Vaginal Discharge Syndromes: Vaginal Infections and Cervicitis

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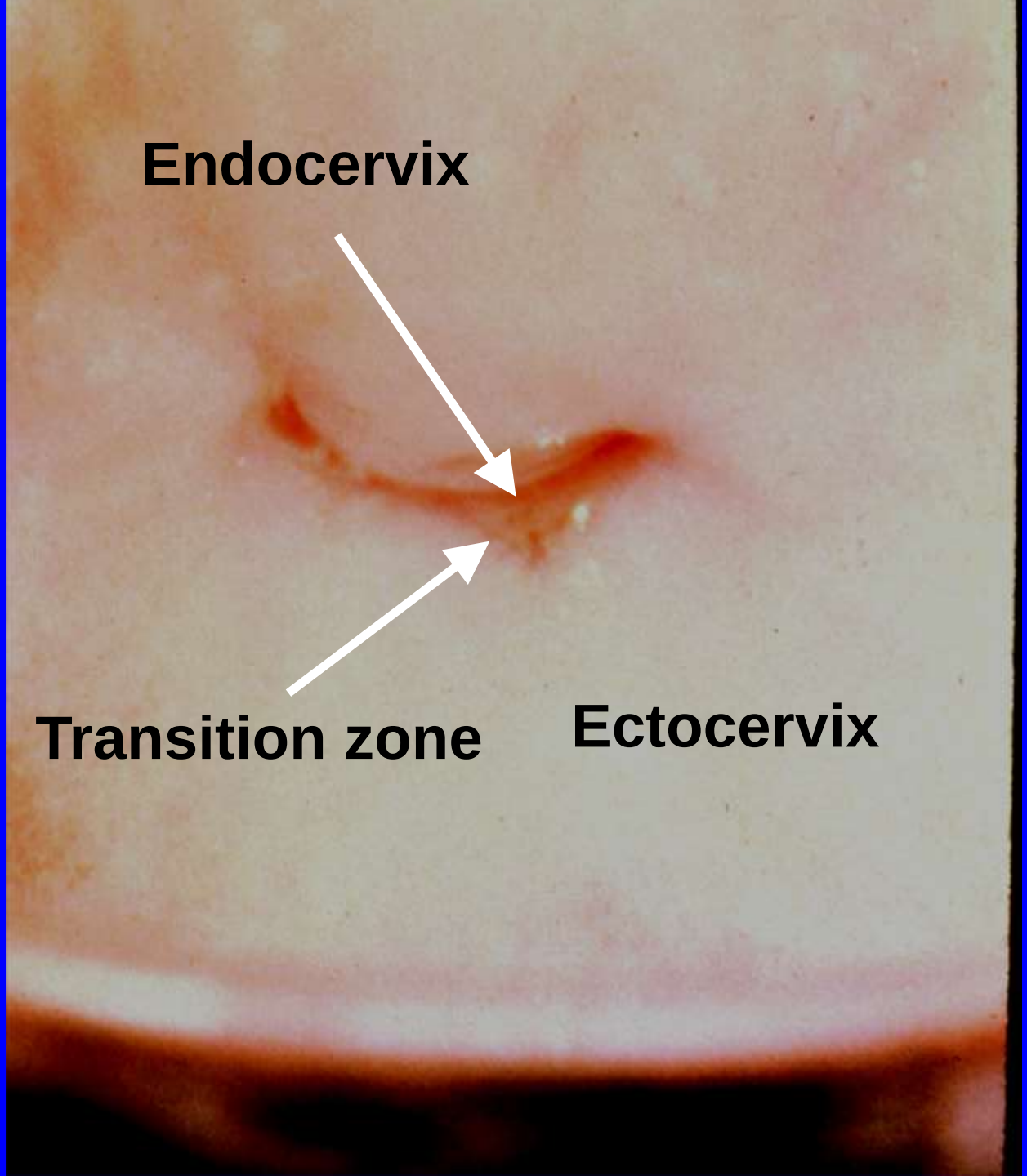
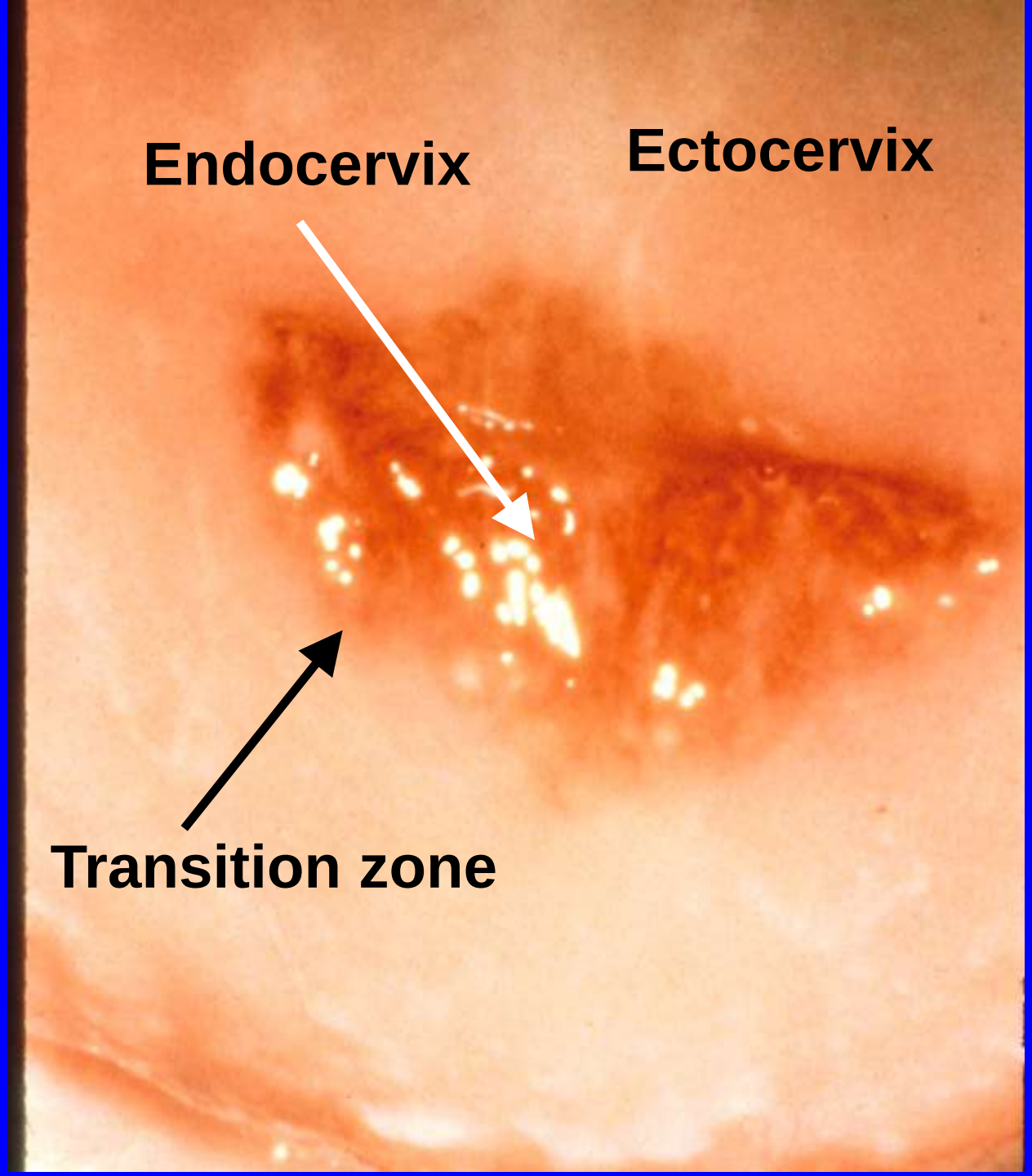
Cervical Anatomy and Terminology

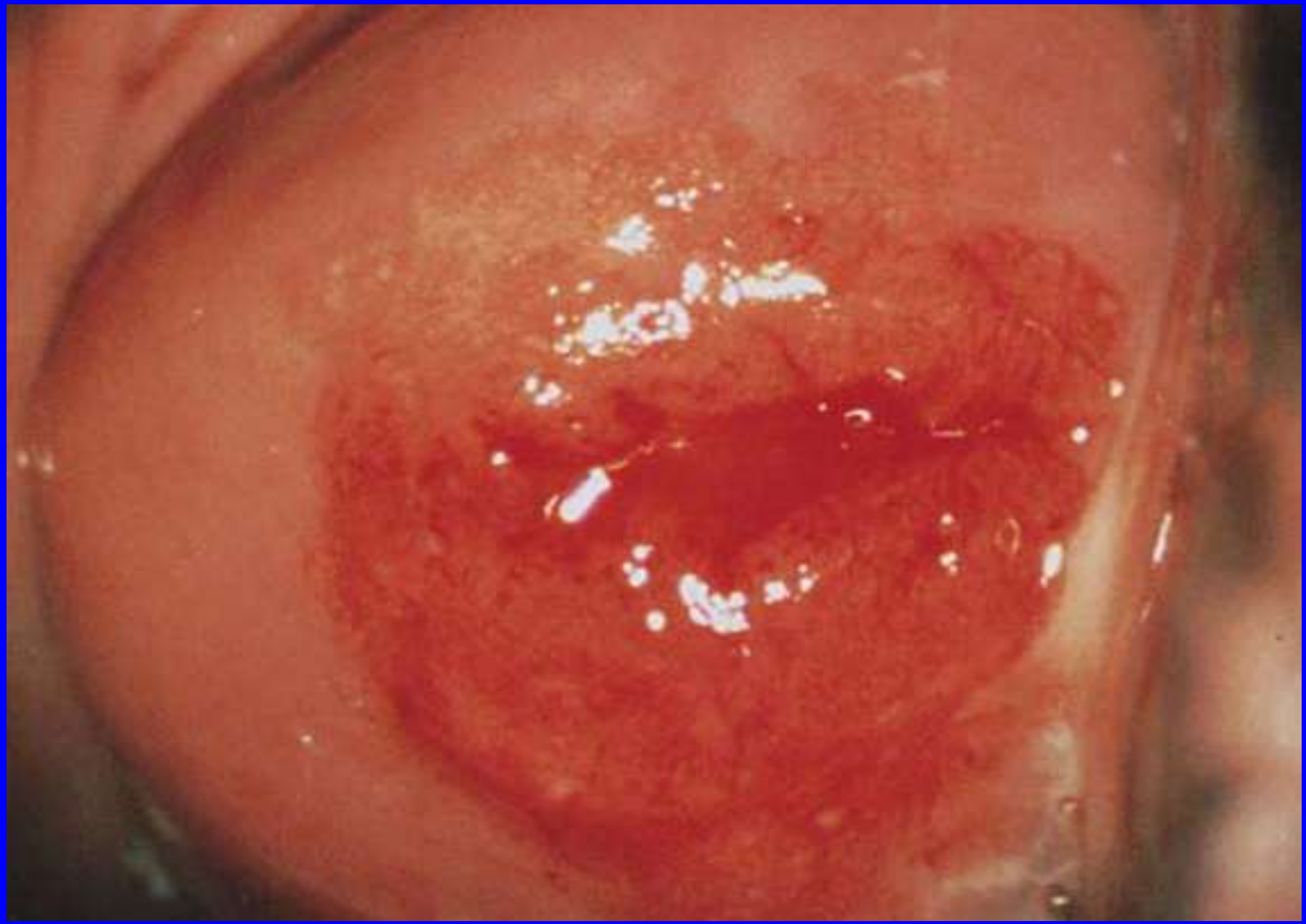
- Ectocervix
- Endocervix

} Transition zone

- Ectopy ("Ectropion", "Erosion")
  - Physiologic ectopy: Migration of endocervical mucosa onto the ectocervix ~menarche
    - Usually regresses age 17-20
    - Can recur during pregnancy or hormonal contraception
    - Probably one reason *C. trachmatis* is so strongly related to young age in women
    - Regression can generate nabothian cysts
  - Pathologic ectopy: Edema due to inflammation (cervicitis) results in eversion ("edematous ectopy")
- Vagina has no mucus-secreting glands; presence of mucus in vaginal secretions denotes cervical origin


