

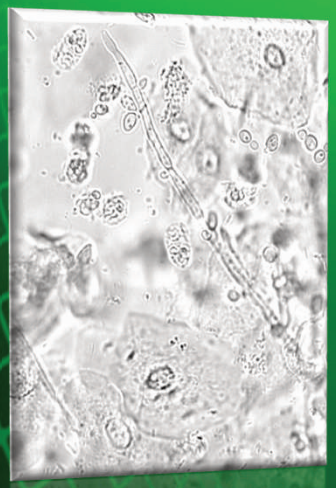
Il problema della candida recidivante o resistente

Filippo Murina-Silvia Oneda

Servizio di Patologia del Tratto Genitale Inferiore

Osp.V. Buzzi –Università degli Studi di Milano

Candidosi Vulvo-Vaginale



Affezione vulvo-vaginale molto frequente:
75-80% almeno un episodio
50% recidiva occasionale
8% ricorrente



Vestibolodinia

GRAVIDANZA
-Infezione 20-75%
-Colonizzazione 35%



I Trimestre 9%

III Trimestre 54%

Sobel.Vulvovaginal candidosis-Lancet 2007; 369: 1961–71

Global burden of recurrent vulvovaginal candidiasis: a systematic review

David W Denning, Matthew Kneale, Jack D Sobel, Riina Rautemaa-Richardson

-138 milioni di donne con RVVC nel mondo
-Prevalenza 3871/100.000 donne
-158 milioni nel 2030

Recurrent vu … ty of life of affected wor … ported. For this systema … sed studies published b … defined as four or mor … e included, consisting o … estimated lifetime inci … of women at risk to 2030. Worldwide, recurrent vulvovaginal candidiasis affects about 138 million women annually (range 103–172 million), with a global annual prevalence of 3871 per 100 000 women; 372 million women are affected by recurrent vulvovaginal candidiasis over their lifetime. The 25–34 year age group has the highest prevalence (9%). By 2030, the population of women with recurrent vulvovaginal candidiasis each year is estimated to increase to almost 158 million, resulting in 20 240 664 extra cases with current trends using base case estimates in parallel with an estimated growth in females from 3·34 billion to 4·181 billion. In high-income countries, the economic burden from lost productivity could be up to US$14·39 billion annually. The high prevalence, substantial morbidity and economic

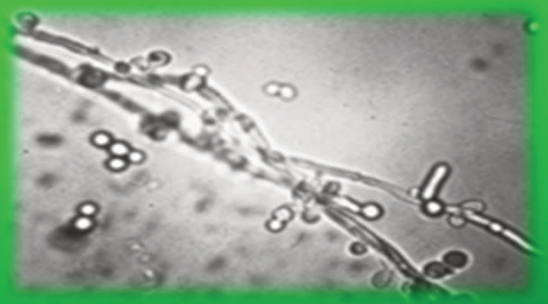
	15–24 years	25–34 years	35–44 years	45–54 years	15–54 years
Global female population (2012)	595 454 000	572 804 000	468 421 000	381 388 000	1 968 068 000
Prevalence (%)	5·39%	9·00%	7·64%	5·95%	7·00%
Estimated prevalence (base case)	32 095 000	47 052 000	35 387 000	22 693 000	137 627 000
Base case +25%	40 012 000	58 082 000	44 073 000	28 037 000	172 034 000
Base case –25%	24 007 000	35 029 000	26 084 000	17 002 000	103 220 000

Table 1: Age-specific prevalence of self-reported recurrent vulvovaginal candidiasis from a survey of 6000 women in six countries and global prevalence by 10-year age group[27]

Lancet Infect Dis 2018

Health-related quality of life as measured with the Short-Form 36 (SF-36) questionnaire in patients with recurrent vulvovaginal candidiasis

Yu-Xia Zhu[1†], Ting Li[1,2†], Shang-Rong Fan[1,3*], Xiao-Ping Liu[4], Yi-Heng Liang[1] and Ping Liu[1]



SF-36 questionnaire

The SF-36 questionnaire consists of 36 items, which are used to calculate eight s (PF), role physical (RP), b (GH), vitality (VT), socia tional (RE), and mental scores can be summed to create the physical composite score (PCS), while the last four can be summed to create the mental composite score (MCS). Scores for the SF-36 scales range between 0 and 100, with higher scores indi- ca

SF-36: Questionario valuta impatto sulla qualità di vita in donne con RVVC

Results: The mean age at first diagnosis of the patients with RVVC was 30.96 years (SD 5.38), and the mean age of the controls was 29.75 years (SD 5.83; $p > 0.05$). The duration of the patients' complaints varied from 6 months to 10 years, with a mean duration of 22.28 (±21.75) months. The most common complaints were increased vaginal discharge (102 cases, 100 %), itching (97 cases, 95.1 %), dyspareunia (65 cases, 63.7 %), burning (79 cases, 77.5 %) and erythema (25 cases, 24.5 %). *C. albicans* was the predominant Candida species (86 strains, 84.3 %) in the patients, followed by *C. glabrata* (12 strains, 11.8 %). *C. parapsilosis* (1 strain, 0.9 %), *C. tropicalis* (1 strain, 0.9 %), *C. krusei* (1 strain, 0.9 %) and *C. lusitaniae* (1 strain, 0.9 %). The mean SF-36 dimension scores for physical function, role physical, bodily p significantly lower in 59.17 vs. 90.20, 80.87, scores of the patients (75.01 and 74.87; $p <$

(Continued on next page)

-Prurito (95%) ; Bruciore (77%); Dispareunia (63%)
-C. albicans 84%
-SF significativamente più basso

Health and Quality of Life Outcomes (2016)

Candidosi Vulvo-Vaginale

Commensalismo

Malattia



Dr. Yeast

Mr. Hypha

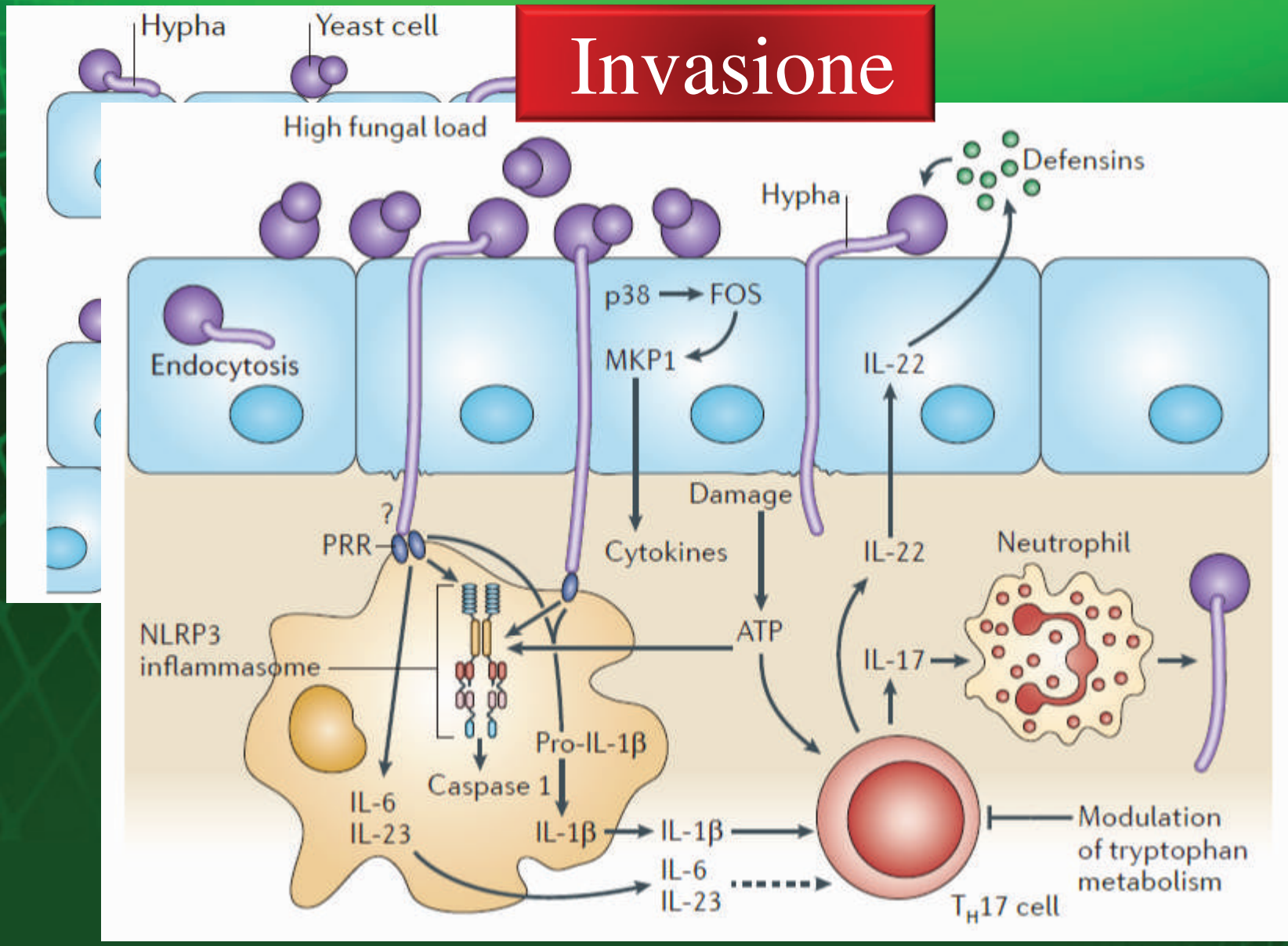
Cassone A. Vulvovaginal Candida albicans infections: pathogenesis, immunity and vaccine prospects. BJOG 2014
Cassone A. NATURE REVIEWS | MICROBIOLOGY -2013

