FACULTY OF
PHARMACEUTICAL SCIENCES

Development of a protocol to question health care workers considering oral thrush in infants

Anne-Florence Moerman

A Master dissertation for the study programme Master in Pharmaceutical Care

Academic year: 2019 - 2020

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The information, conclusions and points of view in this master dissertation are those of the author and do not necessarily represent the opinion of the promoter or his/her research group.

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PREAMBULE

In deze scriptie beoogden we aanvankelijk een onderzoek te voeren naar de diagnosestelling en behandeling van orale spruwinfecties bij zuigelingen tijdens de borstvoedingsperiode in de praktijk. We wensten met behulp van vragenlijsten voor zorgverleners en ouders een beeld te vormen van de noden en uitdagingen die zich voordoen in de huidige praktijk. Daarnaast beoogden we een beeld te vormen van de meest bevraagde alternatieve therapieën en te onderzoeken welke invloed spruwinfecties bij zuigelingen en moeders hebben op de borstvoeding. Verder hadden we graag ook de huidige kennis en praktijk omtrent resistentie van microorganismen aan antimycotische middelen bestudeerd.

Omwille van de maatregelen met betrekking tot COVID-19 is de aanvraag bij het ethisch comité voor het uitvoeren van deze studie verhinderd. Hierdoor was het onmogelijk om vragenlijsten te distribueren en resultaten te bekomen.

Bijgevolg zijn de doelstellingen van dit onderzoek geheroriënteerd naar het ontwikkelen van de vragenlijsten in combinatie met het samenvatten van bestaande richtlijnen omtrent de diagnosestelling en behandeling van spruwinfecties tijdens de borstvoeding, zowel bij de zuigeling als bij de moeder. Ook werd uitgebreid onderzocht welke alternatieve therapieën soms geadviseerd worden. Op deze manier kon een deel van het reeds voorhanden zijnde materiaal (de reeds opgestelde vragenlijsten) toch geïncludeerd worden in de scriptie.

Deze preambule werd in overleg tussen de student en de promotor opgesteld en door beiden goedgekeurd.

SUMMARY

Objectives: In this dissertation we aimed to summarize available Dutch and English guidelines on the diagnosis and treatment of oropharyngeal candidiasis in infants and mammary and/or nipple candidiasis in mothers during lactation. Additionally, we included a review of alternative approaches that may be used in the treatment of oropharyngeal candidiasis and mammary and/or nipple candidiasis during the breastfeeding period. Furthermore, we aimed to evaluate the treatment cost of OPC in infants. Finally, we wished to compose questionnaires for health care workers and parents to examine the diagnosis and treatment of OPC and mammary and/or nipple candidiasis in daily practice.

Methods: Initially, we used four scientific databases (PubMed, Scopus, Google scholar and Web of Science) to search for guidelines concerning OPC in infants and nipple or mammary candidiasis in mothers, followed by a general internet search to ensure inclusion of directives by (online) breastfeeding-focussed organisations. The treatment cost was calculated by using the most affordable commercially available compounds, according to the website of the Belgian Centre for Pharmacotherapeutic Information. Lastly, three questionnaires were designed: one for general practitioners, paediatricians and midwives, one for pharmacists and one for parents. The questionnaires were continuously adapted according to topics discussed in literature and the acquired guidelines and optimized in collaboration with a paediatrician.

Results: Fifteen different guidelines concerning the diagnosis and treatment of OPC in infants and mammary or nipple candidiasis in mothers were included. We acquired two Dutch guidelines, three Belgian guidelines, three British guidelines, three American guidelines, two Australian guidelines and two international guidelines. Concerning treatment cost, the price of treatment of a four-week-old infant is equal to the price of treatment of a six-month-old infant. Nystatin oral suspension appeared to have a total treatment cost of €15,1 (€2,02 with normal compensation) for a fourteen-day treatment, miconazole oral gel (Daktarin®) costs €16 (€2,34 with normal compensation) for a fourteen-day treatment. Treatment with fluconazole (Diflucan®) costs €12,55 (€2,73 with normal compensation) for a seven-day treatment. Concerning the questionnaires, all surveys include questions on the diagnosis and treatment of thrush in infants and mothers during lactation. Contemporary challenges such as resistance to medication, breastfeeding experience and alternative approaches were also included.

Conclusion: We gathered fifteen different guidelines. The contents of the guidelines contain a significant amount of discrepancies. Nystatin oral suspension and miconazole oral gel are the first-choice treatment options for OPC in infants. Future research on the in vivo safety and effectiveness of alternative approaches is necessary. Nystatin oral suspension is the most affordable treatment option for OPC in infants. Finally, three questionnaires were developed.

SAMENVATTING

Objectieven:. In deze scriptie beoogden we een samenvatting te maken van Engelse en Nederlandse richtlijnen met betrekking tot de diagnose en behandeling van spruwinfecties bij zuigelingen en moeders tijdens de borstvoedingsperiode. Daarnaast wensten we een kritische blik te werpen op de mogelijke alternatieve therapieën in de behandeling van spruwinfecties. Verder wensten we de kostprijs van de behandeling van spruwinfecties bij zuigelingen te evalueren. Ten slotte beoogden we vragenlijsten op te stellen voor zorgverleners en ouders om de diagnosestelling en behandeling van spruwinfecties bij zuigelingen en moeders in de dagelijkse praktijk te onderzoeken.

Methodes: We consulteerden vier wetenschappelijke databases (PubMed, Scopus, Google scholar en Web of Science) in de zoektocht naar richtlijnen met betrekking tot spruwinfecties. Vervolgens voerden we een algemene internet-zoekopdracht uit om de inclusie van richtlijnen door (online) borstvoedingsgerichte organisaties te verzekeren. De kostprijs van de behandeling werd berekend door selectie van de meest betaalbare specialiteiten met behulp van de BCFI website. Ten slotte werden drie vragenlijsten opgesteld: één voor huisartsen, pediaters en vroedvrouwen, één voor apothekers en één voor ouders. De vragenlijsten werden voortdurend bijgewerkt naargelang de verzamelde literatuur en richtlijnen en ze werden geoptimaliseerd in samenwerking met een pediater.

Resultaten: We bekwamen vijftien verschillende richtlijnen met betrekking tot de diagnosestelling en behandeling van spruwinfecties bij zuigelingen en moeders. We includeerden twee Nederlandse richtlijnen, drie Belgische richtlijnen, drie Britse richtlijnen, drie Amerikaanse richtlijnen, twee Australische richtlijnen en twee internationale richtlijnen. Met betrekking tot de kostprijs van de behandeling bleek de prijs voor een baby van vier weken hetzelfde te zijn als de prijs voor een bandeling van een zes-maanden-oude baby. Nystatine heeft een totale kostprijs van €15,1 (€2,02 met normale tegemoetkoming) voor een behandeling van veertien dagen. Miconazole orale gel (Daktarin®) heeft een totale kostprijs van €16 (€2,34 met normale tegemoetkoming) voor een behandeling van veertien dagen. De prijs van een behandeling van zeven dagen met fluconazole bedraagt €12,55 (€2,73 met normale tegemoetkoming). Ten slotte bevatten alle enquêtes vragen met betrekking tot de diagnose en behandeling van spruwinfecties bij zuigelingen en moeders tijdens de borstvoedingsperiode. Recente uitdagingen zoals resistentie aan antimycotica, invloed van spruw op de borstvoeding en het gebruik van alternatieve therapieën werden ook geïncludeerd.

Conclusie: We verzamelden vijftien verschillende richtlijnen. De inhoud van de richtlijnen vertoont significante onverenigbaarheden. Nystatine orale suspensie en miconazole orale gel vormen de primaire keuzes in de behandeling van spruwinfecties bij zuigelingen. Onderzoek naar de in vivo effectiviteit en veiligheid van alternatieve therapieën is nodig in de toekomst. Nystatine is de meest betaalbare behandeloptie. Ten slotte werden drie vragenlijsten ontwikkeld.

ACKNOWLEDGMENTS

At the start of this semester I was incredibly excited to conduct the research project ahead of me. Unfortunately, a global pandemic broke out and things dramatically changed. This period has been challenging, especially mentally, and I realise I couldn't have gotten through this and delivered this result on my own. Therefore, there's some people that deserve a special thank you.

First and foremost, I would like to thank my promotor, Eline Tommelein. Thank you for the endless feedback, tips and tricks. Thank you for taking the time to read my dissertation a million times. Thank you for guiding me when I got lost. Thank you for encouraging me by saying I did a good job, I don't think you realise how much that meant to me in this challenging situation. Thank you for always being constructive. Thank you for all the knowledge you passed onto me. Thank you for the contagious enthusiasm you radiate. I will take that with me and put it into every future project. In short: the biggest thank you for being a really good promotor.

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I would also like to thank a small –approx. 50 cm- motivating factor, which got me even more invested into this subject, because I had someone to project it onto. Mathis, welcome to this world. Auntie can't wait to show you this as soon as you can read and understand English.

Lastly, thank you to my partner in crime, Lore, for making me feel like we were in this together. Thank you for tolerating my million questions and telling me it would all be fine in the end. We got this.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AIDS	=	Acquired Immune Deficiency Syndrome
APNO	=	all-purpose nipple ointment
BAPCOC	=	Belgian Antibiotic Policy Coordination Committee
BCFI	=	Belgisch centrum voor farmacotherapeutische informatie
CAM	=	Complementary and Alternative Medicine
CDD	=	candidal diaper dermatitis
GP	=	general practitioner
LLL	=	La Leche League
MFC	=	Minimum Fungicidal Concentration
MIC	=	Minimal Inhibitory Concentration
OPC	=	oropharyngeal candidiasis
UNICEF	=	United Nations International Children's Emergency Fund
WHO	=	World Health Organisation
ZOI	=	zone of inhibition

1. INTRODUCTION

1.1. THRUSH

Thrush is a fungal infection caused by *Candida albicans* or other *Candida* species in 95% of cases. (1) Other *Candida* species include *C. glabrata, C. tropicalis, C. parapsilosis, C. krusei, C. dubliniensis and C. guilliermondii.* (2,3) Thrush in infants is also called **oropharyngeal candidiasis (OPC),** pseudomembranous oral candidiasis or Monilia. (4) A symptomatic infection occurs when there is an overgrowth of *Candida* species in the superficial epithelium of the oral mucosa. This usually affects the infant's mouth and/or tongue, manifesting as white plaques.

Thrush was mentioned for the very first time in Hippocrates' book named "Of the epidemics" and was described as "mouths affected with aphthous ulcerations" (400 B.C.). Up until the 1800's the disease was believed to be of host origin. It took about 200 years to identify the causative agent as a fungal pathogen, starting with the first observation of a fungus as the source of infection in 1846 by Berg. However, it was Charles Philippe Robin, a French mycologist, who classified the fungus as 'Oidium albicans' only one year later, in 1847. In this classification, the term 'albicans', which means 'to whiten', was used for the first time. Almost a century later, in 1923, the fungus was reclassified under the current genus '*Candida*'. *'Candida'* is derived from the Latin 'toga candida'. This referred to white robes, worn by senators in the ancient Roman times. It's presumed the name *'Candida'* was given as a reference to the white oral lesions or possibly the white fungal colonies on agar. Another couple of years later, in 1954, the term *'Candida albicans'* was formally introduced, but it wasn't until the 1980's that oral candidiasis gained more attention. The sudden rise of interest in thrush can be mainly attributed to the escalation of the AIDS epidemic, which meant a greater incidence of OPC in individuals with weakened immune systems. This trend highlights the opportunistic nature of the infection. (1)

In this dissertation, we focus on OPC in children that are breastfed. OPC during breastfeeding is a common fungal infection, most often caused by the bodies' own commensal *Candida albicans*. The buccal area of the neonate already gets colonized with *Candida* when passing through the birth canal while having physical contact with the maternal vaginal mucosa. *Candida* may also be acquired from the hands of the mother or caregivers. Maternal vaginal colonization with *Candida* naturally increases during pregnancy, with 20% to 40% of mothers testing positive during labour. Children born by natural delivery consequently have a greater chance of colonization with *Candida* species. (5)

An infection develops when there is an imbalance in the neonate's local immune response. It can take place at any age after colonization. (2)

The otherwise commensal yeast colonizes the buccal epithelial cells via germ tube formation and relative hydrophobicity of the cell surface, which promotes further colonization. (6) The adherence of *Candida* species to buccal cells is greater in premature infants compared to the adherence to buccal cells of term infants. In term infants, the adherence of the yeast to mucosal cells increases over the first week of life. (7) Up to 80% of the general population carries *C. albicans* asymptomatically. Being a carrier does not automatically lead to infection. However, *C. albicans* possesses an impressive amount of virulence factors, which allow the organism to rapidly transform into a pathogen. This transition is generally inhibited by the host immune system, specifically by secretion of anti-candidal peptides into the saliva, which inhibit the adherence of the yeast to epithelial cells. (1,6) Some important virulence factors produced by the yeast are extracellular enzymes. *Candida* species produce phospholipases and proteinases, which promote cell membrane destruction and aid in nutrient acquisition. (8)

As a commensal organism, C. albicans reversibly adheres to epithelial cells through electrostatic interactions. These interactions can be easily dismissed by salivary flow and swallowing. In addition, the saliva is enriched with anti-candidal peptides. Both functions are considered host defence factors. The attachment of the fungus to the buccal mucosa is mediated by a variety of receptors, such as those of the agglutinin-like sequence family of glycoproteins. Two specific proteins, Alsp3 and Hwp1, were respectively identified as a receptor for bacterial co-adhesion and as a major adhesin. Deletion of the genes responsible for the expression of these proteins showed to make the pathogen significantly less virulent. Other virulent traits of *C. albicans* consist of its' ability to morphologically switch from yeast to hyphal forms after attachment to host surfaces (the hyphal form enables invasion of the host tissue), the ability to invade host cells through endocytosis by using lytic enzymes and invasive proteins and the ability to form biofilms. This is confirmed by a study by Taschdjian and Kozinn, which mentions that the presence of *Candica albicans* blastospores in oral samples for a period of three or four days predicts the development of clinical oral thrush by 98.5% and that the disease is imminent when hyphae can be detected in oral smears. (9) A visual representation of the stages of oral infection with *Candida albicans* can be seen in **Figure 1.1.1**.

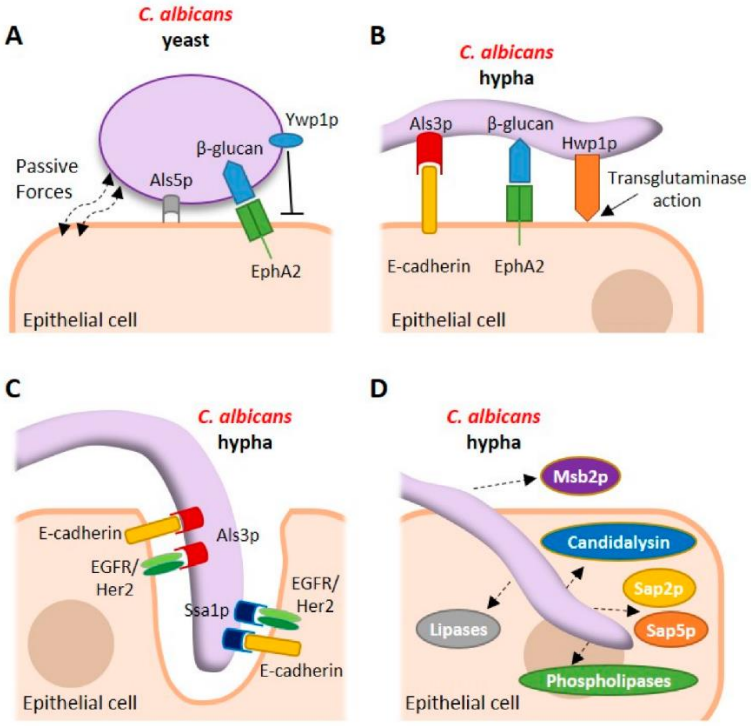

Figure 1.1.1: Schematic interaction of *C. albicans* with host epithelial cells. (A) Colonization with C. albicans through adherence by passive electrostatic forces, the cell surface protein Als5p which functions as an adhesin and a component of the fungal cell wall, β-glucan, binding to a protein-tyrosine kinase receptor (EphA2) on the epithelial surface. Ywp1p is expressed during the growth phase and has antiadhesive properties. A receptor for this protein has not yet been identified. (B) The transition to the hyphal form of *C. albicans* results in stronger interactions with the epithelial cell surface through expression of additional adhesins, including Hwp1p and Als3p. Als3p forms an interaction with E-cadherin and Hwp1p acts as a substrate for epithelial transglutaminase enzymes. The interaction between hyphal β-glucan and EphA2 remains. (C) Invasion of the C. albicans hyphae into the epithelial cell surface is mediated by invasins (Als3p and Ssa1p), which interact with E-cadherin and an EGRF/Her2 receptor complex. The complex consists of the epidermal growth factor receptor and a Her2-receptor. *C. albicans* may also breach the mucosal barrier by direct active penetration but remains passive during the process of pathogen-induced endocytosis. (D) *C. albicans* secretes virulence factors while in contact with the host mucosal tissue. These virulence factors include candidalysin (a peptide toxin), aspartic proteinases (Saps), lipases and phospholipases. To counteract host antifungal peptides, Msb2p is excreted into the extracellular environment. (10)

The immune system of infants is not completely developed at the start of life. This is a possible reason for the higher prevalence of oral thrush in extreme ages, such as infants. Infants get their initial protection mainly from immune factors transmitted through breastmilk at the start of life. Through breastfeeding, the child not only acquires this passive immunity, but also the perfect amount of nutrients for every stage of development. Among other reasons, this led to the advice of WHO and UNICEF to recommend that breastfeeding should be initiated within the first hour postpartum and the aim is to exclusively breastfeed the child for six months. Exclusive breastfeeding means no other foods or liquids are provided, not even water. After six months, safe and adequate complementary foods may be provided to the child while continuing to breastfeed. Breastfeeding should be continued for up to two years and beyond. (11,12)

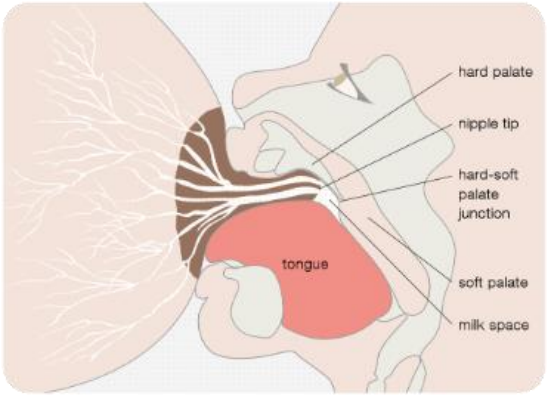

Figure 1.1.2: Anatomy of breastfeeding (13)

However great the benefits of breastfeeding, the fungal infection can also be passed onto the mother by the very act of breastfeeding. When a baby feeds, it makes a teat from the nipple and the surrounding breast tissue, as can be seen in **Figure 1.1.2**. These structures and the underlying breast tissue are drawn deeply into the infant's mouth and are sealed. During the process of suckling, the infant's tongue remains over the lower gum, while the tongue forms a groove around the areola of the breast. The teat ends on the mid tongue, near the junction between the hard and soft palate. All relevant structures of the infant mouth and female breast are schematically presented in **Figures 1.1.3** and **1.1.4**. If a *Candida* overgrowth is present in the infant's mouth, suckling at the breast may easily infect the mother. On the other hand, *Candida spp.* found in or on nipples can also infect the infant. (8)

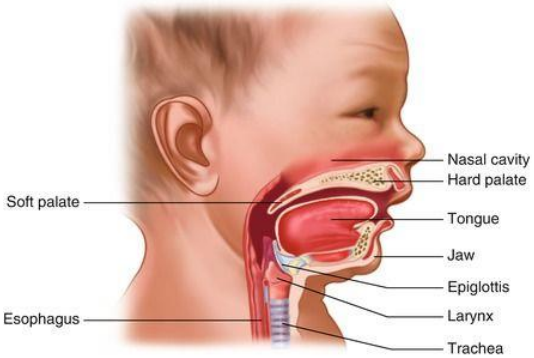

Figure 1.1.3: Anatomy of the infant mouth (14)

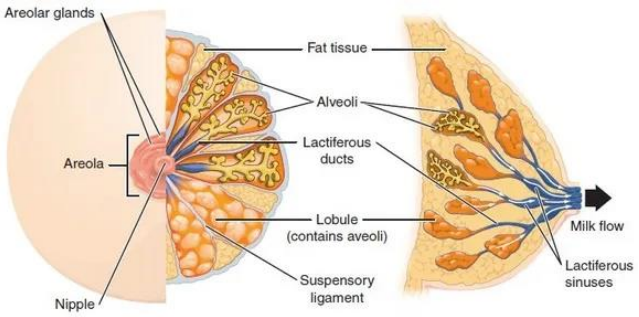

Figure 1.1.4: Anatomy of the female breast (15)

1.1.1 Presentation of thrush

Oral thrush in **infants** often presents as white patches on the mucosal membrane of the mouth. Under these white plaques, the epithelial surface may be tender. (4) The white patches can occur on the tongue, inside of the cheeks, on

the gums, on the palate and/or on the throat. (3) A typical trait of a *Candida* infection is that these plaques come off by gentle scraping, often revealing a red, irritated surface. Health care providers should be attentive not to confuse milk coating from breastfeeding with OPC, as both might – at first sight – present similarly. (16) Although OPC can be caused by multiple *Candida* species, symptoms manifest in the same way, regardless of the causative species. The infant may experience pain or discomfort when having to use the mouth and this may consequently lead to poor nursing and possible failure to thrive. (5)

Candidiasis in the **mother** causes symptoms at the nipple area and/or at the breast tissue. Physical manifestations of nipple thrush include a pink nipple/areola area, a shiny or flaky appearance of the nipple, nipple pain out of proportion to clinical findings, burning nipple pain and pain radiating into the breast or axilla. (17) Also, a sudden and intense pain and sometimes fissures are typical clinical presentations of nipple candidiasis. (8) To this day the involvement of *Candida* with nipple or breast pain remains controversial. Some studies have found an association between thrush symptoms and *Candida* colonization, others haven't. (17) However, there is scientific evidence that the bacterial component of the mouth microbiome in combination with *Candida* pathogenic factors plays a significant role in the development and potential aggravation of oral candidiasis. (18) Research also suggests that co-adhesion of *C. albicans* to buccal bacteria is necessary for persistent colonization. (19)

1.1.2 Prevalence of thrush during breastfeeding

OPC is most frequently reported at four weeks of age. Reported incubation periods are in between four and thirteen days. (5,7) OPC can be seen in up to 37% of otherwise healthy infants. (1,20) Many different prevalences are reported, possibly because of the small study population of the available studies. A study by Yilmaz et al. reported that the prevalence of OPC is not associated with ethnicity. (21) Prevalences reported in more recent studies are shown in **Table 1.1.2.1.**

Table 1.1.2.1. Prevalence of OPC in infants reported by various studies.

Author	Year of publication	Number of children in study population	Age of study population	Prevalence of OPC
Vainionpää et al. (22)	2019	32	Under 12 months	12.5%
Stecksén-Blicks et al. (23)	2015	496	8 weeks 3 months 6 months	11% 11% 15%
Yilmaz et al. (21)	2011	216	2 to 12 months	10.70%
Bessa et al. (24)	2003	746	0 to 4 years	0.99%

1.1.3 Predisposing factors to the development of thrush

First, infants whose mother has an **active vaginal *Candida* infection during birth** are eight times more likely to develop thrush. Thrush develops in approximately 40% of cases where the mother had a symptomatic vaginal infection when giving natural birth. (7,25) Additionally, a study by Tanguay et al. found a significant correlation between the development of nipple candidiasis in mothers and current vaginal candidiasis, previous antibiotic use and nipple trauma at the beginning of the lactation process. (26)

Second, **immature host defence mechanisms** are the main reason why *C. albicans* often acts as a pathogen in the infant. (5) Factors that cause even the slightest imbalance in host defences may be risk factors to the development of thrush. These may include local or systemic treatment of the infant with broad-spectrum antibiotics, the use of steroids, the use of immunosuppressants or the presence of juvenile diabetes. All of these factors can cause a dysbiosis in the infant's microbiome and thus a favourable environment for *Candida* to proliferate in the child's oral mucosa. (1,3,20)

Third, **reduced salivary flow and physical damage to the mouth's mucosa** may also trigger the infection in the infant. (2,6) Additionally, in premature infants in intensive care units a significant association was reported between oxygen deprivation at birth and developing thrush. (7)

Moreover, thrush in bottle fed infants is more common than thrush in infants directly fed at the breast. Bottles and other aids are often not sufficiently cleaned before they are reused. As well as use of a bottle, using an infant soother, a breast pump and other aiding materials can increase the incidence of thrush and be a continuous source of infection, unless they are properly washed and sterilized. Thus, the **use of bottles, breastpumps and pacifiers** are considered predisposing factors to de development of thrush in infants. (5,20,27)

OPC and **candidal diaper dermatitis in the infant** predispose the mother to the development of nipple and/or breast thrush. Other factors that predispose the mother to the development of nipple thrush include the use of corticosteroids, antidepressants and immunosuppressants as they create an imbalance in the local flora and increase the opportunity for *Candida* overgrowth. Other alterations in the endocrine balance, such as diabetes mellitus, renal failure, hyperthyroidism and pregnancy itself predispose the mother to any type of fungal infection. (6,17,26)

1.2. DIAGNOSIS OF THRUSH

Diagnosing OPC in infants is mainly based on physical examination of the infant's mouth, identifying the white plaques and is sometimes accompanied by simultaneous examination of the infant's diaper area in the search for concomitant candidal diaper dermatitis (CDD). (4) In assessing oral thrush in infants, it might be useful to swab the white patches and determine whether it is *Candida* and which species is present. (1) Infants with OPC inevitably have traces of *C. albicans* in their gastro-intestinal tract and faeces. In studies on infants with OPC, *C. albicans* was found in the faeces of up to 90% of patients. The infected faeces showed to lead to a cutaneous candidal infection in almost 50% of cases. The researchers concluded that candidal diaper dermatitis is often the result of oral and consecutive gastro-intestinal candidiasis. The first clinical manifestation of CDD is emaciation of the anal mucosa and perianal skin, followed by scaly papules merging into eroded lesions. CDD is characterized by flaccid vesicopustules outside the main zone of irritation. CDD may be confined to the diaper area, without the presence of oral thrush. On the other hand, diaper dermatitis is not always caused by *Candida* species, thus a differential diagnosis between CDD and other forms of diaper dermatitis must be made. There is no need for routine stool cultures to determine the presence of *C. albicans* if the clinical presentation of candidal diaper dermatitis is typical. (5)

OPC in infants is closely related to nipple and ductal thrush in the mother, as the infection may be transmitted through physical contact by breastfeeding. Diagnosing ductal or nipple thrush in the mother is often based on the sole symptom of nipple pain. (28) Nipple thrush can be suspected when there were no earlier problems during breastfeeding and the mother rapidly developed extremely sore nipples, burning or itching and burning, shooting or stabbing nipple pain that radiates through the chest wall. (4,16) Nipple thrush can also be suspected if the physical manifestations are typical. (8,17) Distinguishing pathologic pain from discomfort commonly reported in the first few weeks of breastfeeding can be challenging. Therewithal, lactation specialists have not yet reached a consensus regarding the cause of deep aching and sharp breast pain. Multiple possible causative agents need to be considered when diagnosing this pain, such as *Candida* overgrowth, bacterial overgrowth, dysbiosis, physical trauma due to poor latch-on, other mechanical problems or even a combination of the previously mentioned. (17,29)

In addition to a physical examination of the breast, it is advised for the breastfeeding mother to have an evaluation of her breastfeeding technique by a midwife, a lactation specialist or other knowledgeable practitioner on the matter.

