

Bugs in the bowel. home grown ones and visitors. IPC view.

3 options for c.diff. more to come

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Bowel Bugs...friend or foe? Friend and foe?

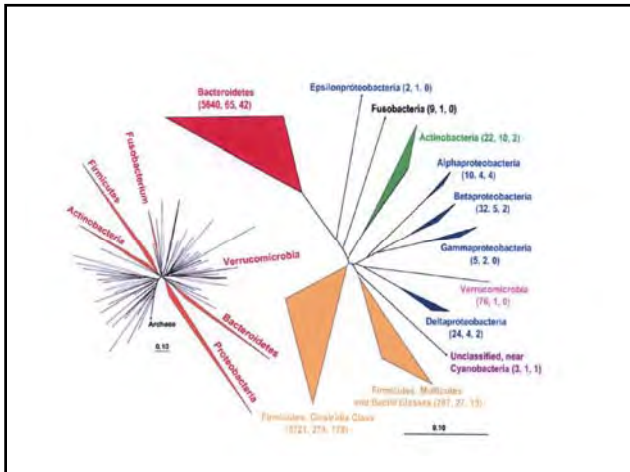
- Normal flora protects?
- VRE
- C. difficile
- ?MRSA
- ESBL, AmpC's, MBL pseudo & coliform, KPC's
- Source of vitamin K, source of fatty acids for enterocyte nutrition, diverse roles of microbe such that the "normal" microbes are part of healthy state.

Normal bowel bugs...the microbiome

- 10 x more cells in gut as all cells comprising human body.....trillions
- Gradual complexity to > 600 + species
- Most are unknown, only a 1/3 are grow-able
- Function poorly understood, but picture getting better
- Generally stable, but can be perturbed e.g. antibiotics, drugs, infections. Comes from lining.

What we know of gut bugs in old days.

- E. coli, E. coli, E. coli
- Pseudomonas
- Enterococcus
- VRE, Salmonella, Shigella, Campylobacter etc
- Bacteroides, C. perfringens, C. septicum
- Ova/parasites
- viruses



