

İNSAN MİKROBİYOM ÇALIŞMALARININ KLİNİĞE YANSIMASI

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VKV Amerikan Hastanesi

13 Mart 2019

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62 yaş erkek hasta

İki haftadan uzun süredir devam eden ateş, perianal bölgede şişlik ve ağrı, halsizlik şikayetleri ile bir başka hastaneden geldi.

22-30.03.2017: Pnömoni? c-ANCA ilişkili vaskülit?, Romatoid artrit ? ile Uludağ Üni Tıp Fak'ne yatış.

03-14.04.2017: Perianal abse ile seftriakson + vankomisin + klaritromisin verilmiş.

20.04.2017'de Cerrahpaşa TF'ye getirilmiş ve tedavisi meropenem + teikoplanin + flukonazol olarak değiştirilmiş.

Mart sonunda başlayan günde 2-3 kez olan sulu vasıfta ishal şikayeti var.

M. pneumoniae IgM: –

C. pneumoniae IgM: –

Brucella RB: -

Q fever CF: -

Sedimentasyon oranı: 73
(30.03.2017)

RF: 10.3

Rubella IgM: -

EBV VCA IgM: Zayıf +

EBNA IgM: Zayıf +

CMV IgM: -

28.03.2017:

Parvovirus IgM: -

TTE: Endokardit bulgusu yok.

BAL: ARB: -

P. jirovecii: -

Galaktomannan: -

Mantar:

Kültür: Üreme yok

İdrarda ARB: -

AH:

WBC: 15.3, CRP: 221,
prokalsitonin: 0.29

En son tedavinin devamını
önerdik.

Quantiferon: lenfosit sayısı düşük
olduğundan test sonuç vermedi.

Anti HIV: negatif

HIV RNA: negatif

CD4: 353

CD4/CD8: 2.7

CMV DNA: 930 kopya/mL

RF: 416

Sedim: 106

ALT: 153, GGT: 287, ALP: 643

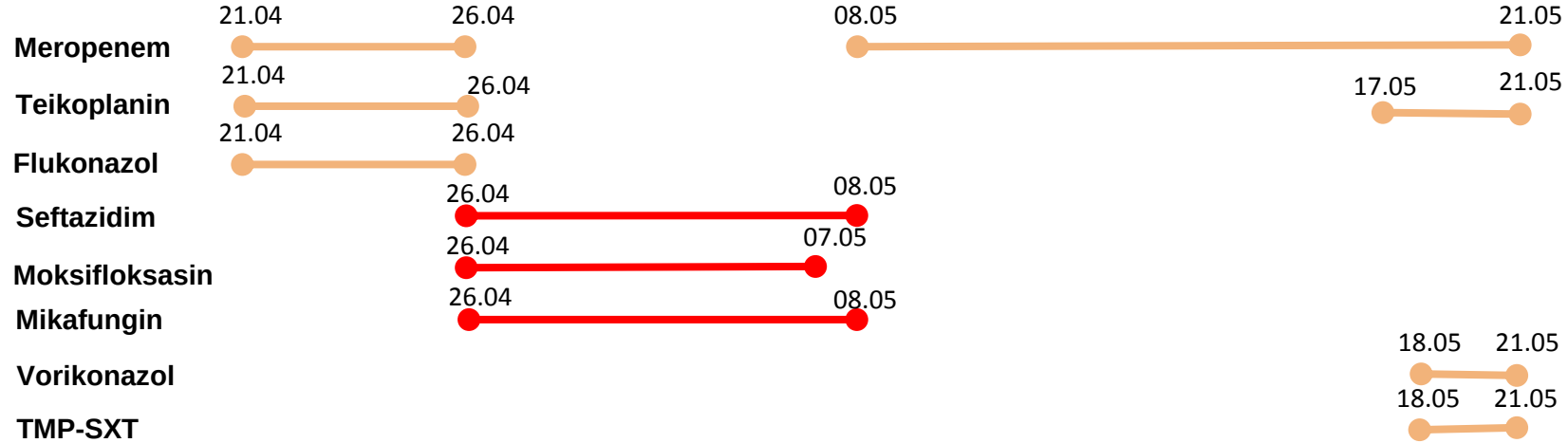
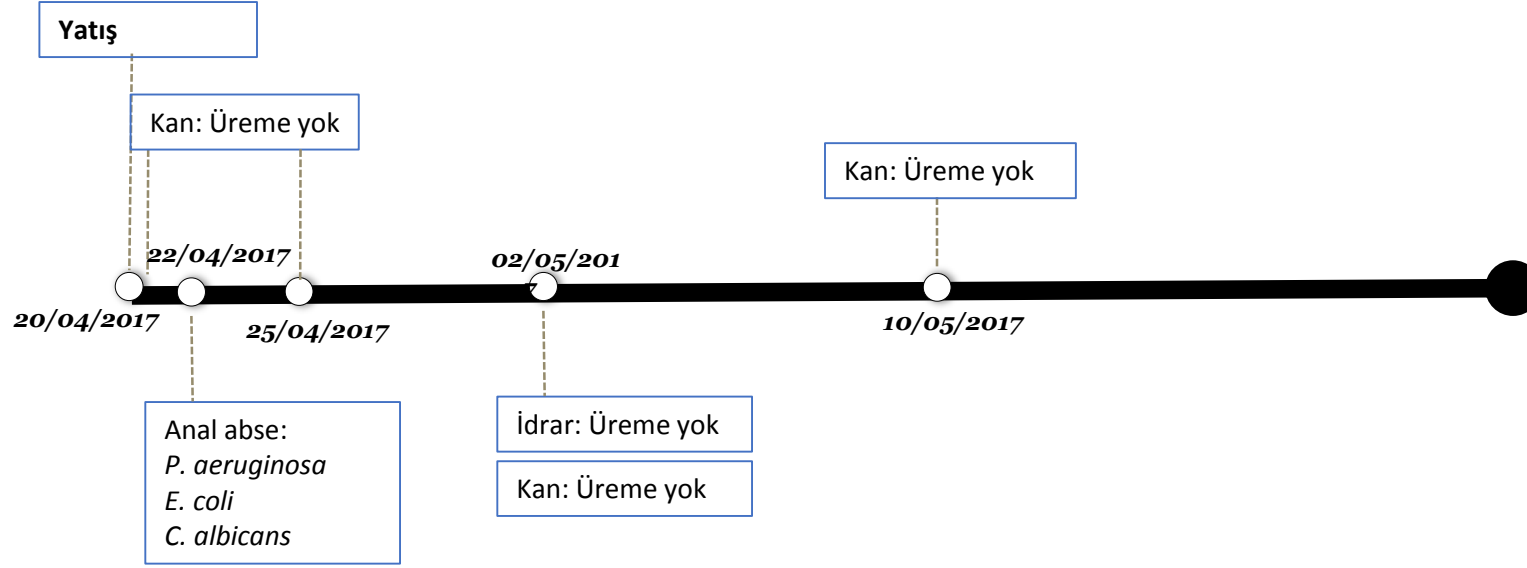
Toxoplasma IgM : -

TPHA ve RPR: -

EBV VCA IgM: -

HSV-1 IgM: -

Sıtma: -



Cinsiyet/Yaş : E / 01.05.1955
Protokol No. : 1435204
Örnek Tarihi/Saati : 22.04.2017 0:53

Örnek No : 5122558
Doktor : TAMER KÖYMEN
Bölümü : KAT 4 A
Rapor Tarihi : 26.04.2017 10:45

30440 - Kültür, Cerahat

KÜLTÜR - ANTİBİYOGRAM RAPORU

MİKROSKOPİK İNCELEME

G RAM : Polimorf çekirdekli lökositler, maya hücreleri ve Gram negatif çomaklar görüldü.

KÜLTÜR YÖNTEMİ

AEROP : 1.SUŞ Pseudomonas aeruginosa ve 2.SUŞ ESBL pozitif Escherichia coli üredi.

