

ANNOTATED BIBLIOGRAPHY
PERSISTENT BREAST AND/OR NIPPLE PAIN IN HUMAN LACTATION
2016

Abbreviations:

CFU	colony-forming units	PCR-DGGE	polymerase chain reaction-denaturing gradient gel electrophoresis
C(o)NS	coagulase-negative Staphylococcus	PFGE	pulsed field gel electrophoresis
EDPS	Edinburgh Postnatal Depression Scale	PP	postpartum
FISH	fluorescent <i>in situ</i> hybridization	SCV	small colony variant
hx	history	TMP/SMX	trimethoprim/sulfamethoxazole
IFPS (II)	Infant Feeding Practices Survey (II) – CDC		
MIC	minimal inhibitory concentration		

Definition of persistent breast pain

Amir, L. H. (2014). "ABM clinical protocol #4: Mastitis, revised March 2014." <i>Breastfeed Med</i> 9(5): 239-243.	Citation for mastitis protocol.	n/a
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Background

DNPAO, National Center for Chronic Disease Prevention and Health Promotion. Infant Feeding Practices Survey II: Results. Centers for Disease Control and Prevention. http://www.cdc.gov/ifps/results/ch2/table2-37.htm Published October 1, 2009. Accessed June 23, 2014.	Relevant data from the Infant Feeding Practices Survey (IFPS II): Pain associated with breastfeeding is common in the early post-partum period, affecting 72.5% of mothers on the first day, 95.1% during the first week, and 79.5% during the second week [or just 75.4% of mothers in the first two weeks total].	II-2
Thulier D, Mercer J. Variables associated with breastfeeding duration. <i>J Obstet Gynecol Neonatal Nurs</i> . 2009 May-Jun;38(3):259-68. doi: 10.1111/j.1552-6909.2009.01021.x.	" Since this is a common cause for early breastfeeding cessation the mother-baby dyad should be evaluated by a lactation specialist"	III
Buck ML, Amir LH, Cullinane M et al. Nipple pain, damage, and vasospasm in the first 8 weeks postpartum. <i>Breastfeed Med</i> . 2014; 9(2): 56-62.	<ul style="list-style-type: none"> - Prospective cohort, 360 primiparous women - After birth and before hospital discharge, 79% had nipple pain - At some point during 8 weeks of study, 58% reported nipple damage, 23% reported vasospasm. - AFTER 8 weeks, 8% still reported nipple damage, and 20% still had nipple pain - Cited McCann et al: "38% of breastfeeding women at 1 mo PP had persistent sore nipples" *common advice is that nipple tenderness should subside after first week or two and that ongoing nipple pain is abnormal - Cited Scott 2001, Odom 2013 regarding cessation of BFing early/before hospital discharge 	II-2
Li R, Fein SB, Chen J, Grummer-Strawn LM. Why mothers stop breastfeeding: mothers' self-reported reasons for stopping during the first year. <i>Pediatrics</i> 2008;122 Suppl 2:S69-76.	Of mothers who stopped breastfeeding during the first month post-partum, 29.3% cited pain and 36.8% identified sore, cracked or bleeding nipples as an important reason. Of those who stopped between the 1 st and 2 nd month, 15.8% cited pain and 23.2% identified sore, cracked or bleeding nipples as important.	II-2
Amir, L. H., L. Dennerstein, et al. (1996). "Psychological aspects of nipple pain in lactating women." <i>J Psychosom Obstet Gynaecol</i> 17(1): 53-58.	Study design: Prospective cohort study of lactating women >2 weeks PP presenting with nipple pain lasting > 1 week. All women with pain were treated for Candida with medication and diet (N=48). Comparison group comprised 37 members of the Nursing Mothers' Association of Australia and 21 women seen in Maternal and Child Health Centres and seven	II-2

	<p>women at postnatal checkup (N=65).</p> <p>Outcome measures: EPDS and Profile of Mood States (POMS).</p> <p>Results: Symptomatic mothers had younger infants than asymptomatic mothers (3.7 vs. 10.5 wks pp). EPDS ≥ 13 was more common among symptomatic mothers (38% vs 14%) and POMS disturbance scores were higher. After resolution of pain, EPDS and POMS scores in the symptomatic group were improved, but 11 women were lost to follow-up, including 4 women who were still experiencing breastfeeding problems and were therefore excluded from the analysis.</p> <p>Conclusion: Elevated depression scores in the setting of nipple pain may reflect situational, rather than chronic, depression, and treatment of underlying pain may resolve mood symptoms.</p> <p>Limitation: Differential loss to follow-up among mothers with mood symptoms and exclusion of mothers with persistent pain may have biased these results. The study does not report what percentage of the mothers who were lost to follow-up were symptomatic at presentation.</p> <p>Additional info: Article states that 96% of BFing women experience nipple pain at some point in the first 6 wks PP.</p>	
<p>Watkins, S., S. Meltzer-Brody, et al. (2011). "Early breastfeeding experiences and postpartum depression." <i>Obstet Gynecol</i> 118(2 Pt 1): 214-221.</p>	<ul style="list-style-type: none"> - Secondary analysis from IFPS data (CDC); cross sectional? - Hypothesized an association between early breastfeeding experiences and postpartum depression at 2 months - PP depression status assessed with Edinburgh Postnatal Depression Scale (EDPS) - 2,586 women reported ever breastfeeding, among whom 223 (8.6%) met criteria for major depression (Edinburgh Postnatal Depression Scale 13 or greater) at 2 months postpartum - Women who disliked breastfeeding in the first week were more likely to experience postpartum depression at 2 months (odds ratio [OR] 1.42, 95% confidence interval [CI] 1.04-1.93) adjusting for maternal age, parity, education, ethnicity, and postnatal WIC participation - Women with severe breastfeeding pain in the first day (adjusted OR 1.96, 95% CI 1.17-3.29), the first week (adjusted OR 2.13, 95% CI 0.74-6.15 compared with no pain), and the second week (adjusted OR 2.24, 95% CI 1.18-4.26 compared with no pain) were more likely to be depressed. - Breastfeeding help appeared protective among women with moderate (adjusted OR 0.22, 95% CI 0.05-0.94) or severe (adjusted OR 0.17, 95% CI 0.04-0.75) pain with nursing. 	II-2
<p>Blair A, Cadwell K, Turner-Maffel C, et al. The relationship between positioning, the breastfeeding dynamic, the latching process and pain in breastfeeding mothers with sore nipples. <i>Breastfeed Rev</i> 2003;11(2):5-10.</p>		II-2
<p>Morland-Schultz, K. and P. D. Hill (2005). "Prevention of and therapies for nipple pain: a systematic review." <i>J Obstet Gynecol Neonatal Nurs</i> 34(4): 428-437.</p>	<p>Review article – articles from 1983 to 2004</p> <ul style="list-style-type: none"> - Studies evaluated: warm water compresses, tea bags, heat, mother’s milk, lanolin, vitamin A, collagenase, dexpanthenol, hydrogel, glycerin gel, moist occlusive dressing, education re: latch and positions, and no tx - No single topical agent showed superiority - Most important is education re proper BFing technique and latch AND anticipatory guidance re high incidence of early PP nipple pain 	I
<p>Woolridge, M. W. (1986b). The ‘anatomy’ of infant sucking. <i>Midwifery</i>, 2, 164-171.</p>	<p>Detailed description of the mechanics of latch and milk removal from the breast.</p> <p>Distinction between nutritive and non-nutritive sucking; proposal that the former helps draw the nipple out, filling the oral cavity, and “reversing any loss of grasp – primary difference is duration of negative pressure applied, not necessarily change in tongue position.</p>	III
<p>Lau, C., E. O. Smith and R. J. Schanler (2003). "Coordination of suck-swallow and swallow</p>	<p>“Infants that are premature, have low oral tone, reflux / aspiration or congenital anomalies may be at risk for disorganized suckling.”</p>	III?