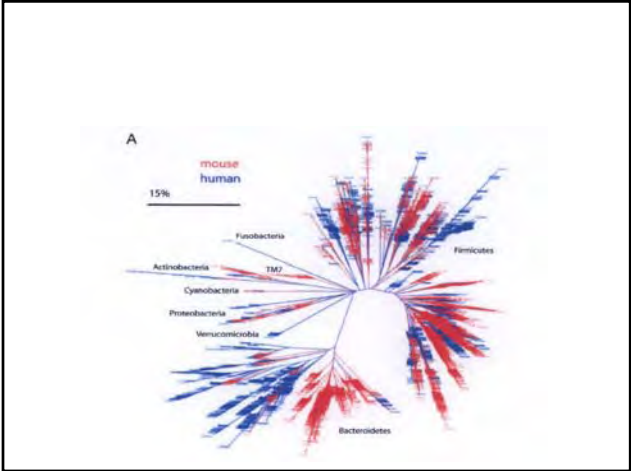
Fast findings about gut NF

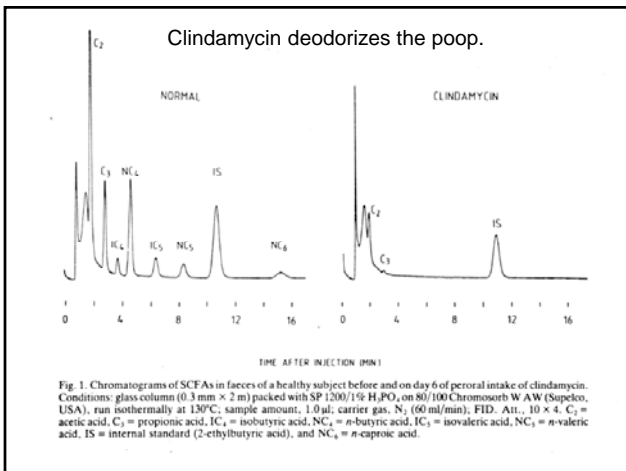
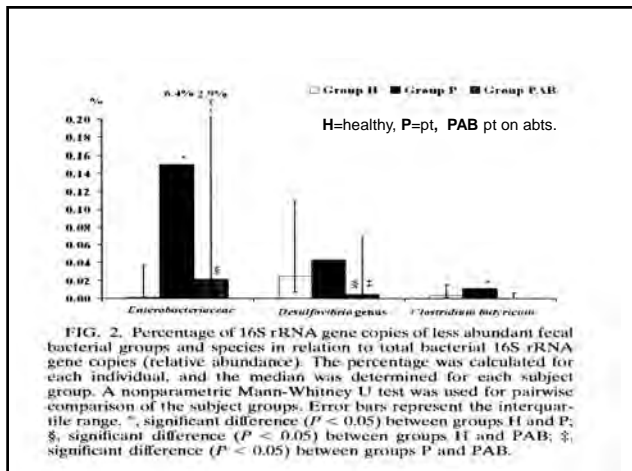
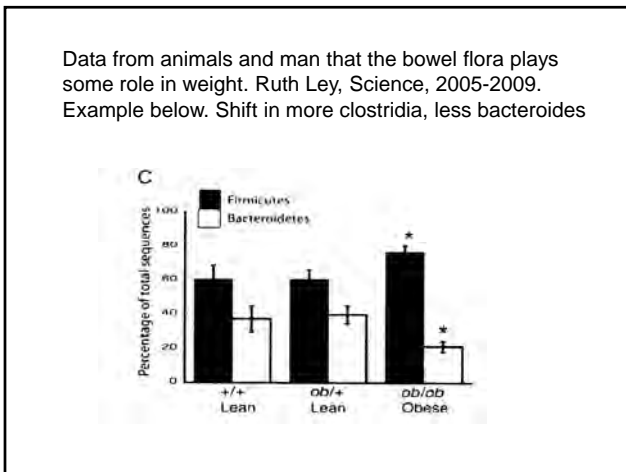
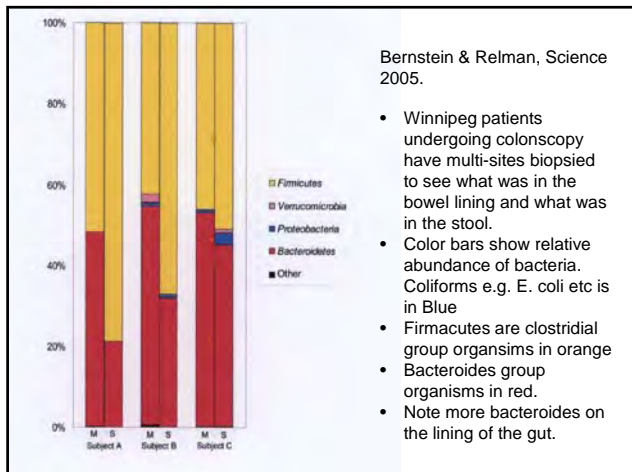
- ~ 1000 species
- 1/3 cultivable
- ½ are live, 20% injured, 30% dead
- *C. coccoides*, *C. leptum*, *Bacteroides* most numerous
- Host genetics govern make up, likely every person has a unique microbial composition

- Within families, genetically linked persons have more similar flora [spouses are different]
- No data about which microbes might confer colonization resistance against *C. difficile*

Genetic diversity of viable, injured and dead fecal bacteria.
Ben-amor, de Vos et al, Appl Env Micro 2005

- FACS/propidium iodide/SYTO BC
- 49% cells viable, 19% injured, 32% dead
- Predominant organisms in *Clos. coccoides*, *Clos. leptum*, *Bacteroides*