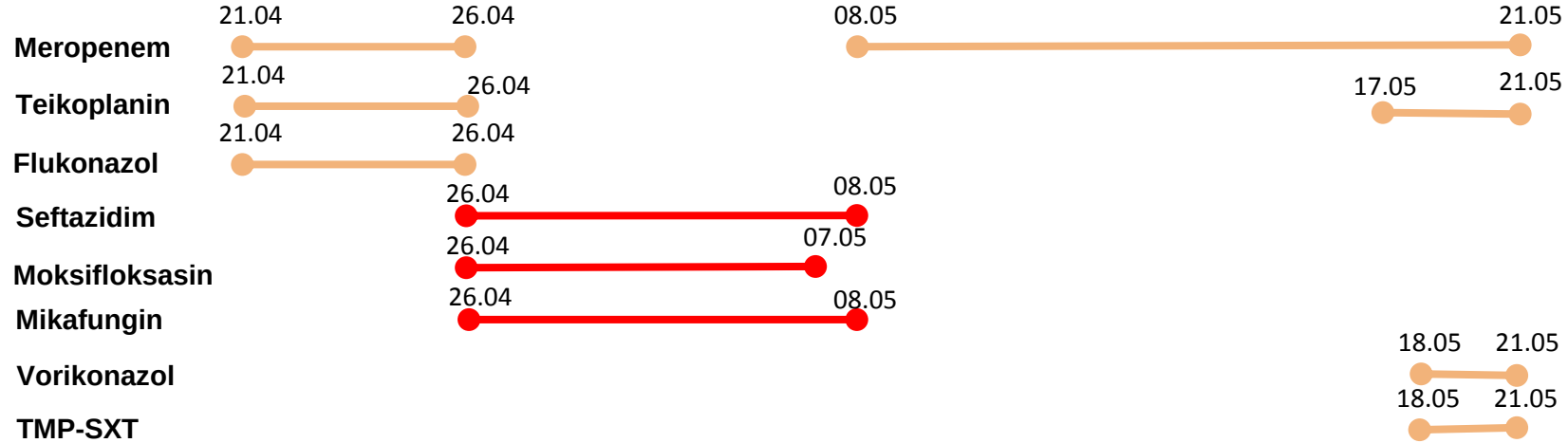
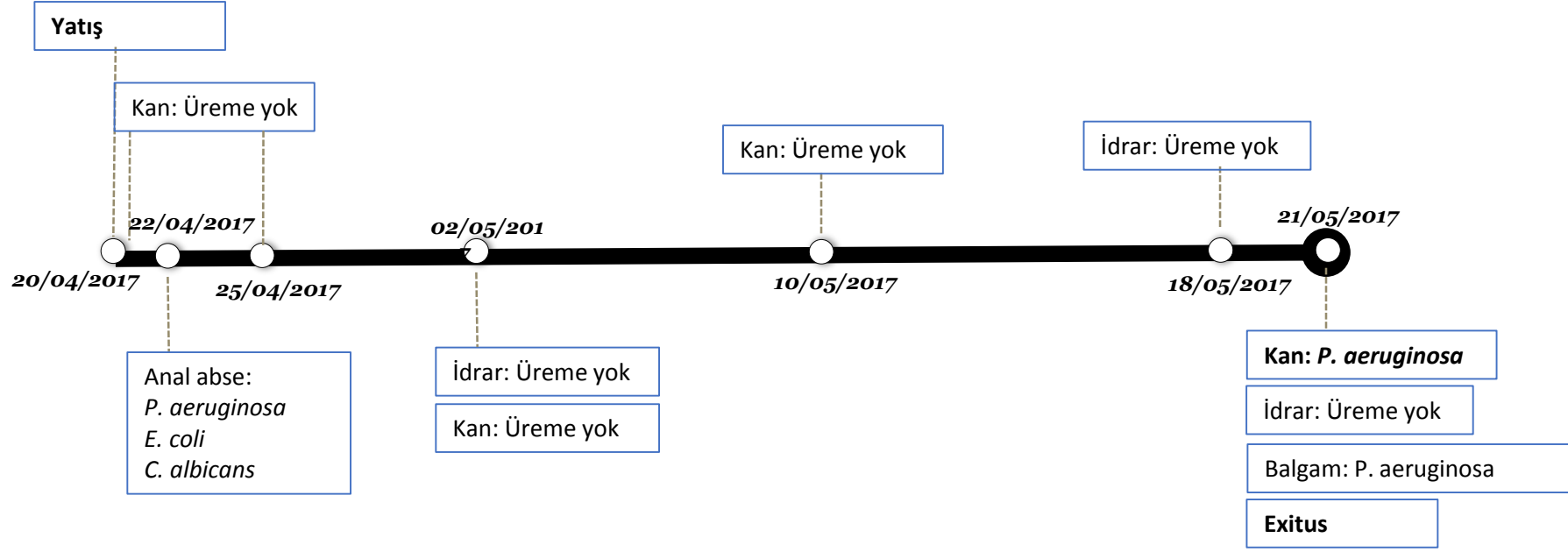
SABOURAUD BESİYERİ : Candida albicans üredi.

ANTİBİYOGRAM

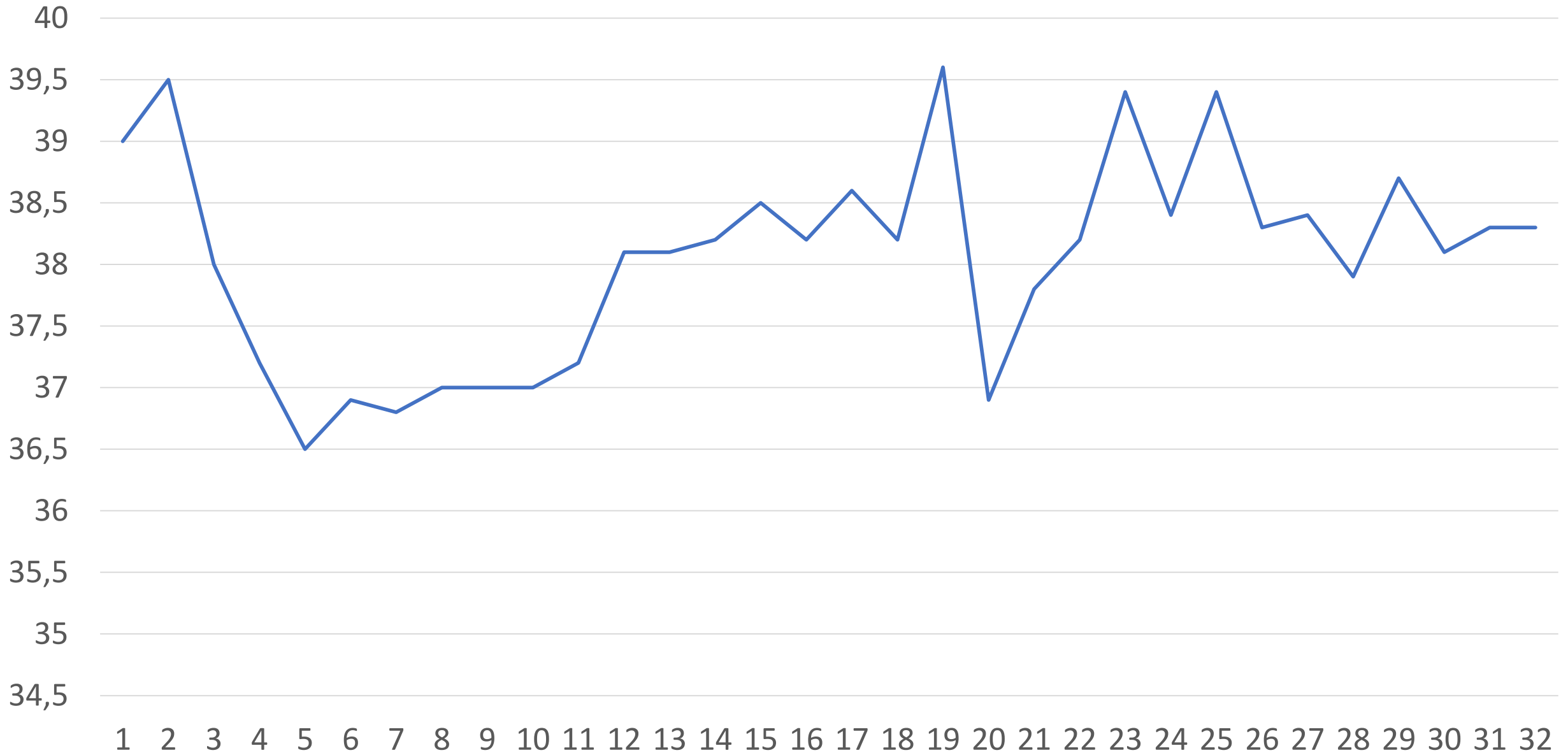
Notu : 1.SUŞ Piperasilin & tazobaktam orta duyarlı, Kolistin (MIC < 0,5 µg/ml) Duyarlı, Meropenem (MIC > 16 µg/ml) Dirençli, 2.SUŞ Piperasilin & tazobaktam orta duyarlı bulunmuştur.

	1.SUŞ <u>DUYARLILIK</u>	2.SUŞ <u>DUYARLILIK</u>
Amikasin	Dirençli	-
Ampisilin / Amoksisilin	-	Dirençli
Ciprofloksazin	Dirençli	Duyarlı
Gentamisin	Dirençli	Duyarlı
İmipenem	Dirençli	Duyarlı
Meropenem	-	Duyarlı
Sefoksitin	-	Dirençli
Seftazidim	Duyarlı	-
Trimetoprim & Sulfametaksazol	-	Duyarlı

