

Enteral nutrition and the gut microbiome

Microbiome in clinical practice Part 2: FODMAPs vs. FADMAs

Kevin Whelan PhD RD

Professor of Dietetics

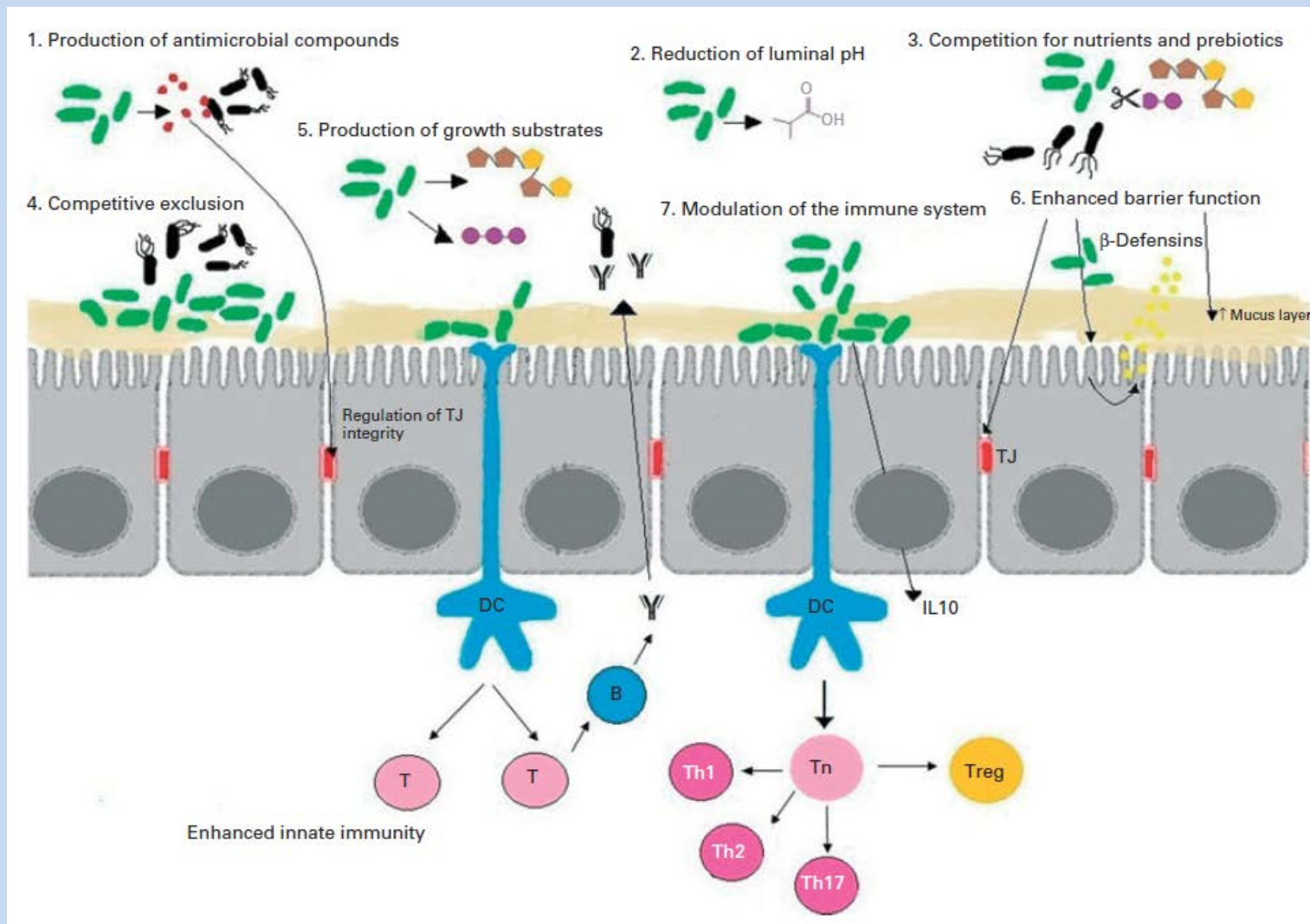
King's College London



@ProfWhelan
#BAPEN2016

KING'S
College
LONDON

Microbiota: beneficial functions in health



Factors influencing the gut microbiome in EN: The 3 Ds

Disease

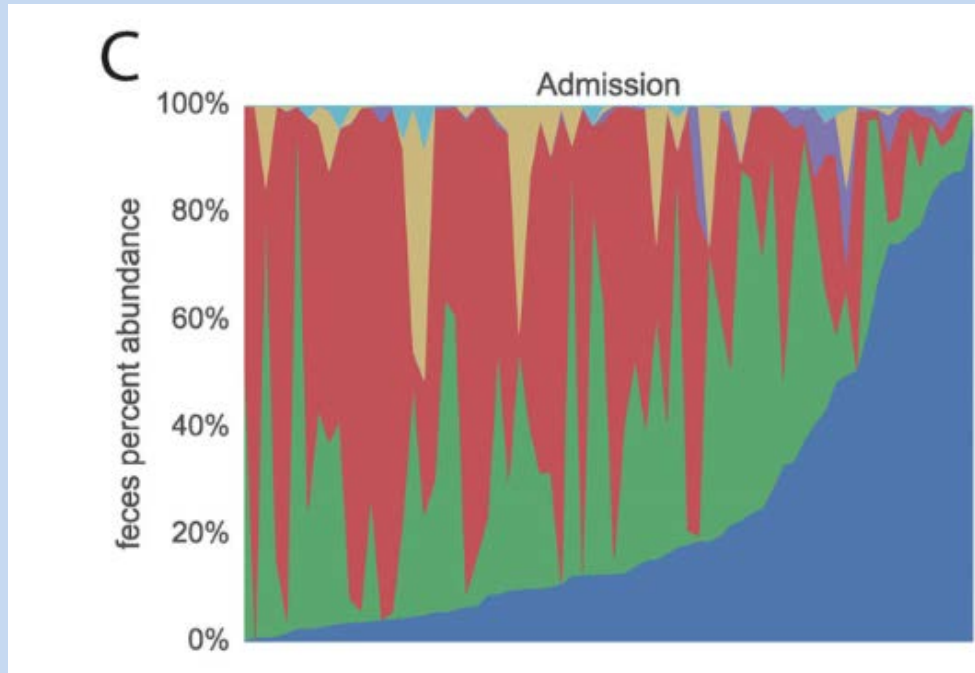


Drugs

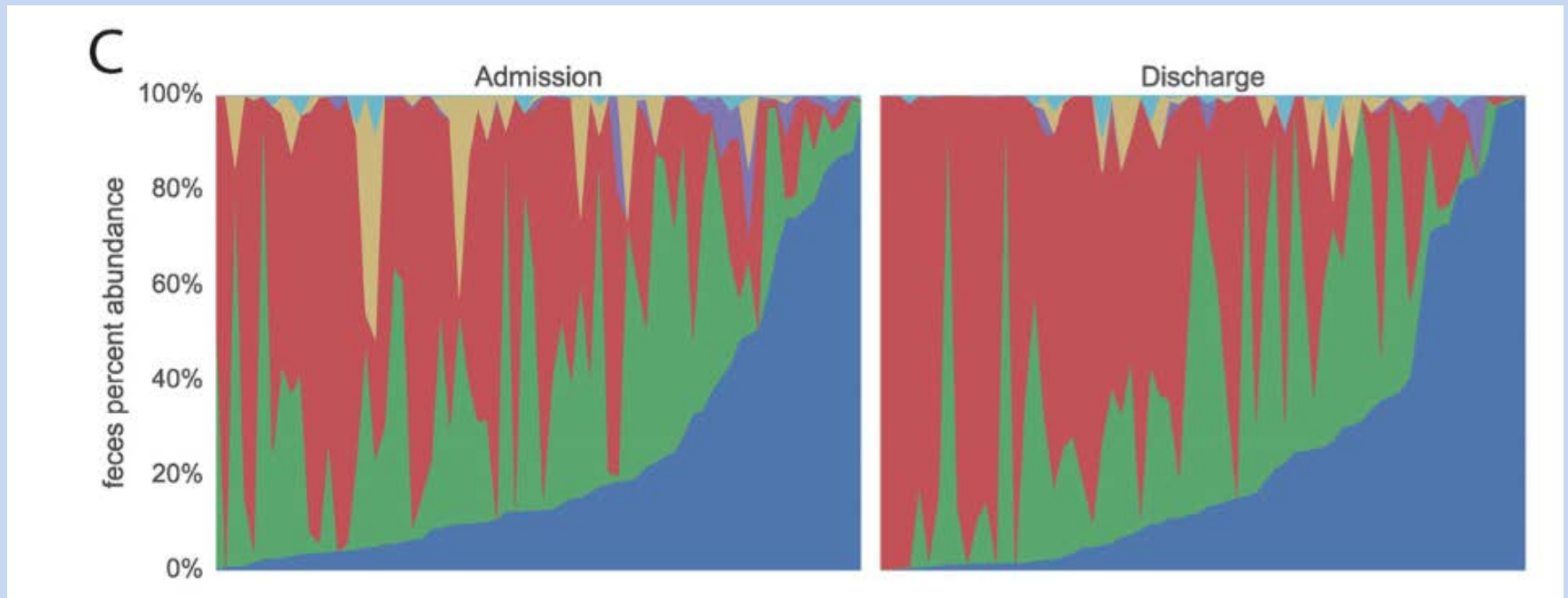
Diet
(enteral formula)



Patients receiving EN have altered gut microbiome



Patients receiving EN have altered gut microbiome



Alterations in gut microbiome in EN are important

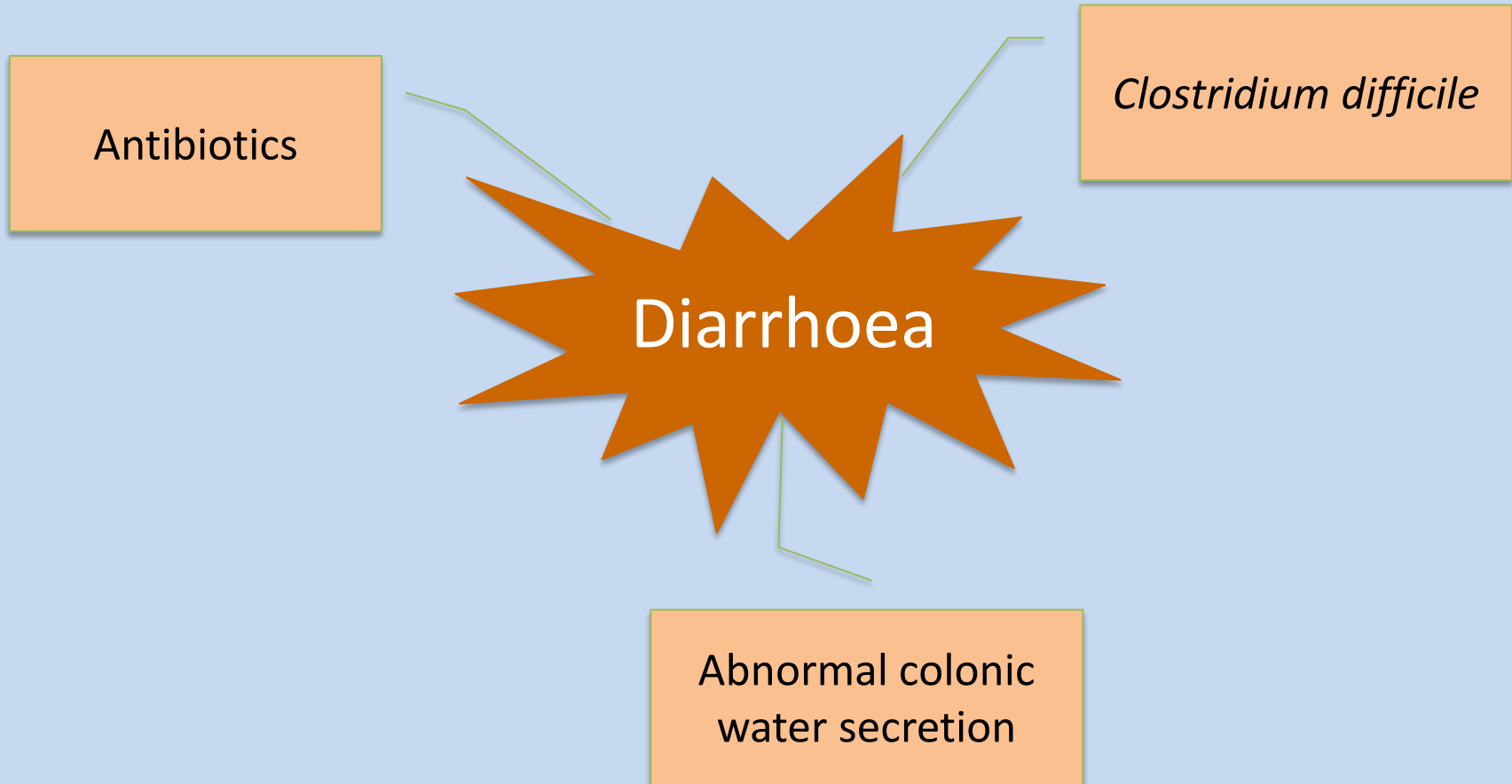


	Start (days 1–4)	Middle (days 6–9)	End (days 11–14)	<i>P</i> value ¹
Microbiota, <i>n</i> = 20 (% of total)				
Bifidobacteria				
No diarrhea	4.3 ± 5.1	9.3 ± 16.0	12.2 ± 18.3	0.029
Diarrhea	0.6 ± 0.5	1.7 ± 3.2	0.4 ± 0.3	