Candida albicans morphogenesis and host defence: discriminating invasion from colonization

Neil A. R. Gow[1], Frank L. van de Veerdonk[2], Alistair J. P. Brown[1] and Mihai G. Netea[2]

Aspetti Patogenetici della Candidosi

Invasione



asica)

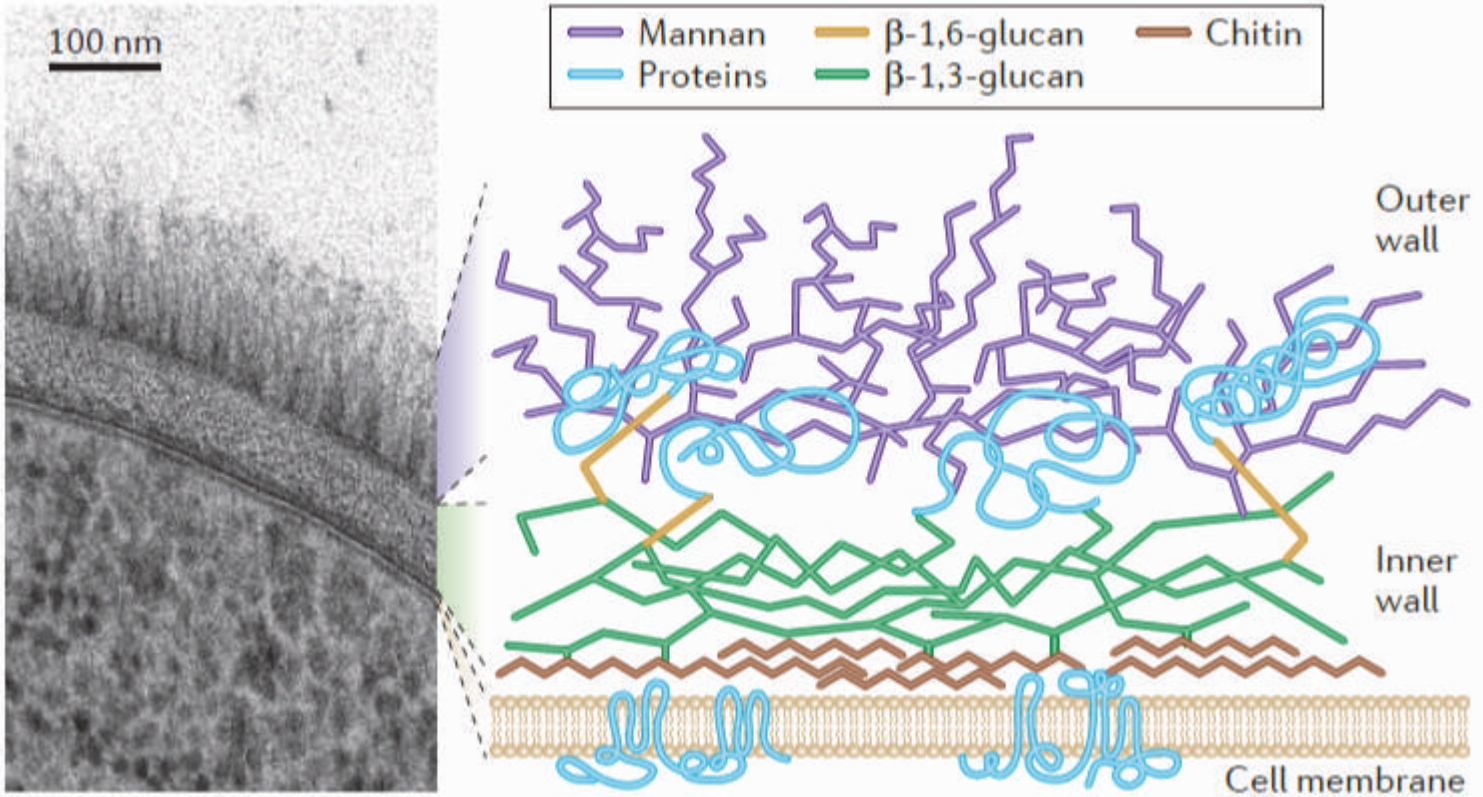
LOGY -2012

Mannose-Binding Lectin Gene Polymorphism and Its Association with Susceptibility to Recurrent Vulvovaginal Candidiasis

Noha M. Hammad,[1] Nissreen E. El Badawy,[1] Ashraf M. Nasr,[2]

Recurrent vulvovaginal candidiasis (RVVC) is a common illness influencing childbearing women worldwide. Most women suffering from RVVC develop infection without specified risk factors. Mannose-binding lectin (MBL) is an important component of innate imm... ...een suggested to play a role ...on 1 codon 54 polymorphism ...rom 59 RVVC cases and ... 1 codon 54 polym... ...P). It was shown th... ...es higher in those ... ...4 variant allele (B)...

Struttura della parete cellulare della candida



Variable		OR (95% CI)
	AA	
	AB	2.65**
	BB	
	A	
	B	.04***

*Significant difference; **OR for genotypes AB/AA. CI = 0.991–7.104; ***OR for alleles B/A. CI = 1.228–7.545.

BioMed Research International 2018

Classification of vulvovaginal candidiasis

Acute Type

Immunosuppressive action being present with high quantities of Candida

Recurrent Type

Hypersensitivity reaction acting with a “small quantity” in subjects with genetic predisposition



The therapeutic challenge of recurrent vulvovaginal candidiasis.
A. Graziottin , F. Murina -2011

Elevated nitric oxide in recurrent vulvovaginal candidiasis – association with clinical findings

CATHRIN ALVENDAL[1], SOPHIA EHRSTRÖM[1], ANNELIE BRAUNER[2], JON O. LUNDBERG[3] &

Acta Obst Gyn Scand (2017)

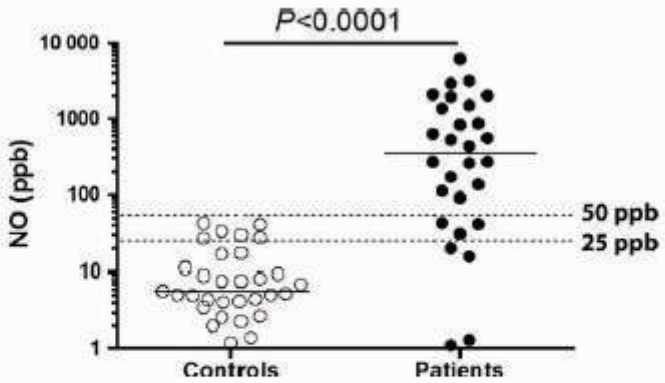


Figure 2. Median levels of vaginal nitric oxide (NO) measured in healthy controls and in women with recurrent vulvovaginal candidiasis during acute exacerbation. ppb, parts per billion. The scale is logarithmic and dotted lines represent NO 25 and 50 ppb.

