Meeting to Transform IBD

Collaborative Solutions in Patient-Centric Care.

CROHN'S & COLITIS CONGRESS™

A Partnership of the Crohn's & Colitis Foundation and the American Gastroenterological Association

FMT for Recurrent *C Difficile* Infection and IBD in the Pediatric Population

Maria Oliva-Hemker, MD

Johns Hopkins University School of Medicine

Baltimore, MD

CROHN'S & COLITIS FOUNDATION

AGA

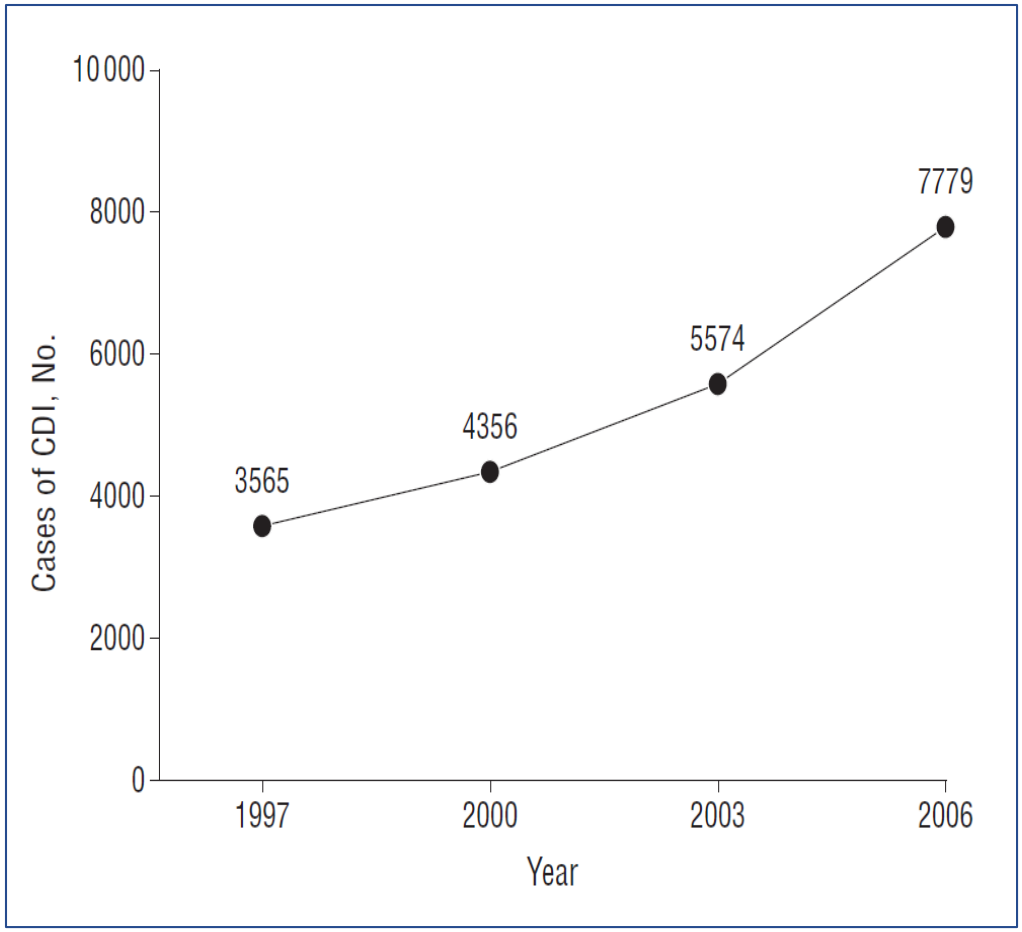
Disclosures

- Grant funding
  - Janssen
  - Prometheus
  - Abbott Immunology
  - Nestle Nutrition
- Consulting
  - Hoffman LaRoche

Objectives:

- Discuss the prevalence of CDI in children
- Review efficacy and safety of FMT for pediatric patients (<18 years) with recurrent CDI and IBD
- Highlight ethical issues unique to children when considering FMT

Prevalence of *C difficile* Infection Increasing in Children

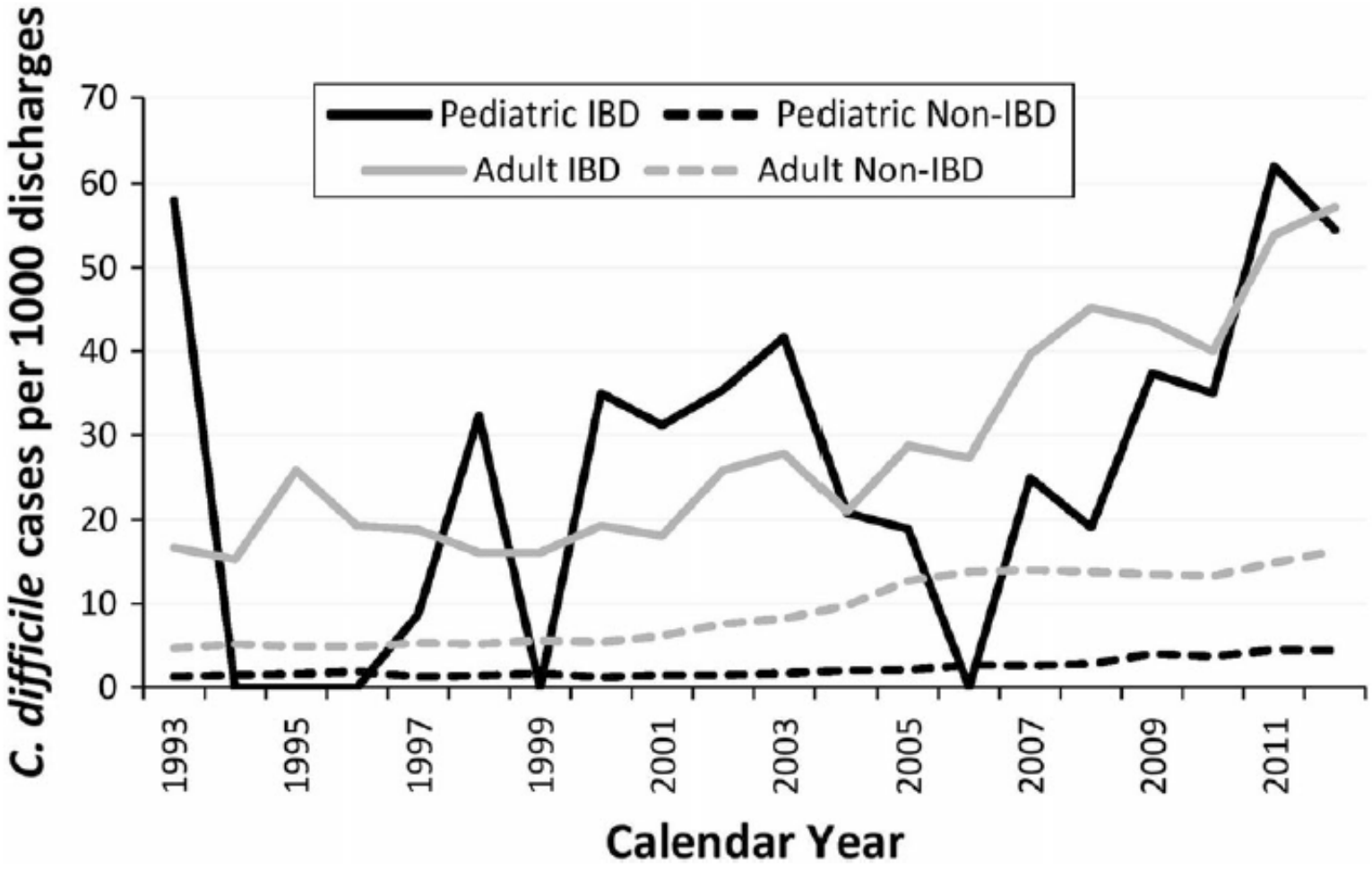


Adjusted Association Between CDI and Health Severity Indicators

Indicator	OR (95% CI)
Mortality	1.20 (1.01-1.43)
Colectomy	1.36 (1.04-1.79)
Length of stay	4.34 (3.97-4.83)
Hosp. charges	2.12 (1.98-2.26)