The majority of cases of nipple pain with minimal visible trauma can be relieved by adjusting the positioning and latch of the infant to the breast. Possible sources of pain can include poor latch-on, slow let-down of milk, the baby not attaching deeply enough so the infant's tongue or roof of the mouth rubs against the nipple, the baby using its tongue incorrectly, too much suction when taking the baby off and vasospasms among others. (30) Furthermore, McClellan et al. reported strong vacuums applied by infants during breastfeeding as a cause of nipple pain. Specifically, the vacuum applied by infants of women reporting pain was of greater force than the maximum comfortable pumping vacuum measured in women who did not report pain. (31) Assessment of breastfeeding practice should include a direct observation of a complete breastfeeding session with a focus on maternal positioning, position of the infant and behaviour at the breast, suckling dynamics and shape and colour of the nipple after feeding. (17)

In the assessment of OPC in the infant, possible sources of the infection must be evaluated simultaneously, considering the colonization of the infant during natural delivery. A significant transmission of micro-organisms from mother to child takes place during labour. The delivery mode determines the type of transmitted micro-organisms: babies delivered through vaginal birth show similar bacterial communities throughout their bodies as found in the mothers vaginal area, whereas babies delivered through caesarean birth show a composition similar to the mothers skin microbiome. (25) OPC in the neonate may be the result of passage through an infected birth canal, therefore it may be useful to assess the mother for vaginal candidiasis. (5) Symptoms of vaginal candidiasis include vaginal itching or soreness, pain during intercourse, pain or discomfort when urinating and abnormal vaginal discharge. Health care providers usually confirm the diagnosis by examining a specimen of vaginal discharge under a microscope in the medical office or send it to a laboratory for a fungal culture. (32)

In assessing for simultaneous ductal and oral candidiasis in the mother-baby dyad, physicians almost never request cultures of breastmilk as a confirmation of the diagnosis. This is mainly because *Candida* is difficult to grow in milk due to assumed inhibition by lactoferrin. There are also hardly any standardized protocols for the collection, storage and analysis of breastmilk samples in case of suspected OPC. (27) In addition, multiple studies suggest no difference in *Candida* species can be found in milk of infected mothers compared to control groups. (29) In a study of 346 healthy breastfeeding women, *Candida albicans* was found on nipples and in breastmilk of 2.6% of all healthy women during the fourth week postpartum. When assessed for all *Candida* species, 5% of the study population tested positive. Multiple studies on healthy breastfeeding women reported the presence of *Candida albicans* in 3% to 23% of breastmilk samples. (16,17,33)

Recently, newer methods such as analyses of 1->3 β-D-glucan in breastmilk were used to assess colonization with *Candida* species. These methods revealed no significant difference in fungal levels in breastmilk between the symptomatic and the control group. The amount of *Candida* species found in the milk samples was too low to be cultured in both groups, even after addition of iron to stimulate the *Candida* growth and inhibit the presumed effect of lactoferrin. (29) Other research on 529 breastmilk samples of women with symptoms consistent with candidiasis reported that no association was found between *C. albicans* presence in breast milk and the symptoms, while a significant association was found between the symptoms and the presence of coagulase negative staphylococci and streptococci on the nipple and in breastmilk. They suggested that the presence of staphylococci and streptococci can induce *Candida* overgrowth, and that consequently the source of the thrush-infection was the mothers nipple. It is known that these bacteria promote fungal growth and may lead to mixed-species biofilm formation. Another study confirms that microbial presence of *Candida albicans* in breast milk is not a reliable source to diagnose a *Candida* infection of the breast. (16)

Contradictory, a study by Amir et al. examined 346 women of which 32% developed burning nipple pain and radiating breast pain within two to eight weeks postpartum. By leaving out the first week they corrected for common nipple pain while adjusting to breastfeeding. Women with and without the case definition of thrush were examined for the presence of nipple damage, presence of *C. albicans* and presence of *S. aureus*. Only the presence of nipple damage and *C. albicans* significantly predicted thrush. The researchers concluded that *Candida* is involved in nipple and breast pain in lactating women. (4,33)

All studies concluded that cultures are an asset to determining colonization with *Candida* species or bacterial overgrowth, but that the management should include treating immediately while awaiting the culture results. (4)

1.3. TREATMENT OF THRUSH

Antifungal agents are the first choice in the treatment of OPC in infants and concomitant nipple or breast thrush in nursing mothers. Antifungal drugs can be divided into three main classes: polyenes, azoles and echinocandins, each with their own benefits and shortcomings. Medication that has been used for almost seventy years is still indicated

as first line therapy today. The main shortcomings include suboptimal selectivity, heightened toxicity and increased risk of resistance, particularly to azole-antifungals. (1)

Available literature advises to routinely treat symptomatic OPC in infants, yet in a letter published in The Pediatric Infectious Disease Journal, a paediatrician with extensive experience questions the need to routinely treat oral candidiasis in immunocompetent infants. He doesn't recall ever seeing infants showing signs of pain due to thrush and consequently feed poorly, show signs of anorexia or develop a systemic infection as a result thereof. He pleads to only treat in case of concomitant persistent CDD, concomitant presumed maternal infection of the nipple or surrounding breast tissue or if the parents are anxious for treatment. He also vocalizes the need for more extensive research on the prevalence of symptoms in infants going through a thrush infection, the risk of development of a more extensive or systemic infection and research on evidence to justify routine use of antifungals. (34)

Important in the treatment of thrush is the concept of the mother-baby dyad, meaning every treatment plan should include the simultaneous assessment and, if necessary, treatment of the mother and the child. (35) Moreover, simultaneous infections such as vaginal candidiasis in the mother or CDD in the child require synchronous treatment. One miconazole vaginal capsule (Gyno-Daktarin®) containing 1200 mg of miconazole is indicated for symptomatic vaginal candidiasis and is considered safe during pregnancy and lactation. (36) For CDD, one application a day of isoconazole 1% cream (Travogen®) is advised and treatment should be continued until two weeks after the lesions have disappeared. (37)

1.3.1. Non-medical approaches

First, pacifiers, breast pumps, bottles and other supplies can increase the prevalence of thrush and be a continuous source of infection, unless properly washed and sterilized. (5,20,27) Pacifiers may develop persistent biofilms and sterilization by boiling water for ten minutes may not be sufficient in this case. A study by Campanha et al. showed that *Candida* on dentures was completely eradicated by microwaving the tool submerged in water on 650W for three minutes. This method damaged the fungal cell membrane and left no viable cells. (38) Other studies by Ribeiro et al. and Sanitá et al. confirmed that microwave sterilization at 650W for three minutes of the aid submerged in a small amount of water resulted in complete fungal sterilization. (39,40)

Second, board certified lactation consultants propose to air dry the mother's nipples and expose them to direct sunlight a few minutes a day. They suggest carefully drying the external genitalia with a hairdryer after washing. Additionally, all underwear and bedding should be washed at the highest possible temperature if there is suspicion of a candidal mammary infection. Anecdotal literature mentions adding one cup of distilled vinegar to the rinse water or treating the fabrics with bleach in order to kill possible spores. Furthermore, disposable breast pads should be disposed of as soon as they become wet. Lactation specialists advise to avoid bathing with other family members, as to avoid spreading the infection. They also recommend decreasing the consumption of alcohol, cheese, bread, wheat products, sugar and honey. (4,28) No research has been done on the effectiveness of these interventions. These non-medical approaches are based on a consensus between health care providers rather than scientific evidence. However, an older study from 1984 reported that *C. albicans* could be found on a cotton sample and a nylon sample after being washed with general detergent at 50°C, but was eradicated at a washing temperature of 70°C. (41)

Advise concerning expressed breastmilk to use in later feedings is very diverse, which is caused by a lack of knowledge about the presence of *Candida* (-spores) in breastmilk. (16,17,33) Due to the many differing scientific findings about whether or not *C. albicans* is present in breastmilk, health care providers agree to give fresh or frozen expressed milk to the infant while still being treated for the infection. Freezing deactivates yeast, but it doesn't kill off spores. (29) Therefore, it is not advised to use milk expressed during the time of infection for consumption after the treatment has been ended. Not using the possibly infected milk minimizes the theoretical risk of reinfection. (42)

Very few research has been done on the effect of pasteurization of breastmilk on fungal organisms. It is however well known that heating breastmilk has an impact on other components present in the maternal milk. High temperatures can lead to denaturation of crucial proteins in the development of the child, such as immunoglobulins and enzymes that play a role in the breastmilk-mediated immunocompetence of the child. (43) In a study by Naicker et al., short-term high-temperature pasteurization (72°C, 15 seconds) showed to inhibit all bacterial growth in 99% of samples. (44) This is not beneficial in the context of breastmilk, as maternal bacteria transmitted through breastmilk lay down and nourish the infant's microflora in the gastro-intestinal tract. (4) In addition, a study by Silvestre et al. reported a significant decrease in lysine content after pasteurisation, representing a decreased nutritional value as lysine is an essential amino acid. (45)

Moreover, heat treatment on milk may induce Maillard reaction. The Maillard reaction or non-enzymatic glycation occurs when a reducing sugar (such as lactose) chemically interacts with an amino group (such as the ε-amino group of lysine residues in milk). A schematic representation of the Maillard reaction can be seen in **Figure 1.3.1.1**. Ultimately, the Maillard reaction generates melanoidins, which give the milk a brown colour. The reaction causes a decrease in organoleptic and nutritional value of the milk. (46) In conclusion, scientific evidence suggests it is not to be advised to pasteurize breastmilk during a thrush infection, as there is no evidence that the benefits outweigh the downsides.

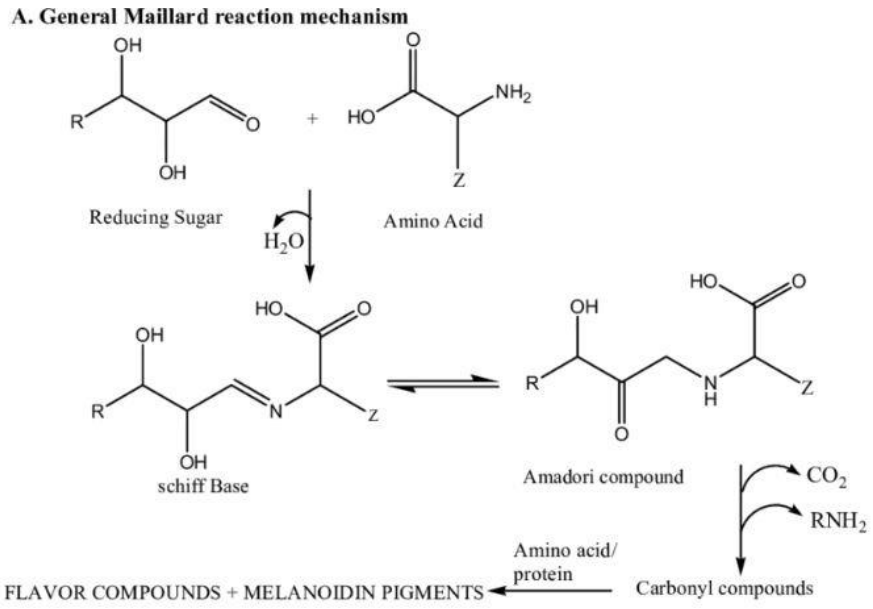

Figure 1.3.1.1: general Maillard reaction mechanism. (47)

1.3.2. Topical medical approaches

Successful treatment of thrush includes use of the most appropriate antifungal drugs, for both the infant and the lactating mother. Administering drugs to an infant eliminates the possibility of certain formulations, such as tablets. As OPC presents as a superficial infection of the buccal mucosa in infants, topical medication has been the number one therapeutic choice. As for breastfeeding mothers, topical treatment is also preferred, as the goal in this scenario is to avoid, as much as possible, transmission of a systemic drug to the infant through breastmilk. Advised topical approaches in Belgium include nystatin oral suspension and miconazole oral gel to treat the infant, and miconazole cream to treat the nipple area of the mother. (48) These therapies have been used for decades and the accumulated experience with them presents a great benefit in the treatment of fragile groups, such as infants. Other topical antifungals that are advised by different organisations include amphotericin B and clotrimazole. (2)

1.3.2.1. Nystatin

Nystatin is a polyene macrolide, naturally produced by *Streptomyces noursei* strains. (6) The fungicidal mechanism is based on the binding of the drug to ergosterol, which is a crucial element in the fungal cell membrane. Due to this bond and the consecutive formation of pores in the membrane, a major loss of intracellular potassium takes place which causes fungal death. Additionally, nystatin possesses the ability to cause secondary cell damage by autooxidation. (2)

For the treatment of oral thrush, nystatin is used topically. The drug is not absorbed into the gastrointestinal tract when applied to intact skin or mucosal membranes. After oral administration, bioavailability is very limited, and the drug can not be detected in plasma when used in normal doses. The drug is only slightly soluble in water, which explains the inability to attain effective blood concentrations after oral administration. (5,7,49) Internationally, nystatin is available as oral suspensions, topical cream, topical ointment, oral pastilles and powder. In Belgium however, only the suspension is marketed. (6)

The advised dosage to treat oral thrush in infants consists of 100 000 to 200 000 units, four times a day, applied after feeding the infant. The dosage and treatment duration should be dependent on the mycological and clinical response. (20) The Belgian Antibiotic Policy Coordination Committee (BAPCOC) advises to continue treatment with nystatin until seven days after the symptoms disappear. (48) The average primary treatment duration with nystatin usually takes up to four weeks. Moreover, when relapse occurs, nystatin should be used for a minimum of four to six weeks. (6)

Older studies with small study populations mention clinical cure rates of up to 80% after two weeks of treatment with nystatin. These studies already reported low mycological cure rates and high relapse rates. More recent studies could not reproduce these results and reported clinical cure rates of maximum 54%. The primary problem with nystatin oral suspension is poor adherence to the oral mucosa. (50) The suspension may be rapidly swallowed, leaving contact between the drug and the plaques to a minimum and therefor limiting the efficacy. (7)

Nystatin oral suspension has been used for nearly 70 years as first-line treatment for OPC in infants. Oral gels with nystatin are also available but also show poor clinical cure rates (below 50%). This might be due to insufficient concentrations in the gels or insufficient adhesion properties of the gel to oral mucosa. (5,20) There is extensive experience with the oral suspension formulation and very few side effects have been reported, which may contribute to the continued practical use, despite the documented inferior effectivity compared to other antifungal drugs (**Table 1.3.2.1.1**). Nystatin seemed inferior to miconazole, fluconazole, gentian violet and ketoconazole in treating oral candidiasis. (8,50)

Very few side effects were reported for nystatin. Poor taste and gastrointestinal side effects such as vomiting, nausea, diarrhoea, anorexia and abdominal pain were the most commonly reported adverse reactions. The main concern may be the frequent refractory reactions with nystatin, which may require systemic treatment with fluconazole. (8)

Table 1.3.2.1.1: Results of studies by Goins et al., Hoppe et al. and Flynn et al. comparing the efficacy of nystatin oral suspension vs. fluconazole syrup suspension and miconazole oral gel in the treatment of thrush in infants. (5,50,51)

Goins et al. (2002)	Dose	Treatment duration	Total patients evaluated	Patients cured (clinical cure rate in %)
Nystatin	100 000 IU (1mL of a 100 000 IU/mL suspension) four times daily (topical)	10 days	19	6 (32%)
Fluconazole (Diflucan®)	3mg/kg once daily (systemic)	7 days	15	15 (100%)
Hoppe et al. (1997)	**Dose**	**Treatment duration**	**Total patients evaluated**	**Patients cured (clinical cure rate in %)**
Nystatin	100 000 IU (1mL of a 100 000 IU/mL suspension) four times daily (topical)	12 days	107	58 (54.1%)
Miconazole gel	25 mg miconazole (1,25g of a 20mg/g gel) four times daily (topical)	12 days	105	104 (99%)
Flynn et al. (1995)	**Dose**	**Treatment duration**	**Total patients evaluated**	**Patients cured (clinical cure rate in%)**
Nystatin	400 000 IU (four mL of a 100 000IU/mL suspension) four times daily (topical)	14 days	73	37 (51%)
Fluconazole	Loading dose of 4 mg/kg on the first day followed by 2mg/kg once daily (systemic)	14 days	86	71 (91%)

1.3.2.2. Miconazole

Miconazole is a first-generation imidazole. (20) Miconazole inhibits fungal cell wall synthesis by inhibiting the 14α-demethylase enzyme and thus exercises a fungistatic effect. Furthermore, the antifungal drug inhibits (per)oxidative enzymes and affects triglyceride synthesis. (3) Miconazole has a broad spectrum activity, even against several *Candida* species that can be resistant to fluconazole, such as *C. albicans* and *C. glabrata*. (52) The reported minimal inhibitory concentration (MIC) of miconazole for *C. albicans* is 1.0 µg/mL. (5)

In the treatment of OPC in infants, miconazole is used as an oral gel. In the oral gel formulation, miconazole is categorized as a systemic agent as it may be ingested. However, miconazole has a bioavailability of 25%-30% and the achieved plasma concentrations (approx. 31 ng/mL) with the use of normal doses (25 mg miconazole) are not sufficient to treat systemic infections. (53) Miconazole is also used in the treatment of nipple thrush for cutaneous application. For nipple candidiasis, miconazole cream is preferred as the gel formulation can dry the nipple area and the ointment is more difficult to wash off. Biological availability of miconazole through cutaneous application is less than 1%. (54)

Miconazole oral gel, best known under the brand name Daktarin®, is considered a first line therapy option for mild OPC. It has been used for nearly 40 years to treat superficial fungal infections safely and effectively. (52) The recommended single dose of oral gel consists of 25 mg miconazole or 1,25 mL of a 20mg/g gel formulation applied four times daily until one week after the symptoms have disappeared. (5,48) The gel should be smeared by finger onto the mucosa of the child's mouth, not including the soft palate. Miconazole oral gel is contra-indicated to use in children under the age of four months, due to risk of suffocation when applied incorrectly. Independent prescribing committees advise miconazole oral gel as the first choice treatment in even younger infants. (55,56) The drug is said to adhere well to the oral mucosa in comparison to nystatin oral suspension. (7)

As well as low prevalence of resistance, another benefit of miconazole is the greater clinical cure rate compared to the current first-line therapy nystatin. Results from multiple trials show that miconazole is clinically superior to nystatin. In addition, results of respectively a 99% eradication rate compared to a 54% eradication rate were reported when mycological outcomes were assessed **(table 1.3.2.2.1.).** (6,7,57) Furthermore, fewer relapses were reported with miconazole and the treatment duration with miconazole was approximately five days shorter than with nystatin. (5)

Very few adverse effects have been mentioned in the available studies. One study mentions about six percent prevalence of gastro-intestinal discomfort, which is similar to nystatin. (7,52) When applied to the nipple area, local irritation might occur, manifesting as an itching or burning sensation. (2)

Table 1.3.2.2.1: Comparison of mycological cure rates between application of miconazole oral gel and nystatin oral suspension. (5)

Agent	Dose	No. of patients	Clinical outcome (n)			Mycologic cure (%)
			Cure	Improvement	Failure	
Miconazole gel	25 mg	14	13 (92.8)	NA	NA	55.6
Nystatin suspension	400 000 units qid	14	12 (85.7)	NA	NA	13.3
Miconazole gel	25-50 mg	23	23 (100.0)	0	0	NA
Nystatin suspension	100 000 units qid	24	18 (75.0)	0	6 (25.0)	NA
Miconazole gel	25 mg	98	97 (99.0)	1 (1.0)	0	59.2
Nystatin suspension	100 000 units qid	85	46 (54.1)	16 (18.8)	23 (27.1)	11.8

NA: data not available
Qid: four times daily

Adopted and edited from (*Treatment of oropharyngeal candidiasis and candidal diaper dermatitis in neonates and infants: review and reappraisal, Hoppe J., 1997)* The Paediatric Infectious Disease Journal, edition 9, volume 6, pages 885-894.

1.3.2.3. Clotrimazole

Clotrimazole is a synthetic trityl imidazole, similar to miconazole. It inhibits ergosterol biosynthesis and therefore disturbs fungal cell membrane production. It also damages the fungal plasma membrane, causing a change in membrane permeability and loss of essential cell components. Clotrimazole is active against dermatophytes, *Candida* species and has an antibacterial effect against certain gram-positive bacteria. (58) The reported MIC for *C. albicans* is 1 µg/mL. (5)

When applied cutaneous, clotrimazole resorption is less than 2%. When applied onto mucosal surfaces, less than 3% is absorbed. (59) The compound is very effective when used orally or topically. Continued oral use is limited due to induction of CYP enzymes that rapidly metabolize the drug to its inactive form. (60,61) Clotrimazole is commercially available in as creams, ovules, sprays and solutions. (58,59,62)

Clotrimazole is mentioned in the treatment of thrush as an off-label suppository formulation used in slit pacifiers **(Figure 1.3.2.3.1)**. The overall impression of this use was effective, safe and practical when treating infants. However,

follow up treatment with nystatin was advised once the fungal load was significantly decreased. (60) Another off-label use of clotrimazole is to smear commercially available cream onto the oral mucosa of the infant three to four times daily. Similar dosages to miconazole were used (25 mg of active compound). Clotrimazole is normally used as a cream in the treatment of vaginal and skin infections and is available in Belgium as Canesten®. (5,58) Common side effects related to the topical use of clotrimazole include red and irritated skin, pain and a burning or stinging sensation. (62)

Figure 1.3.2.3.1: Example of a fillable or 'slit' pacifier containing fruit. (63)

1.3.2.4. Amphotericin B

Amphotericin B is a polyene antifungal. It has fungistatic as well as fungicidal properties by binding to sterols of the fungal membrane, causing increased permeability of the fungal cell membrane and consecutive loss of intracellular potassium and other components. Amphotericin B is naturally produced by a strain of *Streptomyces nodosus.* The compound is active against multiple yeasts and fungal pathogens, including *C. albicans.* (64) The reported MIC for *C. albicans* is between 0,5 µg/mL and 0.86 µg/mL.

Amphotericin B can be used as an oral suspension in the treatment of thrush. The compound is stable in water and the suspension is tasteless, so no sucrose is added. However, the osmolality is still high with 1700 mOsm/L. Amphotericin B is very scarcely absorbed orally. It is in Belgium only available as a solution for intravenous administration in the treatment of systemic fungal infections. (5)

Amphotericin B oral suspension is mentioned in the treatment of uncomplicated OPC as a last choice when standard treatment fails or in case of contra-indication. The suspension is available in Europe under the commercial name Fungizone®. (64) Indicated dosages for infants are presented in **Table 1.3.2.4.1**.

Table 1.3.2.4.1.: Indicated dosages for the use of amphotericin B oral suspension in children. (65)

Weight	Recommended dosage	Usage instructions
5 to 10 kg	75 mg per day divided over three administrations	Keep suspension in mouth as long as possible.
10 to 20kg	150 mg per day divided over three administrations	Keep suspension in mouth as long as possible.
20 to 30 kg	200 mg per day divided over four administrations	Keep suspension in mouth as long as possible.
≥ 30 kg	400 mg per day divided over four administrations	Keep suspension in mouth as long as possible.

1.3.2.5. All Purpose Nipple Ointment (APNO)

APNO was developed in 2009 by dr. Jack Newman, a breastfeeding researcher and founder of the International Breastfeeding Centre in Canada. The name of the ointment suggests the ointment is indicated for multiple causes of nipple pain. In the presentation of his self-invented prescription ointment he clearly states that preventing sore nipples by improving breastfeeding techniques should always be the primary concern of health care providers. The ointment needs to be compounded and contains 2% mupirocin, 0,1% betamethasone and miconazole powder in a Vaseline base to a final concentration of 2%.

Mupirocin is an antibiotic that's active against several bacteria commonly found in abrasions or cracks in the nipple, such as *S. Aureus*. Due to very rapid metabolization and low concentrations in the ointment, it's safe to be swallowed by the baby.

Betamethasone is a corticosteroid, active against inflammation. This compound reduces inflammation and therefore might reduce pain if inflammation is the cause of the discomfort. There has been some controversy about the advised treatment duration, because of this compound. Certain pharmacists and midwives advise to not use the ointment for a period longer than two weeks, at the risk of thinning the skin around the nipple and making it even more vulnerable. (66) Dr. Newman refuted these comments by saying he has not witnessed such events, even in mothers who had used the ointment for over one month.

Miconazole is the antifungal agent in this ointment and is probably the reason why this ointment is a treatment option in the oral/nipple thrush dyad between mother and child. Miconazole powder is added until a final concentration of 2% is reached. Dr. Newman noted that miconazole may be substituted with fluconazole or clotrimazole powder, but that clotrimazole, in his experience, induces irritation more often than the other antifungals. (67)

Instructions for the use of APNO include applying the ointment sparingly after each feeding until the nipple and areola convey a glossy or shiny look. The ointment should not be washed off in between feedings. However, if the child shows signals of reluctance to latch, bad taste due to miconazole in the ointment might be the cause for this behaviour. In that case dr. Newman advises to wipe off any excess ointment. (68)

The effectiveness of APNO therapy has not been extensively researched. As the ointment's origin is found in 2009 in the Canadian city Toronto, not much international research has been done. A study by Dennis et al. on 151 breastfeeding women in Toronto compared the effect of APNO versus plain lanolin ointment on nipple pain. The study concluded there were no significant differences between the two groups when scored on nipple pain after one week of treatment and no significant differences in breastfeeding duration and exclusivity at 12 weeks postpartum. (69)

1.3.3. Systemic medical approaches

1.3.3.1. Fluconazole

Fluconazole belongs to the family of triazoles. The compound is active against *Candida* through disruption of the fungal cell membrane by inhibiting lanosterol 14 α-demethylase and by impairing cell replication. (70) Fluconazole has a high oral bio availability (>90%). It penetrates well into saliva. (71)

Fluconazole is used in the treatment of OPC in infants and in the treatment of nipple and/or breast candidiasis in nursing mothers. For infants, fluconazole suspension, available as Diflucan® in Belgium is most commonly used. For the mother, fluconazole capsules are more common. (50,72) Dosages for infants are represented in **Table 1.3.3.1.1**

The use of orally administered fluconazole in OPC has up until now been restricted to treatment of immunocompromised infants, infants with high risk of developing systemic infections and in persistent recurring fungal infections. (3) The suspension is not used as routine treatment, because the cost is higher than that of nystatin, which is still considered as first line treatment. Moreover, there is a risk of selective development of azole-resistant

species. Azole resistance has mainly been reported in the treatment of severe immunocompromised patients, who require repeated or prolonged therapy with rising dosages. The absence of evidence of selective azole-resistant fungal growth in immunocompetent patients does not justify routine use, as it may put other, more vulnerable patient groups at risk. (50)

Experience with fluconazole in adults is also limited to immunocompromised patients, due to potential occurrence of resistant strains. (7) However, fluconazole is effectively and commonly used against candidiasis that does not respond to topical treatment and severe recurrent candidosis. Recommended treatment plans for adults are 100 to 400 mg daily until the infection has resolved. (70) A single dose of 750 mg was proven to have equal efficacy and no difference in relapse rates. (3)

Fluconazole is transferred in human milk. Kaplan et al. compared multiple studies on fluconazole concentrations found in breastmilk of mothers who were treated with oral fluconazole in dosages from 100 mg to 200 mg a day for a period of up to 30 days. They reported that the infant is exposed to an average of 0,6 mg/kg daily, which is lower than the normal dose used to systemically treat infants (3 to 12 mg/kg daily). Since there are hardly any reports on adverse effects with the normal dose, they concluded fluconazole use to be safe during breastfeeding when using typical doses and treatment durations. For higher doses or longer treatment duration, the liver function of the infant should be monitored. The study concluded that breastfeeding can be continued and poses no harm to the infant when the mother is treated with fluconazole. (70)

Table 1.3.3.1.1.: Recommended doses of fluconazole for infants in the treatment of OPC. (73)

Age	Loading dose	Maintenance dose	Maximum dose per day	Treatment duration
0 to 2 weeks	6 to 12 mg/kg in one administration	3-6 mg/kg in one administration every 72 hours	400 mg	based on clinical and mycological response
2 to 4 weeks	6 to 12 mg/kg in one administration	3 to 6mg/kg in one administration every 48 hours	400 mg	based on clinical and mycological response
1 month to 12 years	6 to 12 mg/kg in one administration	3 to 6 mg/kg in one administration every day	400 mg	based on clinical and mycological response
>1 month (alternative)	/	3 mg/kg in one administration every day	400 mg	7 days

1.3.4. Other antifungal drugs

Other antifungal treatment options include itraconazole, ketoconazole, isavuconazole, voriconazole and posaconazole.

Itraconzole, available as Sporanox® on the Belgian market, is indicated for systemic and recurrent superficial infections, similar to fluconazole. Itraconazole is available as a sirup solution, which makes it possible to administer to infants. Sporanox® is available as 150 mL of a 50mg/5mL solution. (74) The advised starting dose for children aged one month to eighteen years is 10 mg/kg/day for the first two days with a maximum of 400 mg/day, followed by 5 mg/kg/day from the third day with a maximum of 200 mg/day. (5,75)

Ketoconazol is a dibasic imidazole, which is not usually employed in the treatment of oral thrush. In 1989 the use of ketoconazole was evaluated in the treatment of OPC in healthy infants. The drug was significantly superior to nystatin, with a clinical cure rate of 100% compared to 43% with nystatin. However, ketoconazole is limited by its considerable adverse effects such as hepatotoxicity and inhibition of steroid synthesis. Moreover, ketoconazole also has many drug-drug interactions. (6,50)

Isavuconazole, posaconazole and voriconazole are indicated in severe systemic infections and have no place in the treatment of OPC in infants or mammary candidiasis in nursing mothers. (48)

1.4. RISKS ASSOCIATED WITH INAPPROPRIATE TREATMENT OF THRUSH

1.4.1. Antifungal resistance

Azole resistance is a recent, but severe problem in the treatment of any fungal infection. In the treatment of OPC, resistance was observed in isolates of *C. albicans, C. glabrata, C. tropicalis, C. krusei* and *C. dubliensis*. (2) Resistance to first-line therapy such as nystatin and miconazole has mainly been reported in immunocompromised patients, undergoing longer treatment duration and higher doses. (3,76) Acquired resistance to nystatin rarely occurs. In a study by Athar et al. only seven of 626 *Candida* isolates developed resistance to nystatin and the resistant isolates showed reversion to sensitivity when no longer exposed to a polyene environment. (77) Studies have reported 17% of *C. albicans* and 45% in non-albicans species to be resistant to miconazole. The supposed mechanism for this resistance is mutations in genes that code for efflux pumps in fungal organisms. On the other hand, miconazole has proven to be effective against fluconazole-resistant strains. (3) Another possible mechanism for antifungal resistance is biofilm formation. (1)

In a study by Pereira et. al, 51 strains of *Candida albicans* were examined. Three strains showed resistance to fluconazole and one to amphotericin B. The strains were isolated from infant's oral cavities, mother's nipples and mother's oral cavities, so there was no indication for preference of the resistant strains to a specific anatomical site. All resistant strains showed remarkable positive enzymatic activity for phospholipase and proteinase. This indicates that enzymatic activity may predict ineffectiveness of conventional antifungal treatment. (8) Fluconazole resistance poses a particular problem in infections that don't respond to topical treatment with nystatin and miconazole.

