EFFETTI DELLE TERAPIE ORMONALI LOCALI

Costantino Di Carlo

IL MICROBIOTA VAGINALE

La microflora vaginale è dominata dalla presenza di differenti specie di lattobacilli che insieme costituiscono la

“flora di Doderleïn” **(10^6 -10^8 cfu)**

Albert Sigmund Doderlein
(1860-1941)

Table 1 Prevalence of *Lactobacillus* spp. in vaginal tract of different women (expressed in percentage values)

Lactobacillus spp.	Antonio et al. [13] (Seatle, $n = 302$)	Anukam et al. [14] (Nigeria, $n = 24$)	Aslim and Kilic [15] (Turkey, $n = 10$)[a]	Tamrakar et al. [16] (Japan, $n = 98$)	Vitali et al. [17] (Belgium, $n = 26$)	Brolazo et al. [18] (Brazil, $n = 135$)[b]
L. crispatus	32	3.0	14	61.2		30.1
L. jensenii	23		3	29.6		26.5
L. gasseri	5	7.3	21	33.7	Present	22.9
L. ruminis	0.3					
L. reuteri	0.3					2.4
L. fermentum	0.3	1.3				2.4
L. oris	0.3		2			
L. vaginalis	0.3	2.7	16		Present	8.4
L. iners		64.4		39.8	Present	
L. plantarum		6.0	5			
L. suntoryeus		6.0				
L. rhamnosus		2.7				2.4
L. helveticus		1.3				
L. johnsonii		1.3				
L. salivarius		1.3	3			1.2
L. acidophilus			16		Present	
L. delbrueckii			14			2.4
L. cellobiosus			3			
L. curvatus			2			
L. brevis			2			
L. mucosae						1.2
No homology	4					
No lactobacilli	29					
Lactobacillus spp.	15	2.7				
Methodology	Whole-chromosomal DNA probes to 20 *Lactobacillus* strains	Processed by denaturing gradient gel electrophoresis (DGGE) and identified by DNA sequencing	Biochemical tests	PCR with primers for 16S ribosomal DNA	DGGE and real-time PCR analysis	Multiplex PCR

[a] Percentage relative to the number of isolates (58 isolates of *Lactobacillus* spp.)

[b] Percentage relative to the number of isolates (83 isolates of *Lactobacillus* spp.)

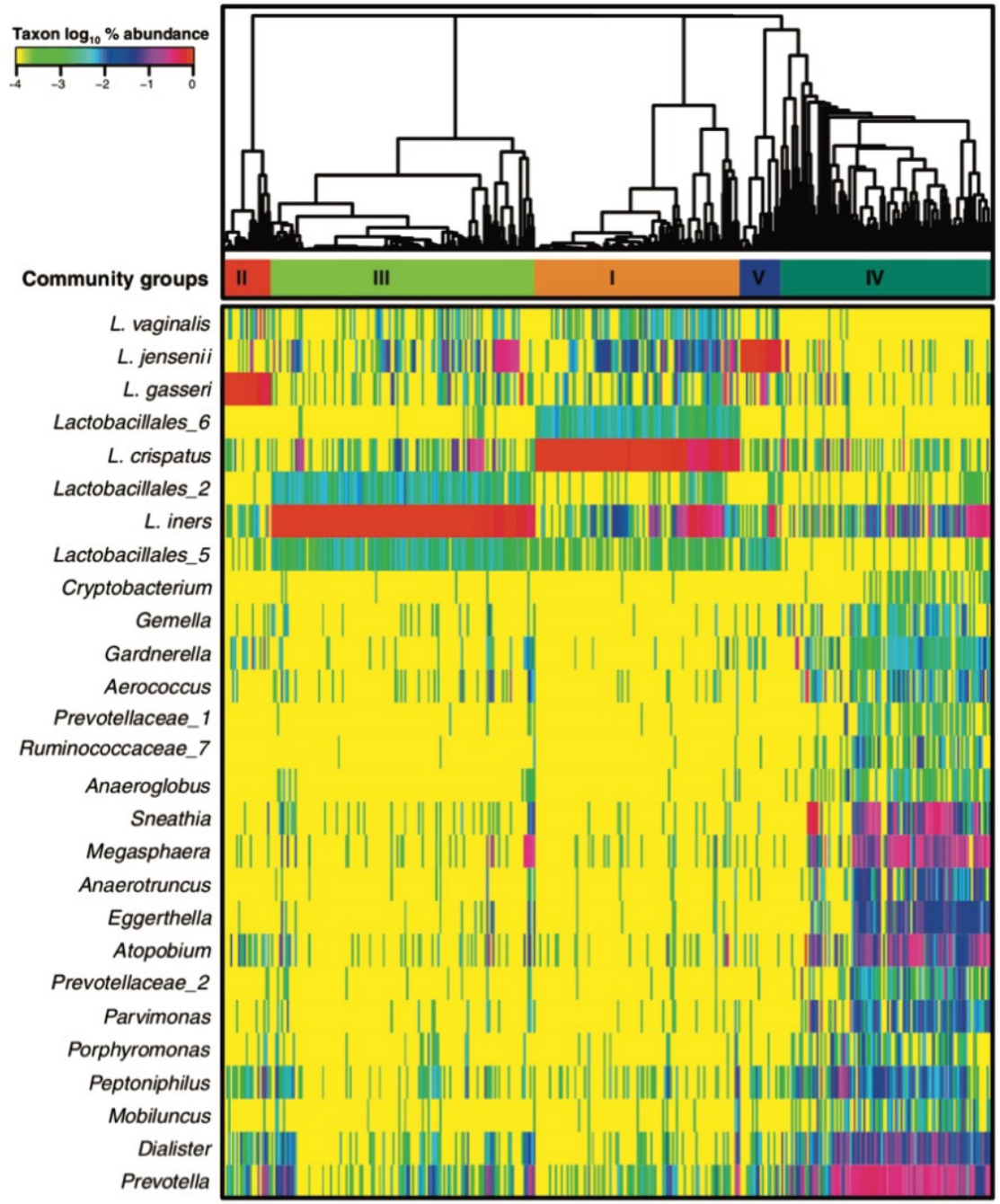
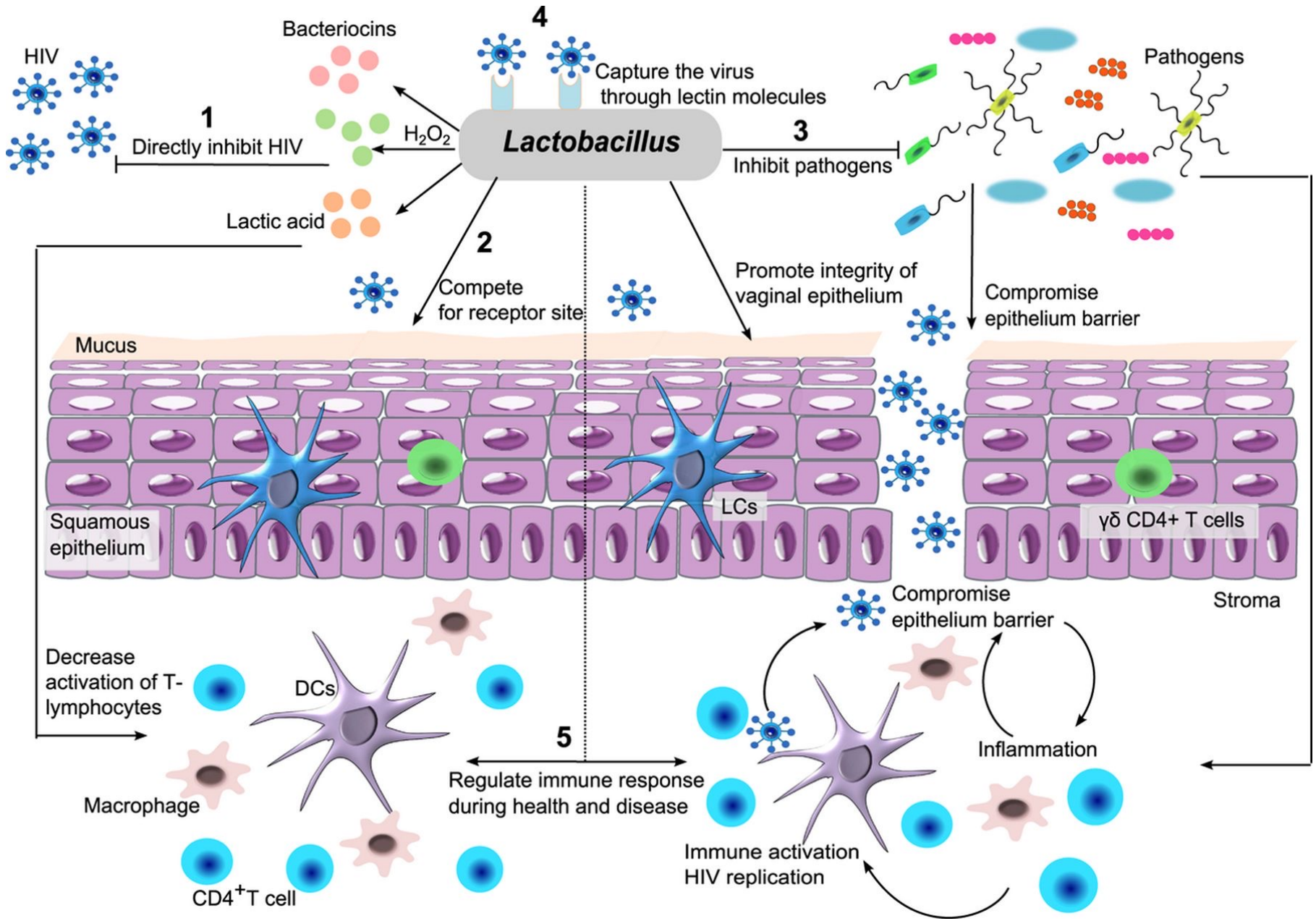
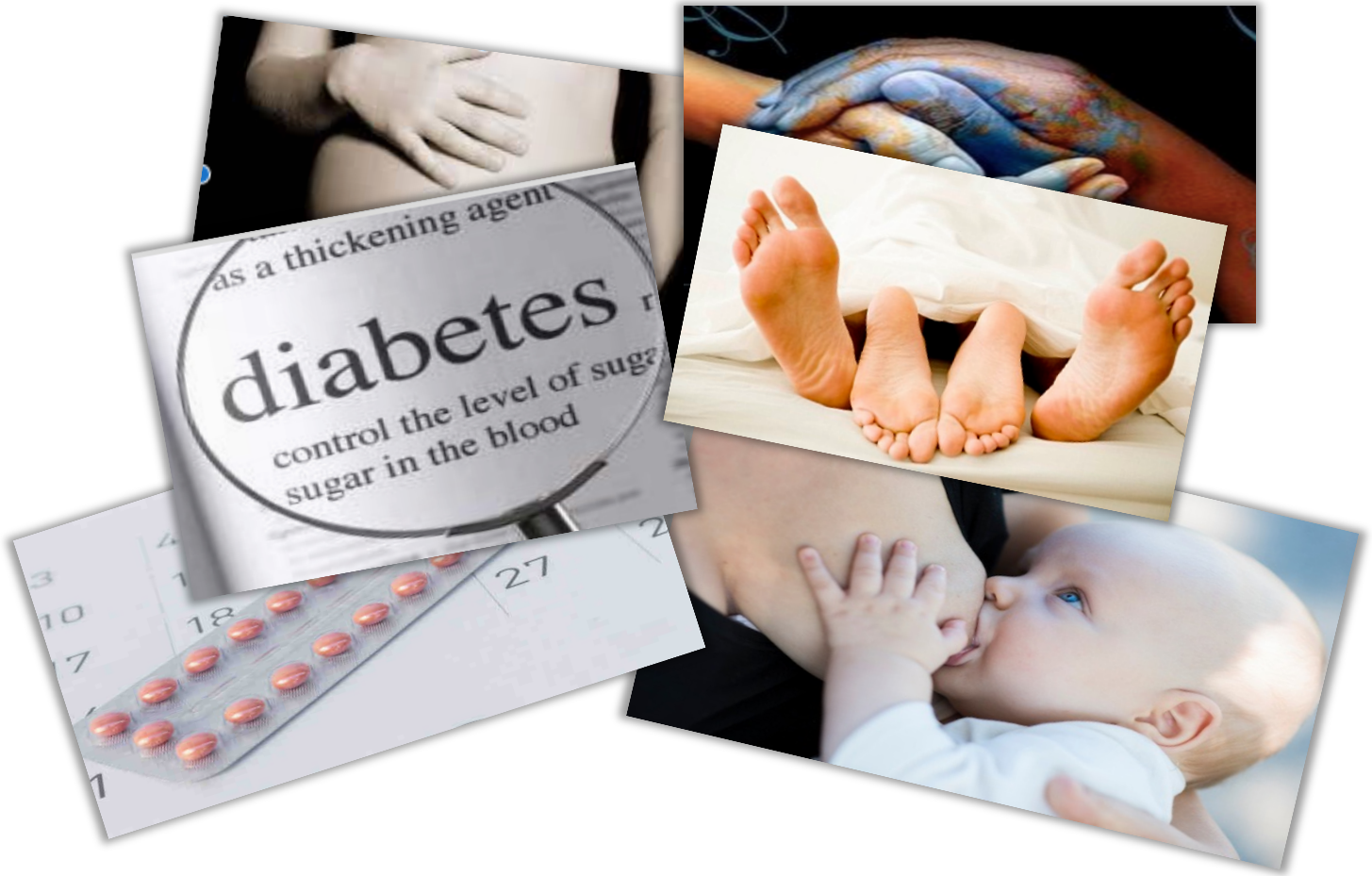