Nylund CM et al, Arch Pediatr Adolesc Med 2011

C difficile Infection Associated with IBD in Hospitalized Children & Adults (Maryland, 1993-2012)



Hourigan, Oliva-Hemker &, Hutfless, Dig Dis Sci 2014

Prevalence of *C difficile* in IBD vs Non-IBD Patients

1993-2012	Ped IBD	Ped non-IBD	IRR*	95%CI	P Value
CDI cases per 1000 discharges	28.6	2.2	12.7	10.0-26.1	<0.0001

1993-2012	Adult IBD	Adult non-IBD	IRR*	95%CI	P Value
CDI cases per 1000 discharges	33.0	9.6	4.0	3.8-4.2	<0.0001

*Incidence rate ratios

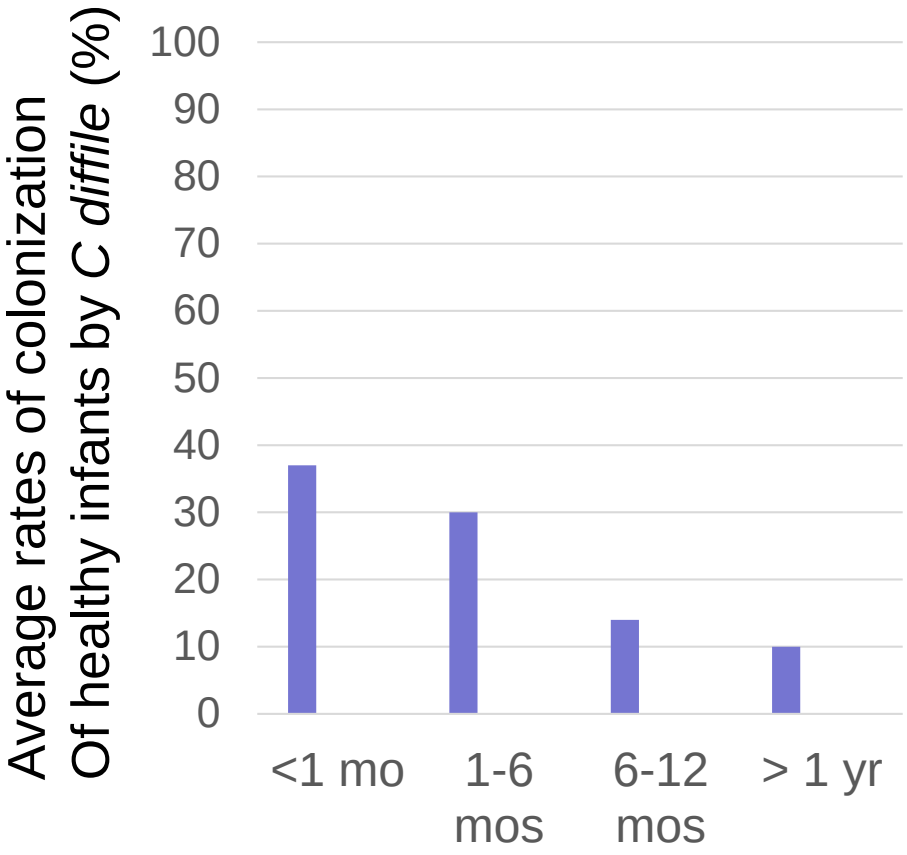
Hourigan, Oliva-Hemker & Hutfless, Dig Dis Sci 2014

