Review

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Overdiagnosis and overtreatment of nipple and breast candidiasis: A review of the relationship between diagnoses of mammary candidiasis and *Candida albicans* in breastfeeding women

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Abstract

Background: Breastfeeding mothers commonly experience nipple pain accompanied by radiating, stabbing or constant breast pain between feeds, sometimes associated with pink shiny nipple epithelium and white flakes of skin. Current guidelines diagnose these signs and symptoms as mammary candidiasis and stipulate antifungal medications.

Aim: This study reviews existing research into the relationship between *Candida albicans* and nipple and breast pain in breastfeeding women who have been diagnosed with mammary candidiasis; whether fluconazole is an effective treatment; and the presence of *C. albicans* in the human milk microbiome.

Method: The author conducted three searches to investigate (a) breastfeeding-related pain and *C. albicans*; (b) the efficacy of fluconazole in breastfeeding-related pain; and (c) composition of the human milk mycobiome. These findings are critiqued and integrated in a narrative review.

Results: There is little evidence to support the hypothesis that *Candida* spp, including *C. albicans*, in maternal milk or on the nipple-areolar complex causes the signs and symptoms popularly diagnosed as mammary candidiasis. There is no evidence that antifungal treatments are any more effective than the passage of time in women with these symptoms. *Candida* spp including *C. albicans* are commonly identified in healthy human milk and nipple-areolar complex mycobiomes.

Discussion: Clinical breastfeeding support remains a research frontier. The human milk microbiome, which includes a mycobiome, interacts with the microbiomes of the infant mouth and nipple-areolar complex, including their mycobiomes, to form protective ecosystems. Topical or oral antifungals may disrupt immunoprotective microbial homeostasis. Unnecessary use contributes to the serious global problem of antifungal resistance.

Conclusion: Antifungal treatment is rarely indicated and prolonged courses cannot be justified in breastfeeding women experiencing breast and nipple pain. Multiple strategies for stabilizing microbiome feedback loops when nipple and breast pain emerge are required, in order to avoid overtreatment of breastfeeding mothers and their infants with antifungal medications.

Keywords

breastfeeding, breast pain, candidiasis, human milk, mammary candidiasis, mycobiome

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Highlights

- Overdiagnosis and overtreatment of medical conditions is common in breastfeeding pairs.
- *Candida albicans* is commonly identified in healthy breast milk and nipple-areolar complex mycobiomes.
- Nipple pain and stabbing pain between breastfeeds is often diagnosed as *C. albicans* and treated with topical and oral antifungals.
- These symptoms are not diagnostic of breast or nipple candidiasis.

Background

Breastfeeding mothers may experience nipple pain that is accompanied by shooting or stabbing breast pain between feeds, sometimes also associated with pink shiny nipples and fine white flakes. Current guidelines diagnose these as symptoms and signs of mammary candidiasis or thrush, for example, the Academy of Breastfeeding Medicine Clinical Protocol #26 for Persistent Pain with Breastfeeding or the Royal Women's Hospital Melbourne guidelines in Australia.[1,2] Courses of maternal oral fluconazole and topical antifungal medications on the nipple-areolar complex and in the infant's mouth are recommended.

Candida albicans is a diploid polymorphic yeast, the most common fungal commensal in the human body. It adheres to epidermal keratinocytes and may exist on the nipple-areolar complex as part of healthy human skin's network of protective and interacting microbiota and biofilms. *C. albicans* may grow hyphae and change shape for epithelial penetration in favourable circumstances. However, epithelial penetration by *C. albicans* is limited by interactions with host immune processes. For example, intertrigo is an inflammatory condition found in skin folds, for example, under pendulous breasts, between the toes, or in an infant's nappy area. This inflammation arises in the context of friction, heat, moisture, reduced pH, and occlusion resulting in carbon dioxide accumulation. Although an intertriginous dermatitis may be complicated by *C. albicans* overgrowth, causing hyperkeratosis and erythema, this overgrowth remains superficial, due to highly efficient skin barrier defences and host immunity. *C. albicans* invades systemically only in immunocompromised patients, for example, who have HIV or are undergoing chemotherapy.[3–6]

Current guidelines for breastfeeding women recommend that nipple and breast pain which continues despite an initial course of antifungal treatment indicates the need for prolonged courses of antifungal treatment, including applications of gentian violet, assuming persistence of treatment-resistant *C. albicans* overgrowth.[1,2] A 2011 Australian study investigated 96 breastfeeding women who had been diagnosed with mammary candidiasis because of continuous burning nipple pain, often associated with post-feed radiating breast pain. These mothers took an average total of 7.3 doses of 150 mg of fluconazole on alternate days as antifungal treatment, with a range of 1–29 doses.[7] Anecdotally, high levels of antifungal medication treatments continue to be prescribed for breastfeeding women with pain, consistent with existing clinical guidelines.

