Opportunistic fungal infections and HIV infection - the current challenges in Africa

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- Fungal opportunistic infections associated with HIV in Africa and Zimbabwe

- Which infections are important

- Effectiveness and availability of fungal laboratory diagnosis and the challenges
How important are fungal infections?

The Fungal Infection Trust (UK based) successor to the Fungal Research Trust was established in 2012 and together with LIFE its “education and advocacy brainchild” is pushing for more attention for fungal infections. Estimated that 300 million people suffer and die from fungal infections every year.

In November 2013 the Global Action Fund for Fungal Infections (GAFFI) was launched with these goals:

1. Increase awareness of the impact of fungal disease
2. Universal access to diagnostics for fungal disease
3. Universal access to appropriate and affordable antifungal therapeutics with a focus on generic agents
4. Improve education of health professionals about fungal disease.

GAFFI Year 1 review Sept. 2014
From these initiatives a campaign has been launched to determine the fungal burden of disease around the world:

In Africa data from several African Countries has been published:

Kenya, Nigeria, Senegal, Tanzania, Uganda, Zambia

**Nigeria**  *R Oladele et al 23rd Congress ECMID 2013*

Estimates > 11.8% of the Nigerian population has a serious fungal infection each year.

**Senegal**  *A S Badiane D W Denning 23rd Congress ECMID 2013*

Estimates 17% of the population have a fungal infection

**Uganda**  *R. Parkes-Ratanshi et al 23rd Congress ECMID 2013*

Estimates 2 million fungal infections occur each year
The prevalence of opportunistic fungal infections has increased amongst those infected with HIV particularly in Africa.

**Zimbabwe (2013)**
- Estimated that 1.4 million people living with HIV
- 15% prevalence rate in adults (15-49)
- 77% of adults and 46% children had access to ARVs

**MOHCC Global AIDS Response Country Progress Report 2014**
Opportunistic infections associated with HIV infection

**Senegal** A S Badiane D W Denning 23rd Congress ECMID 2013

Of 5544 new AIDS cases each year:

- 2.9% have cryptococcal meningitis 160 cases/yr
- 22% Pneumocystis pneumonia 1220 cases/yr
- 53% have oral candidiasis
- 16% dermatophytosis

**Uganda** R. Parkes-Ratanshi et al 23rd Congress ECMID 2013

Cryptococcal disease 2773 cases/yr
Pneumocystis pneumonia 748 cases/yr
oral/vaginal candidiasis (pre-ART) 24290 cases/yr
   (on ART) 7157 cases/yr
Oesophageal candidiasis (pre-ART) 8407
   (on ART) 1475
Important opportunistic fungal infections associated with HIV in Africa

Oral, oesophageal and vaginal Candida infections
Cryptococcosis
Tinea
Pneumocystis Pneumonia (PCP)
Histoplasmosis

The presentation of other fungal infections e.g. sporotrichosis may change in the presence of HIV infection.
Candidiasis
In HIV infection

- Mucocutaneous candidiasis occurs 40-90% in the HIV infected patients and associated with progression to AIDS in both children and adults.

- Pseudomembranous oral candidiasis is the most common type of mucocutaneous candidiasis.

- Oesophageal candidiasis (OC) is the most frequent diagnosed mucosal invasive candidiasis.

- In HIV infection OC occurs in 7-27% in Africa and 9-31% in the West mainly in patients with a CD4+ <100 cells/μl.

- Possible that in Africa many cases of oesophageal candidiasis go undiagnosed and this might contribute the low reported prevalence in Africa.

Photos from hiv.va.gov/provider/image-library
Diagnosis of Candida infections is straightforward

Simple KOH preparations and Gram stains can be used to identify Candida in specimens.

Isolation in culture can be done on blood/Sabouraud dextrose agar (SDA).

Identification to species level remains a challenge.

Many labs in Zimbabwe still send out results as *C. albicans* or yeast not *C. albicans*. Additional tests such as Carbohydrate assimilation are not always available.
Does it matter?