The Infectious Disease society of America (IDSA) guidelines propose treatment with itraconazole solution if failure of therapy with fluconazole occurs. Researchers reported that itraconazole solution is effective in up to 80% of fluconazole-resistant cases. If failure with itraconazole occurs, IDSA suggests to treat with echinocandins. (3) Another treatment option when azole-resistance occurs is the novel triterpenoid, Ibrexafungerp. Ibrexafungerp is a glucan synthase inhibitor that has shown activity against multidrug-resistant *Candida* species. These newer antifungal drugs may be able to resist mechanisms of antifungal resistance. (2,78)

1.4.2. Early cessation of breastfeeding

Human milk provides the perfect composition of nutrients in every stage of the development of the infant. The mother as well as the baby simultaneously benefit from the process of nursing. WHO and UNICEF recommend that breastfeeding should be initiated within the first hour postpartum and the mother should exclusively breastfeed the child for six months. Exclusive breastfeeding means the child should receive no other foods or liquids, not even water. After six months, safe and adequate complementary foods should be added. Breastfeeding should be continued for two years and beyond. (11,12) Breastfeeding aids the good physical and emotional health of the mother on a short and a long-term basis. Specifically, breastfeeding stimulates uterine involution, reduces the risk of bleeding and infection, reduces adiposity and weight, reduces the risk of postpartum depression and reduces stress and anxiety. On a long-term basis breastfeeding reduces the risk of certain cancers and it decreases the risk of developing endometriosis, diabetes, osteoporosis, cardiovascular diseases, metabolic syndrome, rheumatoid arthritis, Alzheimer's disease and multiple sclerosis. (79)

In the infant, exclusive breastfeeding during the first six months postpartum decreases the risk of non-specific gastro-intestinal infections up to 64%. It also decreases the risk of respiratory infections, food allergies, asthma, obesity, diabetes type 1, leukaemia and celiac disease. (80)

Infants with oral thrush may experience discomfort or pain when forced into actions that require contact with the affected oral surfaces. The child may be irritable and show reduced interest in feeding. (7) In mothers, nipple candidiasis can cause discomfort while nursing and lead to premature weaning. (8) Discomfort is common in the first few weeks postpartum but should diminish with proper latching technique and time. Nipple pain is the second most common reason for the early termination of breastfeeding, right after the mothers' perception of insufficient milk production. (4) Poor positioning and poor latch of the infant to the breast are the most common causes for breast and nipple pain. Healthcare providers should therefor always assess breastfeeding technique. However, if adequate treatment of oral and mammary candidiasis can reduce the incidence of (nipple) pain and therefore premature weaning, the argument can be made that symptomatic thrush should be routinely treated, even when there is no consensus on the cause of the pain. The focus should be on alleviating the pain in both the mother and the infant with the goal to continue (exclusive) breastfeeding. (16)

2. OBJECTIVES

The *first objective* of this dissertation is to make a summary of available guidelines concerning the diagnosis of OPC in infants. We aim to make an overview of directives regarding necessary actions in recognizing thrush in infants during the breastfeeding period. Consecutively, we wish to summarize guidelines concerning the diagnosis of nipple candidiasis in the mother of the breastfed child, as it concerns the mother-baby dyad.

In health care practice, professionals often seek evidence-based advice before initiating a treatment. Therefore, the *second objective* of this dissertation is to summarize available guidelines regarding the treatment options for oral thrush in infants. The goal is to include non-medical as well as medical directives, provided by different institutions. We aim to provide a structural overview of advised treatment options. In addition, we aim to provide an overview of the treatment options for nipple candidiasis in the mother, as this is an indispensable part in the treatment of the child. Furthermore, we wish to include an overview of alternative therapies that may be used in the treatment of OPC in infants and nipple candidiasis in the mother during lactation.

Third, we aim to calculate the general treatment cost in Belgium for OPC in infants based on the content of the guidelines. We intend to compare the commercially available medications in Belgium to each other and determine which treatment is least and most expensive.

Finally, we intend to develop questionnaires to evaluate the current practice of diagnosis and treatment of OPC in infants during lactation in Belgium. The goal is to develop surveys for general practitioners, paediatricians, midwives and pharmacists to assess their knowledge and experience concerning the diagnosis and treatment of oral thrush in infants. We wish to include contemporary challenges such as microbial resistance to certain medications and experience with alternative therapies. Simultaneously, we wish to develop a questionnaire to evaluate parents (with a focus on the mother of the breastfed infant) on their experience with the diagnosis and treatment of OPC in their child. We also aim to include related topics, such as which health care provider was consulted, the influence of OPC on their breastfeeding experience, their use of alternative therapies and which non-medical advice they received.

3. METHODS

3.1. GUIDELINES AND THERAPEUTICAL APPROACHES

First, literature on oral thrush in infants was acquired through searching four online databases: PubMed, Scopus, Web of Science and Google scholar. Search terms included "oral thrush", "candidiasis", "infants", "child", "treatment of thrush", "oropharyngeal candidiasis", "*candida* infection", "miconazole oral gel", "nystatin oral suspension", "fluconazole thrush" and combinations of the previously mentioned. Search terms concerning nipple candidiasis included "nipple pain", "nipple candidiasis", "mammary candidiasis" and "nipple thrush" on their own or in combination with "diagnosis" and "treatment". These searches already gave rise to guideline documents and literature mentioning alternative therapies. Further research was done by using specific terms for each topic such as "antifungal effect coconut oil" and "*candida* diet". Dutch and English publications were included

Second, guidelines that were referred to in other documents were either acquired through snowballing or through exploring the websites of the mentioned organisations online. We added the search terms "oral thrush", "oropharyngeal candidiasis", "nipple pain" or "nipple candidiasis".

Third, a general google search on "guidelines oral thrush breastfeeding" was conducted as to specifically select directives by breastfeeding organisations such as International Breastfeeding Centre (IBC). Additionally, a general google search on "oral thrush therapies" and "oral thrush treatment" was conducted. We consequently investigated the alternative treatment approaches these search terms gave rise to. More information regarding gentian violet, coconut oil, plant oils and the effect of processed sugars were acquired through exploring the four earlier mentioned scientific databases. We applied search terms including "sugars" AND "*Candida",* "Gentian violet" AND "thrush" OR "antifungal", "antifungal effect essential oil" and "antifungal mechanism coconut oil".

Lastly, Belgian and Dutch guidelines were acquired by consulting known websites on medication policy. We consulted the BAPCOC antibiotic guide in combination with the website of the Belgian Centre for Pharmacotherapeutic Information (BCFI) and "Farmacotherapeutisch Kompas" (FK). The BCFI website was also used to determine the treatment costs for each commercially available compound. To determine the treatment cost, first, the necessary amount for each drug was calculated for the expected treatment duration. The average duration for each treatment

was deducted from the guidelines, no special cases were taken into account. Subsequently, the content of the available preparations was calculated. Thereafter, we determined the amount of packages that were needed to complete the treatment and then we calculated the price based on the cheapest commercially available option.

3.2. QUESTIONNAIRES

We decided to construct questionnaires for health care workers who come into direct contact with breastfeeding babies and their mothers on a frequent basis. This resulted in the selection of four target groups: general practitioners (GP's), paediatricians, midwives and pharmacists. Simultaneously, we decided to also construct a questionnaire for parents of (an) infant(s) that received medication for OPC during the breastfeeding period. We focussed the latter survey on mothers as we believe they are in the best position to remember and describe their own breastfeeding experience, which is an indispensable part of the subject we aim to evaluate. Sections included in the questionnaires were determined through selection of the main topics discussed in available literature and guidelines. We decided the topics concerning general practitioners, paediatricians and midwives were very similar and that one questionnaire for these target groups was sufficient. In conclusion three types of questionnaires were designed: one for GP's, paediatricians and midwives, one for pharmacists and one for parents. Questions were continuously added and adapted throughout the development process.

The questionnaires were developed by pharmacists and optimized in collaboration with a paediatrician and a midwife. A pilot testing was executed on two pharmacists and two midwives, in an attempt to further optimize the clarity of the questions and suitability for the intended target groups.

3.3. OUTCOMES

The guidelines concerning diagnosis were ordered by year of publication (or publication of the updated version) and divided for OPC and nipple candidiasis. The guidelines concerning treatment were also ordered by year of publication. Treatment directives were split up into three sections: non-medical advice, medical advice and medical advice for persistent or recurrent infections. Two summaries were made, one on the treatment of OPC and one on the treatment of nipple candidiasis. Additionally, we provided a narrative review of (non-medical) alternative therapies that may be used in the treatment of OPC and/or nipple candidiasis.

4. RESULTS

4.1. SUMMARY OF GUIDELINES

We acquired fifteen different guidelines concerning OPC in infants: two Dutch guidelines, three Belgian guidelines, two Australian guidelines, three American guidelines, three British guidelines and two international guidelines. Only few *diagnostic* directives for OPC in infants and nipple candidiasis in mothers are published. They are represented in **Table 4.1.1.** and **Table 4.1.2** for OPC in infants and nipple candidiasis in mothers respectively. A summary of Dutch and English guidelines on the *treatment* of OPC in infants can be found in **Table 4.1.3** and a summary of guidelines on the *treatment* of nipple candidiasis can be found in **Table 4.1.4.**

4.2. TREATMENT COST

Nystatin oral suspension (Nilstat®) for topical use, miconazole oral gel (Daktarin®) for topical use and fluconazole syrup suspension (Diflucan®) for systemic use are in Belgium the only commercially available medications for oral use in the treatment of OPC in infants. Therefore, they are the only preparations included in **Table 4.2.1**, which compares the price of treatment with each of the previously mentioned medications. Amphotericin B and Clotrimazole are not commercially available in Belgium as formulations for oral administration to infants.

Table 4.2.1: Overview of the treatment cost of OPC in infants with commercially available oral preparations.

Infant aged 4 weeks (±4kg) (81)	available preparations	Average treatment plan	Amount of packages needed	Total treatment cost	Cost with normal compensation	Cost with increased compensation
	Nystatine (Nilstat®, Pharma logistics) 30 mL 100 000 IE/ 1 mL (€7,55)	100 000 IE four times daily for 14 days	2	€15,1	€2,02	€1,22
	Miconazole (Daktarin®, Janssen-Cilag) 40 g 20 mg/ 1g (€8,00)	25 mg miconazole or 1,25 mL gel four times daily for 14 days	2	€16	€2,34	€1,40
	Fluconazole (Diflucan® sirup susp, Pfizer) 35 mL 50 mg/5 mL (€12,55)	Min/max: 24 /48 mg loading dose followed by 12/24 mg every 48 hours for 7 days	1	€12,55	€2,73	€1,64
Infant aged 6 months (±8kg) (81)	available preparations	Average treatment plan	Amount of packages needed	Total treatment cost	Cost with normal compensation	Cost with increased compensation
	Nystatine (Nilstat®, Pharma logistics) 30 mL 100 000 IE/ 1 mL (€7,55)	100 000 IE four times daily for 14 days	2	€15,1	€2,02	€1,22
	Miconazole (Daktarin®, Janssen-Cilag) 40 g 20 mg/ 1g (€8,00)	25 mg miconazole or 1,25 mL gel four times daily for 14 days	2	€16	€2,34	€1,40
	Fluconazole (Diflucan® sirup susp, Pfizer) 35 mL 50 mg/5 mL (€12,55)	Min/max: 24/48 mg loading dose followed by 12 /24 mg every day for 7 days	1	€12,55	€2,73	€1,64

Table 4.1.1: Summary of guidelines concerning the **diagnosis** of OPC in **infants.**

Institution	Year	Diagnostic recommendations
Government of West Australia North Metropolitan health service (King Edward Memorial Hospital)– Australia (82)	2019	A thorough history and physical examination are required. The baby may have recently received treatment with antibiotics. Oral signs of thrush such as white plaques on the gums, cheeks and palate and a red papular rash with satellite lesions around the anus or genitals may be present. A white appearance of the tongue must not be confused with milk coating and may be indicative of poor tongue movement rather than thrush.
JAPC (Derbyshire joint area prescribing committee) - United Kingdom (83)	2019	**Symptoms** of thrush in the infant's mouth include creamy white patches that do not rub off in the mouth, a whitish sheen to saliva and inside of lips and gums, the infant continually coming off the breast, breast refusal, flatulence, nervous behaviour at the breast, clicking sounds during feeding, poor weight gain and nappy rash. A differential diagnosis of a white tongue (milk coating) due to tongue tie should be made.
La Leche League Vlaanderen – Belgium (84)	2019	**Signs and symptoms:** the baby may have a thick white coating in the mouth that does not rub off. Sometimes it may be small local spots. The baby may have red, dry and chapped lips and the inside of the lips may show a pearl shine. The tip of the infant's tongue may be red. The infant may have an early outlined rash in the diaper area. Not all infants with thrush show visible symptoms. Some babies are agitated and want to be fed more often, while others refuse the breast as it is painful for them to drink with an infected mouth. Most babies often detach from the breast multiple time during a feeding session as the created vacuum is uncomfortable for them. Feeding may be accompanied by clicking or smacking sounds.
Kind en Gezin – Belgium (85)	2019	Symptoms include white spots in the mouth that don't rub off. Beneath the spots are small ulcers. The child may behave agitated and may show difficulty feeding.
The women's royal hospital – Australia (86)	2017	**Symptoms** of thrush include white oral plaques in the mouth (tongue and inside of cheeks) or red papular rash with satellite lesions around the anus and genitals. Although these signs are not always present, it should be assumed that the baby is colonised with the organism if the mother has evidence of nipple thrush.
NHG (Nederlands Huisartsen Genootschap) – The Netherlands (87)	2015	The infant continuously detaches from the breast and may cry. This might be accompanied by pain in the mother during and after feeds.

Table 4.1.2: Summary of guidelines concerning the **diagnosis** of nipple and/or mammary candidiasis in **mothers** during lactation.

Institution	year	Diagnostic advice
Government of West Australia North Metropolitan health service (King Edward Memorial Hospital)– Australia (82)	2019	Thorough history and physical examination are required. The mother may have a history of nipple trauma, a predisposition to *candida* infections, a history of antibiotic treatment antepartum, intrapartum or postpartum or a recent history of vaginal thrush. **Symptoms** may include a burning or stinging nipple/areola area during and after feeds, a pink, shiny appearance of the nipple, a red, dry or flaky appearance of the areola and the nipple may be very tender to any touch. The pain may be bilateral or localised to one nipple or breast. Shooting, stabbing or deep aching pain in the breast during and after feeds can be perceived as candidiasis, however it is vital to exclude staphylococcal infection. Nipple swabs and milk samples should be taken and sent to the laboratory for microscopy, culture and sensitivity to ensure there is no bacterial infection.
IBC (International breastfeeding centre) and Canadian breastfeeding foundation – International (88)	2019	Exclude underlying causes and evaluate technique of positioning and latching the baby on.
JAPC (Derbyshire joint area prescribing committee) - United Kingdom (83)	2019	A person skilled in breastfeeding management should observe a breastfeeding session to ensure poor attachment is not causing the problem. Thrush should not be diagnosed if pain is present only in one nipple/breast. **Signs and symptoms** in the mother include sudden onset of nipple pain in both breasts after a period of pain-free breastfeeding, nipple pain so intense the mother dreads feeding the infant, no relieve of pain with improved attachment, cracked nipples that don't heal, nipples that are sensitive to touch and might be itchy, loss of colour of nipples or areola and a red and shiny appearance of nipples. The mother may have a recent history of antibiotic use or vaginal thrush. Pain sensation may be described as excruciating, stabbing, grazing, unbearable burning or the impression that the breast is full of glass. The pain may start at the end of each feed and last up to an hour. The symptoms are the same at every feed and are present in both breasts. Thrush should not be diagnosed if pain is present only in one nipple/breast. Swabs of the mother's nipple and/or the baby's mouth are useful to confirm the presence of fungal or bacterial infection.
La leche league vlaanderen – Belgium (84)	2019	**Signs and symptoms**: Thrush often causes a discolouration of the nipple and areola. The skin may appear pink or purple, tight, dry and sometimes shiny or flaky. The most obvious sign is an itching sensation that merges into a sharp, burning pain sensation. These signs are often accompanied by nipple cracks that won't heal. Sometimes, deep breast pain might be present at the end of a feeding session and continue for a long time after. Visible signs are not always present. The diagnosis should be made if improving the breastfeeding technique does not relieve the pain and the pain intensifies when the child feeds. Breastfeeding may become unbearable when thrush is left untreated. Therefore, a fast and correct diagnosis is crucial when breastfeeding becomes uncomfortable.

Institution	year	Diagnostic advice
Kind en gezin - Belgium (85)	2019	**Symptoms include** red, painful nipples, a burning sensation at the nipple, nipple cracks, white spots in the nipple creases that can't be rubbed off, a severe itching sensation at the nipple, the areola may appear tight, shiny or flaky and a stabbing pain sensation in the breast. Sometimes there are no visible symptoms.
The women's royal hospital – Australia (86)	2017	Early diagnosis is important as it can avoid early weaning. The mother may complain of nipple pain that does not resolve despite improved attachment of the baby to the breast. The mother may have a history of antibiotic treatment, vaginal thrush or nipple trauma. **Symptoms** include a burning, stinging nipple pain which continues during and after the feed, nipples tender to touch and light clothing, pink and/or shiny nipples, reddened, a dry or slightly flaky areola area, shooting, stabbing, or deep aching breast pain and localised or bilateral nipple or breast pain. Consider dermatitis if significant itching and/or rash is present. If nipple pain is exacerbated by cold and/or nipples blanch, consider nipple vasospasm. If nipple/breast is inflamed, consider mastitis.
ABM (The Academy of Breastfeeding Medicine) – International (17)	2016	Assessment of nipple pain should include a history and examination of both mother and child with a focus on breastfeeding history, pain history, maternal history and infant history. Additionally, examination of the mother's general appearance, breast, nipple area, milk expression and maternal mood and examination of the infant's facial features, oral anatomy, airway, head and neck range of motion, muscle tone and behaviour are recommended. A direct observation of a breastfeeding session by a knowledgeable health care provider is necessary to exclude poor latch-on as the cause of the pain. Other causes of persistent nipple pain should also be excluded such as nipple damage, dermatosis, infection, vasospasm and functional pain. **Symptoms** include a pink nipple/areola area, shiny or flaky appearance of the nipple, nipple pain out of proportion to the clinical findings, burning nipple pain and pain radiating into the breast.
NHG (Nederlands Huisartsen Genootschap) – The Netherlands (87)	2015	A stabbing pain during breastfeeding sessions with absence of thrush in the infant is not an indication to treat with antifungal medication.
Rotherham clinical commissioning group – United Kingdom (89)	2013	**Signs and symptoms** include sudden onset of pain in both nipples after a period of pain-free breastfeeding, painful nipples to the point where the mother dreads feeding the child, no relieve of the pain by improved attachment, cracked nipples and no healing, very sensitive nipples (to any touch), itchy nipples and loss of colour of the areola and/or nipple. Mothers may have had vaginal thrush or taken a recent course of antibiotics.
American college of nurse-midwives – United states of America (35)	2006	Evaluate proper positioning and latch of the baby to the breast. A complete history of pain, labour, delivery, and breastfeeding is essential, including the use of antibiotics in labour or postpartum, prior history of cracked nipples and the infant's use of pacifiers and bottles. Exclude other possible causes for nipple pain such as eczema of the nipple/areola, Raynaud's syndrome, contact dermatitis and bacterial infection. Exclude possible causes for breast pain, such as plugged ducts, mastitis and breast abscess. **Symptoms** may include a shiny or flaky appearance of the nipple/areola, burning pain of the nipple/areola, sore nipples and stabbing pain in the breast.

Table 4.1.3: Summary of the available guidelines concerning the **treatment** of OPC in **infants**.

Institution	Year	Non-medical advice	Medical advice		Medical advice for recurrent or persistent infection
BAPCOC (Belgian Antibiotic Policy Coordination Committee) – Belgium (48)	2019	Pacifiers need to be carefully sterilized. (Grade 1C)	*infants < 6 months*: **nystatin oral suspension** 4 ml per day (of a 100 000 IU/mL suspension) in 4 administrations until 1 week after disappearance of the injuries.	*infants > 6 months*: **miconazole oral gel** 4 applications of 1,25 mL per day until one week after disappearance of the injuries. (Smear out gel very thoroughly with finger over the mucosal epithelium of the child's mouth, do not include the soft palate)	*infants > 1 month*: **oral fluconazole** 3 mg/kg/day for 7 days
Government of West Australia North Metropolitan health service (King Edward Memorial Hospital)– Australia (82)	2019	If mother or baby have signs and symptoms of Candida overgrowth then both should be treated simultaneously. Clean expressing equipment, teats and dummies thoroughly after use and boil for 5 minutes or steam sterilize. Dummies should be replaced weekly.	**Miconazole oral gel** (Daktarin) Administer a quarter of a teaspoon, 4 times a day. Apply with a clean finger or cotton bud to the inside of the cheeks and over the tongue. Healthcare providers must ensure that the client understands how to apply the product safely. If the client is unsure about the application, she can be advised to use **nystatin oral drops**. It should be noted that nystatin drops are not as effective for oral thrush as miconazole oral gel. Treat any other site of fungal infection in the whole family such as the mother's vagina, nappy rash and feet.		/
JAPC (Derbyshire joint area prescribing committee) - United Kingdom (55)	2019	Mother and infant need to be treated simultaneously even if only one shows symptoms of thrush.	**Miconazole oral gel** *Neonates (< 1 month):* 1 mL in divided doses in the mouth 4 times a day *1 month- 23 months:* 1.25 mL in divided doses in the mouth 4 times a day *2 years and above:* 2.5 mL 4 times a day	Off-label when used in children younger than 4 months of age. Use after feeds, smearing around the mouth. The dose should be measured by oral syringe then administered by a clean fingertip. Care should be taken to ensure that the gel does not obstruct the throat in infants. Initial treatment should be 7 days, extend if infection has not resolved.	/

Institution	Year	Non-medical advice	Medical advice	Medical advice for recurrent or persistent infection
La Leche League Vlaanderen – Belgium (84)	2019	/	**Nystatin** oral suspension or **miconazole oral gel (Daktarin®)** are available prescription drugs. Miconazole oral gel poses a slight choking hazard, but if the parents carefully apply small amounts of gel with their fingertips to the inside of the cheeks and tongue, there should be no hazard. Treat the infant for seven days after the symptoms have disappeared. If the baby has nappy rash: treat diaper area with antifungal zinc ointment. A 1% gentian violet solution may be applied to the infant's mouth once daily. Apply with a cotton bud. Treat for a minimum of 4 days and a maximum of 7 days. Treat baby up to 2 days after symptoms have disappeared.	**Fluconazole (Diflucan):** use according to instructions on leaflet.
Kind en gezin – Belgium (85)	2019	Use separate bottles and pacifiers for each child. Sterilize all aids and toys daily. Clean toys with a 70% alcohol solution. Treat mother and child simultaneously.	Local treatment of infant's mouth with antimycotic medication. Consult doctor. Sometimes gentian violet, propolis, grapefruit seed extract, vinegar, coconut oil and essential oils are used. Sometimes probiotics are recommended. More research is necessary on the effectiveness and safety of these methods.	/
The women's royal hospital - Australia	2017	both mother and baby should be treated at the same time to prevent re-infection	**miconazole oral gel (Daktarin®).** Apply a quarter of a teaspoon 4 times a day for 1 week, then once daily for 1 week after signs/symptoms resolve. The spoon should not be used for administering the gel. Using a clean finger, apply small amounts of gel at a time to the inside cheeks and over the tongue. If the client/ mother is unsure about how to use the gel or is unable to purchase the product from her pharmacy, she can be advised to try another pharmacy or to use nystatin oral drops. However, it should be noted that the drops are not as effective for oral thrush in infants as the gel.	/
IDSA (Infectious Diseases Society of America) and CDC (Center for disease control and prevention) – United states of America (90)	2016	/	**clotrimazole troches** 10 mg 5 times daily **miconazole mucoadhesive buccal tablet** 50 mg applied to the mucosal surface over the canine fossa once daily for 7–14 days **nystatin suspension** (100 000 U/mL) 4–6 mL 4 times daily **nystatin pastilles** (200 000 U) one to two pastilles 4 times daily, for 7–14 days **oral fluconazole** (for moderate to severe disease) 100–200 mg daily for 7–14 days (12 mg/kg daily for infants)	**itraconazole solution** 200 mg once daily or **posaconazole suspension** 400 mg twice daily for 3 days, then 400 mg once daily, for up to 28 days or **voriconazole** 200 mg twice daily or **amfotericin B deoxycholate oral suspension** 100 mg/mL 4 times daily

Institution	Year	Non-medical advice	Medical advice		Medical advice for recurrent or persistent infection
ABM (The Academy of Breastfeeding Medicine) – International (17)	2016	/	**Nystatin suspension** or **miconazole oral gel**		/
NHG (Nederlands Huisartsen Genootschap) – The Netherlands (87)	2015	If no symptoms are present in mother and baby, treatment is not necessary. Wash hands after every diaper change. Boil all things that come into contact with the baby's mouth for 3 minutes daily	*Infants aged 1-3 months*: **Nystatin oral suspension** 1-2 mL four times daily or 0,5-1mL after every feed with a maximum of 8 mL per day. If therapy fails, replace by off-label miconazole oral gel.	*Infants > 4 months*: **Miconazole oral gel** Apply gel by finger or cotton swab and make sure the child can't suffocate in leftover gel. Do not apply gel to nipple as this increases the chance of suffocation.	/
Farmacotherapeutisch kompas – The Netherlands (91)	2015	/	*Infant aged 1-3 months:* **Nystatin oral suspension** Continue treatment for 7 days after lesions have disappeared	*Infants > 4 months*: **Miconazole oral gel** Continue treatment for 7 days after lesions have disappeared	/
British national formulary for children (BNFC), NICE guidelines – United Kingdom (92)	2014	The mother's breast, nipples and teats of feeding bottles should be cleaned adequately.	If thrush is causing feeding problems or you or your baby are in pain, you should be given antifungal cream or gel. **Miconazole oral gel** or **nystatin oral suspension** are used for the treatment of OPC in neonates.		**Fluconazole** **Itraconazole** for fluconazole-resistant infections

Institution	Year	Non-medical advice	Medical advice		Medical advice for recurrent or persistent infection
Rotherham clinical commissioning group – United Kingdom (89)	2013	The mothers' breast, nipple and the teats of feeding bottles must be cleaned adequately.	**Miconazole oral gel** *Neonate (< 1 month):* 1 mL 2-4 times daily *1 month-2 years:* 2.5 mL twice daily Apply to cheeks, gums, roof of mouth and the tongue with clean fingertip. Caution is required to ensure that the gel does not obstruct the throat. Use after food and retain near lesions. Treatment should continue for 48 hours after lesions have disappeared. Not licensed for use in infants under 4 months or during the first 5-6 months of life in a pre-term infant	**Nystatin oral suspension** *Neonate (< 1 month):* 100,000 u (1ml) four times a day after feeds *1 month -18 years:* 100,000 u (1ml) four times a day after meals Treatment duration is usually 7 days and should continue for 48 hours after lesions have disappeared. Not licensed for infants under 1 month of age.	/
Family physicians inquiries network – United states of America (57)	2008	/	**Nystatin oral suspension** or **miconazole oral gel** or **gentian violet** or **fluconazole**		/
American college of nurse-midwives – United states of America (35)	2006	/	**Nystatin suspension** or **oral fluconazole** Always treat mother and child simultaneously.		/

Table 4.1.4: Summary of the available guidelines concerning the **treatment** of nipple candidiasis in **mothers** during lactation.

