Hastane İnfeksiyonlarının Önlenmesinde Yeni bir Hedef: Mikrobiyota

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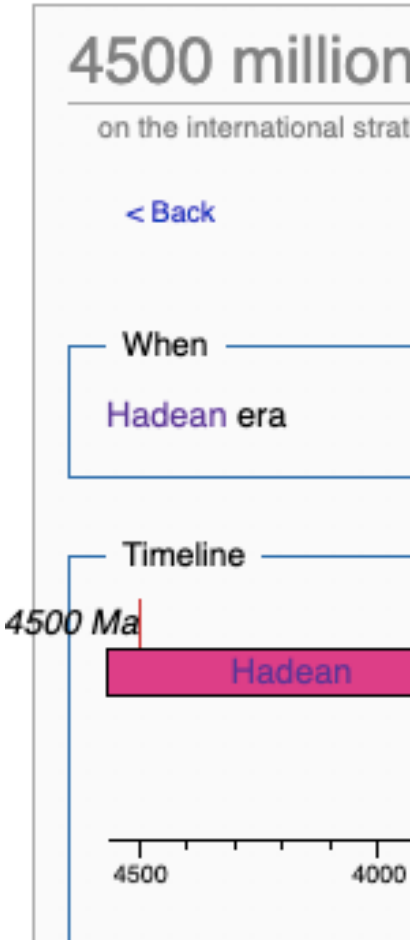
Sunum Planı

- Barsak Mikrobiyotasının tanımı ve yapısı
- Mikrobiyota yapısını etkileyen faktörler
- Barsak mikrobiyotasının fonksiyonları (Simbiyozis)
- Barsak mikrobiyotası ve İmmünite
- Hastane infeksiyonları ve mikrobiyota.
- Fekal Mikrobiyota Transplantasyonu ile tedavi..

THE ROYAL SOCIETY

Archaean metabolic evolution of microbial mats



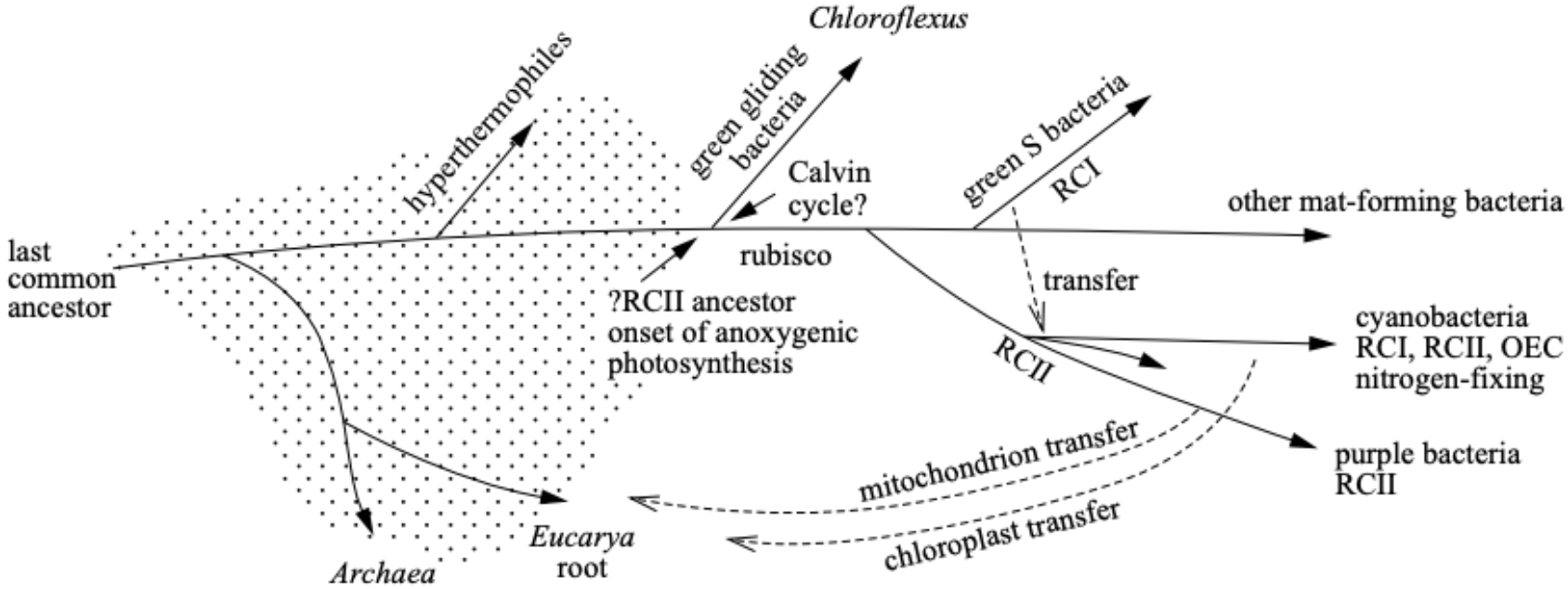
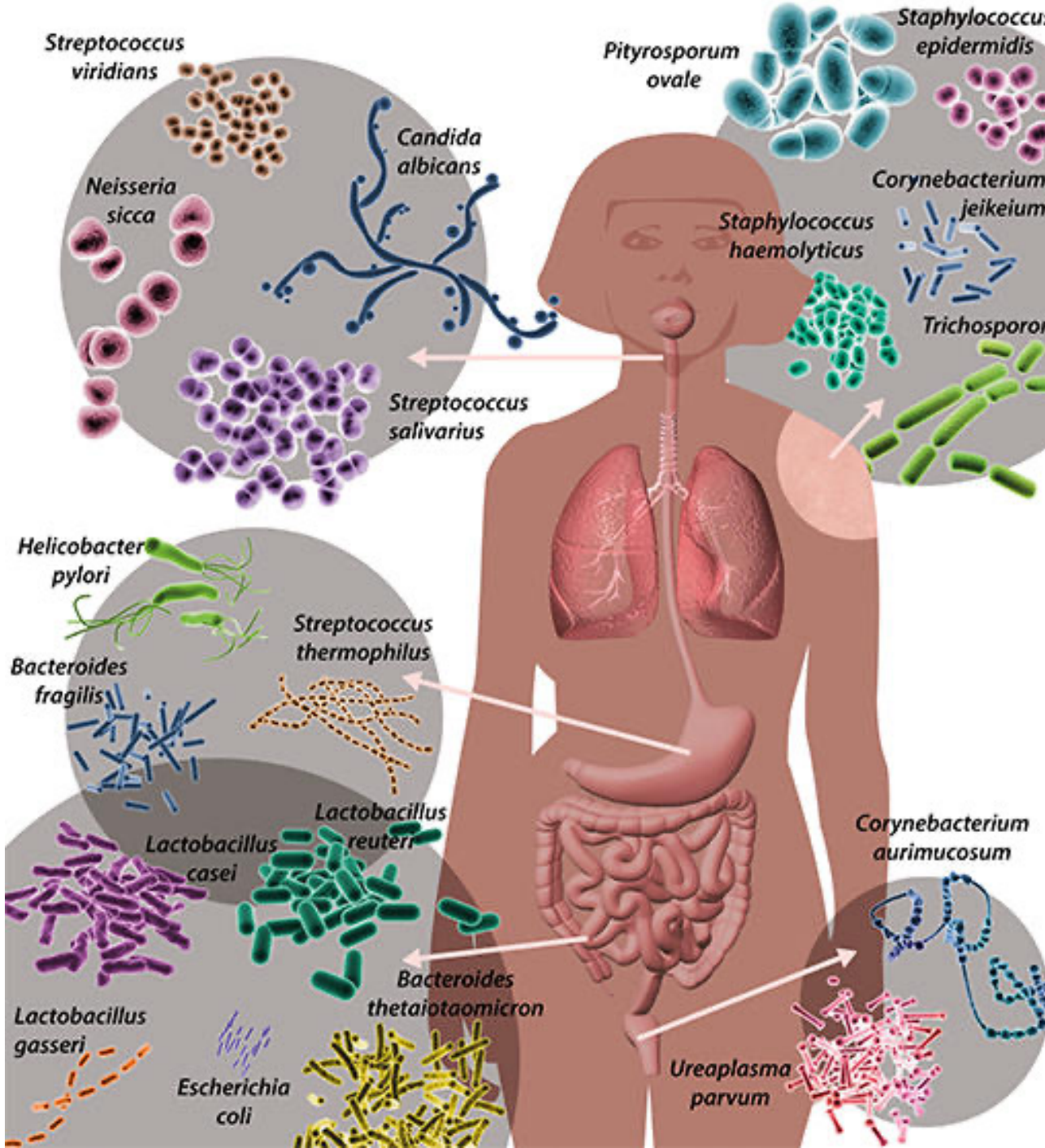


Figure 1. Possible metabolic descent of photosynthetic organisms (after Woese 1987; Blankenship 1992; Barnes *et al*. 1996; Pace 1997; Blankenship & Hartman 1998). The stippled region represents the hyperthermophile setting. The figure is based on what Doolittle (1999) termed the 'standard' model. The onset of anoxygenic photosynthesis (ancestral RCII?) allowed escape from the hyperthermophile setting; the symbiosis of RCII (purple bacteria) and RCI (green sulphur bacteria) formed the ancestral cyanobacterium (see the text for an alternative hypothesis); and chloroplast transfer from a cyanobacterium and mitochondrial transfer from a purple bacterium into a Korarcheota-like organism formed the Eucarya (assuming amitochondrial eukaryotes are descended from earlier mitochondrial ancestors).

- Çevresel faktörlere maruz kalan her türlü vücut yüzeyi ve vücudun parçası kendine özgü bir mikrobiyoma sahiptir..
- Deri ve mukoz membranlar
- Dış kulak yolu
- Üst solunum yolu
- Üretranın dışa açılan kısmı
- Dış genital organlar
- Vajina
- Gözün dış kısmı (Göz kapağı, konjuktiva)..

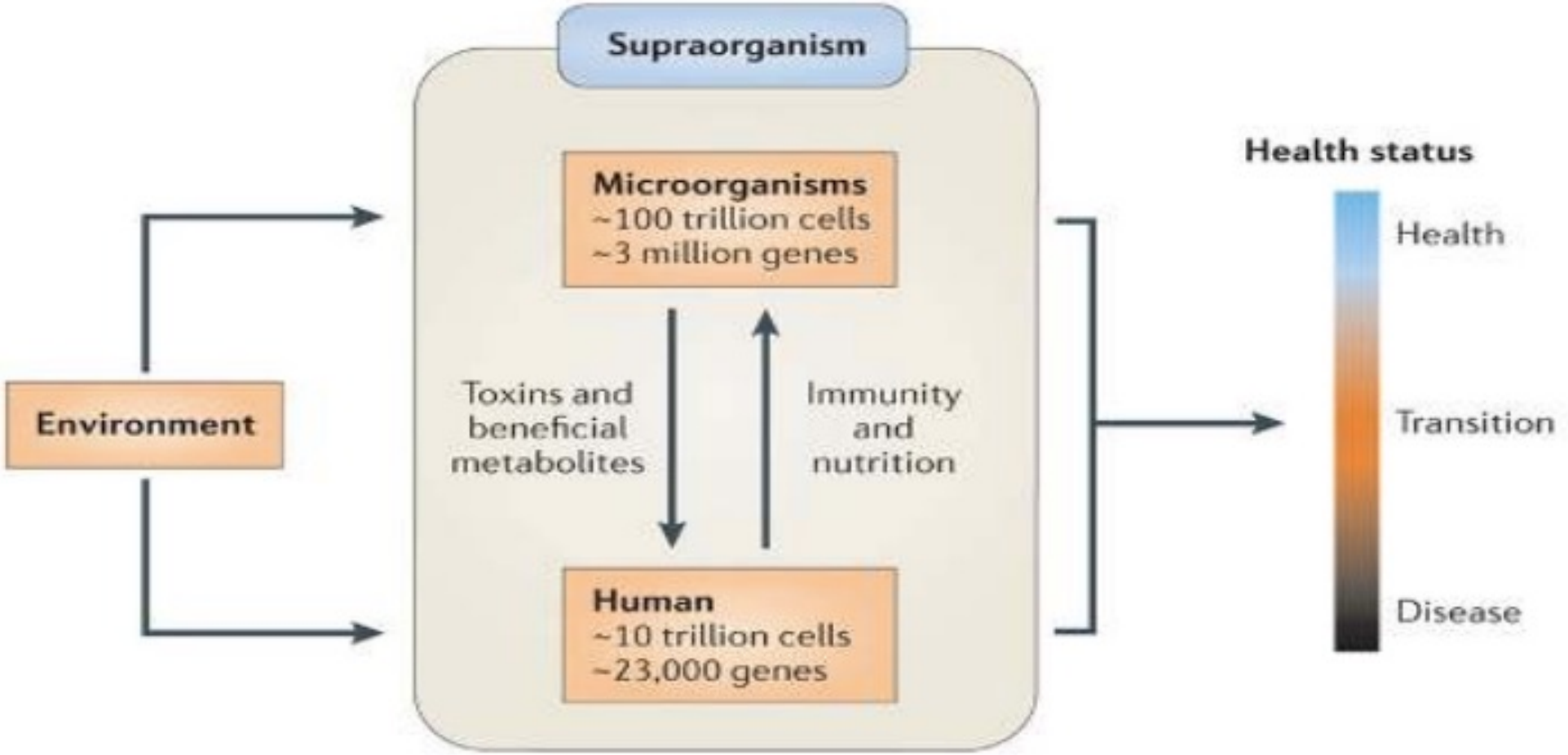


We Are Really More Bug than Man.....

Humans as micro biomes:-

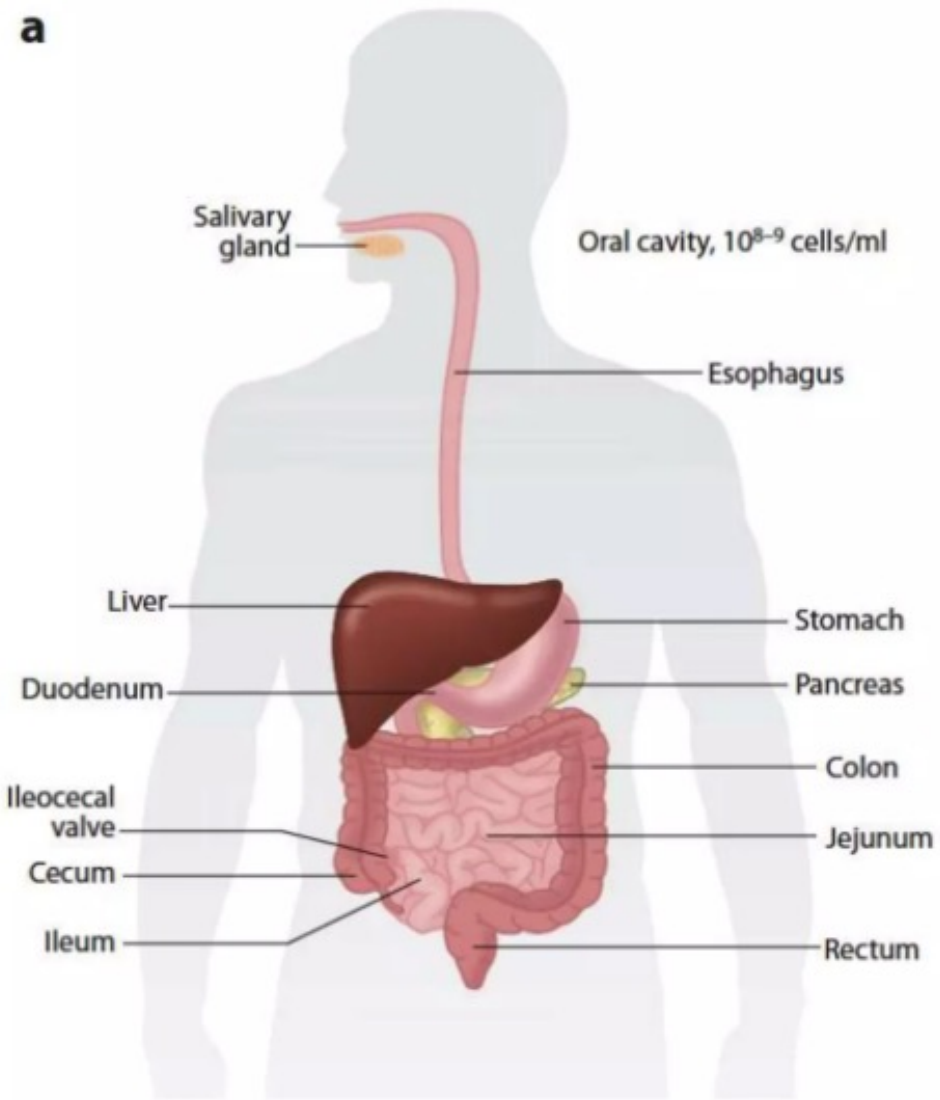
- 10-100 trillion microbes in human intestine.
- 3 million genes (100X).
- 2 kg weight.
- 300-1000 species of bacteria.
- control almost all body functions.

