Medizinische Universität Graz

Mikrobiomtransfer bei Clostridium difficile Infektion

PRO

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Mikrobiomtransfer
= fäkale Mikrobiota Transplantation
FMT

- **Definition:** Übertragung von Stuhl (und damit Stuhlbakterien u.a.) eines Gesunden in den Darm eines Erkrankten
- ☐**Ziel:** Wiederherstellung eines gestörten intestinalen Mikrobioms

Zhang. Am J Gastro 2012

FMT

- CDAD
- Colitis ulcerosa
- Intestinale Dysbiose mit GI Trakt Funktionsstörung bei ICU Patienten

PRO FMT

- Indikation
  - Studien
  - Leitlinien
- Sicherheit und Nebenwirkungen
- Standardisierbarkeit
  - Spender, Stuhlverarbeitung, Lagerung, Applikationsroute
- Verfügbarkeit
- Legistische Überlegungen
  - Österr. Leitlinie, AGES
- Akzeptanz/Erwartungshaltungen der Patienten

C. Diff Therapie

- Metronidazol
  - „mild-to-moderate CDI“
    - Keine Resistenzinduktion
    - Billiger als Vanco
- Vancomycin
  - „severe CDI“
    - Besser als Metronidazol (Heilungsrate, Komplikationen etc)
- Teicoplanin
  - „severe CDI“
    - Besser als Metronidazol (Heilungsrate, Komplikationen etc)
- Fidaxomicin
  - „severe CDI“ und Risiko für Rezidiv
- Rifaximin
  - Folgetherapie nach Vanco bei Rezidiven
    - Keine Studie zur Primärtherapie
    - Resistenzinduktion
    - „Primärresistenz“ 8% (Lit 2)
    - Kreuzresistenz zu Rifampicin (Lit 4,5)

Zar. CID 2007;45:302–7
Goldstein AAC 2011;55:5194–5199
Debast. Clin Microbiol Infect. 2013 Oct 5. doi: 10.1111/1469-0691.12418
Valentin. J of Infection 2011;62, 34e38
Krause NEJM 2011; 364:1467-1468

C. diff. Therapie

- Bis 25% Therapieversagen bei Erst-Therapie
- 40% Therapieversagen beim ersten Rezidiv (Vanco)
- 70% Therapieversagen bei mehrfachen Rezidiven

- → FMT

Els van Nood et al. NEJM 2013;368:407

Clinical Studies FMT for recurrent CDI

Study	Indication	No. of Patients	Mode of Administration	Outcome
Eiseman et al,[9] 1958	Severe PMC	4	Fecal enema	Dramatic resolution of PMC in all patients (100%)
Cutolo et al,[10] 1959	PMC	1	Cantor tube, then fecal enema	Resolution
Fenton et al,[11] 1974	PMC	1	Fecal enema	Symptom resolution within 24 h; sigmoidoscopy at 4 d revealed normal mucosa.
Bowden et al,[12] 1981	PMC	16	Fecal enema (n = 15); enteric tube (n = 1)	Rapid/dramatic response in 13/20 (65%). 3/20 (15%) patients died; no PMC on autopsy in 2 the third patient had small-bowel PMC.
Schwan et al,[13] 1984	Relapsing CDI	1	Fecal enema	Prompt/complete normalization of bowel function.
Tvede and Rask-Madsen,[14] 1989	Relapsing CDI	6	Fecal enema	Prompt *C difficile* eradication and symptom resolution. Normal bowel function within 24 h.
Flotterod and Hopen,[15] 1991	Refractory CDI	1	Duodenal tube	*C difficile* eradication
Paterson et al,[16] 1994	Chronic CDI	7	Colonoscope	Rapid symptom relief. Resolution in all (100%).
Harkonen,[17] 1996	PMC	1	Colonoscope	Diarrhea ceased immediately and symptoms had not recurred by 8 mo post FMT.
Lund-Tonneson et al,[18] 1998	CDI	18	Colonoscope (n = 17); gastrostoma (n = 1)	15/18 (83.3%) Clinically cured post-FMT without relapse
Persky and Brandt,[19] 2000	Recurrent CDI	1	Colonoscope	Immediate symptom resolution; *C difficile* eradication persisted at 5-year follow-up.
Faust et al,[20] 2002	Recurrent PMC	6	Unknown	All patients (100%) clinically cured postinfusion.
Aas et al,[21] 2003	Recurrent *C difficile* colitis	18	Nasogastric tube	15/18 (83.3%) Cured; 2 (11.1%) patients died of unrelated illnesses; 1 treatment failure (5.5%).
Borody et al,[5] 2003	Chronic CDI	24	Colonoscope and/or rectal enema and/or nasojejunal tube	Eradicated CDI in 20/24 patients (83.3%) with negative toxins and stool culture.

