Is it Gluten Intolerance or is it IBS?

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Aims

- What defines gluten intolerance and IBS
- Pathophysiology
- Diagnostic approaches/therapy
- Future developments & directions

Patient RJW, 34 yers, female

GI symptoms

- Relapsing abdominal pain,
- bloating,
- Severe postprandial pain, fullness
- Loose stool/diarrhea, occasional constipation
- Symptoms affect normal life, stopped her work as teacher

History

- Cholecystectomy 5 years ago

Extraintestinal

- Recurrent back pain, migraine
- Complains of lack of energy, fatigued

…broad spectrum of gastrointestinal and extraintestinal symptoms…

?

15 - 40 % of the population experiences digestive symptoms

50% of those with symptoms seek medical attention

50% of those have functional GI disorders

Coeliac disease?
H. pylori?
IBD?
NERD?
Diverticulosis?
Postcholecystectomy-syndrome?
IBS
…

If cancer and IBD are ruled out, FGIDs (e.g. FD, IBS, NERD) or a FGID-like disease are the most likely cause for symptoms

Patient RJW, 34 yers, female

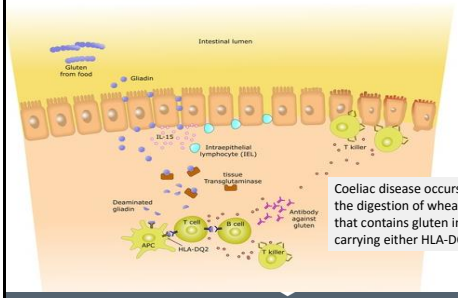
Laboratory tests

- FBC, LFT etc.: very mild IDA
- Stool, no evidence for parasites
- Glucose breath test (SIBO) negative
- Stool microbiome: inconclusive
- *H. pylori* serology: positive
- tTGA IgA: pending
- Serum IgA normal
- Calprotectin normal

Coeliac disease?

What is gluten?

- **Gluten is a protein complex**
- **75 to 85% of the total protein in bread wheat**
- **Gluten = glutenin molecules cross-link, network attached to gliadin, which contributes viscosity (thickness)**



Coeliac disease occurs in response to the digestion of wheat, rye and barley that contains gluten in individuals carrying either HLA-DQ2 or HLA-DQ8

Symptoms of coeliac disease

- Abdominal symptoms, diarrhea, bloating fullness (constipation)
- Weight loss (infrequent)
- Anaemia, usually resulting from iron deficiency
- Loss of bone density (osteoporosis)
- Itchy, blistery skin rash (dermatitis herpetiformis)
- Headaches and fatigue
- Nervous system injury, including numbness and tingling in the feet and hands, possible problems with balance, and cognitive impairment
- Joint pain
- Acid reflux and heartburn

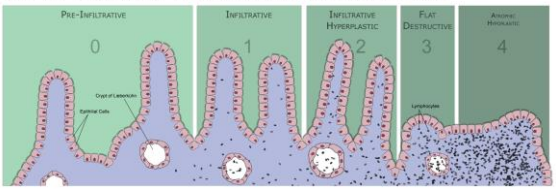
Why and how is the gluten sensitive enteropathy linked to a broad spectrum of GI and non-GI symptoms?

Diagnosis of coeliac disease

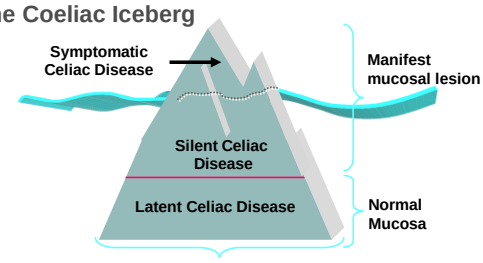
- **Tissue Transglutaminase Antibodies (tTG-IgA)** – tTG-IgA positive in about 98% of patients with **celiac disease** who are on a gluten-containing diet.
- A positive blood test always needs to be followed by a **small bowel biopsy** to **confirm** the **diagnosis**.

Coeliac disease: Marsh Criteria

UPPER JEJUNAL MUCOSAL IMMUNOPATHOLOGY



The Coeliac Iceberg



Genetic susceptibility: - DQ2, DQ8
Positive serology

Non coeliac gluten sensitivity?

