1

NO CONFLICTS OF INTEREST TO DECLARE

2

AGENDA

- EPIDEMIOLOGY
- THE AGENT
- CLINICAL SYNDROMES
- DIAGNOSIS
- TREATMENT

3

EPIDEMIOLOGY

Restrepo A. Sem Resp Crit Care Med 2008;29:182-97.

- Endemic systemic mycosis, no outbreaks reported
- Geographically restricted to Latin America: Mexico, Central America, Colombia, Ecuador, Venezuela, **Brazil (80% of cases in LA)**, Peru, Argentina, Bolivia
- Significant rainfall (2000-3000mm), humid forest, watercourses, limited temperature variation (17-24C), 1000-1500m above sea level, coffee/tobacco crops
- The fungus has been rarely isolated from nature; possible animal reservoirs identified recently (nine-banded armadillo and dogs)
- Exposure of humans to fungus habitat

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EPIDEMIOLOGY

- Incidence rates in Brazil: 1-3 per 100,000, mortality rates 0.14 per 100,000 (not a reportable disease; 10M infected in LA)
- Transmission: respiratory route, primary lesion in the lung, exceptionally through direct skin contact
- Rare in children and below 30yo, most cases occur in males between 30-50yo (70%)
- Male/female ratio 14/1 (10/1 to 70/1)
- No race predominance
- Farmers: coffee/tobacco crops

Sem Resp Crit Care Med 2008;29:182-97.

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Environment
Coffee and sugar cane plantation / rural workers
Agriculture activities / Climate conditions (soil humidity)
Inhalatic
P. brasiliensis
P. lutzii
Yeast phase (body temperature)
Armadillo (Pb) (Pl?) immunotolerant / signalling
Hosts
Human beings predominance of infection predisposing factors for disease genetic gender (male) great inoculum
Animals – infection; rare cases of disease
Mendes & Bagagli

Rev Soc Bras Med Trop 2017;50:715

FIGURE 2 - Spread of *Paracoccidioides brasiliensis* and *Paracoccidioides lutzii*. Pb: *Paracoccidioides brasiliensis*; Pl: *Paracoccidioides lutzii*.

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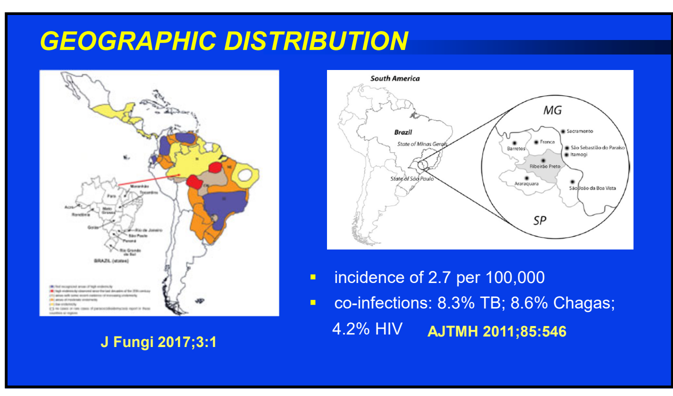
GEOGRAPHIC DISTRIBUTION



- incidence of 2.7 per 100,000
- co-infections: 8.3% TB; 8.6% Chagas; 4.2% HIV

J Fungi 2017;3:1

AJTMH 2011;85:546

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REPORTS FROM THE DEVELOPED WORLD

- Not reported from travelers yet; opposite to histoplasmosis
- Several cases have been reported from immigrants: Europe
  - Spain (25 cases; 1997-2014), Austria, Germany
  - Immigrants from Latin America: Brazil, Colombia, Ecuador
  - All patients were males; one-third had evidence of immunosuppression
  - Long latency period (10-50 years)
  - Classical clinical presentation of chronic multi-focal disease
  - Wrong initial diagnosis (mostly TB) and delay in initiation of treatment

