Advances in the Prevention of Infection-Related Preterm Birth

OBK Meeting, Odense, October, 2014
Infection as a Cause of Spontaneous Early Preterm Labour (SPTL)

- Bacterial products added to amnion cells *in vitro* results in a significant increase in PGE$_2$ production
  - (Lamont et al, Lancet, 1985)

- Between 26 and 34 wks GA, women in SPTL compared to women not in SPTL, are significantly more likely to have:
  - Abnormal vaginal flora (47% v 15%)
  - Neonatal infection
  - Chorioamnionitis (56% v 10%)
  - (Lamont et al, BJOG, 1986)

- Between 26 and 34 wks GA, women in SPTL compared to women not in SPTL, are significantly more likely to be colonised by high numbers Mycoplasmas and Ureaplasmas (18% v 0%)
  - (Lamont et al, J Med Microbiol, 1987)

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**EFFECT OF BACTERIAL PRODUCTS ON PROSTAGLANDIN E PRODUCTION BY AMNION CELLS**

R. F. LAMONT*, M. ROSE
M. G. ELDER
Department of Obstetrics and Gynaecology, Hammersmith Hospital, London

*British Journal of Obstetrics and Gynaecology*
August 1986, Vol. 93, pp. 804–810

Spontaneous early preterm labour associated with abnormal genital bacterial colonization

R. F. LAMONT, D. TAYLOR-ROBINSON, M. NEWMAN, J. WIGGLESWORTH, M. G. ELDER

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**The role of mycoplasmas, ureaplasmas and chlamydiae in the genital tract of women presenting in spontaneous early preterm labour**

R. F. LAMONT*, D. TAYLOR-ROBINSON, J. S. WIGGLESWORTH, P. M. FURRIT, R. T. EVANS* and M. G. ELDER

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© 1987 The Pathological Society of Great Britain and Ireland
Late Miscarriage (<24w) and Early PTB (<34w) According to Grade of Vaginal Flora before 16 weeks

<table>
<thead>
<tr>
<th>Grade</th>
<th>Late Miscarriage (%)</th>
<th>Early PTB (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>16.7</td>
<td>3.4</td>
</tr>
</tbody>
</table>

Odds ratio = 5.35 (2.73 – 10.5)
Relative risk = 3.12 (2.23 – 4.37)
P-value = 0.000001

It would appear logical to consider using antibiotics to prevent PTB of infectious etiology.
‘Different studies have used different diagnostic methods, with different outcome parameters or differing definitions of success, to treat women of differing risks, with different susceptibilities and hence different host response, with different degrees of abnormal genital tract flora, at different gestational ages, using different antibiotics in different dose regimens by different routes of administration and not surprisingly DIFFERENT results’

Lamont 2001
<table>
<thead>
<tr>
<th></th>
<th>Clindamycin</th>
<th>Metronidazole</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>McGregor</td>
<td>1995 Hauth*</td>
<td></td>
</tr>
<tr>
<td>1995</td>
<td>Vermeulen</td>
<td>1997 McDonald</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>Kurkinen-Raty</td>
<td>2000 Carey (NICHD/MFMU)</td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>Rosenstein</td>
<td>2001 Porter</td>
<td></td>
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<tr>
<td>2001</td>
<td>Kekki</td>
<td>2002 Odendaal</td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>Guaschino</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>Lamont</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>Ugwumadu</td>
<td>* plus erythromycin</td>
<td>** amoxicillin</td>
</tr>
<tr>
<td>2004</td>
<td>Kiss</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>Larsson</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year</td>
<td>Author</td>
<td>Year</td>
<td>Author</td>
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</tr>
<tr>
<td>2001</td>
<td>Guise</td>
<td>2002</td>
<td>Koumans</td>
</tr>
<tr>
<td>2003</td>
<td>Leitich</td>
<td>2004</td>
<td>Klein</td>
</tr>
<tr>
<td>2004</td>
<td>Riggs</td>
<td>2005</td>
<td>Okun</td>
</tr>
<tr>
<td>2006</td>
<td>Varma</td>
<td>2007</td>
<td>Simcox</td>
</tr>
<tr>
<td>2007</td>
<td>McDonald</td>
<td>2008</td>
<td>Hutzal</td>
</tr>
<tr>
<td>2008</td>
<td>Swadpanich</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Overall conclusions = antibiotics of no benefit
So why the confusion?
Antibiotic choices

What?
- Co-Amoxiclav?
- Clindamycin?
- Erythromycin?
- Metronidazole?

Who?
- Low BMI?
- High Risk?
- Contracting?
- Previous PTB?
- FFN+ve?

