대변이식의 효과와 현황

가톨릭대학교 부천성모병원
소화기내과
권태근
Function of intestinal microbiota

• Metabolic
  – Fermentation of non-digestible dietary residue
  – Short chain fatty acid
    • Butyrate, propionate, acetate
    • Energy source for epithelial cell of gut

• Trophic
  – Control of epithelial cell proliferation and differentiation
  – Development and homeostasis of the immune system

• Protective
  – Protection against pathogens
  – Tolerate beneficial commensal bacteria

Lancet 2003; 361:512-19
Blood 2017;129:927-933
Stability and complexity of the gut microbiome

Factors affecting the microbiome
- Genetics
- Birth route
- Geography
- Hygiene
- Stress
- Diet/nutrition
- Drugs

Microbiome complexity and stability

Healthy

Perturbation

Infectious diseases, metabolic diseases, and inflammatory disorders
- Protect against pathogens
- Train/activate immune function
- Supply nutrients, energy, vitamins, SCFA
- Inflammation (local > systemic)
- Oxidative stress
- Increase in Gram negative bacteria
- Infection (opportunistic/pathogenic)
- Altered metabolite production

Disease

Birth  3 years  Adult  Elderly

Early onset  Adult onset  Late onset

Gastroenterology 2014;146:1489-1499
Diet

- High fat diet → perturbation of microbiota
- Omega 3 → beneficial bacteria (*Bifidobacterium* and *Lactobacillus* species)
- Low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet → Treatment for IBS

### Eliminate foods containing FODMAPs

<table>
<thead>
<tr>
<th>excess fructose</th>
<th>lactose</th>
<th>fructans</th>
<th>galactans</th>
<th>polyols</th>
</tr>
</thead>
<tbody>
<tr>
<td>fruit</td>
<td>milk</td>
<td>artichoke</td>
<td>legumes</td>
<td>fruit</td>
</tr>
<tr>
<td>apple, mango,</td>
<td>milk from cows, goats</td>
<td>asparagus,</td>
<td>baked beans,</td>
<td>apple, apricot, avocado,</td>
</tr>
<tr>
<td>rashi, pear,</td>
<td>or sheep, custard, ice</td>
<td>beetroot,</td>
<td>chickpeas,</td>
<td>blackberry, cherry,</td>
</tr>
<tr>
<td>tinned fruit</td>
<td>cream, yoghurt</td>
<td>broccoli,</td>
<td>kidney beans,</td>
<td>longon, lychee, nashi,</td>
</tr>
<tr>
<td>in natural juice,</td>
<td>cheeses</td>
<td>brussels sprouts,</td>
<td>lentils,</td>
<td>nectarine, peach, pear,</td>
</tr>
<tr>
<td>watermelon</td>
<td>soft unp pissed cheeses</td>
<td>cabbage,</td>
<td>soy beans</td>
<td>plum, prune, watermelon</td>
</tr>
<tr>
<td>sweeteners</td>
<td>eg, cottage, cream,</td>
<td>fennel, garlic, leek,</td>
<td>vegetables</td>
<td><em>vegetables</em></td>
</tr>
<tr>
<td>fructose, high fructose</td>
<td>mascarpone, ricotta</td>
<td>okra, onion (all),</td>
<td>cauliflower, green</td>
<td><em>capicum</em> (bell pepper),</td>
</tr>
<tr>
<td>corn syrup</td>
<td></td>
<td>shallots, spring onion</td>
<td>cabbage</td>
<td>mushroom, sweet corn</td>
</tr>
<tr>
<td>large total</td>
<td></td>
<td>cereals</td>
<td>legumes</td>
<td><strong>sweeteners</strong></td>
</tr>
<tr>
<td>fructose dose</td>
<td></td>
<td>wheat and rye, in large</td>
<td>baked beans,</td>
<td>sorbitol (420)</td>
</tr>
<tr>
<td>concentrated fruit</td>
<td></td>
<td>amounts</td>
<td>chickpeas,</td>
<td>mannitol (421)</td>
</tr>
<tr>
<td>sources, large serves</td>
<td></td>
<td>of legumes</td>
<td>kidney beans,</td>
<td>isomalt (952)</td>
</tr>
<tr>
<td>of fruit, dried fruit, fruit juice</td>
<td></td>
<td>lentils</td>
<td></td>
<td>maltitol (965)</td>
</tr>
<tr>
<td>honey</td>
<td></td>
<td>legumes</td>
<td>legumes</td>
<td>xylitol (967)</td>
</tr>
<tr>
<td>corn syrup, frusiana</td>
<td></td>
<td>legumes</td>
<td>legumes</td>
<td><strong>miscellaneous</strong></td>
</tr>
</tbody>
</table>