respiration in preterm infants." Acta Paediatr 92(6): 721-727.		
Power, R. F. and J. F. Murphy (2015). "Tongue-tie and frenotomy in infants with breastfeeding difficulties: achieving a balance." Arch Dis Child 100(5): 489-494.	"Ankyloglossia (tongue-tie), recognized in 0.02-10.7% of newborns, involves the restriction of tongue movement (projection) beyond the lower gum"	I

Differential Diagnosis

Nipple damage

Ballard JL, Auer CE, et al. Ankyloglossia: assessment, incidence, and effect of frenuloplasty on the breastfeeding dyad. Pediatrics. 2002; 110 (5): e63.	<p>Study Design: A study of mothers having problems breastfeeding to determine 1) the significance of ankyloglossia, 2) incidence in breastfeeding infants, and 3) the effectiveness of frenuloplasty in regards to solving breastfeeding issues.</p> <p>Methods: 2763 inpatient breastfeeding infants and 273 outpatient infants with breastfeeding issues. Hazelbaker Lingual Assessment Tool was used to score function and appearance of infant tongue. Scores were related to quality of infant latch and severity of maternal nipple pain. On infants that qualified, frenuloplasty was performed. Maternal nipple pain and infant latch were reassessed.</p> <p>Results: Ankyloglossia was diagnosed in 3.2% of the inpatient infants and 12.8% of the outpatients. Mean scores for the presenting sx's of poor latch and maternal nipple pain were similar. All frenuloplasty cases were performed successfully and saw improvements in latch. Maternal nipple pain decreased significantly from 6.9 +/- 2.31 prior to the procedure to 1.2 +/- 1.52 after.</p> <p>Conclusion: Ankyloglossia is common among newborns and is frequently associated with poor latch and maternal nipple pain. Frenuloplasty is shown to be a successful option when attempting to facilitate breastfeeding in cases of significant ankyloglossia.</p>	II-2
Segal, L. M., R. Stephenson, et al. Prevalence, diagnosis, and treatment of ankyloglossia: methodologic review. Can Fam Physician. 2007; 53 (6): 1027-1033.	<ul style="list-style-type: none"> - Methodologic review of current lit re: ankyloglossia - No well-validated clinical method for dx of ankyloglossia - Prevalence 4-10% (5 studies) - Effectiveness of frenotomy for improving nipple pain, sucking, latch, continuation of BFing (from 6 non-random and 1 randomized study) – "all suggested frenotomy was beneficial" 	I
Wall V, Glass R. Mandibular asymmetry and breastfeeding problems: experience from 11 cases. J Hum Lact. 2006; 22 (3): 328-334.	<p>Study Design: Case series</p> <ul style="list-style-type: none"> - "Low jaw asymmetry is an early identifiable sign of torticollis, and a possible contributor to latch difficulties, nipple pain, and poor milk transfer." - During 2 years, researchers collected stories of babies with difficult latch (11 babies; unable to latch or could not sustain latch for more than a few sucks) and associated maternal nipple soreness (8 of 11 mothers) - Babies' lower alveolar ridge or gumline appeared depressed on one side and/or elevated on the opposite side – none had dx of torticollis upon presentation - All the mothers had "normal nipples" and "milk production was appropriate" - 2 infants had sepsis workups in the hospital; 5 lost more than 8% of birth weight; 9 received supplementation at some point (formula/expressed milk via finger feeding / bottle / tube at breast) in the first week – 2 of those 9 also tried a nipple shield - Signs of torticollis: 1) preference for holding head to one side, 2) one ear "cupped" forward, 3) lower jaw tilted to one side, 4) mild flattening of the head, 5) one eye smaller/higher - Solutions for these infants: 1) positioning infant on the side that allows for most effective suckling and milk transfer (and maintenance of this body position regardless of which breast the infant feeds from), 2) chin support (mother's / father's hand) --- until weight velocity is appropriate for the 	III

	first 2-3 weeks (correction of head position can begin afterwards)	
Qi Y, Zhang Y, Fein S et al. Maternal and breast pump factors associated with breast pump problems and injuries. <i>Journal of human lactation (J Hum Lact)</i> . 2014; 30(1) 62 -72. doi: 10.1177/0890334413507499	<ul style="list-style-type: none"> - Prevalence of injuries: 14.6% (at least 1 breast pump-related injury; - Most common were: sore nipples [12.5% of all mothers, 85.8% of mothers with an injury], a pressure bruise [3.6% of all mothers, 24.5% of injured], nipple injury [2.2% of all mothers, 15.2% of injured]) (Qi 2014) - Sore nipples not necessarily caused by pump (latch more likely, soreness exacerbated by pump) -Predictors of injuries: <p>Note: paper used survey data from mostly advantaged women with full-term babies (no preemies, LBW babies, few minorities), recall or reporting bias may have played role</p> <ul style="list-style-type: none"> - type of pump (Becker 2011, Sisk 2006) – specifically, a battery-operated pump (173% higher risk for injury compared to mothers using an electric pump) (Qi 2014) --- less powerful / stable motor and poor suction? *less than 2% of surveyed mothers used this type of pump, so predictive power is actually quite low - pregnancy complications, primiparity, and anxiety with pump use (Boo 2001, D’Amico 2003) - breastfeeding intentions: not intending to BF at least 12 mo (Qi 2014) --- less effort in preparation, less support? - type of delivery (anything except planned cesarean assoc with higher risk of injury, Qi 2014) --- unclear why ... medication use, mother’s fatigue level, edema after longer labors? - problems with breast pump (Qi 2014) - other sources: literacy level, age, education, income level (Sisk 2006, Boswell-Penc 2007), unmarried, higher BMI, smoker (Qi 2014 – univariate analysis only, association not sig with covariate analysis) 	II-2

Differential Diagnosis (continued)

Dermatoses

Barankin B, Gross MS. Nipple and areolar eczema in the breastfeeding woman. <i>Journal of Cutaneous Medicine and Surgery</i> . 2004; 126-130.	<p>This review (protocol) describes the clinical presentation, etiology, differential diagnosis, and management of nipple/areolar eczema (the clinical manifestation of several types of dermatitis) in lactating women. Erythema, crusting, and/or erosions may signify an acute presentation while subacute, chronic eczema may appear as a dry, erythematous, lichenified and scaling dermatitis. Lesions may cause pain, itching and/or a burning sensation. The authors note that half of women who developed nipple/areolar eczema in their patient panel had a prior hx of eczema while the other half developed it as a contact dermatitis following the introduction of solids in the baby’s diet. Water, soaps, detergents, fragrances, and other topical agents may also contribute to irritation and hypersensitivity, leading to the development of eczema. Differential diagnosis includes bacterial infection of the breast, mammary candidiasis (?), and mammary Paget’s disease. A thorough maternal hx (atopy, eczema, dermatitis, allergens/irritants), introduction of solids to the infant at or after 6 months, and adequate moisturization are cited as preventative strategies. Topical corticosteroids are noted as the primary treatment approach, though the authors place emphasis on careful monitoring for side effects as well as prevention of steroid ingestion by the infant. The authors also note a strong prevalence of <i>S. aureus</i> colonization in women with atopic dermatitis. They suggest either topical (mupirocin, polysporin, or fusidic acid) or oral antibiotics for infected eczema, although oral medication is cited as more effective at treating the infection and preventing recurrence.</p>	III
Schalock PC, Hsu JTS, Arndt KA. <i>Lippincott's Primary Care Dermatology</i> . Lippincott Williams & Wilkins, Sep 15, 2010 p. 29, 232-236	<p>p 29, 232-236 Overview of atopic dermatitis including physical findings. P 146-147 Overview of varicella zoster virus / transmission pp 174-175 Overview of breastfeeding during varicella infection</p>	n/a

