Leiden University Medical Center

NDFB
Nederlandse Donor Feces Bank

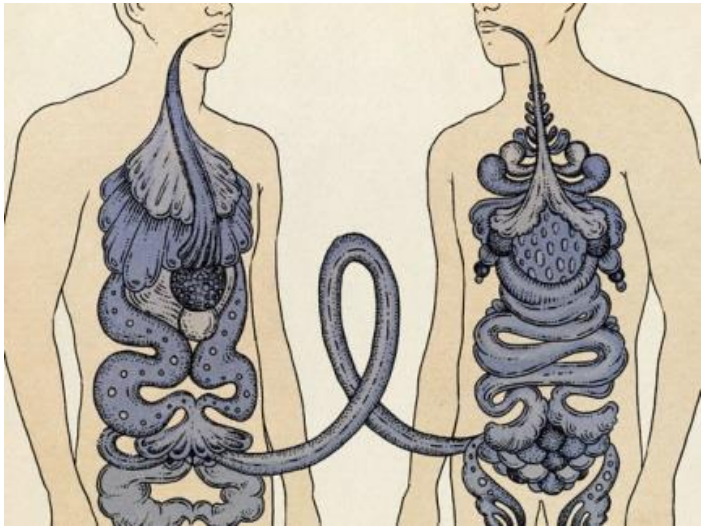
Het nieuwe bruine goud

Feces Microbiota Transplantaties via de Nederlandse Donor Feces Bank

Dr. E.M. Terveer
Medical microbiologist, LUMC

November 16th 2022

TRIP

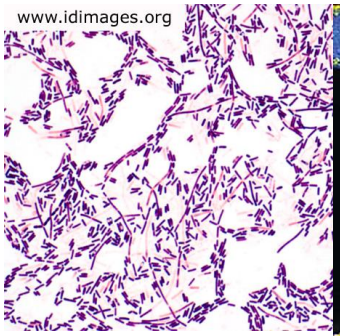


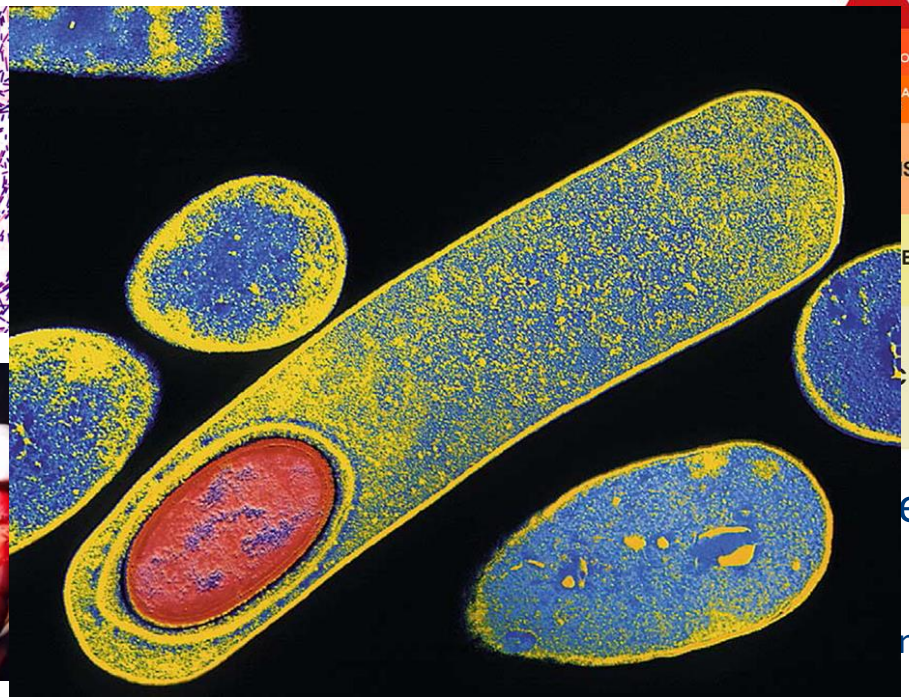
What to discuss in 30 minutes

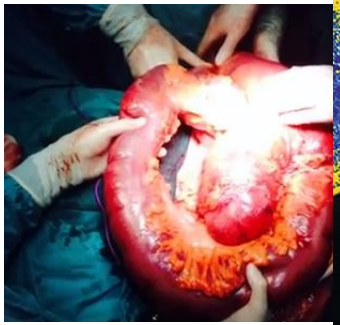
- The indication of fecal microbiota transplantation
- The stool bank: Netherlands Donor Feces Bank
- Results of the NDFB
  - Donor selection & screening
  - Processing fecal suspension
  - Patients
- Regulation of FMT

