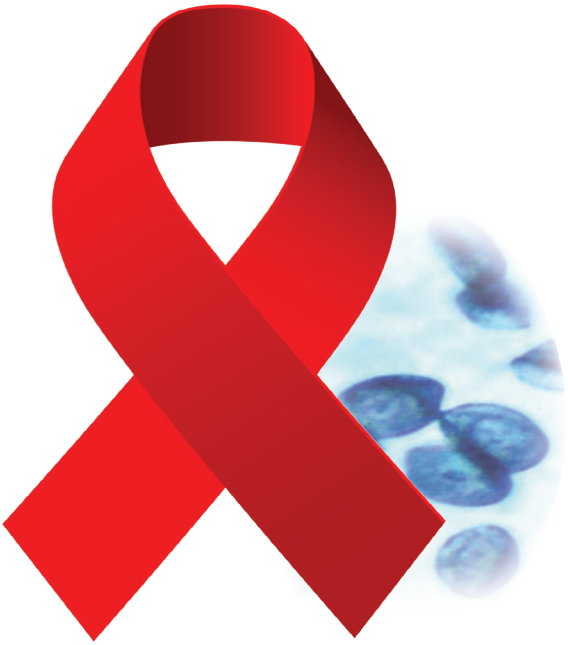
Clinical Practice Guidelines & HIV Opportunistic Infections

Clinical Practice Guidelines for the Prevention, Diagnosis and Treatment of Opportunistic Infections in Human Immunodeficiency Virus-infected Adults and Adolescents in the Philippines 2016



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CLINICAL PRACTICE GUIDELINES FOR THE PREVENTION, DIAGNOSIS AND TREATMENT OF OPPORTUNISTIC INFECTIONS IN HUMAN IMMUNODEFICIENCY VIRUS-INFECTED ADULTS AND ADOLESCENTS IN THE PHILIPPINES 2016

Philippine Society for Microbiology and Infectious Diseases

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INTRODUCTION

Background

Human Immunodeficiency Virus (HIV) is the causative agent of Acquired Immune Deficiency Syndrome (AIDS). HIV infection affects 33.3 million people worldwide, with 2.6 million new cases annually. Over the last decade, major advances in the understanding and treatment of HIV have led to a dramatic decrease in AIDS-related deaths to the point that this once inevitably fatal disease has been transformed into a chronic illness. From 2001 to 2009, 33 countries have decreased HIV incidence by over 25%, while 23 others have stabilized their case numbers. The Philippines is one of only seven countries, and the only one in Southeast Asia, to have seen an increase of more than 25% HIV prevalence in this time period (UNAIDS, 2011). While doubling time for new cases in the Philippines took 10 years from 1996 to 2006, acceleration of the doubling time to just 2 years between 2007 and 2009, and to 1 year from 2009 to 2010 is alarming. New infections are currently being diagnosed at a rate of six new cases per day (NEC, 2012). The DOH declared an HIV epidemic in July 2010, and case numbers continue to increase. While government and private efforts to address the epidemic through ramped up prevention and education programs and the provision of specialized clinical care and free antiretroviral (ARV) treatment have been met with some success, the rapid increase in case numbers threatens to overwhelm the limited resources and expertise available. The rapid increase of persons presenting in full-blown AIDS with opportunistic infections (OIs) that most Filipino physicians are unfamiliar with has led to a delay in recognition as well as inappropriate or inadequate treatment (Farr and Wilson, 2010).

Epidemiology of Opportunistic Infections in HIV in the Philippines

OIs are a heterogenous group of infections that are more likely encountered in immunocompromised states. OIs include diseases caused by viruses, bacteria, fungi, protozoans, helminths and other life forms. OIs in immunocompromised hosts are not only more common; they also tend to present with more severe and disseminated courses and may require prolonged and increased doses of treatment. The characteristic OIs in persons living with HIV are usually encountered at specific CD4 counts and can be a surrogate marker for gauging the severity of immunosuppression. Multiple OIs can present in persons with severely depressed CD4 counts, and gauging treatment response to one OI can be difficult since a concurrent OI may be causing additional symptoms and confound clinical resolution of symptoms of an adequately treated OI (Kaplan et al., 2009).

As HIV cases continue to rise in the Philippines, the number of patients presenting with opportunistic infections will continue to increase as long as patients continue to be diagnosed late in the course of their illness. Consequently, guidelines which serve as a template for treatment for clinicians who are as of yet inexperienced in the treatment of OIs but who will increasingly encounter these illnesses in their practice as the AIDS epidemic spreads are needed.

While updated international guidelines exist for the treatment of opportunistic infections in HIV, the information contained therein may not be applicable to our setting due to the unavailability of specific medications or other reasons. Moreover, there may be inadequate emphasis on specific infections such as tuberculosis (TB) due to the difference in epidemiology. For instance, OI rates in the Philippine General Hospital show that TB by far is the most common opportunistic infection (Table 1). While median CD4 counts, in general, were lower than those reported in literature, recommendations for prophylaxis still fall within the limits of internationally accepted guidelines and are therefore validated.

The objective of this guideline is to provide a framework for the treatment of Filipino HIV patients using an evidence-based approach, with emphasis on locally available treatment. The target audience is not only the infectious diseases subspecialist who treats HIV but also internists, family physicians, pulmonary specialists and other subspecialists who are taking care of or who wish to care for persons living with HIV.

Table 1. OIs and associated characteristics (Salvaña et al. 2012).

Rank	OI	Cases	%Prevalence N=476	% of OIs n=155	CD4 Mean (cells/mL)	Range (cells/mL)	CD4 Median (cells/mL)	95% CI (cells/mL)	Deaths	Mortality
1	PTB	73	15.3	47.1	161	1-663	88	118-203	5	6.8
2	PCP	50	10.5	32.3	86	1-576	34	51-121	4	8
3	ePTB	27	5.7	17.4	160	2-429	135	93-227	0	0
4	dis TB	11	2.3	7.1	30	2-164	30	14-108	1	9.1
5	othrush	11	2.3	7.1	136	2-347	104	54-218	1	9.1
6	CMV	9	1.9	5.8	48	3-189	6	0-111	1	11.1
7	crypto	6	1.3	3.9	35	24-49	35	21-49	1	16.7
8	ethrush	5	1.1	3.2	64	6-218	16	0-165	0	0
9	toxo	3	0.6	1.9	13	11-15	12	10-15	0	0

Legend: OI - opportunistic infection; PTB - pulmonary tuberculosis; PCP - Pneumocystis pneumonia; ePTB - extrapulmonary tuberculosis; dis TB - disseminated tuberculosis; othrush - oral thrush; CMV - cytomegalovirus; crypto - Cryptococcus meningitis; ethrush - esophageal thrush; toxo - toxoplasmosis

Scope of Work

Evidence-based local guidelines for the prevention, diagnosis and treatment of OIs in adults and adolescents infected with HIV have not been formulated. The present HIV Working Group (HWG) was formed by the Philippine Society for Microbiology and Infectious Diseases (PSMID) and tasked with collecting and reviewing local and international data and literature for the purpose of producing a set of evidence-based clinical practice guidelines for the prevention, diagnosis, and treatment of OIs in HIV-infected adults and adolescents in the Philippines. The HWG has made recommendations on prevention, diagnosis, and treatment of OIs in adults and adolescents infected with HIV but did not make specific recommendations on government health policy, as this may overlap with the functions of the Department of Health (DOH). The data sources include, among others, the DOH, including the National Epidemiology Center and the Philippine National AIDS Council, as well as the Joint United Nations Programme for HIV and AIDS (UNAIDS). Literature searched and reviewed included local and international peer-reviewed publications up to 2013.

Guideline Development Methodology

1. *Composition of the HWG*

The HWG is made up of representative experts from the academe and the DOH. These include an epidemiologist (Dr. Marissa Alejandria); adult clinical infectious diseases and HIV medicine experts (Dr. Edsel Maurice T. Salvaña, Dr. Jodor Lim, Dr. Arthur Dessi Roman); an immunologist (Dr. Allan Tenorio); a parasitologist and public health expert (Dr. Sonia Salamat); a neurologist (Dr. Paul Pasco); and a blood bank expert (Dr. Angela Mirasol), assisted by infectious diseases fellows and a hematology fellow at the Philippine General Hospital. Dr. Rosanna Ditangco served as senior adviser and DOH liaison while Dr. Rontgene Solante and Dr. Manolito Chua also acted as senior advisers. Dr. Salvaña, as head of the subcommittee for HIV and AIDS of the PSMID, was designated as the lead person. The lead organization is the PSMID. The complete HWG is as follows:

Dr. Edsel Maurice Salvaña	Dr. Arthur Dessi Roman
Dr. Allan Tenorio	Dr. Karen Gregorio
Dr. Marissa Alejandria	Dr. Oliver Sanchez

Dr. Jodor Lim	Dr. Jill Itable
Dr. Angela Mirasol	Dr. Katha Ngo-Sanchez
Dr. Paul Pasco	Dr. Katryn Roa
Dr. Sonia Salamat	Dr. Marinela Juan
Dr. Roxan Perez	Dr. Manolito Chua
Dr. Rosanna Ditangco	Dr. Rontgene Solante

2. *Preparation of the Evidence-Based Draft*

The HWG identified and formulated the questions to be addressed in the guideline. These questions were presented and approved in a consensus meeting. Upon approval, literature search and retrieval was done by a technical working committee supervised by the HWG. Relevant literature was appraised and the level of quality of the evidence was rated using the GRADE system (see below). The results of the literature search and appraisal were summarized in an evidence-based draft.

3. *Rating System for Recommendations and Evidence*

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used to determine the strength of each recommendation and to assess the quality of evidence. For the purpose of these guidelines, only two strengths of recommendation were used: strong and weak. For grading the evidence, three grades were used: high (at least one well-designed randomized controlled trial [RCT]); moderate (at least one well-designed cohort with long-term follow-up); and low (case-control studies, case series and expert opinion) (Guyatt et al., 2008). To facilitate analysis, the GRADE profiler program was used (Schünemann et al., 2009).

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PNEUMOCYSTIS PNEUMONIA

Introduction

Pneumocystis pneumonia (PCP) is caused by the fungus *Pneumocystis jirovecii*. Historically, the etiologic agent was referred to as *Pneumocystis carinii*, but the species *jirovecii* was used to distinguish the causative agent of human PCP from PCP in mice (Stringer et al., 2002). *P. jirovecii* is a ubiquitous environmental organism with detectable antibodies in two-thirds of children by the age of four (Pifer et al., 1978). *P. jirovecii* does not

typically cause disease in immunocompetent individuals. Early cases of PCP in non-HIV patients typically occurred in patients treated with high doses of steroids or those undergoing chemotherapy (Kovacs et al., 1984).

PCP is one of the most frequent presenting OIs in HIV patients prior to the routine use of anti-retroviral therapy. It typically occurs at CD4 counts below 200 cells/μL (Phair et al., 1990). In the Philippines, PCP is the second most common AIDS-defining illness at presentation, next only to TB (Salvaña et al., 2012). PCP in HIV is associated with a mortality rate of 10%-20% and substantially increases if mechanical ventilation is needed, even with appropriate treatment (Randall Curtis et al., 2000). In a case series at the University of the Philippines–Philippine General Hospital (UP-PGH) SAGIP clinic, the mortality rate was 8% in 50 cases, but this is likely an underestimation since some patients who presented with PCP as their AIDS-defining illness died before being enrolled in clinic.

Prevention of PCP through prophylaxis as well as early initiation of ARV therapy remains the best option for avoiding significant morbidity and mortality from this disease.

I. What are the clinical signs and symptoms of PCP?

1. **HIV-infected patients presenting with exertional dyspnea, cough and fever should be suspected to have PCP and worked up accordingly.**

Strong recommendation, Moderate quality of evidence

Summary of Evidence

HIV-infected patients with PCP present with a prolonged, subacute course. The most common symptom is dyspnea, especially on exertion. A dry or minimally productive cough is typical and may be associated with pleuritic chest pain. Patients become increasingly febrile and more debilitated as the disease progresses. On examination, auscultation findings are usually normal, but diffuse fine crackles may be appreciated (Kales et al., 1987; Selwyn et al., 1998). Signs of hypoxia, including cyanosis and tachypnea, accessory muscle use with intercostal retractions and diaphragmatic breathing, may be present, depending on the severity of illness (Thomas

and Limper, 2004).

Patients may have been already treated with several courses of antibiotics for bacterial pneumonia with poor response, and the diagnosis entertained only afterwards. A retrospective chart review identified exertional dyspnea plus interstitial infiltrate as the most likely predictor of PCP disease (sensitivity 58%, specificity 92%; OR, 16.3), with interstitial infiltrate (OR, 10.2), exertional dyspnea (OR, 4.9), and oral thrush (OR, 2.9) as independent predictors (Selwyn et al., 1998).

II. What tests are needed to diagnose PCP?

2. All patients with suspected PCP should be evaluated with a chest x-ray (CXR), which can be normal early in the course but typically shows bilateral, fluffy infiltrates.

Strong recommendation, Moderate quality of evidence

3. Pleural effusions are rare in PCP, and alternative or additional etiologies should be sought.

Strong recommendation, Low quality of evidence

4. A high-resolution CT scan of the chest can demonstrate typical ground glass opacities, and a normal finding is sufficient for ruling out disease.

Strong recommendation, Moderate quality of evidence

5. Gram stain and culture of sputum is useful for diagnosing concurrent bacterial pneumonia but cannot be used to rule out PCP.

Strong recommendation, Low quality of evidence

6. Specialized stains, when available, can be used for ruling in PCP with a positive test but cannot be used for ruling out PCP due to insufficient sensitivity.

Strong recommendation, Moderate quality of evidence

7. **An elevated lactate dehydrogenase (LDH) can provide supporting evidence for a diagnosis of PCP and can be used to monitor response to treatment. A persistently elevated LDH after 3 to 5 days of treatment is suggestive of poor response to treatment or elevation from another source (e.g., liver pathology, lymphoma, etc.).**

Strong recommendation, Moderate quality of evidence

Summary of Evidence

A wide variety of laboratory tools are available to diagnose PCP. However, clinical suspicion in a patient with compatible risk factors as well as typical signs and symptoms should not preclude appropriate intervention while waiting for laboratory confirmation.

CXR findings may be variable. About one-fourth have a normal CXR early in the course of the disease. The most typical picture of PCP in HIV-infected patients is bilateral, fluffy infiltrates starting from the perihilar area. Unilateral infiltrates (which mimic bacterial pneumonia), as well as nodular and apical infiltrates (which can mimic TB), are not uncommon. Cavitary disease may be present in advanced disease (DeLorenzo, et al., 1987). Pleural effusions are rare, occuring in about 6% of cases, and its presence should prompt the search for an alternative or additional diagnosis (Afessa, 2000). High-resolution computed tomography (CT) scanning of the chest may show characteristic ground glass opacities, and a normal CT can rule out disease (Benito et al., 2012).

Sputum Gram stain and culture are useful in cases of mixed etiology or for ruling out other sources of infection. A negative Gram stain does not rule out PCP since the cysts typically do not retain crystal violet or safranin. Specialized stains for demonstrating PCP include methenamine silver and Wright-Giemsa, which have a sensitivity of 50%-70% and are best employed using induced sputum to maximize yield (Shelhamer et al., 1996). Direct fluorescence antibody can increase yield. PCR of oral secretions has been shown to be highly sensitive but may yield false positive results in cases of colonization. If PCR is used, it should be

performed in a well-experienced lab because quality control is important. Sputum induction and oral washing have been used to improve sensitivity. Patients with scanty secretions despite nebulized saline may undergo bronchial alveolar lavage (BAL). In non-HIV patients, the low number of organisms may preclude diagnosis even from BAL and may necessitate a lung biopsy in cases that are highly suspected (Limper et al., 1989).

Common laboratory abnormalities in patients with PCP include an elevated LDH and a low PaO2 on arterial blood gas (Zaman and White, 1988; Selwyn et al., 1998). A complete blood count typically shows a normal white blood cell (WBC) count unless there is concomitant bacterial infection. LDH can be used to follow the disease course and can aid in treatment decisions in patients with an equivocal clinical response. Baseline creatinine should be checked since the mainstay of treatment, TMP-SMX, can lead to a benign increase in creatinine levels due to decreased tubular secretion of creatinine from the trimethoprim (Shelhamer et al., 1996).

Ambulatory pulse oximetry, with a subsequent drop in oxygenation after ambulation for five minutes, is highly sensitive for PCP, especially in the earlier stages. Continuous pulse oximetry can also be used to monitor the patient's status (Balestra et al., 1992).

III. What are the standard and alternative treatments for PCP?

8. The drug of choice for the treatment of severe PCP is TMP-SMX.

Strong recommendation, High quality of evidence

9. The typical oral adult dose for the treatment of PCP is two double strength tablets (800/160 mg per tablet) three times a day for 21 days. If the IV formulation is available, dosing is 5 mg/kg IV q8 of the trimethoprim component for severe disease.

Strong recommendation, High quality of evidence

10. Clindamycin 300-450 mg PO/IV q6 to q8 plus primaquine 30 mg daily is the typical alternative regimen, to be given for 21 days.

Strong recommendation, High quality of evidence

11. In patients being treated with the alternative regimen, G6PD testing (if available) should be done prior to initiation of primaquine (30 mg a day), but a lower dose of primaquine (15 mg a day) can be started in patients with severe disease with close monitoring for hemolysis while awaiting G6PD results.

Strong recommendation, Low quality of evidence

Summary of Evidence

Several RCTs have proven the efficacy of trimethoprim-sulfamethoxazole (TMP-SMX) in the treatment of PCP (Safrin et al., 1996; Hughes et al., 1993). Dosing is based on the trimethoprim component. Trimethoprim 5 mg/kg IV q8 hours x 21 days is preferred in cases of severe disease, but the oral tablets are highly bioavailable and are more easily procured. In recent years, IV TMP-SMX has been unavailable locally, and so oral treatment is used even in severe disease. Liquid preparations of TMP-SMX may be used in a comatose or ventilated patient with a nasogastric tube.

Adverse reactions to TMP-SMX include a whole spectrum of allergic reaction such as rash, angioedema, all the way to Stevens-Johnson syndrome. Approximately 20%-85% of AIDS patients on TMP-SMX will develop some adverse reaction to the drug. Patients with a history of severe reactions to TMP-SMX should be treated with an alternative regimen. Milder reactions can usually be treated through. Other side effects include hemolysis in patients with G6PD deficiency, as well as anemia with chronic use due to depression of folate metabolism (Kaplan et al, 2009).

Alternative treatments for patients who are allergic or cannot tolerate TMP-SMX include IV pentamidine, clindamycin plus primaquine, atovaquone, trimethoprim plus dapsone, and trimetrexate plus leucovorin. Only clindamycin plus primaquine is available in the Philippines. While dapsone is locally available, trimethoprim is co-formulated with sulfamethoxazole and is not available as a single agent.

If G6PD testing has not been done, a sample can be sent for testing, and the clindamycin can be given immediately. A lower dose of primaquine (15

mg daily) can be initiated in patients with severe disease while waiting for the result of the G6PD assay. If G6PD testing is not available, low-dose primaquine can be started and, if tolerated, can be increased to full dose in a few days if there is no evidence of hemolysis (Smego et al., 2001).
The clindamycin plus primaquine regimen has also been shown to be the best alternative regimen in patients who do not respond to TMP-SMX or IV pentamidine (if available) (Smego et al., 2001; Klein et al., 1992; Toma et al., 1993; Toma et al., 1998). Treatment failure was defined as clinical deterioration within 4–5 days from the start of therapy, or the lack of improvement in 7 or more days after initiation therapy.

Table 2. Available treatment regimens for PCP in the Philippines

Regimen	Dosage	Remarks
TMP-SMX	800/160 mg tab, 2 tabs TID **IV formulation 5 mg/kg IV q8 of trimethorim component**	First line High bioavailability for oral preparations For severe disease, adjunctive steroids (see next section)
Clindamycin plus Primaquine*	300 mg PO QID or 450 mg IV q8 30 mg PO daily	Best second-line regimen in trials Test G6PD, may begin primaquine at 15 mg PO daily while waiting for result

*Primaquine is only available through the DOH.

IV. What adjunctive treatments for PCP are necessary?

12. Adjunctive steroids for severe PCP pneumonia should be started if the patient has a PaO2 of less than 70 mm Hg on arterial blood gas at room air or if the alveolar-arterial oxygen gradient is more than 35 mm Hg.

Strong recommendation, High quality of evidence

13. The preferred steroid regimen is prednisone 40 mg PO BID x 5 days, then 20 mg PO BID x 5 days, then 20 mg PO daily x 11 days. If the patient cannot take oral medication, IV methylprednisolone at 75% of the prednisone dose can substituted.

Strong recommendation, High quality of evidence

14. If methylprednisolone is not available, an equivalent dose of IV hydrocortisone q8 can be used.

Strong recommendation, Low quality of evidence

15. If concurrent TB is suspected and steroids need to be started, send specimens for TB work-up and the start empiric anti-TB treatment.

Strong recommendation, Low quality of evidence

16. In patients presenting with severe PCP pneumonia, and concurrent bacterial etiology cannot be ruled out, broad-spectrum antibiotics with coverage for Pseudomonas should be started empirically.

Strong recommendation, Low quality of evidence

Summary of Evidence

In a metanalysis by Briel et al., (2006), risk ratios for overall mortality for adjunctive corticosteroids were 0.56 (95% CI 0.32–0.98) at 1 month and 0.68 (95% CI 0.50–0.94) at 3–4 months of follow-up. Steroids should be started with, or shortly after, the initiation of antibiotics, at most within 72 hours (Nielsen et al., 1992; Bozette et al., 1990; Montaner et al., 1990; Kaplan et al, 2009).

Because of the severe immunocompromised condition of an AIDS patient, it is not unusual for multiple etiologic agents to be present. TB in particular can be present and may be exacerbated by empiric steroids. Cryptococcal pneumonia may also coexist and should be evaluated as appropriate. In patients with suspected PCP pneumonia, it is usually prudent to give broad-spectrum antibiotic therapy with Pseudomonas coverage until bacterial or mixed-etiology pneumonia can be ruled out (Benito et al., 2001).

Proton pump inhibitors (PPIs) or H2-blockers should be used adjunctively in any patient treated with high-dose steroids. This should be continued for the duration of steroid therapy. In patients on ARVs who are being treated with protease inhibitors, H2-blockers are preferred since PPIs can cause

significant drug interactions (McCabe et al, 2007).

Mechanical ventilation to maintain oxygenation may be necessary in severe disease. This is typically a poor prognostic factor, with a mortality rate in excess of 50% for patients requiring ventilator support. Onset of acute respiratory distress syndrome (ARDS) is not uncommon, and ARDS treatment protocols, including low-volume and positive end-expiratory pressure should be initiated in accordance with usual practice. Non-invasive positive pressure ventilation with BiPap or CPAP can be attempted in awake and coherent patients and has been successfully used to avoid the need for endotracheal intubation (Sarkar and Rasheed, 2013).

V. How can response to therapy be assessed?

17. Continuous pulse oximetry, serial ABGs and serum LDH can be used to gauge the patient's response to therapy.

Strong recommendation, Low quality of evidence

18. Patients with suspected PCP should remain in the hospital for at least 72 hours, even in the presence of dramatic clinical improvement with treatment, due to the risk of developing ARDS.

Strong recommendation, Low quality of evidence

Summary of Evidence

HIV-infected patients with PCP typically present with a delay in diagnosis, since most persons who develop this OI are unaware of their HIV status. They have been typically treated with multiple antibiotics, and the lack of response is what prompts HIV testing. By the time the PCP diagnosis is made, most patients have moderate to severe disease.
Initiation of appropriate antibiotics for PCP, usually trimethoprim-sulfamethoxazole, with or without steroids, is typically accompanied by a dramatic response and improvement in clinical status in 4–8 days, sometimes in as little as 24 hours (Smego et al., 2001). The patient defervesces and requires less oxygen support. The response may be less profound in those with severe disease and those on mechanical ventilation. Serum LDH can be used to assess treatment response in those who have

equivocal clinical improvement, with a decreasing level associated with a better prognosis.

Serial ABGs and continuous pulse oximetry can be helpful in monitoring patients who are sick enough to be admitted in the hospital. Patients who are improving still need to be observed carefully due to a significant risk of ARDS (Sarkar and Rasheed, 2013).

VI. What are the criteria for discharge from the hospital?

Hospital discharge can be considered for patients who have defervesced and are weaned off oxygen and are taking oral antibiotics and steroids. Patients are typically kept in the hospital for at least 72 hours to rule out the subsequent development of ARDS after the initial improvement in clinical status (Smego et al., 2001).

VII. What complications can occur as a result of PCP?

ARDS is the most dreaded complication of PCP. Even patients who seemingly have mild disease can develop it, and those who have had a profound clinical response to therapy can rapidly decompensate. The need for mechanical ventilation is of poor prognostic significance. Prolonged mechanical ventilation carries a dismal outcome.

PCP can cause the formation of cavitary lesions and can reduce lung capacity significantly. In patients treated with ARVs, immune reconstitution may occur and result in significant lung pathology.

VIII. What measures can be taken to prevent occurrence and recurrence aside from ARV (i.e., primary and secondary prophylaxis)?

19. HIV-infected individuals with a CD4 count equal to or less than 200 cells/μL should be started on a prophylaxis regimen to significantly reduce the risk of developing PCP.

Strong recommendation, High quality of evidence

20. Patients who are suspected of having CD4 counts lower than 200 cells/μL and are newly diagnosed with HIV should be started

on primary PCP prophylaxis while awaiting a formal CD4 count. These include patients with oral thrush or a history of an AIDS-defining illness, including TB.

Strong recommendation, Moderate quality of evidence

21. **The preferred prophylaxis regimen is TMP-SMX 400/80 mg or 800/160 mg (double strength) PO daily, and this should be continued until the CD4 count is consistently above 200 cells/μL for at least 3 months.**

Strong recommendation, High quality of evidence

22. **The preferred alternative regimen for patients who develop allergy to TMP-SMX is dapsone 100 mg PO daily, but should not be used if the allergy to TMP-SMX is severe, due to possible cross-reactivity.**

Strong recommendation, High quality of evidence

23. **The only other locally available regimen for prophylaxis, clindamycin plus primaquine, has limited effectiveness for prophylaxis and should not be used routinely.**

Strong recommendation, Moderate quality of evidence

24. **Desensitization to cotrimoxazole allergy can be attempted with the assistance of an allergologist in cases where the perceived benefit outweighs the risk of desensitization.**

Strong recommendation, Low quality of evidence

Summary of Evidence

Prophylaxis with TMP-SMX has made a tremendous impact on the survival of patients with HIV, particularly prior to the discovery of effective ARV therapy. Several regimens have been proven effective (see Table 3) (Bozette et al., 1995; Schneider et al., 1992; Schneider et al., 1995). The TWG prefers the first regimen due to simplicity of administration and continued effectiveness even with missed doses.

