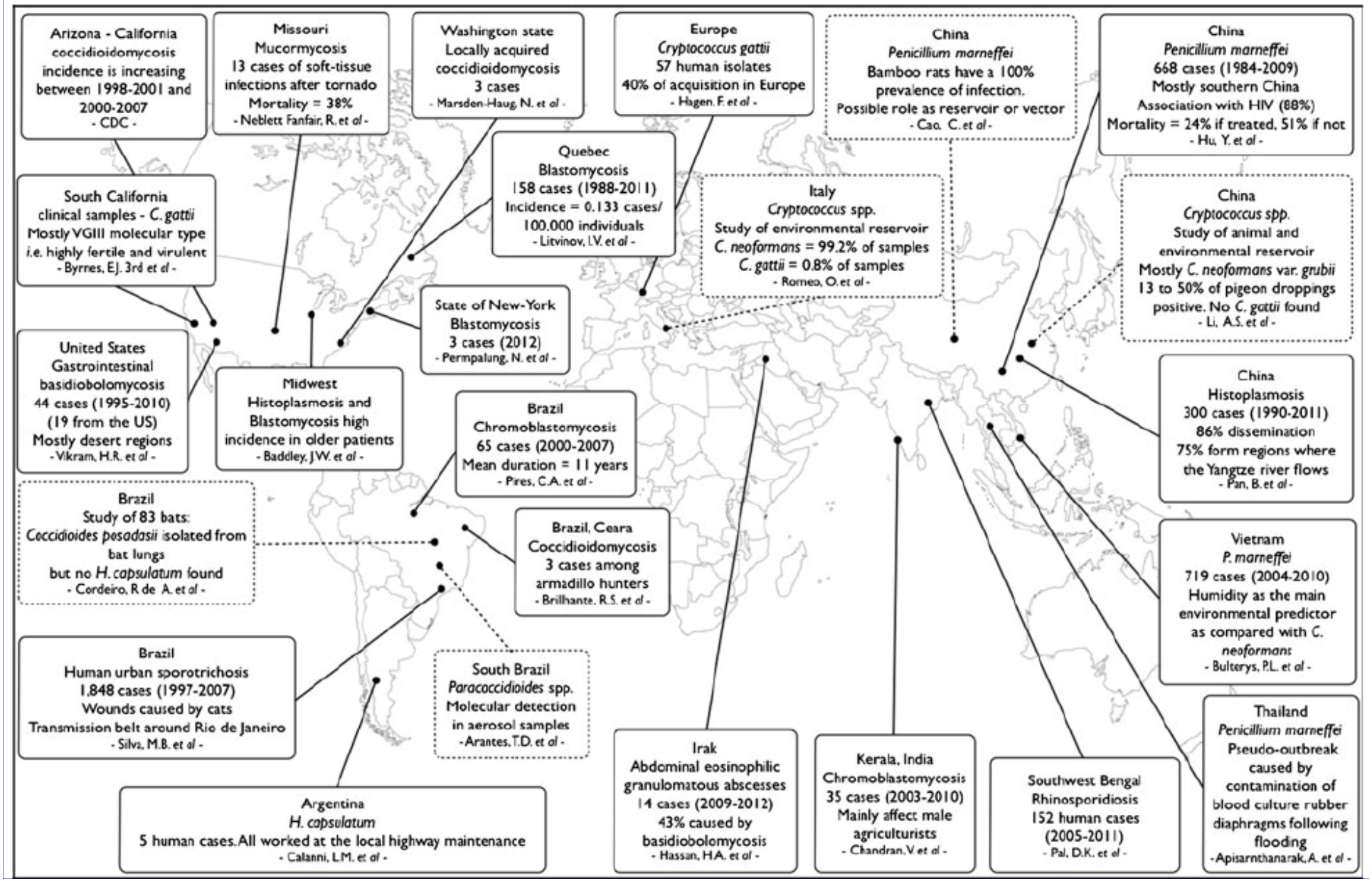
Guidelines of the American Society of Transplantation, Infectious Diseases Community of Practice [Singh, AJT 2012]

Medication	Indication	Dose	Duration
Lipid formulations of amphotericin B	Life-threatening or rapidly progressing infection	5 mg/kg/d	Until the rapid progression of infection is controlled, then transition to an azole alone
Fluconazole	Most non-life-threatening infections	400 – 800 mg/d	Full treatment dose until clinically resolved, then lifelong secondary prophylaxis 200-400 mg
Fluconazole	Meningitis (FCZ preferred)	400 – 800 mg/d (or higher)	Lifelong
Itraconazole	Most non-life-threatening infections	200 mg BID - TID	Indefinite duration; full treatment dose until completely resolved, then change to the lower dose or fluconazole as secondary lifelong prophylaxis
Itraconazole	Skeletal infections (Itra preferred)	200 mg BID – TID	Indefinite duration; full treatment dose until infection resolved, then continued secondary prophylaxis.

IFI/immunosuppressed patients returning from the tropics

- Travel medicine:
  - Quickly moving = regular updating
  - Online information systems
- Fungal infections associated with travel
  - Rare ± severe = early recognition
  - Recently recognized endemic areas
  - Natural disasters included in the medical history

Travel-associated fungal infections: 2012-2013! Richaud et al. 2013



IFI/immunosuppressed patients returning from the tropics

Lortholary, CID 2013.