Institution	year	Non-medical advice	Medical advice		Medical advice for recurrent or persistent infection
IBC (International breastfeeding centre) and Canadian breastfeeding foundation – International (88)	2019	Exclude underlying causes and evaluate technique of positioning and latching the baby on.	**APNO (All-Purpose Nipple Ointment)** sometimes adding ibuprofen powder so that the final concentration of ibuprofen is 2% helps when the regular ointment does not. Apply *sparingly* after each feeding, meaning that the nipple and areola will shine but you won't be able to see the ointment. Do not wash or wipe it off.	And/or: **Grapefruit Seed Extract (GSE)** (active ingredient must be "citricidal") should be used in conjunction with the APNO. Apply diluted solution directly on the nipples. It does not need to be refrigerated. It may be covered and used until solution is finished.	**Oral GSE**: Grapefruit seed extract (not grape seed extract). Tablets or capsules, 250 mg three or four times a day orally or liquid extract can be taken orally: 10 drops in water three times per day. **Fluconazole** 400 mg loading dose, then 100 mg twice daily for at least two weeks, until the mother is pain free for a week.
Government of West Australia North Metropolitan health service (King Edward Memorial Hospital)– Australia (82)	2019	Corrective position and attachment is important to resolve nipple pain and trauma and to ensure adequate drainage and an ongoing milk supply. Expressing and giving expressed breast milk is an option if feeding is too painful. If mother or baby have signs and symptoms of Candida growth, then both should be treated simultaneously. Keep nipples dry by frequently changing breast pads. Reduce intake of refined sugars and saturated fats.	**miconazole cream** Apply to nipples after each feed. Removal is not indicated as this may cause further nipple trauma and the medication is compatible with breastfeeding (poor oral absorption).		**Fluconazole** 150mg once every 48 hours until breast pain is resolved.
JAPC (Derbyshire joint area prescribing committee - United Kingdom (55)	2019	/	Surface thrush: **miconazole 2% topical cream** Apply a small amount to nipples after every feed. Continue treatment for 14, even if symptoms resolve.	Ductal thrush: **oral fluconazole** 150-300 mg loading dose followed by 50-100 mg twice daily for 10 days.	Larger doses of **fluconazole**
La Leche League Vlaanderen – Belgium (84)	2019	Cook all things that come into contact with the infected breast daily. If cooking is impossible, rinse with hot vinegar water. Expressed milk during the time of infection may be given to the baby while still being treated for infection, after treatment the milk should be pasteurized (62,5°C, 30 min) and frozen.	**nystatin** or **miconazole ointment** (not gel or suspension). Apply at least 8 times a day, or after every feeding session, not four times as mentioned in the leaflet. Treat for seven days after symptoms have disappeared. Apply a 1% gentian violet solution to the breast once daily. Treat for a minimum of 4 and a maximum of 7 days. Treat up to 2 days after symptoms have disappeared.		**Fluconazole:** loading dose of 400 mg followed by 100 mg, twice daily for 2 to 4 weeks.

Institution	year	Non-medical advice	Medical advice	Medical advice for recurrent or persistent infection
Kind en gezin – Belgium (85)	2019	Treat mother and child simultaneously. Improve breastfeeding technique. Expressed milk during time of infection may be given to the child while still being treated. Do not keep this expressed milk for later use. Clean and sterilize expressing device, pacifiers and toys daily. Wash hands after every contact with infected area. Keep nipples dry. Wash underwear at 60°C.	Local treatment with antifungal medication. Sometimes gentian violet, propolis, grapefruit seed extract, vinegar, coconut oil and essential oils are used. Sometimes probiotics are recommended. More research is necessary on the effectiveness and safety of these methods.	Oral medication
The women's royal hospital – Australia (86)	2017	Treat mother and baby at the same time to prevent re-infection. Parental hand cleaning with an alcohol-based hand sanitizer after nappy changes may be helpful to reduce the risk of transmission.	**miconazole oral gel/cream or nystatin cream** Apply after each feed (or 3-4 hourly during the day). It is not necessary to wipe the gel/cream from the nipples before the next breastfeed. **Nipple pain only**: **fluconazole** 150 mg capsules, one capsule every 48 hours for 3 doses, followed by course of oral **nystatin** 2 tablets of 500 000 units, 3 times per day preferably with food AND apply **miconazole oral gel** to nipples 4 times a day **Nipple AND breast pain**: **fluconazole** 150 mg capsules, one capsule every 48 hours for 3 doses, plus a repeat prescription for a further course of fluconazole. If pain is not significantly reduced after the first 3 fluconazole capsules, then the repeat prescription of **fluconazole** should be filled to have another course of 150mg fluconazole every 48 hours for 3 doses, followed by a course of oral **nystatin** (2 tablets of 500 000 units, 3 times per day preferably with food AND apply miconazole oral gel to nipples four times per day.	**Persistant nipple pain:** further course of **fluconazole** 150mg capsules, either one capsule every 48 hours for 3 doses or one capsule daily up to 10 days (available only on private prescription), followed by a further course of oral **nystatin** (2 tablets/capsules) 3 times per day preferably with food If nipple pain remains unresolved, consider **gentian violet** 0.5% aqueous paint **Persistent breast pain:** reconsider the diagnosis or consider oral **nystatin** capsules
ABM (The Academy of Breastfeeding Medicine) – International (17)	2016	/	**Topical azole** antifungal ointment or cream on nipple area (miconazole and clotrimazole also inhibit the growth of Staphylococcus species) or **gentian violet** less than 0.5% aqueous solution daily for no more than 7 days	**Oral fluconazole** 200 mg once, then 100 mg daily for 7–10 days

Institution	year	Non-medical advice	Medical advice	Medical advice for recurrent or persistent infection
NHG (Nederlands Huisartsen Genootschap) – The Netherlands (87)	2015	/	**Miconazole cream** (first choice) **or Miconazole ointment** (second choice as it's harder to wash off)	/
Farmacotherapeutisch kompas – The Netherlands (91)	2015	Let the child empty the breasts as much as possible. Make sure the breasts are clean and dry. Wash mother and baby's hands before every feeding session and after every diaper change. Boil pacifiers and breast pumps every day. Replace pacifiers every week.	**miconazole cream** (first choice) or **miconazole ointment** (second choice) or **clotrimazole cream** (third choice)	/
British National Formulary (BNF), NICE guidelines – United Kingdom (92)	2014	You should be given information and guidance about relevant hygiene practices.	If thrush is causing feeding problems or you or your baby are in pain, you should be given antifungal cream or gel. Treatment with **nystatin** or **miconazole** may be needed.	**Fluconazole** for unresponsive infections
Rotherham clinical commissioning group – United Kingdom (89)	2013	/	**Miconazole 2% Cream, 45g** Apply a small amount to nipples after every feed. Gently wipe off any cream, which can be seen before next feed.	/
American college of nurse-midwives – United states of America (35)	2006	Always treat mother and child simultaneously.	**Nystatin suspension** or **miconazole cream** or **clotrimazole cream** In case of nipple fissures: add **mupirocine** or **Neosporine ointment** In case of red and inflamed nipples: add a **low-potency topical steroid**	In case of ductal candidiasis: **Fluconazole** 200 to 400 mg loading dose followed by 100 to 200 mg once daily for 14 to 21 days. Recommendation to continue breastfeeding when taking fluconazole.

4.3. REVIEW OF ALTERNATIVE APPROACHES

4.3.1. Gentian violet

Among the first therapies employed in the treatment of thrush was **gentian violet** or methylrosaniline chloride, introduced in 1925. The topically used purple dye is moderately active against thrush. However, it stains tissue, clothing and epithelial cells (of the child's mouth and mother's breast) and thus is not well accepted by parents. This staining also interferes with clinical assessment of the condition. The MIC of gentian violet for *C. albicans* is 10 µg/mL. (5,20) Gentian violet has a greater clinical and mycological efficacy compared to nystatin with 62% vs. 42% respectively. (6) However, prolonged use of the agent causes irritation and ulceration. Moreover, several studies suggested that gentian violet is possibly mutagenic or carcinogenic. The compound is therefore contra-indicated in the treatment of OPC by the Canadian government. (5,7) Despite these unwelcome problems, gentian violet is to this day still recommended as a treatment option in three guidelines. (17,84,86)

4.3.2. Coconut oil

A second alternative approach to the treatment of oral thrush and concomitant mammary candidiasis is topical application of certain oils onto the mucosa or the nipple area. Two studies by Ogbolu et al. and Shino et al. compared the antifungal effectiveness of **coconut oil** to fluconazole and ketoconazole **in vitro**. They found a coconut oil to be effective against *C. albicans* with slightly lower – but not significantly different – effectiveness than the comparing drugs. (93,94) Coconut oil contains a large concentration of medium chain fatty acids of which approximately 50% consists of lauric acid. Lauric acid and its monoglyceride form, monolaurin, principally disrupt membranes of pathogenic microorganisms and interfere with nutrient transfer and signal transduction, consequently disturbing the membrane function. A review by Mardia et al. reports multiple studies have found that fatty acids disrupt the cell membrane of *C. albicans* resulting in cell death. (95) Coconut oil is not recommended in any of the acquired guidelines.

4.3.3. Essential oils

A study by Devkatte et al. investigated the **in vitro** antifungal effect of 38 plant oils against four *C. albicans* strains and categorized them according to their Minimum Fungicidal Concentration (MFC). Fluconazole and amphotericin B were used as positive controls. Fifteen essential oils appeared to be ineffective: Chandan oil, Cedarwood oil, Jyotishmati oil, Jojoba oil, Olive oil, Jasmine oil, Lavender oil, Orpl oil, Walnut oil, Almond oil, Khus oil, Neem oil, Wheatgerm oil, Chaulmoogra oil and Cade oil. The other 23 oils showed significant antifungal effects. An overview of

the analysed plant oils, their MFC and their average achieved zone of inhibition (ZOI) over the four strains are represented in **Table 4.3.2.1.** Additionally, a study by Höfling et al. showed that *M. Piperita* or mint extract showed significant inhibition of the proteinase activity. Proteinases are virulence factors secreted by *C. albicans* in its pathogenic form. (96) Essential oils are not recommended in any of the guidelines.

Table 4.3.2.1. Classification of plant oils according to their Minimum Fungicidal Concentration.

Most effective (0.01%-0.15%)	Oil	MFC (%)	ZOI (mm)
	Cinnamon oil	0.03	24 (±3.60)
	Lemongrass oil	0.12	30.3 (±2.50)
	Clove oil	0.12	20.3 (±0.50)
	Japanese mint oil	0.06	26.6 (±3.50)
	Geranium oil	0.12	19.0 (±2.88)
	Motiarosha oil	0.12	13.6 (±2.88)
	Ginger grass oil	0.12	16.0 (±3.50)
Moderately effective (0.16-1.0%)	Oil	MFC (%)	ZOI (mm)
	Peppermint oil	0.25	15.6 (±0.50)
	Tulsi oil	0.25	12.0 (±0.00)
	Tea tree oil	0.25	14.6 (±2.50)
	Camphor oil	1.0	16.3 (±0.50)
	Ocimum oil	1.0	16.6 (±0.50)
	Lemon oil	1.0	17.6 (±2.08)
	Ylang-ylang oil	1.0	16.0 (±1.00)
	Orange oil	1.0	25.3 (±1.52)
Less effective (>1%)	Oil	MFC (%)	ZOI (mm)
	Bergamot oil	2.0	19.3 (±1.52)
	Rosemary oil	2.0	12.3 (±2.52)
	Eucalyptus oil	3.0	10.0 (±1.00)
	Citronella oil	2.0	06.1 (±1.50)
	Rose oil	3.0	02.0 (±0.00)
	Clarysage oil	3.0	12.3 (±0.50)
	Juniper oil	>3.0	05.0 (±0.00)
	Ginger oil	>3.0	02.0 (±0.00)

Minimum fungicidal concentration (MFC) is defined as the lowest concentration of oil resulting in the death of 99.9% of the inoculum.

Adapted and edited from (Potential of plant oils as inhibitors of Candida albicans growth, Devkatte A., 2005) Federation of European Microbiological Societies yeast research, volume 5, issue 9, pages 867-873

Another study on **the essential oil of *B. Dracunculifolia*** leafs showed that it also has antifungal properties. The essential oil is extracted from the leaves of the plant with the same name which can be found in Brazil. The *Dracunculifolia* leaf oil, also known as "Vassoura oil", inhibited growth in strains that were resistant to fluconazole and amphotericin B. (97) The study mentions earlier literature about *B. Dracunculifolia* having antifungal activity against *C. krusei, C. Glabrata and C. albicans* with an MIC50 from 65-150 mg/ml. The researchers reported that the oil's antimicrobial activity is mainly due to the presence of derivative compounds of p-coumaric acid, flavonoids, diterpens and triterpens. Other herbal products on the market such as green propolis are derived from the same plant and

contain diluted active ingredients. The MIC50 values for *B. Dracunculifolia* reported in this study by Pereira et al., which are represented in **Table 4.2.1** are significantly lower than in previous literature. (8)

Table 4.2.1: Minimum inhibitory concentrations of *Baccharis Dracunculifolia* essential oil on *Candida* species isolated from infants mouths, mothers' mouths and mothers' nipples. (8)

Candida isolates	MIC (mg/mL)		
	Ranges	MIC50	MIC90
Infants mouth			
C. albicans	0.4-6.25	0.8	6.25
C. parapsilosis	0.2-1.625	0.4	1.625
C. tropicalis	0.8	0.8	0.8
Mothers' mouths			
C. albicans	0.4-6.25	1.625	3.125
C. tropicalis	0.8	0.8	0.8
C. glabrata	0.8-1.625	0.8	1.625
Mothers' nipples			
C. albicans	0.8-6.25	1.625	6.25
C. parapsilosis	0.4-3.125	1.625	3.125
C. tropicalis	0.8-3.125	3.125	3.125

MIC: minimum inhibitory concentration. The values of MIC50 and MIC90 represent, respectively, the concentrations of antifungals that resulted 50 or 90% of the inhibition of the growth.

Adapted and edited from (Enzymatic Activity, Sensitivity to Antifungal Drugs and Baccharis dracunculifolia Essential Oil by Candida Strains Isolated from the Oral Cavities of Breastfeeding Infants and in Their Mothers' Mouths and Nipples, Pereira C., 2011) Mycopathologia, issue 2, volume 17, pages 103-109.

4.3.4. Diet

Another frequently used approach is the '***Candida* diet'**, meaning a reduction of the intake of alcohol, processed sugars and certain types of dairy in an attempt to reduce or prevent candidal yeast infections. A case report mentions resolution of persistant nipple candidiasis through alteration of the diet after failure of therapy with nystatin suspension. (28) No studies have been done on the effect of a diet in the treatment or prevention of thrush. However, an in-vitro study on the effect of sugars on *Candida albicans* adherence to epithelial cells does exist. A study by Samaranayake and Macfarlan found that the adhesion of two strains of *Candida albicans* (a laboratory reference and a fresh clinical isolate) to buccal cells increased significantly after incubation with glucose, sucrose and maltose. Incubation with maltose showed a six-fold increase in enhancement of adhesion. Exact values can be found in **Table 4.2.2.**. (98) In addition, a study by Hudson et al. identified glucose as the main component in serum that is responsible for the yeast to hyphal morphological switch of *C. albicans*. (99) One guideline advises to reduce the intake of refined sugars and saturated fats. (82)

Table 4.2.2.: The effect of dietary carbohydrates on the adhesion of two *Candida* strains to buccal epithelial cells. The used *Candida albicans* strains were MRL3153 (laboratory reference) and GDH1957 (fresh clinical isolate). (98)

The effect of dietary carbohydrates on the adhesion of *C. albicans* strains MRL3153 and GDH197 to human buccal epithelial cells.				
Strain	Preincubation of *Candida* in	Mean number of yeasts/mm² (± SEM)	Test-control	P (Wilcoxon's test)
C. albicans MRL3153	MP + glucose	146 (± 18)	1-2	< 0.05
	MP control	118 (± 13)		
	MP + sucrose	180 (± 18)	1-5	< 0.05
	MP control	118 (± 13)		
	MP + galactose	261 (± 31)	2-2	< 0.005
	MP control	118 (± 13)		
	MP + xyilitol	319 (± 33)	2-7	< 0.05
	MP control	118 (± 13)		
	MP + maltose	408 (± 60)	3-5	< 0.05
	MP control	118 (± 13)		
C. albicans GDH1957	MP + glucose	211 (± 18)	1-4	< 0.05
	MP control	151 (± 15)		
	MP + sucrose	377 (± 36)	2-5	< 0.05
	MP control	151 (± 15)		
	MP + maltose	998 (± 72)	6-6	< 0.005
	MP control	151 (± 15)		

Adapted and edited from (The effect of dietary carbohydrates on the in-vitro adhesion of Candida albicans to epithelial cells, Samaranayake, L. P., 1982) Journal of Medical Microbiology, volume 15, edition 4, pages 511-517.

4.3.5. Grapefruit seed extract

Lastly, **grapefruit seed extract (GSE)** or citrus seed extract is a product derived from the seeds and pulp of grapefruit. (100) GSE contains flavonoids, ascorbic acid, citric acid and tocopherols among other components. (101)

A study by Cao et al. described that GSE induces cell death in yeast cells in a similar pattern to apoptosis. (102) Additionally, GSE has the ability to dissolve *Candida* biofilms when submerged in a 1% solution for five minutes at 25°C. (101) Research has shown GSE also has antibacterial effects by disrupting the bacterial membrane and leading to cell lysis after only fifteen minutes of contact. (103) However, not all research supports the claim that GSE has antifungal properties. This research attributes the antifungal effects to known antimicrobial agents such as benzalkonium chloride and benzethonium chloride, used in processing and creating commercial GSE preparations. (104,105) GSE is recommended in one guideline. (88)

4.4. HEALTH CARE PROVIDERS' SURVEY

General practitioners, paediatricians and midwives are eligible to participate in the survey if they have treated at least one patient with thrush during breastfeeding in the year previous to filling out the survey. Pharmacists are informed of the requirement to be able to consult their delivery software before consenting and starting the questionnaire.
The questionnaire for midwives, GP's and paediatricians contains 5 sections: demographics, diagnosis, treatment, antimycotic medication and a general section. The complete survey can be found in **annex 8.1.** The questionnaire for pharmacists consists of four sections: demographics, delivery protocol, medication and alternative therapies. The complete questionnaire for pharmacists can be found in **annex 8.2.**

The pilot test on midwives revealed that terms such as "have you ever *prescribed* a certain drug" do not always apply to midwives as they, for example, are not authorised to prescribe certain medications such as fluconazole. This may lead to wrong interpretation of the question. We therefore added the term "or *advised"* to questions concerning the prescription of drugs to avoid confusion in the target population. In addition, the pilot testing revealed that midwives would prefer selecting symptoms of thrush out of a list, instead of numerating symptoms themselves.

4.5. PARENTS' SURVEY

Parents are eligible to fill out the survey if they are eighteen years or older and (one of) their child(ren) received medication for oral thrush during breastfeeding no more than two years ago. The questionnaire for parents consists of five sections: demographics, underlying pathology, medication, alternative therapies and breastfeeding. The questions are primarily focussed on mothers and their experience with OPC in the infant and possible mammary candidiasis. The entire list of questions for parents can be found in **annex 8.3**. In the medication section, parents are only asked to answer questions concerning medication that was prescribed or advised to their infant and they have experience with.

5. DISCUSSION

5.1. MAIN FINDINGS OF THIS STUDY

In this dissertation we summarized fifteen guidelines concerning the diagnosis and treatment of OPC in infants and mammary and/or nipple candidiasis in mothers during the breastfeeding period. We separated diagnostic directives from treatment directives which resulted in six guidelines mentioning directives on diagnosing infants with OPC, ten guidelines mentioning how to diagnose mothers with mammary and/or nipple candidiasis, fourteen guidelines containing directives on how to treat infants with OPC and twelve guidelines containing treatment advice for mammary and/or nipple candidiasis. Furthermore, we found that in Belgium, the most affordable treatment option for OPC in infants (assuming the treatment is prescribed) is nystatin, closely followed by miconazole oral gel (Daktarin®) and fluconazole (Diflucan®). Concerning alternative approaches, we found topical application of gentian violet to be the most mentioned alternative therapy across the acquired guidelines, despite the disadvantages. Other possible alternative approaches include application of grapefruit seed extract, coconut oil, certain plant oils and reducing the intake of processed sugars. In vitro testing of these approaches appears promising, but no studies have been carried out on the in vivo effectiveness and safety of these compounds.

5.2. WHAT IS ALREADY KNOWN

Nystatin oral suspension and miconazole oral gel (Daktarin®) are both first choice topical antifungal agents in the treatment of OPC in infants. Indeed, all but one guideline (85) considering treatment of thrush mention at least one of both therapies. It's clinically proven that miconazole is more effective in the treatment of OPC in infants compared to nystatin, with clinical cure rates of 99% compared to 54% respectively, as previously stated in the introduction. **Miconazole oral gel** is licensed for use in children from the age of four months old. The oral gel is therefore not the first treatment choice in the age group *under* four months, in spite of its superior effectiveness compared to nystatin. This was however not always the case. After nearly 30 years of unchanged use, the manufacturer (Janssen-Cilag) chose to change the license in 2008 so it was no longer recommended in infants under the age of four months. In a review by dr. S. Ainsworth, a neonatologist, this measure is criticized. (106) The license change was based on a paper published in 2004 that mentions the case of a seventeen-day-old infant choking on the gel after the mother was told by her pharmacist to apply the gel onto the nipple and let the child feed. When the mother realised the infant couldn't

breathe, she scooped the gel out of the child's mouth and the child made a full recovery. The paper mentions nine similar cases. (107)

Dr. Ainsworth questions the license change, which is based on incorrect usage instructions and poses the question whether the update of the product information leaflet could not have sufficed. (106) The current leaflet clearly states to apply small amounts of the gel by finger four times daily after feeds. (108) We observe that seven out of the fourteen guidelines (50%) concerning the **treatment** of OPC in infants specifically mention the application method for miconazole oral gel. (48,55,82,84,86,87,89,109) This amount could be higher, but miconazole oral gel (Daktarin®) is not licensed in the US and Canada and is consequently not mentioned in two out of three American guidelines. The one American guideline that mentions the gel clearly states it is not commercially available in the US. (57,110)

5.3. WHAT THIS STUDY ADDS

To the best of our knowledge, no previous studies have summarized available guidelines in the diagnosis and treatment of oral thrush in infants and mammary or nipple thrush in mothers during lactation. There has also been no previous review of multiple possible alternative approaches in the treatment of OPC and mammary and/or nipple candidiasis in mothers.

A first notable finding is the small amount of guidelines mentioning **diagnostic** directives. Only six out of fifteen guidelines (40%) mention diagnostic directives concerning OPC in infants (82–88) and ten out of fifteen (66%) guidelines mention diagnostic directives for mammary and/or nipple thrush. (17,35,82–89) This can be considered as a crucial shortcoming, as a correct diagnosis indicates whether or not treatment should be initiated and what medication it should include. Of the fourteen guidelines mentioning *treatment* directives for OPC in infants, only six (42%) include how to recognize the infection in children in contrast to nine (64%) mentioning how to recognize mammary and/or nipple thrush in mothers. This might be due to some guidelines recommending simultaneous treatment of mother and child, even if only one of them shows signs or symptoms and therefore guidelines focussed on mammary and/or nipple candidiasis also include treatment directives for infants. Nonetheless, in the light of the mother-baby dyad, signs and symptoms of an oral *Candida* infection in infants should be included in all guidelines, even if they are focussed on mammary and/or nipple candidiasis. Specifically, five guidelines (33%) advise to treat mother and child simultaneously. (35,82,83,85,86)

A second alarming observation concerns the significant amount of **discrepancies** between the content of guidelines regarding diagnostic as well as treatment directives. For example, we notice that the BAPCOC guideline contra-indicates Daktarin® oral gel below the age of six months, whereas all other guidelines follow the licensed use and advise miconazole oral gel from the age of four months. Personal communication with the BAPCOC-team revealed that the guidelines will be adapted in the near future (the contra-indication will be lowered to four months) in light of a recent decision on the matter by the European Medicines Agency (EMA). (48) Of the thirteen remaining guidelines concerning the treatment of OPC in infants, four (31%) -all British and Australian- advise Daktarin® oral gel as the primary treatment option, even in infants *under* four months of age. (82,83,86,89) Two guidelines (15%) -both Dutch- advise nystatin oral suspension as the primary treatment option for children under four months. (87,91) Four guidelines (31%) mention both nystatin suspension and miconazole gel, without preference or age differentiation. (17,57,84,92) Two guidelines (15%) -both American- only mention nystatin as a paediatric treatment option. (35,111) Finally, one guideline (8%) does not advise specific medications. (85) There clearly is no consensus on the primary treatment option of OPC in infants.

For nipple and/or mammary thrush, the content of the guidelines are less divided but not unanimous. One out of twelve (8%) advises APNO for thrush of the nipple or breast. (88) Seven guidelines (58%) advise miconazole cream, five of which (41% of total) alone and two of which (17% of total) along with other treatment options such as nystatin cream or clotrimazole cream. (35,82–84,86,87,89,91) Three guidelines (25%) did not specify medication options. (17,85,92) This indicates that for candidiasis of the breast or nipple, miconazole cream is the most advised treatment option. Furthermore we notice that only three out of fourteen guidelines (21%) advise a treatment option for persistent thrush in infants. (48,84,92) For mothers, eight out of fourteen guidelines (57%) advise fluconazole in case of recurrent or persistent infection or when ductal candidiasis is suspected. (17,35,82–84,86,88,92) Two of these do not mention a specific treatment plan. (83,92) The other six guidelines advise three different treatment plans (including different doses) for fluconazole. (17,35,82,84,86,88) We can conclude that there is also no consensus on the treatment plan for recurrent or persistent thrush. Moreover, only two guidelines (14%) concerning the treatment of OPC in infants mention an alternative in case of fluconazole resistance. (92,111) This proves that alternative options in case of resistance to antifungal therapy are not sufficiently included in the current guidelines.

Furthermore, we notice that six out of fourteen guidelines (43%) concerning the treatment of OPC in infants do not provide **non-medical advice**. (17,35,57,84,91,111) Neither do four out of twelve guidelines (33%) concerning the treatment of mammary and/or nipple thrush. (17,83,87,89). Additionally, the contents of the directives significantly differ. Regarding cleaning and sterilization of breast pumps, pacifiers, bottles and toys over all fifteen acquired guidelines, eight guidelines (53%) mention the aids should be adequately cleaned. However, only four of those specify boiling as a sterilization technique and of those four, only two specify how long the aids should be boiled. (44,84,87,91) A consensus on practical sterilization techniques might be useful in the further development of guidelines concerning thrush in infants and mothers during lactation. In a study on microwave sterilization of dentures (3 minutes on 650W in 200 mL of water) with possible *Candida* biofilms, complete eradication of *Candida species* was achieved. (39) This method proves to be practical, fast and easy. A study by Lopez et al. confirmed *C. albicans* was able to grow and adhere to silicone pacifiers, but complete eradication was achieved by washing the pacifier for one minute with neutral detergent (they used a 3,5% concentration to submerge the pacifier) and by boiling the pacifier for fifteen minutes. These results indicate that multiple sterilization techniques are successful, but more research should be done to determine the most effective *and* practical method to eradicate *Candida* from breast pumps, pacifiers, bottles and toys in the prevention of spreading thrush. (112) Regarding breastfeeding technique, only three out of fifteen acquired guidelines (20%) mention that positioning and latch of the infant to the breast should be evaluated and improved. (82,85,88) This is remarkable, since improving breastfeeding technique is an efficient manner to alleviate pain. A study by Darmangeat et al. showed improving the latch-on of the baby resolved 65% of cases of breast pain. The question remains whether breast pain due to a candidal infection is also relieved by improvement of the latch-on. This non-medical intervention should be further investigated. Nonetheless, it appears that not much value is attached to non-medical interventions for pain relief in the treatment of mammary and/or nipple thrush. Regarding expressed milk, only three out of fifteen acquired guidelines (20%) mention what to do with expressed milk. (82,84,85) One of these directives – by La Leche League (LLL) - advises pasteurizing and freezing the milk for use after the infection has healed. There is however no scientific evidence that supports the benefits of pasteurization (killing off the fungal cells) outweigh the downsides (denaturation of essential proteins). Another guideline – by the Western Australia North Metropolitan Health Service – mentions expressing milk is an option if breastfeeding is too painful but does not specify storage conditions. The last guideline - by “kind en gezin” – specifically mentions that expressed milk may be given to the child while the child is still receiving treatment but should not be kept for later use.

We can also remark that breastfeeding-focussed organisations (i.e. LLL and IBC) mention more **alternative therapies** without referencing scientific evidence compared to medical institutions such as hospitals or medical societies. E.g., only IBC advises the use of grapefruit seed extract. (88) It is however gentian violet that is the most prevalent alternative therapy mentioned. The purple dye is mentioned in three out of fourteen guidelines (22%) considering the treatment of OPC in infants and three out of thirteen guidelines (23%) considering the treatment of mammary and/or nipple candidiasis. (57,84,85) Gentian violet has been on the market since the early 1900's, therefore there is extensive experience with the solution, including in infants. However, use of gentian violet goes not without risk. A case report clarifies gentian violet may be used in a concentration of 0,5% to 1% once or twice daily for no more than a few days, as overuse of gentian violet is toxic. This includes excessive use of the 0,5% and 1% solutions and use of solutions with a higher concentration. Short term toxic effects include exacerbation of OPC, macroglossia and oral lesions. No epidemiological studies on chronic toxicity of gentian violet in humans are available, but a study on chronic toxicity in mice was executed by N. Littlefield et al. The two-year research project concluded that gentian violet seemed to be carcinogenic in mice in a dose-response related manner. (113–116)

The known toxicity of typically used alternative therapies, such as gentian violet, and the increased resistance to antifungal medications in combination with the shortage of new antimicrobial drugs on the market increases the public's interest in Complementary and Alternative Medicine (CAM). This includes worldwide interest in plant extracts for the prevention and treatment of candidiasis. Our review included several in vitro studies on the effectiveness of plant oils, showing promising results. At this point however, these CAM approaches often lack in vivo safety and effectiveness studies to support them. Essential oils are nevertheless commonly used in everyday practice and experience is therefore not scarce. Of the seven most effective antifungal plant oils mentioned in this dissertation, the international childbirth education association does not recommend the use of mint oil during breastfeeding. The association also advises pregnant and lactating women should use dilutions of maximum 2%. No more than 0.25% to 0.5% dilutions should be applied cutaneous to children between three and 24 months. (117) It should be noted that essential oils may cause a series of adverse effects. For example, they may cause sensitization and irritation of the skin and some essential oils are phototoxic and may cause blistering, inflammation and burning when exposed to UV light. (118–120) Taking into account the risks of essential oils, the use of these products is **not recommended** until more research on the in vivo safety and effectiveness is available.