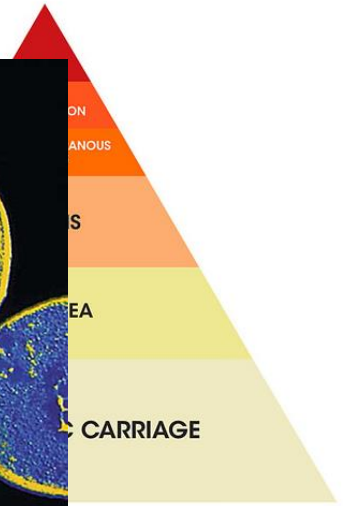
Clostridioides difficile

Gram positive, spore producing rod









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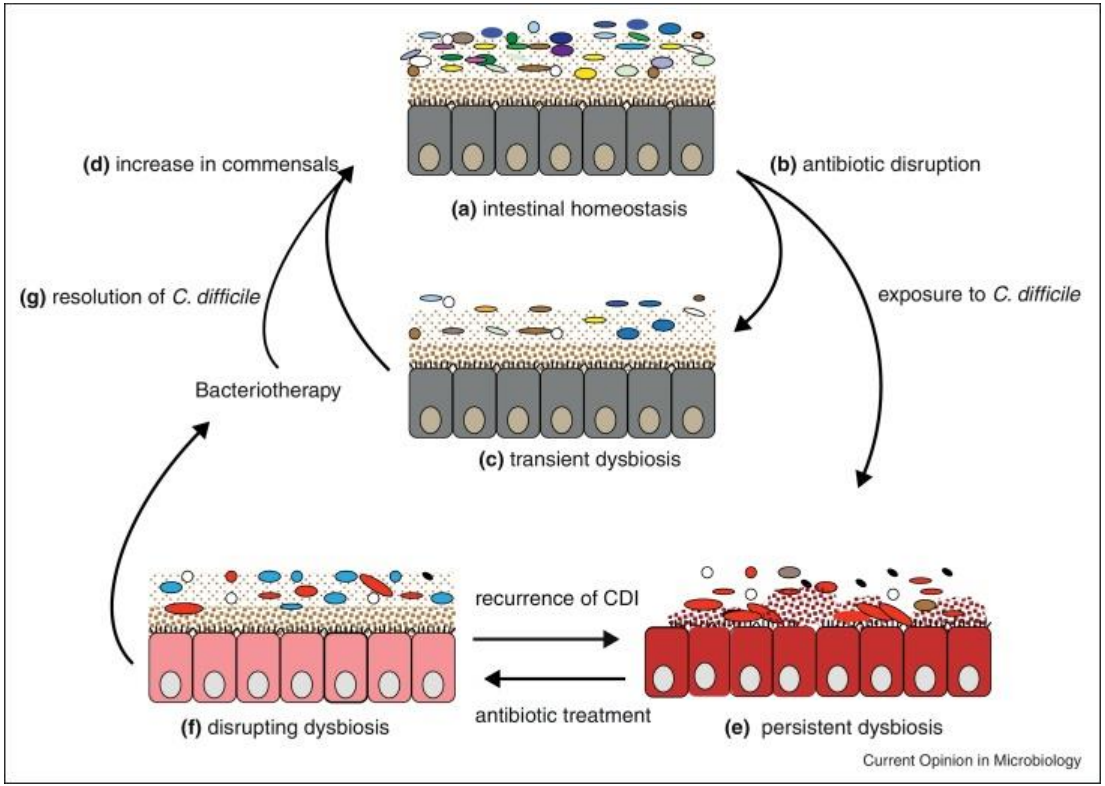
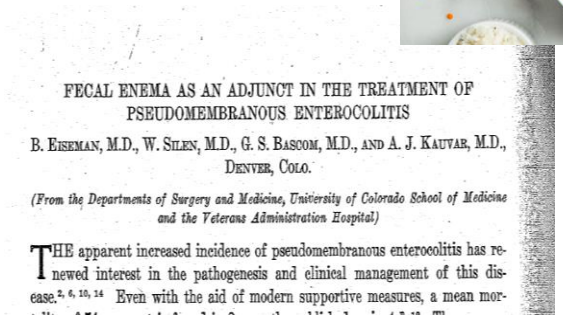
Perturbed microbiota



Adamu et al., Curr Opin Microbiol, 2013

Fecal microbiota transplantation, anecdote to RCT

- First described as ‘Yellow soup’ 400 AD
- First case-series: 1958
- First RCT: 2013



FECAL ENEMA AS AN ADJUNCT IN THE TREATMENT OF PSEUDOMEMBRANOUS ENTEROCOLITIS

B. Eiseman, M.D., W. Silen, M.D., G. S. Bascom, M.D., and A. J. Kauvar, M.D., Denver, Colo.

(From the Departments of Surgery and Medicine, University of Colorado School of Medicine and the Veterans Administration Hospital)

THE apparent increased incidence of pseudomembranous enterocolitis has renewed interest in the pathogenesis and clinical management of this disease.[2, 6, 10, 14] Even with the aid of modern supportive measures, a mean mor-

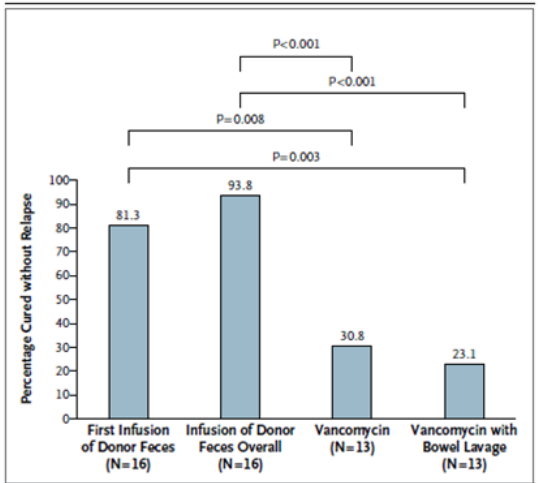


Figure 2. Rates of Cure without Relapse for Recurrent *Clostridium difficile* Infection.