Figure 1: Composition and structure of vaginal bacterial communities found in 396 reproductive age women. The bacterial populations in each sample were classified based on partial 16S rRNA gene sequences and the communities were clustered based on the relative abundances of these bacterial populations. Major groups of communities were used to define community state types I to V. This heatmap shows the relative abundance (see color key) of bacterial taxa (listed on the left) in each community. (From [3]. Reprinted with permission from the *Proceedings of the National Academy of Sciences USA.*)

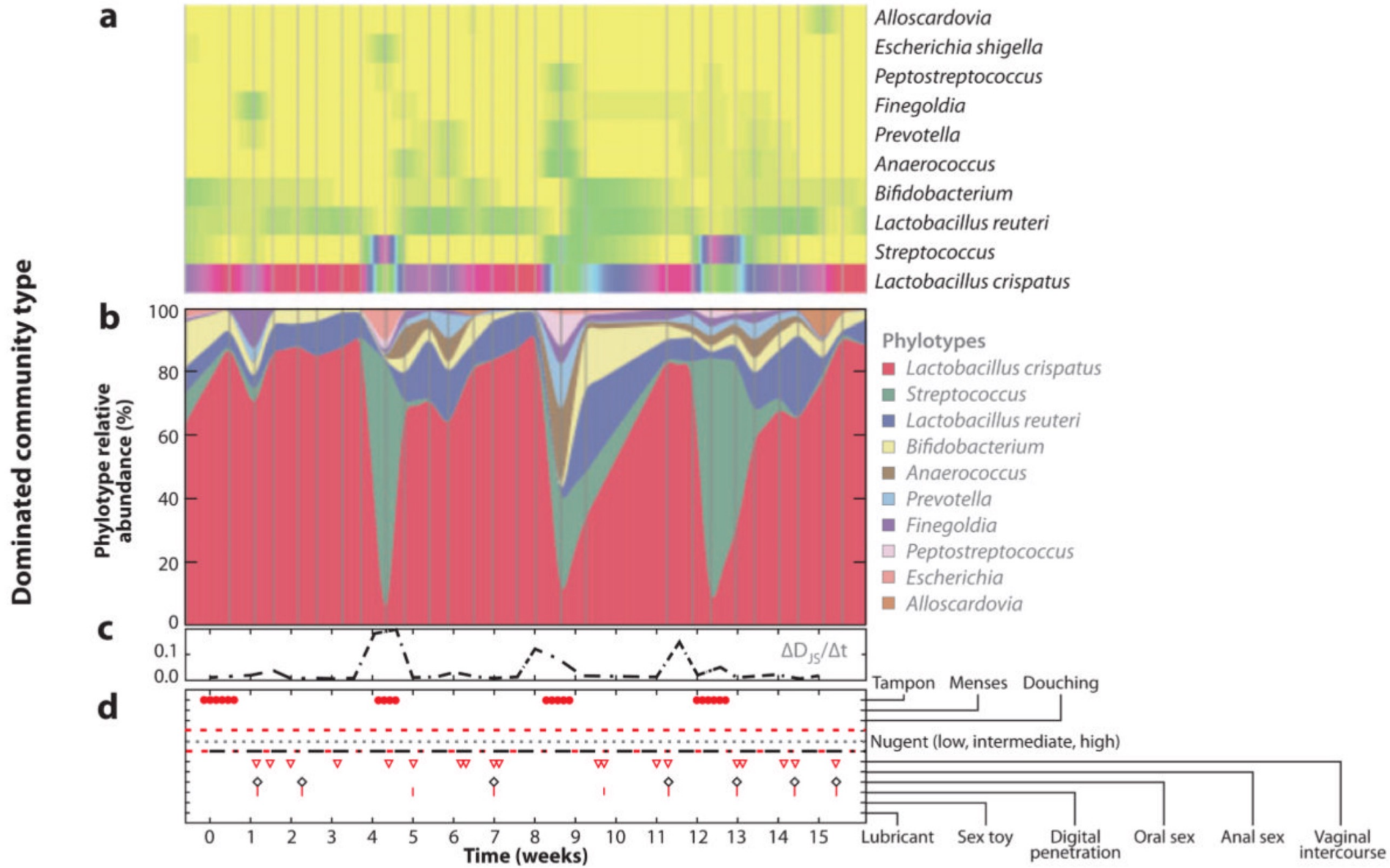

HIV
Bacteriocins
4
Capture the virus
through lectin molecules
Pathogens
1
Directly inhibit HIV
H_2O_2
Lactobacillus
3
Inhibit pathogens
Lactic acid
2
Compete
for receptor site
Promote integrity of
vaginal epithelium
Compromise
epithelium barrier
Mucus
Squamous
epithelium
LCs
γδ CD4+ T cells
Stroma
Compromise
epithelium barrier
Decrease
activation of T-
lymphocytes
DCs
5
Regulate immune response
during health and disease
Inflammation
Macrophage
Immune activation
HIV replication
CD4+T cell

