Pesaro, 20 Marzo 2015

Sindrome dell'intestine irritabile (IBS): Ruolo del farmacista nell'inquadramento del paziente ed opzioni terapeutiche di Sua competenza

Dott. Andrea Lisotti
UOC Gastroenterologia – Ospedale di Imola
DIMEC - Università di Bologna

Conflitto di interesse

Nessun conflitto di interesse *nella preparazione e nella esposizione di tale presentazione*

Agenda

Background

Presentazione clinica

Approccio terapeutico

Agenda

Background

Definizione di malattie funzionali gastroenterologiche

Patogenesi (microbiota, micro-infiammazione, asse intestino-cervello)

Eziopatogenesi del sintomo

Presentazione clinica

Approccio terapeutico

Agenda

Background

Presentazione clinica

Diagnosi differenziale con patologie organiche

Sintomi o «campanelli» d'allarme

Approccio terapeutico

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Presentazione clinica

Approccio terapeutico

Modifiche nello stile di vita

Dieta

Farmaci

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Definizione di malattie funzionali gastroenterologiche

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Definizioni

Disordini funzionali gastrointestinali (FGIDs) un insieme di condizioni idiopatiche dell'apparato GI:

Rome Foundation, Gut 2014

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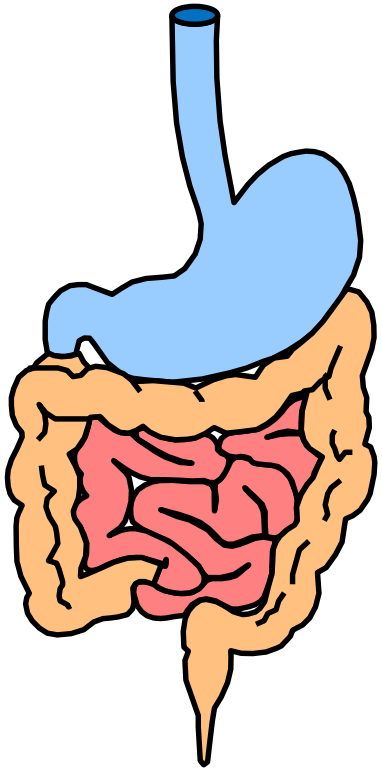

Rome Foundation, Gut 2014

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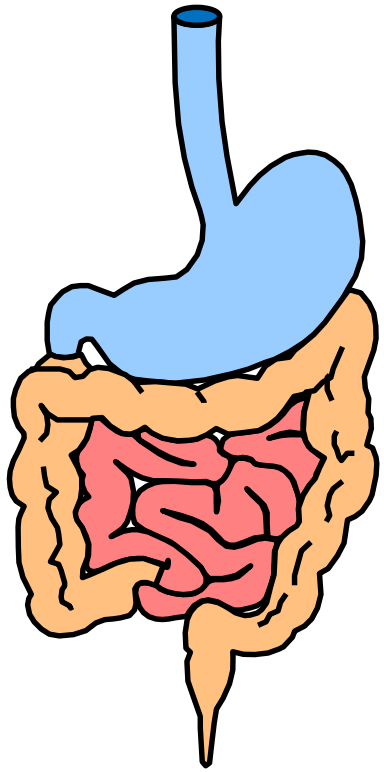
- **Disordini funzionali esofagei;**



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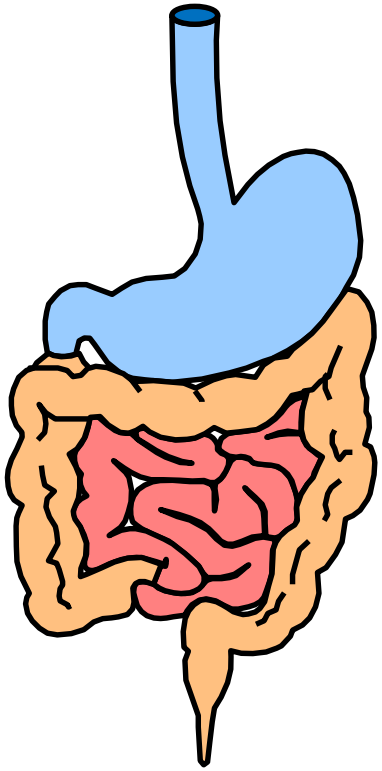

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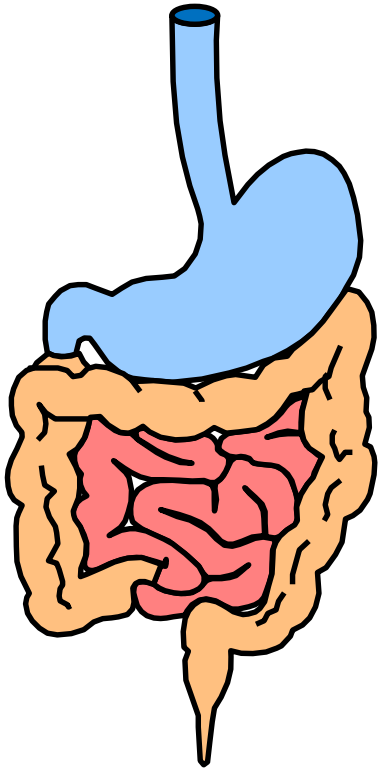

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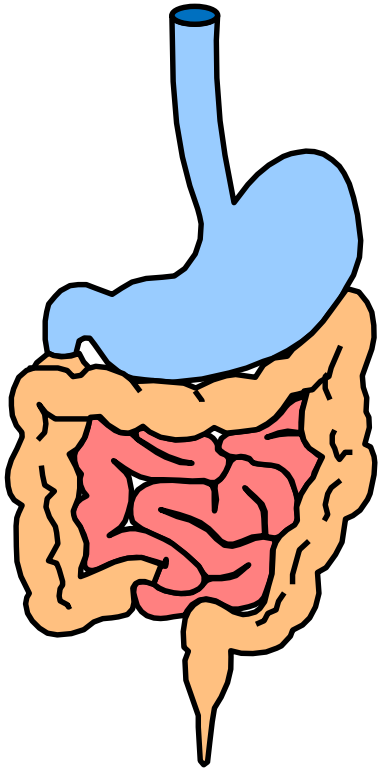

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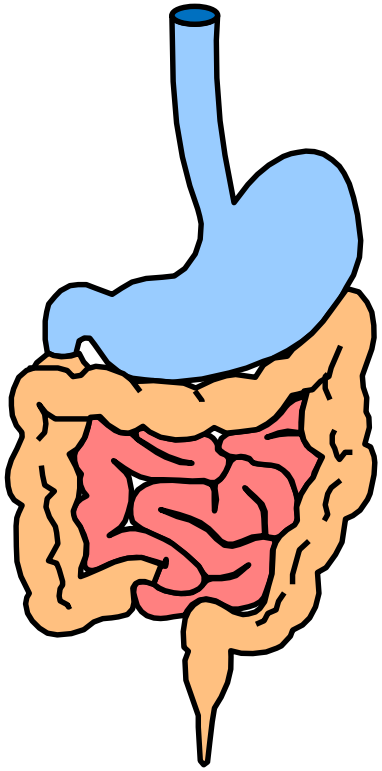
- **Disordini biliari funzionali;**



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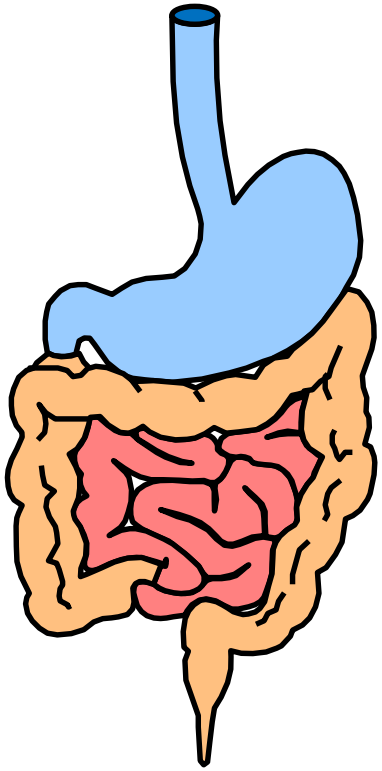
- **Disordini ano-rettali.**



Rome Foundation, Gut 2014

Definizioni

A. Functional Esophageal Disorders

Rome Foundation, Gastroenterology 2006

Definizioni

A. Functional Esophageal Disorders

A1. Functional Heartburn

*Diagnostic criteria** *Must include **all** of the following:*

1. Burning retrosternal discomfort or pain
2. Absence of evidence that gastroesophageal acid reflux is the cause of the symptom
3. Absence of histopathology-based esophageal motility disorders

* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Rome Foundation, Gastroenterology 2006

Definizioni

B. Functional Gastroduodenal Disorders

Rome Foundation, Gastroenterology 2006

Definizioni

B. Functional Gastroduodenal Disorders

B1. FUNCTIONAL DYSPEPSIA

*Diagnostic criteria** *Must include:*

1. *One or more* of the following:
   a. Bothersome postprandial fullness
   b. Early satiation
   c. Epigastric pain
   d. Epigastric burning

AND

2. No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms

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B1a. Postprandial Distress Syndrome

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B1a. Postprandial Distress Syndrome

B1b. Epigastric Pain Syndrome

Rome Foundation, Gastroenterology 2006

Definizioni

B. Functional Gastroduodenal Disorders

B3. NAUSEA AND VOMITING DISORDERS

Rome Foundation, Gastroenterology 2006

Definizioni

B. Functional Gastroduodenal Disorders

B3. NAUSEA AND VOMITING DISORDERS

B3a. Chronic Idiopathic Nausea

B3b. Functional Vomiting

B3c. Cyclic Vomiting Syndrome

B4. Rumination Syndrome in Adults

Rome Foundation, Gastroenterology 2006

Definizioni

C. Functional Bowel Disorders

C1. Irritable Bowel Syndrome

*Diagnostic criterion**

Recurrent abdominal pain or discomfort** at least 3 days/month in the last 3 months associated with *two or more* of the following:

Rome Foundation, Gastroenterology 2006

Definizioni

C. Functional Bowel Disorders

C1. Irritable Bowel Syndrome

*Diagnostic criterion**

Recurrent abdominal pain or discomfort** at least 3 days/month in the last 3 months associated with *two or more* of the following:

1. Improvement with defecation
2. Onset associated with a change in frequency of stool
3. Onset associated with a change in form (appearance) of stool

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Subtyping IBS by Predominant Stool Pattern

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1. IBS with constipation—hard or lumpy stools ≥25% and loose or watery stools <25% of bowel movements

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2. IBS with diarrhea—loose or watery stools ≥25% and hard or lumpy stools <25% of bowel movements
3. Mixed IBS—hard or lumpy stools ≥25% and loose or watery stools ≥25% of bowel movements

Rome Foundation, Gastroenterology 2006

Definizioni

C. Functional Bowel Disorders

C3. Functional Constipation

*Diagnostic criteria**

1. Must include *two or more* of the following:
   a. Straining during at least 25% of defecations
   b. Lumpy or hard stools in at least 25% of defecations
   c. Sensation of incomplete evacuation for at least 25% of defecations
   d. Sensation of anorectal obstruction/blockage for at least 25% of defecations
   e. Manual maneuvers to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor)
   f. Fewer than three defecations per week
2. Loose stools are rarely present without the use of laxatives
3. Insufficient criteria for irritable bowel syndrome

* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Rome Foundation, Gastroenterology 2006

Definizioni

C. Functional Bowel Disorders

C4. Functional Diarrhea

*Diagnostic criterion**

Loose (mushy) or watery stools without pain occurring in at least 75% of stools

* Criterion fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Rome Foundation, Gastroenterology 2006

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Chey WD et al., JAMA 2015

Patogenesi

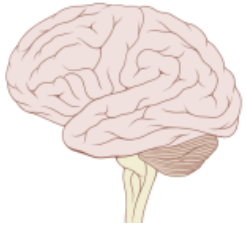
Percezione del dolore

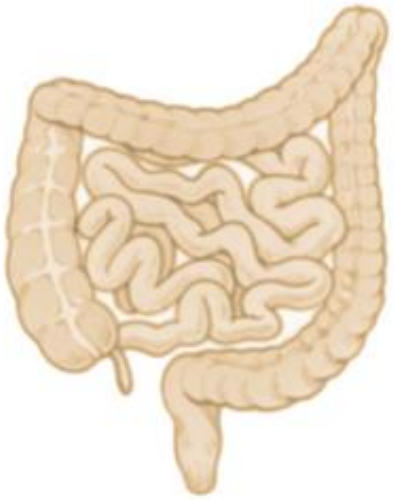
Turbe dell'alvo

Chey WD et al., JAMA 2015

Patogenesi

Percezione del dolore





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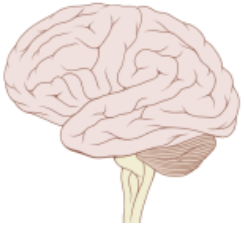

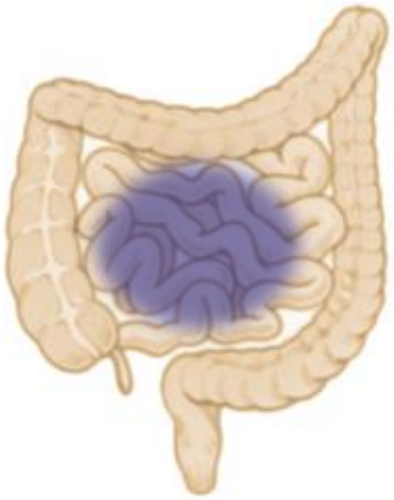

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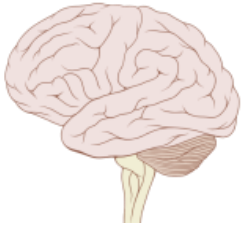
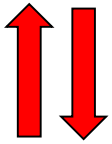
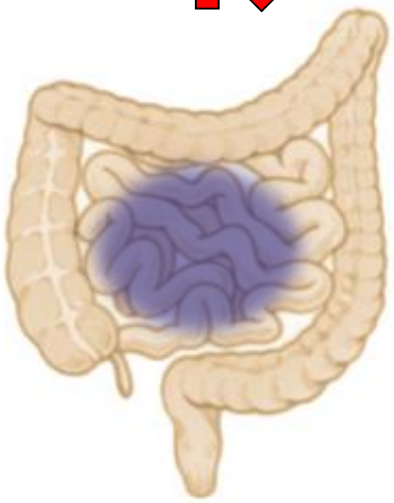


Brain-Gut axis





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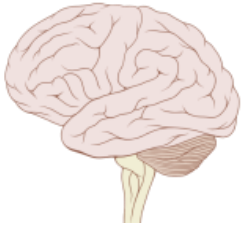

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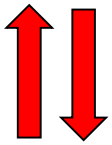

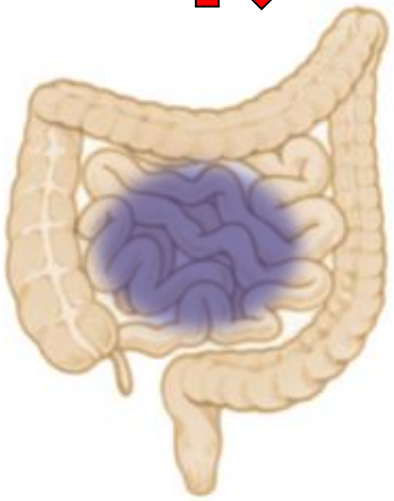

Turbe dell'alvo

- Fattori psicologici
- Alterazioni della motilità
- Ipersensibilità viscerale

Chey WD et al., JAMA 2015

Patogenesi

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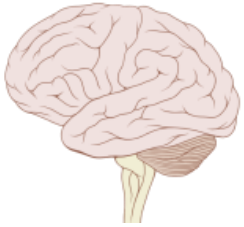

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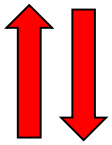

