What causes Burning Pain in Lactating Mothers?

Systematic Review and Meta-analysis

Christine Betzold NP IBCLC MSN
Outline

Ductal Infections

- Differentials
- Definitions
- Case Study

Literature Summary - Problems and Controversies

Systematic Review

- Search Strategy
- Study Description/Inclusion Criteria
- Biases
- Findings/Percentages/OR’s

Explanations for Controversies

- More Case Presentations
1. Breast Fullness
2. Engorgement: Milk and/or Vascular
3. Plugged Duct w/ or w/out a Bleb
4. Galactocele (Milk Cyst)
5. Non-Infectious Mastitis
6. Infectious Mastitis
7. Abscess
8. Vasospasm
9. Latching Problems w/ or w/out Nipple Trauma
Nipple Vasospasm-(Raynauds)

Primary vs. Secondary
# Bacterial Profile of Mothers with Vasospasm vs. Infectious Mastitis

**Curr Microbiol (2009) 59:59–64**

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**Table 3** Detection of bacterial DNA in the milk samples by QRT-PCR. Data are expressed as \( \log_{10} \) genome equivalent ml\(^{-1} \) (Mean and SD)

<table>
<thead>
<tr>
<th>Sample</th>
<th>Total bacteria</th>
<th>Staphylococcus</th>
<th>Bifidobacterium</th>
<th>Bacteroides</th>
<th>Clostridium cluster XIVa</th>
<th>Enterococcus</th>
</tr>
</thead>
<tbody>
<tr>
<td>RS1</td>
<td>2.84 (0.42)</td>
<td>2.70 (0.44)</td>
<td>Nd</td>
<td>Nd</td>
<td>Nd</td>
<td>2.37 (0.08)</td>
</tr>
<tr>
<td>RS2</td>
<td>2.86 (0.19)</td>
<td>2.65 (0.32)</td>
<td>Nd</td>
<td>Nd</td>
<td>Nd</td>
<td>2.68 (0.50)</td>
</tr>
<tr>
<td>RS3</td>
<td>2.74 (0.33)</td>
<td>2.60 (0.29)</td>
<td>Nd</td>
<td>2.13 (0.57)</td>
<td>Nd</td>
<td>2.75 (0.50)</td>
</tr>
<tr>
<td>RS4</td>
<td>2.79 (0.53)</td>
<td>2.57 (0.39)</td>
<td>Nd</td>
<td>Nd</td>
<td>Nd</td>
<td>2.06 (0.06)</td>
</tr>
<tr>
<td>RS5</td>
<td>2.80 (0.60)</td>
<td>2.73 (0.45)</td>
<td>Nd</td>
<td>Nd</td>
<td>2.06 (0.22)</td>
<td>2.49 (0.66)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2.81 (0.05)</td>
<td>2.65 (0.07)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>2.47 (0.27)</td>
</tr>
</tbody>
</table>

**Prevalence**

- **RS1**: 5/5
- **RS2**: 5/5
- **RS3**: 1/5
- **RS4**: 1/5
- **RS5**: 5/5
- **Mean (SD)**: 5/5

**P**: 0.000 < 0.001

Nd, not detected
1. Ruptured breast cyst
2. Fat necrosis
3. Breast cancer
4. Costochondritis
5. Granulomatous Disease
6. Mastalgia-cyclic or non-cyclic
7. Subareolar Abscess-Duct Ectasia
8. Mondor’s Disease-a superficial phlebitis of the chest wall
9. Cat Scratch Disease-presenting as a breast mass
What To Call it!

Name....?