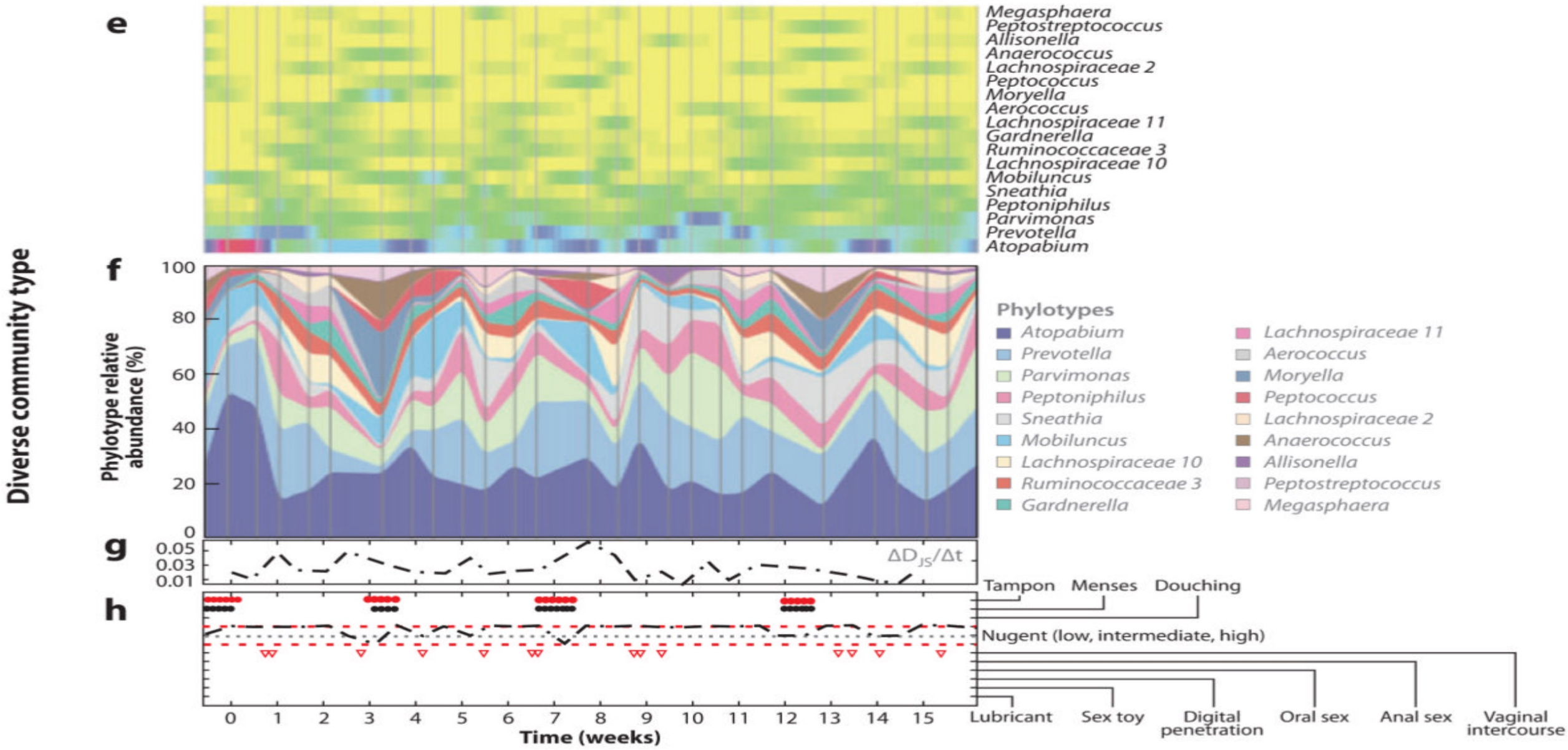
La composizione dell'ecosistema vaginale non è statica e diverse consizioni fisiologiche (es. stato ormonale) o fattori patologici possono indurre modificazioni quantitative e/o qualitative

Età
Etnia
Fattori dietetici
Diabete
Abitudini igieniche
Antibiotici
Attività sessuale
Stato ormonale
Gravidanza
Allattamento
Ciclo mestruale
Contraccezione



Martin DH. Am J Med Sci 2012;343:2-9.


a
Alloscardovia
Escherichia shigella
Peptostreptococcus
Finegoldia
Prevotella
Anaerococcus
Bifidobacterium
Lactobacillus reuteri
Streptococcus
Lactobacillus crispatus
b
Phylotype relative abundance (%)
100
80
60
40
20
0
Phylotypes
Lactobacillus crispatus
Streptococcus
Lactobacillus reuteri
Bifidobacterium
Anaerococcus
Prevotella
Finegoldia
Peptostreptococcus
Escherichia
Alloscardovia
c
0.1
0.0
ΔD_JS/Δt
d
Tampon
Menses
Douching
Nugent (low, intermediate, high)
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Time (weeks)
Lubricant
Sex toy
Digital penetration
Oral sex
Anal sex
Vaginal intercourse
Dominated community type


Diverse community type
e
Megasphaera
Peptostreptococcus
Allisonella
Anaerococcus
Lachnospiraceae 2
Peptococcus
Moryella
Aerococcus
Lachnospiraceae 11
Gardnerella
Ruminococcaceae 3
Lachnospiraceae 10
Mobiluncus
Sneathia
Peptoniphilus
Parvimonas
Prevotella
Atopabium
f
Phylotype relative abundance (%)
100
80
60
40
20
0
Phylotypes
Atopabium
Prevotella
Parvimonas
Peptoniphilus
Sneathia
Mobiluncus
Lachnospiraceae 10
Ruminococcaceae 3
Gardnerella
Lachnospiraceae 11
Aerococcus
Moryella
Peptococcus
Lachnospiraceae 2
Anaerococcus
Allisonella
Peptostreptococcus
Megasphaera
g
0.05
0.03
0.01
ΔD_JS/Δt
h
Tampon
Menses
Douching
Nugent (low, intermediate, high)
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
Time (weeks)
Lubricant
Sex toy
Digital penetration
Oral sex
Anal sex
Vaginal intercourse

LA COMPOSIZIONE DEL MICROBIOTA VAGINALE CAMBIA DRASTICAMENTE NEL TEMPO, CONDIZIONATO DAI VARI LIVELLI DI ESTROGENI DURANTE LA VITA

	Neonata	1 mese	Pubertà	Maturità sessuale	Gravidanza	Dopo la menopausa
Estrogeni	++	-	+	++	+++	-
Glicogeno	+	-	- →+	+	++	-
pH	4/5	7	7→5	4/5	3,5/4,5	6/7
Presenza microrganismi	Sterile, o con lattobacilli	scarsa	mista	lattobacilli		misto

La riduzione dei Lattobacilli favorisce la proliferazione dei patogeni

Germi potenzialmente patogeni, alloctoni o autoctoni

Lattobacilli

La **vaginosi batterica** (VB) è caratterizzata da:

1. alterazione della flora batterica vaginale ("ecosistema vaginale"), con **ridotta concentrazione dei diversi ceppi di Lactobacillus** produttori di acido lattico e H2O2, che contribuiscono a mantenere basso il pH vaginale, difendendo l'ecosistema vaginale da germi patogeni. **In condizioni fisiologiche i lattobacilli rappresentano la quota maggiore dell'intera popolazione di batteri, che è composta di più di 40 ceppi diversi**;

2. **aumento dei germi Gram negativi e dei batteri anaerobi**. Di solito il rapporto tra lattobacilli e anaerobi varia tra 2:1 fino a 5:1 in condizioni fisiologiche. Tale rapporto si inverte, fino a raggiungere l'**1:100**, fino all'**1:1000**, a favore quindi degli anaerobi, con il ridursi dei lattobacilli e il progressivo aumento del pH vaginale.

