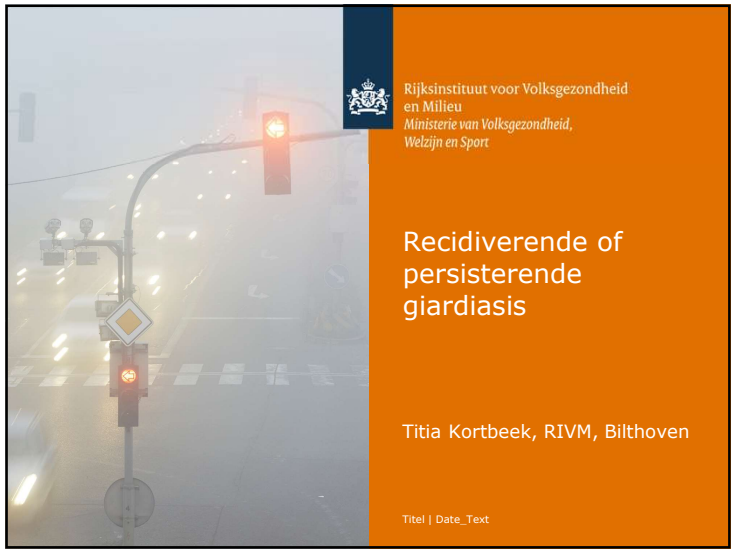
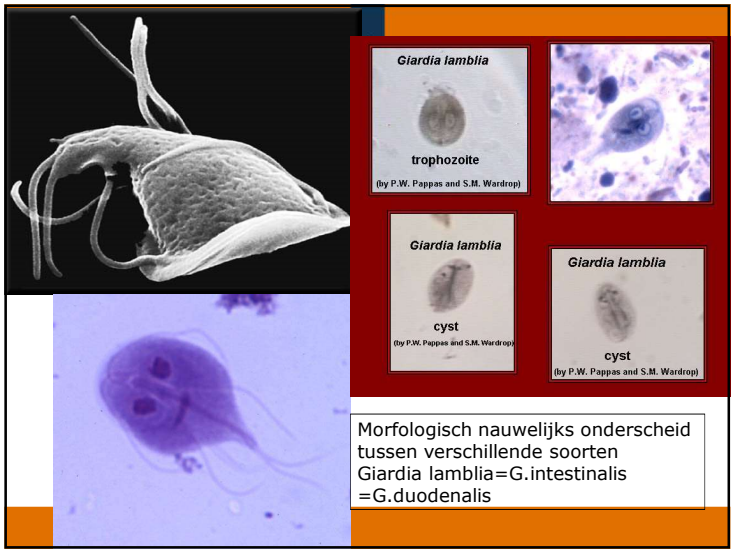


Rijksinstituut voor Volksgezondheid en Milieu
Ministerie van Volksgezondheid, Welzijn en Sport

Recidiverende of persisterende giardiasis

Titia Kortbeek, RIVM, Bilthoven



Morfologisch nauwelijks onderscheid tussen verschillende soorten
Giardia lamblia=G.intestinalis
=G.duodenalis

Giardia infectie: therapie resistentie casus

- Vrouw
- 1950
- Lengte : 168 cm
- Gewicht: 98 kg
- diarreeklachten
- werkzaam in kinderopvang

- Diagnose: Persisterende *Giardia lamblia* infectie

Therapie schema

- Juni 1999 Flagyl 3 dd 250 mg ged. 10 dagen (AZG)
- Aug 1999 Flagyl 3 dd 250 mg ged. 1 week (HA)
- Nov 1999 Flagyl 3 dd 500 mg ged. 10 dagen (HA)
- Jan 2000 Tinidazole 4 x 500 mg in een keer (zkh elders)

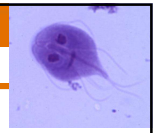
- Nov 2000 Flagyl
- Mei 2001 Flagyl 3 dd 750 mg ged. 1 week, gevolgd door Tinidazol 1 dd 2 gram ged. 6 dagen
- Mei 2001 Albendazol 1 dd 400 mg ged. 7 dagen

- In de brieven wordt wel gesproken dat ze vaker antibioticakuren heeft gehad, maar het is niet duidelijk welke en welke periode.
- Bij herhaling is Giardia lamblia gezien in de faeces
- Oktober 2001: Giardia opgestuurd naar RIVM: Veel cysten; gezuiverd voor typering

Advies:
- **albendazol** 400 mg 2dd , 7 dagen;
- daarna
- **metronidazole** of **tinidazol** 2 gram 7 dagen.
- 1 week na het beeindigen van de therapie parasitologische controle.

