Vulvovaginal Contact Dermatitis: why Biofilm matters

Paul Summers, M.D.

Department of Obstetrics and Gynecology
University of Utah School of Medicine
Today’s Contact Dermatitis Message

Characterized by itching, burning or pain without visible changes unless scratching or secondarily infected with staph, strep, or yeast

Treatment with non irritating moisturizer and non irritating steroid moderates infection and cancer risk

Chronicity of symptoms and failed treatment are related in part to biofilm formation

Over time, activation of nerve growth factor as part of the inflammatory process results in an increased population of nerve endings
Biofilm

- A high population of microbes that adhere to the skin surface

- Microbes join together in a mutually supportive cluster

- A polysaccharide matrix coating is produced, restricting the entry of antibiotics

- Substances that impede local immune defenses are produced
Clue Cells

Biofilm is visible on the cell cytoplasm

Lactobacilli disappear if the mucus is disrupted

No Mucus
No Lactobacilli
Normal flora, lactobacilli

No biofilm
Vulvovaginal contact dermatitis causes the skin to flake (scale formation).

Flaking skin exposes fibronectin, allowing yeast and staph aureus adherence, with risk of biofilm formation.

* Some lactobacilli, mucus present
Vulvovaginal Levels of Defense

1. Vulvar and vaginal pH around 4.5

2. Lactobacillus and other commensals

3. Mucus (biofilm prevention)

4. Innate Immunity, antimicrobial peptides (AMPs)

5. Skin Barrier

6. Cell Mediated Immunity
Levels of Defense

1. Vulvar and vaginal pH around 4.5

2. Lactobacillus and other commensals

Concepts originating in the 1920’s and 1930’s are still presented as fact in our GYN textbooks

No understanding in the 1920’s of mucosal immune defenses

No understanding in the 1920’s of microbial pathologic mechanisms
Levels of Defense

Mainly research in the last 2 or 3 decades
NOT currently addressed in Gynecology Textbooks

3. Mucus (biofilm prevention)

4. Innate Immunity, antimicrobial peptides (AMPs)

5. Skin Barrier

6. Cell Mediated Immunity
2,423 pages
4 paragraphs mention lactobacilli
No mention of pH
References are mainly from the last two decades
Contact Dermatitis Compromises all Levels of Defense

1. Vulvar and vaginal pH rise

2. Lactobacillus and other commensals?

3. Mucus penetration (biofilm risk)

4. Innate Immunity, antimicrobial peptides (AMPs) suppressed

5. Skin Barrier compromised

6. Cell Mediated Immunity shift to Th2
Vulvar and Vaginal pH

Damaged skin (dermatitis, abrasion, etc) has an elevated pH (5.5+) which returns to 4.5 with healing

But Not likely critical importance
Soren Sorensen
The concept of pH was introduced in 1909 by the Danish Chemist, Soren Sorensen.

He formulated: Acidity is the negative logarithm of the hydrogen ion concentration \( \text{pH} = -\log[H^+] \).

In 1934, Arnold Beckman developed the “acidimeter” that could measure pH.
Soren Sorensen was not awarded the Nobel Prize (first award was in 1901)

Yet, pH is a central concept in medicine

“H” stands for hydrogen

Soren Sorensen failed to document what he meant by the “p” in pH (He also used qH)
pH Regulates Microbes?

The majority of microbes are classed as “neutrophiles”

Optimal growth is in the neutral pH range of 6.5 to 7.5

Acidophiles and alkaliophiles are typically found only in unusual natural environments
Vulvovaginal acid pH does not prevent sexually transmitted diseases

Neutrophilic microbes can become vaginal pathogens through inducible acid pH protective defenses
Acid pH Survival (Gram positive bacteria)
Vulvovaginal Staph and Strep

1. Proton pumps
2. Production of alkali
3. Stress sigma factor
4. Cell membrane changes
5. Altered cell density
6. Biofilm production

Cotter PD, Hill C. Surviving the Acid Test: Responses of Gram Positive Bacteria to Low pH Microbiology and Molecular Biology Reviews 2003:67.3 429-53
Acid pH Survival (Gram negative bacteria)
Vulvovaginal flora and Pathogens