IBS Self Help and Support Group - www.ibs-group.org

Gastroenterology 2014;146:1489-1499
Probiotics and prebiotics

• Probiotics
  – Live microorganism
  – Health benefit
  – In diet: 피클, 김치 (Leuconostoc spp., Weissella spp., and Lactobacillus spp), 간장, 요구르트
  – Efficacy
    • Improve integrity of the gut epithelium
    • Promote innate immunity in the gut
    • Reduce local and systemic inflammation

• Prebiotics
  – Non-digestible fiber compounds
  – Stimulate the growth or activity of advantageous bacteria (substrate)

Dhiman RK et al. Gastroenterology 2014;147:1327 – 1337
생물학적 분류

생명 (Life)
역 (Domain)
계 (Kingdom)
문 (Phylum)
강 (Class)
목 (Order)
과 (Family)
속 (Genes)
종 (Species)
<table>
<thead>
<tr>
<th>영문</th>
<th>국문</th>
<th>예 1</th>
<th>예 2</th>
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</thead>
<tbody>
<tr>
<td>Life</td>
<td>생명</td>
<td></td>
<td></td>
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<tr>
<td>Domain</td>
<td>역</td>
<td>Bacteria</td>
<td>Bacteria</td>
</tr>
<tr>
<td>Kingdom</td>
<td>계</td>
<td>Bacteria</td>
<td>Bacteria</td>
</tr>
<tr>
<td>Phylum</td>
<td>문</td>
<td>Firmicutes</td>
<td>Proteobacteria</td>
</tr>
<tr>
<td>Class</td>
<td>강</td>
<td>Clostridia</td>
<td>Gammaproteobacteria</td>
</tr>
<tr>
<td>Order</td>
<td>목</td>
<td>Clostridiales</td>
<td>Enterobacteriales</td>
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<tr>
<td>Family</td>
<td>과</td>
<td>Peptostreptococcaceae</td>
<td>Enterobacteriaceae</td>
</tr>
<tr>
<td>Genus</td>
<td>속</td>
<td>Clostridium</td>
<td>Eschericia</td>
</tr>
<tr>
<td>Species</td>
<td>종</td>
<td>C. difficile</td>
<td>E. coli</td>
</tr>
</tbody>
</table>
C. difficile infection
항생제

"안아키"라는 것이며 약을 쓰지 않고 자연으로 치유한다는
취지의 깨끗한 애정의 개념으로 이는 사람들이 드мысл하기도 하면서도
약을 너무 많이 쓰지 않는 것이요 또는 생길 때만 치료하는가?
이 정도면 병치고 약에 먹어가는가?

"무식한 사람이 씨앗을 가지고는 것만큼 무서운게 없다"

한 아이 아빠가 ‘안아키’의 실체를 만천하에 공개하며
논란이 시작되었습니다.

이후 안아키 때문에 위험한 상황에 처한 아이들의 근이
우후죽순 올라오기 시작했습니다.