Buitrago MJ. J Travel Med 2010;18:1195

Molina-Morant D. PNTD 2018;12(2):e0006425

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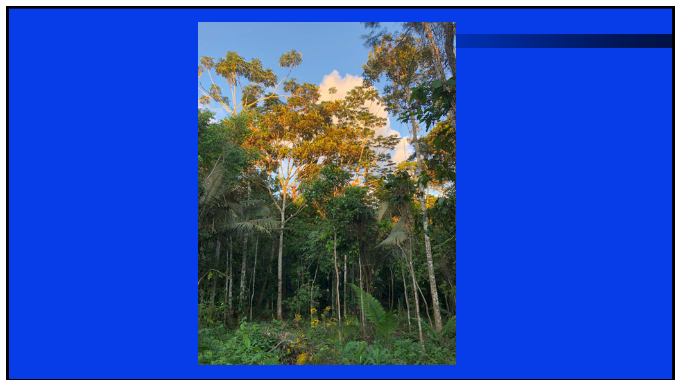

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THE AGENT

- *Paracoccidioides braziliensis* is a thermally dimorphic fungus
  - grows as a mould *(mycelial or infective form)* at temperatures < 28C
  - grows as a yeast in culture or host' s tissues at 36-37C
- Yeast colonies appear within a week in dextrose-agar medium at 28-37C
  - soft, wrinkle, and tan to cream
  - size: 4-35µm, mother cell surrounded by multiple buds of equal size resembling a pilot' s wheel
- Virulence factors not well known
- Female hormones inhibit the transformation to yeast

Shankar J. Clin Microbiol Revs 2011;24:296-313

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CLINICAL SYNDROMES

- Asymptomatic infection
- Progressive disease forms:
  - acute/sub acute or juvenile form (rapidly progressive)
  - chronic or adult type: unifocal or mutifocal
- Sequelae

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CLINICAL SYNDROMES

Infection by inhalation
(endemic areas)

Lung primary complex followed by resolution with or without quiescent foci

Lung primary complex followed by lympho-hematogenous dissemination; mononuclear-phagocytic involvement
(acute form disease)*

Persists asymptomatic
(healthy carrier)

Reactivation of quiescent foci in immunocompetent host; oral/respiratory tract involvement
(chronic form disease)

Reactivation of quiescent foci in immunocompromised host; disseminated disease (with or without oral/respiratory tract involvement)
(mixed form disease)

Bernard G, Duarte AJ. Clin Infect Dis 2000;31:1032-9.

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PATHOGENESIS

- Host' s immune response determines the outcome of the infection
- Patients with the acute/sub acute form show:
  - polyclonal activation (IgA, IgG); non-protective (high titers correlates with disease severity)
  - depressed cell mediated immunity; lack of T cell response to mitogens and antigens, negative skin tests, CD_4 depression
  - predominance of Th2 cytokine pattern (ILs 2,4,10, TNF- α), eosinophilia
- Patients with the chronic form show:
  - mild or absent immunoglobulin activation
  - normal or minimally depressed cell mediated immunity

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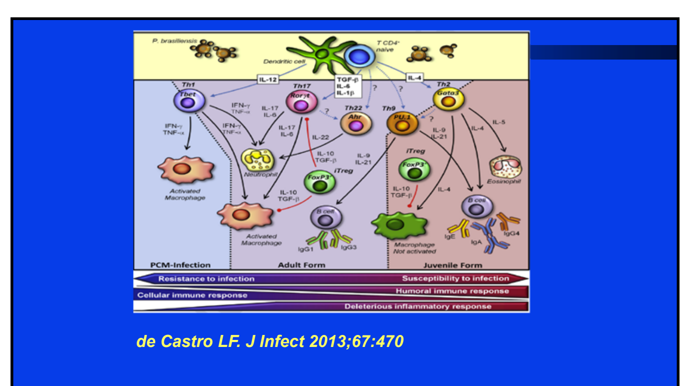

de Castro LF. J Infect 2013;67:470

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COMPARISON OF MAIN CLINICAL SYNDROMES
Paniago AM. Rev Soc Bras Med Trop 2003;36:455-9

	Acute (n=65)	Chronic (n=357)
Prevalence	15%	85%
Mean age, y (M/F)	22 (3/1)	47 (15/1)
Clinical course	rapid (weeks)	slow (years)
Skin test	negative	positive
Organ involvement, %		
fever	79	40
lungs	22	100
oral mucosa	22	66
liver-spleen	46	8
lymph nodes	95	48
skin	35	23

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REASONS FOR THE MARKED GENDER DIFFERENCE