Shown are the proportions of patients who were cured by the infusion of donor feces (first infusion and overall results), by standard vancomycin therapy, and by standard vancomycin therapy plus bowel lavage.

Eiseman, 1958 & van Nood, NEJM, 2013

Total clinical activity of FMT in Europe

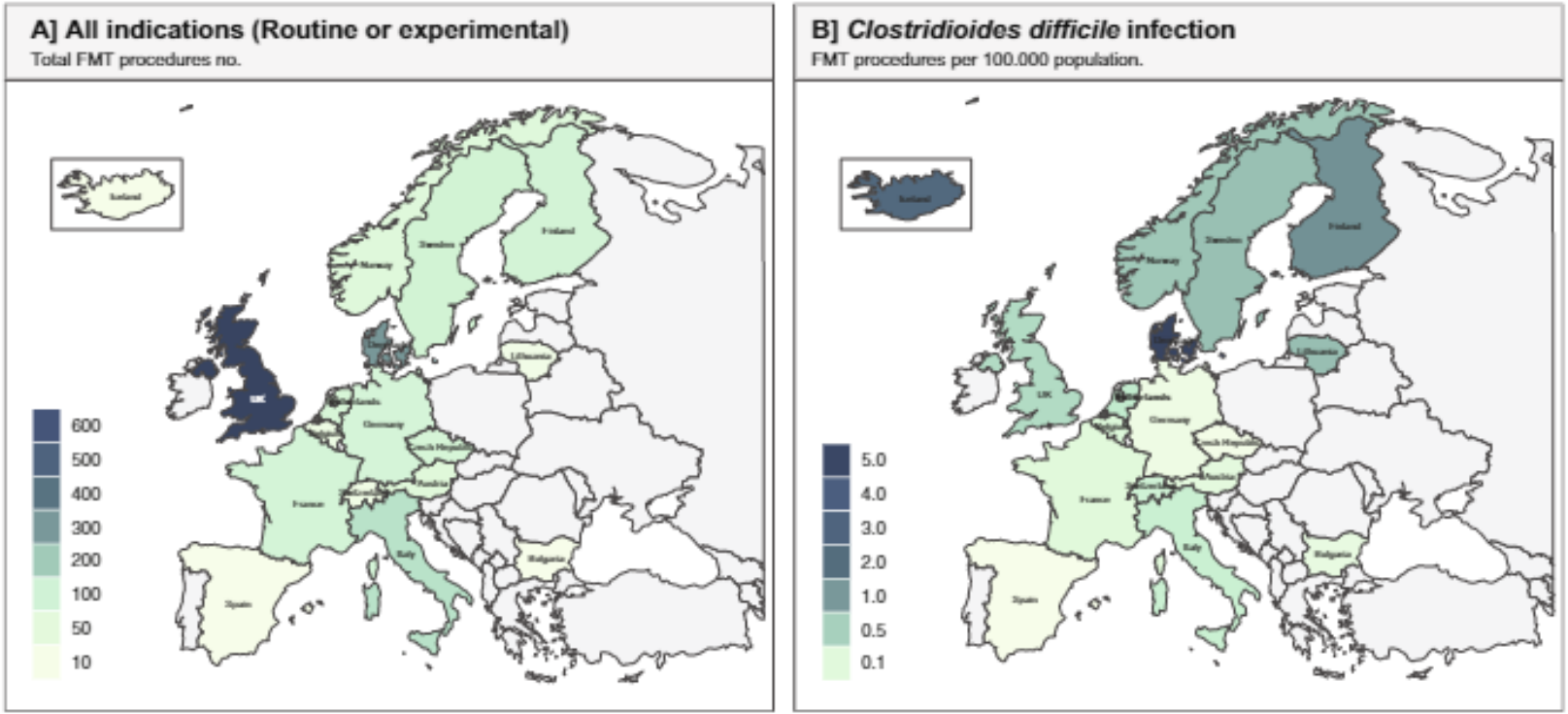
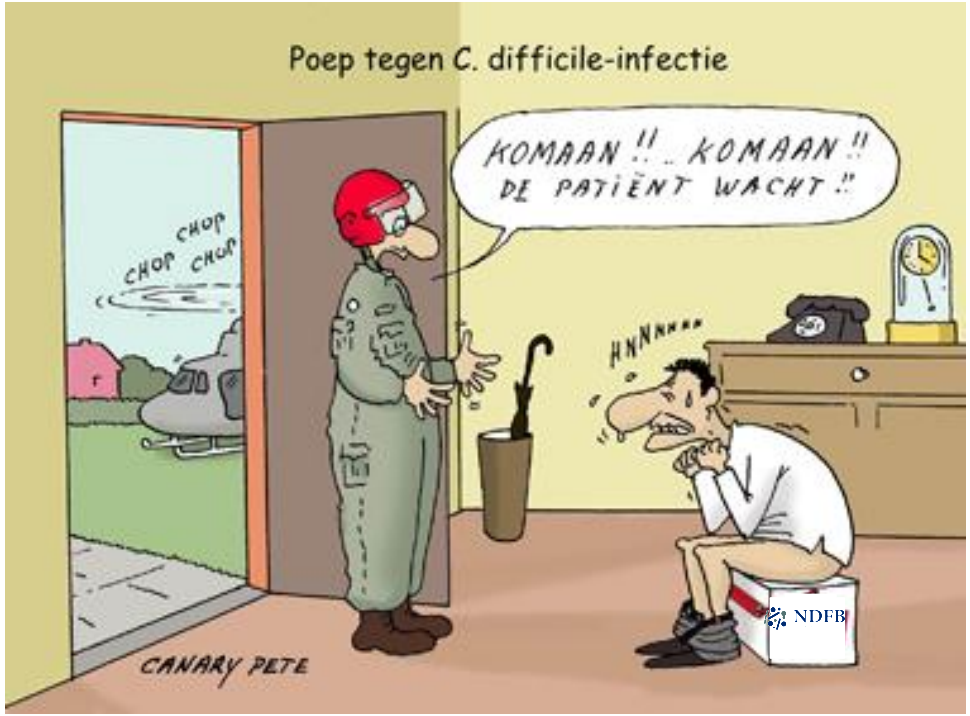