There has been a large amount of research in the past few decades elucidating the composition of human milk and demonstrating the benefits of breastfeeding for infant and maternal well-being. But there remains, relative to most aspects of health care, a paucity of methodologically sound research investigating the management of common clinical breastfeeding problems. Clinical breastfeeding support remains a research frontier. Much of what is offered women with breastfeeding difficulty, including interventions for fit and hold (also known as latch and positioning), is based on experience or opinion.[8–11] The popularly used cross-cradle hold with the other hand shaping the breast, for example, has been shown to increase the risk of nipple pain.[12] When women are taught baby-led or laid-back breastfeeding in hospital immediately after the birth (also known as skin-to-skin or the physiologic initiation of breastfeeding), the incidence of nipple pain and damage decreases.[13,14] A 2021 Chinese randomized controlled trial (RCT) of 504 pairs demonstrated that implementing baby-led self-attachment from birth results in a 12% increase in exclusive breastfeeding at day 3, and an 8% and 5% decrease in the number who reported nipple pain at 3 days and 3 months postpartum, respectively.[15] However, baby-led approaches have not been demonstrated effective as therapeutic interventions for breastfeeding problems. A 2013 Swedish RCT of 103 mothers with infants up to 16 weeks of age with severe latch-on difficulties found that a baby-led or skin-to-skin intervention did not increase the likelihood that the infant would latch on.[16]

Aim

This study aims to critically analyse existing research which investigates:

a. The relationship between *C. albicans* and the symptoms of burning or radiating nipple and breast pain in breastfeeding women who have been diagnosed with mammary candidiasis;
b. The efficacy of fluconazole in treatment of breastfeeding-related nipple and breast pain;
c. The presence of *C. albicans* in the human milk microbiome.

Method

On 1 November 2020, the author used PubMed for three literature searches. First, the terms 'breastfeeding AND (candida OR thrush)' were searched. Studies published after 2000, which were either randomised controlled trials (RCTs),

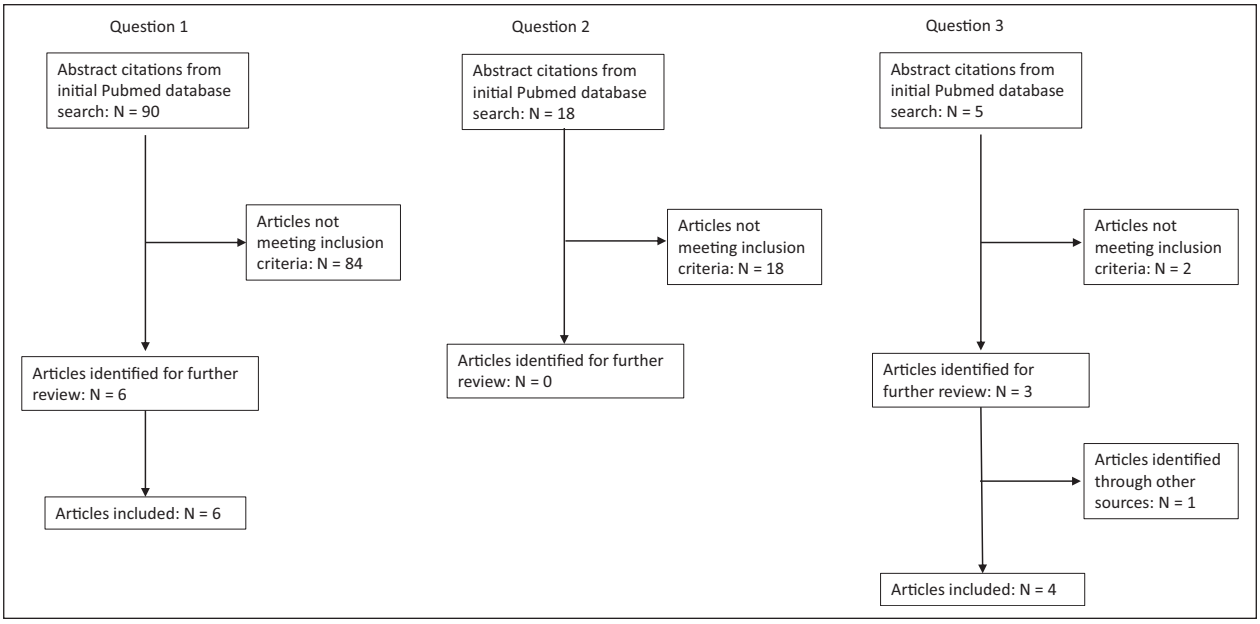

Figure 1. Flow diagram of studies reviewed for inclusion.

comparative studies, or prospective cohort studies, were selected. Second, the terms 'fluconazole AND breastfeeding' were searched, with the intention of selecting only RCTs, comparative studies or prospective cohort studies published after 2000. Third, the term 'human milk mycobiome' was searched. The author integrated the findings of these searches with iterative snowball searches of the literature and critically analysed these studies to develop a narrative review.