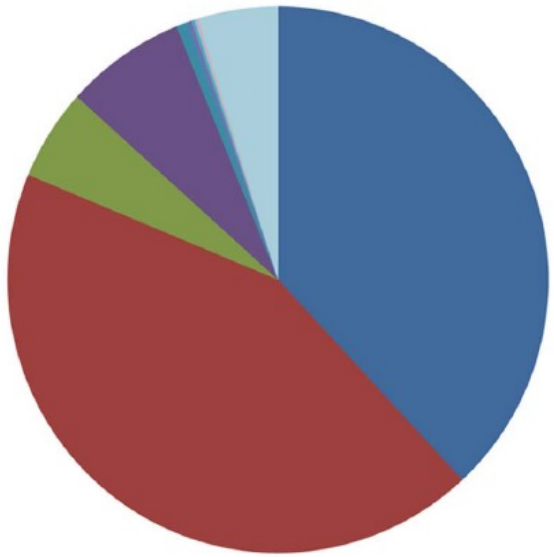
Concetto chiave: la vaginosi è caratterizzata da un'alterazione solo numerica, quantitativa e non qualitativa, dei diversi tipi di microrganismi presenti nell'ecosistema vaginale.

OPEN ACCESS Freely available online PLOS ONE

Composition of the Vaginal Microbiota in Women of Reproductive Age – Sensitive and Specific Molecular Diagnosis of Bacterial Vaginosis Is Possible?

Elena Shipitsyna[1], Annika Roos[2], Raluca Datcu[3], Anders Hallén[4], Hans Fredlund[5], Jørgen S. Jensen[3], Lars Engstrand[2], Magnus Unemo[5]*

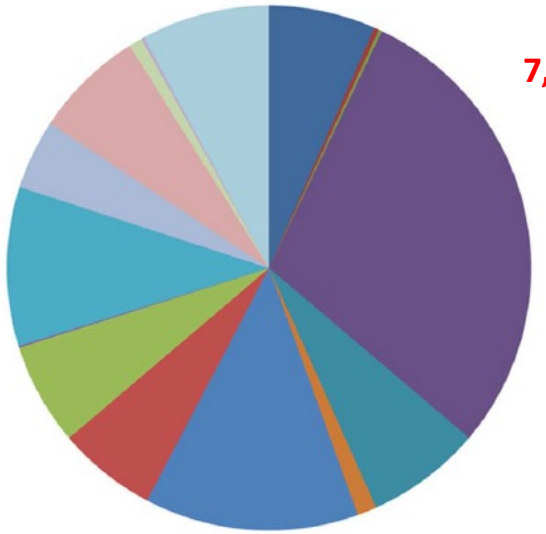
Controls



86,7%

- Lactobacillus iners (38.1%)
- Lactobacillus crispatus (43.2%)
- Other Lactobacillus species (5.4%)
- Gardnerella vaginalis (7.2%)
- Atopobium vaginae (0.6%)
- Eggerthella (0.001%)
- Prevotella (0.2%)
- BVAB 1 (0.02%)
- BVAB 2 (0.01%)
- Finegoldia magna (0.1%)
- Megasphaera type 1 (0.2%)
- Megasphaera type 2 (0%)
- Sneathia sanguinegens (0.1%)
- Leptotrichia amnionii (0.1%)
- BVAB-TM7 (0.002%)
- Mobiluncus curtisii/mulieris (0.002%)
- Other non-Lactobacillus species (4.8%)

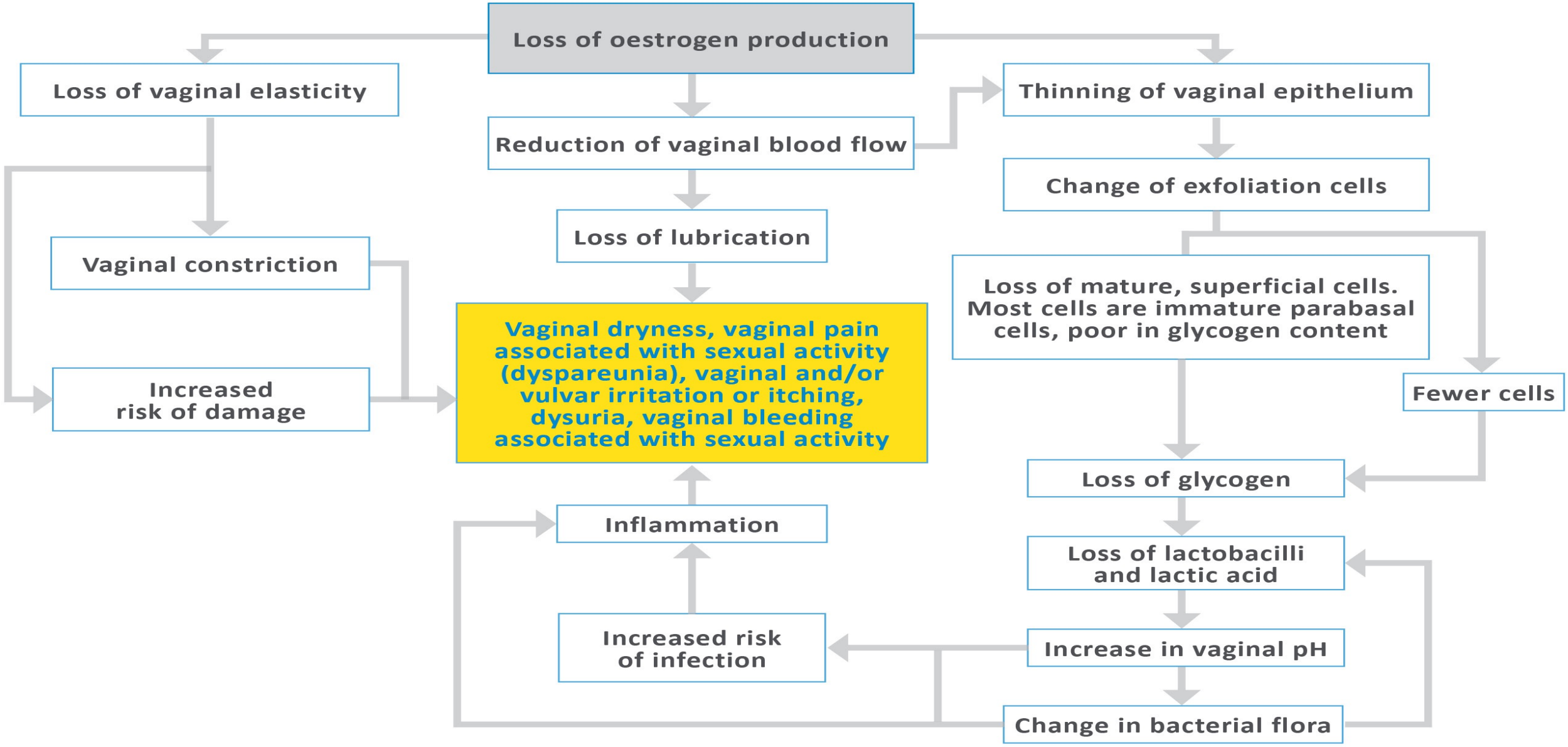
BV



7,1%

- Lactobacillus iners (6.6%)
- L. crispatus (0.3%)
- Other Lactobacillus species (0.2%)
- Gardnerella vaginalis (29.1%)
- Atopobium vaginae (7.1%)
- Eggerthella (1.2%)
- Prevotella (13.2%)
- BVAB 1 (6.1%)
- BVAB 2 (6.3%)
- Finegoldia magna (0.1%)
- Megasphaera type 1 (9.8%)
- Megasphaera type 2 (0.1%)
- Sneathia sanguinegens (4.3%)
- Leptotrichia amnionii (6.8%)
- BVAB-TM7 (0.8%)
- Mobiluncus curtisii/mulieris (0.2%)
- Other non-Lactobacillus species (7.9%)

Modificazioni della vagina dopo la menopausa



Local oestrogen for vaginal atrophy in postmenopausal women (Review)

Suckling JA, Kennedy R, Lethaby A, Roberts H

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in The Cochrane Library 2006, Issue 4.

http://www.thecochranelibrary.com

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Main results

Nineteen trials with 4162 women were included in this review. The overall quality of the studies was good, although not all trials measured the same outcomes. All trials measured efficacy ,with various outcome measures. When comparing the efficacy of different oestrogenic preparations (in the form of creams, pessaries, tablets and the oestradiol-releasing vaginal ring) in relieving the symptoms of vaginal atrophy, results indicated significant findings favouring the cream, ring, and tablets when compared to placebo and non-hormonal gel.