- Not unique to PCM: amebic liver abscess, leishmaniasis, schistosomiasis
- Marked male predominance in clinical manifestations; similar rates of infection as measured by skin and serological tests
- In-vitro data suggest an inhibitory role for 17β-estradiol in transformation of mycelial forms-conidia to pathogenic yeast cells
- 17β-estradiol stimulates a protective Th1 response in females
- Role of smoke and alcohol in males

Bernin H. JID 2014;209(S3):S107 Shankar J. Clin Microb Revs 2011;24:296

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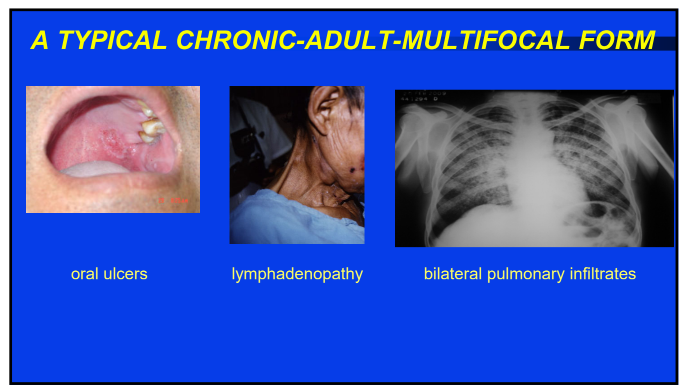
A TYPICAL CHRONIC-ADULT-MULTIFOCAL FORM



oral ulcers lymphadenopathy bilateral pulmonary infiltrates

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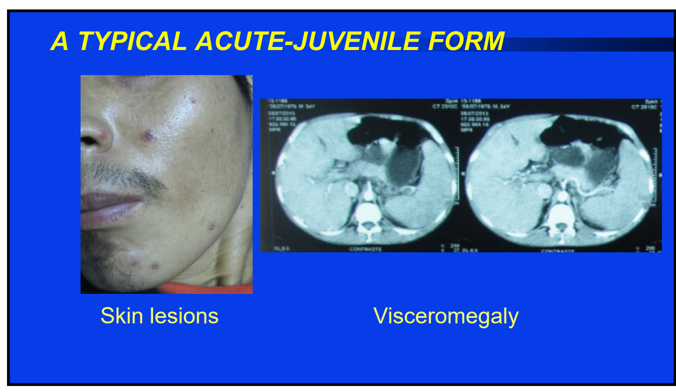
A TYPICAL ACUTE-JUVENILE FORM



Skin lesions Visceromegaly

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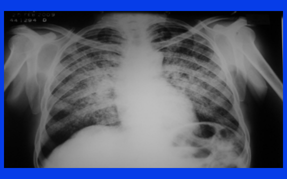
PULMONARY INVOLVEMENT

- 90% in autopsy series
- scarcity of symptoms and prominent radiographic abnormalities
- cough (57%), hemoptysis (11%), dyspnea (34-72%)
- bilateral infiltrates preferentially located in central and lower lobes; alveolar, interstitial, mixed patterns, fibrosis
- cavitary lesions and pleural effusion are less common



concomitant TB in 10% of patients

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PULMONARY INVOLVEMENT

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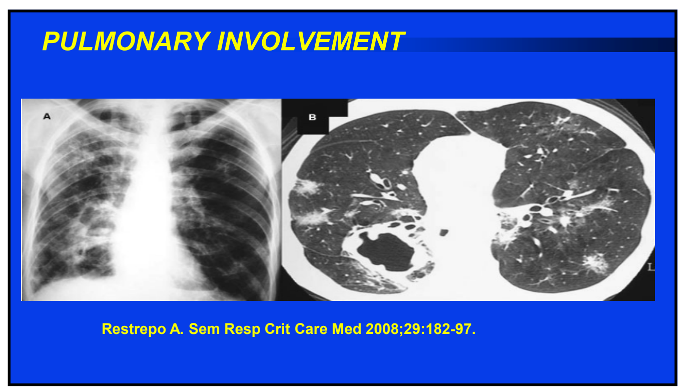