Table 3. Available prophylaxis regimens for PCP in the Philippines

Regimen	Dosage	Remarks
TMP-SMX	800/160 mg tab daily or 400/80 mg tab daily	First line High rate of development of rash and other adverse reactions; milder reactions typically resolve with supportive care; severe reactions include Stevens-Johnson Syndrome.
Dapsone	100 mg daily	Potential cross-reaction in sulfa allergy, do not use in cases of severe TMP-SMX allergy
Clindamycin plus Primaquine	300 mg PO daily 15 mg daily	Test G6PD before starting primaquine

PCP prophylaxis may be discontinued after the patient has been started on ARVs and has a CD4 count greater than 200 cells/μL on two separate determinations within a 3-month period (Lopez, 2001). This is true regardless of whether the patient is on primary prophylaxis (no previous PCP disease) or on secondary prophylaxis (previous PCP disease).

Local data from the Philippine General Hospital (PGH) SAGIP clinic has shown that PCP occurs at a mean CD4 count of 86 cells/μL (51–121) (Salvaña et al., 2012). This supports the use of PCP prophylaxis for Filipino patients with CD4 counts under 200 cells/μL.

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BACTERIAL PNEUMONIA

Introduction

HIV-infected individuals are 25 times at risk of developing bacterial pneumonia (Hirschtick et al., 1995). Historically, the incidence of bacterial pneumonia among this set of patients has ranged from 3.9 to 7.3 episodes per 100 person-years (Wallace et al., 1997). This has declined with the introduction of ARV therapy. However, this decline in the overall rate of bacterial pneumonia has not decreased proportionally to as great an extent as PCP with the advent of ARV and cotrimoxazole prophylaxis (Grubb et al., 2006). It remains the most common cause of pulmonary infections in HIV patients, having replaced PCP in the ARV era (Benito et al., 2012). Locally, there is no comparable data, but pneumonia from all causes remains the number one cause of morbidity and the sixth cause of mortality among Filipinos (Republic of the Philippines Department of Health [DOH], 2013). At the Research Institute for Tropical Medicine (RITM), the most common reason for admission among HIV/AIDS patients is pneumonia of any etiology, similar with foreign reports (Benito et al., 2012; RITM Medical Department, 2013). Due to the difficulty in clinically differentiating a bacterial cause from other causes such as PCP or TB, empiric antibacterial coverage is almost always warranted. Failure to address bacterial pneumonia may result in adverse clinical outcomes because even a single episode of bacterial pneumonia is associated with increased mortality among HIV-infected patients (Hirschtick et al., 1995). Risk factors associated with an increased risk for bacterial pneumonia, include low CD4 count, injection-drug use, and cigarette smoking (Benito et al., 2012; Hirschtick et al., 1995).

An episode of bacterial pneumonia may be the first manifestation of underlying HIV infection and can occur at any stage of HIV disease and at any CD4 count. According to both the Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO) HIV Classification, recurrent bacterial pneumonia (>2 episodes in 12 months) is an AIDS-defining condition, thereby warranting ARV treatment regardless of CD4 count (CDC, 1993; WHO, 2007). It is important, therefore, for every clinician to elicit this history as it may be a clue to the diagnosis of an underlying HIV infection.

IX. What are the clinical signs and symptoms of bacterial pneumonia among HIV-infected individuals?

25. HIV-infected persons with pneumonia present similarly to those without HIV infection, with acute onset of fever, chills, rigors, chest pain, cough productive of purulent sputum, and dyspnea.

Strong recommendation, Low quality of evidence

Summary of Evidence

The clinical and radiographic presentation of bacterial pneumonia in HIV-infected persons is similar to that in persons without HIV infection (Benito et al., 2012; Kaplan et al, 2009). Persons with pneumonias caused by *Streptococcus pneumoniae* and *Haemophilus* species characteristically have an acute onset (3–5 days) of symptoms, including fevers, chills, rigors, chest pain, cough productive of purulent sputum, and dyspnea (Donowitz and Mandell, 2000; Fine et al., 1999; Selwyn et al., 1998). On examination, patients are often febrile. Tachycardia, hypotension, tachypnea, and decreased arterial oxygen saturation indicate moderate-to-severe pneumonia and in-hospital care should be strongly considered (Kaplan et al, 2009).

Leukocytosis may be present but may be appreciated only when compared to a baseline value. The CBC may also show a neutrophilic shift. Persons with bacterial pneumonia usually exhibit unilateral, focal, segmental, or lobar consolidation on chest radiograph. However, the frequency of these typical radiographic findings might depend on the underlying bacterial pathogen. HIV-infected persons may present with multifocal or multilobar involvement and with parapneumonic effusions more frequently than persons without HIV infection, based on a retrospective chart review of 137 patients (21% in HIV patients vs. 13% in non-HIV patients) (Gil Suay et al., 1995).

X. What tests are needed to diagnose bacterial pneumonia in HIV-infected individuals?

26. A chest radiograph should be ordered when pneumonia is suspected. It can help assess severity and aid in prognostication.

Strong recommendation, Low quality of evidence

27. **Blood culture, Gram stain and culture with antibiotic susceptibility tests of respiratory specimens should be requested for patients presenting with pneumonia requiring hospital admission.**

Strong recommendation, Low quality of evidence

28. **For patients with no indications for hospital admission and are well enough to be managed on an outpatient basis, routine microbiologic tests are not recommended.**

Weak recommendation, Low quality of evidence

Summary of Evidence

Chest Radiography

Guidelines for the management of community-acquired pneumonia (CAP) in persons without HIV infection also apply to HIV-infected persons (Benito et al., 2012; Kaplan et al, 2009). Chest radiography remains an important tool in the diagnosis of pneumonia, which requires a demonstrable infiltrate. Aside from confirmation of the diagnosis, the chest radiograph also helps provide clues to the etiologic agent, assess severity, identify other lung diseases, or rule out other non-infectious causes of patient symptoms (Mandell et al., 2007). When available, previous radiographs should be reviewed for comparison in order to assess new findings and monitor the progression or resolution of old lesions.

In terms of radiographic features, a study done in a tertiary care referral hospital in Ethiopia assessed the accuracy of CXR interpretations, inter-observer agreement, degree of CXR overlap, and distinguishing features of PCP, TB, and bacterial pneumonia (Assefa et al., 2011). One hundred thirty-one CXRs of smear-negative, HIV-positive patients with atypical laboratory data were independently assessed by two radiologists blinded to the clinical diagnoses. The CXR interpretation had high sensitivity (88%), negative predictive value (90%), and inter-observer agreement (84%) for PCP. In an earlier study involving 153 HIV-positive patients with proven pulmonary infections and 10 HIV-positive patients with no active

disease, the median percent accuracies were 84% for TB (n=9), 75% for PCP (n=73), 64% for bacterial pneumonia (n=7) and 100% for no active disease (Boiselle et al., 1997). Both studies concluded that an accurate diagnosis of these three common etiologies of pneumonia can be made radiographically in majority of cases. However, overlapping clinical and radiographic features often occur (9.8–36% of cases), as do coexisting infections in HIV/AIDS patients with respiratory symptoms.

Microbiologic Studies

Similar to persons without HIV infection, *Streptococcus pneumoniae* and *Haemophilus* species are the most frequently reported etiologic agents of community-acquired bacterial pneumonia in HIV-infected persons (Benito et al., 2011; Burack et al., 1994; Madeddu et al., 2010; Park et al., 2001; Mundy et al., 1995). However, HIV-infected individuals experience more episodes of bacteremia when infected with *Streptococcus pneumoniae* (Falco et al., 1994; Feldman et al., 1999). Drug resistance of *Streptococcus pneumoniae* is likewise a problem for HIV-infected individuals in most countries (Benito et al., 2011). According to the most recent Philippine DOH Antimicrobial Resistance Surveillance Program Report for 2014, resistance rates of *Streptococcus pneumoniae* to penicillin, erythromycin and chloramphenicol remain relatively low at 7%, 4.3% and 4% respectively (n=257, 67% of which are from respiratory isolates, using breakpoints for meningitis) compared with other countries (Antibiotic Resistance Surveillance Reference Laboratory [ARSRL], 2014). There is no significant change in resistance rates for penicillin, erythromycin and chloramphenicol for the past 3 years (2012–2014) (ARSRL, 2014). Resistance rate to cotrimoxazole has remained high over the past few years, with the latest at 17.3%.

Several studies have highlighted the importance of ***Staphylococcus aureus*** and *Pseudomonas aeruginosa* as etiologic agents of community-acquired bacterial pneumonia among persons with HIV infection (Afessa and Green, 2000; Arnold et al., 2007; Madeddu et al., 2010). **These pathogens should be suspected on the basis of epidemiologic, clinical, or radiologic clues. *Staphylococcus aureus* should be considered in persons with recent viral (or influenza) infection; history of injection-drug use; or severe, bilateral, necrotizing pneumonia (Levine et al., 1990).** *Pseudomonas aeruginosa* should be considered in HIV-

infected persons with CD4 count <50 cells/μL, preexisting lung disease (i.e., bronchiectasis and cavitary infiltrates), underlying neutropenia, corticosteroid therapy, severe malnutrition, hospitalization within 90 days or residence in a healthcare facility or nursing home, and those on chronic hemodialysis (Afessa and Green, 2000; Benito et al., 2011; Kaplan et al, 2009). However, infections caused by *Pseudomonas aeruginosa* have declined with the advent of ARV due to immune reconstitution leading to fewer healthcare contact and hospitalizations (Benito et al., 2011).

Atypical bacterial pathogens such as *Legionella pneumophila, Mycoplasma pneumoniae*, and *Chlamydophila* species have been infrequently reported as causes of community-acquired bacterial pneumonia in HIV-infected persons (Benito et al., 2011; Park et al., 2001; Mundy et al., 1995; Tarp et al., 1999). Diagnostic tests for atypical pneumonia are not routinely done and may be warranted only in cases of treatment failure (Tarp et al., 1999). However, since atypical pathogens are a common cause of CAP in all regions of the world, with a global incidence of 22%, they are important to consider when deciding coverage of empiric antibiotic treatment (Arnold et al., 2007).

In RITM, from 2007 to 2011, the most common bacterial organisms isolated from respiratory specimens of admitted HIV/AIDS patients in whom pneumonia is considered include *Haemophilus* spp. (17%), *Klebsiella pneumoniae* (22%), *Pseudomonas aeruginosa* (15%) and *Streptococcus pneumoniae* (10%). No methicillin-resistant *Staphylococcus aureus* (MRSA) has been isolated (Roman, personal correspondence).

The differential diagnosis of pneumonia in HIV-infected persons is broad. Moreover, a study reported that about 9% of pulmonary infiltrates were polymicrobial in nature, and that inability to come up with an etiologic diagnosis resulted in a higher mortality (OR 23 95% CI 2–283) (Tarp et al., 1999). Several conditions that can alter antimicrobial therapeutic decisions are dependent on the isolation of the etiologic agent. These include (1) the growth of bacteria not covered by the empiric antibiotic, (2) drug resistance, and (3) other organisms such as mycobacteria, *Pneumocystis jiroveci*, and viruses (Task Force on Community-Acquired Pneumonia [TFCAP], 2010). While it is appealing to come up with a single diagnosis, as in the case of immunocompetent individuals, this may not hold true for HIV patients especially when immunosuppression is severe.

An HIV patient can have multiple co-infections at any given time. For these reasons, the importance of sending appropriate clinical specimens and coming up with a microbiologic diagnosis cannot be overemphasized.

The decision to request for microbiologic studies for patients with no indications for hospital admission and are well enough to be managed on an outpatient basis lies on specific clinical scenarios and clinician judgment (Kaplan et al, 2009). This is especially true if microbiologic studies cannot be performed promptly or if there is difficulty in obtaining clinical specimens.

The increased incidence of bacteremia in HIV-infected persons (especially at low CD4 count and if S. *pneumoniae* is the etiologic agent) with *pneumonia*, the high specificity of blood cultures, and the increased risk for infection with drug-resistant organisms are very important bases for blood culture collection (Kaplan et al, 2009; TFCAP, 2010). Blood cultures taken at two sites are recommended prior to starting any antibiotic treatment. However, obtaining clinical samples for culture should not significantly delay timely antibiotic administration. Gram stain and culture of appropriate respiratory secretions should also be part of the initial work up especially for patients who require hospital admission and those requiring intensive care. Gram stain and culture of expectorated sputum should be performed only for properly collected, transported and processed specimens to ensure adequacy, appropriateness, and reliability of results (Kaplan et al, 2009). Gram stain results should be correlated with sputum culture to increase their diagnostic utility. A good expectorated sputum is not inferior to a sputum induction sample with a high overall yield of >50% among HIV-infected patients with pulmonary infiltrates (Anderson et al., 1995; Benito et al., 2001; Conde et al., 2000). For intubated patients, an endotracheal aspirate sample should be obtained. More invasive procedures are recommended only for specific clinical indications or if initial results of non-invasive tests/specimens are not diagnostic (See Table 4). In addition to the above tests, urinary antigen tests for *Legionella pneumophila* and *Streptococcus pneumoniae* can be requested if available.

Table 4. Important considerations in the choice of invasive procedures for the microbiologic diagnosis of pneumonia

Invasive Diagnostic Procedures to Obtain Clinical Specimens for Microbiologic Diagnosis	Points to Consider
Fiberoptic bronchoscopy	• Procedure of choice for diagnosing many pulmonary diseases in HIV-infected patients • Can achieve a microbiologic diagnosis in 56% of cases (Benito et al., 2001) • Use a double-lumen catheter system or a protected BAL to avoid contamination with upper airway flora • Semi-quantitative cultures of the collected specimens should be performed • Diagnostic sensitivity is markedly decreased by antibiotic use prior to procedure • Useful for the diagnosis of TB and PCP
CT-guided transthoracic needle aspiration Surgical lung biopsy (performed by means of thoracotomy or video-assisted thoracoscopic surgery) Diagnostic thoracentesis	• High yield in diagnosing the cause of peripheral nodules and localised infiltrates (Benito et al., 2011) • Has the greatest sensitivity in the diagnosis of parenchymal lung disease (Benito et al., 2011) • Very invasive • Can proceed with therapeutic interventions during procedure • Recommended for patients with pleural effusion or empyema (Park et al., 2001) • Can proceed with therapeutic thoracentesis for drainage (source control) and to relieve respiratory distress secondary to a moderate-to large-sized effusion

Given the increased incidence of *Mycobacterium tuberculosis* in HIV-infected persons, the diagnosis of TB should always be suspected in HIV-infected persons who have pneumonia. Those persons with a clinical and radiographic evidence suggestive of TB should be managed as potential TB (e.g., respiratory isolation if hospitalized), and at least two sputum specimens should be obtained for acid-fast bacilli (AFB) smear and culture (Tuberculosis Coalition for Technical Assistance [TCTA], 2009). Please refer to the section on TB for a detailed discussion on the diagnosis and management of TB among HIV/AIDs patients.

Other Diagnostic Tests

An assessment of disease severity and arterial oxygenation should be performed in all persons with pneumonia. Non-invasive measurement of arterial oxygen saturation via pulse oximetry is an appropriate screening test. However, ABG analysis is indicated for persons with evidence of hypoxemia suggested by non-invasive assessment and for persons with tachypnea and/or respiratory distress. This is also important since PCP is a significant differential diagnosis for bacterial pneumonia, and hypoxemia in PCP warrants steroid therapy. Please refer to the section on PCP for a detailed discussion on the management of hypoxemia with PCP.

XI. Should all HIV-infected patients who develop pneumonia be admitted?

29. Site-of-care decisions should be based on the stability of the patient's clinical condition, presence or absence of other active medical problems, and risk of death and complications.

Strong recommendation, Low quality of evidence

30. The presence of any of the following should warrant admission: RR ≥30/min, PR ≥125/min, temperature ≥40ºC or ≤36ºC, SBP <90 mm Hg or DBP ≤60 mm Hg, altered mental status of acute onset, suspected aspiration, unstable comorbid conditions, or CXR showing multilobar affectation, pleural effusion, or abscess.

Strong recommendation, Moderate quality of evidence

31. Patients with a high risk for mortality and complication (severe sepsis, septic shock, need for mechanical ventilation) warrant ICU admission.

Strong recommendation, Moderate quality of evidence

Summary of Evidence

The diagnosis of HIV in patients presenting with pneumonia does not, in itself, warrant hospital admission. The physician's decision to hospitalize

a patient should be based on the stability of the patient's clinical condition, the presence or absence of other active medical problems, the risk of death and complications and, in some cases, psychosocial considerations. Site-of-care decisions often determine the type and extent of diagnostic testing; the choice, spectrum and route of administration of antimicrobial therapy; the intensity of clinical observation; and the cost of treatment (TFCAP, 2015).

Disease-specific prognostic indicators may be used to assess the initial severity of pneumonia and may help guide the physician to determine the site of care: whether the patient can be managed in an outpatient setting or whether a ward or ICU admission is necessary. Criteria that were developed to assess CAP disease severity in HIV-uninfected persons have been found to be valid for HIV-infected persons (Cordero et al., 2000). According to the CAP Guidelines of 2010, patients with any one of the following physical findings have a higher mortality rate of 8%–10%, and are thus categorized as moderate-risk CAP: RR ≥30 breaths/minute, pulse rate ≥125 beats/minute, or temperature ≤36ºC or ≥40ºC; DBP ≤60 mm Hg and SBP <90 mm Hg, and those with suspected aspiration or altered mental status of acute onset (TFCAP, 2010). Patients with decompensated comorbid conditions (chronic obstructive airway disease, diabetes mellitus, congestive heart failure, chronic renal failure, chronic liver disease, chronic alcohol abuse, or malnutrition) which may aggravate or be aggravated by the pneumonia are also included in this category. Radiographic findings may include bilateral or multilobar involvement, pleural effusion, or abscess. These patients need to be hospitalized for closer monitoring and/or parenteral therapy (TFCAP, 2010).

In the ARV era, HIV infection alone is no longer a driving factor for ICU admission and prognostication in patients with HIV infection and respiratory failure (Masur, 2009; Olaechea et al., 2009). In fact, critically ill HIV-infected patients may have comparable overall survival rates with non-HIV ICU patients, depending on the degree of immunosuppression (Benito et al., 2011). Thus, the decision to admit a patient to the ICU would depend on the patient's risk for mortality and complication. Respiratory failure (the most common indication for ICU admission in the ARV era), together with severe sepsis and septic shock, is among the indications for ICU admission (Benito et al., 2011; TFCAP, 2010).

XII. What are the treatment recommendations for HIV-infected individuals suspected to have pneumonia?

32. For patients who can be treated on an outpatient basis, an oral β-lactam/β-lactamase inhibitor combination (BLIC) OR second-generation oral cephalosporins with or without a macrolide are recommended.

Strong recommendation, Moderate quality of evidence

33. A fluoroquinolone should NOT be used as the first-line antibiotic for HIV patients presenting with pneumonia who can be treated in an outpatient basis. It should only be used for those who are allergic to penicillin or those who have received a beta-lactam within the previous 3 months.

Strong recommendation, Moderate quality of evidence

34. HIV-infected persons who are being treated as inpatients or in the ICU should receive an IV non-antipseudomonal β-lactam (BLIC, cephalosporin or carbapenem) PLUS a macrolide (IV for critically ill patients).

Strong recommendation, Moderate quality of evidence

35. Empiric coverage for MRSA or Pseudomonas should be based on proper clinical and epidemiologic predisposition of individual patients.

Strong recommendation, Low quality of evidence

36. When the etiology of pneumonia has been identified on the basis of reliable microbiological methods, antimicrobial therapy should be directed at that pathogen.

Strong recommendation, Low quality of evidence

37. Stepping down to an equivalent oral antibiotic regimen can be done once clinical improvement is achieved.

Strong recommendation, Low quality of evidence

38. Duration of antibiotic therapy is usually 7 days except for certain pathogens (enteric Gram-negatives, Pseudomonas, MSSA, MRSA and atypical pathogens) that warrant longer treatment duration.

Strong recommendation, Low quality of evidence

Summary of Evidence

The principles of the treatment of community-acquired bacterial pneumonia are the same for HIV-infected persons as for HIV-uninfected persons (Benito et al., 2001; Kaplan et al, 2009). Antibiotic therapy should be administered promptly, without waiting for the results of diagnostic testing. Outpatient antibiotic therapy consists of a BLIC or a second-generation oral cephalosporin with or without an extended macrolide (TFCAP, 2015). For patients who require hospital or ICU admission, IV non-antipseudomonal β-lactam (BLIC or cephalosporin,or carbapenem for critically ill patients) PLUS an extended macrolide (use IV for critically ill patients) are recommended (TFCAP, 2015). The reason for including a macrolide, despite reports that atypical pathogens are rarely isolated from HIV patients, is that in three local studies, atypical pathogens are among the most common etiologic agents of CAP in the Philippines (Bernas and Galvez, 1997; Davidson et al., 1976; San Diego et al., 2001). Preferred β-lactams are oral amoxicillin-clavulanate (for low-risk individuals), PO/IV ampicillin-sulbactam, PO/IV cefuroxime and the IV drugs ceftriaxone and ertapenem for those requiring admission. Preferred macrolides are azithromycin and clarithromycin (Kaplan et al, 2009). It is important to note that patients who are receiving a macrolide for *Mycobacterium* avium complex prophylaxis should never receive macrolide monotherapy for empiric treatment of bacterial pneumonia (Kaplan et al, 2009).

The majority of pathogens causing CAP will be covered adequately with these recommended empiric regimens; however, the increased incidence of *P. aeruginosa* and *S. aureus* as a cause of pneumonia among HIV patients is an exception. These pathogens occur among patients with specific risk factors and clinical presentation (as enumerated earlier) for which empiric antibiotic coverage should be tailored accordingly. For these pathogens, sputum Gram stain and culture are likely to be high yield, allowing early

discontinuation of empiric treatment if results are negative (Kaplan et al, 2009). For hospitalized or ICU patients with risk factors for Pseudomonas infection, an IV antipneumococal, antipseudomonal β-lactam (BLIC, cephalosporin or carbapenem) PLUS an IV extended macrolide PLUS an aminoglycoside should be used (TFCAP, 2015). Preferred β-lactams are piperacillin-tazobactam, cefepime, imipenem, or meropenem. For persons who are allergic to penicillin, aztreonam can be used in place of the β-lactam (Kaplan et al, 2009). If risk factors for *Staphylococcus aureus* infection, including community-acquired methicillin-resistant S. aureus, are present, vancomycin or linezolid should be added to the antibiotic regimen (Kaplan et al, 2009).

Table 5. Recommended empiric antibiotic regimen for specific clinical settings among HIV patients suspected with bacterial pneumonia

Clinical setting	Recommended empiric therapy
Outpatient	β-lactam/β-lactamase inhibitor combination (BLIC) OR second-generation oral cephalosporins +/- extended macrolides
Ward or ICU admission	IV non-antipseudomonal β-lactam (BLIC, cephalosporin or carbapenem) + extended macrolide
	With risk for Pseudomonas infection IV antipneumococal antipseudomonal β-lactam (BLIC, cephalosporin or carbapenem)g + IV extended macrolide + aminoglycoside
Risk for MRSA and other pathogens	See specific agents

Adapted from the Philippine Clinical Practice Guidelines on the Diagnosis, Empiric Management, and Prevention of Community-acquired Pneumonia (CAP) in Immunocompetent Adults: 2010 Update

Table 6. Usual recommended dosages of antibiotics in 50–60 kg adults with normal liver and renal function

Clinical setting	
Macrolides Azithromycin dihydrate 500 mg OD Clarithromycin 500 mg BID	**Second-generation cephalosporin** Cefuroxime axetil 500 mg BID
β-lactam with β-lactamase inhibitor combination (BLIC) Amoxicillin-clavulanic acid 625 mg TID or 1 g BID Amoxicillin-sulbactam 1 gm TID Sultamicillin 750 mg BID	**Oral third-generation cephalosporin (used ONLY as a step-down oral drug from an IV third-gen cephalosporin)** Cefpodoxime proxetil 200 mg BID Cefixime 200 mg BID (for susceptible isolates)
Inpatient or ICU Setting	
Macrolides Azithromycin dihydrate 500 mg q24h Clarithromycin, PO/IV 500 mg q12h **β-lactam with β-lactamase inhibitor combination (BLIC)** Ampicillin-sulbactam 1.5 gm IV q6h	**Second-generation cephalosporin** Cefuroxime Na 1.5 gm IV q8h **Third-generation cephalosporin** Ceftriaxone 2 gm IV q24h **Non-anti-Pseudomonal carbapenem** Ertapenem 1 gm IV q24h
Risk for Pseudomonas present	
Aminoglycosides Amikacin 15 mg/kg q24h Gentamicin 3 mg/kg q24h **Carbapenems** Imipenem-cilastatin 0.5–1 gm q6-8h Meropenem 1–2 gm q8h	**Anti-Pseudomonal, anti-pneumococcal β-lactams (BLIC, cephalosporin)** Cefepime 2 gm IV q8-12h Piperacillin-tazobactam 2.25–4.5 gm IV q6-8h
Other risk factors present	
Oxacillin (*Staphylococcus*) 1–2 gm q4-6h Clindamycin (*Staphylococcus* and *anaerobes)* 600 mg IV q6-8h Metronidazole (*anaerobes*) 500 mg IV q6-8h Linezolid (MRSA) 600 mg IV q12h Vancomycin (MRSA) 1 gm IV q12h	

Data taken from the Philippine Clinical Practice Guidelines on the Diagnosis, Empiric Management, and Prevention of Community-acquired Pneumonia (CAP) in Immunocompetent Adults: 2010 Update

Stepdown to Oral Therapy

When the etiology of pneumonia has been identified on the basis of reliable microbiological methods, antimicrobial therapy should be directed at that pathogen. Similar with immunocompetent individuals, switching to

an equivalent oral antibiotic regimen should be considered once clinical signs of improvement have been achieved, including the ability to tolerate oral feeding and intake of medications. Suggested criteria for clinical stability include oral temperature <37.8°C, heart rate <100 beats/minute, respiratory rate <24 breaths/minute, systolic blood pressure >90 mm Hg, and room air oxygen saturation >90% or partial pressure of oxygen in arterial blood (PaO2) >60 mm (TFCAP, 2010).

Additionally, the CAP Guidelines 2015 Update lists a number of indications for the streamlining of antibiotic therapy:

1. Resolution of fever for >24 hours

2. Less cough and the resolution of respiratory distress (normalization of respiratory rate)

3. Improving WBC count; no bacteremia

4. Etiologic agent is not a high-risk (virulent/resistant) pathogen e.g., *Legionella, S. aureus* or Gram-negative enteric bacilli

5. No unstable comorbid condition or life-threatening complication such as myocardial infarction, congestive heart failure, complete heart block, new atrial fibrillation, supraventricular tachycardia, etc.