Non Coeliac Gluten Sensitivity

- **Symptoms in response to ingestion of foods with gluten and improvement after discontinuation.**
- **The symptoms may be accompanied with an increase in levels of antibody to gluten. No identifiable structural changes.**

Wheat allergy, celiac disease, gluten intolerance

- Differences between **Wheat Allergy** and Celiac Disease or **Gluten Intolerance**. A **wheat allergy** should not be confused with "**gluten intolerance**" or celiac disease.
- A food **allergy** is an **overreaction of the immune system** to a specific food protein. ... People who are **allergic** to **wheat** often may tolerate other grains.

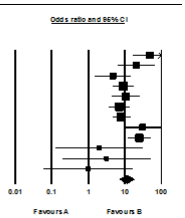
Diagnostic approach

- **Serology:** Tissue Transglutaminase Antibodies (tTG-IgA) while on Gluten diet (if serum IgA normal, if not anti Gliadin ab IgG)
- **Endoscopy/histology:** verification of inflammatory changes
- **Dietary intervention:** Improvement of symptoms and inflammatory changes

IBD?

IBD in coeliac disease

Study name	Subgroup within study	Statistics for each study				
		Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Cooper et al	UK	48.679	16.912	140.117	7.203	0.000
Nielsen et al	Denmark	20.451	6.411	65.237	5.099	0.000
Breen E et al	Ireland	4.749	1.508	14.956	2.662	0.008
Leeds et al	UK	9.054	4.782	17.143	6.766	0.000
Saleem A et al	Ireland	10.828	4.270	25.962	5.112	0.000
Yang et al	USA	7.000	3.705	13.226	5.994	0.000
Dalton F et al	USA	8.048	4.592	14.103	7.285	0.000
Masachs et al	Spain	31.123	9.697	99.893	5.778	0.000
Kocsis D et al	Hungary	24.756	12.012	51.144	8.687	0.000
Fine et al	USA	1.961	0.123	32.021	0.481	0.630
Abdulkarim A et al	USA	3.142	0.193	51.042	0.805	0.421
Hopper et al	UK	0.984	0.061	15.846	-0.011	0.991
		11.426	7.219	18.085	10.398	0.000



A Shah, DDW 2016

Functional GI disorder?

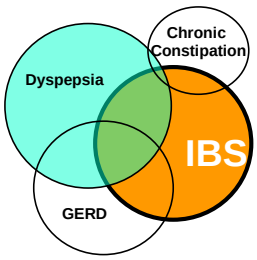
Rome IV Diagnostic Criteria: IBS

IBS a chronic, episodic *disorder* characterized by abdominal pain or discomfort associated with altered bowel function and often bloating

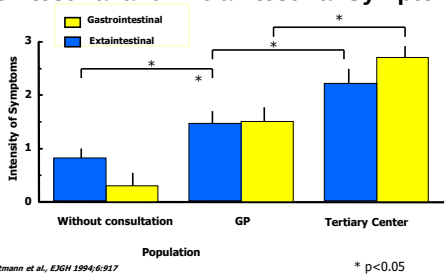
- Abdominal pain/discomfort associated with two of three features:
  - <3 bowel movements (BM) per week or >3 BMs per day
  - hard or lumpy stools, or loose or watery stools (stool form)
  - relieved by defecation

Rome IV (2016):

Overlap of symptoms



Gastrointestinal and Extraintestinal Symptoms

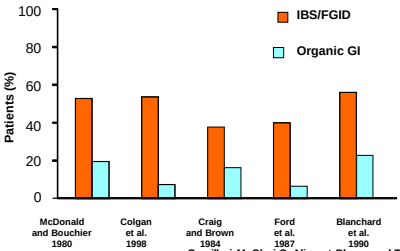


Holtmann et al., EJGH 1994;6:917

* p<0.05

There is considerable overlap of extraintestinal symptoms and symptoms of functional gastrointestinal disorders

IBS – a psychiatric disease?



Camilleri M, Choi C. Aliment Pharmacol Ther 11:3–15; 1997

Why and how is the gluten sensitive enteropathy linked to a brought spectrum of GI and non-GI symptoms?

Pathophysiology

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Pathophysiology

- Motility
- Unrecognised PI
- Visceral sensory function
- *H. pylori*
- Molecular mechanisms
- Inflammation/Microbiome

Infection/inflammation in FGID

a paradigm shift!