극단적인 예로 제가 잘 아는 유명 여류 환경
운동가는 세명의 자녀에게 예방접종을 전혀
해주지 않았다고 합니다. 아이가 아파도
자연요법으로 치료하고 항생제나 감기약을
거의 주지 않은 것은 물론이요.
미생물 불균형 \(\rightarrow\) \textit{C. difficile} infection (CDI)

증례

• 75/F

폐렴으로 타병원에서 항생제 치료 도중 설사 발생. 일주일 후에도 호전 없어 내원.
## Laboratory Findings

<table>
<thead>
<tr>
<th>CBC</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WBC count</strong></td>
<td>16,840 /µL</td>
</tr>
<tr>
<td>seg. Neutrophils</td>
<td>81.4%</td>
</tr>
<tr>
<td><strong>Hb</strong></td>
<td>12.7 g/dL</td>
</tr>
<tr>
<td><strong>Platelet count</strong></td>
<td>192K/µL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BC</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BUN/Cr</strong></td>
<td>15.8/0.58 mg/dL</td>
</tr>
<tr>
<td><strong>TP /Alb</strong></td>
<td>6.2/3.7 g/dL</td>
</tr>
<tr>
<td><strong>TB/DB</strong></td>
<td>0.78/0.18 mg/dL</td>
</tr>
<tr>
<td><strong>AST /ALT</strong></td>
<td>29/22 U/L</td>
</tr>
<tr>
<td><strong>ALP/γ-GTP</strong></td>
<td>71/18 U/L</td>
</tr>
<tr>
<td><strong>CRP</strong></td>
<td>6.57 mg/dl</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stool study</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C. difficile culture</strong></td>
<td>(+)</td>
</tr>
<tr>
<td><strong>C. difficile toxin</strong></td>
<td>(+)</td>
</tr>
<tr>
<td>Occult blood</td>
<td>(+)</td>
</tr>
<tr>
<td><strong>WBC</strong></td>
<td>3-5</td>
</tr>
</tbody>
</table>
HD#4 Sigmoidoscopy
HD#4 Sigmoidscopy

- S: diarrhea
- O: abdominal distension
- A: #1. Aspiration pneumonia
  #2. Parkinson’s disease
  #3. Pseudomembranous colitis
- P: metronidazole IV → oral metronidazole
1st case of FMT in refractory CDI in Korea
HD#27 (POD#3) Sigmoidscopy
Two Cases of Refractory Pseudomembranous Colitis that Healed Following Fecal Microbiota Transplantation
Conventional treatment of CDI

- 원인 항생제 사용 중단
- 경구 metronidazole
- 경구 vancomycin
- Severe, complicated
  - IV metronidazole + 경구 vancomycin and/or vancomycin enema

- Treatment efficacy: 80-90%

- Recurrence
  - 20% after 1\(^{st}\) episode
  - 30-40% after 2\(^{nd}\) episode
Refactory CDI

- Tends to be severe
Severe or fulminant CDI: FMT


Clin Endosc. 2022 E-pub
Development of FMT

• Historic data
  - 1\textsuperscript{st} FMT around the world
    • 4\textsuperscript{th} Century China: Dr. Ge Hong
      • Patient with food poisoning and severe diarrhea
    - 2\textsuperscript{nd} Century
      • 17\textsuperscript{th} Century Italia: Fabricius Aquapendente

• 1\textsuperscript{st} literature (1958)
  – Eiseman B, et al., 4 case series
  – Fecal enema in pseudomembranous enterocolitis

Zhang F et al. 2012 Am J Gastroenterol
Surgery 1958; 44:854-9
Traditional FMT

- Stool: Normal saline = 1 : 3-5
- Homogenization, blending
- Fecal suspension: 200-500ml
- Infusion
  - Colonoscopy
  - Upper endoscopy
  - L-tube, enema
Development of FMT

• 2012
  – Frozen stool preparation
  – 43 patients
  – Success rate : 86%

• 2013
  – 1st FMT in Korea

• 2014
  – Oral capsule
  – Centrifuge : 용량감소, 1/10
  – 20 patients, success rate : 90%

Gweon et al. 대한내과학회지 2013;84:395-399
Youngster I et al. JAMA 2014;312:1772-1778
Stability and complexity of the gut microbiome