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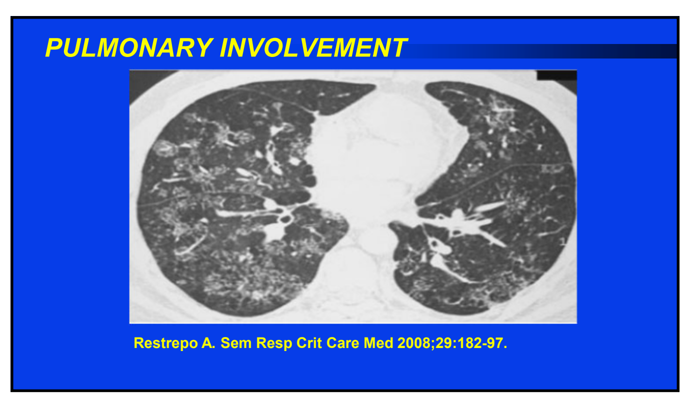

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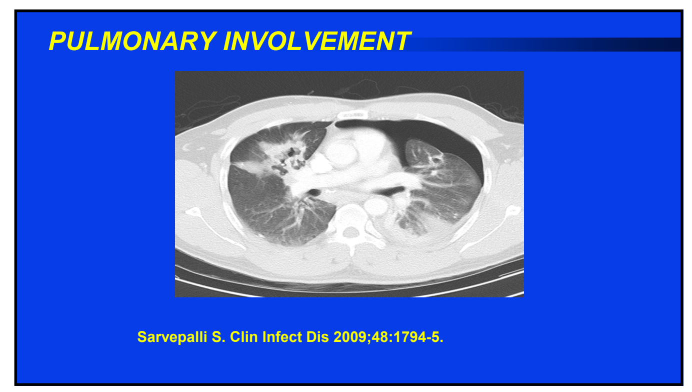

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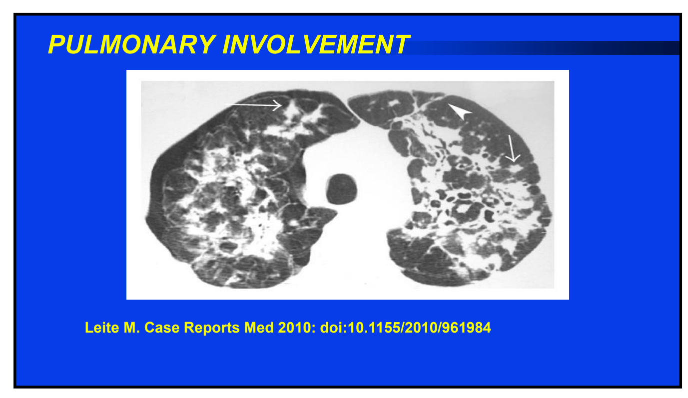

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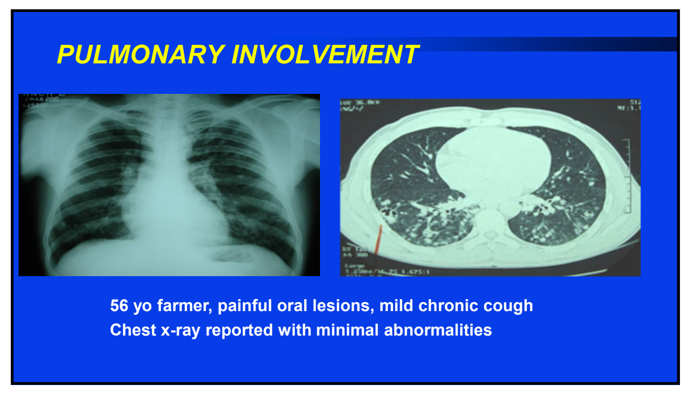

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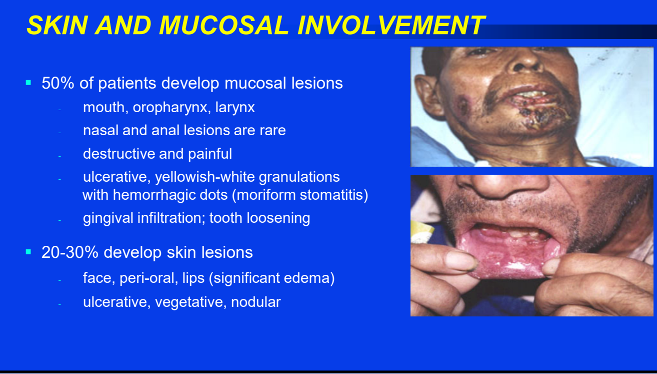

