In the Name of God

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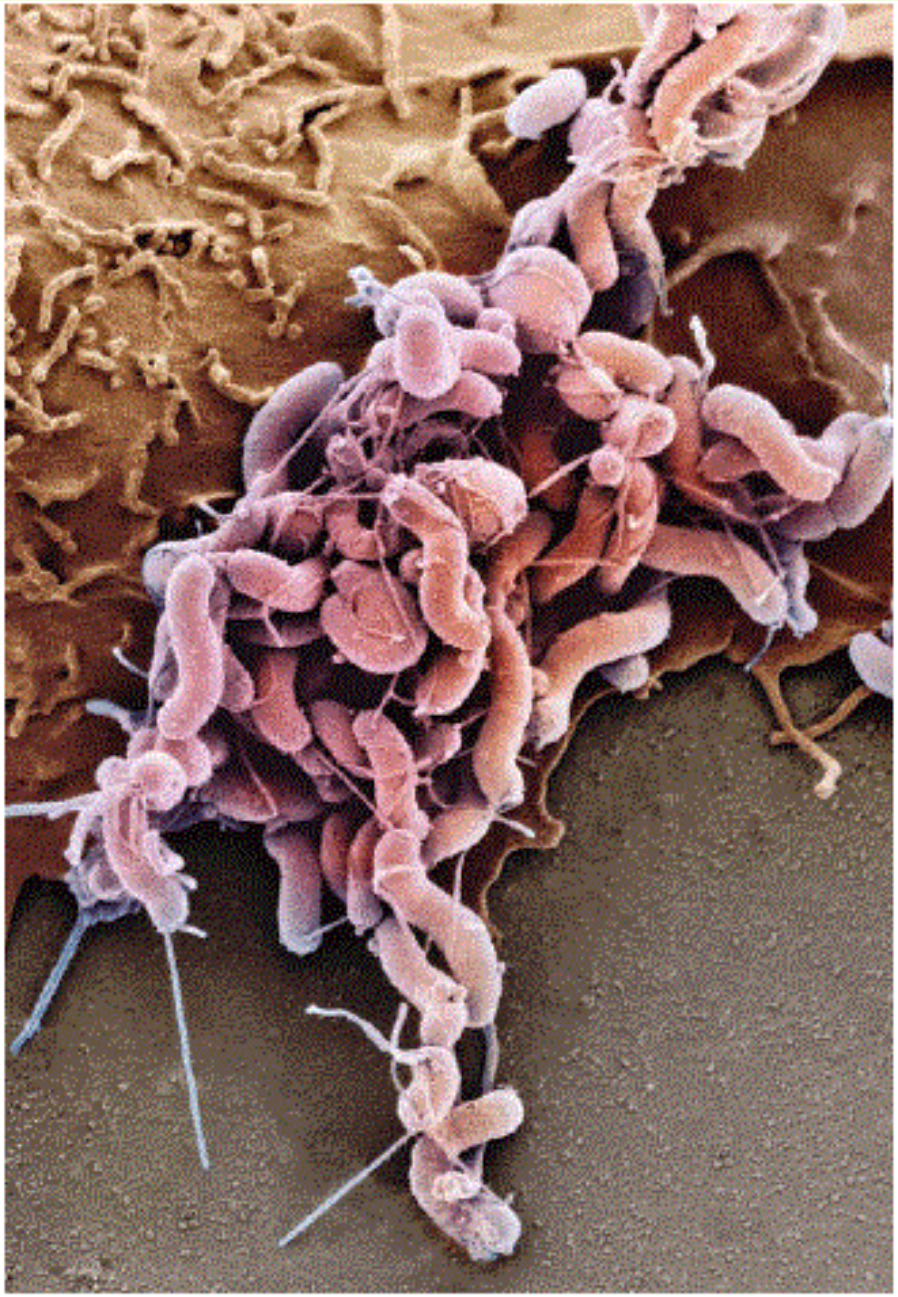
Probiotics & Abdominal Pain



Probiotics

Definition:

Live non pathogenic microorganisms, when consumed in appropriate amounts, cause benefits in the host.

Stay in GI tract for longer time after use.

All probiotics are not the same

- Different kinds of Probiotics have different kinds of effects.
- Never talk about Probiotics generally.
- Always mention the type or strain of probiotics in order to stay scientific

Introduction

- Perturbation of bacterial microflora of the gastrointestinal (GI) tract may play an important role in the pathophysiology of some GI disorders.
- Probiotics have been used as a treatment modality for over a century.
- They may restore normal bacterial microflora and effect the functioning of the GI tract by a variety of mechanisms.