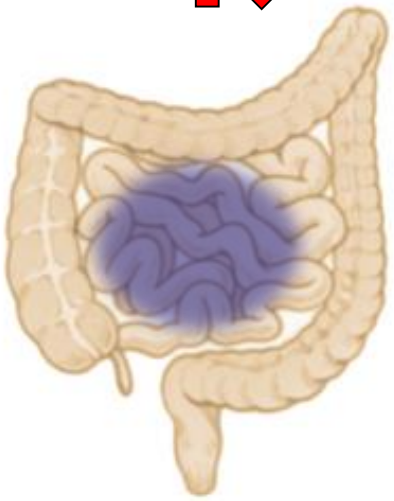

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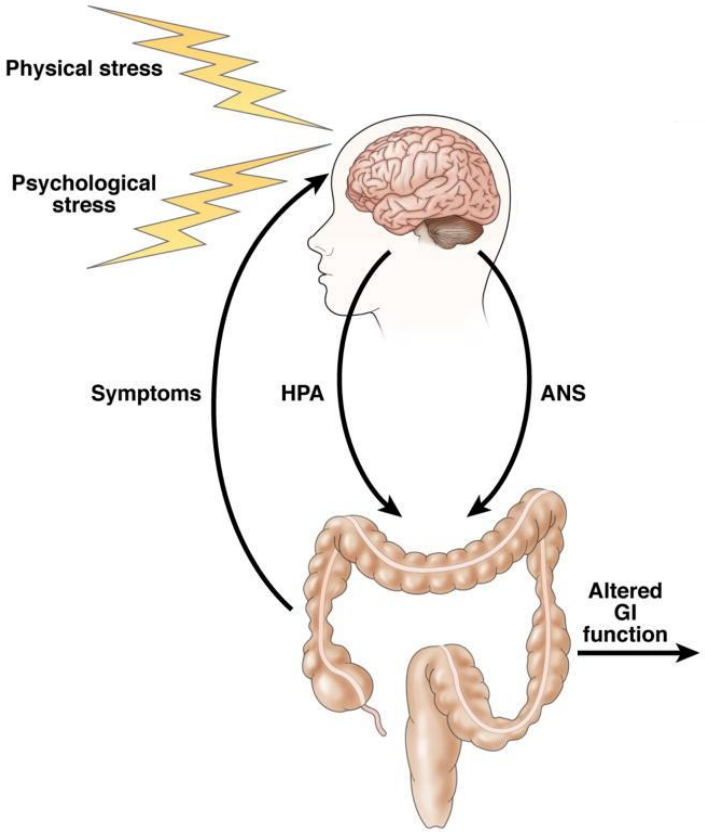
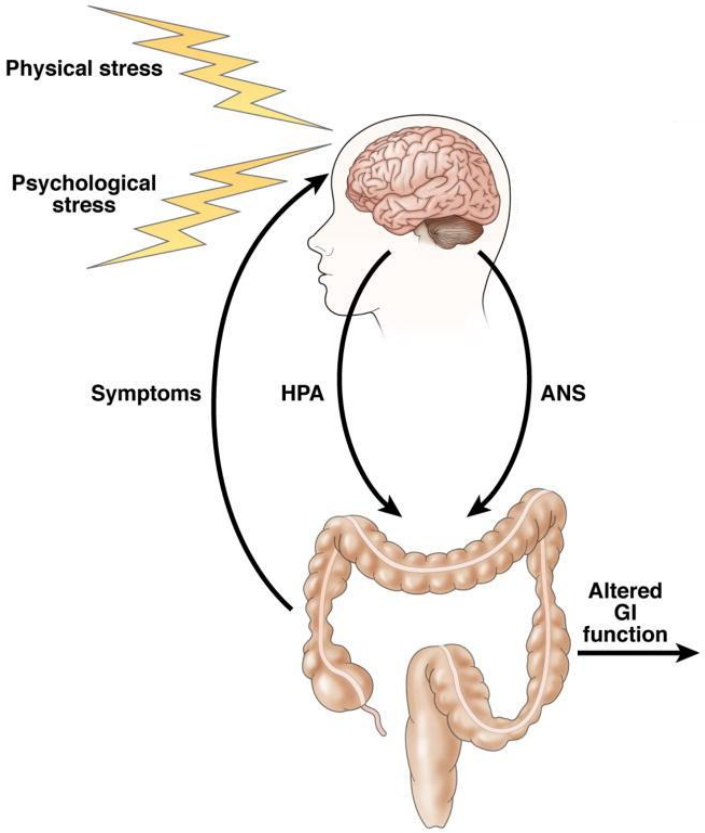
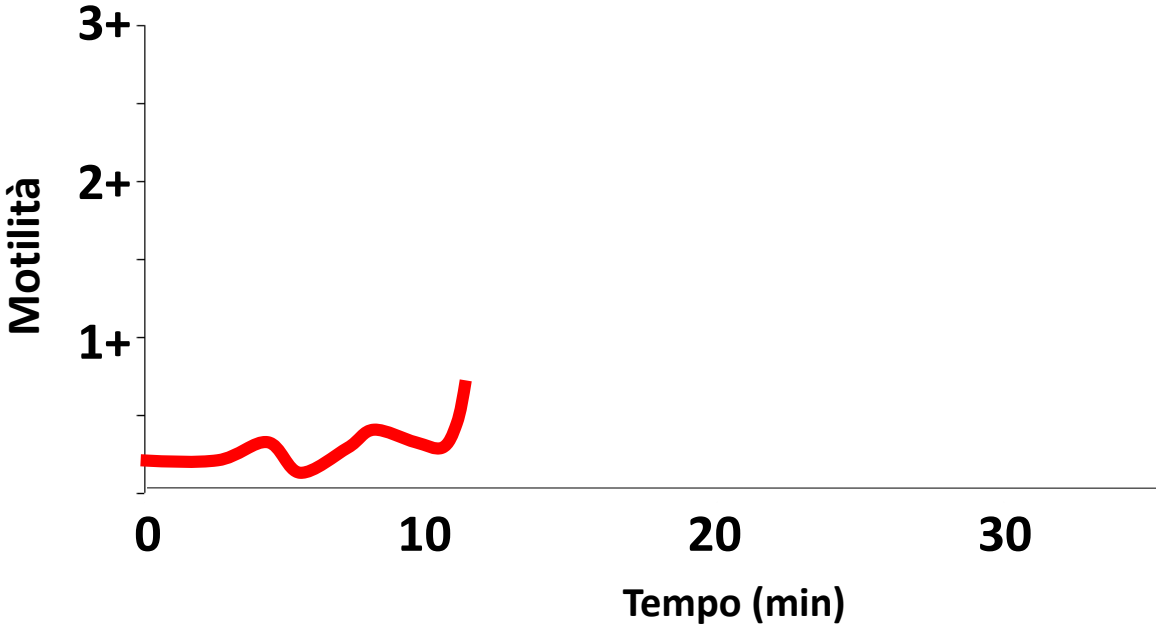


Almy, Gastroenterology 1949

Patogenesi





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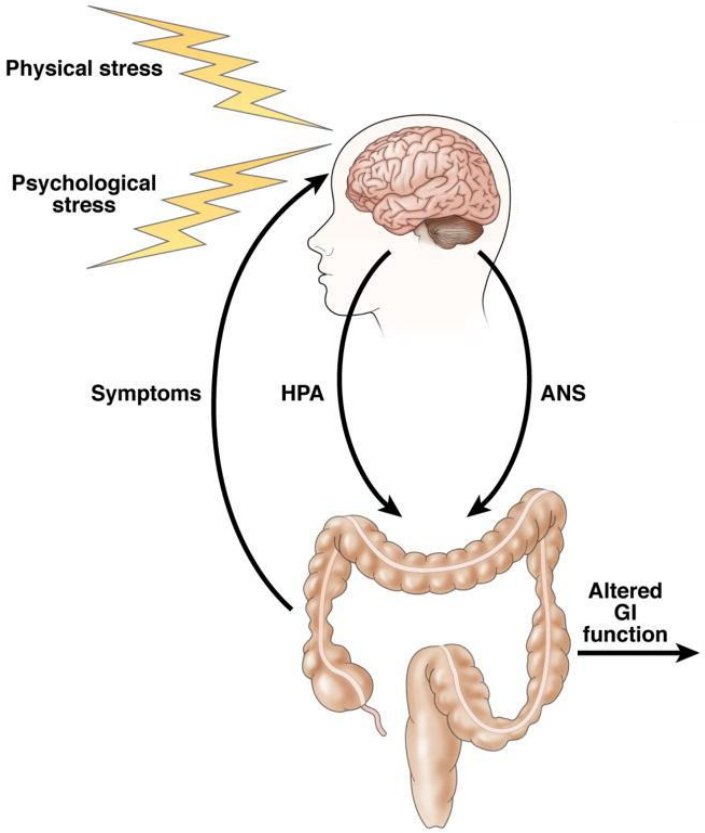

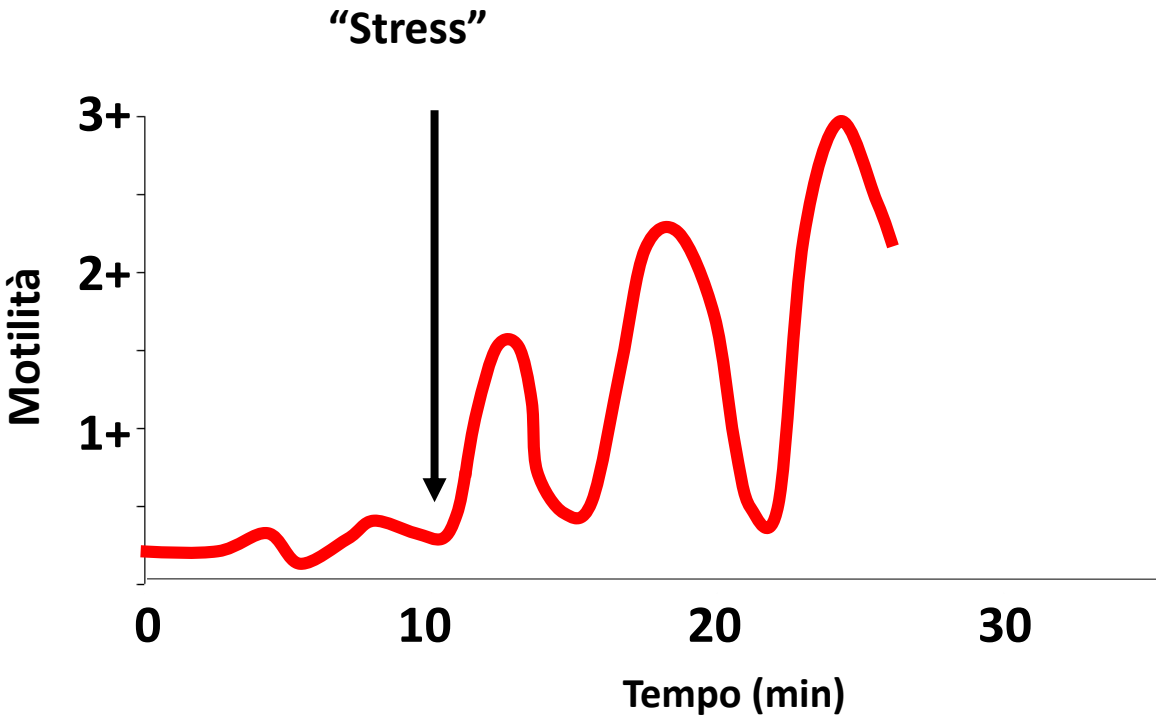

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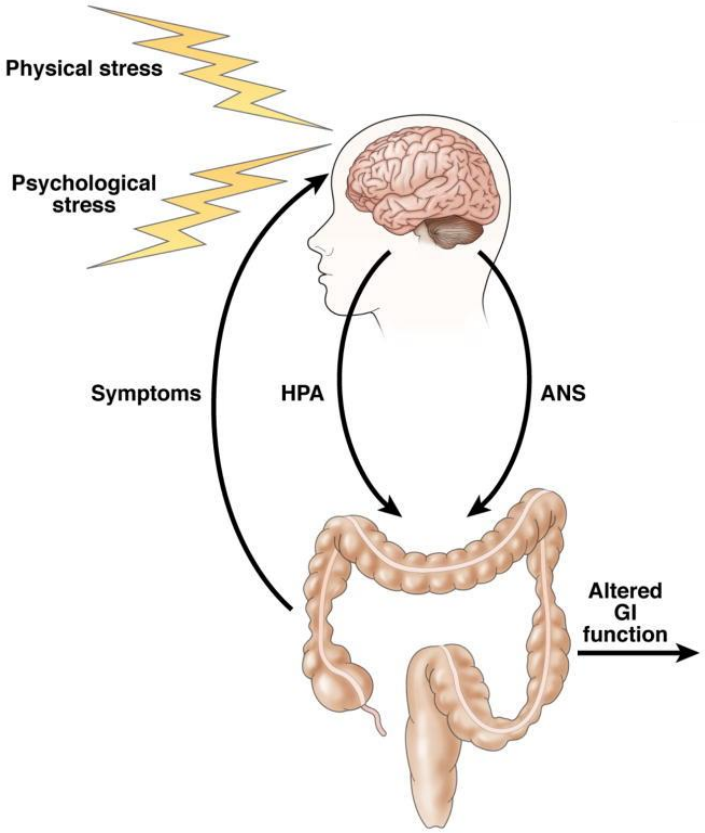

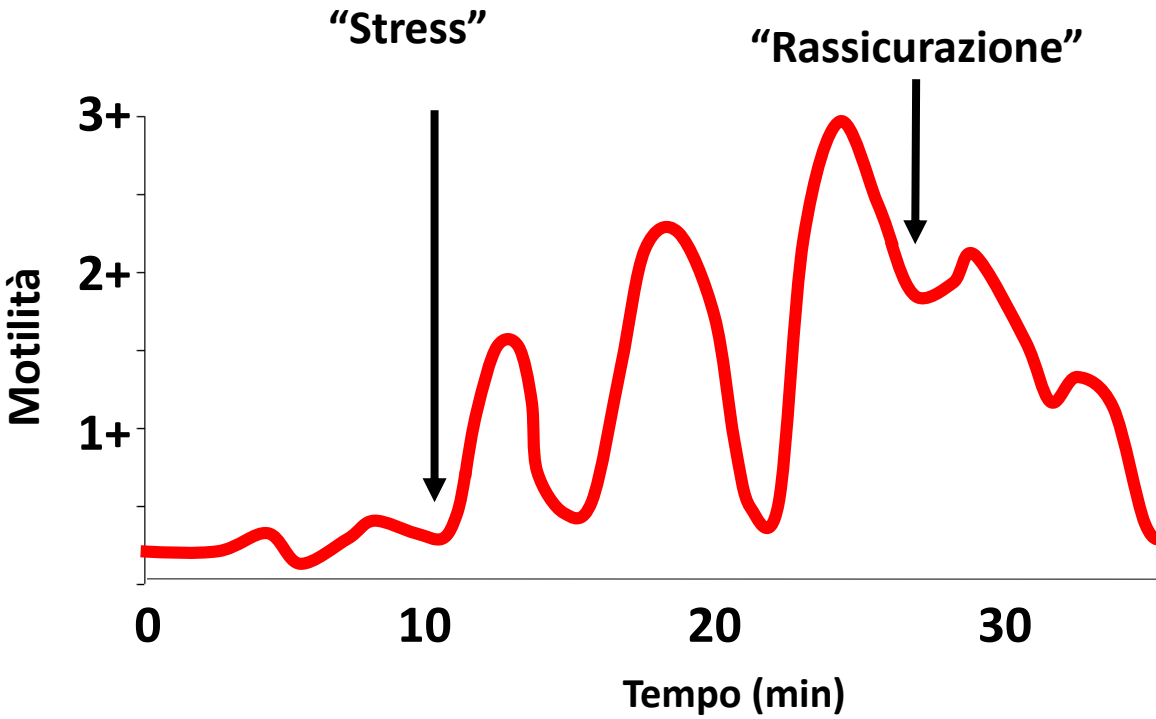

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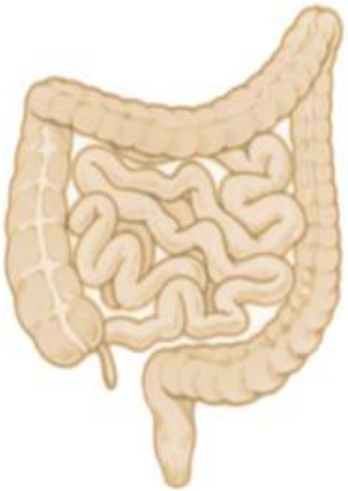
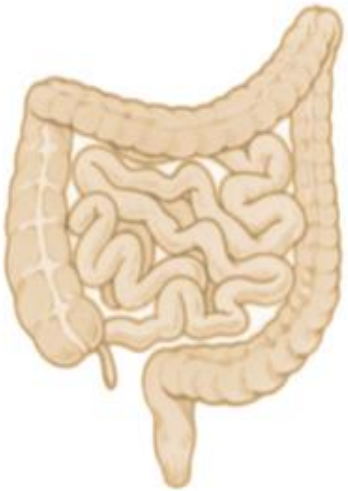
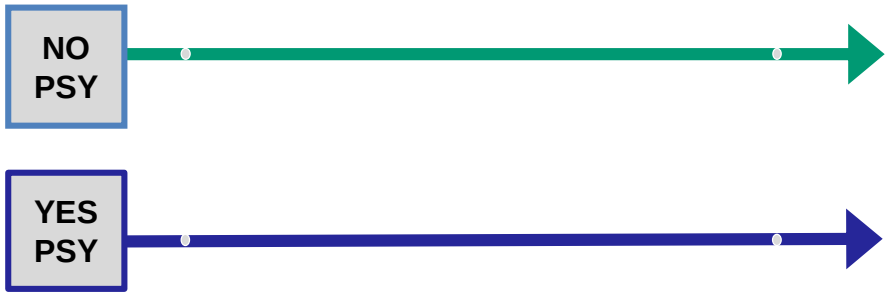


Patogenesi

The brain—gut pathway in functional gastrointestinal disorders is bidirectional: a 12-year prospective population-based study





Koloski NA et al., Gut 2012

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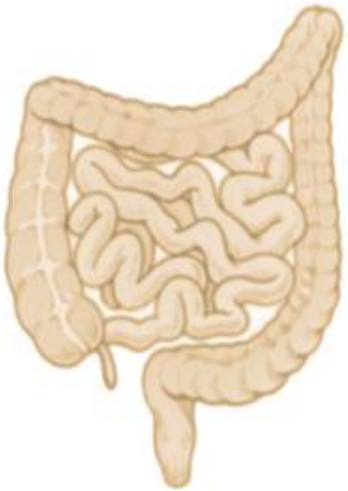

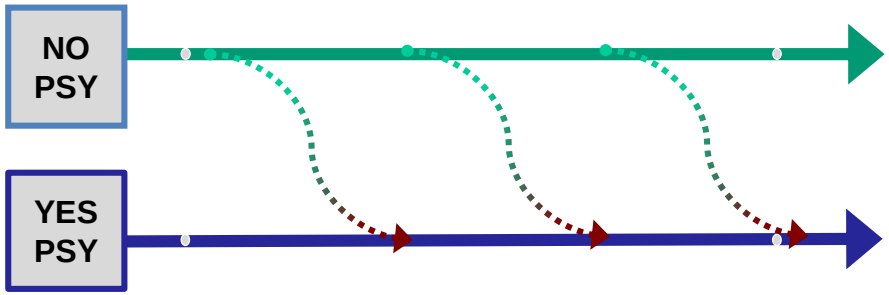

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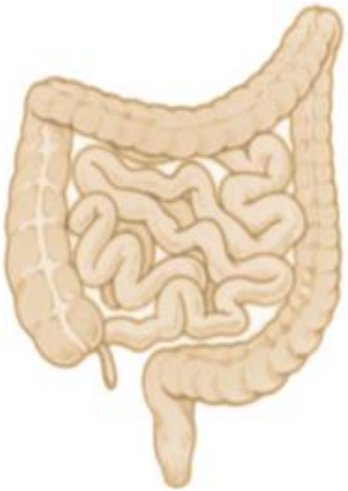

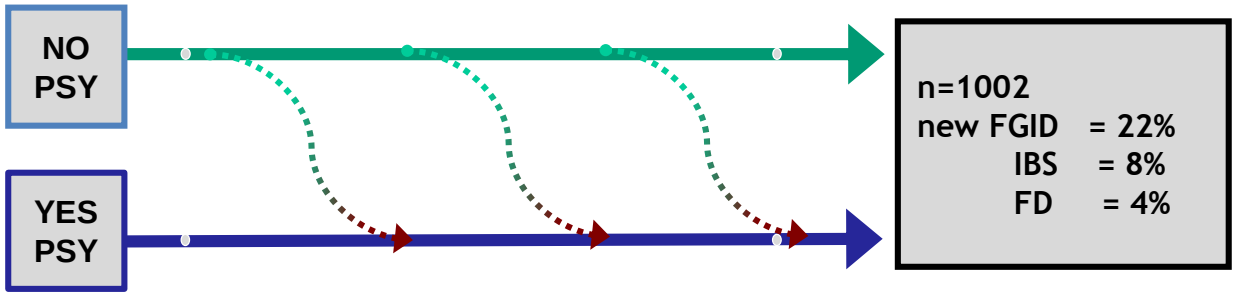

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Patogenesi

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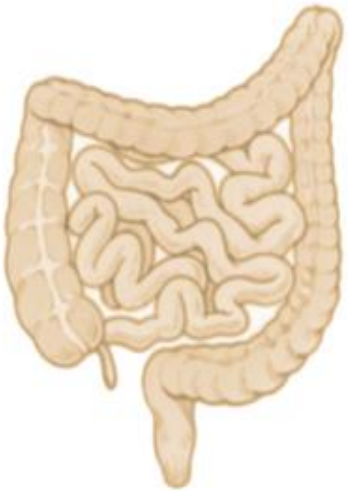
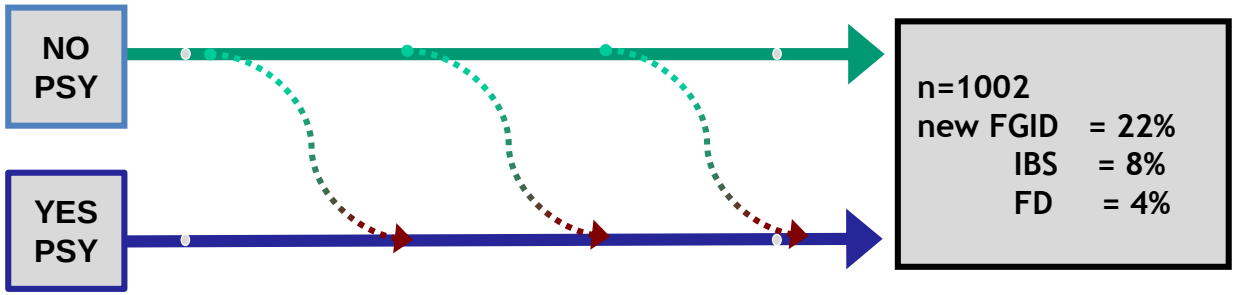