Increased Prevalence of *C difficile* in Asymptomatic IBD Patients

- Prospective studies investigating frequency of detectable *C difficile* in outpatients with IBD in clinical remission:
  - Children with IBD (n=85) vs controls (n=78): **17% vs 3%,** P=0.012
  - Adults with IBD (n=122) vs healthy controls (n=99): **8.2% vs 1%,** P=0.02

Hourigan SK et al, Inflamm Bowel Dis 2013
Clayton EM et al, Am J Gastroenterol 2009

High *C difficile* Colonization in Healthy Infants



Potential Mechanisms of Resistance to CDAD in Infants
Absent machinery for processing toxin
Breast milk components
Competition from maturing flora

Jangi & Lamont, J Pediatr Gastroenterol Nutr 2010

Pediatric Studies of FMT for recurrent CDI

Author	Year of publication	Age (years)	Number of children	Route FMT	Cure rate	Complications
Kronman *et al.* (25)	2015	1–13	10	Nasogastric	90%	Transient vomiting and mucoid stool
Russell *et al.* (26)	2014	1–19	10	Nasogastric (2); Colonoscopy (8)	90%	None
Pierog *et al.* (27)	2014	1–21	6	Colonoscopy	100%	None
Walia *et al.* (28)	2014	1–2	2	Colonoscopy	100%	None
Hourigan *et al.* (29)	2015	6–17	8	Colonoscopy	100%	None
Kahn *et al.* (30)	2012	1	1	Colonoscopy	100%	None
Wang *et al.* (31)	2015	1	1	Nasojejunal	100%	None
Rubin *et al.* (32)	2013	6–8	2 children with adult series	Upper tract (route unclear)	50%	None
Kelly *et al.* (33)	2014	6–16	5 immuno-comprised children with adult series	Not specified for children	89% (whole series)	No infectious complications

Hourigan S & Oliva-Hemker M, Pediatr Res 2015

Multicenter Retrospective Pediatric FMT Study for CDI

Sites	
Vanderbilt Children's Hospital (TN)	Baylor College of Medicine (TX)
Boston Children's Hospital	University of Chicago
Mayo Clinic (MN)	University of Connecticut
University of Utah	Children's Hospital of Philadelphia
Johns Hopkins Children's Center (MD)	Weill Cornell (NY)
Seattle Children's Hospital	Nationwide Children's Hospital
Children's Healthcare of Atlanta	Cedars Sinai
Children's Hospital of Wisconsin	INOVA Fairfax (VA)
Mass General Hospital for Children	University of Southern California

Primary Aim: To measure success rate (no relapse in 2 months) of FMT in pediatric patients with rCDI

Secondary Aims: 1) Identify risk factors associated with failed FMT
2) Quantify and describe potential adverse outcomes

Pediatric FMT Study for CDI (1/1/2006-1/1/2017)

Subject characteristics (N=373)	N (%)
Age (yrs); Median (IQR)	10 (3-15)
Female	186 (49.9%)
Race	
White	332 (89.0%)
Black	15 (4.0%)
Asian	7 (1.9%)
Unknown or Other	22 (5.9%)
Comorbidities	
IBD	120 (32.2%)
Feeding Tube	72 (19.3%)
GERD	36 (9.7%)
Solid Organ Transplant	9 (2.4%)
Stem Cell Transplant	5 (1.3%)
Indication for FMT	
Recurrent CDI	364 (97.6%)
Refractory CDI	32 (8.6%)
Severe or complicated CDI	11 (3.0%)