(repeat citation for Barankin and Gross 2004- above)		
Barrett ME, Heller MM, Fullerton Stone H, Murase JE. Dermatoses of the breast in lactation. <i>Dermatologic Therapy</i> . 2013 26: 331-336.	Abstract: Dermatoses of the breast during lactation can be difficult to diagnose because of their overlapping clinical appearances. It is important to properly diagnose and treat nipple dermatitis since it can be a significant source of pain when nursing. Poorly controlled nipple pain in nursing mothers is one of the primary reasons for breastfeeding to be discontinued earlier than is recommended. Therefore, it is relevant for practicing dermatologists to be aware of certain facts in a patient's history, specific physical exam findings, and the most appropriate laboratory tests used to diagnose these conditions. In addition, the therapeutic approach should be effective and safe for the mother and infant. This review article provides dermatologists with a detailed discussion on the clinical features and management of various breast dermatoses seen in lactation, including atopic dermatitis, irritant contact dermatitis, allergic contact dermatitis, psoriasis, bacterial infections, yeast infections and herpes simplex virus infections.	III
Mervic L. Management of moderate to severe plaque psoriasis in pregnancy and lactation in the era of biologics. <i>Acta Dermatovenerol Alp Pannonica Adriat</i> . 2014;23(2):27-31.	"Flares can occur during lactation sporadically, usually 4-6 weeks after delivery"	III
(repeat citation for Barankin and Gross 2004 - above)		
Kollmorgen DR, Varanasi JS, Edge SB, et al. Paget's disease of the breast: a 33-year experience. <i>J Am Coll Surg</i> . 1998 Aug;187(2):171-7.	Clinical features associated with Paget's disease (PD) include: "nipple or areolar eczema, ulceration, moist erythema, chronic vesicles, or granular erosions"	II-3

Differential Diagnosis (continued)

Infection

Amir LH, Donath SM, Garland SM, et al. Does Candida and/or Staphylococcus play a role in nipple and breast pain in lactation? A cohort study in Melbourne, Australia. <i>BMJ Open</i> 2013;3:e002351. doi:10.1136/bmjopen-2012-002351	<ul style="list-style-type: none"> - Prospective cohort study; n=360 (340 completed study); f/u x6: hospital, weekly until 4 wk pp, phone at 8 wk pp - Cases: "Nipple/breast thrust" = Burning nipple pain and breast pain "(not related to mastitis)" - Samples taken at recruitment (> or = 36 wks gestation during preg) and at weekly visits (maternal: nasal, nipple, breastmilk [both sides]; infant: oral, nasal) - Nipple swabs: "standard charcoal swab for microbiological analysis" and "flocked swab for molecular analysis" - Oral, vaginal swabs cultured for S aureus and Candida - BM samples cultured for S aureus, CoNS, and Candida - Nasal swabs cultured only for S aureus - Candida detected via culture and PCR; tested mother's vagina, nipple, breast milk, baby's mouth - S aureus detected in breast milk or on mother's nipple - Cases more likely to have Candida spp in samples from nipple/BM/baby's mouth (54% vs 36%, p=0.014) - S aureus equally likely in cases and asymptomatic women (82% vs 79%, p = 0.597) - Candida detection and nipple damage predicted pain symptoms; S aureus colonization did not 	II-2
Cucarella C, Solano C, Valle J, Amorena B, Lasa I, & Penadés JR. Bap, a Staphylococcus aureus	A biofilm-producing <i>Staphylococcus aureus</i> isolate was used to generate mutants in order to elucidate the locus responsible for adherence to <u>abiotic</u> surfaces. The identified locus, <i>bap</i> (for biofilm associated protein), encodes	III?

<p>surface protein involved in biofilm formation. <i>Journal of Bacteriology</i>. 2001; 183(9): 2888-2896.</p>	<p>a cell wall associated protein found in 5% of the 350 <i>S. aureus</i> bovine mastitis isolates studied. The amino acid sequence was absent from the 75 clinical human <i>S. aureus</i> isolates analyzed. The <i>bap</i> gene has little sequence similarity to other genes but is organizationally similar to surface proteins on both gram-negative and -positive organisms. An interesting feature of <i>bap</i> is its extensive repeat region, which may play a role in evasion of the host response (as is demonstrated with group B streptococci). This study explores biofilm formation in vivo using an indwelling catheter in mice, but makes conjectures about the role of <i>bap</i> in “subclinical mastitis” without solid evidence of its relevance in adherence to <u>biotic</u> surfaces.</p>	
<p>von Eiff C, Proctor RA, & Peters G. Coagulase-negative staphylococci. <i>Postgraduate Medicine</i>. 2001; 110(4): 63-76.</p>	<p>This review articles highlights the recent recognition of coagulase-negative staphylococci (in humans, <i>S. epidermidis</i>, <i>S. haemolyticus</i>, <i>S. schleiferi</i>, <i>S. saprophyticus</i>, <i>S. xylosus</i>, and <i>S. lugdunensis</i>) as potentially pathogenic bacteria. Antibiotic resistance is a capability noted in 80-90% of isolates from humans. Identification and discrimination between invasive and contaminating strains to elucidate implication in disease are current barriers and thus active areas of research. Clinical manifestations appear to be substantially different than those caused by <i>S. aureus</i> and are usually subtle, nonspecific, and/or chronic. The <i>ica</i> (intercellular adhesion gene cluster) and <i>mecA</i> (methicillin resistance) genes have been detected more often in infecting strains than in contaminating strains. The basics of staphylococcal biofilms are also presented.</p>	III
<p>Fox L, Zadoks RN, Gaskins CT. Biofilm production by <i>Staphylococcus aureus</i> associated with intramammary infection. <i>Veterinary Microbiology</i>. 2005; 107: 295-299.</p>	<p>Isolates of <i>S. aureus</i> (n=221) from milk, teat skin or milking machine liner samples from 45 dairy cow herds (random sample of 30-100 cows per herd) were evaluated for biofilm-forming ability. Milk isolates formed biofilm more readily (41%) than those from teat skin (24.7%) or liners (14.7%). The authors suggest that the ability to form biofilm assists in the attachment to mammary mucosal surfaces and thus permits the establishment of persistent infection. Biofilm-positive isolates tended to cluster into two PFGE genotypes, suggesting that strain or PFGE subtype is predictive of biofilm-forming ability rather than the isolate source. Biofilm formation was measured indirectly (extracellular stain); a methodology suggested as preferable by others is testing for the <i>ica</i> gene implicated in biofilm formation.</p>	III
<p>Melchior MB, Vaarkamp H, Fink-Gremmels J. Biofilms: A role in recurrent mastitis infections? <i>The Veterinary Journal</i>. 2006; 171: 398-407.</p>	<p>This review article discusses the current challenges of antibiotic therapy in acute and chronic [bovine] mastitis and the nature of bacterial biofilms (formation, maturation, resistance to antibiotics). Especially noteworthy is the description of biofilm dynamics, whereby cells shed from one biofilm may form a new biofilm elsewhere and thus contribute to the relapse of infection and necessitate extended therapy. Three classes of antibiotics, including tetracyclines, quinopristine-dalfopristins and erythromycin, have been shown to actually <u>stimulate</u> the expression of the <i>ica</i> genes in <i>S. epidermidis</i> that <u>facilitate</u> biofilm formation. Phosphomycin and cephalosporins (cefuroxime and cefazolin) were active against biofilm bacteria; cephalosporins affect cell walls and may increase the efficacy of other antibiotics such as rifampin (against CoNS), macrolides, and aminoglycosides, which are effective against cells in suspension. Cephalosporin efficacy has been shown in biofilms of up to 4 days old (from reference: Amorena et al 1999).</p>	III
<p>Oliveira M, Bexiga R, Nunes SF et al. Biofilm-forming ability profiling of <i>Staphylococcus aureus</i> and <i>Staphylococcus epidermidis</i> mastitis isolates. <i>Veterinary Microbiology</i>. 2006; 118: 133-140.</p>	<p>Thirty-two (32) subclinical mastitis isolates of <i>S. aureus</i> (n=16) and <i>S. epidermidis</i> (n=16) from dairy cows in Portugal were evaluated for biofilm production. The authors also investigated the utility of FISH for direct observation of biofilm in liquid milk samples, as compared to the standard of optical density measurement. After 24 hours, approx. 37.5% of all <i>Staphylococcus</i> isolates were biofilm-producers, with rates nearly equivalent between <i>S. aureus</i> and <i>S. epidermidis</i>, as determined by phenotypic assay [milk plated on culture dishes]. The use of FISH with milk samples identified the same 37.5% <i>Staphylococcus</i> isolates as biofilm-producers while optical density measurement produced results less consistent with the phenotypic assay. The authors assert that FISH can be</p>	III