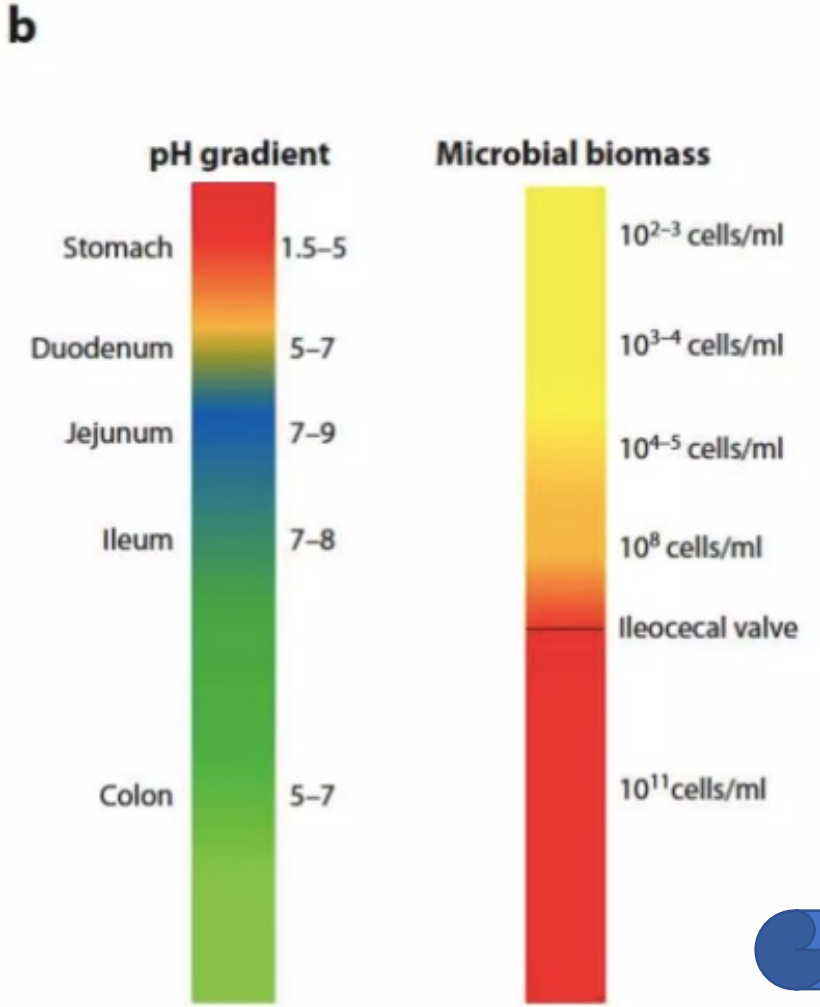
Barsak Mikrobiyotası



- İnsan mikrobiyotası 100 Trilyon (10^{14}) bakteri içerir
- İnsan vücudunda da 10 Trilyon (10^{13}) hücre yer alır

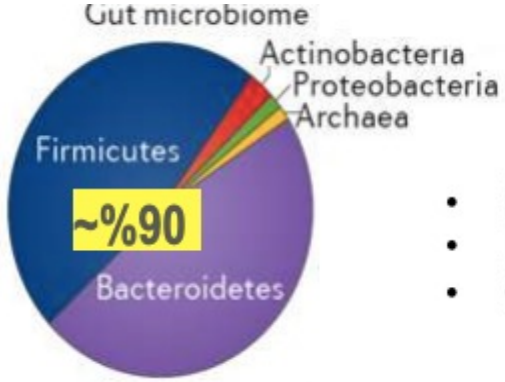
Distribution of Gut Microbiota





Mikrobiyota çeşitliliğini belirleyen faktörler, ortamın besin kaynağı, pH, O2 ve CO2 miktarı ile metabolik ve biyokimyasal işlevlerine uygun ekolojik çevredir..

Barsak Mikrobiyota Bileşenleri



- İnsan mikrobiyomunun %99'u bakteri kökenli
- Bunun dışında kalanların da çoğunluğu Archea kökenli
- Genlerin ancak %0,1'i ökaryot ve viruslara ait

Filum (Şube)	Order (Takım)	Aile	Cins	Tür(~5000)
1-Bacteroidetes (anaerob GNB)	Bacteroides	Bacteroidaceae	Bacteroides	B.fragilis
2-Firmicutes (anaerob GPK)	Clostridia	*Ruminococcaceae*	Clostridium	C. difficile C.perfringens
3-Proteobacteria	Enterobacterales	Enterobacteriaceae		
3-Actinobacteria	Bifidobacterium	Actinomyces, Nocardia, Corynebacterium, Propionibacterium Mycobacterium		

Bakteriyel çeşitlilik fekal 16S rDNA ile ölçülmektedir

- Sağlıklı barsak mikrobiyota bileşenleri baskın olan 4 bakteri filum (şube)'sinden oluşmaktadır.:
- Bacteroidetes > Firmicutes > Proteobacteria > Actinobacteria

Barsak Mikrobiyotasını Oluşturan Önemli Bakteriler ve Kökenleri

Phyla	Representative genera
Firmicutes (60-80%)	– Ruminococcus – Clostridium – Lactobacillus – Enterococcus
Bacteroidetes (20-30%)	– Bacteroides – *Prevotella* – *Xylanibacter*
Actinobacteria (< 10%)	– Bifidobacterium
Proteobacteria ((< 1%)	– *Escherichia* – *Enterobacteriaceae*

Munoz-Garach A, Diaz-Perdigones C, Tinahones FJ.
Microbiota y diabetes mellitus tipo 2. Endocrinol Nutr. 2016;63:560---568.

PROTEOBACTERIA (GNB)

- GNB, 16S rRNA gen sekans çalışmalarıyla 6 sınıfa ayrılmıştır:

1-Alpha-proteobacteria: Bin kadar tür yer alır. Fonksiyonel açıdan ileri çeşitlilik gösterir (*Rickettsia, Wolbachia, Brucella, Bartonella*.....)

2-Beta-proteobacteria: Beşyüz kadar tür yer alır (*Neisseria, Burkholderia*...)

3-Gamma-proteobacteria: En geniş ve en fazla çeşitlilik gösteren grup (*Enterobacteriaceae, Pseudomonas, Vibrio, Pasteurella, Legionella..*)

4-Delta-proteobacteria: Sülfat ve sülfür indirgeyen bakteriler

5-Epsilon-proteobacteria: *Campylobacter, Helicobacter, Wolinella*...

6-Zeta-proteobacteria: Tek tür yer alır

Mikrobiyota bariyerinin yıkılması ve AB kullanımı sonucu en fazla artış Gamma Proteobacteria'da görülür..

Bağırsak Mikrobiyotasının İşlevleri

Savunma:

- Patojen mikroorganizmalara karşı bariyer oluşturmak
- Kommensal ve patojen mikroorganizmaları ayrıştırmak
- Toksik bileşikleri parçalamak.
- Zararlı bakterilerin çoğalmasını baskılar
- Kanser ve çeşitli otoinflamatuar hastalıkların gelişimini engeller

Beslenme:

- Vücudun normalde sindiremeyeceği çeşitli besinleri (örneğin diyet lifi) sindirmek.
- Diyet liflerini parçalayarak kısa zincirli yağ asitleri gibi işlevsel ürünler oluşturmak
- Diyet minerallerinin (örneğin, magnezyum, kalsiyum ve demir) emilimini kolaylaştırmak.
- Bazı temel vitaminleri (örneğin, K vitamini ve folat (B9)) ve amino asitleri (yani proteinlerin yapı taşları) sentezlemek.

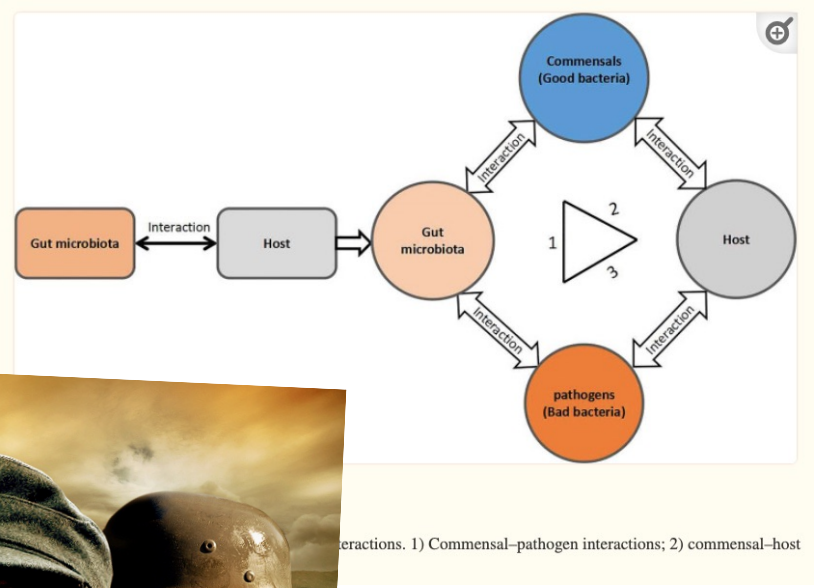
Emosyonel Davranış:

- Ruh halini ve davranışları şekillendirmek.

Büyüme ve Gelişme

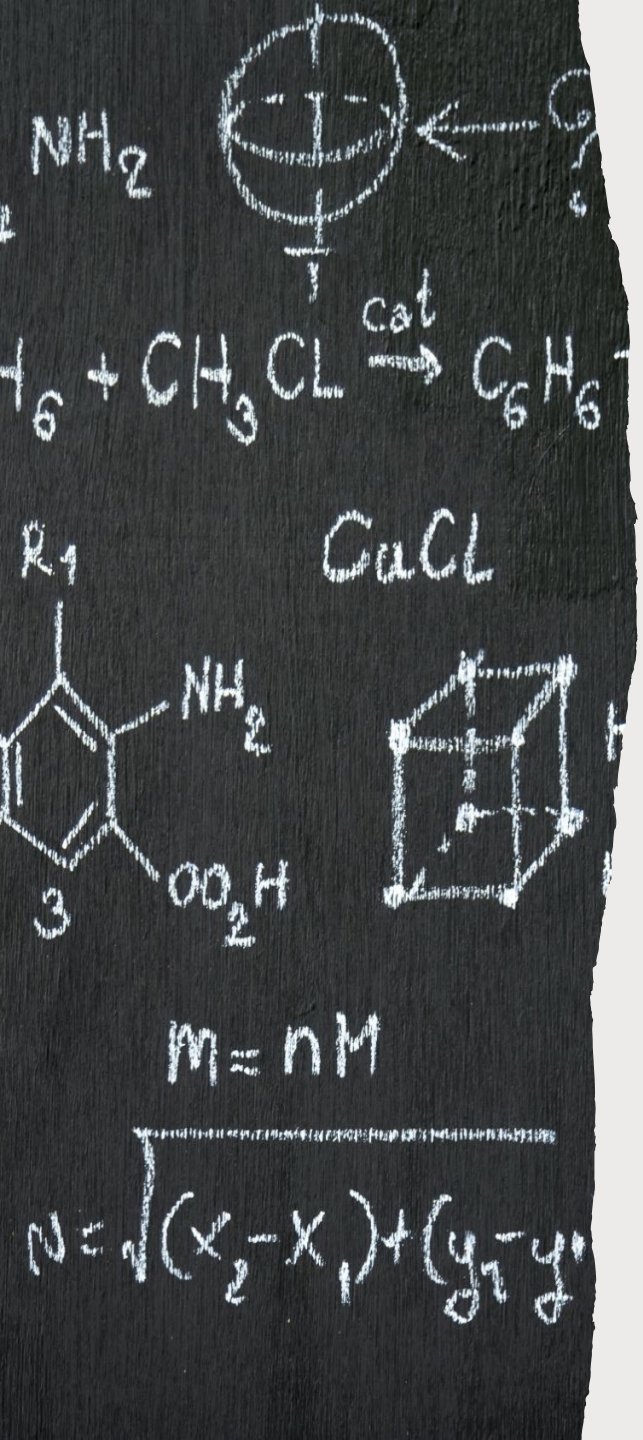
- Hücre büyümesine katkı sağlar

Kolonizasyon Direnci ve AB Dirençli İnfeksiyonlar



teractions. 1) Commensal–pathogen interactions; 2) commensal–host

- Kolonizasyon direnci barsak epitel hücreleri,fizyolojik aktiviteleri, salgıladıkları ürünler ve immun sistemin diğer unsurları ile patojen bakterilere karşı oluşturulan bariyer..
- Mikrobiyal bütünlük bozulduğunda diğer bakterilere karşı bariyer fonksyonu kaybolur
- Sonuç olarak, konakçı bir patojen tarafından kolonizasyona duyarlı hale getirilebilir.
- Bu durum, antibiyotik kullanımının ve antibiyotiğe dirençli patojenlere maruz kalmanın daha sık görüldüğü hastane ortamında özellikle önemli bir endişe kaynağıdır.
- Birçok nozokomiyal enfeksiyon gastrointestinal kolonizasyon ve daha sonra gelişen translokasyondan kaynaklanmaktadır.



Kolonizasyon Direncinin Kaybı

Germ free farelerde yapılan deneysel çalışmalarda anibiyotik uygulaması ile;

- S.Typhimurium (Sprinz et al., 1961),
- *Shigella flexneri* (Zachar and Savage, 19
- *Listeria monocytogenes* (Ferreira et al
- *C.rodentium* (Kamada et al., 2012)

Pseudomonas Candida. en fazla..

gibi enterik patojenlerin kolonizasyonunan ve ciddi enterik infeksiyonlara maruz kaldıkları gösterilmiştir.

Kolonizasyon Direncinin Kaybı ve Endojen Bakteriler

- Bazı mikrobiyotada kolonizasyon direncinin kaybı normalde var olan patojenik özellikli mikrobiyal popülasyonda virulans artışıyla sonuçlanır. Bu da translokasyona ve ciddi infeksiyonlara neden olabilir (Cameron and Sperandio, 2015).
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Table 1. Metabolites that Contribute to Pathogenesis

Metabolites Enhance Pathogen Expansion			
Metabolite	Source	Pathogen	References
Sialic acid	Released from mucosa by microbiota	*S.* Typhimurium, *C. difficile*	Ng et al., 2013
Succinate	By-product of microbiota fermentation	*C. difficile*	Ferreyra et al., 2014a, 2014b
Hydrogen	By-product of microbiota fermentation	*S.* Typhimurium	Maier et al., 2013
Ethanolamine	Mammalian and bacterial membranes	EHEC, *S.* Typhimurium, *L. monocytogenes*	Kendall et al., 2012; Bertin et al., 2011; Thiennimitr et al., 2011; Joseph et al., 2006
Sorbitol	Host diet	*C. difficile*	Theriot et al., 2014
Metabolites Influence Virulence Gene Expression			
Metabolite	Virulence Factors Controlled	Regulator(s) Involved	References
Ethanolamine	Enhances LEE expression (EHEC)	EutR	Kendall et al., 2012
Succinate	Enhances LEE expression (EHEC)	Cra	Curtis et al., 2014a, 2014b
Fucose	Inhibits LEE expression (EHEC)	FusKR two-component system	Pacheco et al., 2012
Butyrate	Inhibits SPI-1 expression (*S.* Typhimurium)	unknown	Lawhon et al., 2002; Gantois et al., 2006; Hung et al., 2013
	Enhances LEE expression (EHEC)	Lrp → PchA → LeuO → Ler	Nakanishi et al., 2009; Takao et al., 2014; Tobe et al., 2011
	Enhances flagella expression (EHEC)	Lrp and unknown Lrp-independent pathway	Tobe et al., 2011
Propionate	Inhibits SPI-1 expression (*S.* Typhimurium)	HilD → HilA	Lawhon et al., 2002; Gantois et al., 2006; Hung et al., 2013
Acetate	Enhances SPI-1 expression (*S.* Typhimurium)	BarA/SirA two-component system → HilA	Lawhon et al., 2002
Taurocholate	Enhances *C. difficile* germination		Theriot et al., 2014

• KOLONİZASYON DİRENCİ KAYBI ENDOJEN BAKTERİLERİN VİRULANSINI NASIL ARTIRABİLİR?

Cell Host & Microbe
Review

Frenemies: Signaling and Nutritional Integration in Pathogen-Microbiota-Host Interactions

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http://dx.doi.org/10.1016/j.chom.2015.08.007

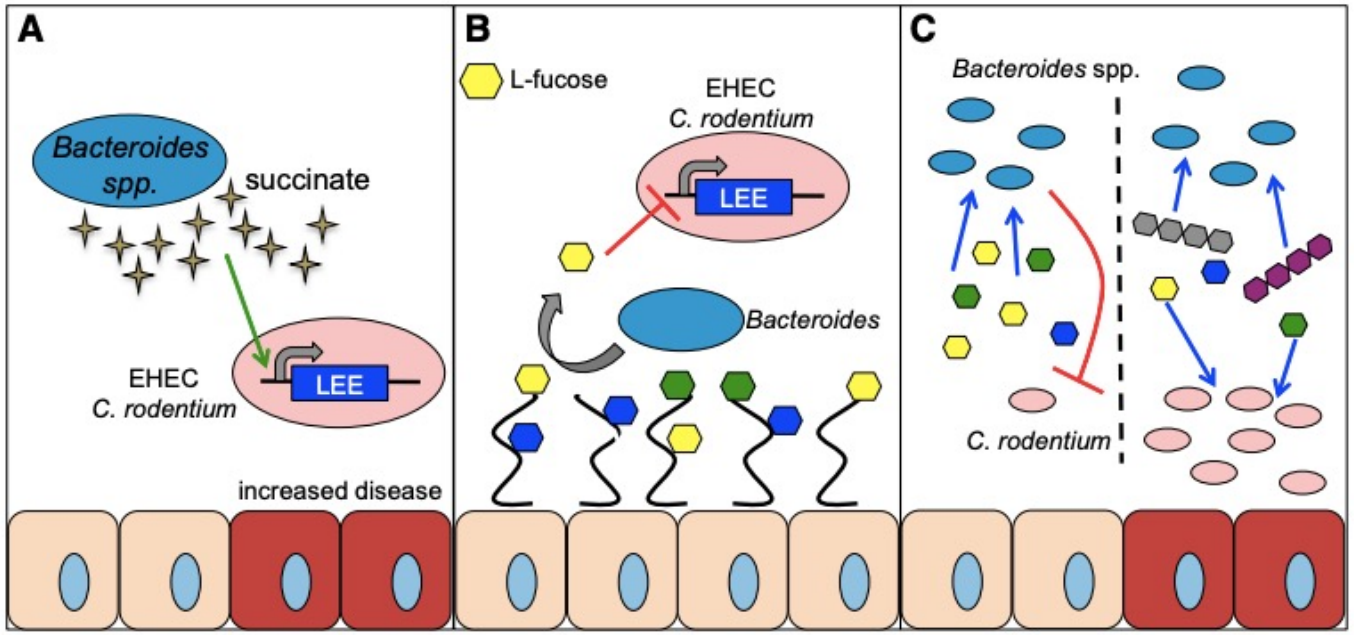

Figure 2. Modulation of Virulence by Commensal *Bacteroides*

Commensal *Bacteroides* affect virulence and progression of disease by AE pathogens in several ways.

(A) *Bacteroides* produce a significant amount of succinate as a by-product of carbohydrate fermentation. Succinate is sensed by EHEC and *C. rodentium* and upregulates expression of the LEE PAI.

(B) L-fucose is liberated from host mucin glycoproteins by fucosidases expressed by members of the microbiota such as *Bacteroides thetaiotaomicron*. Free fucose is sensed by EHEC and represses the LEE PAI to prevent early activation of this virulence factor before reaching the epithelium.