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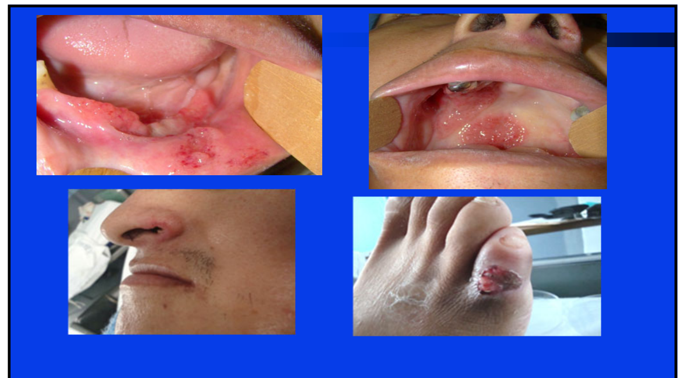

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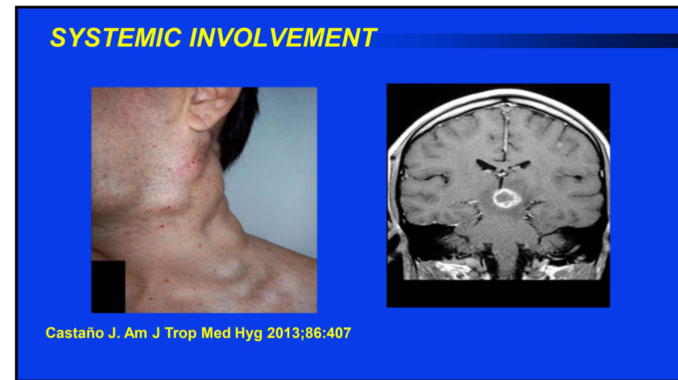

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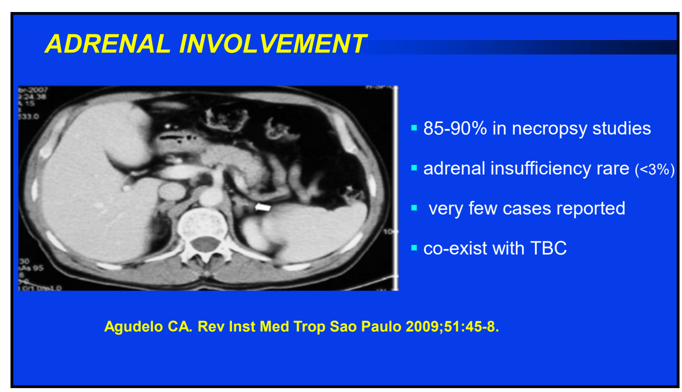

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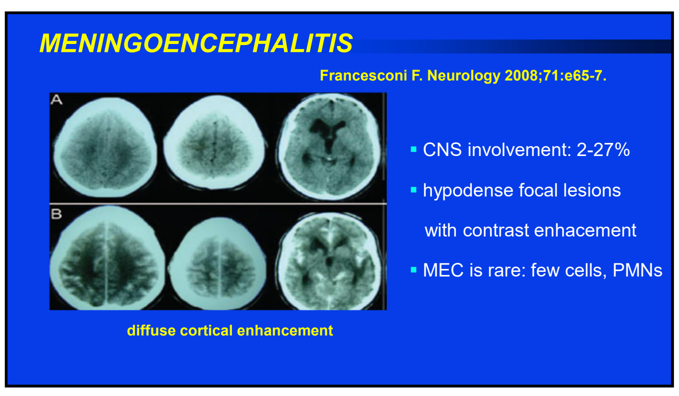

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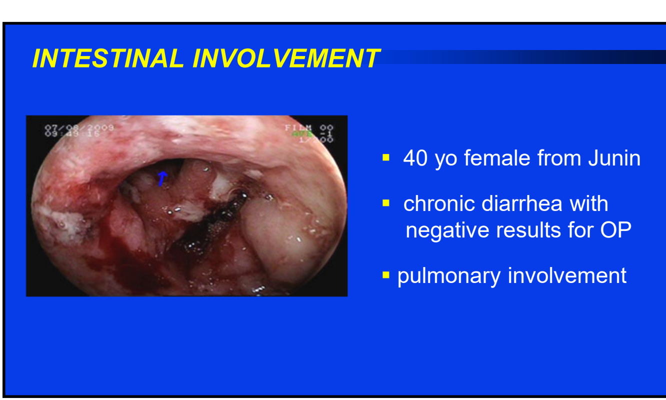