Common Terms Used
- Ductal Infections
- Infections of the Ducts
- Ductal Candidiasis

Other Terms Found
- Moniliasis Breast
- Candidosis
- Deep Breast Pain
Defining Ductal Infections

Maternal Evaluation

• Ductal vs. Nipple Infection?
• *Nipple Pain and Breast Pain are intrinsically related*
• Variations in Presentation

Infant History and Evaluation

• Orally
• Dermatological
• Latch
• Breastfeeding, Mood

Breastfeeding and Thrush. The Practicing Midwife. 2002: 5; (11) www.thepractisingmidwife.com
**The Blood & Burning Breast Case**

Subjective: Burning breast pain for 2 weeks worsening and her 1 mo old infant is hospitalized w/Reflex of bloody milk and Melanocytic stooling

Hx: Maternal Eczema and Told to pump and bottle-feed by MD

**OBJECTIVE:**
Nipples: fissures/scabs (honey crusted)
Infant w/o signs of candida/thrush and tests positive for maternal blood

**ASSESSMENT:** Bacterial Ductal Infection r/o Candida

**PLAN:**
- Cultures (Nipple and Milk)
- Baby Back to Breast
- Tx: Sulfamethoxazole-trimethoprim (Septra DS) 1 bid for 14 days

**OUTCOME:**
Cultures: Positive for C. albicans, S. aureus and Enterococcus.

TX: topical OTC yeast cream
Fluconazole (Diflucan) 200mg 2 po day 1 then 1 po/day until symptoms resolved 100% for 7 days

I Recurrence Resumed Diflucan for another 2-3 wks

Summary of Published Cases, Studies, and Problems
Cases and Studies of Mothers With Variations in Presentation:

1. **Mom treated with antibiotics now has burning pain**
   - Amir, 1996: $P < 0.05$ for Postpartum Antibiotics 62% for Mastitis
   - Tanguay, 1994: Postpartum Antibiotics 52% vs 29% $P < 0.03$

2. **Baby with Candidal Infection-now mom with sore nipples and/or burning pain**
   - Amir, 2004: $P < 0.02$ for Infant with Oral Thrush
   - Tanguay, 1994: 84% vs. 0% Oral or Diaper Candidiasis

3. **Baby Treated with Antibiotics-now mom has sore nipples and/or burning pain**
   - Case Report Amir, 2004

4. **Mom with history of nipple trauma now with burning pain**
   - Rate Ratio 2.3 (1.19 to 4.43) $p = 0.012$ BMJ Open 2013;3:e002351.doi:10.1136
### Summary of History and Physical Findings (N=64)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postpartum History</td>
<td>%</td>
</tr>
<tr>
<td>Nipple cracks and sores</td>
<td>74</td>
</tr>
<tr>
<td>Latch and suck problems</td>
<td>48</td>
</tr>
<tr>
<td>Acute mastitis</td>
<td>52</td>
</tr>
<tr>
<td>Treatment of yeast</td>
<td>63</td>
</tr>
<tr>
<td>Breast or nipple itching</td>
<td>17</td>
</tr>
</tbody>
</table>

# Eglash’s Study: Summary of Most Common Findings n=64

<table>
<thead>
<tr>
<th>Subjective symptoms</th>
<th>Rate</th>
<th>Objective Findings</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Pain with Deep touch</td>
<td>82%</td>
<td>Nipple Cracks, Blisters, Yellow Scabs</td>
<td>73%</td>
</tr>
<tr>
<td>Bilateral Pain</td>
<td>90%</td>
<td>Palpable Breast Tenderness</td>
<td>79%</td>
</tr>
<tr>
<td>Burning Nipple Pain</td>
<td>68%</td>
<td>Palpable Tenderness Behind Areola</td>
<td>29%</td>
</tr>
<tr>
<td>Bruised Nipple Pain</td>
<td>49%</td>
<td>Positive Bacterial Cultures (n=60)</td>
<td>50%</td>
</tr>
</tbody>
</table>

Eglash: Pain Relief and Duration of Antibiotic Use

<table>
<thead>
<tr>
<th>Duration of Use in Weeks</th>
<th>Patients</th>
<th>Pain Relief @ 2 Weeks</th>
<th>@ 4 Weeks</th>
<th>@ 6 Weeks</th>
<th>@ &gt;6 Weeks</th>
<th>No Pain Relief</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-4</td>
<td>25</td>
<td>16%</td>
<td>68%</td>
<td>8%</td>
<td>0%</td>
<td>5%</td>
</tr>
<tr>
<td>5-6</td>
<td>21</td>
<td>0%</td>
<td>0%</td>
<td>81%</td>
<td>14%</td>
<td>5%</td>
</tr>
<tr>
<td>&gt;6</td>
<td>18</td>
<td>0%</td>
<td>5%</td>
<td>11%</td>
<td>78%</td>
<td>6%</td>
</tr>
</tbody>
</table>