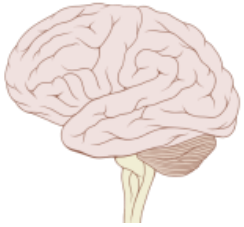


L'IBS precede ed è un fattore di rischio indipendente per lo sviluppo di ansia e depressione

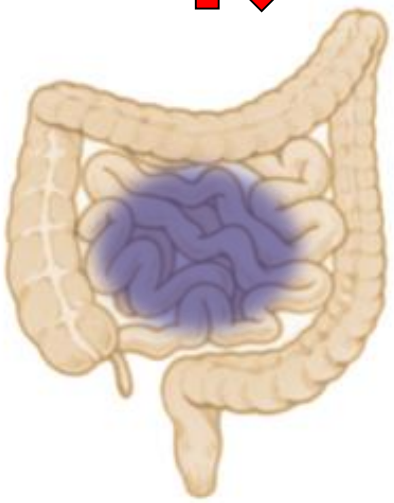
Koloski NA et al., Gut 2012

Patogenesi

Percezione del dolore



Brain-Gut axis

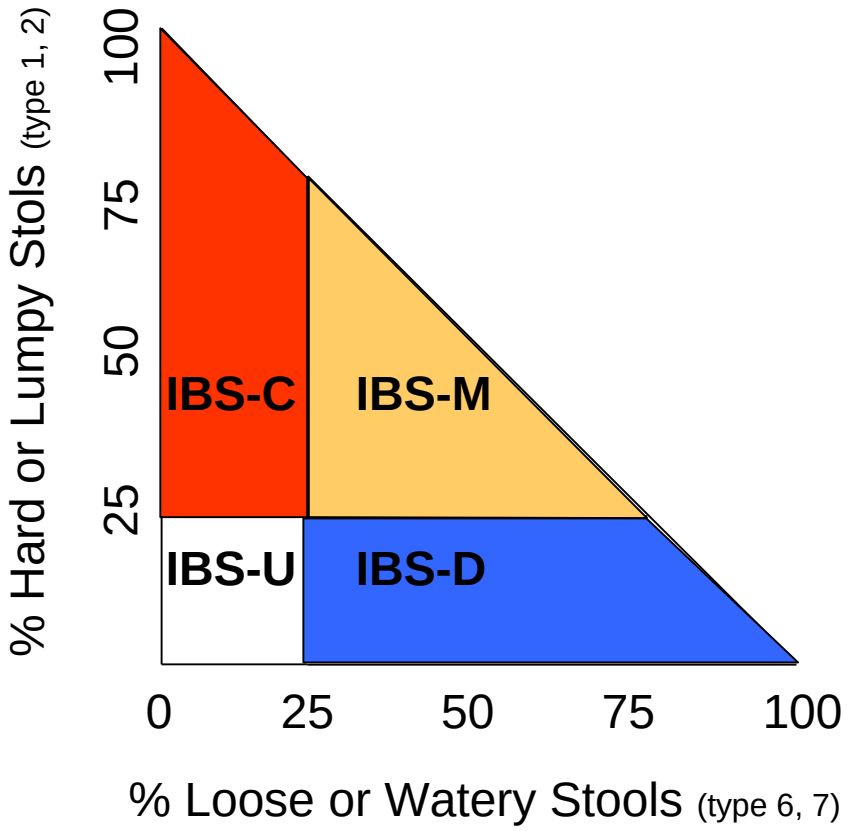


Turbe dell'alvo

- Fattori psicologici
- Alterazioni della motilità
- Ipersensibilità viscerale

Chey WD et al., JAMA 2015

Patogenesi



Chey WD et al., JAMA 2015

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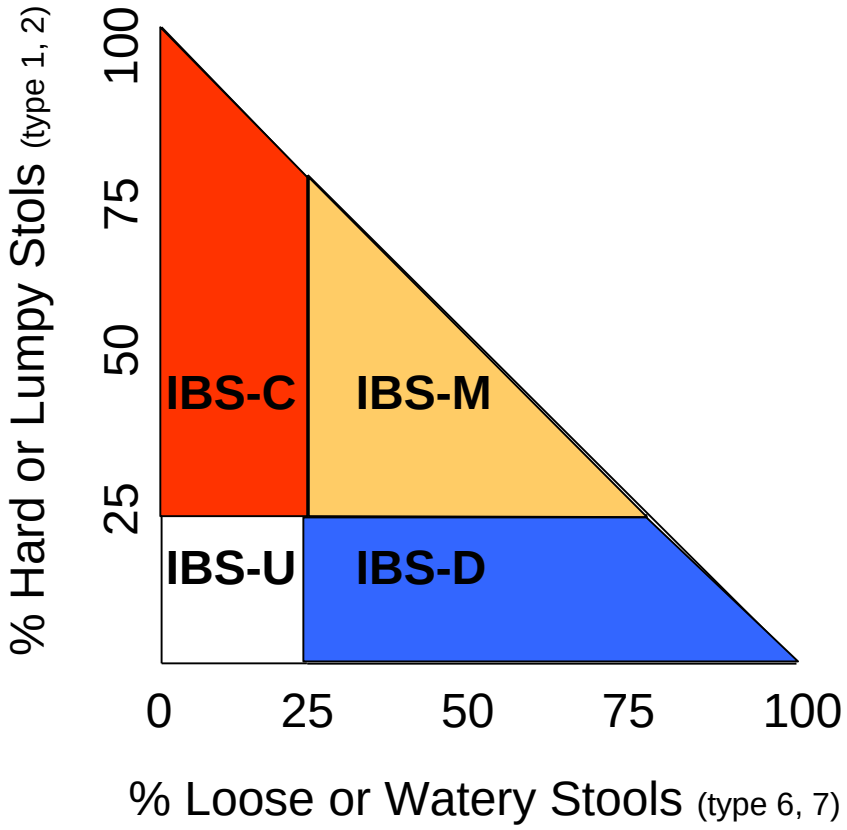
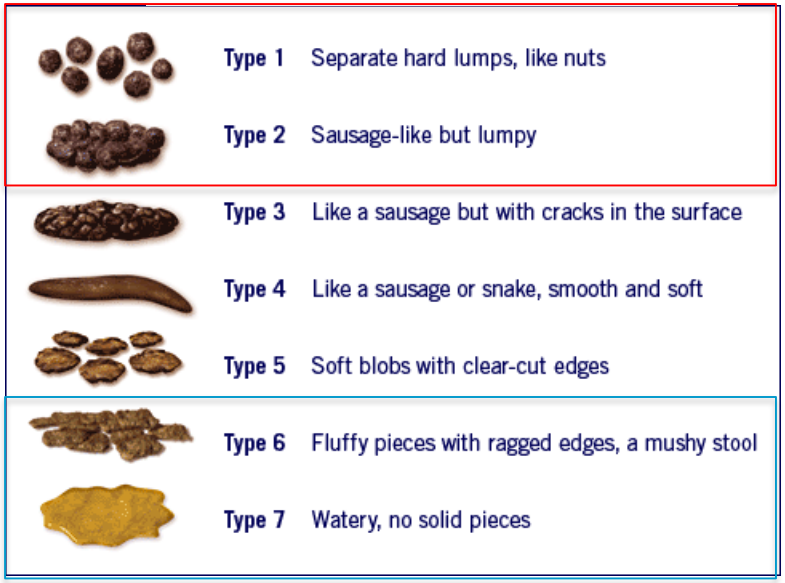


Bristol Stool Form Scale



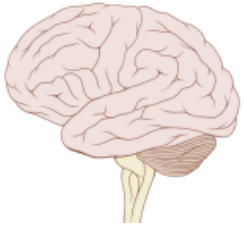
Chey WD et al., JAMA 2015

Patogenesi

O'Donnell, BMJ 1990

Patogenesi

Percezione del dolore



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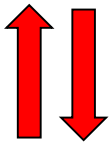
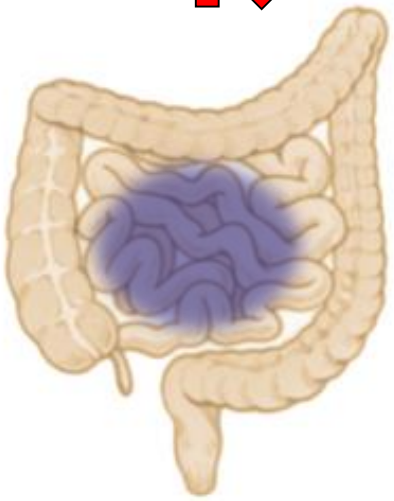




Turbe dell'alvo

- Fattori psicologici
- Alterazioni della motilità
- Ipersensibilità viscerale

Chey WD et al., JAMA 2015

Patogenesi

Normale

3

2

1

0

0 = nulla 1 = fastidio 2 = fastidio intenso 3 = Dolore 4 = Dolore Intenso 5 = Dolore molto intenso

Patogenesi

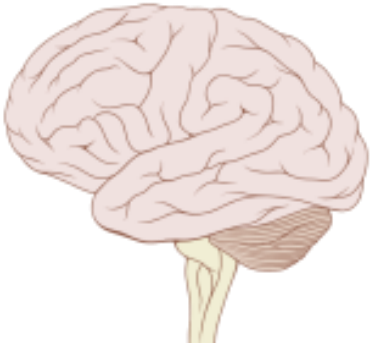
Normale

3

2

1

0



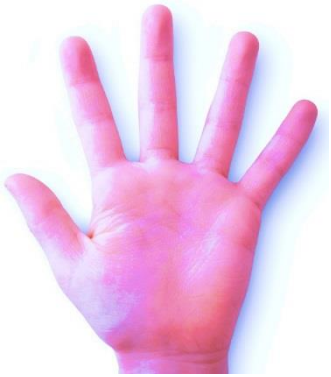
Percezione -Caratteristiche
(corteccia somatosensoriale)

Emotività - Esperienza
(sistema limbico)

Anticipazione

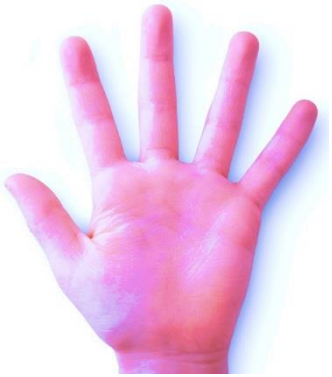
0 = nulla 1 = fastidio 2 = fastidio intenso 3 = Dolore 4 = Dolore Intenso 5 = Dolore molto intenso

Patogenesi

Normale		Allodinia	
	3		5
	2		4
	1		3
	0		1

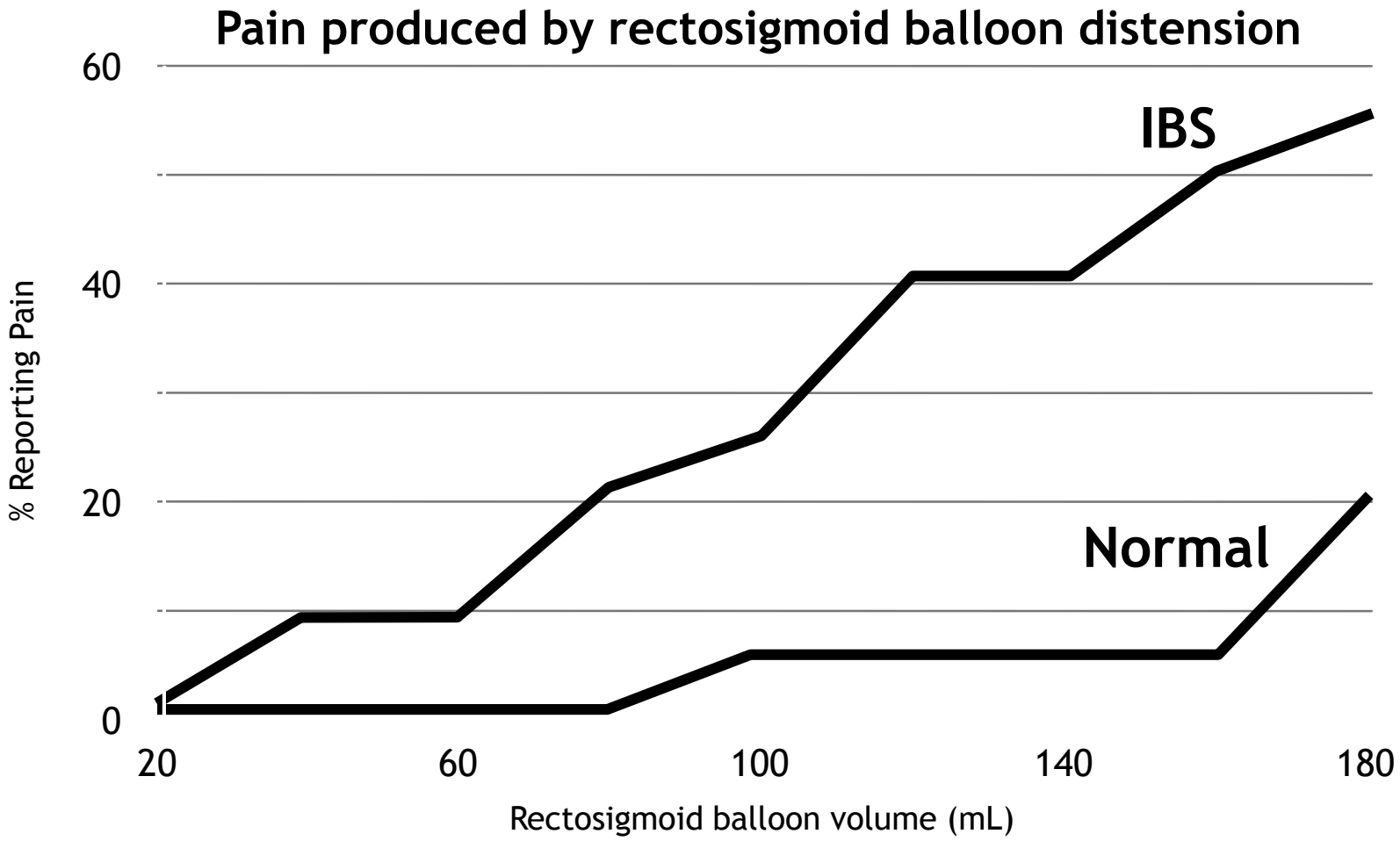
0 = nulla 1 = fastidio 2 = fastidio intenso 3 = Dolore 4 = Dolore Intenso 5 = Dolore molto intenso

Patogenesi

Normale		Allodinia		Iperalgesia	
	3		5		4
	2		4		3
	1		3		2
	0		1		0

0 = nulla 1 = fastidio 2 = fastidio intenso 3 = Dolore 4 = Dolore Intenso 5 = Dolore molto intenso

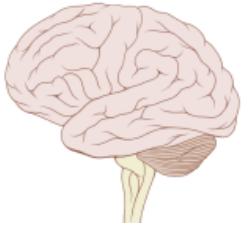
Patogenesi



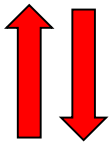
Whitehead et al., Dig Dis Sci 1980

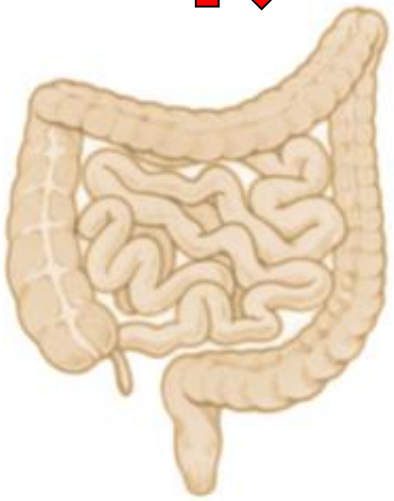
Patogenesi

Percezione del dolore



Brain-Gut axis





Turbe dell'alvo

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- Alterazioni della motilità
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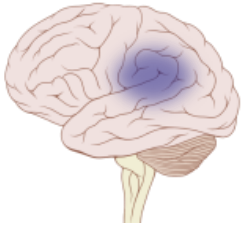
Chey WD et al., JAMA 2015

Patogenesi

Percezione del dolore



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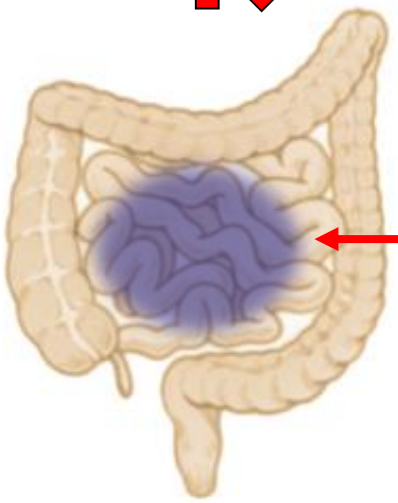

Turbe dell'alvo

- Fattori psicologici
- Alterazioni della motilità
- Ipersensibilità viscerale

Chey WD et al., JAMA 2015

Patogenesi

Environmental Contributors to IBS Symptoms

Early life stressors (abuse, psychosocial stressors)

Food intolerance

Antibiotics

Enteric infection

Chey WD et al., JAMA 2015

Patogenesi

Environmental Contributors to IBS Symptoms

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Enteric infection

Host Factors Contributing to IBS Symptoms

Altered pain perception

Altered brain-gut interaction

Dysbiosis

Increased intestinal permeability

Increased gut mucosal immune activation

Visceral hypersensitivity

Chey WD et al., JAMA 2015

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Chey WD et al., JAMA 2015

Agenda

Background

Definizione di malattie funzionali gastroenterologiche

Patogenesi (**microbiota**, micro-infiammazione, asse intestino-cervello)

Presentazione clinica

Approccio terapeutico

Human Gut Microbiota

“Normal” intestinal microbiome:

- Over 500 bacterial species (less well-described virome and yeast)
- Our intestinal bacteria weight up to 1 Kg
- 10^{14} bacteria cells (outnumber human cells by 10:1)
- The bacterial genome outnumber human genome by 100:1