Ossido Nitrico molto elevato in corso di candidosi segno di marcata risposta infiammatoria

Key Message

Vaginal nitric oxide is greatly increased during episodes of recurrent vulvovaginal candidiasis compared with post treatment and healthy controls. Levels of nitric oxide illustrate the inflammatory tissue response corresponding to symptoms and clinical findings.

Is non-response to fluconazole maintenance therapy for recurrent *Candida* vaginitis related to sensitization to atopic reactions?

Gilbert G. G. Donders[1,2] | Svitrigaile Grinceviciene[1,3] | Gert Bellen[1] | Martin Jaeger[4] |

TABLE 2 Symptom difference between responders and non-responders to maintenar

Characteristics	R (i
Vaginal erythema	3
Vulvar erythema	3
Vulvar pruritus	3
Vulvar excoriation	**1**
Vaginal erosion	1
Vulvar edema	2

Bold numbers indicate stat
[a]Mann-Whitney *U* test.

TABLE 5 Multivariate logistic regression model assessing independency for risk factors for non-response to maintenance therapy with fluconazole in RVVC patients

Risk factors	Odds ratio (95% confidence intervals)	*P* value
Eczema	0.8 (0.1-6.2)	.8
No allergy to medication	**13.8 (1.1-166.7)**	**.04**
IFN−γ (×10)	2.1 (0.7-6.7)	.2
Vulvar excoriation	**3.6 (1.4-9.3)**	**.01**
Atopic disease in family	4.9 (1.1-22.2)	**.04**
Episodes per year	1.6 (0.9-2.6)	.09
Duration of symptoms	1.2 (1.02-1.5)	**.03**

Bold numbers indicate statistical significance ($P < .05$).

Am J Reprod Immunol. 2018

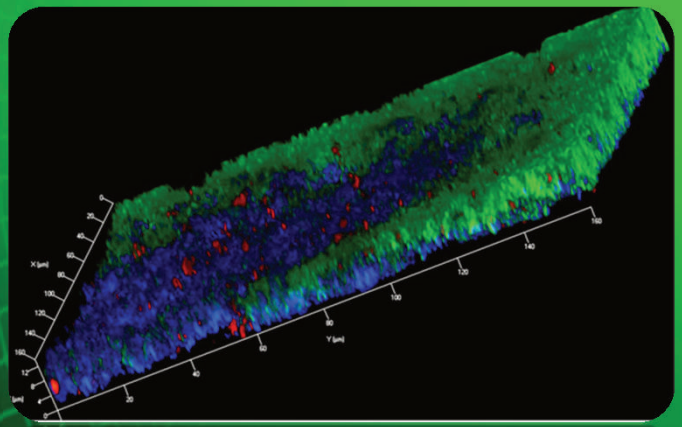
Association between atopy and recurrent vaginal candidiasis

There is a strong association between atopy and recurrent vaginal candidiasis

History of atopy and skin test response to aeroallergens in patients with Recurrent Vaginal Candidiasis (RVC) and Sporadic Vaginal Candidiasis (SVC)

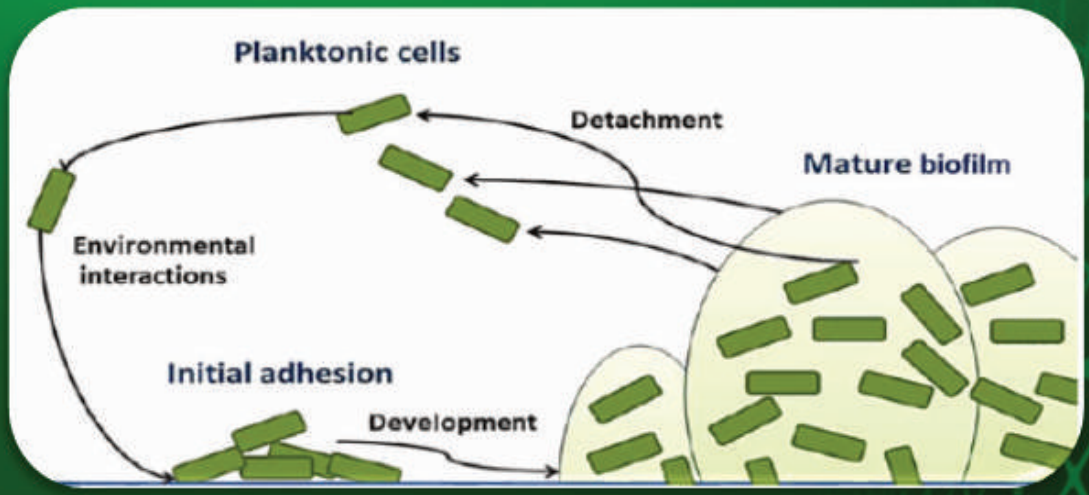
Variables	RVC *n* (%)	SVC *n* (%)
Personal history of atopy	30/44 (68.1)	4/26 (15.3)
Familial history of atopy	25/44 (56.8)	9/26 (34.6)
Positive aeroallergens skin prick test	15/35 (42.8)	2/21 (9.5)

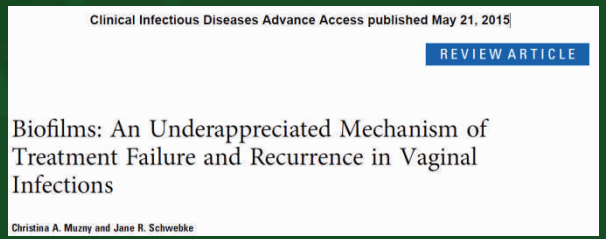
Neves NA.Association between atopy and recurrent vaginal candidiasis. Clin Exp Immunol. 2005
Moraes PS. Recurrent vaginal candidiasis and allergic rhinitis: a common association. Ann Allergy Asthma Imm.1998



"Biofilm"





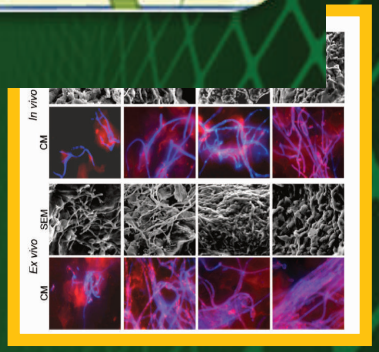


Clinical Infectious Diseases Advance Access published May 21, 2015

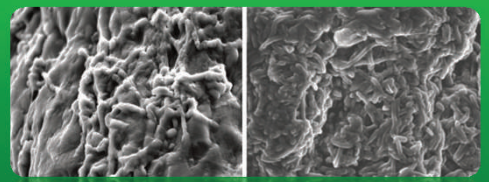
REVIEW ARTICLE

Biofilms: An Underappreciated Mechanism of Treatment Failure and Recurrence in Vaginal Infections