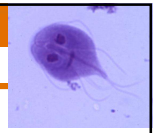
Mee eens ??

Casus 2



- Meisje van 18 maanden :
  - groeit slecht, stinkende poepbroeken, eet slecht
  - Duurt al meerdere weken
  - Geen reizen gemaakt; heeft een broertje van 3 jaar
  - Huisarts doet onderzoek:
    - ***Giardia lamblia***
      - Therapie: metronidazol 10 mg/kg 3dd gedurende 7 dagen
- 2 weken na behandeling nog steeds klachten
- Wat te doen?
  - Onderzoek feces herhalen?
  - Opnieuw behandelen?
  - Onderzoek van de familieleden?

casus



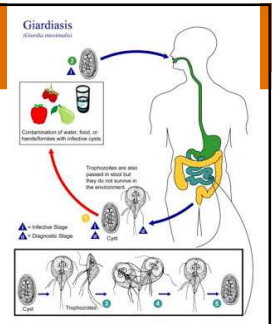
- Wat te doen
  - Onderzoek feces herhalen? Nog steeds Giardia
  - Opnieuw behandeld: metronidazol zelfde dosering
- 2 weken na behandeling nog steeds klachten
- Wat te doen?
  - Onderzoek feces herhalen?
  - Opnieuw behandelen?
  - Onderzoek van de familieleden?

casus

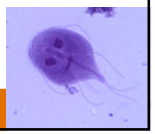
- Onderzoek feces herhalen: Nog steeds *Giardia*
- Onderzoek van de familieleden? Broertje en vader ook *Giardia*; moeder niet
  - Opnieuw behandeld: hele gezin metronidazol
- 2 weken na behandeling nog steeds klachten
- Wat te doen?
  - Gebeld met RIVM en overlegd
  - Typering *Giardia*: broertje en vader hadden ander type
    - Casus had Assemblage B
    - Broertje en vader Assemblage A
- Behandeld met Albendazol: geen *Giardia* meer
  - Volgens de kinderarts : kinderen erg chagrijnig (door Albendazol)

9

Giardia lamblia



- Protozo : flagelaat
- Twee stadia: trofozoiet en cyste
  - Alles dubbel aangelegd
  - Dubbele kern, 2x 4 flagellen
  - Cyste
- Verschillende Assemblages
  - Assemblage A en B humane infecties
- Klachten: stinkende diarree
  - Bij 50 % : asymptomatisch
  - **Acuut**: flatulentie, diarree, misselijk, buikpijn, bloating
  - **Chronisch** (ca.15 %): Recidiverende diarree, gewichtsverlies,steatorrhea
  - Vlokatrofie , failure to thrive



10

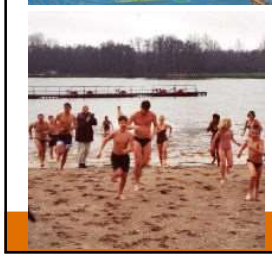
Riskfactors Giardia

	OR univ.	OR multiv.
Swimming	6.8 (2.4-19.3)	15.6 (3.2-77.1)
Contacts with person with gastroenteritis	7.1 (1.8-26.6)	28.6 (3.2-255.6)
Family member attending primary school	2.8 (1.4-5.8)	2.5 (1.0-6.3)

The population attributable risk fraction (PARF) for all these factors was 49% in the GP patients and 76 % for patients in the general population.

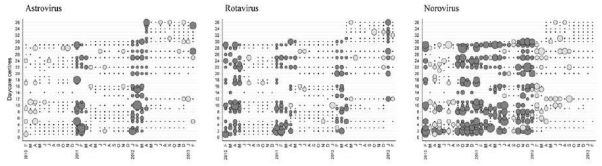
Wat doen nederlanders in de zomer?