Results

Despite three comparative studies, one cohort study, and two prospective cohort studies conducted since 2000, there remains no conclusive evidence to support the hypothesis that C. albicans causes the symptoms commonly attributed to mammary candidiasis

The first search resulted in 90 papers (Figure 1). Studies before the year 2000, and studies that were not RCTs, comparative studies, or prospective cohort studies, were excluded. This yielded 3 comparative studies, one cohort study, and two prospective cohort studies, described below.

In 2007, Andrews et al. published a prospective cohort study which showed 6 of 20 (30%) breastfeeding women with 'sharp, shooting breast pain in the absence of fever, breast redness, or other evidence of mastitis' and 6 of 78 (7.7%) asymptomatic breastfeeding women, cultured yeast in their milk. The yeast in 11 of these 12 samples was *C. albicans*. Although *C. albicans* was cultured more often in breastfeeding mothers who reported pain compared with asymptomatic breastfeeding mothers, it was not cultured in the milk or from the nipple-areolar complex in 70% of women experiencing pain.[17]

In 2009, Hale et al. published a study in which milk cultures from 18 normal control breastfeeding mothers without any breast symptoms were compared with 16 mothers with symptoms fitting the popular definition of mammary candidiasis: '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'. None of 36 control milk samples (right and left breast) cultured *Candida* of any species. In symptomatic women's milk samples, only one of 32 grew a colony of *C. albicans*. The authors concluded that *C. albicans* may not be associated with the syndrome known as mammary candidiasis.[18]

In 2011, Amir et al. published the protocol for the Melbourne CASTLE study, a prospective cohort study which included an aim to resolve the current controversy surrounding the primary organism responsible for the condition known as 'breast thrush'. The study went on to define 'breast thrush' as maternal report of burning nipple pain and radiating or non-radiating breast pain (not associated with breast redness or fever). Each woman was asked if she experienced these symptoms and was sampled for *Candida* spp on 6 occasions from 36 weeks gestation until 4 weeks post-birth. Swabs from the infant mouth and nose, from the mother's nose, vagina and nipples, and samples of milk from each breast were cultured to detect *Candida* spp. In addition, real-time polymerase chain reaction (RT-PCR) was used to detect *Candida* spp on swabs from the maternal nipple and vagina. Milk samples were not analysed with RT-PCR. A final phone call follow-up occurred at 8 weeks post-birth.[19]

In 2013, the CASTLE study reported that 54% of women with symptoms of 'breast thrush' (excluding those with vasospasm) at some time between 2 and 8 weeks post-birth (that is, 54% of the symptomatic 48, out of 346 pairs) had *Candida* spp detected by either RT-PCR or culture in any of the three locations of breast milk, nipple or baby's mouth, compared to 34% of the asymptomatic controls.[20] Importantly, *Candida* spp was cultured from nipple swabs in 14% of the 65 who reported symptoms of 'breast thrush' (including those with vasospasm) at some time between one and 8 weeks post-birth, and in 4% of the 281 who were asymptomatic.[20] The CASTLE study found that RT-PCR significantly increases positive detection rate of *Candida* spp relative to culture across all sites of collection, which did not include human milk.

Amir et al. state that their data shows an association between *Candida* spp and burning nipple pain and breast pain (in the absence of visible epithelial damage) but warn clinicians to be alert to other causes of burning nipple and breast pain. They acknowledge that more than one cause of nipple or breast pain was commonly present, which made it difficult to construct a case definition for 'breast thrush' in their study. For example, they note that burning nipple and radiating breast pain were also associated with nipple damage (defined as visible epithelial damage, such as fissures and ulcers). Nevertheless, the authors conclude under a heading Clinical Implications that: 'The pain clinically associated with *Candida* infection is persistent, ranges from mild to severe, and is not relieved by the use of nipple shields or expressing/pumping, or applying heat'. They assume that burning nipple pain associated with breast pain in the absence of visible epithelial damage, experienced between breastfeeds, is not due to mechanical damage.

