Ateneo Clínico 10/8/12

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Antecedentes

- SM 20 años, HSH.
- VIH de transmisión vertical, multiexperimentado
- Plan actual por test de resistencia : AZT/3TC, TDF, DRV/r (2008)
- En fallo virológico e inmunológico.
- Estado inmunovirológico (04/2012):

  CV: 24.479 copias/ml (log4.38), CD4: 47/mm^3
- Profilaxis: TMP-SMX / Fluconazol.
- NAC en tres oportunidades, última 2011 internado en SEIC.
- No otras EO hasta el momento. No coinfecciones
- Niega consumo de drogas.
- Problema en adherencia a Tto y Px

Enfermedad actual

- Muguet intermitente desde 10/2011, con cortos períodos asintomáticos, tto con Fluconazol y Nistatina local.
- 4/12 comienza con disfagia para sólidos, se constata en policlínica muguet oral.
- Indican Fluconazol y Nistatina.
- FGC (parcial): lesiones compatibles con candidiasis a nivel de EES.
- Perfil lipídico: TGL 570 Col: 103.

- Sin respuesta a tratamiento instituido, peoría de disfagia.
- Ingresa a SEIC 10/5.

- Planteo: Candidiasis esofágica.
  Hipertrigliceridemia.

Evolución

- Muestras para micológico.
- Anfotericina B 50mg/día (peso aproximado 60kg) por 10 días. Excelente respuesta clínica
- Presenta toxicidad medular.
- Posteriormente fluconazol.
- Al 4to día reinstala muguet.
- Nuevo curso de Anfotericina B (29/5 al 4/5) Excelente respuesta clínica.
- Resultado micológico: *Cándida albicans*. Se muestra antibiograma en el cuadro.

fármaco	CMI	Interpretación
Flucitosina	1	S
Fluconazol	>64	R
Voriconazol	0,25	R
Anfotericina	1	S

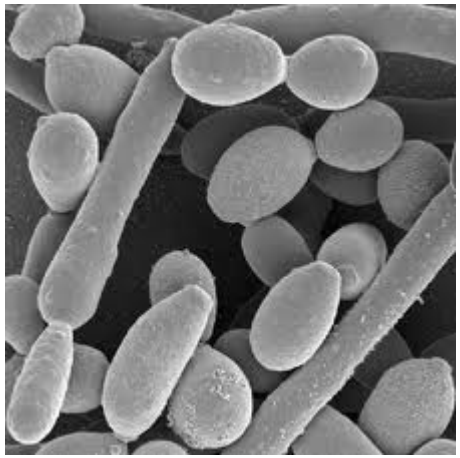
- Alta con Anfotericina B semanal
- Pendiente resultado de test de resistencia para VIH.

En suma:

- Paciente joven, multiexperimentado, en fallo, problemas de adherencia
- Candidiasis orofaríngea con exposición reiterada a azoles
- Candidiasis orofaríngea y esofágica resistente a azoles
- Reacción adversa a Anfotericina (mielodepresión probablemente multifactorial)
- Otras estrategias?

Candida albicans

- Primeras descripciones escritas son de Hipócrates y Galeno (candidiasis orales).



- Más de 100 denominaciones (*Monilia albicans*).
- Nombre actual: Berkhout, 1923.

Características

- Levaduras predominantemente unicelulares, 4-6 µm, ovoideas, pared fina.
- No requieren medios de cultivos especiales para hongos.
- Colonias blancas, cremosas, algodonosas.
- Identificación: parámetros fisiológicos y metabólicos.

- *C. albicans*
- *C. guilliermondii*
- *C. krusei*
- *C. parapsilosis*
- *C. tropicalis*
- *C. pseudotropicalis*
- *C. lusitaniae*
- *C. dubliniensis*
- *C. glabrata*
- *C. inconspicua*.

Epidemiología

- *C. albicans* se recupera en suelos, animales, objetos inanimados, ambiente hospitalario y comida.
- Son comensales de humanos en piel, tracto GI, esputo, tracto genital femenino, orina de pacientes sondados.
- La mayoría de las infecciones son de origen endógeno.
- Ejemplos de transmisión humano-humano: recién nacidos, balanitis, adquisición intrahospitalaria.

Patogénesis

- Inmunidad innata, rol de las células dendríticas. Suero y plasma conteniendo anticuerpos y componentes del complemento son incapaces de destruir *Candida*.
- Complejo rol de linfocitos en inducir la respuesta inmune en el contexto de Th1/Th2 (pacientes no HIV con candidiasis mucocutánea crónica pero con alguna disfunción T; HIV + son altamente susceptibles a candidiasis mucocutánea).

Patogénesis

- Oportunista: se requiere alteración de los mecanismos normales de defensa: diabetes (cutánea), maceración de la piel, HIV-SIDA.

