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Opportunistic Infections

David Dockrell and David Chadwick on behalf of BHIVA OI writing group

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Review of OI Guidelines

- 11 topic sections (assigned authors)
  - Systems; GI, Resp, CNS, Ophthalmology
  - Pathogens; Candida, Herpesviruses, Atypical Mycobacteria
  - Syndromes and special settings: PUO, Pregnancy, travel, ITU

- 2011 version with updates
- Rewrite commenced 2017 section by section
- Completed Candida, Consultation phase GI, PUO, Pregnancy Respiratory all nearing consultation.
- Challenges Some new drugs and tests but limited new HIV OI specific data and few RCTs so much of data historical

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Process

- In line with GRADE system
- Writing Group agrees PICO questions
- Independent literature searches by an information scientist; Catherine Nieman Sims or Jacoby Patterson
- Rounds of searches with refinement
- Literature passed to writing group. Each search screened by one of writing group and results reviewed by second.
- Writing in sections with one of team assigned then review of each section and discussion of recommendations and GRADING in follow up TCs

Infectious diarrhoea

- Amongst HIV-infected MSM in the UK, which of the following pathogens is the commonest cause of diarrhoea?
  - *A Campylobacter spp.*
  - *B Shigella spp.*
  - *C Clostridioides difficile*
  - *D Cryptosporidium spp.*
  - *E Salmonella spp.*

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Infectious diarrhoea

- Meta-analysis post 2008 , 38 clinical trials incidence 18% (Asmuth et al.,Int AIDS Conf Amsterdam 2018)

- In some cohorts *C. difficile* now most common cause (Haines et al., AIDS 2013: 27; 2799)
    - Incidence 8.3 per 1000 in JHCC in US and has doubled

- Shigella incidence increased in HIV-positive MSM
    - Chlamydia positive MSM Shigella, Enteroaggregative *E. coli* and Campylobacter all commonly reported (Hughes et al., Sex Trans Infect 2018)

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Oropharyngeal candidiasis

- A 43 year old man has stopped ART due to longstanding mental health issues 12 months ago. His last CD4 T-cell count 6 months ago was 252 cells/μL. He presents with a sore painful mouth, which and he is struggling to eat but does not report any dysphagia. On inspection has extensive white plaques on the buccal mucosa, plate and tongue. He agrees to restart his antiretroviral regimen of generic TDF/FTC and raltegravir OD. In addition, you should recommend
    - A Nystatin oral suspension 500,000 units for times a day for 7 days
    - B Clotrimazole troches 10 mg five times a day for 7 days
    - C Fluconazole orally 100mg OD for 7 days
    - D Caspofungin 70mg load then 50mg OD IV for 7 days
    - E Itraconazole oral suspension 200mg BD for 7 days

Management of OPC

- ***Fluconazole remains the preferred treatment option for oropharyngeal candidiasis on the basis of an updated Cochrane database systematic review [56] (Grade 1A, high quality of evidence).***
- ***Fluconazole and topical treatment are equally clinically effective at treating oropharyngeal candidiasis with azole-sensitive strains, but azole therapy is associated with a lower risk of relapse. Topical therapy can be considered as an alternative to fluconazole for mild oropharyngeal candidiasis when there is a low risk of relapse (Grade 1B, moderate quality of evidence).***
- ***Fluconazole is the recommended treatment for HIV-seropositive patients with moderate–severe oropharyngeal candidiasis …and azole-sensitive strains (Grade 1A, high quality of evidence).***

BHIVA Candida guidelines Cochrane Systematic Review 2010, Pienaar et al.

Meta-analysis

- 22 RCTs
  - More data needed on mycological cure and relapse
  - Fluconazole showed efficacy and responses as good or better than comparators.
  - Other studies show similar efficacy but lower relapse

Cochrane Systematic Review 2010, Pienaar et al.

Oesophagitis

- A 41 year old man presents with weight loss and dysphagia. An HIV test is positive and the CD4 count is 77 cells/μL. The oral exam reveals several erythematous regions and multiple white plaques in the mouth. Initial management should include.
  - A Oesophago-gastroduodenoscopy
  - B Oral swab and speciation of Candida species
  - C Culture and sensitivity on oral wash
  - D Fluconazole 400 mg for 21 days
  - E Prescription of omeprazole 20 mg nocte in addition to antifungal therapy.