Fig. 2. Total clinical activity of faecal microbiota transplantation (FMT) across Europe and for *Clostridioides difficile* infections adjusted to per 100,000 population.

The set-up of a stool bank



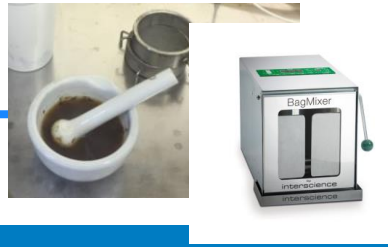
https://www.youtube.com/watch?v=1czGTqTIVZY

Netherlands Donor Feces Bank (NDFB)

- Non-profit
- Provide ready-to-use donor feces samples
  - Widely available, treatment in local hospital
- Guarantee safety and quality of FMT
  - Central donor pool of well screened donors
  - Uniform and standardized procedures (SOPs)
  - Storage of feces quality controls in case of adverse event
- Research & innovation

Feces

Process



Ready to use fecal suspension

How to establish and run a stool bank

Contents lists available at ScienceDirect

Clinical M

ORIGINAL ARTICLE

CMI

ueg journal WILEY

THE LANCET

Gastroenterology & Hepatology

Available online 16 September 2022

In Press, Corrected Proof

· stool banking for faecal microbiota
ısus report from a multidisciplinary

Comment

Minimising the risk of monkeypox virus transmission during faecal microbiota transplantation: recommendations from a European expert panel

Gianluca Ianiro [a, b] ✉, Benjamin H Mullish [c], Tariq H Iqbal [d, e], Elisabeth M Terveer [f, g], Simon Mark Dahl Baunwall [h], Alexander Link [i], Harry Sokol [j, k, l], Juozas Kupcinskas [m], Luca Masucci [n], Maurizio Sanguinetti [n], Maria J G T Vehreschild [o], Christian L Hvas [h], Josbert J Keller [f, p], Antonio Gasbarrini [a, b], Ed J Kujiper [f, g], Giovanni Cammarota [a,

ijevaar[3,4] | Christian L. Hvas[5] |
. Lieberknecht[7] | Christoph Högenauer[8] |
2 | Oleksiy Gridnyev[13] | Francis Mégraud[14] |
15 | Simon D. Goldenberg[16] |
18 | Maurizio Sanguinetti[19] |
orofeev[21] | Olena Gubska[22] |
| Ramesh P. Arasaradnam[23] | Shiv K. Sarin[24] |
| Laurent Alric[27] | Simon M. D. Baunwall[5] |
ink[29] | Abraham G. Goorhuis[30] |
sioen[4] | Georgina L. Hold[32] | Herbert Tilg[33] |
16 | Antonio Gasbarrini[20] | Chris J. J. Mulder[3,4] |
G. T. Vehreschild[7,36,38,39]

Organisation of stool banks

Standards defined by the EU Tissue and Cells Directive (EUTCD)

Feces regarded as substance of human origin (SoHo)

1. Organisational plan for
    1. All intended activities
    2. Responsible persons/qualified personnel
2. Quality system
3. SOPs
4. Auditing (national/international)
5. Data management → traceability
    1. Donors
    2. Fecal suspensions
    3. Patients → Outcome & Adverse events

Donor screening

Questionnaire: Risk assessment

1. transmissible diseases
2. illnesses associated with disturbed microbiota

Exclusion criteria: Age <18 or ≥ 50, BMI <18.5 or > 25, high risk fecal- and or blood transmittable diseases, recent antibiotic use (<6 months), gastrointestinal complaints, recent travel to endemic areas of GI pathogens, (close relative with) inflammatory bowel disease or GI malignancy, auto-immune disease, neuropsychiatric disease, substantial comorbidity, various medication