Diverse array of inducible acid shock proteins including stress sigma factor

Group B Streptococcus

Present in the vaginal flora of up to 30% of normal women with a vaginal pH around 4.5

Will not grow in the laboratory at a pH of 4.5

Group B strep acid pH defenses
1. Biofilm formation
2. Production of intracellular alkaline buffers
3. Proton pump activation
4. Activation of various protective genes

“Vulvovaginal pH of 4.5 maintains a healthy vaginal microflora” is a weak concept

It is more accurate to state:

“Vulvovaginal Contact Dermatitis facilitates pathogens with an inducible ability to survive an acid pH”
CLINICAL SIGNIFICANCE

NORMAL pH DOES NOT AFFIRM NORMAL MICROFLORA

“Fixing” the pH may not eliminate pathogens

HIGH pH MAY BE DUE TO ESTROGEN DEFICIENCY OR TRANSUDATE OF INTERSTITIAL FLUID
Lactobacillus and other Commensals

Vulvovaginal Contact Dermatitis promotes vaginal pathogens in spite of the presence of Lactobacillus
Lactobacilli

• “graze” on the surface of cervicovaginal mucus (Jiri and Mestecky eds. Mucosal Immunology 4th edition. Elsevir 2005;67)

• Lactobacilli fill potential pathogen binding sites on the surface of the mucus but pathogen proteinases allow mucin penetration

• Lactobacilli generally do not contact the vaginal epithelium

• Lactobacilli disappear if the cervicovaginal mucus disappears
• Yeast infection is not reliably prevented by lactobacilli or low pH  (Pirota M et al. BMJ 2004;329:548-51)

Vulvovaginal Contact Dermatitis promotes staph, strep and yeast infection
CLINICAL SIGNIFICANCE

There is no established role for vaginal probiotics.

Probiotics would not be expected to work for BV.

Lactate may be more important than pH.
Vaginal Mucus

Contact dermatitis contributes to vulvovaginal biofilm formation in spite of mucus.
The Dominant Role of Mucus

• **Mucus prevents biofilm formation** (Caldara M et al. Mucin biopolymers prevent bacterial aggregation by retaining cells in the free-swimming state. Curr Biol 2012 Dec 18;22(24):2325-30)

• **Mucus contains important innate antimicrobial substances** (Linden SK et al. Mucins in the mucosal barrier to invasion pgs 1-15)

• **Mucus has structure** (25% protein, 75% carbohydrate)
Innate Antimicrobials in Mucus

Human beta defensin 2 inhibits bacteria and yeast


Secretory leukocyte protease inhibitor (SLPI) inhibits microbial proteinases

Mannose binding lectin
Mucinase allows Biofilm

- Pathogenic microbes must pass through the mucus to attach, then invade the epithelium

- Mucus disruption is achieved with pathogen-produced mucinase, sialidase, and proteinases

- Clue cells present with BV and trichomonas are evidence of biofilm formation due to mucinase production

- Absent mucus increases the risk for infection ascending above the cervix
CLINICAL SIGNIFICANCE

BIOFILM FORMATION ALLOWS MICROBES TO HIDE FROM ATTACK

STAPH, STREP, AND GARDNERELLA VAGINALIS ARE SIGNIFICANT VULVOVAGINAL BIOFILM FORMERS

THE PRESENCE OF ACTINOMYCES IN IUD BIOFILM INCREASES WITH TIME
Bacterial Vaginosis is not a failure of the Lactobacilli

• BV is characterized by mucinase production and biofilm formation (clue cells)

• The growth and proliferation site for lactobacillus is lost

• Lactobacillus ”grazing” on the mucus ends

• With resolution of BV, mucus is restored and lactobacilli (likely from the small bowel) repopulate the vagina
Trichomonas is also associated with mucinase production and the formation of biofilm.
Many Mucosal Pathogens can produce Mucinase

Gardnerella vaginalis

Mycoplasma

Bacteroides

Helicobacter pylori
Cervicovaginal Mucus and Yeast

Yeast do not release mucinase

Proteinases produced by yeast allow penetration into mucus and the vulvovaginal epithelial surface

Vaginal yeast may spread from a primary vulvar site of established infection

BODY GP. Candidiasis. Raven Press 1993;15
CLINICAL SIGNIFICANCE

Inhibition of mucinase producers can help to restore normal flora.