Borody TJ et al Gastroenterol Clin N Am 2012; 41: 781–803

Clinical Studies FMT for recurrent CDI

Jorup-Rönström et al,[22] 2006	Recurrent CDI	5	Fecal enema	All (100%) patients clinically asymptomatic post-FMT.
Wettstein et al,[23] 2007	Relapsing CDI	16	Colonoscope (day 1), then enemas 5, 10, or 24 d.	Eradication of CDI in 15/16 pts (93.8%), confirmed via negative culture or toxin assay.
Louie et al,[24] 2008	Relapsing CDI	45	Rectal catheter	CDI resolved in 43/45 (95.6%) patients.
Niewdorp et al,[25] 2008	Recurrent CDI	7 (2 of Whom with the 027 strain)	Jejunal infusion via duodenal catheter	*C difficile* eradication in all patients (100%), confirmed via culture and/or toxin assay.
You et al,[26] 2008	F-CDI	1	Fecal enema	Bowel function, BP, and leukocytosis normalized; oliguria resolved, and both vasopressin and venous hemofiltration were discontinued.
Hellemans et al,[27] 2009	CDI	1	Colonoscope	*C difficile* eradication
MacChonachie et al,[28] 2009	Recurrent CDI	15	Nasogastric tube	13/15 (86.7%) Asymptomatic post-FMT.
Arkkila et al,[29] 2010	Recurrent CDI	37 (11 of whom with the 027 strain	Colonoscope	*C difficile* eradication in 34/37(92%) patients.
Khoruts et al[30] 2010	Recurrent CDI	1	Colonoscope	*C difficile* eradicated, confirmed via negative culture. Remained negative at 6-month follow-up.
Yoon and Brandt,[31] 2010	Recurrent CDI/PMC	12, 2 of whom had PMC	Colonoscope	12/12 (100%) Exhibited durable clinical response.
Rohlke et al,[32] 2010	Recurrent CDI	19	Colonoscope	18/19 (94.7%) Clinically asymptomatic between 6 mo and 5 y post-FMT.
Silverman et al,[33] 2010	Chronic recurrent CD	7	Low-volume fecal enema	All (100%) patients clinically asymptomatic.
Garborg et al,[34] 2010	Recurrent CDI	40	Colonoscopic = 2; transduodenal = 38	Eradication of *C difficile* in 33/40 patients (82.5%).
Russel et al,[35] 2010	Relapsing CDI	1	Nasogastric tube	Resolved diarrhea by 36 h. *C difficile* toxin negative.
Kelly and De Leon,[36] 2010	Chronic, recurrent CD	12	Colonoscope	All (100%) patients exhibited clinical response.

Borody TJ et al Gastroenterol Clin N Am 2012; 41: 781–803

Clinical Studies FMT for recurrent CDI

Study	Indication	No. of Patients	Mode of Administration	Outcome
Mellow and Kanatzar,[37] 2010	Recurrent and refractory CDI	13	Colonoscope	12/13 (92.3%) *C difficile* toxin negative with rapid resolution of diarrhea.
Kassam et al,[38] 2010	CDI	14	Fecal enema	All (100%) patients complete clinical resolution.
Kelly et al,[39] 2012	Relapsing CDI	26	Colonoscope	24/26 Cured of CDI with resolution of diarrhea.
Hamilton et al,[40] 2012	Recurrent CDI	43	Colonoscope	86% Eradication rate (37/43) by symptom resolution/negative PCR testing for CDI toxin.
Mattila et al,[41] 2012	Refractory CDI	70	Colonoscope	66/70 Recovered (94%) *C difficile* eradicated.
Brandt et al,[42] 2012	Recurrent CDI	77	Colonoscope	Primary cure rate of 91%. Secondary cure rate of 98%. Resolution of diarrhea in 74% of patients by day 3.