Probiotics, different species

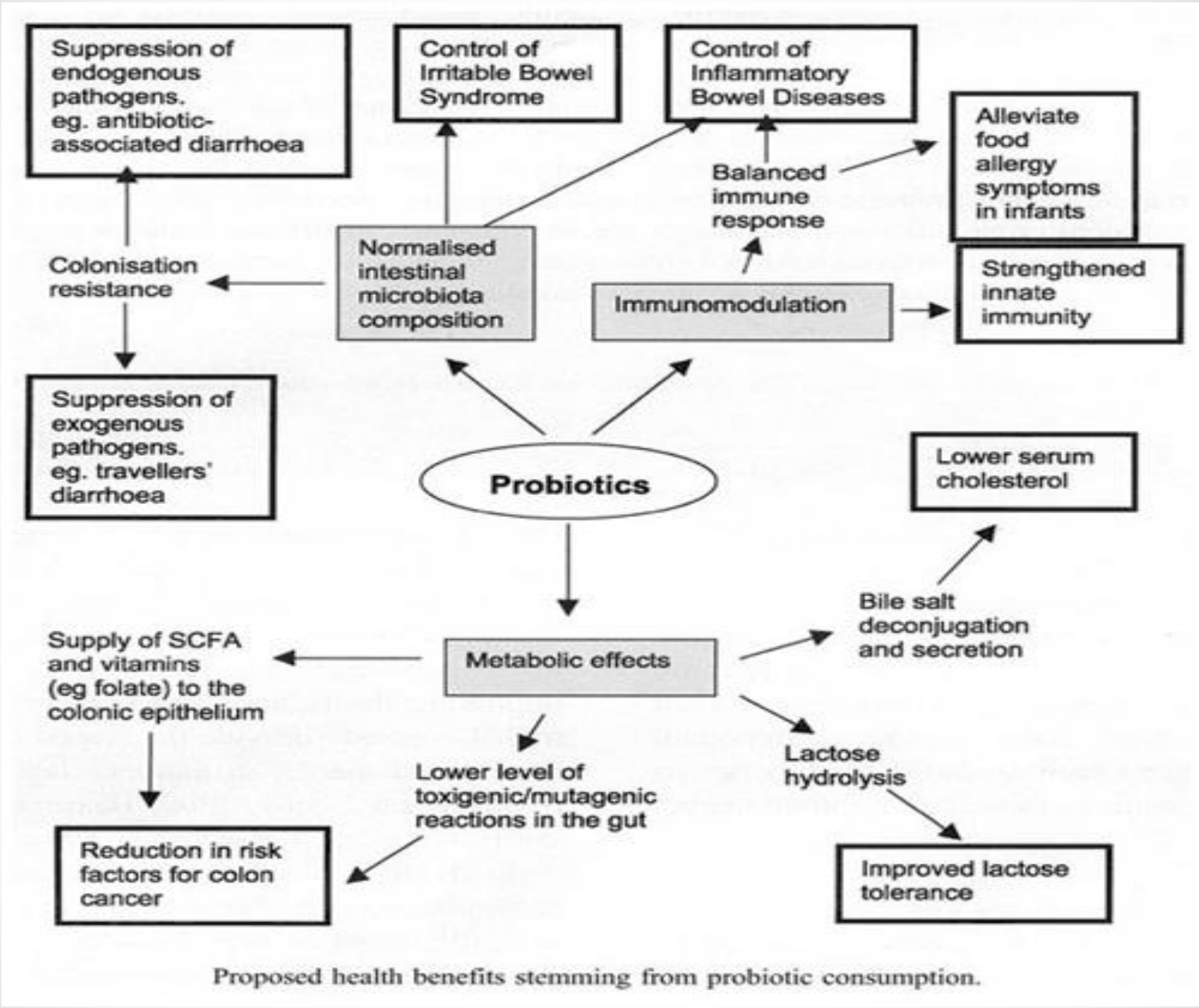
1. Lactobacilli (LGG, L. casei, L. reuteri)
2. Bifidobacteria (B. lactis, B. bifidum, B. langum)
3. Streptococcus (S. thermophilus)
4. Saccharomyces (S. boulardii)
5. E.coli (nissle)

Some biologic characteristics:

- Fermentative
- Obligatory or facultative anaerobic organisms
- Typically non-motile
- Typically lactic acid producer

Clinical Use

- Constipation
- IBS
- Acute diarrhea
- Eczema
- Infantile colic
- Antibiotic-associated diarrhea
- Ulcerative colitis
- Pouchitis
- NEC
- …