(C) Nutrient competition between *Bacteroides* spp. and pathogenic Enterobacteriaceae significantly affects the progression of disease. When only simple sugars (mono- and di-saccharides) are present, commensal *Bacteroides* and pathogens are forced to compete for nutrients, which limits growth and eventually leads to clearance of the pathogen. When both simple sugars and complex carbohydrates are present, *Bacteroides* will preferentially utilize polysaccharides, and pathogenic Enterobacteriaceae are able to utilize simple sugars to proliferate and persist in the intestine.

LEE: Locus Enterocyte Effacement, EHEC: Enterohemorajik E.coli, C.radentium: Citrobacter rodentium

CellPress

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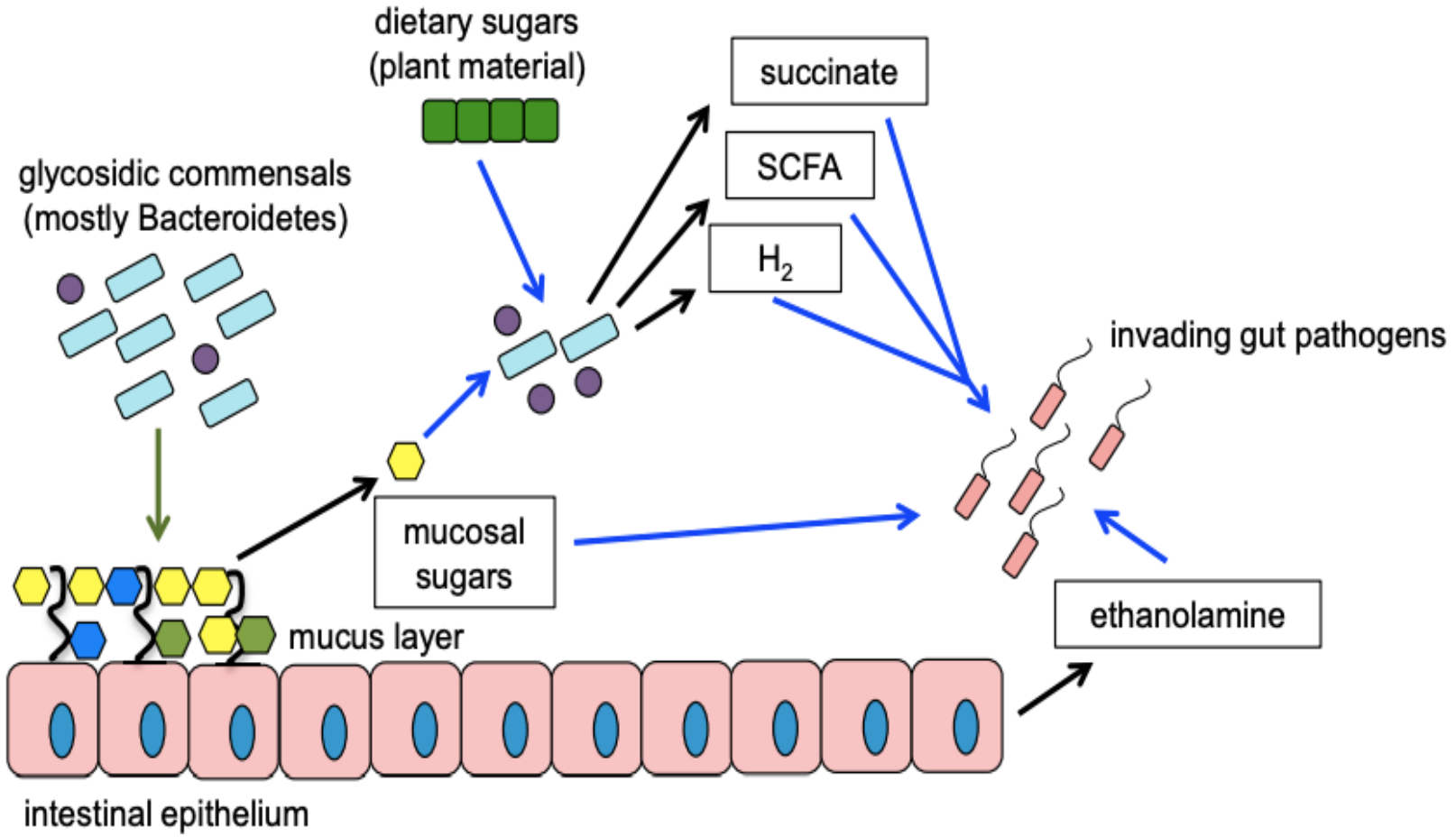


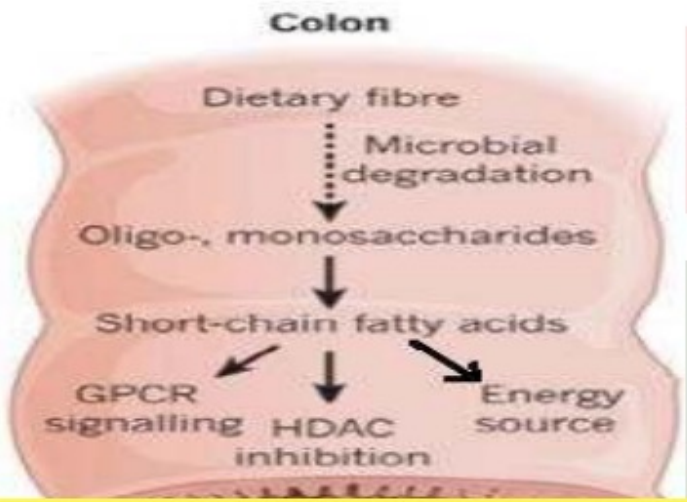
Figure 1. Microbiota-Derived Nutrients Feed Pathogenic Bacteria

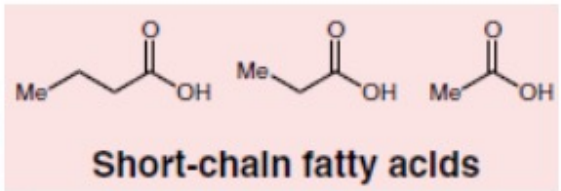
Black arrows indicate production of a particular nutrient; blue arrows indicate consumption of the indicated nutrient. Members of the intestinal microbiota stimulate (green arrow) mucosal sugar production by the host as well as produce glycosidic enzymes that liberate mucosal sugars (galactose, fucose, sialic acid, etc.) from host mucin glycoproteins. Liberated mucosal sugars can directly feed invading pathogen populations. Fermentation of dietary and host-derived sugars by the microbiota leads to production of SCFA, hydrogen, and organic acids like succinate, which can also serve as nutrient sources for pathogens during infection. Epithelial cell turnover releases ethanolamine into the lumen of the gut, where it can serve as a selective nutrient for pathogen proliferation during inflammation.

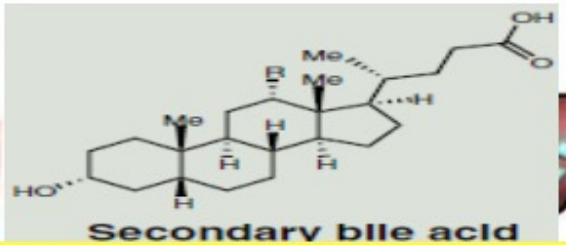
Barsak Mikrobiyota Metabolitleri ve İşlevi

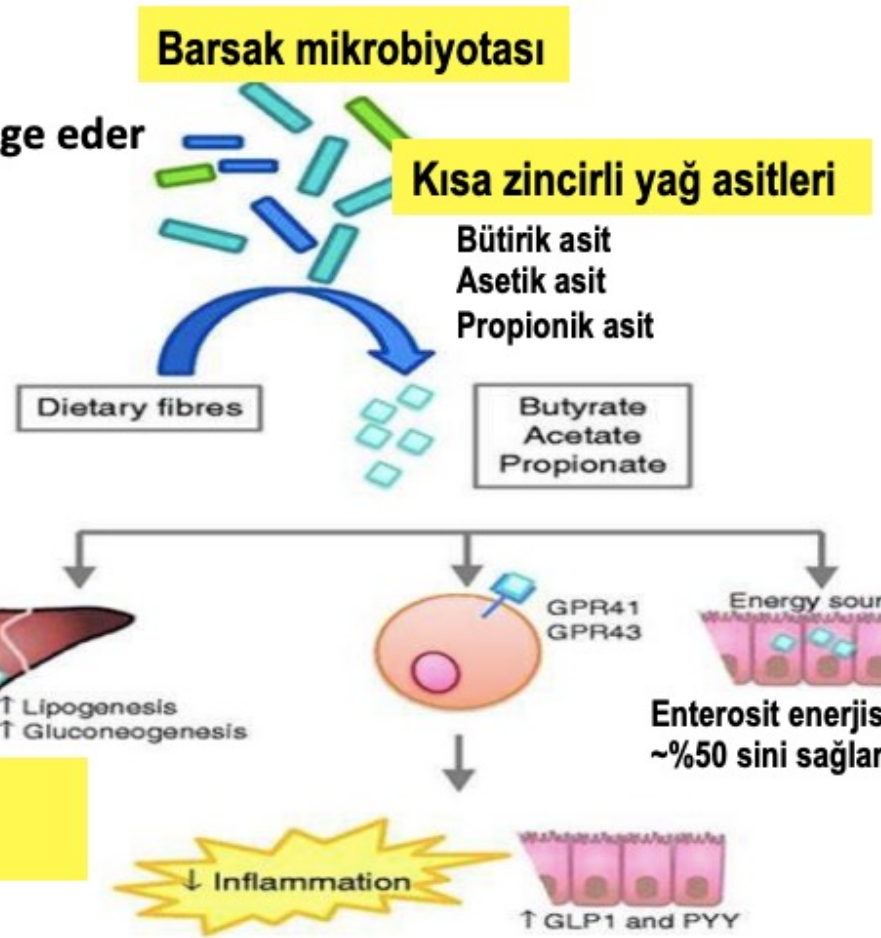
- Kısa zincirli Yağ Asitleri
- Sekonder Safra Asitleri

1-Mikrobiyota alınan lifleri (selüloz) fermantasyonla kısa zincirli yağ asitlerine dönüştürür
Kısa zincirli yağ asitleri;
Goblet hürelerinden müküs üretimini arttırır
Enterosit bütünlüğünü güçlendirir
2-Mikrobiyota kalın barsakda konjuge primer safra asitlerini dekonjuge eder ve sekonder safra asitleri oluşur









Primer safra asitleri: Hepatositlerde kolesterolden sentezlenir (Kolik asit ve Kenodeoksi kolik asit)
Glisin/taurin ile konjuge edilerek safrayla barsağa atılır
Sekonder safra asitleri: Deoksi kolik asit ve Lito kolik asit

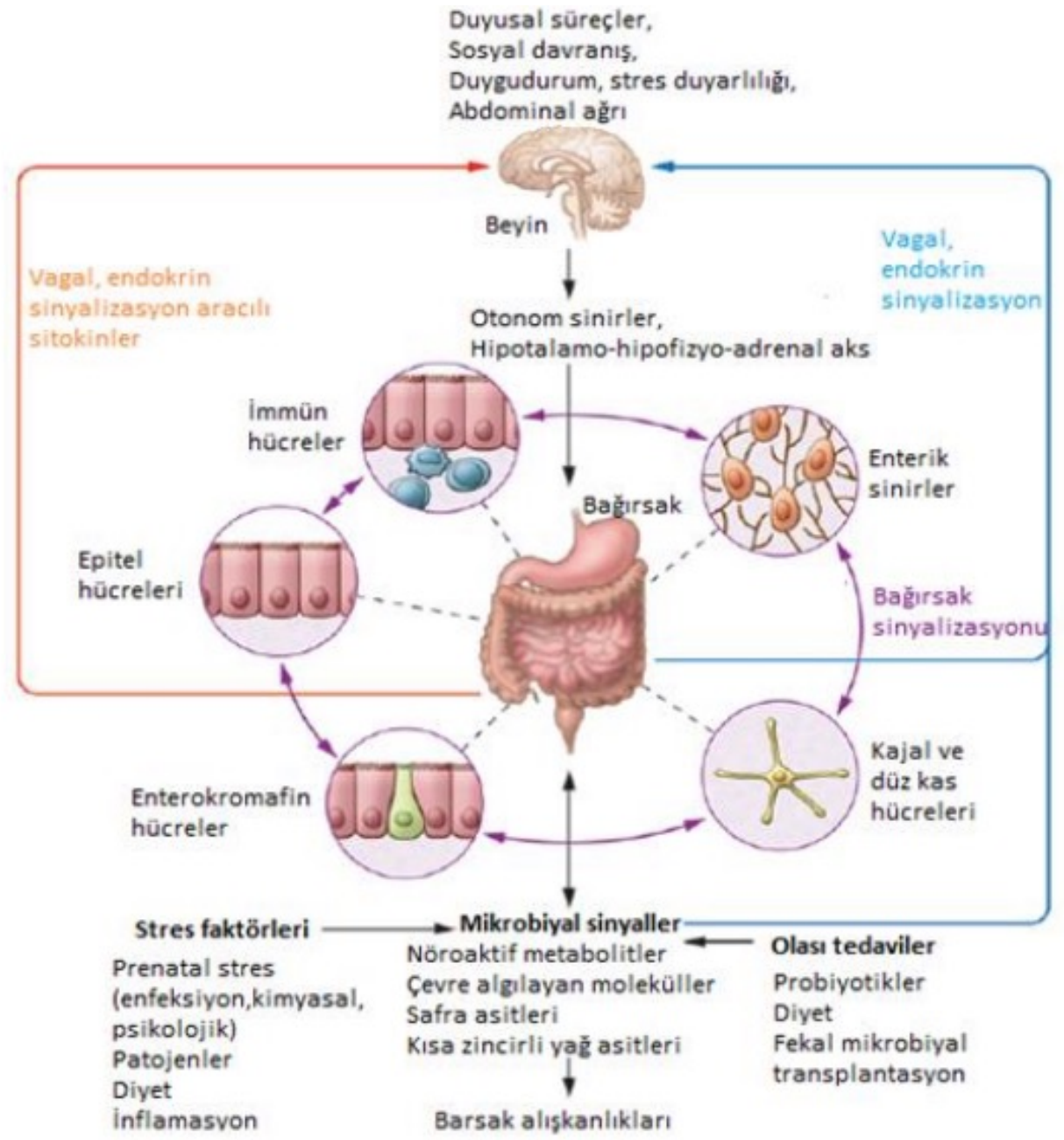
Safra asitleri→Kolik asit ve türevlerinden oluşur

Kısa Zincirli Yağ Asitleri (Short Chain Fatty Acid-SCFA) ve Mikrobiyota

- Enerji substratı olarak görev yapar
- G-protein-Coupled Receptors (GPRs) aracılığıyla intes[illegible] b[illegible]ni ve immün sistemi düzenler
- Regulatory T cell (Treg) hücrelerin diferansiyasyo[illegible] vasıtasıyla IL-10 üretimini sağlar
- GPR43 aracılığıyla inflamazomun kolon epitel[illegible] başlatır
- Kolon epitelinin tamiri ve anti-inflamatuar aktivit[illegible]18 üretimini artırır
- Tight Junction Proteins ekspresyonu artışı, müsin sent[illegible]zi, Dentritik hücre , FOXP3, histon deacetylases, Mp, Macrrophage, PS, HDAC sentezini artırır
- İntestinal hemeostazı düzenler

YBU'sinde mikrobiyota disbiyozunda erken safhada SCFA üretimindeki yetersizlik gelişir.