Sekirov I, Physiol Rev 2010

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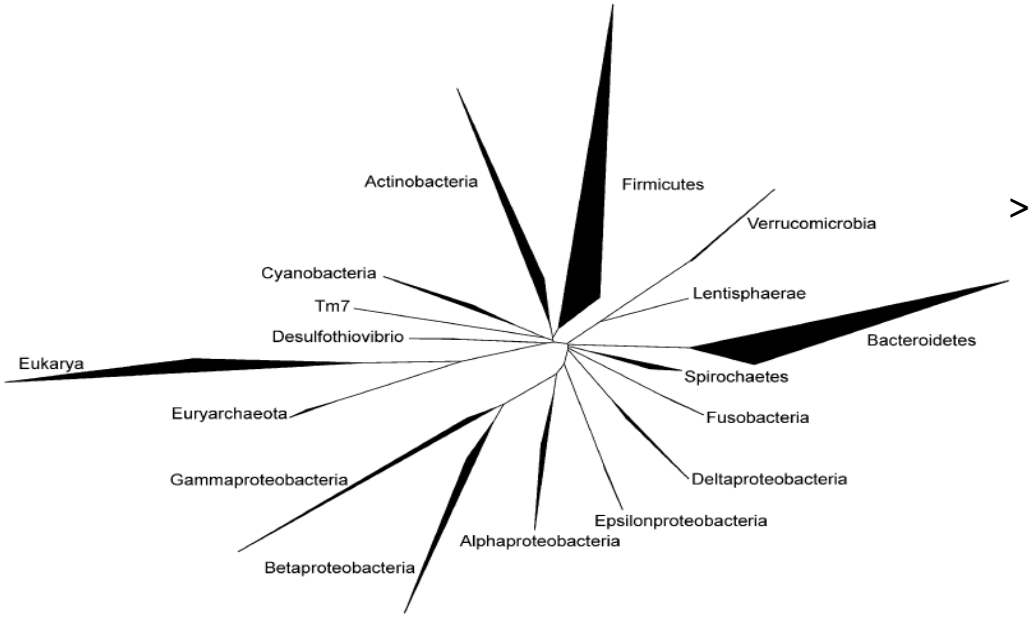
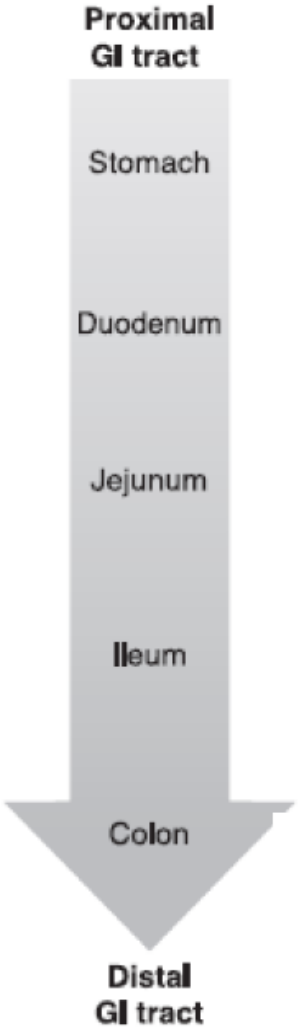


> 90% Bacteroides and Firmicutes

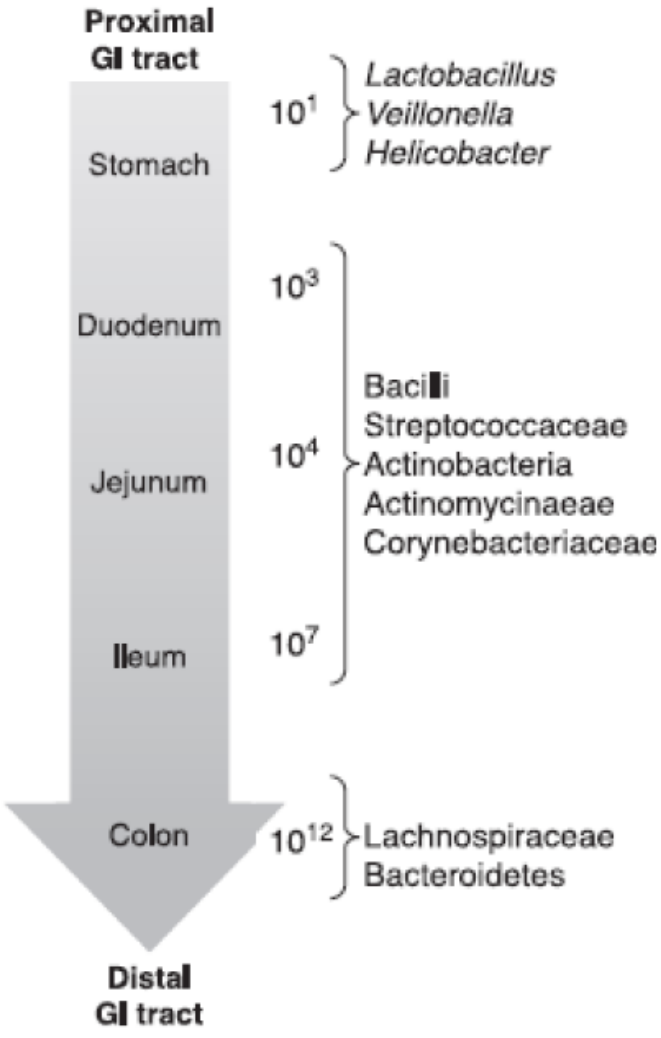
Sekirov I, Physiol Rev 2010

Human Gut Microbiota



Sekirov I, Physiol Rev 2010

Human Gut Microbiota



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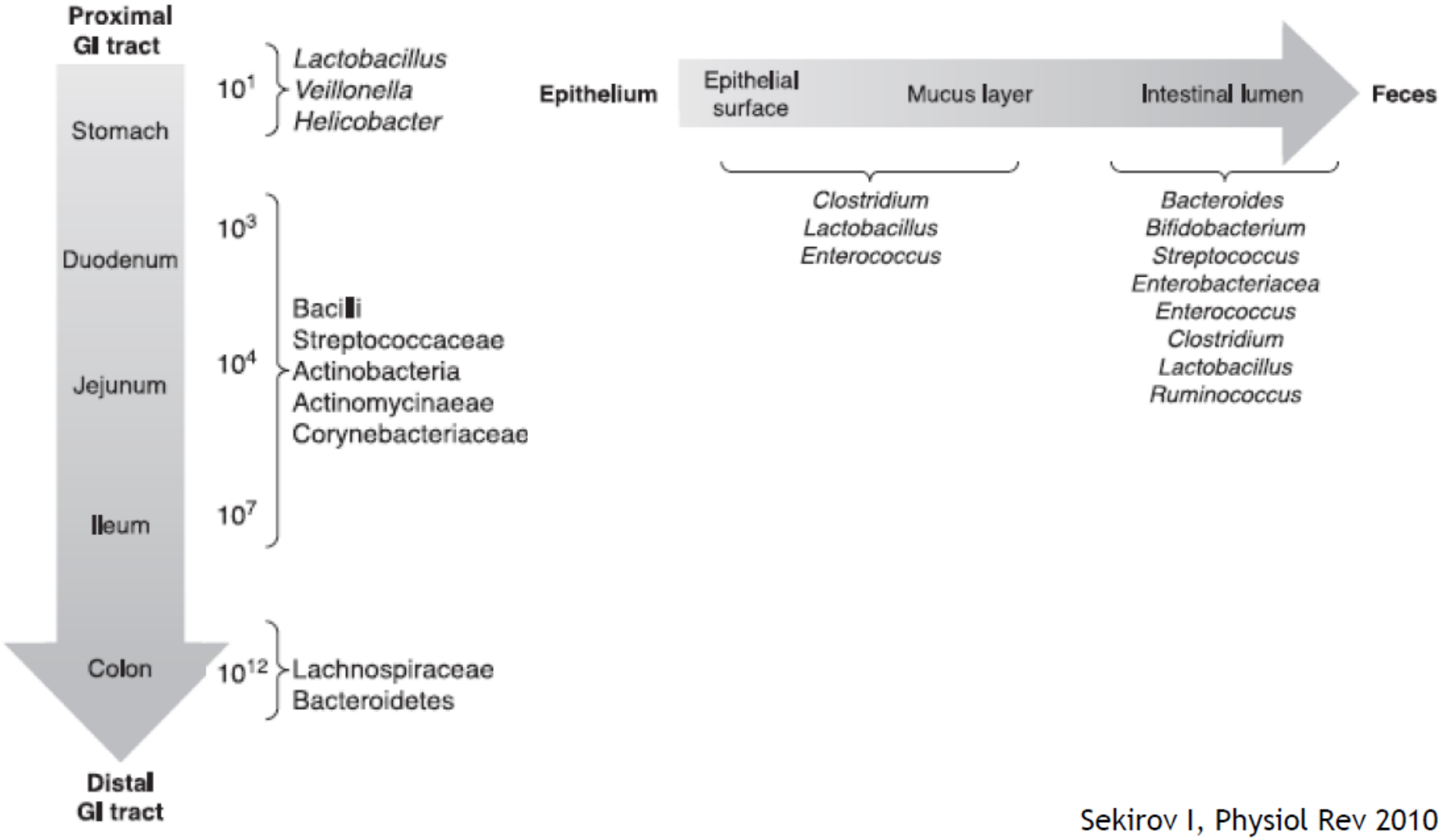
Human Gut Microbiota



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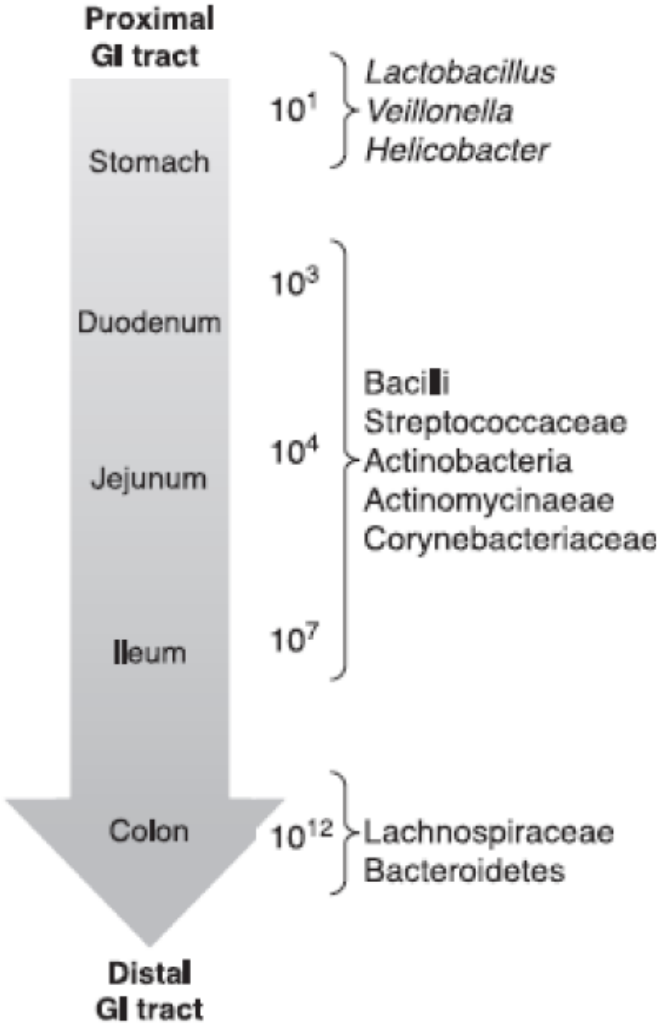

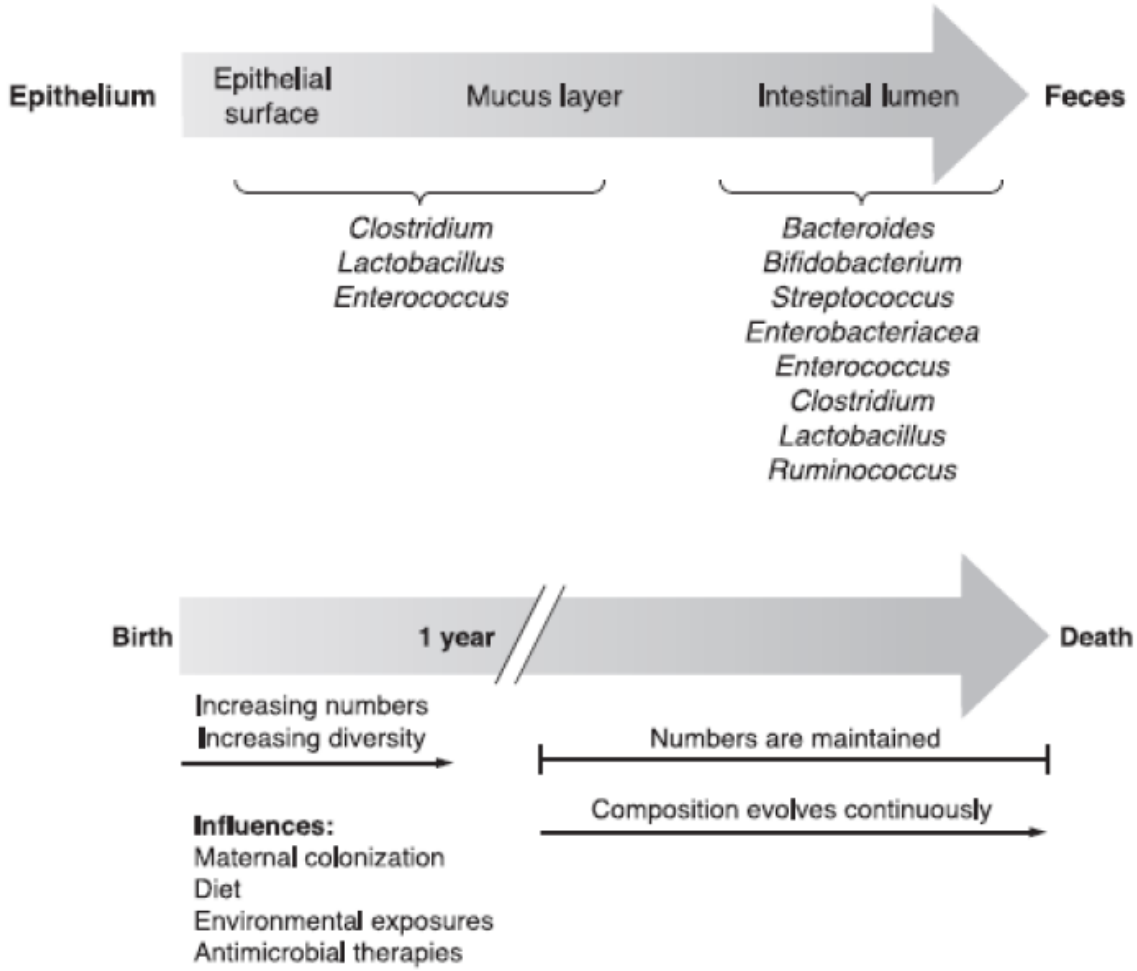

Sekirov I, Physiol Rev 2010

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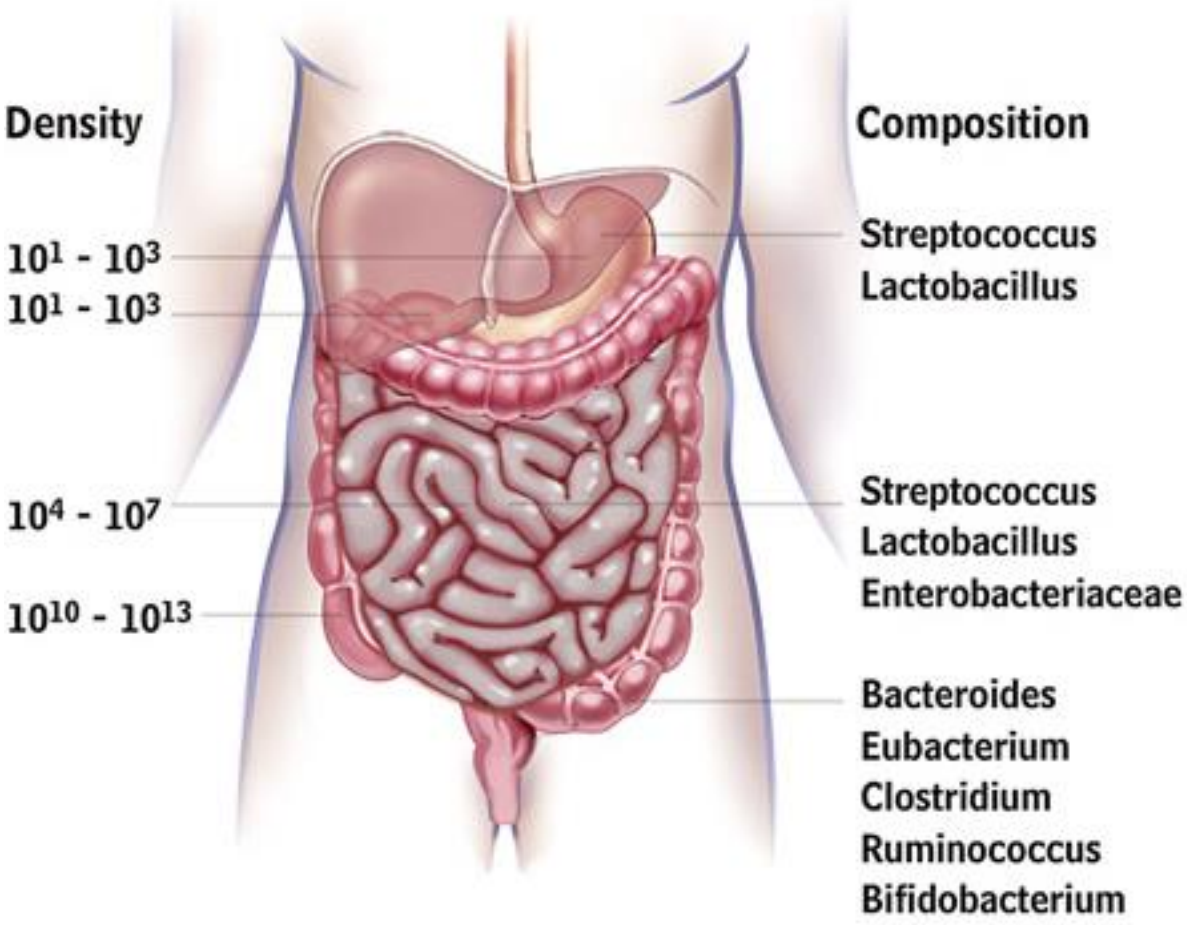
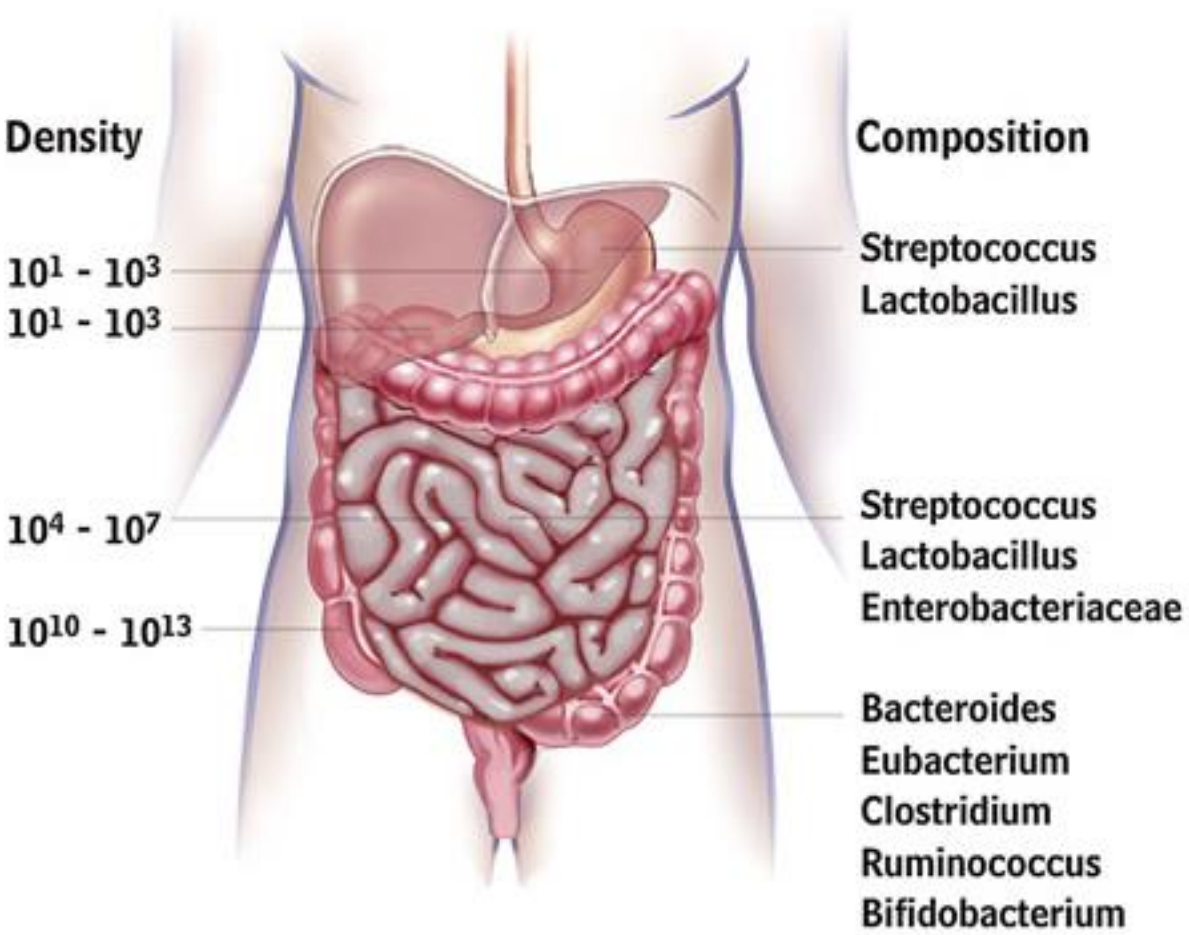