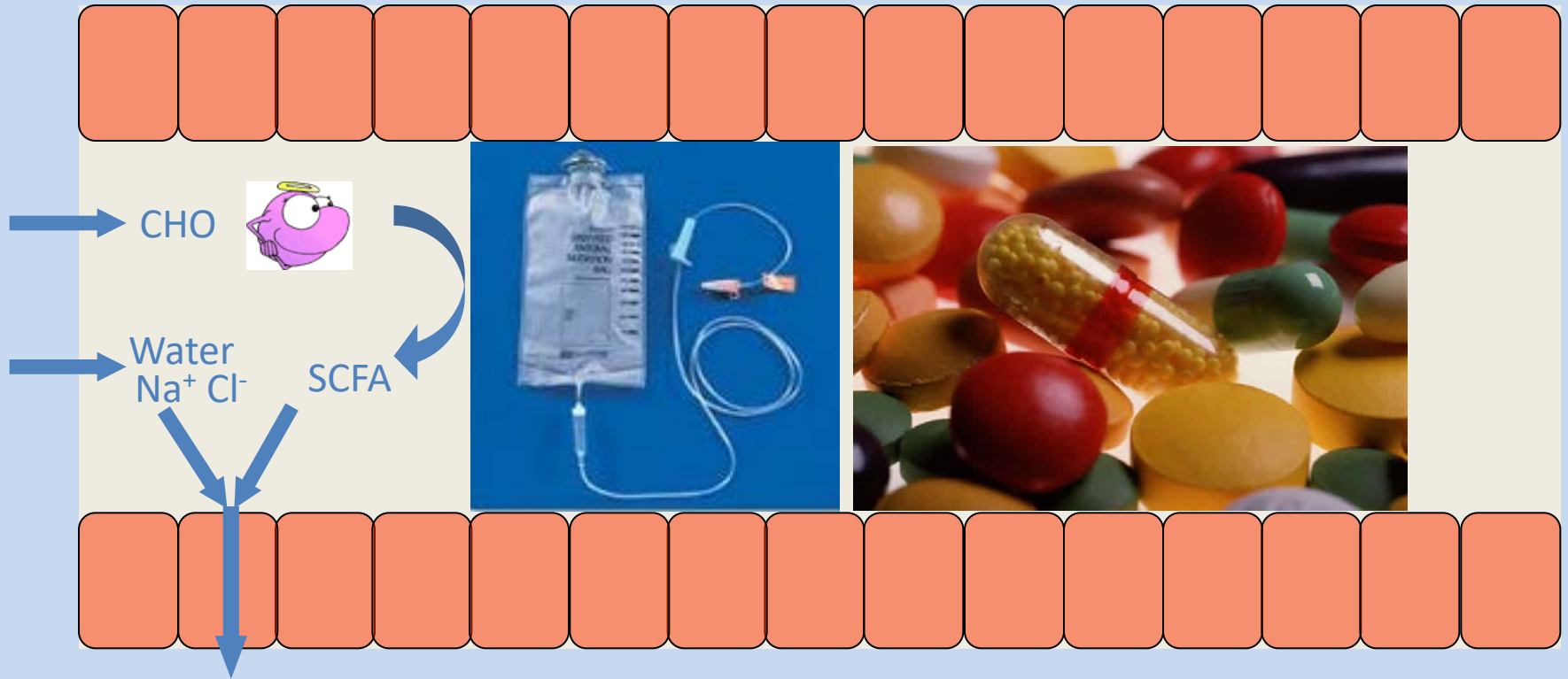


Microbiome, enteral nutrition and diarrhoea:

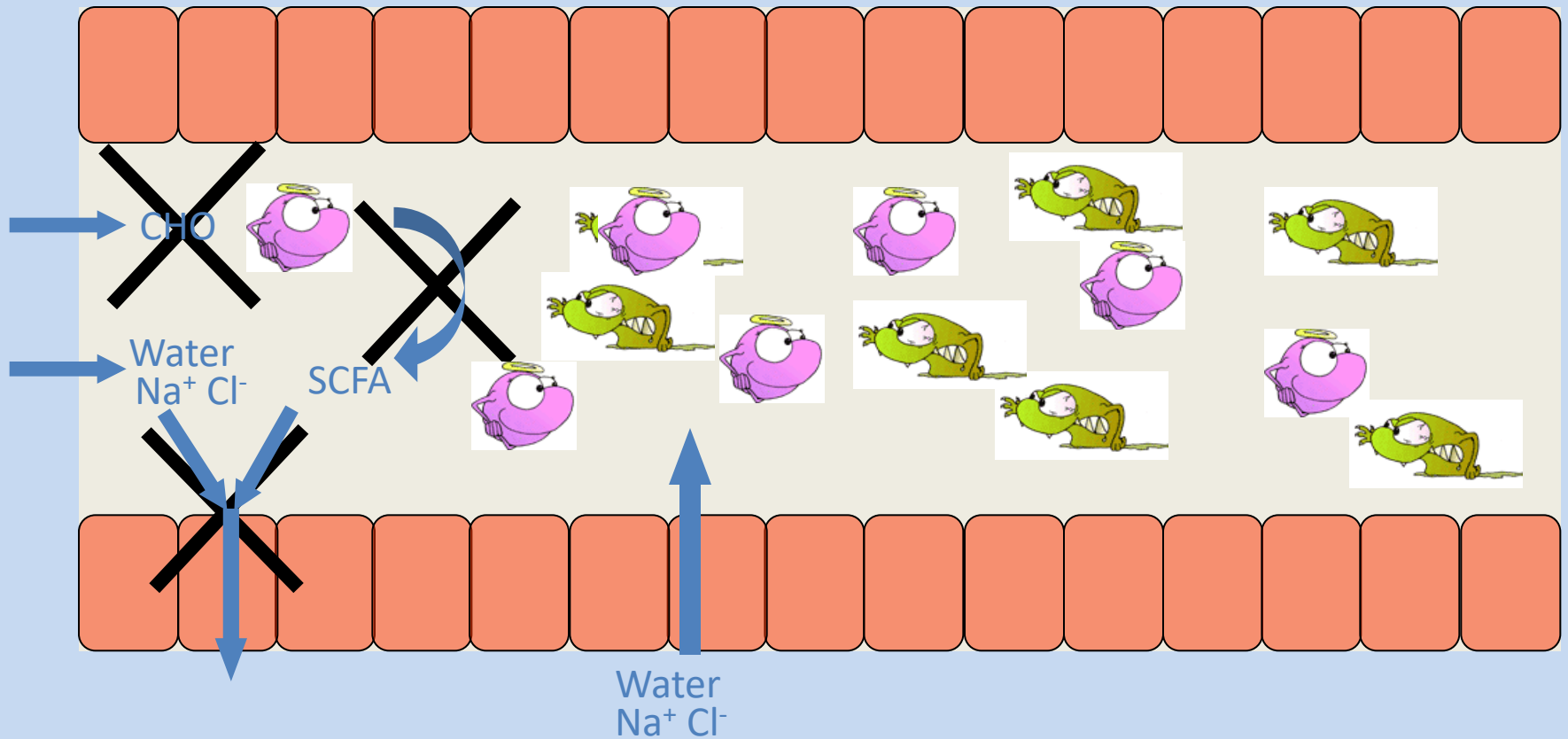
Mechanisms



Microbiome, enteral nutrition and diarrhoea: Mechanisms



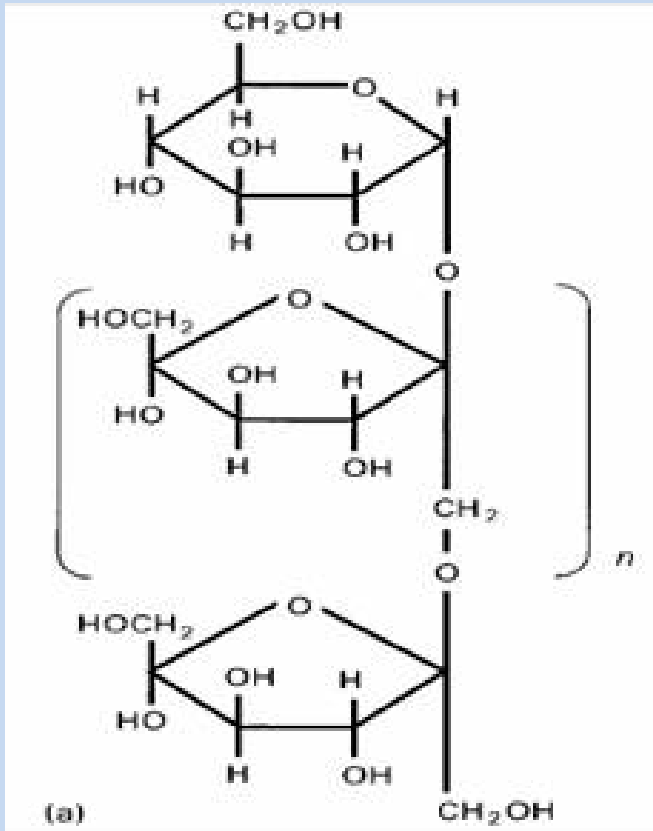
Microbiome, enteral nutrition and diarrhoea: Mechanisms



Do enteral formulas impact gut microbiome?



Prebiotics

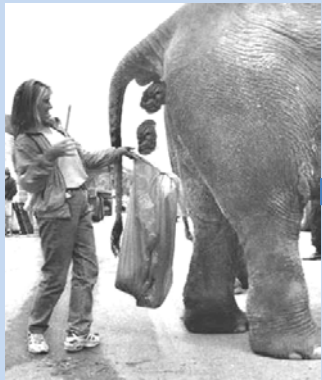


A selectively fermented ingredient that results in specific changes in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefit(s) upon host health (ISAPP, 2008)

Fructans (e.g. oligofructose, inulin, FOS)
Galacto-oligosaccharides)



Do enteral formulas impact gut microbiome?



