

İnfeksiyöz İshalde Probiyotiklerin Yeri

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İshal

► İnfeksiyöz ishaller

- <5 yaş...ilk 5 sıradaki ölüm nedenleri arasında
- Erişkinlerde de sık görülmekte

► İshal: Günde ≥ 3 , normale göre daha sulu gaita

- Akut: 1-14 gün
- Persistan: 14-30 gün
- Kronik: >30 gün

Etiyoloji

- ▶ Genellikle infeksiyöz kaynaklı
- ▶ Akut ishal:

- **Virüsler** (en sık): Rotavirüs, Adenovirüs , Norovirüs, Enterovirüs.....
- **Bakteriler**: Salmonella, Shigella, ETEC, Campylobacter, Yersinia...
- **Protozoalar**: Cryptosporidium, Giardia, Cyclospora, *Entamoeba histolytica* ...

İshal, bulantı, kusma

- Semptomların süresi
- Şiddeti (dehidratasyon, ateş, kan, kilo kaybı, bilinç durumu)
- Epidemiyolojik özellikler (seyahat, gıda, ilaç, salgın, immunosupresyon)

Toplumdan kazanılmış veya
Seyahat ishali

Ateş veya
Gaytada kan

Sulu diyare

Kültür veya test et:
Salmonella
Shigella
Campylobacter
STEC (kanlı gayta)
C. difficile (AB ilişkili)
E. histolytica
(epidemiyolojik maruziyet)

Salgın, şiddetli
hastalık
olmadıkça, ileri
tetkik yapmadan
semptomatik
tedavi ver

Nozokomiyal diyare

Kültür veya *C. difficile* testi
(non-infeksiyöz
nedenleri düşün)

Persistan diyare, özellikle
immunosupresif hasta

Kültür veya Test:
Giardia
Cryptosporidium
Cyclospora
Microsporidia
MAC
C. difficile
Laktaz eksikliği,
malabsorbsiyon...

Probiyotikler-Tarihçe

► 1900'ler...Elie Metchnikoff

- Yoğurt tüketen Bulgar köylülerinin uzun yaşadığını saptaması
- Bulgar bilimci Gregorov'un bulduğu '*Bulgarian bacillus*' ile ilişkilendiriyor
- Kalın barsakta bakterilerin **toksin** oluşturduğunu ve bunların yaşlanma nedeni olduğunu ve
- Barsaklarda zararlı bakterilerin yerine yararlı bakteriler olursa sağlığı olumlu etkileyeceğini öne sürüyor
- Fermente besinlerin sağlığa olumlu etkisi (Süt ve süt ürünleri)

Probiyotik Tanım

- ▶ **Probiotic:** Kelime kökü yunanca (bios) ve latin prefix, 'pro' karışımı: yaşam için "probiyotik"
- ▶ İlk 1953...Alman Werner Kollath: 'yaşam için gerekli aktif ürünler'
- ▶ 1965'te Lilly ve Stillwell: 'bir organizmanın büyümesini sağlayan başka mikroorganizma ürünleri'
- ▶ 1985'te Fuller: 'Bağırsak mikrobiyal dengesini iyileştirerek konakçıya yararlı mikrobiyal takviye'
- ▶ **WHO ve Uluslararası Probiyotik ve Prebiyotik Bilim Derneği'ne göre: Yeterli miktarda tüketildiğinde konağın sağlığı için yararlı canlı mikroorganizmalar**

Tanımlar

- **Prebiyotik:** Konak mikrobiyotasını konakçı yararına düzenleyen gıda ürünleri genellikle sindirilmeyen karbonhidratlar
 - Fruktan/fruktooligosakkaritleri galaktan galaktooligosakkaritler, inülin...
- **Sinbiyotik:** Prebiyotik ve probiyotik karışımı

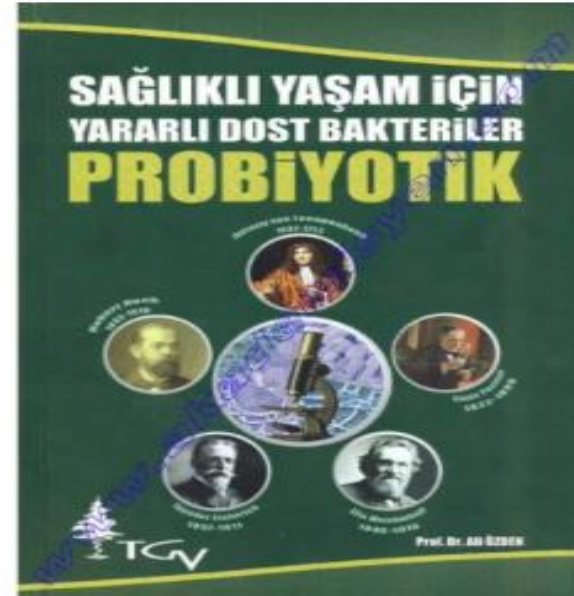
Sık Kullanılan Probiyotikler

- ▶ *Bifidobacterium spp*: *B. bifidum*, *B. breve*, *B. lactis*, *B. longum*, *B. infantis*, *B. adolescents*, *B. paracasei*
- ▶ *Lactobacillus spp*: *L. acidophilus*, *L. casei*, *L. fermentum*, *L. lactus*, *LL rhamnosus*....
- ▶ *Streptococcus thermophilus* group
- ▶ *Saccharomyces baulardii*
- ▶ *Enterococcus faecium*,
- ▶ *Leuconostoc spp*
- ▶ *Escherichia coli* Nissle 1917



Probiyotikler 2 şekilde alınır

- ▶ Besinlere ek olarak (tb, süspansiyon, likit)
- ▶ Besinlerle (fermente gıdalar: yoğurt, kefir...)



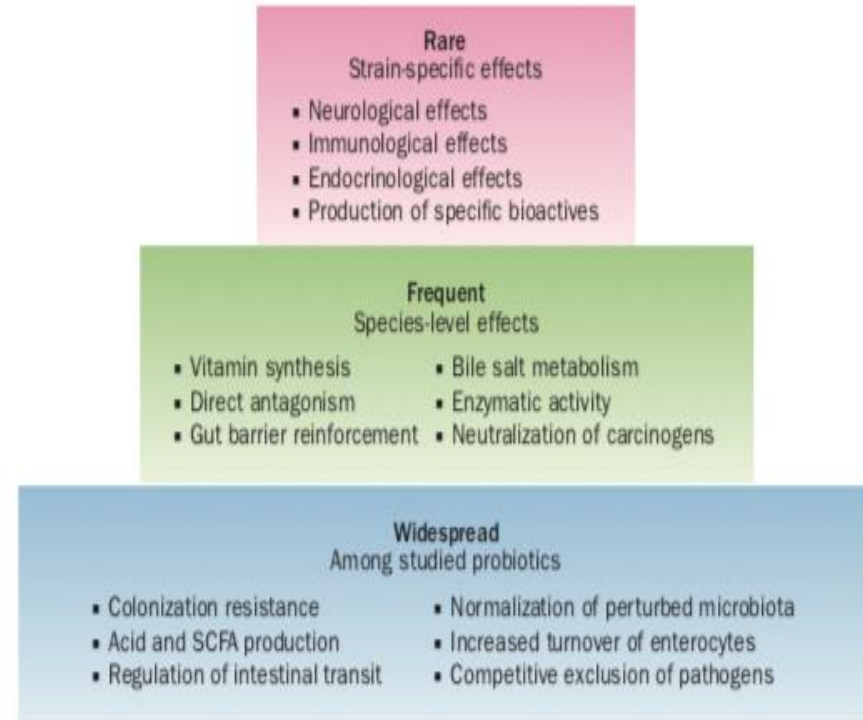
İdeal Probiyotik?



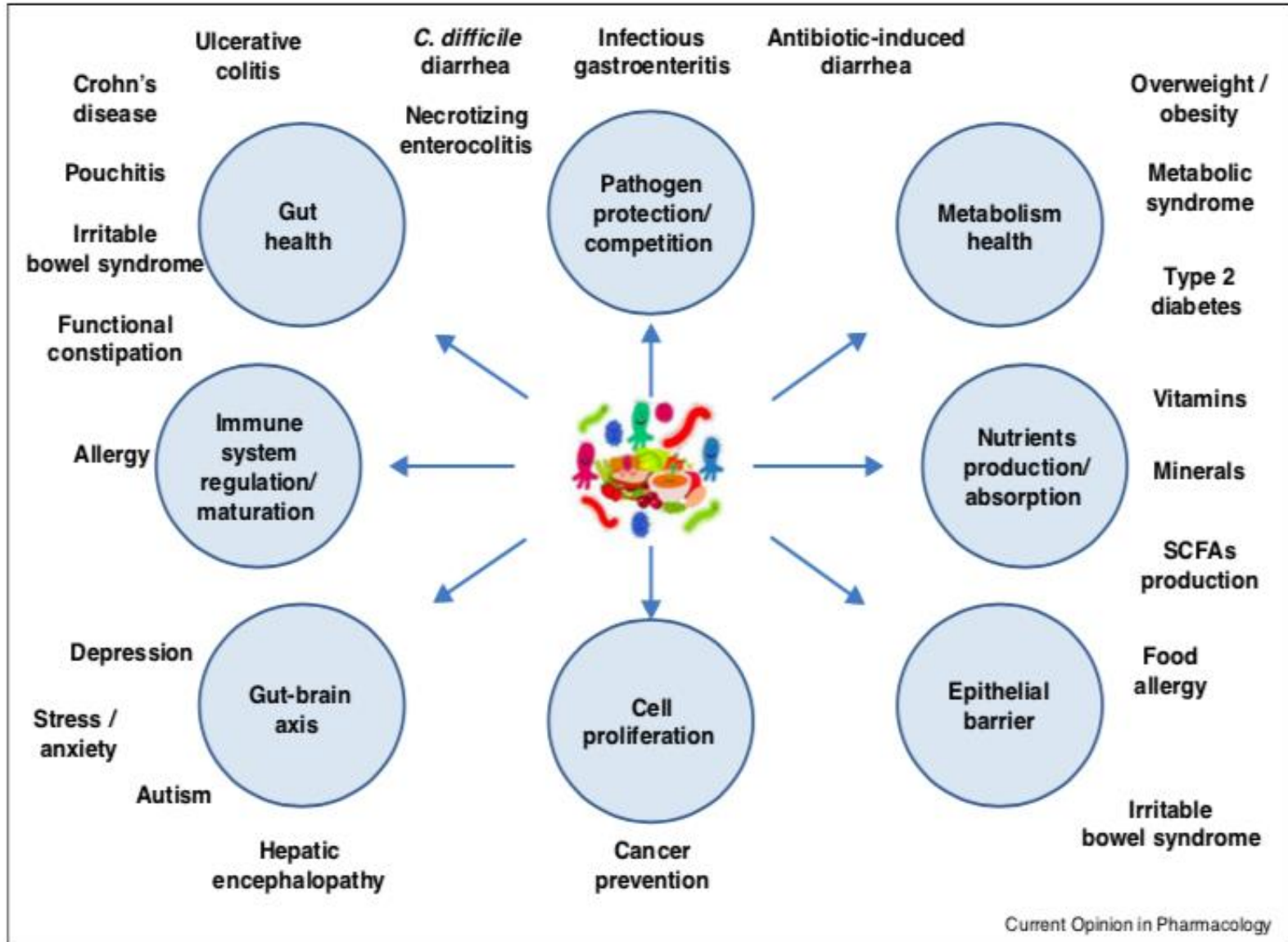
- İnsan orijinli, patojenik olmamalı
- Yeterli canlı hücre içermeli
- Gastrik asit ve safradan etkilenmemeli
- GIS epiteline tutunmalı, GIS'te yaşayabilmeli
- Antimikrobiyal ürün oluşturmali
- İmmün sistemi modüle etmeli
- Klinik yararı dökümente edilmiş olmalı

