Candida in breastfeeding

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Disclosure – conflict of interest

- No relevant financial relationships with companies of breast milk products from producres that go against the WHO code
  - Names of products or brands are related to the discussed cases, without any other intention

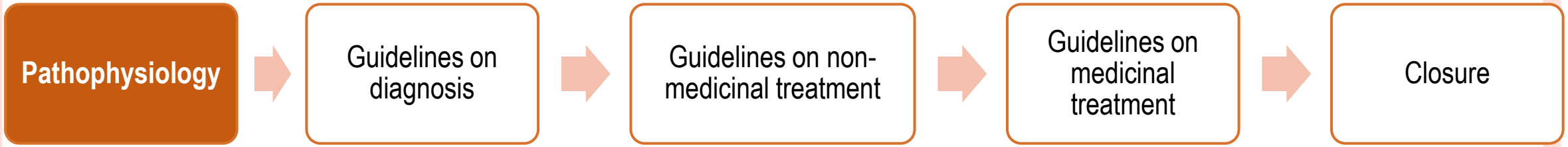
What is thrush or candidiasis?

- Candida albicans
- Nipple / areola
- Ecosystem disruption and overgrowth
- Immunocompression

Douglas, 2021

Risk factors

- Pregnancy
- Recent oral antibiotics
- Birth
- Baby with oral thrush
- Transfer from Candida mother←→child
- Predisposition for Candida


Pathophysiology
Guidelines on diagnosis
Guidelines on non-medicinal treatment
Guidelines on medicinal treatment
Closure

Pathophysiology

- **Fungal infection**
  - 95%*Candida* (*Candida albicans*)

- **Symptomatic**
  - Overgrowth of superficial epithelium oral mucosa
  - White plaques
  - Beneath plaques often red, tender and bleeding

  - Infant co-infection: diaper dermatitis with *candida* surinfection

Vila T et al.*J Fungi. 2020;6(1):1–28*

Pathophysiology

- **"Disease of opportunity"**
  - Colonization mouth during childbirth
    - Contact with vaginal mucosa
    - 20% to 40% women test + on *candida* colonization at time of delivery
  - Transfer through hands
    - Mother / Father / Family / Caregivers

- **Most frequently reported: 4 weeks**
  - Incubation period: 4 to 13 days
  - Reported prevalences: 10% to 15%
    - Outliers up to 37%
    - Small study populations of the available studies
    - Very diverse ages
    - Diversity in diagnosis

Vila T et al.*J Fungi. 2020;6(1):1–28,****Hoppe JE et al****PediatrInfect Dis J. 1997;16(9):885–94*
Can.Paed. Soc.*paediatrChild Health. 2007;5(1):477–82*

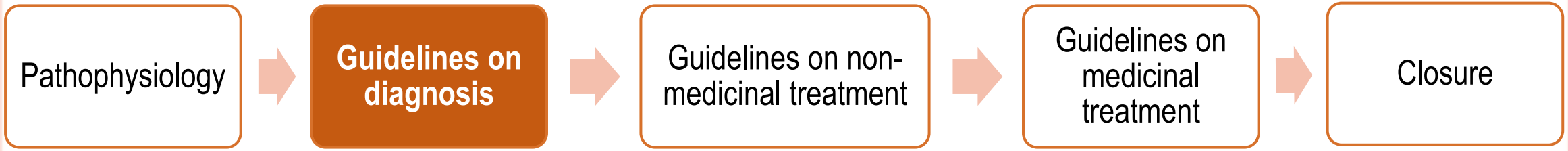
Pathophysiology

- **Transfer to mother**
  - →Candidiosis breast or nipple

- **Symptomatic**
  - Nipple/areola
    - Nipple trauma
    - Shiny, pink/red nipple/red, dry or scaly areola
    - Painful (stinging/burning) and/or itchy
    - Sensitive to touch

  ! Visual symptoms not always present
  - Breast
  - Vaginal co-infection mother

Vila T et al.*J Fungi. 2020;6(1):1–28*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Diagnosis guidelines

- Systematic. literature search (ENG & Dutch), snowballing and breastfeeding organisations