Nicholson M et al, NASPGHAN Annual Meeting, Oct 2017

Pediatric FMT Study for CDI

	N (%)
Number of *C. diff* episodes prior to FMT; Median (IQR)	3 (3-4)
Donor Stool	
Patient-selected	161 (43.2%)
Commercial stool bank	110 (29.5%)
Local stool bank	100 (26.8%)
Stool type	
Fresh	161 (43.4%)
Frozen	210 (56.6%)
Route of FMT	
Colonoscopy	285 (76.4%)
NG/G-tube	35 (9.4%)
ND/NJ/J-tube	33 (8.9%)
Capsule	14 (3.8%)
Enema	4 (1.1%)
Sigmoidoscopy	2 (0.5%)

Nicholson M et al, NASPGHAN Annual Meeting, Oct 2017

Pediatric FMT Study: Recurrent CDI Results

- Outcome known for 342/373 patients (92%)
  - Additional 6 patients excluded due to refractory CDI as primary indication
- 272/336 (81%) successfully responded to a single FMT
- 64 (19%) of patients relapsed within 2 months
  - 35/64 were treated with repeat FMT
  - 20/35 (57%) successful
- Overall success rate 87%

Nicholson M et al, NASPGHAN Annual Meeting, Oct 2017

Pediatric FMT Study for rCDI: Adverse Events

- FMT-related severe AEs: 6 (1.6%)
  - IBD flare with hospitalization (n=4); 2 with colectomy
  - Non-IBD hospitalizations (n=2)
    - Dehydration
    - Aspiration pneumonia
- FMT-related non-severe AEs: 14 (3.8%)
  - Diarrhea, abdominal pain, bloating (n=6)
  - Constipation (n=5)
  - Mild IBD flare (n=3)
- 7/120 (5.8%) IBD patients had a flare post-FMT

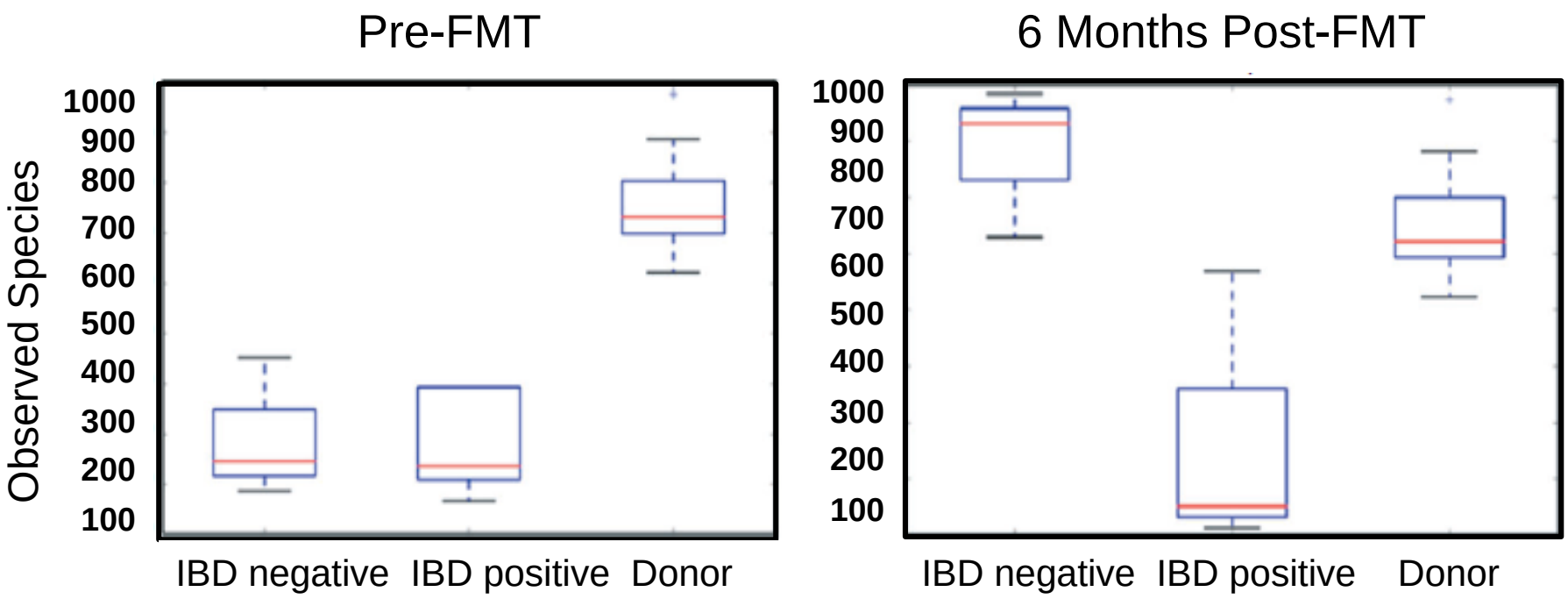
Nicholson M et al, NASPGHAN Annual Meeting, Oct 2017