The authors also assume that detection of *Candida* spp in an infant's mouth and nose is related to the diagnosis of 'breast thrush', even though the presence of *Candida* spp does not constitute a transmissible infection and *Candida* is a common infant commensal, typically acquired at or in the first days after birth.[6] Hale et al.[18] showed that 37% or more of 7-day-old infants are colonized with *Candida* spp, and 82% at 4 weeks postpartum.

In 2016, Mutschlechner et al. investigated the performance of a commercialized RT-PCR for detection of *Candida* spp DNA in human milk. RT-PCR was performed on milk samples from 43 breastfeeding women with symptoms characteristic of mammary candidiasis and from 40 asymptomatic breastfeeding women. A variety of *Candida* spp were cultured in 8.8% of symptomatic and 9.3% of asymptomatic women. *C. albicans* was cultured in the milk of just 2 symptomatic women and was not cultured in the milk of the control group. RT-PCR was positive for *Candida* spp in 67.4% and 79.1% of symptomatic and asymptomatic milk samples, respectively. *C. albicans* was detected in both groups, and either *C. albicans* or *C. parapsilosis* or both were found in 67.4% of symptomatic samples and 58.1% of asymptomatic samples. The authors concluded that RT-PCR technology did not show advantage over use of culture techniques for identification of *Candida* spp in human milk; that RT-PCR technology significantly increases positive detection rate of *Candida* spp in human milk; and that positive PCR data do not identify *Candida* spp as a major fungal pathogen in symptomatic breastfeeding women. The authors concluded that RT-PCR is not a reliable method for identification of symptomatic mammary candidiasis in breastfeeding women.[21]

In 2017, Jiménez et al. published a cohort study which cultured the breast milk of 529 women who reported painful breastfeeding accompanied by radiating or 'shooting' pain into the axilla or back, and also the nipple and areolar complex of the 74% of these women who additionally reported sore, burning, or painful nipples. This study found no association between breast and nipple pain and yeasts in both milk or on the nipples.[22]

The CASTLE study found that 82% of symptomatic and 79% of asymptomatic breastfeeding women cultured *Staphylococcus aureus* in nipple and milk samples and that at least 50% of all participants were colonized with *S. aureus* in nipple or milk samples by 4 weeks postpartum. Amir et al.[20] therefore propose that 'in clinical practice, a finding of *S aureus* in the nipple or breast milk is not evidence that the bacteria are the principal cause of the woman's pain' (p. 6). In contrast, Jiménez et al. propose that coagulase-negative *Staphylococcus* and *Streptococcus*, the predominant organisms cultured from women in their study, must be causative agents, responsible for the breast and nipple pain previously attributed to mammary candidiasis. They recommended that the diagnosis 'subacute mastitis', borrowed from bovine research, be applied to women with these symptoms.[22] Now, symptoms of bilateral dull, deep aching pain +/- burning, and pain during and after breastfeeds with breast tenderness especially in the lower quadrants, may be diagnosed as either 'bacterial dysbiosis' or 'subacute mastitis', receiving antibiotic therapy for up to 6 weeks as recommended in the Academy of Breastfeeding Medicine Clinical Protocol #26 for Persistent Pain with Breastfeeding.[1]

In 2018, Kaski and Kvist published a study comparing 35 breastfeeding women with nipple pain and radiating, burning and penetrating or non-penetrating breast pain during or after breastfeeding, with 35 who were asymptomatic. None of the women in the control group and 8 of the women in the case group showed a growth of *C. albicans* when their breast milk was cultured. However, there were no significant differences in severity or type of symptoms between those in the case group with and without growth of *C. albicans*. Kaski and Kvist conclude that neither clinical symptoms nor microbial cultivation are a reliable means for making a diagnosis of *C. albicans* infection. They also advise against use of the diagnosis of 'subacute mastitis',

which lacks any clinical or pathophysiological definition, cautioning that this diagnosis may 'be of great detriment to the global community' in light of growing anti-microbial resistances (p. 7). Kaski and Kvist[23] suggest that we shift our focus onto identifying other problems, in particular related to breastfeeding technique, rather than attempting to compare between microbiomes.

There are no comparative studies investigating the efficacy of fluconazole for breastfeeding-related pain

The second search found 18 publications (Figure 1). No comparative studies evaluating the efficacy of the oral antifungal medication fluconazole for breastfeeding-related pain relative to controls or other interventions were identified. This absence is corroborated by the website LactMed's statement that 'no adequate clinical studies on fluconazole in *Candida* mastitis have been published'.[24]

New studies elucidate the complexity of the human milk mycobiome, including the common presence of C. albicans

The third search resulted in 5 publications, all published since 2017 (Figure 1). One was a narrative review of maternal-infant microbiota in general, which was excluded. Another was a 2017 Norwegian prospective cohort study of 298 mother-infant pairs by Schei et al., performed over a 2-year period from 36 weeks gestation. This study demonstrated that 90% of the mothers and 60%–80% of the offspring had detectable gut fungi, confirming fungi as an inherent part of the gut microbiome, but did not consider the role of breastmilk.[25] It too was excluded.