When?
- In Labor?
- Pre-Pregnancy?

- 2nd Trimester?
- 1st Trimester?
- <50kg?
- Short Cx?
- BV?
What is the best antibiotic?
Requirements for successful antibiotic prophylaxis

- Active against organisms associated with abnormal vaginal flora
- Used in women whose risk of PTB is due to abnormal flora
- Used early in pregnancy before irreversible changes occur
Active against BV or BV Organisms

- Erythromycin
  - Not recommended for treatment of BV (CDC)
- Co-amoxiclav
  - Not recommended for treatment of BV
- CDC Recommendations for treatment of BV
  - metronidazole
  - clindamycin
Metronidazole vs Clindamycin
The vaginal microbiome: new information about genital tract flora using molecular based techniques

RF Lamont, a, b JD Sobel, c RA Akins, d SS Hassan, a, b T Chaiworapongs a, a, b JP Kusanovic, a, b R Romero a, e

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Department of Infectious Diseases, Wayne State University/Hutzel Hospital, Detroit, MI, USA c Department of Biochemistry and Molecular Biology, Wayne State University Medical School, Detroit, MI, USA e Center for Molecular Medicine and Genetics, Wayne State University, Detroit, MI, USA

Correspondence: RF Lamont, Perinatology Research Branch, NICHD, NIH, DHHS, Bethesda MD and Brush Building, Level 4, 3099 John R, Detroit, MI, 48201, USA. Email rlamont@med.wayne.edu

Accepted 21 November 2010. Published Online 20 January 2011.
HMP Background

- Human Genome Project
  - 100,000 genes predicted
  - 23,000 protein-coding genes found
- Human Supra-organism
  - Human genome + bacterial microbiome
  - Bacterial cells 10x human somatic cells
  - Human microbiome = collective genome of symbionts
  - Bacterial genome provides traits that humans did not need to evolve
- Human Genome + Microbiome > 1,000,000 genes
- NIH investing $100,000,000 roadmap for medical research
What is the best time to administer antibiotics
EARLY!!
Physiology versus Pathology

The earlier in pregnancy at which PTB occurs, the more likely this will be due to an abnormal trigger like infection.

Seo et al, 1992
## Risk of Adverse Outcome According to Maximum Gestational Age at Screening

<table>
<thead>
<tr>
<th>Author</th>
<th>Maximum GA at Screening (RR)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gravette et al 1988</td>
<td>32</td>
<td>(1.1-3.5)</td>
</tr>
<tr>
<td>McDonald et al 1992</td>
<td>28</td>
<td>(1.0-3.2)</td>
</tr>
<tr>
<td>Hillier et al 1995</td>
<td>26</td>
<td>(1.2-1.8)</td>
</tr>
<tr>
<td>Krohn et al 1995</td>
<td>26</td>
<td>(1.1-2.2)</td>
</tr>
<tr>
<td>Germaine et al 1994</td>
<td>26</td>
<td>(1.0-1.3)</td>
</tr>
<tr>
<td>Hillier et al 1995</td>
<td>26</td>
<td>(0.8-3.0)</td>
</tr>
<tr>
<td>McGregor et al 1990</td>
<td>24</td>
<td>(1.1-6.5)</td>
</tr>
<tr>
<td>Riduan et al 1993</td>
<td>20</td>
<td>1.0-3.9</td>
</tr>
<tr>
<td>Hay et al 1994</td>
<td>20</td>
<td>(2.3-13)</td>
</tr>
<tr>
<td>Kurki et al 1992</td>
<td>17</td>
<td>(2.5-19)</td>
</tr>
</tbody>
</table>
Clindamycin Study: Late miscarriage & Preterm Birth According to Grade of Flora

<table>
<thead>
<tr>
<th>Grade of BV</th>
<th>CVC</th>
<th>Placebo</th>
<th>Untreated</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (controls)</td>
<td>-</td>
<td>-</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>I (revertants)</td>
<td>-</td>
<td>-</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>II (intermediate)</td>
<td>16%</td>
<td>28%</td>
<td>-</td>
<td>NS</td>
</tr>
<tr>
<td>III (BV)</td>
<td>17%</td>
<td>30%</td>
<td>-</td>
<td>0.03</td>
</tr>
<tr>
<td>II + III (abnormal)</td>
<td>19%</td>
<td>27%</td>
<td>-</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abnormal genital tract colonization in early pregnancy, even if this resolves, damage occurs early and persists
Genetics of PTB
Genetics of PTB: Susceptibility & Exposure
Host Response: Gene-environmental interaction