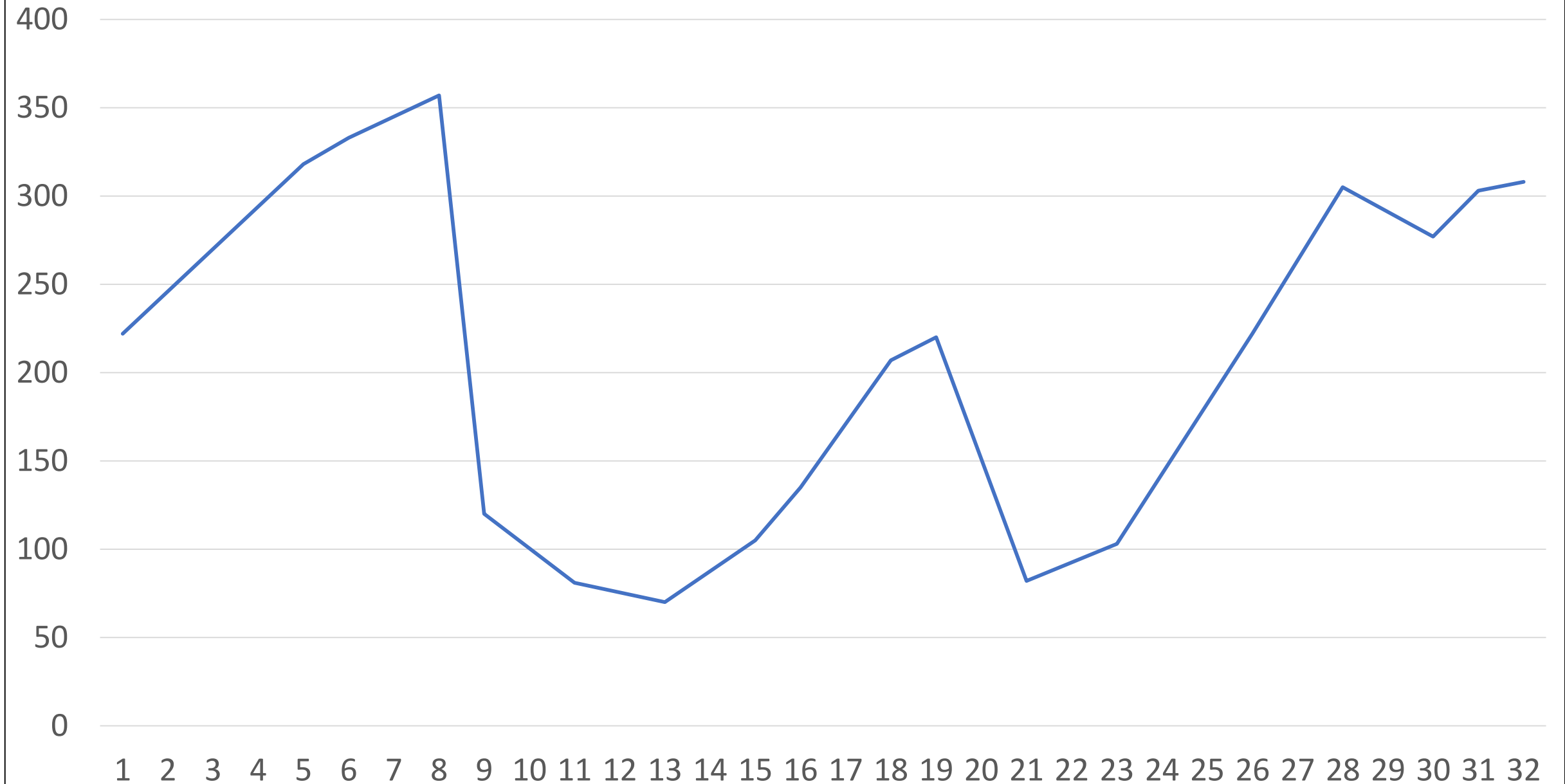
Bilgi Notu: Bakteri tanısı ve antibiyogramı Vitek 2 cihazı ile yapılmıştır. Duyarlılık sonuçları, T.C. Sağlık Bakanlığı Ulusal Mikrobiyoloji Standartları (UMS) ve Klinik ve Laboratuvar Standartları Enstitüsü (CLSI)'ne göre kısıtlı olarak bildirilmiştir.