Christina A. Muzny and Jane R. Schwebke



I biofilm permettono la sopravvivenza di microrganismi in un ambiente ostile





Biofilm "buoni" che difendono la vagina

Biofilm "cattivi" che attaccano la vagina

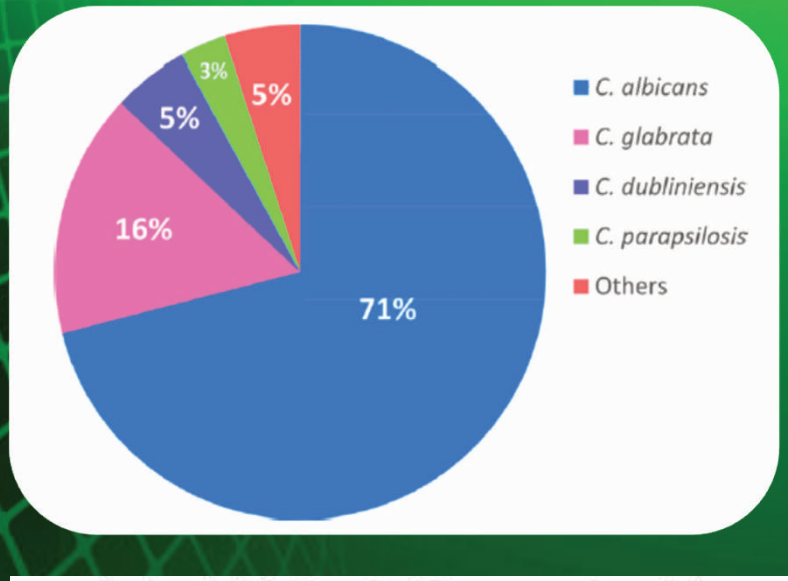
Harriott MM, Lilly EA, Rodriguez TE, Fidel PL Jr, Noverr MC.
Candida albicans forms biofilms on the vaginal mucosa. Microbiology. 2010 Dec;156(Pt 12):3635-44

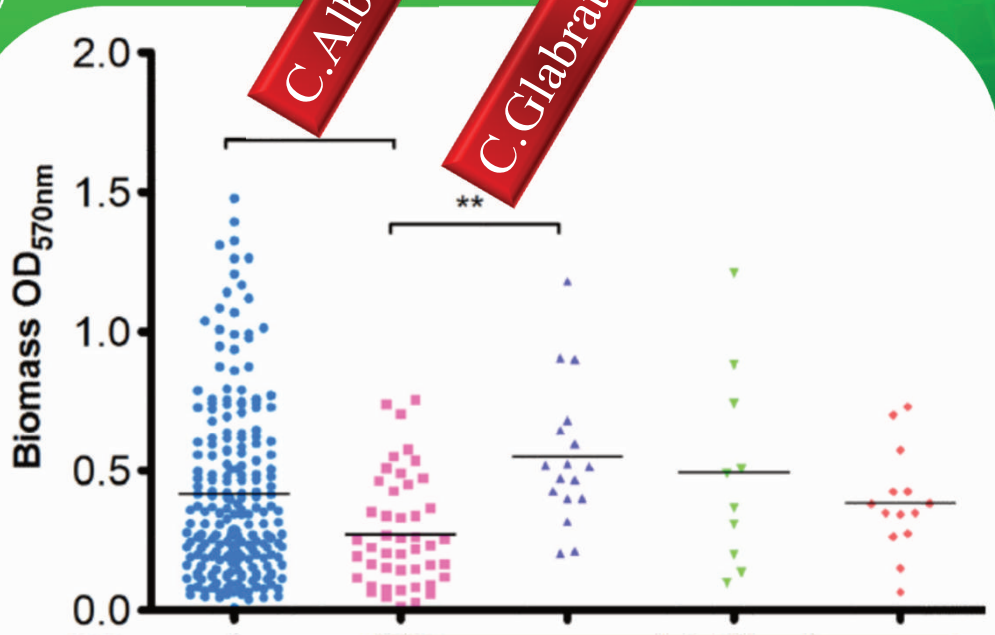
Biofilms Formed by Isolates from Recurrent Vulvovaginal Candidiasis Patients Are Heterogeneous and Insensitive to Fluconazole

Leighann Sherry,[a] Ryan Kean,[a,b] Emily McKloud,[a] Lindsay E. O'Donnell,[a]

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

September 2017





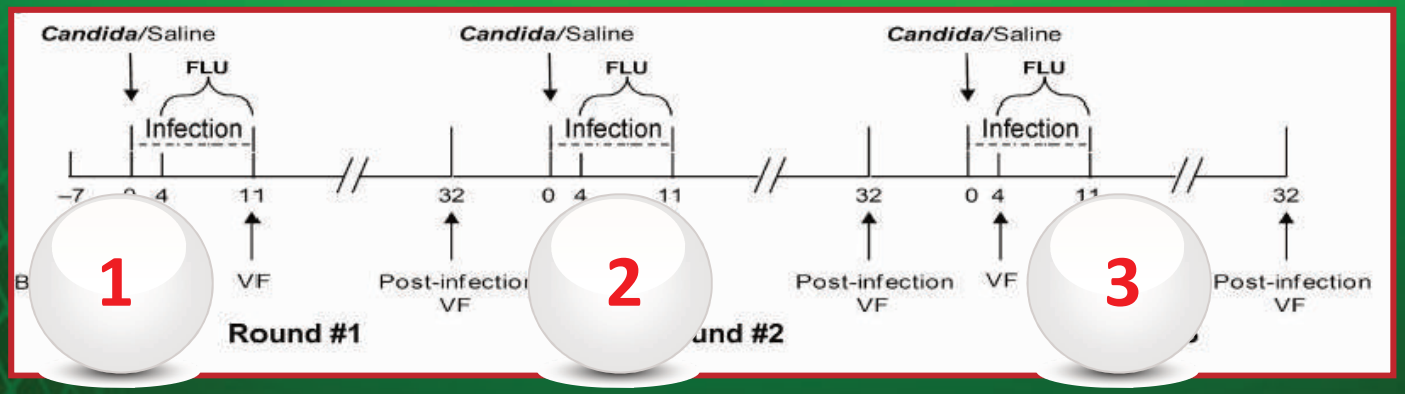
and *C. dubliniensis* ($P < 0.01$), with a mean OD_{570} of 0.271. This apparent biofilm heterogeneity may affect the management of VVC infections, as these sessile communities are known to be notoriously recalcitrant to antifungal therapy and biofilm heterogeneity has been shown to correlate with success of *in vitro* antifungal therapy (17).

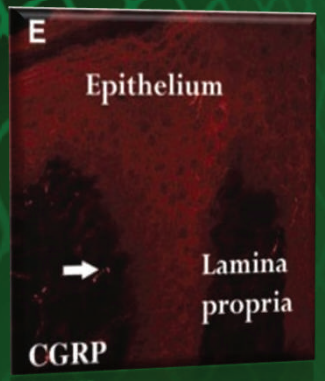
non-*C. albicans* species (NCAS), which accounts for 11 to 80% of infections, depending on geographical location (8). Nevertheless, *C. albicans*, a well-characterized biofilm-forming organism, remains a prominent pathogen in this disease. Resistance to antifungal therapy as a result of biofilm formation is a likely contributor to failed treatment.

Infezione Micotica ⟺ Dolore Vulvare

Science Translational Medicine AAAS

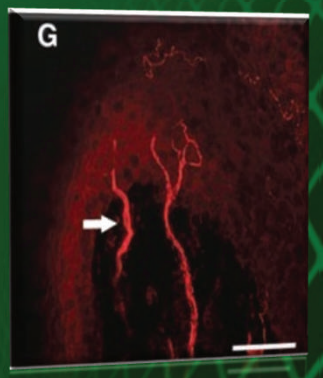
Repeated Vulvovaginal Fungal Infections Cause Persistent Pain in a Mouse Model of Vulvodynia
Melissa A. Farmer, *et al.*
Sci Transl Med **3**, 101ra91 (2011);





Ipersensibilità che si risolve dopo terapia con Fluconazolo (assente dopo 21gg)

Ipersensibilità si mantiene dopo risoluzione infezione con incremento densità fibre nervose



Candidosi Vulvo-Vaginale

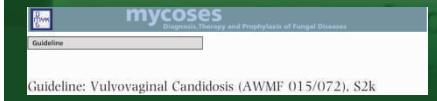
Pazienti con alta colonizzazione micotica possono essere asintomatiche mentre altre con bassa carica hanno sintomi importanti e ricorrenti

3. Summary of recommendations

3.1. The diagnosis
always made based
history, clinical sign
dence of yeast, wh
microscopic examination of a native preparation of
vaginal fluid (400× optical magnification, or prefera-
bly phase contrast
ring and complex ca
determine the species. Serological determination of
antibody titres is not recommended.