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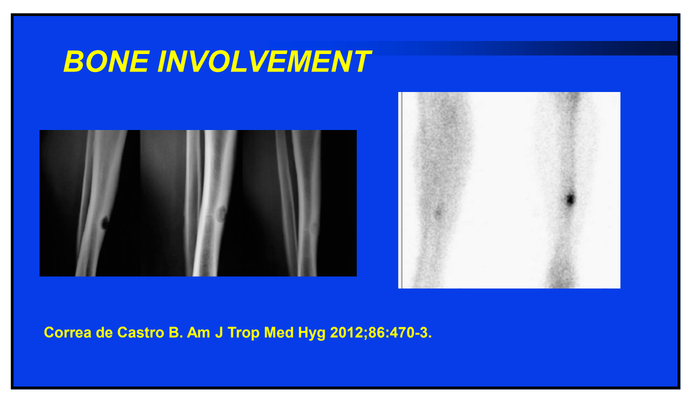

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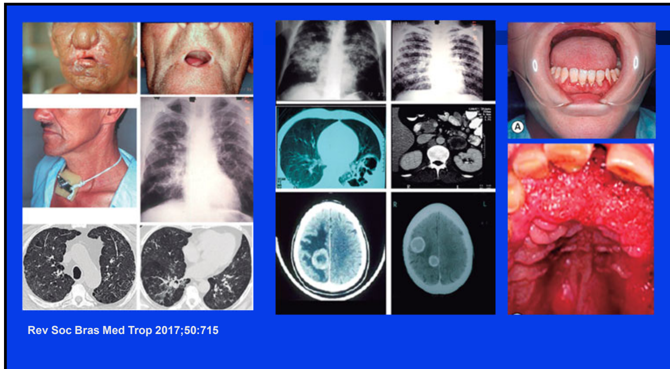

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PCM AND HIV-AIDS

Ramos-e-Silva M. Dermatol Clin 2008;26:257-69.

- Few cases reported, mainly from Brazil
- Disseminated presentation similar to the juvenile form
- Reactivation of a latent foci
- Severe immunosupression with CD4 < 200 cells/mm3
- Skin test usually negative
- High case-fatality rate: 25-30%
- Timing for starting ARVs is unknown

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DISSEMINATED PARACOCCIDIOIDOMYCOSIS AND HIV

Castro G. NEJM 2006;355:2677

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PARACOCCIDIOIDOMYCOSIS AND HIV

Catañao JC. AJTMH 2015;93:433

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PCM AND HTLV-I AT OUR INSTITUTE

- Association previously unreported
- Four cases with extensive involvement:
  - 66 yo male with extensive chronic multifocal presentation
  - 34 yo male with intestinal involvement and progressive disseminated histoplasmosis
  - 40 yo female with intestinal and pulmonary involvement
  - 79 yo female with extensive chronic multifocal presentation
- More studies are needed: prevalence and host immune response

León M. Clin Infect Dis 2010;51:250-1.

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THE EXPERIENCE AT OUR INSTITUTE

- 94 patients
- mean age 48.5y (9-80)
- M/F ratio 21/1, farmers
- chronic form 94%, acute form 6%
- 40% of patients from the rainforest of Junin
- organs involved:
  - oral lesions 74%
  - lung involvement 74%
  - lymph nodes 26%
  - skin 18%

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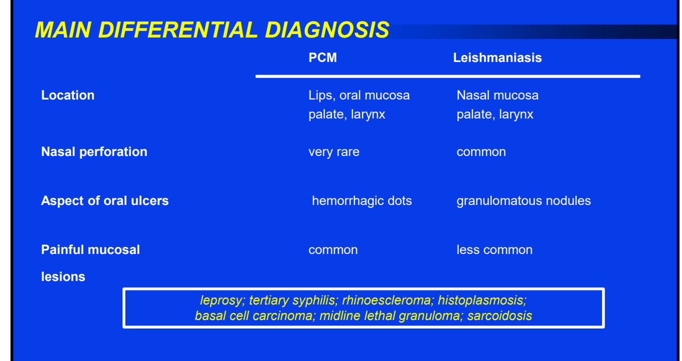