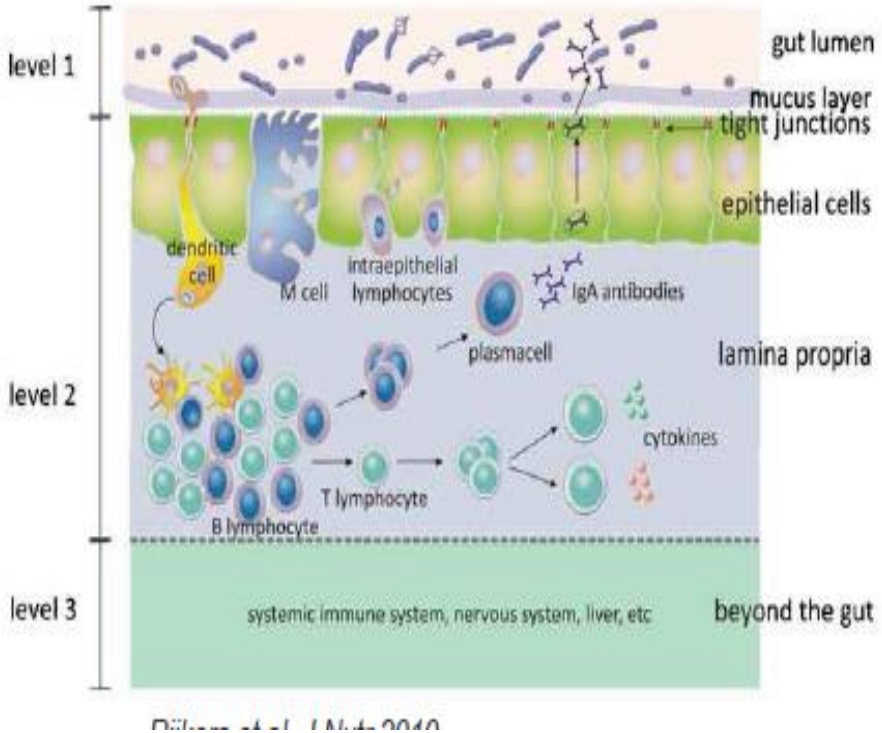


Proposed health benefits stemming from probiotic consumption.

Mechanisms of Action

- Luminal Effects
- Epithelial Effects
- Immune Effects

Mechanisms of Action

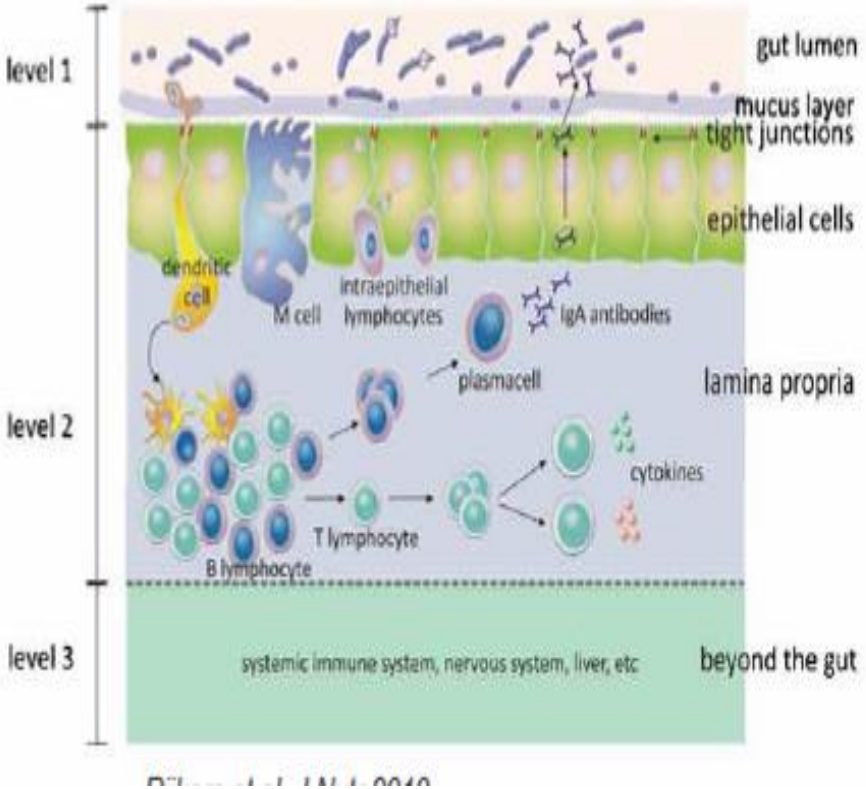


← Luminal Effects

- Competition with pathogens (for substrates, receptors)
- Antimicrobial activity
  - H_2O_2
  - Bacteriocins
  - Organic acids, low pH