Probiyotiklerin Etkileri

- ▶ Suş spesifik etki (antimikrobiyal etki gibi)
- ▶ İmmünolojik ve endokrinolojik etki
- ▶ Spesifik biyoaktif ürünlerin sentezi
- ▶ Tür spesifik etki



Prebiyotik ve Probiyotiklerin Etkileri

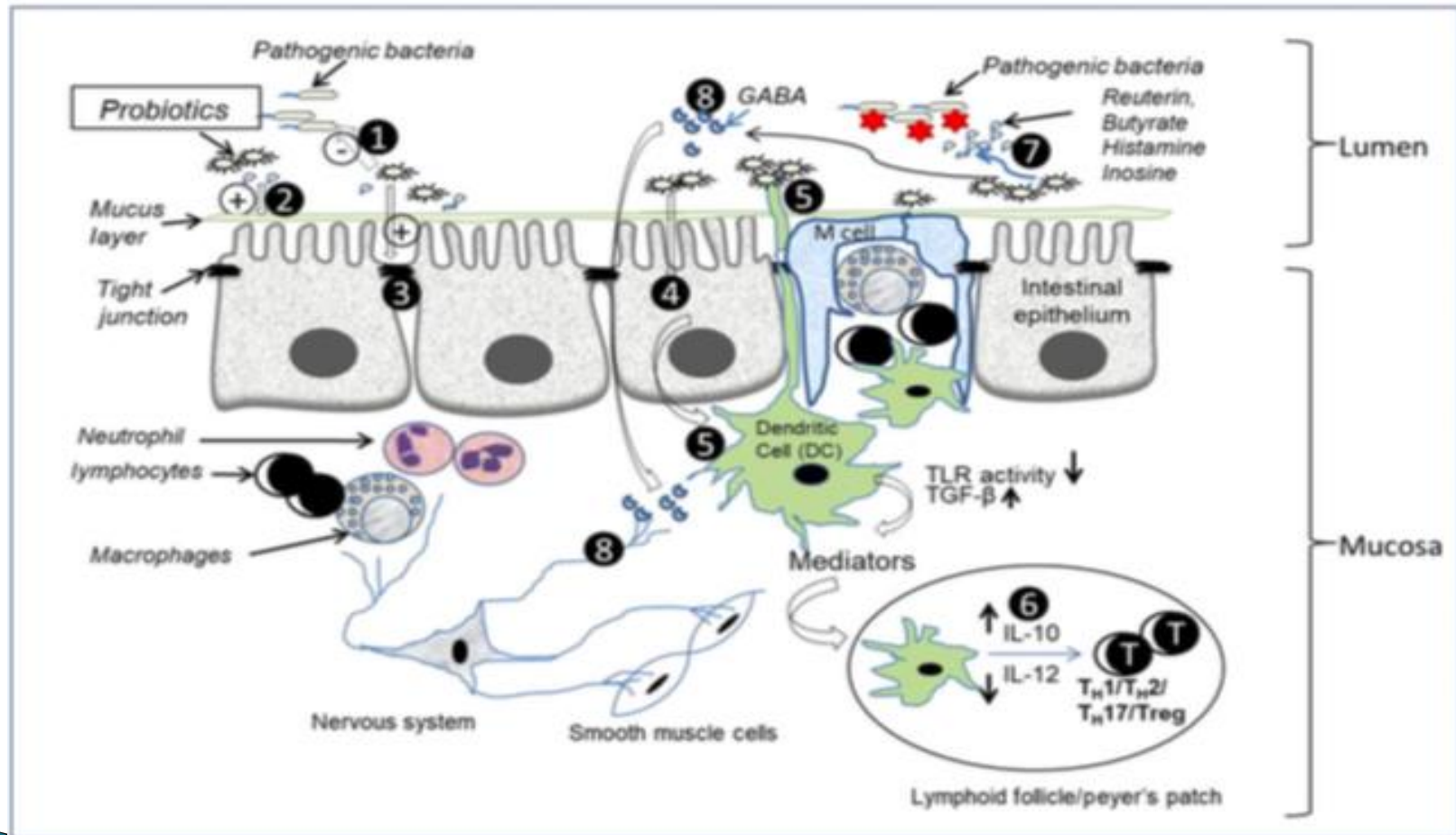


GIS Etki Mekanizması

- ▶ **Mikrobiota değişimi**
- ▶ **Bakteriosinler** ile bakterilerin intestinal mukozaya adezyonunu ve translokasyonunu önler
- ▶ **İntestinal bariyer fonksiyonu:** Müsin yapımı ↑, TLR'e bağlanarak epitelde protein kinaz yapımını ↑
- ▶ **İmmün fonksiyon artışı:** IgA↑, sitoprotektif moleküller ↑, sitokin ekspresyonu modülasyonu (IL-2, IL-6 TNF- α , TGF- β)
- ▶ **Antienflamatuar özellik:** Biyoaktif metabolitler üretir (histamin, inosin, reuterin...)

Probiyotik Etki Mekanizması

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- 1 Inhibit pathogenic bacterial adhesion/translocation
- 2 Increase mucus layer thickness
- 3 Enhance tight junction
- 4 Interact with intestinal epithelial cells

- 5 Mature and phenotype dendritic cells
- 6 Modulate T-cell responses
- 7 Produce bioactive metabolites (reuterin, histamine, butyrate, inosine, GABA)
- 8 Affect nervous system subsequently modulate gut motility and pain

Probiyotik ve GIS Hastalıkları

- İnfeksiyöz ishaller
- Antibiyotik ilişkili ishal
- *C. difficile* infeksiyonları
- Seyahat ilişkili ishal
- Amibiazis
- ...
- *H. pylori*
- İnflamatuvar barsak hastalıkları
- İBS
- Pouchitis
- Nekrotizan enterokolit
- Hepatik ensefalopati
- Pankreatit
-

Probiyotik seçimi



- ▶ Haziran 2018'e kadar
- ▶ Pubmed, Embase, Cochrane,
- ▶ ISI Web of Science
- ▶ RKÇ veya açık kontrollü çalışmalar