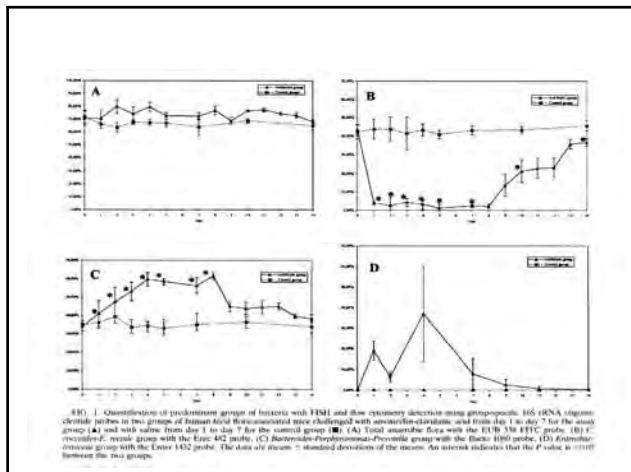


FIG. 1. Quantification of predominant group of bacteria with FISH and flow cytometry detection using group-specific 16S rRNA oligonucleotide probes in two groups of human fecal trans-omental tract challenged with amoxicillin-clavulanic acid from day 1 to day 7 for the control group (A) and with saline from day 1 to day 7 for the control group (B). (A) Total aerobic flora with the EUB 338 FISH probe. (B) *Clostridium* spp. specific oligos with the E-test 462 probe. (C) *Bacteroides-Prevotellaceae-Prevotella* group with the E-test 1493 probe. (D) *Desulfohalobium* group with the E-test 1432 probe. The data are means \pm standard deviation of the means. An asterisk indicates that the *P* value is <0.0001 between the two groups.

APPLIED AND ENVIRONMENTAL MICROBIOLOGY, July 2002, p. 3401-3407
 0099-2240/02/\$14.00+0 DOI: 10.1129/AEM.67.7.3401-3407.2002
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Mucosa-Associated Bacteria in the Human Gastrointestinal Tract Are Uniformly Distributed along the Colon and Differ from the Community Recovered from Feces

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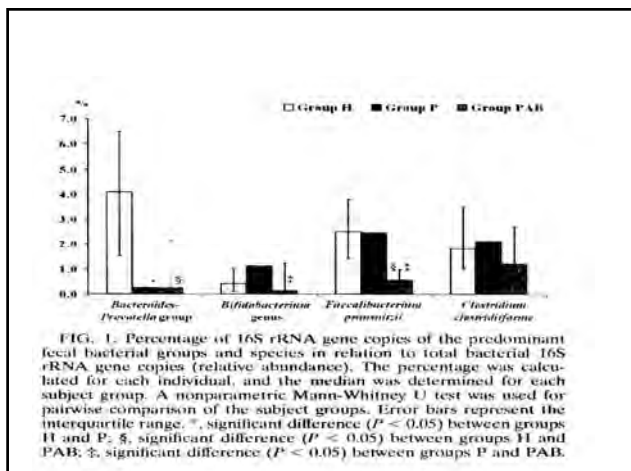


FIG. 1. Percentage of 16S rRNA gene copies of the predominant fecal bacterial groups and species in relation to total bacterial 16S rRNA gene copies (relative abundance). The percentage was calculated for each individual, and the median was determined for each subject group. A nonparametric Mann-Whitney U test was used for pairwise comparison of the subject groups. Error bars represent the interquartile range. *, significant difference ($P < 0.05$) between groups H and P; †, significant difference ($P < 0.05$) between groups H and PAB; ‡, significant difference ($P < 0.05$) between groups P and PAB.

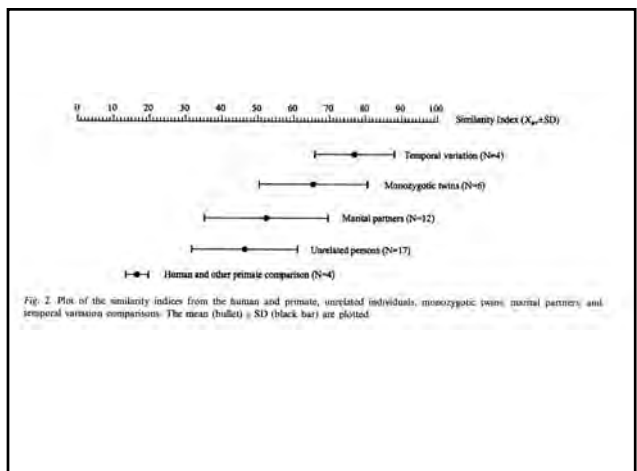


Fig. 2. Plot of the similarity indices from the human and primate, unrelated individuals, monozygotic twins, marital partners, and temporal variation comparisons. The mean (bullet) \pm SD (black bar) are plotted.