- **Scarcity of guidelines regarding diagnosis**

  →Infant oral thrush: 6 guidelines
  →Breast/nipple thrush diagnosis: 10 guidelines

- **Crucial shortcoming**
  - Quick and correct diagnosis determines whether or not to initiate medical intervention

Diagnosis Guidelines – Infant

- **Content-related**
  - Visual recognition: 5/6
  - Indication differential diagnosis milk deposits: 2/6
  - Mention evaluation co-infection diaper zone: 4/6

- **Sometimes very limited**
  - **Child & Family (Belgium organisation for preventive follow-up)**
    - *"Symptoms: white spots in the mouth that won't come off. Under the spots are small blisters. The infant may act agitated and have difficulty feeding."*

Qestion: Diagnosis mother

- Which symptom in the mother is most decisive for you?
  1. Nipple trauma
  2. Itching on the skin
  3. Sore nipple (burning/stinging) at start feeding
  4. Sore nipple (burning/stinging) through nutrition
  5. Stabbing/burning pain in chest
  6. Pink, shiny nipple
  7. White coating on the nipple

Diagnosis Guidelines – Mother

- **Content-related**
  - Visual recognition: 7/10
  - Mention of nipple trauma: 8/10
  - Mention AB use: 5/10
  - Listing differential diagnoses: 4/10
  - Mention evaluation co-infection vaginal: 5/10
  - Swabs: 2/10

- **Sometimes very limited**
  - **NHG**
    - *"A stabbing pain during breastfeeding without symptoms of thrush in the infant is not an indication to treat the mother with antifungal medication."*

Diagnosis Guidelines – Infant

- Evaluation of surinfection diaper zone + (recent) antibiotic use

- Observation breastfeeding session
  - Breast pain sensation (differential)
  - Being agitated and feeding more OR refusing breast due to pain
  - Generally: detachment from the breast more often
  - Clicking sounds

- Mouth symptoms
  - Thick white coating or small local spots in the mouth (differential)
  - Red, dry and cracked lips
  - Inside lips: pearly shine
  - Red tongue tip

Diagnosis Guidelines – Mother

- Evaluation co-infection vaginal + (recent) antibiotic use

- Observation breastfeeding session (idem infant)

- Symptoms nipple/areola (uni/bilateral)
  - (nipple trauma)
  - Shiny, pink/red nipple/red, dry or scaly areola
  - Painful and/or itchy
  - Sensitive to touch

! Visual symptoms not always present

- Breast symptoms
  - Pain

Question: Differential Diagnosis

- What differential diagnosis are you considering?

Concerns – Differential Diagnosis

- **Differential diagnosis**
  - Trauma
  - Functional pain
  - Bacterial infection
  - Dermatitis
  - Vasospasms
  - Mastitis
- **Always consider when infant shows no visual symptoms**

Pijn geassocieerd met de **toeschietreflex**: milde pijn de eerste minuten, kan opnieuw optreden 12 à 15 minuten na start van de voeding; verbetert binnen enkele weken.

Pijn geassocieerd met **candida-infectie**: matige pijn, ergst bij aanhap, duurt de volledige voeding. Zindert soms na, na de voeding. Kan uitstralen in de borst, waar het een brandende pijn geeft, zeker bij terug vullen van de borst. Significant beter na 2 à 4 dagen orale antifungale therapie.

Pijn geassocieerd met **vasospasmen**: matige pijn die continu aanwezig kan zijn, zeker bij contact met koude omgeving. Scherpe, stekende pijn, met kleurwijziging van de tepel.

Tommelein & Muyldermans *(2019)Breastfeeding,practical guide forthehealthcare*


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Treatment guidelines

- Systematic literature search (ENG & Dutch), snowballing and breastfeeding organisations
- **Scarcity of treatment guidelines (15)**

  →6/14 guidelines for infants: no non-drug advice whatsoever

  →4/12 guidelines for mothers: no non-drug advice

- **Scarcity of substantiation of advice**
  - For example: cleaning equipment
  - For example: storing expressed milk

Non-drug advice

- **Cleaning of material**
- Use material: can ↑ incidence of thrush and be persistent source of infection
- Mention in 8/15 guidelines: "sufficient cleaning"
  - 4 specify boiling
  - 2 list specific boiling times
- Consensus about efficient and practical sterilization techniques is urgent