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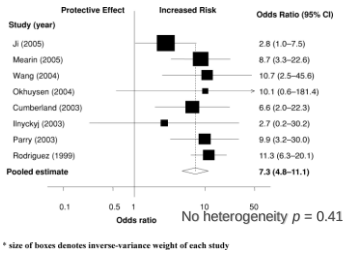
Post-infectious Irritable Bowel Syndrome - A Meta-Analysis

- **Median prevalence of IBS 9.8% (vs. 1.2% in controls)**
- **Pooled odds ratio 7.3 (95% CI, 4.7–11.1)**



Halvorson et al. *Am J Gastroenterol* 2006; 101: 1894-1899

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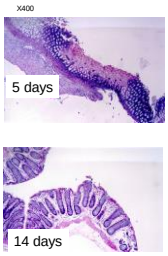
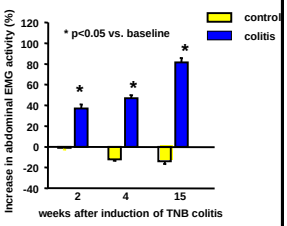
Visceromotor reflex after TNB





Gschossmann Dig. Dis Sci.2004

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Inflammation plays a central role for the manifestation of altered function and central factors modify the effect of inflammation

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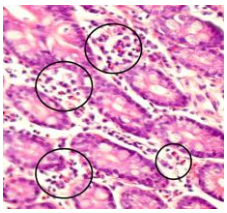
Duodenal eosinophilia in 50% of FD - early satiety



Clusters of eosinophils (circled) in the lamina propria adjacent to glands in a subject with functional dyspepsia

Talley et al. Clin Gastroenterol Hepatol. 2007;5:1175-83.

Inflammatory mediators and FGID?

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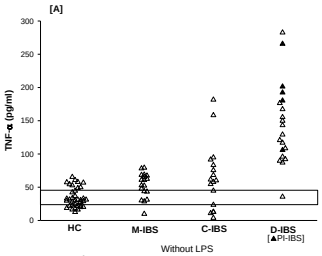
TNF-alpha release from PBMCs in IBS patients



Liebregts et al Gastroenterology, 2007

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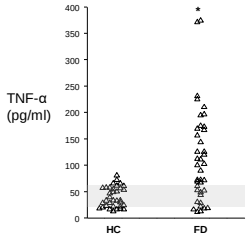
TNF-α release from PBMCs in FD patients



Liebregts et al AJG 2011

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Release of inflammatory mediators significantly increased in patients with IBS & FD

…inflammatory mediators and symptoms/function

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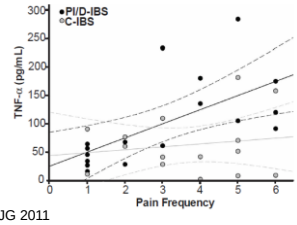
TNF-alpha concentrations in the supernant of cultured PBMCs and Pain frequency



Liebregts et al AJG 2011

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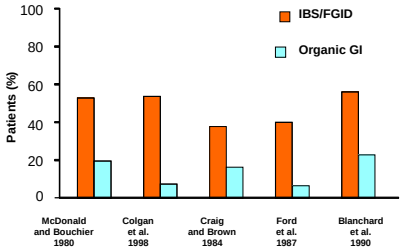
IBS – a psychiatric disease?



Camilleri M, Choi C. Aliment Pharmacol Ther 11:3–15; 1997

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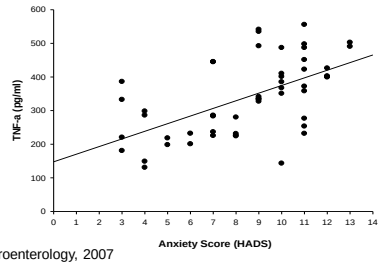
TNF-α and anxiety scores



Gastroenterology, 2007

r=0.384
p=0.030

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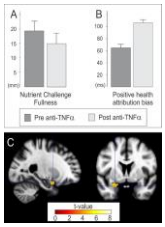
Anti-TNF-alpha alters GI symptom response to nutrient challenge and the cognitive processing of afferences



Anti-TNFα administration reduces visceral sensitivity and improves implicit beliefs about one's health. This is linked to alterations in limbic (amygdala) function.