Average Duration was 5.7 Weeks
Studies Published After Systematic Review

• Castle Study-2013
• Case Control of Bacterial Species-2013
• Role of Antibiotic Treatment-2014
Does Candida and/or Staphylococcus play a role in nipple and breast pain? (CASTLE Study) n=346

<table>
<thead>
<tr>
<th></th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any <em>Candida</em> spp in nipple/breast milk</td>
<td>131</td>
<td>(38%)</td>
</tr>
<tr>
<td>Any <em>Candida</em> spp in nipple/breast milk/baby</td>
<td>133</td>
<td>(38%)</td>
</tr>
<tr>
<td>Any <em>S aureus</em> in nipple/breast milk</td>
<td>231</td>
<td>(67%)</td>
</tr>
<tr>
<td>Any <em>S aureus</em> in nipple/breast milk/baby</td>
<td>277</td>
<td>(80%)</td>
</tr>
</tbody>
</table>

1. Cultured Mothers and Infants Weekly x 4
2. Defined Case Based on Development of Ductal Symptoms
3. Followed for 8 wks

## Time-to-event analysis of predictors of first symptoms of case definition

<table>
<thead>
<tr>
<th>Events</th>
<th>Rate Ratio (95% CI)</th>
<th>P Value</th>
<th>Multivariate Rate Ratio (95%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida Positive</td>
<td>1.87 (1.10 to 3.16)</td>
<td>0.018</td>
<td>2.03 (1.19 to 3.45)</td>
<td>0.009</td>
</tr>
<tr>
<td>S. aureus Positive</td>
<td>1.53 (0.88 to 2.46)</td>
<td>.128</td>
<td>1.41 (0.08 to 2.46)</td>
<td>0.234</td>
</tr>
<tr>
<td>Nipple Damage</td>
<td>2.3 (1.19 to 4.43)</td>
<td>.012</td>
<td>2.39 (1.21 to 4.70)</td>
<td>0.012</td>
</tr>
</tbody>
</table>
The also found a connection between plugged ducts and *S. aureus*.
Table 3. Bacterial Species Growth in Breastmilk and Nipple Cultures

<table>
<thead>
<tr>
<th>Bacterial species</th>
<th>Nipple culture</th>
<th>Breastmilk culture</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CTX</td>
<td>OTX</td>
<td></td>
</tr>
<tr>
<td>Coagulase-negative Staphylococcus</td>
<td>30(88%)</td>
<td>33(77%)</td>
<td>0.194</td>
</tr>
<tr>
<td>S. aureus</td>
<td>5(14.7%)</td>
<td>13(30%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Enterococcus species</td>
<td>1(3%)</td>
<td>2(5%)</td>
<td></td>
</tr>
<tr>
<td>Enterobacter species</td>
<td>2(6%)</td>
<td>0</td>
<td>0.192</td>
</tr>
<tr>
<td>Diphtheroids</td>
<td>1(2.9%)</td>
<td>3(7%)</td>
<td>0.626</td>
</tr>
<tr>
<td>Acinetobacter species</td>
<td>2(6%)</td>
<td>5(12%)</td>
<td>0.445</td>
</tr>
<tr>
<td>Pseudomonas species</td>
<td>0</td>
<td>3(7%)</td>
<td>0.248</td>
</tr>
<tr>
<td>α-Hemolytic Streptococcus</td>
<td>9(27%)</td>
<td>6(14%)</td>
<td>0.168</td>
</tr>
<tr>
<td>E. coli</td>
<td>0</td>
<td>1(2%)</td>
<td>0</td>
</tr>
<tr>
<td>Klebsiella species</td>
<td>0</td>
<td>1(2%)</td>
<td>1</td>
</tr>
<tr>
<td>Candida species</td>
<td>0</td>
<td>2(5%)</td>
<td>0.506</td>
</tr>
</tbody>
</table>

Data are number (%).