Van Nood. NEJM 2013;368:407

Borody TJ et al Gastroenterol Clin N Am 41 (2012) 781–803

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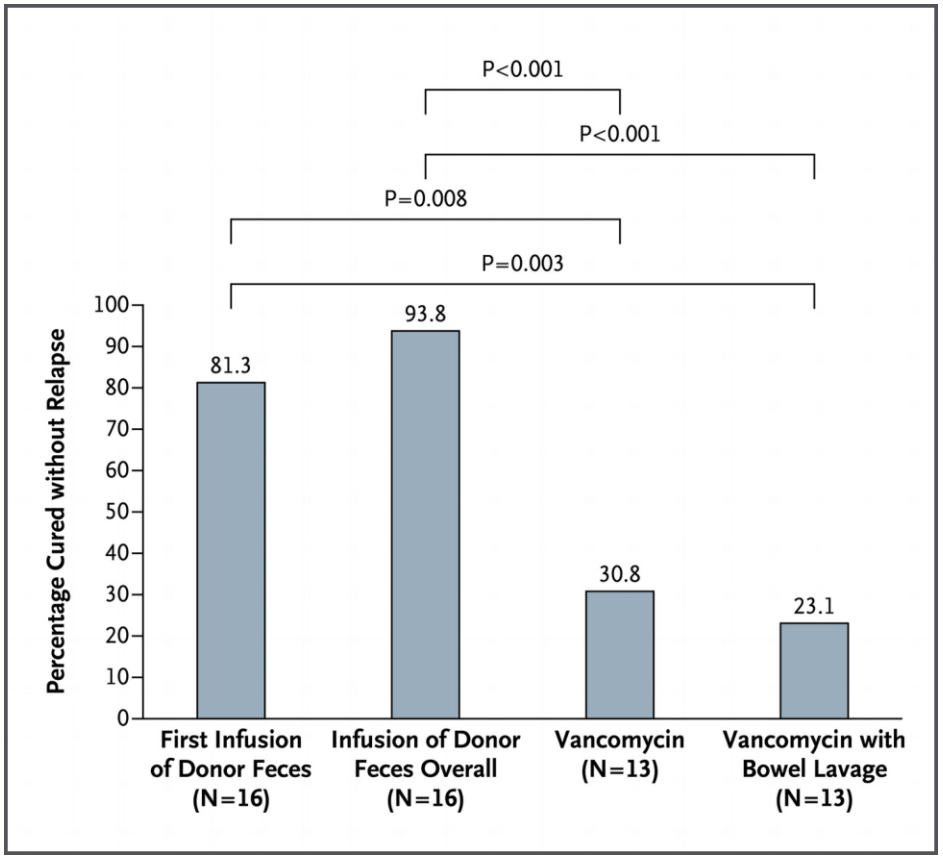
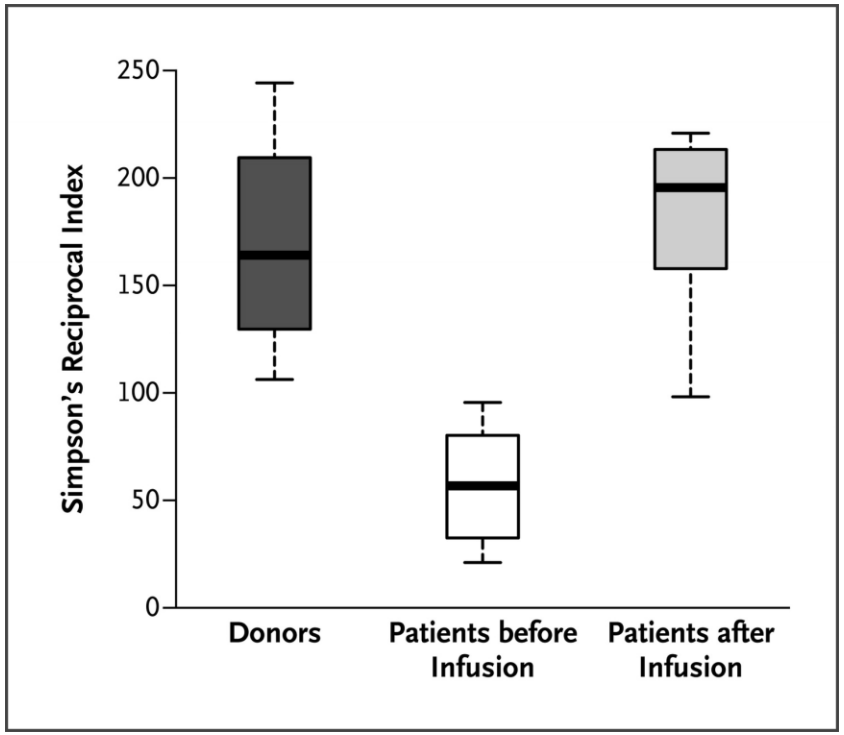
Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