Laboratory screening serum

- Hepatitis A (IgM + IgG)
- Hepatitis B (HBsAg + anti-Hbcore)
- Hepatitis C (anti-HCV)
- Hepatitis E (IgM + IgG)
- HIV (anti-HIV, type 1 and 2)
- Lues (Ig)
- Cytomegalovirus (IgM + IgG)
- Epstein Barr Virus (IgM + IgG)
- Strongyloïdes (IgG1/IgG4)[1]

[1]If travel history to South America, Africa or Asia

Laboratory screening feces

- *Clostridium difficile* (*TcdB* PCR)
- *Helicobacter pylori* (antigen test)
- Bacterial gastro-enteritis (PCR + culture: *Salmonella* spp. *Campylobacter jejuni* and *C. coli*, *Shigella* spp., *Yersinia enterocolitica* and *Y. pseudotuberculosis, Aeromonas* spp. and *Plesiomonas shigelloides*) Shiga-toxin producing *E.coli* (*Stx1/Stx2/EscV*)
- Multidrug-resistant micro-organisms; ESBL and/or carbapenemase producing and/or quinolone and aminoglycoside resistant Gram negatives, VRE, MRSA
- Virus: Norovirus serotype I+II, Astrovirus, Sapovirus, Rotavirus, Adenovirus 40/41, Adenovirus non-40/41, Enterovirus, Parechovirus
- Parasites: *Giardia lamblia*, *Entamoeba histolytica, Cryptosporidium parvum and C. hominis, Microspiridium, Dientamoeba fragilis, Blastocystis hominis, Strongyloides*[1]

Short questionnaire every donation: Recent health-related issues:

Stool frequency/pattern, general health, use of antibiotics, travel history, sexual behaviour

Terveer et al., CMI, 2017 & Terveer UEG journal 2020

Donor screening is extensive

Table 1. Results of the donor selection and screening process.

Donors (%)	Action	Excluded (%)	Exclusion reasons[a]
871	Request for more information by donor	603 (69%)	52% ($n=311$) withdrawal after reading additional information, 22% ($n=132$) unable to deliver faeces 2 h after defaecation, 20% ($n=121$) age >50 years,[b] 8% ($n=49$) increased risk disturbed microbiota (bowel complains, medication use, comorbidity, depression, BMI>25 m^2/kg, etc.), 5% ($n=29$) other
268 (100%) ↓	Donor fills-out an extended questionnaire	185 (69%)	22% ($n=41$) comorbidity/medication use, 22% ($n=40$) BMI<18.5 or >25 m^2/kg, 18% ($n=33$) (history of) depression, 15% ($n=28$) profession of healthcare worker,[c] 14% ($n=25$) age >50 years,[b] 14% ($n=25$) bowel complaints, 12% ($n=22$) inability to deliver faeces <2 h, 10% ($n=19$) withdrawal after completing questionnaire, 6% ($n=12$) (close relative with) IBD, 5% ($n=9$) frequent travelling, 4% ($n=7$) risk factor for colon carcinoma,[d] 3% ($n=6$) high risk sexual behaviour, 7% ($n=13$) other
83 (31%) ↓	Interview	17 (20%)	65% ($n=11$) donors withdrawal or failure to deliver faeces <2 h once a week, 35% ($n=6$) donors excluded based on interview (IBS complaints, comorbidity, psychological evaluation, patient contact, atopy)
66 (25%) ↓	Faeces[e] screening	47 (71%)	89% ($n=42$) *Dientamoeba fragilis*, 15% ($n=7$) MDRO, 9% ($n=4$) *Blastocystis* sp., 4% ($n=2$) *Helicobacter pylori*, 2% ($n=1$) *Campylobacter jejuni*, 2% ($n=1$) *Entamoeba histolytica*
22[f] (8%) ↓	Serum screening	0 (0%)	None
22[f] (8%) ↓	First rescreening and donor withdrawal	6 (27%)	Exclusion of quarantined donor suspensions: 83% ($n=5$) difficulty to implement donation in daily practice, 17% ($n=1$) MDRO and refusal to perform rescreening
16 (6%)	Active donor		

Terveer et al., CMI, 2017 & Terveer UEG journal 2020

How to prepare a fecal suspension?

- 60 gram donor feces < 2h after defecation
- Homogenisation: Saline + bagmixer
- End volume 10% glycerol (cryoprotectant)
- 200 cc fecal suspension
- Storage at -80°C
  - Quality control: suspension 2cc
  - Quality control: feces
  - Fecal suspension 198cc
- Quarantine 2 months

5501177 – 001

FMT Feces

NDFB
Nederlandse Donor Feces Bank

Nederlandse Donor Feces Bank

Fecessuspensie voor Feces Microbiota Transplantatie
Ingrediënten: Donorfeces gefilterd tot 300 micron, glycerol (10%) in NaCl (0.9%).

Bewaren bij -80 °C !