Endocervix
Transition zone
Ectocervix


Endocervix
Ectocervix
Transition zone



Symptoms of Cervicitis

- Most cases are subclinical, either truly asymptomic with minor variations in quantity or quality of vaginal secretions
- Increased vaginal discharge
  - Variable color and staining
  - Little or no odor
- Dysuria (actually represents concomitant urethritis)
- Abnormal bleeding
  - Usually scant
  - Often postcoital
  - Occasionally overt menorrhagia, metrorrhagia

Diagnosis of Cervicitis

- Signs: specific, but insensitive. Include:
  - easily induced bleeding (“friability”)
  - mucopurulent discharge: swab test
  - edematous ectopy
  - discrete lesions (ulcers): can occur anywhere

Endocervicitis, Mucopurulent cervicitis (MPC)

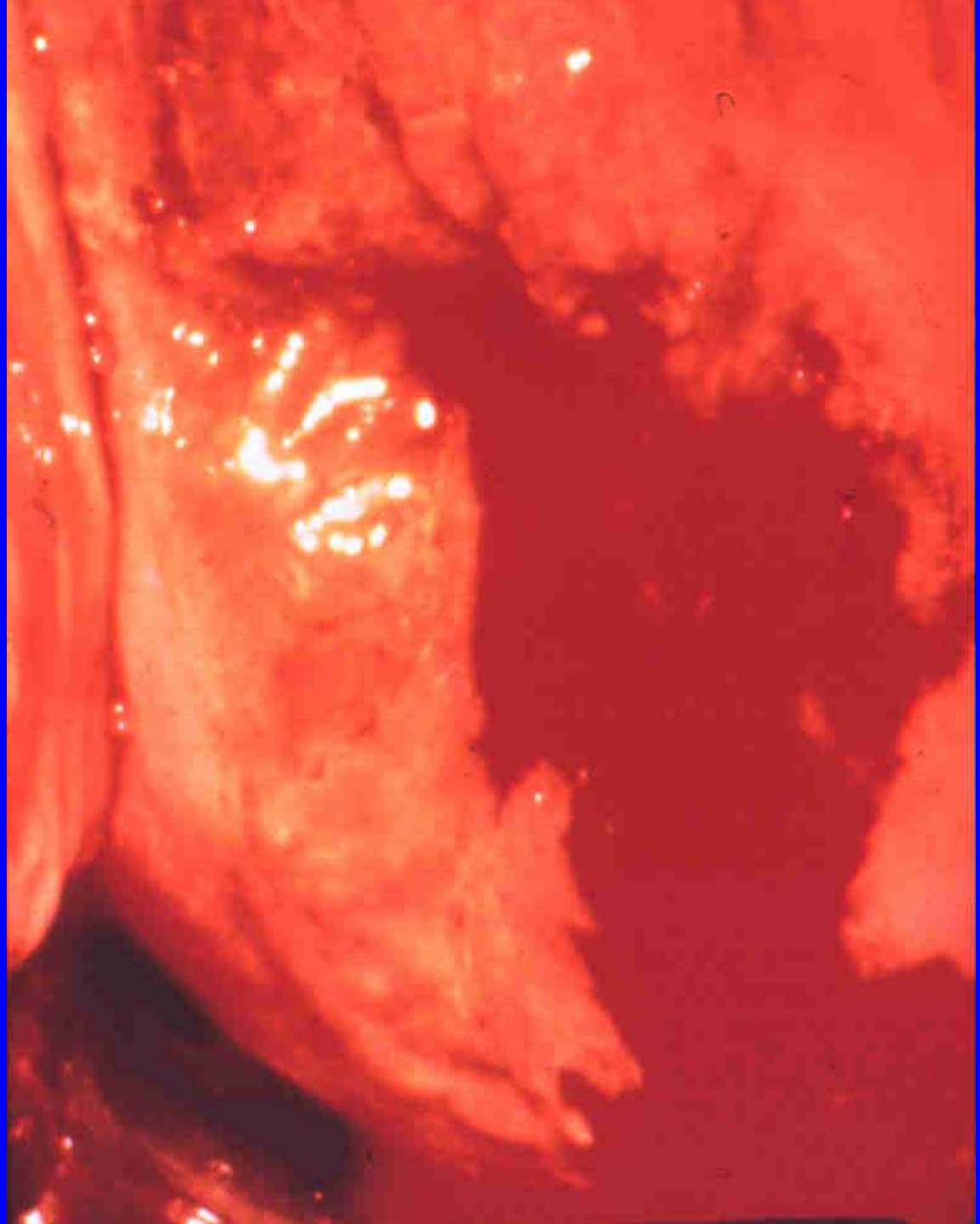
- Increased PMN (“polys;” >10-30/HPF) on Gram stain of endocervical secretions: may be sensitive for endocervicitis, but not specific; variable in ectocervicitis

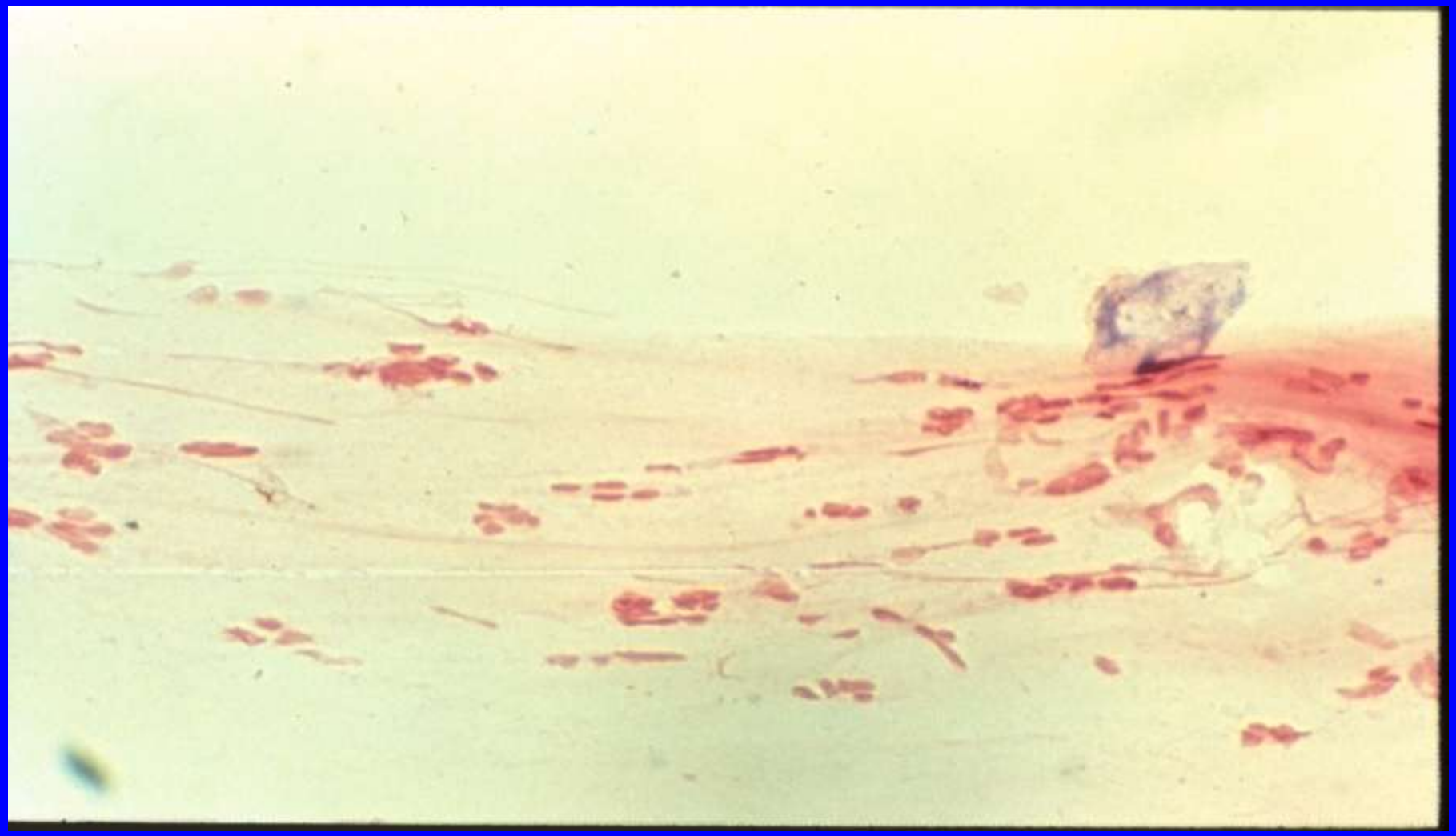
STD as a Cause of Cervicitis

- Endocervicitis (mucopurulent cervicitis, MPC)
  - Gonorrhea
  - Chlamydia

    ~50%
  - *? Mycoplasma genitalium* 10-15%?
  - Other/unknown 40-60%
- Ectocervicitis: often associated with vaginal infection
  - Trichomoniasis
  - *Candida albicans* (probable but infrequent)
  - Bacterial vaginosis (?)
- Discrete lesions
  - Herpes simplex virus (and other ulcerative agents)
  - Syphilis
  - Human papillomavirus
  - Cervical cancer

