Enferm Infecc Microbiol Clin. 2016;34(8):516.e1–516.e18

Enfermedades Infecciosas y Microbiología Clínica

www.elsevier.es/eimc

Consensus statement

Prevention and treatment of opportunistic infections and other coinfections in HIV-infected patients: May 2015☆

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ARTICLE INFO

Article history:
Received 2 November 2015
Accepted 4 February 2016

Keywords:
Opportunistic infections
HIV infection
AIDS

ABSTRACT

Despite the huge advance that antiretroviral therapy represents for the prognosis of infection by the human immunodeficiency virus (HIV), opportunistic infections (OIs) continue to be a cause of morbidity and mortality in HIV-infected patients. OIs often arise because of severe immunosuppression resulting from poor adherence to antiretroviral therapy, failure of antiretroviral therapy, or unawareness of HIV infection by patients whose first clinical manifestation of AIDS is an OI.

The present article updates our previous guidelines on the prevention and treatment of various OIs in HIV-infected patients, namely, infections by parasites, fungi, viruses, mycobacteria, and bacteria, as well as imported infections. The article also addresses immune reconstitution inflammatory syndrome.

Prevención y tratamiento de infecciones oportunistas y otras coinfecciones en pacientes infectados por el VIH: mayo de 2015

Palabras clave:
Infecciones oportunistas
Infección por VIH
Sida

RESUMEN

A pesar del gran avance que ha supuesto el tratamiento antirretroviral (TAR) para el pronóstico de la infección por el VIH, las infecciones oportunistas (IO) continúan siendo causa de morbilidad y mortalidad en estos pacientes. Ello ocurre en muchos casos debido a la inmunodepresión grave, bien ante la falta de adherencia al TAR, el fracaso del mismo o el desconocimiento de la existencia de la infección por el VIH en pacientes que comienzan con una IO.

El presente artículo actualiza las recomendaciones de prevención y tratamiento de diferentes infecciones en pacientes con infección por VIH: parasitarias, fúngicas, víricas, micobacterianas, bacterianas e importadas, además del síndrome de reconstitución inmune.

☆ Readers who prefers to have this review in Castilian, can be obtained from the following address: http://www.gesida-seimc.org/contenidos/guiasclinicas/2015/gesida-guiasclinicas-2015-InfeccionesOportunistasyCoinfeccionesVIH.pdf.

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[1] See Appendix A for the contributions of the Authors and Reviewers.

http://dx.doi.org/10.1016/j.eimc.2016.02.004

Introduction

Opportunistic infections (OIs) have been the main cause of morbidity and mortality in HIV-infected patients since the beginning of the HIV epidemic.[1]

Efficacious regimens for primary and secondary prophylaxis to prevent OIs were the first major advance in therapy for HIV-infected patients, significantly decreasing mortality, even before the advent of highly active antiretroviral therapy (ART).[2] ART brought about a notable change in the progression of HIV infection by dramatically reducing mortality and the incidence of OIs.[3] However, today, we continue to see cases of OI in various settings: patients who are unaware of their HIV infection and whose first manifestation is an OI; patients who do not receive ART; and failure of ART due to poor adherence or other causes.[4] Accordingly, treatment of OIs continues to be a relevant topic in the care of HIV-infected patients.

The present document is an update of our previous recommendations on prevention and treatment of OIs in HIV-infected patients.[5,6] The strength of the recommendation and ranking of the tests that support it are based on a modification of the criteria of the *Infectious Diseases Society of America*.[7] According to these criteria, each recommendation should be offered always (**A**), generally (**B**), or optionally (**C**), based on data from 1 or more randomized clinical trials with clinical or laboratory results (**I**), 1 or more nonrandomized trials or observational cohort data (**II**), or expert opinion (**III**).

Owing to space limitations, the reader should consult the tables, which display the various prophylaxis and treatment regimens (both preferred and alternative) and the corresponding doses.

Parasitic infections (Table 1)

Toxoplasma gondii

Patients who have not been exposed to *Toxoplasma gondii* (confirmed by a negative anti-*Toxoplasma gondii* IgG result) should avoid contact with the parasite. Handwashing is recommended after contact with animals, especially cats, and after handling raw meat. Patients should try to eat meat that has been adequately cooked (or previously frozen to −20 °C) and wash fruit and vegetables that are to be eaten raw (**BIII**).[5,8,9]

Primary prophylaxis should be with cotrimoxazole in patients with anti-*Toxoplasma gondii* IgG and a CD4+ T-lymphocyte count <100 cells/μL (**AII**); alternatives include pyrimethamine combined with dapsone or atovaquone.[5,8,9] These regimens also protect against *Pneumocystis jiroveci* infection. Inhaled pentamidine does not protect against *Toxoplasma gondii* infection.