Fourteen trials compared safety. Four looked at hyperplasia, four looked at endometrial overstimulation and seven looked at adverse effects. One trial showed significant adverse effects of the cream (conjugated equine oestrogen) when compared to tablets (oestradiol) which included uterine bleeding, breast pain and perineal pain (1 RCT; OR 0.18, 95% CI 0.07 to 0.50). Two trials showed significant endometrial overstimulation as evaluated by a progestagen challenge test with the cream (conjugated equine oestrogen) group when compared to the ring (OR 0.29, 95% CI 0.11 to 0.78). Although not statistically significant there was a 2% incidence of simple hyperplasia in the ring group when compared to the cream (conjugated equine oestrogen) and 4% incidence of hyperplasia (one simple, one complex) in the cream group (conjugated equine oestrogen) when compared to the tablet (oestradiol).

Eleven studies compared acceptability to the participants by comparing: comfort of product use, ease of use, overall product rating, delivery system and satisfaction. Results showed a significant preference for the oestradiol-releasing vaginal ring.

2006

Menopause: The Journal of The North American Menopause Society
Vol. 26, No. 4, pp. 431-453
DOI: 10.1097/GME.0000000000001221

Review Article

A systematic review of the efficacy and safety of vaginal estrogen products for the treatment of genitourinary syndrome of menopause

Colton Biehl, BS, Olivia Plotsker, and Sebastian Mirkin, MD

All studies showed superiority of vaginal estrogen products when compared with placebo in objective endpoints such as maturation of the vaginal epithelium and reduction of vaginal pH. Some of the studies demonstrated superiority over placebo for the symptoms of dyspareunia,[11,24,27,30-33] vaginal dryness,[11,12,17,27,30-32] and alleviation of urogenital symptoms including reduced urinary urgency and decreased incidence of cystitis.[10,14] Onset of action for a subjective efficacy endpoint was reported as early as 2 weeks.[30]

Menopause: The Journal of The North American Menopause Society
Vol. 19, No. 10, pp. 1130-1139
DOI: 10.1097/gme.0b013e3182518e9a

The therapeutic effect of a new ultra low concentration estriol gel formulation (0.005% estriol vaginal gel) on symptoms and signs of postmenopausal vaginal atrophy: results from a pivotal phase III study

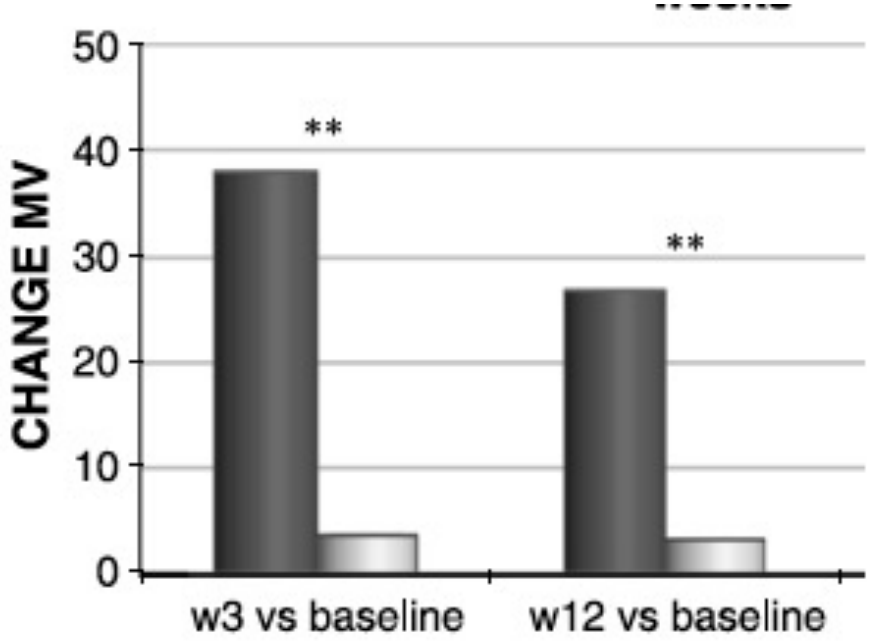
Antonio Cano, MD, PhD,[1] José Estévez, MD,[2] Ramón Usandizaga, MD, PhD,[3] José L. Gallo, MD,[4] Misericord Guinot, MD, PhD,[5] Juan L. Delgado, MD,[6] Elena Castellanos, MD, PhD,[7] Eloy Moral, MD,[8] Concepción Nieto, MD, PhD,[9] Jaime Moscoso del Prado, PhD,[10] and Javier Ferrer, MD, PhD[11]

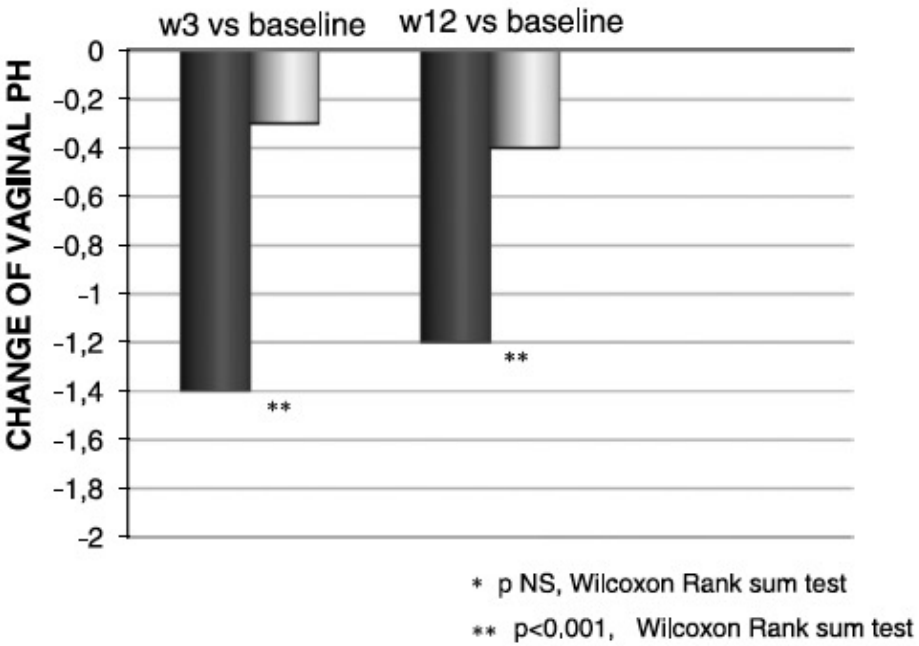
R.C.T. di confronto fra 114 pazienti in postmenopausa con atrofia vaginale trattate con gel contenente estriolo (0,05 mg) e 53 trattate con placebo

TABLE 5. *Possibly related AEs*

	0.005% Estriol gel	Placebo gel
Breast pain	0 (0.0)	1 (1.9)
Vaginal discharge	0 (0.0)	1 (1.9)
Vulvovaginal discomfort	0 (0.0)	1 (1.9)
Application site irritation	1 (0.9)	0 (0.0)
Genital rash	1 (0.9)	0 (0.0)
Vulvovaginal pruritus	5 (4.4)	0 (0.0)
Pruritus	3 (2.6)	2 (3.7)
Candidiasis	1 (0.9)	0 (0.0)
Hyperhydrosis	0 (0.0)	1 (1.9)
Swelling	0 (0.0)	1 (1.9)
Hot flush	0 (0.0)	3 (5.7)
Abdominal pain	1 (0.9)	1 (1.9)
Sensation of leg heaviness	0 (0.0)	1 (1.9)

Data are presented as n (%) of women with the AE.
AE, adverse event.





Maturitas 71 (2012) 360–368

Contents lists available at SciVerse ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Low dose estriol pessaries for the treatment of vaginal atrophy: A double-blind placebo-controlled trial investigating the efficacy of pessaries containing 0.2 mg and 0.03 mg estriol

Henrik Griesser[a], Stefan Skonietzki[b], Thomas Fischer[c], Karin Fielder[c], Marija Suesskind[d,*]