6. No sign of organ dysfunction such as hypotension, acute mental changes, BUN to creatinine ratio of >10:1, hypoxemia, and metabolic acidosis

7. Patient is clinically hydrated, taking oral fluids and is able to take oral medications

Use of oral third-generation cephalosporin is recommended ONLY as a stepdown drug from an IV third-generation cephalosporin (e.g. IV ceftriaxone → cefpodoxime). Cefpodoxime is preferred over cefixime based on lower MIC against Pen-susceptible *Streptococcus pneumoniae*.

Duration of Antibiotic Therapy

Table 7. Duration of antibiotic use based on etiology

Etiologic Agent	Duration of Therapy (days)
Most bacterial pneumonias except enteric Gram-negative pathogens, *S. aureus* (MSSA and MRSA), and *P. aeruginosa*	5–7 days 3–5 (azalides) for *S. pneumoniae*
Enteric Gram-negative pathogens, *S. aureus (MSSA and MRSA),* and *P. aeruginosa*	MSSA CAP a. non-bacteremic: 7–14 days b. bacteremic: longer, up to 21 days MRSA CAP a. non-bacteremic: 7–21 days b. bacteremic: longer, up to 28 days *Pseudomonas aeruginosa* a. non-bacteremic: 14–21 days b. bacteremic: longer, up to 28 days
Mycoplasma and *Chlamydophila*	10–14 days
Legionella	14–21; 10 (azalides)

Adapted from the data taken from the Philippine Clinical Practice Guidelines on the Diagnosis, Empiric Management, and Prevention of Community-Acquired Pneumonia (CAP) in Immunocompetent Adults: 2015 Update

Fluoroquinolone Use in TB-Infected Patients with Bacterial Pneumonia

Respiratory fluoroquinolones are active against *Mycobacterium tuberculosis*. Collateral damage brought about by undue exposure of *Mycobacterium tuberculosis* to fluoroquinolones might cause selection pressure and eventual drug resistance to this second-line antimycobacterial agent. Persons with TB who are treated with fluoroquinolone monotherapy might respond initially; however, this response might be misleading, causing delay in the diagnosis of TB and in the initiation of appropriate multi-drug therapy (Kaplan et al, 2009).

No single study has conclusively demonstrated the effect of fluoroquinolone exposure prior to the diagnosis of TB on hard outcomes such as increased mortality or development of drug resistance, more so with HIV patients. However, several studies including a meta-analysis have showed that empiric treatment of CAP with a fluoroquinolone causes a delay in TB

diagnosis (by ~16 days) and delay in initiation of anti-TB medications (43.1 days SD 40 for those who received prior fluoroquinolones vs. 18.7 days SD 16.9 for those who did not, p=0.04) (Chen et al., 2011; Shen et al., 2012; Yoon et al., 2005). With respect to mortality, a prospective cohort study was performed involving 609 TB cases whose fluoroquinolone exposure within 6 months before TB diagnosis was assessed. Multivariable logistic regression analysis revealed that any fluoroquinolone exposure before TB diagnosis (OR 1.82 95% CI 1.05–3.15) was an independent factor associated with mortality, together with older age (OR 1.05 per year, 95% CI 1.03–9.09) and HIV infection (OR 8.08 95% CI 3.83–17.06) (Van der Heijden et al., 2012).

Results of studies that look into the effect of empiric fluoroquinolone use related to the risk of developing fluoroquinolone-resistant M. tuberculosis are more variable. A meta-analysis of five retrospective studies reported that fluoroquinolone prescription increased the risk of developing fluoroquinolone-resistant M. tuberculosis (OR 2.70 95% CI 1.30–5.60) (Chen et al., 2011). However, in at least two recent studies, fluoroquinolone resistance was found to be associated with MDR-TB and was not related to previous brief fluoroquinolone exposure (Lai et al., 2011; Van den Boogaard et al., 2011).

For the reasons mentioned above, we recommend that caution be taken when prescribing fluoroquinolones especially among the HIV population in which the risk of co-infection with TB is very high. Fluoroquinolones should not be used as a first-line antibiotic and should only be used for specific indications such as penicillin allergy or receipt of a beta-lactam antibiotic within the previous 3 months. When indicated, an oral respiratory fluoroquinolone (moxifloxacin, levofloxacin [750 mg/day]) should be used (Kaplan et al, 2009).

XIII. What is the role of vaccinations in the prevention of bacterial pneumonia among HIV patients?

39. Vaccination for pneumococcal pneumonia is recommended for all HIV patients regardless of CD4 count.

Strong recommendation, Moderate quality of evidence

40. Inactivated influenza vaccine should be administered annually to all HIV-infected persons during influenza season regardless of CD4 count.

Strong recommendation, High quality of evidence

41. Hemophilus influenza type b (Hib) vaccination is not routinely recommended for HIV patients.

Strong recommendation, Moderate quality of evidence

Summary of Evidence

The use of vaccination among HIV-infected individuals has raised specific concerns on safety and immunogenicity given the complex host immune system and HIV interaction. The risk-benefit decision will depend largely on the nature of the vaccine and the level of immunosuppression and partly on several other factors such as malnutrition and concurrent infections (HIV Immunization Guidelines Working Committee [HIGWC], 2010).

A 23-valent polysaccharide pneumococcal vaccination (PPV23) is given as a single dose of 0.5 mL by subcutaneous or intramuscular injection, preferable into the deltoid (HIGWC, 2010). Revaccination can be considered for persons who were initially vaccinated when their CD4 counts were <200 cell/uL and whose CD4 counts have increased to >200cells/uL in response to ARV (HIGWC, 2010; Park et al., 2001). Although data on the safety and immunogenicity on HIV patients are available only for the 7-valent pneumococcal conjugate vaccine (PCV7), the US Advisory Committee on Immunization Practices (ACIP) have recently recommended routine use of 13-valent pneumococcal conjugate vaccine (PCV13) for adults aged ≥19 years with immunocompromising conditions such as HIV (CDC, 2012). Refer to Table 8 for the ACIP recommendation for the administration of pneumococcal vaccine.

Table 8. Summary of recommended intervals for adult patients (19–64 years) with HIV for PCV13 and PPSV23 sequence – ACIP, United States, September 2015

Clinical setting	Primary Dose	Booster Dose	Subsequent doses
Pneumococcal vaccine-naive persons	PCV13	PPV23 at ≥8 weeks	• PPV23 after 5 years • For patients with HIV aged ≥65 years, the recommended interval between PCV13 followed by PPSV23 is ≥8 weeks. For those for who previously received PPSV23 when aged <65 years and for whom an additional dose of PPSV23 is indicated when aged ≥65 years, this subsequent PPSV23 dose should be given ≥1 year after PCV13 and ≥5 years after the most recent dose of PPSV23.
Previous vaccination with PPV23	(≥1 PPV23)	PCV13 at least 1 year after the last PPV23	

Data taken from CDC (2012). Intervals Between PCV13 and PPSV23 Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP)). MMWR. 64(34):944-947.

The recommendation for an annual influenza immunization is important to prevent bacterial pneumonia, which might occur as a complication of influenza illness.

The summary of evidence and further information on the use of pneumococcal and Hib vaccine among HIV/AIDS patients can be found in the Philippine Guidelines on Immunization for Adults Living with Human Immunodeficiency Virus 2010 created by the HIV Immunization Guidelines Working Committee of the PSMID (HIGWC, 2010) and the new Adult Immunization Guidelines of the Philippine Society for Microbiology 2015.

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CRYPTOCOCCAL MENINGITIS

Introduction

Cryptococcosis is the most common life-threatening meningitis in AIDS (Aberg and Powderly, 2006). Most infections worldwide are caused by the yeast *Cryptococcus* neoformans var. neoformans, while a minority of infections due to *Cryptococcus* neoformans var. gattii have been documented. The proportions of infection from each variant in the Philippines is unknown. *Cryptococcus* spp. grow readily from soil contaminated with avian excreta, particularly those from pigeons. It is postulated that transmission occurs via inhalation of the basidiospores or unencapsulated forms, leading to colonization of the airways and subsequent respiratory infection and dissemination mainly in the CNS (Ellis and Pfeiffer, 1990).

Early in the epidemic, approximately 5%–8% of patients with AIDS developed cryptococcal infection. Where effective ARV treatment is available, the incidence of cryptococcosis has decreased markedly (Aberg and Powderly, 2006; Mirza et al., 2003). This OI is mostly seen among patients who have CD4 counts of <50 cells/μL, and is fatal if untreated. In the UP-PGH SAGIP clinic, 1.3% of HIV-infected patients had cryptococcal meningitis, and 100% of these cases had CD4 counts of <50 cells/μL (range: 24–49 cells/μL) (Salvaña et al., 2012).

XIV. What are the clinical signs and symptoms of cryptococcal meningitis?

42. HIV-infected patients presenting with signs and symptoms of meningitis, such as headache, altered mental status, with or without fever, should be suspected to have cryptococcal meningitis and worked up accordingly.

Strong recommendation, Moderate quality of evidence

Summary of Evidence

Cryptococcus meningitis typically presents as a subacute process characterized by headache, fever, and less often, altered mental status; however, presentations characteristic of either acute or chronic

meningitis can occur. Cranial nerve palsies and papilledema are the most common ocular manifestations seen in patients with cryptococcal CNS invasion. Classic meningeal symptoms and signs, such as neck stiffness and photophobia, occur in only one-fourth to one-third of patients. Encephalopathic symptoms, including lethargy, altered mentation, personality changes, and memory loss, usually resulting from elevated intracranial pressure, occurs in small groups of patients (Aberg and Powderly, 2006).

A recent Philippine case series described a tertiary hospital's experience with cryptococcal meningitis. However, HIV serostatus was not determined. In this study, the most common presenting complaint of cryptococcal meningitis was headache (76%), followed by nausea and vomiting (72%) and fever (52%) (Reyes et al., 2006).

When cryptococcosis occurs in the HIV-infected patient, disseminated disease is common. Virtually any organ can be involved, and skin lesions mimicking molluscum contagiosum are frequently observed. The lesions may appear as papules, tumors, vesicles, plaques, abscesses, cellulitis, purpura, draining sinus, ulcers, bullae, or subcutaneous swelling (Durden and Elewski, 1994).

XV. What tests are needed to diagnose cryptococcal meningitis?

43. The following tests are important in the diagnosis of cryptococcal meningitis in HIV patients:

Table 9. Important tests in the diagnosis of cryptococcal meningitis in HIV patients

Test	Expected results	GRADE
Basic CSF Analysis Opening pressure Protein Glucose Differential count Gram stain	 *Elevated* *Mildly elevated* *Low to normal* *Lymphocytic predominance* *Numerous yeasts*	Strong recommendation, High quality of evidence
CSF India Ink	*Positive encapsulated yeast*	Strong recommendation, High quality of evidence

Fungal Culture (Sabouraud's Dextrose Agar) CSF Blood	*Positive growth* *Positive growth*	Strong recommendation, High quality of evidence
Cryptococcal Antigen (CALAS) CSF Serum (if lumbar tap can't be done)	*Elevated titer** *Elevated titer**	Strong recommendation, Moderate quality of evidence
Cranial CT Scan Cranial MRI	*Hydrocephalus, gyral enhancement, or single or multiple nodules; but may be normal in 50% of cases.* *Numerous clustered foci*	Strong recommendation, Low quality of evidence

*False positive results may occur due to invasive infections with the yeast *Trischosporon beigelii, Capnocytophaga species* or *Rothia (Stomatococcus) mucilaginosus*

44. Routine testing of asymptomatic persons for serum cryptococcal antigen is not recommended.

Strong recommendation, Low quality of evidence

Summary of Evidence

Analysis of CSF usually demonstrates a mildly elevated serum protein; glucose ranging from low to normal; a pleocytosis consisting mostly of lymphocytes, although some patients have no cells; and a positive Gram or India ink stain for numerous yeasts. The opening pressure in the CSF is usually elevated, with pressures >20 cm H2O occurring in up to 75% of patients (Powderly et al., 1994).

In the Philippine case series, all patients who had a lumbar tap had elevated opening pressures; 83% had elevated total protein; 61% had hypoglycorrhachia; 83% had CSF WBC count >20 cells/μL; 70% had a positive India ink test; and 89% had a CSF cryptococcal antigen titer of >1:8. (Reyes et al., 2006).

The most widely used method for cryptococcal antigen determination is by latex agglutination, frequently requested as CALAS – Cryptococcal

Antigen Latex Agglutination System. It is almost invariably detected in CSF at high titer in patients with meningitis or meningoencephalitis. The serum cryptococcal antigen is also almost always positive in cases of CNS disease and in other instances of disseminated infection. Therefore, testing for serum cryptococcal antigen is a useful initial screening tool in diagnosing cryptococcosis in HIV-infected patients (Powderly et al., 1994). Positive cryptococcal antigen titers must be confirmed by culture, as false positive results may occur due to invasive infections with the yeast *Trischosporon beigelii*, *Capnocytophaga* species, or *Rothia* (*Stomatococcus*) *mucilaginosus*. Cultures are essential also in order to monitor response to treatment. Up to 70% of patients with HIV-associated cryptococcal meningitis have a positive serum cryptococcal antigen titer, and this may be used as a screening tool for patients in whom a lumbar tap cannot be safely performed. Also, up to 75% of patients with HIV-associated cryptococcal meningitis have routine blood cultures positive for *C. neoformans*.

Approximately 50% of CT scans are normal in CNS infection. However, a CT scan can reveal hydrocephalus, gyral enhancement, or single or multiple nodules that may or may not be enhancing. Cryptococcomas may be single or multiple, and in some populations (e.g., those with *C. gattii* infection), they can occur in up to 25% of non-AIDS and apparently immunocompetent patients. In patients with AIDS, the CT scan differs only in that approximately one-third of patients demonstrate cortical atrophy from the underlying HIV infection. MRI scans are more sensitive than CT scans for detecting abnormalities in cryptococcal meningoencephalitis. MRI findings can include numerous clustered foci that are hyperintense on T2-weighted images and non-enhancing on post-contrast T1-weighted images in the basal ganglia or mid-brain. Rarely, there may also be multiple miliary enhancing parenchymal and leptomeningeal nodules (Cornell and Jacoby, 1982; Tan and Kuan, 1987).

XVI. What are the standard and alternative treatments for cryptococcal meningitis?

45. A standard algorithm for the management of cryptococcal meningitis in patients with HIV is a three-stage regimen: induction phase, consolidation phase, and suppressive/maintenance phase.

The preferred regimen is Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily + fluconazole 800 mg PO or IV daily for 2 weeks or until CSF cultures are negative.

Strong recommendation, High quality of evidence

46. Consolidation phase is fluconazole 400 mg PO or IV once daily given for a total of at least 8 weeks; to begin after at least 2 weeks of successful induction therapy.

Strong recommendation, High quality of evidence

47. Suppressive or maintenace phase is with fluconazole 200 mg PO once daily, given for a total of at least 1 year until there is significant immune reconstitution. (See section on discontinuation of maintence phase for parameters for discontinuation).

Strong recommendation, High quality of evidence

48. Alternative regimens are summarized in Table 10.

Summary of Evidence

Induction Phase

The ideal induction treatment for cryptococcal meningitis and other forms of extrapulmonary cryptococcosis is a lipid formulation of amphotericin B in combination with flucytosine, particularly in patients with, or at risk for, renal dysfunction. Amphotericin B lipid formulations include liposomal amphotericin B, amphotericin B lipid complex and amphotericin B colloidal dispersion. A comparison of amphotericin B deoxycholate (0.7 mg/kg daily) and liposomal amphotericin B (3 mg/kg or 6 mg/kg daily) showed similar efficacies for the three regimens, but nephrotoxicity was lower with the 3 mg/kg daily liposomal amphotericin B (Hamill et al., 2010). A Cochrane review on treatment of acute cryptococcal meningitis in HIV-infected adults, with an emphasis on resource-limited settings, concluded that liposomal amphotericin B is associated with fewer adverse events and may be useful in selected patients where resources allow (Sloan et al., 2008). The non-comparative CLEAR study demonstrated a 58%

response rate in HIV-infected patients treated with amphotericin B lipid complex at a mean dose of 4.4 mg/kg daily (Baddour et al., 2005). A report of four cases showed that amphotericin B colloidal dispersion at 4–6 mg/kg/day was effective and may be an alternative form for those who cannot tolerate conventional amphotericin (Valero and Graybill, 1995). Therefore, liposomal amphotericin B, in a dose of 3–4 mg/kg/daily, is recommended as the preferred amphotericin B formulation for primary induction therapy, based on clinical experience and reduced renal toxicity compared to amphotericin B deoxycholate. Amphotericin B lipid complex at a dose of 5 mg/kg daily is an effective alternative. In areas where lipid formulations are not available, or if cost is prohibitive, conventional amphotericin B deoxycholate is recommended with proper monitoring of renal function and electrolytes.

Amphotericin B formulations should be combined with flucytosine at a dose of 100 mg/kg daily in four divided doses for ≥2 weeks in patients with normal renal function, and it is the preferred regimen for primary induction therapy. The addition of flucytosine to amphotericin B during acute treatment is associated with more rapid sterilization of CSF (van der Horst et al., 1997; Saag et al., 2000; Dromer et al., 2008; Sloan et al., 2008). Flucytosine, however, is not widely available in the Philippines. Amphotericin B deoxycholate in combination with fluconazole 400 mg daily was inferior to amphotericin B in combination with flucytosine for clearing *Cryptococcus* from CSF (Brouwer et al., 2004). However, in two randomized trials, amphotericin B plus fluconazole 800 mg daily compared favorably with amphotericin B alone (Day et al., 2013; Pappas et al., 2009). Therefore, amphotericin B deoxycholate or lipid-formulated amphotericin B alone or combined with fluconazole at 800 mg daily may be viable options.

Fluconazole alone, based on early fungicidal activity, is inferior to amphotericin B for induction therapy and is recommended only for patients who cannot tolerate or do not respond to standard treatment (Bicanic et al., 2007). A prospective longitudinal study of clinical outcomes from cryptococcal meningitis following treatment induction with 800 mg oral fluconazole showed high mortality and treatment failure (Rothe et al., 2013). If it is used for primary induction therapy, the starting daily dose should be 1200 mg (Nussbaum et al., 2010).

Table 10. Three-stage regiment for the management of cryptococcal meningitis in patients with HIV

Treatment Regimens	GRADE	Remarks
INDUCTION PHASE **Preferred regimen**		
Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily + fluconazole 800 mg PO or IV daily	*Strong recommendation, High quality of evidence*	
Alternative regimens that are available:		
Amphotericin B lipid complex 5 mg/kg IV daily + fluconazole 800 mg PO or IV daily	*Strong recommendation, Low quality of evidence*	
Amphotericin B colloidal dispersion 4–6 mg/kg IV daily + fluconazole 800 mg PO or IV daily	*Strong recommendation, Low quality of evidence*	
Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily alone	*Strong recommendation, Low quality of evidence*	
Amphotericin B lipid complex 5 mg/kg IV daily alone	*Weak recommendation, Low quality of evidence*	
Amphotericin B colloidal dispersion 4–6 mg/kg IV daily alone	*Weak recommendation, Low quality of evidence*	
Fluconazole 1200 mg PO or IV daily alone	*Weak recommendation, Low quality of evidence*	
Alternative regimens that are NOT widely available:		
Liposomal amphotericin B 3–4 mg/kg IV daily + flucytosine 25 mg/kg PO QID	*Strong recommendation, High quality of evidence*	This is the preferred regimen in developed countries where both liposomal amphotericin B and flucytosine are available. This is as effective, and it has reduced renal toxicity, compared to amphotericin B deoxycholate.
Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily + flucytosine 25 mg/kg PO QID	*Strong recommendation, High quality of evidence*	
Amphotericin B lipid complex 5 mg/kg IV daily + flucytosine 25 mg/kg PO QID	*Strong recommendation, Moderate quality of evidence*	

Liposomal amphotericin B 3–4 mg/kg IV daily + fluconazole 800 mg PO or IV daily	*Strong Recommendation, Moderate quality of evidence*	
Liposomal amphotericin B 3–4 mg/kg IV daily alone	*Strong recommendation, Moderate quality of evidence*	
Fluconazole 400–800 mg PO or IV daily + flucytosine 25 mg/kg PO QID	*Strong recommendation, Moderate quality of evidence*	
CONSOLIDATION PHASE		
Fluconazole 400 mg PO or IV once daily	*Strong recommendation, High quality of evidence*	Given for a total of at least 8 weeks; to begin after at least 2 weeks of successful induction therapy (defined as substantial clinical improvement AND a negative CSF culture after repeat lumbar puncture)
SUPPRESSIVE / MAINTENANCE PHASE		
Fluconazole 200 mg PO once daily	*Strong recommendation, High quality of evidence*	Given for a total of at least 1 year; see section on discontinuation of suppressive therapy
Important Considerations: • Caution should be observed in treating patients with concomitant TB, due to drug interactions between anti-TB medication containing rifampicin, isoniazid and pyrazinamide and fluconazole. • Flucytosine should be adjusted according to creatinine clearance.		

Consolidation Phase

After at least 2 weeks of successful induction therapy (defined as substantial clinical improvement and a negative CSF culture after repeat lumbar puncture), consolidation therapy with fluconazole 400 mg daily can be initiated. The consolidation phase should continue for at least 8 weeks (van der Horst et al.,1997; Saag et al., 2000; Saag et al., 1999).

Suppressive/Maintenance Phase

After consolidation therapy, fluconazole should be reduced to 200 mg daily and continued as chronic maintenance therapy to complete at least 1 year of azole therapy (Powderly et al., 1992). (See section on discontinuation of suppressive therapy for detailed discussion.)

XVII. What adjunctive treatments for cryptococcal meningitis are necessary?

49. Co-management with a neurologist in patients with cryptococcal meningitis is recommended.

Strong recommendation, Low quality of evidence

50. Daily lumbar punctures are recommended for initial management in patients with persistently elevated pressures.

Strong recommendation, High quality of evidence

51. At the time of diagnosis, all patients with cryptococcal meningitis should have their opening pressure measured in the lateral decubitus position; normal values should be <25 cm H2O.

Strong recommendation, High quality of evidence

52. CSF shunting should be considered for patients in whom daily lumbar punctures are no longer tolerated or whose signs and symptoms of cerebral edema are not relieved by daily lumbar punctures.

Strong recommendation, Moderate quality of evidence

53. Corticosteroids and acetazolamide are not recommended for the management of elevated intracranial pressure.

Strong recommendation, Low quality of evidence

54. Mannitol may be used as an option for the management of elevated intracranial pressure on a case by case basis.

Weak recommendation, Low quality of evidence

Summary of Evidence

A critical management issue in cryptococcal meningitis is increased intracranial pressure (ICP). Increased ICP can cause clinical deterioration despite a good microbiologic response, and it is more likely if the CSF opening pressure is >20 cm H2O (van der Horst et al., 1997; Graybill et al., 2000). In one large clinical trial, 93% of deaths that occurred within the first 2 weeks of therapy and 40% of deaths that occurred within weeks 3–10 were associated with increased ICP (Graybill et al., 2000).

At the time of diagnosis, all patients with cryptococcal meningitis should have their opening pressure measured in the lateral decubitus position with good manometrics assured; normal values are <25 cm H2O. Patients with confusion, blurred vision, papilledema, lower extremity clonus, or other neurologic signs of increased ICP should be managed using measures to decrease ICP. Daily lumbar punctures are usually recommended for initial management in these patients. One approach is to remove a volume (typically 20–30 mL) of CSF that halves the opening pressure (Fessler et al., 1998). CSF shunting should be considered for patients in whom daily lumbar punctures are no longer tolerated or in those whose signs and symptoms of cerebral edema are not being relieved.

Medications other than antifungal drugs are not useful in the management of increased intracranial pressure in cryptococcal meningoencephalitis. A randomized trial in Thailand found severe metabolic acidosis and other complications associated with acetazolamide therapy, causing the study to be stopped prematurely (Newton et al., 2002). Corticosteroids and mannitol have been shown to be ineffective in managing ICP and are not recommended. Despite not being included in the protocol, high-dose corticosteroids were used in 41 of 110 HIV-infected patients during initial therapy (Graybill et al., 2000). Ten of 13 patients with pressures 135 cm of CSF were treated with corticosteroids specifically for intracranial pressure elevation. Of all patients given high-dose corticosteroids, there was no benefit observed, in fact, a trend to higher mortality and clinical deterioration was observed in recipients of corticosteroids (Perfect et al, 2010).

XVIII. How do we monitor response to therapy and adverse events?

55. After the initial 2 weeks of treatment, a repeat lumbar puncture with CSF fungal culture should be performed to ensure the organism has been cleared from the CSF, even among those who have improved after the initial 2 weeks of treatment.

Strong recommendation, Moderate quality of evidence

56. Serum and CSF cryptococcal antigen titers and CSF India ink should not be used to monitor response to treatment.

Strong recommendation, Moderate quality of evidence

57. Patients treated with amphotericin B should be monitored for dose-dependent nephrotoxicity and electrolyte disturbances.

Strong recommendation, Low quality of evidence

58. Preinfusion administration of 500 mL of normal saline may be given to reduce the risk for nephrotoxicity during treatment.

Strong recommendation, Low quality of evidence

59. Infusion-related adverse reactions may be ameliorated by pre-treatment with acetaminophen and diphenhydramine.

Weak recommendation, Low quality of evidence

60. Persons treated with fluconazole should be monitored for clinical signs of hepatotoxicity.

Strong recommendation, Moderate quality of evidence

61. Initiation of ARVs should be delayed for at least 5 weeks for severe cryptococcosis, especially in patients with elevated ICP.

Strong recommendation, High quality of evidence

Summary of Evidence

After the initial 2 weeks of treatment, a repeat lumbar puncture with fungal culture should be performed to ensure the organism has been cleared from the CSF, even among those who have improved after the initial 2 weeks of treatment. Positive CSF cultures after 2 weeks of therapy are predictive of future relapse and typically less favorable clinical outcomes. A combined cohort of 262 patients showed that the rate of clearance of infection is independently associated with clinical outcome in HIV-associated cryptococcal meningitis (Bicanic et al., 2009). If new symptoms or clinical findings occur later, a repeat lumbar puncture, with measurement of opening pressure and CSF culture, should be performed.