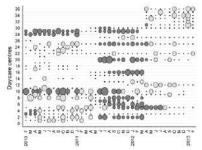



Kinderdagverblijf studie 2010-2013

R. Pijnacker and others



Giardia

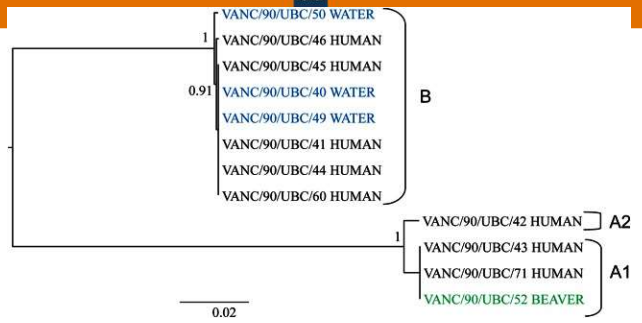


Sommige KDV bijna altijd Giardia positief
Bij enkele nooit Giardia gevonden

Soms altijd assemblage A of B
Soms beide : A en B
Soms alternerend

Fig. 4. Clusters of astrovirus, rotavirus, norovirus, *G. lamblia* and *Cryptosporidium* spp. in Dutch daycare centres from February 2012 to February 2013. The size of the circle correlates with the number of faecal samples positive for the relevant pathogen; no circle indicates absence of samples submitted.

Epidemiol. Infect. (2016), 144, 2527–2539.



Phylogeny of *Giardia* isolates from the Creston outbreak based on four genes (*gdh*, *bg*, *tpi*, and the 18S rRNA gene) and 500 bootstrap replicates. Isolates are colored according to their sources (blue, water; black, human; green, beaver).

Appl Environ Microbiol. 2015 Jul; 81(14): 4827–4834.

Department of Clinical Science

Case – Bergen 2004 outbreak

Hanevik ECCMID

Bergen outbreak Giardia 2004

A prospective follow-up study of 1252 laboratory-confirmed cases of giardiasis (exposed), Bergen, Norway in 2004.

Waterborne outbreak : water reservoir gecontamineerd
Giardia : Assemblage B

Cases: exposed individuals
Controles: non exposed individuals

Patienten langdurig gedocumenteerd door huisartsen

Irritable Bowel Syndrome and Chronic Fatigue 6 Years After *Giardia* Infection: A Controlled Prospective Cohort Study

CID 2014

Kurt Hanevik,[1] Knut-Arne Wensaas,[2] Guri Rortveit,[2,3] Geir Egil Eide,[3,4] Kristine Mørch,[5] and Nina Langeland[1]

[1]Department of Clinical Science, University of Bergen, [2]Research Unit for General Practice, Uni Research Health, [3]Department of Global Public Health and Primary Care, University of Bergen, [4]Centre for Clinical Research, and [5]National Centre for Tropical Infectious Diseases, Department of Medicine, Haukeland University Hospital, Bergen, Norway

The main finding in this study was that there was a high prevalence of CF (30.8%) and IBS (39.4%) 6 years after laboratory-confirmed giardiasis and that these 2 conditions were strongly associated.

Clinical Gastroenterology and Hepatology

Available online 6 March 2018

In Press, Uncorrected Proof — Note to users

Prevalence of Irritable Bowel Syndrome and Chronic Fatigue 10 Years After *Giardia* Infection

Sverre Litleskare[*,‡], Guri Rortveit[*,‡], Geir Egil Eide[*,§], Kurt Hanevik[‖,¶], Nina Langeland[‖,¶], Knut-Arne Wensaas[*,‡]

Results

The prevalence of IBS **10 years** after the outbreak was **43%** (n = 248) among 576 exposed individuals and **14%** (n = 94) among 685 controls (adjusted odds ratio for development of IBS in exposed individuals, 4.74; 95% CI, 3.61–6.23).

At this time point, the prevalence of chronic fatigue was 26% (n = 153) among 587 exposed individuals and 11% (n = 73) among 692 controls (adjusted odds ratio, 3.01; 95% CI, 2.22–4.08). The prevalence of IBS among exposed persons did not change significantly from 6 years after infection (40%) to 10 years after infection (43%; adjusted odds ratio for the change 1.03; 95% CI, 0.87–1.22). However, the prevalence of chronic fatigue decreased from 31% at 6 years after infection to 26% at 10 years after infection (adjusted odds ratio for the change 0.74; 95% CI, 0.61–0.90).