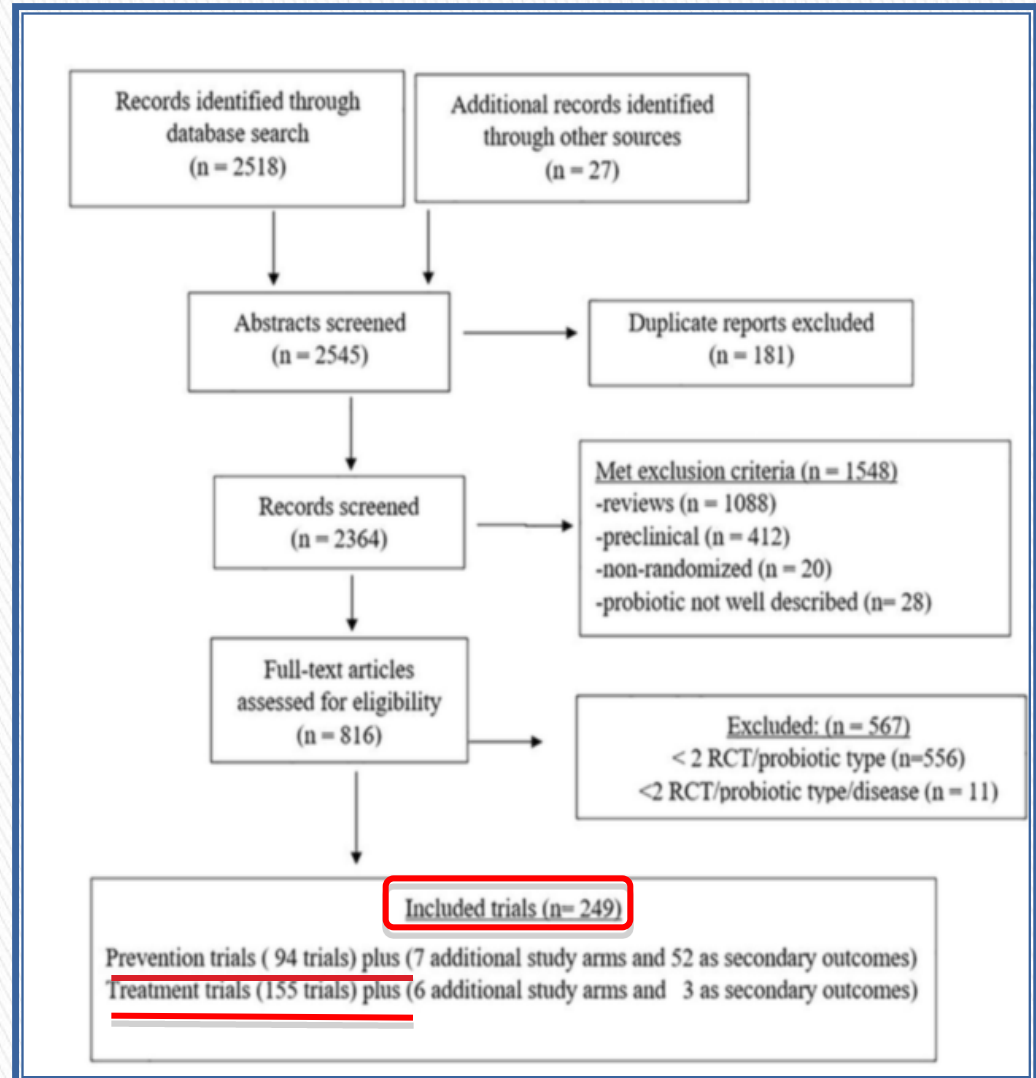


Table 1. Examples of 25 probiotic products available on the commercial market.

Probiotic description (genus, species and strain)	Formulation	Examples of brand names (Manufacturer, Country)	Examples of claims on label
Single strain probiotics			
<i>Bacillus coagulans</i> nr	capsules	ProbioSlim (ProbioSlim, Canada, USA)	"Promotes healthy digestion, helps you lose weight"
<i>B. lactis</i> (<i>animalis</i>) DN-173010 (CNCM I-2494)	yogurt	Activia (Danone, France)	"Supports digestive health"
<i>B. animalis lactis</i> Bb-12 (CNCM I-3446)	capsules, powder in sticks, fermented milk	BB-12 (Chr Hansen, USA)	"Supports bowel function, reduces crying in infants"
<i>B. infantis</i> 35624	drink, capsules	Align (Proctor & Gamble, USA)	"Maintains digestive balance"
<i>Clostridium butyricum</i> 588	tablets, drink	MIYA-BM (Miyarisan Pharm, Japan)	"Intestinal health"
<i>Enterococcus faecium</i> SF 68	powder, sachets	Bioflorin (Sanofi, Germany)	"To treat diarrhea"
<i>Escherichia coli</i> Nissle 1917	capsules	Mutaflor (Pharma-Zentiale, Germany)	"For chronic constipation or ulcerative colitis"
<i>L. acidophilus</i> LB	sachet, capsules	Lacteol (Mirren, South Africa)	"Preserves intestinal peristalsis"
<i>L. casei</i> Shirota	fermented milk	Yakult (Yakult, USA)	"Balance your digestive system"
<i>L. casei</i> DN-114001 (CNCM I-1518)	fermented drink, yogurt	Actimel (in Europe) or DanActive (in USA) (Danone, France)	"Supports normal function of immune system"
<i>L. casei rhamnosus</i> Lcr35	vaginal capsules	Gynophilus (Biocodex, France)	"Helps to recover vaginal flora"
<i>L. johnsonii</i> La1	milk	Bioamicus johnsonii (BioAmicus Probiotics, Canada)	"Assists child's immune system from allergies, eczema, asthma"
<i>L. plantarum</i> 299v (DSM9843)	fermented oat gruel in fruit drink, capsules	Pro Viva (Probi AB, Sweden)	"Relieve symptoms of IBS"
<i>L. reuteri</i> DSM 17938	capsules, yogurt	Protectis (BioGaia, Sweden)	"For digestive comfort"
<i>L. rhamnosus</i> GG (ATCC 53013)	yogurt, capsules	Culturelle (i-Health, Inc, USA)	"Improves digestive health" "Boosts immune system"
<i>S. boulardii</i> CNCM I-745 (ATCC 74012)	capsules, sachets	Florastor (Biocodex, France)	"Strengthens digestive balance" "Boosts immune response"

Mixtures of probiotic strains

<i>L. acidophilus</i> CL1285 + <i>L. casei</i> Lbc80r + <i>L. rhamnosus</i> CLR2	fermented drink, capsules	Bio K+ (BioK+ Intl, Canada)	"Maintains healthy intestinal flora"
<i>L. helveticus</i> R52 (CNCM I-1722) + <i>L. rhamnosus</i> R11 (CNCM I-1720)	capsules, sachets	Lacidofil (Institut Rosell, Canada)	"Maintains normal healthy intestinal microflora"
<i>L. helveticus</i> (bulgaricus) 33409 + <i>L. gasseri</i> 4962	tablets or sachets	Lactinex (Becton, Dickinson and Comp., USA)	"Replaces intestinal flora"
<i>L. reuteri</i> DSM17938 + <i>L. reuteri</i> PTA5289	lozenges, powder, capsules	Protectis (BioGaia, Sweden)	"Helps restore balance in digestive tract"
<i>L. acidophilus</i> La5 + <i>B. lactis</i> Bb12	yogurt	AB Yogurt (President Enterprise Company, Taiwan)	"Improves normal flora"
<i>L. acidophilus</i> nr + <i>B. infantis</i> nr	capsules	Infloran Berna (Berna, Switzerland)	"Helps restore balance of intestinal bacteria" "Used for diarrhea, vaginal and urinary tract infections"
<i>L. acidophilus</i> gasseri + <i>B. infantis</i> nr	capsules	Linex (Sandoz, Bulgaria)	"Normalizes normal flora"
<i>Bacillus clausii</i> (4 strains, O/C, N/R84, T84, Sin8)	capsules, spores in vial	Enterogermina (Sanofi-Aventis, France)	"Management of pediatric diarrhea, for intestinal flora balance disturbed by diarrhea, poisoning and antibiotics"
<i>Bifido. longum</i> BL03, <i>Bifido. infantis</i> subsp. <i>lactis</i> BI04, <i>Bifido. breve</i> BB02, <i>L. acidophilus</i> BA05, <i>L. plantarum</i> BP06, <i>L. paracasei</i> BP07, <i>L. helveticus</i> BD08, <i>Strept thermophilus</i> BT01	sachets	VSL#3 (VSL Pharm, Inc., Italy)	"Management of ulcerative colitis, ileal pouch and IBS"

Table 2. Graded recommendations for probiotic formulations for the prevention or treatment of 19 different types of diseases.

Type of disease	No. of study arms	Strong evidence* (no. + RCTs/no. negative RCTs)	Moderate evidence* (no. + RCTs/no. negative RCTs)	Weak to not effective* (no. + RCTs/no. negative RCTs)
Prevention				
Allergy	3	None	None	<i>L. rhamnosus</i> GG (1+/2-)
Antibiotic-Associated Diarrhea (AAD)	61	<i>S. boulardii</i> I-745 (18+/9-) LaLcLr mix (3+/1-) <i>L. casei</i> DN114001 (2+/0-)	<i>E. faecalis</i> SF38 (2+/1-)	LhLr mix (3+/3-) <i>L. rhamnosus</i> GG (4+/6-) <i>C. butyricum</i> 588 (1+/2-) <i>L. acidophilus</i> La5 + <i>B. lactis</i> Bb12 (1+/5-)
Prevention <i>C. difficile</i> infections (CDI)	23	None	None	<i>S. boulardii</i> (1+/11-) LaLcLr mix (2+/2-) <i>L. rhamnosus</i> GG (1+/4-) <i>L. casei</i> 114001 (1+/1-)
<i>H. pylori</i> (side effects of therapy)	16	<i>S. boulardii</i> I-745 (7+/2-) LhLr mix (2+/0-)	<i>L. rhamnosus</i> GG (3+/2-)	None
Enteral feed associated diarrhea	3	<i>S. boulardii</i> I-745 (3+/0-)	None	None
Necrotizing Enterocolitis (NEC)	17	<i>L. rhamnosus</i> GG + lactoferrin (2+/0-) <i>B. infantis</i> + <i>B. lactis</i> + <i>Strept. thermophilus</i> (2+/0-)	None	<i>L. rhamnosus</i> GG (0+/2-) <i>S. boulardii</i> (0+/3-) <i>L. reuteri</i> 17938 (1+/3-) <i>B. lactis</i> Bb12 (0+/2-) <i>L. acidophilus</i> + <i>B. bifidum</i> (1+/1-)
Nosocomial infections	2	None	None	<i>L. rhamnosus</i> GG (1+/1-)
Respiratory tract infections	10	None	None	<i>L. rhamnosus</i> GG (3+/3-) <i>L. casei</i> 114001 (2+/2-)
Surgical infections	8	Synbiotic PpLmLpLp (4+/1-)	None	<i>L. plantarum</i> 299v (1+/2-)
Traveler's diarrhea	7	<i>S. boulardii</i> I-745 (4+/1-)	None	<i>L. rhamnosus</i> GG (1+/1-)
Urinary Tract Infections	3	None	None	<i>L. rhamnosus</i> GG (0+/3-)