Els van Nood, M.D., Anne Vrieze, M.D., Max Nieuwdorp, M.D., Ph.D., Susana Fuentes, Ph.D., Erwin G. Zoetendal, Ph.D., Willem M. de Vos, Ph.D., Caroline E. Visser, M.D., Ph.D., Ed J. Kuijper, M.D., Ph.D., Joep F.W.M. Bartelsman, M.D., Jan G.P. Tijssen, Ph.D., Peter Speelman, M.D., Ph.D., Marcel G.W. Dijkgraaf, Ph.D., and Josbert J. Keller, M.D., Ph.D.

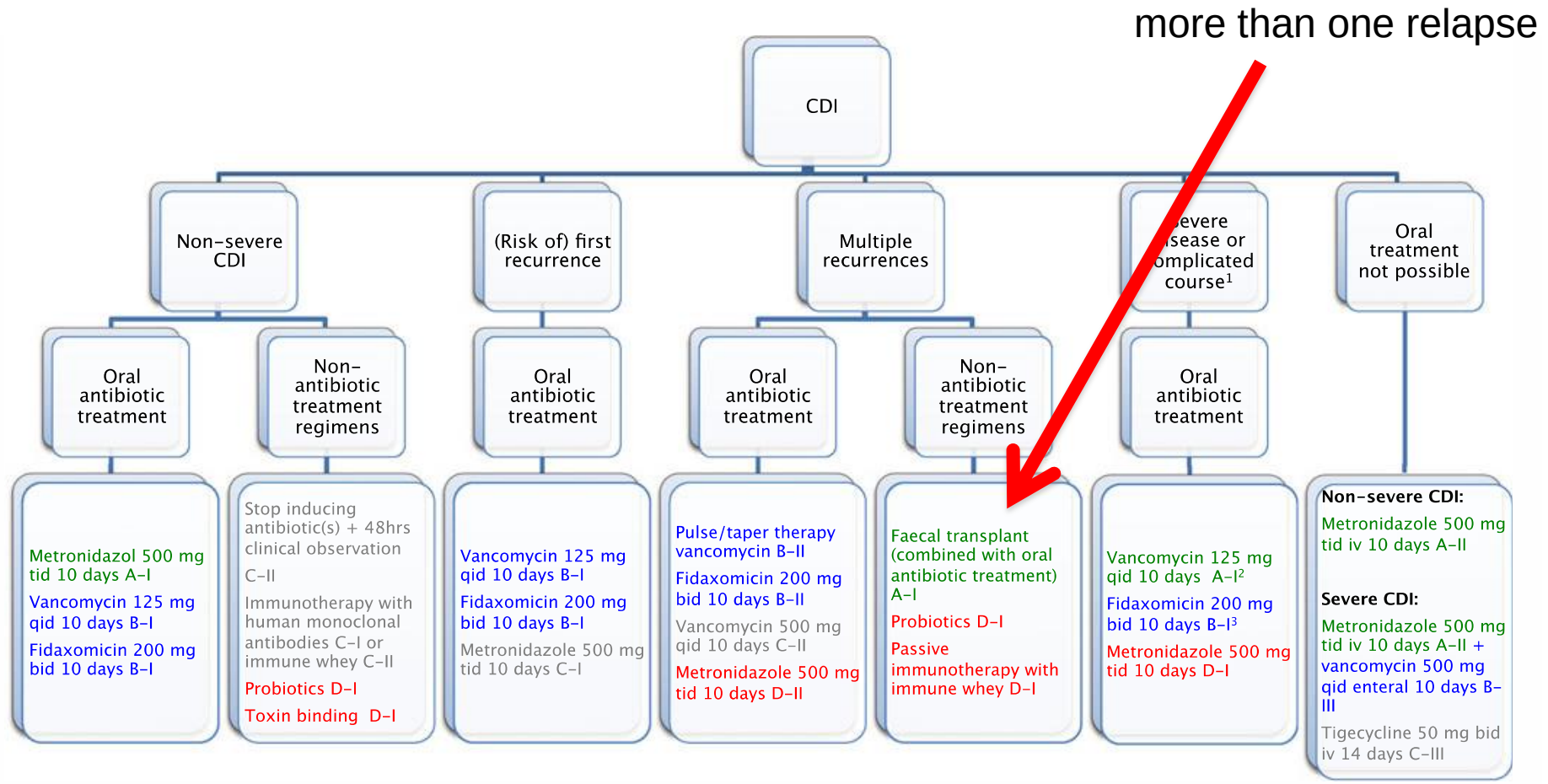


Vielfalt (Diversität)



Els van Nood et al. NEJM 2013;368:407

FMT bei C. diff Infektion
ESMID guideline 2014



Debast. Clin Microbiol Infect. 2013 Oct 5. doi: 10.1111/1469-0691.12418.

Indications for FMT

- Recurrent or relapsing CDI
  - Three or more episodes of mild to moderate CDI and failure of a 6- to 8-week taper with vancomycin with or without alternative antibiotic agents.
  - At least 2 episodes of CDI that result in hospitalization and are associated with significant morbidity.

Moore. CID 2014;58(4):541–5

Indications for FMT

- Recurrent or relapsing CDI
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  - At least 2 episodes of CDI that result in hospitalization and are associated with significant morbidity.
- Moderate CDI not responding to standard therapy (vancomycin or fidaxomicin) for at least 1 week.
- Severe (and perhaps even fulminant CDI) with no response to standard therapy after 48 hours.