Gray et al DDW 2017

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Inflammatory mediators closely associated with symptoms in CD & IBS. Driver for immune activation is the MAM

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Clinical management

- Establish diagnosis (history, tTG-IgA, endoscopy)
- Define targets of therapy (symptoms vs. structural lesions)
- General measures (concerns of the patient!), elimination diet
- Reassurance/Psychological interventions
- Targeted pharmacologic therapy
  - Herbal medications
  - TCA

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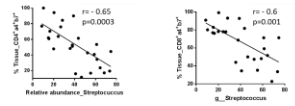
Small intestine bacteria – a link to gut-homing markers

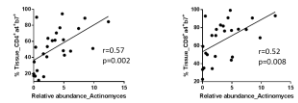
DNA/RNA → Sequencing → Abundance of existing bacteria

Streptococcus – reduction of gut-homing integrins a4, b7



Dr Erin Shanahan

Actinomyces – increase of gut-homing integrins a4, b7



Characterisation of Interactions
Brain - Gut -
Mucosa Associated Microbiome - Immunity

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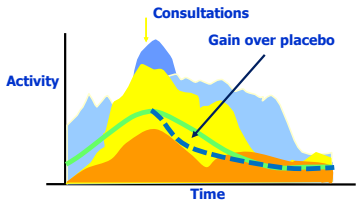
The most effective drug in IBS

P L A C E B O

...The secret of medicine is to distract the patient until nature cures...

Voltaire

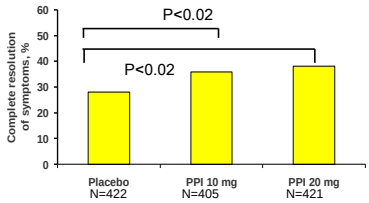
Course of disease activity



The most effective drug in functional dyspepsia

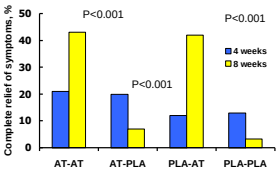
The placebo response reflects spontaneous fluctuations of disease activity

Effects of PPI therapy



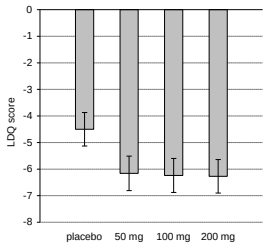
Talley & Lauritsen, Gut 2002; 50: 36-61

Improvement after 4 and 8 weeks of therapy: Herbal preparation



Madisch, Holtmann et al, Digestion 2004

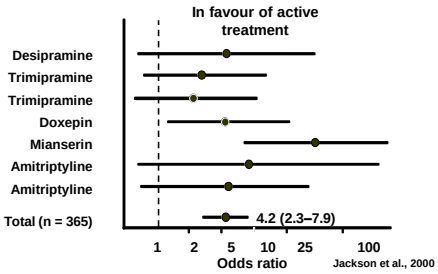
Itopride in Functional Dyspepsia



Improvement of LDQ, p<0.01

Holtmann et al NEJM 2006

Antidepressants in FGID



Jackson et al., 2000

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Summary

- Functional GI disorders are highly prevalent
- Cause substantial morbidity
- Altered function (sensory) relevant for symptom manifestation
- Significant psychiatric comorbidity
- Minimal inflammation key driver
- Future research in the field of gastrointestinal microbiome

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'I have a dream that one day…,

- we will be able to identify the causes of symptoms in all patients with FGID
- recommend therapies that specifically target the underlying causes
- and may cure (or at least provide symptom control for) all patients with these conditions..'

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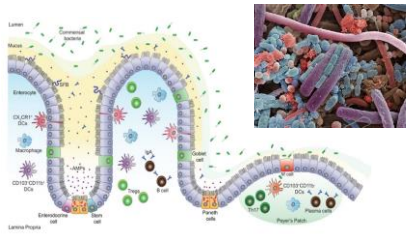
The Future: The Mucosa Associated Microbiome



Muniz et al. Frontiers in Immunology, 2012

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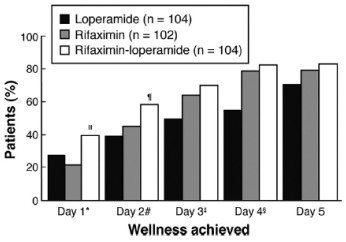
Rifaximin vs. Loperamide in IBS