When cerebral toxoplasmosis is suspected, treatment should be started with sulfadiazine combined with pyrimethamine (and folinic acid to reduce blood toxicity) (**AI**) and maintained for at least 6 weeks (**BII**).[6,8,9] A brain biopsy should be performed if no response is observed at 7–14 days. If the diagnosis is confirmed, switching treatment to clindamycin + pyrimethamine (with folinic acid) should be considered (**AI**).[6,8,9] If therapy cannot be administered through a nasogastric tube, intravenous cotrimoxazole can be used (**BI**).[10] Dexamethasone should be used in cases of intracranial hypertension (**BIII**). Treatment with anticonvulsants—preferably levetiracetam—should be added in patients who experience convulsions (**AIII**).[6,8,9]

Once treatment is complete, secondary prophylaxis can be started (same regimen, reduced dose) (**AI**).[5,8,9]

Prophylaxis can be discontinued after 6 months on ART, providing the patient has maintained an undetectable viral load and a CD4+ T-lymphocyte count >200 cells/μL for ≥3 months (primary) or ≥6 months (secondary) (**AI**),[11] probably owing to recovery of the anti-*Toxoplasma gondii* cellular response (CD4+ T lymphocytes).[12] Prophylaxis should be restarted if the CD4+ T-lymphocyte count returns to <100–200 cells/μL (**AIII**).[5,8,9]

Leishmania *species*

Prevention of exposure to parasites of *Leishmania* species should be based on canine health surveillance in regions where the disease is prevalent (Mediterranean basin, where *L. infantum* is predominant) and avoiding exposure to dogs (especially in the case of immunodepressed patients) (**CIII**), sandfly bites, and needle sharing. There are no primary prophylaxis measures.[5,8,9]

The treatment of choice for visceral leishmaniasis is liposomal amphotericin B (**AII**) or amphotericin B lipid complex,[6,8,9] in various regimens. Alternatives include amphotericin B deoxycholate (renal toxicity) or pentavalent antimonials (pancreatic and cardiac toxicity) (**BII**). The efficacy of miltefosine and paromomycin has not been demonstrated in HIV-infected patients (**CIII**).[13]

Secondary prophylaxis should be administered once the acute infection has been treated (**BII**). Lipid formulations of amphotericin B (liposomal [**AII**] or lipid complex [**BI**]) are also drugs of choice.[5,8,9] In cases of relapse (common in very immunodepressed patients), it is necessary to repeat the initial treatment, use another regimen,[6,8,9] or administer a combination of the drugs mentioned above.

No safe recommendation can be made about withdrawal of secondary prophylaxis against *Leishmania*.[5,8,9] Although some experts recommend maintaining prophylaxis indefinitely, suspension should be considered in patients who remain relapse-free for 6 months, maintain a CD4+ T-lymphocyte count >200–350 cells/μL and an undetectable viral load for >3 months, and, if possible, test negative in PCR for the *Leishmania* antigen in blood or urine[14] (**CIII**). Prophylaxis should be restarted if the CD4+ T-lymphocyte count falls to <200 cells/μL.[5,8,9]

Cryptosporidium *species, microsporidia, and* Isospora belli

These ubiquitous parasites (*Isospora belli* predominates in tropical areas) cause mainly intestinal infection. As they are transmitted through contaminated food and water, contact should be avoided and appropriate hand hygiene measures should be taken to prevent exposure.[5,8,9] There are no efficacious primary prophylaxis regimens.

There is no specific treatment for cryptosporidiosis (**CIII**), and cure is based on ART-associated immune recovery (**AII**).[6,8,9] Treatment of microsporidiosis also depends on ART (**AII**), although efficacious complementary drugs are available. In intestinal infections and infections caused by *Enterocytozoon bieneusi*, the treatment of choice is oral fumagillin (**BIII**). Albendazole is recommended if other species are involved (**AII**). In patients with ocular involvement, albendazole can be combined with topical fumagillin (**BIII**).[6,8,9] The treatment of choice for isosporiasis is cotrimoxazole (**BI**).[6,8,9]

Secondary prophylaxis for microsporidiosis and isosporiasis involves maintaining the same regimen as for treatment. This can be suspended when a CD4+ T-lymphocyte count >200 cells/μL is reached after 6 months of efficacious ART (**CIII** and **BIII**, respectively). Suspension would be questionable in ocular microsporidiosis.[5,8,9] In a recent report, isosporiasis persisted despite appropriate prophylaxis and treatment and optimal immune recovery.[15]