Factors affecting the microbiome

- Genetics
- Birth route
- Geography
- Hygiene
- Stress
- Diet/nutrition
- Drugs

Healthy

Perturbation

Infectious diseases, metabolic diseases, and inflammatory disorders

- Protect against pathogens
- Train/activate immune function
- Supply nutrients, energy, vitamins, SCFA

Disease

- Early onset
- Adult onset
- Late onset

Birth 3 years Adult Elderly

- Inflammation (local > systemic)
- Oxidative stress
- Increase in Gram negative bacteria
- Infection (opportunistic/pathogenic)
- Altered metabolite production

Gastroenterology 2014;146:1489-1499
• Diversity
  – Increased after FMT
  – Single donor < multi-donor

Lancet 2017;389:1218–28
Figure 1. The protocol of the study. Twelve healthy volunteers participated in the study and provided fecal samples 3 times.

- 4주간 투여
  - 혼합제 : Bifidobacterium, Lactobacillus, and Enterococcus
• Composition (before vs after) : no difference
• Overall diversity : no difference
<table>
<thead>
<tr>
<th>Gastrointestinal</th>
<th>Non-gastrointestinal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choledolithiasis</td>
<td>Arthritis</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>Asthma</td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td>Atopy</td>
</tr>
<tr>
<td>Idiopathic constipation(^a)</td>
<td>Autism(^a)</td>
</tr>
<tr>
<td>Inflammatory bowel disease(^b)</td>
<td>Autoimmune disorder</td>
</tr>
<tr>
<td>Irritable bowel syndrome(^b)</td>
<td>Chronic fatigue syndrome(^d)</td>
</tr>
<tr>
<td>Familial Mediterranean fever</td>
<td>Diabetes mellitus and insulin resistance(^b)</td>
</tr>
<tr>
<td>Gastric carcinoma and lymphoma</td>
<td>Eczema</td>
</tr>
<tr>
<td>Recurrent <em>Clostridium difficile</em> infection(^b)</td>
<td>Fibromyalgia(^b)</td>
</tr>
<tr>
<td></td>
<td>Hay fever</td>
</tr>
<tr>
<td></td>
<td>Hypercholesterolemia</td>
</tr>
<tr>
<td></td>
<td>Idiopathic thrombocytopenic purpura(^d)</td>
</tr>
<tr>
<td></td>
<td>Ischemic heart disease</td>
</tr>
<tr>
<td></td>
<td>Metabolic syndrome(^d)</td>
</tr>
<tr>
<td></td>
<td>Mood disorders</td>
</tr>
<tr>
<td></td>
<td>Multiple sclerosis(^d)</td>
</tr>
<tr>
<td></td>
<td>Myoclonus dystonia(^d)</td>
</tr>
<tr>
<td></td>
<td>Nonalcoholic fatty liver disease</td>
</tr>
<tr>
<td></td>
<td>Obesity</td>
</tr>
<tr>
<td></td>
<td>Oxalic acid kidney stones</td>
</tr>
<tr>
<td></td>
<td>Parkinson's disease(^d)</td>
</tr>
</tbody>
</table>

\(^a\)Beneficial effect fecal microbiota transplantation (FMT) in case series; \(^b\)Beneficial effect FMT in randomized clinical trials.
Microbiota based therapy