	used as a rapid, effective screening tool for biofilm production by <i>Staphylococci</i> in milk samples and thus speed treatment of infection.	
Adam B, Baillie GS, Douglas J. Mixed species biofilms of <i>Candida albicans</i> and <i>Staphylococcus epidermidis</i> . <i>Journal of Medical Microbiology</i> . 2002; 51: 344-349.	The development of mixed species biofilms in vitro, using two strains of <i>S. epidermidis</i> (slime-producing wild type and slime-negative mutant) and <i>C. albicans</i> , demonstrated that the two species interact extensively. An extracellular polymer produced by slime-positive wild type <i>S. epidermidis</i> in a 48-hour-old biofilm inhibited fluconazole penetration, and the presence of <i>C. albicans</i> appeared to provide protection for mutant <i>S. epidermidis</i> against vancomycin.	III
Harriott MM, Noverr MC. <i>Candida albicans</i> and <i>staphylococcus aureus</i> form polymicrobial biofilms: Effects on antimicrobial resistance. <i>Antimicrobial Agents and Chemotherapy</i> . 2009; 53(9): 3914-3922.	This study asserts that although <i>S. aureus</i> forms poor monoculture biofilms in serum, it forms a substantial polymicrobial biofilm in the presence of <i>C. albicans</i> . Microcolonies of <i>S. aureus</i> with a novel matrix phenotype (ie. likely coated by <i>Candida</i> matrix) appear to form on/within a scaffolding (comprising of hyphae) of <i>C. albicans</i> and demonstrate increased resistance to vancomycin because of this arrangement.	III
Yang LA. Current understanding of multi-species biofilms. <i>International Journal of Oral Science</i> . 2011; 3: 74-81.	This review article discusses the mechanisms of coaggregation of different species in biofilms (eDNA, pili, adhesins), methods used to identify and quantify constituents of biofilms (16s rRNA and DGGE, real-time PCR, FISH), and common groupings of species (including <i>S. aureus/S. epidermidis</i> and <i>C. albicans</i>). The authors recognize the overall lack of reproducible results due to the specificity of lab techniques used by different groups and call for standardization of this research.	III
Proctor RA, von Eiff C, Kahl BC, et al. Small colony variants: a pathogenic form of bacteria that facilitates persistent and recurrent infections. <i>Nature Reviews: Microbiology</i> . 2006; 4: 295-305.	This review article discusses in detail the characteristics of SCVs that may facilitate their role in persistent infection. The incidence of SCVs in clinical specimens has ranged from 1% to more than 30%. Internalization of SCVs by phagocytes as well as endothelial and epithelial cells, fibroblasts, osteoblasts and keratinocytes has been documented. This process may shield SCVs from antibiotic therapy or host defense mechanisms, explaining the difficulty often encountered in clearing the infection. Increased display of fibronectin-binding adhesins may facilitate internalization. Krebs cycle deficits, causing an abnormal membrane potential, may help explain why SCVs are less susceptible to cationic antimicrobials. Furthermore, the slow growth of SCVs is likely to make them more resistant to cell-wall-active antibiotics such as beta-lactams.	III
Atalla H, Gyles C, Jacob CL, Moisan H, Malouin F, & Mallard B. Characterization of a <i>Staphylococcus aureus</i> small colony variant (SCV) associated with persistent bovine mastitis. <i>Foodborne Pathogens and Disease</i> . 2008; 5(6): 785-799.	Foremilk samples from 11 dairy cows with hx of chronic <i>S. aureus</i> mastitis were cultured and evaluated for growth, genetic/transcription profiles, auxotrophism, antimicrobial susceptibility, and intracellular persistence. Small-colony variant (SCV) isolates were detected in 3 of the 6 "typical" <i>S. aureus</i> colonies, grew in an unstable manner in antibiotic-free broth, and were outgrown by the typical phenotype; in broth with gentamicin, SCV Heba3231 grew seven times more slowly than its parent strain and had a comparatively low cell density. In addition, although as sensitive as other strains to erythromycin, oxacillin, rifampicin, vancomycin and TMP/SMX, SCV Heba3231 was resistant to gentamicin. The number of SCVs internalized by bovine endothelial cells was up to 40 times higher than the number of the parent strain, with minimal cell damage. The authors suggest that this process may play a key role in the persistence of <i>S. aureus</i> mastitis and the difficulty in eliminating the infection. Also noted is the challenge in growing SCVs, which are often found in a mixed population and are easily outgrown by the parent phenotype; sub-inhibitory concentrations of antibiotic were used eliminate most of the parent strain allowing the SCV phenotype to become the majority. This phenomenon is suggested as a possible cause of persistent mastitis that does not respond well to antibiotic treatment.	III
(repeat citation of Barankin and Gross 2004 - above)		
Eglash A, Plane MB, Mundt M. History, physical and laboratory findings, and clinical outcomes of lactating women treated with	Charts of 64 patients who presented to a lactation specialist from 1997 to 2002 and were treated with antibiotics for their breast and/or nipple pain were reviewed. Median time to pain onset was 1 week PP, and 78% of patients had pain begin in the first 1 to 2 weeks. More than 75% of women	II-3