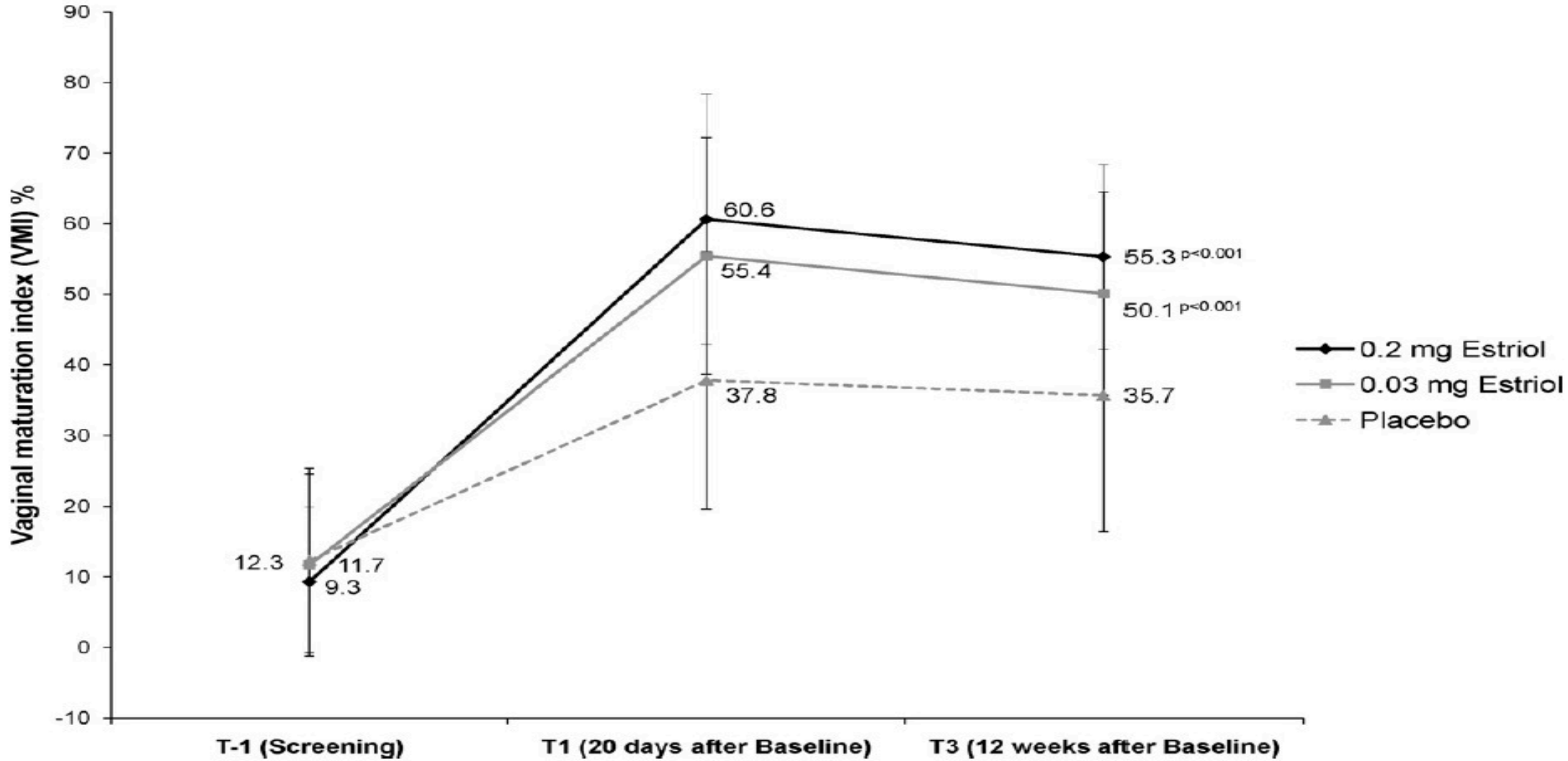


Fig. 2. Improvement in vaginal maturation index. *P*-values (Wilcoxon–Mann–Whitney U test) are given for the comparison of verum and placebo.

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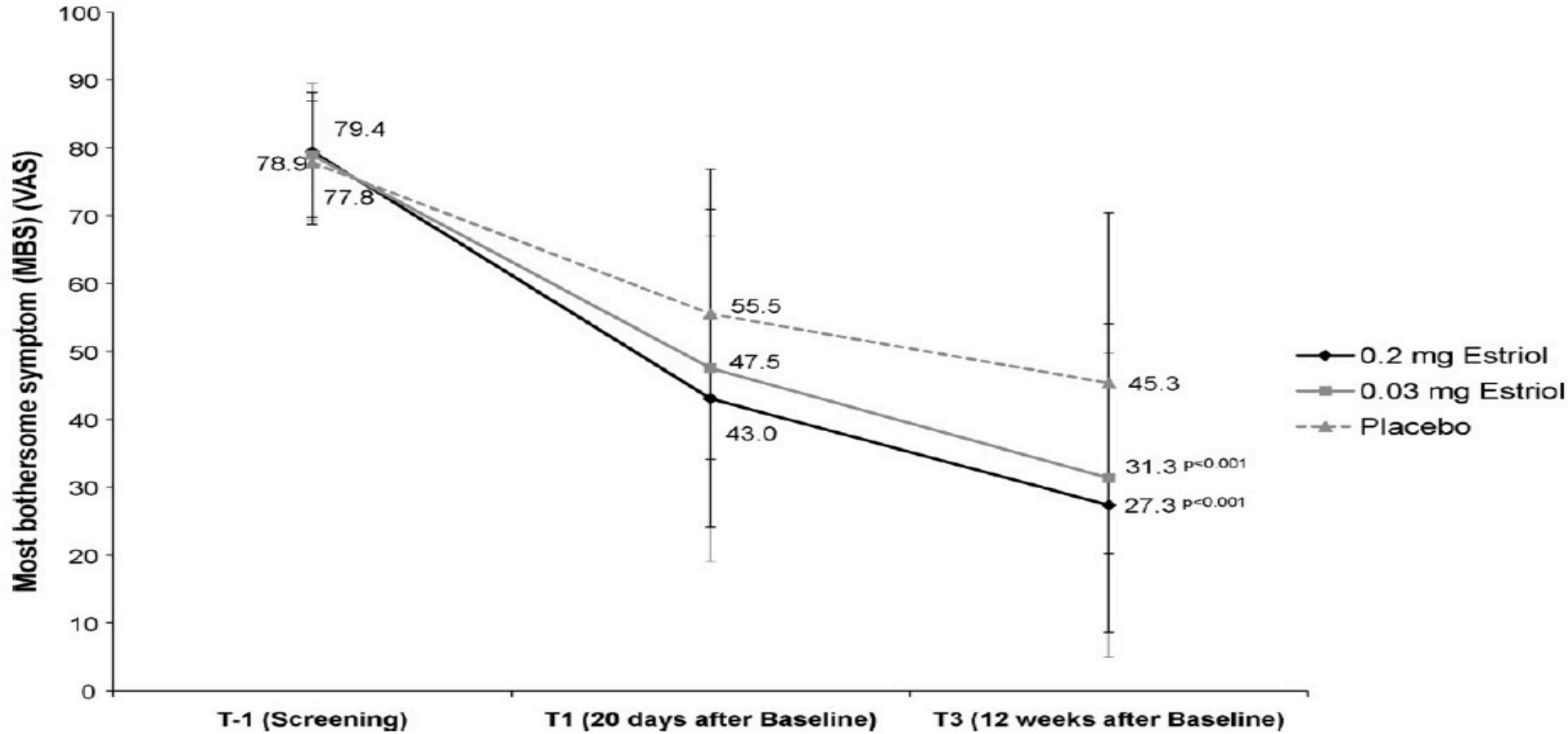

Fig. 4. Improvement in severity of most bothersome symptom. *P*-values (Wilcoxon–Mann–Whitney U test) are given for the comparison of verum and placebo.

A CONTROLLED TRIAL OF INTRAVAGINAL ESTRIOL IN POSTMENOPAUSAL WOMEN WITH RECURRENT URINARY TRACT INFECTIONS

RAUL RAZ, M.D., AND WALTER E. STAMM, M.D.

VARIABLE	ESTRIOL GROUP (N = 36)	PLACEBO GROUP (N = 24)
Positive vaginal cultures — no. (%)		
Pretreatment		
Lactobacilli	0	0
Enterobacteriaceae	24 (67)	16 (67)
After 1 mo of treatment		
Lactobacilli	22 (61)	0†
Enterobacteriaceae	11 (31)	15 (63)‡
After 8 mo of treatment		
Lactobacilli	21 (58)	0†
Enterobacteriaceae	10 (28)	17 (71)‡
Vaginal pH		
Pretreatment	5.5±0.7	5.8±1.2
After 1 mo of treatment	3.8±0.8	6.2±1.2†
After 8 mo of treatment	3.6±1.0	6.1±2.0†

*Only women who had cultures at the one- and eight-month visits were included in the analysis. Plus–minus values are means ±SE.

†$P<0.001$ for the comparison between groups.

‡$P<0.005$ for the comparison between groups.