The three remaining studies analysed the mycobiome of human milk, Boix-Amoros et al.,[26] Heisel et al.[27] and Dinleyici et al.,[28] as did a fourth found through snowballing, Moossavi et al.[29] These studies are integrated in this narrative analysis.

In the 2019 study by Boix-Amoros et al., 80 samples of mature breast milk from healthy breastfeeding women in Spain, Finland, South Africa, and China were analysed by both PCR and culture, demonstrating a diverse mycobiome in each sample regardless of geographic origin, and without significant geographic differences. These normal human milk mycobiomes include *Candida* spp.[26] Also in 2019, a study by Heisel et al. analysed the PCR and cultures of mycobiomes sampled from nine frequently used surfaces of a neonatal intensive care unit in Minnesota, USA, and also the breast milk of an undefined number of healthy lactating NICU mothers. *C. albicans*, *Candida parapsilosis*, and *Saccharomyces cerevisiae* dominated on both NICU surfaces and in breastmilk.[27]

A 2020 Canadian study by Moossavi et al.[29] profiled mycobiota in milk from 271 healthy mothers and detected a range of fungi in 21.4% samples, with *Candida* spp the most prevalent. A 2020 Belgian study by Dinleyici et al. analysed 44 samples from each breast of healthy breastfeeding mothers, finding a range of fungi in 80 of the 88 samples, with mycobiome composition varying depending on gestational age and size at birth, and mode of delivery. Differences in the mycobiome were found also between transient and mature human milk.[28]

Discussion

This narrative review of existing research literature shows little evidence to support the hypothesis that *Candida* spp including *C. albicans* in maternal milk or on the nipple-areolar complex causes the signs and symptoms popularly diagnosed as mammary candidiasis. There is no evidence that antifungal treatments are any more effective than the passage of time in women with these symptoms. Moreover, *Candida* spp including *C. albicans* are commonly identified in healthy human milk and nipple-areolar complex mycobiomes. While this article was under review, a retrospective chart review of 25 breastfeeding women in the United States referred to a breastfeeding medicine clinic for persistent symptoms including nipple and/or breast pain, white nipple lesions, and/or persistent skin redness was published. Each woman had been previously diagnosed with 'yeast infection' and treated with oral and/or topical antifungal therapy, with minimal or no improvement. No woman was confirmed to have a diagnosis of *Candida*, and Betts et al. report that resolution of symptoms occurred within 2–42 days for all women, after revision of diagnosis and treatment for mammary dysbiosis, nipple bleb, dermatitis, vasospasm, milk crust, hyperlactation or postpartum depression. Unfortunately this clinical audit is unable to demonstrate that the range of new treatments was any more effective than the passage of time.

Overuse of interventions is an increasingly serious international problem in health care.[30,31] Both patients and clinicians typically overestimate the benefits of medical interventions and underestimate potential harms.[32,33] It is not surprising then, given our global context of overuse of medical, surgical and pharmaceutical interventions, and relative lack of research into clinical breastfeeding support, that overmedicalisation and overtreatment are significant problems in the care of breastfeeding women and their babies.[34–38]

The Centres for Disease Control and Prevention warn that in addition to the global threat of antibiotic resistance, inappropriate use of antifungal treatments is contributing to growing resistances to antifungal medications, including to *Candida* spp, with potentially catastrophic implications for immunocompromised patients.[39]

Complexity science makes sense of the difference between pathogens and commensals in milk and nipple-areolar-complex microbiomes

Historically, micro-organisms cultured from patients were viewed as dangerous pathogens which threatened human health. Applying a traditional reductionist (or 'cause-and-effect') lens, any micro-organism identified at a disease site was assumed causative, requiring elimination. This strategy has saved countless lives since the advent of antibiotics from the middle of the 20th century but is currently undergoing revision in an era of worsening anti-microbial resistance. Anti-microbial resistance now constitutes a 'slow motion catastrophe' in global health, and all prescribers are responsible for minimizing the rapidly escalating impact of anti-microbial resistance upon human health.[40]