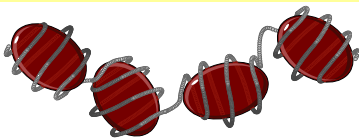
Progress in CDI treatment : finding alternates to metronidazole and vancomycin

Kill the pathogen	Bind / neutralize toxin in lumen of colon
Preserve residual normal microbiota, allow regeneration	Augment host antibodies vs <i>C.difficile</i> toxins, passive, active
Reduction of harmful components of immune responses	Prevention of CDI: infection control, ecologic control :ntcd

Candidates for narrow spectrum CDI treatment

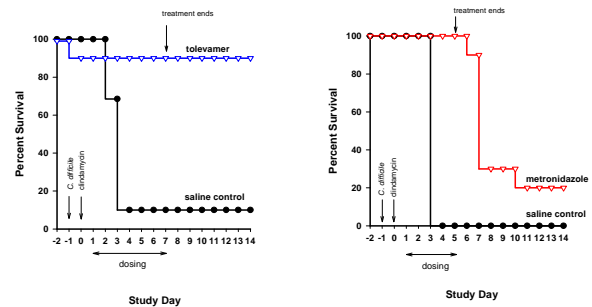
- Tolevamer as 1st attempt at narrow therapy
- OPT-80, now Fidaxomicin: translating promise observed in-vitro to candidate CDI therapy (2004-2010)
- More candidates: Rifaximin, Rep 3123 (methionyl t-RNA synthetase inhibitor), Oritavancin, CB 183,315 (oral lipopeptide)

Tolevamer/Toxin interaction



800 monomer units of tolevamer bind one molecule of toxin A
 Each polymer molecule may bind 3-4 toxin molecules
 Kd Toxin A = 133nM
 Kd Toxin B = 9µM
 (Braunlin *Biophys J* 2004)

Comparison of tolevamer and metronidazole activity in the hamster model of *C. difficile* colitis

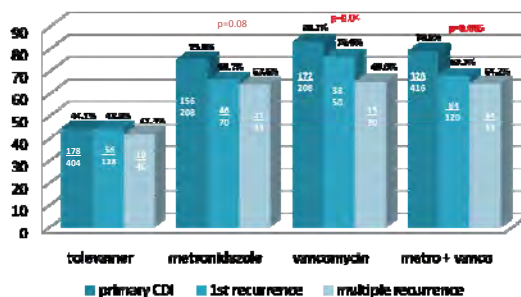


(Kurtz AAC 2001)

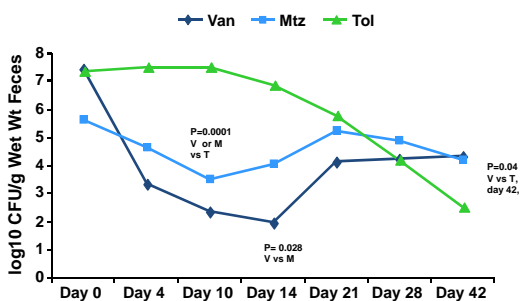
Overall outcome of Genzyme 301/302 trials : tolevamer vs metronidazole vs vancomycin as treatment of Clostridium difficile infection, 1071 patients, FAS=ITT, strain typing by Gerding lab

	Tolevamer	Metronidazole	Vancomycin
Clinical response	236 / 534 (44.2 %)	202 / 278 (72.7%)	210 (259) 81.1%
Recurrence of CDI	10 / 222 (4.5%)	49 / 213 (23.0%)	43 / 209 (20.6%)

Reduction of clinical response with increasing recurrence of CDI; Genzyme 301/302

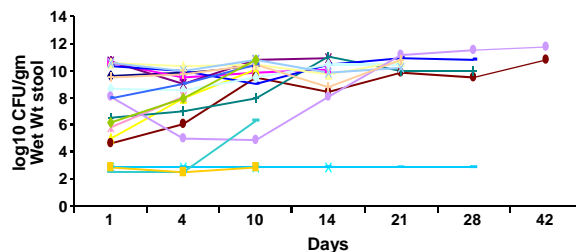


Quantitative *C.difficile* CFUs in patients randomized to Vanco, Metro or Tolevamer, Genzyme 301 (n=43)



Louie TJ , 48th ICAAC/46th IDSA. October 2008; Washington, DC. Abstract K-520.