Cryptococcal antigen titers and India ink are not recommended for monitoring response to treatment. A positive CSF India ink or Gram stain by itself is not sufficient for determining relapse (Perfect et al., 2010). These may represent dead organisms and their viability can only be demonstrated by a positive fungal culture. A study by Powderly et al. (1994) showed a limited role for antigen monitoring during therapy for cryptococcal meningitis in patients with AIDS. There was no correlation between changes in serum titers of cryptococcal antigen and outcome of acute or suppressive therapy. CSF sampling, however, had some value. During acute therapy, an unchanged or increased CSF titer of cryptococcal antigen correlated with a lack of clinical and mycologic response, especially in patients whose baseline titer was >1:8. Similarly, a rise in CSF antigen titer during suppressive therapy was associated with relapse of cryptococcal disease. Although the data suggest that a stable or rising titer of cryptococcal antigen in CSF during antifungal therapy is associated with a greater risk of failure of acute therapy and of relapse during suppressive treatment, a considerable number of patients failed to respond to acute therapy or had a relapse during suppressive therapy despite falling antigen titers in CSF (Powderly et al., 1994).

Patients treated with amphotericin B should be monitored for dose-dependent nephrotoxicity and electrolyte disturbances. Pre-infusion administration of 500 mL of normal saline appears to reduce the risk for nephrotoxicity during treatment. Infusion-related adverse reactions may be ameliorated by pre-treatment with acetaminophen and diphenhydramine. Persons treated with fluconazole should be monitored for hepatotoxicity (Powderly et al., 1994).

An estimated 30% of patients with cryptococcal meningitis and HIV infection experience Immune Reconstitution Inflammatory Syndrome (IRIS) after initiation or reinitiation of ARV (Shelburne et al., 2005). Patients who have cryptococcal IRIS are more likely to be ARV naïve and have higher HIV RNA levels. Appropriate management of presumed IRIS is to continue ARV and antifungal therapy. In patients with severely symptomatic IRIS, short-course glucocorticosteroids are recommended by certain specialists. A recent randomized trial of early (1–2 weeks) or deferred (5 weeks) ARV initiation in cryptococcal meningitis patients undergoing induction therapy showed a increased risk of death (hazard ratio [HR] for death, 1.73; 95% confidence interval [CI], 1.06 to 2.82; p=0.03) for those who underwent early ARV treatment (Boulware et al., 2014).

XIX. How do we manage treatment failure?

62. Treatment failure is rare for those treated with the preferred regimen. For those initially treated with fluconazole alone, therapy should be changed to amphotericin B, with or without fluconazole, and continued until a clinical response occurs.

Strong recommendation, Low quality of evidence

63. Liposomal amphotericin B or amphotericin B lipid complex is better tolerated and may have greater efficacy than the deoxycholate formulation and should be considered when initial treatment with other regimens fails.

Strong recommendation, Low quality of evidence

Summary of Evidence

There is treatment failure if clinical improvement after 2 weeks of appropriate therapy is not observed. This includes management of increased ICP with continued positive cultures, or relapse after an initial clinical response. Although fluconazole resistance has been reported with *C. neoformans*, it is rare (Brandt et al., 2001). At this time, susceptibility testing is not recommended routinely since its applicability is unknown.
There is no established optimal therapy for patients with treatment failure. For those initially treated with fluconazole, therapy should be changed to

amphotericin B, with or without 800 mg fluconazole, and continued until a clinical response occurs. Liposomal amphotericin B (4–6 mg/kg/day) might have improved efficacy over the deoxycholate formulation (Chen and the Australasian Society for Infectious Diseases [ASID] Mycoses Interest Group, 2002; Leenders et al., 1997) and should be considered in treatment failures. Caspofungin and other echinocandins have no in vitro activity against *Cryptococcus* spp. and no role in the clinical management of these patients. The newer triazoles posaconazole and voriconazole have activity against *Cryptococcus* spp. in vitro and might have a role in therapy.

XX. What is the role of antifungal prophylaxis in preventing occurrence and recurrence of cryptococcal meningitis?

64. Antifungals should not be routinely used for primary prophylaxis.

Strong recommendation, Low quality of evidence

65. Patients who have completed the initial 10 weeks of therapy for acute cryptococcal meningitis should be administered chronic maintenance therapy with fluconazole 200 mg daily for at least 1 year.

Strong recommendation, High quality of evidence

Summary of Evidence

HIV-infected persons cannot completely avoid exposure to *C. neoformans*. Limited epidemiologic evidence suggests that specific activities, including exposure to bird droppings, lead to an increased risk for infection. Because the incidence of cryptococcal disease is low, routine testing of asymptomatic persons for serum cryptococcal antigen is not recommended (Powderly et al., 1995).

Prospective controlled trials indicate that fluconazole and itraconazole can reduce the frequency of primary cryptococcal disease among patients who have CD4 <50 cells/μL (McKinsey et al., 1999; Powderly et al., 1995). However, the majority of HIV specialists recommend that antifungal prophylaxis not be used routinely to prevent cryptococcosis because of the relative infrequency of cryptococcal disease, lack of survival benefits

associated with prophylaxis, possibility of drug interactions, potential antifungal drug resistance, and cost. The need for primary prophylaxis or suppressive therapy for other fungal infections should be considered when making decisions concerning primary prophylaxis for cryptococcosis.

Patients who have completed the initial 10 weeks of therapy for acute cryptococcosis should be administered chronic maintenance therapy with fluconazole 200 mg daily, either lifelong or until immune reconstitution with ART. Itraconazole is inferior to fluconazole for preventing relapse of cryptococcal disease (Larsen, 1999; Powderly et al., 1992).

XXI. When do we discontinue suppressive/maintenance therapy?

66. After 1 year of fluconazole maintenance therapy, fluconazole may be discontinued in those with CD4 counts consistently >100 cells/μL for more than 6 months.

Strong recommendation, High quality of evidence

67. Maintenance therapy should be reinitiated if the CD4 count decreases to <100 cells/μL.

Strong recommendation, Moderate quality of evidence

Summary of Evidence

The risk for recurrence of cryptococcosis appears low when patients have successfully completed a course of initial therapy, remain asymptomatic with regard to signs and symptoms of cryptococcosis, and have a sustained increase (i.e., >6 months) in their CD4 count to >100 cells/μL after ARV. The numbers of such patients who have been evaluated remain limited. In a European study, none of 39 subjects in whom antifungal therapy was discontinued had a recurrence of cryptococcosis. The median CD4 count of this cohort was 239 cells/μL, the median HIV RNA concentration was <500 copies/mL, and the median time on potent ARV was 25 months (Kirk et al., 2002). A prospective randomized study of 60 patients in Thailand documented no cases of recurrence after 48 weeks when the CD4 count was >100 cells/μL and HIV RNA was undetectable for 3 months (Vibhagool et al., 2003). On the basis of two published studies and inference from

data regarding safety of discontinuing secondary prophylaxis for other OIs during advanced HIV disease, discontinuing chronic maintenance therapy among such patients who have successfully completed a course of initial therapy when the CD4 count is consistently >100 cells/μL is reasonable (Mussini et al., 2004). Maintenance therapy should be reinitiated if the CD4 count decreases to <100 cells/μL and continued until further immune reconstitution is achieved.

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CANDIDIASIS

Introduction

Candidiasis is a fungal infection caused by the yeast *Candida* spp. *Candida* is part of the normal flora of the skin and mucous membranes but can overgrow and cause disease in immunosuppressed patients. Colonization of the oral cavity with *Candida* among persons living with HIV can occur in up to 81%, and about one-third of these patients can become symptomatic (Thompson et al., 2010; Wu et al., 2011). Prevalence of symptomatic oral candidiasis among persons living with HIV ranges from 31%–90% (Han et al., 2012; Moura et al., 2010; Ianas et al., 2010). According to Philippine data involving HIV-infected patients in a tertiary hospital involving 476 patients, 11 patients or 2.3% had oral candidiasis while 5 patients or 1.1% had esophageal candidiasis (Salvaña et al, 2012). The presence of mucosal candidiasis is a marker of immunosuppression and is associated with a CD4 count of <200 cells/μL among HIV-infected individuals (Bodhade et al., 2011; Han et al., 2012; Tami-Maury et al., 2011). The most common identified causative agent of candidiasis is *Candida albicans* (Thompson et al., 2010; Vasquez et al., 2006). Risk factors associated with mucosal candidiasis among patients living with HIV are a CD4 count <200cells/μL, presence oral leukoplakia, previous use of fluconazole, and viral copies of >3000 copies/mL (Bodhade et al., 2011; Moura et al., 2010). The frequency and severity of disease are associated with the degree of immunosuppression. Patients with CD4 counts of <50 cells/μL were six times more likely to develop oral candidiasis than patients with a CD4 count of >50 cells/μL (Tami-Maury et al., 2011).

Presentation of candidiasis among persons living with HIV

The two most common locations for candidiasis among persons living with HIV are the oropharynx and the esophagus. Oropharyngeal candidiasis is described as painless, creamy white plaque-like lesions of the oral mucosa or at the tongue surface. It can easily be scraped off from the mucosa

with a tongue depressor. A less common presentation is erythematous patches without white plaques that are usually seen in the anterior or posterior palate. Esophageal candidiasis is usually asymptomatic but may present with dysphagia, odynophagia, or retrosternal pain (Thompson et al., 2010). Esophageal candidiasis can occur with or without associated oropharyngeal candidiasis. Episodes are more severe and more frequent among HIV-infected patients with severe immunosuppression and low BMI (Tami-Maury et al., 2011).

XXII. How is candidiasis diagnosed among patients living with HIV?

68. Diagnosis of oropharyngeal candidiasis can be made on clinical characteristics of oral lesions.

Strong recommendation, Low quality of evidence

69. Diagnosis of esophageal candidiasis can be made if there is oropharyngeal candidiasis and dysphagia.

Strong recommendation, Low quality of evidence

70. For suspected esophageal candidiasis, confirmation of the disease may be done through endoscopic findings of lesions similar to oropharyngeal candidiasis.

Weak recommendation, High quality of evidence

71. Biopsy and culture of the lesions can be done to confirm the diagnosis. Culture of the lesions can provide the *Candida* species and drug susceptibility.

Weak recommendation, High quality of evidence

72. If the clinical diagnosis is in doubt, microscopic examination of the scrapings from the lesion using KOH preparation can be done. Culture of the material can determine the species and susceptibility if needed.

Weak recommendation, Low quality of evidence

Summary of Evidence

A study was done involving 85 HIV-infected patients with the presence of oral patchy white plaques. The goal of the study was to evaluate the diagnosis of esophageal candidiasis just by the presence of oral lesions with swallowing symptoms such as odynophagia, dysphagia, or retrosternal burning pain. Results of the study showed that mucosal lesions and swallowing symptoms are diagnostic of oral candidiasis, with sensitivity, specificity, PPV and NPV of 83%, 100%, 100% and 82%, respectively (Ravera et al., 1999).

Another study involving 134 HIV patients compared diagnostic trial with fluconazole and endoscopy for patients with new esophageal symptoms. Patients >18 years old and with problems with swallowing were randomly assigned either in the fluconazole group or in the endoscopy group. Among the fluconazole group, 82% had a complete symptomatic response. The most common endoscopic findings were *Candida* esophagitis comprising 64%. The empirical fluconazole was cost effective, with savings of $738.16 per patient (Wilcox et al., 1996).

XXIII. What are the standards and alternatives of treatment of oral candidiasis among patients living with HIV?

73. Fluconazole is considered the drug of choice at an oral dose of 100–200 mg daily for 7–14 more days.

Strong recommendation, High quality of evidence

74. Itraconazole at 200 mg daily for 7–14 days is as effective as fluconazole but with greater side effects.

Strong recommendation, High quality of evidence

75. Nystatin is inferior to fluconazole as treatment for candidiasis and should not be used as a first-line drug.

Strong recommendation, High quality of evidence

76. Posaconazole oral solution can be used as an effective substitute for fluconazole, with better tolerance than itraconazole; but it is expensive.

Weak recommendation, High quality of evidence

Summary of Evidence

In a prospective randomized third-party blind multicenter trial conducted at 12 centers in the United States involving 179 HIV-infected patients, patients with mycologically documented oropharyngeal candidiasis were assigned either to 200 mg itraconazole for 7–14 days or fluconazole 100 mg/day with a 200 mg loading dose on the first day. Clinical response and relapse were comparable in both arms (97% for itraconazole and 87% for fluconazole). In a meta-analysis involving three trials with a total number of 474 HIV patients with oropharyngeal candidiasis, analysis revealed no benefit of one drug over another with no significant heterogeneity. Relapses were similar in both groups, and there were no differences in the number of adverse events reported in both drugs.

According to a meta-analysis done regarding prevention and management of oropharyngeal candidiasis associated with HIV infection in adults and children, fluconazole favored clinical and mycological cure compared to nystatin (RR 10.37 95% CI 3.89–27.66) (Piennar et al., 2010).

Comparing the efficacy of fluconazole and posaconazole in HIV patients with oropharyngeal candidiasis, a multicenter randomized evaluator-blinded trial involving 358 subjects was done. Dosage for both groups started at 200 mg at day 1, followed by 100 mg/day for 13 days. Clinical success was 91.6% in the posaconazole group, while it was 92.5% on the fluconazole group. In a 42-day follow-up, mycological success was significantly greater in the posaconazole group than the fluconazole group (40.6% vs. 26.4%), and the posaconazole recipients experienced less relapse (31.5% vs. 38.2%) (Piennar et al., 2010).

A prospective randomized double-blind placebo-controlled trial compared the clinical and mycological responses, relapse rate and safety of a single-dose 750 mg fluconazole and a 14-day course of treatment with fluconazole. The trial involved 220 HIV-infected patients with clinical and

mycological evidence of candidiasis. Clinical cure was comparable on both arms (95.5% on the 14-day fluconazole group vs. 94.5% on the single-dose fluconazole group; p=0.99) while mycological cure rates were 75.5% in the 14-day treatment group and 84.5% in the single-dose fluconazole group. The average time to relapse after clinical cure was 20 days in the 14-day group compared to 18 days in the single-dose group (p=0.99). Adverse events were uncommon in both groups (Hamza et al., 2008).

Miconazole microadhesive troches have shown some promise as a topical alternative, may be as effective as systemic therapy in mild cases, but are quite expensive. Due to the small number of studies available, we cannot make a specific recommendation on this drug (Vasquez and Sobel, 2012).

XXIV. What is the treatment of esophageal candidiasis in persons living with HIV?

77. Systemic antifungals are effective for esophageal candidiasis with a 14- to 21-day duration. Fluconazole or itraconazole is highly effective, at similar doses for oropharyngeal candidiasis.

Strong recommendation, High quality of evidence

78. Micafungin and anidulafungin are alternatives for those unable to tolerate itraconazole and fluconazole.

Strong recommendation, High quality of evidence

Summary of Evidence

A multicenter randomized double-blind study in 126 immunocompromised patients with endoscopically and KOH/culture-confirmed esophageal candidiasis compared the efficacy and safety of oral itraconazole solution and fluconazole tablets in the treatment of esophageal candidiasis. Patients received either 100 mg fluconazole or 200 mg itraconazole for a duration of 2 weeks and were followed up for another 4 weeks. Clinical response, mycologic cure, and relapse rate were 94%, 92%, and 18%, respectively, for the itraconazole group; and 91%, 78%, and 27%, respectively, for the fluconazole group. Adverse events were the same for both groups and were generally well tolerated by the patients (Wilcox et al., 2009).

A randomized double-blind parallel-group dose-response study compared micafungin with fluconazole for the treatment of esophageal candidiasis in HIV-infected patients. Patients with history of fluconazole resistant *Candida albicans* infection were excluded from the study. Patients were randomly assigned to either micafungin 50 mg,100 mg, or 150 mg per day; or fluconazole 200 mg IV per day for 14–21 days. Rates of discontinuation were similar in the fluconazole and micafungin group. No statistically significant difference was noted in the endoscopic cure rates between the 150 mg micafungin and fluconazole group and the 100 mg micafungin and fluconazole group. Relapse on 2-week follow-up were noted in 4% of the micafungin group, while none from the fluconazole group had recurrence (De Wet el al., 2004).

According to Krause et al. (2004), a randomized double-blind trial of anidulafungin versus fluconazole was done for the treatment of esophageal candidiasis involving immunocompromised patients with endoscopy and culture-confirmed esophageal candidiasis. Patients were given either anidulafungin 100 mg on day 1, followed by 50 mg per day, versus oral fluconazole 200 mg per day for 7 days beyond the resolution of symptoms but not beyond 21 days. There were 300 patients included in the anidulafungin group, while 301 were included in the oral fluconazole group. The anidulafungin group and fluconazole group had 74% and 77% patients with AIDS, respectively. Endoscopic success was 97.2%, compared to 98.8% in the fluconazole group. Clinical success was also comparable: 98% for the anidulafungin vs. 99% for the oral fluconazole group). Time to resolution of symptoms and episodes of adverse events were similar. Sustained endoscopic success on a 2-week follow-up was 64% for the anidulafungin group, while 89.5% did not relapse in the fluconazole group ($p<0.001$) (Krause et al., 2004).

XXV. What is the optimal management of treatment failure or refractory mucosal candidiasis among patients living with HIV?

79. Posaconazole and itraconazole are recommended for refractory oropharyngeal and/or esophageal candidiasis.

Strong recommendation, High quality of evidence

Summary of Evidence

An open-label study was done to evaluate the efficacy and safety of oral posaconazole for HIV-infected subjects with oropharyngeal and esophageal candidiasis who were clinically refractory to treatment with oral 100 mg fluconazole or 200 mg oral itraconazole. The study involved 199 subjects with documented HIV and evidence of oropharyngeal and/or esophageal candidiasis with lack of improvement or worsening of mucosal candidiasis after fluconazole and itraconazole (10 days for oropharyngeal candidiasis and 21 days for esophageal candidiasis). Groups were assigned either oral posaconazole suspension 400 mg twice a day for 3 days followed by 400 mg daily for another 25 days followed by suppressive treatment 400 mg twice daily, thrice per week, for 3 months (group A); or 400 mg BID for 28 days (group B). Baseline cultures showed refractoriness to prior antifungal therapy in 89% in group A and 80% in group B. In a modified intent-to-treat study, clinical response was 75% in both groups, while mycological response at 1 month of treatment was 35.4% in group A and 37.7% in group B. Follow-up cultures at 4 weeks after treatment were done in 80 patients, with relapses occurring in 80% on regimen A and 68% on regimen B. Clinical response, mycological response and relapse were not statistically different between groups.

A prospective open-label intervention study was done involving 74 patients infected with HIV to evaluate the efficacy of itraconazole oral solution in fluconazole-refractory oropharyngeal candidiasis. There were 36 HIV-infected patients with a history of persistent thrush despite 14 days of 200 mg/day fluconazole in the study. Patients were given itraconazole 100 mg BID for 14–28 days followed by 6 months of suppressive therapy. Clinical response was noted in 55% of patients. Of the 22 patients who entered the maintenance therapy phase, 100% eventually relapsed (Saag et al., 1999). In a prospective open-label intervention study, the efficacy of itraconazole cyclodextrin solution was evaluated in fluconazole-refractory oropharyngeal candidiasis, which was defined as persistence of oral lesions after 10 days of treatment with 100 mg oral fluconazole. All of the cultures collected at baseline were resistant to fluconazole. Patients received 100 mg solution for 2 weeks, followed by maintenance therapy of 200 mg thrice weekly. Clinical response was noted in 65%; and on follow-up, 36% had relapsed (Philips et al., 1996).

XXVI. How do we prevent recurrence of candidiasis among patients living with HIV?

80. Routine prophylaxis with fluconazole is not recommended because mucosal candidiasis is associated with low mortality and increases the risk for drug interactions. Chronic use of antifungals can select for resistance among the *Candida* species.

Strong recommendation, Low quality of evidence

81. Prophylaxis may be considered in HIV-infected patients with frequent or severe mucosal candidiasis.

Weak recommendation, Low quality of evidence

82. If secondary prophylaxis is initiated, fluconazole is the drug of choice.

Weak recommendation, High quality of evidence

83. Initiation of ARVs reduces the risk of recurrent candidiasis.

Strong recommendation, Moderate quality of evidence

Summary of Evidence

In a meta-analysis done on treatment and prevention of candidiasis among HIV patients, nystatin has no significant effect in preventing recurrences of oral candidiasis compared to placebo (RR 85 CI 95% 0.69–1.05). In the same meta-analysis, five trials compared fluconazole with placebo. Prevention of clinical episodes was favored by fluconazole (RR 0.61 95% CI 0.50–0.73). Itraconazole was also compared to placebo with a population size of 298. Results showed that recurrences were similar, and with more adverse reactions in the itraconazole group (Pienar et al., 2010).

A randomized open-label multicenter prevention study of refractory mucosal candidiasis compared episodic fluconazole versus continuous use of fluconazole (200 mg orally 3x weekly) in HIV-infected patients with CD4 <150 cells/μL with a history of oropharyngeal candidiasis. Patients

with a history of continuous use of systemic or oral antifungal drug for more than 1 month within the past 3 months were excluded from the study. The primary endpoint was the time to develop fluconazole refractory oropharyngeal candidiasis or esophageal candidiasis. A total of 413 subjects were randomized in the continuous group and 416 patients in the episodic group. After a follow-up of 42 months, 4.1% and 4.3% in the continuous and episodic fluconazole group, respectively, developed fluconazole-refractory oropharyngeal candidiasis or esophageal candidiasis. There was no difference in the development of fluconazole-refractory infection within 24 months (p=0.88) or before 42 months (p=0.97). Continuous fluconazole was associated with fewer cases of oropharyngeal candidiasis or esophageal candidiasis (p<0.0001) and fewer invasive fungal infections (p=0.04), but it did not improve survival. The proportion of patients in whom the final *Candida* isolate was resistant to fluconazole was 50 of 110 (45%) in the continuous fluconazole arm and 79 of 218 (36%) in the episodic fluconazole arm (p=0.11) (Goldman et al., 2005).

A cross-sectional study was done to investigate the occurrence of mucocutaneous disorders, its relationship with the degree of immunosuppression, and the influence of initiation of ARV on mucocutaneous manifestations. Two hundred fifty-nine patients received ARV (median duration 21 months, 6–33 months) while 89 patients had not started ARV. Oral candidiasis representing 28.74% of the mucocutaneous lesions were more prevalent in patients with CD4 counts below 200 cells/μL (43.78 vs 8.16%, p<0.001). ARV initiation was associated with significant difference in prevalence of oral candidiasis (64% vs 16.6%, p<0.001) (Han et al., 2012).

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CYTOMEGALOVIRUS DISEASE

Introduction

Cytomegalovirus (CMV) is a double-stranded DNA virus belonging to the β-herpes viruses (HHV-5) group. CMV asymptomatically infects a large part of the human population but can cause serious morbidity and mortality among patients with severe immunosuppression. CMV infection involving different organs was one of the most important OIs in AIDS patients prior to the widespread use of ARVs (Meyer-Olson et al., 2010; Straus, 2005). It was a major cause of morbidity and mortality in these patients, and nearly half of untreated HIV-infected patients eventually developed CMV end-organ disease in the form of chorioretinitis, esophagitis, colitis, pneumonia, or central nervous system disease (Hoover et al., 1993; Lerner and Tapper, 1984). Disease is usually from reactivation from latent reservoirs in WBCs and less commonly may arise de novo from reinfection with a novel strain. End-organ disease caused by CMV occurs among persons with CD4 counts <50 cells/μL, who are either not receiving or have failed to respond to ARV. Other risk factors for reactivation include previous OIs and high plasma HIV RNA levels (>100,000 copies/mL) (Arribas et al., 1996; Dieterich and Rahmin, 1991; Jabs et al., 2000).

The most common end-organ affected by CMV is the eye, with CMV retinitis affecting up to 30% of patients with AIDS in the pre-ARV era, and making up nearly 80% of CMV disease in HIV (Dieterich and Rahmin, 1991; Jabs et al., 2000). New cases of CMV disease in AIDS patients in the mid-1990s dramatically declined by 75%–80% of previous estimates with the advent of ARV and now account for less than five cases per 100 person-years (Jabs et al., 2007). The rate of recurrence of active lesions for established CMV retinitis has become substantially lower as well, at 0.58 per person-year for those with CD4 cells <50 cells/μL. However, even for those with immune recovery sufficient to discontinue anti-CMV therapy (i.e., >100 cells/μL), relapse of the retinitis can occur at a rate of 0.03 per person-year and can occur even at normal CD4 counts (Jabs et al., 2004). Therefore, whether anti-CMV therapy is continued, regular ophthalmologic follow-up is needed. Local data from the PGH clinic has shown that CMV occurs at a mean CD4 count of 48 cells/μL with a range of 0–111 and made up 5.8% of the documented OIs (Salvaña et. al, 2012).

HIV-infected MSM patients have been found to have a CMV seroprevalence of above 90% (Meyer-Olson et al., 2010). CMV may also play a significant role in HIV-disease progression (Griffiths, 2006). A few early studies have found evidence of an increased risk for HIV-disease progression for adult CMV-seropositive patients in hemophiliacs (Sabin et al., 1995; Sabin et al., 2000; Webster et al., 1989; Webster et al., 1992). CMV-seropositive HIV-infected patients progress approximately 2.5 times faster than CMV-seronegative patients, and CMV-seropositive HIV-infected patients with CD4 counts over 100 cells/μL have an increased risk for progression to AIDS compared with CMV seronegative counterparts (Meyer-Olson et al., 2010). However, this relationship between CMV seropositivity and HIV-disease progression has not been seen in later studies (Becherer et al., 1990; Rabkin et al., 1993; Touloumi et al., 1998). Aside from overall immune status, host genetic factors may influence mortality, occurrence and progression of retinitis, and retinal detachment (Jabs and Martin, 2010; Sezgin and van Natta, 2011).

XXVII. What are the clinical signs and symptoms of CMV?

84. CMV retinitis can be diagnosed clinically through fundoscopy and compatible symptoms in HIV patients with CD4 count <100.

Strong recommendation, Moderate quality of evidence

85. CMV colitis should be suspected in HIV patients with diarrhea and compatible signs and symptoms and with CD4 count <100.

Strong recommendation, Moderate quality of evidence

Summary of evidence

The risk of CMV end-organ disease HIV is largely dependent on the CD4 count and is rarely observed above 50 cells/μL. Signs of severe immunodeficiency, such as other OIs, should prompt a search for CMV infection when a compatible clinical picture exists. There is a broad range of clinical manifestations of CMV infection, and the presenting symptoms of systemic CMV disease can be nonspecific (Kaplan et. al, 2009; Drew and Lalezari, 2006; Goldberg et al., 2005).

Patients may present with symptoms across different organ systems, particularly visual disturbances such as decreased visual acuity, floaters and visual field defects in CMV retinitis, and severe intractable diarrhea and gastrointestinal bleeding in CMV colitis. AIDS-related CMV retinitis is hematogenously disseminated and occurs after reactivation of latent CMV infection. Unilateral disease occurs in two-thirds of patients at presentation; without treatment or immune recovery, viremic dissemination eventually results in bilateral disease in most patients (Kaplan et al., 2009). This presents as a painless, progressive loss of vision occuring insidiously or rapidly. CMV retinitis is a full-thickness necrotizing retinitis. The characteristic ophthalmologic appearance is fluffy white-yellow lesions, sometimes with intraretinal hemorrhage, and little inflammation of the vitreous, unless immune reconstitution with potent ARV occurs. Blood vessels near the lesions may look sheathed (Kaplan et al., 2009; Goldberg et al., 2005; Holland, 2008; Jacobsen et al., 2012). Without appropriate treatment, retinitis invariably progresses, typically in 10–21 days after initial presentation. The progression of retinitis occurs erratically, causing a characteristic brushfire pattern, with a granular white leading edge advancing before an atrophic gliotic scar (Holland, 2008).