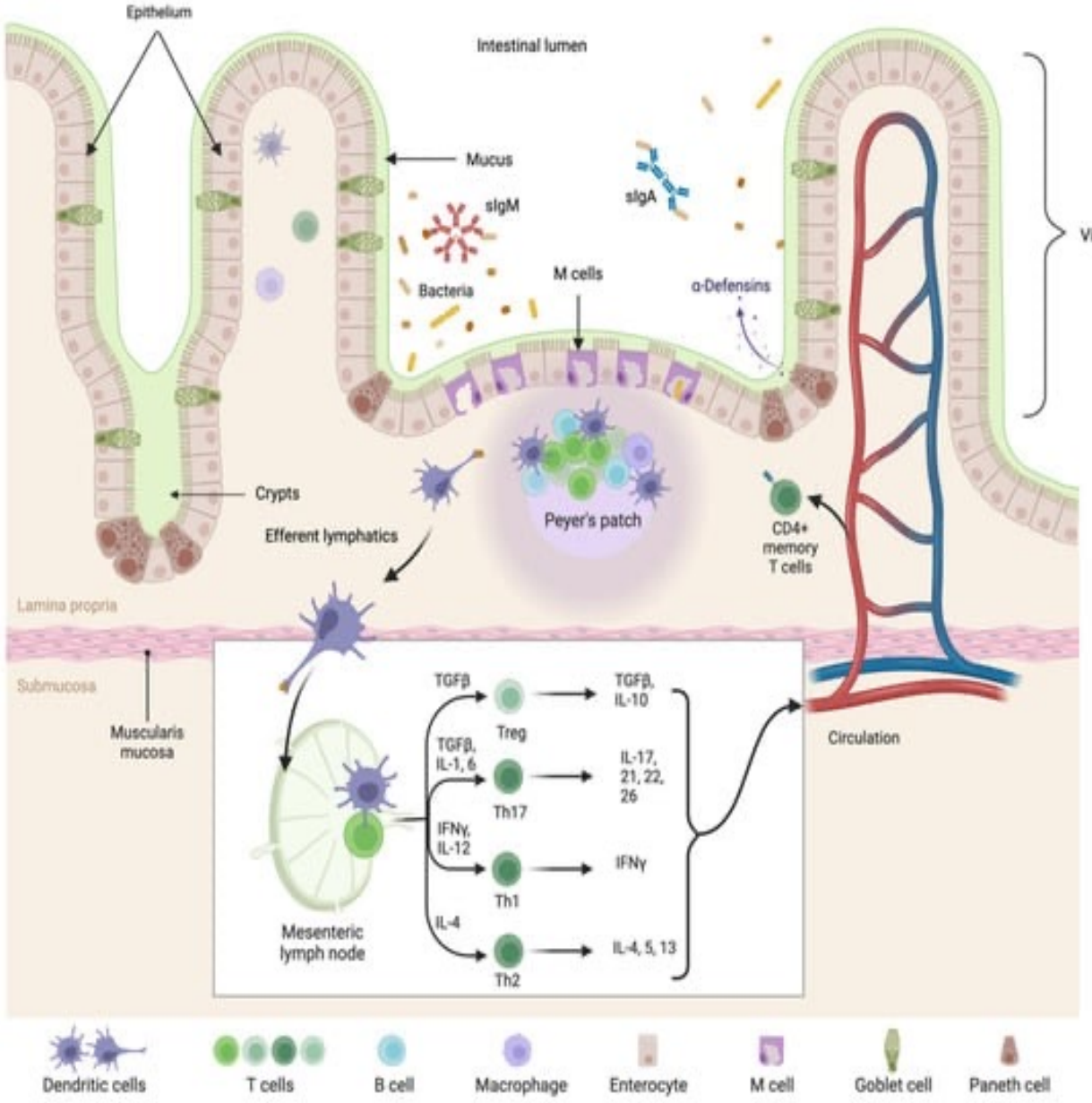
Mikrobiyota ve MSS Etkileşimi



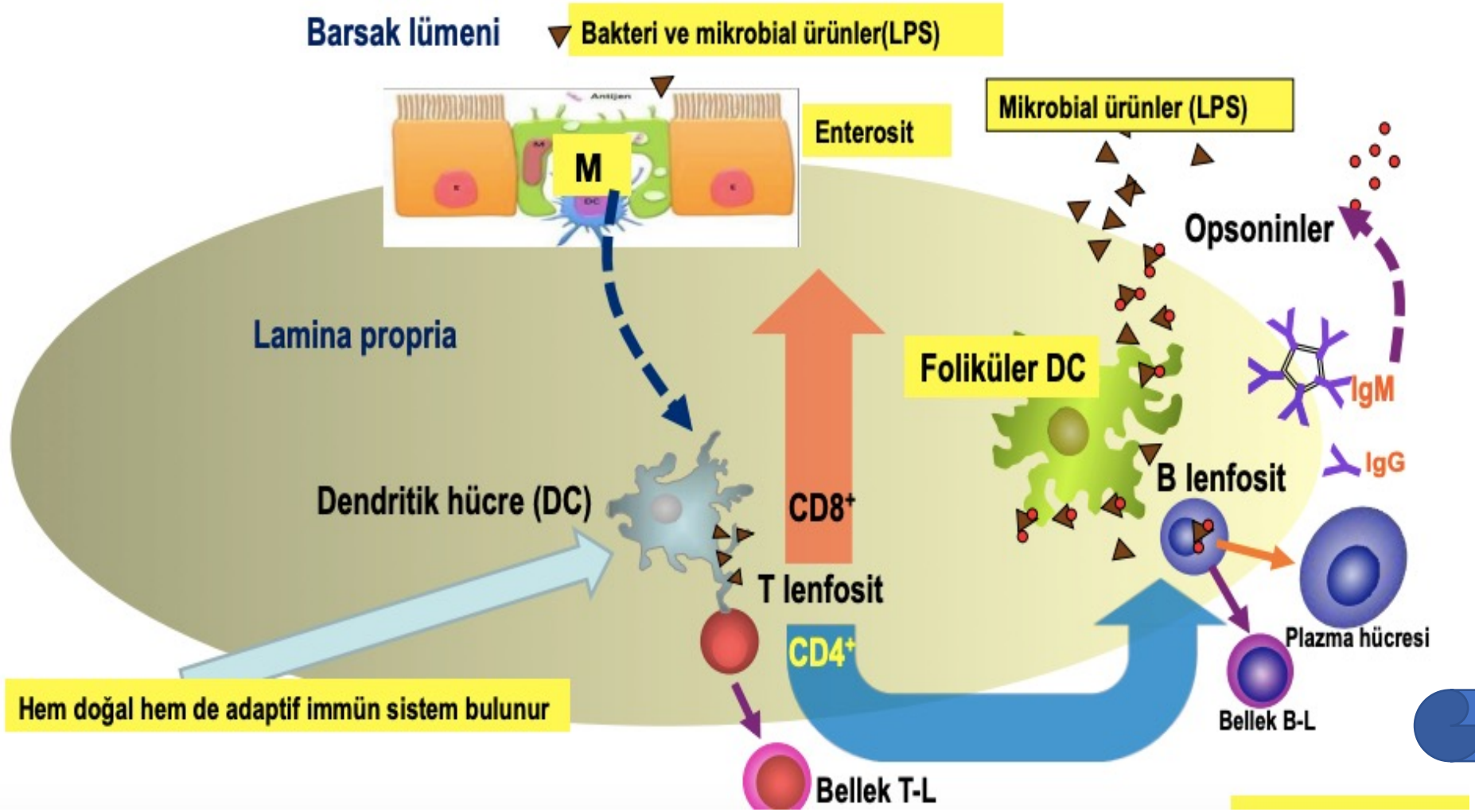
Şekil 2. Beyin-bağırsak aksındaki iki yönlü etkileşimler[14]

Mikrobiyota ve İmmünite

- Vücuttaki lenfoid dokunun büyük bir kısmı bağırsaklarda bulunur.
- Patojenlere karşı oluşturulan mukozal bir tabaka engeli vardır.
- Mukozal epitel içerisine yerleşmiş bağışıklık sistemi hücreleri olan M hücreleri, mukozal bariyerin en önemli bileşenlerinden biridir.
- Bağırsak ilişkili lenfoid doku (GALT) insan vücudunun en büyük lenfoid dokusudur spesifik IgA üretir
- Peyer plaklarında M hücresi tarafından alınan antijen, GALT'da yer alan dendritik ya da makrofaj hücreleri gibi antijen sunan hücrelere verilir.
- M hücrelerinin folikül ilişkili epitel ve kript epitelinde bulunan Lgr5+ kök hücrelerden köken aldığı bilinmektedir
- M hücreleri lenfoid dokuya antijen sunarak hem sistemik hem de mukozal bağışıklığın ilk basamağını gerçekleştirirler.



GALT (Gut Associated Lymphatic Tissue) ve İmmünite



- Mikroorganizma tehditlerinin algılanması
- Dentritik Hücrelerin uyarılması
- CD4/CD8 T Cell uyarımı
- B Cell Lenfosit uyarılması
- Plazma hücresi ve humoral immun yanıt
- Folliküler Dentritik hücre uyarılması
- Opsonik aktivite

Disbiyoz

- Barsak epitel yapısı ve mikrobiyota çeşitliliği ile metabolitlerinin değişmesi sonucunda hormonal, metabolik ve bağışıklık sisteminde gelişen bozukluklara verilen isimdir.

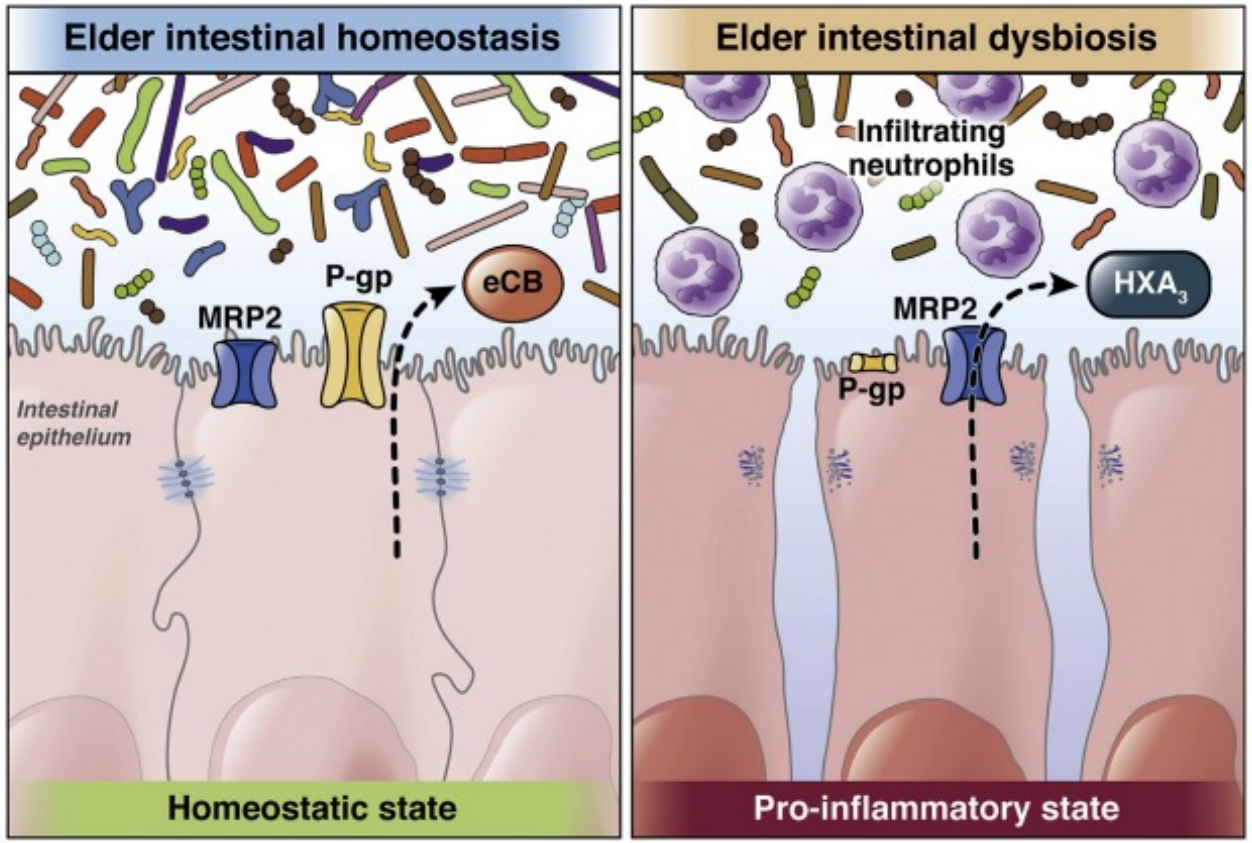
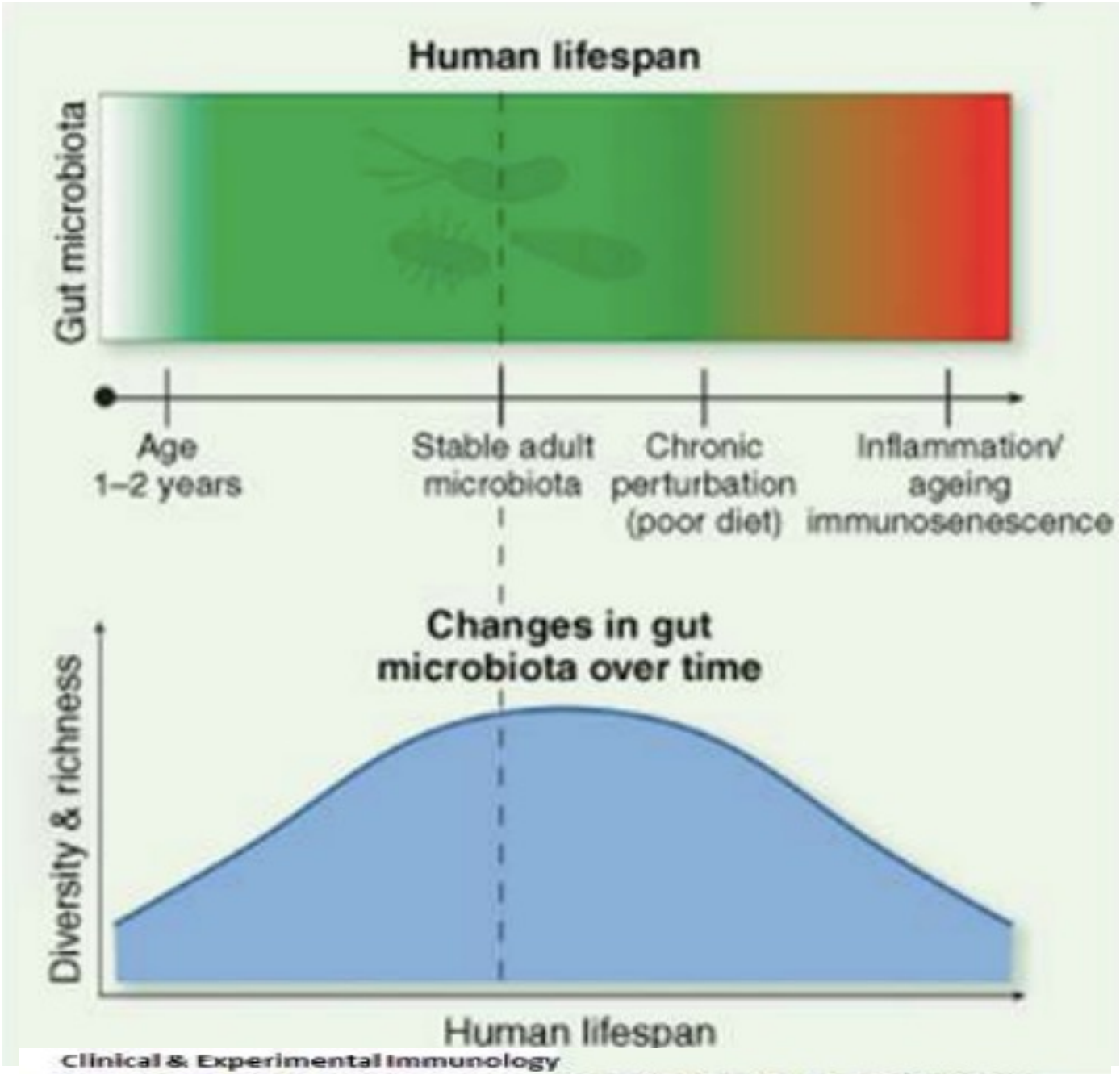


Figure 3. The MRP2/HXA_3 (hepoxilin A3) axis forms the proinflammatory arm of a dynamically regulated system in which inflammatory pathways that activate responses to pathogens or aberrant signals are balanced against the anti-inflammatory P-glycoprotein (P-gp)/endocannabinoid (eCB) pathway that suppresses neutrophil responses in the context of normal commensal colonization. The 2 sets of lipid-based signaling molecules (eCB and HXA_3) are released from the apical surface during periods of either tolerance or inflammation, which control the recruitment of neutrophils to the intestinal lumen. Dysregulation of this critical balance may contribute directly to inflammatory disorders of the intestine.

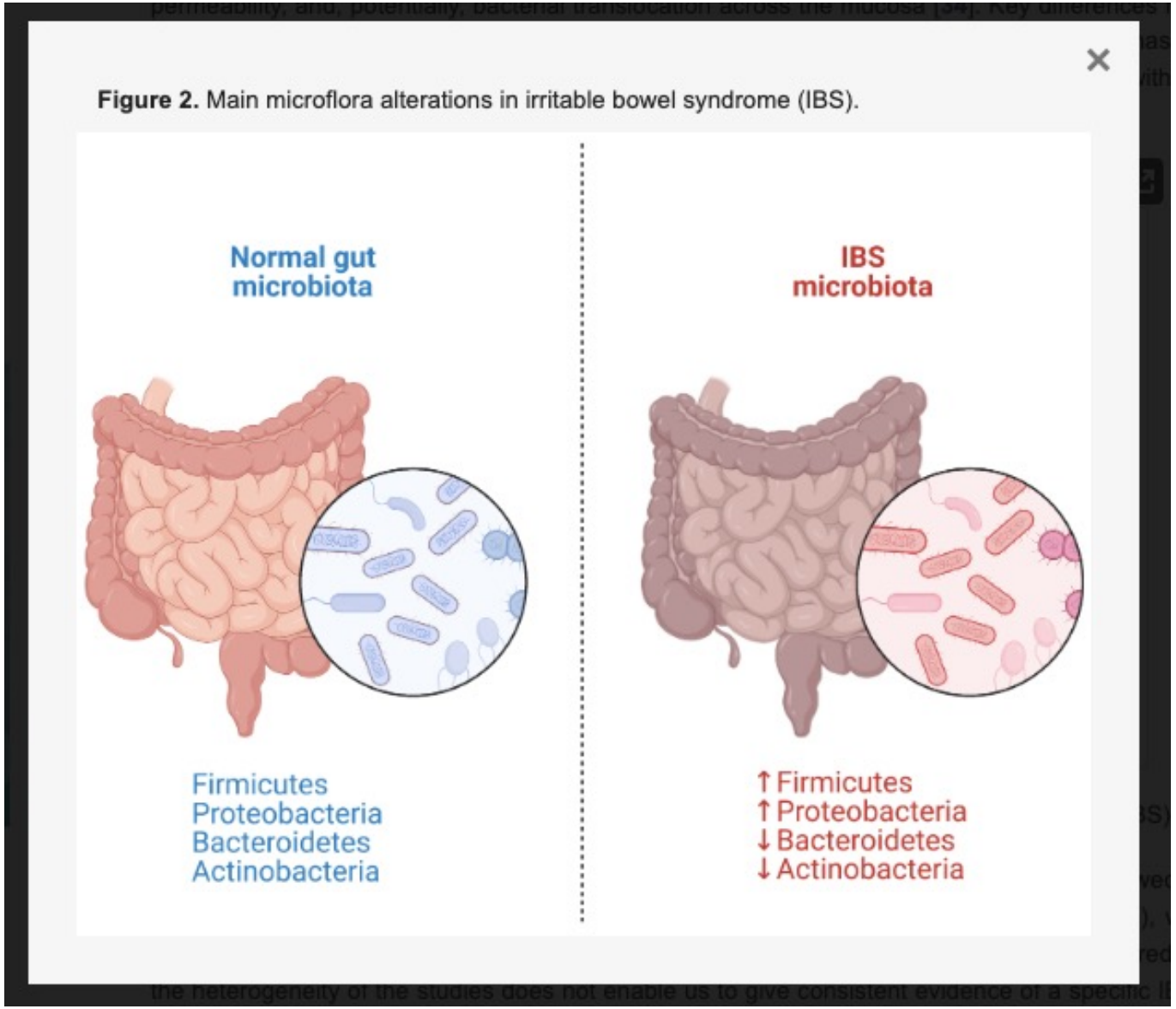
Yaşlanma Disbiyozu Nasıl Etkiler?

Yaşlanmayla disyiboz sıklığı giderek artış gösterir..