Conclusie Giardia

- Verwekker intermitterende en chronische diarree
- Niet alleen diarree maar ook IBS en chronische vermoeidheid
- Na 10 jaar nog klachten
- Resistentie lijkt toe te nemen

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K.Morch ECCMID 2016

Antigiardial agents	Efficacy clinical studies (%)	Effective dosage adults	Comments
Metronidazole	36 - 100	200 – 500mg tid x 5-7d	Efficacy low when shorter than 5 d
Tinidazole	74 - 100	1.5 – 2g sd x 1d	Single dose treatment as effective as longer course due to longer half-life
Ornidazole	90 - 100	1-2g sd x 1d	
Secnidazole	79 - 100	2g sd x 1d	
Nitazoxanide	56 - 94	500mg bid x 3d	
Furazolidone	20 - 92	100mg qid x 10d	
Albendazole	62 - 96	400mg sd x 5d	5 RCTs: Less effective than tinidazole[†] 10 RCTs: Similar effectivenes to metronidazole[#]
Mebendazole	0 - 95	200mg tid x 3 -5d	
Quinacrine	77 - 100	100mg tid x 5d	Risk neuropsychiatric side effects
Paromomycin	40 - 92	500mg tid x 7d	Only drug recommended in first trimester of pregnancy
Chloroquine	86	10mg/kg bid x 5d	
Bacitracin zinc	95	120 000 U bid 10d	One RCT 1995

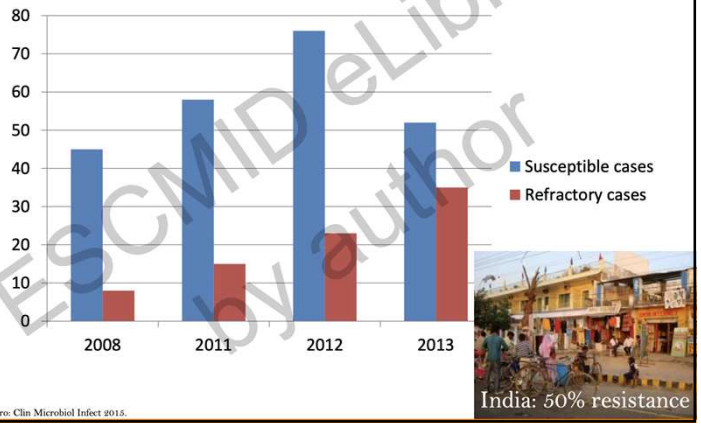
Morch: Giardiasis. PhD thesis http://hdl.handle.net/1956/3996 2010. Granados: Cochrane review 2012. [†]Escobedo: Acta Tropica 2016.
[#]Soumaoro: PLOS Negl Trop Dis 2014.

20

Failure first line treatment

- Retrospective study travellers Spain 2007-09
  - Nitroimidazole-failure
    - Total 22% (21/99)
    - Asia 33% (12/36)
- Bergen outbreak 2004
  - Metronidazole-failure
    - 3% (42/1268)

Nitroimidazole treatment failure - London
Increase from 15% to 40%



Nabarro: Clin Microbiol Infect 2015.

Treatment ladder Bergen outbreak (N=38)

Albendazole 400mg x 2 + metronidazole 250mg x 2 for one week

If failure

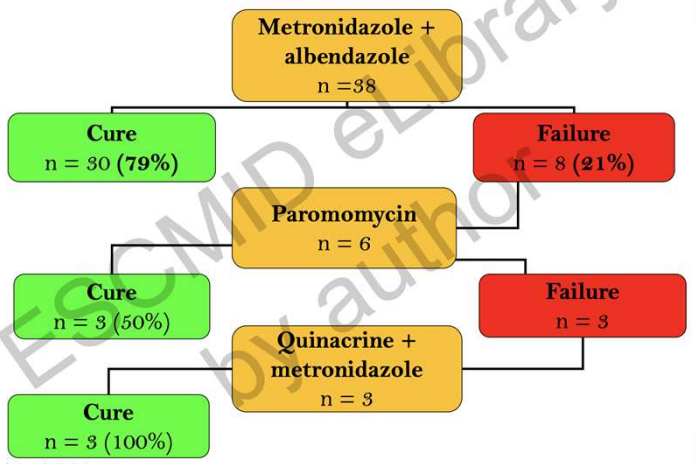
Paromomycin 500mg x 3 for one week

If failure

Quinacrine 100mg x 3 + metronidazole 750mg x 3 for three weeks

March: Journal of Infection 2008.

Results



March: Journal of Infection 2008.

Wat te doen bij resistentie?