Tedavi

Adult acute diarrhea	9	<i>S. boulardii</i> I-745 (4+/2-)	<i>E. faecalis</i> SF68 (2+/1-)	None
<i>C. difficile</i> recurrence	4	<i>S. boulardii</i> I-745 (2+/0-)	None	<i>L. rhamnosus</i> GG (0+/2-)
Colic	4	<i>L. reuteri</i> 17938 (4+/0-)	None	None
Constipation	3	None	<i>B. lactis</i> 173010 (2+/1-)	None
<i>H. pylori</i> eradication	35	LhLr mix (4+/1-)	<i>L. acidophilus</i> La5 + <i>B. lactis</i> Bb12 mix (3+/2-)	<i>S. boulardii</i> I-745 (4+/11-) <i>L. rhamnosus</i> GG (0+/4-) <i>L. acidophilus</i> LB (1+/2-) <i>C. butyricum</i> 588 (0+/3-)
Inflammatory Bowel Disease (IBD)	25	8-strain mix (8+/2-)	<i>S. boulardii</i> I-745 (2+/1-)	<i>L. rhamnosus</i> GG (1+/6-) <i>E. coli</i> Nisse (0+/5-)
Irritable Bowel Syndrome (IBS)	23	<i>L. plantarum</i> 299v (4+/1-) <i>B. infantis</i> 35624 (3+/1-)	None	<i>L. rhamnosus</i> GG (2+/2-) <i>S. boulardii</i> I-745 (2+/2-) 8-strain mix (2+/2-) <i>B. lactis</i> 173010 (1+/1-)
Pediatric acute diarrhea	61	<i>S. boulardii</i> I-745 (25+/4-) <i>L. rhamnosus</i> GG (10+/3-) <i>L. reuteri</i> 17938 (3+/0-) <i>L. acidophilus</i> LB (3+/1-) <i>L. casei</i> DN114001 (3+/0-) <i>Bac. clausii</i> mix (O/C, N/R84, T84, Sin8 (3+/1-) 8-strain mix (2+/0-)	LhLr (2+/1-)	None

Antibiyotik İlişkili İshal-Önlem

- ▶ AİD oral/IV antibiyotik tedavisinden hemen veya kesildikten sonra 1-2 hafta içinde cinsel ilişkiden kaçınılmalıdır.
- ▶ En az 2 hafta boyunca cinsel ilişki.
- ▶ ≥ 3 fazla antibiyotik kullanımı.
- ▶ Antibiyotik ilacı kesildikten 1-2 hafta sonra.
- ▶ Doz 10^7-10^{10} cinsiyet ve enfeksiyon türüne göre değişir.
- ▶ Antibiyotik ilacı kesildikten sonra %5-50'de

Güçlü öneri :

- *S. baulardii* CNCM 1-175

- Antibiyotik ile 1-2 gün içinde başlanmış
- Kesildikten 1-4 hafta sonraya kadar
- Doz 10^7 - 10^{10} cfu/gün

- ▶ 59 çalışma
- ▶ 8 farklı probiyotik, > 22RCT

C. difficile

Önleme

- ▶ Aİİ lerin 1/3'de mg
- ▶ Zayıf öneri
 - ✓ *S. baulardii* CNCM I-745
 - ✓ *L. rhamnosus* GGC
 - ✓ *L. casei* DN1140001
- ▶ *Lactobasillus* miks :
 - *L. acidophilus* CL1285
 - *L. casei* Lbc 80r
 - *L. rhamnosus* CLR2

Tedavi

- ✓ Olguların %20-30'u tekrarlar
 - ✓ *S. baulardii* I-745 (güçlü)
 - ✓ *L. rhamnosus* (zayıf)

Seyahat İlişkili İshal Önleme

- ▶ 5 RKÇ değerlendirilmiş

- ▶ *S. baulardii* CNCM I-745..... güçlü kanıt

- ▶ *L. rhamnosus* GG.....zayıf kanıt düzeyi

- ▶ Doz: $2-5 \times 10^9$ cfu/gün seyahatten bir kaç gün önce başlayıp, 2-5 gün sonrasına kadar

Akut ishal tedavi

▶ Erişkin

▶ 9 çalışma

- ▶ *S. baulardii* CNCM I-745 (güçlü)
- ▶ *E. faecalis* SF-65 (orta)

▶ Çocuk

▶ 61 çalışma

Güçlü öneri

- ✓ *S. baulardii* CNCM I-745
- ✓ *L. rhamnosus* GGC
- ✓ *L. casei* DN1140001
- ✓ *L. reuteri* 17938
- ✓ *L. acidophilus* LB

Suş ve Hastalık Spesifik Probiyotik Etkinliği

- ▶ 1970-2017
- ▶ Sistematik review
- ▶ Meta analiz
- ▶ 2345 çalışma...228'i değerlendirilmiş
 - Önleme 93
 - Tedavi 135

McFarland LV et al. Front. Med. 2018; 5:124.

TABLE 2 | Strength of efficacy for probiotics with identified strain designations and at least two randomized, controlled trials with significant findings for the prevention or treatment of disease.

Disease indication	Net ≥ 2 significant randomized clinical trials (RCTs) (number of significant RCTs/non-significant RCTs)	At least two RCTs with significant efficacy (number of significant RCTs/non-significant RCTs)
Prevention		
Adult AAD	<i>Saccharomyces boulardii</i> I-745 (11+/6-) <i>Lactobacillus acidophilus</i> CL1285 + <i>Lactobacillus casei</i> LBC80R + <i>Lactobacillus rhamnosus</i> CLR2 (4+/0)* <i>L. casei</i> DN114001 (2+/0-)	<i>Enterococcus faecalis</i> SF68 (2+/1-) <i>L. rhamnosus</i> GG (2+/4-) <i>Lactobacillus reuteri</i> 55730 (2+/1-)
Pediatric AAD	<i>S. boulardii</i> I-745 (7+/3-)	<i>L. helveticus</i> R52 + <i>L. rhamnosus</i> R11 (2+/1-)
CDI-primary	None	<i>L. acidophilus</i> CL1285 + <i>L. casei</i> LBC80R + <i>L. rhamnosus</i> CLR2 (2+/2-)*
Nosocomial infections	None	<i>L. rhamnosus</i> GG (2+/2-)
Travelers' diarrhea	<i>S. boulardii</i> I-745 (2+/0-)	
Treatment		
Pediatric acute diarrhea	<i>S. boulardii</i> I-745 (25+/4-) <i>L. rhamnosus</i> GG (12+/3-) <i>L. reuteri</i> DSN 17938 (3+/0-) <i>L. acidophilus</i> LB (3+/1-) <i>L. casei</i> DN114001 (3+/0-) VSL#3* (2+/0-) <i>Bac. clausi</i> OC/SN/R (3+/1-)	<i>L. helveticus</i> R52 + <i>L. rhamnosus</i> R11 (2+/1-)
Irritable bowel syndrome	<i>B. infantis</i> 35624 (2+/0-) <i>L. plantarum</i> 299v (4+/1-) <i>L. rhamnosus</i> GG + <i>L. rhamnosus</i> LC705 + <i>B. breve</i> Bb99 + <i>Prop. freudenreichii shermanii</i> Jc (2+/0-)	<i>L. rhamnosus</i> GG (2+/2-) <i>S. boulardii</i> I-745 (2+/2-) VSL#3* (2+/2-)
Helicobacter pylori eradication	<i>L. helveticus</i> R52 + <i>L. rhamnosus</i> R11 (4+/1-)	<i>S. boulardii</i> I-745 (5+/11-) <i>L. reuteri</i> 55730 (2+/2-) <i>L. acidophilus</i> La5 + <i>B. animalis</i> spp. <i>lactis</i> Bb12 (3+/2-)
Inflammatory bowel disease	VSL#3* (8+/2-)	<i>S. boulardii</i> I-745 (2+/1-)

Suş ve Hastalık Spesifik Probiyotik Etkinliği

Önleme

- ▶ **Aİİ:**
S. baulardii CNCM I-745
L. bacillus miks
- ▶ **Seyahat ishali:**
S. baulardii CNCM I-745

Tedavi

- ▶ *C. difficile* ve erişkin ishal
S. baulardii CNCM I-745
- ▶ **Çocuk ishalleri :**
S. baulardii CNCM I-745
L. rhamnosus GGC
L. casei DN1140001
L. reuteri 17938
L. acidophilus LB

Probiotics for treating acute infectious diarrhoea (Review)



- ▶ Medline 1966 - 2010
Embase 1988 - 2010
- ▶ 120 çalışmadan 63 değerlendirilmiş
 - 56 çocuk, 7 erişkin
- ▶ 8014 kişi
- ▶ Çalışmalarda probiyotik
 - 46: tek mikroorganizma
 - 17: 2-8 mikroorganizma

- ▶ *En sık*
 - 13... *L. casei* GG
- ▶ 10... *S. boulardii*
- ▶ 10... *Enterococcus* laktik asit bakterileri (LAB)
- ▶ 5... SF68

Probiotics for treating acute infectious diarrhoea (Review)



- ▶ Ortalama ishal süresi: 24 sa
 - (95% CI 15.9 - 33.6s ; n=4555), 35 çalışma
- ▶ **Probiyotikler ortalama ishal süresini kısaltıyor**
 - (kontrol grubu 39.1- 173.5 saat /probiyotik -7-79.2 saat)
- ▶ **2. günde ishal sıklığı azalıyor**
 - (ortalama 0.80; 0.45 to 1.14; n=2751), 20 çalışma
- ▶ Rotavirüs ve bakteriyel ishaller: 4 çalışma
 - 3... değişiklik Ø
 - 1...süre ↓

Sonuç: Probiyotikler rehidratasyon tedavisine ek olarak verildiğinde ishal süresini ve şiddetini AZALTIR

The Role of Probiotics in the Treatment of Dysentery: a Randomized Double-Blind Clinical Trial

- ▶ 7 bakteriyel suş karışımı, 5 gün verilmiş :
 - *L. casei*, *L. acidophilus*, *L. rhamnosus*, *L. bulgaris*, *B. infantis*, *B. breve*, *S. termophiles*

50 probiotik	50 kontrol grubu (dizanteri olgu)
↓	↓
ishal süresi 2.62 gün	3.16 gün ($p < 0.05$)

- ✓ İshal ve hastane yatış süresi probiyotik grubunda daha kısa
 - ▶ Yaş, cins , ateş süresi
- } anlamlı fark yok

Akut Amibiazis ve Probiyotikler?