Non-drug advice

Evidence: Pacifiers can develop persistent **biofilms**

- Microwave sterilization *dentures* (3 min at 650W in 200mL water)

→Complete eradication

- Wash for one minute with neutral detergent (concentration of 3.5%)

→Complete eradication

- Boil for 15 minutes

→Complete eradication

Ribeiro DG et al.*J Dent. 2009 Sep 1;37(9):666–72.*
Lopes DF et al.*ClinPediatr(Phila) [Internet]. 2019 Dec 14 [cited 2020 May 15];58(14):1540–3.*

Non-drug advice

- **Milk storage**
- Reference to 3/15 guidelines
  - *"Pasteurize and freeze for later use after the child is cured of the infection"*
  - *"Expression is possible but can only be used while the child is still being treated (no storage possible)"*
- Consensus on preservation is urgent

Non-drug advice

Evidence: Storage of breast milk

- Lack of knowledge about the presence of *Candida*(-spores) in breast milk
- Freezing deactivates but does not kill spores
- Pasteurization
  - Effect on fungalorganisms: unclear
  - Denaturation essential proteins
  - Bacterial growth in 99% samples inhibited = destruction microbiome
  - Decreased nutritional value (e.glysine)
  - Maillard response: decrease in organoleptic & nutritional quality

→**Pragmatic** approach because of the risk of re-infection

Naicker M et al.*Breastfeed Med. 2015;10(2):107–12.*

Hale TW et al.*Breastfeed Med. 2009;4(2):57–61.*

Klotz D et al.*ActapaediatrInt Jpaediatr. 2017;106(5):763–7.*

Silvestre D et al.*BioFactors. 2006;26(1):71–9.*

Non-drug advice

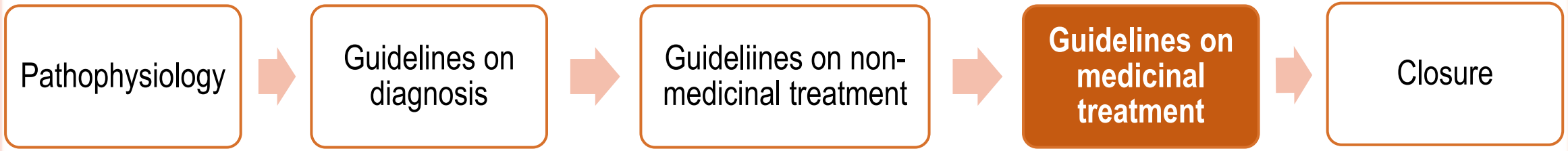
!!! Opinions with no scientific substantiation *(consensus-based)*

- Allow nipples and breasts to air dry
- Expose breast & nipple to direct sunlight
- Gently dry the external genitalia with a hairdryer after washing
- Dispose of nursing pads as soon as they are moist
- Do not recommend communal bathing
- Avoid certain foods

Non-drug advice

!!! Opinions with any scientific substantiation

- Wash bed sheets / underwear / nursing pads at the highest possible temperature
- Cleaning equipment
  - Microwave sterilization (3 min at 650W in 200 mL of water)
  - Wash for one minute with neutral detergent (concentration of 3.5%)
  - Cook for 15 minutes
- Express/storage breast milk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Treatment guidelines

- Systematic literature search (EN & Dutch), snowballing and breastfeeding organisations
- **Scarcity of treatment guidelines** (15)

  →13 with advice on infant care
  →12 with advice on mother's treatment
  →3 with advice on infant recurrence
  →8 with advice on maternal recurrence

- **Scarcity of harmonized advice**

Drug advice - infant

summarizing: drug of choice for infant treatment

- 4/13: Miconazole oral gel (always 1st choice)
- 4/13: Miconazole or Nystatin (no preference)
- 2/13: Nystatin (1st choice <4 months)
- 2/13: Nystatin (always 1st choice)
- 1/13: No specific drug listed