- Iatrogenia: antibióticos (sulfonamidas reducen la muerte intracelular en neutrófilos); tetraciclinas, doxiciclina y aminoglucósidos (reducen la fagocitosis), uso de catéteres y prótesis (válvulas cardíacas), uso de drogas intravenosas, alimentación parenteral, enfermedades neoplásicas y sus tratamientos, uso de corticoesteroides (incluso inhalados), transplantados.

Presentación clínica: candidiasis oral y esofágica.

- Muguet: parches blancos, cremosos, algodonosos en la lengua y otras superficies mucosasa orales.

- Otras manifestaciones: candidiasis aguda atrófica y crónica, queilitis angular, candidiasis leucoplásica.

- Esofagitis candidiásica: disfagia, sensación de obstrucción, dolor subesternal, náuseas, vómitos.

Opciones terapéuticas

- Azoles: fluconazol, itraconazol, voriconazol y posaconazol.
- Polienos: anfotericina B.
- Equinocandinas: caspofungina, micafungina y anidulafungina.
- Flucitosina: nunca en monoterapia.
- Muguet: nistatina local.
- Esofagitis: fluconazol 200mg/día.

Resistencia a azoles / en PVVS

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- Jeddy N, Ranganathan K, Devi U, Joshua E. **A study of antifungal drug sensitivity of Candida isolated from human immunodeficiency virus infected patients in Chennai, South India.** J Oral Maxillofac Pathol.2011;15(2):182-6

- Johnson EM, Warnock DW, Luker J, Porter SR, Scully C. **Emergence of azole drug resistance in Candida species from HIV-infected patients receiving prolonged fluconazole therapy for oral candidasis.** J Antimicrob Chemother. 1995;35(1):103-14.

Resistencia a azoles en pacientes VIH

Exposición a Azoles por EO

- Tratamiento: Cryptococcosis, Histoplasmosis, Aspergillosis, Candidiasis oral, esofágica, vulvogenital, etc.

- Profilaxis secundaria para micosis (fluconazol, itraconazol, etc)

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ORIGINAL ARTICLE

Oral *Candida* isolates among HIV-infected subjects in Nigeria

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Table 2 Antifungal susceptibility profile of 120 oral Candida isolates from HIV patients

Species	Antifungal agents	MIC range	MIC_{50}	MIC_{90}	Resistant number (%)
C albicans ($n = 54$)	Amphotericin B	0.015—0.5	0.125	0.5	—
	Itraconazole	0.015—16	0.03	0.5	6 (11.1)
	Voriconazole	0.015—8.0	0.015	0.03	1 (1.9)
	Fluconazole	0.125—64	0.5	64	9 (16.7)
	Flucytosine	0.12—≥32	0.12	1.0	5 (9.3)
C tropicalis ($n = 22$)	Amphotericin B	0.015—0.25	0.03	0.0125	—
	Itraconazole	0.015—0.25	0.015	0.125	—
	Voriconazole	0.015—1.0	0.015	0.015	1 (7.7)
	Fluconazole	0.25—64	4.0	4	—
	Flucytosine	0.12—≥32	0.5	1.0	2 (9.1)
C parapsilosis ($n = 18$)	Amphotericin B	0.015—0.5	0.125	0.5	—
	Itraconazole	0.015—2.0	0.03	0.5	1 (8.3)
	Voriconazole	0.015—0.5	0.015	0.0125	—
	Fluconazole	0.125—64	1.0	4.0	2 (11.1)
	Flucytosine	0.25—≥32	1.0	2.0	2 (11.1)
C guilliermondii ($n = 11$)	Amphotericin B	0.06—1.0	0.25	1.0	—
	Itraconazole	0.5—16	0.5	16	1 (33.3)
	Voriconazole	0.015—1.0	0.015	0.5	—
	Fluconazole	0.5—8	1.0	8.0	—
	Flucytosine	0.12—≥32	0.12	8.0	—
C dubliniensis ($n = 9$)	Amphotericin B	0.015—0.5	0.125	2.0	—
	Itraconazole	0.015—16	0.015	1.0	1 (11.1)
	Voriconazole	0.015—8.0	0.015	1.0	—
	Fluconazole	0.125—64	2.0	4.0	3 (33.3)
	Flucytosine	0.12—16	1.0	8	1 (11.1)

MIC defined as the lowest concentration, which resulted in no growth for amphotericn B and 50% reduction in turbidity for flucytosine, itraconazole, fluconazole, and voriconazole; MIC_{50} and MIC_{90}: MIC value was able to inhibit 50% and 90% of the isolates tested, respectively.
MIC = minimal inhibitory concentration.