Gastrointestinal CMV infection may present as a stomatitis with oral ulcers; as an esophagitis in up to 10% of persons with AIDS complaining of dysphagia or odynophagia; or as a colitis in up to 10% of persons with AIDS and CMV end-organ disease. Clinical manifestations of CMV colitis include abdominal pain, bloody diarrhea, weight loss, rectal ulcers, fever, anorexia, and malaise. Mucosal ulceration if extensive can lead to hemorrhage and perforation which can be life-threatening (Holland, 2008).

Other less common sites of CMV disease include the nervous, pulmonary, cardiovascular and urogenital systems. These will not be expounded upon in this guideline, and appropriate subspecialty consult is encouraged if CMV in these organs is suspected.

XXVIII. What tests are needed to diagnose CMV?

86. CMV antibodies (IgM and IgG) are not useful for determining CMV disease activity, but CMV IgG may be useful for ruling in reactivation disease and can be ordered as part of the baseline workup.

Weak recommendation, Moderate quality of evidence

87. CMV viral culture is not recommended for the diagnosis of CMV of any form since asymptomatic viral shedding occurs even in those without clinical disease.

Strong recommendation, Low quality of evidence

88. Fundoscopy should be done for all HIV patients with low CD4 counts <100 regardless of the presence symptoms in order to screen for CMV retinitis.

Strong recommendation, High quality of evidence

89. Colonoscopy with biopsy of ulcerated lesions showing typical histopathologic features is recommended for the diagnosis of CMV colitis.

Strong recommendation, High quality of evidence

XXIX. What is the role of CMV antigenemia/CMV PCR in patients with suspected CMV?

90. In cases of suspected CMV end-organ disease where histopathologic diagnosis is not possible, CMV antigenemia or CMV PCR can be used to rule out the diagnosis. CMV antigenemia should not be done in asymptomatic patients.

Strong recommendation, Moderate quality of evidence

Summary of Evidence

CMV viremia can be detected by PCR or p65-antigen assays and is usually observed in end-organ disease, but viremia may also be present in the absence of end-organ disease. In immunocompromised hosts, these assays can detect CMV DNA or antigen from blood even prior to the onset of clinical symptoms, and they can identify individuals at risk for developing CMV disease. These assays are also useful for monitoring response to antiviral treatment and predicting the possibility of clinical

relapse. Preemptive therapy in the absence of end-organ damage has not been shown to improve clinical outcomes in HIV patients, and so the routine monitoring of CMV viral DNA or antigenemia in the blood is not recommended (Brantsaeter et al., 2007; Yoshida, 2008).

The limitations of serologic assays for the detection of CMV-specific antibodies include the inability to differentiate past and current infection and a significant delay in seroconversion in the immunocompromised host. In addition, reactivation from latency may not be detected due to less effective recall immune response in AIDS patients. The presence of serum antibodies to CMV is not diagnostically useful, although a negative IgM and IgG antibody level indicates that CMV is unlikely (Brantsaeter et al., 2007).

The diagnosis of CMV is based on the recognition of characteristic signs and symptoms in end-organ disease. CMV retinitis is diagnosed based on the recognition of characteristic retinal changes observed through a dilated pupil via fundoscopy. When performed by an experienced ophthalmologist, dilated fundoscopy can have up to a 95% positive predictive value. Because retinitis is the most common manifestation of CMV disease, patients with CNS, gastrointestinal, or pulmonary disease should undergo fundoscopy to detect subclinical retinal disease. For CMV colitis, demonstration of mucosal ulcerations on endoscopic examination, combined with colonoscopic or rectal biopsy with histopathologic demonstration of characteristic intranuclear and intracytoplasmic inclusions, clinches the diagnosis. The diagnosis of CMV esophagitis can be established by the presence of extensive large, shallow ulcers of the distal esophagus and biopsy evidence of intranuclear inclusion bodies in the endothelial cells with inflammatory reaction on the ulcer edge. CMV cultures from biopsy or cells brushed from the colon or the esophagus are not sufficient to establish the diagnosis of CMV colitis or esophagitis in the absence of histopathologic changes because certain persons with low CD4 counts might be viremic and have positive cultures for CMV in the absence of clinical disease. Detection of CMV at other sites requires visualization of typical lesions and tissue biopsy. Viral inclusions (“owl’s eye cells”) in biopsy samples indicates invasive disease (Rodriguez-Barradas et al., 1996; Zurlo et al., 1993).

XXX. What are the standard and alternative treatments for CMV and their adverse effects?

91. Treatment of CMV retinitis consists of two phases: initial or induction therapy and chronic maintenance therapy or secondary prophylaxis. Initial therapy for CMV retinitis should be individualized based on the location and severity of disease, the level of immune suppression, and other factors such as concomitant medications and ability to adhere to treatment.

Strong recommendation, Low quality of evidence

92. Recommended initial therapy is intravenous ganciclovir at 5 mg/kg q12H or oral valganciclovir 900 mg twice a day. Duration of initial treatment is 14–21 days in ophthalmologic disease. For esophagitis or colitis, duration of initial treatment is 21–42 days or until signs and symptoms have resolved.

Strong recommendation, High quality of evidence

93. Serial fundoscopy for monitoring of response should be done prior to switching to maintenance therapy, as well as periodically for any signs of recurrence.

Strong recommendation, Low quality of evidence

94. Switching to chronic maintenance therapy for CMV retinitis can be done in a clinically improving patient after the initial prescribed duration of therapy. Chronic maintenance therapy is either oral valganciclovir 900 mg daily or intravenous ganciclovir 5 mg/kg five to seven times weekly for at least 3–6 months.

Strong recommendation, High quality of evidence

95. Gastrointestinal CMV does not require chronic maintenance therapy unless relapse occurs.

Weak recommendation, Low quality of evidence

96. Ganciclovir and valganciclovir can cause neutropenia, thrombocytopenia, and anemia. Patients receiving these antivirals should be monitored closely with periodic complete blood counts and other appropriate laboratory examinations.

Strong recommendation, Moderate quality of evidence

Summary of Evidence

The incidence of CMV end-organ disease in AIDS patients has fallen substantially since the widespread use of ARV therapy; it is currently <6 cases per 100 person-years (Meyer-Olson et al., 2010). Recurrence of disease for patients with known CMV retinitis has likewise dramatically fallen to around 0.58/person-year in patients with persistently depressed CD4 cell counts below 50 cells/μL. Relapse of the retinitis can still occur even with substantial immune reconstitution, and so ophthalmologic follow-up even in those who have discontinued maintenance therapy remains necessary (Kaplan et al., 2009; Meyer-Olson et al., 2010).

The most effective form of treatment for CMV with the least toxicity is still intravenous ganciclovir and its oral prodrug valganciclovir. Earlier studies also used oral ganciclovir, which was less effective, but treatment was in combination with an intraocular ganciclovir implant which is no longer available commercially. In a study by Martin et al. (1999) using three modalities for treating CMV disease, the incidence of new CMV disease at 6 months was 44.3% in the group assigned to the ganciclovir implant alone, 24.3% in the ganciclovir implant plus oral ganciclovir ($p=0.002$) and 19.6% in those treated with intravenous ganciclovir alone ($p<0.001$). Intravenous foscarnet and cidofovir have also been shown in clinical trials to be effective but are associated with substantial toxicity and are not readily available in the Philippines (Kaplan et al., 2009; Jabs et al., 2004).

Initiation of ARVs can control CMV retinitis in patients who experience immune recovery. However, treatment is recommended for all patients even if ARVs are initiated since it may take some time to control viral replication and recover immune function, as well as the risk of immune reconstitution retinitis and detachment (Kaplan et al., 2009; Jabs et al., 2004).

Maintenance therapy can be safely discontinued among patients with CMV retinitis with sustained CD4 counts of >100 cells/μL in response to ARV (Kaplan et al. 2009; Jabs et al., 2004; Jabs, 2004; Jabs et al., 2007). Patients on ARVs who experienced immune recovery and sustained high CD4 levels have remained disease-free in clinical trials, compared to those who did not start ARVs where retinitis reactivated in about 8 weeks after stopping maintenance CMV therapy. Discontinuing secondary prophylaxis (chronic maintenance therapy) is reasonable for patients with a sustained (3–6 months) increase in CD4 counts >100 cells/μL in response to ARV. This decision should be made in consultation with an ophthalmologist who should still perform regular ophthalmologic monitoring once off treatment. The relapse rate among patients whose anti-CMV therapy has been discontinued for immune recovery is 0.03 per person-year (3% per year), and no level of CD4 count is absolutely safe. All patients who have had CMV retinitis and are off maintenance therapy should continue to undergo regular ophthalmologic monitoring for early detection of relapse, ideally every 3 months.CMV viral load is of poor positive predictive value for relapse and is not recommended (Kaplan et al., 2009).

XXXI. What adjunctive treatments are necessary?

97. Ganciclovir intravitreal injections especially in sight-threatening infections can be given as an adjunct to systemic therapy of CMV retinitis but should be administered by a trained ophthalmologist and in consultation with an infectious diseases specialist.

Weak recommendation, Low quality of evidence

Summary of Evidence

Ganciclovir intraocular implants were previously used as adjunct treatments for sight-threatening CMV retinitis in combination with systemic therapy, but they are no longer available from the manufacturer. Intravitreal injection of ganciclovir can deliver high concentrations of the drug to the target organ while waiting for steady-state concentrations in the eye to be achieved with systemically delivered medications (Martin et al., 1999).

XXXII. What measures can be taken to prevent occurrence and recurrence?

98. ARV treatment is the most effective preventive measure for CMV. It should be initiated after 2 weeks of CMV treatment to minimize the risk of severe immune reconstitution but should not be delayed further unless contraindicated.

Strong recommendation, Low quality of evidence

99. Chronic maintenance therapy/secondary prophylaxis for CMV retinitis can be discontinued once ARVs have been initiated, the CD4 count improves and remains >100 cells/uL for 3–6 months, and there is no evidence of active disease on ophthalmologic examination.

Strong recommendation, Moderate quality of evidence

100. Reinstitution of secondary prophylaxis for CMV retinitis should be done if the CD4 count again decreases to <100 cells/μL.

Strong recommendation, Moderate quality of evidence

101. After induction therapy, continuous secondary prophylaxis (chronic maintenance therapy) is recommended to prevent recurrence until immune reconstitution occurs as a result of ARV. In patients who do not recover their CD4 cell count above 100 cells/μL, lifelong therapy is recommended.

Strong recommendation; Moderate quality of evidence

Summary of Evidence

CMV end-organ disease in HIV-infected patients is best prevented by initiating ARVs before the CD4 count goes below 100 cells/μL. In patients with counts below this threshold, there is no evidence that preemptive therapy with ganciclovir or valganciclovir is cost-effective, and it may lead to the emergence of resistance. Early detection of CMV disease can prevent progression to its more severe forms. Patients should be educated to watch for floaters and should be advised to report anychanges in vision to their physicians promptly. Regular funduscopic examinations should be performed by an ophthalmologist in HIV patients with low (<100 cells/μL)

CD4 counts especially prior to the initiation of ARVs which may exacerbate subclinical CMV retinitis through immune reconstitution (Ausayakhun et al., 2010).

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TOXOPLASMA GONDII

Introduction

Toxoplasmic encephalitis (TE) among HIV-infected individuals is usually a complication of the late phase of immunodeficiency. It is a leading cause of a central nervous system disorder among patients with AIDS (Luft and Remington, 1992). However, among all OIs, TE is relatively uncommon, accounting for only 1.2% of OIs in a particular cohort (Ho et al., 2008).

In Taiwan, *T. gondii* infection seroprevalence was estimated at 10.2% in HIV-infected patients, and the incidence of TE was reported to be 0.59 per 100 person-years (Hung et al., 2005). The prevalence of TE among HIV-infected patients in the United States varies from 15% to 40% (Luft and Remington, 1992). In the PGH, approximately 3 cases of cerebral toxoplasmosis were seen among 522 HIV-infected individuals (Salvaña et al., 2012).

Factors associated with an increased risk of TE are severe immunodeficiency, absence of TE prophylaxis, and non-initiation of ARV therapy (Antinori et al., 2004). In one study in Taiwan, 68.4% of patients with TE and HIV presented with TE as the first clinical clue of the diagnosis of AIDS. These patients had depleted CD4 lymphocyte counts and high plasma HIV RNA load and did not receive prophylaxis or ARV therapy (Ho et al., 2008). In an Italian study, it was noted that male sex, previous exposure to ARV therapy, and higher CD4 cell count at neurological diagnosis significantly decrease the probability of TE (Antinori et al., 2004).

XXXIII. What are the clinical manifestations of TE?

102. Patients with CD4 counts <100 cells/μL presenting with altered mental status, headache and fever associated with focal neurologic deficits should be worked up for TE.

Strong recommendation; Moderate quality of evidence

Summary of Evidence

In a study by Ho et al. (2008) on HIV-infected patients with TE, neurologic signs and symptoms include headache (15.8%), focal neurologic deficit (60.0%), cognitive dysfunction (47.4%), altered mental status (31.6%), seizures (10.5%), and meningismus (5.3%). Fever was present in 73.7% of patients. The common focal neurologic deficits were hemiparesis (31.6%), aphasia (21.1%), ataxia (21.1%), and diplopia (15.8%). Disease progression results in seizures, stupor, and coma.

Magnerou et al. (2012) studied 60 HIV-infected patients with TE, and the main presenting complaints were motor deficits (65%), seizures (40%), headaches (31.7%), and language and speech disturbances (35%). Moreover, signs of meningeal irritation were found in 21%, while 10% had symptoms of increased intracranial pressure.

Maggi et al. (1996) states that in 50 AIDS patients with cerebral toxoplasmosis, 6% had hemichoreoathetosis. Patients can also present with cranial nerve abnormalities, visual field defects, sensory disturbances, cerebellar dysfunction, meningismus, movement disorders, and neuropsychiatric manifestations. Rapid fatal diffuse form of the disease is rare (Ho et al., 2008; Magnerou et al., 2012).

XXXIV. How do we diagnose TE?

103. The presence of multiple, focal, ring-enhancing lesions on CT or MRI are suggestive of TE in HIV-infected patients with a clinically compatible course, but are not pathognomonic of the disease.

Strong recommendation, Moderate quality of evidence

104. MRI is preferred over CT for diagnosing and monitoring response to treatment because MRI is more sensitive for TE than CT is.

Strong recommendation, Moderate quality of evidence

105. Serological testing for anti-*Toxoplasma gondii* IgG should be done for those in whom acute TE is suspected since TE in HIV is almost always a reactivation disease, while anti-T gondii IgM has nearly no diagnostic value.

Strong recommendation, Moderate quality of evidence

106. Lumbar puncture to obtain CSF for the diagnosis of TE is not required for presumptive diagnosis, and it may be harmful, especially in the presence of mass lesions.

Strong recommendation, Low quality of evidence

Summary of Evidence

A study in Taiwan showed that in 18 HIV-infected patients found to have TE, the most common location on neuroimaging was the cerebral hemispheres (94.7%), followed by the basal ganglia (57.8%), cerebellum (36.8%), and the brainstem (15.8%). Most lesions are multiple and show typical contrast enhancement and perifocal edema (Ho et al., 2008). MRI is the choice of imaging for HIV-infected patients with focal brain lesions because of its increased sensitivity in diseases involving white matter or the posterior fossa (Post et al., 1986).

A presumptive diagnosis of TE is made based on the presence of all of the following findings: progressive neurological deficits, contrast enhancing mass lesion or lesions on imaging studies (CT/MRI), and successful response within 2 weeks to specific treatment in an HIV-positive patient with a low CD4 lymphocyte count, typically less than 100 cells/μL (Portegies et al., 2004). The definitive diagnosis of TE entails clinical signs and symptoms compatible with the disease; one or more mass lesions identified on CT or MRI; and the presence of the organism on brain biopsy or postmortem tissue (Kaplan et al, 2009).

Cranial CT usually shows multiple bilateral, hypodense foci with ring-like contrast enhancement involving the basal ganglia and hemispheric corticomedullary junction (Levy et al., 1986; Post et al., 1985). T1 weighted MRI findings show multiple hypointense lesions, while T2 weighted imaging show hyperintense lesions. Gadolinium-enhanced MRI demonstrates a ring-enhancing lesion with surrounding edema (Dina, 1991). Several studies have shown that MRI is more sensitive in detecting multiple lesions than CT and is thus considered as the modality of choice (Ciricillo and Rosenblum, 1990; Dina, 1991; Levy et al., 1990). Single Photon Emission Computed Tomography (SPECT) when available may help differentiate

malignancy (such as CNS lymphoma) in HIV-infected patients, wherein there is increased uptake of thallium 201 (with a sensitivity for CNS lymphoma is between 86% and 100% while its specificity ranges from 76% to 100%) (Lorberboym et al., 1996; Lorberboym et al., 1998; O'Malley et al., 1994). However, it is not routinely used and cannot be recommended at this time.

The most commonly used serologic markers detect the presence of anti-*Toxoplasma gondii* IgG and IgM. A negative IgG serologic test makes the diagnosis of acute toxoplasmosis unlikely but will not definitively exclude it. IgM antibodies are typically absent in those with reactivated disease; since TE in HIV-infected patients is most often due to reactivated disease, IgM antibody test is not very useful. Several studies have suggested that 97%–100% of HIV-infected patients with TE have anti-*Toxoplasma gondii* IgG antibodies (Grant et al., 1990; Luft and Remington, 1992; Navia et al., 1986).

In a Brazilian study, CSF samples from all patients with cerebral toxoplasmosis presented with positive PCR results, and a sample from one of the 18 AIDS patients with other neurological diseases also presented with a positive PCR result; hence, a 100% sensitivity and a 94.4% specificity (Vidal et al., 2004). CSF findings may include elevated protein, variable glucose levels, and mildly elevated WBC counts with a mononuclear predominance. In a study by Alfonso et al. (2009), results from 190 CSF samples from HIV-positive and HIV-negative patients showed good sensitivity (83.3%) and specificity (95.7%) for the diagnosis of TE in AIDS patients using PCR.

Definitive diagnosis of the TE is the demonstration of tachyzoites or cysts with surrounding inflammatory reaction in the affected brain tissue (Conley et al., 1981). Other histopathological findings typical of the disease include a granulomatous reaction with gliosis and microglial nodules to necrotizing encephalitis (Farkash et al., 1986; Navia et al., 1986).

XXXV. What are the standard and alternative treatments?

107. Patients with suspected TE encephalitis with compatible imaging and clinical manifestations should be started empirically on treatment.

Strong recommendation, High quality of evidence

108. Treatment of TE in the acute phase is with TMP-SMX at 5 mg/kg intravenously of the trimethoprim component twice a day. TMP-SMX 800/160 mg tablet, two tablets twice a day, is effective oral therapy when the IV preparation is not available.

Strong recommendation, High quality of evidence

109. In the absence of or a negative IgG serology, presumptive diagnosis of TE is made based on demonstration of all the following findings: progressive neurological deficits, contrast-enhancing mass lesion or lesions on imaging studies (CT/MRI), and successful response within 2 weeks to specific treatment in an HIV-positive patient with a low CD4 lymphocyte count.

Strong recommendation; High quality of evidence

110. The total duration of acute treatment should be 6 weeks or longer until complete clinical and radiologic resolution. A chronic maintenance phase of TMP-SMX 800/160 mg tablet, one tablet once a day, should be continued until there is immune reconstitution with CD4 count >200 cells/μL for at least 6 months.

Strong recommendation, High quality of evidence

111. In the event of intolerance to TMP-SMX, consultation with an infectious disease specialist should be made for possible alternative regimens.

Strong recommendation, Low quality of evidence

112. Definitive diagnosis of TE entails clinical signs and symptoms compatible with the disease; one or more mass lesions identified on CT or MRI; and the presence of the organism in brain tissue.

Strong recommendation; High quality of evidence

113. Brain biopsy should be considered in cases where brain lesions do not respond to empiric therapy for TE.

Strong recommendation, Low quality of evidence

Summary of Evidence

In a cohort study by Leport et al. (1988) prior to widespread availability of effective ARV therapy, 35 patients with AIDS and CNS toxoplasmosis seen over a 30-month period were treated with a combination of pyrimethamine and sulfadiazine. Of the 24 patients evaluated for long-term therapy, 58% achieved complete resolution, suggesting that the combination is highly efficacious and that life-long therapy is needed to prevent relapses in patients with AIDS.

In a trial comparing the efficacy and safety of TMP-SMX with the standard therapy (pyrimethamine and sulfadiazine) for the treatment of TE in patients with AIDS, there was no difference in clinical efficacy during acute therapy; however, patients randomized to TMP-SMX appeared more likely to achieve a complete radiologic response after acute therapy and suffer fewer adverse reactions (Torre et al., 1998).

A cohort study by Luft et al. (1993) evaluating clinical outcome of HIV-infected patients with toxoplasmosis after treatment with clindamycin 600 mg four times a day and pyrimethamine 75 mg OD for 6 weeks showed that 71% responded to therapy. They concluded that combination oral clindamycin and pyrimethamine is an effective treatment regimen for TE.

Table 11. Recommended therapy for toxoplasmic encephalitis in patients

Drug	Dosage
TMP-SMX	5 mg/kg TMP + 25 mg/kg SMX IV or PO q12
Pyrimethamine* + Sulfadiazine + Leucovorin*	200 mg loading followed by 50–75 mg q24 PO + Sulfadiazine 1–1.5 gms q6 PO + Leucovorin 10–25 mg OD
Pyrimethamine* + Clindamycin + Leucovorin*	200 mg loading followed by 50–75 mg q24 PO + Clindamycin 600–1200 mg q6 IV or PO + Leucovorin 10–25 mg OD

*not readliy available locally

In another trial, effectiveness and tolerance of atovaquone suspension 1500 mg PO BID plus either pyrimethamine 200 mg loading dose followed by 75 mg OD or sulfadiazine 1500 mg four times a day as treatment for acute disease for 6 weeks and as maintenance therapy for 42 weeks for TE were studied. Results showed that 75% receiving pyrimethamine and 82% receiving sulfadiazine responded to treatment for acute disease. Moreover, 28% discontinued treatment due to adverse events of nausea, vomiting, or intolerance to the taste of atovaquone suspension (Chirgwin et al., 2002).

Martin studied the efficacy of a pyrimethamine-clarithromycin combination for the treatment of acute TE in a cohort of 13 AIDS patients. Results showed that the clinical and CT scan responses at 6 weeks were 80% and 50%, respectively; thus, the combination was shown to be comparable to the conventional regimen (Fernandez-Martin et al., 1991).

Table 12. Alternative therapy for toxoplasmic encephalitis in patients with AIDS

Drug	Dosage
Pyrimethamine* + Atovaquone* + Leucovorin*	200 mg loading followed by 50–75 mg q24 PO + Atovaquone 1500 mg q12 + Leucovorin 10–25 mg OD
Pyrimethamine* + Clarithromycin + Leucovorin*	200 mg loading followed by 50–75 mg q24 PO + Clarithromycin 1000 mg q12 PO + Leucovorin 10–25 mg OD
Pyrimethamine* + Azithromycin + Leucovorin*	200 mg loading followed by 50–75 mg q24 PO + Azithromycin 1200 mg – 1500 mg q24 PO + Leucovorin 10–25 mg OD
Pyrimethamine* + Dapsone + Leucovorin*	200 mg loading followed by 50–75 mg q24 PO + Dapsone 100 mg q24 PO + Leucovorin 10–25 mg OD

*not readily available locally

XXXVI. What are the adjunctive treatments needed?

114. Patients with associated mass effect of focal lesions and edema may be given adjunctive corticosteroids such as dexamethasone.

Weak recommendation, Moderate quality of evidence

115. Patients who develop seizures should be given anticonvulsants. These should be continued for at least the entire period of acute therapy. Anticonvulsant prophylaxis prior to an actual seizure event is not recommended.

Strong recommendation, Low quality of evidence

116. Comanagement with a neurologist in neurologically symptomatic TE patients is recommended.

Strong recommendation, Low quality of evidence

Summary of Evidence

In one retrospective cohort, results showed that in patients treated with pyrimethamine-sulfadiazine, the use of adjunctive steroids to treat cerebral edema associated with focal lesions appeared safe but was not associated with better neurologic outcomes (Sonneville et al., 2012).

XXXVII. How can TE be prevented among HIV patients?

117. HIV-infected patients should be tested for IgG antibody to Toxoplasma soon after the diagnosis of HIV infection to determine whether they are at risk for reactivation disease from latent infection with T. gondii.

Weak recommendation, Moderate quality of evidence

Summary of Evidence

In a study in Serbia, the prevalence and infection risk factors of *Toxoplasma gondii* were analyzed in 765 women, and the infection risk factors were additionally analyzed in 53 women with acute infection and compared to an age-matched seronegative group. Results showed that the overall prevalence of infection was 33%, and infection risk factors include undercooked meat consumption and exposure to soil. Undercooked meat consumption was noted to be a single predictor of infection in women with acute infection. Finally, of all meat types consumed, only beef consumption was shown to influence *Toxoplasma* infection rates (Bobic et al., 2007).

In another study by Jones et al. (2009), the risk of recent *Toxoplasma gondii* infection was associated with the following: eating raw ground beef; eating rare lamb; eating locally produced, cured, dried, or smoked meat; working with meat; drinking unpasteurized goat's milk; and having three or more kittens. While nearly all infection in HIV-infected patients is from reactivation disease, patients who are not latently infected may still acquire primary infection and should take precautions against exposure.

XXXVIII. Is there a need for prophylaxis?

118. *Toxoplasma* seropositive patients with CD4 counts of <100 cells/μL should be administered prophylaxis against TE. TMP-SMX 800/160 mg once a day is the preferred prophylaxis and is effective against TE.

Strong recommendation, Moderate quality of evidence

119. Prophylaxis against TE can be discontinued among adult and adolescent patients who have responded to ARV therapy characterized by an increase in CD4 counts to >200 cell/μL for more than 3 months. Prophylaxis should however be reintroduced if the CD4 count decreases to <200 cell/μL.

Strong recommendation, Moderate quality of evidence

Summary of Evidence

A case-control study by Weigel (1997) showed that among patients with TE, none had used TMP-SMX (cotrimoxazole) for >70% of the observation time and that the 1-year incidence was 0% in the control group vs. 41% in patients without sufficient cotrimoxazole use.

