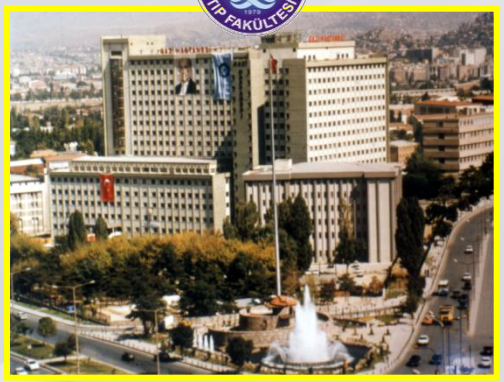
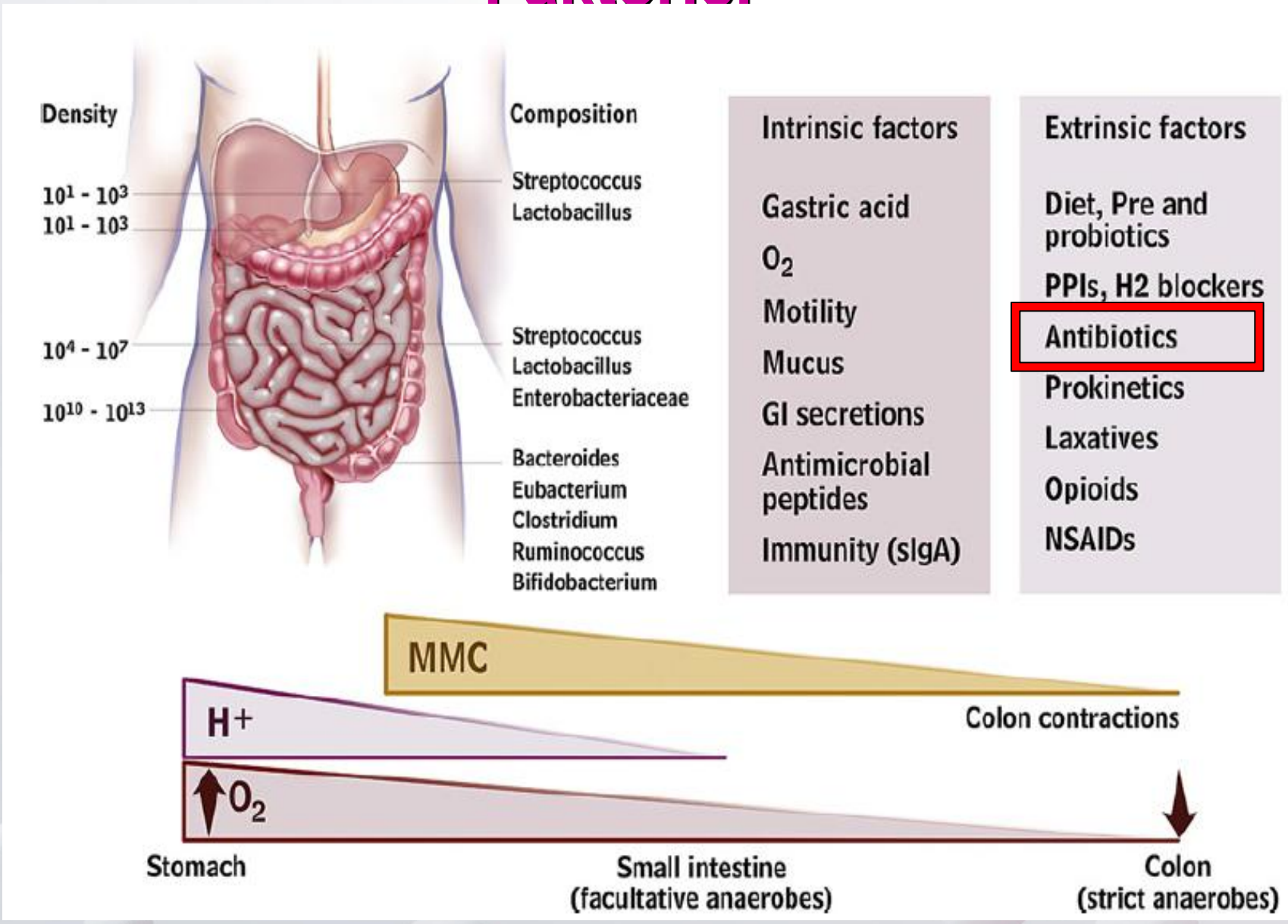
Clostridium difficile –Tedavi Prensipleri

Esin ŞENOL

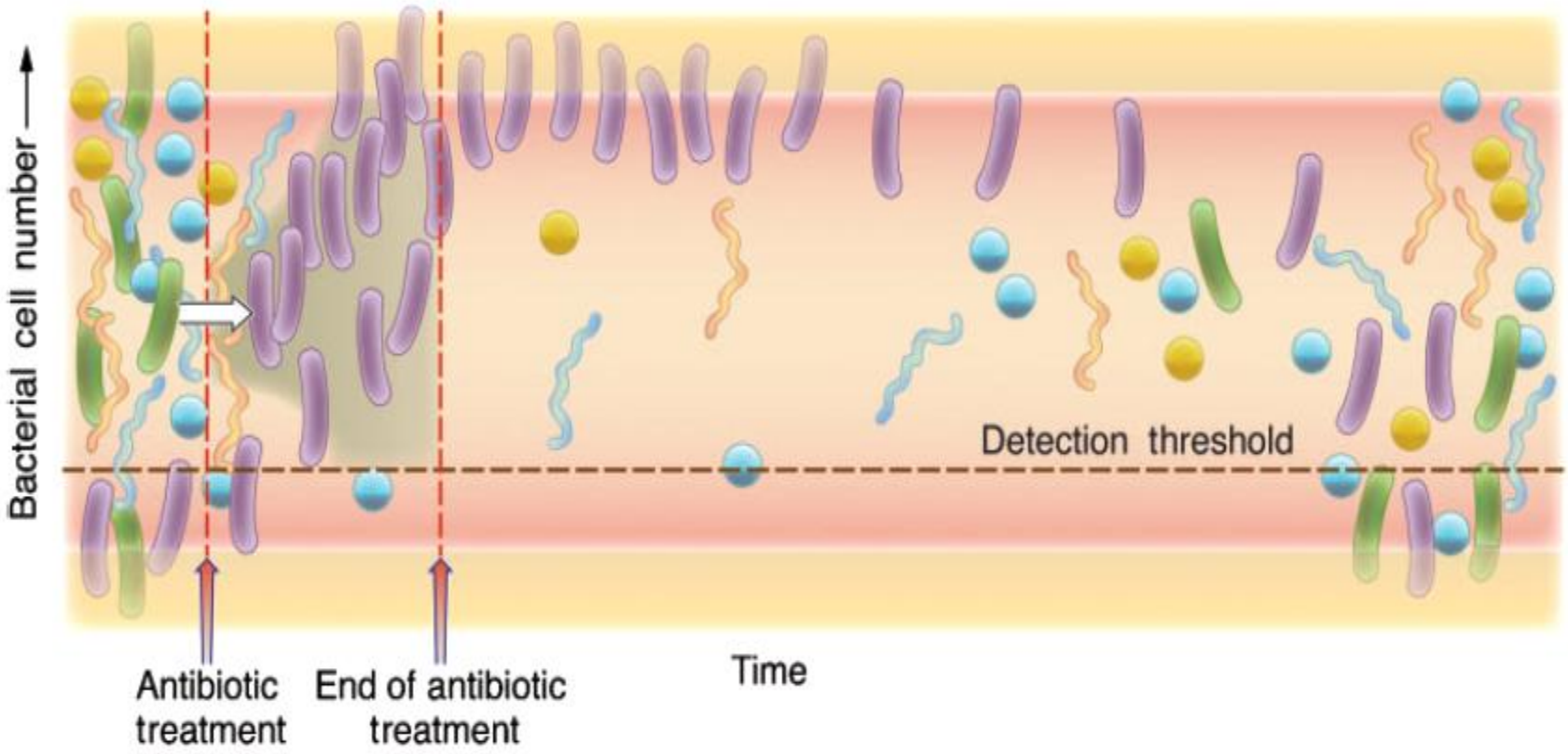
G.Ü.T.F. Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji-AD



Barsak Mikrobiyotasını Etkileyen Faktörler



Antibiyotik kullanımının mikroflora üzerine etkisi



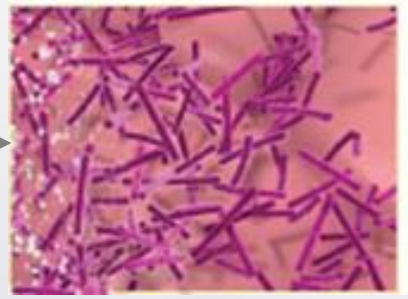
Microbiology (2010), **156**, 3216–3223

Antibiyotik-İlişkili ishal

ANTİBİYOTİK

Normal B Florası

Antibiyotiklerle karşılaşan floranın bozulması (Beyaz)