Simrén M, Gut 2012

Human Gut Microbiota

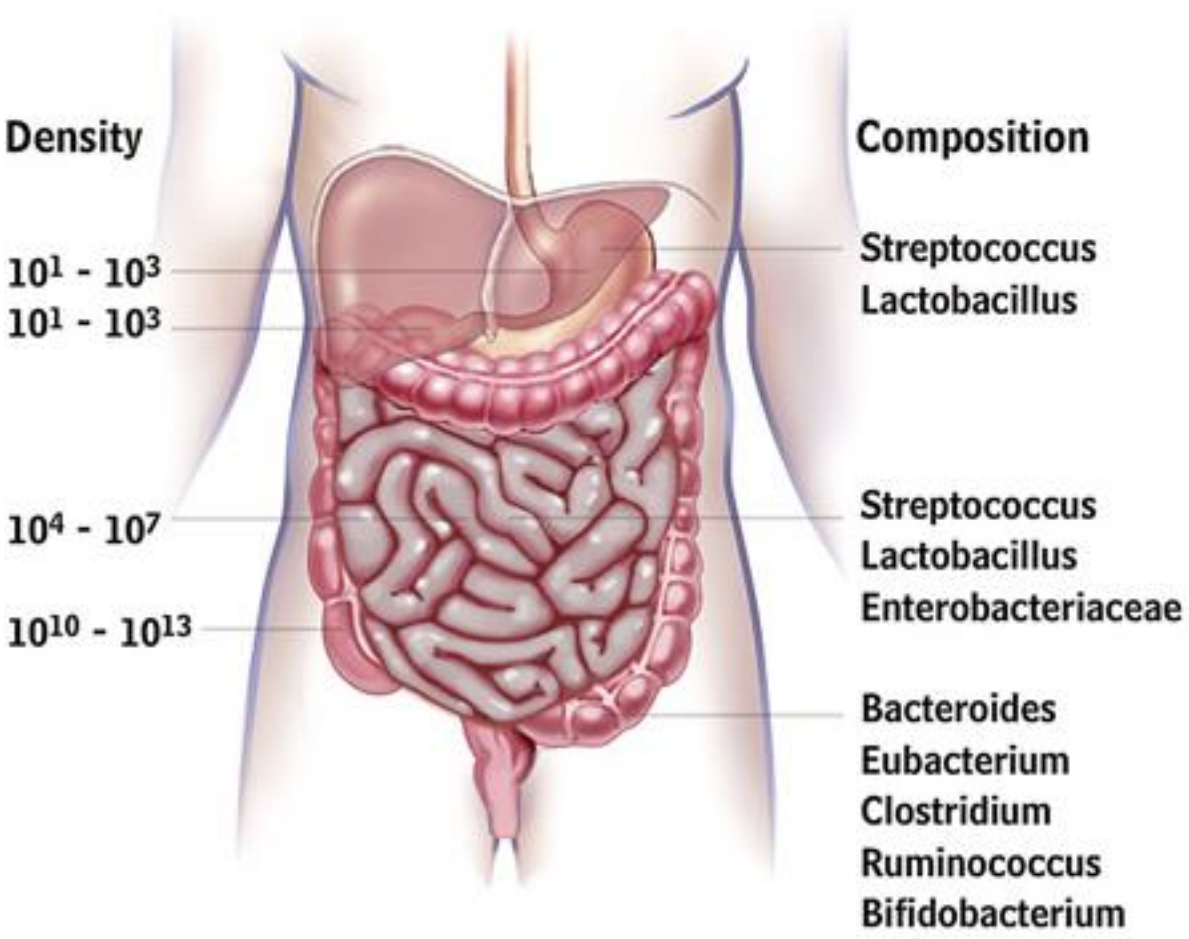


Intrinsic factors

- Gastric acid
- O_2
- Motility
- Mucus
- GI secretions
- Antimicrobial peptides
- Immunity (sIgA)

Simrén M, Gut 2012

Human Gut Microbiota



Extrinsic factors

Diet, Pre and probiotics

PPIs, H2 blockers

Antibiotics

Prokinetics

Laxatives

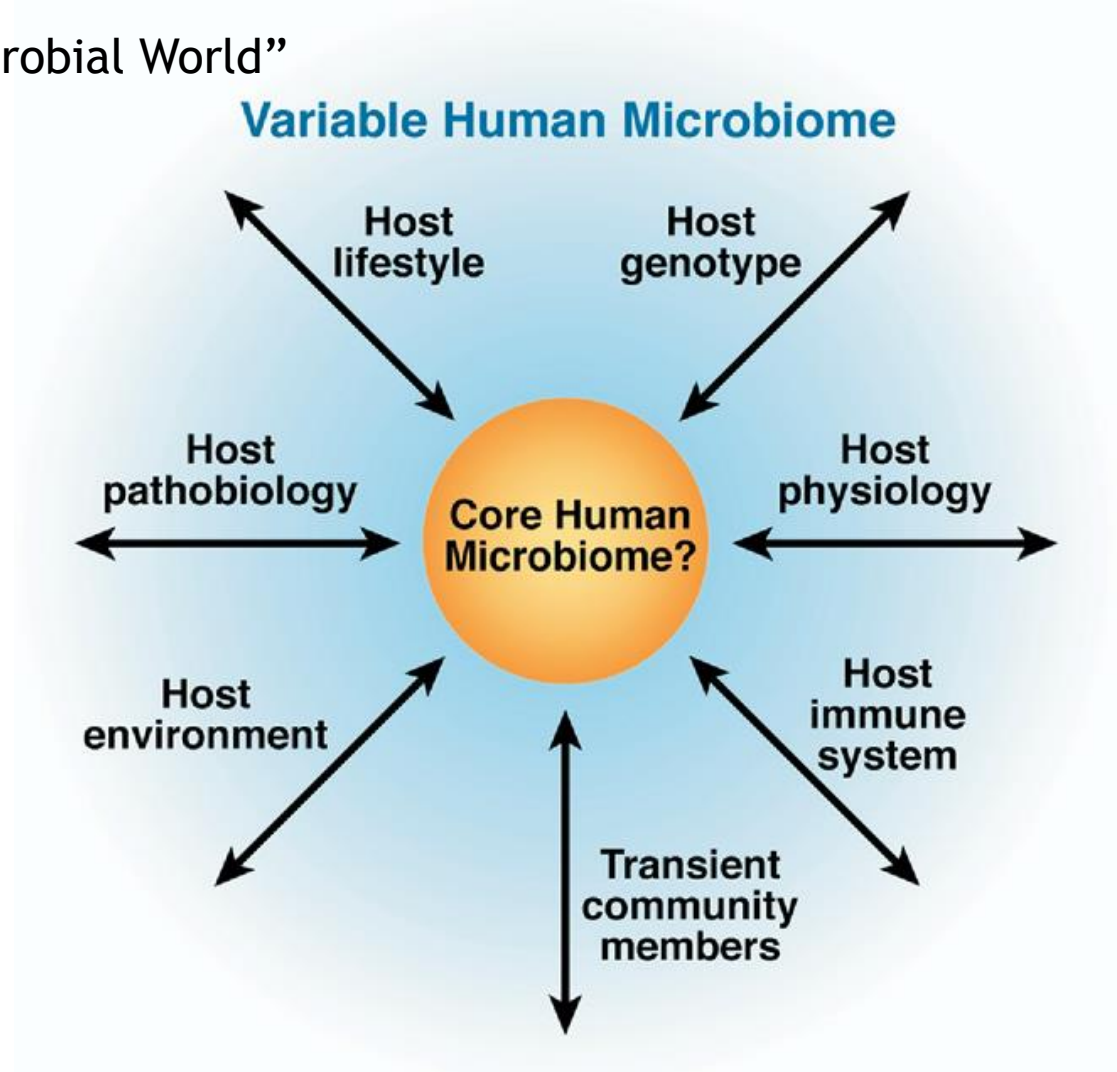
Opioids

NSAIDs

Simrén M, Gut 2012

The “Microbial World”

The “Microbial World”



Preidis GA, Gastro 2009

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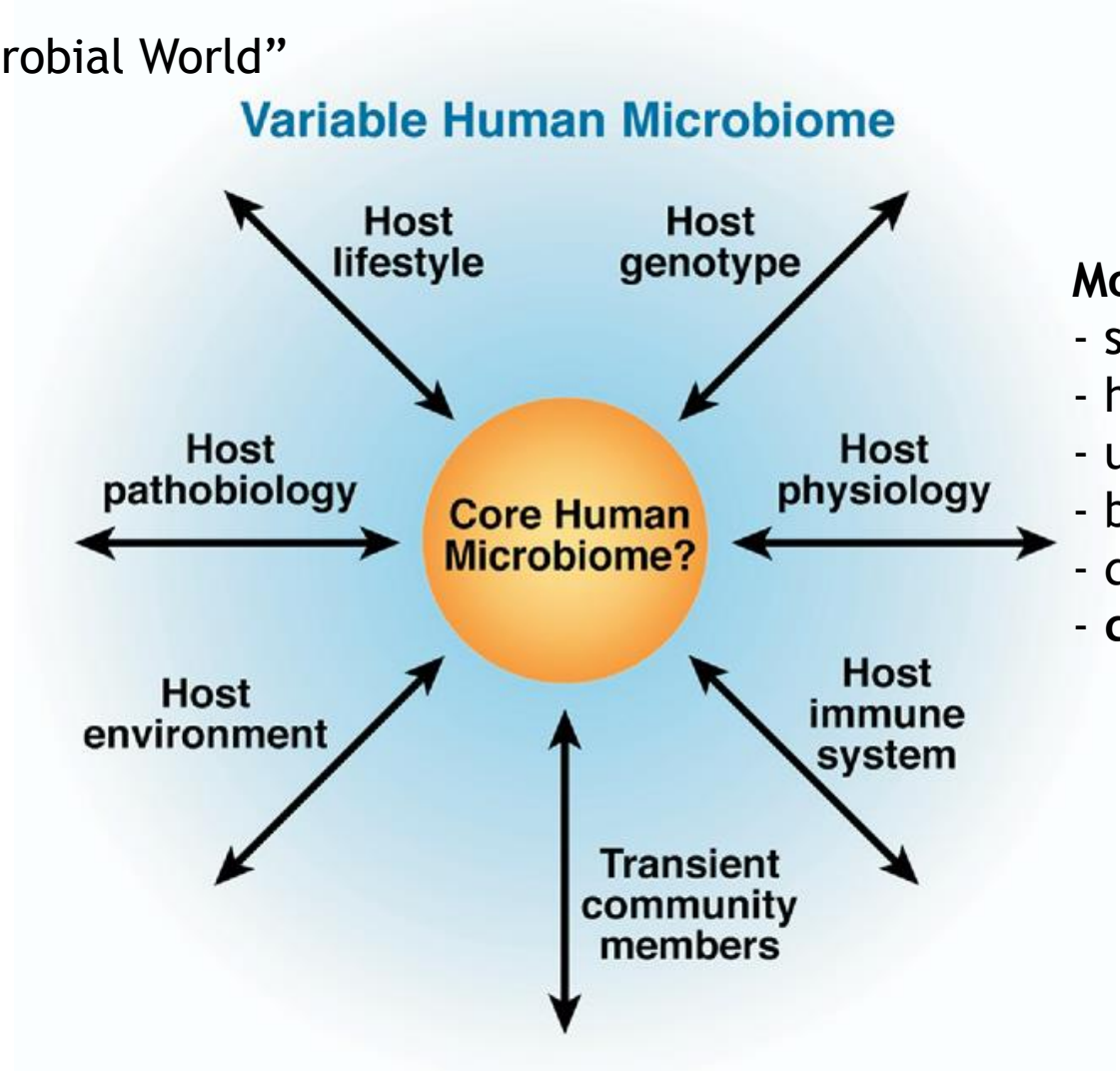


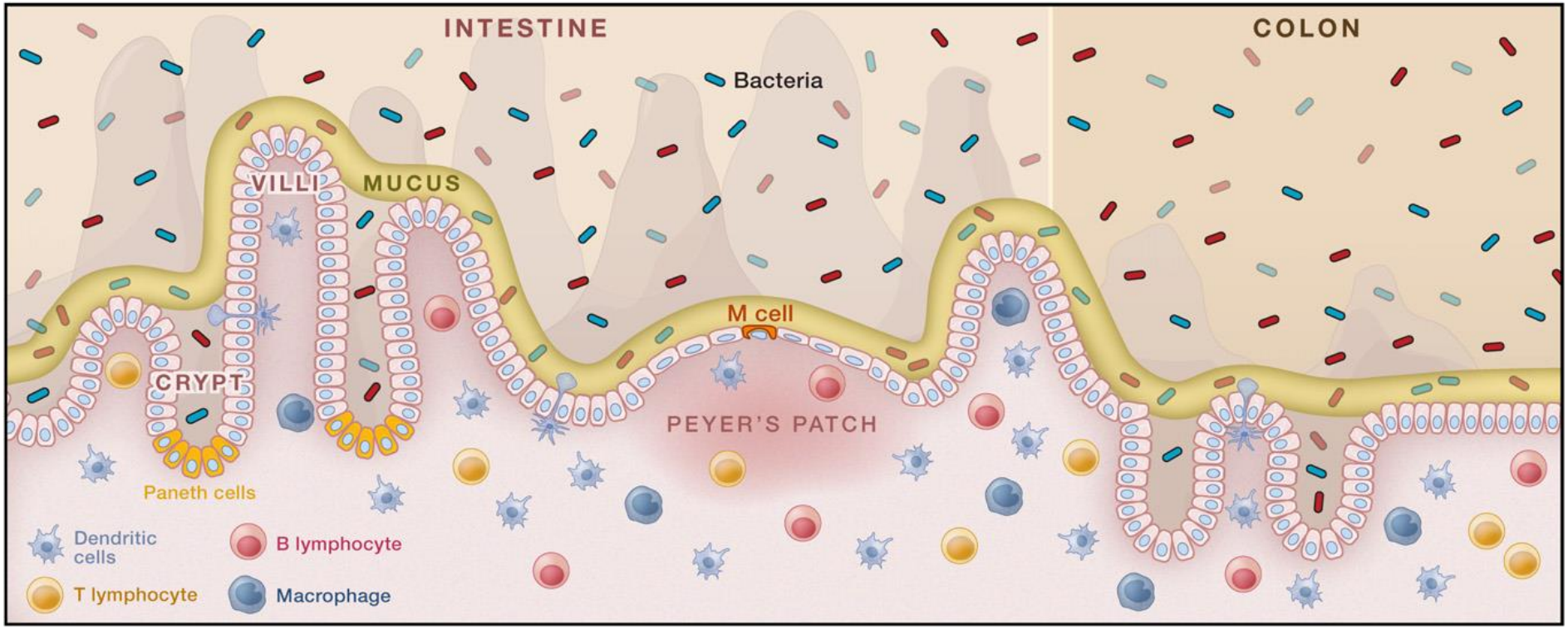
Modern lifestyle
- sanitation
- hygiene
- urbanization
- birth delivery
- drug exposure (antibiotic)
- **diet**

Preidis GA, Gastro 2009

Homeostasis and Inflammation in the Intestine

Cell

Microbiota is an **healthy asset** (and may become a **risk factor** for disease).



Garrett WS, Cell 2010

Homeostasis and Inflammation in the Intestine

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The human genome does not contain enough information for full mucosal and extraintestinal development.