Grup 1: 27 hasta
metranidazol+ iodoquinol

Grup 2: 27 hasta
metranidazol+ iodoquinol+ *S. baulardii*
2x250 (10 gün)

Tedavi sonrası 2 ve 4. hf

► İshal süresi, ateş ve karın ağrısı
S. baulardii grubunda daha kısa ($p<0.05$)

► 4 hf sonunda amebik kist
► grup 1 'de 5 hastada (+)
► grup 2'de Ø

Ghanaei FM et al. World J Gastroenterol 2003;9(8)

Grup 1: 45 hasta
metranidazol

Grup 2: 40 hasta
metranidazol + *S. baulardii*
(10 gün)

► İshal süresi, ateş, karın ağrısı, kusma gibi semptomların süresi benzer

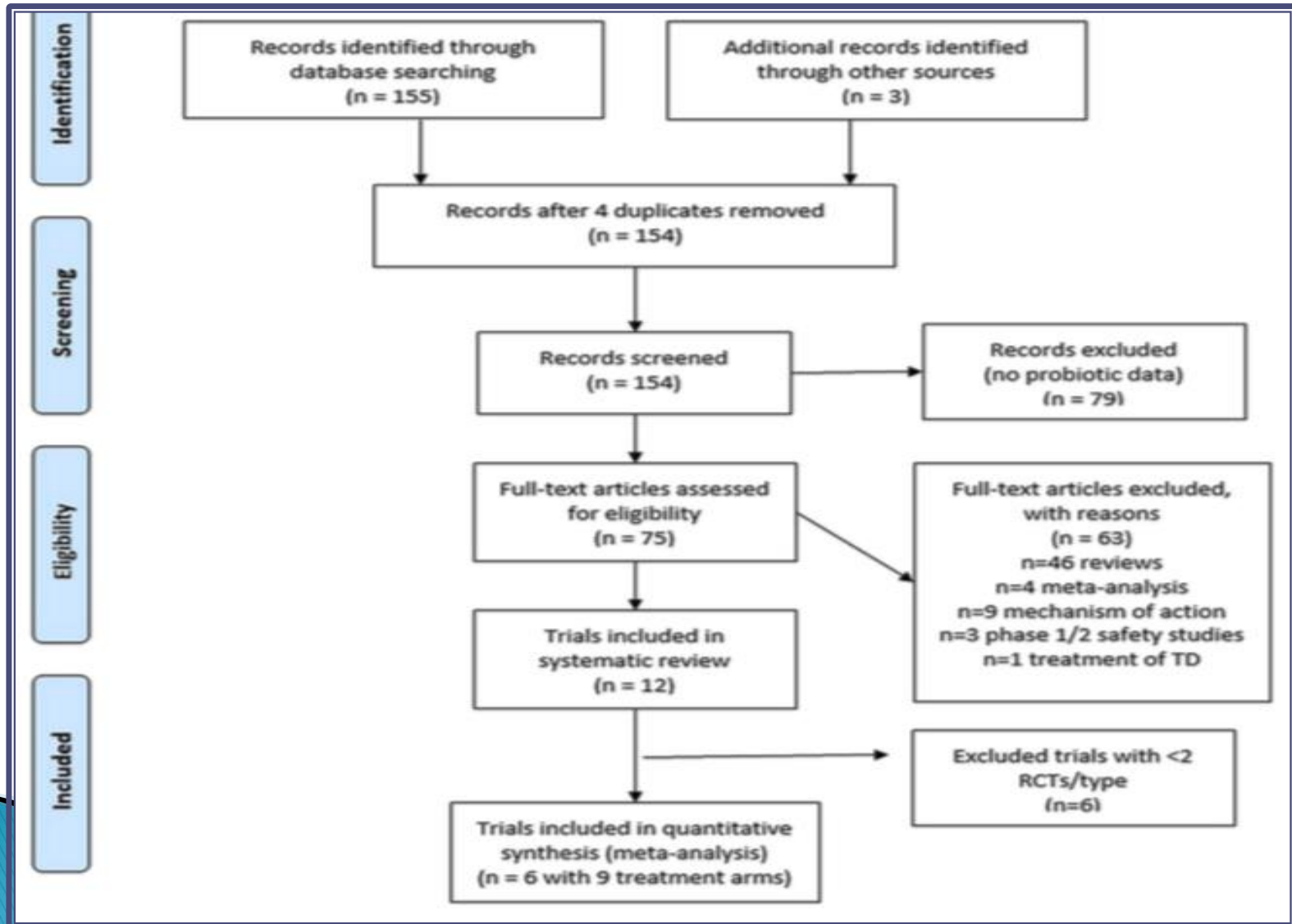
Savaş-Erdeve S et al. Turk J Pediatr 2009;
51(3)

Seyahat İlişkili İshal (Turist İshali)

- ▶ Seyahat edilen yer, mevsime göre değişir
- ▶ Gelişmekte olan ülkelere seyahatte ↑ (%38-79)
- ▶ Sıklık: 20-40 milyon kişi/yıl
- ▶ Süre: 1-4 gün (ort 2 gün)
- ▶ Genellikle kendi kendini sınırlar
- ▶ %10 medikal tedavi, %3 hastane yatış
- ▶ Tedavi:
 - Hafif-orta... ORS
 - Şiddetli... ORS ve antibiyotik
- ▶ %3-30: postinfeksiyöz komplikasyonlar (IBS, dispepsi, konstipasyon...)



Are probiotics and prebiotics effective in the prevention of travellers' diarrhea: A systematic review and meta-analysis





Are probiotics and prebiotics effective in the prevention of travellers' diarrhea: A systematic review and meta-analysis

Table 1
Characteristics of included randomized, controlled trials of probiotics or prebiotics for the prevention of travellers' diarrhea.

Reference	Study population (mean age)	Travel destination	No. enrolled: probiotic or prebiotic (control)	Attrition (%)	Follow-up post-therapy (days)	Type of control	Compliance (%)
Kollaritsch 1989 ^a [46]	Austrian tourists (42 y)	varied, hot climates	426 (406)	nr	0	placebo	nr
Kollaritsch 1989 ^b [46]	Austrian tourists (42 yrs)	varied, hot climates	299 (-) ^d	nr	0	placebo	nr
Kollaritsch 1993 ^a [47]	Austrian tourists (69 y)	varied, hot climates	727 (727)	51%	0	placebo	65%
Kollaritsch 1993 ^b [47]	Austrian tourists (70 y)	varied, hot climates	695 (-) ^d	56%	0	placebo	61%
Oksanen 1990 [49]	Finnish tourists (44 y)	2 cities, Turkey	402 (418)	8%	0	placebo	92%
Hilton 1997 [50]	U.S. tourists (55 y)	varied	200 (200)	39%	0	placebo	64%
Kollaritsch 1989 ^c [46]	Austrian tourists (35 y)	varied, hot climates	154 (-) ^d	nr	0	placebo	nr
Katellaris 1995 [48]	British soldiers (nr)	Belize	101 (101)	nr	7	placebo	76%
Briand 2006 [51]	French tourists (38 y)	West Africa or Asia	174 (174)	29%	4	placebo	71%
Katellaris 1995 ^c [48]	British soldiers (nr)	Belize	80 (-) ^d	nr	7	placebo	76%
de Dios Pozo-Olano 1978 [52]	U.S. tourists (nr)	Mexico	26 (24)	nr	28	placebo	nr
Black 1989 [53]	Danish tourists (50 y)	Egypt	47 (47)	14%	0	placebo	nr
Virk 2013 [54]	U.S. tourists (49 y)	high risk areas	94 (102)	22%	0	placebo	58%
Cummings 2001 [55]	British tourists (50 y)	varied	181 (182)	29%	7	placebo	nr
Drakoularakou 2010 [56]	British tourists (38 y)	low-high risk, varied	100 (101)	21%	0	placebo	nr
Krokowicz 2014 [57]	Polish adult tourists (nr)	varied sub-tropical	30 (30)	30%	0	placebo	nr

Characteristics of probiotic or prebiotic intervention and outcome for the prevention of travellers' diarrhea.