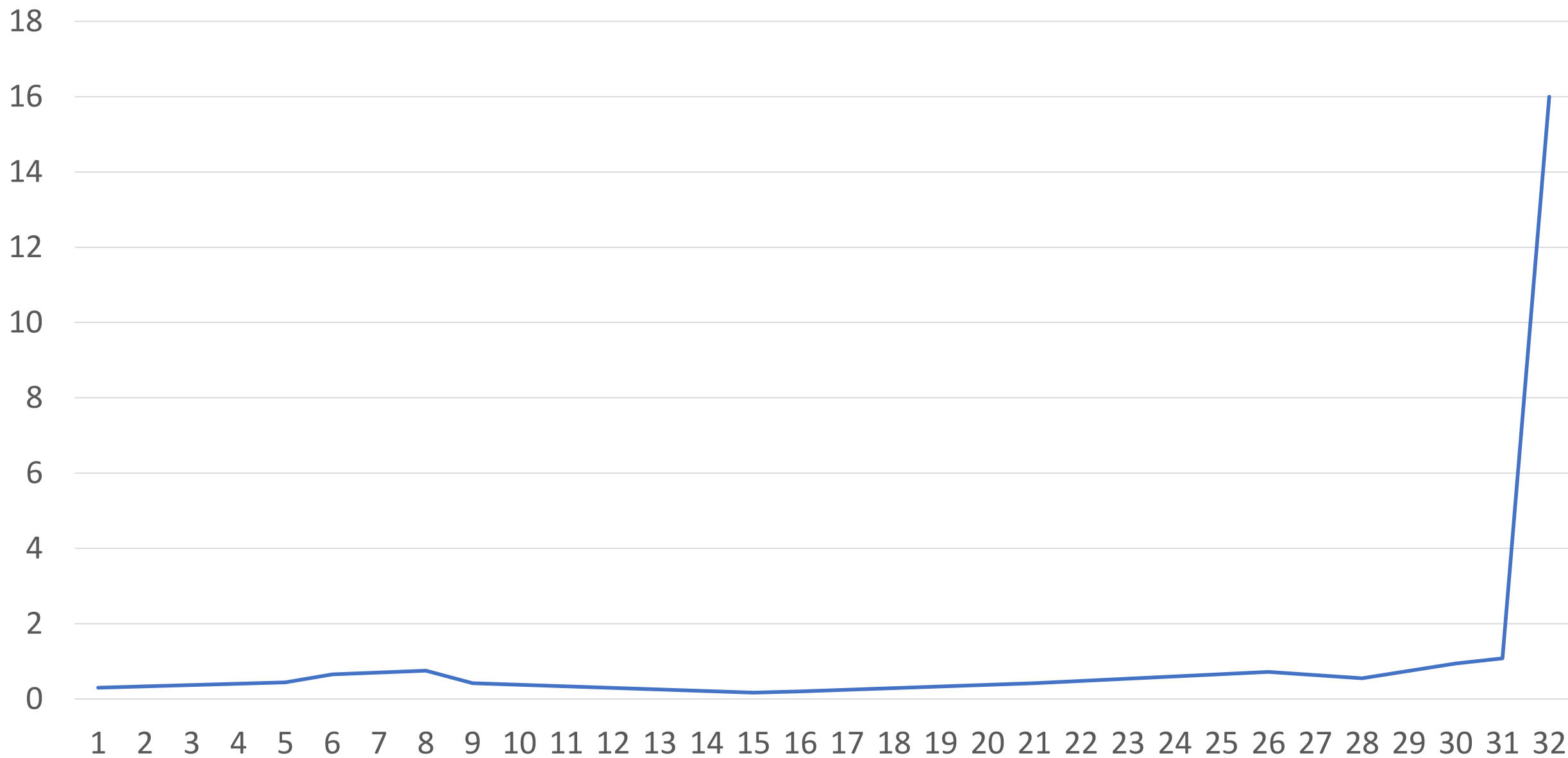
Ateş



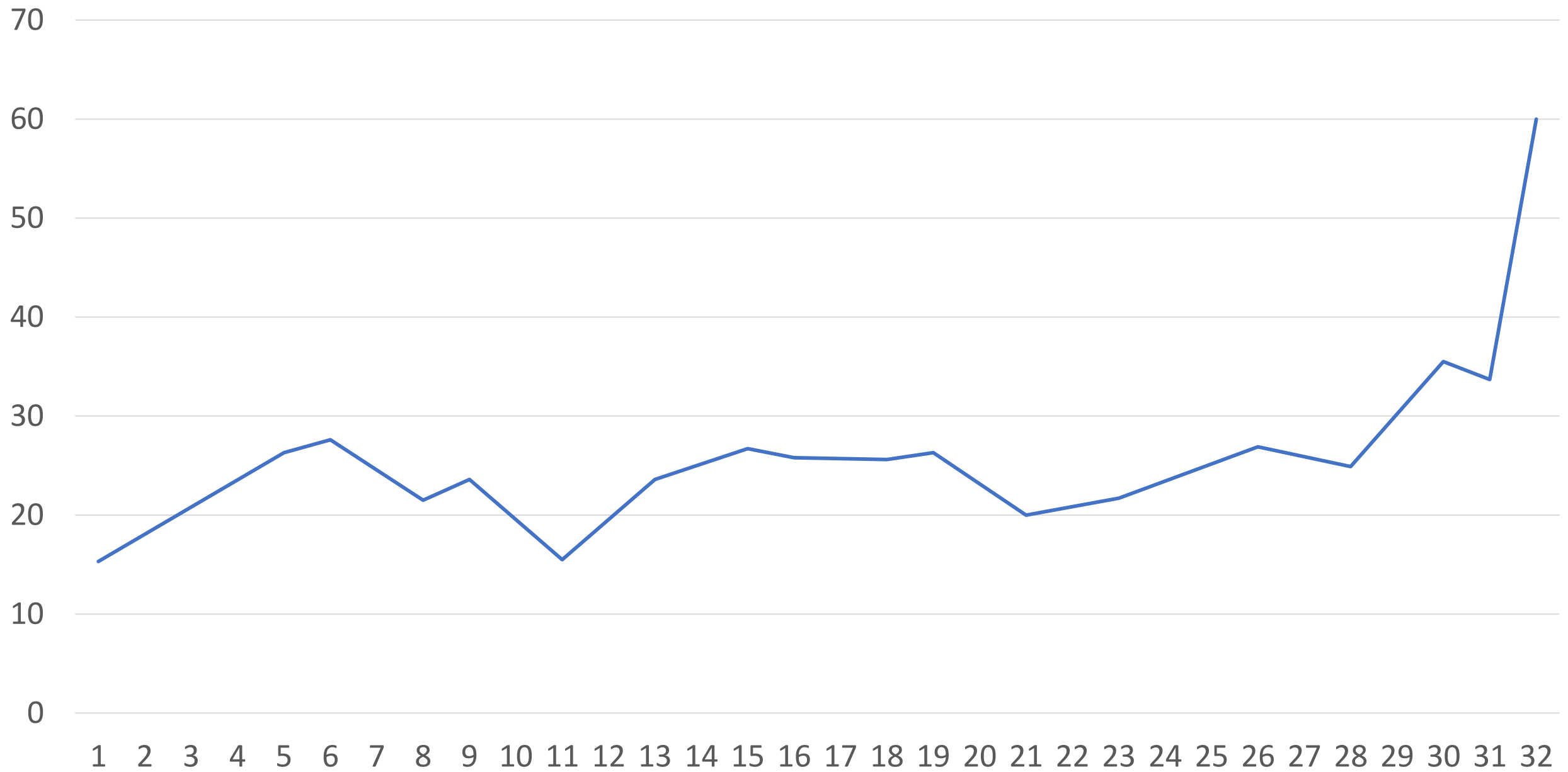
CRP



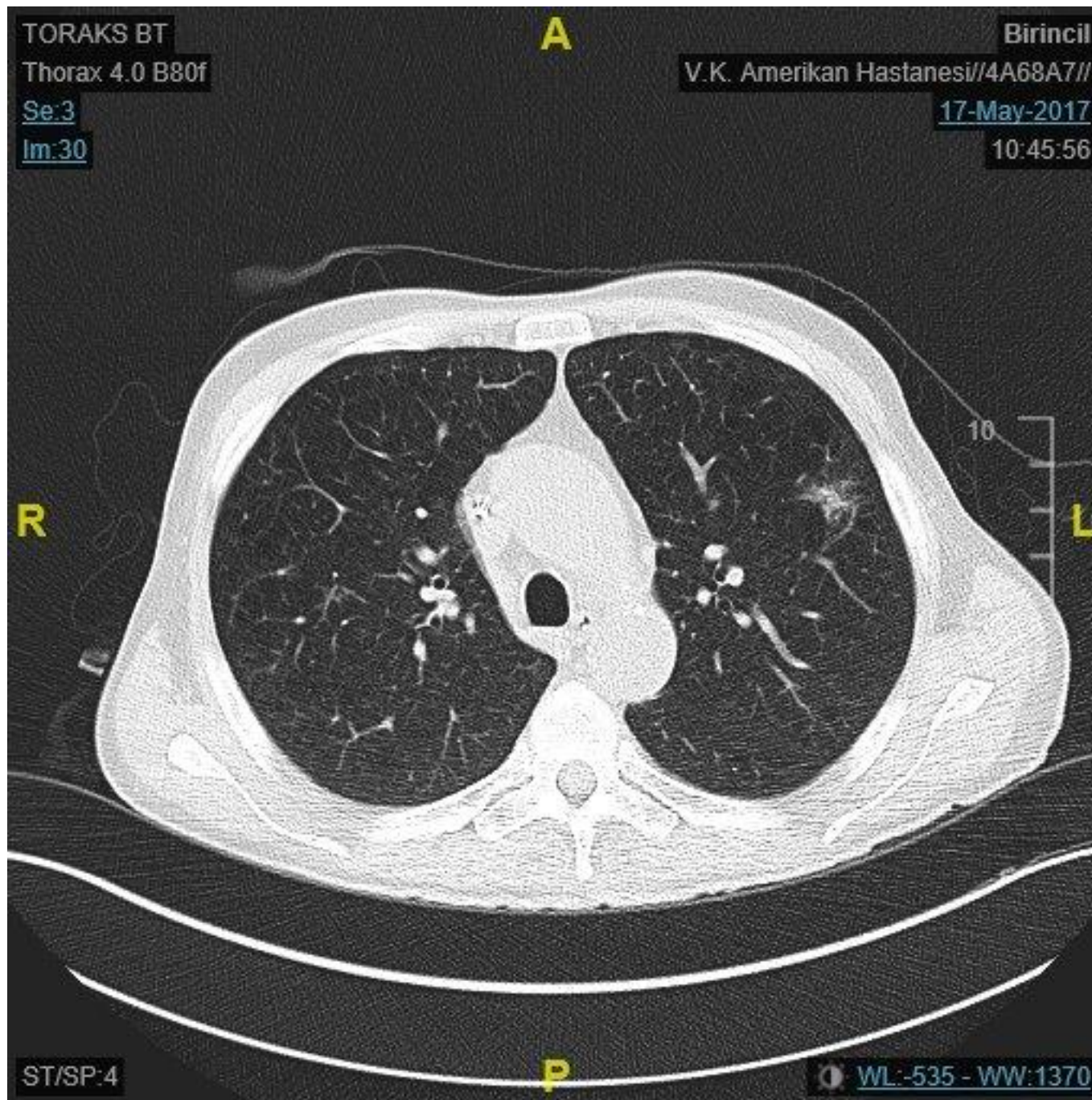
Prokalsitonin



Lökosit



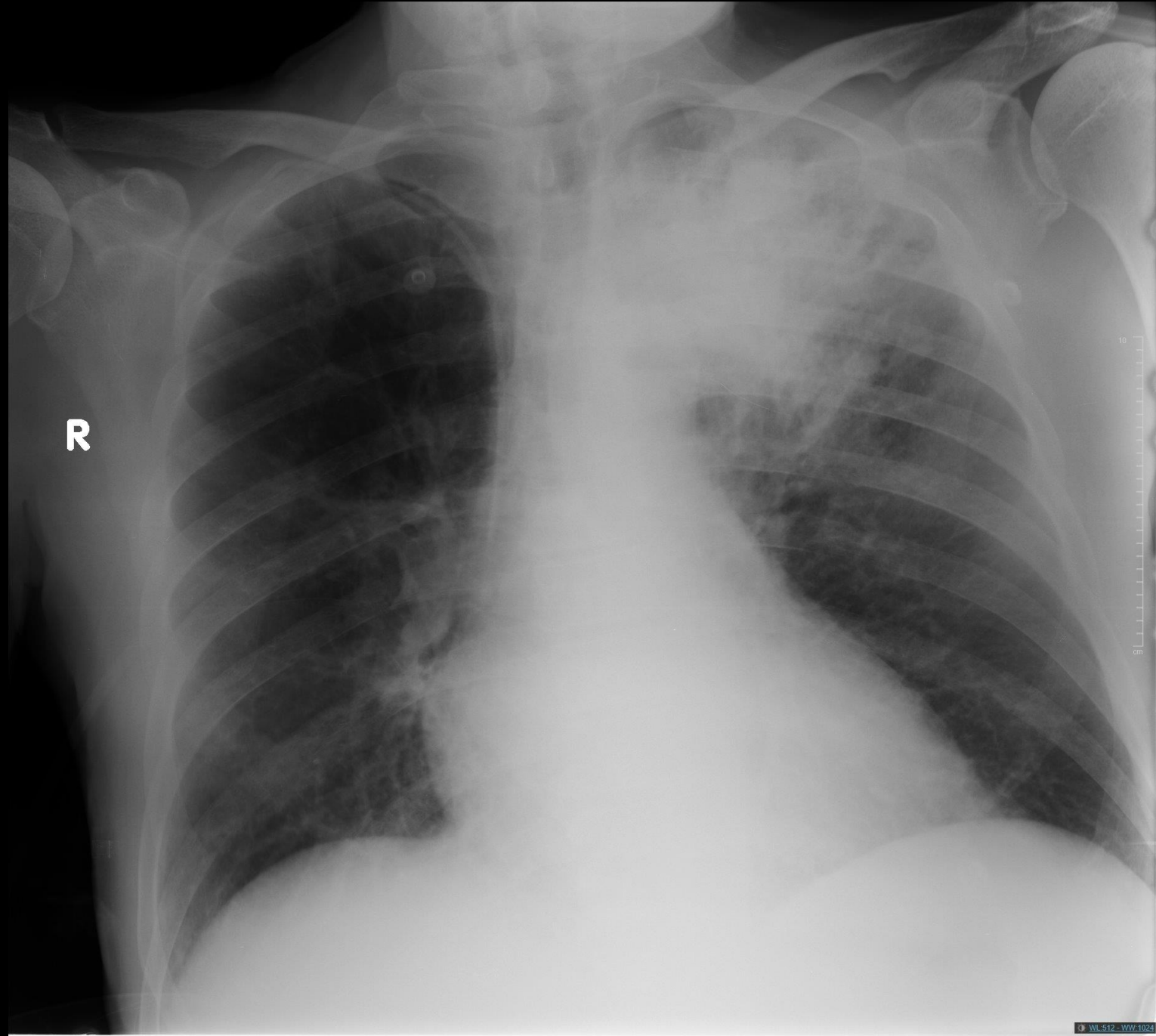
17 Mayıs 2017



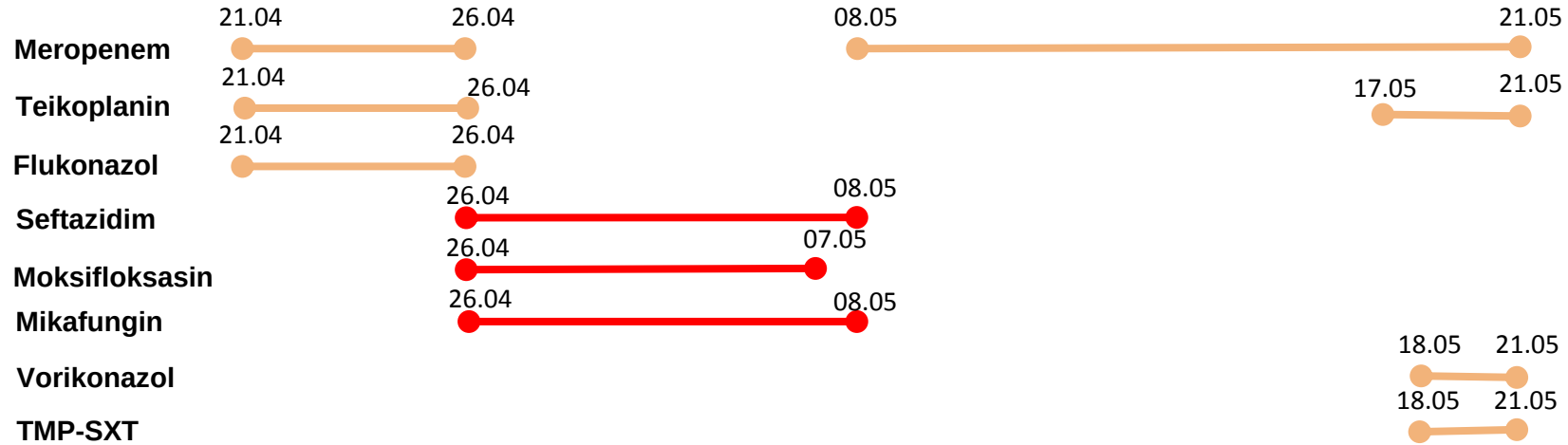
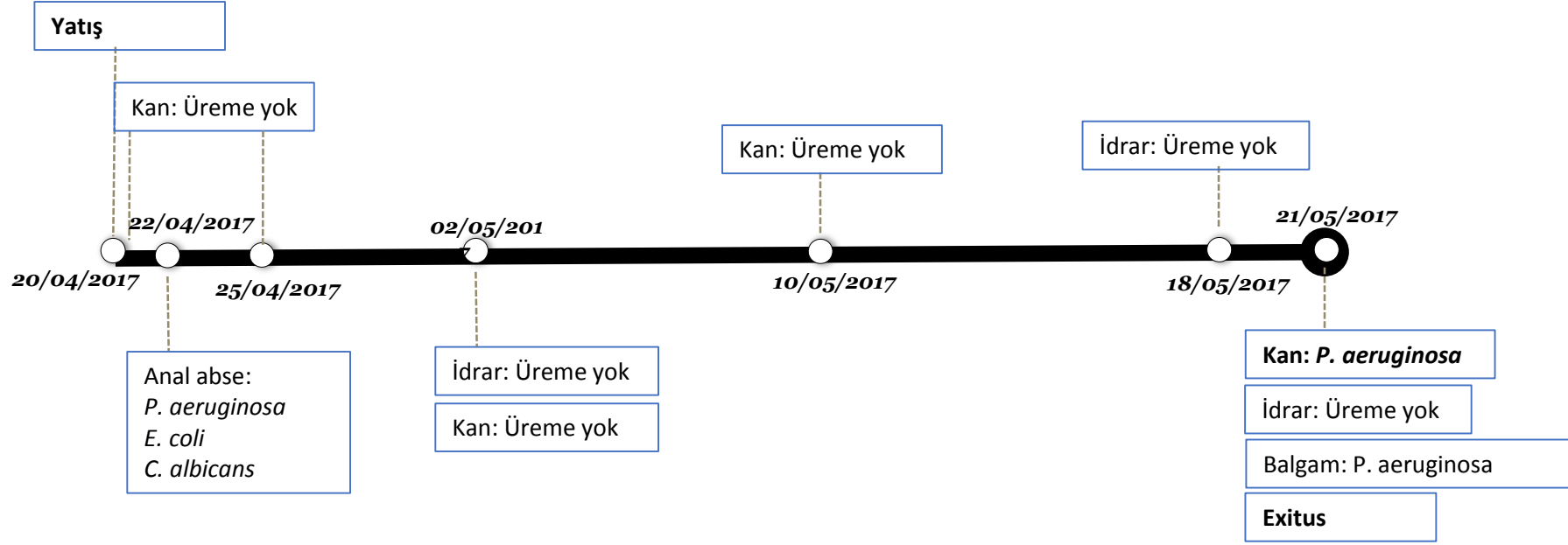
21 Mayıs 2017

PORTABLE GRAFI, TEK YON
Se:1001
Im:1001

Birinci
AMERIKAN HASTANESİ
21-May-2017
03:11:48



WL-512-WW-1024



30340 - Kültür, Balgam

KÜLTÜR - ANTİBİYOGRAM RAPORU**MİKROSKOBİK İNCELEME**

E. ZIEHL-NEELSEN : Aside dirençli bakteri görülmedi.

GRAM : Her alanda 1-3 epitel hücresi, 5-7 lökosit, Gram pozitif koklar ve Gram negatif çomaklar görüldü.

KÜLTÜR YÖNTEMİ

AEROP : Pseudomonas aeruginosa üredi.

ANTİBİYOGRAM

Notu : Kolistin (MIC < 0,5 µg/ml) Duyarlı ve Piperasilin & tazobaktam, Seftazidim Orta duyarlı bulunmuştur.

	1.SUŞ DUYARLILIK	2.SUŞ DUYARLILIK
Amikasin	Dirençli	-
Siprofloksasin	Dirençli	-
Gentamisin	Dirençli	-
Meropenem	Dirençli	-
Trimetoprim & Sulfametaksazol	Dirençli	-

