Fecal Microbiota Transplant Current Role and Potential Future

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Outline

- Fecal Microbiota Transplant
  - Current use – C. difficile infections
  - What this is and how it's done
  - FDA involvement
  - Role in other treating other conditions now
- Probiotics – no beneficial role proven for most conditions and will not be discussed

Clostridium difficile

- Clostridium difficile is a bacterial pathogen capable of causing severe diarrhea in susceptible patients

- Found if soil, air, water, and in human and animal feces. Perhaps 10% of population carries this in their GI tracts with no ill effects.

Clostridium difficile

- Capable of being spread from individual to individual through contact and unclean hand washing practices.
- Spores of this bacterium are difficult to kill and can persist on various surfaces despite routine cleaning for long periods of time.

Why does this happen?

- Human colon: 100 trillion bacteria; 500 – 1000 different species; 60% stool volume are bacteria

- Normal healthy human microbiota: protection against invasion and infections by CDI and other pathologic infectious organisms.

Why does this happen?

- Also has other functions:
  - Digestion of complex carbohydrates and proteins
  - Energy generation and storage
  - Immune functions
  - Brain-gut nervous system interactions
- Antibiotics disrupt this normal flora and allow infectious organisms to take over

Clostridium difficile colitis

- Result: severe diarrheal illness
- Inflammation of the colon (sometimes the small intestine)
- Hospitalization and occasionally death can result.

Clostridium difficile colitis

- The most common cause of disease: antibiotics for some unrelated infection.
  - Immunosuppressive medications or disease - less common.
  - Rarely, healthy patients can develop this spontaneously.

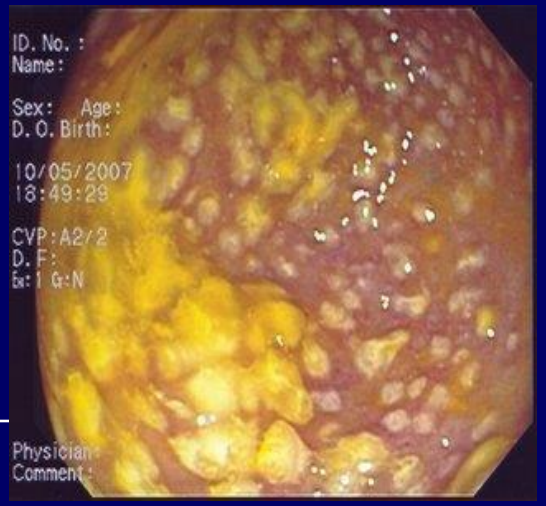
Clostridium difficile colitis

- Beneficial bacteria normally prevent Clostridium difficile from becoming a dominant intestinal bacterium and causing disease.

- Antibiotics can lead to a change in the flora of the gut such that these good bacteria are eradicated and a pathogen can emerge.

Diagnosis

- Symptoms of diarrhea and abdominal pain, possibly fever, weakness, dehydration
- Stool testing: Clostridium difficile toxins (A and B) and/or now C. difficile PCR
- Colonoscopy or flex sig → pseudomembranes



Clostridium difficile diarrhea

- Growing problem over the past 20 years, increasing in severity and frequency related to increasingly virulent strains of this bacterium that have emerged
- 500,000 people develop this infection each year; 14,000 die.

Clostridium difficile diarrhea

- 80% recover with one course of antibiotics, but **relapse** following an initial response to treatment is becoming a more common problem.
- Relapse becomes an increasingly frequent problem with each relapse event.

Clostridium difficile diarrhea

- Relapse following initial response to treatment: 20 – 30%
- After 2nd relapse, the rate increases to 40 – 60%
- Following 3 or more relapses, the response rate is down to 20%

Recurrence and relapse

Risk factors:

- Older age (>65 yrs)
- Intercurrent antibiotic use for non-CDI infections
- Renal insufficiency
- Immune deficiency
- Antacid medications
- Female sex
- Initial severe disease
- Continued antibiotic exposure after initial CDI Rx predictive of almost 90% relapse rate!!