<table>
<thead>
<tr>
<th>Susceptibility and exposure</th>
<th>BV status</th>
<th>Gene variation</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
<td>–</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>–</td>
<td>+</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>+</td>
<td>SPTL and PTB</td>
</tr>
</tbody>
</table>

Host response to sepsis†

- Normal flora
  - Infection
  - Adhesion
  - Invasion

- Abnormal flora
  - Infection
  - Adhesion

Gene-environmental interaction*

<table>
<thead>
<tr>
<th></th>
<th>PTB risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>BV only</td>
<td>3.3</td>
<td>1.8–5.9</td>
</tr>
<tr>
<td>TNF-α only</td>
<td>2.7</td>
<td>1.7–4.5</td>
</tr>
<tr>
<td>BV and TNF-α</td>
<td>10.1</td>
<td>4.4–23.5</td>
</tr>
</tbody>
</table>

Morbidity/mortality BPD/PVL/CP
Recovery and repair
Morbidity/mortality

Developing Sepsis Schematically

- Normal flora
- Abnormal flora
- Infection
- Adhesion
- Invasion
- Inflammation
- Tissue Damage
Developing Sepsis Schematically

- Normal flora
- Abnormal flora
- Infection
- Adhesion
- Invasion
- Inflammation
- Tissue Damage

Too late, the damage is already done
Developing Sepsis Schematically

Normal flora

Abnormal flora

Infection

Adhesion

Invasion

Inflammation

Tissue Damage

May be early enough to prevent damage
Which pregnant women should receive antibiotics?
Choice of Patient

- Objective evidence of abnormal genital tract colonization
  - otherwise decimating normal flora
- Exclude previous PTB of non-infectious etiology
  - iatrogenic
  - APH, Twins, PIH
- Grade III gram stain (Barn door BV)
  - Responds to antibiotic treatment
Treatment of abnormal vaginal flora in early pregnancy with clindamycin for the prevention of spontaneous preterm birth: a systematic review and metaanalysis

Ronald F. Lamont, BSc, MB, ChB, MD, FRCOG; Chia-Ling Nhan-Chang, MD; Jack D. Sobel, MD; Kimberly Workowski, MD; Agustin Conde-Agudelo, MD, MPH; Roberto Romero, MD

Hypothesis

The conclusions of individual studies/systematic reviews/meta-analyses on the use of antibiotics used prophylactically for the prevention of PTB are flawed by the fact that undue reliance is placed on:

- Studies with suboptimal choice of antibiotics (mainly metronidazole)
- Used too late in pregnancy to influence outcome (23-27 weeks)
- In women whose risk of PTB was not due to BV (previous PTB, Low BMI, FFN, Ureaplasmas, GBS, TV, etc.)

Conversely, that antibiotics active against BV related organisms, used in women whose risk of PTB is due to abnormal flora, and used early in pregnancy before irreversible inflammatory damage occurs, can reduce the rate of PTB

Results
Intravaginal Clindamycin to Reduce Preterm Birth in Women With Abnormal Genital Tract Flora

Ronald F. Lamont, DM, FRCOG, Sheila L. B. Duncan, MD, FRCOG, Debasish Mandal, MBBS, FRCP, and Paul Bassett, MSc

Prospective randomised controlled trial of an infection screening programme to reduce the rate of preterm delivery

Herbert Kiss, Ljubomir Petricevic, Peter Huttsein

Late miscarriage and preterm birth after treatment with clindamycin: a randomised consent design study according to Zelen

P-G Larsson, a L Fähræus, b B Carlsson, b T Jakobsson, b U Forsum, b the premature study group of the Southeast Health Care Region of Sweden

a Department of Obstetrics and Gynaecology, Kårrsjukhuset, Skövde, Sweden b Department of Molecular and Clinical Medicine, Linköping University Hospital, Linköping, Sweden