MAIN DIFFERENTIAL DIAGNOSIS

	PCM	Leishmaniasis
Location	Lips, oral mucosa palate, larynx	Nasal mucosa palate, larynx
Nasal perforation	very rare	common
Aspect of oral ulcers	hemorrhagic dots	granulomatous nodules
Painful mucosal lesions	common	less common

leprosy; tertiary syphilis; rhinoescleroma; histoplasmosis; basal cell carcinoma; midline lethal granuloma; sarcoidosis

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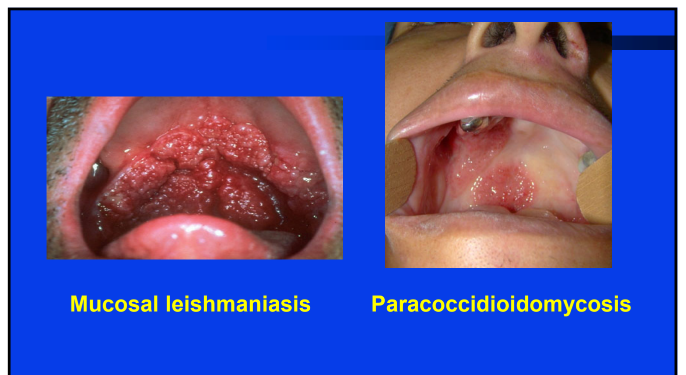

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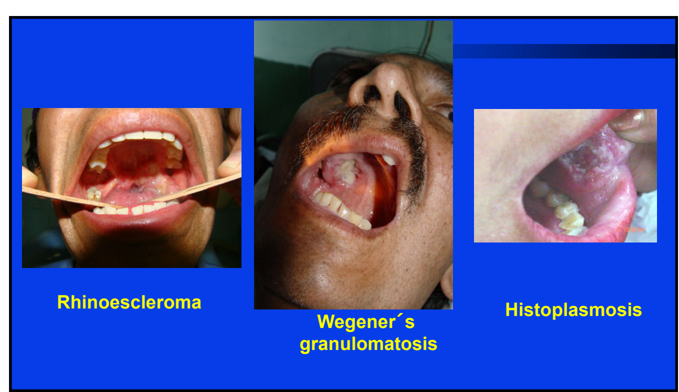

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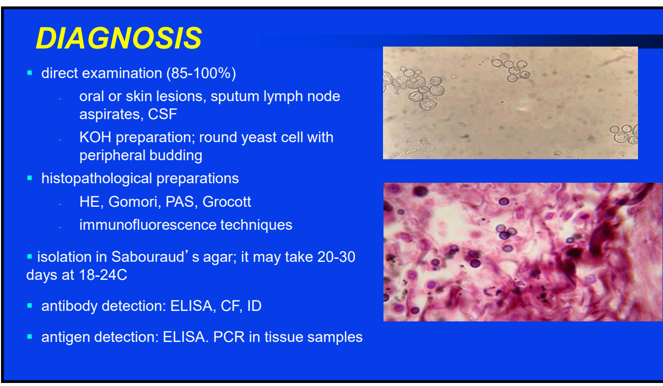

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DIAGNOSIS

Fig. 1 - Polygemulating yeast and wooden ship's wheel.

Andrade-Filho JS. Rev Inst Med Trop Sao Paulo 2012;54:330

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HISTOPATHOLOGY: CHRONIC FORM

- epitheliod granulomas
- caseation is rare
- plasma cells, multinucleated giant cells, lymphocytes
- typical yeast structures are identified with specif stains: PAS, Grocott
- microabscesses in oral and skin lesions
- fibrosis in chronic stages

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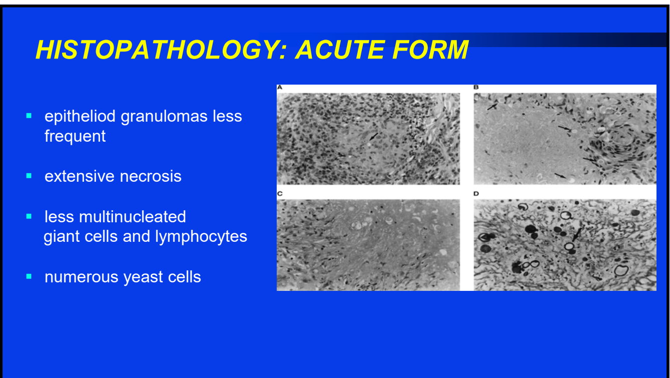
HISTOPATHOLOGY: ACUTE FORM