Dupont et al CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2007;5:451– 456

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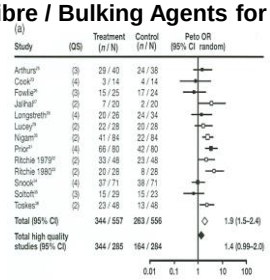
Fibre / Bulking Agents for IBS



- All have significant methodological flaws
- Psyllium/ispaghula husk (20-30 g/day) improves constipation
  - Wheat bran does not appear to be effective
- Data does not support the use of fiber for abdominal pain or diarrhea
- No RCTs have evaluated other laxatives for IBS

A placebo in IBS??

Lesbros-Pantoflickova et al *APT* 2004; 20: 1253-69

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Bulking agents, antispasmodics and antidepressants for the treatment of irritable bowel syndrome (Review)

Ruepert L, Quartero AO, de Wit NJ, van der Heijden GJ, Rubio G, Muris JWM

THE COCHRANE COLLABORATION®

WILEY

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Conclusions IBS:

- '…There is **no evidence that bulking agents are effective for treating IBS**..'
- '... There is evidence that **antispasmodics are effective for the treatment of IBS**. The individual subgroups which are effective include: cimetropium/dicyclomine, peppermint oil, pinaverium and Trimebutine..'.
- '…There is ***good evidence that antidepressants are effective for the treatment of IBS.*** The subgroup analyses for SSRIs and TCAs are unequivocal and their effectiveness may depend on the individual patient…'.

Cochrane data

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Conclusions FD:

- ***Prokinetics*** (19 trials with dichotomous outcomes evaluating 3178 participants; relative risk reduction (RRR) 33%; 95% confidence intervals (CI) 18% to 45%),
- ***H_2RAs*** (12 trials evaluating 2,183 participants; RRR 23%; 95% CI 8% to 35%) and
- ***PPIs*** (10 trials evaluating 3,347 participants; RRR 13%; 95% CI 4% to 20%) were significantly more effective than placebo

Cochrane data

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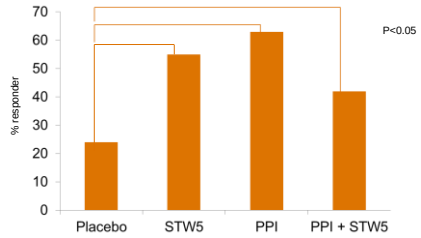
Response rates to PPI and STW5



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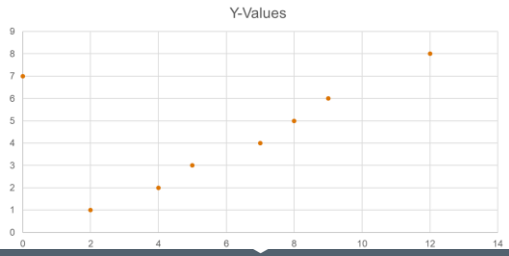
Conclusions IBS:

- **'…There is *no evidence that bulking agents* are effective for treating IBS..'**
- **'... There is *evidence that antispasmodics* are effective for the treatment of IBS. The individual subgroups which are effective include: cimetropium/dicyclomine, peppermint oil, pinaverium and Trimebutine..'.**
- **'…There is *good evidence that antidepressants are effective* for the treatment of IBS. The subgroup analyses for SSRIs and TCAs are unequivocal and their effectiveness may depend on the individual patient…'.**
- **Dietary advice? FODMAP**
- **Antibiotic therapy?**

Other measures?



Meta analysis: psychological interventions

- 4 trials
- Various interventions (psychotherapy, relaxation, cognitive behavioral, psychodrama)
- All suggested benefit (12 months)
- Baseline adjusted outcome measurements, drop out rates

=> Insufficient evidence to confirm efficacy of psychological interventions

Soo et al Cochrane Database Syst Rev. 2004

Ingredients and potential effects of STW5 (Iberogast®)

Iberis amara
15%
tonicising
anti-inflammatory

Angelica
10%
spasmolytic, acid inhibition

Caraway
10%
spasmolytic
bacteriostatic

Celandine
10%
prokinetic
tonicising,
cholekinetic

Chamomille
20%
spasmolytic
anti-inflammatory

Milk thistle
10%
anti-dyspeptic,
spasmolytic,
cytoprotective

Liquorice
10%
spasmolytic
anti-inflammatory

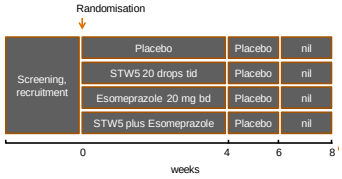
Lemon balm
10%
spasmolytic
anti-inflammatory

Peppermint
5%
spasmolytic,
anti-emetic

Herbal medicine:
Shotgun approach

What about relapse rates?