<p>antibiotics for chronic breast and/or nipple pain. <i>Journal of Human Lactation</i>. 2006; 22(4): 429-433.</p>	<p>had breast tenderness and bilateral deep, dull, aching breast pain during and after feeding. Half of women had sharp, shooting pain and nearly all had either a bruised or burning type of nipple pain. Recent hx of nipple cracks and sores was reported for 75% of women. Most women did not have signs of acute inflammation. All women were treated with antibiotics for 3 to >6 weeks, with type and dose depending on known allergies/intolerances of mother/infant, patient preference for frequency of administration, bacterial sensitivities based on culture results, and medication cost. Antibiotics used include: cephalexin (500 mg 4x/day), dicloxacillin (500 mg 4x/day), clindamycin (300 mg 4x/day), erythromycin (333 mg 3x/day), and amoxicillin/clavulanate (875 mg 2x/day). Sixteen percent of all patients weaned because of the pain even though 70% had pain resolution with tx. Ninety-four percent of all patients had pain resolution; most patients had pain resolution by 6 weeks after starting antibiotics, and average duration of antibiotic use was 5.7 weeks. Future prospective RCTs are needed to distinguish symptoms and clinical signs of chronic breast infections as well as to determine appropriate treatment.</p>	
<p>Delgado S, Arroyo R, Jiménez E, Fernández L, Rodríguez JM. Mastitis infecciosas durante la lactancia: un problema infravalorado (I) <i>Acta Pediatr. Esp</i>. 2009; 67(2): 77-84.</p> <p>Title (English): Infectious mastitis during lactation: an underrated condition (I).</p>	<p>This literature review highlights the need for more prospective studies on infectious mastitis in which cellular, biochemical, immunologic and complementary microbiological data is collected in order to define the etiology of the disorder. The authors assert that the most likely cause is a dysbiosis of bacteria in the breasts, with <i>S. aureus</i> and <i>epidermidis</i> – especially in the form of biofilms - as the species overshadowing the normal diversity of the region. They also suggest that genetic predisposition may contribute to vulnerability of the host to dysbiosis caused by normally commensal bacteria. Delgado et al. also assert that faulty experimental design and logic have led to an ingrained assumption of the role of <i>C. albicans</i> despite no strong evidence supporting it as a major causative agent.</p>	II-2
<p>(repeat citation for Eglash and Plane 2006)</p>		
<p>Hale TW, Bateman TL, Finkelman MA, Berens PD. The absence of <i>Candida albicans</i> in milk samples of women with clinical symptoms of ductal candidiasis. <i>Breastfeeding Medicine</i>. 2009; 4(2): 57-61.</p>	<p>BM samples were obtained from eighteen (18) asymptomatic and sixteen (16) symptomatic breastfeeding mothers, plated on <i>Candida</i> growth medium and tested for (1→3)-β-D-glucan (comprises 40% of the cell wall of <i>C. albicans</i>). The symptomatic group included those with sore, inflamed or traumatized nipples, intense stabbing or burning pain that radiated into the axilla often persisting after feeding, and painful breastfeeding without alternate diagnosis. There was no significant difference in (1→3)-β-D-glucan levels between the control (mean = 94 pg/mL) and symptomatic (mean = 68 pg/mL) groups (p = 0.75). No <i>Candida</i> colonies were present in the control group, and only one pair of samples from a symptomatic woman grew colonies (1 and 5 colonies each per 15-μL sample), even after the addition of exogenous iron. The observation of unencumbered colony growth after adding pure <i>C. albicans</i> to control milk samples, with or without added iron, suggests that BM does not inhibit <i>Candida</i> growth. <i>C. albicans</i> does not appear to be present in large quantities of milk ducts and may not be associated with the clinical symptoms presented above.</p>	II-2
<p>Graves S, Wright W, Harman R & Bailey S. Painful nipples in nursing mothers: fungal or staphylococcal? A preliminary study. <i>Aust Fam Physician</i>. 2003; 32(7): 570-1.</p>	<p>Twenty-eight (28) women with tender nipples and clinical diagnosis of “breast thrush” and 23 control lactating women recruited at a breastfeeding conference were evaluated. “Breast thrush” is characterized by intense nipple pain radiating into the breast, burning, tenderness, absence of masses or fever, nipple fissures, and/or areolar erythema. Maternal nipples, anterior nares, and lower vagina, as well as the infant’s oropharynx, were swabbed and the samples tested for the presence of <i>Candida</i> and bacteria. Milk samples were also collected and tested. <i>S. aureus</i> was present in 57% of nipple swabs from symptomatic women and in none from the control group. Similarly, <i>S. aureus</i> was found in 48% of milk samples from symptomatic women and in none from the control group. Colonization of the anterior nares was not significantly different between the two groups, and colonization of the vagina with either <i>S. aureus</i> or</p>	II-2

	<p><i>Candida</i> was uncommon (1 and 0 out of 17 samples, respectively). No vaginal samples were collected from control group women for comparison. The presence of <i>S. aureus</i> in nipple/milk cultures did not correlate with infant oropharyngeal colonization. Similarly, the presence of <i>Candida albicans</i> in infant oropharyngeal cultures did not correlate with “breast thrush” symptoms in the mother.</p> <p>The authors propose that the mild staphylococcal infection may follow nipple trauma due to attachment problems and precede a more extensive infection of the lactiferous ducts. Sample collection methods were not described in this short article. A brief mention is made of antibiotic treatment for women who grew <i>S. aureus</i> in both nipple and milk samples, but information about treatment course and outcomes were not included.</p>	
<p>Jiménez, E., de Andrés, J., Manrique, M., Pareja-Tobes, P., Tobes, R., Martínez-Blanch, J., & Rodríguez, J. M. (2015). Metagenomic analysis of milk of healthy and mastitis-suffering women. <i>Journal of Human Lactation</i>, 31(3), 406-415. doi: 10.1177/0890334415585078</p>	<p>No evidence of <i>Candida</i> present with breast pain sx</p>	<p>II-2</p>
<p>Andrews JI, Fleener DK, Messer SA, et al. The yeast connection: is <i>Candida</i> linked to breastfeeding associated pain? <i>American Journal of Obstetrics & Gynecology</i>. 2007; 197:424.e1-424.e4.</p>	<p>This prospective cohort study of 98 postpartum women planning to breastfeed (women with acute mastitis, fever, or breast redness, as well as those using antibiotics/antifungals in the last 14 days were excluded) evaluated whether self-reported pain during lactation was associated with isolation of <i>Candida</i> from BM. The study was conducted from May 2004 to July 2006 and included a single evaluation of each mother-infant pair. Mothers answered a demographic/pain questionnaire and samples from the infant’s oral mucosa, mother’s areolar skin, and BM were collected in sterile containers without cleaning the areola/nipple other than with the saline swab used to collect skin flora. Six of the 78 asymptomatic women and 6 of the 20 symptomatic women had BM cultures positive for yeast (30% vs 7.7%, p = 0.015). Among these 12 positive BM samples, 11 were positive for <i>C. albicans</i>, and in each woman from whom yeast was isolated, yeast also grew from infant oropharyngeal cultures. Fifteen of the 78 asymptomatic women and 5 of the 20 symptomatic women had BM cultures positive for <i>S. aureus</i> (p > 0.05). The etiology of breastfeeding-associated pain is not clear, as the majority of patients with pain (70%) had no <i>Candida</i> isolated from BM or areola/nipple cultures.</p>	<p>II-2</p>
<p>(repeat citation for Amir, Donath 2013 – above)</p>		

Differential Diagnosis (continued)

Viral infection

<p>Parra J, Cneude F, Huin N et al. Mammary herpes: a little known mode of neonatal herpes contamination. <i>J Perinatol</i>. 2013; 33 (9): 736-7. doi: 10.1038/jp.2013.67.</p>	<ul style="list-style-type: none"> - Incidence of neonatal herpes infection: 1-3 newborns per 100,000 births - Mortality from systemic infection ~85% (etiology: 73% HSV2, 27% HSV1) - 10% of HSV transmission to neonates occurs postnatally - Only 2% of extragenital lesions are on the breast (citations 1-3) - Erythema, induration, pruritis, pain, +/- ulceration - Case report: mother with erosive breast lesion, appeared days prior to delivery (Cesarean section); baby breastfed from birth - Two other cases cited from literature - Recommendation: Breast lesions should not be presumed benign cold sores; questionable lesions should be tested for HSV; breastfeeding should be discontinued until resolution of sore and samples are negative 	<p>III</p>
<p>(repeat citation for Schalock et al 2010 – above)</p>		
<p>Jaiyeoba O, Amaya MI, Soper DE, Kilby JM.</p>	<p>Information about zoster</p>	<p>III</p>

Preventing neonatal transmission of herpes simplex virus. Clin Obstet Gynecol. 2012 Jun;55(2):510-20		
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Differential diagnosis (continued)