Probiotic	Daily dose (cfu/d)	Formulation	Duration (mean days)	Incidence TD in probiotic or prebiotic	Incidence TD in controls	AEs	Reference
<i>S. boulardii</i> CNCM 1-745 ^a	2.5 x 10 ⁹			14/186 (38.5%)	37/186 (49.5%)	none	Kollaritsch 1989 ^b [46]
<i>S. boulardii</i> CNCM 1-745 ^a	5 x 10 ⁹			14/186 (38.5%)	37/186 (49.5%)	none	Kollaritsch 1989 ^c [46]
<i>S. boulardii</i> CNCM 1-745 ^a	5 x 10 ⁹			5/186 (3.8%)	13/186 (17.5%)	5%, ns	Kollaritsch 1993 ^b [47]
<i>S. boulardii</i> CNCM 1-745 ^a	2 x 10 ¹⁰			5/186 (3.8%)	13/186 (17.5%)	5%, ns	Kollaritsch 1993 ^c [47]
<i>L. rhamnosus</i> GG	2 x 10 ⁹			14/186 (38.5%)	37/186 (49.5%)	none	Oksanen 1990 [49]
<i>L. rhamnosus</i> GG	2 x 10 ⁹			14/186 (38.5%)	37/186 (49.5%)	none	Hilton 1997 [50]
<i>L. acidophilus</i> nr	2 x 10 ⁸⁻⁹			14/186 (38.5%)	37/186 (49.5%)	none	Kollaritsch 1989 ^d [46]
<i>L. acidophilus</i> nr	2 x 10 ¹¹			14/186 (38.5%)	37/186 (49.5%)	none	Katellaris 1995 [48]
<i>L. acidophilus</i> nr	2 x 10 ¹⁰			14/186 (38.5%)	37/186 (49.5%)	3%, ns	Briand 2006 [51]
<i>L. fermentum</i> KLD	2 x 10 ¹¹			14/186 (38.5%)	37/186 (49.5%)	none	Katellaris 1995 ^d [48]
<i>L. helveticus</i> ATCC33409 + <i>L. gasseri</i> ATCC4962 ^e	7 x 10 ⁹	tablet	Trip=8 d	9/26 (34.6%) ns	7/24 (29.1%)	nr	de Dios Pozo-Olano 1978 [52]
<i>L. acidophilus</i> + <i>L. bulgaricus</i> + <i>Bifido. bifidum</i> + <i>Strept. thermophilus</i>	9 x 10 ⁹	capsules	Pre (2d) + trip = 14 d	17/40 (42.5%)*	29/41 (70.7%)	none	Black 1989 [53]
<i>Enter. faecium</i> SF68 + <i>S. cerevisiae</i> CNCM I-4444 + FOS	1 x 10 ¹⁰	capsules	Pre (3 d) + trip + post (7 d) = 21 days	52/94 (55.3%)ns	55/102 (53.9%)	less constipation in probiotic (30%) vs placebo (54%)	Virk 2013 [54]
FOS	10 g/d	sachet	Pre (14d) + trip = 28 d	45/117 (38.5%) ns	58/127 (45.7%)	34% gas vs 19%*	Cummings 2001 [55]
GOS	5.5 g/d	sachet	Pre (7d) + trip = varied	19/81 (23.4%)*	30/78 (38.5%)	none	Drakoularakou 2010 [56]
Sodium butyrate	1.5 g/d	capsule	Pre (3d) + trip = varied	1/22 (4.5%)*	8/20 (40.0%)	none	Krokowicz 2014 [57]

S. baulardii CNCM I -745



Erişkin seyahat ishallerinin önlenmesinde etkili

Original Article

Guidelines for the prevention and treatment of travelers' diarrhea: a graded expert panel report

Pre-travel	Providers should consider the following in counseling the traveler: (1) Definitions of travelers' diarrhea and severity classification (2) Importance of oral rehydration through fluid and salt intake for all travelers' diarrhea (3) Information on effectiveness of treatments for travelers' diarrhea and the risk of travel, travelers' diarrhea, and antibiotic use with the acquisition of multi-drug resistance bacteria. (4) B...		
During Travel	Probiyotikler ve prebiyotikler ↓ Tedavi ve önlemede <u>önerilmiyor</u> (yetersiz kanıt)		
	subsalicylates	as an adjunct to antibiotics	adjunct to antibiotics
	±		+
Post-travel	May use antibiotic (Table 2)		Should use antibiotic (Table 2)
	Acute travelers' diarrhea should be treated empirically as above.		
	Microbiologic testing is recommended in returning travelers with severe or persistent symptoms or in those who fail empiric therapy		
	Multiplex molecular diagnostics are preferred in patients with persistent or chronic symptoms		

Seyahat İshali

- ▶ *Lactobacillus GG* ve *S. baulardii* gibi probiyotiklerin seyahat ishallerinin önlenmesi ile ilgili çalışmalar
 - Az sayıda hastada yapılmış
 - Veriler yetersiz
 - Bu bakterilerin standardize edilmiş preparatları Ø
- ▶ Prebiyotiklerle ilgili çalışmalar devam ediyor
- ▶ Kullanımlarını önermek için veriler yetersiz

Antibiyotik ilişkili ishal

Open Forum Infectious Diseases

MAJOR ARTICLE

IDSA
Infectious Diseases Society of America

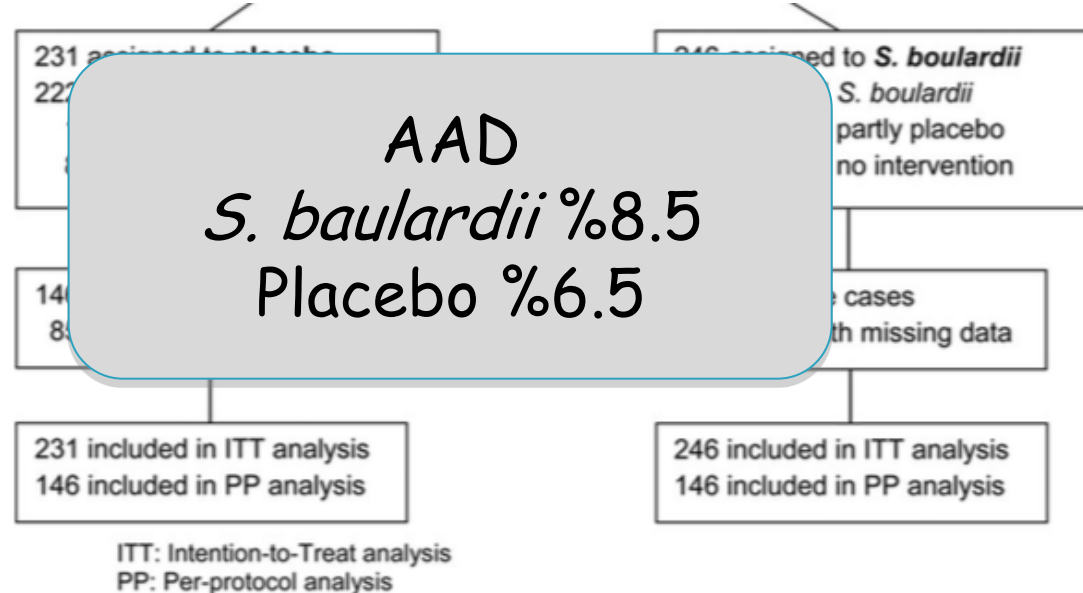
hivma
hiv medicine association

OXFORD

Saccharomyces boulardii to Prevent Antibiotic-Associated Diarrhea: A Randomized, Double-Masked, Placebo-Controlled Trial

Haziran 2010- Ekim 2012 , Almanya, 15 merkez 477 erişkin ve sistemik AB ted alan hasta

► Perenterol (1.8×10^{10} *S. boulardii* canlı hücre) 2x1/gün



Probiotic Yogurt for the Prevention of Antibiotic-associated Diarrhea in Adults: A Randomized Double-blind Placebo-controlled Trial.

Velasco M¹, Requena T², Delgado-Iribarren A³, Peláez C², Guijarro C¹.

⊕ Author information

Abstract

GOAL: To evaluate the effect of yogurt supplemented with probiotic bacteria on the prevention of antibiotic-associated diarrhea (AAD) in hospitalized patients.

BACKGROUND: Diarrhea following antibiotic administration is a frequent clinical problem. The usefulness of probiotics for the prevention of AAD in the hospitalized adult population remains unclear.

STUDY: A randomized, double-blind, placebo-controlled clinical trial was conducted in hospitalized patients who started antibiotic treatment. Patients were randomized (2:2:1) to receive a daily amount of 200 mL of placebo-yogurt (Streptococcus thermophilus and Lactobacillus delbrueckii subsp. bulgaricus), 200 mL of probiotic yogurt (previous plus Lactobacillus acidophilus La-5, Bifidobacterium animalis subsp. lactis Bb-12 and Lactobacillus casei subsp. casei Lc-01) or no yogurt (unblinded control) within 48 hours of beginning the antibiotic therapy and up to 5 days after stopping the antibiotic. Patients were followed up with for 1 month to determine occurrence of diarrhea.

RESULTS: We included 314 patients, mean age 76 years. The rate of diarrhea was 23.0% in the probiotic group versus 17.6% in the placebo group, absolute risk reduction -5.35% (95% confidence interval, -15.4% to 4.7%; P=0.30). Rate of diarrhea was similar in the unblinded external control and in the blinded study groups combined (20.9% vs. 20.2% respectively; P=0.91). There was no difference in the duration of diarrhea, maximum number of bowel movements or prolonged admission because of diarrhea among the groups. All-cause mortality did not differ between groups.

CONCLUSIONS: The combined probiotic strains LA-5, BB-12, and LC-01 do not have an effect in the prevention of AAD in hospitalized

Lactobacilli and bifidobacteria in the prevention of antibiotic-associated diarrhoea and *Clostridium difficile* diarrhoea in older inpatients (PLACIDE): a randomised, double-blind, placebo-controlled, multicentre trial

Stephen J Allen, Kathrin Winkler, David Wootton, Caroline Beal, Helen Hocking, Michael B Graven, Helen Brown, Alison Eden, Michael B Graven

Summary

Background

AAD is a common complication of broad-spectrum antibiotic therapy underlying diarrhoea (AAD). However, to reliably assess the impact of those administered a number of patients

Methods

We recruited older inpatients aged 65 years and over

to participate in a randomised

controlled trial to evaluate the

effectiveness of a multistrain

preparation of lactobacilli and

bifidobacteria compared with a

placebo in the prevention of

antibiotic-associated diarrhoea

and *Clostridium difficile* diarrhoea

in older inpatients.

The trial was conducted in

four UK hospitals.

Patients were randomised

to receive either a multistrain

preparation of lactobacilli and

bifidobacteria or a placebo.

The primary outcomes were

occurrence of AAD within 8

weeks and *C. difficile* diarrhoea

(CDD) within 12 weeks of

recruitment. Analysis was by

modified intention-to-treat.

This trial is registered, number ISRCTN70017204.

Findings

Of 17 420 patients screened, 1493 were randomly assigned to the microbial preparation group and 1488 to the placebo group. 1470 and 1471, respectively, were included in the analyses of the primary endpoints. AAD (including CDD) occurred in 159 (10.8%) participants in the microbial preparation group and 153 (10.4%) participants in the placebo group (relative risk [RR] 1.04; 95% CI 0.84–1.28; $p=0.71$). CDD was an uncommon cause of AAD and occurred in 12 (0.8%) participants in the microbial preparation group and 17 (1.2%) participants in the placebo group (RR 0.71; 95% CI 0.34–1.47; $p=0.35$). 578 (19.7%) participants had one or more serious adverse event; the frequency of serious adverse events was much the same in the two study groups and none was attributed to participation in the trial.