Experimental design



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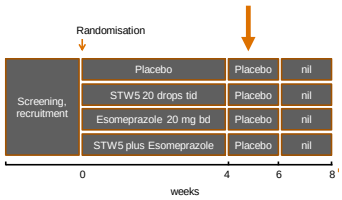
Experimental design



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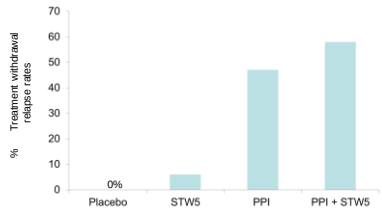
'Active' treatment withdrawal relapse rates (% of responders)



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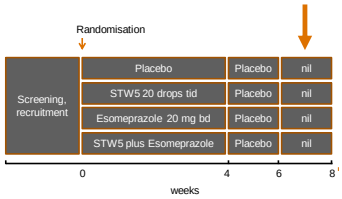
Experimental design



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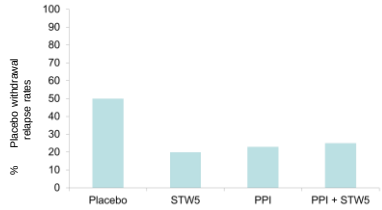
Placebo withdraw relapse rates



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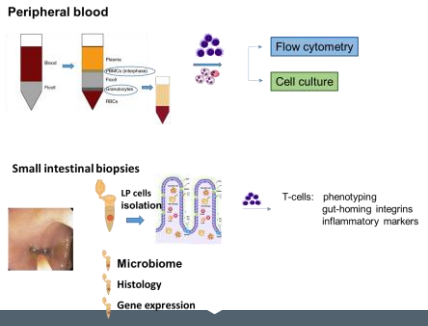

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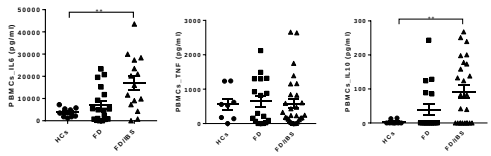
Results

Increase of cytokine secretion in FD and FD/IBS patients



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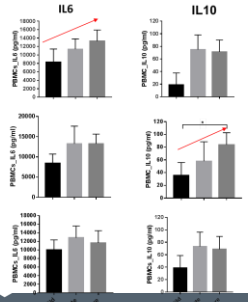
Increase of cytokine secretion in FD and FD/IBS patients - GI symptoms



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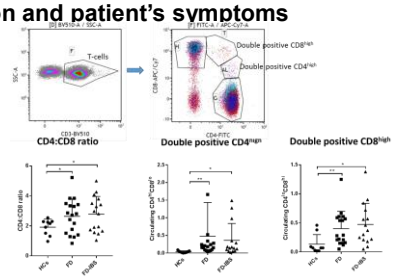
T-cells subpopulations - inflammatory marker expression and patient's symptoms



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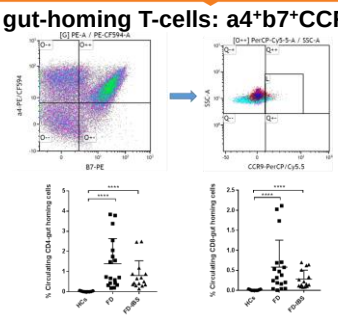
Small gut-homing T-cells: a4+b7+CCR9+



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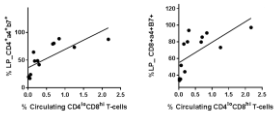
Relation between Circulating T-cells and Lamina propria T-cells

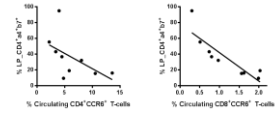
Increase of double positive CD8hi ↔ expression of gut-homing integrin a4 & b7