Ontdooi advies voor gebruik:
- Ontdooi de donor fecessuspensie na aankomst overnacht bij 4°C (in koelkast) of 5 uur bij kamertemperatuur.
- Indien de donor fecessuspensie in de koelkast is ontdooid, laat de suspensie dan circa 1 uur op kamertemperatuur komen voorafgaand aan infusie.
- Op kamertemperatuur is de fecessuspensie maximaal 3 uur houdbaar (eventueel nog 6 uur op ijs/in de koelkast).
- De donor fecessuspensie kan niet opnieuw worden ingevroren.

Waarschuwing:
Dit product kan voedselallergenen bevatten.

Adverse event:
Direct melden aan info@NDFB.nl en/of een van de artsen van de Nederlandse Donor Feces Bank werkgroep (zie formulier Toediening Feces Microbiota Transplantatie).

Houdbaarheidsdatum:
xx-xx-xxxx (productiedatum +2 jaar).

FMT Feces suspensie

Donornr.:	5501177
Suspensienr.:	5501177 – 001A
Productiedatum:	08 – 03 – 2016
Houdbaarheidsdatum:	08 – 03 – 2018
Volume suspensie:	198 ml

Bewaren bij – 80°C

5501177 – 001QCSA
08 – 03 – 2016
FMT QC

5501177 – 001QCFA
08 – 03 – 2016
Feces QC

Evaluation FMT request by FMT expert team

Evaluation of 241 FMT candidates:

- 177 (73%) suitable for FMT
- 64 (27%) not suitable
  - Mostly due underlying bowel disease + *C. difficile* carriership

→ Limit unnecessary use

→ Appropriate use of unstandardized therapy

NDFB – Clinical results

May 2016 – Sept 2022:

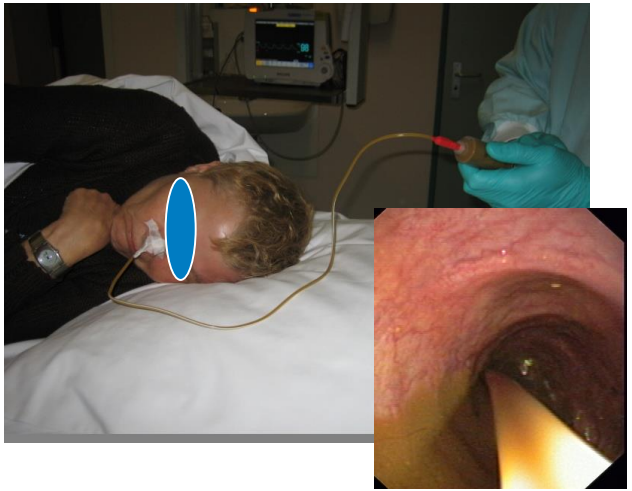
- 248 FMTs in 220 patients with rCDI
- >200 FMTs clinical studies
- 64 hospitals
- 18 donors

Patient characteristics:

- 1st episode – 9th recurrence
  - median 3 relapses (average 3.2)
- Mean age: 70 year
- 60% female

Preparation patient

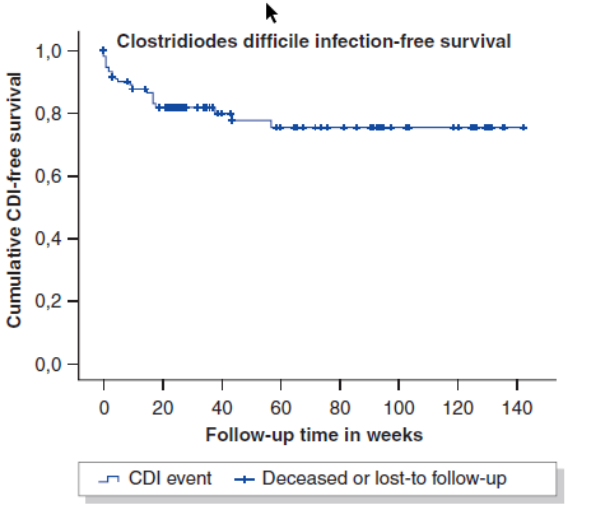
- Antibiotic anti-CDI pretreatment antibiotic ≥ 4 days, stop 1-day prior FMT
- Klean-prep (bowel lavage)
- Nasoduodenal tube
- 198cc in 20 minutes



- Remove nasogastric tube after 30 min
- Monitor patient at least 2 hours (p/RR/T)
- Advise patient → toilet before leaving → loose stools after FMT

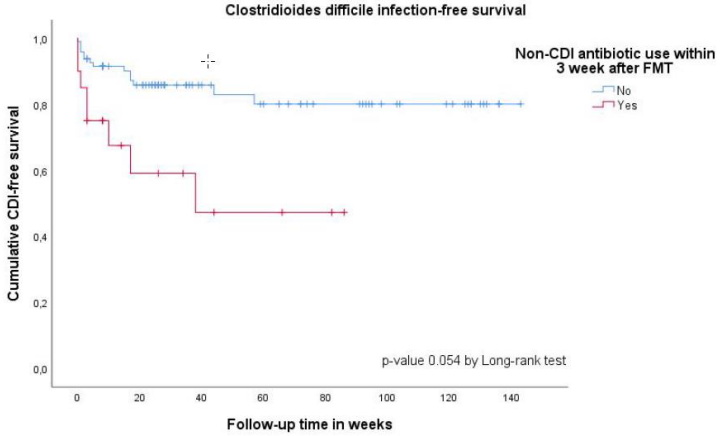
Cure rate after FMT

- Cure rate 90% after 2 months (142/158)