- epitheliod granulomas less frequent
- extensive necrosis
- less multinucleated giant cells and lymphocytes
- numerous yeast cells



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TREATMENT

- No large randomized-controlled clinical trials have been conducted
- Several drugs have in-vitro activity: TMP/SMX, amphotericin B, azoles (ketokonazole, itraconazole, fluconazole, posaconazole, isavuconazole)
- Prolonged treatment is advised: mean duration is 6 months (3-12 months)

	Cure rates	Relapse rates
TMP/SMX (160/800 mg bid)	80	20
Ketoconazole (400/200 mg/d)	90	10
Fluconazole (600 mg/d)	60	40
Itraconazole (200/100 mg/d)	**98**	**< 5**
Amphotericin B (1-2g)	70	30

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TRIMETHOPRIM-SULFAMETHOXAZOLE

- Versatile antimicrobial: bacteria, parasites, fungi
- First line therapy in Brazil for chronic non life-threatening disease in adults and children: cheap and affordable
- Loading dose of 160/800 mg tid for 30 days
- Maintenance dose: 160/800 mg bid *(4-6mg/kg, children)*
- Side effects:
  - Hypersensitivity reactions; renal toxicity
  - Liver toxicity: elevation of ALT
  - Hematologic toxicity; anemia, leucopenia, thrombocytopenia

Ramos-e-Silva M. Dermatol Clin 2008;26:257-69.

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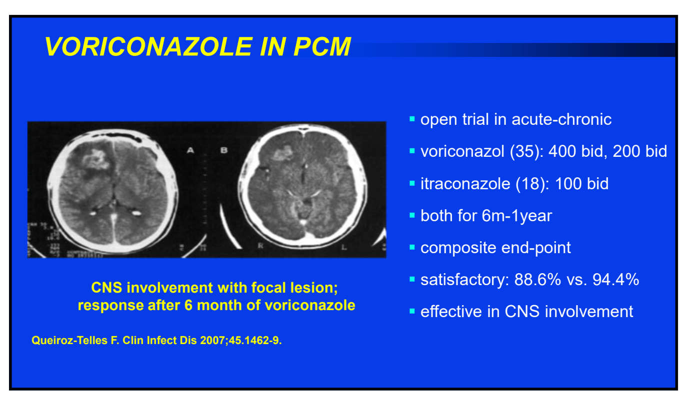
VORICONAZOLE IN PCM



CNS involvement with focal lesion; response after 6 month of voriconazole

- open trial in acute-chronic
- voriconazol (35): 400 bid, 200 bid
- itraconazole (18): 100 bid
- both for 6m-1year
- composite end-point
- satisfactory: 88.6% vs. 94.4%
- effective in CNS involvement

Queiroz-Telles F. Clin Infect Dis 2007;45.1462-9.

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OTHER TREATMENT CONSIDERATIONS

- Duration of treatment is unknown
- Composite criteria:
  - Clinical: resolution of signs and symptoms
  - Mycologic: elimination from clinical sites
  - Radiologic cure: dissapearance, fibrosis
  - Serologic: serum ID titers 1:2
- Chronic form: 2 years if serologic criteria is achieved
- Acute form: duration unknown; *1 year after ID negativization*

Rev Soc Bras Med Trop 2017;50:715

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A TRULY NEGLECTED MYCOSIS

NEGLECTED TROPICAL DISEASES	PARACOCCIDIOIDOMYCOSIS
Affect people in remote areas	**10M people infected in rural LA**
Are linked to poverty	**Affects mostly poor farmers**
Affect low income countries	**Remote areas of LA countries**
Disabling-disfiguring, mortality	**Extensive fibrosis (oral, lungs)**
Low priority in national health programmes	**Only 1 country with national guidelines**
Social stigma-discrimination	**Patients are stigmatized**

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SALIENT FEATURES

- Endemic mycosis, no outbreaks reported to date
- Geographically restricted to Latin America
- Mainly seen in males, farmers
- Pulmonary origin with further dissemination to oral mucosa, skin, reticulo-endothelial system, adrenal glands
- Long latency period, chronic course, acute presentation is rare
- Itraconazole is the drug of choice
- Significant sequelae after successful treatment

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