3-day total stool collection



Healthy people stop eating for 2-weeks and consume enteral formula (+/- prebiotics)



3-day total stool collection



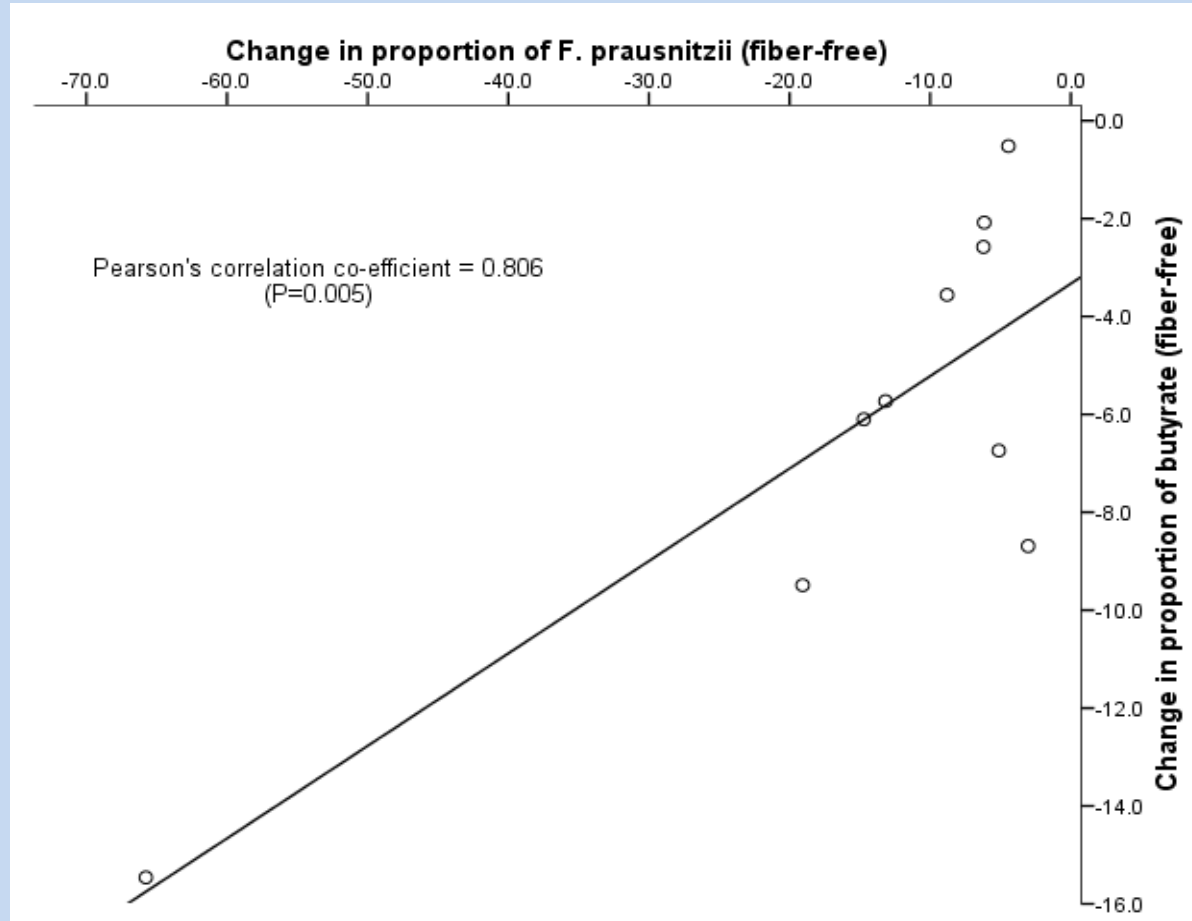
Healthy people stop eating for 2-weeks and consume enteral formula (+/- prebiotics)



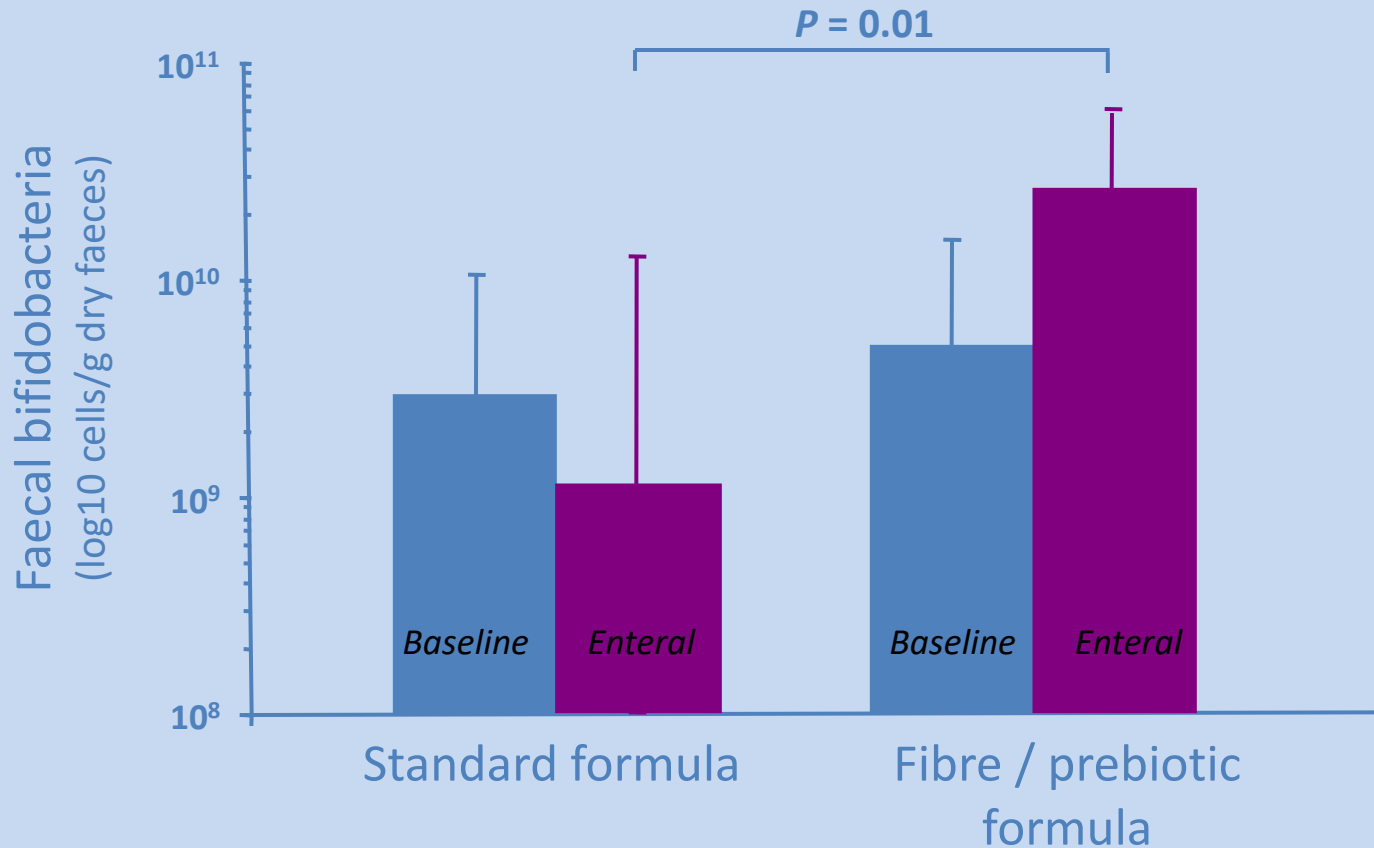
3-day total stool collection



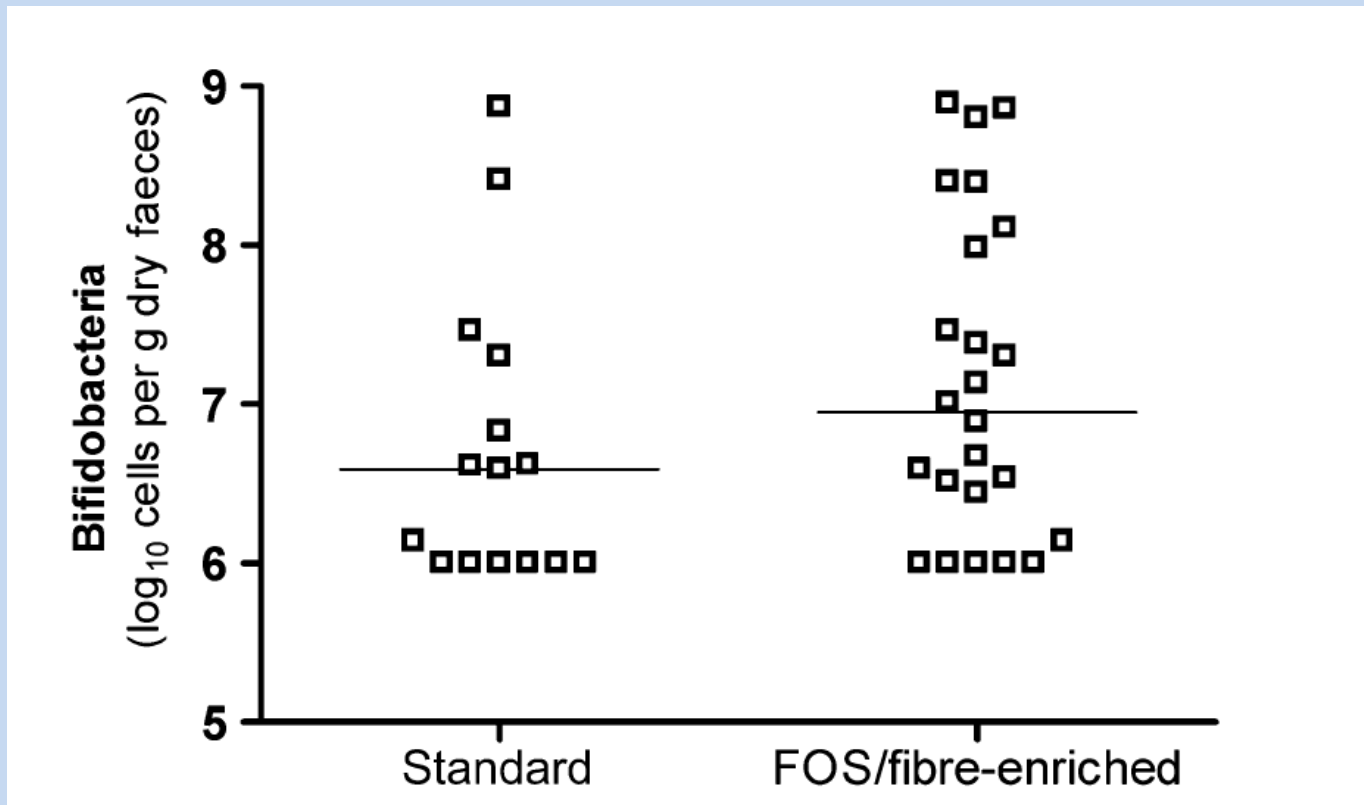
Standard formulas reduce butyrate and *Faecalibacterium prausnitzii*



Fibre / prebiotic formulas can “beneficially” impact gut microbiome (in healthy volunteers)



Fibre / prebiotic formulas in acute in-patients receiving EN

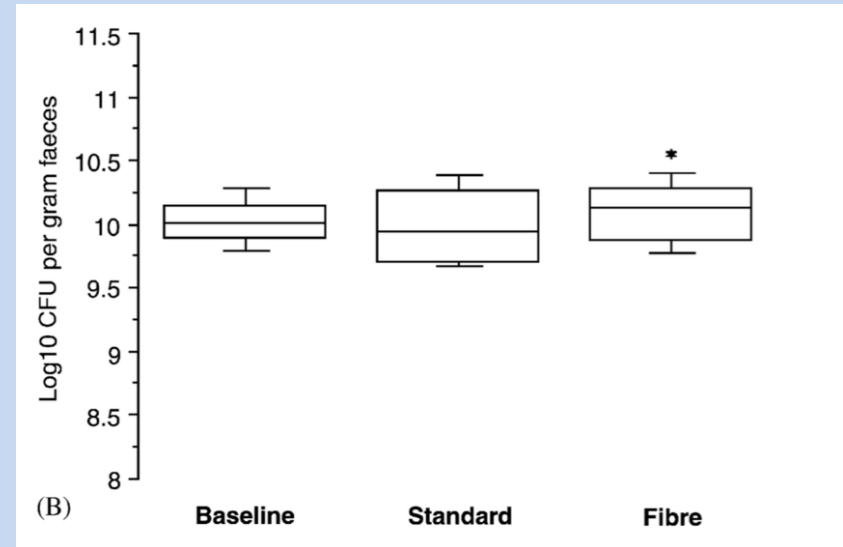


Fibre / prebiotic formulas in long term EN

Effects of total enteral nutrition supplemented with a multi-fibre mix on faecal short-chain fatty acids and microbiota