Bilgi Notu: Bakteri tanısı ve antibiyogramı Vitek 2 cihazı ile yapılmıştır. Duyarlılık sonuçları, T.C. Sağlık Bakanlığı Ulusal Mikrobiyoloji Standartları (UMS) ve Klinik ve Laboratuvar Standartları Enstitüsü (CLSI)'ne göre kısıtlı olarak bildirilmiştir.

30270 - Kan Kültürü (Aerop / Anaerop)

KÜLTÜR - ANTİBİYOGRAM RAPORU**ÖRNEK**

AÇIKLAMA : Arterden alınan Kan Kültürü

MİKROSKOBİK İNCELEME

GRAM : Gram negatif çomaklar görüldü.

KÜLTÜR YÖNTEMİ

AEROP : Pseudomonas aeruginosa üredi.

ANTİBİYOGRAM

Notu : Kolistin (MIC < 0,5 µg/ml) Duyarlı ve Piperasilin & tazobaktam, Seftazidim Orta duyarlı bulunmuştur.

	1.SUŞ DUYARLILIK	2.SUŞ DUYARLILIK
Amikasin	Dirençli	-
Siprofloksasin	Dirençli	-
Gentamisin	Dirençli	-
Meropenem	Dirençli	-
Trimetoprim & Sulfametaksazol	Dirençli	-

Bilgi Notu: Bakteri tanısı ve antibiyogramı Vitek 2 cihazı ile yapılmıştır. Duyarlılık sonuçları, T.C. Sağlık Bakanlığı Ulusal Mikrobiyoloji Standartları (UMS) ve Klinik ve Laboratuvar Standartları Enstitüsü (CLSI)'ne göre kısıtlı olarak bildirilmiştir.

Sorular

Mikrobiyotan “**Kaderin**” midir” ?

ÇiD *P. aeruginosa* eradike edilebilir miydi?

Karbapenem dirençli *P. aeruginosa* ile kolonizasyonun etkisi?

In the human body:

10^{13} « human cells »

10^{14} « microbial cells »