Before travel:

- Specific medical visit before travel
- Parameters of immunodeficiency (CD4 cell count (HIV+ pts) /graft function / immunosuppressive drugs, dosage and duration)
- Some IFI may reactivate years after the return

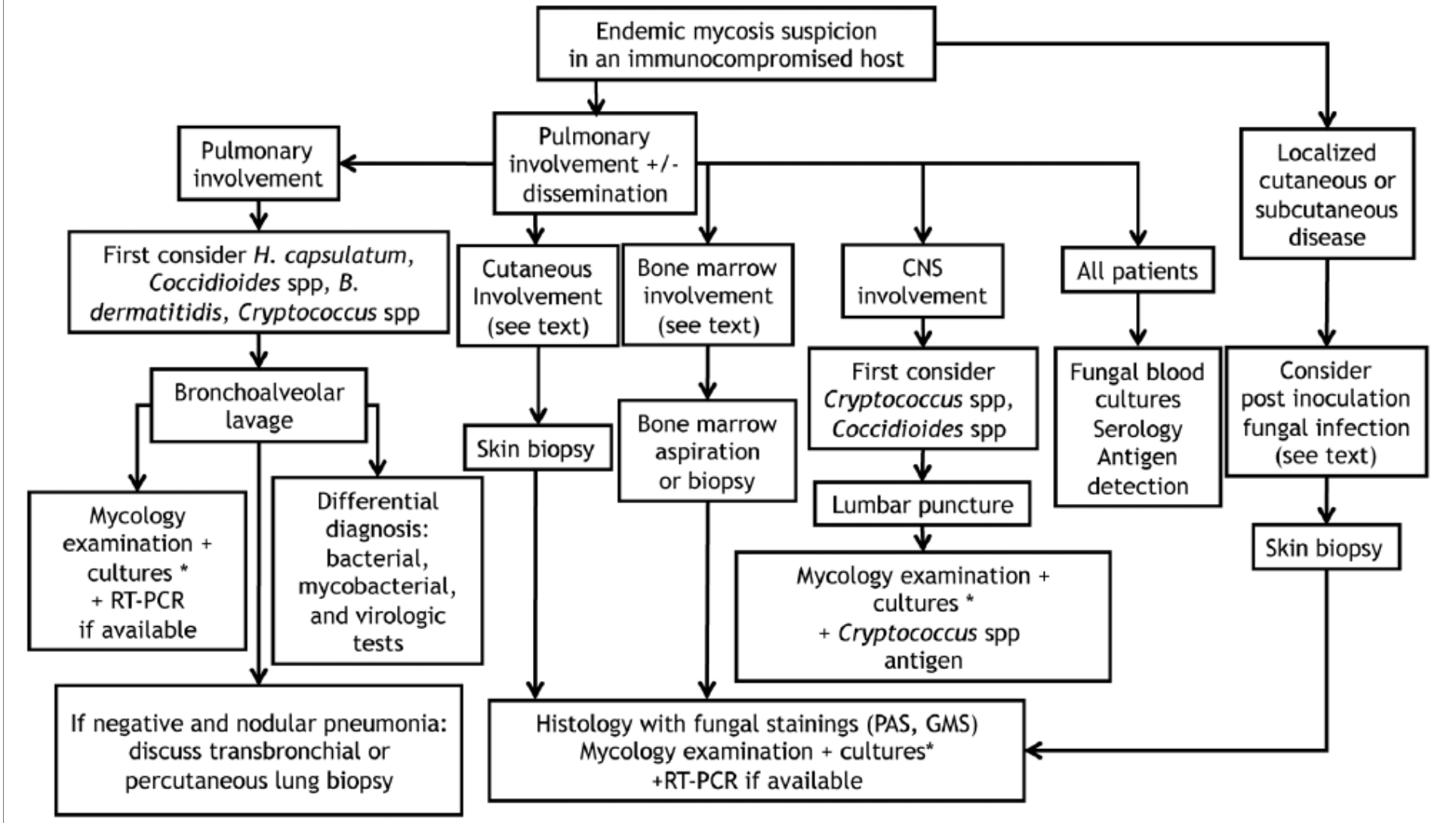
After travel:

- Which precise geographical area ?
- Particular epidemiological event (earthquake, windy conditions, construction work, cave, trauma with vegetal) ?

IFI/immunosuppressed patients returning from the tropics

- Pulmonary manifestations should suggest dimorphic fungi
- Papules should suggest IFI: cryptococcosis, but also histoplasmosis/penicilliosis

- Advanced age and diabetes mellitus should be considered as extra risk factors for IFI acquired in endemic areas



Lortholary, CID 2013.

IFI/immunosuppressed patients returning from the tropics

Lortholary, CID 2013

- In SOT, the donor may have traveled or lived in an endemic area [2012 AST guidelines]
- Endemic areas are moving (*P. marneffei* and *R. mackenziei* in India/Afghanistan)... and even Europe!
- Suspicion of IFI in an immunosuppressed traveler often requires a reference mycology laboratory (P3)

Further readings…?

INVITED ARTICLE IMMUNOCOMPROMISED HOSTS

David R. Snydman, Section Editor

Fungal Infections in Immunocompromised Travelers

Olivier Lortholary,[1,2,3] Caroline Charlier,[1] David Lebeaux,[1] Marc Lecuit,[1,4,5] and Paul Henri Consigny[6]

Clinical Infectious Diseases 2013;56(6):861–9

Fungal Infections Associated with Travel

Clémence Richaud, David Lebeaux & Olivier Lortholary

Current Fungal Infection Reports

ISSN 1936-3761

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TAKK !