Moore. CID 2014;58(4):541–5

Sicherheit/Nebenwirkungen

Table 2. Adverse Events in 16 Patients in the Infusion Group.*

Adverse Event	On Day of Infusion of Donor Feces	During Follow-up
	no. of events	
Belching	3	0
Nausea	1	0
Vomiting	0	0
Abdominal cramps	5	0
Diarrhea	15	0
Constipation	0	3
Abdominal pain	2 (associated with cramping)	0
Infection	0	2†
Hospital admission	NA	1‡
Death	0	0
Other adverse event	1§	1‡

1xHarnwegsinfekt, 1x ohne Keim/Fokus

1xCholedocholithiasis, ERCP

vanNood. N Engl J Med 2013;368:407-15.

Sicherheit und Nebenwirkungen

- Symptome IBS (6 von 317)
- 13 Todesfälle (4% of 317) während des follow up – CDI oder durch Grunderkrankung

- 1 Tod durch Pneumonie (FMT durch Nasogastralsonde, Aas et al. CID 2003)
- Tod durch V.a. Magensondenfehllage, akutes Abdomen

- Fieber (V.a. bei Applikation in den oberen GI Takt bei IBD)
- 4 of 70 Pat. mit Autoimmunerkrankungen bei Langzeit - follow up

- 2 Todefälle von 80 immuspprimierten FMT Patienten, 1 wg Aspiration während Coloskopie und Sedierung, 1 ohne Zusammenhang

Gough E et al. Clin Inf Dis 2011; 53:554
Borody TJ et al Gastroenterol Clin N Am 2012; 41: 781–803
Brandt LS et al. Am J Gastro 2012;107:1079

Högenauer, Kump. Krause. Clin Infect Dis. 2014;59:1348-1349
Solari. Clin Infect Dis. 2014 Jul 15;59:319
Kelly. *Am J Gastroenterol* 2014; 109:1065–1071