Vasospasm

Anderson, J. E., N. Held, et al. (2004). "Raynaud's phenomenon of the nipple: a treatable cause of painful breastfeeding." Pediatrics 113(4): e360-364.	<p>Background: Affects "up to 20% of women of childbearing age"</p> <p>Study design: Case series of 12 mothers with Raynaud's syndrome of nipple.</p> <p>Sxs precipitated by cold, assoc with nipple blanching / cyanosis / erythema. 8 of 12 mothers received multiple courses of antifungal tx without relief before Raynaud diagnosis made.</p> <p>To diagnose: precipitation by cold stimulus, occurrence of sxs during preg (seen in 6 of 12 women) or when not BFing, biphasic or triphasic color change. 3 of 12 women also had hx of breast surgery.</p> <p>Tx options: avoidance of cold stimuli, avoidance of vasoconstrictive drugs and nicotine, medication (nifedipine; very little in milk, safe to – see ref below for LactMed)</p> <p>6/12 tx'd with nifedipine and "responded well"</p> <p>5 mg (3 times daily) OR 30 mg slow-release tab daily; 2 week course (some patients may require a 2nd or 3rd course)</p> <p>Other anecdotal tx options: aerobic exercise, biofeedback, Ca and Mg supplements, vitamin B6 supplements, evening primrose oil, fish oil</p>	II-3
Barrett ME, Heller MM, Fullerton Stone H et al. Raynaud Phenomenon of the Nipple in Breastfeeding Mothers: An Underdiagnosed Cause of Nipple Pain. JAMA Dermatol. 2013; 149(3): 300-306	<ul style="list-style-type: none"> - Case series: Retrospective review of 22 cases of breastfeeding mothers who fit the diagnostic criteria for Raynaud of the nipple - Previous tx for Candida with oral or topical antifungals ineffective in 20/22. - Chronic deep breast pain ("in general, > or = 4 weeks"); many described as occurring all the time - Also had at least 2: (1) nipple color change, (2) cold sensitivity or color change of hands/feet with cold exposure, [note: 20/22 had hx of this] (3) failed tx with oral antifungals - Another diagnostic clue: "other autoimmune diseases, esp connective tissue disorders" - Trial of nifedipine in 12 patients; 10 reported decreased/resolved pain - All 22 patients also received (at some point in tx of pain): topical corticosteroid, advice to apply emollients 2-3 times daily, "standard course of oral fluconazole ... 400 mg PO on day 1 and then 200 mg PO on days 8-10" - Bacterial cx performed on 9 patients, 2 yielded S aureus; these pts received oral abx; other cx yielded "mixed skin flora" <p>*****</p>	II-3

Differential diagnosis (continued)

Allodynia/functional pain

de Boer, M. J., M. M. Struys and G. J. Versteegen (2012). "Pain-related catastrophizing in pain patients and people with pain in the general population." Eur J Pain 16(7): 1044-1052.	Pain disorders are associated with catastrophization	II-2
de Boer, M. J., H. E. Steinhagen, G. J. Versteegen, M. M. Struys and R. Sanderman (2014). "Mindfulness, acceptance and catastrophizing in	Pain disorders are associated with reduced psychological acceptance	II-2

chronic pain." PLoS One 9(1): e87445.		
Bergbom, S., K. Boersma, T. Overmeer and S. J. Linton (2011). "Relationship among pain catastrophizing, depressed mood, and outcomes across physical therapy treatments." <i>Phys Ther</i> 91(5): 754-764.	Psychological factors are associated with diminished treatment response	II-2
Williams, A. C., C. Eccleston and S. Morley (2012). "Psychological therapies for the management of chronic pain (excluding headache) in adults." <i>Cochrane Database Syst Rev</i> 11: CD007407.	Benefit from psychological therapy designed to treat chronic pain.	I

Recommendations for future research

Chelimsky G, Madan S, Alshekhlee A, Heller E, McNeeley K, Chelimsky T. A comparison of dysautonomias comorbid with cyclic vomiting syndrome and with migraine. <i>Gastroenterology research and practice</i> 2009;2009:701019.	"Future studies should quantify maternal mood, pain catastrophization ..."	n/a
Ossipov MH, Dussor GO, Porreca F. Central modulation of pain. <i>J Clin Invest.</i> Nov 2010;120(11):3779-3787.	"Future studies should quantify maternal mood, pain catastrophization ..."	n/a
Tchivileva IE, Lim PF, Smith SB, Slade GD, Diatchenko L, McLean SA, Maixner W. Effect of catechol-O-methyltransferase polymorphism on response to propranolol therapy in chronic musculoskeletal pain: a randomized, double-blind, placebo-controlled, crossover pilot study. <i>Pharmacogenet Genomics</i> 2010;20(4):239-48.	"Future studies should quantify ... comorbid dysautonomias" "...propranolol, starting at 20 mg TID, can be helpful, based on evidence of efficacy for Temporomandibular Joint Disorder."	I
(repeat citation of Adam, Baillie et al 2002 – above)		

Table 1: Conditions, symptoms, and management

Dollberg S, Botzer E, et al. Immediate nipple pain relief after frenotomy in breast-fed infants with ankyloglossia: a randomized, prospective study. <i>J Pediatr Surg.</i> 2006; 41(9): 1598-1600.	Background: Tongue tie estimated in 5% of neonates. Study Design: A randomized, double-blind, prospective study; hypothesis: frenotomy alleviates sx's associated with Bfing difficulties in infants with ankyloglossia. Inclusion criteria: Full-term, healthy infants aged 1 to 21 days. Setting: Lactation clinic at the Lis Maternity Hospital. Methods: Mothers experiencing nipple pain were referred to the study (n=25). Infants were examined for ankyloglossia by neonatologist. Patients were randomized into one of two sequences: 1) frenotomy, immediately followed by breastfeeding, then sham, immediately followed by breastfeeding or 2) sham, immediately followed by breastfeeding, then frenotomy, immediately followed by breastfeeding. In both sequences, after each sham or frenotomy procedure a standardize pain and latch score were taken. Results: There	I
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	<p>was a significant decrease ($p=0.001$) in the frenotomy pain scores as compared to the sham scores. There were nearly significant ($p=0.06$) improvements in the frenotomy latch scores. Conclusion: Frenotomy procedures appear to immediately alleviate nipple pain. It is speculated that ankyloglossia plays a significant role in breastfeeding difficulties and this can be effectively treated with frenotomies.</p>	
<p>Srinivasan A, Dobrich C, et al. Ankyloglossia in breastfeeding infants: the effect of frenotomy on maternal nipple pain and latch. <i>Breastfeed Med.</i> 2006; 1(4): 216-224.</p>	<p>Study Design: A study to determine effectiveness of frenotomies in ankyloglossic infants by using standardized tools to measure quantitative changes in latch and maternal nipple pain. Inclusion criteria: Mothers with full-term, singleton infants younger than 12 weeks, who presented to the clinic between August 2004 and February 2005 and intended to begin or continue breastfeeding. Infants who met the standards of the Frenotomy Decision Rule for Breastfeeding Infants (FDRBI), which awaits future validation. Setting: Goldfarb Breastfeeding Program at the Jewish General Hospital. Methods: A total of 27 mother-infant dyads participated in the study. Infants were evaluated based on (FDRBI). Latch was assessed using the Latch Tool, and Maternal pain was assessed using R. Melzack's Short Form McGill Pain Questionnaire containing Pain Rating Index and Presenting Pain Index subsets. Frenotomies performed on infants. Latch and pain were reassessed within 10 minutes of the frenotomy. Mothers were given breastfeeding counseling before the pain questionnaire was administered as well as throughout and after the frenotomy. Three months after the procedure mothers were contacted by phone to complete a follow-up questionnaire. Results: All infants had an equal or higher latch score after the frenotomy. The mean latch score showed an improvement of 2.5. All mothers had a significant decrease in nipple pain after the procedure (-11.4 points on the PRI subset and -1.5 points on the PPI subset). At the 3-month questionnaire, 21 of the 27 mothers were still breastfeeding, 23 of 25 were pain free, and 22 of 25 felt the frenotomy had helped. Two mothers stopped breastfeeding during the study and were not contacted at the 3-month point. Conclusion: Frenotomies in addition to breastfeeding counseling is effective in improving latch and maternal nipple pain experienced during breastfeeding ankyloglossic infants.</p>	II-2
<p>(repeat citation of Segal, Stephenson et al 2007 - above)</p>		
<p>Geddes DT, Langton DB, et al. Frenulotomy for breastfeeding infants with ankyloglossia: effect on milk removal and sucking mechanism as imaged by ultrasound. <i>Pediatrics.</i> 2008; 122(1): e188-194.</p>	<p>Study design: A study to evaluate the effectiveness of frenulotomies in infants experiencing breastfeeding difficulties by evaluating milk production, breastfeeding characteristics, and sucking dynamics of infants with ankyloglossia before and after frenulotomy. Inclusion criteria: mothers with persistent breastfeeding difficulties despite professional advice. Setting: Breastfeeding Centre of Western Australia. Methods: Submental ultrasound scans of the infant's oral cavity were performed before and after the frenulotomy. Milk transfer, LATCH (latch, audible swallowing, type of nipple, comfort, and hold) scores, and maternal pain were recorded before and after frenulotomy. Results: Milk transfer, LATCH scores, and maternal pain improved significantly for all mother-infant dyads postfrenulotomy. Ultrasound results revealed two types of groups: one group compressed the base of the nipple, and the other compressed the tip of the nipple. In all but one of these cases, these features were resolved or lessened after frenulotomy. Conclusion: Infants with ankyloglossia and experiencing persistent breastfeeding difficulties showed less compression of the nipple and significant improvements in regards to breast attachment, milk production, and maternal pain.</p>	II-2
<p>Buryk M, Bloom D, et al. Efficacy of neonatal release of ankyloglossia: a randomized trial. <i>Pediatrics.</i> 2011; 128(2): 280-288.</p>	<p>Study design: A single-blinded, controlled, randomized trial to determine whether frenotomies in infants with ankyloglossia was effective in improving breastfeeding and reducing maternal nipple pain. Inclusion criteria: Maternal report of nipple pain or difficulty breastfeeding paired with significant ankyloglossia in infant. Setting: Naval Medical Center Portsmouth, newborn nursery, newborn care clinic, and otolaryngology clinic. Methods: Over a 12 month period infants with significant ankyloglossia and difficulty breastfeeding were enrolled in the study. Prior</p>	I