Management alternatives

- Antibiotics
  - Metronidazole 250 – 500 mg IV or po TID
  - Vancomycin 125 mg po TID (not IV)
    - Duration 10 – 14 days

Alternatives

Rifaxamin

Fidaxomicin

Management alternatives

- Relapse or recurrence treatments
  - Antibiotics with tapered or pulsed dosing
    - Vancomycin 125 mg QID x 14 days, then TID x 7 days, then BID x 7 days, then QD x 7 days, then QOD x 7 days, then d/c
    - Vancomycin 125 mg x 14 days, the rifaxamin (“chaser”) x 7 days
- Success rates: 65 – 70%

Expense

- Vancomycin 14 d treatment course costs ~ $1500
- Fidaxomicin $3000: new, most insurances do not cover this

History of fecal transplant

- Chinese are known to have used this in the 4th century
- 1958 – Denver surgeons treated 4 post-op patients
- Next report 1983 – FT used for CDI
- Rapid increase in use in past decade

Non-antibiotic alternative Fecal transplant (FT)

TERMINOLOGY

- Fecal Microbiota Transplantation (FMT)
- Fecal Microbiota Restoration (FMR)
- Fecal Microbiota Reconstitution
- Fecal Bacteriotherapy
- Intestinal Microbiota Transplantation (IMT)

What is fecal transplant?

- Transfer of stool and bacteria from the colon of a healthy person to the colon of a person ill with a disease felt to be related to having acquired a harmful altered bacterial flora.
- The idea is to restore the altered bacteria population of the ill person to a normal healthy bacterial flora and make the disease better or cure this disease.

What is the process?

- Healthy donor stool and blood is tested for possible infections that could be transmitted to the ill patient
- Stool passed on day of the treatment and processed to create liquid suspension

What is the process?

- This suspension with healthy, normal intestinal flora is then given to the patient if one of a few different ways.

What is the process?

- Colonoscopy
- Upper GI endoscopy or tube placed into patient's upper intestine (naso-jejunal tube)
- Retention enema

Results

- Success rates vary by route of the transplant
- Colonoscopy: **90 – 95%**
- Upper GI delivery: **80 – 85%**
- Enema: **80 - 85%**
- Speed of recovery and resolution of symptoms is usually within 2 – 7 days, but can sometimes take 2 weeks.

Conclusions

- Clostridium difficile infection is an increasing problem
- Relapsing or recurring course is common
- Antibiotic use is not guaranteed to work, and is expensive
- Fecal flora transplant is highly effective in breaking this cycle and curing these patients with rates over 90%.

Conclusions

- Evidence is now convincing enough to make this an acceptable and necessary practice in our hospitals and endoscopy centers.

- Better scientific studies are needed – random controlled trials

FDA story

- May 2013

FDA declared fecal material used to treat diseases like Clostridium difficile a “biologic drug” subject to all the rules and regulations of any other investigational new drug.

  - **Investigational new drug (IND)** number required for any patient treated in this manner

FDA story

- July 2013
  - Public outcry – FMT life-saving procedure in many cases
  - Decision modified: FDA to "exercise enforcement discretion" regarding IND number requirement for FMT used to treat CD

FDA story

- Adequate "informed consent" required
- Patients need to be informed that this is "investigational treatment".
- All other uses require an IND number

Other uses for this treatment?

- IBD
- IBS
- Metabolic syndrome
- Diabetes
- Obesity

- PSC?

Inflammatory Bowel Disease

ACG meeting 10/13 Abs P1791 L. Brandt

- 16 pts: 14 CUC, 2 Crohns; IBD duration 7.5 yr av. (1 – 33 yrs)]
- Given FMT by colonoscopy (1 NJ admin.), then enema (self admin.) at scheduled intervals, tapered; f/u 14 mo. mean (4.5 – 30 mos.)