The Swab Test to Detect Mucopurulent Endocervical Discharge





Neutrophils embedded in cervical mucus

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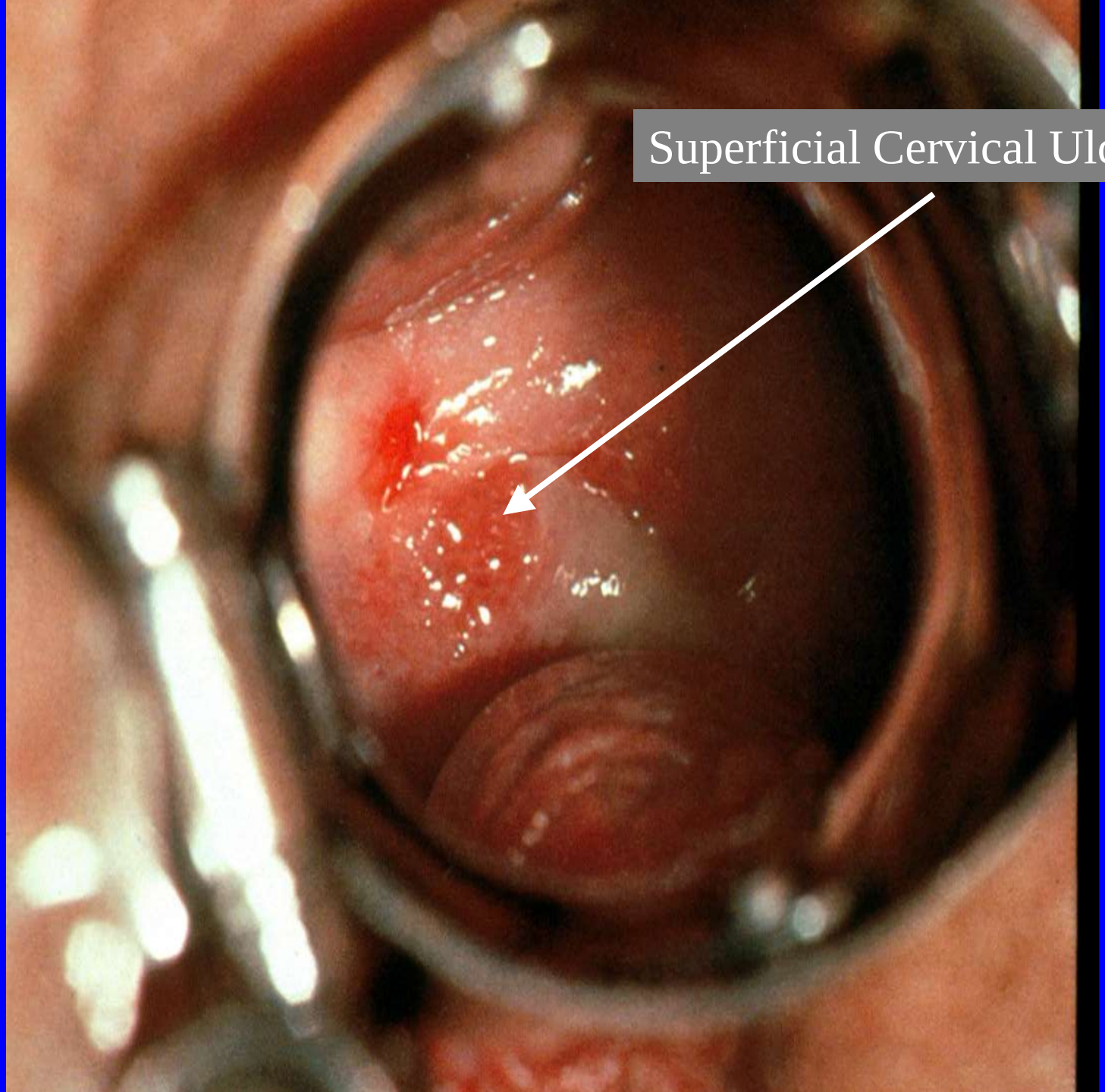

Superficial Cervical Ulcer

Workup of Cervicitis

- Bimanual pelvic examination to rule out PID
- Test for chlamydia and gonorrhea using most sensitive test available
- Careful examination of vaginal fluid, pH
  - Look for BV, trichomoniasis, *Candida*
- Additional diagnostic tests based on clinical judgement (HSV culture, syphilis serology)
- Consideration of STD risk (partner history etc.)

Treatment of Cervicitis

- Treat for gonorrhea and chlamydia, unless either or both has been excluded by specific testing or prior adequate treatment

- Persistent or recurrent cervicitis
  - Azithromycin (*M. genitalium*)
  - Metronidazole (trichomoniasis)

Chronic or Persistent Non-GC, non-CT Mucupurulent Cervicitis

- A very common clinical problem, but no useful data exist on prevalence, incidence, or natural history
- Clinical significance unknown
  - One study suggests adverse pregnancy outcomes (Nugent)
- Re-evaluate at least once for for gonorrhea and chlamydia
- Treat with azithromycin at least once to cover *C. trachomatis* and *M. genitalium*
- Be sure partner treated (azithromycin or doxycycline)
- Ablative therapy (laser or cryotherapy) is often used and is anecdotally successful; no data

Vaginal Infections

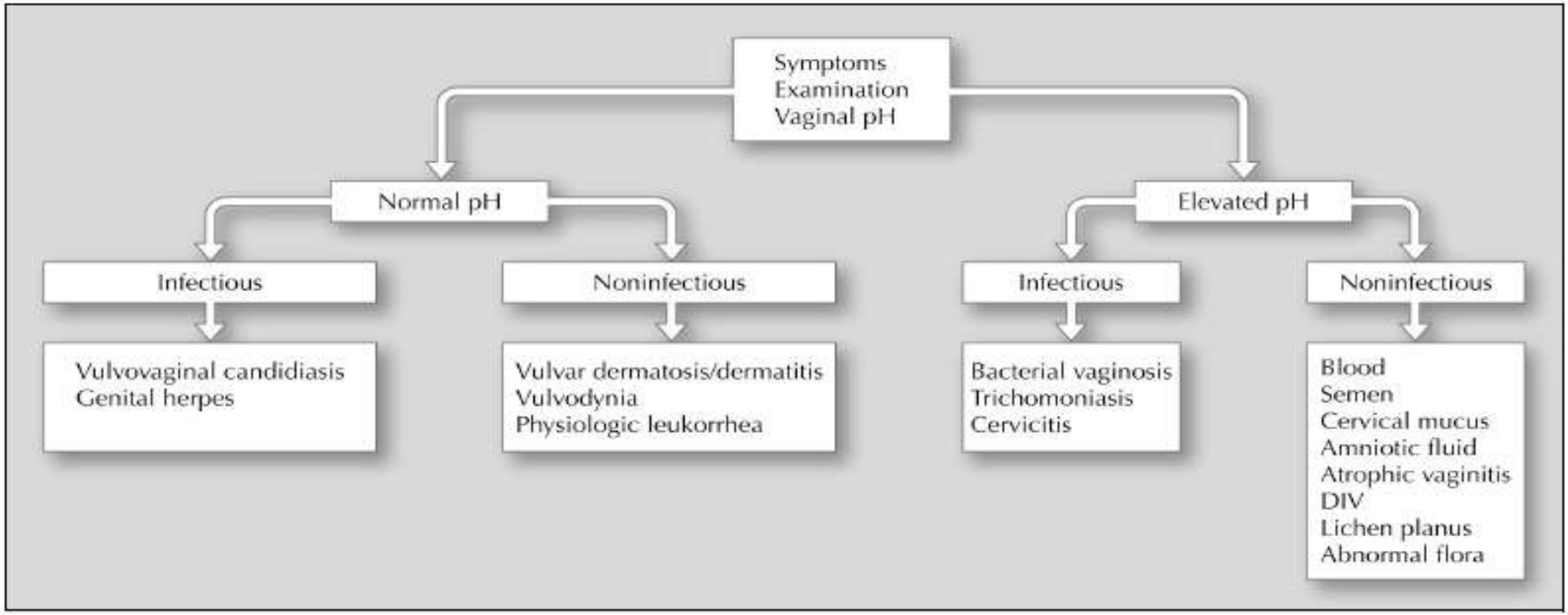
- Trichomoniasis (~10%)
  - *Trichomonas vaginalis* (protozoan)
  - Sexually transmitted
  - Vaginal discharge, odor, elevated pH
- Bacterial vaginosis (~40%)
  - Overgrowth of mostly normal vaginal bacteria; depletion of protective *Lactobacillus*
  - Sexually associated; sexually transmitted in lesbian women
  - Odor, vaginal discharge, elevated pH
- Candida vulvovaginitis (yeast infection, thrush)
  - *Candida albicans, C. glabrata*
  - Intestinal reservoir; not an STD
  - Vulvar itching, irritation; variable discharge; normal pH

Epidemiology of Vaginitis: NHANES, 2001-2002

Koumans 2007, *Sex Transm Dis*
Sutton 2007, *Clin Infect Dis*

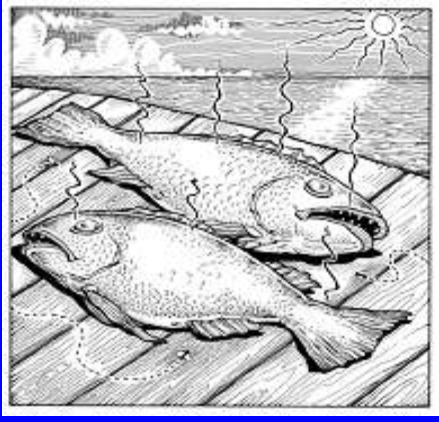
- Population-based survey in U.S.
- Women 14-49 y.o. asked to self-collect vaginal swab
  - 28% reported symptoms
- Swabs used to prepare Gram stain for Nugent scoring and trichomonas culture
- BV prevalence 27.4% in
  - Higher among non-white women, douching, WSW, higher no. lifetime sex partners, smoking
- Trichomoniasis prevalence 3.1% in 1,999 women
  - 13.5% non-Hispanic blacks
  - Only 15% reported symptoms
  - Higher among 30-49 y.o., lower income/education level, higher no. lifetime sex partners, douching

A pH-Based Framework for Evaluating Common Causes of Vaginal Infection



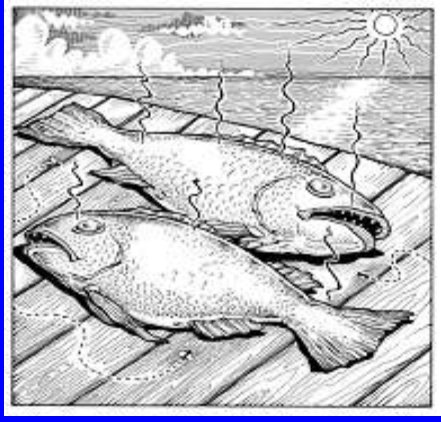
Nyirjesy & Sobel, *Curr ID Reports* 2005

Bacterial Vaginosis
The Basics



- The most common vaginal infection
  - Sexually associated disease (SAD)…
  - but sexual transmission per se remains uncertain
- Symptoms
  - Odor
    - Often spontaneously described as fishy
    - May be prominent after sex
  - Vaginal discharge
    - Usually scant
    - White or gray
    - Non-staining