Garrett WS, Cell 2010

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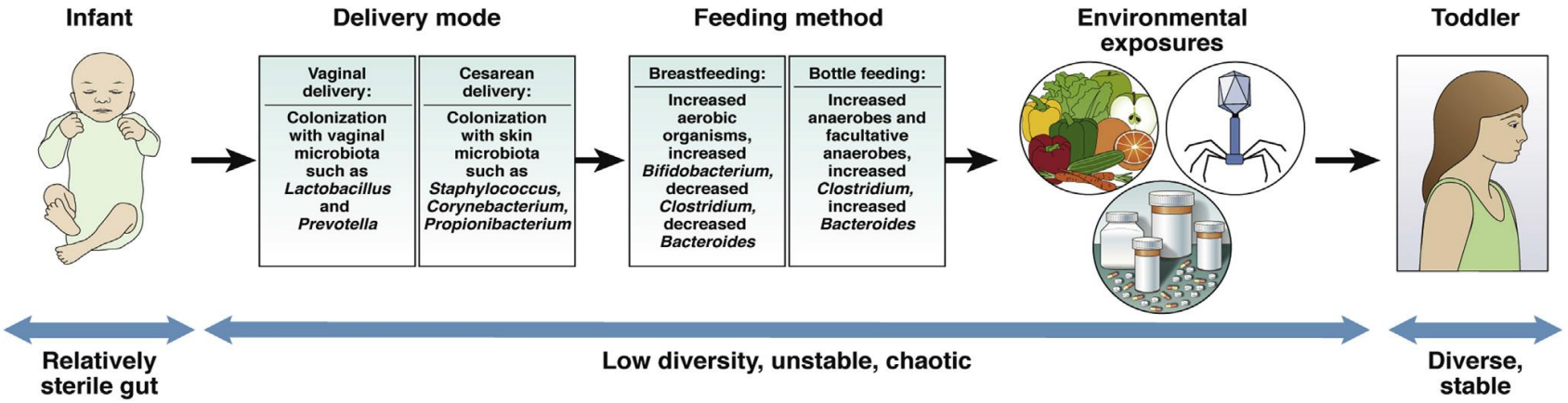

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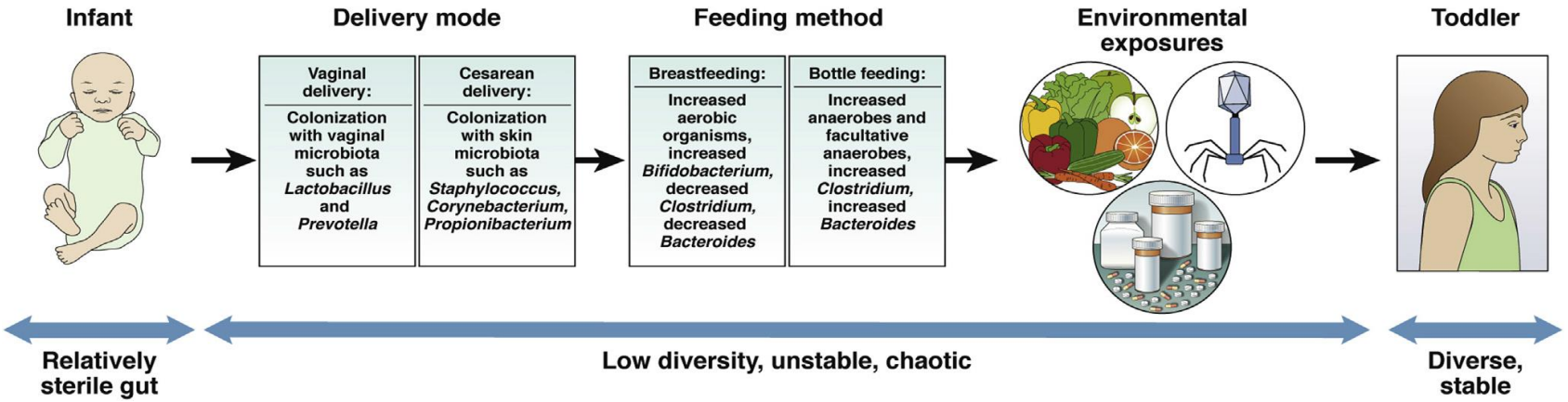


The colonizing **microbiota provides:**

- **Trophic signals** for immune and digestive systems
- **Vitamins and nutrients** for metabolic activity
- **Protective role** against pathogens
- **Immuno-modulations**

Garrett WS, Cell 2010

Agenda

Background

Definizione di malattie funzionali gastroenterologiche

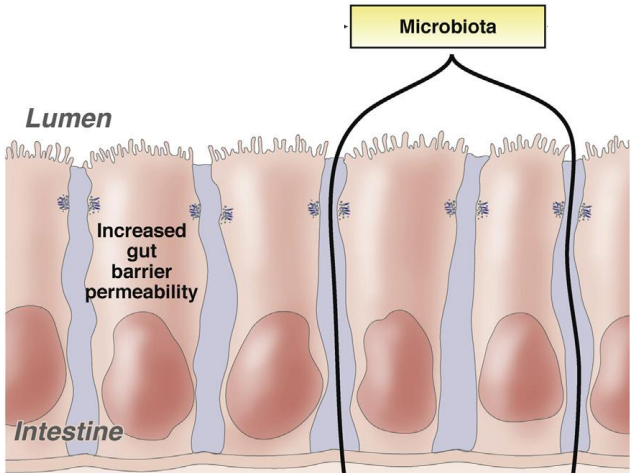
Patogenesi (microbiota, micro-infiammazione, asse intestino-cervello)

Eziopatogenesi del sintomo

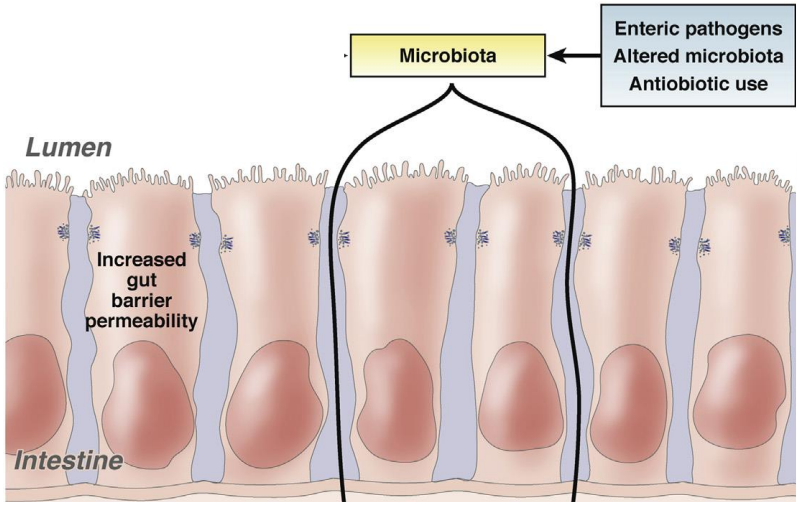
Presentazione clinica

Approccio terapeutico

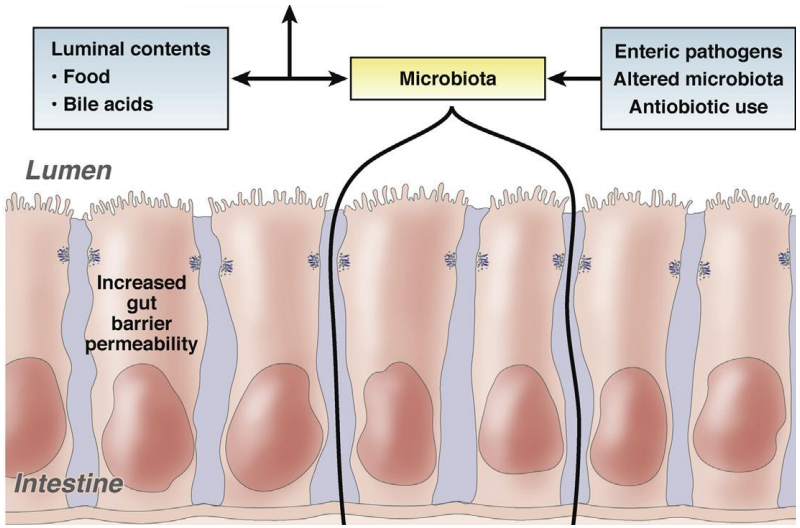
Pathogenesis



Pathogenesis



Pathogenesis



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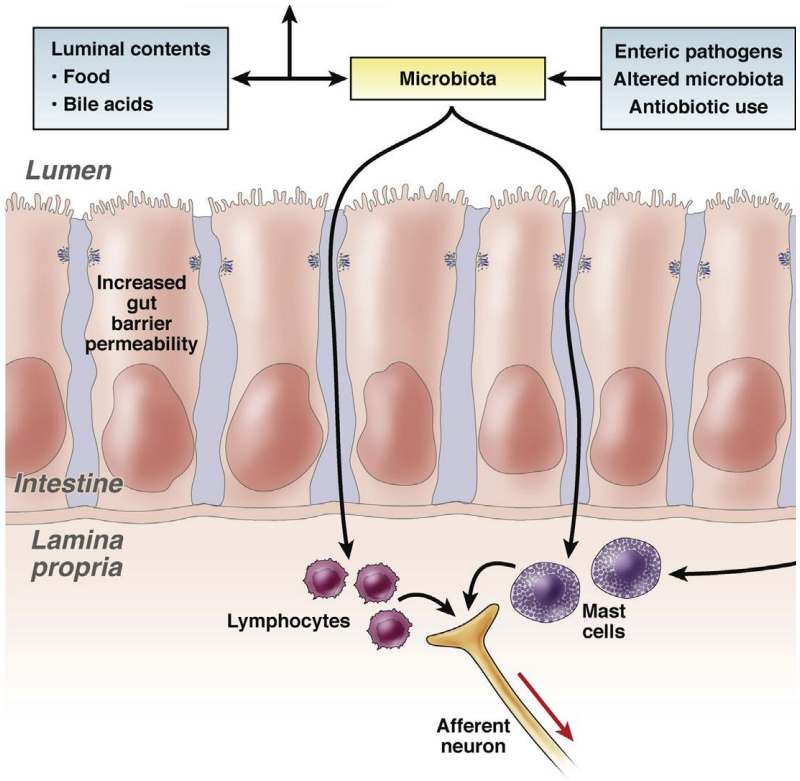

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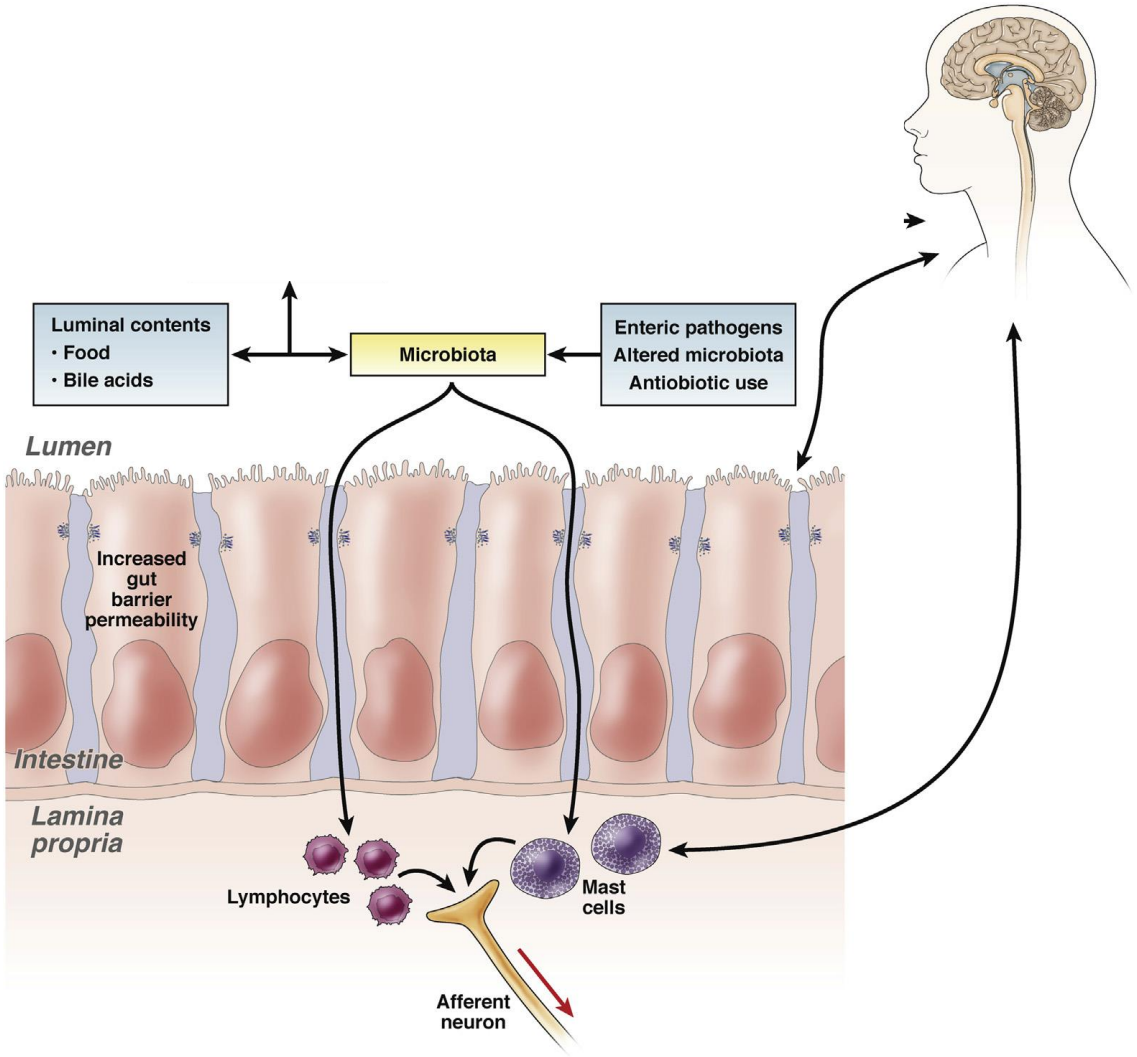

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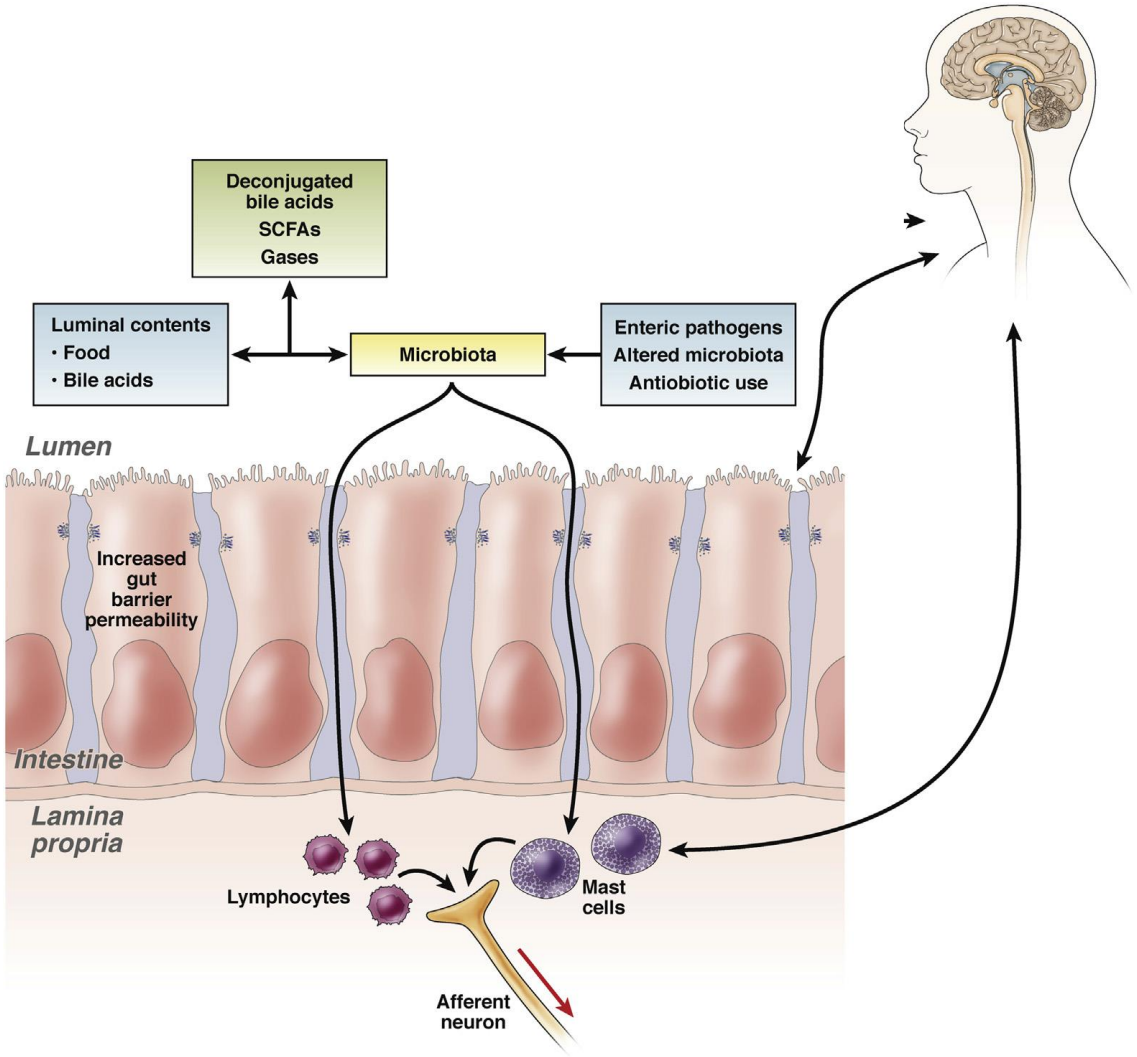

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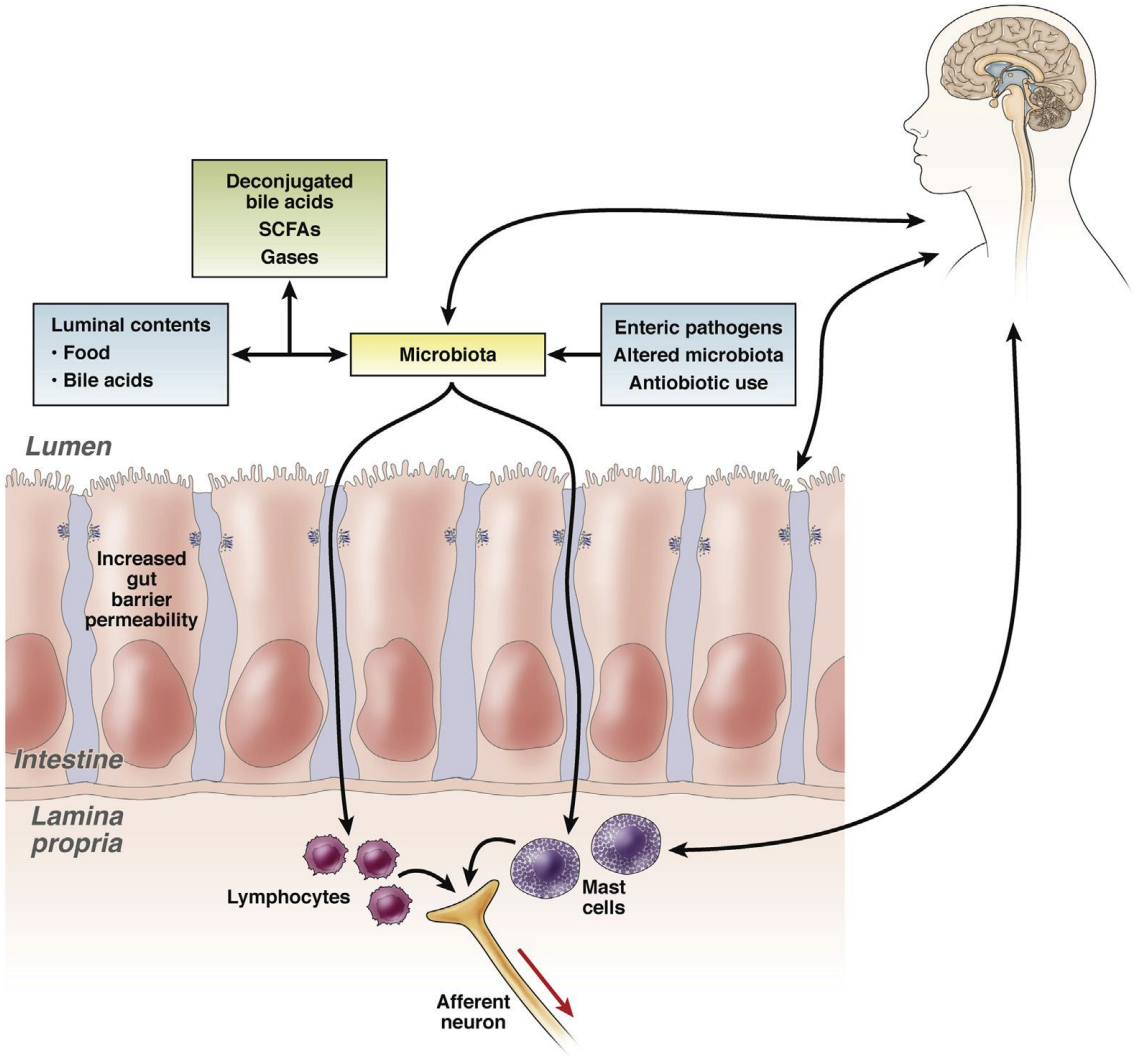

Take home messages - 1

- criteri diagnostici basati su **sintomi cronici e/o ricorrenti**, in assenza di condizioni patologiche organiche identificate.