10^{12} bacteriophages/g of fecal material

10^{11} bacteria/g of fecal material

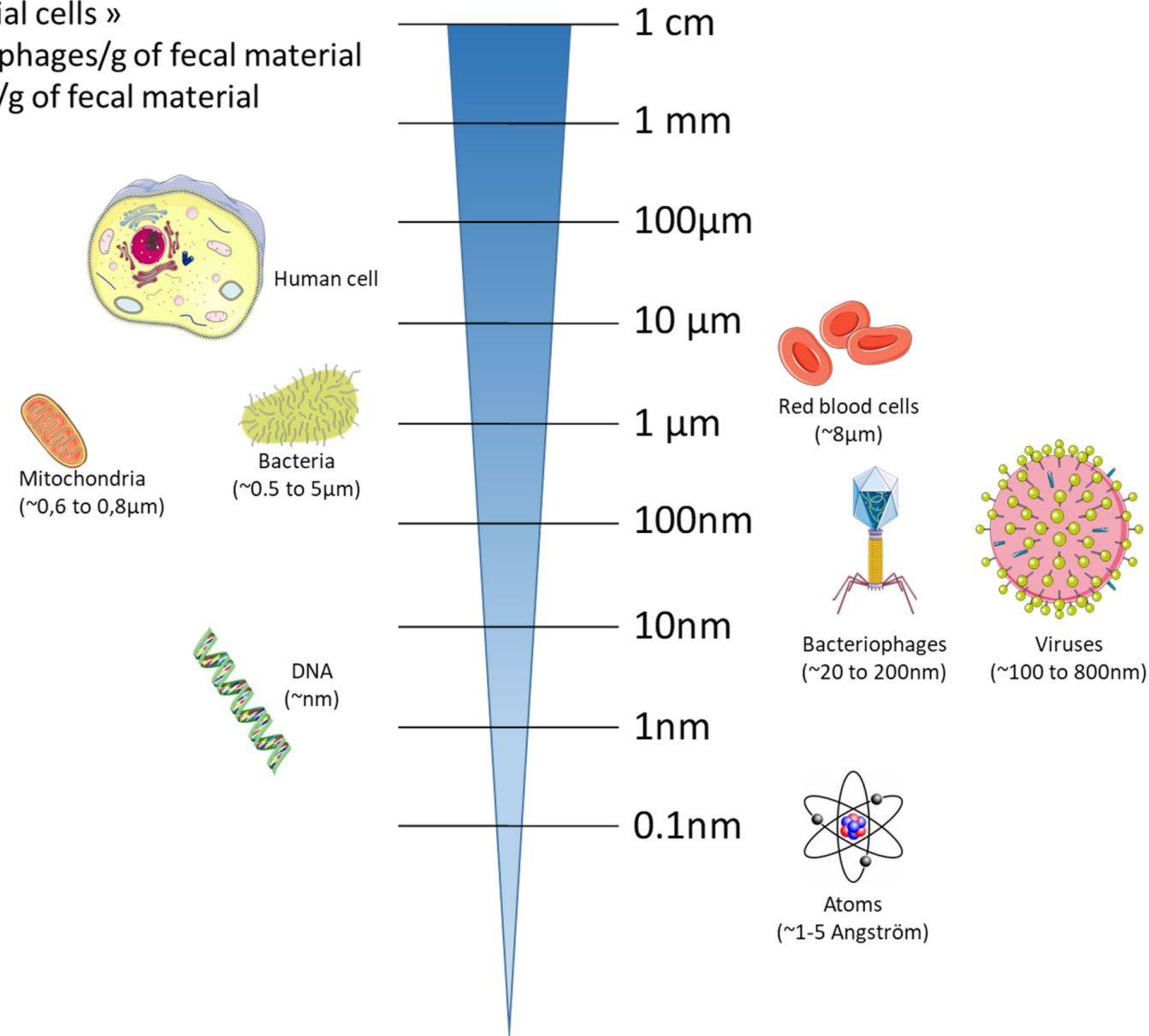


Figure 1 Relative sizes of major host cells and their components versus those of bacteria and viruses.

Healthy situation

Genes / Food / Drugs

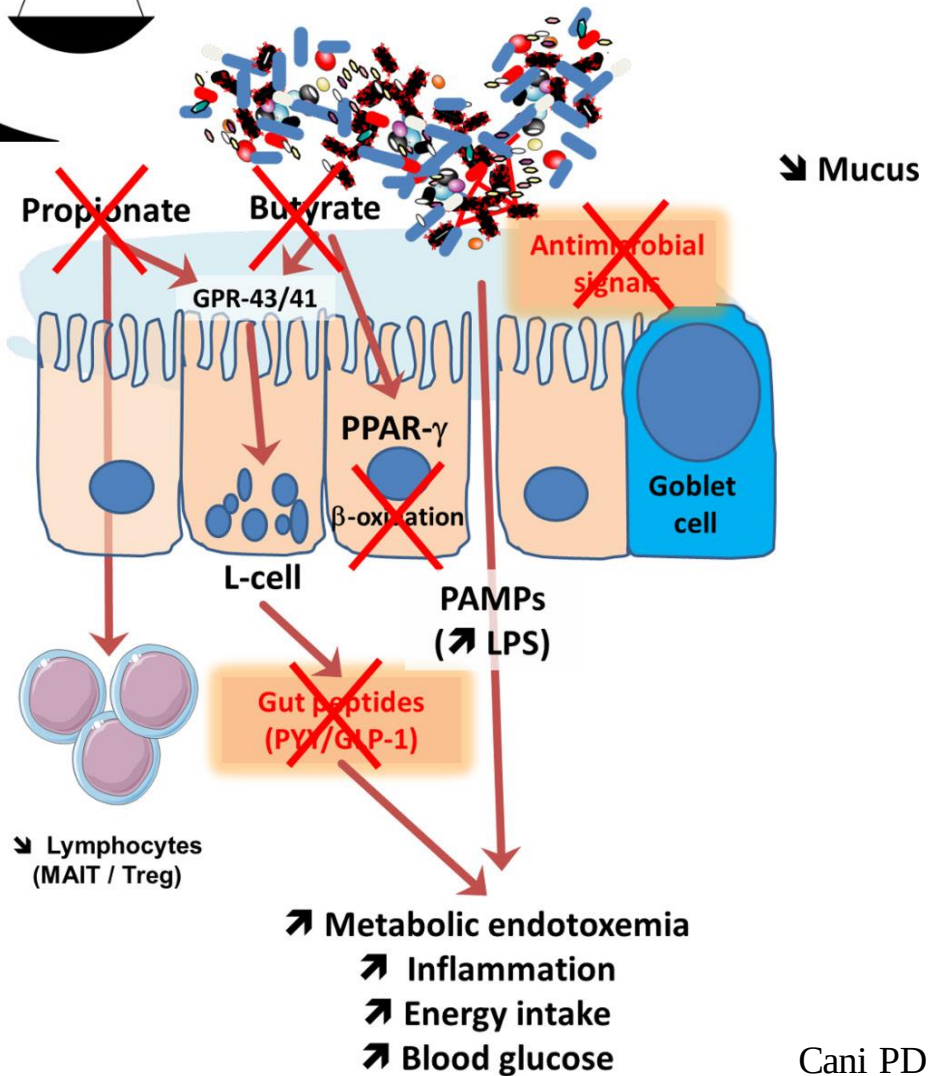
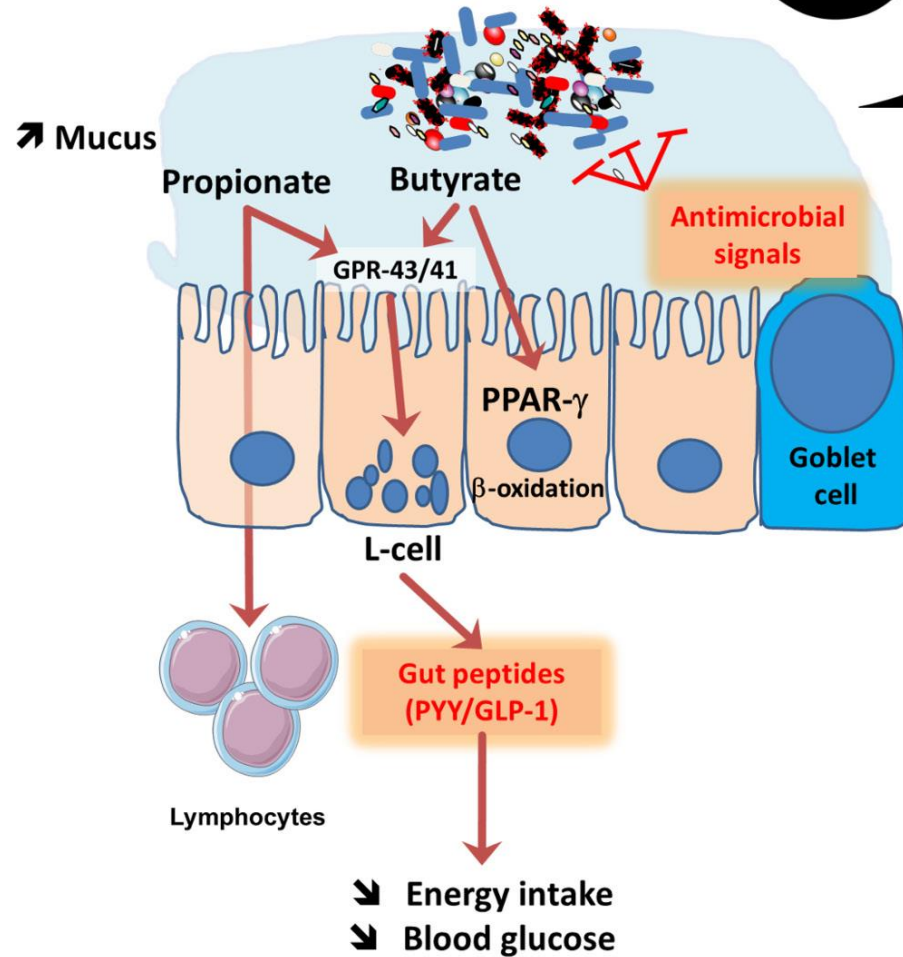
Metabolic disorders