Bozulan mikroflora (ör, *C difficile*)

Anaerobik bakteri supresyonu

Karbonhidrat metabolizmasındaki bozulma

Ozmotik

Azalmış Kısa Zincirli Yağ Asitleri inflamasyon

İSHAL

Klavulonate, Eritromisin

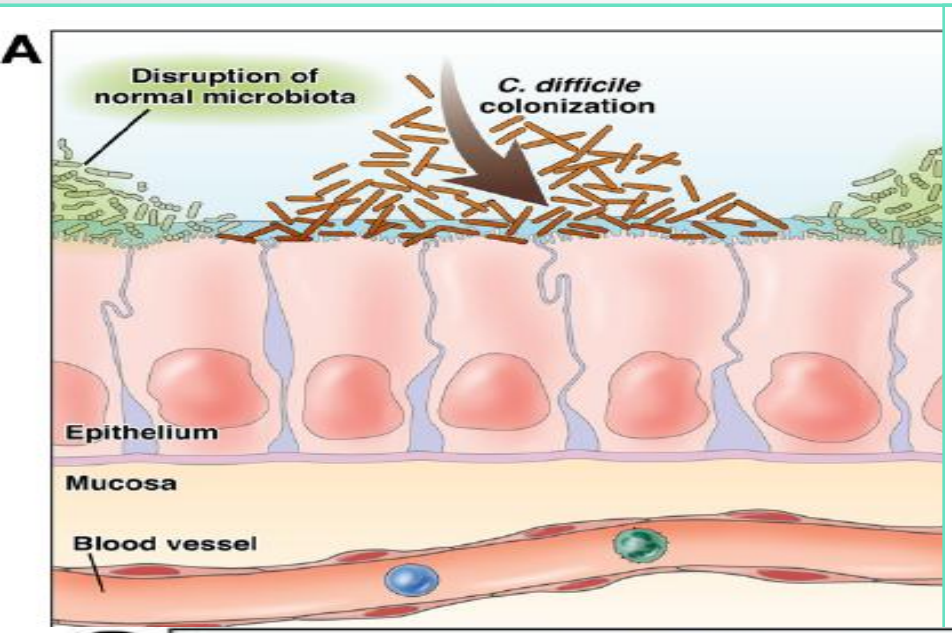
Prokinetik

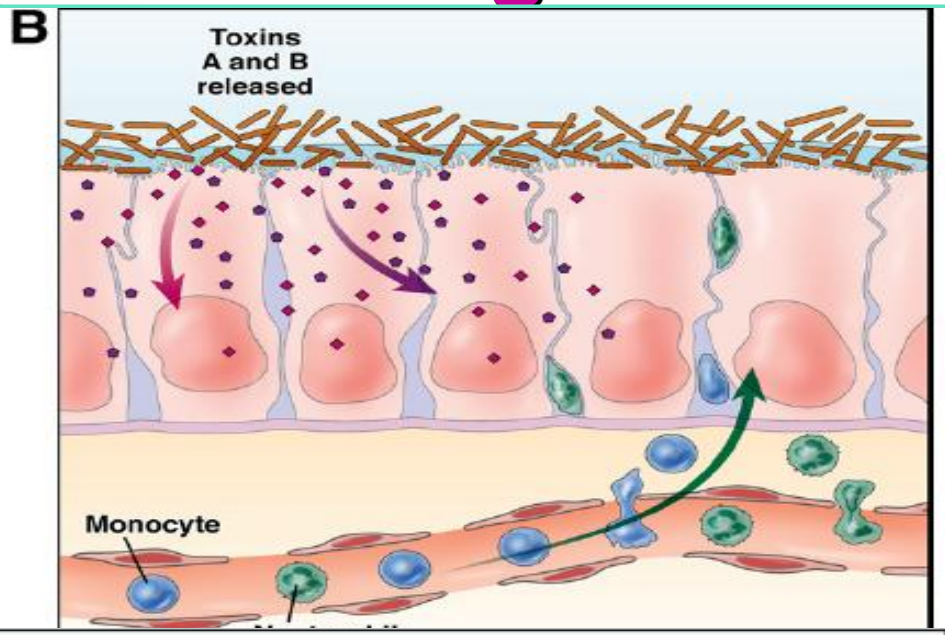
Bouhnik Y. *Gut Microflora Digestive Physiology And Pathology*. Paris; 2009:181-197.

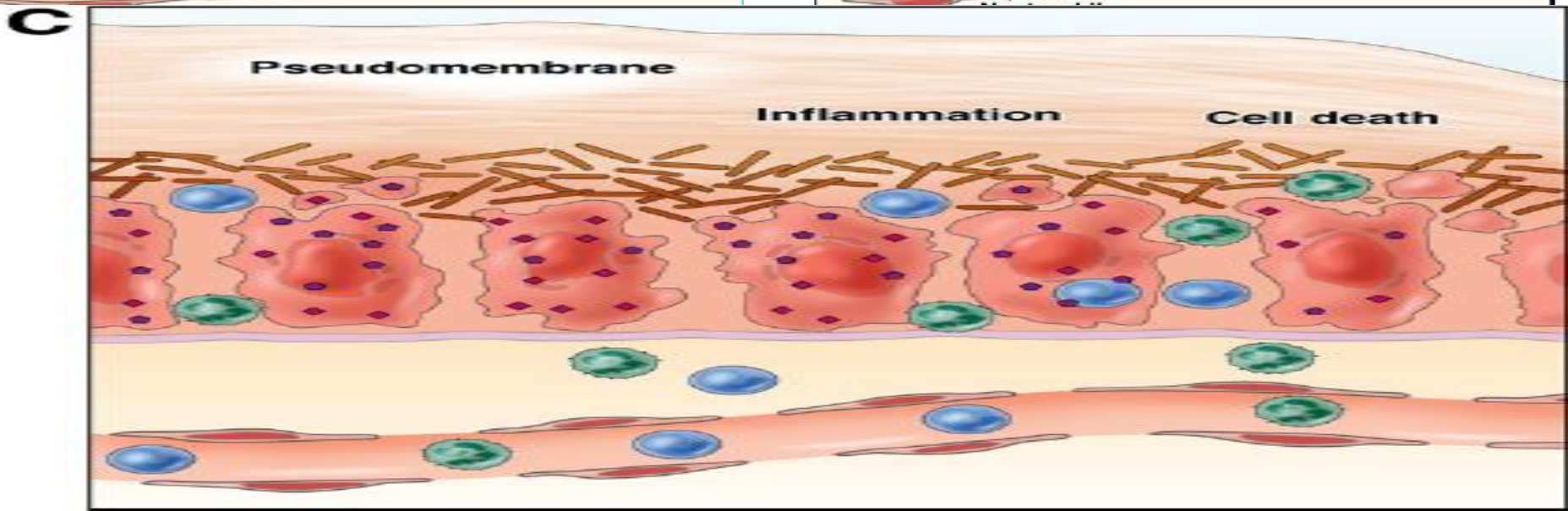
ANTİBİYOTİK SONRASI İSHAL VE *C.difficile* İLE İLİŞKİSİ

- ✓ Koliti olmayan olguların % 15 -25 i
- ✓ Koliti olan olguların %50-70 i
- ✓ Psödomembranöz enterokoliti- % 100

Clostridium difficile- Patogenez







C. difficile ilişkili ishal

- CDC tarafından *C. difficile* infeksiyonun şiddetinin ve sıklığının arttığı bildirilmiştir.
- HİPERVİRULAN SUŞ
- Kanada hastanelerinde ise
  - 1997-2005 yılları arasında
    - 10000 hasta gününde 3,8'den 9,5'a ve
    - Her 1000 yatışta 3,4'den 8,4 artığı gösterilmiştir

Cohen SH et al. IDSA Guidelines 2010
Hall Aj, et al. The roles of C. difficile and norovirus among gastroenteritis-associated deaths in the United States, 1999-2007. CID 2012