- 2/13: Diaper zone treatment advice

- **No clear consensus**

Drug advice - infant

Evidence:Clinical effectiveness

	Design	Groep	Groep 1	Effect	Bijwerkingen	Groep 2	Effect	Bijwerkingen	Verschil
Hoppe et al (1997)	Niet geblindeerde RCT	83 kinderen	Miconazol orale gel	99% klinische genezing	4.5%	Nystatine orale suspensie	54% klinische genezing	3.5%	P<.001
Hoppe et al (1996)	Niet geblindeerde RCT	95 kinderen	Miconazol orale gel	85% klinische genezing	4.5%	Nystatine orale suspensie	45% klinische genezing	3.5%	P<.001

- Contraindication miconazole oral gel < 4 months
  - Choking incidents
  - 7/13 specific advice regarding method of administration

Hoppe JE et alinfection.*1996 Mar-Apr;24(2):136-9;****Hoppe JE et al****PediatrInfect Dis J. 1997;16(9):885–94*
Ainsworth S & Jones*BMJ. 2009 Jan 5;338.*

Drug advice - mother

summarizing: practical application for treatment mothers

- 7/12: Miconazole cream (1st choice)
- 3/12: No drug specification
- 6/12: Advice on dosage (after each feeding)
- 1/12: Advice on (not) removing for next feeding

- **Mainly incompleteness in the guidelines**
  - dosing schedule (duration, application, removal)

Drug advice - mother

Evidence: practical application for treatment mothers

- Clotrimazole & Miconazole: similar spectrum of activity
- Removing cream not recommended
  - Cause unnecessary damage
  - BA is low (mic: 25% /clo: <3%)

Table 1. *In vitro* activity of the main antifungal drugs against main *Candida* species causing oral infection.

Antifungal drugs	**Species of *Candida***						
	Candida albicans	*Candida glabrata*	*Candida parapsilosis*	*Candida tropicalis*	*Candida krusei*	*Candida dubliniensis*	*Candida* spp.
Nystatin	●●	●●	●●	●●	●●	●●	●●
Amphotericin B	●●	●●	●●	●●	●●	●●	●●
Miconazole	●●	■ ○	●●	●●	○	●●	●
Clotrimazole	●●	■	●●	●●	○	●●	●

Antifungal activity: ●● very active, ● active, ■ variable activity, ○ resistant.

Bron figuur: Quindos et al (2019)

Summary of ProductCharacteristics:*Daktarin® Cream &Canestene® cream*

Drug advice - recurrence

Summarizing: dosing schedule for treatment of recurrence / alternative in case of resistance

- Infants
  - 2/3 with dose
  - 1/3 with alternative in case of resistance: itraconazole

- Mother
  - Fluconazole oral (1st Choice) – Mother
  - Varying treatment plans
    - 400 mg loading dose, followed by 100-200 mg twice a day (2-4 weeks)
    - 200 mg loading dose, followed by 100 mg daily for 7 to 10 days
    - 150 mg every 48 hours until chest pain is gone
  - No mention of alternative in case of resistance

- Insufficient scientific substantiation

Drug advice - recurrence

Evidence: Compatibility with breastfeeding

- Maternal dose
  - Oral 200mg daily → $C_{max, mm}$ 4.1mg/L

- Therapeutic child dose
  - Children's Formulary: 3 - 6 mg/kg/day in 1 dose (from 1 month)
  - BCFI: 3 mg/kg/day for 7 days (from 1 month)

	Ingestion through milk	Therapeutic dose
4 kilos	2.46mg/day	12mg/day
6 kilos	3.69mg/day	18mg/day
8 kilos	4.92mg/day	24mg/day

__Hale__– Medications and Mother's Milk, __Briggs__– Drugs in pregnancy and lactation, __Lactmed__application, __Kinderformularium.nl__

Drug advice - recurrence

- **Evidence**: Alternative for resistance
  - Azole-resistance: mainly immuno compromised children who received oral treatment with azoles

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Clotrimazole	●●	■	●●	●●	○	●●	●
Fluconazole	●●	■ ○	●●	●●	○	■ ○	●
Isavuconazole	●●	●●	●●	●●	●●	●●	●●
Itraconazole	●●	■ ○	●●	○	○	■ ○	●

Antifungal activity: ●● very active, ● active, ■ variable activity, ○ resistant.