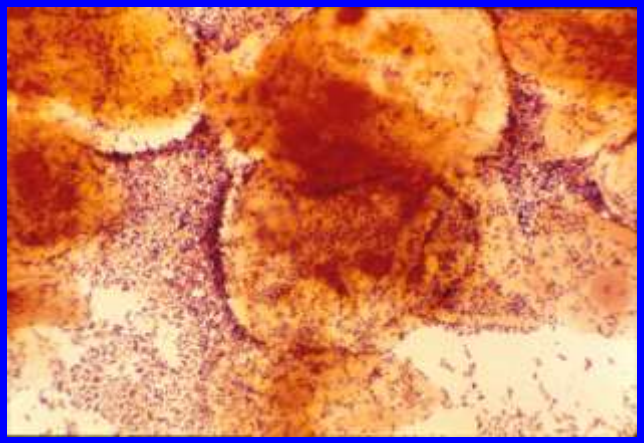
Bacterial Vaginosis
The Basics



- Bacteriology
  - Depletion of H_2O_2 producing *Lactobacillus sp.*
  - Overgrowth of multiple components of normal flora
    - Anaerobes
    - *Gardnerella vaginalis*
  - Novel, non-cultured “BV associated bacteria” (BVAB)
- Main diagnostic findings
  - pH >4.5
  - Amines, voltalized by alkalinization (KOH/sniff test; semen)
    - Direct effects of anaerobes’ glycosidase activity & metabolism
    - Putrescine, cadaverine
  - Microscopy
    - Clue cells
    - Altered bacterial flora

The Vaginal Milieu in Bacterial Vaginosis

Nugent = 0



Nugent = 10

- Profound loss of H_2O_2 - producing *Lactobacilli*
- Overgrowth of “commensal” anaerobes
- Production of sialidase (IgA destruction), glycosidase, volatile amines
- ↑ Il-1B, IL-10; ↓ IL-8, SLPI (secretory leukocyte protease inhibitor)

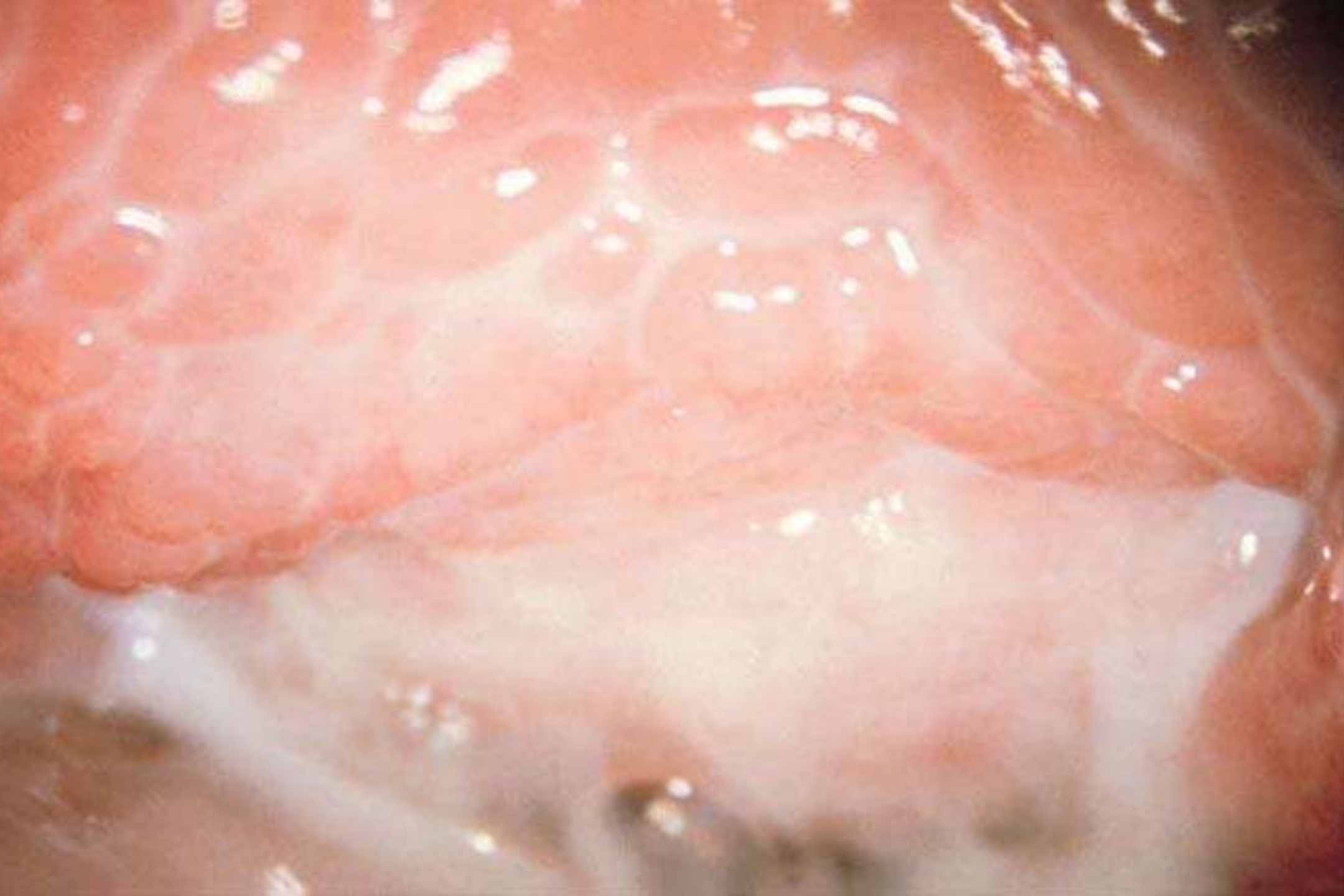
Cauci 2004; Cherpes 2008

BV: an STI?

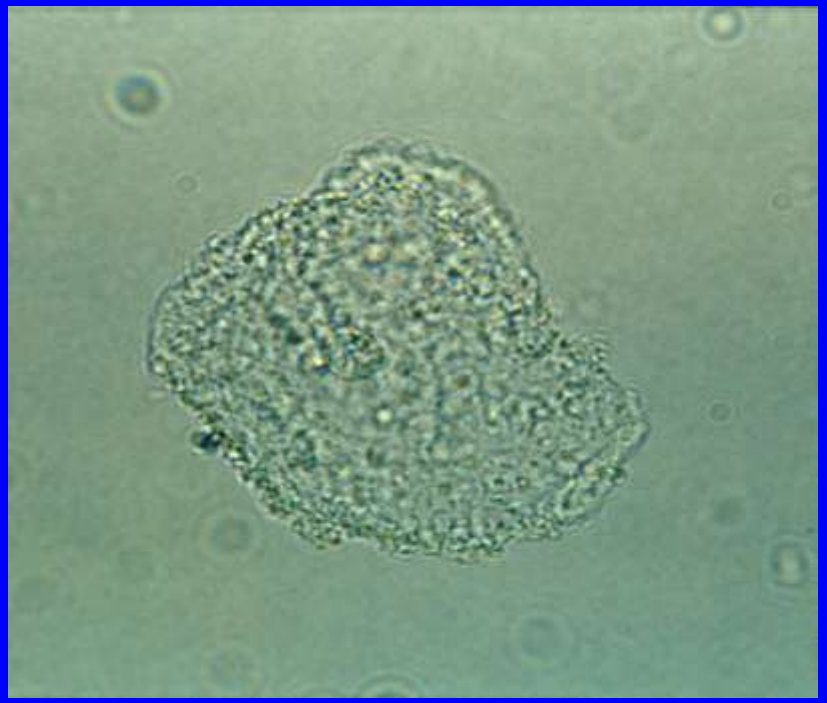
Yes	No
• Increasing no. sex partners and other epidemiologic markers of STI risk • Concordance within female sex partnerships (shared vaginal secretions?) • Rare in women with no/little sexual experience • BVAB detected in male genital tract • Protective effect of condoms	• Incident BV occurs in sexually experienced but abstinent women • Seemingly random varation in BV symptoms and Nugent scores in untreated women • Prevalence in some populations seems too high • Treatment of male partners has not improved BV-related outcomes ▪ Suboptimal regimens?

Diagnosis of BV

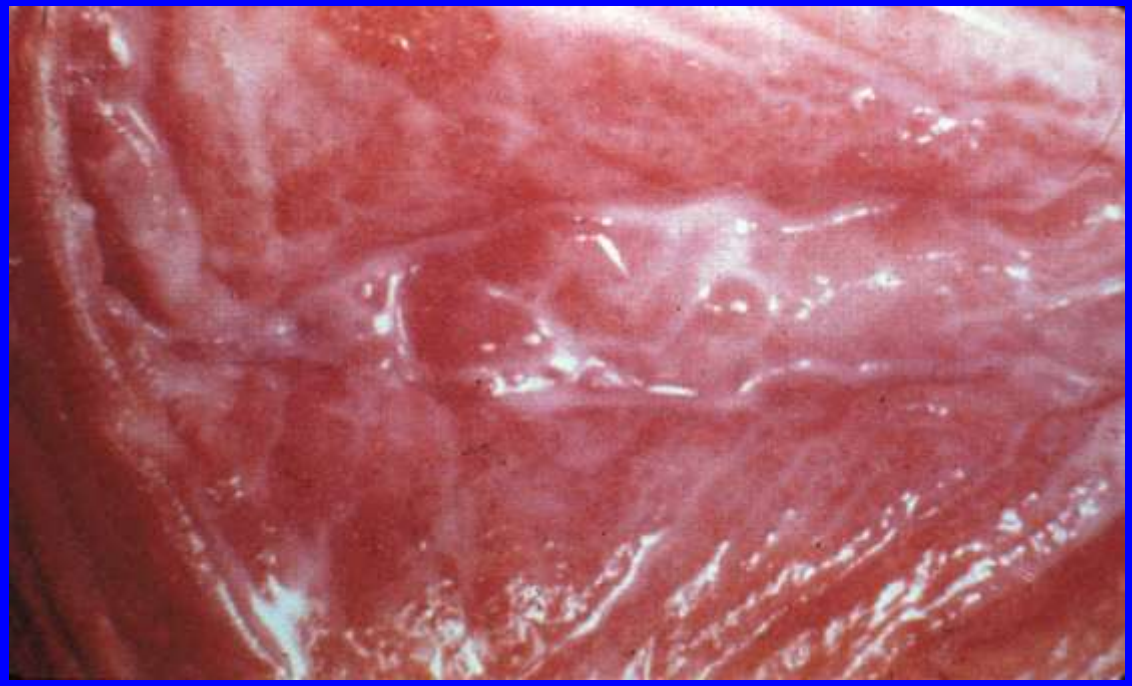
- Clinical findings (Amsel criteria): ≥3 of the following:
  - Homogeneous discharge, smoothly coating vaginal walls and introitus
  - pH >4.5
  - Clue cells (>20%) on saline microscopy
  - Amine odor on addition of KOH (+whiff test)
    - Putrescine, cadaverine
    - BV Blue® test: uncertain clinical utility
- Gram stain findings (Nugent scale)
  - Based on number of lactobacilli and other bacterial morphotypes
  - 0-9 scale: 0-3 normal, 4-6 borderline, 7-9 definite BV
  - Primarily research, but clinically useful in trained hands