	<p>to initiation into the study, nipple pain and breastfeeding were assessed using a nipple-pain scale and the Infant Breastfeeding Assessment Tool. Infants were randomly assigned to one of two groups: frenotomy (30 neonates) or sham (28 neonates). After the procedure or sham, infants were returned to moms for breastfeeding. Patients were then reassessed, and were followed-up 2 weeks later and at regularly scheduled visits over 1 year using the same tools. Mothers enrolled in the sham group were offered a frenotomy at or prior to the 2-week follow-up. Results: Both groups showed a significant decrease in nipple pain after intervention. The frenotomy group improved more than the sham group. Of the sham group all but 1 chose to have the frenotomy when offered at 2-weeks. This prevented further comparison. Conclusion: There were immediate improvements in nipple pain despite a possible placebo effect. This provides convincing evidence for the effectiveness of frenotomies in improving breastfeeding and reducing nipple pain.</p>	
(repeat citations of Barrett, Heller et al 2013 – above)		
Butler DC, Heller MM, Murase JE. Safety of dermatologic medications in pregnancy and lactation: Part II. Lactation. J Am Acad Dermatol. 2014 Mar;70(3):417.e1-10; quiz 427. doi: 10.1016/j.jaad.2013.09.009.		
Bae YS, Van Voorhees AS, Hsu S, et al. Review of treatment options for psoriasis in pregnant or lactating women: from the Medical Board of the National Psoriasis Foundation. J Am Acad Dermatol. 2012 Sep;67(3):459-77. doi: 10.1016/j.jaad.2011.07.039. Epub 2011 Oct 22.	Treatment of psoriasis	?
Livingstone, V. and L. J. Stringer (1999). "The treatment of Staphylococcus aureus infected sore nipples: a randomized comparative study." Journal of Human Lactation 15(3): 241-246.	<p>Study design: A prospective, randomized comparative study to compare four treatment regimens for S. Aureus infected, sore, cracked nipples, and test the hypothesis that optimal breastfeeding technique alone is an effective cure. Inclusion criteria: Mothers with sore, cracked nipples and S. aureus positive cultures. Setting: Vancouver Breastfeeding Center. Methods: Women complaining of sore nipples were approached to participate. Signs and symptoms of sore nipples were recorded followed by breastfeeding observation to assess latch, positioning, and infant sucking dynamics. Lactation consultants gave instructions on basic breastfeeding techniques. Nipple cultures were obtained to test for S. aureus colonization. 84 eligible mothers were enrolled and randomly assigned to 1 of 4 treatment groups: (1) review of basic breastfeeding technique alone; (2) topical treatment with 2% mupirocin ointment applied to each nipple after breastfeed; (3) topical fusidic acid ointment applied to nipples after each feed; (4) oral cloxacillin/ erythromycin 500 mg every 6 hours for 10 days. All participants were assessed by a physician at 7 days of treatment or sooner, if requested. At this time, physicians assessed signs and symptoms of wound healing. Mothers ranked nipple soreness on pain scale. Results: Of the mothers who received advice alone, 9% showed improvements, 16% of the topical mupirocin group showed improvements, 36% showed improvements in the topical fusidic acid group, and 79% improved with oral antibiotics. Mastitis developed in 12 to 35% of mothers not treated with systemic antibiotics compared to 5% of mothers treated with systemic antibiotics. Conclusion: S. aureus infected, sore, cracked nipples should be treated aggressively with systemic antibiotics to improve healing and avoid further infection.</p>	I
(repeat citation of Barankin and Gross 2004 – above)		
(repeat citation of Eglash, Plane et		