Stéphane M. Schneider^{a,*}, Fernand Girard-Pipau^b, Rodolphe Anty^a, Esmeralda G.M. van der Linde^c, Bertine J. Philipsen-Geerling^d, Jan Knol^c, Jérôme Filippi^a, Kamel Arab^a, Xavier Hébuterne^a

15 patients on long term EN (3.5 years)
Randomised cross-over trial (14 d)



	Baseline
Bifidobacteria	6.0 (6.0–10.4)
<i>Bacteroides</i>	8.2 (6.0–9.1)
<i>Clostridium</i>	8.4 (6.0–9.2)
Streptococci–Lactococci	7.7 (6.0–8.2)
<i>Escherichia coli</i>	6.7 (6.0–8.8)
Lactobacilli–Enterococci	8.7 (7.9–9.5)
<i>Eubacterium</i>	9.0 (7.9–9.4)
<i>Atopobium</i>	6.0 (6.0–9.0)

	Fibre-free EN	Multi-fibre EN
	6.0 (6.0–10.4)	6.0 (6.0–10.4)
	8.2 (6.0–9.1)	8.4 (6.0–9.2)*
	8.2 (6.0–9.1)	8.5 (6.0–8.9)
	7.8 (6.0–8.7)	7.7 (6.0–8.3)
	7.1 (6.0–8.7)	6.0 (6.0–8.4)
	8.6 (7.7–9.4)	8.9 (7.4–9.4)
	8.9 (8.4–9.6)	8.9 (6.0–9.5)
	6.0 (6.0–8.6)	6.0 (6.0–8.8)



Fibre / prebiotic formulas in long term EN

Effects of total enteral nutrition supplemented with a multi-fibre mix on faecal short-chain fatty acids and microbiota

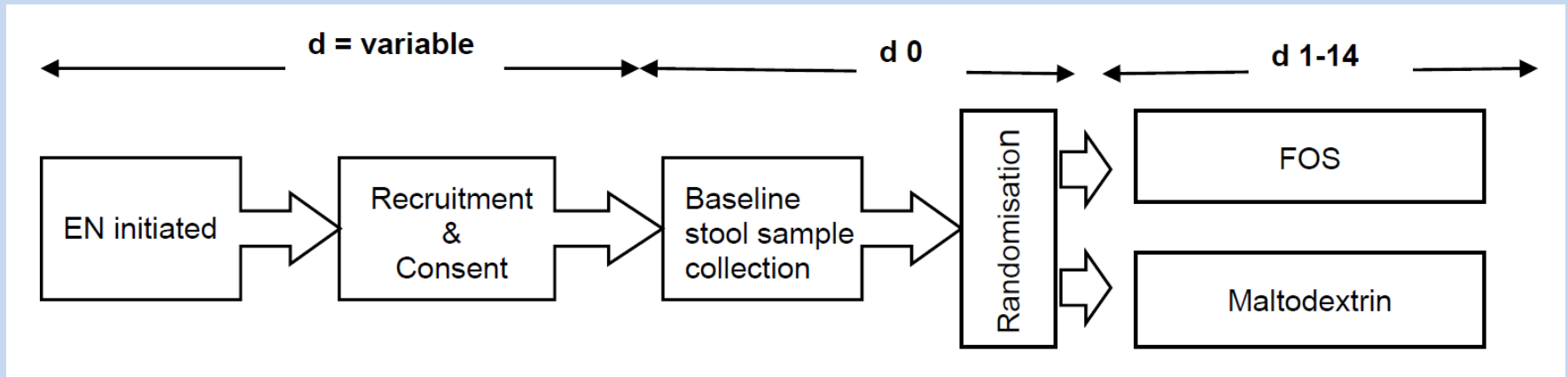
Stéphane M. Schneider^{a,*}, Fernand Girard-Pipau^b, Rodolphe Anty^a, Esmeralda G.M. van der Linde^c, Bertine J. Philipsen-Geerling^d, Jan Knol^c, Jérôme Filippi^a, Kamel Arab^a, Xavier Hébuterne^a

15 patients on long term EN (3.5 years)
Randomised cross-over trial (14 d)

	Baseline	Fibre-free EN	Multi-fibre EN
Acetic acid	29.1 (3.8–61.7)	35.8 (0–92.5)	49.6 (9.2–125.2)*
Propionic acid	9.9 (0–20.6)	10.4 (0–19.3)	12.4 (0–34.4)
Butyric acid	1.2 (0–17.8)	3.5 (0–10.1)	4.6 (0–25.8)**
Total SCFAs	37.1 (12.7–138.9)	51.4 (5.5–130.1)	66.6 (16.3–185.5)**



Add-FOS: RCT of 7 g/d additional prebiotics in enteral nutrition in patients on ICU



Add-FOS: additional prebiotics actually lowered *F. prausnitzii* in patients on ICU

		Post-intervention Adjusted mean ^a (SD)	P value ANCOVA
Total cells	Placebo	10.4 (0.4)	0.47
	Oligofructose/inulin	10.2 (0.4)	
<i>Bacteroides-Prevotella</i>	Placebo	9.9 (0.9)	0.05
	Oligofructose/inulin	9.1 (1.0)	
<i>C. coccoides-E. rectale</i>	Placebo	8.6 (0.9)	0.85
	Oligofructose/inulin	8.6 (1.0)	
<i>F. prausnitzii</i>	Placebo	8.4 (1.3)	0.01
	Oligofructose/inulin	7.0 (1.0)	
Bifidobacteria	Placebo	7.8 (1.3)	0.15
	Oligofructose/inulin	6.9 (1.4)	
<i>Lactobacillus-enterococci</i>	Placebo	7.4 (1.3)	0.51
	Oligofructose/inulin	7.0 (1.4)	



Probiotics



Live microorganisms that when administered in adequate amounts confer a health benefit on the host
(FAO/WHO, 2002)



(Some) probiotics may be beneficial

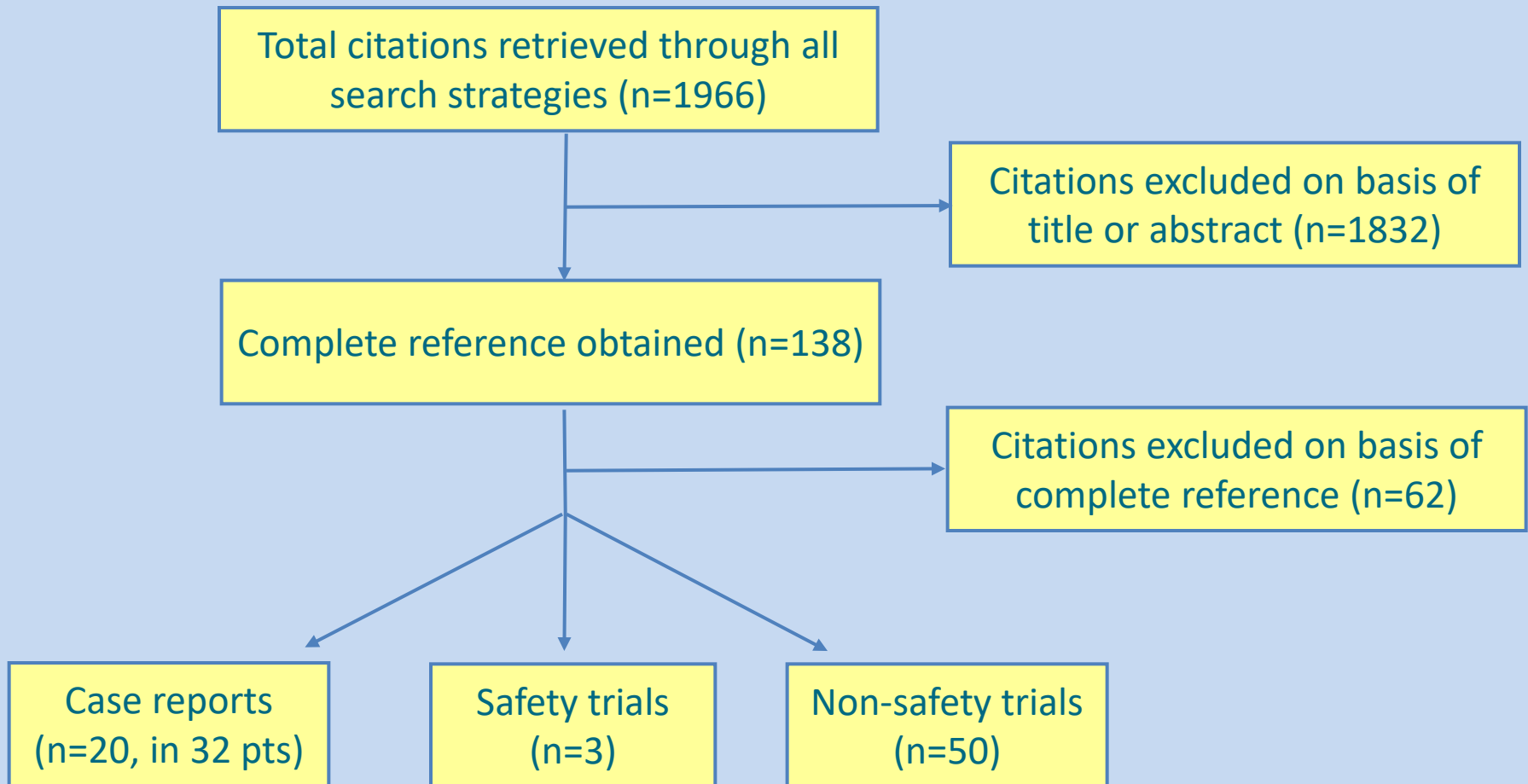
Meta-analyses

Necrotizing enterocolitis	24 RCTs	RR 0.43 (0.33-0.56)	Cochrane Database 2014, CD005496
Antibiotic-associated diarrhoea	63 RCTs	RR 0.58 (0.50-0.68)	J Am Med Assoc 2012; 307:1959-69
<i>Clostridium difficile</i> - associated diarrhoea	20 RCTs	RR 0.34 (0.24–0.49)	Ann Intern Med 2012; 157: 878-888
Post-operative infections	7 RCTs	OR 0.26 (0.12-0.55)	Eur J Clin Pharmacol 2009; 65: 561-70

RCTs

Ventilator-associated pneumonia	n 146	Lacto GG Placebo	19.1% 40.0%	Am J Resp Crit Care 2010; 182: 1058-64
Enteral diarrhoea	n 128	<i>S. boulardii</i> Placebo	14.2% 18.9%	Intensive Care Med 1997; 23: 517-23

Probiotics in enteral nutrition: safety



Probiotics in enteral nutrition: safety

52 papers reporting 53 trials

Probiotics (4131 pts) vs placebo (3643)

ICU, premature, surgical, transplant etc

Probiotics: Lactobacilli, Bifidobacteria, *S. boulardii*,

Mixtures (e.g. VSL#3)

Safety trials (n 3)

L. plantarum, *B. breve*, *L. casei* Shirota

No adverse events

No bacterial colonisation

Non-safety trials (n 50)

No increase in any negative outcomes (47)

Significant increase in negative outcome (3)

Generally “non-infectious”

Liver transplant (stenosis)

Neonatal ICU

Pancreatitis (ischaemia, mortality)

PRObiotics in PANcreatitis TRIAl (PROPATRIA)

Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial

Marc GH Besselink, Hjalmar C van Santvoort, Erik Buskens, Marja A Boermeester, Haryvan Goor, Harro M Timmerman, Vincent B Nieuwenhuijs, Thomas L Bollen, Bert van Ramshorst, Ben JM Witterman, Camiel Rosman, Rutger J Ploeg, Menna A Brink, Alexander FM Schaapherder, Cornelis HC Dejong, Peter J Wahab, Cees JH M van Laarhoven, Erwin van der Horst, Casper HJ van Eijk, Miguel A Cueta, Louis MA Akkermans, Hein G Goosen, for the Dutch Acute Pancreatitis Study Group

Summary

Background Infectious complications and associated mortality are a major concern in acute pancreatitis. Enteral administration of probiotics could prevent infectious complications, but convincing evidence is scarce. Our aim was to assess the effects of probiotic prophylaxis in patients with predicted severe acute pancreatitis.