Ribera et al. (1999) evaluated the influence of the dose of cotrimoxazole prophylaxis on the risk of toxoplasmosis among HIV-infected patients using a case-control study. Results showed that higher doses of cotrimoxazole appear to be more effective than low doses for lowering the risk of toxoplasmosis in HIV-infected patients.

In a trial by Leport et al. (1996), 50 mg pyrimethamine plus 15 mg folinic acid three times weekly was assessed as primary prophylaxis for TE in 554 HIV-infected patients seropositive for *Toxoplasma gondii* and with CD4 counts <200 cells/cubic mm. Results showed that the incidence of TE after 1 year between pyrimethamine and placebo (12% and 13%, respectively) and the survival rate (85% and 80%, respectively) were similar. Rash was the only adverse event and was significantly more frequent in the pyrimethamine arm. Moreover, the incidence of TE was lower in the pyrimethamine group (4% vs. 12%) than placebo in the on-treatment analysis. Thus, pyrimethamine is not recommended as first line but rather an alternative in patients intolerant to TMP-SMX. Pyrimethamine is not available locally and so is not recommended in these guidelines.

A study by Opravil et al. (1995) showed dapsone with pyrimethamine was as effective as aerosolized pentamidine as prophylaxis for PCP and significantly reduced the incidence of TE among those study participants who tolerated it. A trial by Miro et al. (2006) evaluating 381 patients concluded that in HIV-infected adult patients receiving effective and highly active ARV therapy, primary and secondary prophylaxis against TE can be safely discontinued after the CD4 T-cell count has increased to ≥200 cells/μL for more than 3 months.

Table 13. Primary prophylaxis against TE

Drug	Dosage
TMP-SMX	1 double strength tablet once a day
Pyrimethamine + Dapsone + Folinic Acid (not available locally)	50 mg once/week + 50 mg OD + 25 mg OD 50 mg 2x/week + 100 mg 2x/week + 25 mg OD 75 mg once/week + 200 mg once/week + 25 mg OD

XXXIX. How do we prevent recurrence of TE?

120. Chronic maintenance therapy should be administered as lifelong suppressive therapy in the absence of adequate immune reconstitution from ARV therapy.

Strong recommendation, Moderate quality of evidence

121. In patients who, after acute therapy, have resolution of signs and symptoms and have immune reconstitution (CD4 counts >200cell/μL) for more than 6 months on ARV therapy, maintenance therapy can be discontinued. Patients must, however, be observed for recurrence of symptoms and chronic maintenance therapy restarted once CD4 count decreases to <200 cell/μL.

Strong recommendation, High quality of evidence

Summary of Evidence

Katlama et al. (1996) showed in a trial that during the maintenance phase of treatment, the relapse rate was twice as high among patients in the pyrimethamine-clindamycin group as compared to the pyrimethamine-sulfadiazine group. The rate of side effects was similar between the two groups although the toxic effects of pyrimethamine-clindamycin led to fewer discontinuations of therapy than the pyrimethamine-sulfadiazine group; thus, pyrimethamine-sulfadiazine combination is the most effective treatment of TE, while pyrimethamine-clindamycin combination is a valuable alternative but less effective for long-term prevention of relapses.

Podzamczer et al. (2000) showed in a trial that the efficacy of thrice-weekly pyrimethamine-sulfadiazine combination was similar to that of the daily regimen in the prevention of relapses of TE.

In a study by Duval et al. (2004), median follow-up of 31 months of a cohort of patients receiving TMP-SMX as maintenance therapy showed that the TE relapse incidence was 2.1 cases per 100 patient-years; thus, this strategy could be useful for patients awaiting immune reconstitution which allows the interruption of TE maintenance therapy.

Table 14. Recommended maintenance therapy for TE in patients with AIDS

Drug	Dosage
Trimethoprim + Sulfamethoxazole	1 double-strength tablet BID
Pyrimethamine + Sulfadiazine + Leucovorin	25–50 mg q24 PO +Sulfadiazine 500–1000 mg q6 PO + Leucovorin 10–25 mg OD
Pyrimethamine + Clindamycin + Leucovorin	25–50 mg q24 PO + Clindamycin 600 mg q6 PO + Leucovorin 10–25 mg OD

XL. What are the common adverse drug events?

Patients on TMP-SMX should be monitored for adverse events.

Table 15. Drug toxicities

Drug	Dosage
Pyrimethamine	Rash, nausea and bone marrow suppression (neutropenia, anemia, thrombocytopenia)
Sulfadiazine	Rash, fever, leukopenia, hepatitis, nausea, vomiting, diarrhea and crystalluria
Clindamycin	Fever, rash, nausea, diarrhea (including pseudomembranous colitis or diarrhea related to *Clostridium difficile* toxin) and hepatotoxicity
Cotrimoxazole (TMP-SMX)	Rash, fever, leukopenia, thrombocytopenia and hepatotoxicity

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MICROSPORIDIOSIS

Introduction

Microsporidia are ubiquitous in nature and can cause enteric infections in HIV patients. They are small, spore-forming, obligate intracellular protozoan parasites that can invade tissues like muscle, kidney, liver, brain, and the cornea. They can infect humans, as well as a wide range of animals like dogs, cattle, and pigs, suggesting that infections occur via horizontal transmission between humans or via zoonotic reservoirs (Santin and Fayer, 2009). Transmission is through the fecal-oral route via the ingestion of spores released from the gastrointestinal tract or in the urine of infected animals (Bryan et al., 1991). Less commonly, microsporidiosis has been associated with a history of surface water exposure (Leder et al., 1998). *Enterocytozoon bieneusi* is the causative agent of most cases of microsporidiosis in HIV-infected patients, mostly as intestinal disease (Weber et al., 1994). Another species, *Encephalitozoon intestinalis*, is associated with disseminated as well as intestinal disease. Replication of the protozoan occurs in the enterocytes of the intestinal epithelial villi, causing shortening of the villous height, extensive cell degeneration, death and shedding of the epithelial lining. Areas of predilection for microsporidiosis include the jejunum, followed by the duodenum. The large intestines are less likely to be involved (Modigliani et la., 1985; Orenstein et al., 1990). Prior to widespread use of ARV therapy, the reported prevalence rate of microsporidiosis ranged from 2% to 70% among HIV-infected patients with diarrhea. A CD4 count <100 cells/μL in immunocompromised patients is usually associated with clinical signs of microsporidiosis (Kaplan et al, 2009).

In a prospective study done among 134 HIV-infected patients, the prevalence of microsporidiosis was 22% among patients with chronic diarrhea (6 of 27 patients) and 29% among those with unexplained chronic diarrhea (6 of 21 patients) (Weber et al., 1992).

In three US hospitals, a prospective study of HIV-infected patients with diarrheal illnesses revealed that the median age at diagnosis of microsporidiosis was 34 years (range 29 to 46 years). In this study, the median CD4 count within 6 months of diagnosis was found to be 33 cells/μL (range 3–319 cells/μL) (Dworkin et al., 2007). A cross-sectional study of 242 HIV patients done in Congo showed that an advanced stage of immunodepression manifesting as a CD4 count <100 cells//μL increased the risk of opportunistic intestinal parasites five-fold. Logistic regression analysis showed that a CD4 count of <100 cells/μL (OR 4.60 95% CI 1.70–12.20; p=0.002), no ARV (OR 5.00 95% CI 1.90–13.20; p=0.001), and exposure to surface water (OR 2.90 95% CI 1.01–8.40; p=0.048) were identified as the significant and independent determinants for the presence of opportunistic intestinal parasites including microsporidia (Wumba et al., 2012).

XLI. What are the clinical signs and symptoms of the microsporidiosis?

Clinical manifestations of disease most commonly include gastrointestinal manifestations such as anorexia, nausea, weight loss, abdominal pain, malabsorption, fever and chronic non-bloody diarrhea (McWhinney et al., 1991). Other clinical syndromes vary depending on the infecting species. E. bieneusi is associated with malabsorption, diarrhea, and cholangitis; while *E. cuniculi* is associated with hepatitis, encephalitis, and disseminated disease. *E. intestinalis* is associated with diarrhea, disseminated infection, and superficial keratoconjunctivitis; and *E. hellem* is associated with superficial keratoconjunctivitis, sinusitis, respiratory disease, prostatic abscesses, and disseminated infection. *Nosema, Vittaforma*, and Microsporidium are associated with stromal keratitis following trauma in immunocompetent hosts. *Pleistophora, Anncaliia*, and *Trachipleistophora* are associated with myositis. *Trachipleistophora* is associated with encephalitis and disseminated disease (Kaplan et al, 2009).

XLII. What tests are needed to diagnose microsporidiosis?

122. Stool exams using light microscopy with Kinyoun staining for microsporidia should be performed in suspected cases (Wumba et al., 2012).

Strong recommendation, Moderate quality of evidence

123. Microsporidiosis can also be diagnosed by histology, either from tissue biopsies or secretions. Electron microscopy, special stains and light microscopy, immunohistochemical and molecular techniques can be done for a more specific diagnosis.

Strong recommendation, Moderate quality of evidence

124. If the stool exam is negative and microsporidiosis is still suspected, small intestinal biopsy should be performed.

Strong recommendation, Moderate quality of evidence

Summary of Evidence

Differential staining that provide contrast between the spores of the microsporidia and the cells and debris in clinical samples is useful for morphological demonstration of microsporidia in stool. Determination of the microsporidial species can also be done through transmission electron microscopy, by staining with species-specific antibodies or by PCR using species- or genus-specific primers (Weiss and Vossbrinck, 1998).

XLIII. What are the standard and alternative treatments and its side effects?

125. Albendazole (400 mg PO BID x 3 weeks) can be used to treat *Encephalitozoon intestinalis*.

Strong recommendation, Moderate quality of evidence

126. ARVs to effect immune reconstitution is an essential part of the treatment of microsporidial infection.

Strong recommendation, Moderate quality of evidence

Summary of Evidence

Blanchard et al. (1992) used albendazole to treat six HIV patients with *microsporidia* as the only identified cause of diarrhea. Diarrhea responded in all patients within 1 week of starting treatment, with body weight stabilizing or increasing. Four patients relapsed at 19–31 days, but all of them responded to a second course of albendazole. A prospective study in London was done by following up six HIV patients infected with microsporidia using stool samples and duodenal biopsies taken pre-ARV, 1–3 months and then 6 months post-ARV. They found that patients treated with ARV were 94% less likely to die compared with those that had no ARV (HR 0.06 95% CI 0.03–0.10). The median survival of patients without ARV was 10 months; for those treated with ARV, the median survival to date was 35 months (Miao et al., 2000).

The clinical course of 37 *E. bieneusi*-infected HIV patients with diarrhea revealed parasitic clearance in 15 patients (40.5%). Nine patients noted resolution of diarrhea and improvement (25%–75% decrease in stool frequency) in six patients in an average of 2.5 months. It was also noted that 72.7% of patients on albendazole failed to clear the parasite (Conteas et al., 1998). Peripheral blood CD4 cell counts ≥100/μL, the use two or more anti-HIV medications, and the use of a protease inhibitor were associated with an increased likelihood of clearing microsporidiosis, as well as a decrease in time to clearance of the parasite among subjects whose infection was self-limited. In fact, most of the 15 patients who cleared their infection did so in a self-limited fashion in the absence of antiparasitic therapy or any change in their anti-HIV medications (Conteas et al., 1998).

XLIV. How can response to therapy be assessed?

Resolution of diarrhea signals improvement.

XLV. What measures can be taken to prevent occurrence and recurrence?

The prevention of microsporidia infection via individual and population-based prophylaxis should be established in terms of hygiene. Patients with HIV/AIDS should shun untreated water sources. Strict rules should be respected to avoid oro-fecal transmission, including hand washing, washing fresh vegetables, drinking boiled water, and limiting contact with animals susceptible to transmission of microsporidia. No chemoprophylactic regimens are known to be effective in preventing microsporidiosis.

Summary of Evidence

In a cohort study done (September 2000-December 2002) among 2652 HIV-positive patients in two Lima hospitals, the median CD4 count was 131 cells/mL, 67 patients (3%) had microsporidiosis. The strongest risk factor for microsporidiosis was low CD4 count <100 cells/mL associated with 12-fold increase. In addition, an increased risk was associated with the presence of animals in the household, especially ducks, chickens, rabbits, and sheep. Contact with duck and/or chicken droppings in the month before interview was also associated with an increased risk. A number of factors related to poor sanitary conditions, like the lack of municipal garbage collection, no running water, or no flush toilet, led to an increased risk of microsporidial infection (Bern et al., 2005).

A small RCT measured the safety and efficacy of albendazole for preventing relapse of intestinal microsporidiosis among adult HIV-positive patients (Molina et al., 1998). Three patients received albendazole 400 mg twice a day for 12 months or until parasitological relapse or death, and five patients received no treatment. All three patients on albendazole did not relapse, while three of the five patients receiving no treatment relapsed (p=0.04). However, the small study sample size precludes recommending albendazole prophylaxis for microsporidiosis.

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CYCLOSPORA INFECTION

Introduction

Cyclospora cayetanesis is a coccidian protozoan that causes a self-limited diarrhea in immunocompetent individuals but causes a severe diarrhea among the immune-suppressed population, particularly HIV-infected individuals (Stark et al., 2009). This protozoan is endemic in certain parts of the globe such as Haiti, Guatemala, Peru, Indonesia, and Nepal (Ortega and Sanchez, 2010). Humans are the only known host for *Cyclospora*. Transmission is via the ingestion of oocysts present in contaminated food and water (Stark et al., 2009). Data from the United States show that the incidence of infection ranges from 0.01 to 0.07 per 100,000 persons (Hall et al., 2011). A study in India showed that *Cyclospora* is the third most common parasite isolated in HIV patients presenting with diarrhea (Tuli et al., 2008). HIV patients with CD4 count <200cells/µl are at higher risk for acquiring *Cyclospora* infection (Asma et al., 2011; Tuli et al., 2008). Diarrhea due to *Cyclospora* can cause malnutrition that contributes to the morbidity and mortality among HIV-infected patients (Mukhopadhyay et al., 2007). Risk factors for acquiring the infection include consumption of untreated water and contaminated food, lack of adequate sanitation, and the presence of animals in the household. A history of travel to endemic areas should trigger suspicion of *Cyclospora* infection (Ortega and Sanchez, 2010).

XLVI. What are the clinical signs and symptoms of Cyclospora infection?

Cyclospora may be present in both symptomatic and asymptomatic HIV-infected individuals (Asma et al., 2011). Diarrhea is the most common presenting symptom and may be acute or chronic (Tuli et al., 2008). Other symptoms include abdominal cramps, fatigue, weight loss, nausea, anorexia, fever, and vomiting (Hall et al., 2011, Ortega and Sanchez, 2010). HIV patients with *Cyclospora* infection have greater weight loss and a longer duration of diarrhea compared to non-HIV patients with the infection (Ortega and Sanchez, 2010). Disseminated infection is unusual and, if present, usually involves the biliary tract (Stark et al., 2009).

In a summary of US national data on 1110 laboratory-confirmed cases of *Cyclospora* reported to the CDC from 1997 to 2008, diarrhea was the most common symptom that is present in 97% of cases. Abdominal cramps were observed in 82%, fatigue in 75%, weight loss in 72%, nausea in 69%, anorexia in 65%, fever in 43.3%, and vomiting in 30.4% of cases (Hall et al., 2011). Right upper-quadrant pain may be present in patients with involvement of the biliary tract (Zar et al., 2001).

In an investigation of an outbreak of *Cyclospora* involving 1465 cases showed that diarrhea, loss of appetite, weight loss, and fatigue were present in more than 90% of cases (Herwaldt and Ackers, 1997).

A retrospective study done in Mexico involving 12 patients with laboratory-confirmed *Cyclospora* infection and of whom seven had HIV co-infection showed that patients with HIV presented with more weight loss (p=0.04) and had more prolonged illness compared with patients without HIV. Two of the seven patients with HIV also had concomitant biliary disease that resolved with *Cyclospora* treatment (Sifuentes-Osornio et al., 1995).

XLVII. What tests are needed to diagnose Cyclospora infection?

127. Modified Kinyoun staining after stool concentration using the formalin ether stool concentration technique (FECT) is recommended.

Strong recommendation, High quality of evidence

128. Submission of multiple stool specimens may be required to increase the diagnostic yield.

Strong recommendation, High quality of evidence

Summary of Evidence

In a prospective study done in India to compare different techniques for evaluating enteric protozoans, stools were collected from 450 HIV patients with diarrhea. *Cyclospora* was the third most often isolated parasite next to cryptosporidium and microsporidium. Sensitivity of direct microscopy for detecting *Cyclospora* was 65.22% and specificity was 97.21%. Sensitivity increased to 78.26% after formalin ether concentration of stool specimens. Safranin staining showed a sensitivity of 89.13% and a specificity of 99.16% for detecting *Cyclospora*, while modified Kinyoun staining showed a sensitivity of 85.87% and specificity of 98.6% (Tuli et al., 2010).

In a study done in Colombia, 100 concentrated stool samples known to be positive for *Cyclospora* were used to compare the capability of modified Ziehl-Neelsen stain and modified safranin staining for detecting *Cyclospora* oocyst in stool samples. Modified Ziehl-Neelsen stain had a sensitivity of 95% and a specificity of 90%. On the other hand, modified safranin staining showed a sensitivity of 98% and a specificity of 100%. A high degree of agreement between the two tests was demonstrated (Galvan-Díaz et al., 2008).

XLVIII. What are the standard and alternative treatments for Cyclospora infection?

129. *Cyclospora* infection is treated using TMP-SMX 160/800 mg orally four times a day for 7–10 days, followed by prophylaxis.

Strong recommendation, High quality of evidence

130. Ciprofloxacin 500 mg orally twice a day for 7 days may be used as an alternative to TMP-SMX.

Strong recommendation, High quality of evidence

Summary of Evidence

In a randomized placebo-controlled trial involving 40 non-HIV-infected expatriate persons with gastrointestinal complaints and *Cyclospora* detected on examination in Kathmandu and Nepal, participants were assigned to receive either TMP-SMX 160/800 mg or placebo twice a day for 7 days. Twenty-one patients received TMP-SMX and 19 patients received placebo. The two groups of patients had no significant differences in baseline characteristics. After 7 days, *Cyclospora* was detected in 1 of 16 (6%) patients treated with TMP-SMX who submitted stool specimens compared with 15 of 17 (88%) patients receiving placebo ($p<0.0001$). Eradication of the organism was correlated with clinical improvement. There was no evidence of relapse of infection among treated patients followed for an additional 7 days (Hoge et al., 1995).

In a 3-year cohort study done in Haiti involving 43 HIV-positive participants with diarrhea lasting for at least 3 weeks and a laboratory diagnosis of *Cyclospora*, patients were treated with TMP-SMX 160/800 mg orally four times a day for 10 days. Participants with recurrent diarrhea and parasitologic recurrences after 10 days of treatment were retreated with the same regimen. All participants had clinical and parasitological cure after 2.5 days of initiation of treatment. Symptomatic infection recurred in 12 of 28 patients who were followed for 1 month or more. The recurrent infections responded to retreatment using trimethoprim-sulfamethoxazole for 10 days (Pape et al., 1994).

In a RCT done in Haiti involving 20 HIV-infected patients with *Cyclospora*, 1-week treatment with oral TMP-SMX 160/800 mg twice a day was compared with 1-week treatment employing oral ciprofloxacin 500 mg twice a day. Results showed that 100% of participants exhibited a clinical response, and 95% showed a microbiological response to TMP-SMX treatment. Among the participants who received ciprofloxacin, 87% manifested a clinical response and only 70% demonstrated a microbiological response (Verdier et al., 2000).

XLIX. How can response to therapy be assessed?

A decrease in the frequency and amount of bowel movements signals improvement. Secondarily, parasitological clearance may also be monitored to track response to treatment.

L. What measures can be taken to prevent occurrence and recurrence?

131. Secondary prophylaxis should be administered using TMP-SMX 800/160 mg orally three times a week until CD4 count is >200 cells/µl.

Strong recommendation, High quality of evidence

132. An alternative drug for secondary prophylaxis is ciprofloxacin 500 mg orally three times a week until CD4 count is >200 cells/µl.

Weak recommendation, High quality of evidence

133. Adequate processing of water and food, as well as abstaining from consumption of raw produce when travelling to endemic areas, will help reduce the risk of *Cyclospora* infection.

Strong recommendation, High quality of evidence

Summary of Evidence

In a 3-year cohort study done in Haiti involving 43 HIV-positive patients with diarrhea lasting for at least 3 weeks and *Cyclospora* documented in the stool, 12 participants who had recurrent infection received secondary prophylaxis using oral trimethoprim-sulfamethoxazole 160/800 mg three times a week. Only a single recurrence was reported after 7 months of follow-up (Pape et al., 1994).

In a RCT done in Haiti involving 20 HIV-infected patients with *Cyclospora,* nine patients received secondary prophylaxis with TMP-SMX 800/160 mg orally three times a week for 10 weeks, while seven patients received secondary prophylaxis with ciprofloxacin 500 mg orally three times a week for 10 weeks. No recurrences of infection occurred in the TMP-SMX group. On the other hand, one of seven patients receiving ciprofloxacin had a recurrence of infection on the fourth week (Verdier et al., 2000).

Adequate processing of water and foods and abstaining from eating raw produce when traveling to areas of endemicity will aid in reducing the risk of acquiring *Cyclospora* infection (Ortega and Sanchez, 2010).

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CRYPTOSPORIDIOSIS

Introduction

Cryptosporidium is a protozoan genus with 20 recognized species (Cabada and White, 2010) that cause cryptosporidiosis. The most common species causing disease in humans are *C. parvum*, *C. hominis*, and *C. meleagridis* (Cabada and White, 2010; Kaplan et al, 2009). *Cryptosporidium* is an intracellular, extracytoplasmic organism that can cause diarrheal disease in both immunocompetent and immunocompromised persons. Disease is more severe in people who are immunosuppressed (Cabada and White, 2010).

LI. What are the clinical signs and symptoms of cryptosporidiosis?

134. HIV-infected patients presenting with acute, chronic, or fulminant diarrhea, especially with CD4 <100 cell/µL, should be suspected to have cryptosporidiosis and worked up accordingly.

Strong recommendation, Moderate quality of evidence

Summary of Evidence

The most common symptom of cryptosporidiosis in immunocompromised hosts is acute, chronic, or fulminant diarrhea (Cabada and White, 2010; Kaplan et al, 2009). Diarrhea is profuse, watery, and non-bloody. Accompanying symptoms may include nausea, vomiting, abdominal pain (Kaplan et al, 2009).

Cryptosporidiosis often leads to chronic diarrhea with weight loss and dehydration (Nissapatorn and Sawangjaroen, 2011). Small and large bowel involvement are also possible and biliary disease is the most frequent form of extra-intestinal involvement. HIV-infected people with CD4 <100 cells/L are at the greatest risk of disease (Kaplan et al, 2009).

Cryptosporidium has a low infective dose (Abubakar et al., 2009). Infection is acquired through the ingestion of oocysts from contaminated drinking or recreational water (Cabada and White, 2010), contact with persons or animals with diarrhea, and person-to-person transmission, i.e., among men who have sex with men. Cryptosporidium has a potential for fomite transmission (Kaplan et al, 2009).

A hospital-based study from Ethiopia showed that more parasitic infections were detected in HIV patients whose CD4 counts are <200/□L (OR 12.1 95% CI 5.5–26.3) (Assefa et al., 2009)..Several hospital- and clinic-based cross-sectional studies have shown varying prevalences of *Cryptosporidium* among HIV patients: between 20% (Assefa et al., 2009) and 25% (Getaneh et al., 2010) in Ethiopia; 54.2% in Nigeria (Ojurongbe et al., 2011); and 9.1% in Iran (Dehkordy et al., 2010). Among patients with HIV and diarrhea, the prevalence was found to be 86.5% compared to the general population (p<0.001) in one study (Ojurongbe et al., 2011). In a one-year study of 3456 diarrheic patients in the Philippines, Natividad et al. (2008) found that 1.9% of the stool samples of patients were positive for *Cryptosporidium*.

LII. What tests are needed to diagnose the cryptosporidium?

135. Stool specimens should be examined by employing stool concentration methods (formalin-ether concentration technique) and acid-fast staining modified AFB/Kinyoun stains in all HIV patients suspected of having symptomatic cryptosporidiosis.

Strong recommendation, Moderate quality of evidence

136. Stool samples for examination should be obtained on at least three consecutive days.

Strong recommendation, Moderate quality of evidence

137. If available, enzyme-linked immunosorbent assays (ELISAs) for antigen detection should be performed to detect *Cryptosporidium* in stool specimens in symptomatic.

Strong recommendation, High quality of evidence

Summary of Evidence

Microscopy-based tests to detect oocysts are the most widely available tests. Acid-fast staining is done to detect oocysts, which will appear red or pink against a blue background. Concentration methods are generally used to increase the amount of stool examined (Swierczewski et al., 2012).

Unfortunately, microscopy is generally believed to underestimate the prevalence of *Cryptosporidium* because of the high dependence on the microscopist's expertise and also the possibility of misidentification of the organism. The amount of oocysts shed in the stool varies from day and to day, and microscopy may fail to detect the infection if low numbers of oocysts are shed (Swierczewski et al., 2012).

Less widely available tests for *Cryptosporidium* are tests for antigen detection that employ immunofluorescence and ELISAs. Commercial kits for testing stool specimens that detect specific antigen of *Cryptosporidium* may be available in some centers. These kits often also contain antibodies for detecting other common parasitic stool pathogens, e.g., Giardia and Entamoeba. One study that evaluated an antigen detection kit for *Cryptosporidium* showed a sensitivity of 73% and a specificity of 100%, higher than that for microscopy-based methods (Swierczewski et al., 2012).

Other methods for detecting *Cryptosporidium* are intestinal biopsy and polymerase chain reaction (PCR).

LIII. What are the standard and alternative treatments?

138. No antibiotics are currently recommended for the treatment of cryptosporidiosis in HIV-infected persons.

Strong recommendation, High quality of evidence

139. HIV-infected patients with cryptosporidiosis should be started on ARV therapy as soon as possible to improve chances of resolution.

Strong recommendation, High quality of evidence

Summary of Evidence

Several drugs have been evaluated for treating cryptosporidiosis, including nitazoxanide, paromomycin, spiramycin, and bovine dialyzable extract. None of these are recommended for treating *Cryptosporidium* diarrhea in HIV patients.

To date, paromomycin, nitazoxanide, spiramycin, and bovine dialyzable extract have not been found to significantly speed up the resolution of diarrhea (decrease stool frequency and stool volume) or the clearance of *Cryptosporidium* in HIV patients with *Cryptosporidium* diarrhea (Abubakar et al., 2009; Kaplan et al, 2009; Hewitt et al., 2000); they are not recommended.