Oropharyngeal carriage of *Candida* species in HIV-infected patients in India

Oropharyngeale *Candida*-Besiedlung bei HIV-Infizierten in Indien

H. C. Gugnani,[1] K. Becker,[2] W. Fegeler,[2] S. Basu,[1] D. Chattopadhya,[3] U. Baveja,[3] S. Satyanarayana,[4] T. Kalghatgi[4] and A. Murlidhar[4]

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Both the *C. krusei* isolates as well as the *C. glabrata* isolate were classified as resistant to itraconazole (MIC 1 mg l^{-1}). In contrast, they were shown to be susceptible to voriconazole (Table 2). Complete resistance to azoles including fluconazole (MIC ≥ 64 mg l^{-1}), voriconazole (MIC ≥ 8 mg l^{-1}) and itraconazole (MIC ≥ 8 mg l^{-1}) was found only in one *C. tropicalis* isolate recovered from a patient without previous azole exposure. In view of recently undetermined breakpoints of voriconazole, an MIC of ≥8 mg l^{-1} may be classified as resistant to voriconazole.

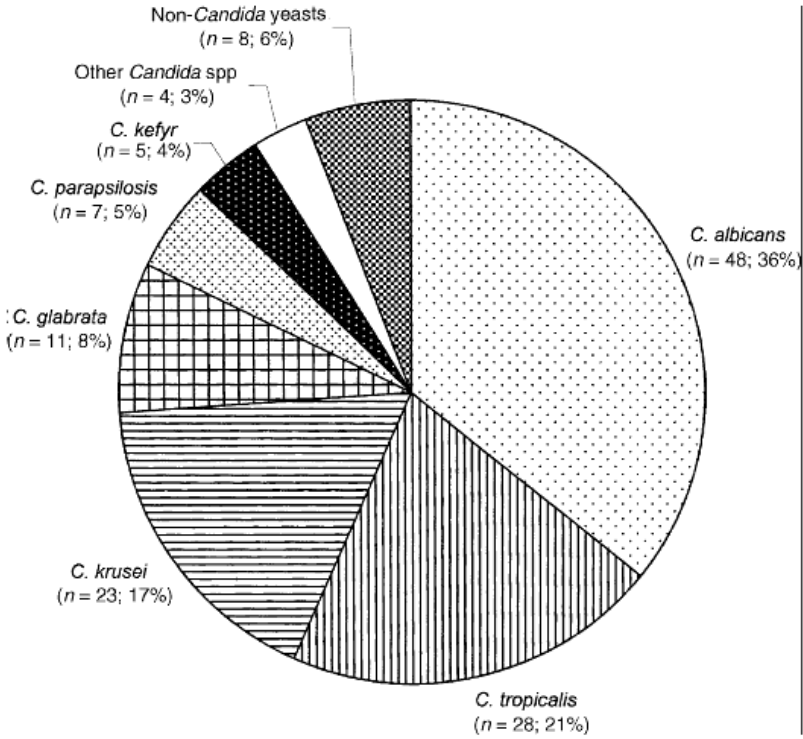

Figure 1 Distribution of *Candida* and other yeast species among the 134 isolates recovered from Indian AIDS patients.

Mycopathologia (2006) 162: 45–50
DOI 10.1007/s11046-006-0032-y

Species distribution and antifungal susceptibility profile of oral *Candida* isolates from HIV-infected patients in the antiretroviral therapy era

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Table 1. Antifungal susceptibility profile of 62 oral *Candida* isolates from HIV-infected patients

Species	Antifungal agent	Minimal Inhibitory Concentration (μg/ml)[a]			Resistant number (%)
		Range	MIC_{50}[b]	MIC_{90}[b]	
C. albicans (*n* = 31)	Itraconazole	0.015–16	0.03	0.5	3 (9.7)
	Fluconazole	0.125–64	0.5	64	4 (12.9)
	Amphotericin B	0.015–0.5	0.125	0.5	–
	Voriconazole	0.015–8.0	0.015	0.03	1 (3.2)
C. tropicalis (*n* = 13)	Itraconazole	0.015–0.25	0.015	0.125	–
	Fluconazole	0.25–64	4.0	64	–
	Amphotericin B	0.015–0.25	0.03	0.125	–
	Voriconazole	0.015–1.0	0.015	0.015	1 (7.7)
C. parapsilosis (*n* = 12)	Itraconazole	0.015–2.0	0.03	0.5	1 (8.3)
	Fluconazole	0.125–64	1.0	4.0	1 (8.3)
	Amphotericin B	0.015–0.5	0.125	0.5	–
	Voriconazole	0.015–0.5	0.015	0.125	–
C. guilliermondii (*n* = 3)	Itraconazole	0.5–16	0.5	16	1 (33.3)
	Fluconazole	05–8.0	1.0	8.0	–
	Amphotericin B	0.06–1.0	0.25	1.0	–
	Voriconazole	0.015	0.015	0.015	–

[a]The MIC was defined as the lowest concentration which resulted in no growth for amphotericin B and a 50% reduction in turbidity for itraconazole, fluconazole and voriconazole.
[b]MIC_{50}: MIC value able to inhibit 50% of the samples tested; MIC_{90}: MIC value able to inhibit 90% of the samples tested.