Bacteroides Group Counts in Patients Responding to Tolevamer Therapy



Louie TJ , 48th ICAAC/46th IDSA. October 2008; Washington, DC. Abstract K-520.

Quantitative *B. fragilis* group counts in 103 patients at study entry,

Genzyme and Phase 2a OPT-80

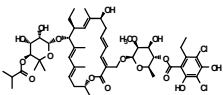
<i>Log</i> ₁₀ CFU/gm	number of patients
≥ 11	3 (2.9%)
8.1 to 10.95	34 (33%)
3.1 to 8.0	29 (28%)
≤ 3	37 (36%)

5 normals had counts ≥ 11.5 with on average 4 spp./ donor

Learnings from tolevamer

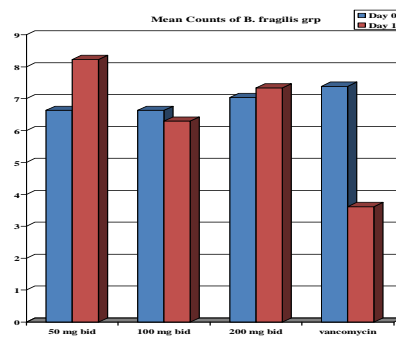
- Seems desirable to kill the pathogen (first?)
- For responders to Tolevamer, recurrence is uncommon. Biome features to be sorted out.
- Vanco most consistent CD reduction, less so with metrodazole. Biome features of metro to be sorted out in patients.
- Recurrent disease is more difficult to treat

Fidaxomicin (OPT-80)



- New class of antibacterial
 - macrocyclic antibiotic, targets RNA polymerase
 - no cross-resistance with known antibacterials
 - low rate of *C. difficile* resistance development
- Active against *C. difficile*, including BI (NAP1/027)
 - MIC90 vs *C. difficile*, 0.125 µg/mL
 - Bactericidal activity against *C. difficile*
 - Long postantibiotic affect (>24 h)
- “Narrow spectrum”
 - No activity vs Gram negative bacilli
 - Moderate vs some Gram pos
- Low systemic absorption
 - ng/mL plasma concentrations
 - High fecal concentrations
 - >10,000 × the MIC₉₀

Log 10 CFU/gm *Bacteroides* group organisms by increasing doses of OPT-80 BID or vancomycin 125 mg qid; Phase 2a study (AAC Jan'09)



Response: 12/14 13/15 16/16

Microbial signatures by FISH/FLOW study of patients in the OPT-80 (fidaxomicin) phase 2a study. Gerald Tannock et al (Dunedin, NZ), submitted.

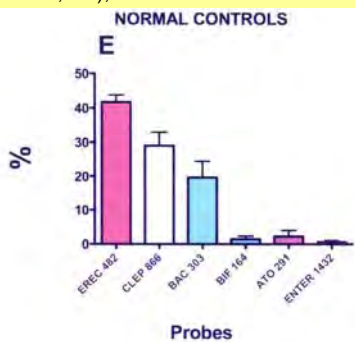
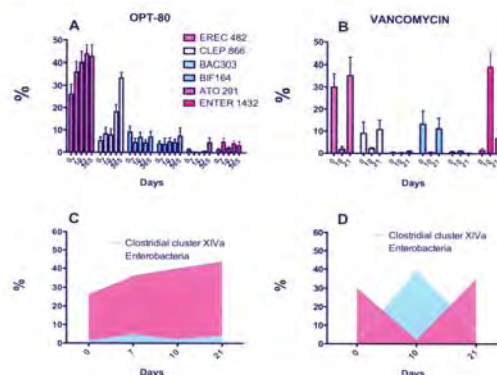


Figure 3 Results of FISH/FLOW study of OPT-80 or Vancomycin treatment of CDI, Tannock et al.