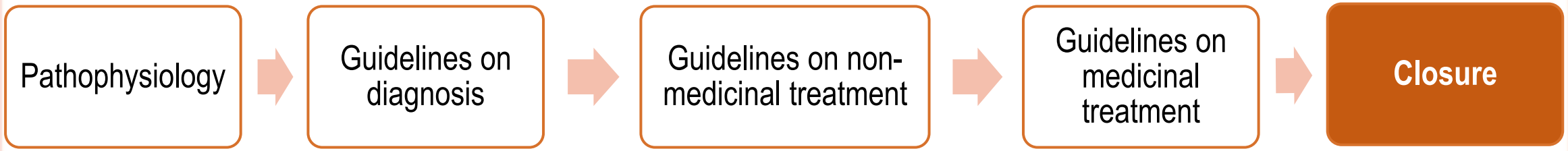
Bron figuur: Quindos et al (2019)

Drug advice

- **Infant**
  - Miconazole oral gel 4 x per day 1.25 mL, after feeding, symptom free for up to 7 days
  - Fingertip on jaws, gums, palate and tongue. Airway obstruction alert.
  - Diaper zone co-infection: miconazole / isoconazole pasta
- **Mother**
  - Topical miconazole cream after each feeding ½ FTU, until 7 days after symptom-free
  - Do not wash off before next feeding or new application
  - Co-infection vaginal: miconazole / clotrimazole ovule / cream

Drug advice

- **Recurrent infections**: evaluate necessity
  - Infant: fluconazole 3 mg/kg/day
  - Mother: fluconazole
    - 400 mg loading dose, then 100 to 200 mg,2x/day (2 to 4 weeks)
  - Swab for resistance evaluation (alternative: nystatin)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Conclusion

- Recommendations for practice
  - Validated screening tool
  - Harmonization & completion of guidelines
    - Diagnosis & Treatment
- Recommendations for research
  - Screening tool
  - Adapted to skin diversity
  - When to start therapy?
  - Effectiveness of non-drug therapies
    - Research into breast milk storage
    - Research into effective and practical sterilization method
  - Effectiveness of drug therapies
    - Different treatment schedules for recurrences
    - Alternative for resistance

RESEARCH CALL

STUDY ON THE KNOWLEDGE OF EUROPEAN HEALTHCARE PROVIDERS ABOUT MASTITIS AND CANDIDIASIS

- Are you a lactation consultant or health care provider?
- Do you work with breastfeeding mothers?
- Do you work in Europe?

THEN WE NEED YOU !

FILL IN THIS QUESTIONNAIRE AND HELP US DISCOVER NEW INSIGHT!

https://vub.fra1.qualtrics.com/jfe/form/SV_6yw3GiSf1uov3Ey

Study set up at University of Brussels
Head researcher: eline.tommelein@vub.be
Researcher: joke.muyldermans@vub.be

VUB VRIJE UNIVERSITEIT BRUSSEL

A timely and correct diagnosis of thrush is crucial to protect long-term breastfeeding.

Thrush causes significant pain for the breastfeeding mother and child which – when not managed appropriately – can lead to unwanted weaning

E. Tommelein

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Study set up at University of Brussels
Head researcher: eline.tommelein@vub.be
Researcher: joke.muyldermans@vub.be

VUB VRIJE UNIVERSITEIT BRUSSEL

Included diagnosis guidelines

Infant

- **Clinical MidwiferyConsultantBreastfeedingcentre.** Breastfeeding challenges:Thrushinlactation. 2019.
- **Child & Family:** Thrush [Internet]. [cited2020 May 13].Available from: https://www.kindenfamily.be/gezondheid-en-vaccineren/ziek/schimmel-gistfections/spruw/
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Mother

- Berens P,EglashA,MalloyM,SteubeAM,BrodribbW,NobleL, et al. **ABMClinicalProtocol** #26: PersistentPain with Breastfeeding.Breastfeeding Med. 2016;11(2):46–53.
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Included treatment guidelines

- *INFANT*

  - *Berens P et al. ABM Clinical Protocol #26: Persistent Pain with Breastfeeding. Breastfeed Med. 2016;11(2):46–53.*
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Included treatment guidelines

- *MOTHER*

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