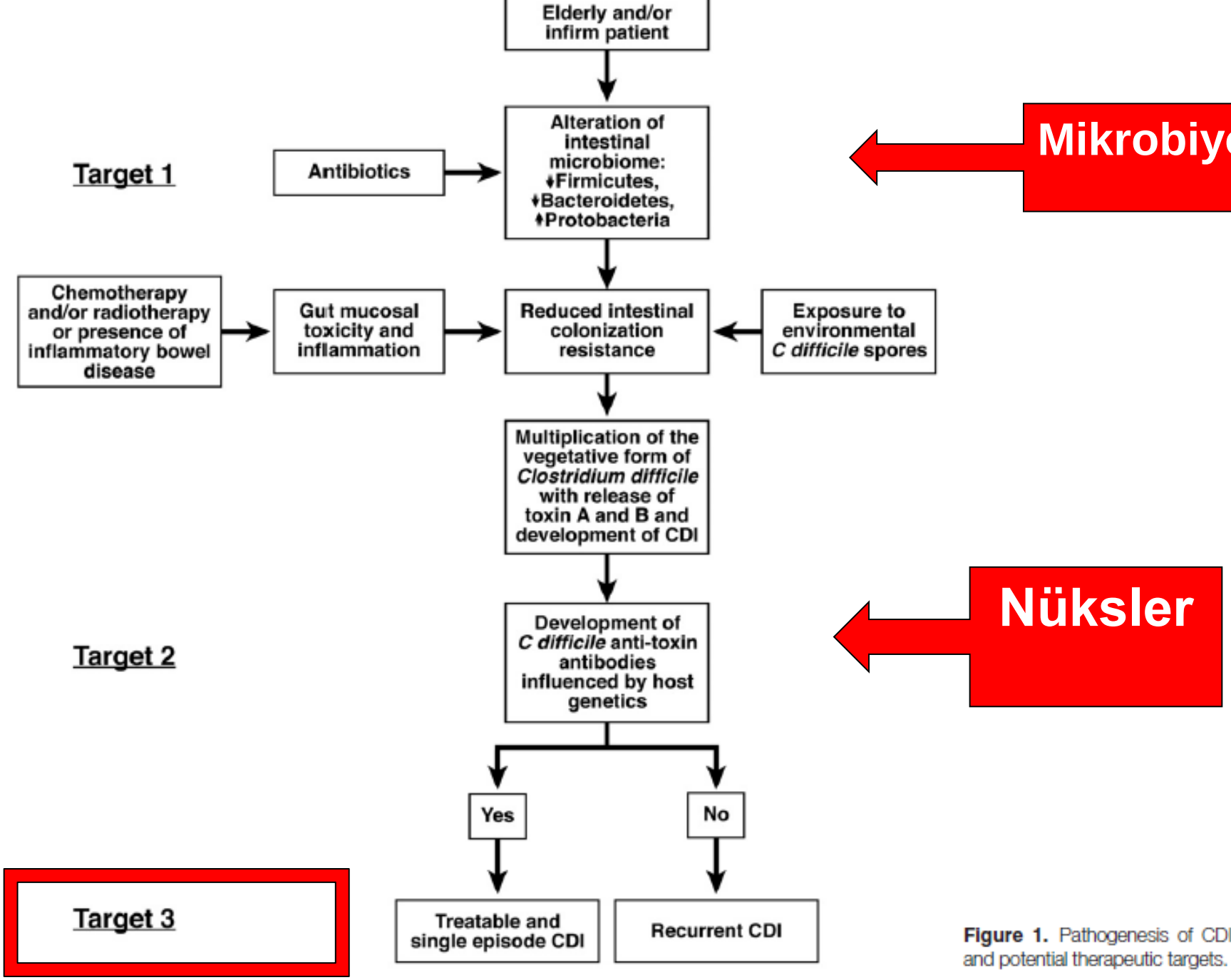


Figure 1. Pathogenesis of CDI and potential therapeutic targets.

C.difficile tedavi

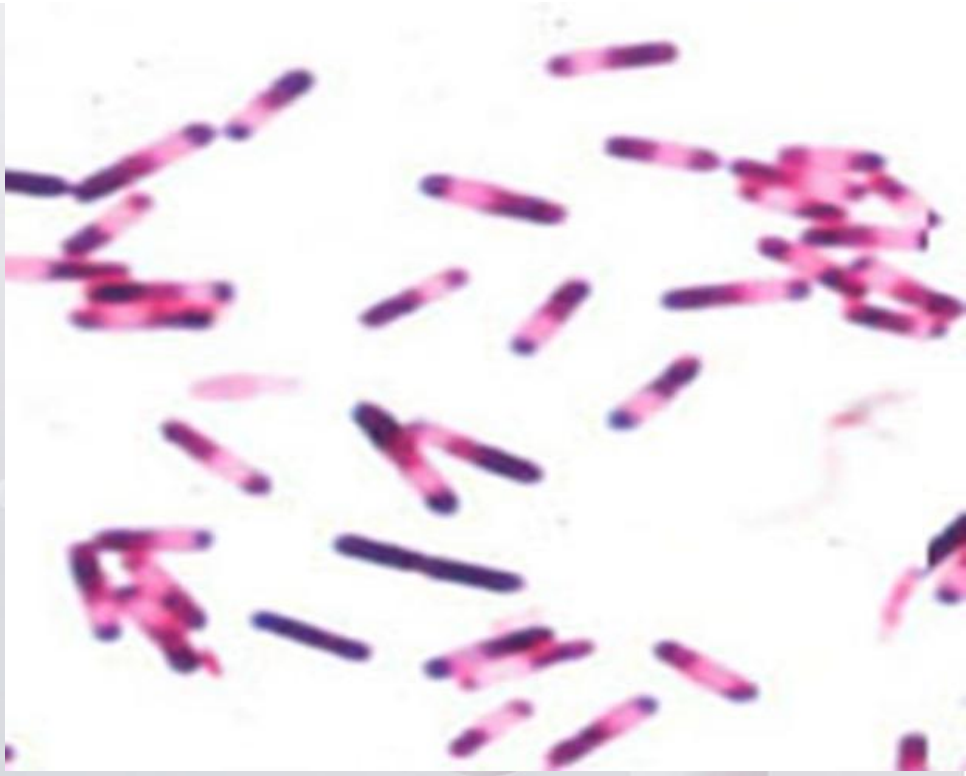
- Metronidazol (PO, IV)
- Vankomisin (po, rektal yoldan)
- Fidaxomicin(PO)
- Alternatifler
  - IVIG-ÖNERİLMİYOR
  - Rifaximin-ÖNERİLMİYOR
  - TİGESİKLİN
  - NÜKSLERİN ÖNLENMESİNDE PROBİYOTİKLER

INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY MAY 2010, VOL. 31, NO. 5

SHEA-IDSA GUIDELINE

Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults: 2010 Update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA)

Stuart H. Cohen, MD; Dale N. Gerding, MD; Stuart Johnson, MD; Ciaran P. Kelly, MD; Vivian G. Loo, MD; L. Clifford McDonald, MD; Jacques Pepin, MD; Mark H. Wilcox, MD



CME

Guidelines for Diagnosis, Treatment, and Prevention of *Clostridium difficile* Infections

Christina M. Surawicz, MD[1], Lawrence J. Brandt, MD[2], David G. Binion, MD[3], Ashwin N. Ananthakrishnan, MD, MPH[4], Scott R. Curry, MD[5], Peter H. Gilligan, PhD[6], Lynne V. McFarland, PhD[7,8], Mark Mellow, MD[9] and Brian S. Zuckerbraun, MD[10]

Clostridium difficile **infection (CDI) is a leading cause of hospital-associated gastrointestinal illness and places a high burden on our health-care system. Patients with CDI typically have extended lengths-of-stay in hospitals, and CDI is a frequent cause of large hospital outbreaks of disease. This guideline provides recommendations for the diagnosis and management of patients with CDI as well as for the prevention and control of outbreaks while supplementing previously published guidelines. New molecular diagnostic stool tests will likely replace current enzyme immunoassay tests. We suggest treatment of patients be stratified depending on whether they have mild-to-moderate, severe, or complicated disease. Therapy with metronidazole remains the choice for mild-to-moderate disease but may not be adequate for patients with severe or complicated disease. We propose a classification of disease severity to guide therapy that is useful for clinicians. We review current treatment options for patients with recurrent CDI and recommendations for the control and prevention of outbreaks of CDI.**

Am J Gastroenterol 2013; 108:478–498; doi:10.1038/ajg.2013.4; published online 26 February 2013

Kuvvetli şüphe varlığında laboratuvar tetkikleri beklenilmeden- EMPİRİK TEDAVİ

C. difficile toksinin ya da toksijenik C. difficile'nin dışkı testinde pozitif saptanması ya da pseudomembranöz kolitin kolonoskopik ve histopatolojik olarak saptanması olarak tanımlanmış- ÖNCEKİ REHBER

Tedavi

İlk CDI atağında tedavi başlarken

Ağır/Komplike

- Yaş(>65 yaş),
- Lökosit (>15 000hücre/mL)
- Kreatinin düzeyindeki 1,5kat artış olmasına göre yapılmaktadır.