Zie ESCMID library (vrije toegang!)
https://www.escmid.org/escmid_publications/escmid_elibrary

- Kurt Hanevik (Noorwegen): 2013 S217
- Kristine Mørch (Noorwegen) : 2016 S630

- **Treatment ladder**:
  - Eerst metronidazol **of** albendazol
    - Als dat niet werkt: metronidazol **en** albendazol
      - Als dat niet werkt: quinacrine en metronidazol

VIIth International *Giardia* and *Cryptosporidium* Conference

Conference Abstracts on USB Key

June 23-26, 2019

Rouen 2019 Nieuwe inzichten

- Recirculation of *Giardia duodenalis* genotype A in children after treatment with metronidazole: reinfection or parasitic resistance?

Fantinatti M1, Oliveira LAPL1, Cascais T1, Austriaco-Teixeira P1, Verrissimo E2, Bello AR2, Da-Cruz AM1,2. (Brasil)

- Understanding metronidazole resistance in *Giardia duodenalis*: Identifying patterns by transcriptomics combined with biochemical analysis of two oxygen-insensitive nitroreductases

Krakovka1,S; Svärd1, SG (Sweden)

- Metronidazole drug-resistance in *Giardia*: emerging roles of epigenetic and post-translational modifications and sub-species variation

Samantha J. Emery-Corbin1, Louise Baker2, Brendan R.E. Ansell2, Mehdi Mirzaei3,4, Paul A. Haynes3, Ernest Lacey3,5, Malcom J. McConville6, Staffan G. Svärd7, Aaron R. Jex1,2 (Australia, Sweden)

- Exploring genomic variation in Giardia duodenalis using well characterised reference isolates

Aaron R. Jex1,2 Xaidong Fang3, Feifei Xu4, Filip Wiesz5, Swapnil Tichkule2, Brendan Ansell2, Emery S2, Norbert Mü ller5, Marco Lalle6, Cacciò S6, Staffan Svärd GS7 and Robin B. Gasser1 (Australia, Switserland, China, Italy)

- Mtz resistance phenotypes in *Giardia* is complex:
  - *in vivo* isolates often lose resistance *in vitro*,
  - and resistance *in vitro* is rarely genetically fixed, with reversion to sensitivity after drug selection ceases, or via passage through the life cycle.

Nieuwe inzichten

TISSUE BARRIERS
2017, VOL. 5, NO. 1, e1274354 (16 pages)
http://dx.doi.org/10.1080/21688370.2016.1274354

Taylor & Francis

REVIEW

Interactions of *Giardia sp.* with the intestinal barrier: Epithelium, mucus, and microbiota

Thibault Allain[a,b,c], Christina B. Amat[a,b,c], Jean-Paul Motta[a,b,c], Anna Manko[a,b,c], and André G. Buret[a,b,c]

[a]Department of Biological Sciences, University of Calgary, Calgary, AB, Canada; [b]Inflammation Research Network, University of Calgary, Calgary, AB, Canada; [c]Host-Parasite Interactions, University of Calgary, Calgary, AB, Canada

ABSTRACT
Understanding how intestinal enteropathogens cause acute and chronic alterations has direct animal and human health perspectives. Significant advances have been made on this field by studies focusing on the dynamic crosstalk between the intestinal protozoan parasite model *Giardia duodenalis* and the host intestinal mucosa. The concept of intestinal barrier function is of the highest importance in the context of many gastrointestinal diseases such as infectious enteritis, inflammatory bowel disease, and post-infectious gastrointestinal disorders. This crucial function relies on 3 biotic and abiotic components, first the commensal microbiota organized as a biofilm, then an overlaying mucus layer, and finally the tightly structured intestinal epithelium. Herein we review multiple strategies used by *Giardia* parasite to circumvent these 3 components. We will summarize what is known and discuss preliminary observations suggesting how such enteropathogen directly and/ or indirectly impairs commensal microbiota biofilm architecture, disrupts mucus layer and damages host epithelium physiology and survival.

ARTICLE HISTORY
Received 2 November 2016
Revised 13 December 2016
Accepted 14 December 2016

KEYWORDS
commensals; *Giardia duodenalis*; Giardiasis; host-parasite interactions; intestinal microbiota biofilm; mucus layer; poly-microbial infection