Probiotics
~ Consortia

~~~~~~ Fecal microbiota transplantation (FMT)
FMT indication

• *C. difficile* infection (CDI)

• Non-CDI
  – GI disease
    • Inflammatory bowel disease (IBD)
    • Irritable bowel syndrome (IBS)
  – Non-GI disease
    • Autism
    • Cardiometabolic disorder
    • 다제내성균주 집락: Multi-drug resistant organism (MDRO)
      – Vancomycin Resistant Enterococcus
      – Carbapenem Resistant Enterobacteriaceae
Clinical Practice Guidelines for Fecal Microbiota Transplantation in Korea

Tae-Geun Gweon,¹ Yoo Jin Lee,² Kyeong Ok Kim,³ Sung Kyun Yim,⁴ Jae Seung Soh,⁵ Seung Young Kim,⁶ Jae Jun Park,⁷ Seung Yong Shin,⁸ Tae Hee Lee,⁹ Chang Hwan Choi,⁸ Young-Seok Cho,¹⁰ Dongeun Yong,¹¹ Jin-Won Chung,¹¹ Kwang Jae Lee,¹² Oh Young Lee,¹³ Myung-Gyu Choi,¹ and Miyoung Choi¹⁴; Gut Microbiota and Therapy Research Group Under the Korean Society of Neurogastroenterology and Motility

Fecal Microbiota Transplantation Indications

Statement 1: Fecal microbiota transplantation is recommended for patients with recurrent *Clostridioides difficile* infection who have had at least 2 recurrences and can be considered in patients with refractory or severe *Clostridioides difficile* infection.

(Strong recommendation, high quality of evidence)
FMT 방법

• 상부위장관 vs 하부위장관

• 공여자대변 vs 자가대변

• Single vs multiple

• 대변처리
  – Aerobic vs anaerobic

• 대변제형
  – Fresh stool, frozen stool, capsule
  – Novel product
FMT 방법

• 50～150g of fresh stool
• 최소 : 50g
• 누구의 대변?
  – Family donor stool
  – Healthy donor stool
• Infusate : (stool : normal saline = 1:3)
• Blender로 3분 grinding (제품의 종류에 따라 다를 것으로 보임)
• 체로 거를 필요 없음
FMT efficacy for recurrent CDI

- Overall cure rate: 80-90%
- Superior than conventional treatment
  - Cure rate
  - Days to resolution

Kelly CR et al. *Am J Gastroenterol* 2014;78:785-793
Severe or fulminant CDI

- 대변이식 + 반코마이신

- Success rate : 93%
  - Severe CDI: 100% (10/10)
  - Fulminant CDI: 89% (17/19)
Traditional FMT
CDI, fresh stool

Indication
IBS, IBD, MDRO

FMT product
Traditional FMT
We are a nonprofit stool bank, expanding safe access to fecal transplants and catalyzing research into the human microbiome.
Openbiome

- 1st stool bank in the world
- Founded in 2012
- Non-profit organization
Frozen stool
Fig. 2. Fecal microbiota transplantation procedures. (A) Donor stool and normal saline (1:3) ground in a blender. (B) Fecal suspension in 50-ml syringes. (C) Infusion using colonoscopy.

Choi HH, Cho YS Clin Endosc 2016;49:257-265
Capsule

- Aerobic processing
- Centrifuge (volume 1/10)
- Freeze
- 1 Capsule
  - 0.65mL: 1.6g stool
- 30 capsule: 48g stool
  - 2 consecutive days

Liquid material → Lyophilization

JAMA. 2014;312(17):1772-1778
Am J Gastroenterol 2017; 112:940–947
Non-CDI
Non-CDI diseases

• 방법이 매우 상이
  – 대변이식 횟수 (multiple FMT)
  – 대변용량

• 치료효과 상이

• 표준화 힘들다
과민성 장증후군
(irritable bowel syndrome, IBS)

• 만성 복통, 복부 팽만감, 배변습관 변화

• 기능성 질환
  – No structural abnormality

• No biomarker
IBS: Multifactorial pathogenesis

- Stress
- Microbiota
- Diet
- Brain-gut axis
- Visceral hypersensitivity

Lacy BE at al. *Gastroenterology* 2016;150:1393 – 1407
IBS: Multifactorial pathogenesis

- Stress
- Diet
- Visceral hypersensitivity
- Brain-gut axis
- Microbiota

Lacy BE at al. Gastroenterology 2016;150:1393 – 1407
• Microbiota 조성 변화
  - 증가 : Firmicutes
  - 감소 : Bacteroidetes

**IBS** 에 의한 2차적인 결과 vs IBS 의 원인 ???

Jeffery IB et al. *Gut* 2012;61:997-1006