Hipoalbüminemi+Lökositoz/ Abdominal hassasiyet

Kolektomi

Serum laktat düzeyi >5mmol/L + WBC>50.000 perioperatif mortalite ile yakın ilişkili

Cohen SH et al. Clinical practice guidelines for C. difficile infection in adults: 2010
http://www.uptodate.com/contents/clostridium-difficile(18.02.2013

Table 3. **CDI severity scoring system and summary of recommended treatments**

Severity	Criteria	Treatment	Comment
Mild-to-moderate disease	Diarrhea plus any additional signs or symptoms not meeting severe or complicated criteria	Metronidazole 500 mg orally three times a day for 10 days. If unable to take metronidazole, vancomycin 125 mg orally four times a day for 10 days	If no improvement in 5–7 days, consider change to vancomycin at standard dose (vancomycin 125 mg four times a day for 10 days)
Severe disease	Serum albumin <3 g/dl plus ONE of the following: WBC ≥15,000 cells/mm^3, Abdominal tenderness	Vancomycin 125 mg orally four times a day for 10 days	
Severe and complicated disease	Any of the following attributable to CDI: Admission to intensive care unit for CDI Hypotension with or without required use of vasopressors Fever ≥38.5 °C Ileus or significant abdominal distention Mental status changes WBC ≥35,000 cells/mm^3 or <2,000 cells/mm^3 Serum lactate levels >2.2 mmol/l End organ failure (mechanical ventilation, renal failure, etc.)	Vancomycin 500 mg orally four times a day and metronidazole 500 mg IV every 8 h, and vancomycin per rectum (vancomycin 500 mg in 500 ml saline as enema) four times a day	Surgical consultation suggested
Recurrent CDI	Recurrent CDI within 8 weeks of completion of therapy	Repeat metronidazole or vancomycin pulse regimen	Consider FMT after 3 recurrences

CDI, *Clostridium difficile* infection; FMT, fecal microbiota transplant; IV, intravenous; WBC, white blood cell.

RÇT Θ
Tigesiklin/fidaxomicin

10 g.4x125 mg 3 günde bir
125 mg/gün/..10 doz.

Fidaxomicin

- FDA Mayıs 2011 onaylandı,hafif-orta şiddetli CDİ
- Makrosiklik antibiyotik
- *C. difficile*'ye bakterisidal etkili ilaç
- Daha dar spektrumlu olması nedeniyle kolon anaerobik mikroflorayı daha az bozmaktadır.
- Barsak emilimi zayıftır
- Postantibiyotik etkili
- 200 mg PO BID x 10 gün
- Yan etki: Bulantı, kusma

Louie TJ et al. NEJM 2011

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Fidaxomicin versus Vancomycin for *Clostridium difficile* Infection

Thomas J. Louie, M.D., Mark A. Miller, M.D., Kathleen M. Mullane, D.O., Karl Weiss, M.D., Arnold Lentnek, M.D., Yoav Golan, M.D., Sherwood Gorbach, M.D., Pamela Sears, Ph.D., and Youe-Kong Shue, Ph.D., for the OPT-80-003 Clinical Study Group*

N Engl J Med 2011;364:422-31.

Fidaxomicin:

- **Nüks CDİ önlenimindeki üstünlük yalnızca hipervirulan suş için**
- **Rekürrens riski yüksek hastaların başlangıç tedavisinde verildiğinde, vankomisine göre daha az tekrarlama oranları gösterilmiştir. (fidaxomisin%19, vankomisin%35)**

Cornely OA. Treatment of first recurrence of *C. difficile* infection: fidaxomicin versus vancomycin. CID 2012

Table 4. Cost of antibiotic therapy for *C. difficile* infection

	Cost per dose	Regimen	Cost per 10-day regimen
Metronidazole 500 mg	$0.73	500 mg three times a day	$22.00
Vancomycin 125 mg pills	$17.00	125 mg four times a day	$680.00
Vancomycin 125 mg IV compounded for oral	$2.50–$10.00	125 mg four times a day	$100.00–$400.00
Fidaxomicin 200 mg	$140.00	200 mg twice a day	$2,800.00

IV, intravenous.

Vancomycin IV form can be compounded for oral use as well as used for enema therapy.

Fekal bakterioterapi

- Sağlıklı donörden alınan feçes belli oranlarda dilüe edilerek, nazogastrik, nazojejunal, kolonoskopik veya enema yoluyla verilebilmektedir.
- Nüks CDİ- kür oranı %81-94 arasındadır

- En sık yan etkisi 3 saat içinde hafif diare, kramplar ve geğirme olabilmektedir.
- Etkisi 24 saat-12 gün arasında gözleniyor
- ishal ve eşlik eden semptomlar tamamen düzeliyor
- Psödomembranlar ortadan kalkıyor

Tvede M, et al. Bacteriotherapy for chronic relapsing C. difficile diarrhoea in six patients. Lancet 1989
Chang JY, et al. Decreased diversity of the fecal Microbiome in recurrent C. difficile-associated diarrhea. J Infect Dis 2008

Fekal bakterioterapi-yöntem

Donor gaita incelemesi (parazit, patojen bakteriler (*C.difficile* dahil), viral etkenler,)

Kan: CBC, HIV-1,HIV-2, Hepatit A,B,C

Sağlıklı donör kararı : son 6 ay içinde antibiyotik kullanmamış ve inflamatuvar barsak hastalığı olmayan olan donörden günlük gaita 200-300g donör gaita 200-300 mL steril SF homojenize edilerek

- **Enema yoluyla 10 dk verilmekte (5 gün içinde günlük tekrarlanmakta) loperamid verilerek enema retansiyonu engellenmektedir**
- **Kolonoskopi ile terminal ileuma verilebilir kolonik inflamasyon nedeniyle kolon perforasyonu riski olabilir son derece dikkatli yapılmalıdır**
- **Nazogastrik tüp (nazogastrik veya nazojejunal) ile verilebilir**
  - **vankomisin 4x500mg 4 gün tedavi takiben hazırlanmış infüzyon 25-30g gaita 50mL tuzlu su ile dilue edilerek üst GIS yoluyla verilmekte**

Fecal transplantation poses dilemma for FDA

Box 1 Stool bank shut down

In 2011, Eric Alm, an associate professor at MIT and an associate member of the Broad Institute in Cambridge, and Mark Smith, a PhD candidate in Alm's laboratory, became interested in fecal transplant. At the time, the procedure was limited in scope. "We were trying to figure out where to get samples so we could sequence patients," Smith says. As they delved into the area, they also became aware of the treatment risks individuals were taking with stool obtained without adequate quality checks. "[We feared] a black market of people doing this at home when there's no access in a way that's potentially dangerous," Smith says. Banking stool, making it available in a standardized, quality-controlled manner to clinicians, seemed like "a good solution to make compliance a little easier and probably safer from the FDA's perspective," he says.

But FDA thought otherwise. Its decision to allow FMT only when the stool source is known to either the physician or the patient was aimed at and has effectively shut down Open Biome's efforts in the US. "We are the only organization that would be affected by [the ruling], and our conversation with FDA was consistent with that," Smith says. Open Biome is working on an IND that investigators will be able to reference for their studies. "We will provide the Master Drug File [an essential part of an IND] as a material supplier," Smith says, easing the IND process for clinicians. In the meantime, Open Biome is looking at supplying stool for researchers outside the US. "I'd like to create an international registry on FMT—a universal database for clinical and scientific studies."

Table 1. Available antibiotics and investigational new agents for the management of CDI. (Adapted from Cornely [2012] and Venugopal and Johnson [2012].)

Agent	Dose	Relative efficacy	Recurrence risk	Resistance in clinical isolates	Adverse events	Comments
Fidaxomicin	200 mg po bid for 10 days	+++	+	Not reported	Abdominal pain, nausea, vomiting, anemia, neutropenia bowel obstruction and gastrointestinal hemorrhage	FDA approved for CDI; first-in-class oral macrocyclic antibiotic with targeted bactericidal activity against *C. difficile* and minimal impact on normal flora
Vancomycin	125 mg po qid for 10 days or 'taper/pulse' for recurrence: 125 mg po qid for 10–14 days, then 125 mg po bid per day for 1 week, then 125 mg po daily for 1 week, then 125 mg po every 2 or 3 days for 2–8 weeks	+++	++	Not reported	Nausea, not absorbed so systemic symptoms unlikely	FDA approved for CDI; potential for resistance induction in other clinically important pathogens (VRE)
Metronidazole	500 mg po tid for 10 days or 250 mg po qid for 10 days	++	++	Increased MICs noted in some studies	Nausea, neuropathy, abnormal taste in mouth	Not FDA approved for CDI, increased reports of treatment failures and slow response, less effective in severe CDI
Nitazoxanide	500 mg po bid for 10 days	++	++	Not reported	Nausea, diarrhea, abdominal pain	Not FDA approved
Rifaximin	400 mg po tid for 10 days or 'chaser' regimen 400 mg po bid for 14 days	++	+?	Potential for development of high-level resistance	Headaches, abdominal pain, nausea, flatulence, not absorbed	Not FDA approved for CDI, used primarily as post-vancomycin
Teicoplanin	400 mg po bid for 10 days	+++	++	Not reported	Not absorbed so systemic symptoms unlikely	Not FDA approved for CDI, similar results to vancomycin.
Tigecycline	50 mg iv every 12 hours for 10 days	++?	?	Not reported	Nausea, vomiting, diarrhea	Not FDA approved for CDI; limited case reports of treatment success and failures
Bacitracin	25,000 units po qid for 10 days	+	+++	Increased resistance noted	Minimal absorbed, poor taste	Not FDA approved for CDI; limited efficacy secondary to resistance
Fusidic acid	250 mg po tid for 10 days	++	++	Reported *in vivo*	Nausea, vomiting, epigastric pain, anorexia	Not FDA approved for CDI, concern about use as a single agent

bid, twice daily; CDI, *Clostridium difficile* infection; FDA, United States Food and Drug Administration; po, *per os*; qid, four times daily; tid, three times daily.