Cure of CDI by Fidaxomicin or Vancomycin, Two DB-RCTs, involving 1164 patients

	Fidaxomicin (200 mg bid)	Oral Vancomycin (125 mg qid)
003 (NA) study	92.1% (244/265)	89.8% (254/283)
004 (Int'l) study	91.7% (198/216)	90.6% (213/235)

Per Protocol: Patient group with CDI confirmed by diarrhea with a positive toxin assay, protocol compliant, and received at least 3 days of therapy if failure and at least 8 days of therapy for cure

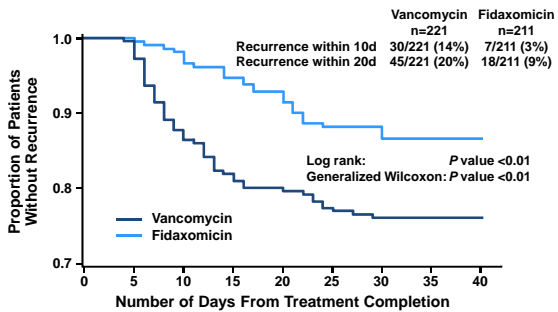
Louie T et al. Presented at: 19th ECCMID, May 17, 2009; Helsinki, Finland. Abstract. Miller M et al. *Gastroenterology*. 2009;136 (Suppl 1):Abstract 751a. Golan Y et al. Presented at: 49th ICAAC, Sept. 14, 2009; San Francisco, CA. Abstract L1-1639. Crook D et al. LB2401, ECCMID 2010, Vienna Austria April 2010.

Recurrence within 4 weeks post treatment
Fidaxomicin had a 47% lower recurrence rate

	Fidaxomicin (200 mg bid)	Vancomycin (125 mg qid)	P value (95% CI)
003 (NA) study	13.3% (28/211)	24.0% (53/221)	0.004 (-17.9, -3.3)
004 (Int'l) study	12.8% (23/180)	25.3% (46/182)	0.002 (-20.3, -4.4)

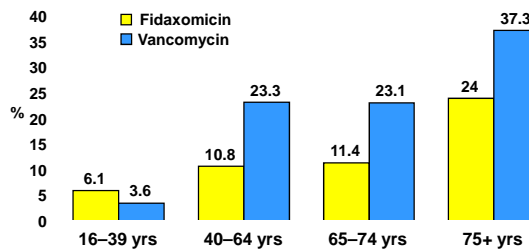
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Time to Recurrence (003 trial)



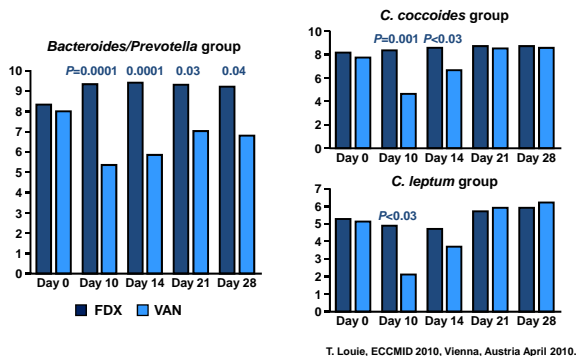
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Miller M et al. *Gastroenterology*. 2009;136 (Suppl 1):Abstract 751a.
Golan Y et al. Presented at: 49th ICAAC, Sept. 14, 2009; San Francisco, CA. Abstract L1-1639.

Recurrence of CDI by Age Groups, Vancomycin vs Fidaxomicin (003)



Golan Y et al. Presented at: 49th ICAAC, Sept. 14, 2009; San Francisco, CA. Abstract L1-1639.

Log₁₀ CFU/gm Feces of Major Cultivable and Noncultivable Genera of the Normal Fecal Microbiota; n=20 (Optimer phase 3 [003] protocol)



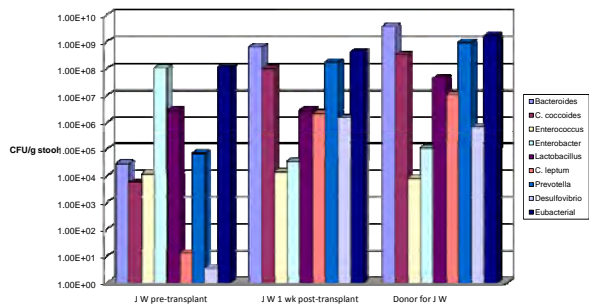
Lower incidence of VRE acquisition with Fidaxomicin during 003 trial