Proper and adequate hydration, which is the standard of care for persons with diarrheal diseases, should be carried out in all HIV patients with *Cryptosporidium* diarrhea.

ARV to achieve restoration of the immune system is the central component in the treatment of cryptosporidiosis.

LIV. What adjunctive treatments are necessary?

Antimotility agents (e.g., loperamide) may decrease the severity of symptoms but are not routinely recommended (Kaplan et al, 2009).

LV. How can response to therapy be assessed?

Severe dehydration, malabsorption, and malnutrition may result from *Cryptosporidium* diarrhea (Cabada and White, 2010; Kaplan et al, 2009). Cryptosporidiosis may also cause complications in extraintestinal sites, i.e., pancreatitis and sclerosing cholangitis.

A decrease in the frequency and amount of bowel movements signals improvement. Secondarily, parasitological clearance may also be monitored to track response to treatment. Patients who required hospitalization may be discharged once hydration status has been optimized and electrolyte abnormalities are corrected. Diarrhea may not necessarily have resolved before discharge.
No primary or secondary prophylaxis is currently recommended for the prevention of cryptosporidiosis.

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STRONGYLOIDIASIS

Introduction

The causative agent of strongyloidiasis is *Strongyloides stercoralis*, a soil-transmitted nematode that is capable of autoinfection. Healthy persons are usually asymptomatic even if they have a chronic infection from *Strongyloides* (Segarra-Newnham, 2007). However, hyperinfection and disseminated disease may result in immunocompromised patients (Segarra-Newnham, 2007). Hyperinfection refers to an increase in the total worm burden while the worm is limited to its normal migration path in the human body consisting of the gastrointestinal tract, respiratory tract, and peritoneum (Segarra-Newnham, 2007; Siddiqui and Berk, 2001). In disseminated infections, worms are found in ectopic sites such as the brain (Segarra-Newnham, 2007; Siddiqui and Berk, 2001). Mortality from disseminated disease may be as high as 50%–80% in patients with impaired cellular immunity (Segarra-Newnham, 2007).

According to a hospital-based cross-sectional study by Getaneh et al. (2010), the prevalence of strongyloidiasis among HIV-positive persons was 12%, and 2.1% among HIV-negative persons. The odds ratio for *Strongyloides* infection among people with HIV was 6.4 (95% CI 2.2–18.9) using three techniques for detection of the worm (Getaneh et al., 2010).

In another hospital-based cross-sectional study by Assefa et al. (2009), the prevalence of strongyloidiasis was found to be 12.6% among HIV-positive persons and 0.6% among those who were HIV-negative. Among HIV-positive persons with a CD4 count <200 cells/l, the OR of *Strongyloides* infection was 3.1 (95% CI 1.1–8.9).

The question of HIV as a true risk factor for *Strongyloides* hyperinfection and dissemination has been raised (Siegel and Simon, 2012). The Th2 immune response is believed to predominate in persons with helminth infections. Th2 activity is relatively preserved in patients with HIV; there is a greater decline in Th1 cells among these patients. Therefore, Th2-mediated cytokine activity may be maintained even in patients with advanced AIDS. This may prevent dissemination of *Strongyloides* in patients with HIV (Siegel and Simon, 2012).

LVI. What are the clinical signs and symptoms of Strongyloides infection?

Patients with strongyloidiasis may manifest with a migratory, serpiginous, urticarial rash (larva currens) that may affect the buttocks, trunk, and groin more commonly (Siddiqui and Berk, 2001). Abdominal discomfort, including bloating, diarrhea, nausea, and anorexia, may also be present (Siddiqui and Berk, 2001). Persons with hyperinfection may have fever, chills, malabsorption, paralytic ileus, ulcerative enteritis, bleeding, cough, dyspnea, and possibly ARDS (Segarra-Newnham, 2007; Siddiqui and Berk, 2001). Secondary bacterial infections (including bacteremia) and fungal infections may result from translocation of bacteria from the intestines or from the transfer of gut bacteria to other parts of the body by adhering to the worm integument (Segarra-Newnham, 2007; Siddiqui and Berk, 2001).

LVII. What tests are needed to diagnose strongyloidiasis?

140. Stool exam using stool concentration methods (e.g. Kato Katz and formalin ether concentration techniques [FECT]) should be requested for all patients suspected of having strongyloidiasis.

Strong recommendation, Moderate quality of evidence

141. If the first stool exam is negative for larvae, a series of three exams should be done.

Strong recommendation, Moderate quality of evidence

142. If they are available, serology for antibodies against Strongyloides and other methods of direct detection of *Strongyloides* (i.e., Baermann method and agar plate culture) should be requested.

Strong recommendation, Moderate quality of evidence

Summary of Evidence

The most common method for diagnosing strongyloidiasis is the stool examination to detect larvae. However, there may only be a small number of larvae in stool in low-density infections. Also, the number of larvae deposited in the stool varies from day to day (Lim et al., 2004; Segarra-Newnham, 2007).

The detection rate for *Strongyloides* using stool examination is only approximately 25%–30% (Segarra-Newnham, 2007; Siddiqui and Berk, 2001). The detection rate increases to 50% with three serial examinations (Segarra-Newnham, 2007) and to 90%–100% with seven serial examinations (Siddiqui and Berk, 2001; Smith et al., 1985).

A comparison of three techniques for detecting *Strongyloides* showed that out of 27 positive stool samples positive with at least one technique, the water-emergence technique (Baermann method) was positive in 85.2%, the direct saline mount in 55.6%, and FECT in 51.9% (Getaneh et al., 2010).

In patients with hyperinfection, a sputum exam may be used to detect *S. stercoralis* (Segarra-Newnham, 2007), as well as examination of bronchial washings and brushings and pleural fluid (Siddiqui and Berk, 2001). Larvae may be detected in Gram-stained specimens (Siddiqui and Berk, 2001; Smith et al., 1985).

ELISA serology using antigens from *Strongyloides* larvae has shown a sensitivity of 82%–95% and a specificity of 84%–92% (Carroll et al., 1981; Lim et al., 2004; Loutfy et al., 2002; Segarra-Newnham, 2007). However, the performance of the test is likely to be affected by the choice of antigens to be used, as certain antigens may cross-react with antibodies against other helminth infections (Loufty et al., 2002; Neva et al., 1981).

The agar plate culture may be used to diagnose strongyloidiasis (Siddiqui and Berk, 2001), but this is not available in most laboratories. Other methods of diagnosing *Strongyloides* infection are duodenal fluid/aspirate examination (Segarra-Newnham, 2007; Siddiqui and Berk, 2001) and small bowel biopsy (Segarra-Newnham, 2007; Siddiqui and Berk, 2001).

PCR has been shown to be highly sensitive and specific for detecting *Strongyloides* in the stool (Kramme et al., 2011; Moghaddassani et al., 2011).

Patients with strongyloidiasis usually show eosinophilia on the complete blood count. This is not a conclusive finding, however (Lim et al., 2004; Segarra-Newnham, 2007).

LVIII. What are the standard and alternative treatments for strongyloidiasis?

143. HIV-infected persons with uncomplicated strongyloidiasis should be treated with albendazole 400 mg daily for 7 days. Patients with hyperinfection or disseminated infection may need to be given repeat doses.

Strong recommendation, High quality of evidence

144. Alternative drugs that may be used are ivermectin 200g/kg given as a single dose and thiabendazole 25 mg/kg/day in two daily doses for 2–3 days. These two drugs, however, are not routinely available in the Philippines.

Strong recommendation, High quality of evidence

Summary of Evidence

The recommended drugs for treating strongyloidiasis are albendazole, ivermectin and thiabendazole (Kaplan et al, 2009; Segarra-Newnham, 2007).

A prospective, open-label, randomized, controlled study compared ivermectin 200g/kg given as a single dose, as two doses given 2 weeks apart, and albendazole 400 mg twice a day for 7 days among 151 patients positive for rhabditiform larvae in the stool. Half of the patients were symptomatic at enrollment. Parasite elimination was achieved in 63.3% of patients in the albendazole arm, in 96.8% in the single-dose ivermectin arm, and 93.1% in the two-dose ivermectin arm (p=0.006). There were more patients who had reinfection/relapse in the albendazole group. Transient changes in transminases were observed to result from both ivermectin and albendazole (Suputtamongkol et al., 2011).

Several studies have similarly found that ivermectin is superior to albendazole in terms of parasitological clearance of *Strongyloides* (Datry et al., 1994; Marti et al., 1996; Pitisuttithum et al., 1995; Toma et al., 2000).

A prospective, randomized, open-label, phase III trial comparing ivermectin single dose at 200g/kg and thiabendazole 25 mg/kg in two daily doses for 2 days was conducted among 198 patients diagnosed with strongyloidiasis using immunofluorescence antibody test (IFAT). HIV patients were included but not those with CD4 count <400/l. Approximately half of participants in each arm were asymptomatic. Using a negative stool agar culture, negative IFAT, or a decrease of two or more antibody titers at 4 and 6 months after recruitment as outcomes constituting cure, the efficacy of ivermectin was 56.6% and that of thiabendazole was 52.2% (p=0.53). More side effects were observed in the thiabendazole arm, i.e., dizziness, nausea and vomiting, and day somnolence. These findings were similar to those of Gann et al. (1994).

LIX. What adjunctive treatments are necessary?

No adjunctive treatments are necessary.
Prompt treatment must be given for conditions resulting from *S. stercoralis* infection, e.g., diarrhea, paralytic ileus, secondary bacterial infections, and ARDS.

LX. How can response to therapy be assessed?

Response to therapy may be assessed by improvement of signs and symptoms and by parasitological clearance from the stool. If antibody determination is available, a fall in titers as a response to treatment may be monitored. Improvement of signs and symptoms as well as of complicating conditions resulting from strongyloidiasis should be used as the criteria for discharge for patients who are hospitalized.

LXI. What measures can be taken to prevent occurrence and recurrence?

Primary and secondary prophylaxis are not recommended for strongyloidiasis.

Patients should be advised to avoid reexposure and reinfection. Patients should be advised to avoid contact of skin with soil that may contain the infective larvae of *Strongyloides*.

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MYCOBACTERIUM AVIUM COMPLEX

Introduction

Mycobacterium avium complex (MAC) is made up of nontuberculous mycobacteria *(M. avium* and *M. intracellulare*) that present as a disseminated infection in people living with HIV in the advanced stage of their natural course of illness (Kaplan et al, 2009; Khosravi et al.,

2012; Tan et al., 2010). Disseminated MAC was exceedingly rare before the era of HIV but rose markedly with the advent of the HIV pandemic (Nightingale et al., 1993). The incidence of disseminated MAC disease is related to the level of immunosuppression from the depletion of CD4 T-helper cells. The risks substantially decrease once the patient's immune system has recovered in response to ARVs (Kaplan et al, 2009; Chaisson et al., 1992). In patients not receiving ARVs or MAC prophylaxis, the risk of MAC infection ranges from 20%–40% (Chaisson et al., 1992; Nightingale et al., 1993). Prevalence of MAC among HIV-infected patients ranges from 14%–55% depending on the country (Corti and Palmero, 2008, McCarthy et al., 2012; Lazaro et al., 2006). Inhalation or ingestion of environmental mycobacteria is the main route of transmission. Water is the main source of the mycobacteria, where they have the ability to survive in chlorine or other biocides (Kaplan et al, 2009; Corti and Palmero, 2008).

Risk factors for developing MAC among HIV-infected individuals are a viral load of more than 100,000 copies/mL, previous history of any OI, CD4 count of less than 100 cells/μL, and MAC colonization of either the respiratory or gastrointestinal tract (Kaplan et al, 2009).

LXII. What is the clinical presentation and physical examination of MAC?

In ARV naïve HIV-infected patients, MAC usually presents in a disseminated form (Torriani et al., 1994; Inderlied et al., 1993). Symptoms may be present months before the first episode of MAC bacteremia (Gordin et al., 1997). Clinical manifestations of disseminated MAC are very nonspecific, and may overlap with symptoms of other OIs. The disseminated form of MAC commonly presents with more than 4 weeks of cough, fever, night sweats, weakness, and weight loss. In HIV-infected patients receiving ARV treatment, MAC usually manifests as a localized infection. Localized infection may present as lymphadenitis, skin and soft infection, pneumonitis, pericarditis, osteomyelitis, and genital ulcers (Kaplan et al, 2009; Griffith et al., 2007; Tan et al., 2010). Physical examination may aid in localizing the source of infection such as lymphadenopathy, hepatomegaly, splenomegaly, or abnormalities on lung auscultation. Radiograph and imaging studies are helpful in locating the site involved. Nonspecific laboratory abnormalities include anemia, elevated alkaline phosphatase, and an elevated LDH (Kaplan et al, 2009; Torriani et al.,

1994). Since the signs and symptoms of MAC are very non-specific, a high index of suspicion is necessary especially among persons living with HIV.

In a nested case-control study involving 90 HIV-infected patients to describe the clinical presentation of MAC infection matched with 180 controls, patients infected with MAC had lower weights (p=0.001) and lower Karnofsky scores (p<0.001); a higher proportion had fever (p<0.003), decreased hemoglobin (p<0.001), elevated alkaline phosphatase (P<0.04), and elevated LDH (p<0.02). Symptoms present prior to isolation of MAC bacteremia were weight loss at 3 months prior (p=0.002), fever at 2 months prior (p=0.02) and anemia/LDH at 1 month prior (p<0.001) to diagnosis (Gordin et al., 1997).

In a cohort study done in 1060 HIV-infected patients residing in Southeast Asian countries and diagnosed with nontuberculous-mycobacterium infection, factors independently associated with MAC infections were manifestations of more than 4 weeks of fever (OR 6.8 CI 2.3–19.9 p<0.001), more than 4 weeks of cough (OR 4.6 CI 1.6–13.1), pain in muscle/joints (OR 3.1 CI 1.1–8.6 p<0.091). According to the guidelines of management of MAC endorsed by IDSA/ATS, the most common presentation of disseminated MAC is fever (80%), night sweats (35%), and weight loss. Chest radiographs are abnormal in 66% of those with pulmonary MAC. Laboratory findings may include elevated alkaline phosphatase, elevated LDH, as well as anemia.

LXIII. How is MAC diagnosed in patients with HIV?

Diagnosis is based on the presence of signs and symptoms, along with identification of MAC by culture of a sterile tissue or body fluids such as blood, lymph node, and bone marrow. Species identification can be performed using specific DNA probes, high-performance liquid chromatography or biochemical tests (Kaplan et al, 2009; Griffith et al., 2007). Other diagnostic modalities that provide diagnostic information are AFB smear, biopsy, and imaging studies (Kaplan et al, 2009).

LXIV. What is the treatment of MAC in patients living with HIV?

145. Treatment of MAC should include two or more active drugs to prevent the development of resistance. Clarithromycin 500 mg

twice a day plus ethambutol 15 mg/kg/day is the recommended regimen for disseminated MAC. A minimum of 1 year of treatment is recommended.

Strong recommendation, High quality of evidence

146. Azithromycin 250 mg once a day can be substituted for clarithromycin and is more convenient to take and is associated with less drug interactions.

Strong recommendation, High quality of evidence

Summary of Evidence

Treatment of MAC disease should consist of two or more antimycobacterial drugs to prevent the development of resistance (Dube et al., 1997; Dunne et al., 2000; May et al., 1997; Parenti et al., 1998; Piscitelli et al., 1997; Singer et al., 2000; Ward et al., 1998). Macrolides remain the backbone of the treatment regimen (Dube et al., 1997; Dunne et al., 2000; May et al., 1997; Parenti et al., 1998; Piscitelli et al., 1997; Singer et al., 2000; Ward et al., 1998). Clarithromycin is associated with faster clearance of bacteremia compared to azithromycin (Dunne et al., 2000; Ward et al., 1998). However, clarithromycin can be substituted with azithromycin because once a day dosing is convenient and is associated with less drug interactions (Kaplan et al, 2009; Piscitelli et al., 1997). Ethambutol is the recommended second drug in the regimen (Dube et al., 1997; Dunne et al., 2000; May et al., 1997; Ward et al., 1998). A third or fourth drug can be added in cases of severe immunosuppression, high mycobacterial loads, and in the absence of ART. Rifabutin is the recommended third drug for prevention of resistance and improved survival (Kaplan et al, 2009), but it is not locally available.

A fourth drug can be an injectable agent such as amikacin or streptomycin (Parenti et al., 1998; Sim et al., 2010). Evidence has shown that rifabutin in addition to clarithromycin and ethambutol may prevent resistance and improved survival; however, it is not available here in our country.

In a randomized control trial comparing azithromycin with clarithromycin involving 59 HIV-infected patients diagnosed with disseminated with

MAC, the study was stopped due to an interim analysis that demonstrated faster clearance of bacteremia at 16 weeks (azithromycin 45.5% vs. clarithromycin 94.4% p=0.22) with both regimens containing ethambutol as a second agent (Ward et al., 1998). In another randomized control trial comparing azithromycin and ethambutol vs. clarithromycin and ethambutol, the study involved 239 patients infected with HIV, and sterilization of blood was similar at week 24. Relapse was more common in azithromycin than in clarithromycin, although the difference was not statistically significant. No significant change in mortality was noted in either study (Dunne et al., 2000).

LXV. What is the recommended prophylaxis for MAC?

147. For primary prophylaxis, HIV-infected patients with CD4 count of <50cells/μL should receive either clarithromycin 500 mg once a day or azithromycin 1000 mg once a week. Azithromycin prophylaxis should be continued until CD4 count is >100 cells/μl in response to ARV treatment.

Weak recommendation, Moderate quality of evidence

148. For secondary prophylaxis, adult and adolescent patients with a diagnosis of disseminated MAC disease should be maintained on antimycobacterial treatment unless CD4 count recovers to >100 cells/μL in response to ARV.

Strong recommendation, Moderate quality of evidence

Summary of Evidence

Primary prophylaxis for MAC should be initiated if CD4 is <50 cells/μL (Brooks et al., 2005; Kaplan et al, 2009; El-Sadr et al., 2000; Pierce et al., 1996). Azithromycin or clarithromycin is the recommended drug for prophylaxis (Kaplan et al, 2009; El-Sadr et al., 2000; Pierce et al., 1996). No studies have shown the superiority of one over the other with regards to efficacy. Azithromycin may be preferred because it is given at a once a week dosing and is associated with less drug interactions than clarithromycin. Primary prophylaxis should be continued until the CD4 is >100 cells/uL for >3 months. In a cohort study comparing azithromycin vs.

no prophylaxis in patients with CD4 count <50 cells/uL, episodes of MAC was decreased in patients receiving azithromycin prophylaxis (p<0.002) (El-Sadr et al., 2000). A double-blind RCT comparing placebo vs. clarithromycin in preventing disseminated MAC was stopped prematurely because 16% developed MAC in the placebo group compared to 6% in the control group (p<0.001). Mortality was also higher in the placebo group compared to the clarithromycin group (32% vs. 41%, p=0.026) (Pierce et al., 1996).

A multicenter double-blind randomized trial of treatment with azithromycin 1200 mg weekly compared with placebo in HIV-infected patients was done to assess whether prophylaxis can be discontinued once CD4 is more than 100 cells/μL in response to ARV. After a median follow-up of 12.7 months, there was no confirmed MAC in both groups (Pierce et al., 1996). Another cohort study was done involving 962 HIV-infected patients to assess whether primary prophylaxis for MAC can be discontinued in patients responsive to ARV. Among the 962 patients who became eligible to discontinue prophylaxis, 592 discontinued the treatment. After an average follow-up of 2.47 years, only one case of relapse was noted, resulting to an incidence of 0.68 infections per 1000 person-years (Brooks et al., 2005). In a large national cohort using a surveillance monitoring HIV-related illness, they noted HIV patients with history of primary MAC maintained on prophylaxis. Five hundred ninety-two patients discontinued their prophylaxis because CD4 count was already >100 cells/uL. They were followed up for a total duration of 1465 person-years, and no recurrences of MAC were noted. In a prospective cohort to assess the safety of discontinuing prophylaxis (primary and secondary) for OIs in response to ARV, MAC prophylaxis was discontinued in 28 patients. No MAC cases were reported after a median follow-up of 28–31 months (Green et al., 2004). In a retrospective study involving HIV-infected patients receiving secondary prophylaxis for MAC to assess whether prophylaxis can be discontinued after a favorable response to ARV, favorable response was defined as plasma HIV RNA level to less than level of detection. After a median follow-up of 50 months, there was only one case of relapse (Shafran et al., 2002).

AIDS-related morbidity and mortality have decreased since the introduction of ARV (Aberg et al., 2003). Initiation of ARV decreased the incidence of OIs and its related death (Zeller et al., 2002). Proportions of MAC infection among advanced HIV disease have fallen from 16% in the era before

ARV to 4% after the era of ARVs, with a current rate of 1% (Karakousis et al., 2004). HIV-infected patients with disseminated MAC should be maintained on secondary prophylaxis with a macrolide until there is a sustained increase of CD4 >100 cells/μL in response to ARV (Aberg et al., 2003; Kaplan et al, 2009; Green et al., 2004; Shafran et al., 2002).
The incidence of MAC infection in the Philippines is unknown, and a stronger recommendation for MAC prophylaxis cannot be made at this time. This may be an important topic for research.
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Protease inhibitors can increase the serum levels of clarithromycin, but no recommendations can be made for drug adjustment (Kaplan et al, 2009). Efavirenz can induce the metabolism of clarithromycin but increases the active metabolite of clarithromycin. The effect of this interaction is still unknown. Azithromycin has no interaction with protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs) because azithromycin is not affected by cytochrome P450 system (Kaplan et al, 2009). Simultaneous administration of clarithromycin and zidovudine may affect the absorption of the latter; hence, it is advised that the drugs be given 2 hours apart (Polis et al., 1997).

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PULMONARY TUBERCULOSIS

Introduction

In 2011, there were 8.7 million new cases of TB, of which 1.1 million (13%) were among people living with HIV. And of the 1.4 million people who died from TB, 430,000 (24%) were living with HIV (WHO, 2012). Furthermore, of the 1.8 million HIV-related deaths in 2010, 350,000 (22%) were due to TB (UNAIDS, 2010). TB continues to be the most common OI worldwide for people with HIV and remains a leading cause of death for people living with HIV in low- and middle-income countries (UNAIDS, 2008). It may develop at any stage of the disease.

LXVI. When should one suspect that an HIV patient may have pulmonary TB (PTB)?

149. All HIV patients with any of the screening symptoms (cough of any duration, fever of any duration, weight loss, and night sweats lasting 3 weeks) and/or an abnormal CXR should be suspected of having PTB.

Strong recommendation, High quality of evidence

Summary of Evidence

At higher CD4 counts, HIV-related TB presents like TB among HIV-negative patients. However, with decreasing CD4 counts, extrapulmonary tuberculosis (ePTB) becomes more common, and the CXR findings more commonly involves the middle and lower lobes. Although the clinical

presentation of PTB in people living with HIV may be different from the presentation of PTB in HIV-uninfected patients, the most common symptoms are still cough, fever, night sweats and significant weight loss (Bruchfeld et al., 2002, Batungwanayo et al., 1992). Relative to HIV-uninfected patients, weight loss and fever are more common, whereas hemoptysis is less common. Some studies have reported a decreased proportion of patients with cough (Kassu et al., 2007; Selwyn et al., 1998). The latter observations relate to a reduced inflammatory response, resulting in less pulmonary cavitation and endobronchial involvement (Harries et al., 1998; Raviglione et al., 1992). In a large study in Thailand looking at screening for TB in HIV-1 infected patients, weight loss occurred in 50% of patients who were screened and had a negative predictive value of 92% (Cain et al., 2010). Furthermore, TB HIV patients may also be asymptomatic. Four out of 14 Tanzanian HIV-1 infected patients with CD4 <200 cells/uL diagnosed with PTB (positive sputum microscopy or culture) during screening for a vaccine study were asymptomatic with a normal chest radiograph (Mtei et al., 2005).

A 2010 study in Uganda comparing clinical manifestations and radiographic presentation of PTB based on their relationship to the CD4 count (Chamie et al., 2010) also showed that HIV patients differed significantly from HIV-negative patients with PTB. Among 873 HIV-infected patients with PTB, decreasing CD4 count was significantly associated with an increase in the likelihood of having experienced subjective fever ($p<0.001$), weight loss ($p=0.001$), malaise ($p=<0.005$), diarrhea ($p=0.001$), and loss of appetite ($p<0.001$). On the other hand, hemoptysis declined with decreasing CD4 count ($p=0.004$) and so did the mean duration of cough ($p<0.001$). This is also correlated with an increasing likelihood of having fever ($p<0.001$) and normal chest examination ($p=0.025$).

Cain et al. (2010) proposed an algorithm for TB screening and diagnosis in people with HIV. In their study which enrolled 1768 patients from Thailand, Cambodia, and Vietnam, the first step was inquiring about the presence of any of the three screening symptoms, namely cough of any duration, fever of any duration, and night sweats lasting 3 weeks or more. The presence of these symptoms in the past 4 weeks was found to be 93% sensitive and 36% specific for TB. Those with positive screens underwent two sputum smears for AFB as the first step. Chest radiography was done on patients with two negative sputum smears. According to the authors, this algorithm

reduced the number of false negative results by 83% compared to the WHO algorithm. Furthermore, they said that adding chest radiography to symptom screening further improves its sensitivity.

In a meta-analysis (Getahun et al., 2011) of 12 studies, the above algorithm was also recommended as the best performing one with the addition of weight loss in the screening questions. The overall sensitivity of the rule was 78.9% (95% CI 58.3%–90.9%) and specificity was 49.6% (95% CI 29.2%–70.1%).

LXVII. How does one reliably diagnose PTB in HIV patients?

150. The evaluation for PTB should include a chest radiograph.

Strong recommendation, High quality of evidence

151. A normal CXR result does not rule out PTB, so when clinical suspicion is high, sputum samples should still be obtained for Xpert MTB/RIF.

Strong recommendation, High quality of evidence

152. Drug susceptibility testing is recommended for suspected drug-resistant tuberculosis (DRTB).

Strong recommendation, High quality of evidence

Summary of Evidence

Chest X-ray

The spectrum of radiographic manifestation of PTB is dependent on the relative level of HIV-related immunosuppression. CXR findings vary with CD4 count. At lower CD4 counts, findings of a normal CXR, miliary disease, adenopathy, and pleural effusion were more likely, while at higher CD4 counts, cavitary disease, fibrosis, and upper lobe disease were more likely findings. After adjusting for age, sex, and cough duration, the factors of never having smoked, a negative AFB smear, and CD4 cell count <150 cells/uL were all significantly associated with an increased likelihood of having a normal CXR (Chamie et al., 2010).