Rijkers et al, J Nutr 2010

Mechanisms of Action



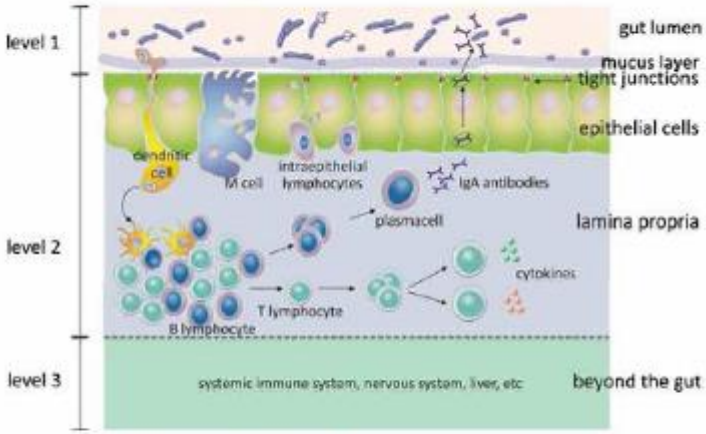
← Epithelial Effects

- ↑ Barrier function
- ↑ Mucin secretion
- ↑ IgA secretion
- ↓ Toxin recptors

Rijkers et al, J Nutr 2010

Mechanisms of Action

Actions of gut bacteria / probiotics



Rijkers et al, J Nutr 2010

← Immune Effects

- Modulation of cytokines
- Stimulated innate immunity
- Dendritic cell and monocyte function
- ↑ Expression of Foxp3 & Treg cells

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Clinical Use

- functional abdominal pain disorders
- IBS
- functional constipation

FAPD(functional abdominal pain disorders)

Functional abdominal pain	▪ Episodic or continuous abdominal pain ▪ Insufficient criteria for other functional gastrointestinal disorders
Functional abdominal pain syndrome	▪ Functional abdominal pain for at least 25% of the time and one or more of the following: 1. Some loss of daily functioning 2. Additional somatic symptoms such as headache, limb pain, or difficulty sleeping
Functional dyspepsia	▪ Persistent or recurrent pain or discomfort centred in the upper abdomen ▪ Not relieved by defecation or associated with a change in stool frequency or form
Irritable bowel syndrome	▪ Abdominal discomfort or pain associated with two or more of the following at least 25% of the time: 1. Improved with defecation 2. Onset associated with a change in frequency of stool 3. Onset associated with a change in form of stool