Correspondence: Dr P-G Larsson, Department of Obstetrics and Gynaecology, Kårrsjukhuset, S 44 47 Skövde, Sweden.
Email p-g.larsson@vgregion.se
Preterm Birth 24-36 completed weeks of gestation
(5 Studies – Fixed Effects Model)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Clindamycin Events</th>
<th>Total</th>
<th>Placebo/no treatment Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
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<tbody>
<tr>
<td>Kekki 2001</td>
<td>9</td>
<td>187</td>
<td>7</td>
<td>188</td>
<td>9.6%</td>
<td>1.29 [0.49, 3.40]</td>
</tr>
<tr>
<td>Kiss 2004</td>
<td>5</td>
<td>149</td>
<td>8</td>
<td>143</td>
<td>11.2%</td>
<td>0.60 [0.20, 1.79]</td>
</tr>
<tr>
<td>Lamont 2003</td>
<td>8</td>
<td>208</td>
<td>19</td>
<td>201</td>
<td>26.6%</td>
<td>0.41 [0.18, 0.91]</td>
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<tr>
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<td>11</td>
<td>395</td>
<td>10</td>
<td>390</td>
<td>13.8%</td>
<td>1.09 [0.47, 2.53]</td>
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<td>Ugwumadu 2003</td>
<td>11</td>
<td>244</td>
<td>28</td>
<td>241</td>
<td>38.7%</td>
<td>0.39 [0.20, 0.76]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1183</td>
<td></td>
<td>1163</td>
<td>100.0%</td>
<td></td>
<td>0.60 [0.42, 0.86]</td>
</tr>
</tbody>
</table>

Total events 44 72

Heterogeneity: \( \chi^2 = 6.82, df = 4 \) (\( P = 0.15 \)); \( I^2 = 41\%

Test for overall effect: \( Z = 2.74 \) (\( P = 0.006 \))
Preterm Birth 24-36 completed weeks of gestation
(5 Studies – Fixed Effects Model)

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<td></td>
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<td>1163</td>
<td>100.0%</td>
<td>0.60 [0.42, 0.86]</td>
</tr>
</tbody>
</table>

Total events: 44
Total events: 72
Heterogeneity: Chi² = 6.82, df = 4 (P = 0.15); I² = 41%
Test for overall effect: Z = 2.74 (P = 0.006)

Late miscarriage 16-23 completed weeks of gestation (two studies)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Clindamycin</th>
<th>Placebo/no treatment</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events Total</td>
<td>Events Total</td>
<td>M-H, Fixed, 95% CI</td>
<td>M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td>Larsson 2006</td>
<td>0 395</td>
<td>2 390</td>
<td>0.20 [0.01, 4.10]</td>
<td></td>
</tr>
<tr>
<td>Ugwumadu 2003</td>
<td>2 244</td>
<td>10 241</td>
<td>0.20 [0.04, 0.89]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>639</td>
<td>631</td>
<td>0.20 [0.05, 0.76]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>2</td>
<td>12</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 2.35 (P = 0.02)

Late miscarriage 16-23 completed weeks of gestation (two studies)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Clindamycin</th>
<th>Placebo/no treatment</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
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<tbody>
<tr>
<td></td>
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<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Larsson 2006</td>
<td>0</td>
<td>395</td>
<td>2</td>
</tr>
<tr>
<td>Ugwumadu 2003</td>
<td>2</td>
<td>244</td>
<td>10</td>
</tr>
<tr>
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<td>639</td>
<td></td>
<td>631</td>
</tr>
</tbody>
</table>

Total events: 2

Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%

Test for overall effect: Z = 2.35 (P = 0.02)

Results Summary

- Preterm birth significantly reduced by 40%
- Late miscarriage significantly reduced by 80%
- Of those infants born preterm:
  - Antibiotics: babies <2500g = 20%
  - No treatment: babies <2500g = 80% (p<0.009)
  - Antibiotics versus no treatment
    - 32.5 day difference in mean gestation age in favor of antibiotics (p<0.024)
- Delivery before 33 completed weeks of gestation
  - Statistically significant 86% reduction for those who received antibiotics
- Women with Barn Door BV
  - Late Miscarriage & Preterm Birth
    - Antibiotics = 5.4%
    - Placebo = 35.7%

## Results: Secondary Outcomes

<table>
<thead>
<tr>
<th>Category</th>
<th>Late Misc/PTB</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent BV</td>
<td>28%</td>
<td>2.9</td>
<td>1.3-5.2</td>
</tr>
<tr>
<td>Cured BV</td>
<td>10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cured but recurrent BV</td>
<td>15%</td>
<td>9.3</td>
<td>1.6-53.5</td>
</tr>
<tr>
<td>Cured BV/ no recurrence</td>
<td>2%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Kekki 2001
Conclusions

- The *appropriate* antibiotics
  - (clindamycin)
- Given to the *appropriate* women
  - (those with objective evidence of abnormal genital tract flora)
- At the *appropriate* time in pregnancy to prevent infection and inflammatory tissue damage
  - (<22 weeks)
- Significantly reduces the risk of LM (80%) & PTB (40%)

Thank you for your attention
Requirements for successful antibiotic prophylaxis

- Active against organisms associated with abnormal vaginal flora
- Used in women whose risk of PTB is due to abnormal flora
- Used early in pregnancy before irreversible changes occur
New Information from Molecular Based Techniques