Radiographic characteristics such as mediastinal lymphadenopathy, pleural effusion, and lower lobe and miliary disease have been shown to be relatively more common in HIV-infected compared with non-HIV-infected persons (Post et al., 1995, Abouya et al., 1995), as was a normal CXR (Pepper et al., 2008). Adding CXR to symptom screening increases the number of TB cases detected, but it is nonspecific and adds to the cost of screening (Padmapriyadarsini et al., 2011).

In the Getahun (2011) meta-analysis for the development of a standardized screening rule for TB in HIV patients in resource-constrained settings, it was shown that abnormal chest radiographic findings increased the sensitivity of the rule by 11.7% (90.6% vs 78.9%), with a 10.7% reduction of specificity (49.6% vs 38.9%). In a 2011 study in Uganda (Yoo, 2011), out of 334 HIV patients with cough ≥2 weeks, 54 (16%) had a normal CXR, and these patients were younger, had lower CD4 counts (median 13 vs. 57 cells/uL, $p<0.001$), and were less likely to be AFB smear positive (17% vs. 39%, $p=0.002$) than those with abnormal x-rays. PTB was the most frequent (44%) diagnosis of those with normal CXRs which was established via bronchoalveolar lavage TB culture. Also, the frequency of normal CXRs among culture-positive PTB patients were 9% (14/148), compared with 20% (10/50, $p=0.048$) among culture-negative PTB patients.

Sputum Smear Microscopy

The most frequent method of TB detection involves microscopic examination of sputum for AFB. It is inexpensive, relatively rapid to perform, and specific in most settings. However, in order to be positive, a specimen needs to contain approximately 105 mycobacteria per milliliter. The sensitivity in HIV infection ranges from 43% to 51% (Cattamanchi et al., 2009; Wilkinson and Sturm, 1997).

A 2009 study in Thailand (Mongkongdee et al., 2009) showed that of 126 HIV patients with PTB, the first sputum smear diagnosed 36 (29%, 95% CI 21–37), the second sputum added nine patients (incremental yield 7%; 95%CI 4–12) and the third smear added two patients (incremental yield 2%; 95% CI 0–6). It is worth noting that out of 96 culture-positive patients diagnosed from the first collected specimen, sputum smear diagnosed 35 patients.

TB Culture

Culture of *M. tuberculosis* is much more sensitive than smear microscopy. It also allows subsequent strain identification and drug susceptibility tests. The traditional method of inoculating solid media is slow, as growth may not be visible until after 6–8 weeks of incubation. However, since HIV patients have a higher mortality due to DRTB (Gandhi et al., 2006, Park et al., 1996), it is recommended that HIV patients be subjected to TB culture as part of the diagnostic process. In a cohort of multi-drug resistant TB (MDR-TB) patients in New York, of which 90 were HIV-positive and 41 were HIV-negative, the mortality rates were 75% and 24% ($p<0.01$), respectively (Park et al., 1996).

A study in Thailand (Mongkongee et al., 2009) also showed that differences in yield can depend on the culture technique used, whether solid media like LJ culture, or broth-based media like MGIT (Mycobacterial Growth Indicator Tube) is used. This study showed that performing LJ culture on the three sputum specimens diagnosed 68% of cases while MGIT diagnosed 98% of cases.

Molecular Techniques

Nuclear acid amplification testing (NAAT) provides a reliable way of increasing the specificity of diagnosis, but sensitivity is variable due to paucibacillary disease. A recent meta-analysis showed high sensitivity (>95%) and specificity (100%) for line probe assays when culture isolates were used (Morgan et al., 2005). The WHO has endorsed the use of LPA, which detect both M. tuberculosis complex as well as INH and rifampicin resistance on smear-positive sputum or on early positive growth on culture. Recently, the WHO endorsed the use of GeneXpert-Rif for the rapid diagnosis of TB as well as rifampicin resistance among HIV-infected individuals with clinical suspicion of TB. Clinical validation trials done showed that 92.2% of culture-positive patients were detected by a single direct Xpert MTB/RIF test (in comparison to the sensitivity of a single direct smear of 59.5%) (Rachow et al., 2011). HIV co-infection substantially decreased the sensitivity of microscopy (to 47%) but did not significantly affect Xpert MTB/Rif performance (Van Rie et al., 2010).

LXVIII. What is the recommended treatment regimen for HIV-infected PTB patients?

153. Considering the variability of yield from smear microscopy and NAAT, empiric treatment should be initiated and continued in HIV-infected persons in whom TB is suspected until all diagnostic work-up (smears, cultures, or other identification results) is complete.

Strong recommendation, Moderate quality of evidence

154. When active TB is diagnosed or suspected, a combination anti-TB treatment regimen should be started as soon as possible.

Strong recommendation, High quality of evidence

155. TB patients with known HIV-positive status and all TB patients living in HIV-prevalent settings should receive daily TB treatment.

Strong recommendation, High quality of evidence

156. Directly observed treatment is recommended for all patients with HIV-related TB.

Strong recommendation, High quality of evidence

157. Recommendations for anti-TB treatment regimens in HIV-infected adults follow the same principles as for adults without HIV infection. It is recommended that TB patients who are living with HIV should receive at least the same duration of TB treatment as HIV-negative TB patients.

Strong recommendation, High quality of evidence

158. Until further RCTs elucidate the optimal duration of treatment, 6 months of therapy is probably adequate for the majority of patients, but prolonged therapy (up to 9 months) is recommended (as in HIV-uninfected patients) for patients with a

delayed response to therapy (smear positive after completion of 2 months of therapy), with cavitary disease on chest radiograph.

Strong recommendation, Moderate quality of evidence

159. All HIV-infected patients treated with isoniazid should receive pyridoxine supplementation.

Strong recommendation, Low quality of evidence

160. In all TB co-infected HIV patients, cotrimoxazole preventive therapy should be considered when CD4 testing is not readily available.

Strong recommendation, High quality of evidence

Summary of Evidence

Combination anti-TB treatment approach promotes rapid killing of tubercle bacilli, prevents the emergence of drug resistance, and decreases the period of contagion (Kaplan et al, 2009). The recommendation that a four-drug regimen be used is because this regimen has similar efficacy rates in both fully sensitive and INH-resistant organisms (PSMID, 2006).

Directly observed treatment is recommended by the WHO for the treatment of HIV-1/TB. So far there have been no RCTs or systematic reviews on the usefulness of combined antiretroviral therapy (ART)/directly observed treatment (DOT) in treating HIV-1/TB co-infection.

A retrospective study of 700 patients with 264 HIV-seropositives (Nahid et al., 2007) showed that the relapse rate among HIV-infected TB patients was 9.3 per 100 person-years vs. 1.0 per 100 person-years in the HIV-uninfected/unknown TB patients ($p<0.001$). HIV patients who received intermittent therapy were more prone to relapse than those treated daily (adjusted HR 4.12; $p=0.04$). The use of ARV was associated with more rapid conversion of smears and cultures and with better survival.

The optimal length and type of TB treatment in patients co-infected with HIV-1 is unknown, and long-term randomized trials are needed to address this question (Schutz et al., 2010). A systematic review and meta-analysis

(Khan et al., 2010) was conducted to evaluate the impact of duration and dosing schedule of rifamycin and the use of ARV in the treatment of active TB in HIV patients. Six RCTs and 21 cohort studies were included. Results show that relapse was more common with regimens using 2 months rifamycin (adjusted risk ratio 3.6; 95% CI 1.1–11.7) than with regimens using rifamycins for at least 8 months. Compared with daily therapy in the initial phase, thrice-weekly therapy was associated with higher rates of failure (adjusted risk ratio 4.0; 95% CI 1.5–10.4) and relapse (adjusted risk ratio 4.8; 95% CI 1.8–12.8). Furthermore, there were trends toward higher relapse rates if rifamycins were used for only 6 months, compared with ≥8 months, or if ART was not used. However, the data quality of the studies included in the review was low and more RCTs are necessary as identified by the reviewers.

Cotrimoxazole prophylaxis has been shown to decrease mortality in patients with TB. Of 1003 patients in a RCT in Zambia (Nunn et al., 2008), the HR for death (cotrimoxazole:placebo) was 0.79 (95% CI 0.63–0.99). In one study in Malawi, case fatality rates in HIV-positive patients fell from 43% to 24% (HR 0.67) after cotrimoxazole prophylaxis was started, and the improvement was most apparent in those with smear-positive TB (HR 0.56) and others with confirmed TB diagnoses (Mwaungulu et al., 2004).

LXIX. What is the management for treatment failure?

161. The management of MDR-TB is complex, and DRTB patients should be referred to Programmatic Management of Drug-resistant TB (PMDT) centers for work-up and treatment.

Strong recommendation, Low quality of evidence

162. The recommended treatment for DRTB is the same for HIV-infected as for non-HIV-infected patients.

Strong recommendation, Moderate quality of evidence

163. Contact investigation and strict infection-control precautions should be implemented according to national guidelines.

Strong recommendation, Low quality of evidence

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LATENT TB INFECTION

Introduction

Latent TB infection (LTBI) occurs when the inhaled TB bacilli persist in an inactive state rather than progressing to active TB disease. At this point, patients are asymptomatic and non-infectious. HIV infection is a leading risk factor for progression from LTBI to active disease (van der Sande et al., 2004, Horsburgh, 2004). In settings where TB is a leading cause of death, the risk of reactivation is around 10% per year (WHO, 2010).

LXX. Who should be treated for LTBI?

164. In the absence of active TB, HIV patients should be treated for presumed LTBI.

Strong recommendation, Moderate quality of evidence

Summary of Evidence

In a meta-analysis (Getahun et al., 2011) of 12 studies, the screening rule of current cough, fever, weight loss and night sweats has an overall sensitivity of 78.9% (95% CI 58.3%–90.9%) and specificity was 49.6% (95% CI 29.2%–70.1%). The absence of these four symptoms had a negative predictive value of 98% (where the prevalence of active TB among HIV-infected patients was 5%).

LXXI. How is LTBI diagnosis done?

165. Tuberculin skin test (TST) is not a requirement for initiating isoniazid preventive therapy (IPT) in people living with HIV.

Strong recommendation, Moderate quality of evidence

166. Interferon gamma release assays (IGRAs) are not recommended to screen HIV patients for eligibility to receive IPT.

Strong recommendation, Moderate quality of evidence

Summary of Evidence

In resource-constrained settings where operational challenges to the implementation of TST exist and can impede access to IPT, the WHO (2011) recommends that TST should not be a requirement for starting IPT.

If TST is used, 0.1 ml of purified protein derivative (PPD) is placed intradermally. It is positive if induration is ≥5mm 48–72 hours after placement. Nontuberculous mycobacterial infection and prior BCG vaccination may cause false-positive TSTs. However, in HIV patients, potential causes of false positive tests should not influence the decision to administer LTBI therapy (Kaplan et al, 2009).

The European Centre for Disease Prevention and Control has declared in 2011 that in general, IGRA cannot differentiate between active TB disease and latent infection. In immunocompromised patients, IGRA responses have been shown to be reduced compared to immunocompetent subjects, with the former exhibiting a higher proportion of indeterminate results.

Furthermore, indeterminate results increase as CD4 counts decrease. Furthermore, the WHO (2011) does not recommend the use of IGRAs in low- and middle-income countries because there is insufficient data on the performance of IGRAs in countries where TB and HIV infections are endemic and IGRAs are more costly and technically more difficult to perform than the TST.

In the preliminary result of the Thibela TB study in South Africa (Churchyard et al., 2010) involving 23,117 miners of which 10.6% received HIV care, it was noted that the addition of chest radiography to symptom screening increased the number of definite cases detected by 2.5-fold (113 to 281 cases). No sub-group analysis for HIV patients was done in this regard.

LXXII. What is the management for LTBI?

167. All HIV patients with presumed LTBI should receive at least 6 months of IPT 300 mg daily under supervised treatment.

Strong recommendation, High quality of evidence

168. Patients who are on isoniazid should receive pyridoxine 25 mg per day to prevent peripheral neuropathy.

Strong recommendation, Low quality of evidence

Summary of Evidence

In a meta-analysis of 12 trials (Akolo et al., 2010) with a total of 8578 participants, TB preventive therapy versus placebo was associated with a lower incidence of active TB (RR 0.68 95% CI 0.54–0.85). This benefit was more pronounced in those with a positive TST (RR 0.38 95%CI 0.25–0.57) than in those with a negative test (RR 0.89 95% CI 0.64–1.24). Efficacies were similar regardless of drug types or frequency or duration of treatment, but short-course multi-drug regimens were more likely to be discontinued due to adverse events compared to INH monotherapy. Overall, there was no evidence that TB preventive therapy vs. placebo reduced all-cause mortality (RR 0.94 95% CI 0.85–1.05).

Preventive chemotherapy reduces the overall risk of developing TB by 33% (relative effect 0.67 95% CI 0.51–0.87). For those who were TST positive, the reduction in developing TB increased to 64% (RR 0.36 95% CI 0.22–0.61) (WHO, 2011).

The major toxicities of isoniazid therapy are peripheral neuropathy and hepatotoxicity, thus the recommendation for pyridoxine intake while on IPT.

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EXTRAPULMONARY TUBERCULOSIS

Introduction

HIV and tuberculosis is a deadly combination in countries where both are endemic. ePTB cases have been increasing in countries where HIV is an epidemic (Aaron et al., 2004). ePTB is associated with higher mortality in HIV-infected individuals compared to HIV-negative individuals. Tuberculosis in HIV-infected patients can be extrapulmonary in 40% of cases (Kingkaew et al., 2009). Lymphatic involvement is still the most

common extrapulmonary manifestation, followed by meningeal and intra-abdominal involvement. Other sites that can be infected are pleural, cutaneous, pericardium, and bone (Kingkaew et al., 2009). In our SAGIP clinic at PGH involving 426 HIV-infected patients, prevalence of ePTB in one site is 5.7% and comprises 17.4% of all OIs (Salvaña et al., 2012). Including disseminated TB, the total prevalence of extrapulmonary disease is 8%, comprising 24.5% of all OIs. Risk factors identified for developing ePTB among HIV-infected individuals included having been diagnosed with HIV for 1–5 years, late diagnosis of pulmonary tuberculosis, and lymphoma (Kingkaew et al., 2009; Kwara et al., 2009). Risk factors for mortality identified included having TB meningitis, CD4 <200 cells/µl, and hospitalization at the time of diagnosis of ePTB (Kingkaew et al., 2009; Kwara et al., 2009). Of the ePTB sites, the most studied in HIV co-infection is tuberculous meningitis (TBM) and tuberculous pericarditis. Initiation of ARV treatment improves survival in HIV patients diagnosed with ePTB and should be started as soon as practical (Garcia de Olalla et al., 2008).

TB PERICARDITIS

TB pericarditis in HIV-infected individuals is associated with higher mortality compared to HIV-seronegative individuals (Mayosi et al., 2008). Eighty-five percent of pericardial effusion in HIV-infected patients is associated with tuberculosis. Effusive pericarditis in HIV seropositive patients is associated with a lower risk for TB constrictive pericarditis (Ntsekhe et al., 2008).

A multicenter prospective observational study enrolled 119 patients with suspected tuberculous pericarditis to assess whether patients with HIV are less likely to have constrictive pericarditis compared to HIV seronegatives. Among those who were HIV seropositive, 0% had constrictive pericarditis, in contrast to 24.2% among those in those who were HIV seronegative (p0.005). Among those 42 persons with signs of HIV, 4.8% had constrictive pericarditis vs. 14.3% among the 77 patients without signs of HIV (p=0.08). Multivariate analysis showed that clinical evidence of HIV was associated with less risk of constriction (Ntesekhe et al., 2009).

A prospective observational study to determine predictors of mortality in 174 patients with TB pericarditis in sub-Saharan Africa showed an overall mortality rate of 26%. Patients who had clinical features of HIV had higher

mortality compared to those who did not (40% vs. 17% p=001). The presence of HIV was identified as an independent predictor for mortality (HR 2.28 95% CI 1.14–4.56) (Mayosi et al., 2008).

LXXIII. What is the treatment for TB pericarditis?

169. Prednisolone 60 mg (or 60 mg prednisone if prednisolone is not available) once a day, to be tapered 10 mg per week to complete 6 weeks, should be included in the treatment of TB effusive pericarditis in patients infected with HIV.

Strong recommendation, Moderate quality of evidence

Summary of Evidence

Treatment of tuberculous pericarditis is mainly the initiation of anti-tuberculous chemotherapy. The same treatment applies to HIV-infected individuals (Elliot et al., 1993). The use of adjunctive steroids in managing TB pericarditis among HIV-positive patients is controversial. A systematic review of 543 HIV non-infected patients revealed that steroids have no benefit in the treatment of TB pericarditis (Mayosi et al., 2002). There is also a concern of aggravating immunosuppression if HIV-infected patients were given steroids.

At least one RCT involving HIV-infected patients showed lower mortality and faster resolution of symptoms among those given steroids (Hakim et al., 2000). This was a double-blind randomized placebo-controlled trial involving 58 HIV seropositive patients assigned to receive either prednisolone or placebo for 6 weeks. The aim of the study was to assess the effect of steroids on mortality, morbidity, and resolution of fluids in HIV-infected patients diagnosed with TB pericarditis. Mortality was noted in 5/29 patients in the prednisone group vs. 10/29 in the placebo group (OR 2, p=0.004). Death in the first 6 months was mainly due to disseminated TB, while after 6 months was mainly due to complications of HIV. None died due to constriction. Improvement in physical activity (p=0.02), decrease in jugular venous pressure (p=0.017), resolution of hepatomegaly (p=0.007), and ascites (p=0.015) were faster in the prednisolone group compared to placebo. The rates of resolution of pericardial fluid were the same in both groups. No excess OIs occurred in the prednisolone group.

TB MENINGITIS

TBM is associated with high mortality, especially in patients infected with HIV, with the rate of death ranging from 29% to 67% (8–10). Tuberculosis is a common etiology of meningitis among patients infected with HIV (Marais et al., 2010). Clinical presentations of TBM among HIV-infected vs. non-HIV patients vary in different studies. In some studies, cognitive dysfunction, absence of (or minimal) meningeal symptoms, and absence of hydrocephalus were more frequent in HIV-infected patients. On the other hand, one prospective study showed that seizures, hydrocephalus, and cerebral infarction were more common in HIV-infected patients. Factors that increased the risk for death in TBM were a low CD4 count, as well as grade 2 or 3 TBM. Factors for the development of severe neurologic deficit were hydrocephalus, infarction, and cranial nerve involvement (Marais et al., 2010). MDR-TB on CSF culture was associated with increased mortality (Tho et al., 2012).

In a retrospective study done to assess the etiology of 211 cases of meningitis in an area with a high HIV/TB prevalence country, 57% of meningitis cases were due to TB meningitis and 88% of those infected have HIV. A decrease in all-cause mortality was noted in those who received ART during treatment (HR 0.3 95% CI 0.08–0.82). Risk for mortality identified in the study were low CD4 count (OR 1.4 95% CI 1.03–1.96) and grade 2 or 3 TBM (OR 4.8 95% CI 1.45–15.87) (Marais et al., 2010).

LXXIV. How is TB meningitis diagnosed?

170. Xpert/RIF MTB should be done on CSF of HIV patients with suspected TB meningitis.

Strong recommendation, High quality of evidence

171. A normal CSF cell count does not rule out TB meningitis in HIV-infected patients presenting with signs of chronic meningitis. Diagnosis should not be based solely on CSF cell counts but should be associated with clinical and epidemiological information.

Strong recommendation, Moderate quality of evidence

Summary of Evidence

A prospective study was done to compare the clinical presentation of TBM between HIV-positive and HIV-negative patients. There were 82 patients with definite or probable TBM who were enrolled, 40 of whom were HIV positive. Fever >38.3°C was more common in HIV-negative (12% vs. 38%), while seizures were more common in HIV positive patients (30% vs. 9.5%). On imaging, hydrocephalus (30% vs. 7%) and cerebral infarction (27.5% vs. 4.76%) were more common in HIV infection. No differences on CSF results were noted between the two groups. On multivariate analysis in HIV-infected patients, death was associated with GCS <9, seizures, and CD4 <200/μL (RR 2.01,1.4, and 3.3, respectively) while factors associated with severe neurologic deficit were hydrocephalus, infarction, and cranial nerve involvement (RR 1.6, 1.8, and 1.29, respectively) (Bandyopadhyay et al., 2009).

The typical CSF findings in TBM seen in HIV-seronegative individuals (lymphocytic predominance, low glucose, high total protein) are not always seen in those patients infected with HIV. A normal CSF finding cannot be used to rule out TBM because in some patients, CSF findings can be normal and may have a neutrophilic predominant instead of lymphocytic (Cohen et al., 2010; Croda et al., 2010; Torok et al., 2008).

In a retrospective study involving 5576 lumbar puncture in an area highly endemic for TB and HIV, 820 had microbiological diagnosis. Around 28% accounted for TBM. Of those tested, 94%(134/158) of those who were positive for TBM had HIV. CSF findings were mostly lymphocytic predominant, with normal total protein and glucose. CSF was normal in 5% of cases (Jarvis et al., 2010). In another study in Vietnam involving 58 patients with HIV and TB meningitis, CSF findings showed that most presented with increased WBC, mostly neutrophilic, and normal total protein (Torok et al., 2008). In a study involving 108 HIV-infected patients with definite TBM, CSF analysis showed normal findings in 19% of the patients (Croda et al., 2010). Xpert/RIF on CSF was recently recommended by WHO as a replacement for conventional microscopy and culture as an initial test for TB meningitis (WHO, 2010. It has a calculated sensitivity of 59.3% and a specificity of 99.5%, with a positive predicitive value of 99.1% and a negative predictive value of 72.5% (Nhu et al, 2014).

LXXV. What is the role of steroids in TB meningitis?

172. Patients with TB meningitis should receive dexamethasone as adjunctive treatment regardless of HIV status, as early possible after initiation of appropriate first-line anti-tuberculosis drugs.

Strong recommendation. High quality of evidence

Summary of Evidence

TB meningitis patients with focal neurologic deficits or decreased mental status should be treated with intravenous dexamethasone for 7 weeks: intravenous dexamethasose at 0.4 mg/kg/day x 1 week, then 0.3 mg/kg/day x 1 week, then 0.2 mg/kg/day x 1 week, then 0.1 mg/kg/day x 1 week, then switch to oral dexamethansone at 4 mg/day x 1 week, then 3 mg/day x 1 week, then 2 mg/day x 1 week, then 1 mg/day x 1 week, then stop.

TB meningitis patients with no focal neurologic deficits or decreased mental status should be treated with intravenous dexamethasone for 5 weeks: intravenous dexamethasose at 0.2 mg/kg/day x 1 week, then 0.1 mg/kg/day x 1 week, then switch to oral dexamethasone at 4 mg/day x 1 week, then 3 mg/day x 1 week, then 2 mg/day x 1 week, then 1 mg/day x 1 week, then stop.

A randomized double-blind placebo-controlled trial was done in Vietnam on patients with TBM regardless of HIV status to assess the efficacy of adjunctive therapy with dexamethasone in reducing the risk of death and disability with 9 months of follow-up. A total of 5455 patients were enrolled in the study. Treatment with dexamethasone was associated with a reduced risk of death but was not associated with significant reduction in disability. The benefits were seen in all subgroups, including HIV seropositive individuals where 44 patients were in the dexamethasone group while 54 were in the placebo groups, in both outcomes (RR 0.78 95% CI 0.59–1.04 p=0.55) and death/disability (RR 0.87 95% CI 0.62–1.24 p=0.44) (Thwaites et al., 2004).

In a meta-analysis done of seven trials involving 1140 participants to assess the effects of corticosteroids, as an adjunct to antituberculous treatment, on death and severe disability in people with TBM, corticosteroids reduced

the risk of death on all seven trials (RR 0.78 95% CI 0.67 -0.91). Three trials showed that corticosteroids reduced the risk of death or disabling residual neurological deficit (RR 0.82 95% CI 0.70-0.97). In one trial, it was mentioned that 98 of the patients were HIV seropositive. In subgroup analysis, the results did not reach statistical significance. There is not enough evidence to support the use of steroids in HIV positive patients for reducing death and disabling residual neurological deficit (Prasad and Singh., 2008.

LXXVI. When is the optimal time to start ART in TB patients?

173. For ART-naïve, HIV-infected persons who are diagnosed with active TB, anti-TB treatment must be started as soon as possible, preferably within 4 weeks.

Strong recommendation, High quality of evidence

174. When TB occurs in patients already on ART, treatment for TB must be started immediately and ART should be modified to reduce the risk for drug interactions and maintain virologic suppression.

Strong recommendation, Moderate quality of evidence

Summary of Evidence

The CAMELIA (Cambodian Early vs. Late Introduction of Antiretrovirals) (Blanc et al., 2011) trial enrolled 661 TB-HIV patients to determine the timing for initiation of ARV relative to the start of anti-TB therapy. In this open-labelled RCT, it showed a significant decrease in mortality in early ARV (2 weeks after the start of TB treatment) among HIV patients with CD4 ≤200 cells/uL, adjusted HR 0.62 (95% CI 0.44–0.86 p=0.006) but showed an increase in IRIS events in the same group, HR 2.51 (95%CI 1.78–3.59 p<0.001).

In the SAPiT (Starting Antiretroviral Therapy at Three Points in Tuberculosis) (Abdool Karim et al., 2010) trial of patients with CD4 count <500 cells/uL, the risk of AIDS-defining illness or death did not differ between the two integrated arms – early or late initiation. However, in a subgroup of

72 patients with CD4+ count <50 cells/uL, the risk of AIDS or death was lower among those who initiated ART within 4 weeks of anti-TB treatment compared with 8–12 weeks. The decreased AIDS or death rate outweighs the higher IRIS rate (incidence rate ratio 4.71 95% CI 1.48–19.64 p=0.01). On the other hand, deferral of ARV to the first 4 weeks of the continuation phase of TB therapy in those with higher CD4 counts reduced the risks of IRIS (incidence rate ratio 2.18 95% CI 1.12–4.47 p=0.02) and other adverse events related to ART without increasing the risk of AIDS or death.

The AIDS Clinical Trials Group 5221 reported by Havlir et al. (2011) was a multinational open-label RCT of 806 patients of suspected TB and CD4 <250 cells/uL with a follow-up for 48 weeks. Similar to the SAPiT trial, there was no significant difference between early and late ART arms of the combined outcomes of AIDS-defining illnesses or death. But in a subgroup of 285 patients with CD4 <50 cells/uL, the rate of a new AIDS-defining illness or death was significantly reduced but was accompanied by a significant increase in IRIS events (11% vs. 5%, p=0.002).

These results were also shown by a retrospective cohort done in Rwanda (Franke et al., 2011), reviewing charts of 308 HIV patients. Their data showed that for individuals with CD4 counts of 50 or 100 cells/uL, ARV initiation at day 15 yielded 2-year survival probabilities of 0.82 (95% CI 0.76–0.89) and 0.86 (95% CI 0.80–0.92), respectively.

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