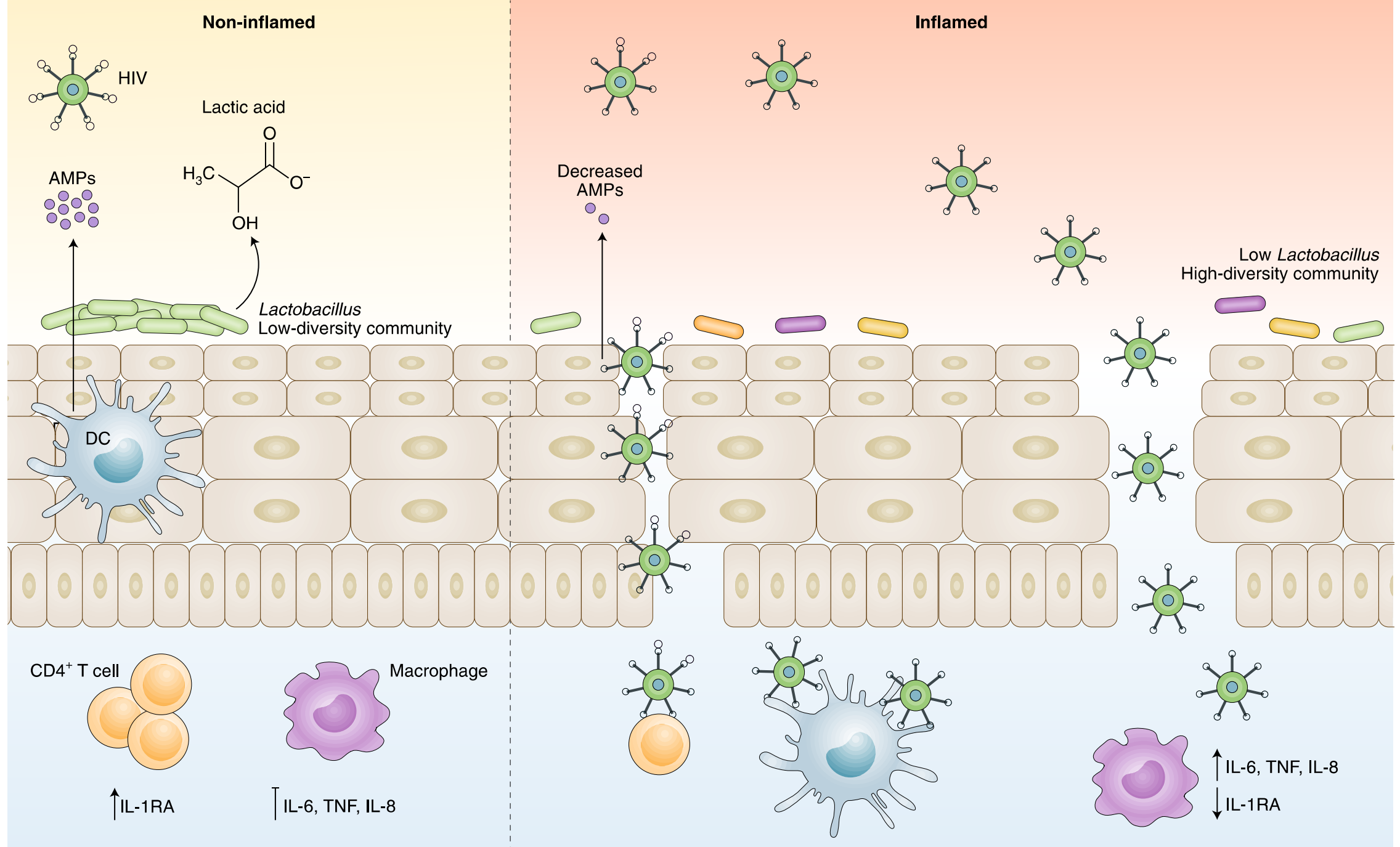
Bacteria

Quantity

Metabolites

Immunity





Nekrotizan enterokolit

- Barsak mikrobiyomu bozulduktan sonra ortaya çıkar.
- Proteobacteria ve anaerobların azalması ile korelasyon gösterir.
- Meta-analiz: Enteral probiyotikler ciddiyeti ve mortaliteyi azaltır.
- En son yapılan RCT'de faydası gösterilemedi.
- Doz, yol, süre, içerik hakkında bilgi yok.
- FDA onayı yok

Enterik Bakteriyel İnfeksiyonlar

- Mikrobiyota direkt olarak patojeni öldürebilir
- Ya da indirekt olarak barsak müsinini artırarak immün yanıtı indükleyerek patojeni öldürür.
- Bozulmuş mikrobiyotada patojen invazyonu daha kolay olmaktadır.

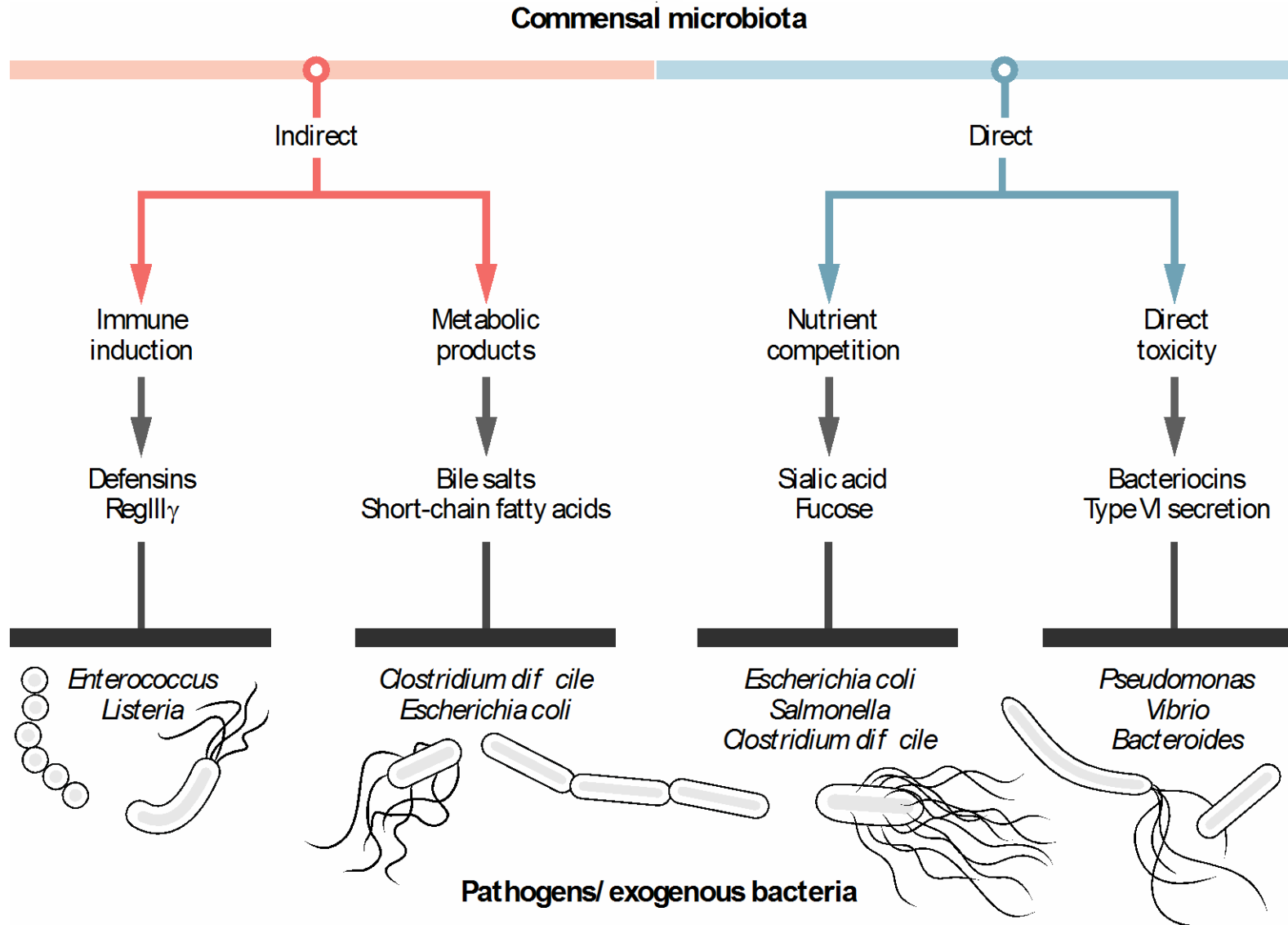
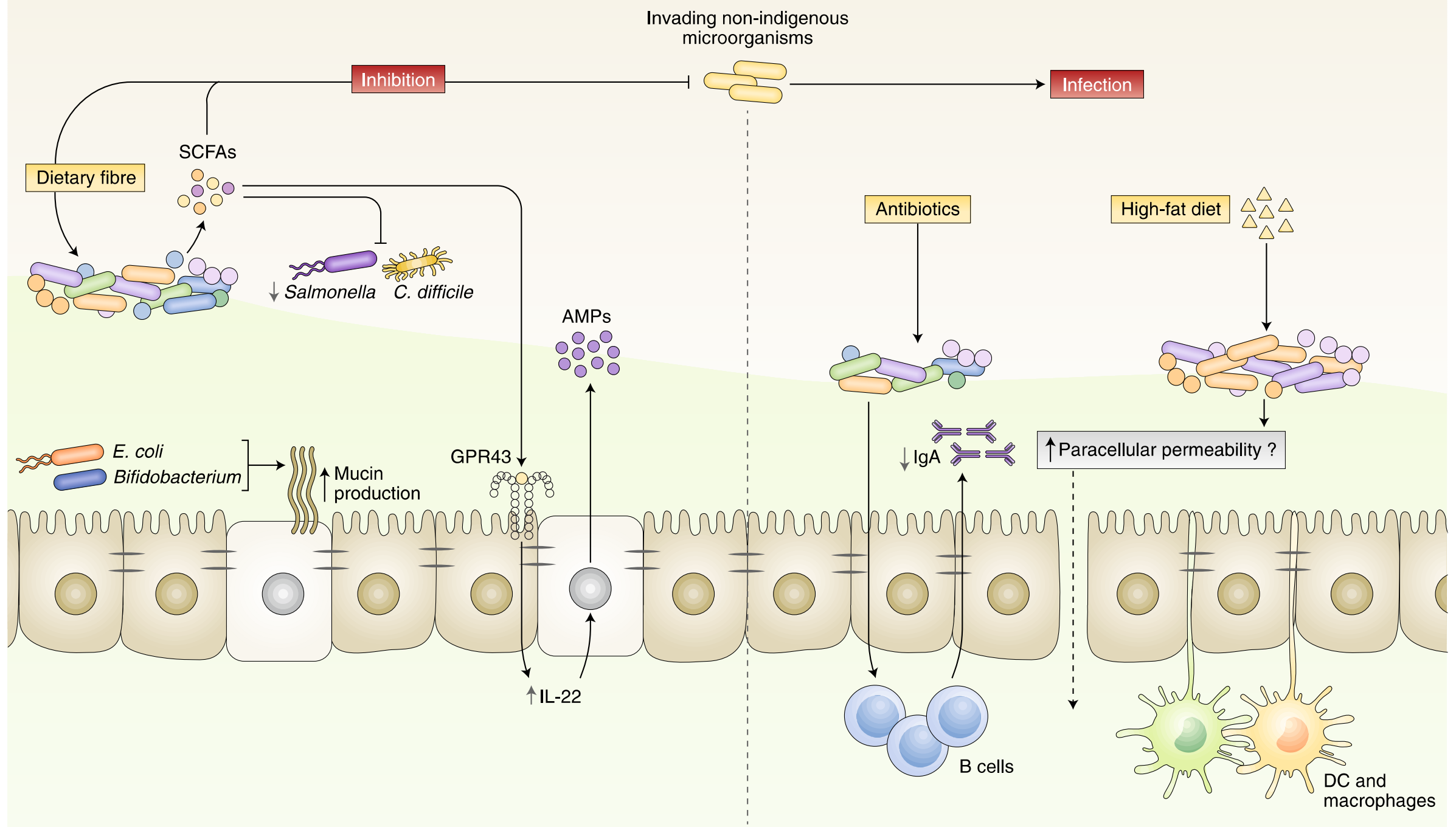
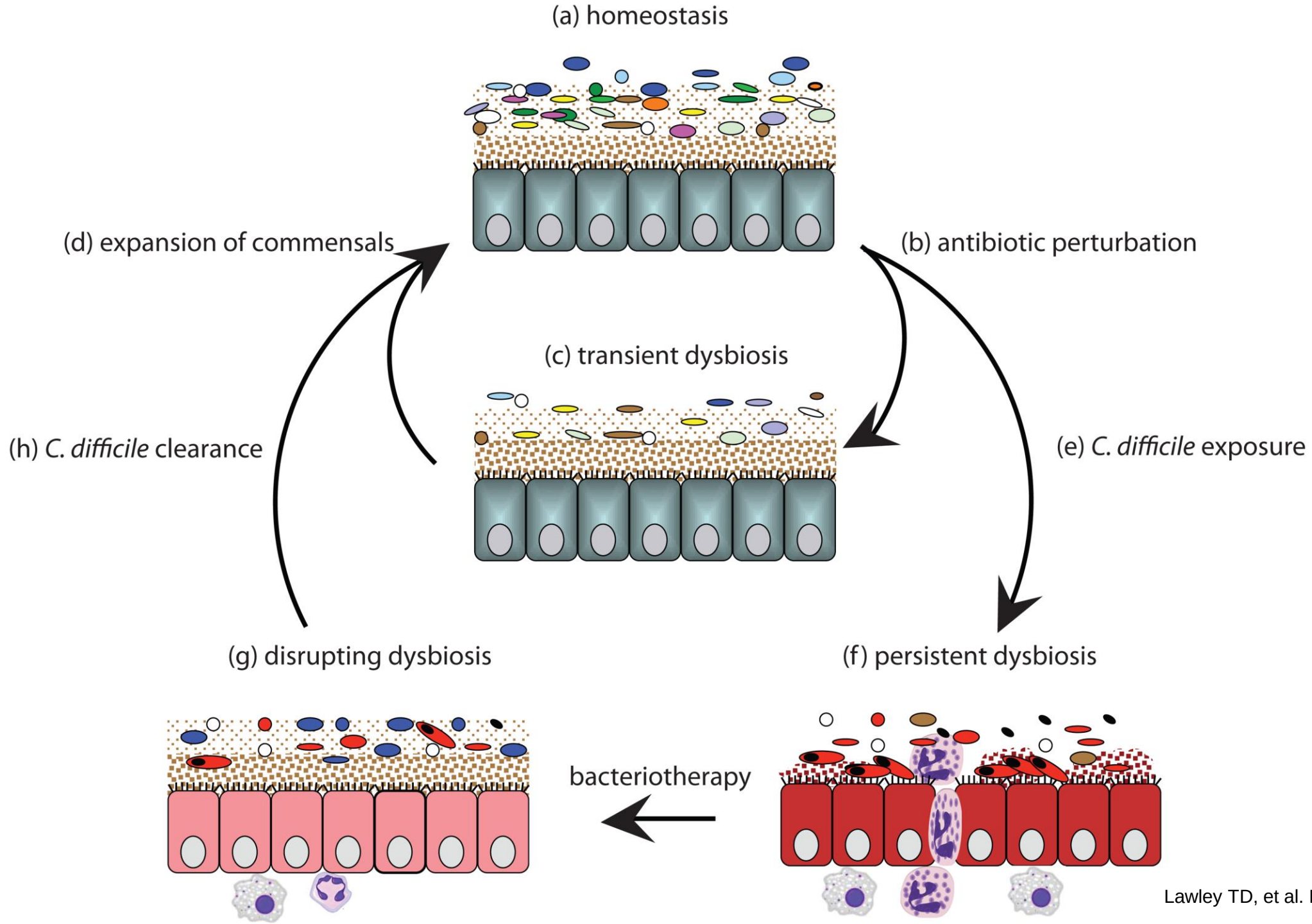