The gut, mouth, genitourinary system and skin are each colonized by complex microbiomes, which are co-regulatory ecosystems of microbes composed of bacteria, protozoa, parasites, viruses and fungi. The fungal component of a microbiome is the mycobiome. Bacterial cells vastly outnumber fungi in human microbiomes, composing more than 99% of a microbiome, but fungal cells are typically 100-fold larger than bacterial cells, and are part of the normal ecology of human bodies. The fungal domain interacts with and stabilizes the microbial domain in human milk in protective association networks, which together strengthen host health and immunity and resist pathogen colonization. The mechanisms by which bacteria and fungi co-regulate in commensal communities are complex and diverse. In the gut, bacteria are known to limit fungal colonization because bacterial metabolites activate mucosal immunity to fungi. Yeasts are known to have a beneficial, probiotic effect, interacting with and containing certain bacterial pathogens. *C. albicans* is the most common fungal commensal in the human body and is part of mycobiome interactions with millions of bacteria, which keep immune and epithelial barriers healthy.[41,42]

In the past decade, we have learnt that the human milk microbiome consists predominantly of stable populations of *Staphylococcus*, *Streptococcus*, and *Propionibacterium*, with much smaller and more variable numbers of other organisms such as *Lactobacillus* and *Bifidobacterium*.[43] But the composition of the fungal fraction of the human milk microbiome has only recently been elucidated, as detailed in Moossavi et al., Dinleyici et al., Boix-Amoros et al. and Heisel et al.

Applying the lens of complexity science to this new research concerning the human milk mycobiome, dynamic networks of interactions between the microbiome (including the mycobiome) of human milk and also with the breastfeeding woman's immune system act as an immunomodulatory ecosystem, protective not only of the infant gut, but of the lactating mammary gland. Healthy microbiomes, including of the skin, vary in composition between individuals in response to multiple environmental factors.

It may not be possible to define dysbiosis of human milk or nipple-areolar complex, or to understand clinical implications of the microbiome, until the complex normal composition of the microbiota, including of the mycobiome, of human milk and the nipple-areolar complex have been fully elucidated. Importantly, scientists are increasingly more interested in the interactions between microbes than in attempts to catalogue which microbes are present.[41–43] Dysbiosis is less likely to be causative of pathology in a linear sense, but a marker of adaptation and disruption, as the complex adaptive system of a microbiome activates multiple feedback loops (between micro-organisms including fungi, metabolites, and the immune system) to maintain physiological integrity and health. Applying the lens of complexity science, pathology emerges when dynamic feedback loops fail to stabilize complex adaptive systems. Depending on the virulence of the organism, feedback loops may be overwhelmed, and in some cases antibiotic or antifungal treatment will be required. But in most cases, the microbiome will successfully suppress positive feedback loops and protect the host in collaboration with the host's immune system.

Some clinicians believe that *C. albicans* overgrowth fails to respond to antifungal treatment because of biofilm formation, justifying prolonged courses of antifungal medications. This hypothesis lacks supporting evidence, and confuses normal skin biofilms (composed of aggregates of dozens or hundreds of cells) with the complex, extensive and microbial resistant biofilms which form when medical devices are inserted in the human body or when vascular insufficiency or diabetes cause chronic wounds. As Kavi and Krist recommend, the health of the breastfeeding woman and her infant are best served by strengthening the resilience of the multiple feedback loops than by unilateral attempts to eliminate an emergent organism.[23] Antibiotics and antifungals should be reserved for rare occasions when the feedback loops within the complex adaptive system of the human microbiome cannot be stabilized through other strategies (See Box 1).

What are the risks of unnecessary antifungal treatment of breastfeeding women and their infants?

Simplistic, unilateral interventions in complex adaptive systems are known to risk unintended consequences. The following unintended consequences may accompany antifungal treatment.

1. Promotion of antifungal medication resistance in the community, with potentially catastrophic effects in immunocompromised patients;[42]

Box 1. The treatment of oral thrush in infants and painful breast and nipples in lactating mothers in an era of antifungal stewardship.

C. albicans is a member of the normal mycobiome of the infant's oral cavity from birth or shortly afterwards, and there is no rationale to proceed with infant oral treatment in the absence of visible plaques of *C. albicans*.[6] When there is visible infant oral thrush, sparingly applied oral miconazole gel, one millilitre on the parent's fingertip smeared around mouth or gums four times daily or nystatin oral drops may be prescribed. Miconazole gel has been recommended in product guidelines for infants older than 4 months, after a single report of transient choking in a 17-day-old baby. That baby suckled on a copious application of miconazole gel applied to the mother's nipple. There was no long-term effect after the mother scooped out the gel. Some clinicians maintain that oral miconazole gel may be used in babies younger than 4 months if smeared sparingly in the mouth.[44] Both nystatin and miconazole have been demonstrated to be effective treatments for adult oral candidiasis, but there is no efficacy research in infants.[45]