• **Country**
  - Norway

• **ROME III patients**
  - Moderate to severe IBS (SSS ≥ 175)
  - Placebo: 환자대변
  - FMT (n=55)
    - Fresh (n=26)
    - Frozen (n=29)

• **치료효과**
  - 3개월 후 SSS 75이상감소

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• FMT vs placebo
  - 3개월: 65% vs 43% ($p=0.049$)
  - 12개월: 56% vs 36% ($p=0.075$)

### 캡슐 (donor feces vs placebo)

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>FMT</th>
<th>Placebo</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>51</td>
<td>25</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Age (mean (SD))</td>
<td>36.39 (11.47)</td>
<td>37.28 (12.48)</td>
<td>35.54 (10.58)</td>
<td>0.593</td>
</tr>
<tr>
<td>Weight (mean (SD))</td>
<td>77.02 (17.86)</td>
<td>76.60 (19.89)</td>
<td>77.42 (16.07)</td>
<td>0.872</td>
</tr>
<tr>
<td>BMI (mean (SD))</td>
<td>25.99 (5.35)</td>
<td>25.96 (5.84)</td>
<td>26.02 (4.95)</td>
<td>0.966</td>
</tr>
<tr>
<td>Height (mean (SD))</td>
<td>1.72 (0.08)</td>
<td>1.72 (0.09)</td>
<td>1.72 (0.07)</td>
<td>0.784</td>
</tr>
<tr>
<td>Male (%)</td>
<td>16 (31.4)</td>
<td>8 (32.0)</td>
<td>8 (30.8)</td>
<td>1</td>
</tr>
<tr>
<td>Type of IBS (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.591</td>
</tr>
<tr>
<td>IBS with constipation</td>
<td>17 (33.3)</td>
<td>7 (28.0)</td>
<td>10 (38.5)</td>
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</tr>
<tr>
<td>IBS with diarrhea</td>
<td>15 (29.4)</td>
<td>7 (28.0)</td>
<td>8 (30.8)</td>
<td></td>
</tr>
<tr>
<td>IBS mixed</td>
<td>19 (37.3)</td>
<td>11 (44.0)</td>
<td>8 (30.8)</td>
<td></td>
</tr>
<tr>
<td>Continue use of IBS medication (%)</td>
<td>29 (56.9)</td>
<td>14 (56.0)</td>
<td>15 (57.7)</td>
<td>1</td>
</tr>
<tr>
<td>Former tried IBS medication (%)</td>
<td>43 (84.3)</td>
<td>23 (92.0)</td>
<td>20 (76.9)</td>
<td>0.274</td>
</tr>
<tr>
<td>Former tried new diet (%)</td>
<td>38 (74.5)</td>
<td>17 (68.0)</td>
<td>21 (80.8)</td>
<td>0.469</td>
</tr>
</tbody>
</table>

- **Country**
  - Demark

- **ROME III patients**
  - Moderate to severe IBS (SSS ≥ 175)
  - Placebo : 식용첨가물

- 치료효과
  - 3개월 후 SSS 감소

Halkjær Sì, et al. Gut 2018;0:1–9
캡슐 (donor feces vs placebo)

- Diversity
  - FMT 이후 증가함

Halkjær SI, et al. Gut 2018;0:1–9
### Table 2: IBS-SSS and IBD-QoL score between groups and their change over time

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>FMT</th>
<th>Placebo</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IBS-SSS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>n</strong></td>
<td>51</td>
<td>25</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>At inclusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mean (SD))</td>
<td>343.39</td>
<td>341.68 (95.02)</td>
<td>345.04 (79.56)</td>
<td>0.892</td>
</tr>
<tr>
<td>First month</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mean (SD))</td>
<td>250.49</td>
<td>273.67 (113.86)</td>
<td>228.24 (112.67)</td>
<td>0.167</td>
</tr>
<tr>
<td>Third month</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mean (SD))</td>
<td>251.57</td>
<td>287.14 (118.30)</td>
<td>218.96 (121.87)</td>
<td>0.061</td>
</tr>
<tr>
<td>Sixth month</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mean (SD))</td>
<td>263.47</td>
<td>297.73 (130.58)</td>
<td>230.70 (126.35)</td>
<td>0.087</td>
</tr>
<tr>
<td>Difference between inclusion and first month (mean (SD))</td>