- Zimbabwe participates in a “Free access” programme for Fluconazole with use restricted to the treatment of oropharyngeal candidiasis and cryptoccasis.
- Increasing resistance of Candida albicans to azoles and the reports of highly resistant species of *Candida glabrata* (*sometimes multi-drug resistant*) require monitoring for anti-fungal resistance of isolates (*M. Pfaller Amer.J.Med 2012*)

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<td><em>C. albicans (39)</em></td>
<td>72%</td>
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<td><em>C. dubliniensis (6)</em></td>
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<td><em>C. krusei (3)</em></td>
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<td><em>C. glabrata (7)</em></td>
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<td><em>C. tropicalis (1)</em></td>
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(unpubl. Data Sichewo 2007)
CRYPTOCOCCOSIS

Caused by two species of Cryptococcus
C. neoformans and C. gattii
CRYPTOCOCCOSIS

- Affects 1 million people world-wide annually
- Causes 530,000 deaths annually
- Sub-Saharan Africa is region with the highest number of estimated cases - 720,000 cases;
- AIDS defining illness in 25-30% in South-East Asia and 64-91% in Sub-Saharan Africa (Park et al; AIDS 2009, Vol 23 No 4)
- Responsible for 13-42% of all deaths amongst HIV positive people
- Mortality in Sub-Saharan Africa is estimated to be 70% compared with 55% in other low- and middle-income countries and 20% in high-income countries.

Remains one of the most challenging opportunistic infections to treat
Comparison of deaths in sub-Saharan Africa (2006) due to HIV-related Cryptococcosis and common infectious diseases excluding HIV, as estimated by World Health Organization.
Encapsulated yeasts of the *Cryptococcus* genus, *C. neoformans* and *C. gattii*

- Both have a teleomorphic phase *Filobasidiella neoformans* and *Filobasidiella bacillispora*

- *C. neoformans* has 2 varieties var. neoformans and var grubii, 3 serotypes A and D and AD and 4 molecular types

- *C. gattii* has two serotypes B and C and 2 molecular types

- *Cryptococcus neoformans* var grubii is implicated in 90% of CM cases

- *Cryptococcus gattii* prevalence varies:
  - South Africa 1-2%
  - Botswana 13.7% (161 isolates, Litvintseva et al 2005)
  - Zimbabwe 3% [Heyderman et al 1998]
  - Zimbabwe >10% [unpubl. Nyazika et al 2014].

**Cause of infection**
Does it make a difference?

- *C. gattii* more likely than *C. neoformans* to be involved in infections in immune competent individuals. Case series described in Canada, Australia and an infection recently described in Zimbabwe in an 18yr HIV negative old male patient (*Centr.Afr. J. Med 2014*)

- Australia study suggested differences in presentation between *C. gattii* and *C. neoformans* and immune-competent and immune-compromised. Lung Cryptococcomas associated with *C. gatti* in immune competent (*S Chen et al CID 31 1999*)

- In a South African study of 46 *C. gattii* (serotype Band C) infections there was no significant difference in the clinical presentation and mortality between the serotypes and *C.gattii* non-infected patients who presented with Cryptococcal meningitis (*J. Morgan et al CID 2006*)
Source of infection:

*C. neoformans*  bird, pigeon excreta associated with nests and old buildings, soil and decaying wood. In DRC (Zaire) identified in chicken and pigeon droppings, air dust and cockroaches from households of AIDS patients (*Swynne et al Ann.Soc.Med trop 1986*)

*C. gattii* found in association with several tree species first identified in Australia in association with *Eucalyptus camaldulensis*.

*C.gattii* identified as a significant pathogen on Vancouver island, Canada. Extensive environmental investigations demonstrated presence in/on tree surfaces, soil, air, freshwater, and seawater. There was no difference between the seasons but concentration of potential infectious propagules <3.3μm was higher in the warm dry months (*S.Kidd et al Appl.Env Microbiol 2007*)
AIDS associated cryptococcal infection

• May present with severe progressive pneumonia + acute dyspnoea

• Disseminated cutaneous lesions – pustular + papular, nodular, ulcerated lesions (10-15% patients)

• Meningitis is the most common presentation in Africa

Amerson EH, Maurer TA, *Topics in HIV Medicine* 18 1 2010
Underdiagnosis of pulmonary Cryptococcosis?

Zimbabwe  
CID 200518–27 S Munyati et al

Investigation of the aetiology chronic cough of 544 adults - 454 HIV positive

- Cryptococcosis diagnosed in 1.1% (5) but only one from a sputum specimen
- Three additional isolates from sputum from patients diagnosed with LRTI and 2 bacterial pneumonia (suggesting colonisation)

South Africa  

Autopsy of cardiorespiratory organs 8421 miners 1996-2000 (compensation for occupational lung disease)

7% (589) had cryptococcal pneumonia
(97 had concomitant respiratory disease 51.5% PCP and 42.3% mycobacterial)

In life only 2.7% had cryptococcal pneumonia but 46.9% had cryptococcal meningitis
Under-diagnosis of pulmonary Cryptococciosis?