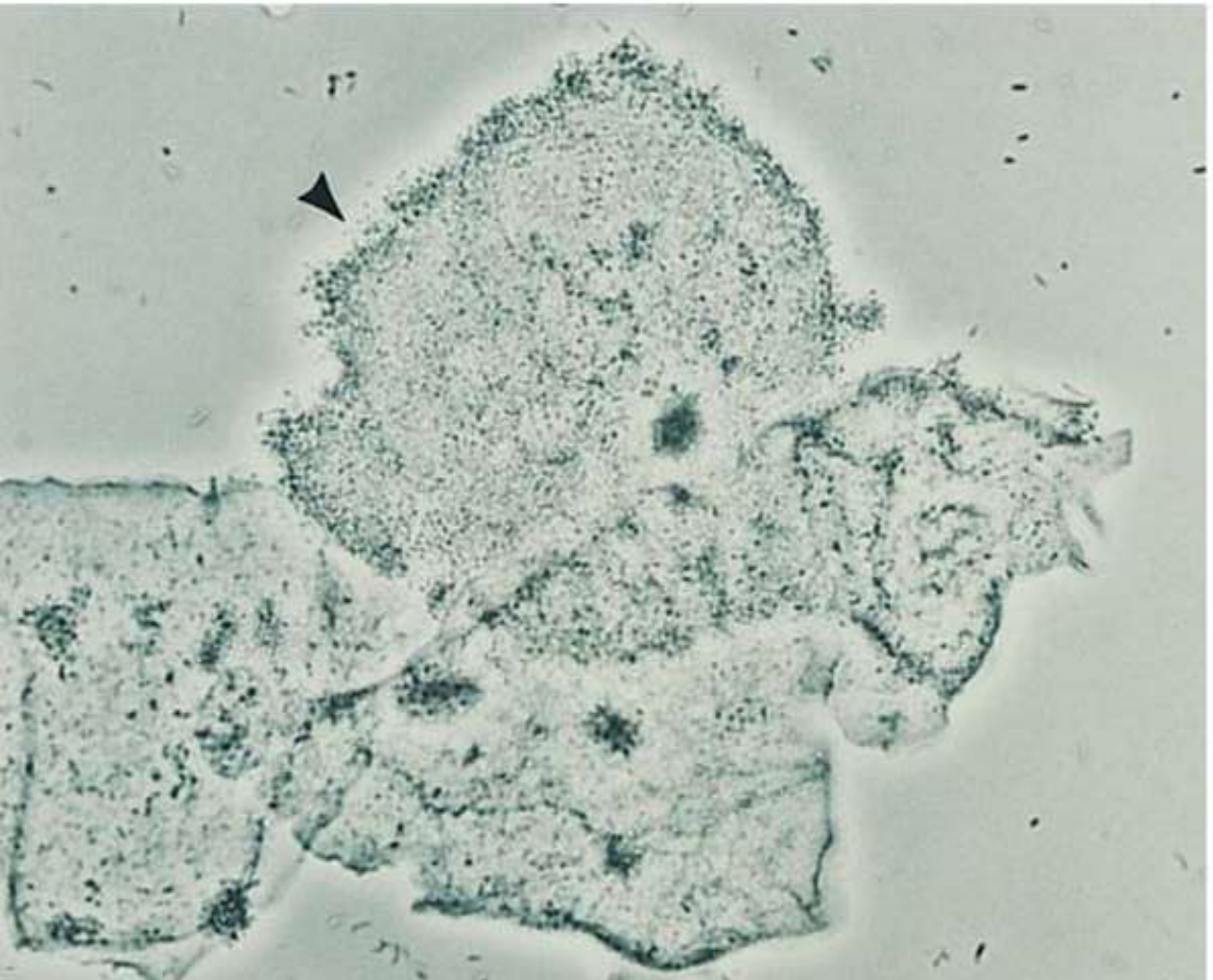
Bacterial Vaginosis

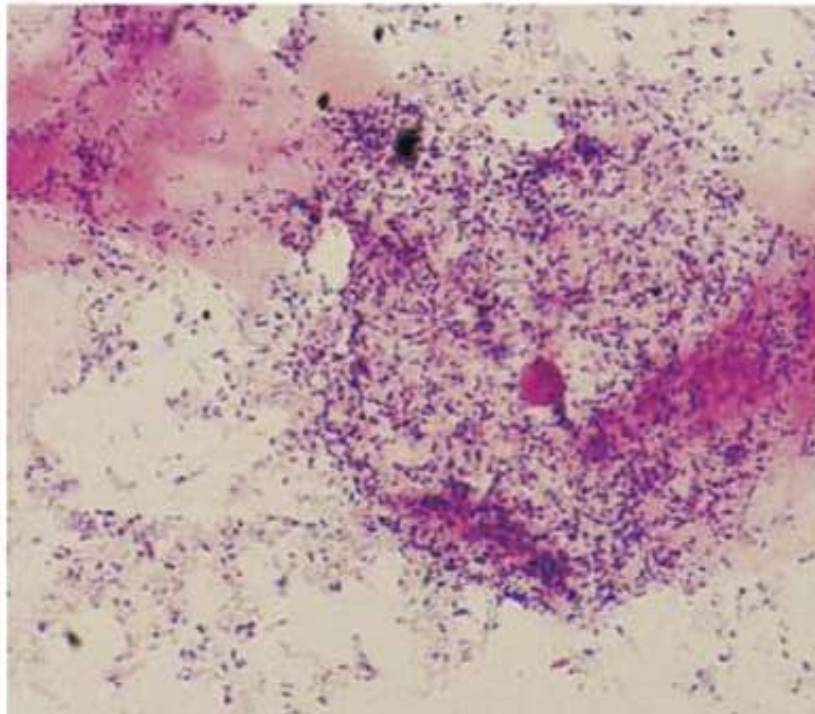


Wet Prep:
Clue Cell



Vaginal
Discharge





Complications Associated with BV

- Pelvic inflammatory disease
- Post-hysterectomy infection
- Pregnancy related complications
  - Postpartum endometritis
  - Postabortal endometritis and PID
  - Preterm labor and delivery
  - Premature rupture of membranes
  - Intra-amniotic infection
    - Histological chorioamnionitis
  - Spontaneous abortion in first trimester (IVF)

Treatment of Bacterial Vaginosis (CDC)

Nonpregnant Women

- Recommended
  - Metronidazole 500 mg PO bid x 7 d
  - Metronidazole gel 0.75% intravag qHS x 5 d
  - Clindamycin cream 2% intravag qHS x 7 d
- Alternatives
  - Clindamycin 300 mg PO bid x 7 d
  - Clindamycin ovules 100 g intravag qHS x 3 d

Treatment of Bacterial Vaginosis (CDC)

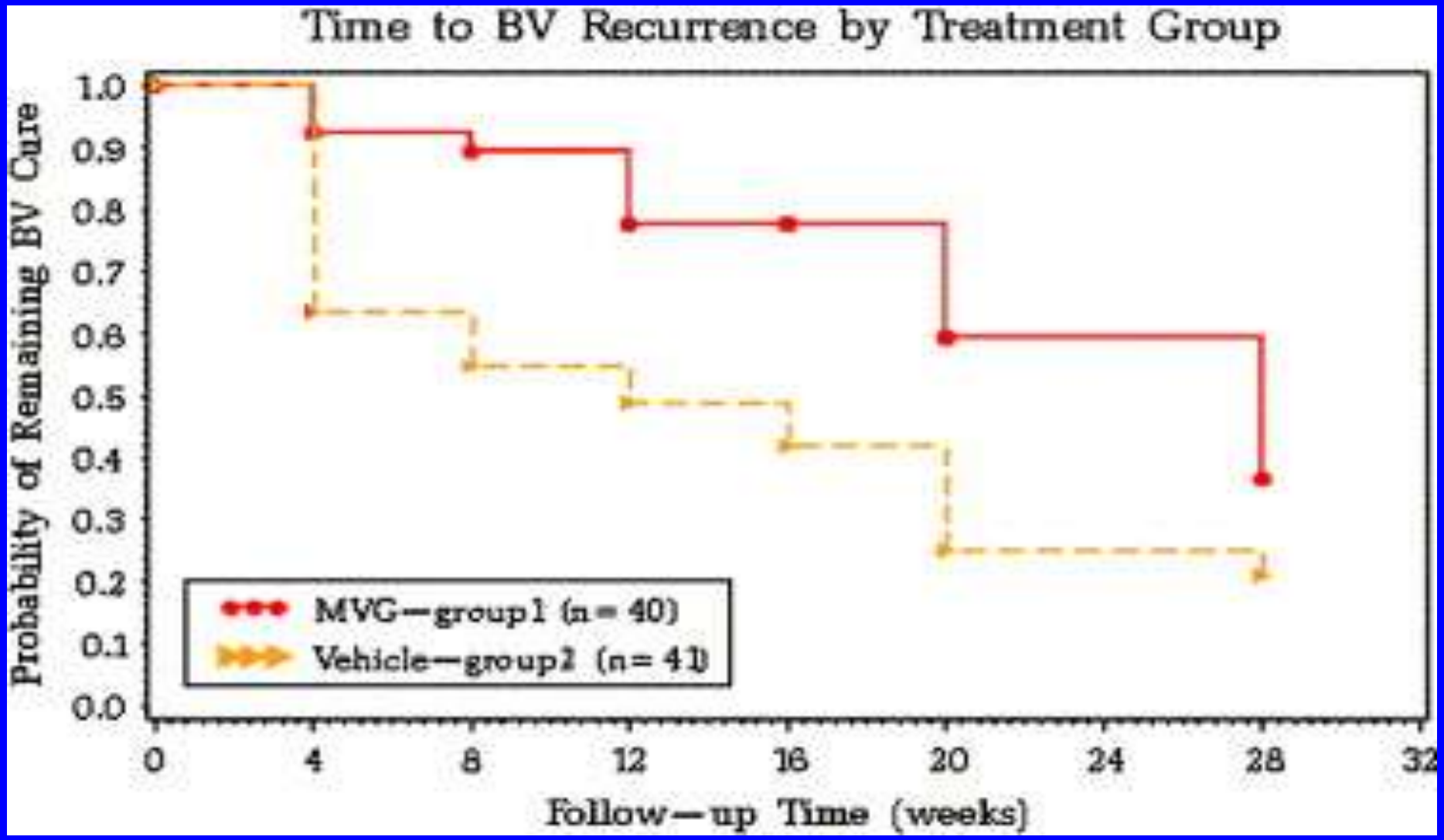
Pregnant Women

Systemic therapy preferred, especially for women at high risk for preterm delivery:

- Metronidazole 250 mg PO tid x 7 d
- Metronidazole 500 mg bid x 7 d
- Clindamycin 300 mg PO bid x 7 d