<td>-93.53 (105.38)</td>
<td>-65.00 (91.52)</td>
<td>-120.92 (112.19)</td>
<td>0.063</td>
</tr>
<tr>
<td>Difference between inclusion and third month (mean (SD))</td>
<td>-90.67 (100.22)</td>
<td>-52.45 (97.72)</td>
<td>-125.71 (90.85)</td>
<td>0.012*</td>
</tr>
<tr>
<td>Difference between inclusion and sixth month (mean (SD))</td>
<td>-79.53 (114.34)</td>
<td>-41.86 (84.24)</td>
<td>-115.57 (128.83)</td>
<td>0.029*</td>
</tr>
</tbody>
</table>

- **Donor vs Placebo**
  - 3개월
    - SSS ∆ : 52.5 vs 125.7 (p=0.012)
    - SSS ∆ 50 : 36.4% vs 79.2% (p=0.008)
  - 6개월
    - SSS ∆ : 41.9 vs 128.8 (p=0.029)

Halkjær SI, et al. Gut 2018;0:1–9
캡슐 (donor feces vs placebo)

Microbiota modulation

X

Symptom improvement

Halkjær SI, et al. Gut 2018;0:1–9
Other indications
The experts panel took into account other clinical indications for a possible use of FMT in the clinical practice, such as IBD, IBS, metabolic disorders, paediatrics, but for none of them emerged an evidence-based recommendation to use FMT except that in a context of research (see online supplementary 1).

2.2.2.3. Other comorbidities and FMT
i. We recommend that FMT should be offered to those with recurrent CDI and inflammatory bowel disease (IBD), but patients should be counselled about a small but recognised risk of exacerbation of IBD (GRADE of evidence: moderate; strength of recommendation: strong).
Fecal microbiota transplantation in gastrointestinal disorders: time for precision medicine
Donor effect

• Multi-donor
  – Diversity: multi-donor > single donor

• Super donor
  – 대변이식을 하였을 때 다른 공여자보다 우수한 효과를 보이는 공여자

Lancet 2017;389:1218–28
Front Cell Infect Microbiol 2019;21;9:2
궤양성 대장염

- Retention enema
  - 6주: 주 1회

- 50ml stool

- Donor B vs others (p=0.06)
  - 39% (7/18) vs 10% (2/20)
과민성 장증후군

• Single super-donor
  – 36세, 백인남성
  – 비흡연
  – BMI: 23.5
  – Vaginal delivery, 모유수유
  – 항생제 복용 3회

• 연구대상자: > IBS-SSS 175

• Primary endpoint
  – 3개월 후 SSS 50감소

• Bowel preparation
  – Not done

• Infusion
  – Endoscopic duodenal infusion

Microbiota-gut-social brain axis

- **Mechanism**
  - Vagus nerve activation
  - Microbial metabolite
  - Neurotransmitter
  - Immune system
  - Sensory pathway

Sherwin E et al. Science 2019; 1;366(6465)
• Autism
  – Children with autism
    • Destabilized microbiota
    • *Prevotella copri* : decreased
  – GI symptoms
    • Constipation
    • Diarrhea
    • Correlation: autism severity

Sherwin E et al. *Science* 2019; 1;366(6465)
**Autism**

- **Lactobacillus plantarum**
  - Improve antisocial and anxiety

- **Microbiota cocktail (L acidophilus, L rhamnosus, Bifidobacterium longum)**
  - Improved behavior and GI symptom

---

<table>
<thead>
<tr>
<th>Species</th>
<th>Behavior</th>
<th>Ranking of dominant phyla in the microbiota</th>
<th>Relationship between social behavior and microbiota</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Honey bee</td>
<td>(Apis mellifera) The eusocial insect species exists within colonies consisting of a queen bee along with worker and soldier bees. Worker and soldier bees interact in a cooperative manner to ensure maintenance and survival of the colony.</td>
<td>1. Firmicutes 2. Actinobacteria 3. Proteobacteria</td>
<td>Social interaction facilitates horizontal transmission of microbiota that confers immune resistance against pathogens.</td>
<td>(50)</td>
</tr>
<tr>
<td>S. bovis</td>