Diagnosi come combinazione di sintomi e segni con il supporto dell'evidenza di miceti

In casi particolari ricorso all'esame colturale



Mycoses, 2015,



Scor

Segno

zioni



Am J Obstet Gynecol 2001;185:363-69.


ar skin has
asymmetrical
d to intense
ma of the labia
ossible edema
ia majora.



Scor

Segno

zioni



Am J Obstet Gynecol 2001;185:363-69.

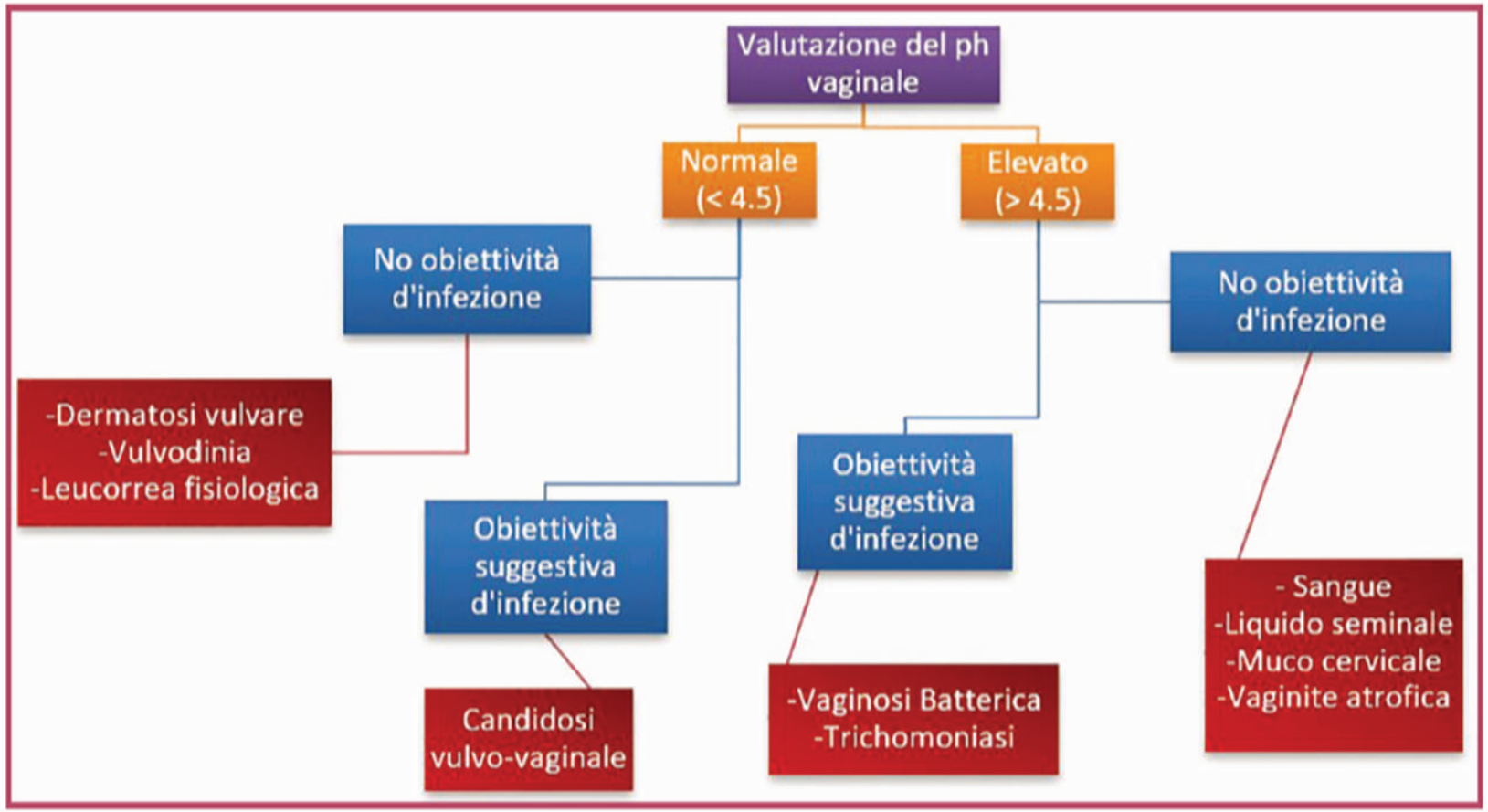


Figura 11.5. Algoritmo diagnostico delle vulvovaginiti attraverso l'ausilio della valutazione del pH vaginale.

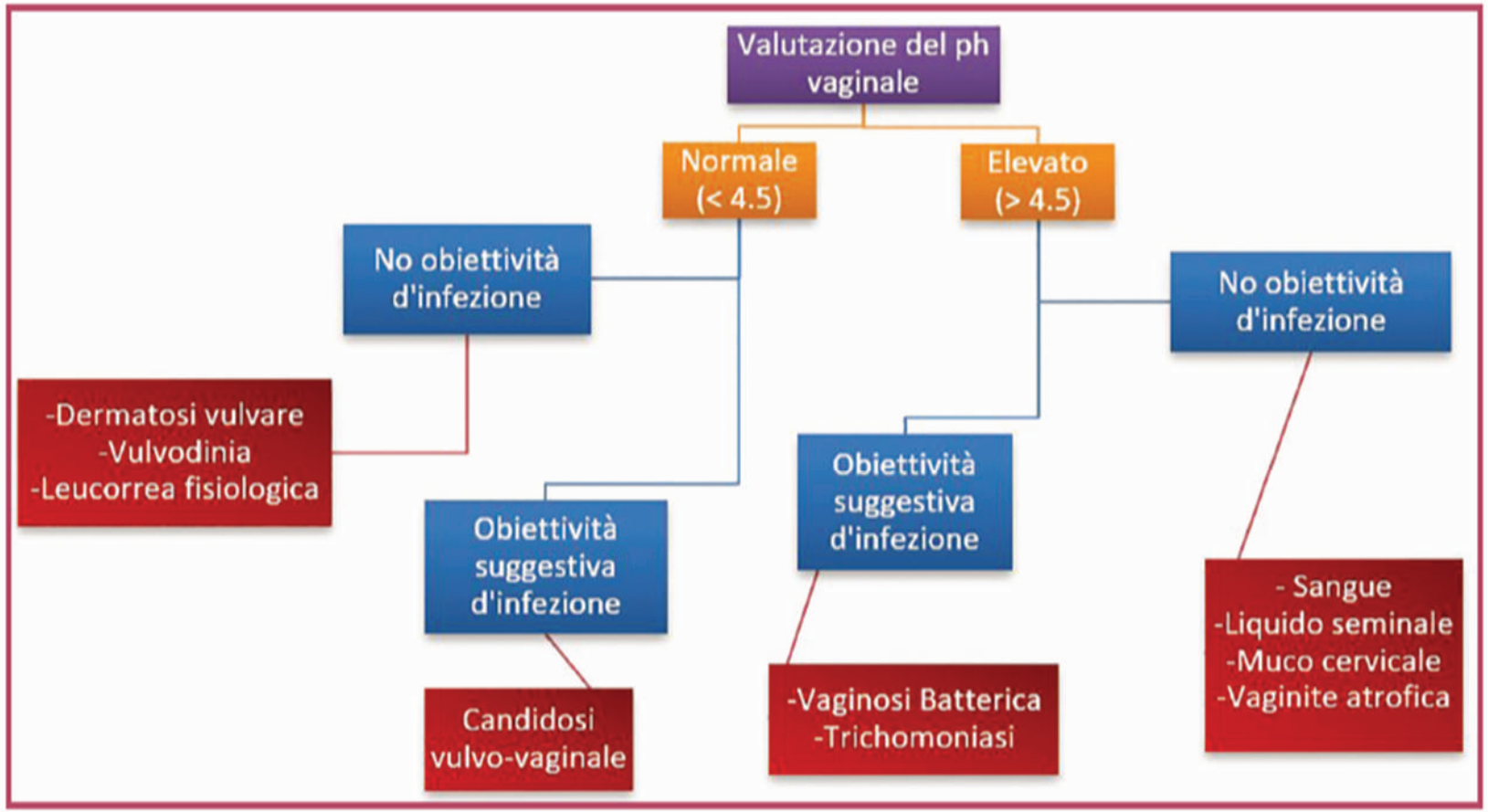
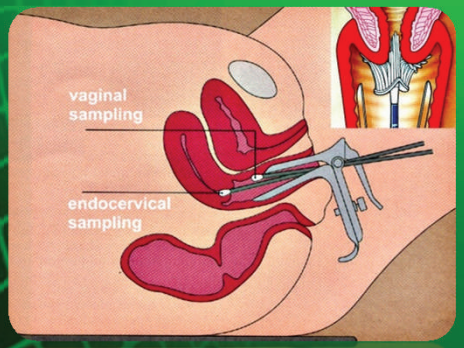
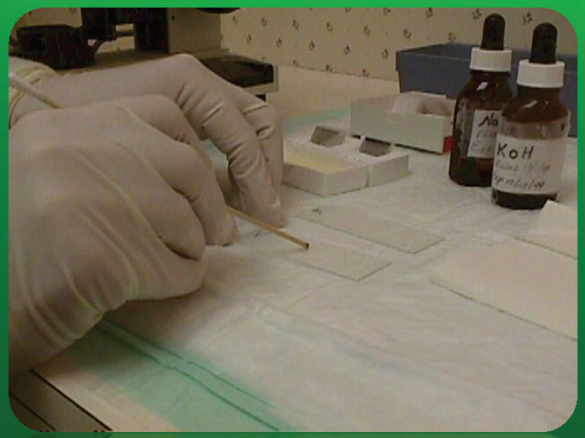