- Normal & abnormal vaginal flora composed of different population subtypes
  - Normal:
    - *Lactobacillus* dominated
    - Other lactic acid producing communities
  - Abnormal
    - Anaerobe dominated
    - G. vaginalis/A. vaginae dominated
    - Other mixed organisms
    - Sexually transmitted subtype

- Metronidazole:
  - Ineffective *in-vitro* against BV related organisms
  - Effective *in vivo*
    - Metabolites
    - Effect on synergism
  - Metronidazole in black/hispanic women in North America
    - no benefit
  - Clindamycin in white North European women
    - benefit
NICHD/MFMU Study

- Metronidazole
- "Low risk population"
  - 85% black/hispanic
- Placebo effect (37%)
- Delay in start of treatment
  - 8 weeks
  - 25% change in flora
- Late treatment
  - <16 weeks = 0%
  - >20 weeks = 44%
- Numbers
  - 29,626 screened
  - 6,540 BV
  - 1,936 recruited
- Exclusions
  - 4,604
  - 999 (other)

Carey et al NEJM 2003; Lamont RF NEJM 2003
ORACLE II

- Erythromycin and co-amoxiclav
  - Not recommended for treatment of BV (CDC)
  - Ureaplasmas
- No objective evidence of infection
  - 13-22% subclinical
  - Infections excluded!
- Diagnosis of PTL
  - 50% tocolytics
  - 90% undelivered <48 hours
  - 85% undelivered <7 days
  - Mean GA at delivery 38 weeks
- Timing
  - In labor
- Self fulfilling prophecy

Kenyon 2001 and 2008

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Interpretation of ORACLE Studies I & II

• A badly conceived albeit well-conducted study has self-fulfilled its own prophecy that inappropriate antibiotics given to women whose risk of PTB is not infection based will not prevent PTB

• Long term follow up using sub-optimal methodology confirms that such ill-conceived interventions do not improve outcome and may cause more harm than good
Relative abundance of vaginal microbial communities using culture-independent, molecular-based techniques

Unpublished data pertaining to PPROM, Marian Kacerovsky, Czech Republic
Relative Abundance in Normal Flora (molecular techniques)

- Lactobacillus crispatus
- Lactobacillus jensenii
- Lactobacillus gasseri
- Lactobacillus iners

Normal vaginal flora dominated by one, or at most two of these four *Lactobacillus* species

*Lactobacillus crispatus* dominated

Minimal diversity!
Relative Abundance in Abnormal Flora (molecular techniques)

- Lactobacillus iners dominated

Maximal diversity?

- Definitely abnormal

- Lactobacillus iners
- Gardnerella vaginalis
- Lactobacillus sp.
- Atopobium vaginae
- Butyrate-producing bacterium GM2/1
- Dialister propionicifaciens
- Eubacterium biforme
- Dialister sp. oral taxon 502
- Klebsiella granulomatis
- Eubacterium coprostanoligenes
- Clostridium lactatifermentans
- Ruminococcus flavaei
- Ruminococcus callidus
- Sneathia sanguinegens
- Streptococcus agalactiae
- Eubacterium ramulus
- Eubacterium coprostanoligenes
- Leptotrichia amnionii
- Gardnerella vaginalis
- Chlamydia trachomatis
- Lactobacillus sp.
- Clostridium leptum
- Ureaplasma urealyticum; (serovar 2)
- Atopobium vaginae
- Sneathia sanguinegens
- Butyrate-producing bacterium GM2/1
- Eubacterium biforme
- Dialister propionicifaciens
- Eubacterium ramulus
- Eubacterium coprostanoligenes
- Ureaplasma urealyticum; (serovar 1)
- Finegoldia magna
- Roseburia hominis

- ?abnormal
Relative Abundance in Abnormal Flora (molecular techniques)

Maximal diversity!
What have we learned about BV using molecular based techniques?

- Diversity greater than in normal flora
- Not a single entity
  - Number of different sub-types of BV
  - Anaerobe dominated
  - L.iners dominated
  - G. vaginalis + A. vaginae dominated
- Racial differences
- Likely to be different etiologies
  - sexually transmitted
- Likely to induce different host responses
- Possibly different phenotypic outcomes
- Likely to respond differently to different antibiotics
- Explains a lot:
  - Etiology,
  - Bacteriology,
  - Diagnosis,
  - Treatment
- The “Bacterial Vaginosis Syndrome”
Anti-Inflammatory Activity of Macrolide Antibiotics

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