On the other hand, **coconut oil** is considered a carrier oil and does not pose the same challenges as essential oils. A study on topical application of coconut oil in 72 preterm infants showed no adverse effects. (121) In vitro testing shows coconut oil is an effective antifungal agent when it comes to *C. albicans.* (122) In a study on 30 children aged five to ten years old, no adverse effects were reported after two weeks of coconut oil mouth wash, three times daily. (123) These results imply coconut oil does not irritate buccal mucosa. Coconut oil could be the safest alternative therapy for OPC in infants, although more research on the effectiveness and safety in infants is necessary.

Finally, there are a few remarks to be made about **APNO**. Sometimes ibuprofen may be added to the ointment to a final concentration of 2%. Ibuprofen is a non-steroid anti-inflammatory drug that relieves pain. (124) This may be useful in mothers suffering from severe nipple pain. If the ointment were to be compounded in Belgium, the ointment base of choice would be lanolin, as plain lanolin ointment is often given to new mothers while getting used to breastfeeding as to prevent or treat nipple damage. In the comparing study of APNO versus plain lanolin by Dennis et. al it is not defined which ointment base is used to compound APNO. (69) The recipe, available on the IBC website does not mention any preference or indication as to what ointment base to use either. (68) Other bases do not pose particular advantages. Zinc ointment is mainly used to treat itching skin, but may dry the skin of the nipple area. (125) Coconut oil as a base is not advised as it poses stability issues. Virgin coconut oil is solid at room temperature but has a melting temperature of 24°C. (126) However, if more research would be done into the antifungal effects of coconut oil and its MFC was determined, it could be useful to incorporate coconut oil into known stable bases.

5.4. LIMITATIONS OF THIS RESEARCH

Only Dutch and English guidelines were included in this dissertation. We did not include any French, German or other European sources. It might be useful to summarize European guidelines, as we know all compounds would be commercially available in each country and we would have a better view on the off-label recommendations and the place of miconazole oral gel (Daktarin®) in the treatment of OPC in infants. Unfortunately, the language barrier is a limitation that obstructed us from realizing this goal.

5.5. IMPLICATIONS FOR FUTURE RESEARCH

First and foremost, more information should be acquired about the need for medical interventions in the treatment of OPC in infants. There are no epidemiological studies on how many colonized children develop OPC and how many of those are symptomatic. Asymptomatic thrush is known to resolve by itself, but the idea may leave parents and health care providers waiting too long to initiate adequate treatment. Future research should focus on determining clear diagnostic directives, including at which point to initiate a medical intervention. This could ensure a fast and effective treatment and avoid adverse consequences such as early weaning.

Additionally, research should be conducted on the effects of OPC and mammary and/or nipple candidiasis on breastfeeding practice, specifically the amount of cases leading to early cessation of breastfeeding and how to prevent this. Furthermore, it might be useful to investigate the adherence and persistence of *Candida species* on pacifiers, breast pumps or other aids, bottles and toys. Current sterilization techniques should be evaluated regarding effectiveness and practical use and a consensus should be reached and included into future guidelines. Additionally, we noticed that resistance to fluconazole is barely discussed and few options in case of resistance are listed. The prevalence of azole resistance should be further investigated and alternative treatment options in case of resistance should be explored.

6. CONCLUSION

We summarized fifteen different guidelines concerning the diagnosis and treatment of OPC in infants and mammary and/or nipple candidiasis in mothers. We separated diagnostic directives from treatment directives and directives concerning infants from directives concerning mothers. We can conclude there is a significant amount of discrepancies between the guidelines and a consensus is needed on diagnostic directives as well as treatment directives. 43% of guidelines concerning the treatment of OPC in infants and 33% of guidelines concerning the treatment of mammary and/or nipple thrush do not provide non-medical advice. Non-medical advice regarding sterilization of aids (i.e. breast pumps, pacifiers and bottles) and expressed milk that was included often lacked specificity and scientific evidence. Additionally, hardly any directives included advice concerning improvement of breastfeeding technique (only 20%), even though it can significantly decrease breast pain.

Concerning medical advice, nystatin oral suspension and miconazole oral gel are the most commonly advised treatment options for OPC in infants. Moreover, 31% of guidelines recommend Daktarin® oral gel as the primary treatment option, even in infants *under* four months of age (off license), provided that specific usage instructions are applied. Miconazole cream is the most advised (58%) treatment option for mammary and/or nipple thrush in mothers. Fluconazole remains the first-choice treatment option in case of recurrent or persistent infections, but few alternatives are presented in case of resistance to therapy. We can conclude that resistance to antimycotic drugs is a topic that requires more research.

Furthermore, a lack of research regarding the effectiveness and safety of alternative therapies on a short- and long-term basis poses a problem, but new discoveries such as plant oils, coconut oil, grapefruit seed extract and diet restrictions are promising subjects for future research. Gentian violet is the most often mentioned alternative therapy (22% for OPC and 23% for mammary and/or nipple thrush), but coconut oil seems to currently be the safest choice.

The most affordable prescribed treatment option for OPC in infants is nystatin oral suspension (Nilstat®), closely followed by miconazole oral gel (Daktarin®) and fluconazole (Diflucan®).

Lastly, three different questionnaires were developed to question GPs, paediatricians, midwives, pharmacists and parents on their experience with the diagnosis and treatment of thrush in infants and mothers.

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8. APPENDIX

8.1. Questionnaire for GPs, paediatricians and midwives.

Beste arts/vroedvrouw,

Een spruwinfectie tijdens de borstvoedingsperiode wordt meestal veroorzaakt door candida albicans en kan zowel voorkomen bij zuigelingen als bij de moeders die borstvoeding geven.

Een snelle en correcte diagnosestelling is noodzakelijk aangezien een medicamenteuze behandeling en verlichting van de pijn een groot verschil kunnen maken voor de voortzetting van de borstvoeding. Uit onderzoek blijkt dat pijn aan de tepel of de borst de op één na meest voorkomende reden is om de borstvoeding stop te zetten. Het vroegtijdig stopzetten van de borstvoeding is nadelig voor zowel moeder als zuigeling.

In het kader van mijn masterthesis onderzoek ik de huidige praktijk ter diagnosestelling en behandeling van spruwinfecties tijdens de borstvoedingsperiode. In een gelijklopend onderzoek worden de bevindingen van ouders geëvalueerd.

Het invullen van deze enquête duurt een tiental minuten. Alle antwoorden zullen anoniem (hierbij is er totaal geen terugkoppeling meer mogelijk naar uw persoonlijk dossier) verwerkt worden en enkel gebruikt worden in het kader van dit onderzoek. Graag verduidelijken we dat het geenszins de bedoeling is een oordeel te vellen, maar een idee te krijgen van de noden om later onderzoek hierop af te stemmen.

Bij vragen of opmerkingen kan u steeds mailen naar AnneFlorence.Moerman@Ugent.be
Alvast hartelijk bedankt voor uw medewerking!

Anne-Florence Moerman
1ste masterstudente farmaceutische zorg (Universiteit Gent)

Onder begeleiding van
Prof. Dr. Apr. Eline Tommelein

☐ "Ik verklaar mij akkoord dat ik er mij bewust van ben dat deze vragenlijst volledig vrijwillig is, steeds kan onderbroken worden, en dat alle gegevens anoniem zullen verwerkt worden.
☐Ik heb in het jaar voorafgaand aan deze vragenlijst minimum één patiënt met een spruwinfectie tijdens de borstvoedingsperiode behandeld."

Deze studie werd goedgekeurd door een onafhankelijke Commissie voor Medische Ethiek verbonden aan het UZ Gent, en zal worden uitgevoerd volgens de richtlijnen voor de goede klinische praktijk (ICH/GCP) en de verklaring van Helsinki opgesteld ter bescherming van mensen deelnemend aan klinische studies. In overeenstemming met de Belgische wet van 8 december 1992 en de Belgische wet van 22 augustus 2002, zal uw persoonlijke levenssfeer worden gerespecteerd. De experimentenwet van 7/05/2004 verplicht ons om deelnemers aan wetenschappelijke projecten te verzekeren voor de deelname en het risico (hoe klein ook) dat men loopt. De waarschijnlijkheid dat u door deelname aan deze studie enige schade ondervindt, is extreem laag. Indien dit toch zou voorkomen, wat echter zeer zeldzaam is, werd een verzekering afgesloten conform de Belgische wet van 7 mei 2004, die deze mogelijkheid dekt.

Demografische gegevens

1. Geslacht: ☐ Man ☐ Vrouw ☐Ander, specifieer:.....
2. Leeftijd: .....
3. Heeft u kinderen? ☐ Ja ☐ Nee

   Indien ja: heeft (één van) uw kind(eren) een antimycoticum (Nystatine, Miconazole, Fluconazole,..) gebruikt tijdens de borstvoedingsperiode?

   ☐Ja ☐ Nee

4. Beroep: ☐Huisarts ☐Huisarts in opleiding ☐ Vroedvrouw
   ☐Pediater ☐Pediater in opleiding
   ☐ Ander:.....
5. Aantal jaren ervaring: .....
6. Stad/gemeente waar u tewerkgesteld bent: .....
7. Universiteit/Hogeschool waar u de opleiding tot arts of vroedvrouw gevolgd heeft:

☐ UGent ☐ KULeuven ☐ VUB ☐ HoGent ☐ UC Leuven ☐ Artevelde

☐ UAntwerpen ☐ UHasselt ☐ KULAK ☐ Odisee ☐ HoWest ☐ VIVES

☐ Andere: .....

Universiteit waar u een vorvolgopleiding gevolgd heeft indien van toepassing:

☐ UGent ☐ KULeuven ☐ VUB

☐ UAntwerpen ☐ UHasselt ☐ KULAK

☐Andere: .....

Opgelet! Deze enquête gaat specifiek over spruwinfecties bij zuigelingen en moeders tijdens de borstvoedingsperiode

Diagnosestelling

8. Welke symptomen correleert u met een orale spruwinfectie bij <u>zuigelingen</u>?

.....

.....

.....

9. Welke symptomen correleert u met een spruwinfectie bij moeders die borstvoeding geven?

.....

.....

10. Wanneer u een spruwinfectie vermoed of de diagnose stelt, vraagt u dan een laboratoriumtest aan ter bevestiging of verwijst u de patiënt door voor een cultuurname?

☐ Ja ☐ Nee

Indien ja, hoe wordt het staal afgenomen?

.....

.....

11. Welke andere aandoening(en) sluit u uit die mogelijks eenzelfde klachtenpatroon vertonen?

.....

.....

.....

☐ Ik weet het niet, ik moet dit opzoeken

12. Vindt u dat er duidelijke richtlijnen zijn voor het stellen van de diagnose van een spruwinfectie tijdens de borstvoedingsperiode?
☐ Ja ☐ Nee

13. Welke richtlijnen gebruikt u voor het stellen van de diagnose van een spruwinfectie tijdens de borstvoedingsperiode?

.....

.....

14. Neemt u aan dat spruw de oorzaak is van pijn tijdens het geven van borstvoeding, wanneer er geen visuele symptomen aanwezig zijn?

.....

.....

15. Bij hoeveel moeder/kind duo's heeft u tijdens de borstvoedingsperiode het afgelopen jaar de diagnose 'spruw' gesteld?

☐ 0 ☐ 1-4 ☐ 5-9 ☐ 10-19 ☐20 of meer

16. Bij de laatste 10 patiënten met een spruwinfectie, bij hoeveel patiënten bent u concomitant ook nagegagaan of er een vaginale schimmelinfectie aanwezig was bij de moeder?

    .....patiënten

    ☐ Ik herinner dit mij niet

17. Bij de laatste 10 patiënten met een spruwinfectie, bij hoeveel patiënten bent u concomitant ook nagegagaan of er luierdermatitis met een candida surinfectie aanwezig was bij de zuigeling?

    .....patiënten

    ☐ Ik herinner dit mij niet

18. Bij de laatste 10 patiënten met een spruwinfectie, bij hoeveel patiënten hebt u een cultuur genomen van de mond en/of de tepel of hebt u de patiënt doorverwezen voor een cultuurname?

    .....patiënten

    ☐ Ik herinner dit mij niet

Behandeling van spruw

19. Vindt u dat u beschikt over duidelijke richtlijnen voor de behandeling van spruwinfecties bij zuigelingen en moeders tijdens de borstvoedingsperiode?
    ☐ Ja ☐ Nee

20. Welke richtlijnen gebruikt u?

.....

.....

21. U stelt de diagnose **spruw (primo-infectie).**
Welk niet-medicamenteus advies geeft u voor de infectie?

.....

.....

.....

☐ Ik weet het niet, ik moet dit opzoeken

Welk medicamenteus advies geeft u voor de infectie?

.....

.....

.....

☐ Ik weet het niet, ik moet dit opzoeken

Welke therapie stelt u in voor de pijn?

.....

.....

.....

☐ Ik weet het niet, ik moet dit opzoeken

.

22. U stelt de diagnose **spruw (recidiverende infectie – tweede keer).**

Welk niet-medicamenteus advies geeft u voor de infectie?

.....

.....

.....

☐ Ik weet het niet, ik moet dit opzoeken

Welk medicamenteus advies geeft u voor de infectie?

.....

.....

.....

☐ Ik weet het niet, ik moet dit opzoeken

Welke therapie stelt u in voor de pijn?

.....

.....

.....

☐ Ik weet het niet, ik moet dit opzoeken

23. U stelt de diagnose **spruw (recidiverende infectie – derde of meerdere keer).**

Welk niet-medicamenteus advies geeft u voor de infectie?

.....

.....

.....

☐ Ik weet het niet, ik moet dit opzoeken

Welk medicamenteus advies geeft u voor de infectie?

.....

.....

.....

☐ Ik weet het niet, ik moet dit opzoeken

Welke therapie stelt u in voor de pijn?

.....

.....

.....

☐ Ik weet het niet, ik moet dit opzoeken

Antimycotische medicatie

NYSTATINE lokale therapie voor de mond van de zuigeling

24. Voor hoeveel unieke zuigelingen heeft u de afgelopen **maand nystatine (orale suspensie)** voorgeschreven of geadviseerd ter behandeling van spruw?
    - ☐ 0
    - ☐ 1 – 4
    - ☐ 5 – 9
    - ☐ 10 of meer

25. Wat is de dosering van **nystatine ter behandeling van de mond van de zuigeling**?

    dosering: ☐ .....

    ☐ Ik ken dit niet van buiten, ik zoek dit op*

    *welke bronnen gebruikt u om dit op te zoeken?

☐ BCFI

☐ Commentaren Medicatiebewaking

☐ Apotheek.nl

☐ Farmacotherapeutisch kompas

☐ Wetenschappelijke studies/reviews

☐ Kinderformularium

☐ Wetenschappelijke bijsluiter

☐ Andere: .....

26. Welke gebruiksinstructies geeft u mee aan de ouders wanneer u **nystatine (orale suspensie)** voor de behandeling van orale spruwinfecties bij zuigelingen tijdens de borstvoedingsperiode voorschrijft of adviseert?

.....

.....

27. Welke bijwerkingen van **nystatine (orale suspensie)** kent u?

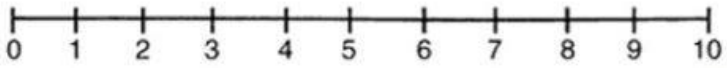
☐Ik weet dit niet vanbuiten, ik zoek dit op

.....

.....

28. Hoe effectief vindt u nystatine (orale suspensie) op een schaal van 0 tot 10 waarbij 0= helemaal niet effectief en 10=zeer effectief ?

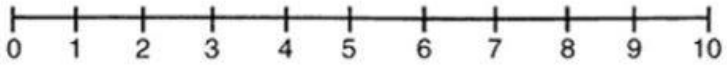
☐Ik weet dit niet



0= helemaal niet effectief **10=zeer effectief**

29. Hoe veilig vindt u nystatine (orale suspensie) op een schaal van 0 tot 10 waarbij 0= helemaal niet veilig en 10=zeer veilig ?

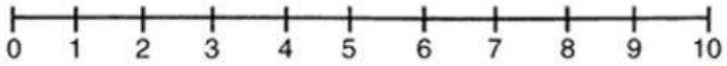
☐Ik weet dit niet



0= helemaal niet veilig **10=zeer veilig**

30. Hoe geschikt vindt u nystatine(orale suspensie) op een schaal van 0 tot 10 waarbij 0= helemaal niet geschikt en 10=zeer geschikt ?

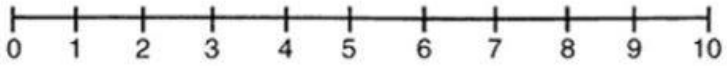
☐Ik weet dit niet



0= helemaal niet geschikt **10=zeer geschikt**

31. In welke mate beïnvloedt de prijscategorie van nystatine (orale suspensie) uw beslissing om dit geneesmiddel al dan niet voor te schrijven of te adviseren?

☐Ik weet dit niet



0= De prijs beïnvloedt mijn voorschrijf-/adviseergedrag helemaal niet **10=De prijs beïnvloedt mijn voorschrijf-/adviseergedrag aanzienelijk veel**

MICONAZOLE ORALE GEL (DAKTARIN ®) lokale therapie voor de mond van de zuigeling

32. Voor hoeveel unieke zuigelingen heeft u de afgelopen maand **miconazole orale gel (Daktarin®)** voorgeschreven of geadviseerd ter behandeling van spruw?
    - ☐ 0
    - ☐ 1 – 4
    - ☐ 5 – 9
    - ☐ 10 of meer

33. Miconazole orale gel (Daktarin®) is sinds 2008 vergund voor gebruik in kinderen vanaf vier maanden. De vergunning werd aangepast wegens een risico op verstikking. Volgens de BAPCOC richtlijnen is miconazole orale gel (Daktarin®) gecontra-indiceerd bij kinderen jonger dan zes maanden omwille van dezelfde reden. Wat vindt u van deze contra-indicatie?

.....

.....

.....

.....

.....

34. Wat is de dosering van **miconazole orale gel (Daktarin®) ter behandeling van de mond van de zuigeling**?

    dosering: ☐ .....

    ☐ Ik ken dit niet van buiten, ik zoek dit op*

    *welke bronnen gebruikt u om dit op te zoeken?

☐ BCFI

☐ Commentaren Medicatiebewaking

☐ Apotheek.nl

☐ Farmacotherapeutisch kompas

☐ Wetenschappelijke studies/reviews

☐ Kinderformularium

☐ Wetenschappelijke bijsluiter

☐ Andere: .....

35. Welke gebruiksinstructies geeft u mee aan de ouders wanneer u **miconazole orale gel (Daktarin®)** voor de behandeling van orale spruwinfecties bij zuigelingen tijdens de borstvoedingsperiode voorschrijft of adviseert?

.....

.....

36. Welke bijwerkingen van **miconazole orale gel (Daktarin®)** kent u?

☐Ik weet dit niet vanbuiten, ik zoek dit op

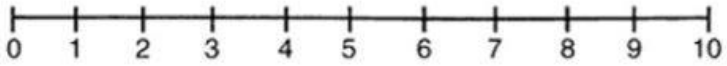
.....

.....

.....

37. Hoe <u>effectief</u> vindt u miconazole orale gel (Daktarin®) op een schaal van 0 tot 10 waarbij 0= helemaal niet effectief en 10=zeer effectief?

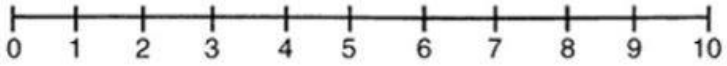
☐Ik weet dit niet



0= helemaal niet effectief **10=zeer effectief**

38. Hoe <u>veilig</u> vindt u miconazole orale gel (Daktarin® op een schaal van 0 tot 10 waarbij 0= helemaal niet veilig en 10=zeer veilig ?

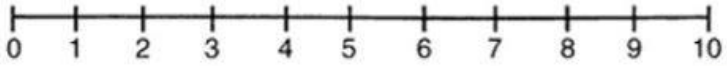
☐Ik weet dit niet



0= helemaal niet veilig **10=zeer veilig**

39. Hoe <u>geschikt</u> vindt u miconazole orale gel (Daktarin®) op een schaal van 0 tot 10 waarbij 0= helemaal niet geschikt en 10=zeer geschikt ?

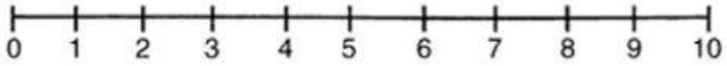
☐Ik weet dit niet



0= helemaal niet geschikt **10=zeer geschikt**

40. In welke mate beïnvloedt de <u>prijscategorie</u> van miconazole orale gel (Daktarin®) uw beslissing om dit geneesmiddel al dan niet voor te schrijven of te adviseren?

☐Ik weet dit niet



0= De prijs beïnvloedt mijn voorschrijf-/adviseer gedrag helemaal niet **10=De prijs beïnvloedt mijn voorschrijf-/adviseergedrag aanzienelijk veel**

MICONAZOLE CRÈME lokale therapie voor de borst/tepel van de moeder

41. Voor hoeveel unieke moeders die borstvoeding geven heeft u de afgelopen maand **miconazole crème** voorgeschreven of geadviseerd ter behandeling van spruw?
    - ☐ 0
    - ☐ 1 – 4
    - ☐ 5 – 9
    - ☐ 10 of meer

42. Wat is de dosering van **miconazole crème (Daktarin®) ter behandeling van de tepel en/of borst van de moeder**?

    Dosering : ☐ .....
    ☐ Ik ken dit niet van buiten, ik zoek dit op*

    *welke bron(nen) gebruikt u om dit op te zoeken?

☐ BCFI

☐ Commentaren Medicatiebewaking

☐ Apotheek.nl

☐ Farmacotherapeutisch kompas

☐ Wetenschappelijke studies/reviews

☐ Kinderformularium

☐ Wetenschappelijke bijsluiter

☐ Andere: .....

43. Welke gebruiksinstructies geeft u mee wanneer u **miconazole crème ter behandeling van de tepel en/of borst van de moeder** voorschrijft of adviseert?

.....

.....

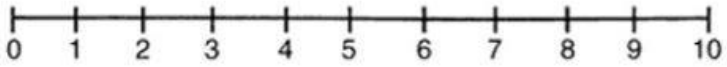
44. Welke bijwerkingen van **miconazole crème** kent u?
    - ☐Ik weet dit niet vanbuiten, ik zoek dit op

.....

.....

45. Hoe effectief vindt u miconazole crème (Daktarin®) op een schaal van 0 tot 10 waarbij 0= helemaal niet effectief en 10=zeer effectief?

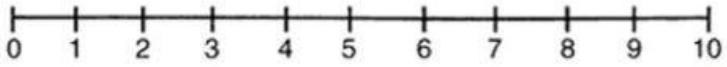
☐Ik weet dit niet



0= helemaal niet effectief **10=zeer effectief**

46. Hoe veilig vindt u miconazole crème (Daktarin®) op een schaal van 0 tot 10 waarbij 0= helemaal niet veilig en 10=zeer veilig ?

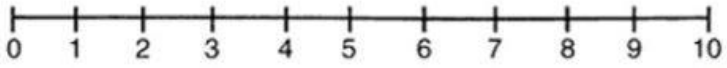
☐Ik weet dit niet



0= helemaal niet veilig **10=zeer veilig**

47. Hoe geschikt vindt u miconazole crème (Daktarin®) op een schaal van 0 tot 10 waarbij 0= helemaal niet geschikt en 10=zeer geschikt ?

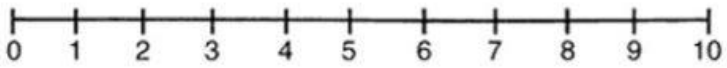
☐Ik weet dit niet



0= helemaal niet geschikt **10=zeer geschikt**

48. In welke mate beïnvloedt de prijscategorie van miconazole crème (Daktarin®) uw beslissing om dit geneesmiddel al dan niet voor te schrijven of te adviseren?

☐Ik weet dit niet



0= De prijs beïnvloedt mijn voorschrijf-/adviseergedrag helemaal niet **10=De prijs beïnvloedt mijn voorschrijf-/adviseergedrag aanzienelijk veel**

ALL PURPOSE NIPPLE OINTMENT (APNO ZALF) lokale therapie voor de borst/tepel van de moeder

De all purpose nipple ointment is een magistrale bereiding die bestaat uit een zalfbasis (lanoline/vaseline) met

- *2% mupirocine (antibioticum)*
- *0,1% bètamethasone (corticosteroïd)*
- *2% miconazole poeder (antimycoticum)*

49. Voor hoeveel unieke moeders die borstvoeding geven heeft u de afgelopen maand **all purpose nipple ointment (APNO zalf)** voorgeschreven of geadviseerd ter behandeling van spruw?
    - ☐ 0
    - ☐ 1 – 4
    - ☐ 5 – 9
    - ☐ 10 of meer

50. Wat is de dosering van **all purpose nipple ointment (APNO zalf) ter behandeling van de tepel en/of borst van de moeder**?

    dosering: ☐ .....

    ☐ Ik ken dit niet van buiten, ik zoek dit op*

    *welke bronnen gebruikt u om dit op te zoeken?

☐ BCFI

☐ Commentaren Medicatiebewaking

☐ Apotheek.nl

☐ Farmacotherapeutisch kompas

☐ Wetenschappelijke studies/reviews

☐ Kinderformularium

☐ Wetenschappelijke bijsluiter

☐ Andere: .....

51. Welke gebruiksinstructies geeft u mee wanneer u **APNO zalf** ter behandeling van een spruwinfectie bij de moeder voorschrijft of adviseert?

.....

.....

52. Welke bijwerkingen van **APNO zalf** kent u?

    ☐ Ik weet dit niet vanbuiten, ik zoek dit op

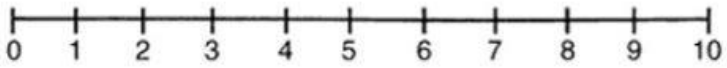
.....

.....

.

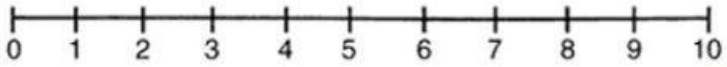
53. Hoe effectief vindt u APNO zalf op een schaal van 0 tot 10 waarbij 0= helemaal niet effectief en 10=zeer effectief?

    ☐Ik weet dit niet



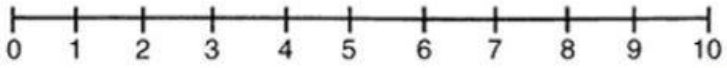
0= helemaal niet effectief **10=zeer effectief**

54. Hoe veilig vindt u APNO zalf op een schaal van 0 tot 10 waarbij 0= helemaal niet veilig en 10=zeer veilig ?
    ☐Ik weet dit niet



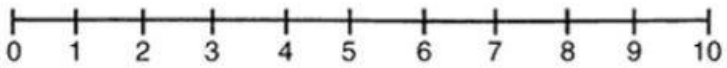
0= helemaal niet veilig **10=zeer veilig**

55. Hoe geschikt vindt u APNO zalf op een schaal van 0 tot 10 waarbij 0= helemaal niet geschikt en 10=zeer geschikt ?
    ☐Ik weet dit niet



0= helemaal niet geschikt **10=zeer geschikt**

56. In welke mate beïnvloedt de prijscategorie van APNO zalf uw beslissing om dit geneesmiddel al dan niet voor te schrijven of te adviseren?
    ☐Ik weet dit niet



0= De prijs beïnvloedt mijn voorschrijf-/adviseergedrag helemaal niet **10=De prijs beïnvloedt mijn voorschrijf-/adviseergedrag aanzienelijk veel**

FLUCONAZOLE (Diflucan® siroop susp) systemische therapie voor de zuigeling

57. Voor hoeveel unieke zuigelingen heeft u de afgelopen maand **fluconazole (Diflucan® siroop susp)** orale therapie voorgeschreven of geadviseerd ter behandeling van spruw?
    ☐ 0
    ☐ 1 – 4
    ☐ 5 – 9
    ☐ 10 of meer

58. Wat is de startdosis en wat is de maximale dosis van **fluconazole (Diflucan® siroop susp) voor de zuigeling**?

Startdosering: ☐ .....

☐ Ik ken dit niet van buiten, ik zoek dit op*

Max. dagdosis: ☐ .....

☐ Ik ken dit niet van buiten, ik zoek dit op*

*welke bronnen gebruikt u om dit op te zoeken?

☐ BCFI

☐ Commentaren Medicatiebewaking

☐ Apotheek.nl

☐ Farmacotherapeutisch kompas

☐ Wetenschappelijke studies/reviews

☐ Kinderformularium

☐ Wetenschappelijke bijsluiter

☐ Andere: .....

59. Welke gebruiksinstructies geeft u mee wanneer u **fluconazole (Diflucan® siroop susp.)** ter behandeling van een orale spruwinfectie bij de zuigeling voorschrijft of adviseert?

.....

.....