Persistent Gardnerella vaginalis is typically Flagyl resistant.

Persistent Gardnerella vaginalis may respond to Cleocin cream combined with Augmentin or possibly Azithromycin.
Innate Immunity

Vulvovaginal contact Dermatitis suppresses important innate defenses of the vulva and vagina Contributing to VULVAR and VAGINAL biofilm formation
Antimicrobial Peptides (AMPs)

Over 100 antimicrobial peptides and antimicrobial lipids have been identified in Skin

A normal level of AMPs helps to inhibit skin pathogens

Cathelicidin is deficient in contact dermatitis

Excessive Cathelicidin contributes to rosacea and psoriasis  
Innate Antimicrobials in Mucus and Vulvar Skin

Human beta defensin 2 inhibits bacteria and yeast


Secretory leukocyte protease inhibitor (SLPI) inhibits microbial proteinases
CLINICAL SIGNIFICANCE

Antimicrobial peptides (AMPs) contribute significantly to vulvovaginal pathogen prevention

Some pathogens suppress AMPs, contributing to coinfections

Restoration of mucus and control of contact dermatitis can restore key AMPs
Contact Dermatitis flaking skin compromises the vulvovaginal Skin barrier allowing staph and other microbe overgrowth, contributing to Biofilm formation.
Skin Barrier

• Healthy skin only allows entry of chemicals with a molecular weight less than 500

• Microbes, skin irritants and allergens have a molecular weight greater than 500

• Dermatitis and skin trauma significantly compromise this barrier function

• Yeast and bacteria bind to fibronectin that is exposed by flaking skin (dermatitis)
Skin Flakes in the Wet Prep

Hyperkeratotic skin flake

Folded edge of skin flake

Skin flake melting in KOH

Thin skin flake
CLINICAL SIGNIFICANCE

A compromised vulvovaginal skin barrier exposes fibronectin binding sites for pathogens.

Skin flakes, as evidence of a compromised skin barrier is a common finding in the saline wet prep.

Flaking skin is typically evidence of Vulvovaginal contact dermatitis or lichen sclerosus.
Cell Mediated Immunity

Vulvovaginal Contact Dermatitis And Colonizing Microbes shift immune defenses from protective Th1 to ineffective Th2 (allergy) response Contributes to biofilm
Th1 Immune Response

- Stimulated by foreign antigen exposure in the skin
- The appropriate response to help eliminate infection and individual malignant cells
- Auto-immune skin disease is an excessive Th1 response
- Rejection of a transplanted organ is a Th1 response
Th2 Immune Response

Mediates allergy and humoral immune response

Down-regulates key innate defenses (AMPs)

Does not effectively clear yeast, bacteria, viruses or malignant cells from the epithelium

History of asthma, hay fever, eczema, sensitivity to cheap jewelry (nickel sensitivity)
Vulvovaginal Immune Defects

- HIV (Th1 absent)
- Vulvovaginal contact dermatitis (Th2)
- Lichen Sclerosus with superimposed contact dermatitis (Th2)
Contact Dermatitis

- Itching, burning or pain, depending on severity

- Typically, there is no visible change

- Flakes of skin in the wet prep

- Spongiotic change in the biopsy read by a dermatopathologist
## Irritants in Commercial Preparations

**Blue squares** indicate irritants present in the respective product.

<table>
<thead>
<tr>
<th></th>
<th>Propylene Glycol</th>
<th>Parabens</th>
<th>Butylated Hydroxyanisole (BHA)</th>
<th>Cetyl Alcohol</th>
<th>Sodium Lauryl Sulfate</th>
<th>Mineral Oil</th>
<th>Scorbic Acid</th>
<th>Benzoic Acid</th>
<th>Fragrance</th>
<th>Benzyl Alcohol</th>
<th>Stearyl Alcohol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gynecotrimin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monistat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Terazol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femstat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premarin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K-Y Jelly</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ortho Gynol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gynol II</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Allergic Vulvar Dermatitis (Th2)