al 2006 – above)		
(repeat citation of Barrett, Heller et al 2013 – above)		
Arroyo R, Martín V, Maldonado A, Jiménez E, Fernández L, & Rodríguez JM. Treatment of infectious mastitis during lactation: Antibiotics versus oral administration of Lactobacilli isolated from breast milk. <i>Clinical Infectious Diseases</i> . 2010; 50(12): 1551-1558.	A total of 352 women with symptoms of mastitis (breast inflammation, painful breastfeeding, milk bacterial count >4 log ₁₀ CFU/mL, milk leukocyte count >6 log ₁₀ cells/mL) were randomly assigned to 3 groups (two probiotic: “A” and “B”, one antibiotic group: “C”). Many women (n=74) also presented with fissures in the mammary areola and/or nipple. No women ingested commercial probiotic foods or supplements during the 21-day study and treatment was double-blinded. Groups A and B consumed daily one capsule of <i>Lactobacillus fermentum</i> or <i>Lactobacillus salivarius</i> (isolated from human milk), respectively. Group C received standard antibiotic treatment at their primary care centers. BM samples, evolution of symptoms and breast pain scores were obtained at day 0 and day 21. On day 0, mean bacterial counts in the milk samples and breast pain ratings were similar between the 3 groups. On day 21, mean bacterial counts in the probiotic groups (2.61 and 2.33 log ₁₀ CFU/mL) were lower than that of the control antibiotic group (3.28 log ₁₀ CFU/mL, p < 0.001). Breast pain ratings were also significantly lower on day 21 in probiotic groups compared to the control group (p < 0.001). Recurrence of mastitis was less common (8.8%) in probiotic groups than in the antibiotic group (30.7%, p < 0.001). Predominant bacteria isolated in this study include: <i>Staphylococcus epidermidis</i> , <i>Staphylococcus aureus</i> , and <i>Streptococcus mitis</i> .	I
Fernandez L, Arroyo R, Espinosa L, Marin M, Jimenez E, Rodriguez JM. Probiotics for human lactational mastitis. <i>Beneficial Microbes</i> . 2014; 5(2): 169-183.	***Abstract: The use of culture-dependent and -independent techniques to study the human milk microbiota and microbiome has revealed a complex ecosystem with a much greater diversity than previously anticipated. The potential role of the milk microbiome appears to have implications not only for short- and long-term infant health but also for mammary health. In fact, mammary dysbiosis, which may be triggered by a variety of host, microbial and medical factors, often leads to acute, subacute or subclinical mastitis, a condition that represents the first medical cause for undesired weaning. Multiresistance to antibiotics, together with formation of biofilms and mechanisms for evasion of the host immune response, is a common feature among the bacterial agents involved. This explains why this condition uses to be elusive to antibiotic therapy and why the development of new strategies for mastitis management based on probiotics is particularly appealing. In fact, selected lactobacilli strains isolated from breast milk have already shown a high efficacy for treatment.	?
(repeat citation of Barrett, Heller et al 2013 - above)		
Kayama. 2006. ?	Use of gentian violet	?
van Veldhuizen-Staas CG. Overabundant milk supply: an alternative way to intervene by full drainage and block feeding. <i>Int Breastfeed J</i> . 2007; 2: 11.	Oversupply/hyperlactation/overabundant milk supply: - Caused by: BFinng mismanagement, hyperprolactinemia, congenital predisposition - Mother may have constant feeling of “(over-) fullness, engorgement and tension,” may leak between feeds or from opposite breast during feeds - Mother has increased risk for mastitis - Infant may appear to be a “greedy feeder” and struggle not to choke or aspirate milk, may spit up frequently and/or have reflux-like sxs, suffer from gas, colic, and explosive, often green and foamy stools (rapid gastric passage of relatively high sugar/low fat milk) - Infant may have either very low (may not be able to empty the breast far enough to obtain fatter milk) or very high weight gain - Infant may show restless or even aversive nursing behavior (refusal, shortened feeds) - Infant may slip from optimal latch to clamp down and slow the flow, resulting in nipple trauma Managing oversupply:	III

	<p>“Full drainage and block feeding” method (FDBF)</p> <ul style="list-style-type: none"> - Start with “as-complete-as-possible” mechanical drainage of both breasts - Offer both breasts immediately afterwards (goal is to get infant high-fat hindmilk) - Rest of day divided into equal time blocks (usually starting with 3 hours) during which the infant is fed on only one side, whenever hunger cues or other signs of interest are shown - At the end of each time block, the baby is offered the other breast for all feeds for the next time block - Sxs may require increasing block to 4, 6, 8 or even 12 hours - Multiple mechanical drainages may be necessary - Requires caution so as not to drain the breasts too often - Also requires close follow-up/monitoring for over-fullness, plugged ducts, mastitis 	
Lactmed. http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/*92Bfx1:1 Accessed September 6, 2014).	Role of estrogen in decreasing supply	II-2? II-3?
Thompson and Pope 2005	Use of nifedipine for vasospasm	I
(repeat citation of Tchivileva, Lim et al 2010 – above)		
(ABM Protocol #18 - Use of Antidepressants in Breastfeeding Mothers)		
Kernerman E, Park E. Severe Breast Pain Resolved with Pectoral Muscle Massage. J Hum Lact. 2014 May 29;30(3):287-291. [Epub ahead of print]	Many mothers stop breastfeeding because of breast and/or nipple pain, despite recommendations by the World Health Organization to exclusively breastfeed for the first 6 months. Most commonly, such pain is thought to be caused by fungal or bacterial infection; however, many women do not respond to usual treatments for such diagnoses. Furthermore, there is much dispute in the literature about these diagnoses and treatments. We submit a series of 3 cases of mothers who presented with severe mastalgia (breast pain) and who did not respond to conventional treatments. After treating the patients with pectoral muscle massage and stretching, they each had complete resolution of their pain. We suggest that each of these mothers experienced constriction of the upper thoracic muscles on their mammary neurovasculature.	II-3
UNC School of Medicine at Chapel Hill staff. Health Care Professionals :: OB Algorithms :: Breastfeeding: Culture Collection Protocol. UNC Center for Maternal & Infant Health. Available at: http://mombaby.org/PDF/culture_protocol.2.0.pdf . Updated/published ****. Accessed 1 Nov 2014.	Protocols for culturing / collecting breastmilk.	III

Future Work

Chronic and/or recurrent breast infections have been largely misunderstood until quite recently. Research from the dairy industry has spurred similar investigations in human cases of breast infection in the last twenty years, and both fields often refer to the condition as “mastitis.” Rather than the textbook set of symptoms that include reddening, warmth, swelling and hardness within a wedge of breast tissue, chronic infection is often manifested by breast and/or nipple pain without obvious outward signs of infection and in cases where latch and positioning have been ruled out as potential causes of symptoms. The clarification of symptoms that constitute “mastitis” versus “lactiferous duct infection” or “infectious mastitis” (both of which have been newly proposed in the literature) is thus the first challenge in determining the relevancy and usefulness of previous work, and in turn understanding and treating this condition.

The initiation of high-quality studies evaluating treatment modalities for lactiferous duct infection/infectious mastitis is just beginning, and additional prospective randomized controlled trials are needed to replicate the promising results of these early studies. Secondary outcomes such as neonatal side effects and/or complications, hospitalization, cost of treatment, and adverse reactions should also be considered.

The largest trial to date investigated the efficacy of oral administration of the probiotic strains *Lactobacillus fermentum* or *Lactobacillus salivarius* compared to standard antibiotic treatment for 3 weeks in 352 lactating women in Spain. Results largely favored the use of probiotics over traditional antibiotic therapy due to the significant decline in both bacterial counts and reported breast pain in women treated with probiotics. The previous work by this research group, led by Susana Delgado, has elucidated various related microbiological research questions – an area of expertise previously underrepresented in the literature on chronic breast infection.

A wide variety of new potential antimicrobial substances are being investigated at the level of animal models and/or in vitro inhibition assays, including berberine, phenolic acids, farnesol, flavonoids, and lantibiotics. Based on the results of these studies, the eventual development of human trials to study safety and efficacy will be needed.

Evidence also exists for the role of nipple cracks and sores in the development of lactiferous duct infection/infectious mastitis. The breakdown of maternal skin on the breasts and chronic infection appear to coincide, but not every woman presents with both problems. More work must be done to determine the etiological role, if any, of skin damage and which risk factors determine whether such damage will lead to infection.

Several groups have been working on improving assays for the detection and identification of causative agents within breast milk. Several culture-independent methods, including RT-PCR and FISH, have been used with success to identify organisms that are difficult to culture and to permit analysis on a direct milk sample, respectively. Additional work is still needed to determine the clearest biochemical and bacteriologic markers for this type of infection in breast milk.

Some evidence, especially in veterinary research on other mammals, suggests a role for small colony variants in the etiology of persistent infections. Although they have been implicated in many other kinds of infection, including bovine mastitis, SCVs have yet to be isolated from breast milk samples of women with lactiferous duct infection/infectious mastitis.

The potential for implicated bacteria to form biofilms is another outcome that, while widely discussed in bench and animal model research, deserves greater attention in future human studies. Delgado et al. found that the biofilm-related *icaD* gene was more common in milk samples from women with mastitis, and subsequently made a case in a later review article for the role of biofilms in the persistence of human intramammary infection.

US Preventive Services Task Force Evidence Standards

I Evidence obtained from at least one properly randomized controlled trial

II-1 Evidence obtained from well-designed controlled trials without randomization

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions of respected authorities, based on clinical experience, descriptive studies and case reports; or reports of expert committees