60. Welke bijwerkingen van **fluconazole (Diflucan® siroop susp.)** kent u?

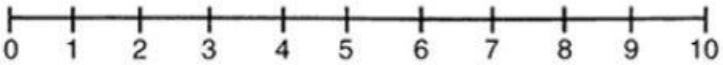
☐ Ik weet dit niet vanbuiten, ik zoek dit op

.....

.....

61. Hoe effectief vindt u **fluconazole (Diflucan® siroop susp.)** op een schaal van 0 tot 10 waarbij 0= helemaal niet effectief en 10=zeer effectief?

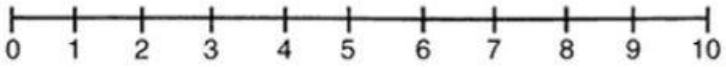
☐Ik weet dit niet



0= helemaal niet effectief **10=zeer effectief**

62. Hoe veilig vindt u **fluconazole (Diflucan® siroop susp.)** op een schaal van 0 tot 10 waarbij 0= helemaal niet veilig en 10=zeer veilig ?

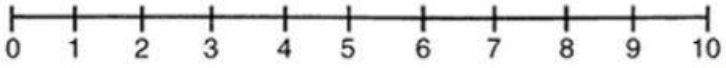
☐Ik weet dit niet



0= helemaal niet veilig **10=zeer veilig**

63. Hoe geschikt vindt u **fluconazole (Diflucan® siroop susp.)** op een schaal van 0 tot 10 waarbij 0= helemaal niet geschikt en 10=zeer geschikt ?

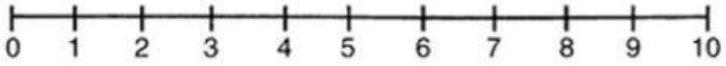
☐Ik weet dit niet



0= helemaal niet geschikt **10=zeer geschikt**

64. In welke mate beïnvloedt de prijscategorie van **fluconazole (Diflucan® siroop susp.)** uw beslissing om dit geneesmiddel al dan niet voor te schrijven of te adviseren?

☐Ik weet dit niet



0= De prijs beïnvloedt mijn voorschrijf-/adviseer gedrag helemaal niet **10=De prijs beïnvloedt mijn voorschrijf -/adviseergedrag aanzienelijk veel**

FLUCONAZOLE systemische therapie voor de moeder

65. Voor hoeveel unieke moeders die borstvoeding geven heeft u de afgelopen maand **fluconazole** orale therapie voorgeschreven of geadviseerd ter behandeling van spruw?

☐ 0

☐ 1 – 4

☐ 5 – 9

☐ 10 of meer

66. Wat is de startdosis en wat is de maximale dosis van **Fluconazole voor de moeder**?

Startdosering: ☐ .....

☐ Ik ken dit niet van buiten, ik zoek dit op*

Max. dagdosis: ☐ .....

☐ Ik ken dit niet van buiten, ik zoek dit op*

*welke bronnen gebruikt u om dit op te zoeken?

☐ BCFI

☐ Commentaren Medicatiebewaking

☐ Apotheek.nl

☐ Farmacotherapeutisch kompas

☐ Wetenschappelijke studies/reviews

☐ Kinderformularium

☐ Wetenschappelijke bijsluiter

☐ Andere: .....

67. Welke gebruiksinstructies geeft u mee wanneer u **fluconazole** ter behandeling van een spruwinfectie bij de moeder voorschrijft of adviseert?

.....

.....

68. Welke bijwerkingen van **fluconazole** kent u?

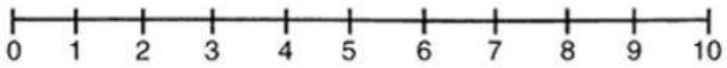
☐Ik weet dit niet vanbuiten, ik zoek dit op

.....

.....

69. Hoe effectief vindt u **fluconazole (oraal voor de moeder)** op een schaal van 0 tot 10 waarbij 0= helemaal niet effectief en 10=zeer effectief?

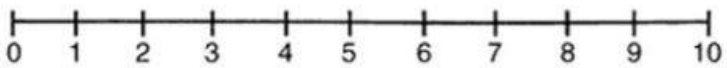
☐Ik weet dit niet



0= helemaal niet effectief **10=zeer effectief**

70. Hoe veilig vindt u **fluconazole (oraal voor de moeder)** op een schaal van 0 tot 10 waarbij 0= helemaal niet veilig en 10=zeer veilig ?

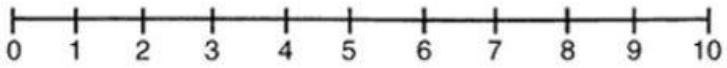
☐Ik weet dit niet



0= helemaal niet veilig **10=zeer veilig**

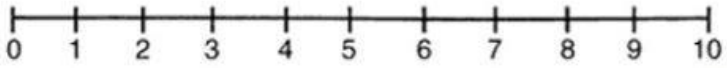
71. Hoe geschikt vindt u **fluconazole (oraal voor de moeder)** op een schaal van 0 tot 10 waarbij 0= helemaal niet geschikt en 10=zeer geschikt ?

☐Ik weet dit niet



0= helemaal niet geschikt **10=zeer geschikt**

72. In welke mate beïnvloedt de prijscategorie van **fluconazole (oraal voor de moeder)** uw beslissing om dit geneesmiddel al dan niet voor te schrijven of te adviseren?
☐Ik weet dit niet



0= De prijs beïnvloedt mijn voorschrijf-/adviseergedrag helemaal niet **10=De prijs beïnvloedt mijn voorschrijf-/adviseergedrag aanzienelijk veel**

73. Op welke andere geneesmiddelen in de medicatiehistoriek van de patiënt bent u aandachtig bij het voorschrijven van antimycotica ? Waarom?

☐ Ik let hier niet op

.....

.....

74. Wat weet u over resistentie aan azole-antimycotica?

.....

.....

Algemeen

75. Over welke van onderstaande therapieën werd u **ooit** bevraagd door ouders waarvan de zuigeling een orale spruwinfectie heeft/had tijdens de borstvoedingsperiode?

☐ gentiaan violet
☐ topische applicatie van azijn
☐ verwijderen van 'processed sugars' uit het dieet
☐ topische applicatie van (kokos)olie
☐ topische applicatie van grape seed oil of orale inname ervan
☐ miconazole of clotrimazole geëmulsifieerd in suppositoria die toegediend werden aan de zuigeling via een fopspeen
☐ Andere.....

76. Adviseert u soms nog andere middelen dan bovenvernoemde geneesmiddelen voor bij de behandeling van spruw bij zuigelingen?
    ☐ Nee
    ☐ Ja, welke?
        ☐ itraconazole
        ☐ voriconazole
        ☐ Amfotericine B
        ☐ Clotrimazole
        ☐ Andere: .....

77. Heeft u al gehoord van miconazole of clotrimazole geëmulsifieerd in suppositoria die toegediend werden aan de zuigeling via een fopspeen?
    ☐ Ja ☐ Nee

78. In het <u>afgelopen jaar</u>, in hoeveel gevallen vermoedde u resistentie aan azole-antimycotica bij de behandeling van een spruwinfectie tijdens de borstvoedingsperiode?
    (indien u geen exact aantal kan geven, mag u een schatting maken)

    In ..... gevallen vermoedde ik een resistentie aan azole-antimycotica.

☐ Ik herinner dit mij niet

79. In hoeveel van bovenstaande gevallen heeft u dit bevestigd via een laboratotiumtest / doorverwijzing naar laboratoriumtest ?
    (indien u geen exact aantal kan geven, mag u een schatting maken)

    In ..... gevallen vroeg ik een laboratoriumtest aan bij vermoeden van resistentie.

☐ Ik herinner dit mij niet

80. Indien u niet in alle gevallen van vermoeden van een azole-resistentie een laboratoriumtest aanvroeg ter bevestiging of doorverwees, waarom niet en wat was uw behandelplan voor de verdere aanpak van de spruwinfectie?

Ik vroeg geen laboratoriumtest aan / verwees niet door omdat

.....

.....

☐ Ik weet dit niet, ik moet dit opzoeken

Ik pakte de spruwinfectie verder aan op volgende manier:

.....

.....

☐ Ik weet dit niet, ik moet dit opzoeken

Bedankt voor uw deelname aan deze vragenlijst

☐ Ik wens de resultaten van de studie doorgestuurd te krijgen via volgend e-mailadres: .....

8.2. Questionnaire for pharmacists

Beste apotheker(es)/farmaceutisch-technisch assistent(e),

Spruw is een infectie, veroorzaakt door candida albicans. De symptomen bij zuigelingen komen voor ter hoogte van de mond en de symptomen bij moeders die borstvoeding geven komen voor ter hoogte van het borstweefsel. Spruwinfecties worden meestal behandeld met antimycotica. In het kader van mijn masterthesis onderzoek ik de afleveringsprocedure van verschillende antimycotica ter behandeling van spruw. Ook de gebruikte magistrale formules worden geëvalueerd. Tenslotte evalueren we ook de gepercipieerde effectiviteit van de verschillend behandelingen.

Het invullen van de enquête duurt slechts 10-15 minuten. Alle antwoorden zullen anoniem (hierbij is er totaal geen terugkoppeling meer mogelijk naar uw persoonlijk dossier) verwerkt worden en enkel gebruikt worden in het kader van dit onderzoek. Graag verduidelijken we dat het geenszins de bedoeling is een oordeel te vellen, maar een idee te krijgen van de noden om later onderzoek hierop af te stemmen.

Let op: u heeft toegang nodig tot uw afleversoftware om de enquête te vervolledigen

Bij vragen of opmerkingen kan u steeds mailen naar AnneFlorence.Moerman@Ugent.be.

Alvast hartelijk bedankt voor uw medewerking!

Anne-Florence Moerman
1ste masterstudente farmaceutische zorg (Universiteit Gent)

Onder begeleiding van
Prof. Dr. Apr. Eline Tommelein

"Ik verklaar mij akkoord dat ik er mij bewust van ben dat deze vragenlijst volledig vrijwillig is, steeds kan onderbroken worden, en dat alle gegevens anoniem zullen verwerkt worden."

☐Ik ga akkoord en ga verder met de vragenlijst

Deze studie werd goedgekeurd door een onafhankelijke Commissie voor Medische Ethiek verbonden aan het UZ Gent, en zal worden uitgevoerd volgens de richtlijnen voor de goede klinische praktijk (ICH/GCP) en de verklaring van Helsinki opgesteld ter bescherming van mensen deelnemend aan klinische studies. In overeenstemming met de Belgische wet van 8 december 1992 en de Belgische wet van 22 augustus 2002, zal uw persoonlijke levenssfeer worden gerespecteerd. De experimentenwet van 7/05/2004 verplicht ons om deelnemers aan wetenschappelijke projecten te verzekeren voor de deelname en het risico (hoe klein ook) dat men loopt. De waarschijnlijkheid dat u door deelname aan deze studie enige schade ondervindt, is extreem laag. Indien dit toch zou voorkomen, wat echter zeer zeldzaam is, werd een verzekering afgesloten conform de Belgische wet van 7 mei 2004, die deze mogelijkheid dekt.

Demographische gegevens

1. Wat is uw geslacht? ☐ Man ☐ Vrouw ☐Ander, specifieer:.....
2. Hoe oud bent u? .....
3. Heeft u kinderen? ☐ Ja ☐ Nee

   Indien ja: heeft (één van) uw kind(eren) een antimycoticum ter behandeling van een spruwinfectie gekregen tijdens de borstvoedingsperiode ? ☐Ja ☐ Nee ☐ Ik herinner mij dit niet
4. Aantal jaren ervaring in de officina-apotheek: .....
5. Postcode apotheek: .....
6. Aantal full-time equivalenten in de apotheek waar u werkzaam bent:

..... Apothekers

..... Farmaceutisch-Technisch Assistenten

7. Uw functie:

☐ Apotheektitularis ☐ Apotheker-vervanger*

☐ Adjunct-apotheker ☐ FTA

☐ Stagiair

*Neem enkel de apotheek in beschouwing waar u op dit moment werkzaam bent.

8. Gemiddeld aantal patiënten per dag in de apotheek waar u werkt:

...../dag ☐Dit varieert sterk

Afleveringsprotocol

9. Welke klachten bij <u>de zuigeling</u> wijzigen volgens u op de aanwezigheid van een orale spruwinfectie tijdens de borstvoedingsperiode?

.....

.....

.....

10. Welke klachten bij de moeder wijzigen volgens u op de aanwezigheid van een spruwinfectie tijdens de borstvoedingsperiode?

.....

.....

.....

11. Welke andere zaken bevraagt u ter verificatie van het vermoeden van een orale spruwinfectie tijdens de borstvoedingsperiode?

.....

.....

.....

.....

☐ Ik bevraag niets extra

12. Verwijst u bij vermoeden van een orale spruwinfectie tijdens de borstvoedingsperiode altijd de patiënt door naar een arts?

    ☐ Ja

    ☐ Nee

    Indien nee, wat zijn de doorverwijsciteria die u hanteert?

.....

.....

13. Welk niet-medicamenteus advies geeft u mee aan ouders van een zuigeling en/of de moeder met een spruwinfectie tijdens de borstvoedingsperiode wanneer u van mening bent dat deze **in zelfzorg** kan behandeld worden?

.....

.....

.....

.....

.....

14. Welk niet-medicamenteus advies geeft u, **complementair aan de aflevering van voorgeschreven medicatie door een arts of vroedvrouw**, mee aan ouders van een zuigeling en/of de moeder met een spruwinfectie tijdens de borstvoedingsperiode?

.....

.....

.....

.....

.....

15. Op welke richtlijnen baseert u zich voor de aanpak van spruwinfecties tijdens de borstvoedingsperiode in de officina-apotheek?

.....

.....

.....

16. Vindt u dat u beschikt over voldoende richtlijnen om adequate informatie mee te geven aan de ouders over gebruik van **antimycotica** bij zuigelingen? ☐ Ja ☐ Nee

    Indien ja, welke richtlijnen?

.....

.....

.....

Medicatie

NYSTATINE voor behandeling van de mond van de zuigeling

17. Voor hoeveel unieke zuigelingen heeft u de afgelopen **drie** maanden **nystatine (orale suspensie)** afgeleverd ter behandeling van spruw bij zuigelingen? (u kan dit opzoeken in uw afleveringssoftware)

    .....zuigelingen

18. Wat is de dosering van **nystatine ter behandeling van de mond van de zuigeling**?

    dosering: ☐ .....

    ☐ Ik ken dit niet van buiten, ik zoek dit op*

*welke bronnen gebruikt u om dit op te zoeken?

☐ BCFI

☐ Commentaren Medicatiebewaking

☐ Apotheek.nl

☐ Farmacotherapeutisch kompas

☐ Wetenschappelijke studies/reviews

☐ Kinderformularium

☐ Wetenschappelijke bijsluiter

☐ Andere: .....

19. Welke gebruiksinstructies geeft u mee aan de ouders wanneer u **nystatine (orale suspensie)** voor de behandeling van orale spruwinfecties bij zuigelingen tijdens de borstvoedingsperiode aflevert?

.....

.....

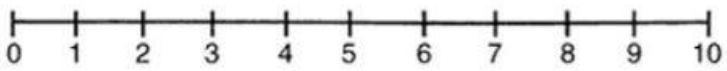
20. Welke bijwerkingen van **nystatine (orale suspensie)** kent u?

☐Ik weet dit niet vanbuiten, ik zoek dit op

.....

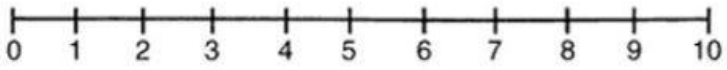
.....

21. Hoe <u>effectief</u> vindt u nystatine (orale suspensie) op een schaal van 0 tot 10 waarbij 0= helemaal niet effectief en 10=zeer effectief ?
☐Ik weet dit niet



0= helemaal niet effectief **10=zeer effectief**

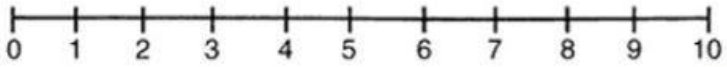
22. Hoe <u>veilig</u> vindt u nystatine (orale suspensie) op een schaal van 0 tot 10 waarbij 0= helemaal niet veilig en 10=zeer veilig ?
☐Ik weet dit niet



0= helemaal niet veilig **10=zeer veilig**

23. Hoe geschikt vindt u nystatine(orale suspensie) op een schaal van 0 tot 10 waarbij 0= helemaal niet geschikt en 10=zeer geschikt ?

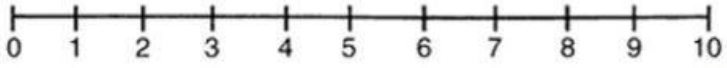
☐Ik weet dit niet



0= helemaal niet geschikt **10=zeer geschikt**

24. Hoe verantwoord vindt u de prijs van nystatine (orale suspensie) in het kader van antimycotica ter behandeling van spruw op een schaal van 0 tot 10 waarbij 0= helemaal niet verantwoord en 10=zeer verantwoord?

☐Ik weet dit niet



0= helemaal niet verantwoord **10=zeer verantwoord**

MICONAZOLE ORALE GEL (DAKTARIN ®)

25. Voor hoeveel unieke zuigelingen heeft u de afgelopen drie maanden **miconazole orale gel (Daktarin®)** afgeleverd ter behandeling van spruw? (u kan dit opzoeken in uw afleveringssoftware).

..... zuigelingen

Hoeveel van deze zuigelingen waren jonger dan vier maanden oud?

..... zuigelingen waren jonger dan vier maanden oud

Hoeveel van deze zuigelingen waren tussen vier en zes maanden oud ?

..... zuigelingen waren tussen vier en zes maanden oud

81. Miconazole orale gel (Daktarin®) is sinds 2008 vergund voor gebruik in kinderen vanaf vier maanden. De vergunning werd aangepast wegens een risico op verstikking. Volgens de BAPCOC richtlijnen is miconazole orale gel (Daktarin®) gecontra-indiceerd bij kinderen jonger dan zes maanden omwille van dezelfde reden. Wat vindt u van deze richtlijn?

.....

.....

26. Wat is de dosering van **miconazole orale gel (Daktarin®) ter behandeling van de mond van de zuigeling**?

dosering: ☐ .....

☐ Ik ken dit niet van buiten, ik zoek dit op*

*welke bronnen gebruikt u om dit op te zoeken?

☐ BCFI

☐ Commentaren Medicatiebewaking

☐ Apotheek.nl

☐ Farmacotherapeutisch kompas

☐ Wetenschappelijke studies/reviews

☐ Kinderformularium

☐ Wetenschappelijke bijsluiter

☐ Andere: .....

27. Welke gebruiksinstructies geeft u mee aan de ouders wanneer u **miconazole orale gel (Daktarin®)** voor de behandeling van orale spruwinfecties bij zuigelingen tijdens de borstvoedingsperiode aflevert?

.....

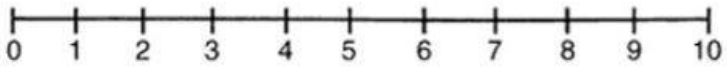
.....

28. Welke bijwerkingen van **miconazole orale gel (Daktarin®)** kent u?
☐Ik weet dit niet vanbuiten, ik zoek dit op

.....

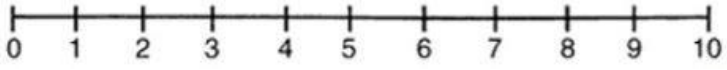
.....

29. Hoe <u>effectief</u> vindt u miconazole orale gel (Daktarin®) op een schaal van 0 tot 10 waarbij 0= helemaal niet effectief en 10=zeer effectief?
☐Ik weet dit niet



0= helemaal niet effectief **10=zeer effectief**

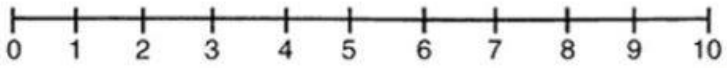
30. Hoe <u>veilig</u> vindt u miconazole orale gel (Daktarin® op een schaal van 0 tot 10 waarbij 0= helemaal niet veilig en 10=zeer veilig ?
☐Ik weet dit niet



0= helemaal niet veilig **10=zeer veilig**

31. Hoe geschikt vindt u miconazole orale gel (Daktarin®) op een schaal van 0 tot 10 waarbij 0= helemaal niet geschikt en 10=zeer geschikt ?

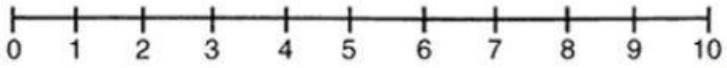
☐Ik weet dit niet



0= helemaal niet geschikt **10=zeer geschikt**

32. Hoe verantwoord vindt u de prijs van miconazole orale gel (Daktarin®) in het kader van antimycotica ter behandeling van spruw op een schaal van 0 tot 10 waarbij 0= helemaal niet verantwoord en 10=zeer verantwoord?

☐Ik weet dit niet



0= helemaal niet verantwoord **10=zeer verantwoord**

MICONAZOLE CRÈME (Daktarin®)

33. Voor hoeveel unieke moeders die borstvoeding geven heeft u de afgelopen drie maanden **miconazole crème (Daktarin®)** afgeleverd ter behandeling van spruw tijdens de borstvoedingsperiode? (u kan dit opzoeken in uw afleveringssoftware)

..... moeders

34. Wat is de dosering van **miconazole crème (Daktarin®) ter behandeling van de tepel en/of borst van de moeder**?

Dosering : ☐ .....

☐ Ik ken dit niet van buiten, ik zoek dit op*

*welke bron(nen) gebruikt u om dit op te zoeken?

☐ BCFI

☐ Commentaren Medicatiebewaking

☐ Apotheek.nl

☐ Farmacotherapeutisch kompas

☐ Wetenschappelijke studies/reviews

☐ Kinderformularium

☐ Wetenschappelijke bijsluiter

☐ Andere: .....

35. Welke gebruiksinstructies geeft u mee wanneer u **miconazole crème ter behandeling van de tepel en/of borst van de moeder** aflevert?

.....

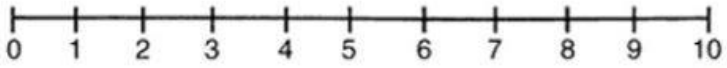
.....

36. Welke bijwerkingen van **miconazole crème** kent u?
☐Ik weet dit niet vanbuiten, ik zoek dit op

.....

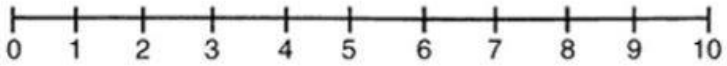
.....

37. Hoe <u>effectief</u> vindt u miconazole crème (Daktarin®) op een schaal van 0 tot 10 waarbij 0= helemaal niet effectief en 10=zeer effectief?
☐Ik weet dit niet



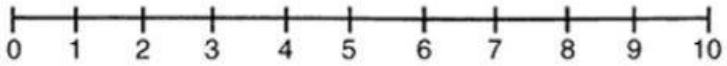
0= helemaal niet effectief **10=zeer effectief**

38. Hoe <u>veilig</u> vindt u miconazole crème (Daktarin® op een schaal van 0 tot 10 waarbij 0= helemaal niet veilig en 10=zeer veilig ?
☐Ik weet dit niet



0= helemaal niet veilig **10=zeer veilig**

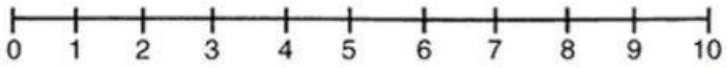
39. Hoe <u>geschikt</u> vindt u miconazole crème (Daktarin®) op een schaal van 0 tot 10 waarbij 0= helemaal niet geschikt en 10=zeer geschikt ?
☐Ik weet dit niet



0= helemaal niet geschikt **10=zeer geschikt**

40. Hoe verantwoord vindt u <u>de prijs</u> van miconazole crème (Daktarin®) in het kader van antimycotica ter behandeling van spruw op een schaal van 0 tot 10 waarbij 0= helemaal niet verantwoord en 10=zeer verantwoord?

☐Ik weet dit niet



0= helemaal niet verantwoord **10=zeer verantwoord**

ALL PURPOSE NIPPLE OINTMENT (APNO CRÉME)

De all purpose nipple ointment is een magistrale bereiding die bestaat uit een zalfbasis (lanoline/vaseline) met

- *2% mupirocine (antibioticum)*
- *0,1% bètamethasone (corticosteroïd)*
- *2% miconazole poeder (antimycoticum)*

41. Voor hoeveel unieke <u>moeders</u> die borstvoeding geven heeft u de afgelopen drie maanden **all purpose nipple ointment (APNO zalf)** afgeleverd ter behandeling van spruw? (u kan dit opzoeken in uw afleveringssoftware)

..... moeders

42. Wat is de dosering van **all purpose nipple ointment (APNO zalf) ter behandeling van de tepel en/of borst van de moeder**?

dosering: ☐ .....

☐ Ik ken dit niet van buiten, ik zoek dit op*

*welke bronnen gebruikt u om dit op te zoeken?

☐ BCFI

☐ Commentaren Medicatiebewaking

☐ Apotheek.nl

☐ Farmacotherapeutisch kompas

☐ Wetenschappelijke studies/reviews

☐ Kinderformularium

☐ Wetenschappelijke bijsluiter

☐ Andere: .....

43. Welke gebruiksinstructies geeft u mee wanneer u **APNO zalf** ter behandeling van een spruwinfectie bij de moeder aflevert?

.....

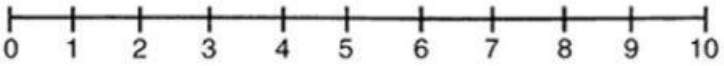
.....

44. Welke bijwerkingen van **APNO zalf** kent u?
☐ Ik weet dit niet vanbuiten, ik zoek dit op

.....

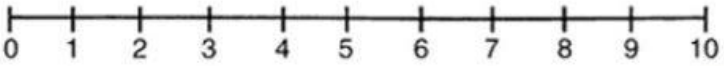
.....

45. Hoe <u>effectief</u> vindt u APNO zalf op een schaal van 0 tot 10 waarbij 0= helemaal niet effectief en 10=zeer effectief?
☐Ik weet dit niet



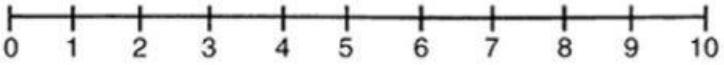
0= helemaal niet effectief **10=zeer effectief**

46. Hoe <u>veilig</u> vindt u APNO zalf op een schaal van 0 tot 10 waarbij 0= helemaal niet veilig en 10=zeer veilig ?
☐Ik weet dit niet



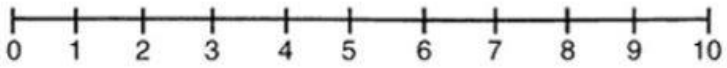
0= helemaal niet veilig **10=zeer veilig**

47. Hoe <u>geschikt</u> vindt u APNO zalf op een schaal van 0 tot 10 waarbij 0= helemaal niet geschikt en 10=zeer geschikt ?
☐Ik weet dit niet



0= helemaal niet geschikt **10=zeer geschikt**

48. Hoe verantwoord vindt u <u>de prijs</u> van APNO zalf in het kader van antimycotica ter behandeling van spruw op een schaal van 0 tot 10 waarbij 0= helemaal niet verantwoord en 10=zeer verantwoord?
☐Ik weet dit niet



0= helemaal niet verantwoord **10=zeer verantwoord**

FLUCONAZOLE oraal voor de zuigeling

49. Voor hoeveel unieke zuigelingen heeft u de afgelopen drie maanden **fluconazole (Diflucan® siroop susp.)** orale therapie afgeleverd ter behandeling van spruw tijdens de borstvoedingsperiode? (u kan dit opzoeken in uw afleveringssoftware)

    ..... zuigelingen

50. Wat is de startdosis en wat is de maximale dosis van **fluconazole (Diflucan® siroop susp) voor de zuigeling**?

    Startdosering: ☐ .....
    ☐ Ik ken dit niet van buiten, ik zoek dit op*
    Max. dagdosis: ☐ .....
    ☐ Ik ken dit niet van buiten, ik zoek dit op*

    *welke bronnen gebruikt u om dit op te zoeken?

☐ BCFI

☐ Commentaren Medicatiebewaking

☐ Apotheek.nl

☐ Farmacotherapeutisch kompas

☐ Wetenschappelijke studies/reviews

☐ Kinderformularium

☐ Wetenschappelijke bijsluiter

☐ Andere: .....

51. Welke gebruiksinstructies geeft u mee wanneer u **fluconazole (Diflucan® siroop susp.)** ter behandeling van een orale spruwinfectie bij de zuigeling aflevert?

.....

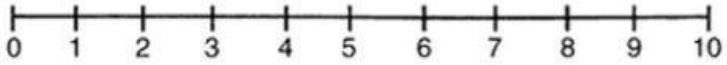
.....

52. Welke bijwerkingen van **fluconazole (Diflucan® siroop susp.)** kent u?
☐ Ik weet dit niet vanbuiten, ik zoek dit op

.....

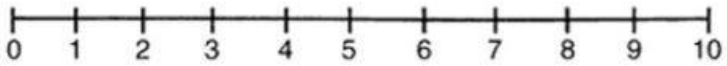
.....