Because *C. albicans* overgrowth is known to sometimes complicate an intertriginous dermatitis, it is possible that moisture associated skin damage of the nipple, in conjunction with multiple other factors such as the heat, low pH, high CO2 and high humidity which build up over long periods in the occlusive environment of a bra, may predispose to mycobiome imbalances and vulnerability to *C. albicans* overgrowth. This is more likely if there has been previous steroid or antibiotic use, and emollient, ointment or cream applications worsening epidermal overhydration. These factors should be remedied as part of a multi-lateral approach to downregulate possible *C. albicans* imbalance, including as much exposure of the nipples to the air as possible, prior to antifungal use. The critical issue of persistent breast tissue drag during breastfeeding must also be addressed, as a matter of priority. Breastmilk may be applied to the nipple-areolar complex, due to the immunoregulatory properties of breastmilk, which include the antagonistic effects of *Lactobacillus* on *C. albicans*.[6]

On rare occasions, if these multi-lateral interventions do not decrease the breast and nipple pain, treatment for yeast infection of the nipples may be deemed clinically appropriate. A standard antifungal course of miconazole cream four times daily on the nipples and fluconazole 150 mg stat, three doses taken on alternate days for a week, may be prescribed. The clinician should bear in mind that vulvovaginal candidiasis is usually effectively treated with a single oral dose of fluconazole 150 mg, and there is no rationale for prolonged courses of antifungals for persistent breastfeeding pain.[46] Persistent pain is most likely due to failure to effectively address underlying micro-trauma. There is no evidence to suggest that infant nappy rash or maternal vaginal thrush predispose a breastfeeding woman to nipple thrush, since *Candida* does not constitute a transmissible infection. Finally, an RCT showed that a nipple application containing miconazole 2% was no better than lanolin in reducing nipple pain or nipple healing time, or improving maternal satisfaction.[47]

Multiple conservative strategies to downregulate any possible *C. albicans* overgrowth when there are predisposing factors, and careful attention to eliminating breast tissue drag and persistent micro-trauma, are the treatments of choice.

2. Clinical focus shifted away from fit and hold interventions which address the primary cause of repetitive mechanical micro-trauma resulting in pain of the nipple and breast;[34]
3. Alteration of the protective ecosystem of the milk and skin microbiomes, with unknown effects;
4. Fluconazole side-effects including:
    a. Interaction with domperidone and erythromycin to prolong QT intervals in cardiac electrophysiology;[48,49]
    b. Transient and asymptomatic hepatoxicity in 10% of patients, in particular with daily doses when monitoring of liver enzymes is recommended (discontinuation is not required);[50]
    c. Fulminant and fatal hepatotoxicity, which is extremely rare in otherwise healthy patients but has been reported.[50]
    d. Breastfeeding mothers taking fluconazole report:
        i. Gastro-intestinal symptoms or headache (13%)
        ii. Infant side-effects, including flushed cheeks, gastrointestinal upset, and runny or mucous stools (7%);[7]
5. Topical miconazole, in particular with long courses prescribed for persistent nipple pain, risks overhydration of the epithelium and associated contact dermatitis and worsened pain;[51]
6. Gentian violet applications to the nipple-areolar complex, recommended as an option in clinical protocols, risk infant buccal ulceration and necrotic maternal skin reactions.[1,52]

If it's not thrush, what causes burning nipple pain and associated radiating breast pain including between feeds?

In establishing the diagnosis of mammary candidiasis, existing protocols require the clinician to first eliminate the possibility of fit and hold (or latch and positioning) problems. However, most significantly, there is little evidence to support the therapeutic efficacy of the range of fit and hold, or latch and positioning, interventions commonly applied by International Board Lactation Consultants or other health professionals, and these approaches remain predominantly experience or opinion based.[8–11]

The physiologic approach to breastfeeding initiation, including skin-to-skin contact postpartum, has been a

major advance in the field of clinical breastfeeding support over the past two decades, with positive impacts on breastfeeding outcomes.[53–56] But the range of fit and hold interventions currently offered, including 'baby-led' or mammalian methods, have not been demonstrated to resolve maternal pain or breastfeeding-related unsettled infant behaviour, including in RCTs.[9,57–63]