- Lichen simplex, spongiotic change

- May have history of asthma, hay fever, eczema, nickel sensitivity (11% of women)

- Beta defensin 2 and 3 and human cathelicidin are suppressed (Nomura I et al Cytokine milieu of atopic dermatitis, as compared to psoriasis, skin prevents induction of innate immune response genes J Immunol 2003 Sept 15;171(6);3262-9)

- Allergy worsens with menstrual secretory phase and pregnancy
Severe Allergic Dermatitis
(Deficient innate immunity, flaking skin)

History of asthma, hay fever, eczema, sinusitis

Scratching here
Consequences of Contact Dermatitis

Chronic irritation, soreness

Increased sensitivity to mechanical and chemical irritants

Proliferation of nerve endings in the skin due to increased nerve growth factor

Increased staph, strep, yeast and herpes

Increased risk for squamous carcinoma
Severe Yeast

Suspicious for diabetes

Satellite lesions
1% clotrimazole 7 is the least irritating topical agent (no propylene glycol)
Non-albicans Yeast

Blastospores, no hyphae

30% of C. glabrata strains are resistant to fluconazole

600 mg boric acid vaginally BID for 7 days has a 60% success rate. Compounded Flucyosine cream costs around $3000.

May consider combined oral fluconazole and topical clotrimazole.
Therapy for Vulvar Atopic Dermatitis

- Avoid allergens (and irritants)

- Non irritating topical corticosteroid ointment

- Moisturize with Vaseline, Crisco, or coconut oil

- Consider the long-term risk of squamous cancer

- Oral or non irritating topical yeast therapy for superimposed infection
CLINICAL SIGNIFICANCE

Contact Dermatitis typically causes little or no visible skin changes

History of sensitivity to nickel, propylene glycol, etc

Increased risk for staph, strep, yeast or encapsulated viral disease

Moisturize and judicial use of a non irritating topical steroid
Antibiotic-Induced Vaginal Yeast Infection

• Most directly related colonization of vulvovaginal contact dermatitis with Staph and other microbes
Staph aureus Colonization of Skin

- Normal skin has $10^4$ bacteria per square cm
- Atopic skin is populated by up to $10^7$ per square cm (Biofilm)
Staphylococcus aureus

- 40% colonization of nasopharynx
- 60% colonization of the vulva
- Potentially universal cofactor for contact dermatitis
- Staph toxins promote a Th2 response and provide biofilm support
Consequence of Antibiotics

- Staph aureus cell wall is disrupted, releasing toxin
- More pronounced Th2 response in the biofilm
- Free up some biofilm fibronectin binding sites
- Yeast organisms move in and join the biofilm
- Cell wall antibiotics cause a stronger Th2 shift than metabolic inhibitors
Antibiotic Induced Staphyloccoccus Toxin Release (contributes to the vulvovaginal Th2 Response)

CLINICAL SIGNIFICANCE

Staphyloccocal colonization of vulvo-vaginal dermatitis contributes to the Th2 environment

Contact dermatitis associated staphylococcal biofilm is difficult to eradicate

Yeast infection is a risk when antibiotics kill the staph
SUMMARY

PH CORRECTION, LACTOBACILLI, OR ADDITION OF PROBIOTICS MAY NOT PREVENT VULVOVAGINAL INFECTIONS

MUCUS CONTAINING AMPS HAS A STRONG INFLUENCE ON VAGINAL MICROBES

VULVOVAGINAL CONTACT DERMATITIS COMPROMISES THE SKIN BARRIER, BLOCKS KEY AMPS, AND RESULTS IN A TH2 IMMUNE RESPONSE

CONTACT DERMATITIS TREATMENT MAY LOWER THE RISK FOR VULVOVAGINAL YEAST INFECTION AND RECURRENT HERPES
BIOFILM FORMATION REMAINS A PROBLEM TO BE RESOLVED

Staphyloccus aureus contributing to contact dermatitis

Gardnerella vaginalis in recurrent / persistent BV

Actinomyces on the long term IUD