Figura 11.5. Algoritmo diagnostico delle vulvovaginiti attraverso l'ausilio della valutazione del pH vaginale.

Esame microscopico a fresco











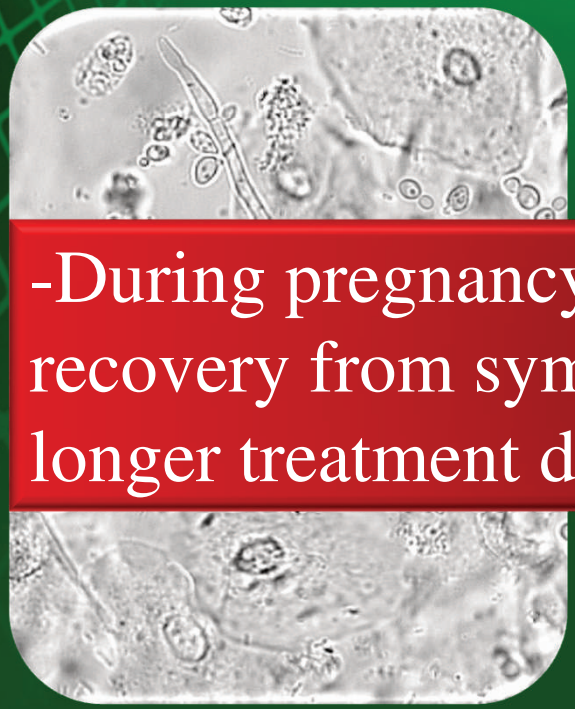
GYNECOLOGY

Recurrent vulvovaginal candidiasis

Jack D. Sobel, MD

-Azoli topici od orali in short therapy in acuto

-Fluconazolo 150-200 mg nelle recidivanti



-During pregnancy, VVC is more severe and recovery from symptoms is prolonged, indicating longer treatment days (7-14 gg)

TABLE 1
Treatment of recurrent vulvovaginal candidiasis

1. Regimens for *Candida albicans*, *C tropicalis*, *C parapsilosis*
   a. Oral
      1) Fluconazole induction 150 mg q 72 h for 3 doses
         Fluconazole maintenance regimen 150 mg q weekly for 6 mo

         or 6 mo

      Induction

         Miconazole 4% vaginal cream for 3 nights
         Tioconazole 6.5% ointment for 1 night
         Terconazole 0.4% vaginal cream for 7 nights
         Terconazole 0.8% vaginal cream for 3 nights
         Terconazole 89 mg vaginal suppository for 3 nights
         Butoconazole 2% vaginal cream single dose

      Maintenance regimen

         Nystatin (see above)
         Amphotericin B vaginal cream/suppositories 5-10% nightly for 14 d
         Flucytosine cream 17% per vagina, nightly for 14 d
         Combination amphotericin B/flucytosine

bid, twice daily; *MIC*, minimal inhibitory concentration; *q*, every.

Sobel. Recurrent vulvovaginal candidiasis. Am J Obstet Gynecol 2016.

American Journal of Obstetrics & Gynecology-2016

Tools for Practice

Recurrent vulvovaginal candidiasis

Mathieos Belayneh Evan Sehn Christina Korownyk MD CCFP

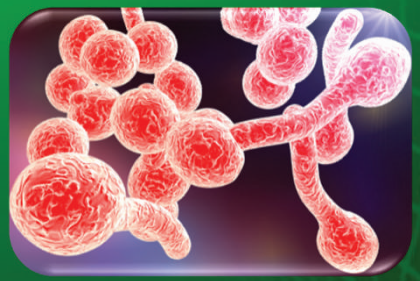
Clinical question

What is the most effective management for women with recurrent vulvovaginal candidiasis (≥4 episodes within 1 year)?

Evidence

Two double-blind RCTs of 373[1] and 64 women[2] with symptoms and culture-confirmed recurrent vulvovaginitis compared 150 mg of oral fluconazole weekly for 6 months (after an initial 150 mg of oral fluconazole every 72 hours for 3 days) with placebo:

- There was a
  cal relapse r
  -After 6 mor
  sus 50% to 6
- At the 12-m
  78% (NNT = 5
  relapse in th
  tance in either study.[1,2]

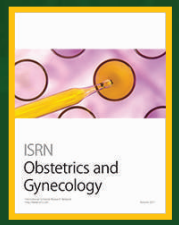


One observational study of 136 women individualized decreasing doses (200 mg of fluconazole 3 times a week, weekly for 2 months, biweekly for 4 months, then monthly for 6 months) based on clinical symptoms[5]:

- There was a 30% clinical relapse rate during 12 months of treatment and a 45% rate at the 18-month follow-up.

Terapia Candidosi vulvo-vaginale ricorrente
Protocollo terapeutico personalizzato

Fluconazolo 200mg	**Fluconazolo 200mg**	**Fluconazolo 200mg**	**Fluconazolo 200mg**	**Fluconazolo 200mg**	**Fluconazolo 200mg**
1 cpr tre volte la settimana per 1 settimana	1 cpr alla settimana x 4 settimane	1 cpr dopo 10 giorni	1 cpr dopo 15 giorni	1 cpr dopo 20 giorni	1 cpr dopo 30 giorni



Recurrent vaginal candidiasis: proposal for an individualized protocol
F. Murina, et Al . 7/2011

Research Article

The Recurrent Vulvovaginal Candidiasis: Proposal of a Personalized Therapeutic Protocol

F. Murina,[1] A. Graziottin,[2] R. Felice,[1] G. L. Radici,[1] and S. Di Francesco[1]

[1] *Outpatient Department of Vulvar Disease, V. Buzzi Hospital, Via Castelvetro 32, 20124 Milan, Italy*
[2] *Center of Gynecology, San Raffaele Resnati Hospital, 20124 Milan, Italy*

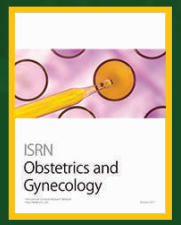
3. Results

All the 55 patients enrolled (average age 29, range 21–44)

Two problems still exist

-The subsection of women suffering recurrent VVC

-Antifungal therapy is not designed to restore the normal microbiota of the vagina



Recurrent vaginal candidiasis: proposal for an individualized protocol
F. Murina, et Al . 7/2011

Long-Term Outcomes of Women With Recurrent Vulvovaginal Candidiasis After a Course of Maintenance Antifungal Therapy

Tess Crouss, MD,[1] Jack D. Sobel, MD,[2] Katharine Smith, PhD,[1] and Paul Nyirjesy, MD[1]

TABLE 2. Comorbid Conditions (n = 201)

	n	%
Diabetes		
Obesity		
Any comorbid vaginal condit		
Bacterial vaginosis		
Atrophic vaginitis		
Lichen Scler		
Vulvodynia		
Desquamativ		

In the entire RVVC group (n = 201), the mean number of maintenance treatment regimens that patients had undergone was 1.98, with a median of 2 and range of 0 to 10. On average, treatment duration was 9.4 months, with a median of 8 months and a range of 1 to 33 months. Of the 120 complete charts, 62 (51.7%) of patients [illegible] maintenance [illegible] %) con- [illegible] d to ex- [illegible] tenance [illegible] ths. For average [illegible] o even- [illegible] nfection [illegible] py, with or without sporadic use of antifungals.