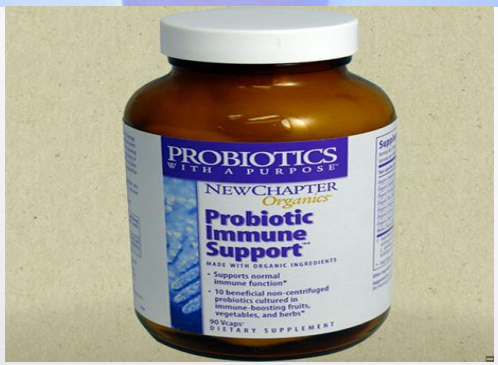
Table 2. Nonantibiotic alternatives and investigational new agents for the management of CDI. (Adapted from Cornely [2012] and Venugopal and Johnson [2012].)

Agent	Comments
IVIG	Multisystemic side-effects profile. Most commonly renal failure. Efficacy for use in adults is inconclusive; in pediatrics, evidence favors efficacy.
Fecal transplantation	Infusion of feces from a healthy donor. Most evidence comes from single-center case series and case reports. A recent multicenter, long-term follow-up study has shown positive results.
Probiotics	Multiple studies favor the use of probiotics for the prevention of CDI and antibiotic associated diarrhea (Hempil *et al.* 2012; Johnson *et al.* 2012; McFarland, 2006); however, appropriately powered studies are needed to confirm these findings. Guidelines do not recommend the routine use of probiotics given the lack of definitive evidence of effectiveness and potential risk of blood stream infection.
Investigational new agents	
Agent	Comments
Ramoplanin	Under investigation (phase III) for the treatment of CDI. Lipoglycodepsipeptide with spectrum activity similar to vancomycin but considerably more potent.
CB-183,315	Narrow spectrum, Gram-positive lipopeptide antibiotic in phase III: development status (Mascio *et al.* 2012; Rege *et al.* 2012; NTC 01597505; NTC 01598311).
Cadazolid	Hybrid oxazolidinone-quinolone antibiotic. Currently in phase II [ClinicalTrials.gov identifier: NCT01222702].
CDAI and CDBI	Human monoclonal antibodies against *C. difficile* toxins A and B. Phase III trials for prevention of CDI, recurrence (MODIFY I [ClinicalTrials.gov identifier: NCT01241552] and MODIFY II [ClinicalTrials.gov identifier: NCT01513239]).
ACAM-CDIFF	Active *C. difficile* toxoid vaccine. Phase II placebo-controlled for primary CDI prevention [ClinicalTrials.gov identifier: NCT00772343].
VP 20621	Nontoxigenic *C. difficile*. Phase II trial for prevention of CDI recurrence [ClinicalTrials.gov identifier: NCT01259726].

IVIG, intravenous immunoglobulins; CDAI, Human monoclonal antibody to *C. difficile* toxin A; CDBI, Human monoclonal antibody to *C. difficile* toxin B.

Probiyotik nedir?

- İnsan orijinli
- GİS'de canlı kalabilen
- Asit ve safraya dayanıklı
- Mukozaya adezyon yapabilen
- Klinik olarak yararı gösterilmiş
- GÜVENLİ (GRAS)
- WHO, Birleşmiş Milletler ve FAO



(Food and Agriculture Organization) tanımı:

«yeterli miktarda verildiğinde sağlık yönünden yarar sağlayan canlı mikroorganizmalar»

Table 1 Microorganisms used as probiotics [17, 18]

Lactobacilli[a]	Bifidobacteria	Others
L. acidophilus-group	*B. longum* (BB536)	*Enterococcus faecalis*[b]
	B. longum (SP 07/3)	
L.acidophilus (LA-5)	*B. bifidum* (MF 20/5)	*Enterococcus faecium*[c]
L. crispatus (*L. acidophilus* "Gilliland")	*B. infantis*	*Lactococcus lactis*
L. johnsonii (LA1)	*B. animalis* (*B. animalis* ssp. *lactis* BB-12)	*Streptococcus thermophilus*
L. gasseri(PA 16/8)	*B. adolescentis*	*Propionibacteria*
L. casei- group	*B. breve*	*E. coli*[c] (*E. coli* "Nissle 1917")
L. (para)casei (*L. casei*) "shirota"		*Sporolactobac. Inulinus*[c]
L. casei "defensis")		
L. rhamnosus (LGG)		*Spores of Bacillus cereus* "toyoi"
L. reuteri		
L. plantarum (*299 and 299v*)		*Saccharomyces boulardii*[d]

Probiyotiklerin bozulmuş florayı düzeltmesi

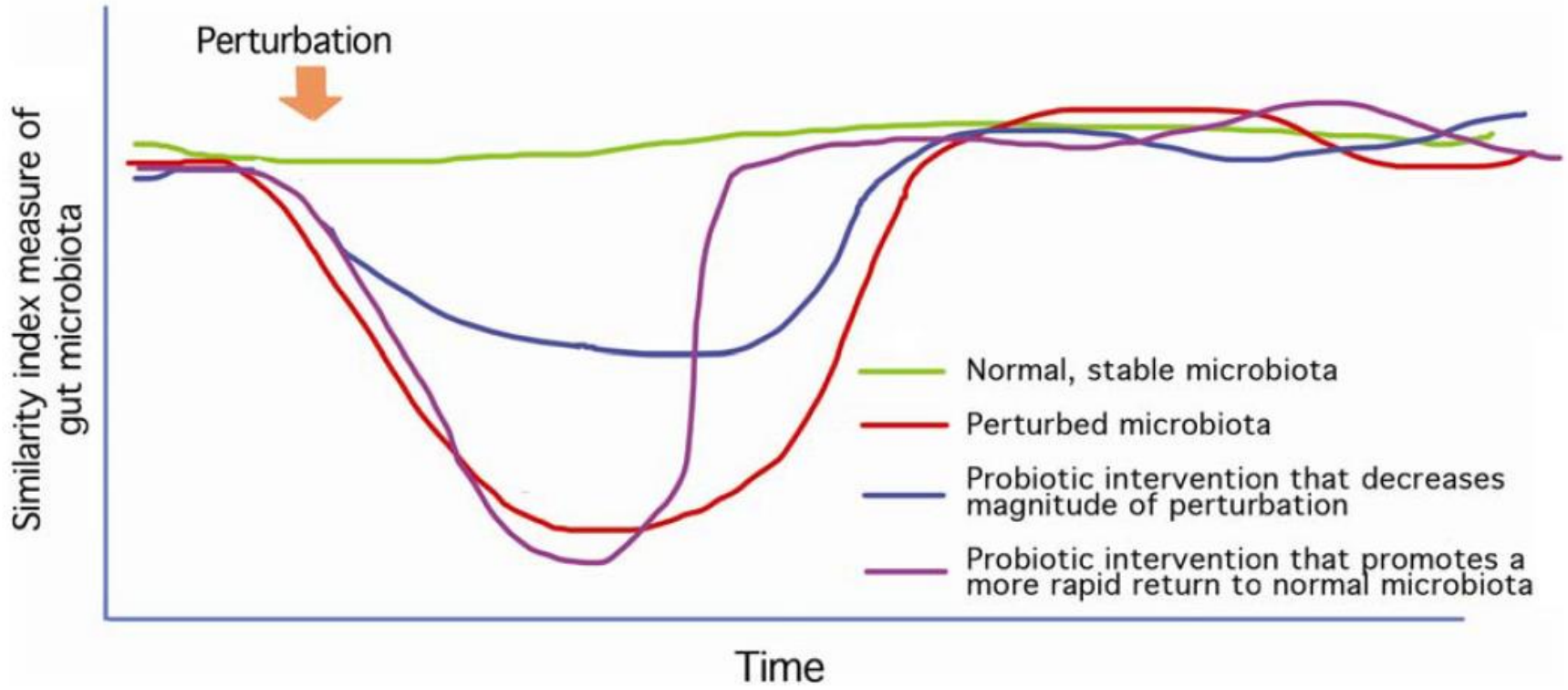
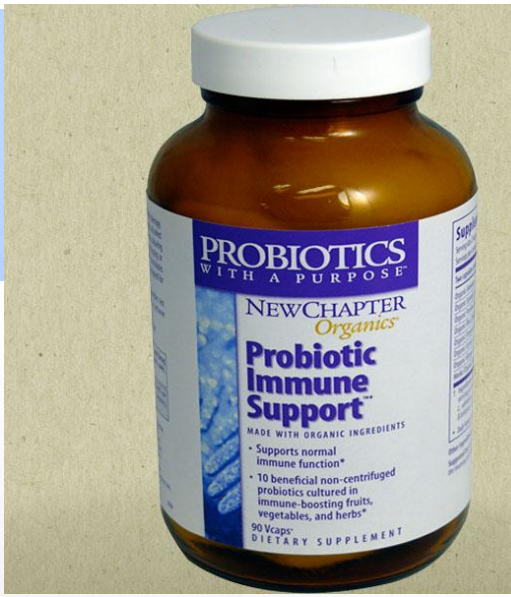


FIGURE 1. Probiotic intervention that decreases the magnitude of change or promotes a more rapid return to normal in a perturbed gut bacterial community. (Sanders et al. In Press). Reprinted with permission from Gut Microbes.