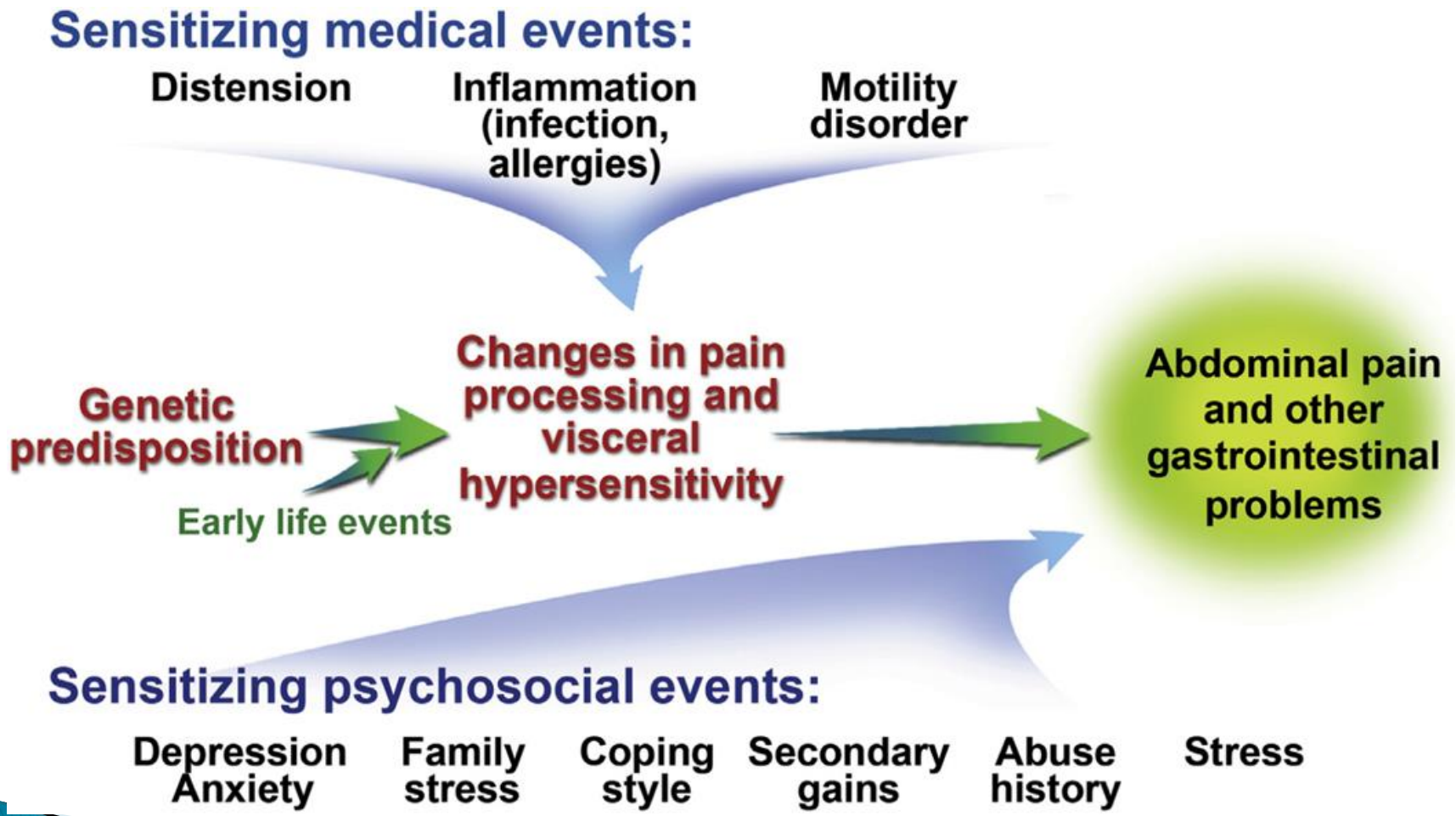
Alarm Findings in Children with Recurrent Abdominal Pain

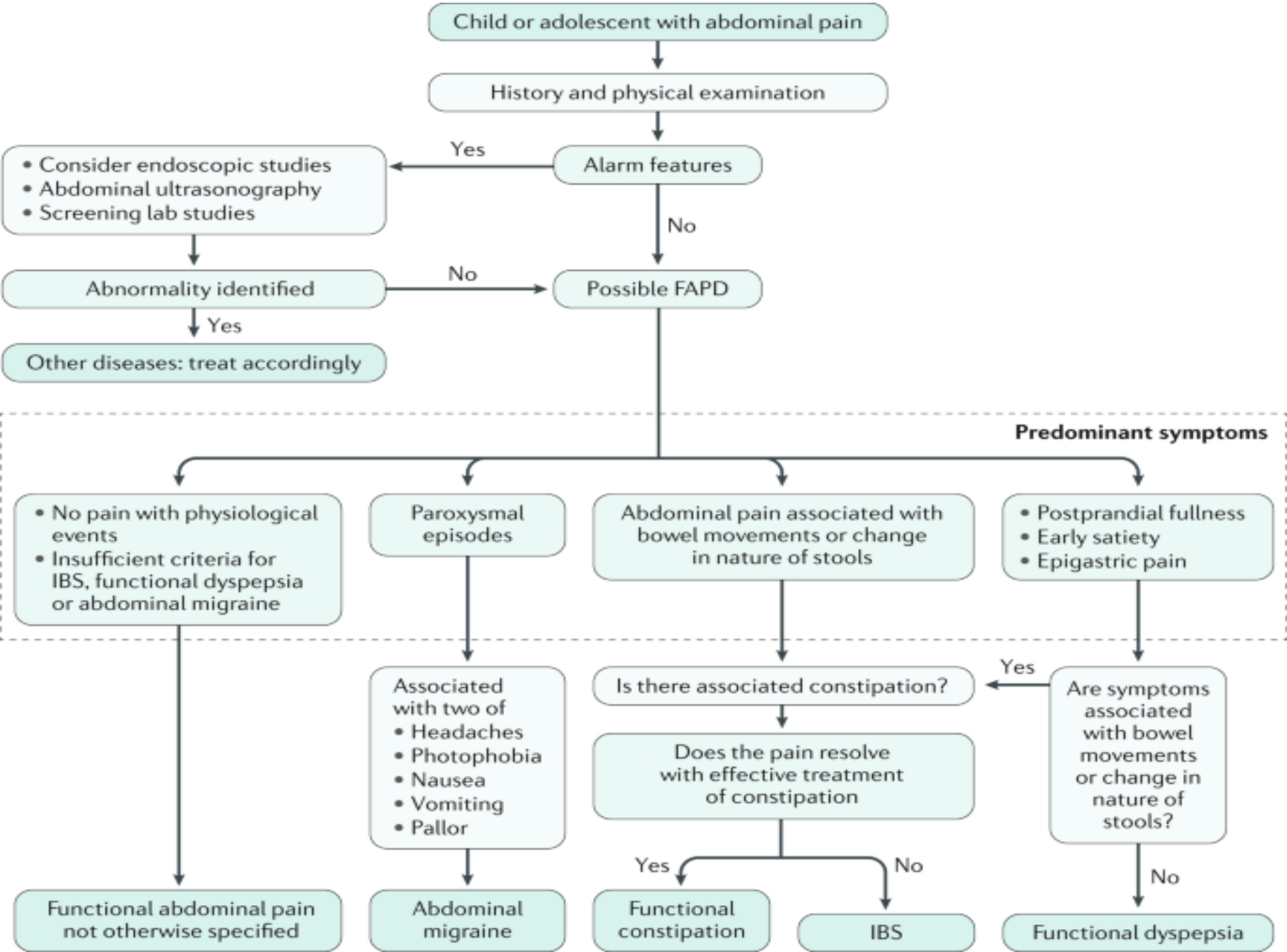
- Chronic, severe, or nocturnal diarrhea
- Deceleration of linear growth
- Delayed puberty
- Dysphagia
- Family history of inflammatory bowel, celiac, or peptic ulcer disease
- Gastrointestinal blood loss
- Genitourinary tract symptoms
- Involuntary weight loss
- Pain that wakes the child from sleep
- Persistent right upper or lower quadrant pain
- Significant vomiting
- Unexplained fever