Nieuwe inzichten

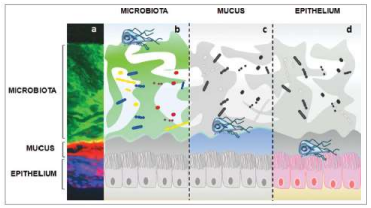


Figure 1. *Giardia* interactions with gut triple barrier (microbiota, mucus, epithelium). a) characterization of intestinal barriers geographical distribution in mice immunostaining Colonic sections were stained with EUB-388 (bacteria; αDNA), WGA (mucus; Life Technologies) and DAPI (epithelial cells; SIGMA). b) commensals are mostly organized in biofilms throughout the gastrointestinal tract. It has been observed that this resident microbiota plays a role in host susceptibility to *Giardia* infection. Some commensals (ex: lactic acid bactaria) even exhibit anti-giardial effects. In turn, *Giardia* has the ability to modulate commensals to pathobionts by inducing virulence factors and also disrupting intestinal biofilms. The resulting shift of gut microbiota may help explain the production of post- infectious symptoms. c) To attach the epithelium, trophozoites must breach the mucus layer, which acts as a biochemical / physical barrier. Little is known regarding the role of mucus during *Giardia* infection. Ongoing research indicates that *Giardia*'s proteolytic activity may disrupt MUC2 mucin, the major constituent of intestinal mucus in humans; d) Trophozoites strongly attach to epithelial microvilli, and disrupt the epithelial barrier. Disaccharidase deficiencies, diffuse microvillous shortening, arginine starvation, increased permeability, disruption of tight junctions and enterocyte induced apoptosis have been associated with *Giardia* infection. Extracellular factors such as cathepsin B-like cysteine proteases contribute to the parasite virulence by degrading CXCL 8 (IL-8) and inducing villin breakdown.

Nieuwe inzichten

Trends in Parasitology

CellPress

Review

Pathogenic Mechanisms of *Cryptosporidium* and *Giardia*

Gabriela Certad,[1,2,*] Eric Viscogliosi,[1] Magali Chabé,[1] and Simone M. Cacciò[3]

Intestinal protozoa are important etiological agents of diarrhea, particularly in children, yet the public health risk they pose is often neglected. Results from the Global Enteric Multicenter Study (GEMS) showed that *Cryptosporidium* is among the leading causes of moderate to severe diarrhea in children under 2 years. Likewise, *Giardia* infects approximately 200 million individuals worldwide, and causes acute diarrhea in children under 5 years. Despite this recognized role as pathogens, the question is why and how these parasites cause disease in some individuals but not in others. This review focuses on known pathogenic mechanisms of *Cryptosporidium* and *Giardia*, and infection progress towards disease.

Trends

Infection by *Cryptosporidium* or *Giardia* can result in symptoms in some individuals but can lead to an asymptomatic state in others.

Common effects on host epithelial cells include disruption of the mucus layer, attachment to (*Giardia* and *Cryptosporidium*) and/or invasion of epithelial cells (*Cryptosporidium*), release of effector molecules into the host cell cytoplasm and secretion of toxins.

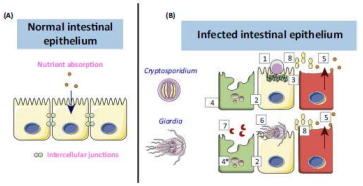
However, pathogenic mechanisms are not identical. For instance, *Giardia* is

Cryptosporidium and *Giardia*: Two Neglected Intestinal Parasites

Nieuwe inzichten

Trends in Parasitology

CellPress



Trends in Parasitology

Figure 1. The Pathogenesis of *Cryptosporidium* and *Giardia*. Schematic view of the main interactions between the two protozoa and intestinal epithelial cells in the luminal and mucosal environment. (A) The intestinal epithelium is formed by a single layer of epithelial cells (normal epithelial cells are represented in yellow) that functions as a physical barrier between the lumen and the subepithelial tissue. Within the barrier, epithelial cells are held together by complex structures known as intercellular junctions. This barrier controls nutrient absorption and prevents the passage of microorganisms, luminal antigens, and toxins to the mucosal tissue. Normal epithelial cells are represented in yellow. (B) After invasion, *Cryptosporidium* is located in an extracytoplasmic niche inside a parasitophorous vacuole (1). Interaction between *Cryptosporidium* and the apical surface of the epithelial cell results in the localized activation of signaling cascades, culminating in barrier disruption (2) and polymerization of actin filaments (3) in the region of host–parasite interaction. *Cryptosporidium* inhibits cell apoptosis (apoptotic cells are represented in green with fragmented nuclei) at the trophozoite stage, but promotes this process at the sporozoite and merozoite stages (4). Several molecules, such as phospholipases, proteases, and hemolysins, may cause cellular damage, enhancing fluid secretion from the crypts and supporting diarrhea due to active secretion and malabsorption. As a consequence, cell death (dead cells are represented in red) may occur (5). *Giardia* trophozoites adhere to epithelial cells via a specialized ventral structure, the adhesive disc (6). Attachment to epithelial cells may target specific signaling networks, including those of caspases (7), that can activate apoptosis (4*). This leads to the loss of intercellular junctions (3), cytoskeleton rearrangement, and barrier dysfunction, which can contribute to the pathophysiological mechanisms, such as electrolyte secretion and malabsorption, underlying diarrhea (5). Complex interactions between *Cryptosporidium* and *Giardia* with the microbiota (8) in luminal and mucosal environments likely influence **infectivity** and disease outcomes.