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- **interazione bi-direzionale** tra sistema nervoso e gastrointestinale: **percezioni centrali** (dolore, fastidio, gonfiore) e le **funzioni gastrointestinali** (motilità, funz.immunitaria).

Take home messages - 1

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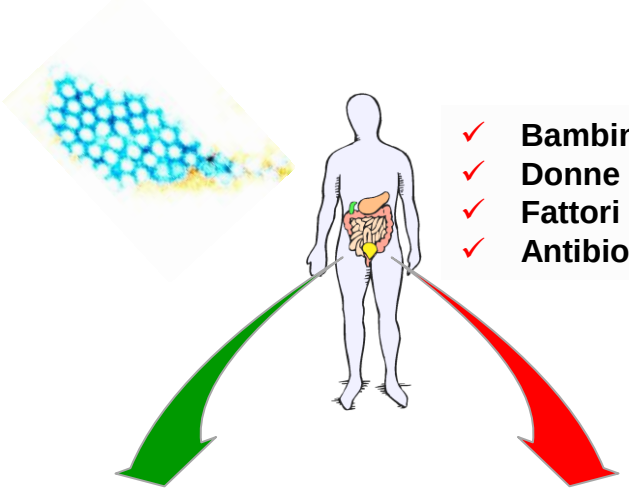
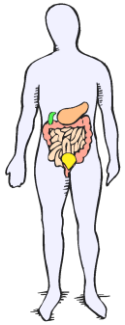
- **disbiosi** contribuisce alla patogenesi dell'IBS: alterazione della sensibilità neuro-motoria intestinale, la funzione di barriera ed alterando l'asse cervello-intestino.