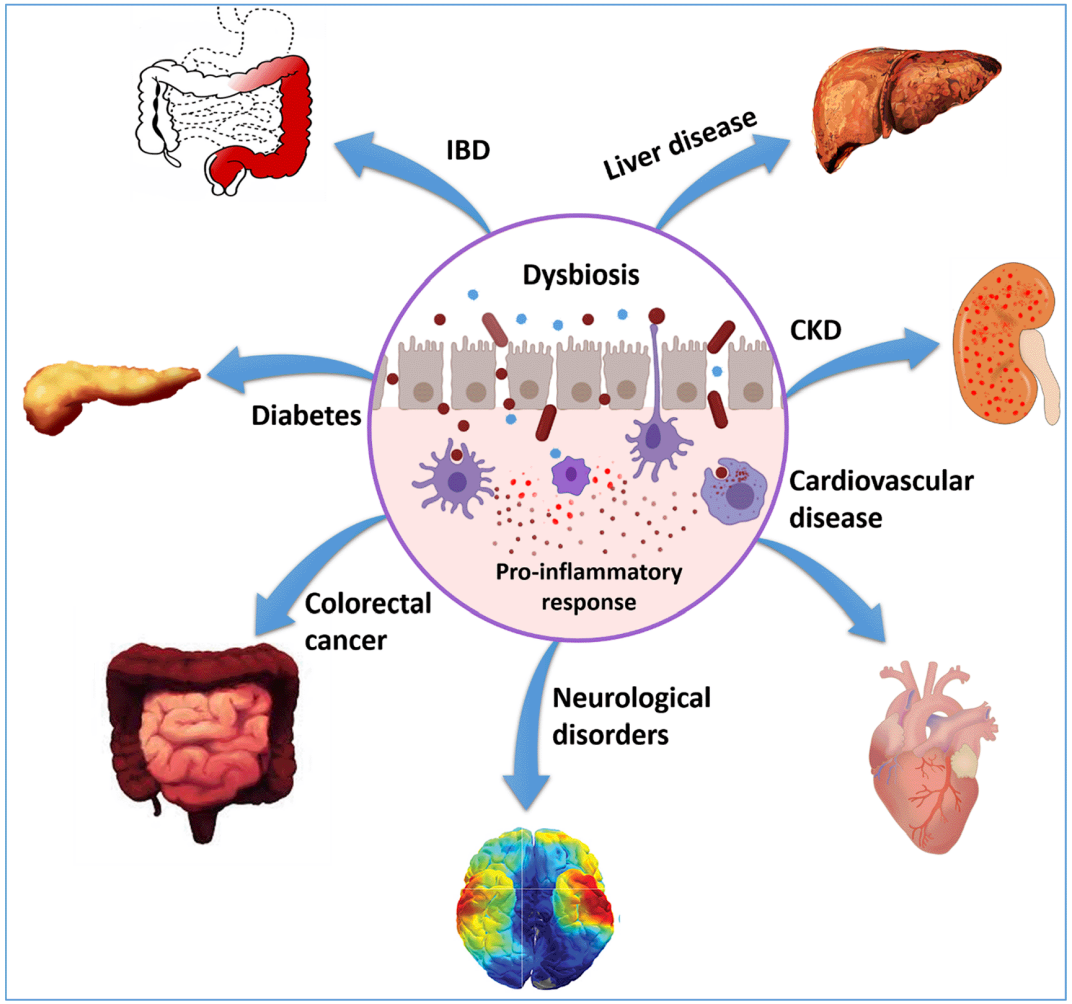


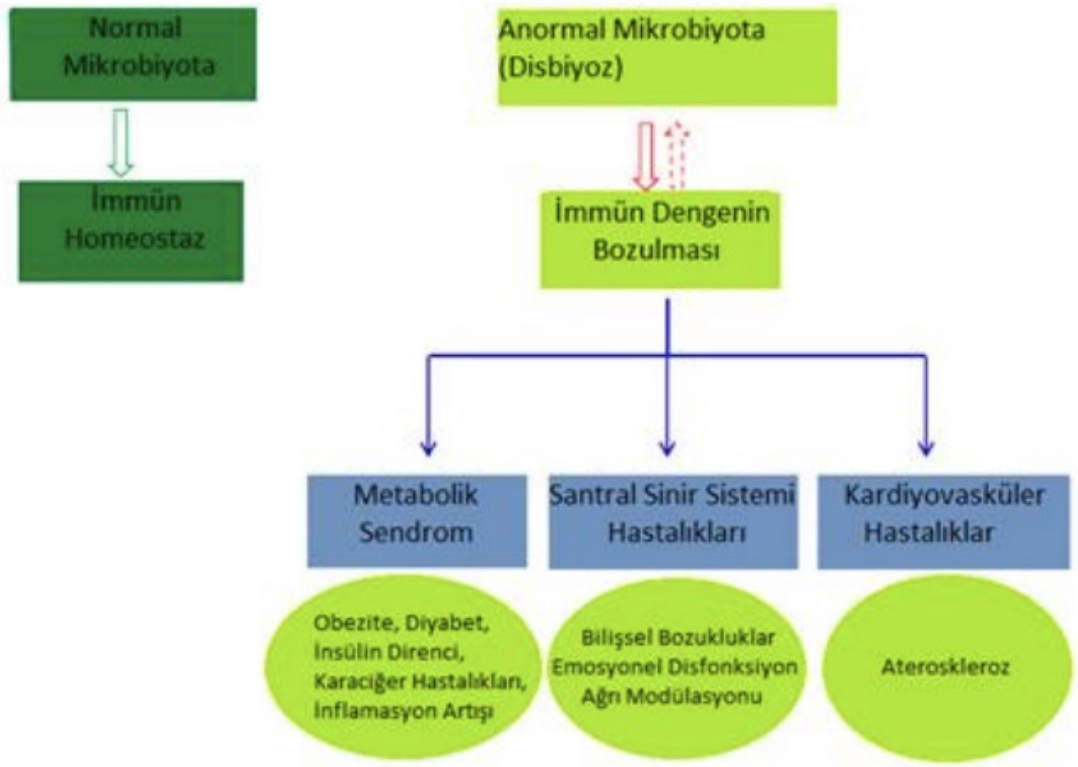
Clinical & Experimental Immunology
Volume 179, Issue 3, pages 363-377, 16 FEB 2015 DOI: 10.1111/cei.12474
http://onlinelibrary.wiley.com/doi/10.1111/cei.12474/full#cei12474-fig-0001

Disbiyoz ve İntestinal Değişim

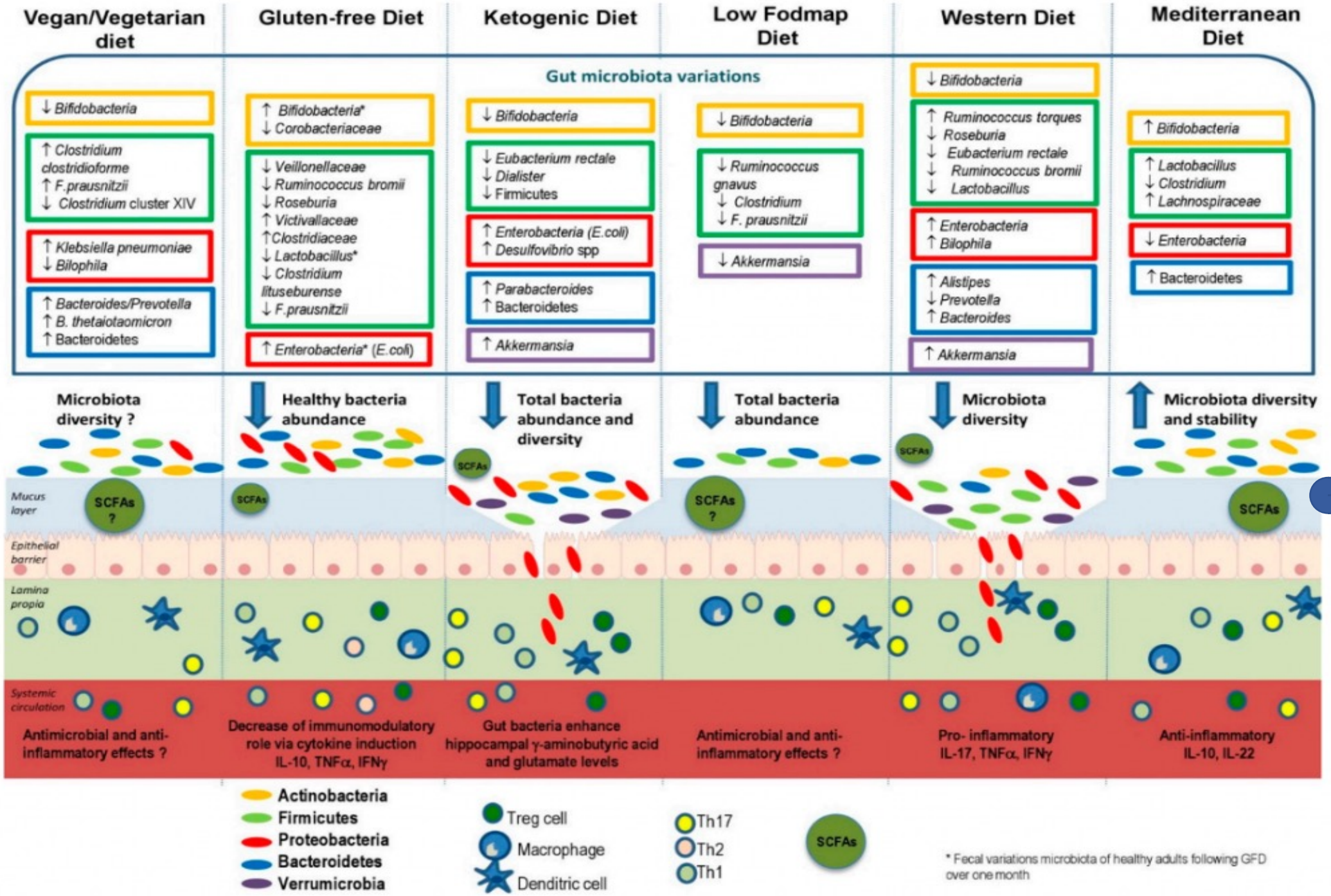


İntestinal Mikrobiyota Düzensizliği (Disbiyoz)





Şekil 3. Bağırsak mikrobiyotasının perifer dokulardaki etkileri[24]

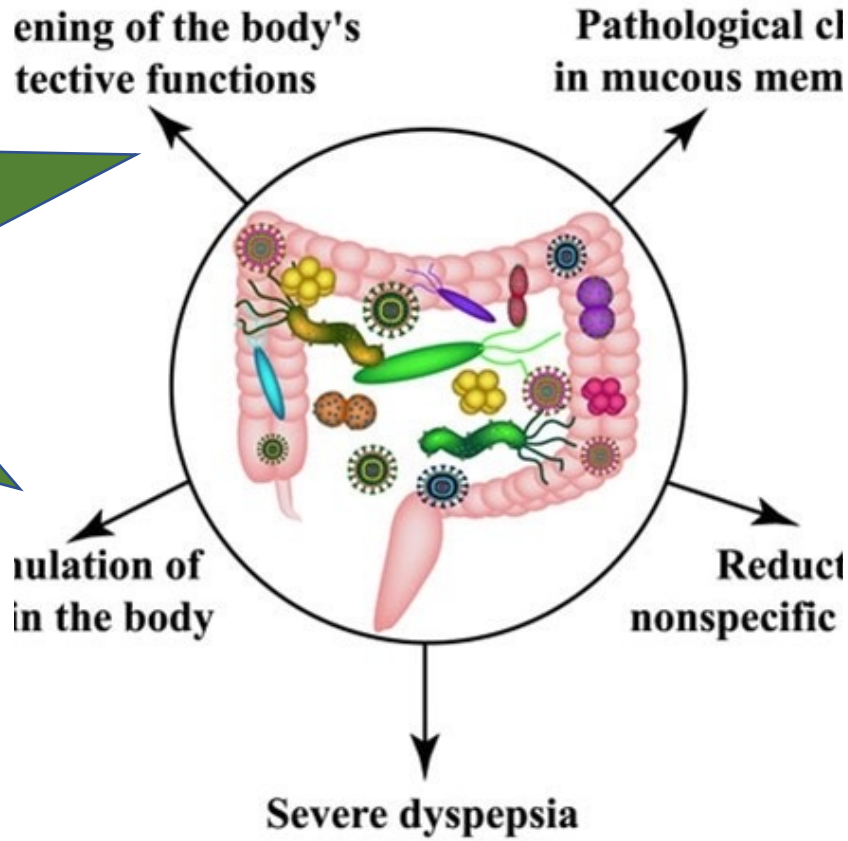


Fermente edilebilir kısa zincirli karbonhidratlar (Fodmap) diyet en uygunu..

Disbiyoz Nelere Yol Açar?

- Epitel hücrelerin bariyer özellikleri
- Mukus membranda patolojik değişiklik
- Toksinlerin birikimi
- Ciddi dispepsi
- Nonspesifik immünite azalması
- M hücrelerin Antijen sunumları
- Sitokin salımı ve inflamasyon artışı
- Sıkı bağlantı yapısının bozulması
- CD4, CD8, T ve B Lenfosit, DC ve Makro[illegible] yanıtı
- Kanser gelişimi (B.fargilis Toksini, BFT- Kolon Kanseri)
- Patojen bakteri kolonizasyonunda artış..

MDR ve PDR bakteri Kolonizasyonu



Disbiyoz ve İnfeksiyon

Patojen Bakteri Translokasyonu

İnfeksiyon gelişimi

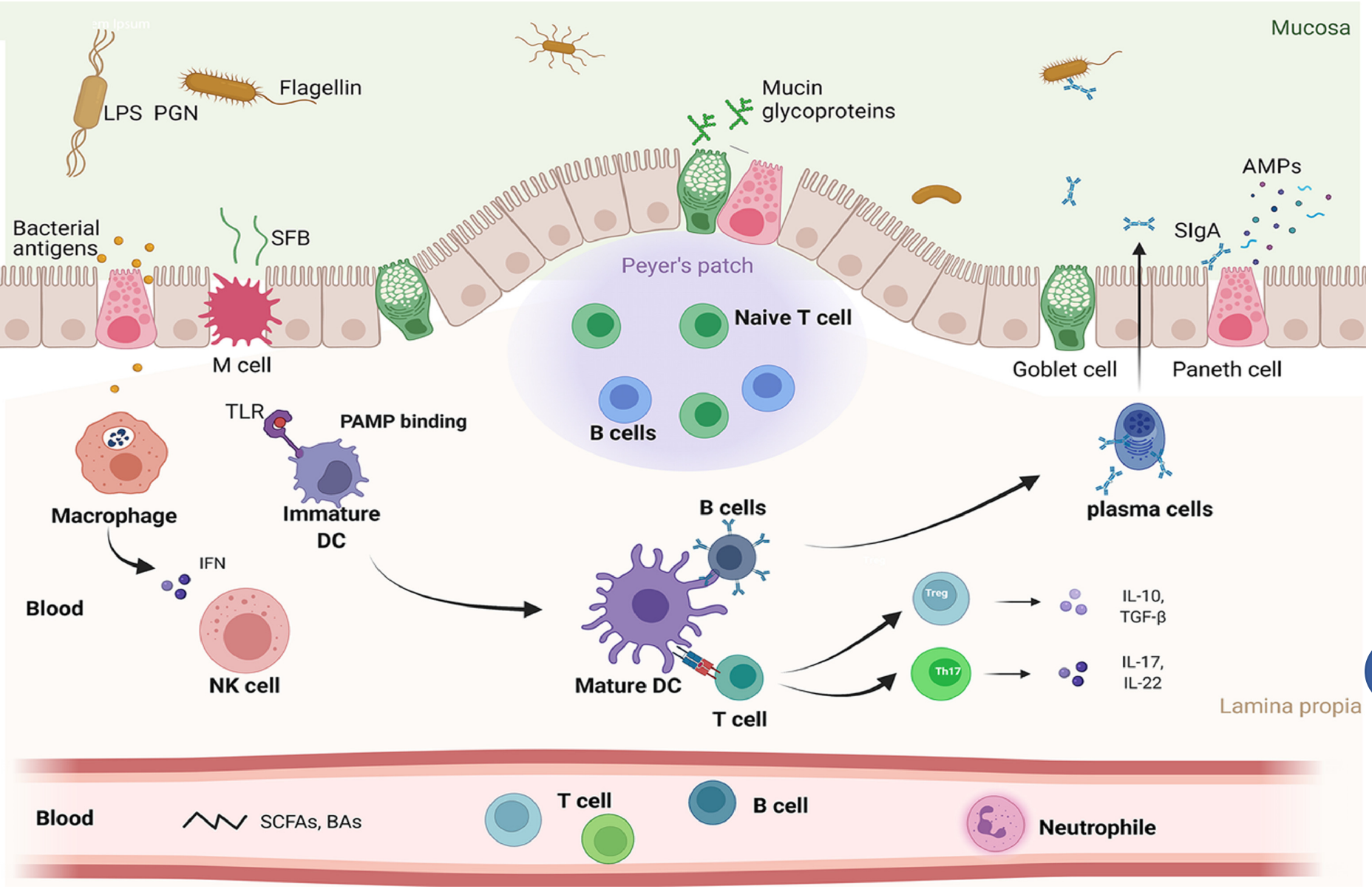
Antibiyotik kullanımı..

Kolon kaynaklı patojen bakterilerde seçici AB Direnç Etkisi

Mukozal ve sistemik (doğal / adaptif) immun sisteminin sürekli aktive olmaktadır (sürekli antijenik stimülasyon)

Bacterial Translocation from the Gut to the Distant Organs: An Overview

R. Nagpal, H. Yadav • Published in Annals of Nutrition and... 1 September 2017 • Medicine, Biology



- Disbiyoz intestinal bariyeri ortadan kaldırır
- Bakteriyel translokasyon artar
- Lümen içerisinde immun sistem hücreleri aktive olur
- Yoğun sitokin salınımı ve patojen bakteriler infeksiyonu artırır..