SWAB & NVP

- Initiatief Foekje Stelma om advies SWAB en NVP te controleren op discrepanties en eventueel aan te passen
- Giardia voorstel Bert Mulder en Theo Mank

Gastroenteritis **Giardia lamblia** https://adult.swabid.nl/en/node/7994 ja

Advices

Priority	**Score**	**Medication**	**Remarks**
≥ 18 years			
1e keus		Metronidazol po 500mg 3dd 7 d	
Alternatieve 1e keus		Albendazol po 400mg 1dd 5 d	
≥ 18 years			
Indicatie: Bestaande zwangerschap		Paromomycine po 500mg 3dd 7 d	

1 – 18 jaar

1e keus metronidazol po 10 mg/kg 3dd 7 days

1e keus alternatief po albendazol 5 mg/kg 1dd 5 days

Comments

- Symptoomloos draperschap komt voor; in voorkomende gevallen (bijvoorbeeld bij recidiverende infecties binnen een gezin) behandeling overwegen
- Meestal is behandeling met metronidazol of albendazol effectief (± 90 %). Therapie resistente infecties kunnen voorkomen. In deze gevallen kan een combinatie van metronidazol en albendazol effectief zijn.
- Tijdens zwangerschap is de eerste keus om bij weinig klachten de behandeling uit te stellen tot na de bevalling. Indien behandeling wel geïndiceerd is, heeft paromomycine de voorkeur.
- Metronidazol dient niet tegelijkertijd met alcoholische drank genuttigd te worden.
- Albendazol tijdens zwangerschap alleen op strikte indicatie gebruiken. Bij dieren is albendazol in therapeutische doseringen schadelijk gebleken.
- Albendazol is geregistreerd voor kinderen vanaf 6 jaar. Bij kinderen tussen 1 en 6 jaar is albendazol wereldwijd uitvoering gebruikt en kan overwogen worden (Keijzer et al).
- Albendazol innemen met vetrijke maaltijd (verhoogd resorptie).

An algorithm for Ddx

- should we make a difference in age groups?
- are clinical symptoms indicative?
- are costs and lab logistics most important ?

- Algoritm for laboratory investigation of intestinal parasites
  - For patients of GPs and in hospital
  - Method of choice: PCR for Giardia and Cryptosporidium
    - Within 2 years all Dutch labs that offer diagnostic tests have to implement PCR

Richtlijn Laboratoriumdiagnostiek van intestinale parasieten

INITIATIEF
Nederlandse Vereniging voor Medische Microbiologie

IN SAMENWERKING MET
Nederlandse Vereniging voor Parasitologie
Nederlandse Internisten Vereniging
Nederlandse Vereniging Infectieziektebestrijding
Nederlands Huisartsen Genootschap
Nederlandse Vereniging voor Kindergeneeskunde

MET ONDERSTEUNING VAN
B.S. Niël-Weise, zelfstandig richtlijnmethodoloog

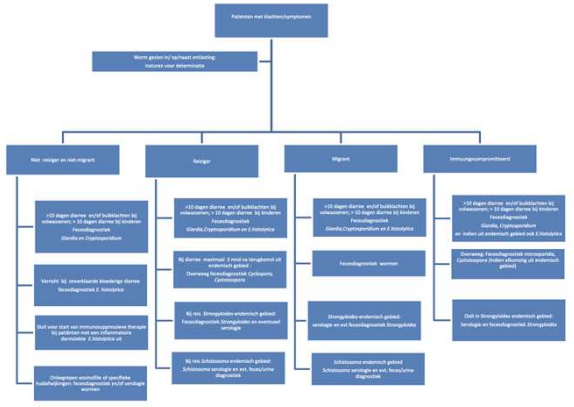
FINANCIERING
De richtlijnontwikkeling werd gefinancierd uit de Kwaliteitsgelden Medisch Specialisten (SKMS)