Interpretation

We identified no evidence that a multistrain preparation of lactobacilli and bifidobacteria was effective in prevention of AAD or CDD. An improved understanding of the pathophysiology of AAD is needed to guide future studies.

	Probiyotik	Placebo
AAD	159 (%10.8)	153 (%10.4)
CDI	12 (%0.8)	17 (%1.2)

C. difficile

Probiotics for the prevention of *Clostridium difficile* associated diarrhea in adults and children



- ▶ 21 Mart 2017'e kadar olan RKÇ (pubMed, EMBASE, Central, Cochrane IBS)
 - ▶ Primer sonuç: *C.difficile* insidansi
 - ▶ Sekonder sonuç: *C.difficile* saptanması, istenmeyen etkiler, AAD ve hastane yatış süresi
-
- ▶ 31 çalışma, 8672 hasta
 - ▶ Probiyotikler... CD insidansini ↓
 - ▶ Probiyotik grubunda %1.5
 - ▶ Kontrol grubunda % 4

Kılavuz önerileri

Clinical Practice Guidelines for *Clostridium difficile*
Infection in Adults and Children: 2017 Update by the
Infectious Diseases Society of America (IDSA) and Society
for Healthcare Epidemiology of America (SHEA)

Probiyotiklerle *C. difficile*
infeksiyonlarının önlenmesi için
klinik çalışmalar dışında yeterli
veri YOK

2017 Infectious Diseases Society of America Clinical
Practice Guidelines for the Diagnosis and Management of
Infectious Diarrhea

- ▶ **İnfeksiyöz ishalde probiyotikler**
 - **İmmümkompetan erişkin ve çocuklarda**
 - **İnfeksiyöz veya antibiyotik ilişkili ishalde**
- ↓
- **Semptomların şiddetini ve süresini azaltmak için önerilebilir (zayıf, orta öneri)**

Çocuk yaş grubu ishalleri ve probiyotikler



Use of Probiotics for Management of Acute Gastroenteritis: A Position Paper by the ESPGHAN Working Group for Probiotics and Prebiotics

**Hania Szajewska, †Alfredo Guarino, ‡Iva Hojsak, §Flavia Indrio, ‡Sanja Kolacek,
||Raanan Shamir, ¶Yvan Vandenplas, and #Zvi Weizman,
on Behalf of the ESPGHAN Working Group for Probiotics and Prebiotics*

- AGE li çocuk ve YD'da
- Sistematik review ve RKÇ incelenmiş
- ▶ Probiyotik olarak
 - *Lactobacillus*
 - *Bifidobacterium*
 - *Saccharomyces*
 - *Streptococcus*
 - *Enterococcus*
 - *Bacillus*

Use of Probiotics for Management of Acute Gastroenteritis: A Position Paper by the ESPGHAN Working Group for Probiotics and Prebiotics

**Hania Szajewska, †Alfredo Guarino, ‡Iva Hojsak, §Flavia Indrio, ‡Sanja Kolacek,
||Raanan Shamir, ¶Yvan Vandenplas, and #Zvi Weizman,
on Behalf of the ESPGHAN Working Group for Probiotics and Prebiotics*

- ▶ Primer sonuç: İshal miktarı ve süresi
- ▶ Diğer sonuçlar: hastane yatışı, süresi, rehidratasyon sonrası kilo kazanımı, kusma olup olmadığı

- **AGE esas tedavi: Rehidratasyon**
- **Probiyotikler: Diare süresini 1 gün kısaltır**
Yardımcı tedavi

Probiotics for gastrointestinal disorders: Proposed recommendations for children of the Asia-Pacific region

Table 2 Proposed recommendations for the Asia-Pacific region with grade and strength of recommendations

Disease		Recommendation	Strains	Grade	Weak
<u>Acute gastroenteritis</u>	T	Should be considered ¹	<i>S. boulardii</i> , <i>L. rhamnosus</i> GG <i>L. reuteri</i>	Moderate quality	Strong Strong Weak
<u>AAD</u>	P	May be considered	<i>L. rhamnosus</i> GG <i>S. boulardii</i>	Moderate quality	Strong Strong
<u>CDAD</u>	P	May be considered	<i>S. boulardii</i>	Low quality	Weak
<u>Nosocomial diarrhea</u>	P	Can be considered	<i>L. rhamnosus</i> GG	Moderate quality	Weak
<u>Traveler's diarrhea</u>	P	Not recommended		Very low quality	Weak
Functional intestinal disorders	T	Not recommended		Very low quality	Weak
Infant colics	T	May be considered	<i>L. reuteri</i>	Moderate quality	Weak
IBD (Crohn's disease, ulcerative colitis)	T	Not recommended		Low quality	Weak
<i>Helicobacter pylori</i> infection	T	May be considered	<i>S. boulardii</i> , others	Very low quality	Weak ² Weak
Necrotizing enterocolitis		Decision to be discussed with parents	Various (<i>Bifidobacterium</i> , <i>Lactobacillus</i> species)		

Table 1 Recommendations for use of probiotics in childhood intestinal diseases by geographic region

Diseases		Europe ^[14,40]	United States ^[36]	Latin America ^[50]	World ^[51]
Acute gastroenteritis	T	<i>L. rhamnosus</i> GG, <i>S. boulardii</i> , <i>L. reuteri</i>	<i>L. rhamnosus</i> GG, <i>S. boulardii</i>	<i>L. rhamnosus</i> GG, <i>S. boulardii</i> , <i>L. reuteri</i>	<i>S. boulardii</i> , <i>L. rhamnosus</i> GG, Indian Dahi
AAD	P	<i>L. rhamnosus</i> GG, <i>S. boulardii</i>	<i>L. rhamnosus</i> GG, <i>S. boulardii</i>	<i>L. rhamnosus</i> GG, <i>S. boulardii</i>	<i>S. boulardii</i> ; <i>L. rhamnosus</i> GG, <i>B. lactis</i> Bb12 + <i>S. thermophilus</i> , <i>L. rhamnosus</i> strains E/N, Oxy and Pen
CDAD	P	<i>S. boulardii</i>			
Nosocomial diarrhea	P	<i>L. rhamnosus</i> GG	<i>L. rhamnosus</i> GG	<i>L. rhamnosus</i> GG, <i>B. lactis</i> Bb12, <i>S. thermophilus</i> , <i>B. bifidum</i>	<i>L. rhamnosus</i> GG, <i>B. lactis</i> Bb12 + <i>S. Thermophilus</i>
Traveler's diarrhea	P			<i>S. boulardii</i>	
Functional intestinal disorders (IBS)	T	Insufficient evidence		<i>L. rhamnosus</i> GG, VSL#3	<i>L. rhamnosus</i> GG, <i>L. reuteri</i> DSM 17938
Infant colic	T	<i>L. reuteri</i> DSM 17938		<i>L. reuteri</i> DSM 17938	<i>L. reuteri</i> DSM 17938
IBD (CD, UC, pouchitis)	T	<i>E. coli</i> Nissle 1917, VSL#3 ¹		VSL#3 ¹	VSL#3 ²
<i>Helicobacter pylori</i> infection	T			Not recommended	<i>L. casei</i> DN-114 001

AGE Çocuk Hasta

- ▶ ABD, 10 merkez, 2014-2017
- ▶ 3 ay- 4 yaş, AGE
- ▶ Prospektif, randomize, çift kör

761 hasta

- ▶ **468**... *L. rhamnosus GG*
1x10¹⁰, 2x1/gün (5 gün)
- ▶ **475**... placebo

- ▶ İzlem: 5 gün boyunca, 14. gün ve 1. ay



- ▶ **Primer sonuç:** hastalık ciddiyeti (Vesikari skalası)
- ▶ **Sekonder sonuç:** ishal süresi, sıklığı, kusma, bakım ihtiyacı, evdekilere geçiş

Table 1. Modified Vesikari Scale.*

Scale component	Score on the Vesikari Scale			
	0 Points	1 Point	2 Points	3 Points
Duration of diarrhea (hr)	0	1–96	97–120	≥121
Maximum no. of watery stools per 24 hr	0	1–3	4–5	≥6
Duration of vomiting (hr)	0	1–24	25–48	≥49
Maximum no. of vomiting episodes per 24 hr	0	1	2–4	≥5
Maximum recorded rectal temperature (°C)†	<37.0	37.1–38.4	38.5–38.9	≥39.0
Unscheduled health care visit	None	NA	Primary care	Emergency department
Treatment	None	Rehydration with intravenous fluids	Hospitalization	NA

* In the modified Vesikari scale score, one variable (percent dehydration) in the original score was replaced with the variable of unscheduled health care visits to better measure the effect of acute gastroenteritis in outpatients, given that the ability to perform frequent in-person assessments in an outpatient cohort of children can be challenging. Scores range from 0 to 20, with higher scores indicating more severe disease. Children with a score of 9 or more were considered to have moderate-to-severe gastroenteritis.^{25,26} NA denotes not applicable.