53. Hoe <u>effectief</u> vindt u **fluconazole (Diflucan® siroop susp.)** op een schaal van 0 tot 10 waarbij 0= helemaal niet effectief en 10=zeer effectief?
☐Ik weet dit niet



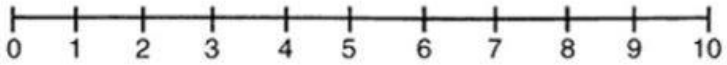
0= helemaal niet effectief **10=zeer effectief**

54. Hoe <u>veilig</u> vindt u **fluconazole (Diflucan® siroop susp.)** op een schaal van 0 tot 10 waarbij 0= helemaal niet veilig en 10=zeer veilig ?
☐Ik weet dit niet



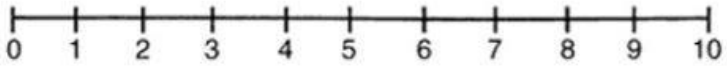
0= helemaal niet veilig **10=zeer veilig**

55. Hoe <u>geschikt</u> vindt u **fluconazole (Diflucan® siroop susp.)** op een schaal van 0 tot 10 waarbij 0= helemaal niet geschikt en 10=zeer geschikt ?
☐Ik weet dit niet



0= helemaal niet geschikt **10=zeer geschikt**

56. Hoe verantwoord vindt u <u>de prijs</u> van **fluconazole (Diflucan® siroop susp.)** in het kader van antimycotica ter behandeling van spruw op een schaal van 0 tot 10 waarbij 0= helemaal niet verantwoord en 10=zeer verantwoord?
☐Ik weet dit niet



0= helemaal niet verantwoord **10=zeer verantwoord**

FLUCONAZOLE oraal voor de moeder

57. Voor hoeveel unieke moeders die borstvoeding geven heeft u de afgelopen drie maanden **fluconazole** orale therapie afgeleverd ter behandeling van spruw tijdens de borstvoedingsperiode? ? (u kan dit opzoeken in uw afleveringssoftware)

    ..... moeders

58. Wat is de startdosis en wat is de maximale dosis van **Fluconazole voor de moeder**?
    Startdosering: ☐ .....
    ☐ Ik ken dit niet van buiten, ik zoek dit op*
    Max. dagdosis: ☐ .....
    ☐ Ik ken dit niet van buiten, ik zoek dit op*

    *welke bronnen gebruikt u om dit op te zoeken?

☐ BCFI

☐ Commentaren Medicatiebewaking

☐ Apotheek.nl

☐ Farmacotherapeutisch kompas

☐ Wetenschappelijke studies/reviews

☐ Kinderformularium

☐ Wetenschappelijke bijsluiter

☐ Andere: .....

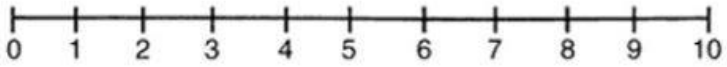
59. Welke gebruiksinstructies geeft u mee wanneer u **fluconazole** ter behandeling van een spruwinfectie bij de moeder aflevert?

.....
.....

60. Welke bijwerkingen van **fluconazole** kent u?
    ☐Ik weet dit niet vanbuiten, ik zoek dit op

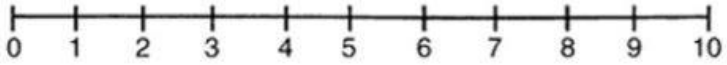
.....
.....

61. Hoe effectief vindt u **fluconazole (oraal voor de moeder)** op een schaal van 0 tot 10 waarbij 0= helemaal niet effectief en 10=zeer effectief?
☐Ik weet dit niet



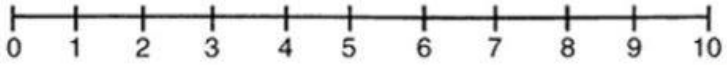
0= helemaal niet effectief **10=zeer effectief**

62. Hoe veilig vindt u **fluconazole (oraal voor de moeder)** op een schaal van 0 tot 10 waarbij 0= helemaal niet veilig en 10=zeer veilig ?
☐Ik weet dit niet



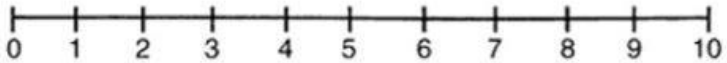
0= helemaal niet veilig **10=zeer veilig**

63. Hoe geschikt vindt u **fluconazole (oraal voor de moeder)** op een schaal van 0 tot 10 waarbij 0= helemaal niet geschikt en 10=zeer geschikt ?
☐Ik weet dit niet



0= helemaal niet geschikt **10=zeer geschikt**

64. Hoe verantwoord vindt u de prijs van **fluconazole (oraal voor de moeder)** in het kader van antimycotica ter behandeling van spruw op een schaal van 0 tot 10 waarbij 0= helemaal niet verantwoord en 10=zeer verantwoord?
☐Ik weet dit niet



0= helemaal niet verantwoord **10=zeer verantwoord**

65. Op welke andere geneesmiddelen in de medicatiehistoriek van de patiënt bent u aandachtig bij het afleveren van antimycotica ? Waarom?

☐ Ik let hier niet op

.....

.....

66. Wat weet u over resistentie aan azole-antimycotica?

.....

.....

.....

.....

Alternatieve therapieën

67. Hebt u in het **afgelopen jaar** andere producten of geneesmiddelen afgeleverd ter behandeling van spruw tijdens de borstvoedingsperiode?

☐ Ja ☐ Nee

Indien ja, welke ?

.....

.....

68. Over welke van onderstaande therapieën werd u **ooit** bevraagd door ouders waarvan de zuigeling een orale spruwinfectie heeft/had tijdens de borstvoedingsperiode?

☐ gentiaan violet
☐ topische applicatie van azijn
☐ verwijderen van 'processed sugars' uit het dieet
☐ topische applicatie van (kokos)olie
☐ topische applicatie van grape seed oil of orale inname ervan
☐ miconazole of clotrimazole geëmulsifieerd in suppositoria die toegediend werden aan de zuigeling via een fopspeen
☐ Andere.....

69. Welk van bovenstaande alternatieve therpiën heeft u effectief afgeleverd ?

.....

.....

.....

☐ Ik heb geen enkele alternatieve therapie afgeleverd (ga naar einde enquête)

70. Indien u een alternatieve therapie afleverde, welk **advies** gaf u over de werking, gebruiksinstructies en bijwerkingen van de therapie?

Therapie:.....

Werking:

.....

.....

.....

Gebruiksinstructies:

.....

.....

.....

Bijwerkingen:

.....

.....

.....

Welke feedback kreeg u over deze therapie?

☐ Ik kreeg geen feedback over deze therapie

☐ De ouders ervaarden deze therapie als effectief

☐ De ouders ervaarden deze therapie NIET als effectief

☐ Andere:

.....

71. Indien u nog een andere therapie afleverde, welk advies gaf u over de werking, gebruiksinstructies en bijwerkingen van de therapie?

☐ Ik leverder geen andere therapie af

Therapie:.....

Werking:

.....

.....

Gebruiksinstructies:

.....

.....

Bijwerkingen:

.....

.....

Welke feedback kreeg u over deze therapie?

☐ Ik kreeg geen feedback over deze therapie

☐ De ouders ervaarden deze therapie als effectief

☐ De ouders ervaarden deze therapie NIET als effectief

☐ Andere:

.....

Bedankt voor uw deelname aan deze vragenlijst

☐ Ik wens de resultaten van de studie doorgestuurd te krijgen via volgend e-mailadres:

.....

8.3. Questionnaire for parents

Beste ouder,

Wetenschappelijk onderzoek hecht vandaag de dag meer en meer belang aan verwachtingen en bevindingen van patiënten. Wanneer de patiënt een kind of een zuigeling is, zijn het de primaire zorgverleners –meestal de ouders- die de belangrijkste rol spelen in de patiëntenervaringen. In het kader van mijn masterthesis onderzoek ik de ervaring en de kennis van ouders die medicatie tegen een spruwinfectie gebruik(t)en bij de behandeling van een spruwinfectie tijdens de borstvoedingsperiode. Het invullen neemt ongeveer 10 à 15 minuten in beslag.

De resultaten geven ons zeer waardevolle informatie en helpen zorgverleners om u en andere ouders in de toekomst de gewenste en noodzakelijke informatie te geven. Deze enquête is voornamelijk gericht op de moeders van zuigelingen die een spruwinfectie doormaken of doormaakten.

Alle antwoorden zullen anoniem verwerkt worden en enkel gebruikt worden in het kader van dit onderzoek. Hierbij is er dus geen terugkoppeling meer mogelijk naar uw persoonlijke gegevens. Bij vragen of opmerkingen kan u steeds mailen naar AnneFlorence.Moerman@Ugent.be

Alvast hartelijk bedankt voor uw medewerking.

Anne-Florence Moerman
1ste masterstudent farmaceutische zorg (Universiteit Gent)

Onder begeleiding van
Prof. Dr. Apr. Eline Tommelein

☐ "Ik verklaar mij akkoord dat deze vragenlijst volledig vrijwillig is, dat steeds kan onderbroken worden, en dat alle gegevens anoniem zullen verwerkt worden.
☐Ik ben meerderjarig
☐Mijn kind kreeg maximaal twee jaar geleden medicatie voor een spruwinfectie tijdens de borstvoedingsperiode

Deze studie werd goedgekeurd door de onafhankelijke Commissie voor Medische Ethiek. Deze studie wordt uitgevoerd volgens de richtlijnen voor de goede klinische praktijk (ICH/GCP) en de verklaring van Helsinki (versie 2013) opgesteld ter bescherming van mensen deelnemend aan klinische studies. In geen geval dient U de goedkeuring door de Commissie voor Medische Ethiek te beschouwen als een aanzet tot deelname aan deze studie. In overeenstemming met de Belgische wet van 8 december 1992 en de Belgische wet van 22 augustus 2002, zal uw persoonlijke levenssfeer worden gerespecteerd. U heeft het recht om een klacht in te dienen over hoe uw informatie wordt behandeld, bij de Belgische toezichthoudende instantie die verantwoordelijk is voor het handhaven van de wetgeving inzake gegevensbescherming: Gegevensbeschermingsautoriteit (GBA) Drukpersstraat 35,1000 Brussel Tel. +32 2 274 48 00 e-mail: contact(at)apd-gba.be Website: www.gegevensbeschermingsautoriteit.be. De experimentenwet van 7/05/2004 verplicht ons om deelnemers aan wetenschappelijke projecten te verzekeren voor de deelname en het risico (hoe klein ook) dat men loopt. De waarschijnlijkheid dat u door deelname aan deze studie enige schade ondervindt, is extreem laag. Indien dit toch zou voorkomen, wat echter zeer zeldzaam is, werd een verzekering afgesloten conform de Belgische wet van 7 mei 2004, die deze mogelijkheid dekt.

Demografische gegevens

1. Wat is uw geslacht? ☐ Man ☐ Vrouw ☐Ander, specifieer:.....
2. Hoe oud bent u? .....
3. Welke afkomst (etnische achtergrond) heeft u? (meerdere mogelijkheden)

   ☐ Kaukasisch (Blank) ☐ Noord-Afrikaans ☐ Overig Afrikaans ☐ Latijns-Amerikaans ☐ Aziatisch

   ☐ Andere: .....
4. Wat is de leeftijd van uw kind(eren)? (Indien u geen tweede, derde, vierde,... kind hebt, dan schrijft u een 0. Als uw kind jonger is dan 1 jaar, dan schrijft u 'x maanden'.)
   a. Oudste kind?.....
   b. Tweede kind? .....
   c. Derde kind? .....
   d. Vierde kind?.....
   e. Andere kinderen?.....
5. Wat is uw postcode? .....
6. Welke opleiding heeft u gevolgd of volgt u?

   ☐ Lager onderwijs

   ☐ Middelbaar onderwijs (evt. met 7e jaar)

   ☐ Hogeschool

   ☐ Universiteit

   ☐ Andere: .....
7. Welk beroep beoefent u? .....

Onderliggende pathologie

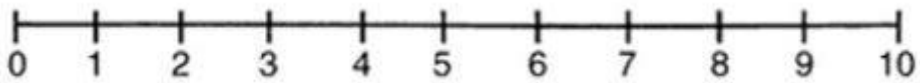
8. Welke symptomen waren aanwezig bij de zuigeling tijdens de spruwinfectie?

.....
.....
.....
.....
.....

9. Welke symptomen waren bij u aanwezig tijdens de spruwinfectie?

.....
.....
.....
.....
.....

10. Beoordeel de ernst van de pijn die u ervaarde op een schaal van 0 tot 10 waarbij 0= geen pijn en 10= ondraaglijke pijn.



0= geen pijn **10= ondraaglijke pijn**

11. Waar ervaarde u de pijn? Antwoord zo specifiek mogelijk.

.....
.....

12. Welke pijnsensatie ervaarde u? (brandend, stekend,…)

.....
.....

13. Heeft u zelf iets geprobeerd **vooraleer** u een zorgverlener raadpleegde?

☐ Ja ☐ Neen

Zo ja, wat probeerde u lokaal ter hoogte van de mond van de zuigeling of de tepel van de moeder ?

(meerdere mogelijkheden)

☐ ontsmetten van de tepel/mond met ontsmettende middelen, specifiek:.....
☐ Ik ondernam geen lokale acties
☐ gentiaan violet
☐ (kokos)olie aan de borst smeren
☐ Azijn aan de borst smeren

☐ aanbrengen van grapefruit seed oil

☐ Andere: .....

Zo ja, welke algemene acties ondernam u ? (meerdere mogelijkheden)

☐ Ik ondernam geen lokale acties

☐ verandering van positioneren van de baby tijdens de voeding

☐ uitstellen van voedingsmomenten

☐ probiotica innemen

☐ innemen van grapefruit seed oil

☐ geen verwerkte suikers meer eten

☐ Andere: .....

14. Indien u iets probeerde, ervaarde u deze acties al effectief?

☐ Ik probeerde niets

☐ ja

☐ nee

15. Waarom ervaarde u deze acties als wel/niet effectief?

.....

.....

16. Welke zorgverlener heeft u **eerst** geraadpleegd in het kader van de spruwinfectie?

☐ Vroedvrouw

☐ Vroedvrouw – lactatiekundige

☐ Lactatiekundige (niet-vroedvrouw)

☐ Huisarts

☐ Pediater

☐ Apotheker

☐ Andere: .....

17. Welke zorgverleners heeft u uiteindelijk gezien in het kader van de aandoening van uw kind?

(meerdere mogelijkheden)

☐ Vroedvrouw

☐ Vroedvrouw – lactatiekundige

☐ Lactatiekundige (niet-vroedvrouw)

☐ Huisarts

☐ Pediater

☐ Apotheker

☐ diëtist

☐ Andere: .....

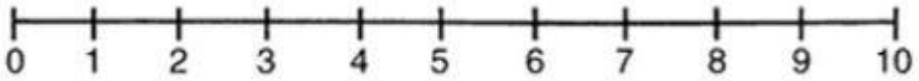
18. Welke onderzoeken werden er uitgevoerd bij u of uw kind? (meerdere mogelijkheden)

☐ Er werden geen onderzoeken uitgevoerd
☐ Er werd een orale inspectie gedaan bij mijn zuigeling
☐ Er werd een volledig lichaamsonderzoek van het kind gedaan
☐ Er werd een cultuur genomen van de mond van mijn kind
☐ Er werd een cultuur genomen van de luierzone van mijn kind
☐ Er werd een cultuur genomen van de borst van de moeder
☐ Er werd een vaginaal onderzoek bij de moeder gedaan
☐ Er werd een fysisch onderzoek van de borst(en) van de moeder gedaan
☐ Ik weet dit niet
☐ Andere: .....

19. Welk niet-medicamenteus advies kreeg u van de zorgverlener(s)?

.....
.....
.....
.....
.....

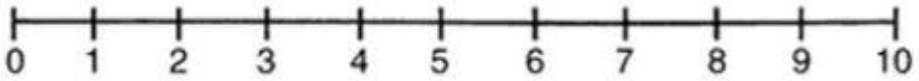
20. In welke mate was u tevreden over de <u>onderzoeken</u> die werden uitgevoerd door de zorgverleners?
0=helemaal niet tevreden
10= zeer tevreden



0= helemaal niet tevreden **10= zeer tevreden**

21. Waarom was u wel/niet tevreden over de onderzoeken?
.....

22. In welke mate was u tevreden over het <u>niet-medicamenteus</u> advies dat de zorgverlener u gaf?
0= helemaal niet tevreden 10= zeer tevreden



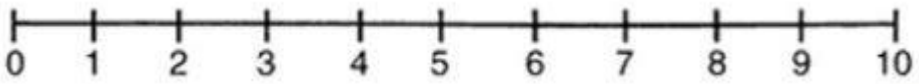
0= helemaal niet tevreden **10= zeer tevreden**

23. Waarom was u wel/niet tevreden over het niet-medicamenteus advies?

.....

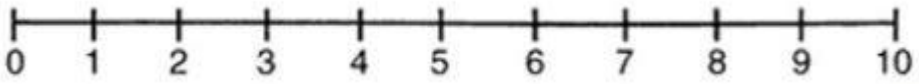
24. Wie of wat raadpleegde u nog in verband met de aandoening of behandeling van uw kind naast de persoon die het geneesmiddel opgestart heeft?
    - ☐ Ik raadpleegde niets/niemand anders
    - ☐ Familie
    - ☐ Vrienden/Vriendinnen
    - ☐ Online Fora of hulpgroepen
    - ☐ Live hulpgroepen
    - ☐ Websites
    - ☐ Andere: .....

25. Wie bepaalde de behandeling van de spruwinfectie van u en uw kind tijdens de borstvoedingsperiode?
    0= de zorgverlener bepaalde de behandeling volledig
    10= de ouders bepaalden de behandeling volledig



0= de zorgverlener **10= de ouders**

26. Wie bepaalt volgens u, in ideale omstandigheden, de behandeling van de spruwinfectie van u en uw kind tijdens de borstvoedingsperiode?
    0= de zorgverlener bepaalt de behandeling volledig
    10= de ouders bepalen de behandeling volledig



0= de zorgverlener **10= de ouders**

27. Zou u (nog) meer betrokken willen worden in het kiezen van de behandeling voor u en uw kind?
    ☐ Ja ☐ Neen
28. Op welke manier zou u nog meer betrokken willen worden?

    .....

    .....

29. Hebt u opmerkingen over hoe de begeleiding beter was kunnen verlopen?

    ☐ Ja ☐ Neen

    Zo ja, welke ?

.....

30. Heeft u een antibioticakuur ondergaan in de 2 weken voor de spruwinfectie?
☐ Ja ☐ Neen ☐ Ik herinner dit mij niet

31. Heeft uw kind een antibioticakuur ondergaan in de 2 weken voor de spruwinfectie?
☐ Ja ☐ Neen ☐ Ik herinner dit mij niet

32. Heeft uw kind een maagzuurremmer (vb. Acidcare®, Losec®, Omeprazol®,…) gebruikt in de maand voor de spruwinfectie?
☐ Ja ☐ Neen ☐ Ik herinner dit mij niet

Medicatie

Medicatie voor de zuigeling

NYSTATINE

33. Werd **nystatine orale suspensie** geadviseerd of voorgeschreven aan uw kind?
☐ Ja ☐ Neen (ga door naar vraag 56)

34. Hoe werd **nystatine orale suspensie** toegediend?
☐ Het werd toegediend met de hand
☐ Het werd toegediend via een lepel
☐ Het werd toegediend via een spuitje
☐ Rechtstreeks uit de fles
☐ Andere: ……

35. Welke problemen waren er gelinkt aan de toediening van **nystatine orale suspensie**? (meerdere mogelijkheden)
☐ Wij ervaarden geen problemen bij de toediening van de medicatie.
☐ Huilen
☐ Weigeren om het geneesmiddel in te nemen
☐ Andere: ……

36. Hoe oud was uw kind toen het voor de eerste keer **nystatine orale suspensie** geadviseerd of voorgeschreven kreeg?
……

37. Hoe lang heeft uw kind het geneesmiddel genomen?
……
☐ Ik herinner mij dit niet

38. Welke gebruiksinstructies kreeg u bij deze therapie? (hoeveel toedienen, hoe lang toedienen, wanneer toedienen, wanneer stoppen,…)

    ……

    ……

    ……

    ☐ Weet ik niet

39. Welke gebruiksinstructies kreeg u bij deze therapie **met betrekking tot de voeding**? (voor of na de voeding, afwassen of niet, bij elke voeding of beperkt,…) ?

    ……

    ……

    ……

    ☐ Weet ik nie

40. Heeft u zelf eens de dosis aangepast?

    ☐ Ja ☐ Neen

    Zo ja, waarom?

    ……

    Hoe vaak heeft u dit gedaan?

    ……

41. Welke van onderstaande problemen ervaarde uw kind bij het stopzetten van Nystatine? (meerdere mogelijkheden)

    ☐ Wij ervaarden geen problemen bij het stopzetten
    ☐ De infectie was nog niet volledig verdwenen bij het stopzetten maar ik schakelde over naar andere medicatie op advies van een zorgverlener
    ☐ De infectie was nog niet volledig verdwenen bij het stopzetten maar ik schakelde op eigen initiatief over naar een alternatieve therapie
    ☐ De infectie was nog niet volledig verdwenen bij het stopzetten maar verdween later vanzelf
    ☐ De infectie was verdwenen maar kwam binnen de week weer terug
    ☐ De infectie was verwenen maar kwam later dan één week weer terug
    ☐ Andere: ……

42. Bent u hierna met een nieuwe behandeling gestart?

    ☐ Ja ☐ Neen

    Zo ja, welke behandeling? ……

43. Hoe vaak vergat u het geneesmiddel toe te dienen aan uw kind?

☐ Ik ben dit nooit vergeten
☐ zelden
☐ af en toe
☐ regelmatig
☐ heel vaak

44. Welke van onderstaande zorgverleners adviseerde of startte het gebruik van Nystatine op?

☐ Vroedvrouw
☐ Vroedvrouw – lactatiekundige
☐ Lactatiekundige (niet-vroedvrouw)
☐ Huisarts
☐ Pediater
☐ Apotheker
☐ Andere:.....

45. Ervaarde u deze behandeling als effectief?

☐ Ja ☐ Neen

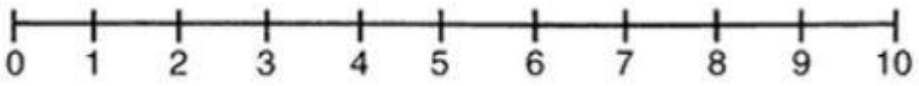
Zo nee, waarom niet? .....

46. Na hoeveel dagen merkte u verbetering van de aandoening of verlichting van de pijn?

..... dagen

47. In welke mate was u tevreden over de informatie die de zorgverlener u gaf in verband met de aandoening?

0= helemaal niet tevreden
10= zeer tevreden



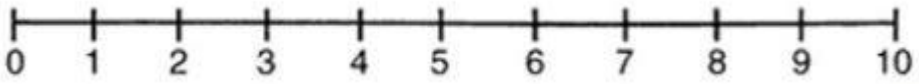
0= helemaal niet tevreden **10= zeer tevreden**

48. Waarom was u wel/niet tevreden?

.....

.....

49. In welke mate was u tevreden over de informatie die de zorgverlener u gaf in verband met de dosering van het geneesmiddel?
    0= helemaal niet tevreden
    10= zeer tevreden



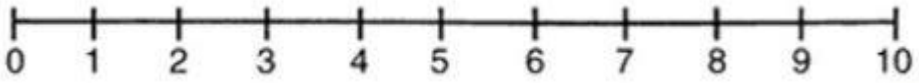
0= helemaal niet tevreden **10= zeer tevreden**

50. Waarom was u wel/niet tevreden?

.....

.....

51. In welke mate was u tevreden over de informatie die de zorgverlener u gaf in verband met de gebruiksinstructies van het geneesmiddel?
    0= helemaal niet tevreden
    10= zeer tevreden



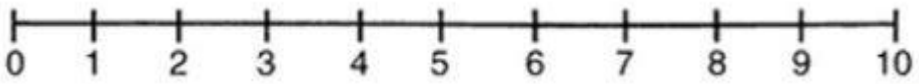
0= helemaal niet tevreden **10= zeer tevreden**

52. Waarom was u wel/niet tevreden?

.....

.....

53. In welke mate was u tevreden over de informatie die de zorgverlener u gaf in verband met de bijwerkingen van het geneesmiddel?
    0= helemaal niet tevreden
    10= zeer tevreden



0= helemaal niet tevreden **10= zeer tevreden**

54. Waarom was u wel/niet tevreden?

.....

55. Heeft u opmerkingen met betrekking tot (de behandeling met) nystatine?

.....

.....

MICONAZOLE ORALE GEL (Daktarin®)

56. Werd **miconazole ORALE gel** voorgeschreven aan uw kind

    ☐ Ja ☐ Neen (ga door naar vraag 79)

57. Hoe werd **miconazole ORALE gel** toegediend?

    ☐ met een lepeltje
    ☐ met de hand
    ☐ rechtstreeks uit de tube
    ☐ op de fopspeen
    ☐ Andere: .....

58. Welke problemen waren er gelinkt aan de toediening van **miconazole ORALE gel**? (meerdere mogelijkheden)

    ☐ Wij ervaarden geen problemen bij de toediening van de medicatie.
    ☐ Huilen
    ☐ Weigeren om het geneesmiddel in te nemen
    ☐ Andere: .....

59. Hoe oud was uw kind toen het voor de eerste keer **miconazole ORALE gel** voorgeschreven kreeg?

    .....

60. Hoeveel dagen heeft uw kind het geneesmiddel genomen?

    .....

    ☐ Ik herinner mij dit niet

61. Welke gebruiksinstructies kreeg u bij deze therapie? (hoeveel toedienen, hoe lang toedienen, wanneer toedienen,...)

    .....

    .....

    .....

    ☐ Weet ik niet

62. Wele gebruiksinstructies kreeg u bij deze therapie met betrekking tot de voeding? (voor of na de voeding, afwassen of niet, bij elke voeding of beperkt,…) ?

……

……

……

☐ Weet ik niet

63. Welke van onderstaande problemen ervaarde uw kind bij het stopzetten van **miconazole ORALE gel**?

(meerdere mogelijkheden)

☐ Wij ervaarden geen problemen bij het stopzetten
☐ De infectie was nog niet volledig verdwenen bij het stopzetten maar ik schakelde over naar andere medicatie op advies van een zorgverlener
☐ De infectie was nog niet volledig verdwenen bij het stopzetten maar ik schakelde op eigen initiatief over naar een alternatieve therapie
☐ De infectie was nog niet volledig verdwenen bij het stopzetten maar verdween later vanzelf
☐ De infectie was verdwenen maar kwam binnen de week weer terug
☐ De infectie was verwenen maar kwam later dan één week weer terug
☐ Andere: ……

64. Bent u hierna met een nieuwe behandeling gestart?

☐ Ja ☐ Neen

Zo ja, welke behandeling?

……

65. Heeft u zelf eens de dosis aangepast?

☐ Ja ☐ Neen

Zo ja, waarom?

……

Hoe vaak heeft u dit gedaan?

……

66. Hoe vaak vergat u het geneesmiddel toe te dienen aan uw kind?

☐ Ik ben dit nooit vergeten
☐ zelden
☐ af en toe
☐ regelmatig
☐ heel vaak

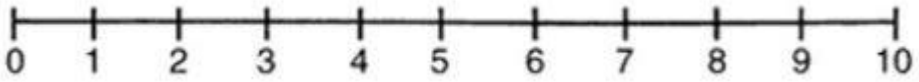
67. Welke van onderstaande zorgverleners adviseerde of startte het gebruik van Miconazole ORALE gel op?

☐ Vroedvrouw
☐ Vroedvrouw – lactatiekundige
☐ Lactatiekundige (niet-vroedvrouw)
☐ Huisarts
☐ Pediater
☐ Apotheker
☐ Andere:.....

68. Ervaarde u deze behandeling als effectief?
☐ Ja ☐ Neen
Zo nee, waarom niet? .....

69. Na hoeveel dagen merkte u verbetering van de aandoening of verlichting van de pijn?
..... dagen

70. In welke mate was u tevreden over de informatie die de zorgverlener u gaf in verband met de aandoening?
0= helemaal niet tevreden
10= zeer tevreden

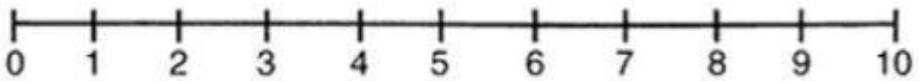


0= helemaal niet tevreden **10= zeer tevreden**

71. Waarom was u wel/niet tevreden?

.....

72. In welke mate was u tevreden over de informatie die de zorgverlener u gaf in verband met de dosering van het geneesmiddel?
0= helemaal niet tevreden
10= zeer tevreden

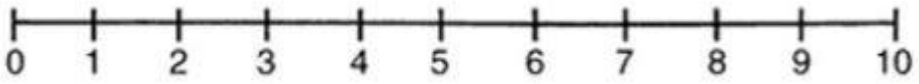


0= helemaal niet tevreden **10= zeer tevreden**

73. Waarom was u wel/niet tevreden?

.....

74. In welke mate was u tevreden over de informatie die de zorgverlener u gaf in verband met de gebruiksinstructies van het geneesmiddel?
    0= helemaal niet tevreden
    10= zeer tevreden

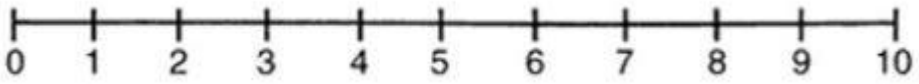


0= helemaal niet tevreden **10= zeer tevreden**

75. Waarom was u wel/niet tevreden?

.....