PROBİYOTİK-ÇALIŞMALAR



- 1973-2010;4500, 2002≥300, 2011≥1000
- EN SIK ENTERİK İNFEKSİYONLAR
- Kritik hastalar, YBÜ

- ✓ GASTROENTERİT
- ✓ Aİİ
- ✓ HIV, RADYOTERAPİ-İSHAL
- ✓ *H.pylori*
- ✓ ÜTİ
- ✓ PANKREATİT
- ✓ SYİ
- ✓ CİLT İNFEKSİYONLARI
- ✓ DİŞ ÇÜRÜKLERİ VE PERİODONTAL

- ✓ İBS
- ✓ İBH
- ✓ LAKTOZ İNTOLERANSI
- ✓ POŞİT
- ✓ KANSER
- ✓ ALLERJİK HASTALIK
- ✓ ATOPİK DERMATİT

The Safety of Probiotics

Clinical Infectious Diseases 2008; 46:S104–11

David R. Snydman

Division of Geographic Medicine and Infectious Diseases and Department of Medicine, Tufts–New England Medical Center, and Tufts University School of Medicine, Boston, Massachusetts

Table 1. Populations in whom *Lactobacillus* GG ha ied and has shown evidence of safety.

Pregnant women
Premature neonates
Elderly individuals
Children with rotavirus diarrhea
Hospitalized children
Hospitalized adults
Finnish and other tourists
Malnourished Peruvian children
Patients with rheumatoid arthritis
Adults with Crohn's disease
Adults with *Helicobacter pylori* infection
Adults with *Clostridium difficile*–associated diarrhea

Table 2. Populations in whom safe use of other probiotics has been studied.

Critically ill children (*Lactobacillus casei* Shirota)
Patients with *Clostridium difficile*–associated diarrhea (*Lactobacillus plantarum, Saccharomyces boulardii,* and *Lactobacillus acidophilus* plus *Bifidobacterium*)
Patients with Crohn's disease (*Lactobacillus johnsonii* LA 1, VSL#3)
Adult women with urinary tract infections
Children attending day care
Liver transplant recipients (*L. plantarum* 299V)
Adults in the intensive care unit (*L. plantarum* 299 V)
Patients with liver failure (*L. plantarum* 299 V)
Patients with rotavirus diarrhea (*Bifidobacterium lactis* BB-12, *Lactobacillus reuteri* SD 2222, and many others)
Patients with necrotizing enterocolitis (*L. acidophilus, Bifidobacterium infantis*)
Patients with HIV infection–associated diarrhea *(S. boulardii*
Adults with diarrhea *(S. boulardii, L. casei, Streptococcus thermophilus, Bacillus bulgaricus, L. acidophilus)*
Adults with antibiotic-associated diarrhea *(L. plantarum, S. boulardii, L. acidophilus, B. bulgaricus)*
Patients with bacterial vaginosis and candida vaginitis (*Lactobacillus fermentum* RC-14 plus *Lactobacillus rhamnosus* GR-1, *L. plantarum*)
Patients with *Helicobacter pylori* infection (many)
Patients with irritable bowel syndrome (many)

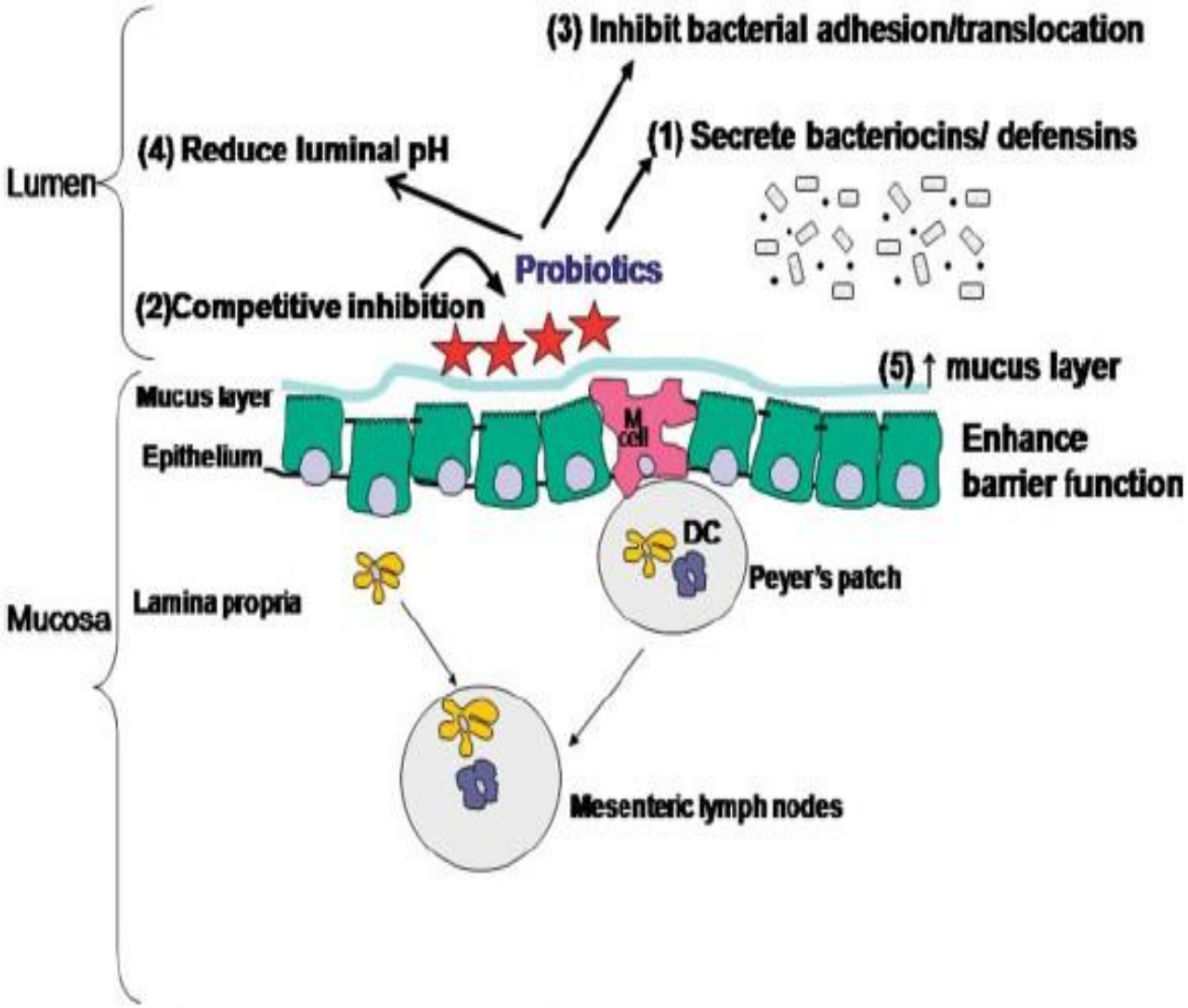


FIGURE 1. Inhibition of enteric bacteria and enhancement of barrier function by probiotic bacteria. Schematic representation of the crosstalk between probiotic bacteria and the intestinal mucosa. Antimicrobial activities of probiotics include the (1) production of bacteriocins/defensins, (2) competitive inhibition with pathogenic bacteria, (3) inhibition of bacterial adherence or translocation, and (4) reduction of luminal pH. Probiotic bacteria can also enhance intestinal barrier function by (5) increasing mucus production. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v16.i18.2202

World J Gastroenterol 2010 May 14; 16(18): 2202-2222
ISSN 1007-9327 (print)

EDITORIAL

Systematic review and meta-analysis of *Saccharomyces boulardii* in adult patients