Number of patients at risk for CDI after FMT:

Time (weeks)	0	3	8	20	40	60	80	100	120	140
Patients (number)	129	119	105	70	37	31	23	14	11	1



Biovigilance

- Tissue Guide: *Systematic monitoring of serious adverse reactions and events from donor selection to follow up of the recipient*

Description adverse event		Number of patients
Definitively or probably related to FMT		
SAE	None	0% (0/128)
AE	Procedure-related AEs	4% (5/128)
	– Regurgitation, no aspiration, patient successfully treated	– 4
	– Sore throat after placing duodenal tube	– 1
Possibly related to FMT		
SAE	Hospitalization within 3 weeks post-FMT due to:	8% (9/115)
	– Lower respiratory tract infection (causing pathogen unknown)[a]	– 5
	– Urinary tract infection (causing pathogen unknown)[b]	– 3
	– Diarrhoea (non-CDI)	– 1
AE	Gastro-intestinal (see Table 4)	11–52%
	Infections	– 5
	– Urinary tract infection (causing pathogen unknown)[b]	– 1
	– Urinary and lower respiratory tract infection[a]	– 1
	Other	– 1
	– Fever	
	– Possible flare IBD (ulcerative colitis), uncertain if it was pre-existent	

Terveer *et al.*, UEG Journal, 2020

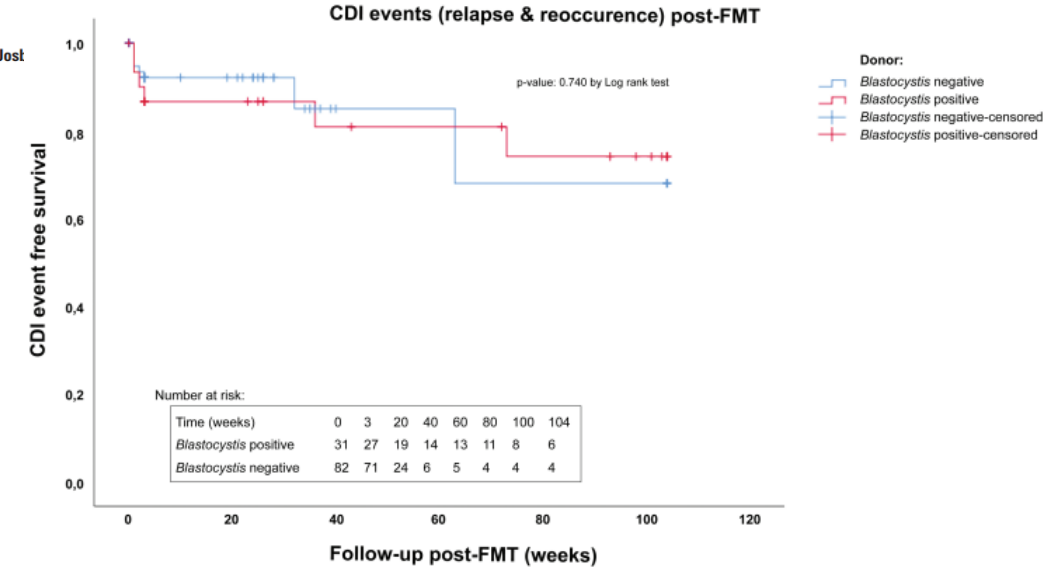
The benefit of tracebility

Clinical Infectious Diseases

MAJOR ARTICLE

Human Transmission of *Blastocystis* by Fecal Microbiota Transplantation Without Development of Gastrointestinal Symptoms in Recipients

Elisabeth M. Terveer,[1,2] Tom van Gool,[3] Rogier E. Ooijevaar,[2,4] Ingrid M. J. G. Sanders,[1] Eline Boeije-Koppenol,[1,2] Jost Ed J. Kuijper[1,2]; for the Netherlands Donor Feces Bank (NDFB) Study Group



Regulation depends on domain

1 **Donor-related**

2 **Processing**

3 **Clinical application**

Recruitment

Screening

Intention of the processing

Preservation

These include e.g.:
- Cryopreservation
- Lyoprotectants

Modifications

These include e.g.:
- Additives for enrichment
- Cultivation
- Mixing of donations

Administration

Follow-up

Becomes comparable to a drug from this point forward, but long-term donor/recipient follow-up is still necessary.

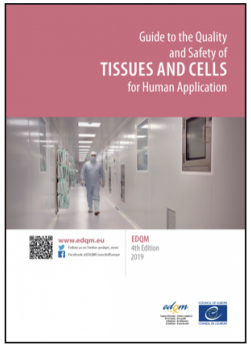
Tissue legislation appropriate

Drug legislation appropriate

Clinical trials: GCP
Routine clinical care: Biovigilance

Organs, Tissues and Cells - Technical Guides

NEW EDITION: Guide to the quality and safety of tissues and cells for human application



Human tissues and cells are being used in an increasing variety of ways, and advances in transplantation therapy have unquestionable benefits. **Human cells and tissues for human application** can save lives or restore essential functions, but the use of human tissues and cells also raises questions of safety and quality.