Inflammatory Bowel Disease

- Results
  - 10/16: dec. flare freq. (63%)
  - 3/10: no relapses over mean 21 mos. (8-30 mos.)
  - 0/16 had more frequent flares

Inflammatory Bowel Disease

- Results
  - Diarrhea dec. 8.2 → 3.6/ day (0/16 had inc. D)
  - Rectal bleeding: resolved 29% Decreased 43% No change 21%
  - IBD+CD: 4 pts – all able to D/C IBD meds
  - Adverse events: 3/16 had transient abd. distention

Inflammatory Bowel Disease

ACG meeting 10/13 Abs P1688 S Khanna **FMT in IBD pts with CDI**

13 pts, 7CD, 6 CUC CDI conventional Rx x 5

Meds: 6 5-ASA; 6 biologic; 3 immunomod.; 5 steroids None DC for FMT

Ages: 21 – 48; IBD median 3 yrs before FMT

Inflammatory Bowel Disease

92% success rate in median 2 weeks after FMT (CDI -)

No adverse events

IBD pts: 46% → higher dose IBD meds, most likely not related to CDI

Irritable Bowel Syndrome

ACG meeting 10/13 Abs P1862 L. Brandt

- 13 IBS patients treated with FMT
- IBS-D: 9; IBS-C:3; IBS-M:1 Mean duration 73 mos. (12-180 mos.) All failed therapies
- Single FMT 11/13; 1/13 x 2; 1/13 x 3

Irritable Bowel Syndrome

- Follow up av. 11 mos (6 – 18 mos.)
- Results: 70% complete or partial remission; remaining 30% no change

Irritable Bowel Syndrome

- Subgroups
  - Abd pain: 73% decreased or resolved
  - Bloating: 50% decreased or resolved
  - Flatulence or dyspepsia: 41% and 66% decreased or resolved

Irritable Bowel Syndrome

- Subgroups
  - Constipation: decreased frequency
  - Diarrhea: decreased frequency
  - Global feeling of well being: “most” (4/13 not)
  - Adverse events: 0

What about FMT and PSC?

- Cause of PSC in unknown
  - Immune activation
  - Genetic factors
  - Ischemic ductal injury
  - Bacterial infection

Bacterial infection

- Strong association between CUC and PSC
- Speculation: gut permeability in CUC → bacteria in portal circulation causing chronic or recurrent cholangitis.
- Or…

Bacterial infection

Or…

- Bacterial products may cause bile duct injury/ inflammation

Evidence contradictory…

Bacterial infection

- Early studies indicated increased risk of portal venous bacteremia in PSC patients
- Subsequent studies do not confirm the portal vein phlebitis
- Small intestinal bacterial overgrowth in some animal studies → similar bile duct appearance as in PSC

What about FMT and PSC?

- Interest in this gut bacteria and PSC relationship raises the possibility still that the gut microbiome might have some bearing on the cause of PSC.

- Therefore, microbiome alterations might, along with other therapies, offer some hope in finding a helpful treatment for this difficult liver disease.

What about FMT and PSC?

- To date, such studies of microbiome alteration with FMT have not been done.
- As more and more interesting aspects of this and other microbiome altering measures are investigated, we might find that this could alter the natural history of this problem.

Summary

- Fecal microbiome transplant is an investigational treatment for all diseases at this stage.
- The FDA now requires all uses of this unique therapy to be done under an approved investigational protocol with an FDA issued IND number…except

Summary

- CDI treatment is allowed if an adequate informed consent is given by the patient, and the patient understands this treatment is "investigational".

- There is strong evidence in several large case series that FMT is highly efficacious in curing patients with relapsing CDI and appears to be very safe.

Summary

- There is a suggestion this treatment might be helpful in other diseases such as IBD and IBS.
- There are several other diseases that theoretically might also be helped by this treatment such as obesity, metabolic syndrome, diabetes,… and PSC. However, these have not yet been investigated.

Thank you!

Questions ?