76. In welke mate was u tevreden over de informatie die de zorgverlener u gaf in verband met de bijwerkingen van het geneesmiddel?
    0= helemaal niet tevreden
    10= zeer tevreden



0= helemaal niet tevreden **10= zeer tevreden**

77. Waarom was u wel/niet tevreden?

.....

78. Heeft u opmerkingen met betrekking tot (de behandeling met) miconazole orale gel?

.....

.....

FLUCONAZOLE (Diflucan ®)

79. Werd **fluconazole (Diflucan ®)** voorgeschreven **aan uw kind**?

    ☐ Ja ☐ Neen (ga door naar vraag 102)

80. In welke vorm werd **fluconazole (Diflucan ®)** toegediend?

    ☐ Capsules
    ☐ siroop suspensie
    ☐ oplossing voor intraveneuze toediening (spuitje)
    ☐ Andere: .....

81. Welke problemen werden er gelinkt aan de toediening van **fluconazole (Diflucan ®)**? (meerdere mogelijkheden)

☐ Wij ervaarden geen problemen bij de toediening van de medicatie.
☐ huilen
☐ Weigeren om het geneesmiddel in te nemen
☐ Andere: .....

82. Hoe oud was uw kind toen het **fluconazole (Diflucan ®)** voor de eerste keer voorgeschreven kreeg?

.....

83. Hoe lang heeft uw kind **fluconazole (Diflucan ®)** genomen?

..... dagen/weken (schrappen wat niet past)

☐ Ik herinner mij dit niet

84. Welke gebruiksinstructies kreeg u bij deze therapie? (hoeveel toedienen, hoe lang toedienen, wanneer toedienen, …)

.....

.....

.....

☐ Weet ik niet

85. Welke gebruiksinstructies kreeg u bij deze therapie met betrekking tot de voeding? (voor of na de voeding, afwassen of niet, bij elke voeding of beperkt,…)

.....

.....

.....

☐ Weet ik niet

86. Welke van onderstaande problemen ervaarde uw kind bij het stopzetten van **fluconazole (Diflucan ®)** ? (meerdere mogelijkheden)

☐ Wij ervaarden geen problemen bij het stopzetten
☐ De infectie was nog niet volledig verdwenen bij het stopzetten maar ik schakelde over naar andere medicatie op advies van een zorgverlener

☐ De infectie was nog niet volledig verdwenen bij het stopzetten maar ik schakelde op eigen initiatief over naar een alternatieve therapie
☐ De infectie was nog niet volledig verdwenen bij het stopzetten maar verdween later vanzelf
☐ De infectie was verdwenen maar kwam binnen de week weer terug
☐ De infectie was verwenen maar kwam later dan één week weer terug
☐ Andere: .....

87. Bent u hierna met een nieuwe behandeling gestart?

☐ Ja ☐ Neen

Zo ja, welke behandeling?

.....

88. Heeft u zelf eens de dosis aangepast?

☐ Ja ☐ Neen

Zo ja, waarom?

.....

Hoe vaak heeft u dit gedaan?

.....

89. Hoe vaak vergat u het geneesmiddel toe te dienen aan uw kind?

☐ Ik ben dit nooit vergeten
☐ zelden
☐ af en toe
☐ regelmatig
☐ heel vaak

90. Welke van onderstaande zorgverleners adviseerde of startte het gebruik van **fluconazole (Diflucan ®)** op?

☐ Vroedvrouw
☐ Vroedvrouw – lactatiekundige
☐ Lactatiekundige (niet-vroedvrouw)
☐ Huisarts
☐ Pediater
☐ Apotheker
☐ Andere:.....

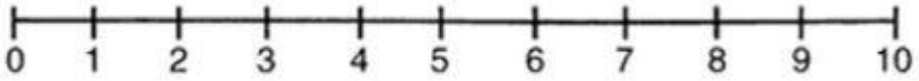
91. Ervaarde u deze behandeling als effectief?

☐ Ja ☐ Neen

Zo nee, waarom niet? .....

92. Na hoeveel dagen merkte u verbetering van de aandoening of verlichting van de pijn?
..... dagen

93. In welke mate was u tevreden over de informatie die de zorgverlener u gaf in verband met de aandoening?
0= helemaal niet tevreden
10= zeer tevreden



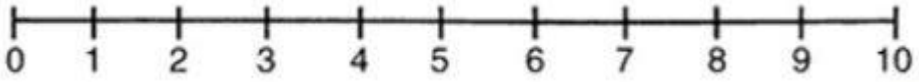
0= helemaal niet tevreden **10= zeer tevreden**

94. Waarom was u wel/niet tevreden?

.....

.....

95. In welke mate was u tevreden over de informatie die de zorgverlener u gaf in verband met de dosering van het geneesmiddel?
0= helemaal niet tevreden
10= zeer tevreden



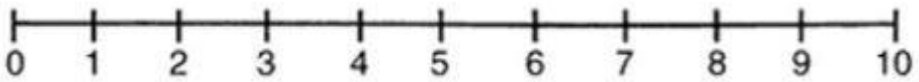
0= helemaal niet tevreden **10= zeer tevreden**

96. Waarom was u wel/niet tevreden?

.....

.....

97. In welke mate was u tevreden over de informatie die de zorgverlener u gaf in verband met de gebruiksinstructies van het geneesmiddel?
0= helemaal niet tevreden
10= zeer tevreden



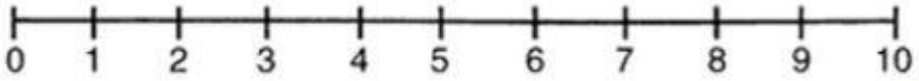
0= helemaal niet tevreden **10= zeer tevreden**

98. Waarom was u wel/niet tevreden?

.....

.....

99. In welke mate was u tevreden over de informatie die de zorgverlener u gaf in verband met <u>de bijwerkingen van het geneesmiddel</u>?
    0= helemaal niet tevreden
    10= zeer tevreden



0= helemaal niet tevreden **10= zeer tevreden**

100. Waarom was u wel/niet tevreden?

.....

.....

101. Heeft u opmerkingen met betrekking tot (de behandeling met) fluconazole voor de zuigeling?

.....

.....

Medicatie voor de moeder

FLUCONAZOLE (Diflucan ®)

102. Werd **fluconazole (Diflucan ®)** aan **u** voorgeschreven tijdens de borstvoedingsperiode?

☐ Ja ☐ Neen (ga door naar vraag 124)

103. In welke vorm werd **fluconazole (Diflucan ®)** voorgeschreven?

☐ Capsules
☐ siroop suspensie
☐ oplossing voor intraveneuze toediening (spuitje)
☐ Andere: .....

104. Welke problemen werden er gelinkt aan de gebruik van **fluconazole (Diflucan ®)** ? (meerdere mogelijkheden)

☐ Wij ervaarden geen problemen bij de toediening van de medicatie.
☐ Nevenwerkingen traden op
☐ Onsmakelijk
☐ Andere: .....

105. Hoe lang heeft u **fluconazole (Diflucan ®)** genomen?

.....dagen

106. Welke gebruiksinstructies kreeg u bij deze therapie? (hoeveel toedienen, hoe lang toedienen, wanneer toedienen,...)

.....

.....

☐ Weet ik niet

107. Welke gebruiksinstructies kreeg u bij deze therapie **met betrekking tot de voeding**? (voor of na de voeding, afwassen of niet, bij elke voeding of beperkt,...) ?

.....

.....

.....

☐ Weet ik niet

108. Welke van onderstaande problemen ervaarde u bij het stopzetten van **fluconazole (Diflucan ®)** ? (meerdere mogelijkheden)

☐ Wij ervaarden geen problemen bij het stopzetten
☐ De infectie was nog niet volledig verdwenen bij het stopzetten maar ik schakelde over naar andere medicatie op advies van een zorgverlener
☐ De infectie was nog niet volledig verdwenen bij het stopzetten maar ik schakelde op eigen initiatief over naar een alternatieve therapie
☐ De infectie was nog niet volledig verdwenen bij het stopzetten maar verdween later vanzelf
☐ De infectie was verdwenen maar kwam binnen de week weer terug
☐ De infectie was verwenen maar kwam later dan één week weer terug
☐ Andere: .....

109. Bent u hierna met een nieuwe behandeling gestart?

☐ Ja ☐ Neen

Zo ja, welke behandeling?

.....

110. Heeft u zelf eens de dosis aangepast?

☐ Ja ☐ Neen

Zo ja, waarom?

.....

Hoe vaak heeft u dit gedaan?

.....

111. Hoe vaak vergat u het geneesmiddel in te nemen?

☐ Ik ben dit nooit vergeten
☐ zelden
☐ af en toe
☐ regelmatig
☐ heel vaak

112. Welke van onderstaande zorgverleners adviseerde of startte het gebruik van **fluconazole (Diflucan ®)** op?

☐ Vroedvrouw
☐ Vroedvrouw – lactatiekundige
☐ Lactatiekundige (niet-vroedvrouw)
☐ Huisarts
☐ Pediater
☐ Apotheker
☐ Andere:.....

113. Ervaarde u deze behandeling als effectief?

☐ Ja ☐ Neen

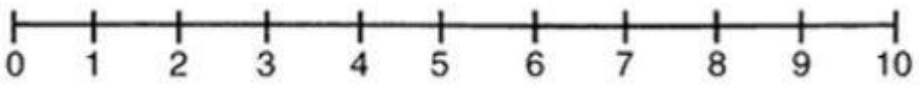
Zo nee, waarom niet? .....

114. Na hoeveel dagen merkte u verbetering van de aandoening of verlichting van de pijn?

..... dagen

115. In welke mate was u tevreden over de informatie die de zorgverlener u gaf in verband met de aandoening?

0= helemaal niet tevreden
10= zeer tevreden



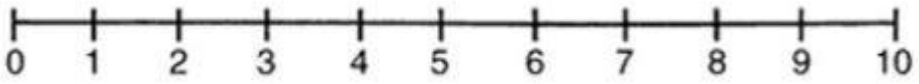
0= helemaal niet tevreden **10= zeer tevreden**

116. Waarom was u wel/niet tevreden?

.....

.....

117. In welke mate was u tevreden over de informatie die de zorgverlener u gaf in verband met de dosering van het geneesmiddel?
0= helemaal niet tevreden
10= zeer tevreden



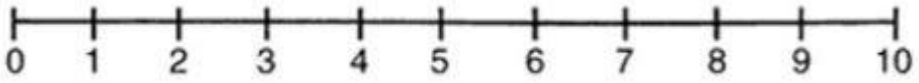
0= helemaal niet tevreden **10= zeer tevreden**

118. Waarom was u wel/niet tevreden?

.....

.....

119. In welke mate was u tevreden over de informatie die de zorgverlener u gaf in verband met de gebruiksinstructies van het geneesmiddel?
0= helemaal niet tevreden
10= zeer tevreden



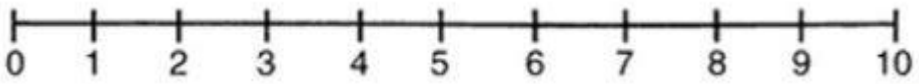
0= helemaal niet tevreden **10= zeer tevreden**

120. Waarom was u wel/niet tevreden?

.....

.....

121. In welke mate was u tevreden over de informatie die de zorgverlener u gaf in verband met de bijwerkingen van het geneesmiddel?
0= helemaal niet tevreden
10= zeer tevreden



0= helemaal niet tevreden **10= zeer tevreden**

122. Waarom was u wel/niet tevreden?

.....

.....

123. Heeft u opmerkingen met betrekking tot (de behandeling met) fluconazole voor de moeder?

.....

.....

MICONAZOLE CRÈME

124. Werd **miconazole crème** voorgeschreven aan **de moeder**?

☐ Ja ☐ Neen (ga door naar vraag 145)

125. Welke problemen werden er gelinkt aan het gebruik van **miconazole crème**? (meerdere mogelijkheden)

☐ Wij ervaarden geen problemen bij de toediening van de medicatie.
☐ Pijn bij het aanbrengen op de borst
☐ Andere: .....

126. Hoe lang heeft u **miconazole crème** gebruikt?

..... dagen/weken (schrappen wat niet past)

127. Welke gebruiksinstructies kreeg u bij deze therapie? (hoeveel toedienen, hoe lang toedienen, wanneer toedienen,...)

.....

.....

.....

☐ Weet ik niet

128. Welke gebruiksinstructies kreeg u bij deze therapie **met betrekking tot de voeding**? (voor of na de voeding, afwassen of niet, bij elke voeding of beperkt,...) ?

.....

.....

.....

☐ Weet ik niet

129. Welke van onderstaande problemen ervaarde u bij het stopzetten van **miconazole crème**? (meerdere mogelijkheden)

☐ Wij ervaarden geen problemen bij het stopzetten
☐ De infectie was nog niet volledig verdwenen bij het stopzetten maar ik schakelde over naar andere medicatie op advies van een zorgverlener
☐ De infectie was nog niet volledig verdwenen bij het stopzetten maar ik schakelde op eigen initiatief over naar een alternatieve therapie
☐ De infectie was nog niet volledig verdwenen bij het stopzetten maar verdween later vanzelf
☐ De infectie was verdwenen maar kwam binnen de week weer terug
☐ De infectie was verdwenen maar kwam later dan één week weer terug
☐ Andere: .....

130. Bent u hierna met een nieuwe behandeling gestart?

☐ Ja ☐ Neen

Zo ja, welke behandeling? .....

131. Heeft u zelf eens de dosis aangepast?

☐ Ja ☐ Neen

Zo ja, waarom?

.....

Hoe vaak heeft u dit gedaan?

.....

132. Hoe vaak vergat u het geneesmiddel in te nemen?

☐ Ik ben dit nooit vergeten
☐ zelden
☐ af en toe
☐ regelmatig
☐ heel vaak

133. Welke van onderstaande zorgverleners adviseerde of startte het gebruik van Fluconazole op?

☐ Vroedvrouw
☐ Vroedvrouw – lactatiekundige
☐ Lactatiekundige (niet-vroedvrouw)
☐ Huisarts
☐ Pediater
☐ Apotheker
☐ Andere:.....

134. Ervaarde u deze behandeling als effectief?

☐ Ja ☐ Neen

Zo nee, waarom niet? .....

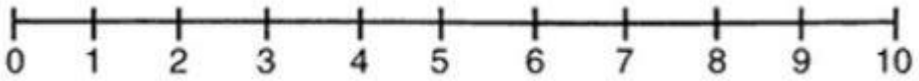
135. Na hoeveel dagen merkte u verbetering van de aandoening of verlichting van de pijn?

..... dagen

136. In welke mate was u tevreden over de informatie die de zorgverlener u gaf in verband met de aandoening?

0= helemaal niet tevreden

10= zeer tevreden



0= helemaal niet tevreden **10= zeer tevreden**

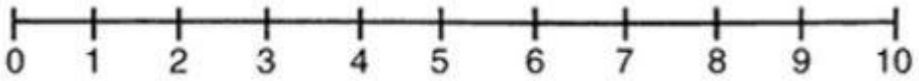
137. Waarom was u wel/niet tevreden?

.....

138. In welke mate was u tevreden over de informatie die de zorgverlener u gaf in verband met de dosering van het geneesmiddel?

0= helemaal niet tevreden

10= zeer tevreden



0= helemaal niet tevreden **10= zeer tevreden**

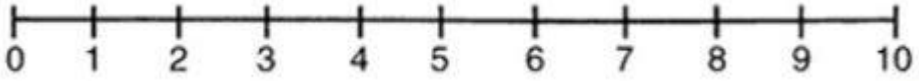
139. Waarom was u wel/niet tevreden?

.....

140. In welke mate was u tevreden over de informatie die de zorgverlener u gaf in verband met de gebruiksinstructies van het geneesmiddel?

0= helemaal niet tevreden

10= zeer tevreden



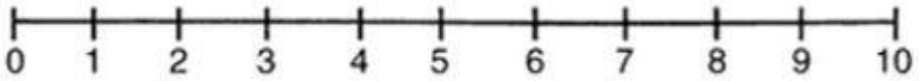
0= helemaal niet tevreden **10= zeer tevreden**

141. Waarom was u wel/niet tevreden?

.....

.....

142. In welke mate was u tevreden over de informatie die de zorgverlener u gaf in verband met <u>de bijwerkingen van het geneesmiddel</u>?
0= helemaal niet tevreden
10= zeer tevreden



0= helemaal niet tevreden **10= zeer tevreden**

143. Waarom was u wel/niet tevreden?

.....

.....

144. Heeft u opmerkingen met betrekking tot (de behandeling met) miconazole crème?

.....

.....

ALL PURPOSE NIPPLE OINTMENT (APNO ZALF)

All purpose nipple ointment is een magistrale bereiding die bestaat uit:

- *2% mupirocine (antibioticum)*
- *0,1% bètamethasone (corticosteroïd)*
- *2% miconazole poeder (antimycoticum)*

145. Werd **APNO zalf** aan **u** voorgeschreven?

☐ Ja ☐ Neen (ga door naar vraag 166)

146. Welke problemen werden er gelinkt aan het gebruik van **APNO zalf**? (meerdere mogelijkheden)

☐ Wij ervaarden geen problemen bij de toediening van de medicatie.
☐ Pijn bij het aanbrengen op de borst
☐ Andere: .....

147. Hoe lang heeft u **APNO zalf** gebruikt?

..... dagen

148. Welke gebruiksinstructies kreeg u bij deze therapie? (hoeveel toedienen, hoe lang toedienen, wanneer toedienen,...)

.....

.....

.....

☐ Weet ik niet

149. Welke gebruiksinstructies kreeg u bij deze therapie met betrekking tot de voeding? (voor of na de voeding, afwassen of niet, bij elke voeding of beperkt,...) ?

.....

.....

.....

☐ Weet ik niet

150. Welke van onderstaande problemen ervaarde u bij het stopzetten van **APNO zalf**? (meerdere mogelijkheden)

☐ Wij ervaarden geen problemen bij het stopzetten
☐ De infectie was nog niet volledig verdwenen bij het stopzetten maar ik schakelde over naar andere medicatie op advies van een zorgverlener
☐ De infectie was nog niet volledig verdwenen bij het stopzetten maar ik schakelde op eigen initiatief over naar een alternatieve therapie
☐ De infectie was nog niet volledig verdwenen bij het stopzetten maar verdween later vanzelf
☐ De infectie was verdwenen maar kwam binnen de week weer terug
☐ De infectie was verwenen maar kwam later dan één week weer terug
☐ Andere: .....

151. Bent u hierna met een nieuwe behandeling gestart?

☐ Ja ☐ Neen

Zo ja, welke behandeling?

.....

152. Heeft u zelf eens de dosis aangepast?

☐ Ja ☐ Neen

Zo ja, waarom?

.....

Hoe vaak heeft u dit gedaan?

.....

153. Hoe vaak vergat u het geneesmiddel te gebruiken?

☐ Ik ben dit nooit vergeten
☐ zelden
☐ af en toe
☐ regelmatig
☐ heel vaak

154. Welke van onderstaande zorgverleners adviseerde of startte het gebruik van **APNO zalf** op?

☐ Vroedvrouw
☐ Vroedvrouw – lactatiekundige
☐ Lactatiekundige (niet-vroedvrouw)
☐ Huisarts
☐ Pediater
☐ Apotheker
☐ Andere:.....

155. Ervaarde u deze behandeling als effectief?

☐ Ja ☐ Neen

Zo nee, waarom niet? .....

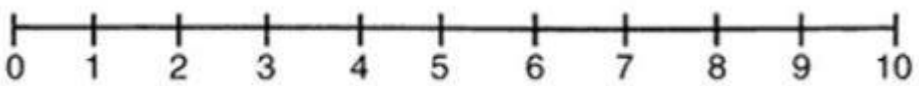
156. Na hoeveel dagen merkte u verbetering van de aandoening of verlichting van de pijn?

..... dagen

157. In welke mate was u tevreden over de informatie die de zorgverlener u gaf in verband met de aandoening?

0= helemaal niet tevreden

10= zeer tevreden

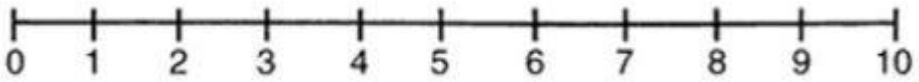


0= helemaal niet tevreden **10= zeer tevreden**

158. Waarom was u wel/niet tevreden?

.....

159. In welke mate was u tevreden over de informatie die de zorgverlener u gaf in verband met de dosering van het geneesmiddel?
0= helemaal niet tevreden
10= zeer tevreden

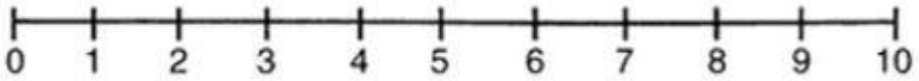


0= helemaal niet tevreden **10= zeer tevreden**

160. Waarom was u wel/niet tevreden?

.....

161. In welke mate was u tevreden over de informatie die de zorgverlener u gaf in verband met de gebruiksinstructies van het geneesmiddel?
0= helemaal niet tevreden
10= zeer tevreden

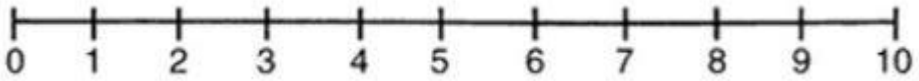


0= helemaal niet tevreden **10= zeer tevreden**

162. Waarom was u wel/niet tevreden?

.....

163. In welke mate was u tevreden over de informatie die de zorgverlener u gaf in verband met de bijwerkingen van het geneesmiddel?
0= helemaal niet tevreden
10= zeer tevreden



0= helemaal niet tevreden **10= zeer tevreden**

164. Waarom was u wel/niet tevreden?

.....

165. Heeft u opmerkingen met betrekking tot (de behandeling met) APNO zalf?

.....

.....

166. De volgende stellingen hebben betrekking op de medicatie die u **uw kind** toedient of toediende.

Stellingen	Helemaal niet akkoord	Eerder niet akkoord	Eerder wel akkoord	Volledig akkoord	Geen mening
Deze geneesmiddelen worden gebruikt om de symptomen onder controle te krijgen.					
Deze geneesmiddelen helpen om de aandoening te genezen.					
Als ik buitenshuis ga gebeurt het wel eens dat ik het geneesmiddel vergeet.					
De meeste geneesmiddelen zijn moeilijk te begrijpen.					
Ik ben constant bang dat ik het geneesmiddel vergeet te geven aan mijn kind.					

Alternatieve therapieën

167. Over welke van onderstaande therapieën hebt u **ooit** advies gevraagd aan uw zorgverlener?

☐ Ik heb nooit advies gevraagd en nooit een alternatieve therapie gebruikt
☐ Ik heb nooit advies gevraagd, maar wel een alternatieve therapie gebruikt
☐ gentiaan violet
☐ topische applicatie van azijn
☐ verwijderen van 'verwerkte suikers' uit het dieet
☐ topische applicatie van (kokos)olie
☐ topische applicatie van grapefruit seed oil of orale inname ervan
☐ miconazole of clotrimazole in suppo's die toegediend werden aan de zuigeling via een fopspeen
☐ Andere.....

168. Aan welke zorgverlener vroeg u advies ?
   - ☐ Vroedvrouw
   - ☐ Vroedvrouw – lactatiekundige
   - ☐ Lactatiekundige (niet-vroedvrouw)
   - ☐ Huisarts
   - ☐ Pediater
   - ☐ Apotheker
   - ☐ diëtist
   - ☐ Andere: .....

169. Had u graag meer uitleg gekregen van uw zorgverlener over alternatieve therapieën in de behandeling van de spruwinfectie?
   ☐ Ja ☐ Neen

170. Over welke therapie/therapieën had u graag meer informatie kregen ?

.....

.....

.....

171. Welk van bovenstaande alternatieve therpieën heeft u effectief gebruikt ?

.....

.....

☐ Ik heb geen enkele alternatieve therapie gebruikt (ga naar vraag 187)

172. Indien u een alternatieve therapie gebruikte **op aanraden van uw zorgverlener**, **welk advies** gaf u zorgverlener u over de werking, gebruiksinstructies en bijwerkingen van de therapie?

☐ niet van toepassing

Therapie:.....
Mijn kind was ..... dagen/maanden/jaar oud toen ik deze therapie toepaste
(schrappen wat niet past)
Werking:

.....

.....

.....

Gebruiksinstructies:

.....

.....

.....

Bijwerkingen:

.....

.....

.....

173. Ervaarde u deze behandeling als effectief?

☐ Ja ☐ Neen

Zo nee, waarom niet? .....

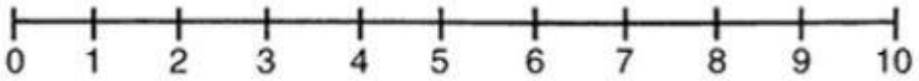
174. Na hoeveel dagen merkte u verbetering van de aandoening of verlichting van de pijn?

..... dagen

175. In welke mate was u tevreden over de informatie die de zorgverlener u gaf in verband met de aandoening?

0= helemaal niet tevreden

10= zeer tevreden



0= helemaal niet tevreden **10= zeer tevreden**

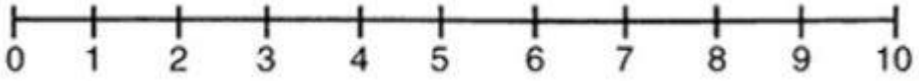
176. Waarom was u wel/niet tevreden?

.....

177. In welke mate was u tevreden over de informatie die de zorgverlener u gaf in verband met de dosering van het alternatief product?

0= helemaal niet tevreden

10= zeer tevreden

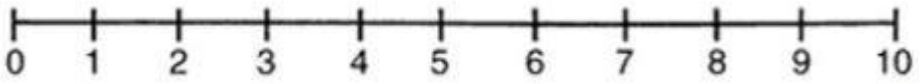


0= helemaal niet tevreden **10= zeer tevreden**

178. Waarom was u wel/niet tevreden?

.....

179. In welke mate was u tevreden over de informatie die de zorgverlener u gaf in verband met de gebruiksinstructies van het alternatief product?
0= helemaal niet tevreden
10= zeer tevreden

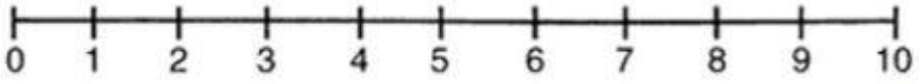


0= helemaal niet tevreden **10= zeer tevreden**

180. Waarom was u wel/niet tevreden?

.....

181. In welke mate was u tevreden over de informatie die de zorgverlener u gaf in verband met de gebruiksinstructies van het alternatief product?
0= helemaal niet tevreden
10= zeer tevreden



0= helemaal niet tevreden **10= zeer tevreden**

182. Waarom was u wel/niet tevreden?

.....

183. Indien u een alternatieve therapie gebruikte **zonder advies van een zorgverlener**: hoe, wanneer en hoelang gebruikte u deze therapie?

☐ niet van toepassing

Therapie:.....
Mijn kind was ..... dagen/maanden/jaar oud toen ik deze therapie toepaste
(schrappen wat niet past)

Hoe geruikte u deze therapie?

.....
.....
.....

Wanneer diende u deze therapie toe?

.....
.....
.....

Hoelang gebruikte u deze therapie?

.....

184. Waar vond u informatie over deze therapie?

.....

.....

185. Ervaarde u deze behandeling als effectief?

☐ Ja ☐ Neen

Zo nee, waarom niet? .....

186. Na hoeveel dagen merkte u verbetering van de aandoening of verlichting van de pijn?

..... dagen

Borstvoeding

187. Welke impact had de diagnose van spruw op uw borstvoeding?

.....

.....

.....

188. Bent u door de **spruwinfectie** vroeger gestopt met borstvoeding geven dan u eigenlijk gepland had?

☐ Ja ☐ Neen

Indien ja,

Hoe lang plande u borstvoeding te geven?.....

Hoe lang hebt u uiteindelijk borstvoeding gegeven?.....

☐ Ik herinner mij dit niet exact, ik maak een schatting

189. Bent u omwille van een **andere reden** dan de spruwinfectie vroeger gestopt met borstvoeding geven dan u eigenlijk gepland had?

☐ Ja ☐ Neen

Indien ja,

Welke reden?

.....

.....

Hoe lang plande u borstvoeding te geven?.....

Hoe lang hebt u uiteindelijk borstvoeding gegeven?.....

☐ Ik herinner mij dit niet exact, ik maak een schatting

190. Kolfde u melk af?

☐ Ja ☐ Neen

Indien ja, welk advies kreeg u van uw zorgverlener in verband met maatregelen voor het afgekolven van melk?

.....

.....

191. welk advies kreeg u van uw zorgverlener in verband met het bewaren van afgekolfde melk?

.....

.....

.....

☐ Ik kreeg geen advies in verband met afgekolfde melk

192. In welke mate paste u de adviezen over afgekolfde melk toe?

.....

.....

.....

193. Indien u geen advies kreeg, wat deed u met de afgekolfde melk?

.....

.....

.....

Bedankt voor uw deelname aan deze vragenlijst

☐ Ik wens de resultaten van de studie doorgestuurd te krijgen via volgend e-mailadres:

.....