*Pearson’s χ² test was used unless the cell count was less than expected, and then Fisher’s exact test was used.

CTX, conservative therapy; OTX, oral antibiotic treatment.
Role of Oral Antibiotics in Treatment of Breastfeeding Women with Chronic Breast Pain Who Fail Conservative Therapy

FIG. 2. Pain in the conservative therapy (CTX) and oral antibiotic treatment (OTX) groups: (A) nipple and (B) breast.
# Related Studies Published After Systematic Review in 2012-2013

## 2013 Cochrane Review of Mastitis TX
- **2 Trials**
  1. One small (n=25)
    - No Difference Between Conservative vs ATB Tx
  2. Found a Difference
    - but problematic design

## US Tx of Blocked Ducts
- n=25 and n=34 treatments (Some with 2-3 Episodes)
- n=23 with Symptom Resolution
- Of 34 Treatments 11 resolved within 1 day and 14 within 2 days

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Summary of and Problems within the Literature

- No RCT of Treatment
- No Established Treatment Recommendations
- No Definitive Methods of Culturing
- Culturing Problematic
- Case reports—The earliest found was in 1964
- Mostly small studies $N \leq 125$
- Studies of microbes—Mostly prospective cohorts
- Investigations of risk factors and symptomatology
- Available Statistical Evidence Supports an Infectious Etiology
1. Why are Positive Culture Results Lower than Expected?

2. Why are There Minimal Objective Symptoms?

3. Why Do Control Moms Sometimes Test Positive?

4. Why Does it Take So Long to Obtain Resolution?
But if it is not infectious then...

- Why do Many Women Respond to Antibiotics and/or Anti-Fungals?

- Why does all the available statistical evidence support infection?

And if it is infectious which microbe is responsible?

- Candida?
- S. aureus?
- Both or a Mixed Infection?
- What about *Coagulase Negative Staphylococcus*?
- What about:
  - *Fungi*?
  - *Adenovirus*?
  - *Streptococcus*?
  - *Enterococci*?
Part II: Systematic Review

1. Methods
   - Search
   - Criteria
2. Identified Studies
3. Biases
4. Findings
Study Criteria

Inclusion:
1. Symptoms of Burning Breast Pain and/or Nipple Pain
2. Objective Testing for Microbes
3. Unable to Consistently Obtain a Case Group Solely with Symptoms of Burning Breast Pain

Exclusion:
1. Only Nipple Pain or subgroups with Only Nipple Pain
2. Subjective Diagnosis of Infection

Search Strategy

1. PubMed Clinical Query  Jan 2010
   • Query: Diagnosis of Candida in Lactation
2. Librarian Assisted Search
   • Terms: Breastfeeding or lactation (subject headings) AND burning pain OR breast pain OR ductal infections OR thrush OR moniliasis breast OR candidaOR mammary candidosis OR candidiasis OR mastitis OR ductal candidiasis OR nipple pain OR mammary ducts) [keywords] = 2,467
Types of Biases/Method Problems and Study Description
Types of Bias

1. Performance: A Source of Bias
2. Attrition: Minimal Not a Source of Bias
3. Selection: A Significant Source of Bias
4. Detection: Likely a Source of Bias
5. Reporting: Outcomes were identified and were not a significant source of bias. However, how they were reported may have lead to detection bias.
Types of Bias

Performance Bias:
- BF Exclusivity?
- Controlled Pacifiers?
- Antifungal usage controlled?
- PP antibiotic usage?