Translocation of gut flora and its role in sepsis

*C Vaishnavi

Abstract

Bacterial translocation is the invasion of indigenous intestinal bacteria through the gut mucosa to normally sterile tissues and the internal organs. Sometimes instead of bacteria, inflammatory compounds are responsible for clinical symptoms as in systemic inflammatory response syndrome (SIRS). The difference between sepsis and SIRS is that pathogenic bacteria are isolated from patients with sepsis but not with those of SIRS. Bacterial translocation occurs more frequently in patients with intestinal obstruction and in immunocompromised patients and is the cause of subsequent sepsis. Factors that can trigger bacterial translocation from the gut are host immune deficiencies and immunosuppression, disturbances in normal ecological balance of gut, mucosal barrier permeability, obstructive jaundice, stress, etc. Bacterial translocation occurs through the transcellular and the paracellular pathways and can be measured both directly by culture of mesenteric lymph nodes and indirectly by using labeled bacteria, peripheral blood culture, detection of microbial DNA or endotoxin and urinary excretion of non-metabolisable sugars. Bacterial translocation may be a normal phenomenon occurring on frequent basis in healthy individuals without any deleterious consequences. But when the immune system is challenged extensively, it breaks down and results in septic complications at different sites away from the main focus. The factors released from the gut and carried in the mesenteric lymphatics but not in the portal blood are enough to cause multi-organ failure. Thus, bacterial translocation may be a promoter of sepsis but not the initiator. This paper reviews literature on the translocation of gut flora and its role in causing sepsis.

Key words: *Bacterial translocation, gut microflora, immunosuppression, multi-organ failure, sepsis*

Introduction

The human gastrointestinal tract is inhabited by a plethora of bacteria belonging to over a 1000 different species[1] comprising of obligate anaerobes (95%) and facultative anaerobes (5%). Obligate anaerobes include *Bifidobacterium, Clostridium, Eubacterium, Bacteroides, Fusobacterium, Peptococcus* and *Peptostreptococcus.* The facultative anaerobes include *Lactobacillus, Bacillus, Streptococcus, Staphylococcus*, *Escherichia coli, Klebsiella* and *Pseudomonas aeruginosa.*[2] *Bifidobacteria* are the predominant cultivable bacteria in 80% of infants and 25% adults.[3] The resident flora comprises of distinct organisms that are constantly present in a given region of the intestine at a particular age. The transient flora organisms that colonise the intestine for different periods of time.[4] Commensal bacteria rarely cause local or systemic disease despite their presence in extremely high numbers. A unicellular epithelial layer on the intestinal mucosa prevents these micro-organisms from migrating to extra-intestinal sites.

The gut microflora has a great role to play. They directly activate the development and differentiation of intestinal epithelium and play an important role in maintaining the integrity of the enterocytes.[2] They contribute to nutrition by producing several enzymes for digestion as well as for mucous secretion[2] and take part in synthesis of vitamins and absorption of minerals.[5] The gut bacterial flora maintains an immunologically balanced

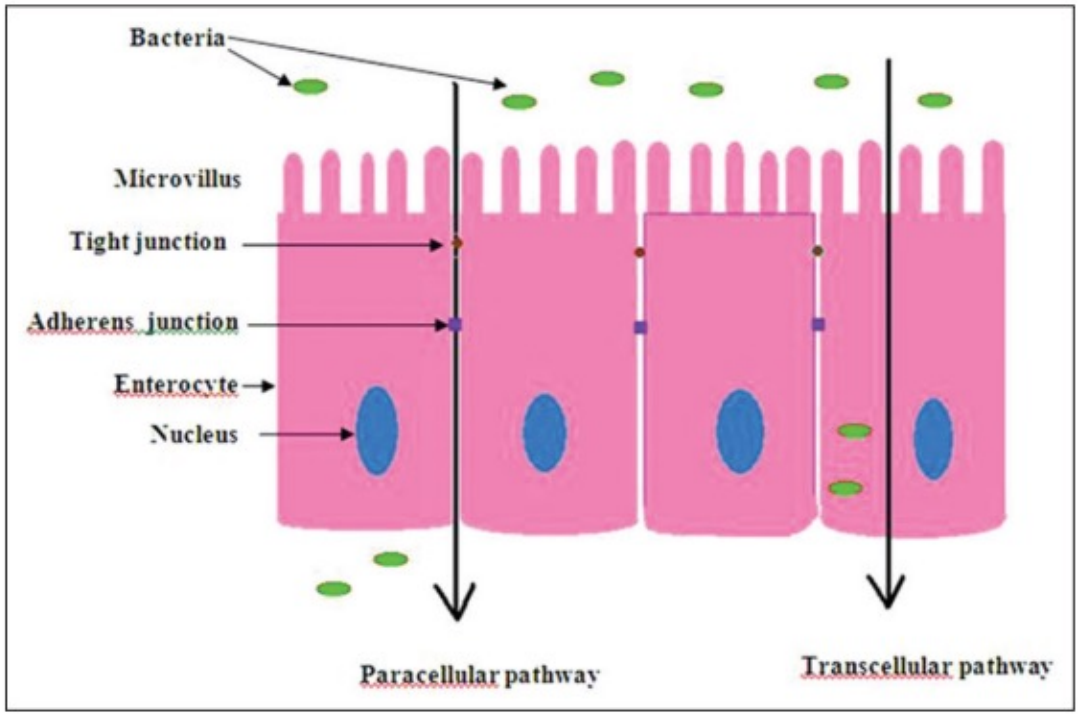


Figure 1: Diagrammatic depiction of pathways of gastrointestinal permeability

Bağırsak florası epitel hücrelerin gelişimini ve farklılaşmasını doğrudan etkiler, Enterositlerin bütünlüğünü korur..

Table 1. List of Microbiota Members by Genus or Species and the Published Disease Conditions With Which Each Has Been Shown to Have an Association

Genus/Species	Related disease conditions	Abundances in disease	References
Butyrate producers			
Anaerostipes	Alzheimer disease/ Cancer/ Colitis	Decreased	1–3
Butyricicoccus	Food allergy/ IBD	Decreased	4,5
Butyrivibrio	Age/ Alzheimer's disease/ Amyotrophic lateral sclerosis	Decreased	6–8
Blautia hansenii	Alzheimer's disease/ Autism/ Obesity	Decreased	9–11
Clostridial clusters IV and XIVa	Cystic Fibrosis/ IBD/ Multiple Sclerosis/ Parkinson's	Decreased	12–15
Clostridium saccharolyticum	Alzheimer's disease/ Parkinson's disease	Decreased	16,17
Eubacterium species	Alzheimer's disease/ Crohn's disease/ Kidney stones	Decreased	18 19–21
Faecalibacterium prausnitzii	Alzheimer's disease/ IBD/ Parkinson's/ Psoriasis	Decreased	20,10,15,27,28,22–24
Roseburia hominis	Allergies/ Autoimmune diseases/ Diabetes Type 2/ Ulcerative Colitis	Decreased	12,24,25
Ruminococcus obeum	Age/ Liver Disease Obesity	Decreased Increased	26,27 28
Ruminococcus bromii	Age/ Crohn's disease/ Parkinson's disease	Decreased	29–31
Lachnospiraceae bacterium	Diabetes / HIV/ Obesity/	Increased	32,33
Frailty associated			
Eggerthella lenta	Autoimmune/ Intestinal Infections	Increased	34,35
Eubacterium dolichum	Obesity	Increased	36,37
Methanobrevibacter	IBD	Decreased	38,39
Ruminococcus gnavus	Age/ Allergies/ Crohn's disease/ Lupus	Increased	31,40–42
Malnutrition associated			
Bifidobacterium	Antibiotic-associated diarrhea/ Cancer/ Eczema/ Ulcerative colitis	Decreased	43–47

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Abstract

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- Bakteriyel translokasyon bağırsak içerisindeki bakterilerin bağırsak mukozasından normalde steril olan Mezenterik lenf nodları ve iç organlara geçiş yapmasıdır.
- Bazı durumlarda mikroorganizma yerine inflamatuar sitokinler geçiş yapar ve SIRS'a neden olabilir.
- SIRS sitokin salınımına neden olan yanık, travma, obstrüktif gastrointestinal injuri, hemorajik şok ve sepsis durumlarında görülür
- Bağırsak mikroflorasında Enterik Gram negatif bakteriler hızla çoğalır, bunlar da endotoksin aracılığıyla mukozal hasarı artırarak bariyer yapısını bozar..

TRANSLOKASYON YAPAN ENTERİK BAKTERİLERİN TÜMÜ İNFEKSİYONA NEDEN OLUYOR MU?

WHAT'S NEW IN GENERAL SURGERY

ANNALS OF SURGERY
Vol. 218, No. 2, 111–119

The Gastrointestinal Tract

The "Undrained Abscess" of Multiple Organ Failure

John C. Marshall, M.D., F.R.C.S.C., F.A.C.S.,*
Nicolas V. Christou, M.D., Ph.D., F.R.C.S.C., F.A.C.S.,†
and Jonathan L. Meakins, M.D., D.Sc., F.R.C.S.C., F.A.C.S.†

From the Departments of Surgery, University of Toronto, Toronto, Ontario, and McGill University, Montreal, Quebec,† Canada*

Objective
This study determined the association between proximal gastrointestinal (GI) colonization and the development of intensive care unit (ICU)-acquired infection and multiple organ failure (MOF) in a population of critically ill surgical patients.

Summary Background Data
ICU-acquired infection in association with progressive organ system dysfunction is an important cause of morbidity and mortality in critical surgical illness. Oropharyngeal and gastric colonization with the characteristic infecting species is common, but its association with ICU morbidity is poorly defined.

- Marshal ve arkadaşları, YBU'sinde enfeksiyon geçiren hastaların >%90'ının üst GIS'de kolonize olan bakterilerle en az bir enfeksiyon atağı geçirdiklerini göstermiştir.
- Her bir atak GİS'de kolonize olan bakterilerin etken olma olasılığını daha da artırmaktadır.

The Gastrointestinal Tract

The "Undrained Abscess" of Multiple Organ Failure

John C. Marshall, M.D., F.R.C.S.C., F.A.C.S.,*
Nicolas V. Christou, M.D., Ph.D., F.R.C.S.C., F.A.C.S.,†
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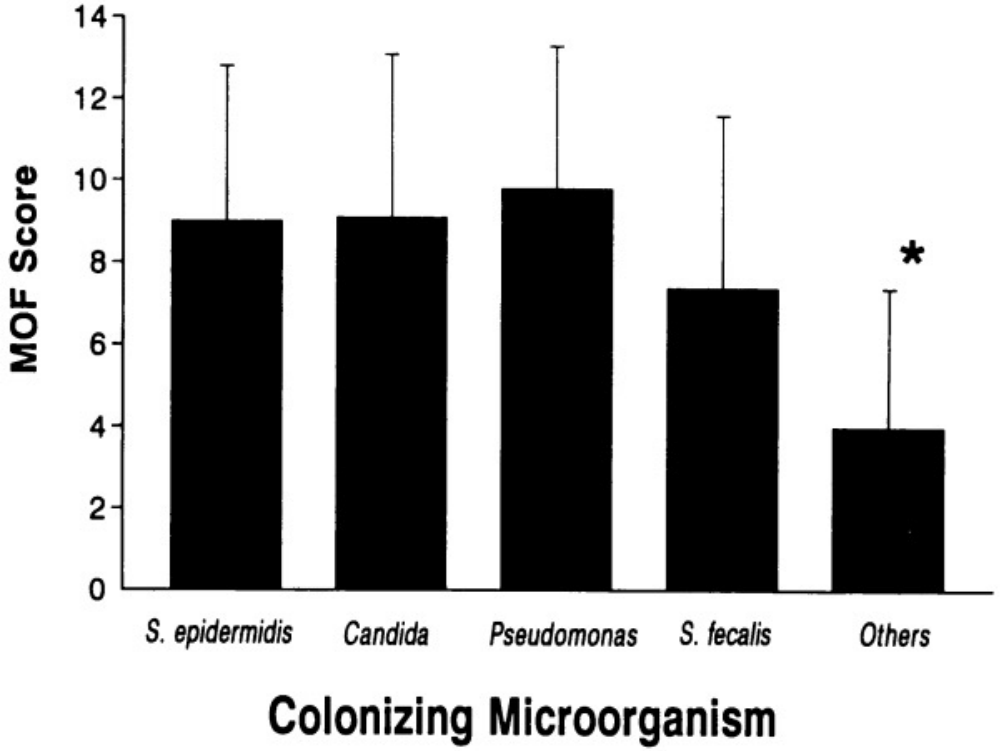

Figure 3. Organ failure (MOF) scores for patients colonized with *Candida* (19 patients), *Pseudomonas* (10 patients), *S. epidermidis* (10 patients), or *S. faecalis* (12 patients) were significantly higher than the scores for the 7 patients who were not colonized with any of these 4 organisms ($p = 0.02$, one-way analysis of variance). MOF scores were calculated as previously described.[9] Results are mean ± SD.

- GIS'de kolonizasyon oluşturan bakterilerden Candida, Pseudomonas, *S.epidermidis* ve *E.faecalis*'in neden olduğu sepsislerde MOF Skoru diğer kolonize olan bakterilerin MOF Skorundan daha yüksekti.
- Bu da dört bakterinin mortaliteye neden olan ciddi infeksiyonlara yol açtığını göstermekteydi..

Enteral Beslenme Mikrobiyotayı Nasıl Etkiler?

INFECTION AND IMMUNITY, Sept. 1992, p. 3556–3565
0019-9567/92/093556-10$02.00/0

Vol. 60, No. 9

Cryptdins: Antimicrobial Defensins of the Murine Small Intestine

PATRICIA B. EISENHAUER,[1] SYLVIA S. S. L. HARWIG,[1] AND ROBERT I. LEHRER[1,2]*

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Received 6 April 1992/Accepted 4 June 1992

Paneth cells are specialized small intestine epithelial cells that contain lysozyme, possess phagocytic properties, and secrete cytoplasmic granules into the intestinal crypt lumen after the entry of bacteria. Recent studies by Ouellette and associates (A. J. Ouellette, R. M. Greco, M. James, D. Frederick, J. Naftilan, and J. T. Fallon, J. Cell Biol. 108:1687–1695, 1989) indicated that murine Paneth cells produce prodefensin mRNA, but the properties of its peptide product were not reported. We purified two closely related defensins, cryptdin 1 and cryptdin 2, from a subcellular fraction of murine small intestine cells that was enriched in Paneth cells. Both peptides contained 35 amino acid residues, including the characteristic defensin "signature" of six invariantly conserved cysteines. Cryptdins 1 and 2 were approximately 90 to 95% homologous to each other and to the carboxy-terminal domain of the 93-amino-acid defensin precursor, cryptdin A, described by Ouellette and associates (Ouellette et al., J. Cell Biol. 108:1687–1695, 1989). Both cryptdins exerted bactericidal activity against *Listeria monocytogenes* EGD and *Escherichia coli* ML-35p in vitro. Their potency exceeded that of human neutrophil defensin HNP-1 but was considerably lower than that of NP-1, a defensin produced by rabbit neutrophils and alveolar macrophages. Both cryptdins killed mouse-avirulent *Salmonella typhimurium* 7953S (*phoP*) much more effectively than its *phoP*$^+$, mouse-virulent, isogenic counterpart, *S. typhimurium* 14028S. Our data indicate that mouse intestinal prodefensins are processed into 35-amino-acid mature defensins (cryptdins) with broad-spectrum antimicrobial properties. The production of defensins and lysozyme by Paneth cells may enable them to protect the small intestine from bacterial overgrowth by autochthonous flora and from invasion by potential pathogens that cause infection via the peroral route, such as *L. monocytogenes* and *Salmonella* species.

- Enteral Beslenme normal proksimal barsak antimikrobiyal defans sistemini aktive eder
- Daha az steril olan Üst GIS'de mikrobiyota devamlılığı gastrik asit, normal barsak motilitesi ve daha az oranda safra tuzları ile etkileşerek sağlanır
- Burada IgA ve Paneth hücrelerinden salınan Defensin'in de katkısı vardır
- Gastrik asit salınımını, safra akışını ve ince bağırsak motiltesini, kolesistokinin ve sekretin salınımını, S-IgA üretimini artırır.
- Asit azaltıcı önlemler stres ülser riskini azaltır. Bu da gastrik gram negatif mikroorganizmaların sayıca hızla çoğalmasına katkı sağlar..

EUROPEAN RESPIRATORY JOURNAL
ORIGINAL RESEARCH ARTICLE
R. CHANDERRAJ ET AL.

In critically ill patients, anti-anaerobic antibiotics increase risk of adverse clinical outcomes

Rishi Chanderraj [1,2], Jennifer M. Baker [3,4], Stephen G. Kay[3], Christopher A. Brown [3,5], Kevin J. Hinkle[3], Daniel J. Fergle[3], Roderick A. McDonald[3], Nicole R. Falkowski[3], Joseph D. Metcalf[3], Keith S. Kaye [6], Robert J. Woods [1,2,7], Hallie C. Prescott [3,8,9], Michael W. Sjoding [3,7,8,10] and Robert P. Dickson [3,4,10]

[1]Division of Infectious Diseases, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, MI, USA. [2]Medicine Service, Infectious Diseases Section, VA Ann Arbor Healthcare System, Ann Arbor, MI, USA. [3]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, MI, USA. [4]Department of Microbiology and Immunology, University of Michigan Medical School, Ann Arbor, MI, USA. [5]Institute for Research on Innovation and Science, Institute for Social Research, University of Michigan, Ann Arbor, MI, USA. [6]Division of Infectious Diseases, Department of Medicine, Rutgers-New Jersey Medical School, Newark, NJ, USA. [7]Computational Medicine and Bioinformatics, University of Michigan Medical School, Ann Arbor, MI, USA. [8]Institute for Healthcare Policy and Innovation, University of Michigan, Ann Arbor, MI, USA. [9]VA Center for Clinical Management Research, Ann Arbor, MI, USA. [10]Weil Institute for Critical Care Research and Innovation, Ann Arbor, MI, USA.