Time to BV Recurrence (ITT), Biweekly MTZ Gel vs. Placebo

Sobel
AJOG
2006

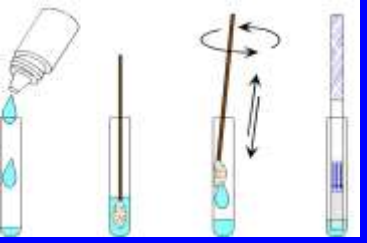


Recurrent BV: Management

- More antibiotic is better: higher cumulative doses (longer therapy, 10-14 days) most effective
  - Mechanism unclear: suppression of overall anaerobic overgrowth allowing for recovery of adequate *Lactobacillus* population, or as yet undefined pathogen
  - Emerging data also support better response of initial BV with higher vaginal doses of MTZ (Sanchez 2004)
- Prevent sexual transmission (condoms, no shared toys): Alkaline pH of sperm (7.5) vs. reinfection? (Trabert 2007; Sanchez 2004)
- Repletion of vaginal lactobacilli
  - Capsules containing human *L. crispatus*
  - First attempted product not effective; second under study
  - Over the counter and yogurt strains don't work

Trichomoniasis: The Basics

- Etiology: *Trichomonas vaginalis*
- Sexually transmitted
  ? colonic reservoir
- Mostly asymptomatic
- Male partners generally asymptomatic; sometimes NGU
- Saline mount insensitive (~50-60%)
  Culture ~70%; PCR requried to detect >90% of cases
- Male partners generally asymptomatic; sometimes NGU



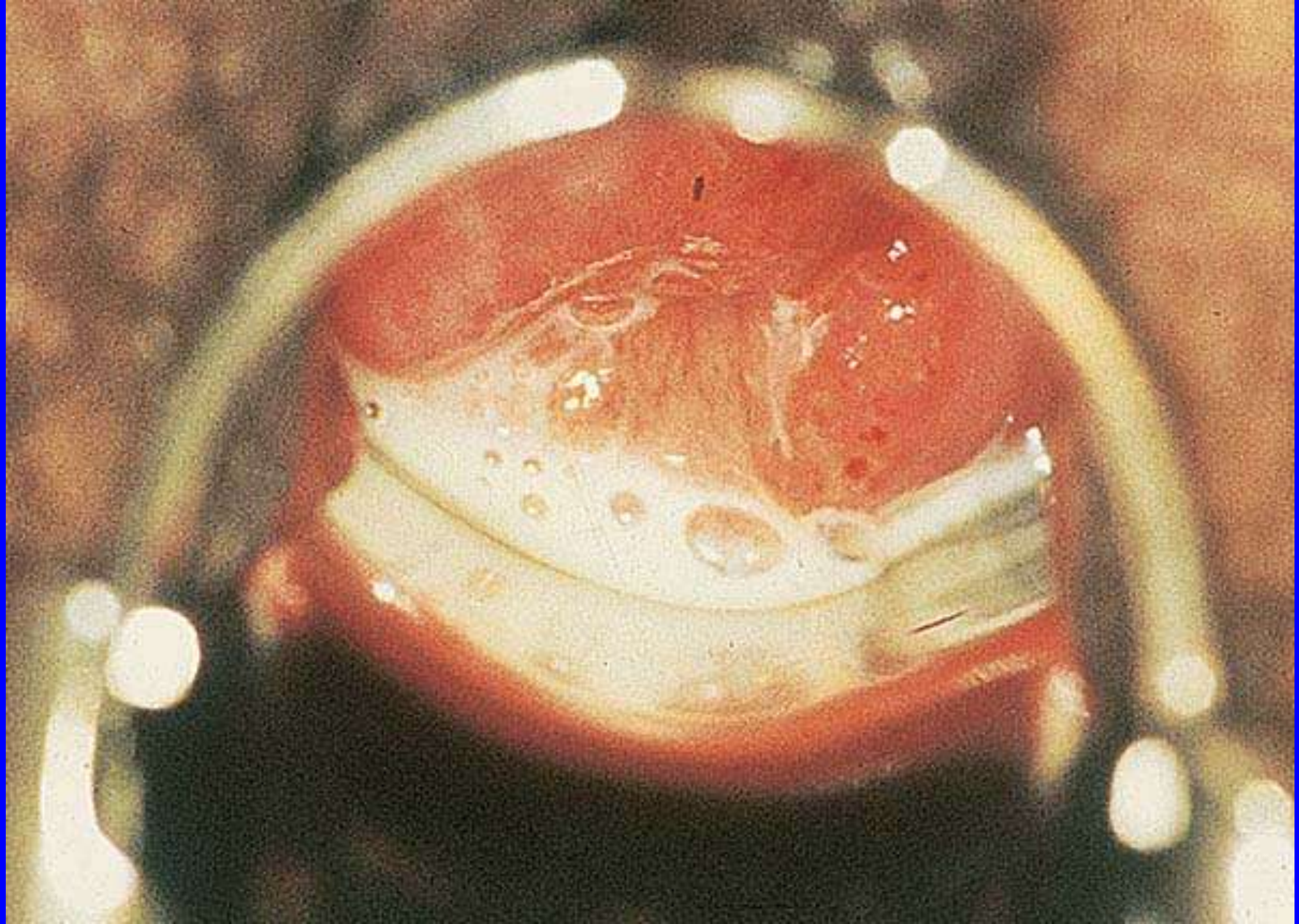
New Testing Options for Trich

- Rapid antigen test (OSOM; Genzyme)
  - Significantly better than wet mount (P = 0.004) (Huppert 2005)

Test	Sensitivity	Specificity
OSOM	83.3%	98.8%
Wet prep	71.4%	100%

- APTIMA TMA Trichomonas Vaginalis Analyte Specific Reagent (ASR; Gen-Probe)
  - Nucleic Acid Amplification Test
  - Utilizes same technology as APTIMA Combo 2 (for CT/GC)
  - May use same specimen type as used with APTIMA Combo 2 (i.e.vaginal swab, endocervical swab, urine)

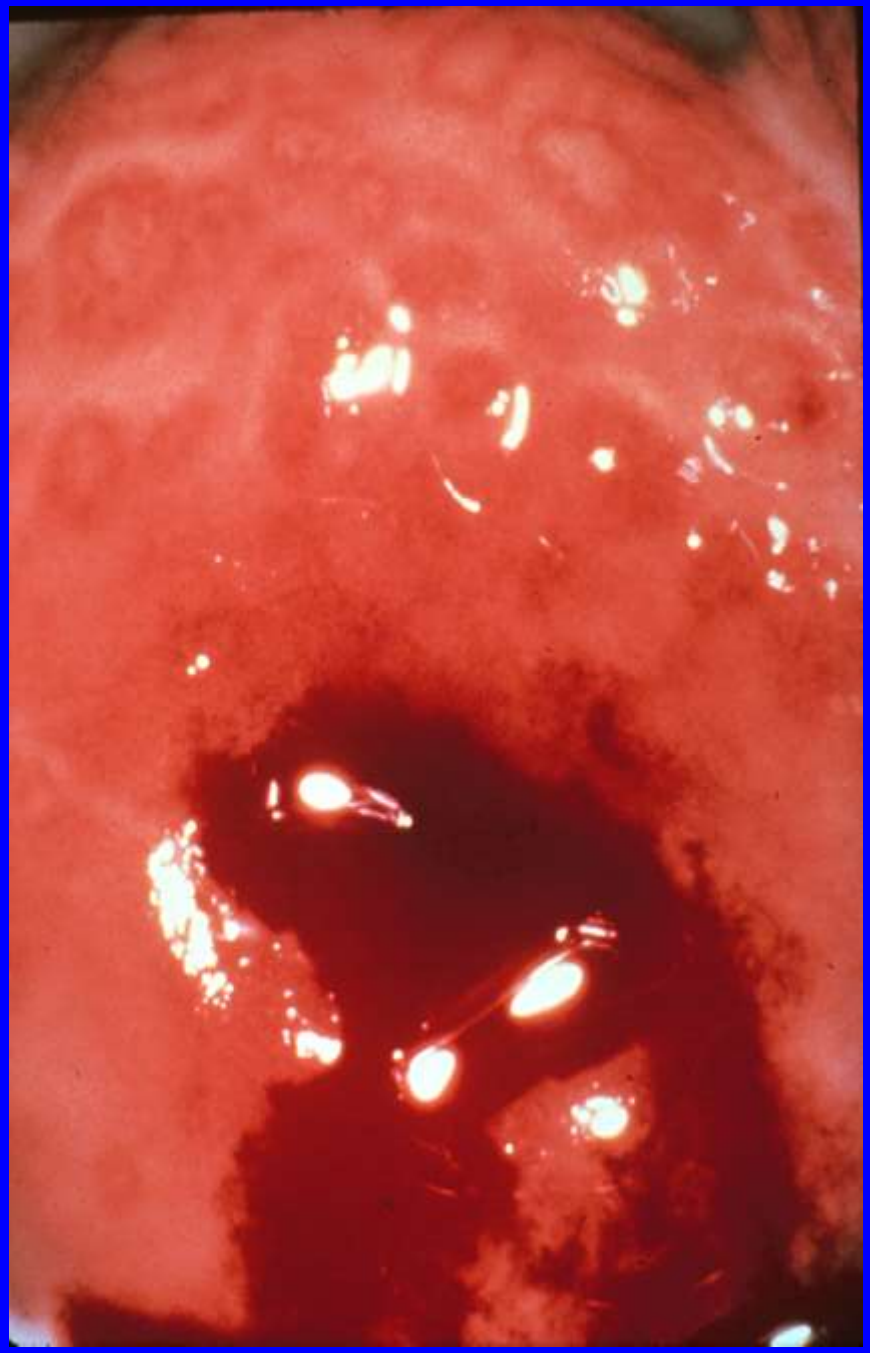
Trichomoniasis: Vaginal discharge



The Cervix and Trichomoniasis

- Classic: “strawberry cervix”
  - Focal areas of superficial hemorrhage surrounded by paler mucosa
  - May also see more subtle petechiae
  - More common with relatively moderate-severe *Trichomonas* vaginitis

Cervicitis due to *Trichomonas vaginalis*



Trichomoniasis Treatment

Recommended regimen

- Metronidazole 2 g PO x 1
- Tinidazole 2 g po x 1

Alternative regimen

- Metronidazole 500 mg PO BID x 7d
- Routine use for recurrent/persistent cases

- Metronidazole is safe at all stages of pregnancy
- Tinidazole Category C (don't use)
- Vaginal therapy is ineffective
- Treat sex partner(s)

Vulvovaginal Candidasis: The Basics

- *Candida albicans* >90% (others <10%, esp. *C. glabrata)*
  - Normal vaginal flora
  - Colonic reservoir
- Not sexually transmitted, although male partners sometimes get superficial balanitis, especially in uncircumcised
- Diagnosis: Clinical appearance, low pH, no odor, microscopy