Selection Bias:
- Studies were not RCT
- Variations in inclusions and exclusions
- Mean infant age
- Symptom Definitions
- Variations in Maternal/Infant Presentations

Detection Bias:
- Testing Methodology
  - BF Exclusivity?
  - Nipple Rinsing?
  - Clean-Catch milk samples?
- Do Pathogens vary by geography?
- Culture Media?
- PCR?
- Types of Bacteria/Degree of Growth
- Presentations
Summary of Findings
### Microbial Growth in Case Mothers with Nipple Pain and/or Deep Breast pain as Compared to Control Mothers Without Pain

<table>
<thead>
<tr>
<th>Study</th>
<th>n=</th>
<th>Findings</th>
<th>Nipple</th>
<th>Milk</th>
<th>Total # Positive</th>
<th>P value/RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amir, 1996</td>
<td>59 vs. 64</td>
<td>C. albicans</td>
<td>15% vs. 3%</td>
<td>9% vs. 2%</td>
<td>19% vs. 3%</td>
<td>0.05, NS, 0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S. aureus</td>
<td>34% vs. 3%</td>
<td>40% vs. 5%</td>
<td>42% vs. 5%</td>
<td>All @ 0.0001</td>
</tr>
<tr>
<td>Thomassen, 1998</td>
<td>40 vs. 20</td>
<td>C. albicans</td>
<td>43% vs. 5%</td>
<td>38% vs. 5%</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Skin Bacteria**</td>
<td>75% vs. 20%</td>
<td>55% vs. 30%</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Graves, 2003</td>
<td>28 vs. 23</td>
<td>C. albicans</td>
<td>0% vs. 4%</td>
<td>0% vs. 0%</td>
<td>N/A</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S. aureus</td>
<td>57% vs. 0%</td>
<td>48% vs. 0%</td>
<td>N/A</td>
<td>Both @ 0.001</td>
</tr>
<tr>
<td>Andrews, 2007</td>
<td>20 vs. 78</td>
<td>Yeast***</td>
<td>30% vs. 8%</td>
<td>20% vs. 3%</td>
<td>30% vs. 8%</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S. aureus</td>
<td>15% vs. 17%</td>
<td>20% vs. 8%</td>
<td>25% vs. 20%</td>
<td>NS</td>
</tr>
<tr>
<td>Panjaniyan, 2008</td>
<td>17 vs. 18</td>
<td>Fungi</td>
<td>65% vs. 33%</td>
<td>N/A</td>
<td>N/A</td>
<td>P&lt;0.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S. aureus</td>
<td>53% vs. 44%</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Morrill, 2005</td>
<td>32 vs. 68</td>
<td>C. albicans</td>
<td>22% vs. 3%</td>
<td>56% vs. 4%</td>
<td>63% vs. 4%</td>
<td></td>
</tr>
<tr>
<td>Hale, 2009</td>
<td>16 vs. 18</td>
<td>C. albicans</td>
<td>N/A</td>
<td>13% vs. 0%</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

*Others Candida, E Coli, Group B Strep, Acinetobacter  **S. aureus found in symptomatic women but not in controls  
***Mostly C. albicans (1 each with C. parapsilosis, C. guillermondii)
Figure 1: Pooled Average Percent of Symptomatic versus Control Mothers with Positive Nipple and Milk Findings*

*Percentile averages based on data from Table 2.
### A. For Candida

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Total Weight</th>
<th>Peto Odds Ratio</th>
<th>Peto Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomasse 1998</td>
<td>5</td>
<td>20</td>
<td>1</td>
<td>0.36 (1.43, 2.62)</td>
<td></td>
</tr>
<tr>
<td>Merril 2005</td>
<td>16</td>
<td>32</td>
<td>5</td>
<td>0.26 (1.05, 1.67)</td>
<td></td>
</tr>
<tr>
<td>Hale 2009</td>
<td>2</td>
<td>35</td>
<td>1</td>
<td>0.35 (0.53, 1.50)</td>
<td></td>
</tr>
<tr>
<td>Andrews 2007</td>
<td>4</td>
<td>20</td>
<td>2</td>
<td>0.42 (2.84, 15.45)</td>
<td></td>
</tr>
<tr>
<td>Amir, 1996</td>
<td>5</td>
<td>59</td>
<td>1</td>
<td>0.38 (1.45, 27.40)</td>
<td></td>
</tr>
<tr>
<td><strong>Total (55%)</strong></td>
<td><strong>147</strong></td>
<td><strong>245</strong></td>
<td><strong>100.2%</strong></td>
<td><strong>1.17 (0.54, 2.37)</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Total events:** 246, **Heterogeneity:** $\chi^2 = 4.62$, df = 4 ($P = 0.37$), $I^2 = 7$