Methods In this multicentre randomised, double-blind, placebo-controlled trial, 298 patients with predicted severe acute pancreatitis (Acute Physiology and Chronic Health Evaluation [APACHE II] score ≥ 8 , Imrie score ≥ 3 , or C-reactive protein >150 mg/L) were randomly assigned within 72 h of onset of symptoms to receive a multispecies probiotic preparation ($n=153$) or placebo ($n=145$), administered enterally twice daily for 28 days. The primary endpoint was the composite of infectious complications—ie, infected pancreatic necrosis, bacteraemia, pneumonia, urosepsis, or infected ascites—during admission and 90-day follow-up. Analyses were by intention to treat. This study is registered, number ISRCTN38327949.

Findings One person in each group was excluded from analyses because of incorrect diagnoses of pancreatitis; thus, 152 individuals in the probiotics group and 144 in the placebo group were analysed. Groups were much the same at baseline in terms of patients' characteristics and disease severity. Infectious complications occurred in 46 (30%) patients in the probiotics group and 41 (28%) of those in the placebo group (relative risk 1.06, 95% CI 0.75–1.51). 24 (16%) patients in the probiotics group died, compared with nine (6%) in the placebo group (relative risk 2.53, 95% CI 1.22–5.25). Nine patients in the probiotics group developed bowel ischaemia (eight with fatal outcome), compared with none in the placebo group ($p=0.004$).

Interpretation In patients with predicted severe acute pancreatitis, probiotic prophylaxis with this combination of probiotic strains did not reduce the risk of infectious complications and was associated with an increased risk of mortality. Probiotic prophylaxis should therefore not be administered in this category of patients.

Introduction

The incidence of acute pancreatitis in Europe and the USA is increasing by about 5% per year, mainly owing to an increase in biliary pancreatitis.¹ About a fifth of patients will develop necrotising pancreatitis, which is associated with a 10–30% mortality rate, mostly attributed to infectious complications and infection of (peri)pancreatic necrotic tissue in particular.¹ These infections are thought to be the sequelae of a cascade of events starting with small-bowel bacterial overgrowth, mucosal barrier failure, and a proinflammatory response leading to bacterial translocation of intestinal bacteria.^{4,5} Systemic antibiotic prophylaxis has long been studied as a measure to prevent secondary infection in acute pancreatitis.¹ However, two double-blind, placebo-controlled trials^{2,3} and two meta-analyses^{4,5} have failed to show a beneficial effect, and many clinicians have abandoned this strategy. In the two antibiotic trials, the incidence of extrapancreatic infections (eg, bacteraemia, pneumonia) and pancreatic infection remained high.^{2,3} Consequently, there is a clear need for other strategies to prevent infectious complications in patients with acute pancreatitis.

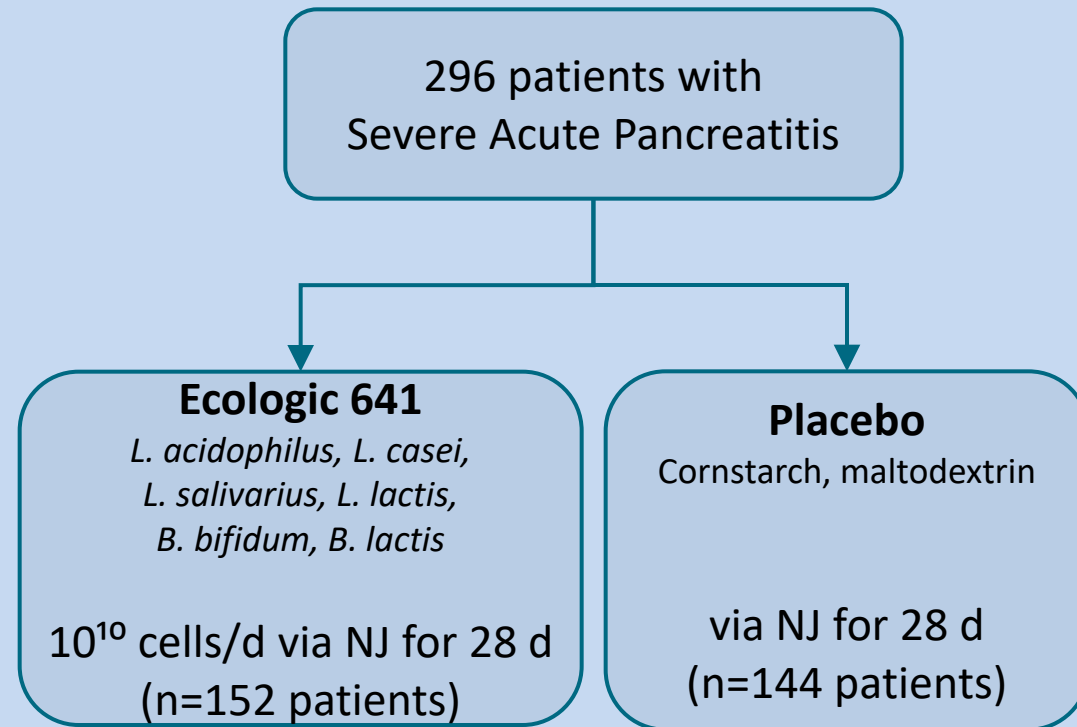
Probiotics, as an adjunct to enteral nutrition, have raised high expectations and are currently gaining worldwide popularity for their presumed health-promoting effects.^{6,7} Certain strains of probiotic bacteria might prevent infectious complications by reducing small-bowel bacterial overgrowth, restoring gastrointestinal barrier function, and modulating the immune system.^{8,9} A reduction of infectious complications has been reported in several clinical studies with probiotics in patients undergoing elective abdominal operations^{10,11} and in patients with acute pancreatitis.¹² However, because of their small size and methodological quality, these studies do not justify global implementation of probiotics as a preventive measure in acute pancreatitis. Accordingly, we embarked on a nationwide multicentre randomised, double-blind, placebo-controlled trial—the PRObiotics in PANcreatitis TRIAl (PROPATRIA)—to assess the effects of probiotic prophylaxis in patients with predicted severe acute pancreatitis.

Methods

Patients

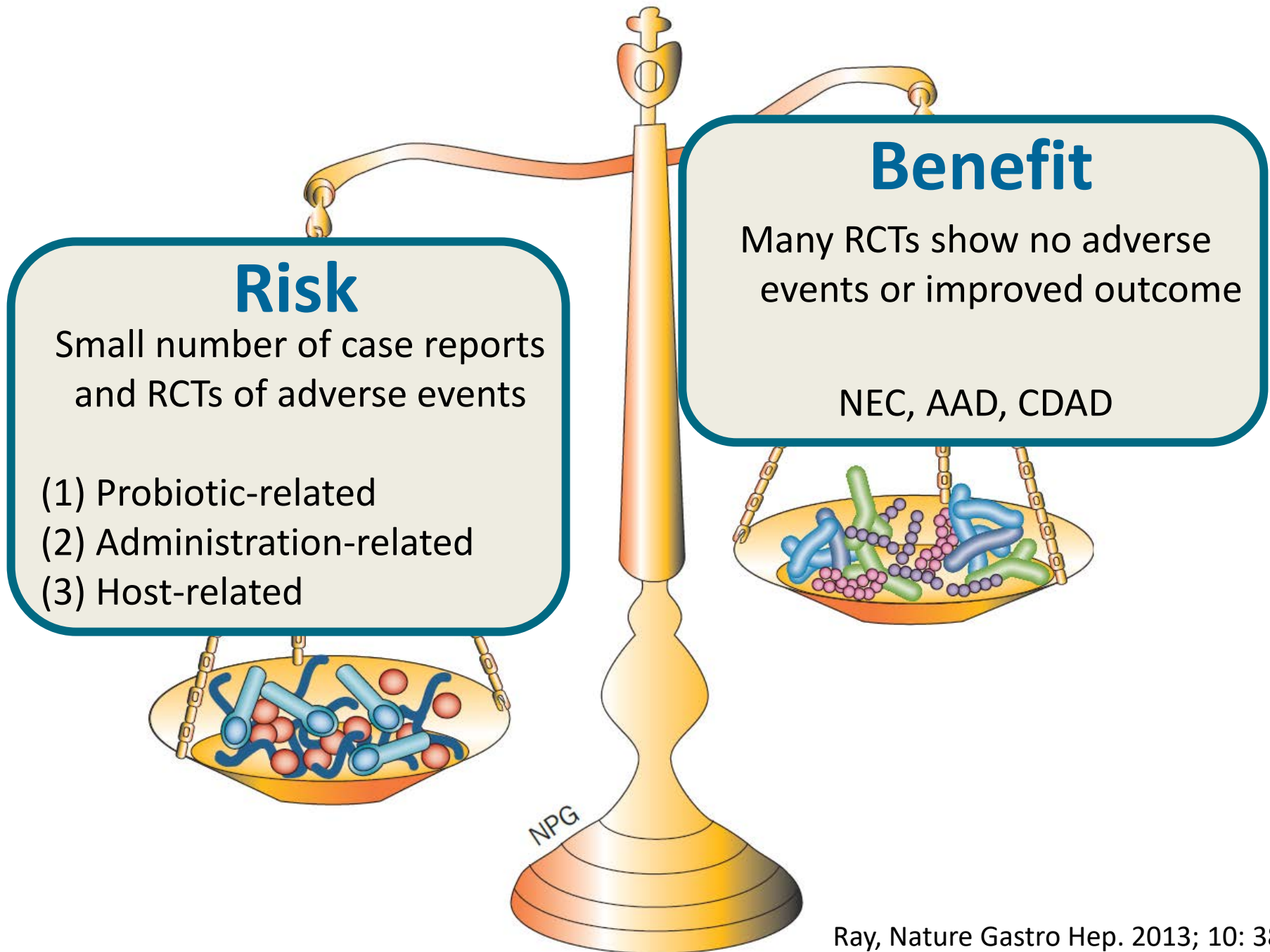
The design and rationale of the study have been described in detail elsewhere.¹³ Adult patients admitted with a first

www.thelancet.com Vol 371 February 23, 2008



	Probiotics (N=152)	Placebo (N=144)	p value
Primary endpoint			
Any infectious complication*	46 (30%)	41 (28%)	0.80
Infected necrosis	21 (14%)	14 (10%)	0.29
Bacteraemia	33 (22%)	22 (15%)	0.18
Pneumonia	24 (16%)	16 (11%)	0.31
Urosepsis	1 (0.7%)	2 (1%)	0.61
Infected ascites	4 (3%)	0 (0%)	0.12
Secondary endpoint			
Use of antibiotics, any indication	75 (49%)	76 (53%)	0.56
Percutaneous drainage	14 (9%)	8 (6%)	0.23
Surgical intervention, any indication	28 (18%)	14 (10%)	0.05
Necrosectomy	24 (16%)	14 (10%)	0.16
Intensive care admission	47 (31%)	34 (24%)	0.19
Intensive care stay (days)	6.6 (17.1)	3.0 (9.3)	0.08
Hospital stay (days)	28.9 (41.5)	23.5 (25.9)	0.98
Nausea	20 (13%)	23 (16%)	0.51
Abdominal fullness	36 (24%)	43 (30%)	0.24
Diarrhoea	25 (16%)	28 (19%)	0.55
Bowel ischaemia	9 (6%)	0 (0%)	0.004
Mortality	24 (16%)	9 (6%)	0.01