FMT rechtliche Situation

- → Erstellung einer österr. Leitlinie und Mitarbeit/Akzeptanz durch AGES/BM für

REVIEW 10.1111/1469-0691.12801

Kump. Clin Microbiol Infect 2014; 20: 1106–1111

Faecal microbiota transplantation—the Austrian approach

P. K. Kump[1], R. Krause[2], F. Allerberger[3] and C. Högenauer[1]

1) *Division of Gastroenterology and Hepatology, Department of Internal Medicine, Medical University Graz,* 2) *Section of Infectious Diseases and Tropical Medicine, Department of Internal Medicine, Medical University of Graz, Graz, and* 3) *Austrian Agency for Health and Food Safety (AGES), Vienna, Austria*

Empfehlungen zur Anwendung der fäkalen Mikrobiotatransplantation „Stuhltransplantation“: Konsensus der Österreichischen Gesellschaft für Gastroenterologie und Hepatologie (ÖGGH) in Zusammenarbeit mit der Österreichischen Gesellschaft für Infektiologie und Tropenmedizin (OEGIT)

Recommendations for the use of faecal microbiota transplantation „stool transplantation“: consensus of the Austrian Society of Gastroenterology and Hepatology (ÖGGH) in cooperation with the Austrian Society of Infectious Diseases and Tropical Medicine

Autoren P. K. Kump[1], R. Krause[2], C. Steininger[3], H. P. Gröchenig[4], A. Moschen[5], C. Madl[6], G. Novacek[7], F. Allerberger[8], C. Högenauer[1]

Kump. Z Gastroenterol 2014; 52: 1485–1492

Durchführung FMT

- Standardisierbarkeit
  - →Leitlinien
  - Spenderauswahl, Spenderuntersuchungen
  - Stuhlvorbereitung, FMT Zubereitung
  - Lagerung
  - Applikation

Kump. Clin Microbiol Infect 2014; 20: 1106–1111
Kump. Z Gastroenterol 2014; 52: 1485–1492

Durchführung FMT

- Verfügbarkeit
  - Akutspender
    - Gescreent
    - im Notfall nicht-gescreente Spender
  - gelagerte Stuhlsuspensionen
  - Verkapselter Stuhl

FMT – Methode
Klinische Ergebnisse

Medical University of Graz

Applikationsform

- koloskopische FMT/Einlauf: 91,4%
  - Rechtes Colon: 94%
  - Linkes Colon: 83%
- Nasogastral/jejunal-Sonde : 82,3%
  - Magen: 81%
  - Jejunum 86%

} Kein head to head Vergleich

Art des Spenders

- Verwandter/Partner/enger Freund: 89,5%
- Anonym: 90,7%

} ?

Kassam Z. et al. Am J Gastro 2013; 108:500-508
Cammarota G et al. J Clin Gastroenterol. 2014 Jan 16.
Borody. Curr Gastroenterol Rep (2013) 15:337

Frozen FMT

- 20 patients (median age, 64.5 years; range, 11-89 years)
- C diff disease, one of
  - ≥ 3 episodes of mild to moderate *C difficile* infection and failure of a 6- to 8-week taper with vancomycin
  - ≥ 2 episodes of severe *C difficile* infection requiring hospitalization
- Unrelated donors
- 15 capsules on 2 consecutive days
- follow up for symptom resolution and adverse events for up to 6 months.

Youngster. Jama 2014. doi:10.1001/jama.2014.13875

Frozen FMT

- Mean 48g stool
- Prepared with glycerol
- Pipetted in 30 capsules
- Stored -80° C
  - mean of 113 days (range, 30-252 days) prior to administration

- CDI treatment stopped 48h prior to FMT

Youngster. Jama 2014. doi:10.1001/jama.2014.13875

Frozen FMT

- Resolution of diarrhea in 14 patients (70%; 95% CI, 47%-85%) after one capsule-based FMT
- All 6 non-responders retreated
  - 4 had resolution of diarrhea

- resulting in an overall 90% (95% CI, 68%-98%) rate of clinical resolution of diarrhea (18/20)

Youngster. Jama 2014. doi:10.1001/jama.2014.13875

Akzeptanz/Erwartungshaltung der Patienten

- 192 Patienten befragt zur potentieller FMT
- Bei 94% akzeptiert, wenn vom Arzt vorgeschlagen
- Tablette bevorzugt 90%
- FMT unattraktiv, wenn verabreicht über Nasogastralsonde
- 77% würden für FMT bezahlen

Zipursky. CID. 2012;55(12):1652–8