Anti-Anaerobik antibiyotik kullanan 116 YBU hastasında yapılan bir Cohort çalışması

- Bağırsak bakteri dansitesinde anlamlı artış (p=0.00038),
- Hastanede yatış süresince Enterik bakteri içerikli mikrobiyom genişlemesinde artış (p=0.011)
- Enterobacteriaceae spp.lerin bağırsak ve solunum yolu patojeni olarak artışı (p=0.045). -

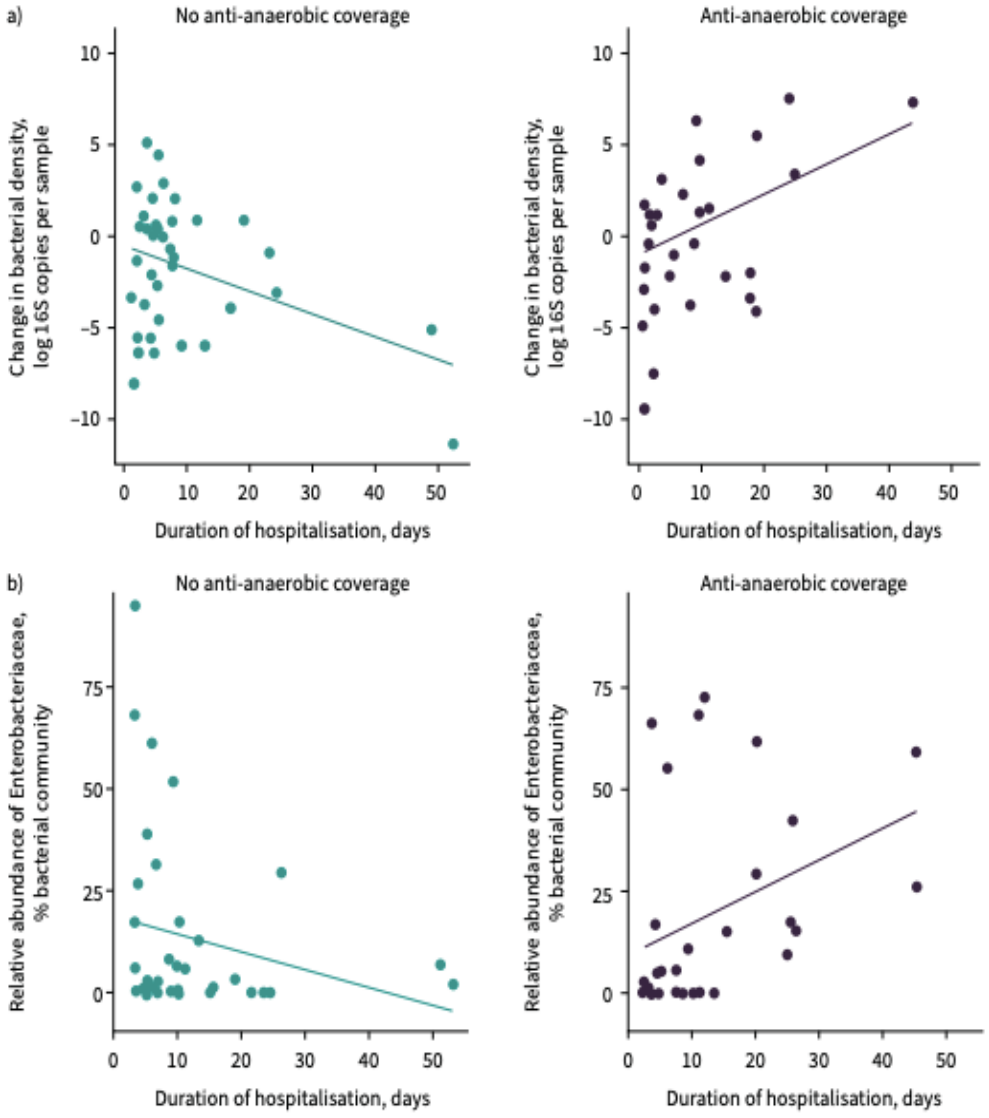


FIGURE 6 Changes in gut microbiota during hospitalisation among patients with and without exposure to anti-anaerobic antibiotic treatment. We measured the bacterial density and relative abundance of Enterobacteriaceae spp. in a subset of 116 subjects with a rectal swab specimen collected at the time of intensive care unit (ICU) admission and ICU discharge. a) Patients treated with anti-anaerobic antibiotics

In critically ill patients, anti-anaerobic antibiotics increase risk of adverse clinical outcomes

Rishi Chanderraj [1,2], Jennifer M. Baker [3,4], Stephen G. Kay[3], Christopher A. Brown [3,5], Kevin J. Hinkle[3], Daniel J. Fergle[3], Roderick A. McDonald[3], Nicole R. Falkowski[3], Joseph D. Metcalf[3], Keith S. Kaye [6], Robert J. Woods [1,2,7], Hallie C. Prescott [3,8,9], Michael W. Sjoding [3,7,8,10] and Robert P. Dickson [3,4,10]

Anti-Anaerobik antibiyotiklerin erken dönemde uygulanması olumsuz sonuçlar doğuruyor:

- VIP ile karşılaşmadan sağ kalım (hazard ratio (HR) 1.24, 95% CI 1.06–1.45)
- İnfeksiyon ile karşılaşmadan sağ kalım (HR 1.22, 95% CI 1.09–1.38)
- Kümülatif Sağkalım (HR 1.14, 95% CI 1.02–1.28)

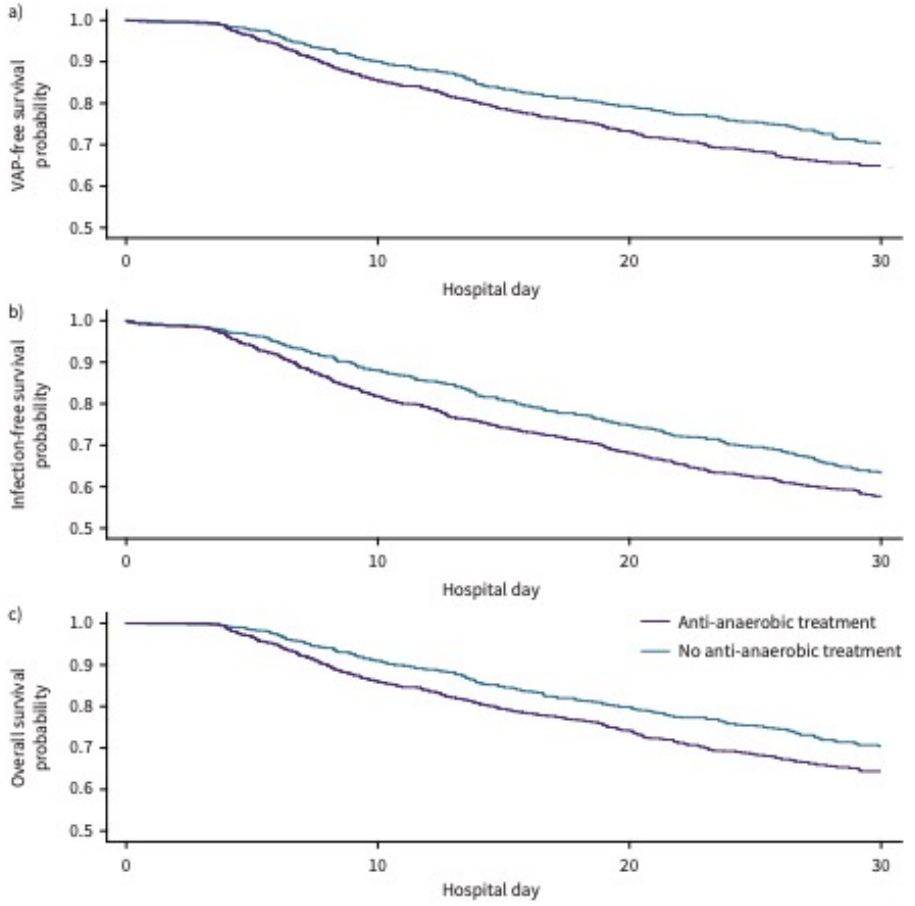


FIGURE 2 Anti-anaerobic antibiotic therapy predicts decreased ventilator-associated pneumonia (VAP)-free survival, infection-free survival and overall survival in critically ill patients. In a cohort of 3032 mechanically ventilated patients treated with *i.v.* antibiotics, the use of anti-anaerobic antibiotic therapy prior to day 3 of mechanical ventilation was associated with a) decreased VAP-free survival at 30 days ($p=0.00074$ by log-rank test), b) infection-free survival at 30 days ($p=0.00044$ by log-rank test) and c) overall survival at 30 days ($p=0.00064$ by log-rank test). There were 842 deaths, 89 cases of VAP and 472 cases of nosocomial infection in the cohort.

In critically ill patients, anti-anaerobic antibiotics increase risk of adverse clinical outcomes

Rishi Chanderraj [1,2], Jennifer M. Baker [3,4], Stephen G. Kay[3], Christopher A. Brown [3,5], Kevin J. Hinkle[3], Daniel J. Fergle[3], Roderick A. McDonald[3], Nicole R. Falkowski[3], Joseph D. Metcalf[3], Keith S. Kaye [6], Robert J. Woods [1,2,7], Hallie C. Prescott [3,8,9], Michael W. Sjoding [3,7,8,10] and Robert P. Dickson [3,4,10]

Anti-anaerob AB kullanımı ile Enterik bakteri ve C.difficile kaynaklı Hİ ve VAP oranlarında artış..

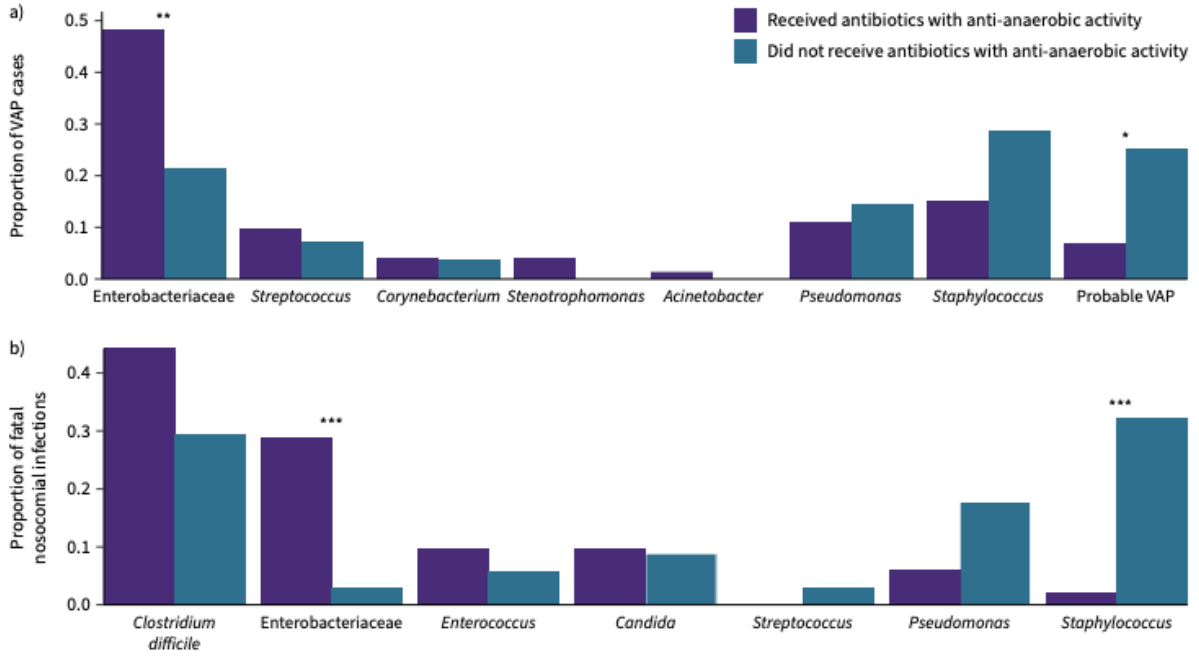
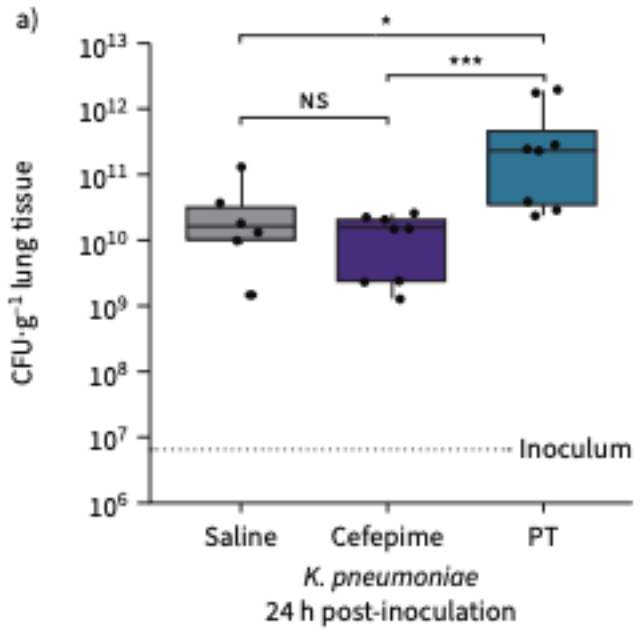
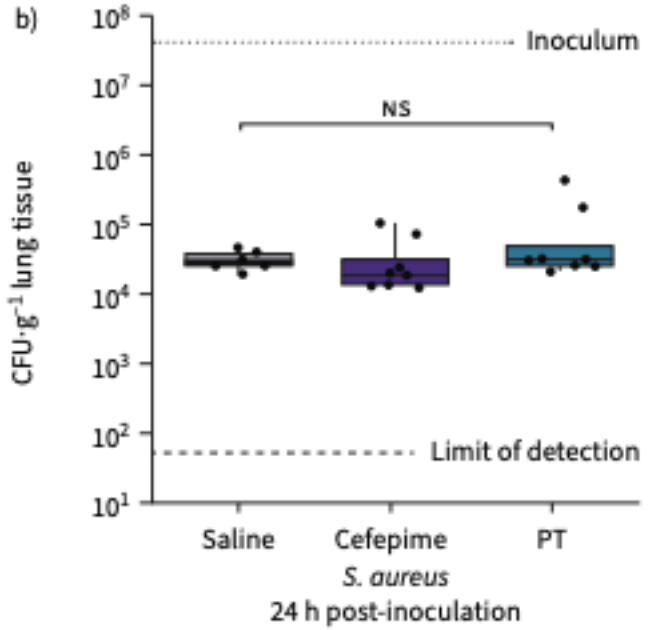
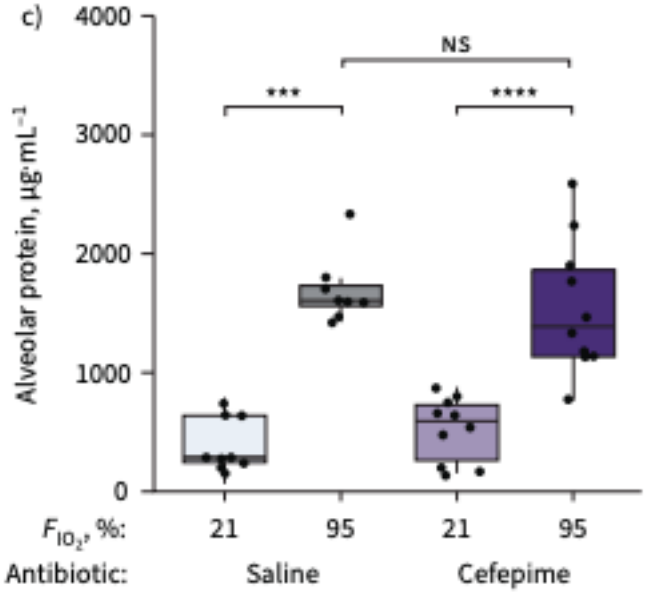
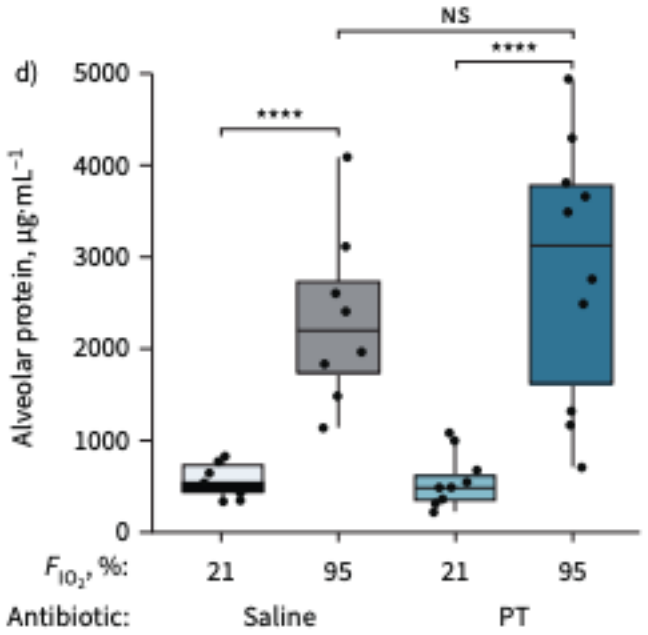


FIGURE 4 Administration of anti-anaerobic antibiotics is associated with increased identification of gut-associated bacteria in respiratory cultures. a) We compared the distribution of pathogens causing ventilator-associated pneumonia (VAP) among treatment groups and found an increased identification of Enterobacteriaceae spp. in patients treated with anti-anaerobic antibiotics (48% of cases of VAP in anti-anaerobic-treated *versus* 21% of cases of VAP without anaerobic treatment; p=0.0090 by t-test). b) We compared the distribution of pathogens causing fatal nosocomial infection among treatment groups and again found an increased identification of Enterobacteriaceae in patients treated with anti-anaerobic antibiotics (29% of cases in anti-anaerobic-treated *versus* 3% of cases without anaerobic treatment; p=0.0004 by t-test). *: p<0.05; **: p<0.01; ***: p<0.001.









Farelerde intraperitoneal olarak uygulanan antibiyotikler sonrasında mikrobiyota ve infeksiyon parametreleri araştırılıyor..

- SF ve Cefepim'e oranla anti-anaerop etkili PIP/TAZ sonrası Klebsiella yoğunluğu artıyor..
- Aynı uygulama sonrası *Staphylococcus aureus* yoğunluğunda değişiklik olmuyor
- Farelerin alveolar dokusunda inflamasyon ve protein artışı en fazla PIP/TAZ sonrası görülüyor..

Mikrobiyota yapısında Enterik bakteri artışı..
Translokasyon..
İnfeksiyon..

Chanderra R, et al. Eur Resp J, 2023; 61: 2200910

GUT MICROBIOTA EFFECTS IN HEMATOPOIETIC STEM CELL TRANSPLANT PATIENTS

ALLOJENİK KÖK HÜCRE NAKİLLERİNDE MİKROBİYOTA ETKİSİ

Ekin Ece GÜRER[1], Fatma SAVRAN OĞUZ[1], Sevgi BEŞIŞIK KALAYOĞLU[2], Zerrin AKTAŞ[3], Zafer GÜLBAŞ[4], Mustafa Oral ÖNCÜL[5], Uğur SEZERMAN[6]

Hematopoetik Stem Cell transplantasyonu sonrasında Mikrobiyota ciddi oranda etkilenmekte..