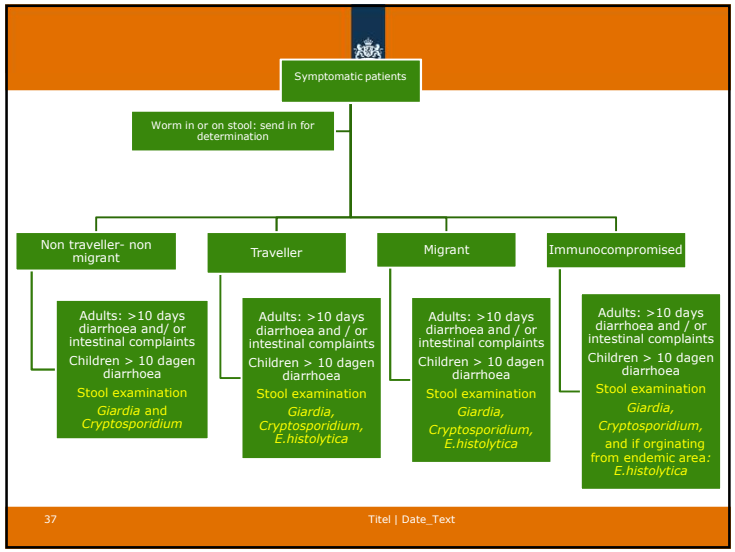
Geautoriseerd door:
Nederlandse Vereniging voor Medische Microbiologie
Nederlandse Internisten Vereniging
Nederlandse Vereniging voor Kindergeneeskunde
Nederlandse Vereniging voor Parasitologie
Nederlandse Vereniging Infectieziektebestrijding

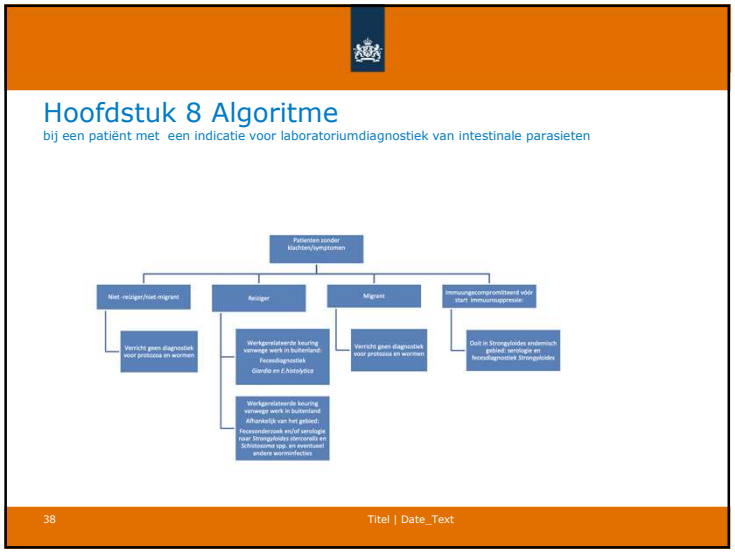
Nederlands Huisartsen Genootschap heeft geen bezwaar.

Hoofdstuk 8 Algoritme

bij een patiënt met een indicatie voor laboratoriumdiagnostiek van intestinale parasieten




Symptomatic patients
Worm in or on stool: send in for determination
Non traveller- non migrant
Traveller
Migrant
Immunocompromised
Adults: >10 days diarrhoea and/ or intestinal complaints
Children > 10 dagen diarrhoea
Stool examination
Giardia and Cryptosporidium
Adults: >10 days diarrhoea and / or intestinal complaints
Children > 10 dagen diarrhoea
Stool examination
Giardia, Cryptosporidium, E.histolytica
Adults: >10 days diarrhoea and / or intestinal complaints
Children > 10 dagen diarrhoea
Stool examination
Giardia, Cryptosporidium, E.histolytica
Adults: >10 days diarrhoea and / or intestinal complaints
Children > 10 dagen diarrhoea
Stool examination
Giardia, Cryptosporidium,
and if orginating from endemic area: E.histolytica
37
Titel | Date_Text


Hoofdstuk 8 Algoritme
bij een patiënt met een indicatie voor laboratoriumdiagnostiek van intestinale parasieten
38
Titel | Date_Text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