132 of a group of 407 HIV patients with chronic cough > 2wks had bronchoscopy if AFB negative on sputum microscopy:

- 11% *C. neoformans* cultured (not suspected on initial investigation)
- 39% Pulmonary tuberculosis
- 23% bacterial pneumonia pulmonary
- 5%, Kaposi sarcoma
- 3% *Pneumocystis jirovecii* pneumonia

15 patients with *C. neoformans*:

- median CD4 count 23 cells/μl
- All initially treated with antibiotics
- 5 patients improved without antifungal suggesting colonisation
Challenges in laboratory diagnosis

Pulmonary infections

• Bronchoscopy improves diagnosis of pulmonary infection in a significant number of patients in the Ugandan study but not widely available in Africa

• What is the significance of colonisation in HIV +ve patients?

• Cryptococcal antigen testing has insufficient sensitivity in pulmonary cryptococcosis

• Use of selective media could increase isolation rate but not widely available but sensitivity unknown
To improve management of Cryptococcal meningitis

- Is it possible to introduce measurement Cryptococcal Colony counts from CSF in monitoring treatment – has proven value (antigen titres are an expensive alternative)

  - Resistance testing
    Both Amphotericin B and Fluconazole used in treatment.
    In South Africa evidence of increasing resistance of *C.neoformans* to fluconazole
    

  - Can we introduce the lateral flow assay for Crypt Ag for urine, serum and plasma

    Recommended by WHO
    Challenges in keeping the price low enough
    Recommended for use as a screening test for patients with a CD4 count < 100 to allow cryptococcal treatment prior to ARV therapy to prevent (IRIS)
HISTOPLASMOSIS
Clinical Features

1. Primary lung infection has been described in Southern Africa in a number of case reports – associated with caves and bat droppings
   Sub-acute/acute (cave’s disease)
   Flu-like illness usually self-limiting
   Acute pneumonia
2. Chronic cavities
3. Disseminated from lung RES Wt. Loss
   Fever
   Liver, spleen
   Ulcers mouth
   Skin lesions

Disseminated skin lesions in a patient with AIDS

A Visser South Afr J Epidemiol Infect 2011;26(4)(Part II) 285 - 287
Histoplasmosis

“Up to 50 million people are thought to have been infected with histoplasmosis, with ~500,000 new infections each year, most asymptomatic and based on skin testing. About 25,000 cases of symptomatic histoplasmosis are estimated in the USA annually. Histoplasmosis may be a life-threatening infection in newborns and AIDS patients, and is common in Central and South America.”


In Africa?

1. Case reports from different countries in Africa, South Africa, Zimbabwe, Botswana
2. 9/970 febrile patients (0.9%) in a series described in northern Tanzania diagnosed using a urine antigen test 6/9 clinically diagnosed as a tuberculous infection or a bacterial infection (S Lofgren et al R Soc Trop Med Hyg. 2012)
Histoplasmosis and AIDS

57 cases reported in patients attending a Central Referral Hospital in Harare, Zimbabwe 1994-2000

12 cases summarised
CDC stage 3 disease:

Pneumonia (50%)
Haematological abnormality (50%)
Oropharyngeal lesions (33%)
Diarrhoea (33%)
Hepatosplenomagaly (25%)

Cutaneous lesions 11/12- nodular/ papular rash
1/12-purulent+haemorrhagic vesicular lesions

T. Gumbo et al
Is this an under-diagnosed infection?

1. Can be diagnosed by Microscopy – stained smears, KOH preparations or histology from biopsy specimens

Detecting *H. capsulatum* by direct microscopy of sputum and bone marrow
Can be grown in culture - Yeast extract + ammonia

Macro and micro-conidia - 25°C

*H. capsulatum* mycelial phase
Comparison of sensitivities of different diagnostic tests for disseminated histoplasmosis in patients with AIDS

A 3rd generation antigen test (MVista test) can be used to measure presence of antigen in urine (95% - 100% sensitivity) and serum (92-100% sens) Higher sensitivity in AIDS patients than immunocompetent Can be only be used in MVista lab in Indianapolis. Other tests by Immy not as sensitive but in the process of improvement and CDC being developed


Conclusions

• ARVs should reduce the prevalence but access although improving is not universal

• Opportunistic fungal infections still remain a problem in HIV-infected individuals

• Improved skills and availability of fungal diagnostic tests would improve outcome in the management of opportunistic infections

• Anti-fungal susceptibility testing is important particularly for monitoring azole resistance
THANK YOU