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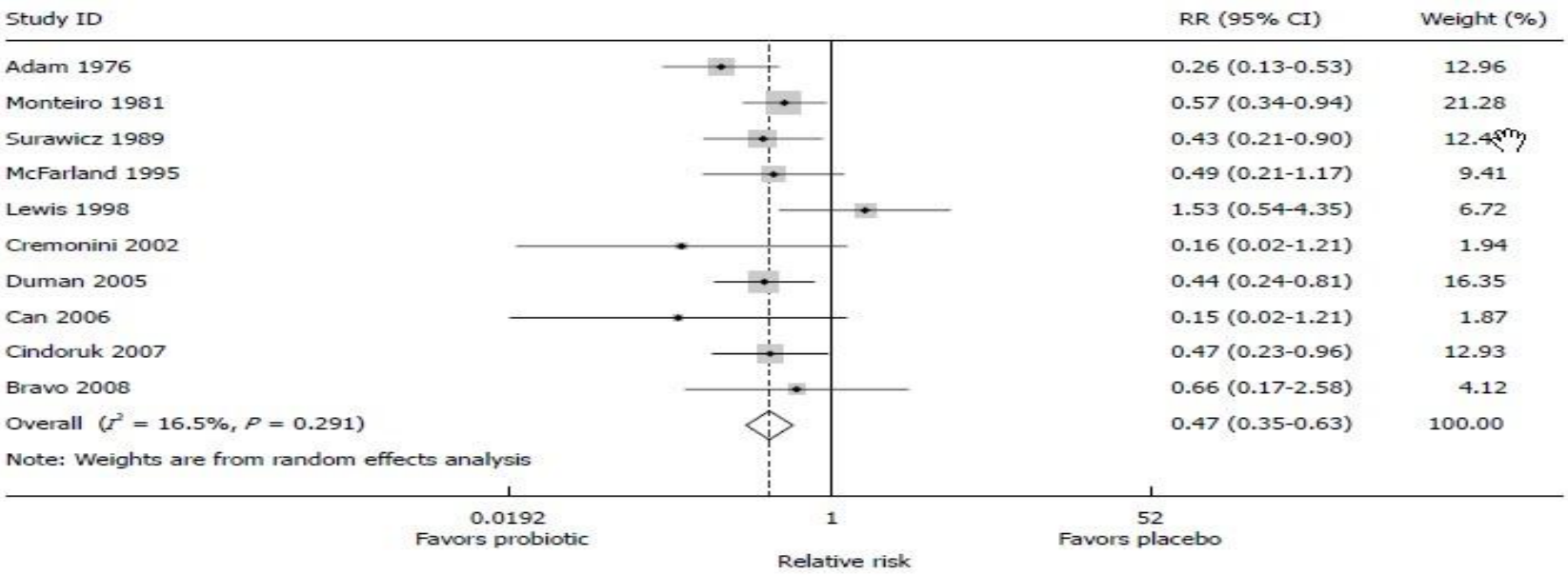
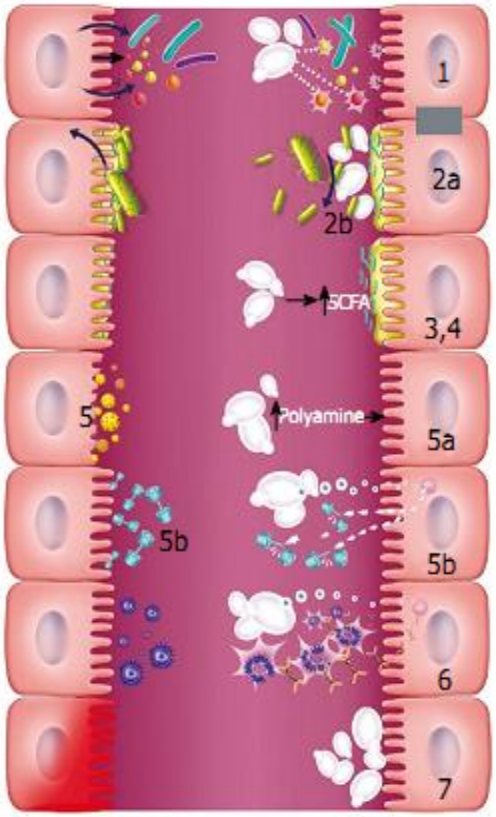
AAD;RR:0.47

Lynne V McFarland

McFarland LV. *Saccharomyces boulardii* in adults



S. Boulardii Etki Mekanizması



Toxins increase water secretion

Bacteria destroy tight junction, invade mucosa

Intestinal flora depleted by antibiotics

Viral infection destroys mature enterocytes

Decrease in disaccharidase causes osmotic diarrhea

Decrease in IgA

Inflammation

Luminal action
1 Anti toxinic effect against
(a) *C. difficile* toxins A and B (54 kDa protease)
(b) Cholera toxin (120 kDa protein)
(c) *E. coli* LPS (63 kDa protein phosphatase)
2 Antimicrobial activity
(a) Preservation of tight junctions
(b) Bacteria adhere to Sb, Sb decreases invasion
3 Modulation of intestinal flora
4 Metabolic activity: Sb increases short chain fatty acids, favors normal colonic function

Trophic action
5 Enzymatic activity
(a) Polyamines favor enterocyte maturation
(b) Increased disaccharidase levels-beneficial in viral diarrhea
6 Increased sIgA levels increases immune defense in the gut

Mucosal action-antiinflammatory effect
7 Acts on the cellular signals and decreases synthesis of inflammatory cytokines

1 *C. difficile* toxin, Cholera toxin and *E. coli* LPS

2a Tight junction

3 Intestinal flora

5 Immature enterocyte with virus

5b Accumulation of disaccharides in lumen

6 sIgA

6 Pathogens, in the absence of sIgA

Lynne V McFarland Systematic review and meta-analysis of Saccharomyces boulardii in adult patientsWorld J Gastroenterol 2010

REVIEW | Annals of Internal Medicine

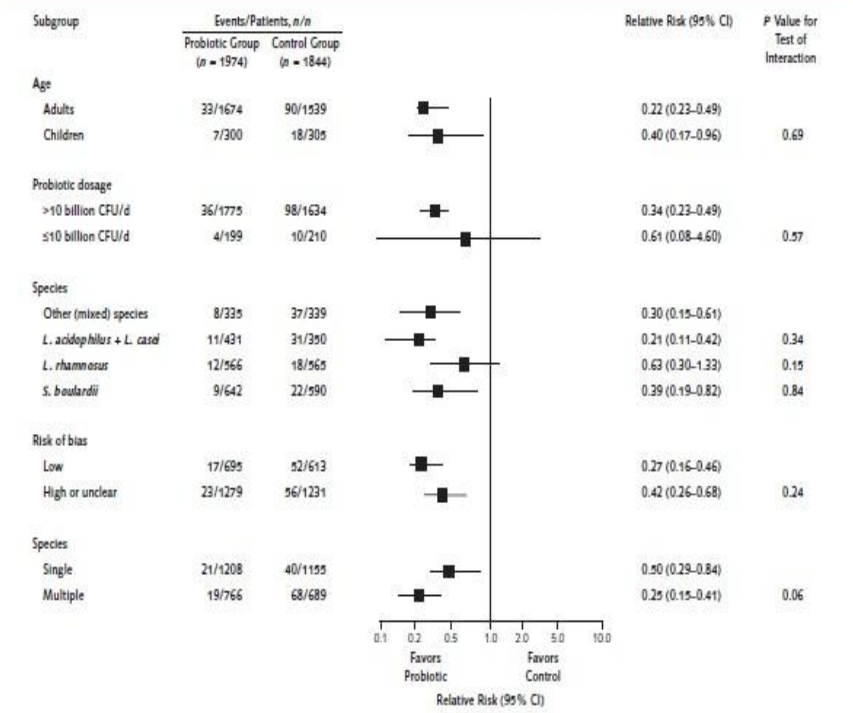
Probiotics for the Prevention of *Clostridium difficile*–Associated Diarrhea

A Systematic Review and Meta-analysis

Bradley C. Johnston, PhD; Stephanie S.Y. Ma, MD; Joshua Z. G
Mark Loeb, MD; and Gordon H. Guyatt, MD

- **20 randomize çalışma; 3818 hasta; CDİ azaltma insidansı %66**

Figure 4. Effect of probiotics on prevention of *Clostridium difficile*–associated diarrhea among subgroups.



CFU = colony-forming units.

Data Synthesis: Twenty trials including 3818 participants met the eligibility criteria. Probiotics reduced the incidence of CDAD by 66% (pooled relative risk, 0.34 [95% CI, 0.24 to 0.49]; I^2 = 0%). In a population with a 5% incidence of antibiotic-associated CDAD (median control group risk), probiotic prophylaxis would prevent 33 episodes (CI, 25 to 38 episodes) per 1000 persons. Of probiotic-treated patients, 9.3% experienced adverse events, compared with 12.6% of control patients (relative risk, 0.82 [CI, 0.65 to 1.05]; I^2 = 17%).

Limitations: In 13 trials, data on CDAD were missing for 5% to 45% of patients. The results were robust to worst-plausible assumptions regarding event rates in studies with missing outcome data.

Conclusion: Moderate-quality evidence suggests that probiotic prophylaxis results in a large reduction in CDAD without an increase in clinically important adverse events.

Primary Funding Source: None.

Ann Intern Med. 2012;157:878-888. www.annals.org
For author affiliations, see end of text.
This article was published at www.annals.org on 13 November 2012.