Fermentable

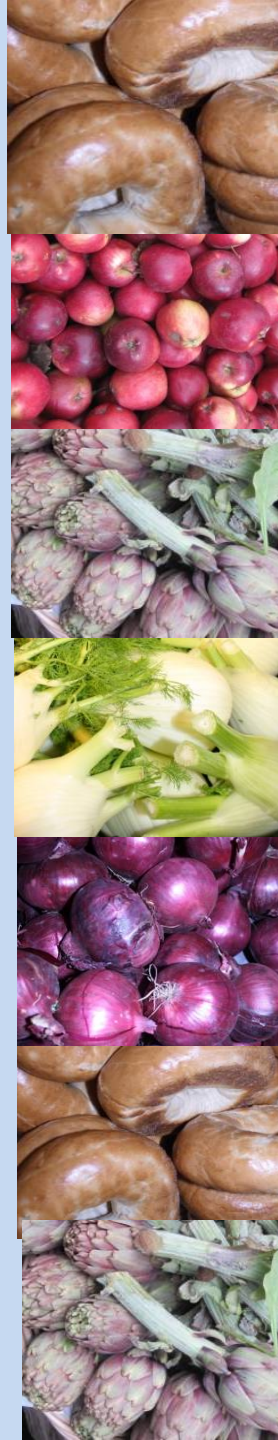
Oligosaccharides (inulin-type fructans)
(α -galacto-oligosaccharides)

Disaccharides (lactose)

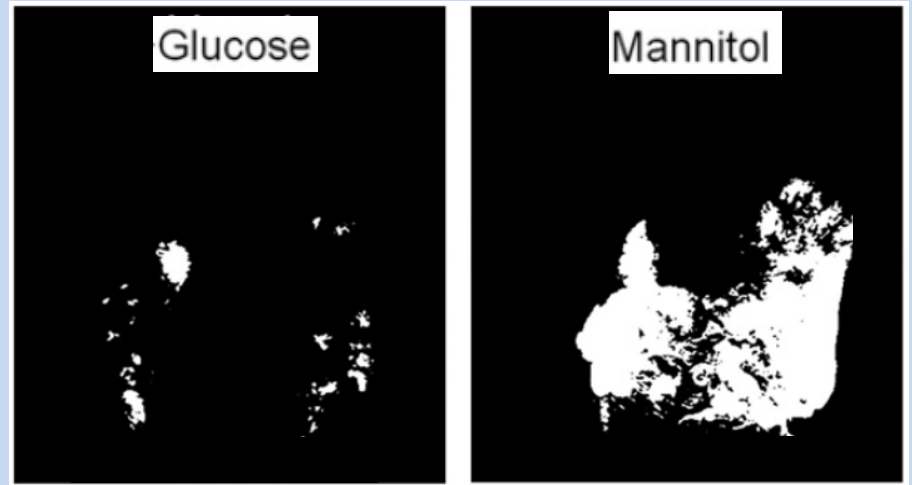
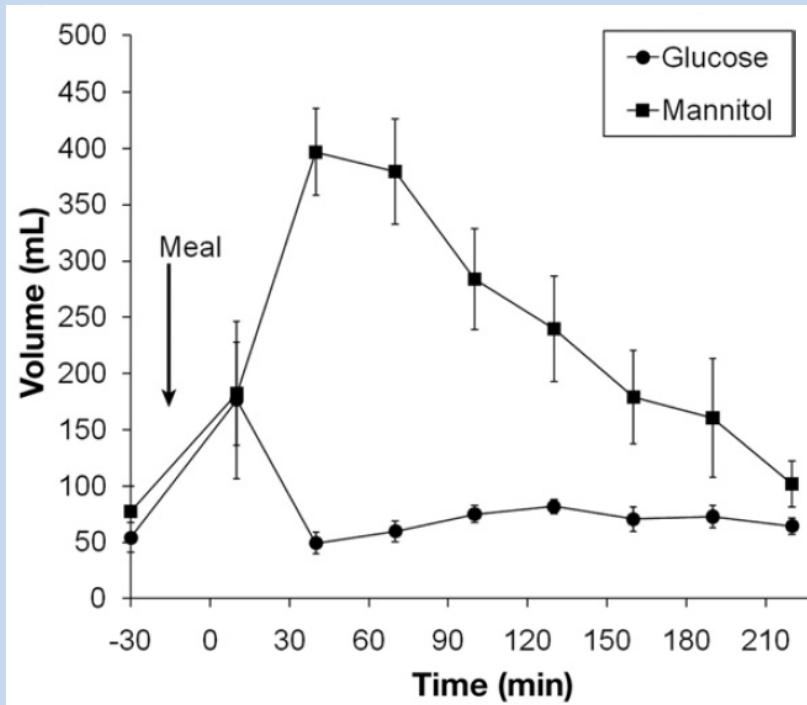
Monosaccharides (fructose)

And

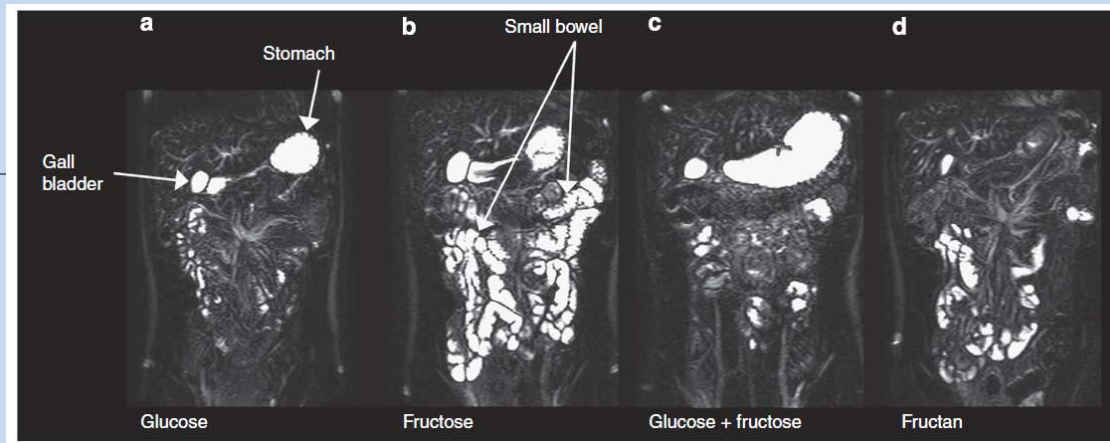
Polyols (sorbitol, mannitol)



Mannitol increases small intestinal water



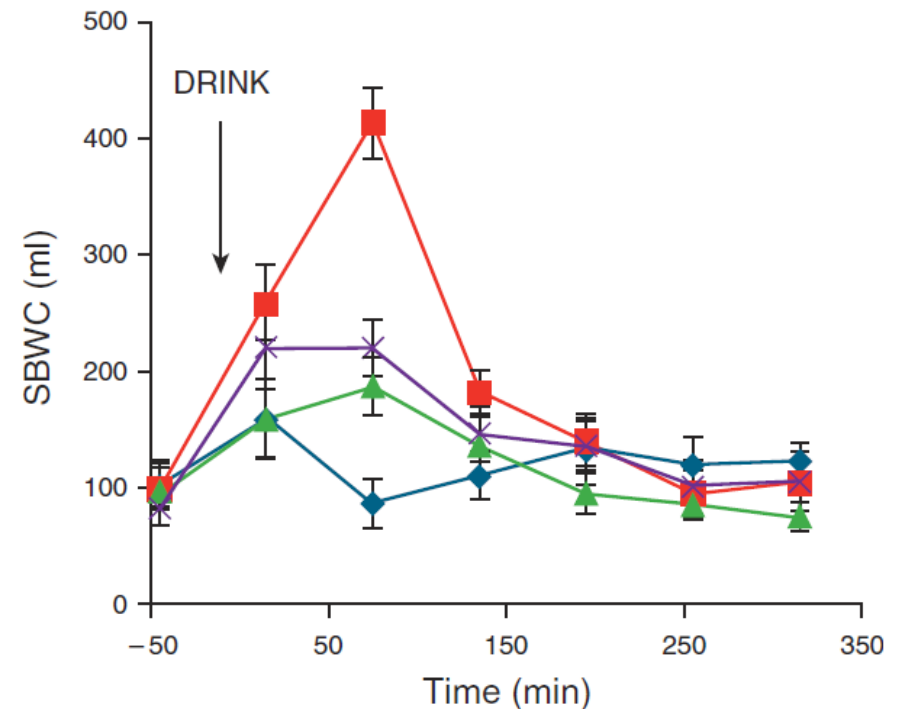
Fructose also increases small intestinal water



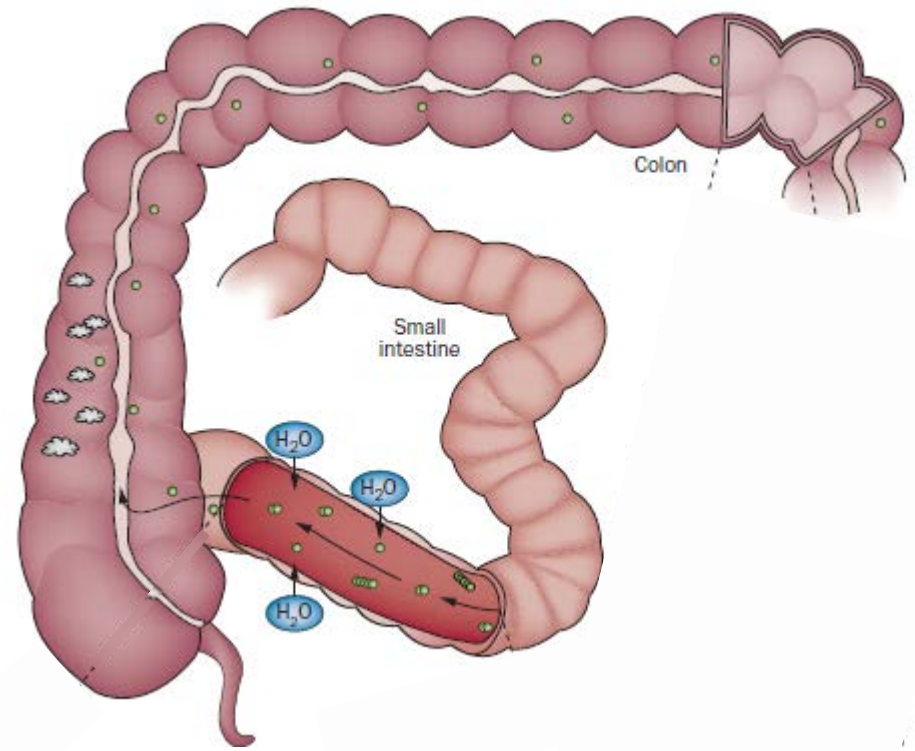
Differential Effects of FODMAPs (Fermentable Oligo-, Di-, Mono-Saccharides and Polyols) on Small and Large Intestinal Contents in Healthy Subjects Shown by MRI

Kathryn Murray, PhD¹, Victoria Wilkinson-Smith, BMedSci², Caroline Head, PhD¹, Carolyn Costigan, MSc¹, Eleanor Cox, PhD¹, Ching Lam, MB BCH², Luca Marciari, PhD², Penny Gowland, PhD¹ and Robin C. Spiller, MD, FRCP²