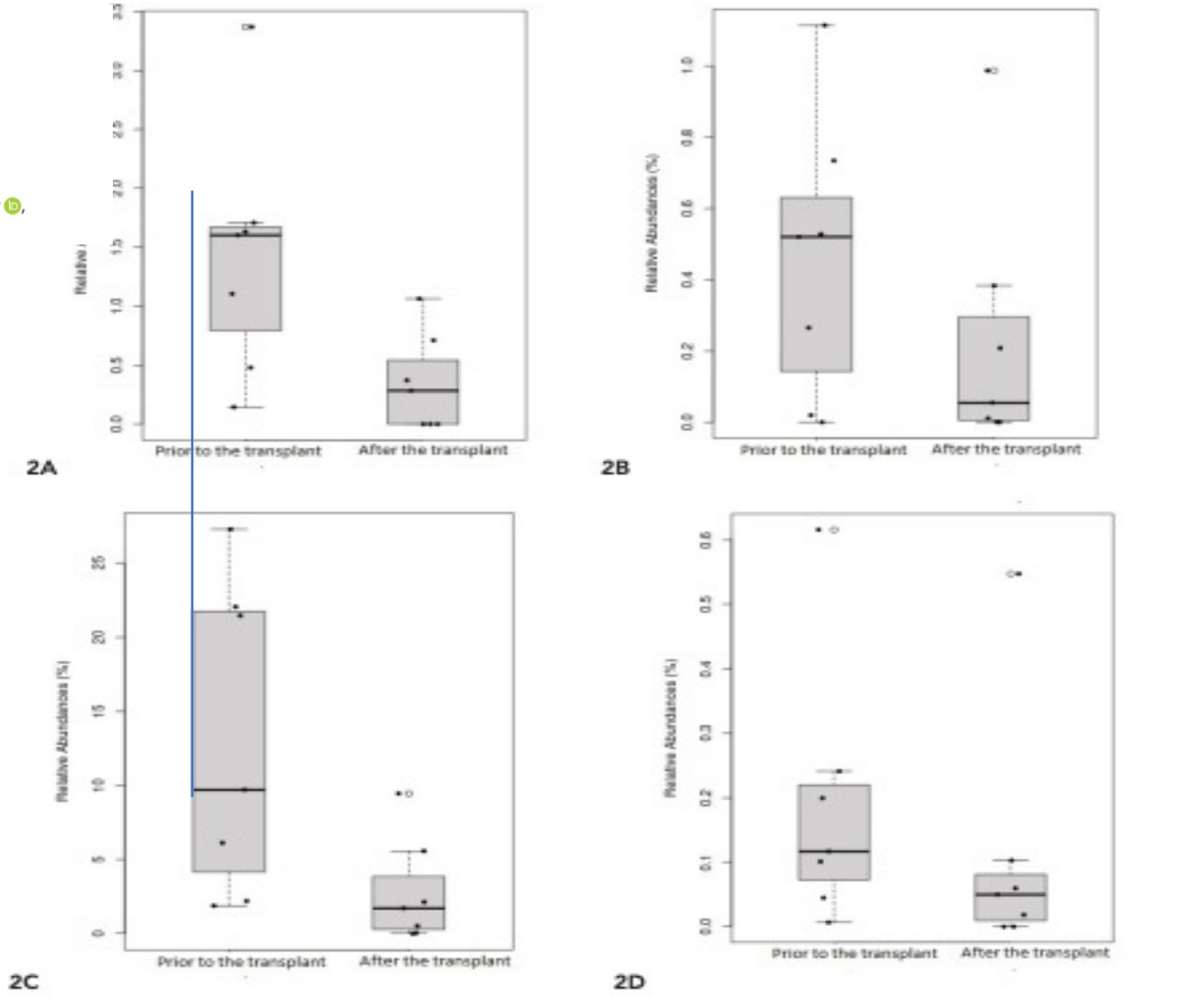


Figure 2: Decreased genus in the microbiota during engraftment. (2A: Genus of *Roseburia* levels prior to and after the transplant, 2B: Genus *of Bifidobacterium* levels prior to and after the transplant, 2C: Genus of *Faecalibacterium* levels prior to and after the transplant, 2D: Genus of Dorea levels prior to and after the transplant)

nature medicine

Article

https://doi.org/10.1038/s41591-023-02243-5

Dysbiosis of a microbiota–immune metasystem in critical illness is associated with nosocomial infections

Received: 5 July 2022

Accepted: 30 January 2023

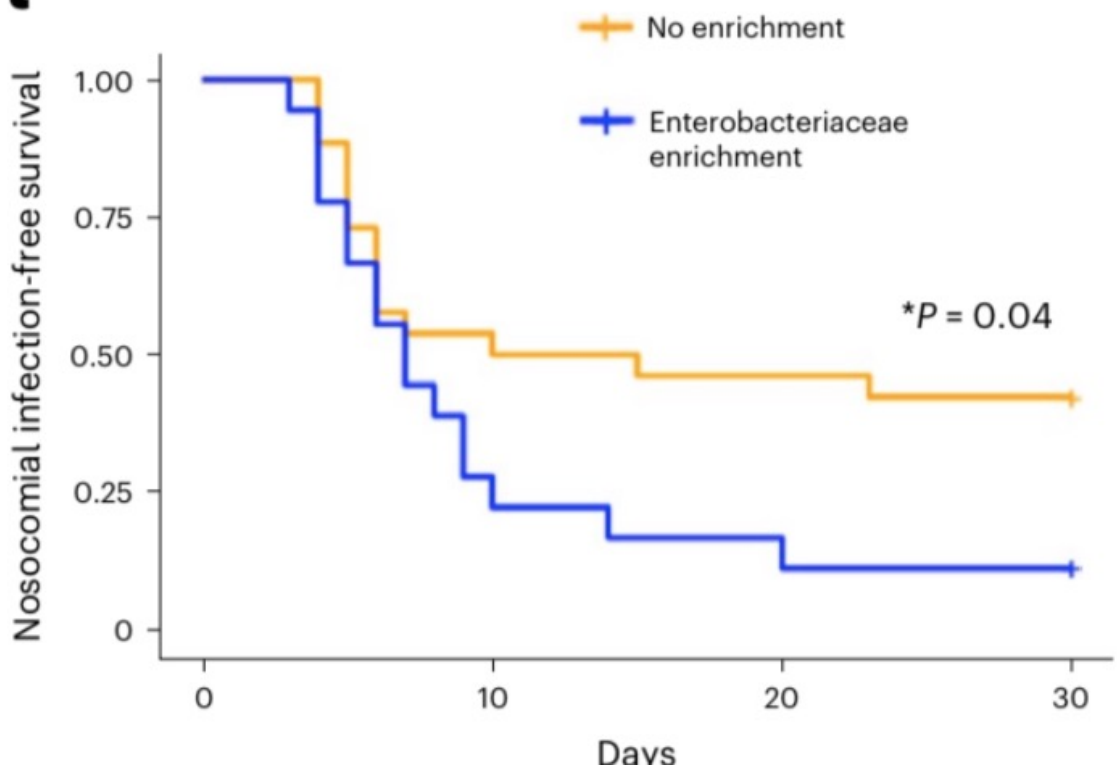
Published online: 9 March 2023

Check for updates

Jared Schlechte[1,2], Amanda Z. Zucoloto[1,2,3], Ian-ling Yu[1,2], Christopher J. Doig[1,2,4], Mary J. Dunbar[4,5,6], Kathy D. McCoy[2,3] & Braedon McDonald[1,2]

Critically ill patients in intensive care units experience profound

	Enterobacteriaceae enrichment (odds ratio, 95% CI)	*P* value
Nosocomial infection	6.8 (1.7–25.3)	*$P = 0.01$
Nosocomial infection by Enterobacteriaceae pathogen	0.97 (0.2–4.7)	$P > 0.99$



nature medicine

Article

https://doi.org/10.1038/s41591-023-02243-5

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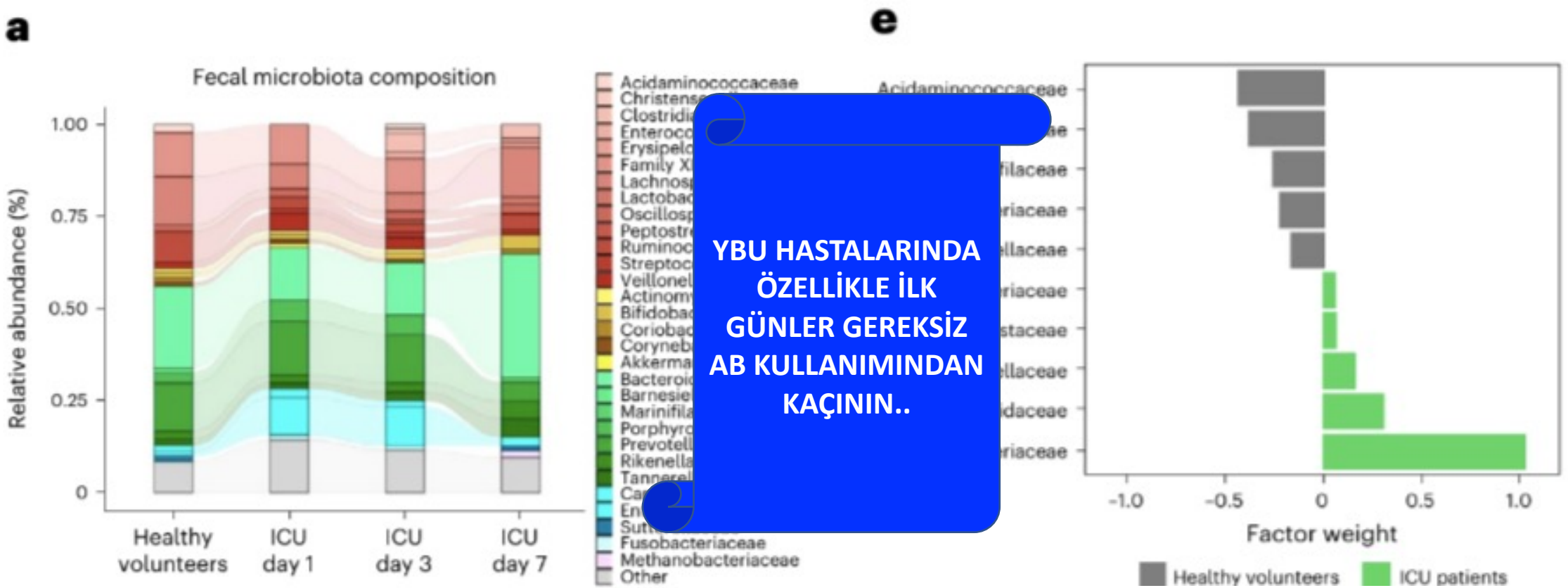
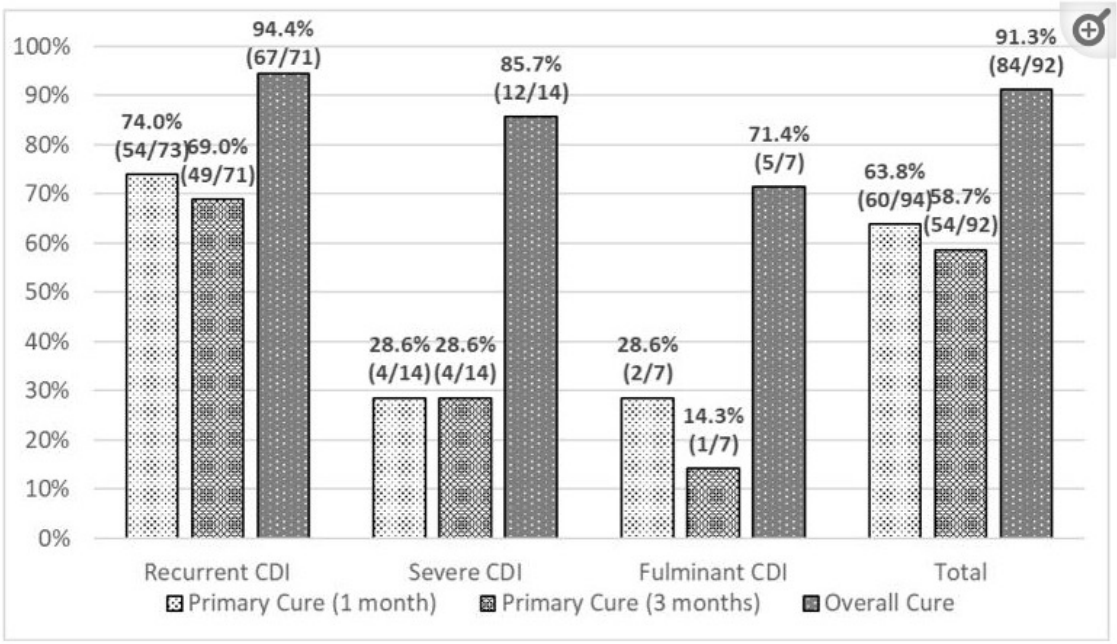


YBU HASTALARINDA ÖZELLİKLE İLK GÜNLER GEREKSİZ AB KULLANIMINDAN KAÇININ..

Fekal Mikrobiyota Transplantasyonu ve *C.difficile* İnfeksiyonlarında Tedavi Etkinliği

- Rekürren *C.difficile* İnfeksiyonu: %94.3
- Ciddi *C.difficile* İnfeksiyonu: %85.7
- Fulminan *C.difficile* İnfeksiyonu: %71.4
- Total Yanıt Oranı: %91.3



frontiers in Public Health

BRIEF RESEARCH REPORT
published: 09 June 2021
doi: 10.3389/fpubh.2021.670941

Does Fecal Microbiota Transplant Have a Role in Treating Recurrent *Clostridioides difficile* Infection in Rural Hospitals?

Krishna Vedala*, Philip Sobash, Parth Shah and Gilbert-Roy Kamoga

Department of Internal Medicine, White River Health System, Batesville, AR, United States

Clostridioides difficile infection possesses a significant economical burden, specifically in the inpatient and rural settings. Fecal Microbiota Transplant has been used for treatment of recurrent *Clostridioides difficile* but its utility is limited by current guidelines and resources. We conducted a retrospective chart review to evaluate the financial benefit of using Fecal Microbiota Transplant after first recurrence of *Clostridioides difficile* infection. We found that while its use was restricted, on average Fecal Microbiota Transplant can save $11,603.49 per patient. In conclusion, our study shows that using Fecal Microbiota Transplant could prove to be economically beneficial in treating recurrent CDI in rural hospitals.

Keywords: *Clostridium difficile* infection, rural healthcare, health economics, fecal microbiota transplant, recurrent C difficile infection

OPEN ACCESS

Edited by:
Sergio Oscar Angel,
CONICET Instituto Tecnológico de Chascomús (INTECH), Argentina

C.difficile infeksiyonlarında FMT uygulaması hasta başına ortalama 11.600 USD kazanç sağlamakta..

TABLE 1 | Costs and savings associated with FMT and recurrent CDI.

	Count	Average cost
>1 Admission for recurrent CDI	43	$16,961.92
Fecal Microbiota transplant	3	$5,358.43
Potential savings		$11,603.49

FMT, Fecal Microbiota Transplant; CDI, Clostridioides difficile infection.

Current Infectious Disease Reports (2019) 21: 22
https://doi.org/10.1007/s11908-019-0680-y

ANTIMICROBIAL DEVELOPMENT AND DRUG RESISTANCE (K CLAEYS AND A VEGA, SECTION EDITORS)

Check for updates

Novel Strategies for the Management of Vancomycin-Resistant Enterococcal Infections

German A. Contreras[1,2] · Jose M. Munita[3,4] · Cesar A. Arias[1,2,4,5,6,7,8]

Published online: 22 May 2019

Abstract

Purpose of Review Vancomycin-resistant enterococci (VRE) are important nosocomial pathogens that commonly affect critically ill patients. VRE have a remarkable genetic plasticity allowing them to acquire genes associated with antimicrobial resistance. Therefore, the treatment of deep-seated infections due to VRE has become a challenge for the clinician. The purpose of this review is to assess the current and future strategies for the management of recalcitrant deep-seated VRE infections and efforts for infection control in the hospital setting.

Recent Findings Preventing colonization and decolonization of multidrug-resistant bacteria are becoming the most promising novel strategies to control and eradicate VRE from the hospital environment. Fecal microbiota transplantation (FMT) has shown remarkable results on treating colonization and infection due to *Clostridiodes difficille* and VRE, as well as to recover the integrity of the gut microbiota under antibiotic pressure. Initial reports have shown the efficacy of FMT on reestablishing patient microbiota diversity in the gut and reducing the dominance of VRE in the gastrointestinal tract. In addition, the use of bacteriophages may be a promising strategy in eradicating VRE from the gut of patients. Until these strategies become widely available in the hospital setting, the implementation of infection control measures and stewardship programs are paramount for the control of this pathogen and each program should provide recommendations for the proper use of antibiotics and develop strategies that help to detect populations at risk of VRE colonization, prevent and control nosocomial transmission of VRE, and develop workers addressing the epidemiology of VRE and the potential impact of these pathogens

December 2, 2022

FDA approves first FMT therapy and issues guidance

What does this mean for GIs and other health care professionals treating CDI?

- Mikrobiyotanın bilinmeyen sırları
- Hiçbir AB ile çözemediğimiz HI sorununu bakterilerin kendisiyle mi çözeceğiz?
- MSS – Mikrobiyota – İmmun Sistem – Konak arasındaki etkileşim
- FMT ile tedavi boyutları nereye kadar?
- Nasıl bir mikrobiyota ile sağlıklı uzun yaşam?
- Kişiye özgü FMT ile tedavi başarısı ne kadar artabilir?
- FMT bugünün gerçeği olan tedavi ajanlarını yarın ne oranda ortadan kaldırabilecek?

Sonuç

- Bağırsak immun sistemin en önemli organlarından biridir
- Kolonizasyon direnci Enterik bakterilerin kolonizasyonunu, translokasyonunu ve infeksiyonlarını önleyen en önemli savunma sistemidir.
- Mikrobiyota ve kolonizasyon direncinin kaybı enterik bakteri kolonizasyonu ve translokasyonu ile sonuçlanır.
- Erken dönemde AB kullanımı MDR/PDR kolonizasyonu ve infeksiyonu riskini artırmaktadır
- FMT bütün bu sorunları çözebilecek umutları taşımaktadır..

- *Teşekkürler..*