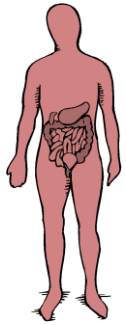
Gastroenterite



- ✓ Bambini
- ✓ Donne
- ✓ Fattori psicologici
- ✓ Antibiotici

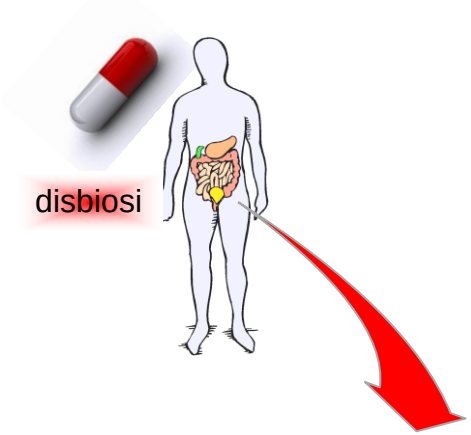


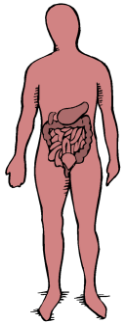
90%
guarigione



10%
IBS

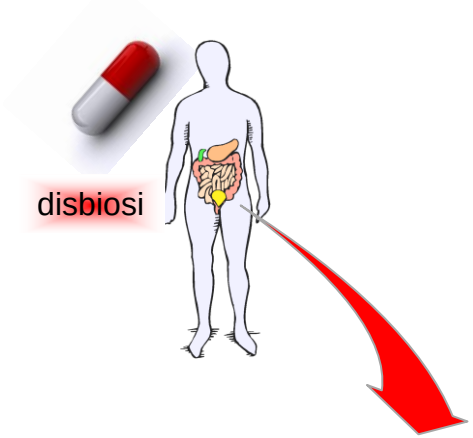
Antibiotici Sistemici

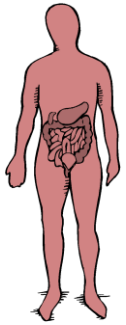




IBS

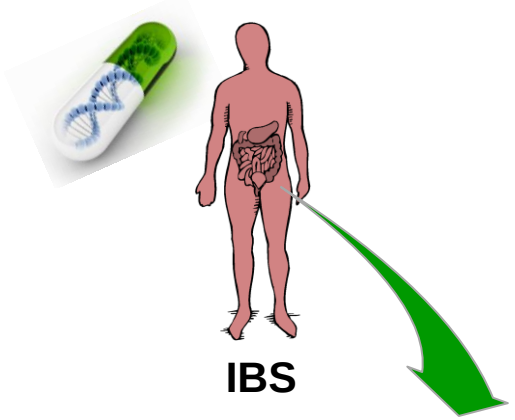
Antibiotici Sistemici



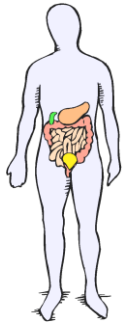


IBS

Probiotici Antibiotics N/A

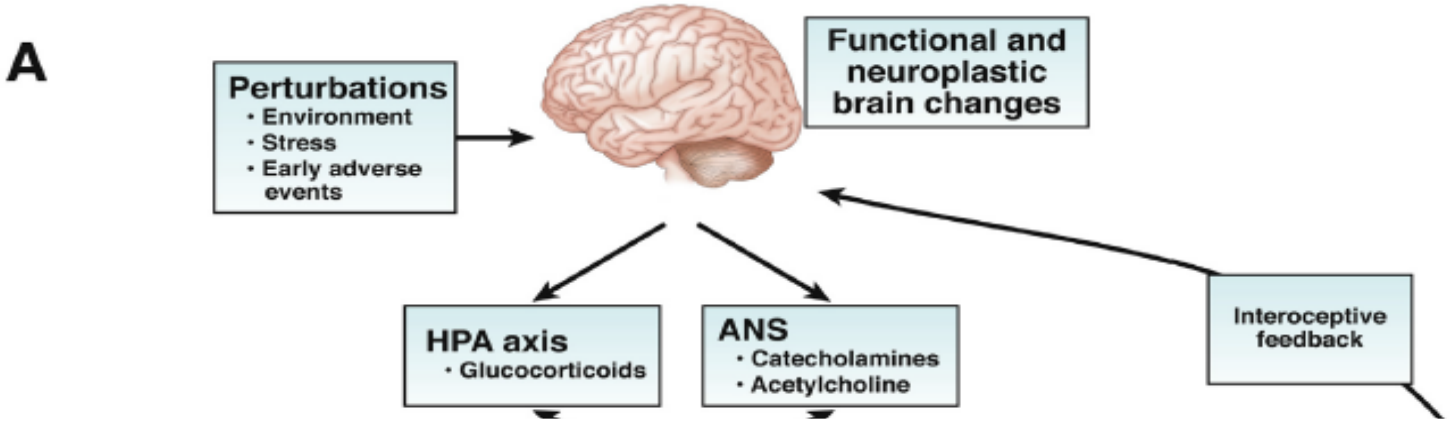


IBS

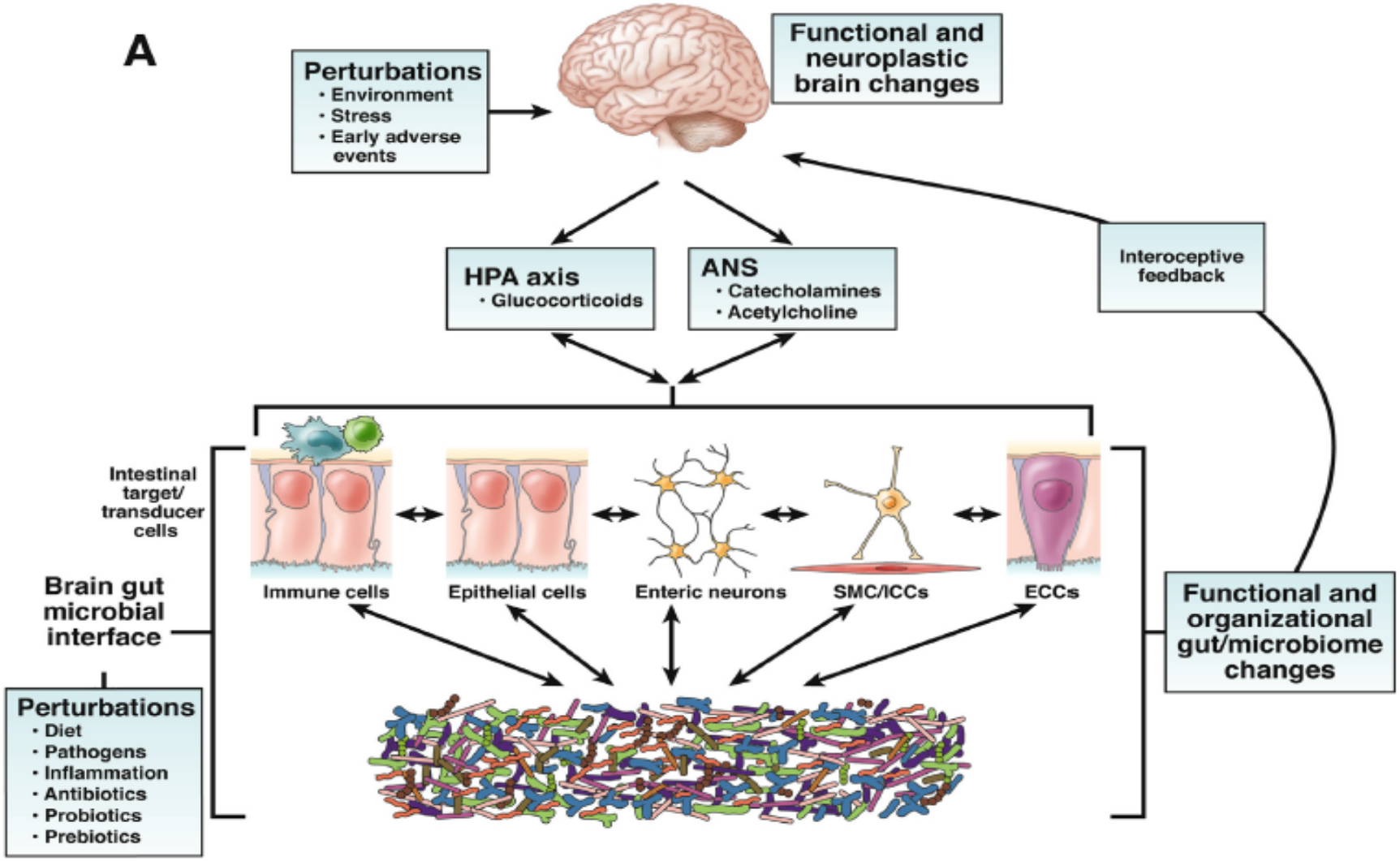


Miglioramento Sintomatologico

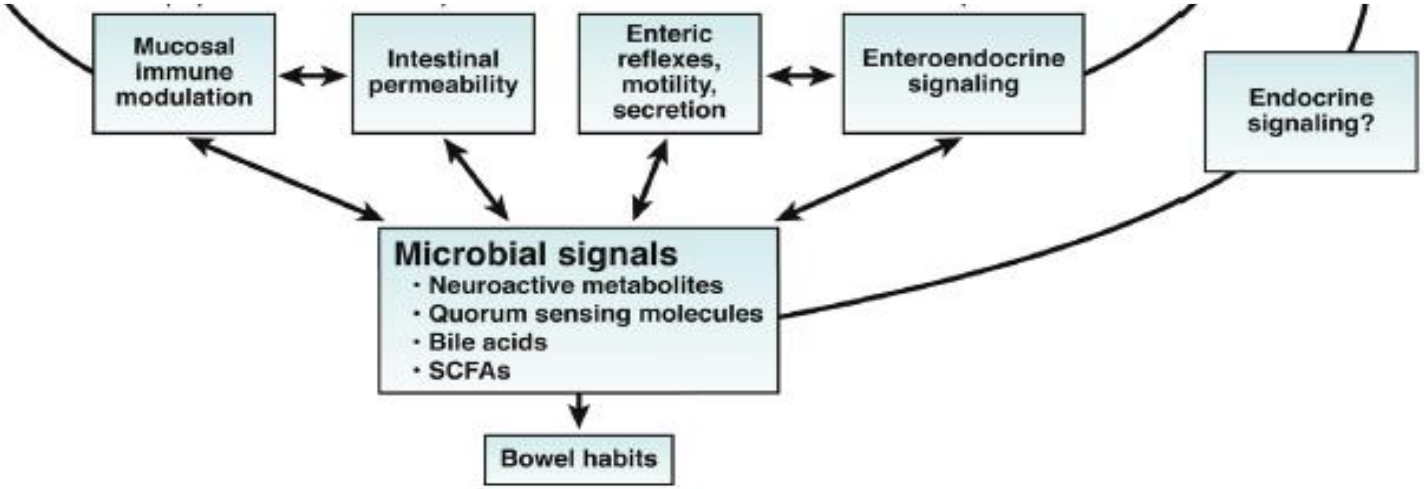
Brain-gut interaction



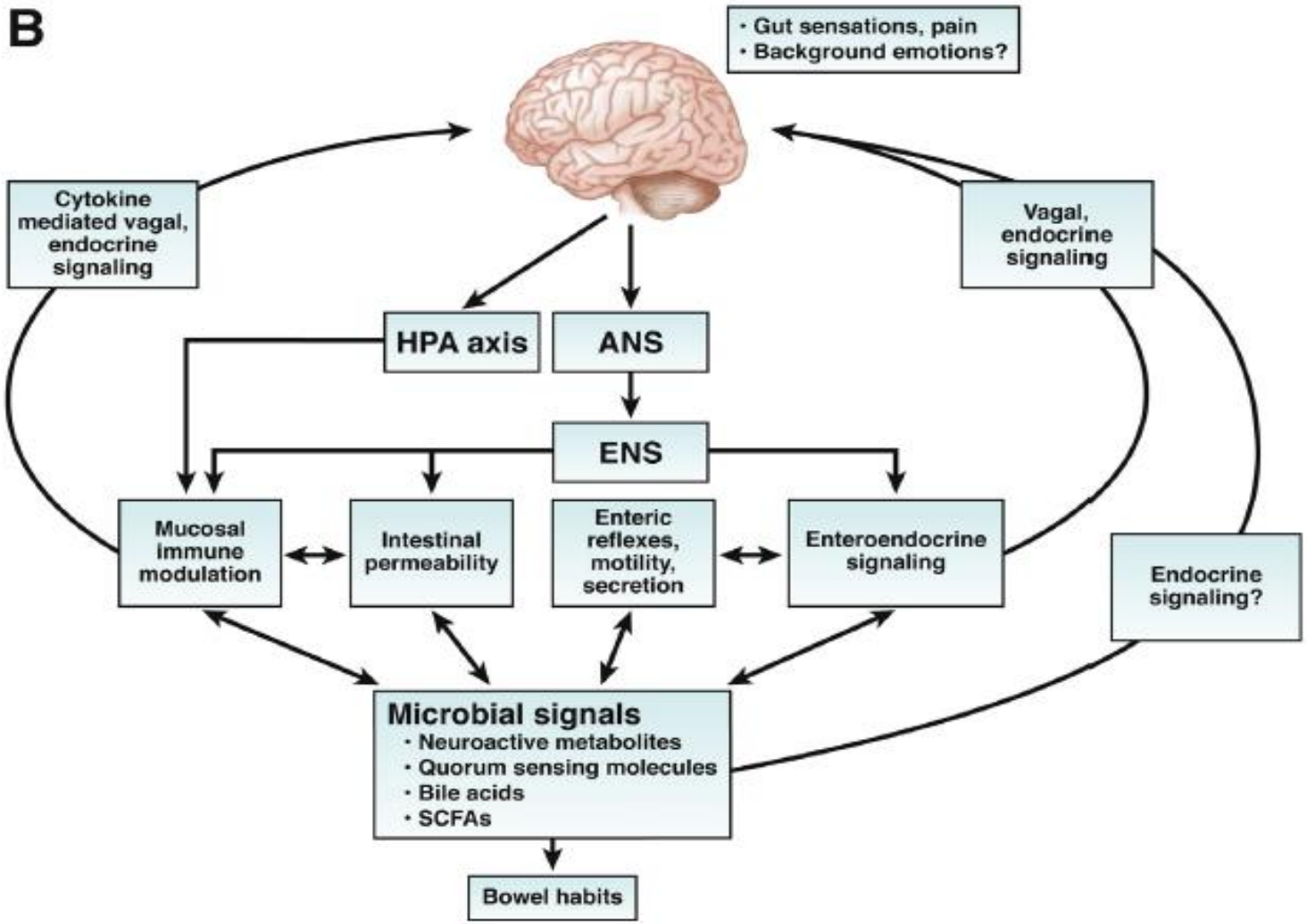
Brain-gut interaction



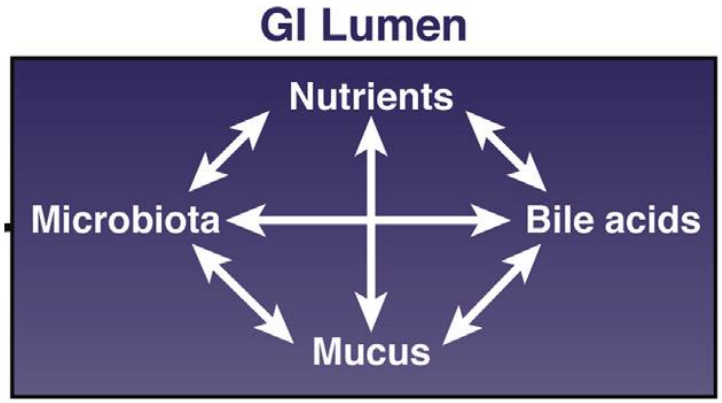
Brain-gut interaction



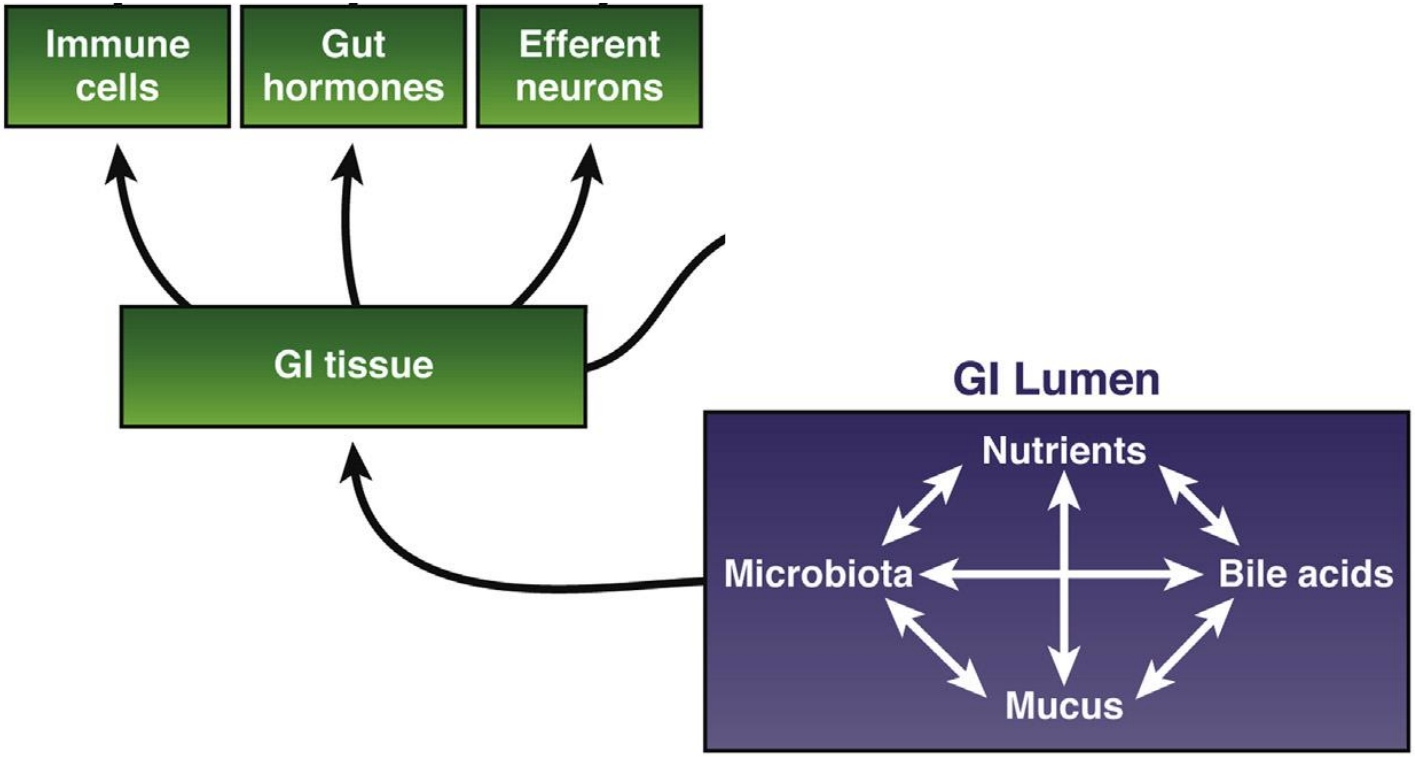
Brain-gut interaction



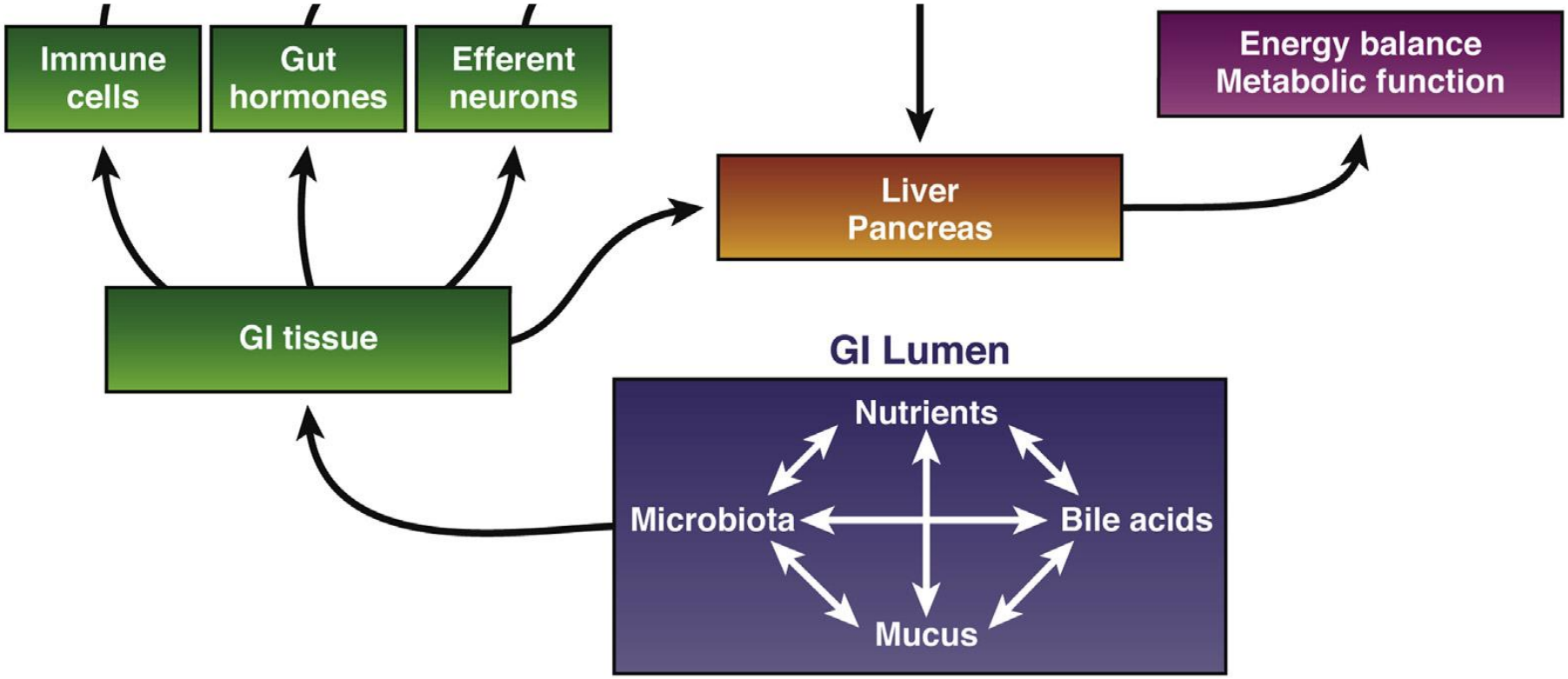
Brain-gut interaction



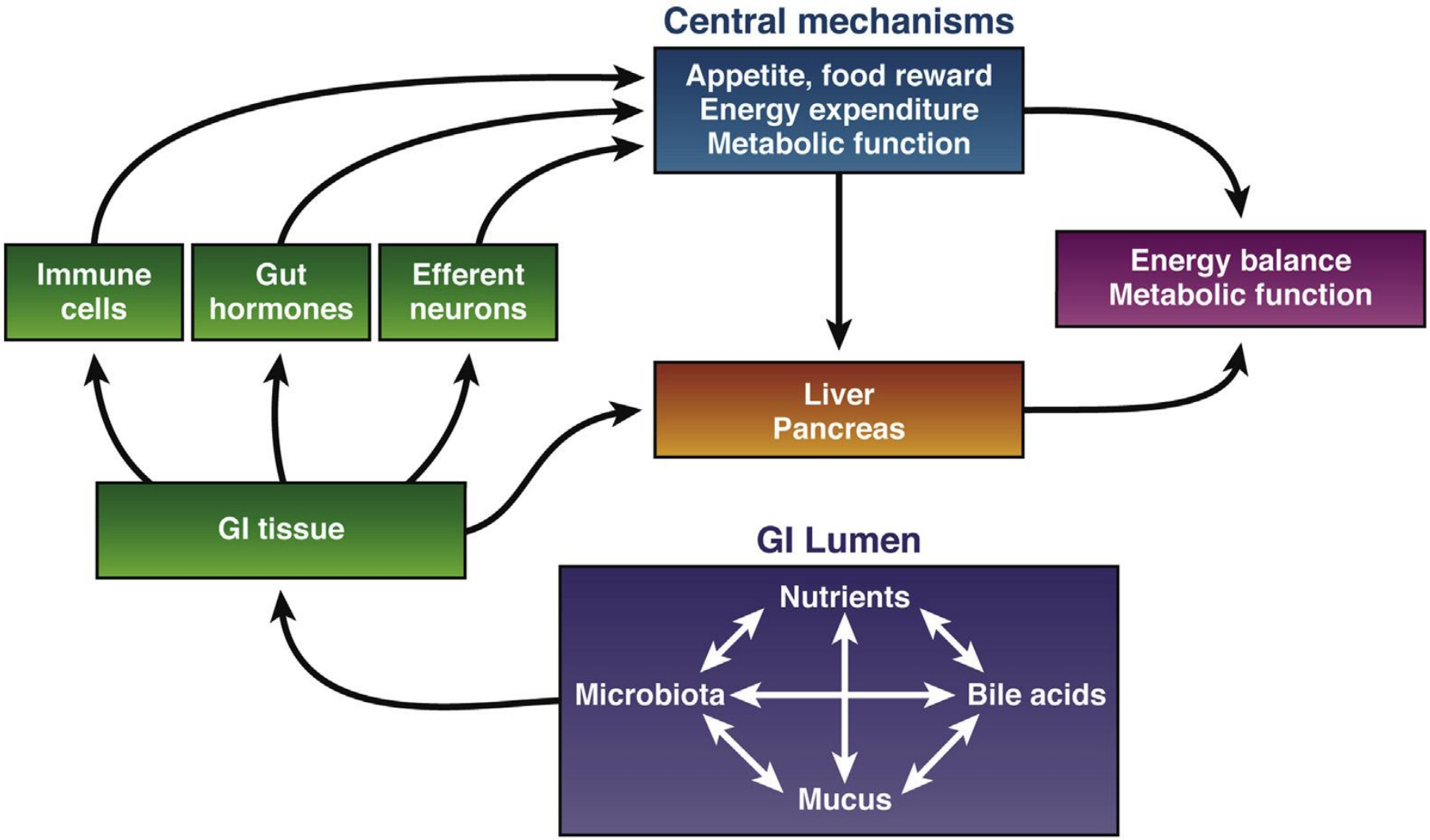
Brain-gut interaction



Brain-gut interaction

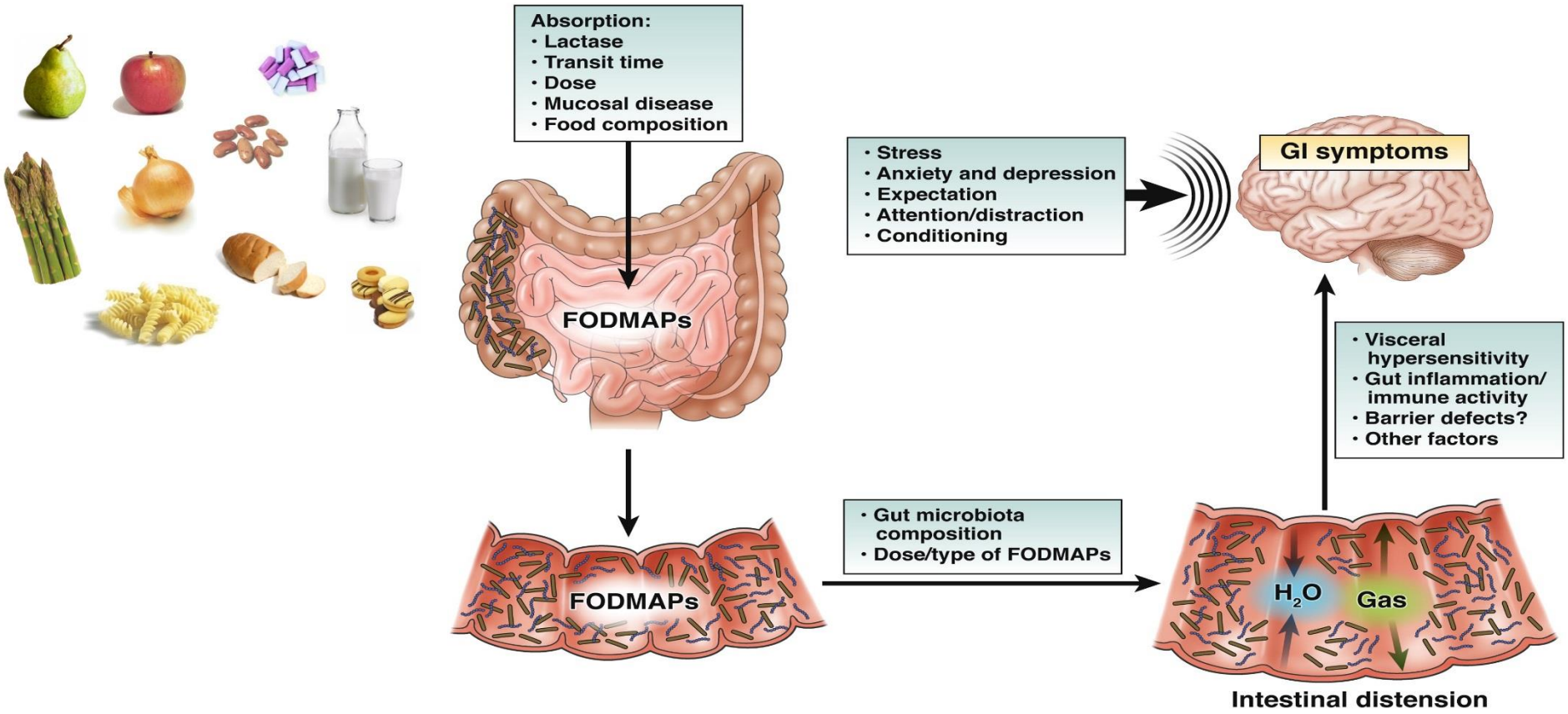


Brain-gut interaction

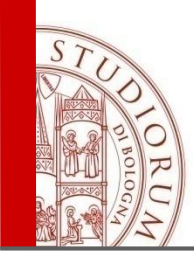


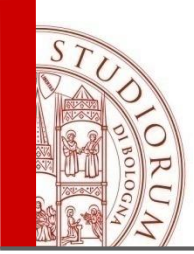
FODMAPS Microbiota e IBS

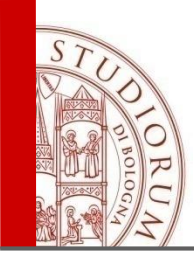
Fermentable oligo-, di-, mono-saccharides and polyols (short chain carbohydrates)



Simren M. Gastroenterology

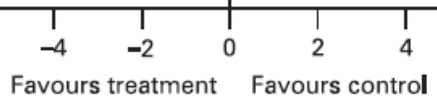






Probiotic bacteria and IBS

Study or subcategory	N	Treatment Mean (SD)	N	Control Mean (SD)	SMD (random) 95% CI	Weight %	SMD (random) 95% CI
01 *Lactobacillus*							
Niv 05	21	270.00 (139.00)	18	230.00 (139.00)		5.93	0.28 (−0.35 to 0.91)
Nobaek 00	25	3.90 (1.00)	27	4.26 (1.67)		6.51	−0.26 (−0.80 to 0.29)
O' Mahoney 05	26	5.25 (2.80)	25	5.68 (2.80)		6.48	−0.15 (−0.70 to 0.40)
Simren 06	29	279.00 (129.00)	29	245.00 (118.00)		6.70	0.27 (−0.25 to 0.79)
Subtotal (95% CI)	101		99			25.63	0.03 (−0.25 to 0.31)
Test for heterogeneity: $\chi^2 = 2.91$, df = 3 ($p = 0.41$), $I^2 = 0\%$							
Test for overall effect: $Z = 0.20$ ($p = 0.84$)							
02 combination							
Drouault-Holowacz 08	48	2.71 (2.16)	52	3.34 (2.24)		7.52	−0.28 (−0.68 to 0.11)
Guyonnet 07	135	5.07 (1.14)	132	5.22 (1.26)		8.43	−0.12 (−0.36 to 0.12)
Kajander 05	41	20.40 (13.88)	40	26.80 (13.88)		7.21	−0.46 (−0.90 to −0.02)
Kajander 08	43	24.00 (16.73)	43	30.00 (18.01)		7.32	−0.34 (−0.77 to 0.08)
Kim 03	11	101.80 (79.72)	10	99.72 (86.81)		4.61	0.02 (−0.83 to 0.88)
Kim 05	24	102.40 (47.03)	24	125.30 (52.79)		6.32	−0.45 (−1.02 to 0.12)
Kim 06	17	1.60 (1.60)	17	1.80 (2.10)		5.68	−0.10 (−0.78 to 0.57)
Simren 07	33	206.00 (113.00)	34	228.00 (125.00)		6.95	−0.18 (−0.66 to 0.30)
Tsuchiya 04	34	1.50 (0.50)	34	2.90 (0.50)		5.66	−2.77 (−3.44 to −2.09)
Subtotal (95% CI)	386		386			59.71	−0.50 (−0.91 to −0.09)
Test for heterogeneity: $\chi^2 = 54.84$, df = 8 ($p < 0.00001$), $I^2 = 85.4\%$							
Test for overall effect: $Z = 2.40$ ($p = 0.02$)							
03 *Bifidobacterium*							
O' Mahoney 05	24	3.70 (2.88)	25	5.68 (2.80)		6.30	−0.69 (−1.26 to −0.11)
Whorwell 06	250	2.01 (0.82)	80	2.09 (0.89)		8.37	−0.10 (−0.35 to 0.16)
Subtotal (95% CI)	274		105			14.66	−0.33 (−0.90 to 0.24)
Test for heterogeneity: $\chi^2 = 3.38$, df = 1 ($p = 0.07$), $I^2 = 70.4\%$							
Test for overall effect: $Z = 1.14$ ($p = 0.25$)							
Total (95% CI)	761		590			100.00	−0.34 (−0.60 to −0.07)
Test for heterogeneity: $\chi^2 = 67.04$, df = 14 ($p < 0.00001$), $I^2 = 79.1\%$							
Test for overall effect: $Z = 2.51$ ($p = 0.01$)							



Moayedi P, Gut 2010

Probiotic bacteria and IBS

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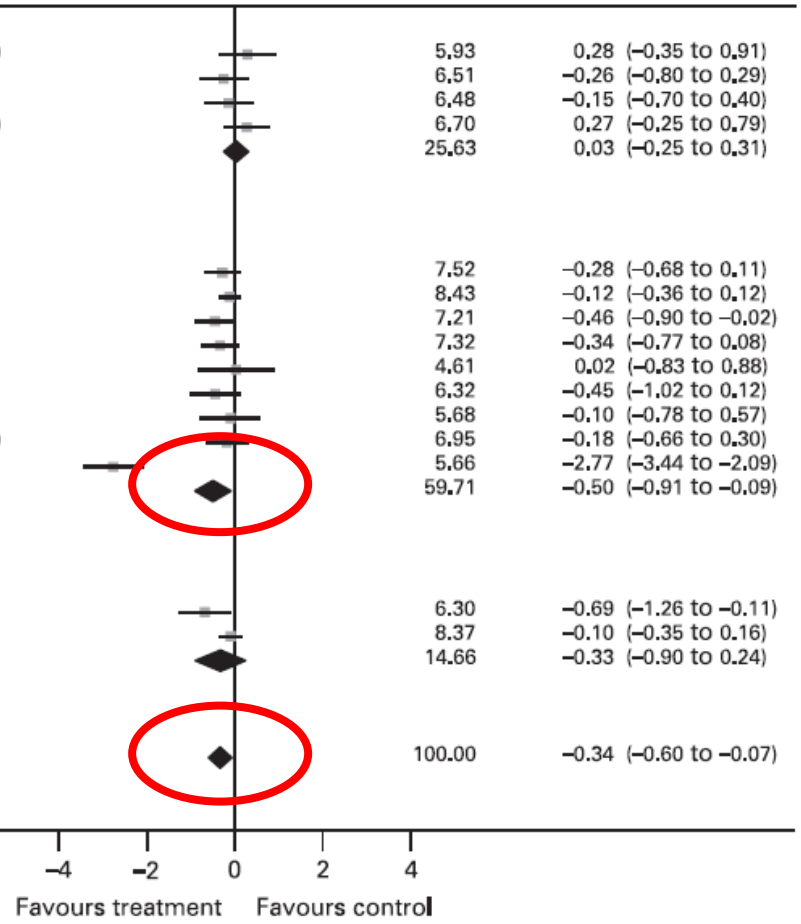

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