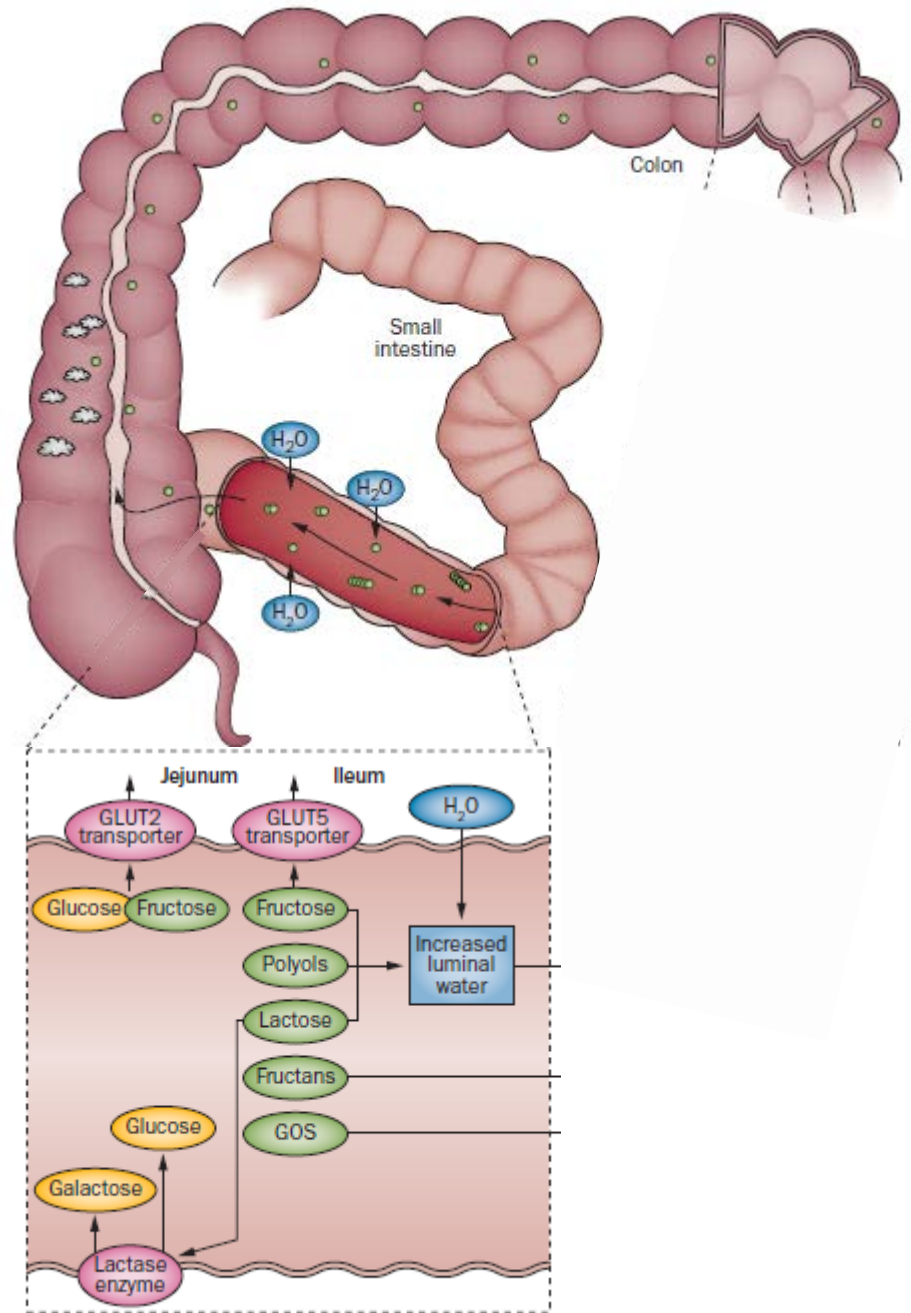
16 healthy people
Normal diet
Challenges (40 g of each)



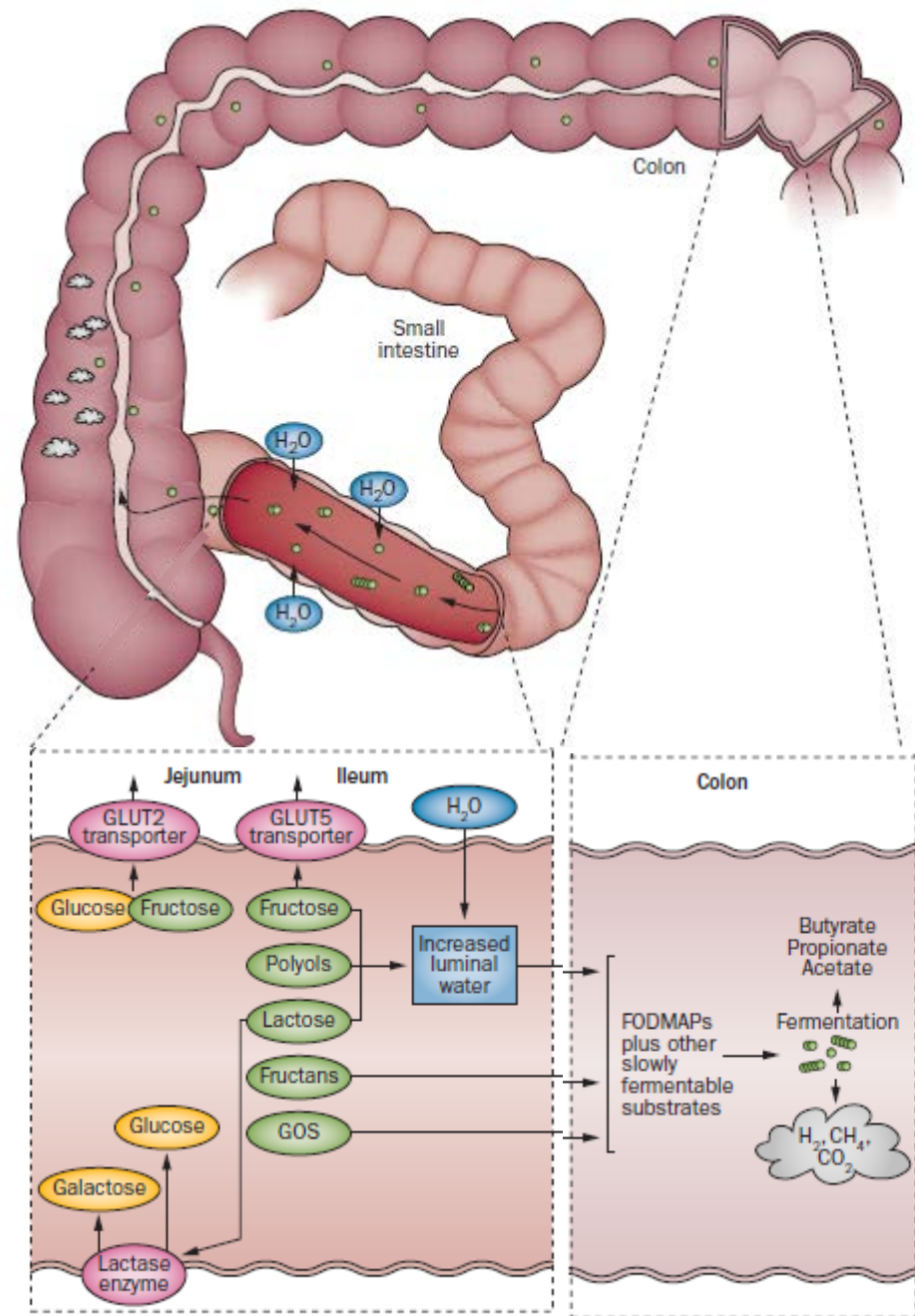
Staudacher et al
Nature Reviews Gastro Hep
2014; 11: 256–266



Staudacher et al
Nature Reviews Gastro Hep
2014; 11: 256–266



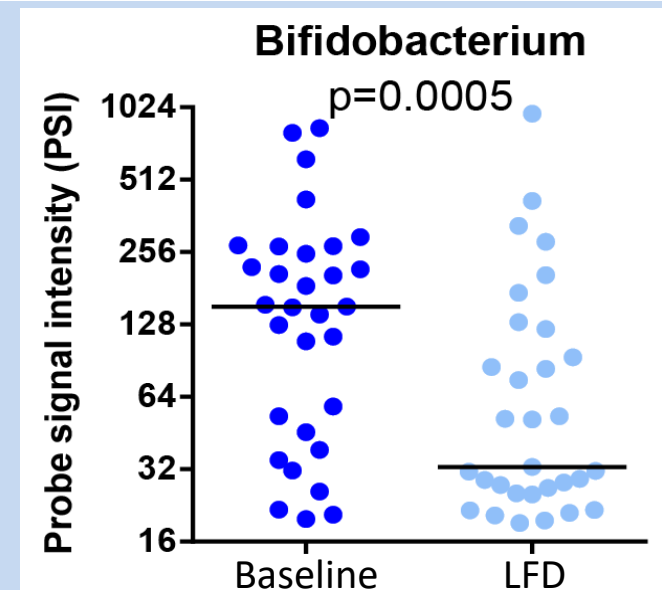
Staudacher et al
Nature Reviews Gastro Hep
2014; 11: 256–266



Low FODMAP diet impacts microbiota (in IBS!)

	Control	Intervention	<i>P</i>	Control	Intervention	<i>P</i>
	Concentration, \log_{10} cells/g feces			Proportion of total bacteria, %		
Total bacteria	9.7 (9.5–9.8)	9.7 (9.6–9.9)	0.52	—	—	—
<i>Bacteroides-Prevotella</i>	8.7 (8.6–8.9)	8.8 (8.6–8.9)	0.52	17.4 (9.2–25.7)	15.2 (6.2–24.3)	0.72
<i>E. rectale-C. coccoides</i>	8.8 (8.6–8.9)	8.7 (8.6–8.9)	0.89	15.7 (10.9–20.5)	11.8 (6.6–17.0)	0.27
<i>F. prausnitzii</i>	8.8 (8.6–9.0)	8.8 (8.5–9.0)	0.58	17.9 (13.3–22.6)	13.1 (8.0–18.2)	0.16
Bifidobacteria	8.2 (7.9–8.5)	7.4 (7.1–7.7)	<0.001	3.2 ⁴ (1.8–5.8)	0.5 ⁴ (0.2–0.9)	<0.001
Lactobacillus, enterococcus	7.4 (7.1–7.7)	7.4 (7.1–7.7)	0.98	1.0 (0.7–1.4)	0.6 (0.2–1.1)	0.17

Bacteria	Australian diet	Low FODMAP diet	p Value
Total bacteria	9.83 (9.72–9.93)	9.63* (9.53–9.73)	<0.001
<i>Clostridium</i> cluster IV	8.33 (8.15–8.52)	8.05* (7.88–8.23)	<0.001
<i>Faecalibacterium prausnitzii</i>	7.72 (7.49–7.95)	7.45* (7.25–7.65)	<0.001
<i>Clostridium</i> cluster XIVa	9.05* (8.93–9.16)	8.03 (7.91–8.15)	<0.001
<i>Roseburia</i>	7.72 (7.59–7.85)	7.49 (7.34–7.63)	<0.001
<i>Lactobacilli</i>	6.35 (6.20–6.50)	6.08 (5.91–6.24)	0.003
<i>Bifidobacteria</i>	7.71 (7.53–7.88)	7.30* (7.11–7.50)	<0.001
<i>Akkermansia muciniphila</i> †	5.46* (4.88–6.04)	4.29 (3.58–4.99)	<0.001
<i>Ruminococcus gnavus</i>	7.26 (7.14–7.37)	7.10 (6.96–7.25)	0.002
<i>Ruminococcus torques</i>	6.08 (5.85–6.31)	6.23 (6.07–6.39)	0.140