Pediatric FMT Case Series for IBD

Reference	Age (yr)	Diagnosis, n	FMT Protocol	Clinical Response Criteria	Response Rate
Kunde et al (2013)	7-21	UC, 9	Serial enemas for 5 d	Decrease in PUCAI by >15 pts	7/9 clinical resp. at 1 wk 6/9 maintained resp. at 4 wk
Kellermayer et al (2015)	14-16	UC, 3	Serial enemas & colonoscopy over 6-12 wk	PUCAI <35	3/3 endo remission at 2 wk 3/3 histologic remission at 2 wk 3/3 clinical response at 4 wk 3/3 w/drawal immunoRx at 15 wk
Suskind et al (2015)	12-19	CD, 9	Single FMT via NGT	PCDAI <10	7/9 clinical resp. at 2 wk 5/9 maintained resp at 6 & 12 wk
Suskind et al (2015)	13-16	UC, 4	Single FMT via NGT	PCDAI <10	No clinical response No laboratory benefit

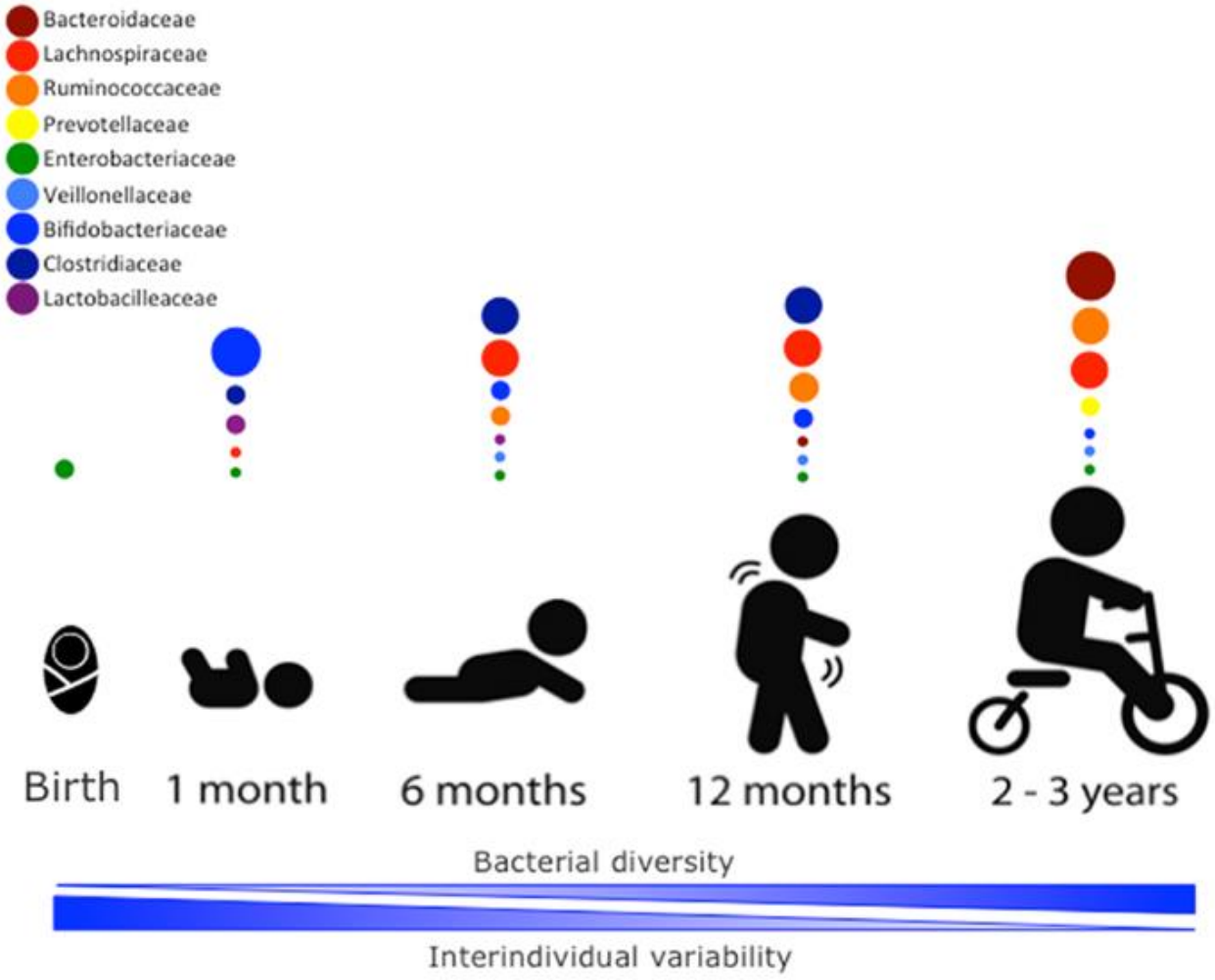
Wang, Popov & Pai, World J Gastroenterol 2016