Probiyotik-metaanalizler

- 3 meta analizin sonucuna göre etkinliği değerlendirilerek Antibiyotik verilen hastalara profilaktik öneriliyor

- 2008 meta analizlerinde veri yetersiz notu ile önerilmekte idi, 2012 meta analizleri- CDİ antimikrobiyal tedaviye ek olarak önermekte

Hempel S,. Probiotics for the prevention and treatment of antibiotic-associated diarrhea: a systematic review and meta-analysis. JAMA 2012; 307:1959.
Ritchie ML, A meta-analysis of probiotic efficacy for gastrointestinal diseases. PLoS One 2012
Johnston BC Probiotics for the prevention of clostridium difficile–associated diarrhea: A systematic review and meta-analysis. Ann Int Med 2012.

ANTİBİYOTİK İLİŞKİLİ İSHAL

Recommendations for Probiotic Use—2011 Update

Martin H. Floch, MD, W. Allan Walker, MD,† Karen Madsen, PhD,‡ Mary Ellen Sanders, PhD,§ George T. Macfarlane, PhD,‖ Harry J. Flint, PhD,¶ Levinus A. Dieleman, MD, PhD,‡ Yehuda Ringel, MD,# Stefano Guandalini, MD,** Ciaran P. Kelly, MD,†† and Lawrence J. Brandt, MD‡‡*

TABLE 1. Recommendations for Probiotic Use—Update 2011

Clinical Condition	Effectiveness	Specific Strain of Organism and Strain References
Diarrhea		
Infectious childhood—treatment	A	*Saccharomyces boulardii*,[15] LGG,[16] *Lactobacillus reuteri* SD2112[17]
Prevention of infection	B	*S. boulardii*,[15] LGG[16]
Prevention of AAD	A	*S. boulardii*.[19] LGG,[20] combination of *Lactobacillus casei* DN114 G01, *Lactobacillus bulgaricus*, snf *Saccharomyces thermophilus*[21]
Prevention of recurrent CDAD	B/C	*S. boulardii*,[11] LGG,[22] bacteriotherapy[14]
Prevention of CDAD	B/C	LGG,[11] *S. boulardii*[22]

World Gastroenterology Organisation Global Guidelines

Probiotics and Prebiotics
October 2011

Review Team, Francisco Guarner, MD (Chair, Spain), Aamir G. Khan, MD (Pakistan), James Garisch, MD (South Africa), Rami Eliakim, MD (Israel), Alfred Gangl, MD (Austria), Alan Thomson, MD (Canada), Justus Krabshuis (France), Ton Lemair, MD (The Netherlands), Invited outside experts, Pedro Kaufmann, MD (Uruguay), Juan Andres de Paula, MD (Argentina), Richard Fedorak, MD (Canada), Fergus Shanahan, MD (Ireland), Mary Ellen Sanders, PhD (USA), Hania Szajewska, MD (Poland), Balakrishnan Siddartha Ramakrishna, MD (India), Tarkan Karakan, MD (Turkey), and Nayoung Kim, MD (South Korea)

J Clin Gastroenterol • Volume 46, Number 6, July 2012

TABLE 8. Evidence-based Pediatric Indications for Probiotics and Prebiotics in Gastroenterology

Disorder, Action	Probiotic Strain/Prebiotic	Recommended Dose	Evidence Level	References	Comments
Treatment of acute infectious diarrhea	*Lactobacillus rhamnosus* GG	10^{10}-10^{11} cfu, twice daily	1a	1	Meta-analysis of RCTs; ESPGHAN/ESPID recommendation
	Saccharomyces boulardii, strain of *Saccharomyces cerevisiae*	200 mg, 3 times daily	1a	2	Meta-analysis of RCTs; ESPGHAN/ESPID recommendation
	Indian Dahi containing *Lactococcus lactis*, *Lactococcus lactis cremoris*, and *Leuconostoc mesenteroides cremoris*	10^{10} cfu of each strain, 2 or 3 times per day	2b	3	—
Prevention of antibiotic-associated diarrhea	*Saccharomyces boulardii*, strain of *Saccharomyces cerevisiae*	250 mg, twice daily	1a	4, 5	Meta-analysis of RCTs
	Lactobacillus rhamnosus GG	10^{10} cfu, once or twice daily	1b	6, 7	—
	Bifidobacterium lactis Bb-12 + *Streptococcus thermophilus*	$10^{7} + 10^{6}$ cfu/g of formula	1b	8	—
	Lactobacillus rhamnosus (strains E/N, Oxy, and Pen)	2×10^{10} cfu, twice daily	1b	9	—
Prevention of nosocomial diarrhea	*Lactobacillus rhamnosus* GG	10^{10}-10^{11} cfu, twice daily	1b	10, 11	—
	Bifidobacterium lactis Bb-12 + *Streptococcus thermophilus*	$10^{8} + 10^{7}$ cfu/g of formula	1b	12	—

PROBİYOTİK KULLANIM ÖNERİLERİ 2013

TABLE 1. Recommendations for Probiotic Use

Clinical Condition	Effectiveness	Organism	References
Diarrhea			
Infectious adult—treatment	A	Saccharomyces boulardii, LGG	2–4
Infectious childhood—treatment	A	LGG, *Lactobacillus reuteri*	4–7
Prevention of infection	B	*S. boulardii*, LGG	3
Prevention of AAD	A	*S. boulardii*, LGG, *L. casei*, *L. bulgaricus*, *S. thermophilus*	8, 9
Treatment of recurrent CDAD	B	*S. boulardii*, LGG	8, 9
Prevention of CDAD	B	LGG, *S. boulardii*	8–12
IBD			
Pouchitis			
Preventing and maintaining remission	A	VSL#3	13–15
Induce remission	C	VSL#3	16
Ulcerative colitis			
Inducing remission	C	*Escherichia coli* Nissle, VSL#3	17–19
Maintenance	C	*E. coli* Nissle, VSL#3	20–22
Crohn's	C	*E. coli* Nissle, *S. boulardii*, LGG	23–26
IBS	B	*Bifidobacterium infantis*	27–29
	C	*Bifidobacterium animalis*, VSL#3, *Lactobacillus plantarum*	30–34
Immune response	A	LGG, *Lactobacillus acidophilus*, *L. plantarum*, *Bifidobacterium lactis*, *Lactobacillus johnsonii*	35, 36
Allergy			
Atopic eczema associated with cow's milk allergy			
Treatment	A	LGG, *B. lactis*	37–43
Prevention	A	LGG, *B. lactis*	44–48
Radiation enteritis	C	VSL#3, *L. acidophilus*	49–52
Vaginosis and vaginitis	C	*L. acidophilus*, LGG, *L. reuteri*	53–55

AAD indicates antibiotic-associated diarrhea; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; CDAD, *Clostridium difficile*-associated diarrhea; LGG, *Lactobacillus* GG.

Table 3 Randomized controlled trials for the treatment of *C. difficile* disease using *S. boulardii*

Ref.	Treatment groups	Study population	Daily dose: cfu/d (mg/d)	Duration of treatment (wk)	Follow-up (wk)	*C. difficile* recurrence in probiotic group	*C. difficile* recurrence in placebo group
McFarland *et al*[53]	*S. boulardii vs* placebo	124 adult patients on varied doses of vancomycin or metronidazole; recurrent and initial CDAD cases; 3 referral sites, US	3×10^{10} (1000 mg)	4	4	15/57 (26.3%)*	30/67 (44.8%)
Surawicz *et al*[60]	*S. boulardii vs* placebo	168 adult patients recurrent CDAD; on vancomycin (2 g/d, $n = 32$) or V (500 mg/d, $n = 83$) or M (1 g/d, $n = 53$); 4 referral sites, US	2×10^{10} (1000 mg)	4	4	V (2 g/d) 3/18 (17%)*; V (500 mg/d) 23/45 (51%); M (1 g/d) 13/27 (48.1%)	V (2 g/d) 7/14 (50%); V (500 mg/d) 17/38 (44.7%); M (1 g/d) 13/26 (50%)

McFarland LV. *Saccharomyces boulardii* in adults

Table 6 Summary of recommendations for clinical use of *S. boulardii* in adults

Use for disease	Dose (mg/d)	Duration	Adjunct to	Strength of evidence[1]
Prevention of antibiotic associated diarrhea	500-1000	During antibiotics with additional 3 d to 2 wk after	Nothing	++++
Prevention of Traveler's diarrhea	250-1000	Duration of trip (3 wk)	Nothing	+++
Enteral nutrition-related diarrhea	2000	8-28 d	Nothing	++
H. pylori symptoms	1000	2 wk	Standard triple therapy	++
Treatment of *Clostridium difficile* infections	1000	4 wk	Vancomycin or metronidazole	+
Acute adult diarrhea	500-750	8-10 d	Nothing	+
Inflammatory bowel disease	750-1000	7 wk to 6 mo	Mesalamine	+
Irritable bowel syndrome	500	4 wk	Nothing	+
Giardiasis	500	4 wk	Metronidazole	+
HIV-related diarrhea	3000	7 d	Nothing	+

[1]Strength of evidence, + (weak, needs more randomized controlled trials) to ++++ (strong, efficacy and safety are evidence based from numerous large randomized controlled trials).


Teşekkürler