Prevalence and Determinants of Vaginal Flora Alterations in Postmenopausal Women

Wendy L. Pabich,[1] Stephan D. Fihn,[2,3] Walter E. Stamm,[2] Delia Scholes,[5] Edward J. Boyko,[2,4] Kalpana Gupta[2]

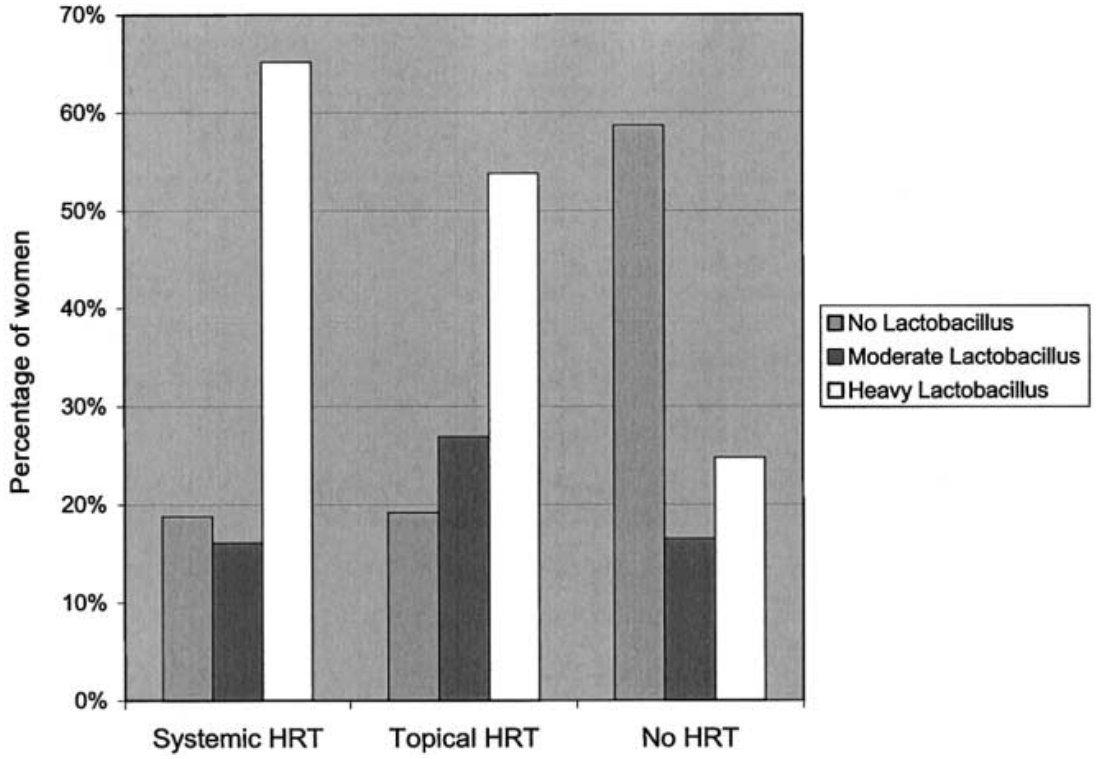

Figure 1. The prevalence of organisms in the vaginal flora of postmenopausal women with (cases) and without (controls) a history of recent urinary tract infection is shown. *Escherichia coli* and enterococci were significantly more prevalent in case women. HRT, hormone replacement therapy.

Efficacy of Vaginal Estradiol or Vaginal Moisturizer vs Placebo for Treating Postmenopausal Vulvovaginal Symptoms

A Randomized Clinical Trial

Caroline M. Mitchell, MD; Susan D. Reed, MD; Susan Diem, MD; Joseph C. Larson, MS; Katherine M. Newton, PhD; Kristine E. Ensrud, MD; Andrea Z. LaCroix, PhD; Bette Caan, DrPH; Katherine A. Guthrie, PhD

OBJECTIVE To compare the efficacy of a low-dose vaginal estradiol tablet and a vaginal moisturizer, each vs placebo, for treatment of moderate-to-severe postmenopausal vulvovaginal symptoms.

DESIGN, SETTING, AND PARTICIPANTS This 12-week multicenter randomized clinical trial enrolled postmenopausal women with moderate to severe symptoms of vulvovaginal itching, pain, dryness, irritation, or pain with penetration.

INTERVENTIONS Vaginal 10-µcg estradiol tablet (daily for 2 weeks, then twice weekly) plus placebo gel (3 times a week) (n = 102) vs placebo tablet plus vaginal moisturizer (n = 100) vs dual placebo (n = 100).

Published online March 19, 2018.

Efficacy of Vaginal Estradiol or Vaginal Moisturizer vs Placebo for Treating Postmenopausal Vulvovaginal Symptoms

A Randomized Clinical Trial

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Gli effetti della terapia estrogenica su pH e indice di maturazione sono significativamente superiori al placebo e all'idratante

	Riduzione pH da >5 a <5	Aum. cell. sup. da>5 a <5
Estradiolo	46%*	57%*
Idratante	9%	11%
Placebo	10%	11%

* p>0.01

Published online March 19, 2018.

Table 2. Most Bothersome Symptom (MBS) Severity Over 4 and 12 Weeks of Treatment for 302 Postmenopausal Women

Parameter	Vaginal Estradiol Tablet + Placebo Gel		Vaginal Moisturizer + Placebo Tablet		Dual Placebo		Difference			
							Estradiol vs Placebo		Moisturizer vs Placebo	
	No.	Mean (95% CI)	No.	Mean (95% CI)	No.	Mean (95% CI)	Mean (95% CI)	*P* Value[a]	Mean (95% CI)	*P* Value[a]
MBS severity[b]										
Baseline	99	2.4 (2.3 to 2.6)	100	2.5 (2.3 to 2.6)	99	2.5 (2.4 to 2.6)	0.0 (−0.2 to 0.1)		0.0 (−0.2 to 0.2)	
Week 4 minus baseline	97	−1.2 (−1.4 to −1.0)	97	−1.0 (−1.2 to −0.8)	97	−1.1 (−1.3 to −0.9)	−0.2 (−0.5 to 0.1)	.25	0.1 (−0.2 to 0.4)	.31
Week 12 minus baseline	96	−1.4 (−1.6 to −1.2)	99	−1.2 (−1.4 to −1.0)	95	−1.3 (−1.5 to −1.1)	−0.1 (−0.4 to 0.2)		0.2 (−0.1 to 0.4)	
Vaginal Symptom Index[c]										
Baseline	102	1.6 (1.5 to 1.7)	100	1.6 (1.5 to 1.7)	100	1.6 (1.5 to 1.7)	0.1 (−0.1 to 0.2)		0.0 (−0.1 to 0.2)	
Week 4 minus baseline	100	−0.7 (−0.8 to −0.5)	97	−0.5 (−0.7 to −0.4)	98	−0.6 (−0.8 to −0.5)	0.0 (−0.2 to 0.2)	.99	0.1 (−0.1 to 0.3)	.05
Week 12 minus baseline	99	−0.9 (−1.1 to −0.8)	99	−0.7 (−0.9 to −0.6)	96	−0.9 (−1.0 to −0.7)	−0.1 (−0.3 to 0.1)		0.1 (−0.1 to 0.3)	
Pain with penetration[d]										
Baseline	75	2.5 (2.3 to 2.6)	84	2.5 (2.4 to 2.6)	87	2.5 (2.4 to 2.6)	−0.1 (−0.2 to 0.1)		−0.1 (−0.2 to 0.1)	
Week 4 minus baseline	74	−1.4 (−1.7 to −1.2)	81	−1.0 (−1.3 to −0.8)	85	−1.2 (−1.4 to −0.9)	−0.3 (−0.6 to 0.1)	.21	0.1 (−0.2 to 0.5)	.08
Week 12 minus baseline	73	−1.5 (−1.7 to −1.2)	83	−1.1 (−1.4 to −0.9)	83	−1.5 (−1.8 to −1.3)	0.1 (−0.3 to 0.4)		0.4 (0.1 to 0.7)	
Dryness[d]										
Baseline	89	2.3 (2.2 to 2.4)	81	2.4 (2.3 to 2.5)	78	2.4 (2.3 to 2.6)	−0.1 (−0.3 to 0.0)		−0.1 (−0.2 to 0.1)	
Week 4 minus baseline	87	−1.1 (−1.3 to −0.9)	78	−1.0 (−1.2 to −0.8)	76	−1.2 (−1.4 to −1.0)	0.2 (−0.1 to 0.5)	.95	0.2 (−0.1 to 0.5)	.36
Week 12 minus baseline	86	−1.4 (−1.6 to −1.2)	80	−1.3 (−1.5 to −1.1)	74	−1.4 (−1.6 to −1.2)	0.0 (−0.3 to 0.3)		0.1 (−0.2 to 0.4)	

Association between postmenopausal vulvovaginal discomfort, vaginal microbiota, and mucosal inflammation