For example, one popularly applied fit and hold technique teaches women to shape their breast and apply a cross-cradle hold as they bring the infant on. In 2002, this technique, when taught to hospital midwives in Bristol, UK, was shown in a prospective cohort study of 1171 new mothers to increase the rate of breastfeeding at 6 weeks post-birth relative to usual care.[64] But in a 2016 Australian study of 653 pairs, this same technique was also shown to worsen the incidence of nipple pain fourfold.[12] In an RCT of 103 of mothers with babies up to 16 weeks of age with severe latch-on difficulties, a 'baby-led' or skin-to-skin intervention did not make it more likely that the infant would latch-on,[16] despite evidence that the 'baby-led' approach when applied from birth modestly decreases the risk of developing nipple pain.[13–15]

This article proposes that overtreatment with antifungal medications is one of a number of examples of overmedicalisation of nipple pain, which result from failure of current approaches to fit and hold to effectively resolve repetitive micro-trauma during breastfeeding.[34] Other examples include overtreatment with infant frenotomy for diagnoses of oral connective tissue restrictions.[34,36,37]

A new 'gestalt' biomechanical model of infant suck and swallow, derived from ultrasound and vacuum studies and corroborated by real-time magnetic resonance imaging (MRI) analysis, contests previous biomechanical conceptions of infant suck and swallow.[34,65,66] In the gestalt approach to fit and hold, which derives from the gestalt biomechanical model, it is understood that women use a wide range of descriptors for their breastfeeding-related nipple and breast pain in the absence of fever or signs of mastitis. These descriptions are not diagnostic, for example, of nipple thrush or restricted oral connective tissues but are a spectrum of descriptions of the effects of repetitive tensile mechanical micro-trauma, causing tissue inflammation and experienced uniquely by each woman. Breastfeeding women may experience a spectrum of epithelial damage ranging from non-visible or deep tissue effects of micro-trauma, to erythema and oedema, fissures, ulceration and bleeding. In the gestalt approach, nipple vasospasm is understood to result from repetitive micro-trauma, whether episodes are temporally associated with feeds or not, though a history of autoimmune disease or diagnosis of Raynaud's syndrome prior to lactation may increase the likelihood of a vasospasm response.

Clinically, nipples subject to repetitive micro-trauma may on occasions appear pink and shiny, with fine scaling and itch, but this appearance is not diagnostic of candidiasis. The fine white scale that is often attributed to nipple candidiasis is a hyperkeratosis of the stratum corneum, which occurs in the context of repetitive micro-trauma and overhydration. Itchiness results from histamine release in response to inflammation; it is hypothesized that histamines stimulate nerve cells during the proliferative phase of healing.[67]

The gestalt model proposes that micro-trauma results from conflicting intra-oral vectors of force during breastfeeding.[34,65,66,68,69] The infant tongue is conceptualized as a supple, adaptive muscular hydrostat, which changes shape to conform to the amount of intra-oral breast tissue that is available. Intra-oral vacuum is generated by the inferior drop of the mandible, which the anterior and mid-tongue follow *en bloc*, in the context of a seal. Breast tissue drag, resulting from suboptimal fit and hold, will create a vector of force which conflicts with the vector of force generated by the intra-oral vacuum, and compromises intra-oral breast tissue volume. As a result, high tensile or mechanical loads are focussed upon a small surface area on the nipple, resulting in discomfort or pain, epithelial inflammation, and also epithelial rupture. A gestalt intervention integrates the foundational evidence-based principles of the 'baby-led' approaches with the clinical implications of the new biomechanical model. It aims to eliminate conflicting vectors of force, which will optimize intra-oral breast tissue volume and allow the intra-oral vacuum and associated mechanical load to be diffused over a larger surface area of the intra-oral nipple-areolar complex, so that concentrated stretching or bending forces no longer cause repetitive micro-trauma and tissue damage.[34,65,66]

Conclusion

Antifungal treatment is rarely indicated for breastfeeding women experiencing nipple pain accompanied by radiating or stabbing or constant breast pain between feeds and by pink shiny nipple epithelium with fine white flakes of skin. Prolonged courses of antifungal medications cannot be justified. Multiple strategies for stabilizing microbiome feedback loops when nipple and breast pain emerge are required, in order to avoid overtreatment of breastfeeding mothers and their infants with antifungal medications. In particular, there is an urgent need for comparative evaluation of an approach to fit and hold (latch and positioning) which aims to eliminate intra-oral breast tissue drag and associated repetitive micro-trauma from conflicting intra-oral vectors of force during breastfeeding, if we are to avoid overmedicalisation of breastfeeding mothers and their infants.

Declaration of conflicting interests

The author(s) is Medical Director of Possums & Co, a charity which educates health professionals in Neuroprotective Developmental Care (or 'the Possums programs'), including in the gestalt approach to clinical breastfeeding support. Possums &

Co sells a Gestalt Breastfeeding Online Self-help program. The charity invests all revenue raised back into education and research which supports the well-being of mothers and babies.

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