-Du

-Microbioma vaginale ed intestinale
-Utilizzo Lattobacilli
-Identificazione aspetti genetici
-Vaccino
-Ruolo dei biofilm

J Low Genit Tract Dis 2018

Probiotics for vulvovaginal candidiasis in non-pregnant women (Review)

Xie HY, Feng D, Wei DM, Mei L, Chen H, Wang X, Fang F

Probiotics used in the prevention and treatment of *Candida* infec-

Lattobacilli



-Produzione Acido Lattico

- Produzione H2O2

- Produzione Batteriocine

during or a
antifungal

microscopic examination or vaginal culture at one, three and six after mycological cure).

Cochrane Database of Systematic Reviews 2017

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Summary of main results

Ten RCTs
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-10 trials randomizzati e controllati con 1656 donne
- Probiotici come terapia adiuvante a farmaci



- Compared with conventional antifungal drugs alone, the addition of probiotics could enhance their effect in improving short-term clinical cure rate (RR 1.14, 95% CI 1.05 to 1.24), regardless of the route of administration, and whether multiple species or single species of probiotics were used. The results did



- Compared with conventional antifungal drugs alone, the addition of probiotics may reduce the first relapse rate at one month after treatment (RR 0.34, 95% CI 0.17 to 0.68).

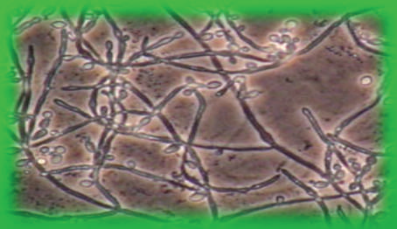
Cochrane Database of Systematic Reviews 2017

Eur J Clin Microbiol Infect Dis (2016) 35:1701–1708
DOI 10.1007/s10096-016-2715-8

ORIGINAL ARTICLE

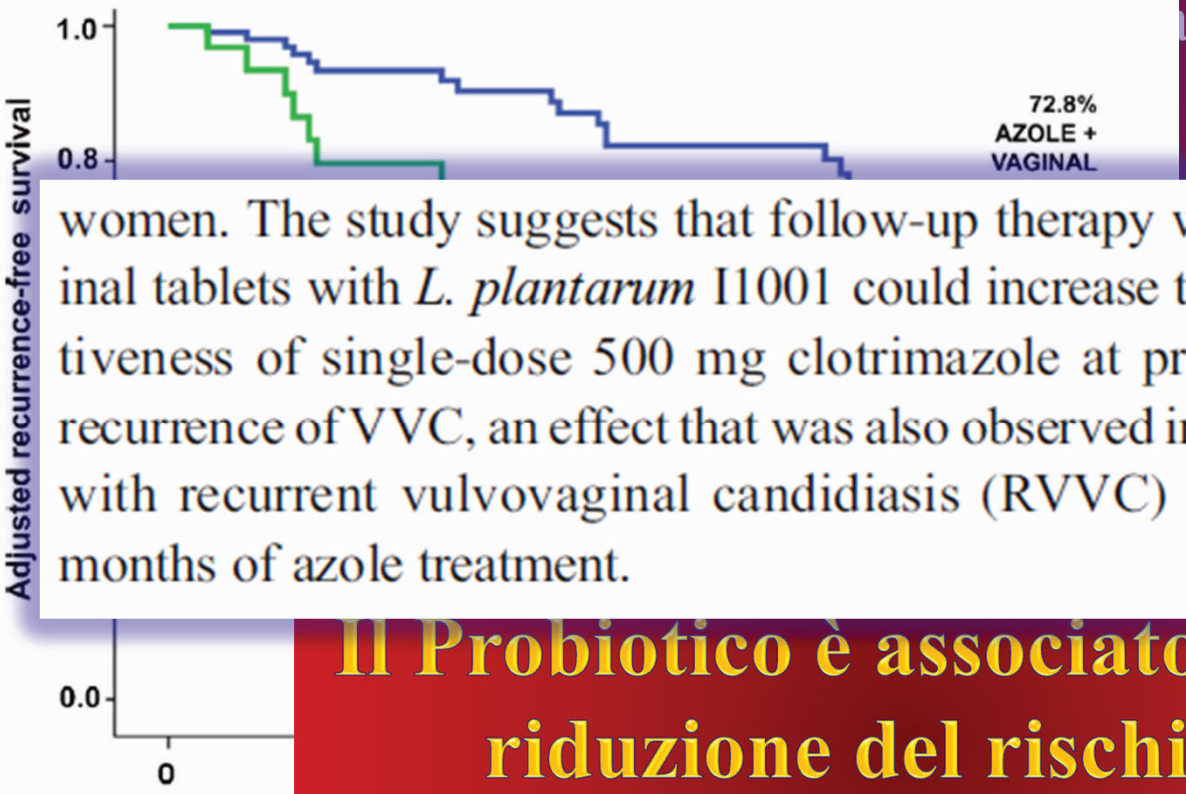
Is it possible to prevent recurrent vulvovaginitis? The role of *Lactobacillus plantarum* I1001 (CECT7504)

S. Palacios[1] · J. Espadaler[2] · J. M. Fernández-Moya[3] · C. Prieto[4] · N. Salas[1]



The first cohort (n = 33) corresponded to sexually active women between 18 and 50 ye
VVC, who were prescribed
500 mg va
L. plantar
Probiotico V
contains *L.*
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week on alt
ing days wi
promised w
single-dose

-33 donne con VVC trattate con Clotrimazolo 500
ginale



women. The study suggests that follow-up therapy with vaginal tablets with *L. plantarum* I1001 could increase the effectiveness of single-dose 500 mg clotrimazole at preventing recurrence of VVC, an effect that was also observed in women with recurrent vulvovaginal candidiasis (RVVC) after six months of azole treatment.

Il Probiotico è associato ad una riduzione del rischio di ricorrenza di tre volte

Can *Lactobacillus fermentum* LF10 and *Lactobacillus acidophilus* LA02 in a Slow-release Vaginal Product be Useful for Prevention of Recurrent Vulvovaginal Candidiasis?

A Clinical Study

Protocol

Induction phase

200 mg of fluconazole orally as an induction dose for 3 alternate days during the first treatment week

At the first follow-up visit (on average after 10 d) all patients who were classified as being clinically cured (severity score<3) were eligible for assignment to the prophylactic phase of the study

F. Murina , et Al - J Clin Gastroenterol 2014

Can *Lactobacillus fermentum* LF10 and *Lactobacillus acidophilus* LA02 in a Slow-release Vaginal Product be Useful for Prevention of Recurrent Vulvovaginal Candidiasis?

A Clinical Study

Protocol

Prophylactic phase

During the **first phase of the prophylactic period** 1 vaginal tablet was inserted into the vagina on alternate days for 10 consecutive nights

Patients who were still free of symptoms and without signs moved on to the **second phase of prophylactic** therapy, consisting in the use of 1 vaginal tablet every week for the subsequent 10 weeks

F. Murina , et Al - J Clin Gastroenterol 2014

Can *Lactobacillus fermentum* LF10 and *Lactobacillus acidophilus* LA02 in a Slow-release Vaginal Product be Useful for Prevention of Recurrent Vulvovaginal Candidiasis?