FAPD(functional abdominal pain disorders)

- Medical interventions may be combined with general behavioral management strategies in children FAPDs.
- Medical approaches
- Probiotics, supplementation with fiber, or peppermint oil.

Mechanism


Sensitizing medical events:
Distension
Inflammation (infection, allergies)
Motility disorder
Genetic predisposition
Early life events
Changes in pain processing and visceral hypersensitivity
Abdominal pain and other gastrointestinal problems
Sensitizing psychosocial events:
Depression Anxiety
Family stress
Coping style
Secondary gains
Abuse history
Stress


Child or adolescent with abdominal pain
History and physical examination
Alarm features
Yes
• Consider endoscopic studies
• Abdominal ultrasonography
• Screening lab studies
No
Abnormality identified
No
Possible FAPD
Yes
Other diseases: treat accordingly
Predominant symptoms
• No pain with physiological events
• Insufficient criteria for IBS, functional dyspepsia or abdominal migraine
Paroxysmal episodes
Abdominal pain associated with bowel movements or change in nature of stools
• Postprandial fullness
• Early satiety
• Epigastric pain
Associated with two of
• Headaches
• Photophobia
• Nausea
• Vomiting
• Pallor
Is there associated constipation?
Yes
Are symptoms associated with bowel movements or change in nature of stools?
Does the pain resolve with effective treatment of constipation
Yes
No
No
Functional abdominal pain not otherwise specified
Abdominal migraine
Functional constipation
IBS
Functional dyspepsia

FGIDs & FAPDs

- Not well established in treatment algorithms.
- low risk of harm and reasonable short-term trials.

- Probiotics in patients with normal bowel movements and probiotics plus fiber in patients with constipation.

- Probiotics combined with general management strategies

Alterations to commensal bacterial populations:

- dysmotility
- visceral hypersensitivity
- abnormal colonic fermentation
- immunologic activation

FGIDs & FAPDs

- Restoring the microbial balance in the gut through metabolic competition with pathogens
- Enhancing the intestine's mucosal barrier
- Altering the intestinal inflammatory response.

- The most effective probiotic strain, dose, or treatment duration is not known .
- Beeing generally safe, the decision to use probiotics is based on the potential benefits, costs, and patient preferences.

FGIDs & FAPDs

- Preparations of strains that have some evidence of benefit in gastrointestinal disease (eg, Lactobacillus rhamnosus, Lactobacillus reuteri).

- Probiotic should be tried for four to six weeks before reassessment of symptoms.