**Test for overall effect:** $Z = 6.19$ ($P < 0.000001$)

### B. For S. aureus

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Total Weight</th>
<th>Peto Odds Ratio</th>
<th>Peto Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amir, 1996</td>
<td>25</td>
<td>59</td>
<td>1</td>
<td>0.19 (1.25, 18.24)</td>
<td></td>
</tr>
<tr>
<td>Andrews 2007</td>
<td>4</td>
<td>20</td>
<td>6</td>
<td>0.27 (0.75, 18.99)</td>
<td></td>
</tr>
<tr>
<td>Grice 1993</td>
<td>13</td>
<td>27</td>
<td>0</td>
<td>0.34 (3.31, 40.76)</td>
<td></td>
</tr>
<tr>
<td><strong>Total (55%)</strong></td>
<td><strong>106</strong></td>
<td><strong>145</strong></td>
<td><strong>100%</strong></td>
<td><strong>1.66 (1.00, 14.63)</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Total events:** 41, **Heterogeneity:** $\chi^2 = 1.16$, df = 2 ($P = 0.56$), $I^2 = 0$

**Test for overall effect:** $Z = 6.13$ ($P < 0.000001$)

### c. Both or Either

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Total Weight</th>
<th>Peto Odds Ratio</th>
<th>Peto Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amir, 1996</td>
<td>26</td>
<td>59</td>
<td>3</td>
<td>0.15 (1.81, 20.08)</td>
<td></td>
</tr>
<tr>
<td>Andrews 2007</td>
<td>7</td>
<td>20</td>
<td>8</td>
<td>0.32 (1.20, 25.70)</td>
<td></td>
</tr>
<tr>
<td>Grice 1993</td>
<td>13</td>
<td>27</td>
<td>0</td>
<td>0.34 (3.31, 40.76)</td>
<td></td>
</tr>
<tr>
<td>Hale 2009</td>
<td>7</td>
<td>16</td>
<td>0</td>
<td>0.31 (0.53, 15.00)</td>
<td></td>
</tr>
<tr>
<td>Merril 2005</td>
<td>20</td>
<td>32</td>
<td>3</td>
<td>0.72 (1.92, 39.44)</td>
<td></td>
</tr>
<tr>
<td>Thomasse 1998</td>
<td>5</td>
<td>20</td>
<td>1</td>
<td>0.36 (1.43, 2.62)</td>
<td></td>
</tr>
<tr>
<td><strong>Total (55%)</strong></td>
<td><strong>174</strong></td>
<td><strong>271</strong></td>
<td><strong>100%</strong></td>
<td><strong>16.99 (1.66, 17.84)</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Total events:** 73, **Heterogeneity:** $\chi^2 = 4.66$, df = 5 ($P = 0.46$), $I^2 = 0$

**Test for overall effect:** $Z = 9.19$ ($P < 0.000001$)
Odds Ratios and Relative Risk Ratios for Microbes in the Milk, Nipple and Either Site
Explanations of Confusing Characteristics

- Small Colony Variants
- S. Epidermidis
- Biofilms
Small Colony Variants (SCV’s)

One case published*

- Small colonies within the host’s cells.
  - Slower growing
  - Resistant to Medications
  - Hard to culture
  - Cause Low-grade, chronic and recurrent infections
  - Require Prolonged antibiotic therapy necessary for clearance

- Lactoferrin will select for SCV’s

- Treatment Choice: Macrolides penetrate intracellularly

*Eglash. Breastfeeding Medicine 2007;2 (2);99-104
# S. Epidermidis and *Mastitis*