Double positive CD8high T-cells



Chemokine receptor CCR6 ↔ reduction of gut-homing integrin a4 & b7

T-cell trafficking receptor – CCR6+ T-cells



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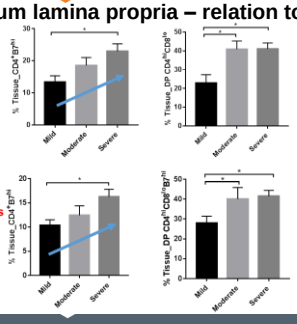
T-cells in FD duodenum lamina propria – relation to GI symptom

Upper GI symptoms
- Gut homing integrin B7

Gas/acid related symptoms
- Gut-homing intergrin B7



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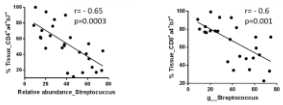
Small intestine bacteria – a link to gut-homing markers

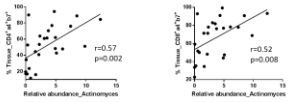
DNA/RNA → Sequencing → Abundance of existing bacteria

Streptococcus – reduction of gut-homing integrins a4, b7



Dr Erin Shanahan

Actinomyces – increase of gut-homing integrins a4, b7



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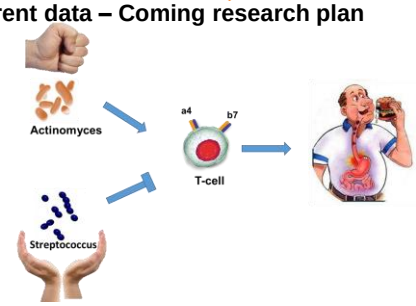
Current data – Coming research plan



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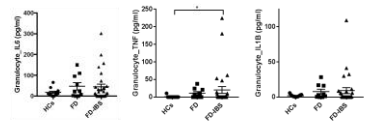
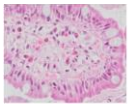
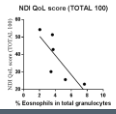
Granulocytes - FD & FD/IBS patients

Cytokine secretion





Postprandial pain patients



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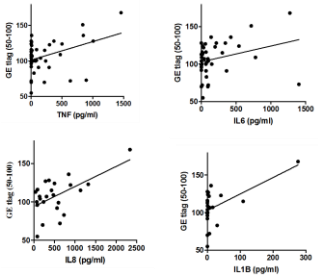
Association of Granulocyte responses to symptoms



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Prof. Gerald Holtmann group
Dr Anh Do
Dr Erin Shanahan
Dr Yuwen Li
Miss Teressa Hansen
A/Prof. Linda Fletcher

NHMRC Grant

The University of Queensland AUSTRALIA

Metro South Health Queensland Government

Thank you for your attention

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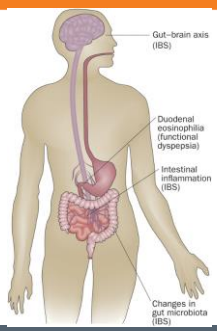
What we have known?

Local immune activation
- Focal aggregate of T-cells
- Increase macrophage/eosinophil counts in FD and mast cell in IBS

Systemic inflammation
- Increased circulating lymphocyte
- Elevated systemic pro-inflammatory cytokine levels

Micobiota – symptomatics
- correlation b/w anxiety score and inflammatory cytokine level

Gut–brain axis
- correlation b/w anxiety score and inflammatory cytokine level



N. Talley, Nature reviews

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What we want to know?

Whether immune activation is a target for therapeutics?

- Targeting immune activation improve symptoms?
  - → diversity of FGIDs
  - → what immunological factors – what symptoms?

Need to define the true target and strategy for therapy

+ Directly suppress specific immune marker - Risk level required medication?

+ Indirectly via targeting the microbes?

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Designing the research

Patient recruitment : FD and FD/IBS

Structural assessment GI symptoms

Nepean Dyspesia index

Depression and anxiety score (HADs)

Clinical test:

- Nutrient challenge test
- Gastric emptying test

Sample collection

Blood

Endoscopy

Eosophageal, gastric, duodenal biopsies

http://www.mydr.com.au/gastrointestinal-health/stomach-and-duodenum