Reviews

- A 2017 systematic review and meta-analysis of seven randomized trials in England compared probiotics with placebo in 722 children with functional gastrointestinal disorders (FGIDs).
- The study found moderate quality evidence that probiotics improve pain at zero to three months (absolute rate of improvement 54 versus 42 percent).
- The meta-analysis also found low quality evidence that probiotics reduce pain frequency and pain intensity.

Reviews

- Meta-analysis of four randomized trials comparing probiotics with placebo in 344 children with irritable bowel syndrome (IBS) found moderate quality evidence that probiotics improve pain at zero to three months (absolute rate of improvement 63 versus 36 percent).

Reviews

- Differences in probiotic strains, formulation, and dose make it difficult to generalize about the efficacy of supplementation across available probiotic formulations.

- The duration of treatment ranged from four to eight weeks.

Clinical trials

Number	Type
5	*L. rhamnosus GG*
3	*L. reuteri*
1	*L. plantarum*
1	VSL#3 (a probiotic mixture of eight species)
1	mixture of *Bifidobacterium* species
1	Bacillus coagulans plus fructooligosaccharides (FOS)

IBS

At least 12 weeks, which need not be consecutive, in the preceding 6 months of:

Abdominal pain/discomfort associated with two or more of the following:

- Altered stool frequency
- Altered stool consistency
- Relieved with BM

May also be associated with:

- Bloating, feeling of abdominal distension, passage of mucus, straining
- Incomplete evacuation
- May alternate with diarrhea

IBS

- Irritable bowel syndrome (IBS) is a common disorder affecting millions of people worldwide.
- Mechanisms include alterations in gut motility, small-bowel bacterial overgrowth, microscopic inflammation, visceral hypersensitivity, and changes related to the brain-gut axis.
- Probiotic therapeutic agents may have a role in the management of IBS.

Probiotic for IBS

- Probiotics have a beneficial effect on intestinal mucosa via several proposed mechanisms:
- Suppression of the growth and binding of pathogenic bacteria
- Improvement of the barrier function of the epithelium
- Alteration of the immune activity of the host.

Probiotic for IBS

- Probiotics secrete short chain fatty acids, that results in decreased luminal pH and production of bactericidal proteins.
- Butyric acid, has been shown to nourish colonic enterocytes, enhancing mucosal integrity.
- The DNA of probiotic organisms may inhibit apoptosis of epithelial cells.
- In addition, probiotics may improve bowel dysmotility.

Clinical Studies

Clinical Studies

- Kim and colleagues performed double-blind, placebo-controlled trial.
- A combination of probiotics that contains live bacteria including *Bifidobacterium*; *Lactobacillus* and *Streptococcus salivarius.*
- Probiotic, as compared to placebo, led to a reduction in flatulence and a delay in colonic transit.

Clinical Studies

- Another probiotic combination (*L. acidophilus, Lactobacillus helveticus,* and *Bifidobacterium sp.*), was evaluated by Tsuchiya and coworkers.

- There was an improvement in overall efficacy in 80% of patients at 12 weeks, as well as improvement in bloating, abdominal pain, and bowel habits throughout the 12-week period.

Clinical Studies

- A study by Guyonnet and colleagues assessed 274 constipation-predominant IBS patients and randomized them to placebo or fermented milk yogurt .

- In the treatment group, bloating symptoms improved, and there was an increase in stool frequency in patients with fewer than 3 stools per week.

Clinical Studies

- Brenner and coworkers conducted a meta-analysis in 2009 that included 16 randomized controlled trials evaluating the efficacy, safety, and tolerability of probiotics in IBS patients.

- *Bifidobacterium.infantis* showed significant benefit in the symptom score and symptom relief of IBS patients.
- The available data are inadequate and further well-designed trials are still needed.

Important points:

- The most effective probiotic strain, dose, and duration of therapy.

- Cost-effectiveness analysis and safety profiles still need to be addressed in large, well-designed trials.

Probiotics for IBS

- IBS-D (D for Diarrhea): *Lactobacillus rhamnosus, Saccharomyces boulardii*
- IBS-C (C for Constipation): Lactobacillus reuteri, Bifidobacteria & fibre
- IBS and Bloating :Lactococcus lactis
- IBS-A (A for alternating digestive symptoms)

Functional Constipation

Functional Constipation

- Strong evidences to support the use of single or combination probiotics in children with functional constipation are lacking.

- Multiple small, randomized, placebo-controlled trials of probiotics in patients with chronic constipation without irritable bowel syndrome, suggest effective role.

- Defecation frequency, stool consistency, and intestinal transit time.