† Temperatures were adjusted for the location of measurement: 1.1°C was added to axillary temperatures and 0.6°C was

Characteristic	<i>L. rhamnosus</i> GG (N=483)	Placebo (N=488)	Overall (N=971)
37.1 to 38.4°C	31 (6.4)	24 (4.9)	55 (5.7)
38.5 to 38.9°C	35 (7.3)	37 (7.6)	72 (7.4)
≥39°C	130 (27.0)	137 (28.2)	267 (27.6)
Dehydration score§			
No. of participants assessed	480	481	961
Median (IQR)	0 (0–1)	0 (0–1)	0 (0–1)
Distribution — no. (%)			
0	347 (72.3)	348 (72.3)	695 (72.3)
1 to 4	124 (25.8)	124 (25.8)	248 (25.8)
5 to 8	9 (1.9)	9 (1.9)	18 (1.9)
Duration of symptoms <48 hr — no. (%)	175 (36.2)	197 (40.4)	372 (38.3)
Receipt of antibiotics in previous 14 days — no./total no. (%)	39/478 (8.2)	36/480 (7.5)	75/958 (7.8)
Receipt of any dose of rotavirus vaccine — no./total no. (%)	210/313 (67.1)	206/319 (64.6)	416/632 (65.8)
Stool sample for multiplex polymerase-chain-reaction assay			
No. of participants from whom stool sample was obtained (%)	379 (78.5)	382 (78.3)	761 (78.4)
Result — no. (%)			
Negative	153 (40.4)	173 (45.3)	326 (42.8)
Norovirus GI or GII	79 (20.8)	70 (18.3)	149 (19.6)
Rotavirus A			
Adenovirus 40 or 41			
<i>Clostridium difficile</i> toxin			
<i>Shigella</i>			
<i>Campylobacter</i>			
<i>Salmonella</i>			
<i>Escherichia coli</i> O157			
Enterotoxigenic <i>E. coli</i> L			
Shiga toxin-producing <i>E. coli</i>			
<i>Giardia</i>			
<i>Cryptosporidium</i>			
<i>Entamoeba histolytica</i>			
<i>Vibrio cholerae</i>	0	1 (0.3)	1 (0.1)
<i>Yersinia enterocolitica</i>	0	0	0

Etkenler	probiyotik	plasebo
Norovirüs	79	70
Rotavirüs	75	60
Adenovirüs	28	41
C. difficile	25	31
Shigella	23	15
Camplobacter	5	4

Table 3. Trial Outcomes, According to Assigned Trial Group.*

Outcome	<i>L. rhamnosus</i> GG (N=468)	Placebo (N=475)	Relative Risk (95% CI)	P Value†
Primary outcome‡				
Modified Vesikari scale score of 0 to 8 — no. (%)	413 (88.2)	415 (87.4)		
Modified Vesikari scale score ≥9 — no. (%)	55 (11.8)	60 (12.6)	0.96 (0.68–1.35)	0.83
Secondary outcomes and individual components of 14-day modified Vesikari scale score				
Median modified Vesikari scale score (IQR)	4 (2–6)	4 (2–6)		0.85
Diarrhea				
Median time to the last watery stool (IQR) — hr	49.7 (18.8–86.4)	50.9 (25.0–88.2)		0.26
Median total no. of diarrheal episodes (IQR)	7 (3–12)	7 (3–14)		0.43
Vomiting				
Median time to the last vomiting episode (IQR) — hr§	0.0 (0.0–21.9)	0.0 (0.0–17.8)		0.17
Median total no. of vomiting episodes (IQR)§	0 (0–2)	0 (0–2)		0.20
Receipt of intravenous fluids — no. (%)	19 (4.1)	22 (4.6)		0.59
Hospital admission — no. (%)	15 (3.2)	15 (3.2)		0.93
Repeat health care visit within 2 weeks after the index visit — no. (%)	57 (12.2)	80 (16.8)		0.03¶
Repeat emergency department visit within 2 weeks after the index visit — no. (%)	32 (6.8)	37 (7.8)		0.55
Median no. of days of day care missed (IQR)	2 (1–3)	2 (1–3)		0.67
Median no. of hours of work missed by parent or guardian (IQR)	0 (0–8)	0 (0–8)		0.52
Household transmission — no. (%)**	43 (10.6)	59 (14.1)		0.16

Chinese clinical practice guidelines for acute infectious diarrhea in children

- ▶ Probiyotikler: akut viral ishalde etkili (A)
- ▶ Erken evrede daha iyi (B)
- ▶ İnvaziv bakteriyel ishalde belirgin etkisi yok (A)
- ▶ Aİİ de etkili (D)

▶ Akut infeksiyöz ishal süresini ↓

S. baulardii (A)

L. rhamnosus GG (A)

L. reuteri, *L. bulgaricus*, *L. acidophilus* (B)

Bifidobacterium+ *Lactobacillus* ve *S. termophilus* (C)

Guidance on the use of probiotics in clinical practice in children with selected clinical conditions and in specific vulnerable groups

Table 1 Summary of proposed practice points for every reported clinical indication

Clinical indication	Practice points
Prevention of common infections	Aİ ishal önleme: <i>S. baulardii</i> ve <i>L.rhamnosus GG</i> C. difficile önleme: <i>S. baulardii</i> AGE tedavisi: ORS ek olarak <i>S. baulardii</i> ve <i>L. GG</i> düşünülebilir.
Prevention of nosocomial infections	
Prevention of allergy	Based on the currently available evidence, probiotics cannot be recommended for prevention of atopic diseases.
Prevention of antibiotic-associated diarrhoea	- In prevention of AAD, LGG or <i>S. baulardii</i> should be considered. <i>S. baulardii</i> is also to be considered in the prevention of C difficile-associated diarrhoea. - Other strains of probiotics, single or in combination, are currently not recommended. - No safety data on the use of probiotics for prevention of AAD in severely ill children are available; thus, their use should be subjected to special scrutiny.
Treatment of acute gastroenteritis	- In the treatment of AGE in children, LGG and <i>S. baulardii</i> may be considered as an adjunct to the oral rehydration therapy. - LGG should be administered for 5–7 days, at dose $\geq 10^{10}$ CFU/day. <i>S. baulardii</i> should be administered for 5–7 days, at dose 250–750 mg/day. - Other strains or products containing single or multiple strains of probiotics have currently no recommendation. - Probiotic should ideally be initiated early in the course of diarrhoea.

QUESTION 2

Probiotics in acute infectious diarrhoea: should we run with it?

Table 1 Summary of papers

Citation	Study group	Study type	Outcome	Key result	Comments
Allen <i>et al</i> (2010), ⁷ UK	n=8014; 6489 <18 years, age not specified in 1173 Included 63 RCTs comparing probiotic use with placebo or no	Cochrane review (1a)	Duration of diarrhoea	'Consistent beneficial effect' with different probiotics and	► 56 trials included children only ► Studies deemed at high risk of bias were included as exclusion had no sensitivity (sensitivity review) Probiotics were pooled and interpreted together 'marked variability' in study methods/ the resultant weakening of evidence base probiotics were commenced in the treatment knowledge high interstudy variability npt to consider cost-effectiveness and e required to explore 'specific probiotic lients parate research exploring specific probiotics ding infant atopy analysis confirmed-LGG reduces diarrhoea n European studies es are methodologically sound' yet 2 = 98%) is 'caused by factors other than cal quality' es required to further explore appropriate conflict of interest-She has been a guest speaker s. She also has links with Danone, Dicoform, Hipp, Nutrition Institute, Nutricia, Mead Johnson and Sequoia Arla, Biogaia and Biocodex ► All RCTs were also included in the 2010 Allen Cochrane review
Szajewska <i>et al</i> (2013), ¹⁴ Poland					
Dinleyici and Vandenplas (2014), ¹⁵ Turkey	Multicentre single-blind RCT assessing 'the effect of 1×10^8 CFU <i>L. reuteri</i> DSM 17938 on hospitalised children with acute non-bloody diarrhoea' lasting 12–72 hours; n=127 children (64 in the probiotic group, 63 in the control group)	RCT—multicentre single-blind	Duration of diarrhoea	33-hour shorter duration in <i>L. reuteri</i> group Mean±SD = 70.7±26.1 hours vs 103.8±28.4 hours, p<0.001	► Included children were aged 3–60 months ► Only hospitalised children were included in analysis ► Excluded children presenting in shock ► Both the <i>L. reuteri</i> and placebo group received ORS ► Recommends further studies investigating outpatients and cost-effectiveness
Dinleyici <i>et al</i> (2015), ¹⁶ Turkey	Multicentre single-blind RCT comparing the effect of <i>S. boulardii</i> CNCM I-745 and placebo on diarrhoea duration n=363 children	RCT—multicentre single blind	Duration of diarrhoea	24-hour shorter duration in <i>S. boulardii</i> group Mean±SD = 75.4±33.1 vs	► Study inclusive of hospital and outpatient patients ► 'Significant reduction of diarrhoea duration in hospital, emergency care unit and outpatient settings'

- <18 yaş...probiyotikler ishal süresini kısaltabilir (A kanıt düzeyi)
- Önerilen probiyotikler
 - *S. baulardii*
 - *L. GG* ve
 - *L. reuteri* DSM 17938 (D kanıt düzeyi)

Probiotic Safety- No Guarantees

- Immunsuprese, kateteri olan hastalarda:
 - Bakteriyemi
 - Fungemi
 - Peritonit.....
- Allerjik reaksiyon
- Direnç (kazanılmış veya intrinsik direnç genleri aktarılabiliyor)

Cohen PA. JAMA Intern Med Eylül 2018

The New York Times

THE NEW HEALTH CARE

There are potential harms as well as benefits, and a lot of wishful thinking and imprecision in the marketing of products containing them.



By Aaron E. Carroll

Oct. 22, 2018

Sonuç olarak

- ▶ Probiyotiklerle ilgili çok fazla çalışma olmasına rağmen sonuçlar birbiri ile uyuşmuyor
- ▶ Çocuk ve erişkin ishallerinin süresi ve sıklığını azaltmakta
- ▶ Erişkin hastalarla ilgili tedavi ve önlemle ilgili kılavuz önerileri yetersiz.
- ▶ Aİİ ve seyahat ilişkili ishalin önlenmesinde yararlı
(*S. baulardii*)
- ▶ Bazı hasta gruplarında yararları yanısıra ciddi istenmeyen sonuçlara yol açabilmekte
- ▶ **İnfeksiyöz ishallerde dehidratasyonun tedavisi +/- antibiyotik tedavisi esas tedavi**
- ▶ Probiyotikler yardımcı tedaviler olarak düşünülmeli.

Teşekkürler