<td>(Streptococcus bovis) Bees have cecal flora that consists of a variety of bacterial species that help with digestion and immune function.</td>
<td>Lactobacillus Odoriferous flora</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F. varium</td>
<td>(Fusobacterium varium) The bacterium Enterobacter cloacae present in the feces of F. varium mediates aggregation of caecal cells. The aggregation leads to the horizontal transmission of microbes.</td>
<td>1. Proteobacteria 2. Firmicutes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Termite</td>
<td>(Mastotermes darwiniensis) Termites are an ancient insect species existing within a colony of multiple nests along with soldier and worker termites. Worker termites undertake the most work in the colony, cooperating in food storage as well as brood and nest maintenance.</td>
<td>1. Spirochaetes 2. Bacteroidetes 3. Firmicutes</td>
<td>Social interaction facilitates the horizontal transmission of microbes that aids in food digestion.</td>
<td>(62, 65)</td>
</tr>
<tr>
<td>Zebrafish</td>
<td>(Danio rerio) The species of fish aggregates into large groups, known as shoals. They can also exhibit aggression toward conspecifics, which typically arises as a result of territoriality. These fish can exhibit social behavior when under threat from other animals.</td>
<td>1. Firmicutes 2. Proteobacteria 3. Firmicutes</td>
<td>Modulation of the microbiota has been shown to influence shoaling behavior of zebrafish. Antibiotic treatment reduces shoaling behavior. Conversely, probiotic supplementation can increase shoaling behavior.</td>
<td>(50, 56)</td>
</tr>
<tr>
<td>Zebra finch</td>
<td>(Taeniopygia guttata) The zebra finch is a social species that typically forms monogamous pair bonds during mating season. These birds tend to roost in groups for food rather than individually.</td>
<td>1. Firmicutes 2. Proteobacteria</td>
<td>Zebra finches have been shown to transmit bacteria through allopreening that results in colonization of the gastrointestinal tract.</td>
<td>(60, 64)</td>
</tr>
</tbody>
</table>

Sherwin E et al. *Science* 2019; 1;366(6465)
Microbiota transfer therapy (MTT)

- $2.5 \times 10^{12}$ cells/day mixed in a chocolate milk, milk substitute, or juice for
- 18 weeks treatment
- 18 participants

Kang DW et al. *Microbiome* 2017;5:10
Microbiota transfer therapy (MTT)

- 80% reduction in **GI symptom**

- Significant improvement of **autism related symptom**

Kang DW et al. *Microbiome* 2017;5:10
• 18 participants
• GI symptom: 58% reduction
• ASD behavior
  – 47% lower than baseline
  – 23% lower than week 10

SAFETY
Safety

- 경증: 24-48시간 이내 호전
  - 복통, 펭만감
  - 발열
  - 구역감

- 중증
  - 구토, 흡인
  - 감염
  - IBD flare
  - Bowel perforation: n=2¹,2
  - 사망: 1.4%, under estimation

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¹ Am J Gastroenterol 2014;109(Suppl 2):S629
² Adv Ther. 2019;36(8):2052-2061
³ Aliment Pharmacol Ther 2021;53:33-42
Fecal Microbiota for Transplantation: Safety Alert - Risk of Serious Adverse Events Likely Due to Transmission of Pathogenic Organisms

• Donor stool from stool bank

• 6 cases of *E. coli* transmission
  – Enteropathogenic *E. coli*: 2 cases
  – Shigatoxin-producing *E. coli*: 4 cases
    • Death: 2 patients

• Online report system
Summary

- Effective treatment for CDI
- CDI 이외의 질환에서는 치료효과 등이 상이
- Safety issues
경청해 주셔서 감사합니다