Alpha Diversity Pre- and Post-FMT in Patients with and without IBD



Hourigan SK et al, Aliment Pharamcol Ther 2015

Stages of Gut Microbial Colonization in Infancy and Early Childhood

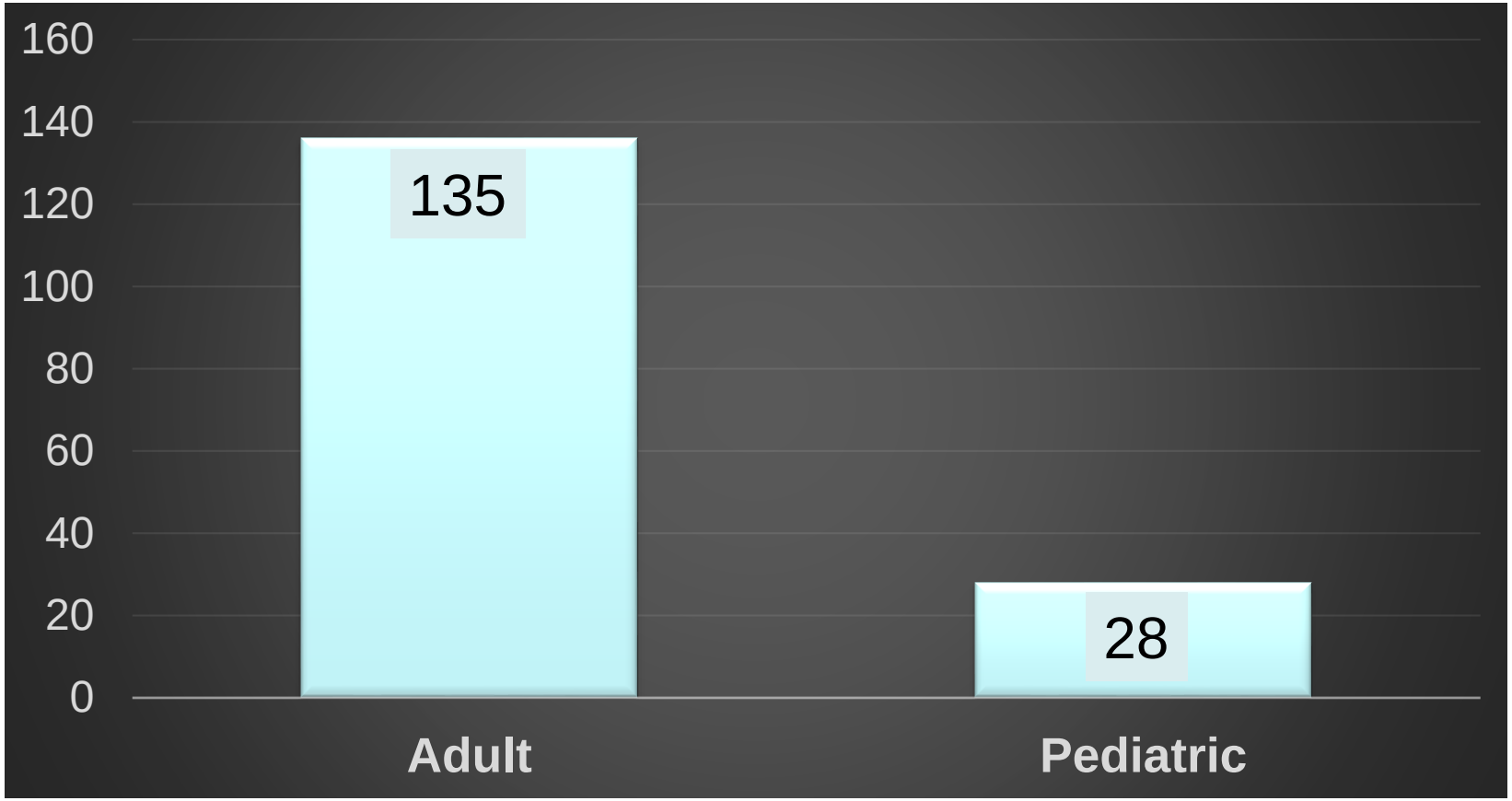


Arrieta MC et al, Front Immunol 2014

Ethical and Clinical Issues for FMT in Children

- Children (especially younger) may be at risk for significant long-term adverse consequences
- Children are a vulnerable population
  - Lack autonomy (parents/guardians decide)
  - Parents eager to treat children with FMT
  - Parents performing FMT on their children at home
- Interventions require more favorable risk/benefit ratio

Open FMT Studies Clinicaltrials.gov



1/15/2017

Unanswered Questions Concerning FMT in Children

- Should donors be age matched?
- Volume of stool required?
- Optimal mode of delivery?
- Infectious risk?
- Unforeseen consequences due to perturbations of the microbiome or the immune system?
- More targeted bacteriotherapy?

Key Points

- ✓ Prevalence of CDI is increasing in children; IBD is the most commonly associated diagnosis
  - ✓ Asymptomatic children with IBD and healthy infants have high rates of colonization with C difficile
- ✓ FMT for recurrent CDI appears to have similar efficacy in children compared with what has been reported in adults
- ✓ Data lacking for use of FMT to treat IBD in children
- ✓ FMT appears to be safe in the short-term but long-term safety data required

Acknowledgements

Johns Hopkins School of Medicine
Cynthia Sears, MD
Grace Felix, MD
Vivian Abadom, RN, PhD

Inova Fairfax
Suchi Hourigan, MD

NYU School of Medicine
Lea Ann Chen, MD

George Washington University
Keith Crandall, PhD
Marcos Perez-Losada, PhD
Michelle Ahn, BS

Robert Wood Johnson University Hospital
Melissa Weidner, MD

NASPGHAN FMT Special Interest Group
Stacy Kahn, MD
Maribeth Nicholson, MD