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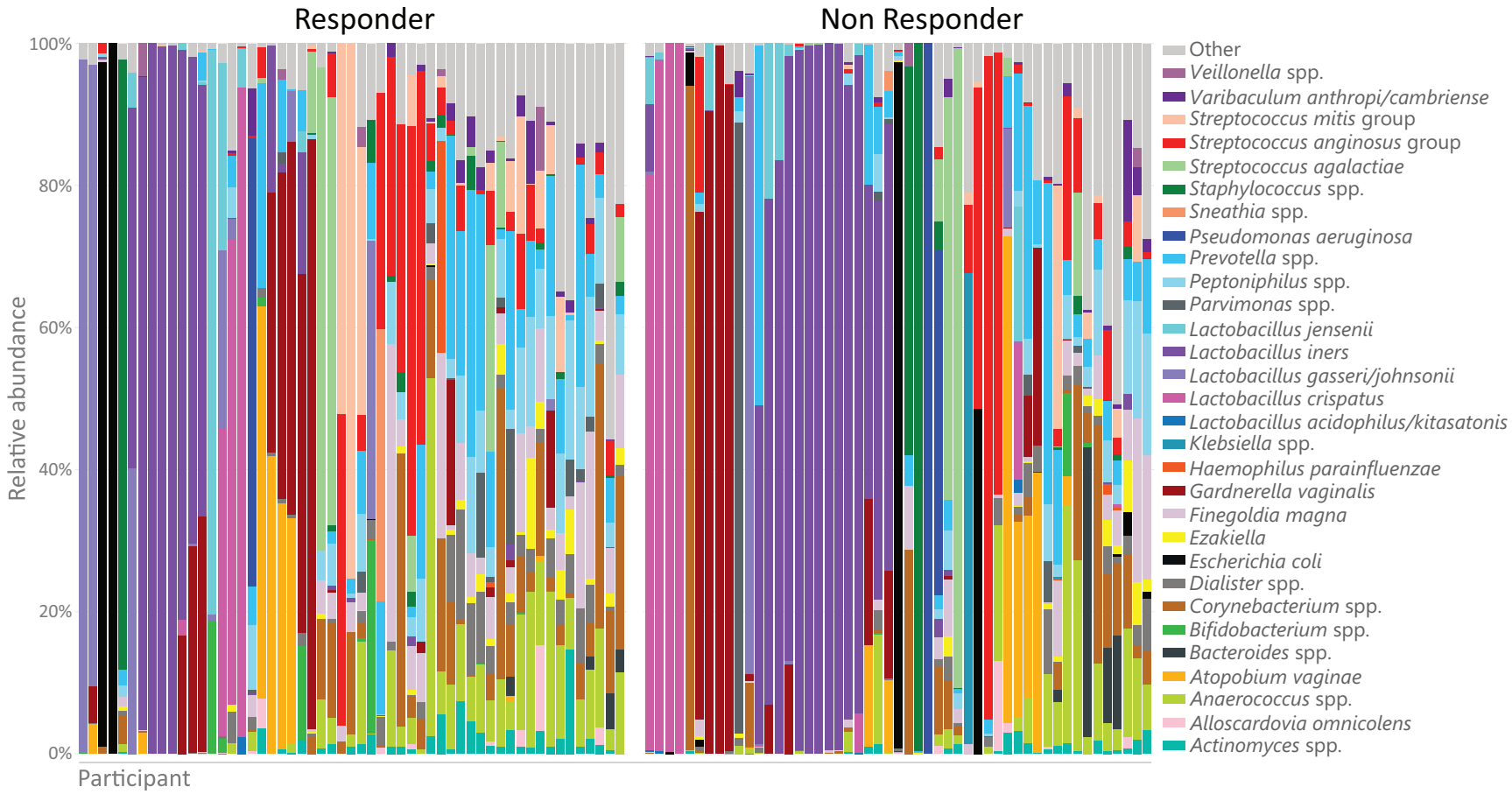
FIGURE 1
Baseline vaginal bacterial communities in responders and nonresponders



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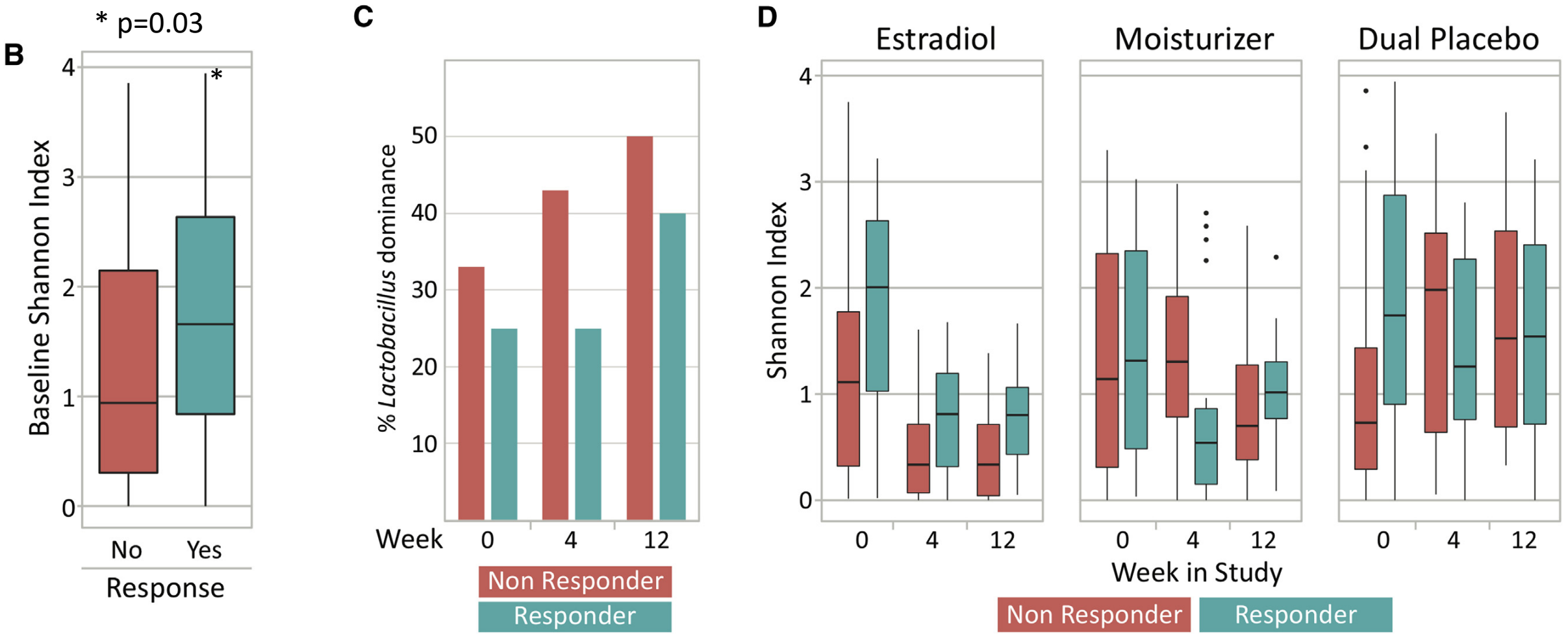

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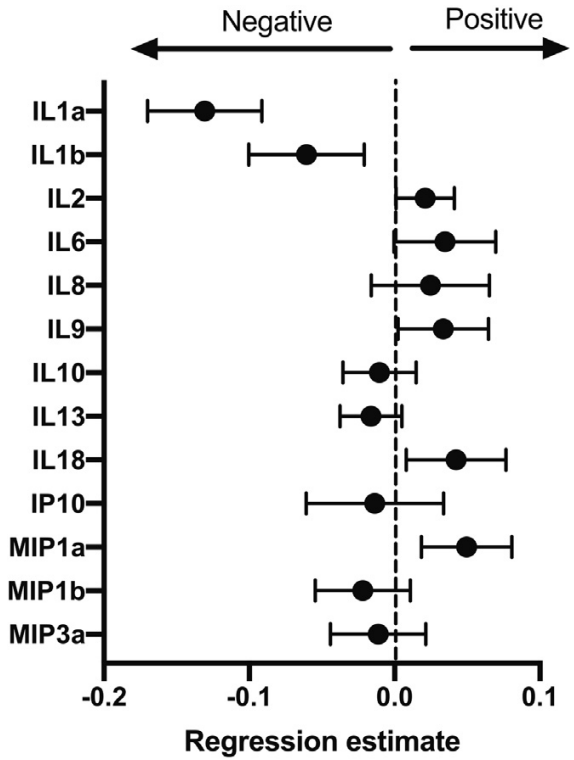
This is the inverse of what we might expect if superficial inflammation were associated with symptom severity, as the IL-1 family of cytokines are key mediators of inflammation. However, symptom severity may be related to deeper features of the vaginal microenvironment not measured with superficial samples like a cervicovaginal lavage, such as mucosal vascularization or elasticity. Of note, in responders, cytokines from both pro- and anti-inflammatory pathways increased over 12 weeks, which could indicate an overall improvement in the health and integrity of the genital tract mucosa.

FIGURE 3
Association between vaginal fluid immune markers and vulvovaginal symptom severity



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Clinical implications

In aggregate, these data demonstrated an association among hormonal status, vaginal microbiota, and vaginal micro-environment; however, the data suggested that vaginal symptoms have an additional underlying pathophysiology that is not clearly understood. For clinicians, this means that vaginal estrogen treatment alone may not be sufficient to relieve symptoms of vaginal discomfort in all postmenopausal women. In addition, this suggested that interventions targeted at changing the postmenopausal microbiota or pH were unlikely to alter symptom severity for most women.

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