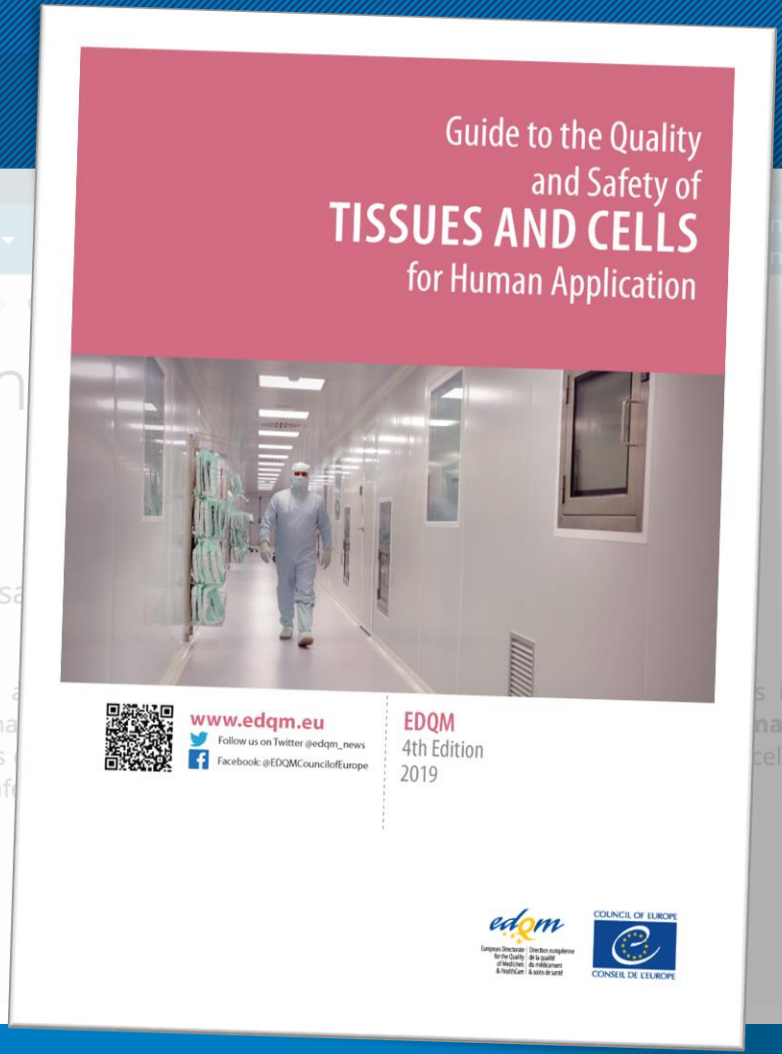
Newsletter Transplant

September 2019

Organs, Tissues an... Guides

NEW EDITION: Guide to the quality and sa...

Human tissues and cells a... transplantation therapy ha... **application** can save lives ... also raises questions of safe...



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Newsletter Transplant

September 2019

Wet veiligheid en kwaliteit lichaamsmateriaal

Wet actualisering lichaamsmateriaalwetgeving

Zorg en gezondheid

In het kort

Dit wetsvoorstel wijzigt wetgeving over het doneren van lichaamsmaterialen, zoals nieren, huid en stamcellen. Huid wordt bijvoorbeeld gebruikt voor het behandelen van mensen met brandwonden. Je wilt dat dit veilig gebeurt. Dit wetsvoorstel zorgt er daarom voor dat de donatie veilig is voor de patiënt die het lichaamsmateriaal krijgt en de mensen die doneren.

tot geneesmiddel. In 2016 is de *Nederlandse Donor Feces Bank* opgericht om donorfeces te verzamelen en te verstrekken. Gedoneerd feces wordt op dit moment gebruikt voor de behandeling van de darminfectie *clostridium difficile*. Onderzoek vindt plaats of een fecestransplantatie ook een oplossing kan bieden bij andere ziektebeelden.

Praktische consequenties

- Erkenning aanvraag indienen bij Farmatec (zie aanvraagformulier op farmatec.nl)
  - Erkenning weefselinstelling / orgaanbank | Vergunning | Farmatec
- Farmatec beoordeelt volledigheid van aanvraag, vraagt zo nodig om meer stukken en vraagt vervolgens advies aan IGJ
  - IGJ gaat op inspectie
- Na advies van de IGJ neemt Farmatec besluit over aanvraag
- Erkenning treedt in werking en instelling wordt periodiek geïnspecteerd door de IGJ
- Instelling houdt zich aan de wet, o.a. aanwijzen verantwoordelijk persoon en actualiseren

Take home messages

- FMT now established treatment
- Consensus about quality standards (guidelines/consensus reports)
- Setting up an international registry both for donor and patient follow-up would lift FMT as quality assured strategy to the next level
- Auditing should be implemented
- FMT probably regulated ‘Wet veiligheid en kwaliteit lichaamsmateriaal’

Thanks to NDFB colleagues

NDFB
Nederlandse Donor Feces Bank