Vulvovaginal Candidiasis

- Vulvar component often dominant
- Most cases still caused by *C. albicans* (>90%)
- Women are often misdiagnosed as having VVC when they really have
  - Genital herpes
  - Lichen planus
  - Recurrent BV
  - Contact dermatitis
  - Atrophic vaginitis
- Uncomplicated VVC defined by all 4:
  - Sporadic
  - Mild-moderate severity
  - Likely to be *Candida albicans*
  - Non-immunocompromised host

Sobel JD, *Lancet* 2007

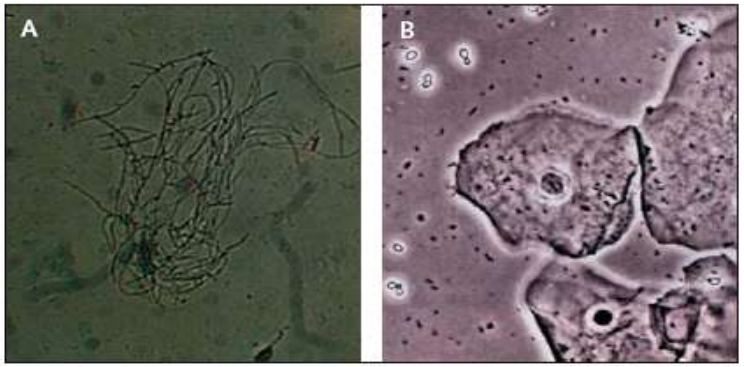
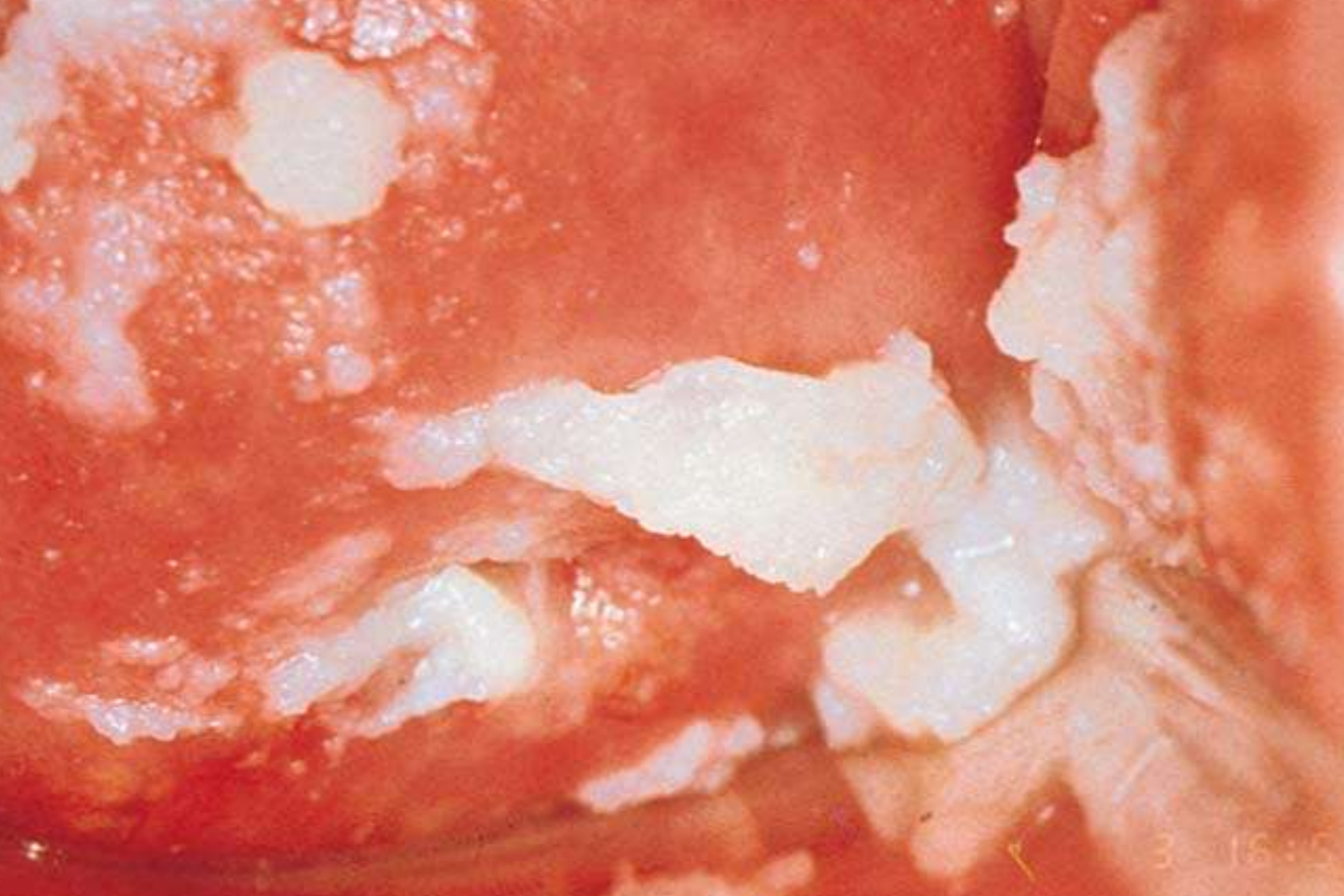
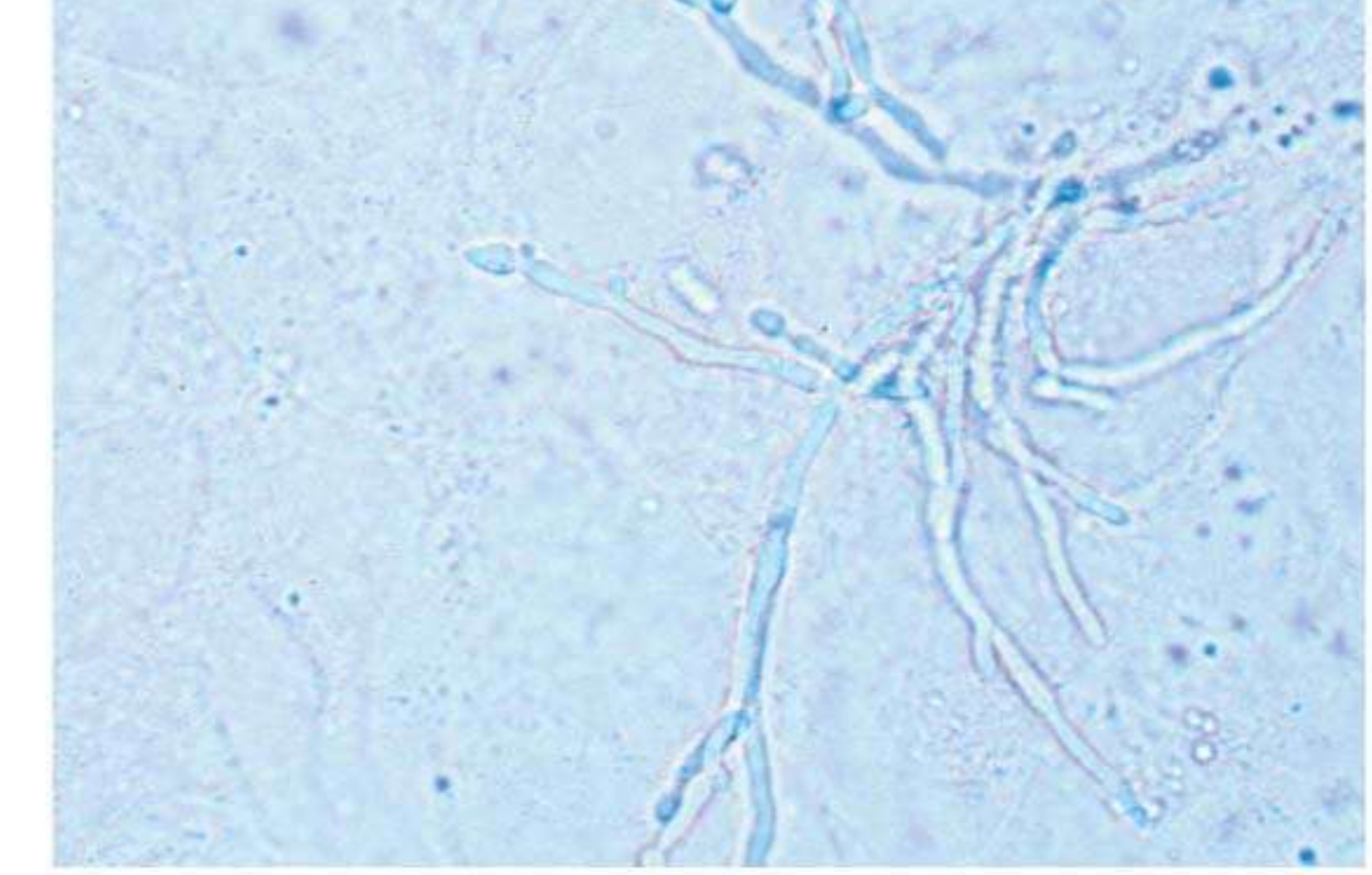


Figure 2: **Wet-mount examination of vaginal discharge from a woman with vulvovaginal candidosis**
(A) *C albicans* hyphae, 10× magnification. (B) Budding *C glabrata*, 40× magnification.

Diagnosis of VVC

- Clinical appearance and symptoms
  - Typically prominent irritative symptoms
  - Minimal discharge
- Laboratory
  - pH <4.5
  - Negative amine odor
  - Microscopy (KOH preparation, Gram stain)
  - Isolation of *Candida* species usually not helpful
    - Nonspecific owing to asymptomatic carriage by most women some of the time and some women all of the time
    - *C. albicans* is normal vaginal flora





