Treatment of Vaginal Dysbiosis

Janneke van de Wijgert, Professor
Institute of Infection and Global Health, University of Liverpool
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Traditional clinical views on bacterial pathogenicity

<table>
<thead>
<tr>
<th>IPI*</th>
<th>Which bacteria?</th>
<th>Colonized</th>
<th>Causes disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.1</td>
<td>Commensals (=microbiota)</td>
<td>100%</td>
<td>Rarely: Immuno-compromized, severe dysbiosis</td>
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<tr>
<td>0.1-0.3</td>
<td>Potential pathogenic microorganisms (PPMs)</td>
<td>20-80%</td>
<td>Sometimes: Specific circumstances / strains only</td>
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<tr>
<td>0.8-1.0</td>
<td>Pathogens (e.g. STI pathogens)</td>
<td>~0%</td>
<td>(Almost) always</td>
</tr>
</tbody>
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* Intrinsic pathogenicity index = # diseased/# colonized = 0 - 1

Current VMB knowledge

The Vaginal Microbiota: What Have We Learned after a Decade of Molecular Characterization?

VMB clusters in 17 molecular studies

From optimal to severe dysbiosis

- **No dysbiosis:**
  - Dominated by *L. crispatus* (11), *L. jensenii* (2), *L. vaginalis*
  - Dominated by *L. iners* (15), *L. gasseri* (5)
  - Multiple Lacto spp with/without *G. vaginalis* (8)

- **Moderate dysbiosis:**
  - Dominated by *G. vaginalis* but with lactobacilli (4)
  - Mixture lactobacilli, *G. vaginalis*, other anaerobes (N=8)

- **Severe dysbiosis:**
  - No dominant taxa but highly diverse mixture of anaerobes with no/few lactobacilli (13); often multiple clusters due to differences in relative proportions of taxa
  - Dominated by PPMs (3)

Why is the VMB important?

VMB dysbiosis associated with:
- Pregnancy complications → pre-term birth
- Pelvic inflammatory disease
- HIV/STI acquisition in women and transmission to infants/male partners
- Infertility? Lower success rate of IVF
- Stigmatizing symptoms

PPMs (particularly GBS) associated with:
- Severe maternal and neonatal infections

Why is the VMB important?

- Chronic (sub)clinical inflammation now proven
  (Kyongo 2015, Borgdorff 2015, Anahtar 2015)
  - Dose-response relationship with severity of dysbiosis
- Adverse outcomes even if asymptomatic

VMB biofilm

- Vaginal biofilm research just starting
- Initial data with FISH probes:
  - Vaginal biopsies, vaginal smears, and urine sediments (Swidsinski 2005, 2010; Machado 2014; Hardy 2015)
  - Endometrial/fallopian tube samples (Swidsinski 2013)
  - In-vitro models (Patterson 2010, Cerca lab 2013)

Current thinking:
- G. vaginalis adheres to vaginal epithelial cells first and provides scaffold to which other taxa bind (Patterson, 2010)
- Multiple G. vaginalis oligotypes (Eren, 2011); some are better biofilm producers than others (Harwich, 2010)
- Other taxa: focus on A. vaginae and BVAB1-3 (Family Lachnospiraceae); many not yet investigated
- G. vaginalis biofilm can also be present under foreskin in men; pieces can be sexually transmitted
- Not yet certain that G. vaginalis is dominant in all vaginal biofilms and which other taxa are important
- Unclear what proportion of first and recurrent BV episodes are associated with presence of biofilm

Traditional BV treatment

- First line tx (oral/vaginal metronidazole or clindamycin):
  - Cure rate 80% but recurrence rate 50+% within 6 months
  - Biofilm damaged and suppressed during tx but reactivated
- Cure rate:
  - Improved by longer first-line tx duration
  - Not improved by first line combinations or adding azithromycin, moxifloxacin, or partner treatment
- Recurrence rate:
  - Reduced by prophylactic use of first line drugs, hormonal contraception, male circumcision


Biofilm disruption

- General strategies: Physical removal, long-term antibiotics, chemical biofilm disruption (targeting structural biofilm components, quorum sensing, attachment and dispersal mechanisms)
- In vaginal dysbiosis:
  - In clinical use: boric acid (Reichman, 2009), add EDTA
  - Tested in women: antiseptic octenidine (Swidsinski, 2014) not effective
  - Experimental BV: DNase (Hymes, 2013), retrocyclin (Eade 2013)
  - Experimental PPMs: lysins, quorum sensing inhibitors
  - BUT: might cause epithelial damage increase HIV acquisition, cell clump embolism, re-activation of infection
- Lactic acid and disinfectants do not disrupt biofilm

Novel approaches to optimize the VMB

- Probiotics:
  - Activity against biofilm (McMillan, 2011) and to restore VMB
  - Many tested with modest effects in short-term and disappointing effects in long-term not recommended
- Vaginal pre/probiotics, ongoing RCTs:
  - Lactin-V (Osel, USA): Cohen et al in USA
  - Gynophilus (Probionov, France) and Ecologic Femi (Winclove, Netherlands): van de Wijgert et al in Rwanda
  - Efficacy may depend on endogenous microbiota

Conceptual VMB dysbiosis framework

1. BV with high loads of planktonic bacteria but no biofilm
   - G. vaginalis common but not required
   - Easy to treat, lower recurrence
2. BV with biofilm
   - G. vaginalis required?
   - Difficult to treat, high recurrence
3. High loads of PPMs
   - Highly inflammatory, severe sequelae
   - PPM biofilm present or not
   - With or without BV
   - PPM-specific treatment required
Diagnostic implications

• Differentiate dysbiosis types
• Differentiate from candidiasis, trichomoniasis, cervical STIs
• If recurrent or severe: need diagnostics to determine if BV and/or PPM biofilm is present

Treatment implications

• If planktonic BV: use BV antibiotic tx
• If planktonic PPMs: use targeted PPM antibiotic tx
• If BV and/or PPM biofilm: disrupt biofilm and use antibiotic tx
• If candidiasis: use antifungal tx
• If trichomoniasis/cervical STI: use pathogen-specific antibiotic tx
• If multiple: use combinations
• In all cases: restore optimal VMB after tx using pre/probiotics, topical/systemic hormones, and/or lactic acid, consider partner treatment

Research priorities

• Increase understanding of:
  – G. vaginalis: genotypes, role in BV biofilm
  – L. iners: how much can be tolerated, role in BV biofilm
  – Role of other taxa in BV biofilm
  – Interactions PPMs and VMB, role in BV and/or PPM biofilm
  – Associations VMB dysbiosis types and clinical outcomes
  – Much VMB dysbiosis is asymptomatic but is still associated with adverse outcomes: When to screen and intervene?
• Develop better/more relevant diagnostics
• Develop better biofilm disruption
• Develop better pre/probiotics to restore optimal VMB
• Continue to test (combinations of) interventions to optimize the VMB and prevent adverse outcomes