Functional Constipation

- Bifidobacterium lactis, Lactobacillus casei, Lactobacillus reuteri.
- Limited heterogeneous studies do not support use of probiotics in children with functional constipation

Functional Constipation

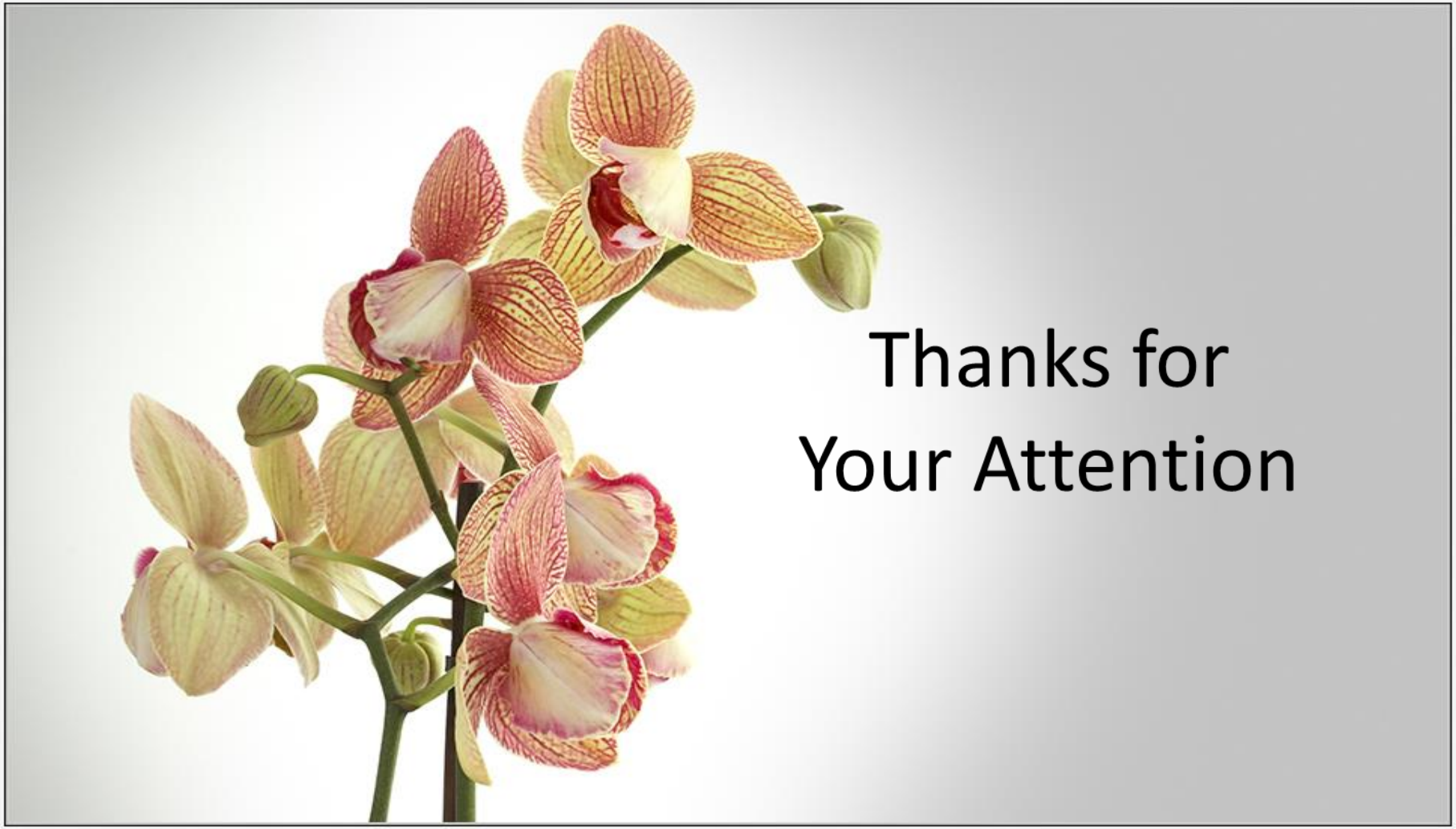
- In a systematic review from China, 6 studies were involved.
- This study shows that probiotics increase stool frequency and have beneficial effects in Asian children.
- Caution is needed when interpreting these outcomes because of the existence of heterogeneity.

Functional Constipation

- Evidence from larger samples and more adequately powered RCTs with results obtained by standardized measurements are necessary.

- Which species and dosage of probiotics and what length of treatment are most efficacious for constipation in children.

- Lactobasillus Reuteri the species most commonly used.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