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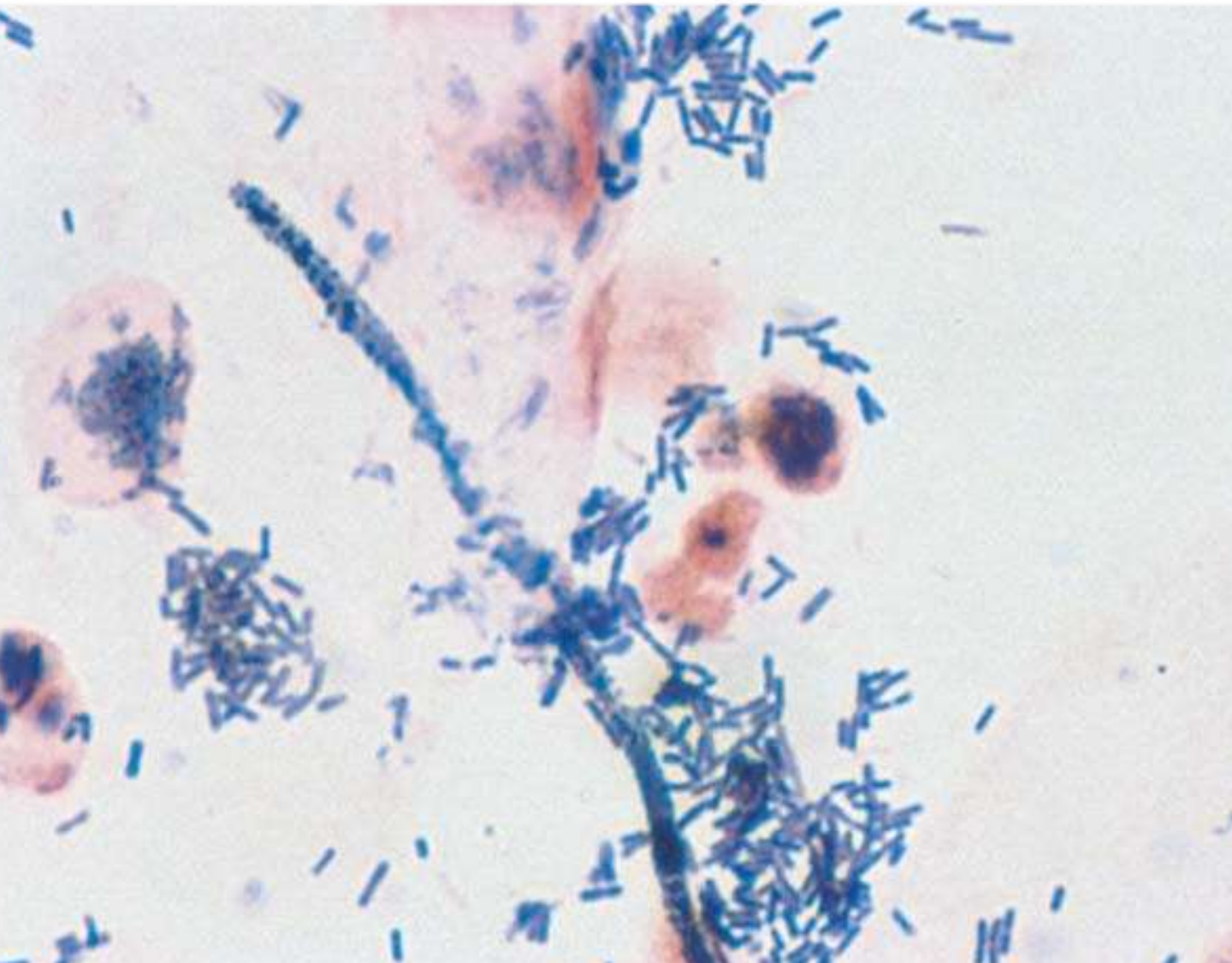
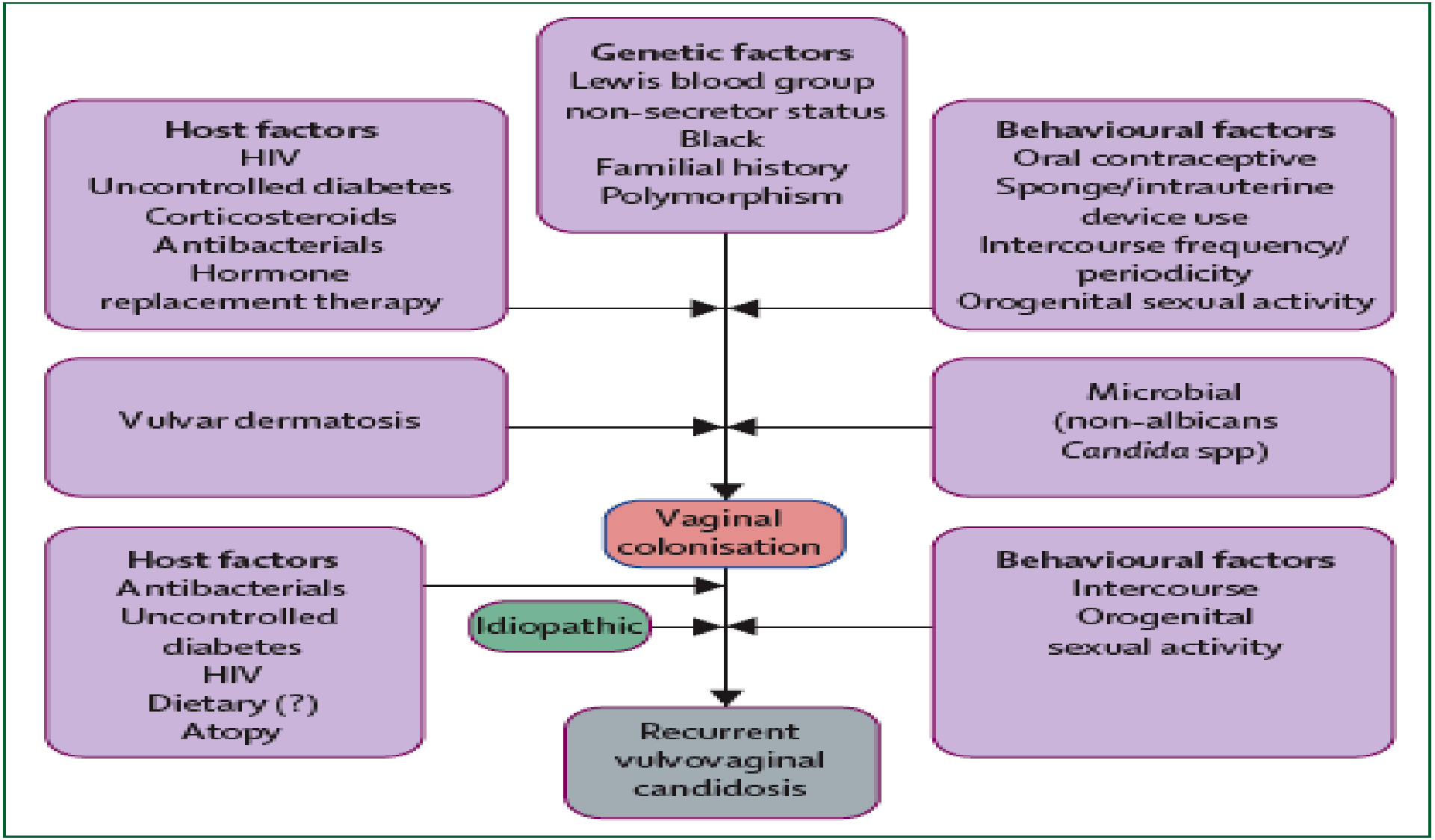


VVC Treatment Regimens

Vulvovaginal candidiasis, uncomplicated			
Intravaginal therapy¶	2% Butoconazole cream (Mycelex-3)	5 g per day for 3 days††	$$
	2% Sustained-release butoconazole cream (Gynazole)	One 5-g dose	$$$
	1% Clotrimazole cream (Mycelex-7)	5 g for 7–14 days††	$
	Clotrimazole (Gyne-Lotrimin 3)	Two 100-mg vaginal tablets per day for 3 days	$
		One 100-mg vaginal tablet per day for 7 days	$
	2% Miconazole cream	5 g per day for 7 days††	$$
	Miconazole (Monistat-7)	One 100-mg vaginal suppository per day for 7 days††	$$
	Miconazole (Monistat-3)	One 200-mg vaginal suppository per day for 3 days††	$$
	Miconazole (Monistat-1 vaginal ovule)	One 1200-mg vaginal suppository††	$
	6.5% Tioconazole ointment (Monistat 1-day)	One 5-g dose††	$
	0.4% Terconazole cream (Terazol 7)	5 g per day for 7 days	$$$
	0.8% Terconazole cream (Terazol 3)	5 g per day for 3 days	$$
	Terconazole vaginal	One 80-mg vaginal suppository per day for 3 days	$$$
	Nystatin vaginal	One 100,000-U vaginal tablet per day for 14 days	$$$
Oral therapy	Fluconazole (Diflucan)	One 150-mg dose orally	$
Vulvovaginal candidiasis, complicated‡‡			
Intravaginal therapy¶	Azole	7–14 days	$$
Oral therapy§§	Fluconazole (Diflucan)	Two 150-mg doses orally 72 hr apart	$$$

Risk Factors for Recurrent VVC

Sobel JD, *Lancet* 2007



Maintenance Therapy For Recurrent VVC

- Most recurrent yeast vaginitis caused by sensitive yeast, but high persistence of vaginal yeast following therapy anyway (about 50%)
- Goal of antifungal maintenance therapy:
  - Suppress vaginal colonization
  - Allow inflamed epithelium opportunity to heal
- Induction therapy with either
  - Vaginal imidazole daily x 14 days
  - Fluconazole 150 mg days 1 and 4 x 2 weeks
- Maintenance therapy with either
  - Fluconazole 100-150 mg PO weekly
  - Clotrimazole 500 mg intravaginally weekly
- Low-potency topical steroids for severe vulvitis; nystatin cream, sitz baths

Non-albicans Candidiasis

- Primarily *Candida glabrata*
- Most have higher MIC to azoles, but still clinically susceptible
- Clinical failures with *C. glabrata* often require >1 dose treatment
- Azole failure may respond to topical boric acid (600 mg in gelatin capsules daily 14 d), nystatin, or flucytosine
  - Recurrence may be controlled by alternate day then twice weekly boric acid
- No routine indication for susceptibility testing in uncomplicated VVC

Desquamative Interstitial Vaginitis (DIV)

- A presumably uncommon condition characterized by:
  - Chronic purulent vaginal exudate, often yellow-green
  - Occasional vestibulitis, diffuse vaginal erythema focal erosions
  - Elevated pH (>4.5, often ~6), no amine odor, many WBC on saline
  - Presence of Gram+ cocci (often Group B strep) on Gram stain, few lactobacilli, increased parabasal cells
- Typically older (peri or post-menopause) patients with lower STD prevalence
- Treat with 2% clindamycin cream x 14 days OR 10% hydrocortisone cream, 5 g x 14 days (probably longer)

Newbern, Ann Epidemiol 2002;12:346-52

And if there is no STI?

Process	Comments
Persistent disruptions of vaginal flora	Mechanism unclear, but may involve effect of glycosidases produced by bacteria associated with BV Treatment of BV associated with enhanced resolution of MPC in one small study
Persistent infection with an undefined pathogen	No direct research in MPC yet, but use of cultivation-independent molecular techniques is rapidly expanding the spectrum of bacteria associated with BV, including *Atopobium vaginalis*
Sustained primary host immune response	Genital mucosa affected in many diseases with immune basis, including psoriasis, Behcet's syndrome May be augmented further by effect of endogenous or exogenous sex hormones
Sustained use of commercial products that disrupt or irritate cervicovaginal mucosa	Many over-the-counter products contain surfactants or other potentially irritating substances (betadine, corn starch, topical anesthetics)

The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL PRACTICE

Acute Vulvovaginitis

Linda O. Eckert, M.D.

This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

A 24-year-old sexually active woman presents with a 3-day history of vaginal pruritus and increased vaginal discharge. One year before presentation, she had the same symptoms, which resolved with use of an over-the-counter antifungal agent. She uses oral contraceptives for birth control. The physical examination reveals vulvar erythema and normal-appearing vaginal discharge. How should she be evaluated and treated?

Eckert, October 2006