Role of endoscopy in oesophageal candidiasis

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- ***Endoscopic diagnosis should be undertaken in patients with oesophageal symptoms without oropharyngeal candidiasis, in patients who do not respond to initial treatment, and in the case of relapse (Grade 1C, low quality of evidence).***
- Confirmation by endoscopy should be used in cases with
  - symptoms of oesophageal candidiasis which fail to respond to initial therapy,
  - cases without concomitant oropharyngeal candidiasis,
  - or cases where an alternative oesophageal condition is suspected, such as oesophageal carcinoma in cases with dysphagia, where barium swallow may have been the initial investigation.
    - Primary oesophageal Ca in era of ART;
      - Sq or Adeno Ca,
      - RF Alcohol, Cigs, benign oesophageal disease
      - Median CD4 -376 and median period since HIV dx 8 y

Stebbing et al Arch Intern Med 2010: 170; 203

CMV oesophagitis

A 34 year old man with newly-diagnosed HIV infection presents with weight loss and dysphagia. His CD4 count was 79 cells/ml. Treatment of oral candida doesn't improve his dysphagia and he undergoes an upper GI endoscopy which reveals only a few solitary ulcers; CMV infection is suspected.

- Which of the following tests is most useful in confirming CMV oesophagitis?
  - a. Biopsy and histology of ulcer
  - b. Blood CMV pp65 antigenaemia
  - c. Blood CMV quantitative PCR
  - d. CMV-specific T-cell assay
  - e. Urine CMV pp65 antigenaemia

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Diagnosis in oesophagitis unresponsive to Fluconazole

- ***Endoscopic diagnosis by swab and/or biopsy should be undertaken in patients with oesophageal symptoms without oropharyngeal candidiasis and in patients who do not respond to initial treatment or who relapse (Grade 1C, low-quality evidence).***
- "Adequate and appropriate specimens must be collected to enable histological and virologic diagnoses, together with cultures and anti-fungal susceptibility testing for the identification of azole-resistant *Candida* strains".
    - Ulcer distal oesophagus typically showing intranuclear inclusion bodies in endothelial cells and infiltrate. Culture alone does not establish diagnosis
    - Blood tests tests usually positive with CMV end-organ disease but have poor positive predictive value and a negative test does not effectively rule out disease (Deayton et al Lancet 2004: 363; 2116 and multiple others)

Cryptosporidiosis

- A 32 year old woman presents with weight loss and chronic diarrhea for 6 weeks. She reports 6-8 liquid bowel motions without blood and some abdominal cramping. She has no fever or systemic features and has no travel history. She is referred to a GI clinic who arrange amongst other tests an HIV test. This is positive and a CD4 count is 21 cells/μL. initial stool cultures are negative. The test which is most likely to exclude a diagnosis of cryptosporidiosis is
  - A Cryptosporidum antigen test by immunochromatographic strip test
  - B Direct microscopy by Modified acid fast stain for oocysts
  - C Culture for Cryptosporidium
  - D Direct microscopy by direct fluorescent antibody
  - E Cryptosporidium PCR

Sensitivity of tests for Cryptosporidium

- Coccidian parasite
- Adapted to human, dog or animal.
- Species *C. hominis* and *C. parvum* most frequent in humans
- testing
    - Culture for Cryptosporidium no role
    - Cryptosporidum antigen test by immunochromatographic strip test
        - Sensitivity 47-70% but less if not *C. hominis* or *parvum*
    - Direct microscopy by Modified acid fast (Kinyoun) stain for oocysts
        - negative test doesn't exclude, repeat x 3
        - Sensitivity 70%
    - Direct microscopy by direct fluorescent antibody
        - Sensitivity approaches 100% if liquid stool less if semi-formed
    - Cryptosporidium PCR
        - 18s rRNA or oocyst wall protein
        - Extraction to disrupt oocyst key enzymatic, chemical, mechanical in combination
        - Sensitivity 93-100%

https://www1.health.gov.au/

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