### S. Epidermidis Strains’ Antibiotic Resistance During Mastitis (Red, Sore Breast, and Fever)

<table>
<thead>
<tr>
<th></th>
<th>Mupirocin MIC&gt;512 ug ml</th>
<th>Erythromycin MIC&gt;4 ug ml</th>
<th>Clindamycin MIC&gt;2 ug ml</th>
<th>Oxacillin MIC&gt;2 ug ml</th>
<th>Streptomycin MIC&gt;1000 ug ml &amp; Vancomycin MIC&gt;16 ug ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mastitis</td>
<td>43%</td>
<td>60%</td>
<td>28%</td>
<td>68%</td>
<td>3 strains (2/1) isolated</td>
</tr>
<tr>
<td>Healthy</td>
<td>22%</td>
<td>33%</td>
<td>8%</td>
<td>39%</td>
<td>NONE</td>
</tr>
<tr>
<td>P Values</td>
<td>0.0437</td>
<td>0.0201</td>
<td>0.0314</td>
<td>0.0125</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Delgado et al. BMC Microbiology 2009, 9:82
<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MIC  $ug/mL</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrofurantoin</td>
<td>32</td>
<td>100%</td>
</tr>
<tr>
<td>Rifampin</td>
<td>1</td>
<td>100%</td>
</tr>
<tr>
<td>Trimethoprim/Sulfamethoxazole</td>
<td>&lt;2/38</td>
<td>90%</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>≤ 4</td>
<td>80%</td>
</tr>
<tr>
<td>Ciprofloxin</td>
<td>≤ 0.5</td>
<td>76%</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>≤ 8</td>
<td>75%</td>
</tr>
</tbody>
</table>

*S. Epidermidis is a Coagulase Negative Staphylococcus*
S. epidermidis from Control Subjects: less likely to have the \textit{biofilms associated} production gene

(11\% Healthy Controls vs. 33\% Mastitis)

Biofilms: Are Slime

- Increases antibiotic resistance
- Increases false-negative culture rates
- Allows slow growth
- Known for causing Recurrent, Chronic, Low-grade Infections
  - Which often present without fever or other systemic symptoms
- Within Biofilms Candida albicans and staphylococci can be synergistic
- Traditionally Explored in Relationship to Medical Devices and Catheters


Characterization of Mucosal Candida albicans Biofilms

Figure 1. C. albicans presence in “white plaque” lesions formed on the tongue of mice with oropharyngeal candidiasis. C. albicans challenged mice were sacrificed after 5 days of oral exposure to the GFP-expressing strain MRL51. Panel A depicts the dorsal aspect of a tongue from an uninfected control. Panel B depicts the white plaque lesions formed on the tongue of an infected mouse. Panel C depicts a three dimensional reconstruction of a live biofilm as visualized via confocal microscopy.

Subjective: Mother of 7 mo old Tx for mastitis early postpartum developed burning breast pain. Re-treated with cephalexin (Kelfex) for burning pain. Pain worsened and she was Dx w/ pulled a muscle or engorgement

OBJECTIVE:

ASSESSMENT: Candida Ductal Infection r/o Bacterial

PLAN:
- Cultures (Nipple and Milk)
- Diflucan 200 mg 2 po today and then one daily until symptoms resolved 100% for 7 days
- Lotrimin or Monistat OTC to Nipple Post-feeding
OUTCOME:
- Cultures: Scant Growth S. aureus and S. epidermidis
- Both Resistant (S. epidermidis resistant to all oral meds except levofloxacin—Levaquin).
- Symptoms 80% better but not resolved
- Levofloxacin initiated for 2 wks w/ resolution

Healed Nipple
Subjective: Hx Nipple Trauma Early Postpartum now Severe Bilateral burning breast pain x wks

OBJECTIVE: 1 ml thin light yellow/off white flake bilateral During Feed: no nipple vasospasm or pain

ASSESSMENT: Vasospasm vs. Infection

PLAN:
✓ Cultures (Nipple and Milk)
✓ Motrin prn
✓ Watch for Vasospasm

OUTCOME:
• Preliminary: Heavy growth of S. aureus (without sensitivities)
• Cephalexin (Keflex) 500mg QID x 14 days with 1 refill
• No relief and Sensitivities showed resistance to Cephalexin
• Resolved w/ Sulfamethoxazole-trimethoprim (Septra DS) BID x 14 days
First E-mail