CID 1996;23 (September)

Resistance to Fluconazole and Amphotericin B in a Patient with AIDS Who Was Being Treated for Candidal Esophagitis

Centers for Disease Control and Prevention. Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents.

MMWR 2009;58 (No. RR-4) April 10, 2009: 45-48.

Management of Treatment Failure or Refractory Mucosal Candidiasis

Refractory oral or esophageal candidiasis is still reported in **approximately 4%–5%** of HIV-infected persons, typically in those patients with CD4counts <50 cells/*μL who have received multiple courses of azole antifungals.*

Treatment failure is typically defined as signs and symptoms of oropharyngeal or esophageal candidiasis that persist after more than 7–14 days of appropriate therapy. Oral itraconazole solution is effective at least transiently in approximately two thirds of persons with fluconazole-refractory mucosal candidiasis **(AII).**

Posaconazole immediate-release oral suspension (400 mg bid for 28 days) is effective in 75% of patients with azole refractory oropharyngeal and/or esophageal candidiasis (AII)

IV amphotericin B is usually effective and can be used among patients with refractory disease **(BII). Both conventional amphotericin B and lipid complex and liposomal amphotericin B have been used (BII).**

Amphotericin B oral suspension (1 mL four times daily of the 100 mg/mL suspension) is sometimes effective among patients with oropharyngeal candidiasis who do not respond to itraconazole **(CIII). (no disponible)**

Azole-refractory esophageal candidiasis also can be treated with posaconazole (AII), anidulafungin (BII), caspofungin (CII), micafungin (CII), or voriconazole (CIII).

Primary prophylaxis

Data from prospective controlled trials indicate that fluconazole can reduce the risk for mucosal (e.g., oropharyngeal, esophageal, and vaginal) candidiasis among patients with advanced HIV disease.

However, routine primary prophylaxis is ***not recommended*** *because mucosal disease is associated with very low attributable mortality, acute therapy is highly effective, prophylaxis can lead to disease caused by drug-resistant species, prophylactic agents can produce drug interactions, and prophylaxis is expensive (****DIII). ART does reduce the likelihood of mucosal candidiasis (AI).***

Secondary prophylaxis

As with primary prophylaxis, the majority of HIV specialists **do not recommend** secondary prophylaxis (chronic maintenance therapy) for recurrent oropharyngeal or vulvovaginal candidiasis because of the effectiveness of therapy for acute disease, the low mortality associated with mucosal candidiasis, the potential for resistant *Candida organisms to develop, the possibility of drug interactions, and the cost of prophylaxis (DIII).*

*However, **if recurrences are frequent or severe,** oral fluconazole can be used for either oropharyngeal (BI) or vulvovaginal (CI) candidiasis.*

Sin embargo…

…documented that the number of episodes of oropharyngeal candidiasis and other invasive fungal infections was statistically significantly lower in HIV patients with CD4count <150 cells/µL when receiving continuous (three times a week) fluconazole versus episodic treatment of recurrences.

This clinical trial also proved that the development of clinically significant resistance was not higher in the group of continuous prophylaxis than in the group with episodic administration of Fluconazole, provided that patients received ART.

Goldman M, Cloud GA, Wade KD, et al. A randomized study of the use of fluconazole in continuous versus episodic therapy in patients with advanced HIV infection and a history of oropharyngeal candidiasis. Clin Infect Dis 2005;41:1473–80.

- The decision to use secondary prophylaxis should take into account the effect of recurrences on the patient's well-being and quality of life; the need for prophylaxis for other fungal infections; cost, toxicities, and most importantly, drug interactions .

- For recurrent esophageal candidiasis, daily fluconazole can be used **(BI). Oral posaconazole bid is also effective (BII). However, potential azole resistance should be considered when long-term azoles are considered.**

- Secondary prophylaxis should be instituted in those patients with fluconazole-refractory oropharyngeal or esophageal candidiasis who have responded to echinocandins, voriconazole, or posaconazole therapy because of high relapse rate until ART produces immune reconstitution **(CI).**

Conclusiones

- Emergencia de resistencia en *Candida*
- Uso prolongado de azoles
- Sospecha
- Necesidad de protocolos de profilaxis alternativos – Disponibilidad de drogas
- En nuestro paciente reforzar adherencia
- Test de resistencia - Cambio de plan

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