Low FODMAP formulas and diarrhoea: Retrospective case note review

AP&T Alimentary Pharmacology and Therapeutics

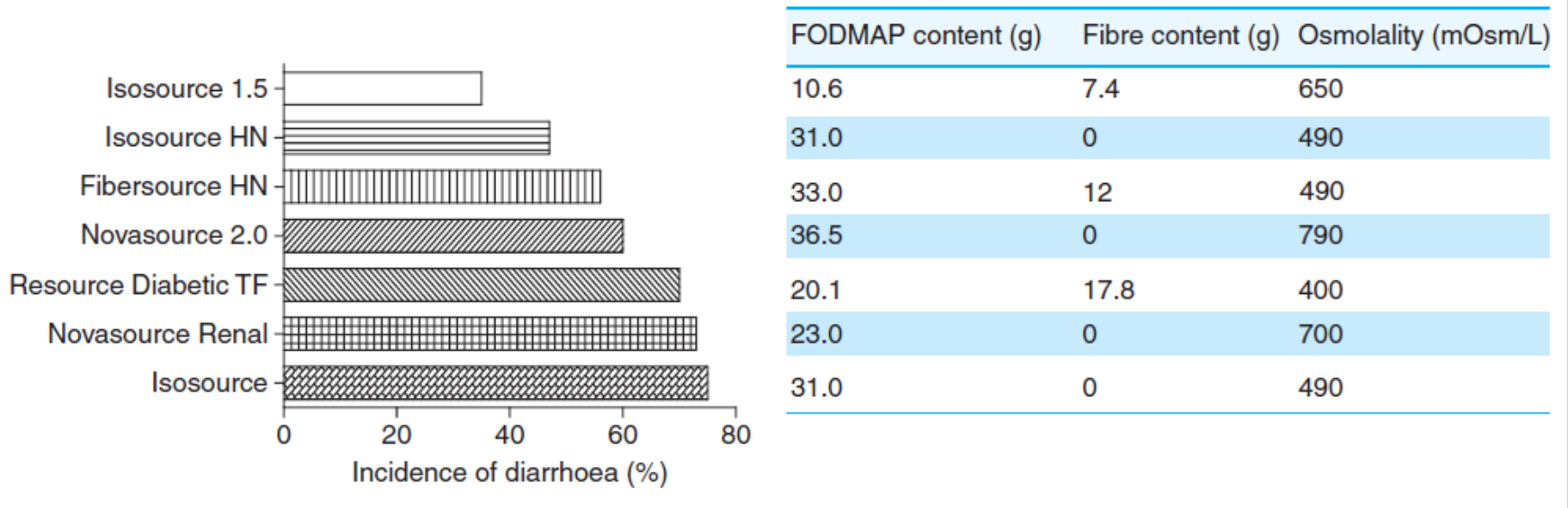
Diarrhoea during enteral nutrition is predicted by the poorly absorbed short-chain carbohydrate (FODMAP) content of the formula

Variable	All (n = 160)
Male	77 (48%)
Age (years)	76 (66–92)*
Length of stay (days)	22 (15–35)*
Duration of EN (days)	11 (6–20)*
Texture modified diet	52 (33%)
Antibiotics	97 (61%)
Proton pump inhibitors	44 (28%)
Laxatives	83 (52%)

**RETROSPECTIVE
CASE NOTE REVIEW**



Low FODMAP formulas and diarrhoea: Retrospective case note review



Low FODMAP formulas and diarrhoea: Retrospective case note review

Variable	<i>n</i>	Diarrhoea present (%)	<i>P</i> value	Estimated OR
Age >65 years	123	77 (63)	0.840	1.10
Stroke unit	65	36 (55)	0.637	0.785
Intensive care unit	42	32 (76)	0.505	1.46
Length of stay >21 days	80	62 (78)	0.026	2.70
EN duration >11 days	79	61 (77)	0.021	2.91
Antibiotics	107	72 (67)	0.443	1.39
Proton pump inhibitors	45	33 (73)	0.642	1.25
Laxatives	83	49 (59)	0.784	0.90
Texture modified diet	52	35 (67)	0.515	1.36
Initiated bolus delivery	32	16 (50)	0.982	1.00
Initiated Isosource 1.5*	20	7 (35)	0.029	0.18
Initiated Fibersource HN/Resource Diabetic TF†	71	41 (58)	0.273	0.49
Initiated Isosource HN/Isosource‡	50	25 (50)	0.213	0.44
Initiated Novasource Renal/Novasource 2.0§	16	11 (69)	0.938	1.07



Low FODMAP formulas and diarrhoea: RCT

Low-FODMAP formula improves diarrhea and nutritional status in hospitalized patients receiving enteral nutrition: a randomized, multicenter, double-blind clinical trial

So Ra Yoon¹, Jong Hwa Lee², Jae Hyang Lee¹, Ga Yoon Na², Kyun-Hee Lee³, Yoon-Bok Lee³, Gu-Hun Jung³ and Oh Yoen Kim^{1*}

Per can (200 mL)	Low-FODMAP	Moderate-FODMAP	High-FODMAP
Calorie (kcal)	200	200	200
Total FODMAPs (g)	0.320	0.753	1.222
Fructose (g)	- (N.D.)	-	-
Lactose (g)	-	-	-
Raffinose (g)	0.079	0.229	0.285
Stachyose (g)	-	-	0.239
1-Kestose (g)	-	-	0.511
Nystose (g)	-	-	-
1-Fructofuranosylnystose (g)	0.233	0.509	0.411

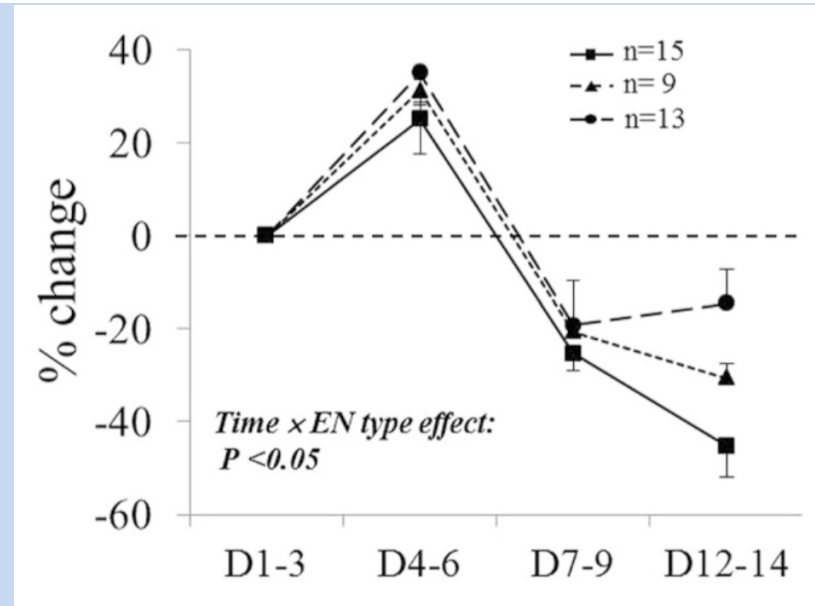
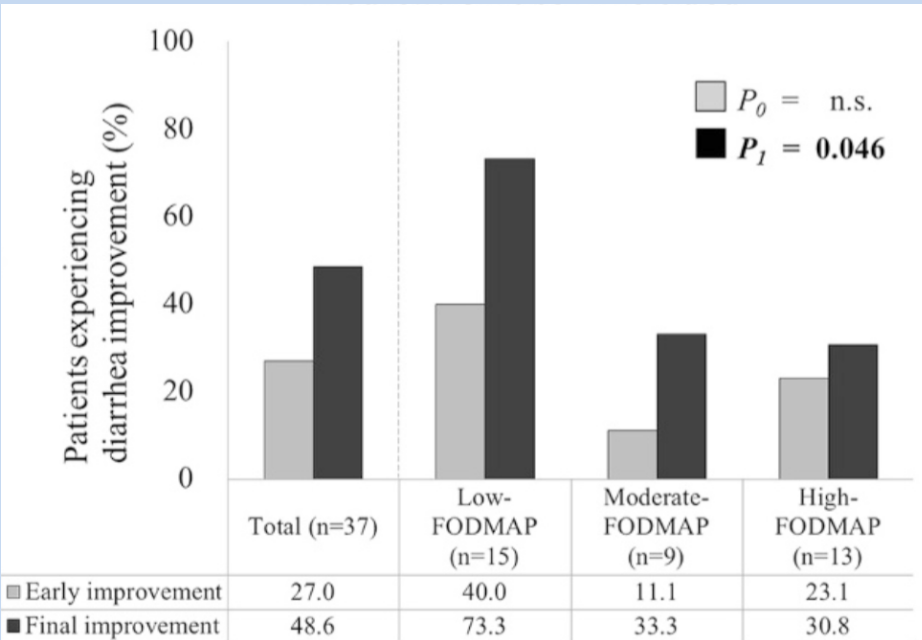


Low FODMAP formulas and diarrhoea: RCT

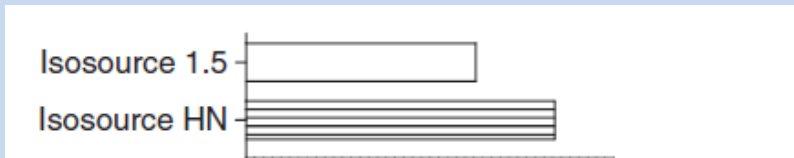
Low-FODMAP formula improves diarrhea and nutritional status in hospitalized patients receiving enteral nutrition: a randomized, multicenter, double-blind clinical trial

So Ra Yoon¹, Jong Hwa Lee², Jae Hyang Lee¹, Ga Yoon Na², Kyun-Hee Lee³, Yoon-Bok Lee³, Gu-Hun Jung³ and Oh Yoen Kim^{1*}

■ Low-FODMAP EN ▲ Moderate-FODMAP EN ● High-FODMAP EN



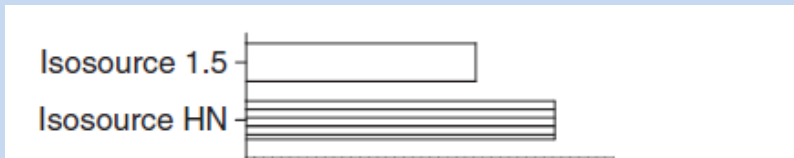
But... problems in measuring FODMAPs in enteral formulas



Enteral Formula and Recommended Daily Volume ^b	FODMAP Content, g/Daily Volume								
	Total FODMAP	Total Fructan		GOS		Free Fructose ^c	Lactose	Polyols	Fiber Content, g/ Daily Volume
		Method	Content	Method	Content				
Isosource 1.5, 930 mL/d	10.6	Fructan	7.9	HPLC	2.7	ND	ND	ND	7.4
Isosource HN, 1200 mL/d	31.0	Fructan	13.7	HPLC	17.3	ND	ND	ND	0



But... problems in measuring FODMAPs in enteral formulas



Enteral Formula and Recommended Daily Volume ^b	FODMAP Content, g/Daily Volume								
	Total FODMAP	Total Fructan		GOS		Free Fructose ^c	Lactose	Polyols	Fiber Content, g/Daily Volume
		Method	Content	Method	Content				
Isosource 1.5, 930 mL/d	10.6	Fructan assay A ^d	7.9	HPLC	2.7	ND	ND	ND	7.4
	1.22	Fructan assay B ^e	0.84	Enzymatic ^f	0.38 ^g				
Isosource HN, 1200 mL/d	31.0	Fructan assay A ^c	13.7	HPLC	17.3	ND	ND	ND	0
	4.04	Fructan assay B ^e	1.68	Enzymatic ^f	2.36 ^g				



Summary

The microbiome is impacted by disease, drugs and diet

Enteral formulas without fibre impact the gut microbiome, which is partially prevented by addition of fibre and prebiotics, although this is not necessarily the case in patients with disease and on drugs

Probiotics also modify the microbiota in EN and may have beneficial effects

Low FODMAP formulas were shown to prevent diarrhoea, but previous studies in this area must be re-analysed due to problems of analysing FODMAPs in enteral formulas



King's College London

Dr Hazreen Abdul Majid

Prof Peter Emery

Prof Victor Preedy

Clio Myers

University of Reading

Professor Glen Gibson

Dr Kieran Tuohy

University of Central Lancashire

Prof Pat Judd

University of Nottingham

Dr Moira Taylor

KING'S
College
LONDON