Day 1: Previously saw OB and Pediatrician
- Infant w/ Thrush x 5 wks - Tx with fluconazole (Diflucan)
- Developed razor sharp pain/burning
- Using monistat/probiotics
- Previously Tx by OB w/ 1 dose fluconazole
- Told Nipple Thrush Doesn’t Exist

Day 3-8: Sees Midwife
- Tx w/ Diflucan x 2 wks
- Refuses to Culture—will only tx for 2 wks
- On fluconazole 5 d and slightly better
- But now w/ nipple cracking

Day 10-11: Urgent Care
- Relapses—entire breast tender to touch
- Refused to Culture
- Tx w/ Sulfamethoxazole-trimethoprim (Septra DS) x 7 d

Day 12: Worse—feeling ill switched to dicloxacillan (Diclox) 500mg BID x 7d
Day 16

OFFICE VISIT: Cracks healing - much improved

ASSESSMENT: Mixed Ductal Infection / Early Mastitis?

Plan:
- Continue DicloxBID for a total of 14 days.
- Continue Diflucan 200mg until symptoms 100% resolved for 7 days
- Get larger cone/flange for pump

OUTCOME:
Day 21: Cracks recurred. Instructed to increase DicloxBID QID
  - Larger flange helped

Day 23: Breast / Nipple very painful again.
  - Decrease DicloxBID
  - Increase Diflucan to 400mg QD x 7 d & F/u.

Day 29: Seen again and Finally Significantly Improved. Completed diclox
  - Continue Diflucan—Continued for @ 7 wks total
Case of Resistant Coagulase Negative Staphylococcus (S. epidermidis?)

Subjective: Self treated with clotrimazole (Gynelotrimin) without resolution. Prior Tx with fluconazole (Diflucan) for mother and Gentian Violet for infant for a Ductal Infection with improvement but not resolution at 4 wks.

OBJECTIVE: Nipples: 2+ pink Scabs Resolving and sensitive to touch

ASSESSMENT: Mixed Ductal vs. Nipple Infection

PLAN:
- Cultures (Nipple and Milk)
- Mupricin (Bactroban)
- Continue fluconazole

OUTCOME:
- Cultures: Moderate growth resistant CNS
- Initially improved w/ mupricin and fluconazole
- Pain Re-exacerbated:
- Rx: Sulfamethoxazole-trimethoprim (Septra DS) 1 bid for 14 days
- Improvement w/in a Few Days with gradual resolution
- Took Fluconazole 5-6 wks total
Subjective: 1 month old hospitalized for bloody emesis. Mom Hx cracked nipples. MD instructed to pump and bottle-feed on right.

Objective: Nipples: 2-3 mm deep by 3 mm wide fissure center of right nipple. Baby w/out signs of thrush.

Assessment: Bacterial Ductal Infection.

Plan:
- Cultures (Nipple and Milk)
- Empiric TX: Bactrim (Trimethoprim/Sulfamethoxazole)

Outcome:
- Cultures: Positive for S. aureus/Negative for Candida. Sensitive to and TX w/ Bactrim (Trimethoprim/Sulfamethoxazole).
- 1-2 wks Later—Fissure healing.
- Symptoms improved but unresolved.
- Mom describes white coating on nipples.
- Tx w/ Diflucan and symptoms resolved within a few days.
Conclusions

- Once you have Corrected Latch problems and R/O Primary Vasospasm

- Statistics/Percentiles Support an Infective Process
  - Candida OR’s in Milk the Highest, Followed by S. aureus

- Biofilm producing Organisms, Small Colony Variants and Resistant CNS May Play a Part

- Application to Treatment:
  - Culture for BOTH Yeast and Bacteria
  - Monitor for Vasospasm
  - Initial TX: Empirically? Wait for C&S?
  - If Cultures Negative; still treat? Or repeat?
Any Questions???