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Protocol

Observation phase

-Patients were monitored without treatment for 7 months

-Patients were required to discontinue the study protocol if they had a clinical recurrence of VVC (score>3)

-The tr an adverse

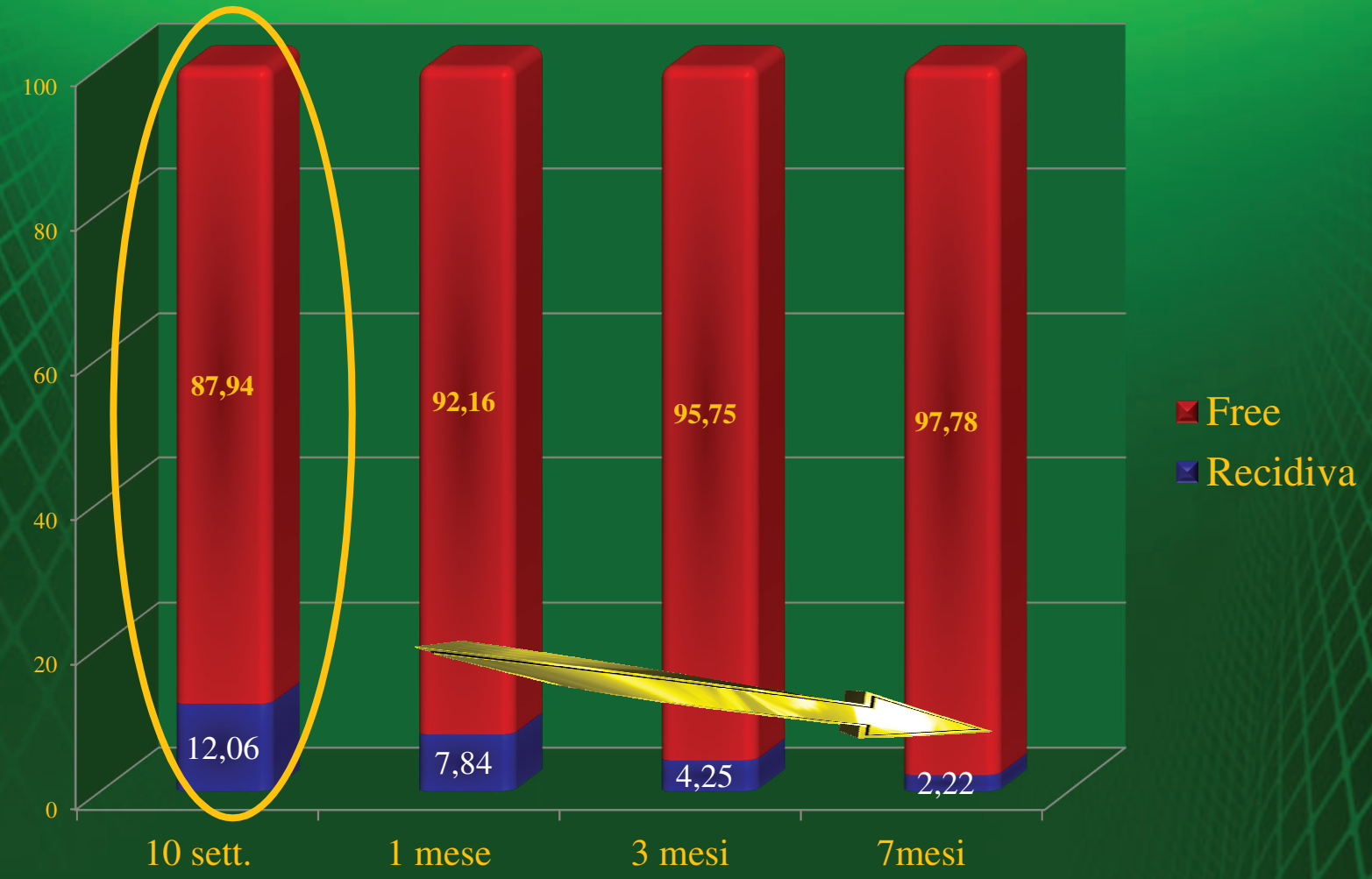
The end point was the proportion of women in clinical remission at the end of the observation period (ie, after 7 mo)

F. Murina , et Al - J Clin Gastroenterol 2014

Can *Lactobacillus fermentum* LF10 and *Lactobacillus acidophilus* LA02 in a Slow-release Vaginal Product be Useful for Prevention of Recurrent Vulvovaginal Candidiasis?

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Results



F. Murina , et Al - J Clin Gastroenterol 2014

Vulvovaginal *Candida albicans* infections: pathogenesis, immunity and vaccine prospects

A Cassone

BJOG 2014

the current antifungal armamentarium. Th
nous cytokines, antibodies and immunor
potential interest[71,72] but the cornerstone
a
a

Immunoterapia approccio di sicuro interesse

Table 4. Some most studied vaccines against RVVC

Vaccine and adjuvant/ carrier	Antigen biological function	Present clinical state	Putative protection mechanism
Als-3 alum	Member of major adhesin family of *C. albicans*. Involved in adherence to epithelia and biofilm formation. Hypha-associated	Phase II	Activation of Th1/Th17 cells Possible role of pre-existent antibodies boosted at high titer in vaccine recipients
Virosomal Sap2	Degradation/deviation of host immune factors. Inflammation Consistently involved in virulence in mucosal pre-clinical models	Closed at Phase 1	Virulence-neutralizing, inflammation-neutralizing antibodies
β-glucan-CRM–conjugate/ MF59	A main pathogen-associated molecular pattern, involved in fungal cell stability. biofilm formation and activatory and inhibitory immune mechanisms	Preclinical	Protection due to universal anti-beta-glucan-antibodies, growth- and adherence inhibitory
Beta-mannan- and Beta-mannoside conjugates	Adhesin, involved in host immune-deviation	Preclinical	Opsonizing antibodies
HyR-1 (no adjuvant defined, probably alum)	Hypha-associated virulence protein involved in protecting the fungus from PMN activity.	Preclinical	Protective antibodies

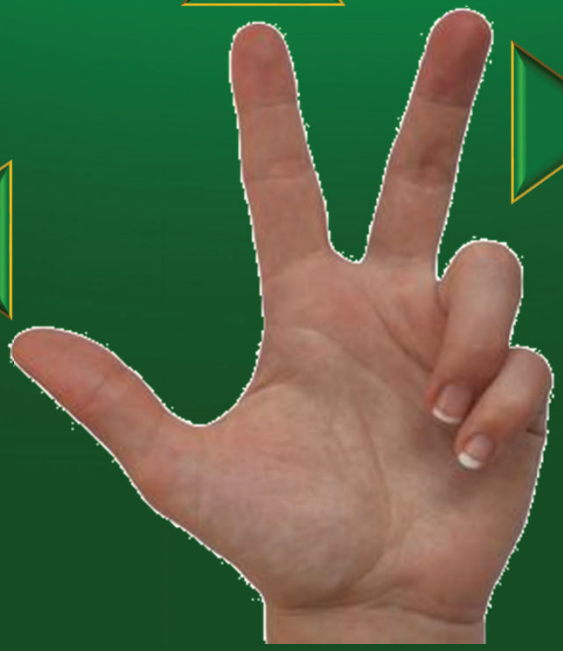
Als-3, adhesin-like substance 3; CRM, cross-reactive material, diphtheria toxoid; Hyr-1, Hyphae-related protein 1; MF59, squalene-derived adjuvant; Sap2, secretory aspartyl proteinase 2. For details, see text and quoted references.

Take home messages

Competere sulla formazione del biofilm

Comprendere la fisiopatologia della candidosi vulvovaginale

Utilizzare schemi di cura razionali ed integrati



Candidosi Vulvo-Vaginale

Grazie per l'attenzione!!!!

Silvia Oneda/Filippo Murina

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