Establishment of VRE colonization ²	FDX	VAN	P value (95% CI)
Negative @ day 1	115	133	
Acquire @ day 10	8	41	
New VRE colonization rate	7%	33%	<0.001

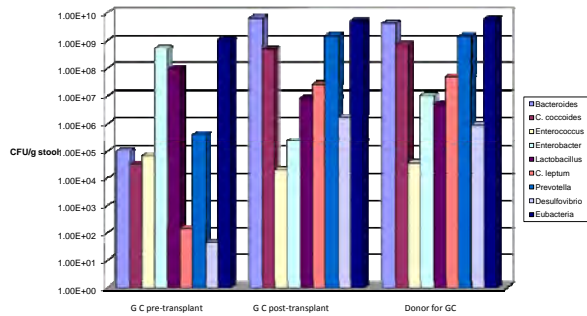
Nerandzic MM et al. Presented at: 49th ICAAC, Sept. 15, 2009; San Francisco, CA. Abstract K1915.

Instant restoration of the microbiome by fecal flora replacement

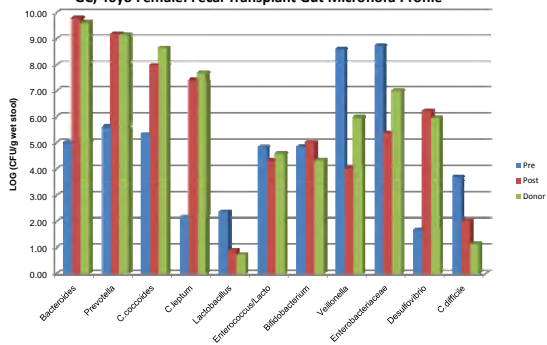
J W- Transplant Patient – biome profiles



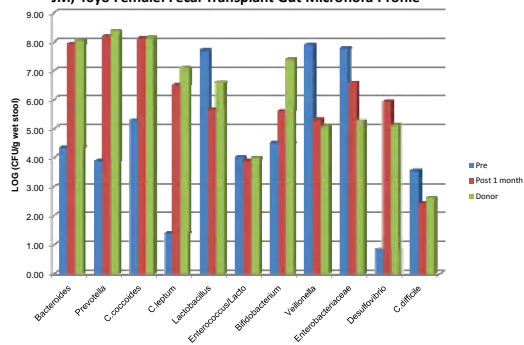
G C - Transplant Patient - Normal Flora

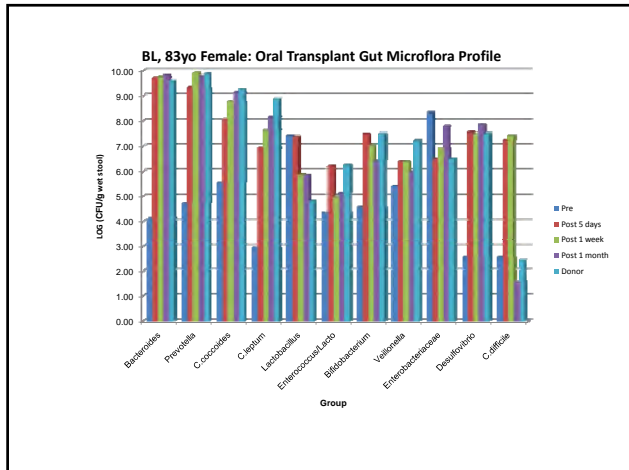


GC, 46yo Female: Fecal Transplant Gut Microflora Profile



JM, 46yo Female: Fecal Transplant Gut Microflora Profile





**Conclusions: *narrow spectrum therapy of CDI:*
on the verge of better treatment options**

- New and novel agents hold the promise of better treatments for both cure and recurrence
- There is still much to be learned in terms of application of these agents..duration, multiple recurrence, effect on biome, resistance
- Addition of biologics and better understanding of CDI pathogenesis should lead to improved outcomes

Conclusions.. Bowel flora

- We are one with our bugs..leave them alone
- As we grow old, our bugs also grow old and deteriorate
- Diverse contributions..even depression, obesity, autism, aging, cancer. We are what we eat.
- Our hate in infection control..source of trouble the fecal 'vener'...all over the place.