Fig. 1. The intestinal commensal microbiota provides colonization resistance against a wide range of pathogens by indirect and direct mechanisms. Commensal bacteria activate innate immune defenses in the mucosa, produce or modify host-derived metabolites, deplete nutrients, or produce substances that are directly toxic to competing bacteria. These mechanisms in aggregate can induce a high level of resistance against colonization by exogenous bacteria.



***C. difficile* infeksiyonu**



***C. difficile* infeksiyonu**

- Fekal transplantasyon tekrarlayan CD infeksiyonunda oral vankomisine göre daha etkili.
- Mikroorganizma içeren ilaçların da tedavide alternatif olabileceği belirtiliyor.

European consensus conference on faecal microbiota transplantation in clinical practice

Giovanni Cammarota,¹ Gianluca Ianiro,¹ Herbert Tilg,² Mirjana Rajilić-Stojanović,³ Patrizia Kump,⁴ Reetta Satokari,⁵ Harry Sokol,⁶ Perttu Arkkila,⁷ Cristina Pintus,⁸ Ailsa Hart,⁹ Jonathan Segal,⁹ Marina Aloï,¹⁰ Luca Masucci,¹¹ Antonio Molinaro,¹² Franco Scaldaferri,¹ Giovanni Gasbarrini,¹ Antonio Lopez-Sanroman,¹³ Alexander Link,¹⁴ Pieter de Groot,¹⁵ Willem M de Vos,^{5,16} Christoph Högenauer,⁴ Peter Malfertheiner,¹⁴ Eero Mattila,¹⁷ Tomica Milosavljević,¹⁸ Max Nieuwdorp,^{12,15,1} Maurizio Sanguinetti,¹¹ Magnus Simren,²⁰ Antonio Gasbarrini,¹ The European FMT Working Group

INFECTIOUS DISEASES

- ▶ History of, or known exposure to, HIV, HBV or HCV, syphilis, human T-lymphotropic virus I and II, malaria, trypanosomiasis, tuberculosis
- ▶ Known systemic infection not controlled at the time of donation
- ▶ Use of illegal drugs
- ▶ Risky sexual behaviour (anonymous sexual contacts; sexual contacts with prostitutes, drug addicts, individuals with HIV, viral hepatitis, syphilis; work as prostitute; history of sexually transmittable disease)
- ▶ Previous reception of tissue/organ transplant
- ▶ Previous (<12 months) reception of blood products
- ▶ Recent (<6 months) needle stick accident
- ▶ Recent (<6 months) body tattoo, piercing, earring, acupuncture
- ▶ Recent medical treatment in poorly hygienic conditions
- ▶ Risk of transmission of diseases caused by prions
- ▶ Recent parasitosis or infection from rotavirus, *Giardia lamblia* and other microbes with GI involvement
- ▶ Recent (<6 months) travel in tropical countries, countries at high risk of communicable diseases or traveller's diarrhoea
- ▶ Recent (<6 months) history of vaccination with a live attenuated virus, if there is a possible risk of transmission
- ▶ Healthcare workers (to exclude the risk of transmission of multidrug-resistant organisms)
- ▶ Individual working with animals (to exclude the risk of transmission of zoonotic infections)

GI, METABOLIC AND NEUROLOGICAL DISORDERS

- ▶ History of IBS, IBD, functional chronic constipation, coeliac disease, other chronic GI disorders
- ▶ History of chronic, systemic autoimmune disorders with GI involvement
- ▶ History of, or high risk for, GI cancer or polyposis
- ▶ Recent appearance of diarrhoea, hematochezia
- ▶ History of neurological/neurodegenerative disorders
- ▶ History of psychiatric conditions
- ▶ Overweight and obesity (body mass index >25)

DRUGS THAT CAN IMPAIR GUT MICROBIOTA COMPOSITION

- ▶ Recent (<3 months) exposure to antibiotics, immunosuppressants, chemotherapy
- ▶ Chronic therapy with proton pump inhibitors

GENERAL BLOOD TESTING

- ▶ Cytomegalovirus
- ▶ Epstein-Barr virus
- ▶ Hepatitis A
- ▶ HBV
- ▶ HCV
- ▶ Hepatitis E virus
- ▶ Syphilis
- ▶ HIV-1 and HIV-2
- ▶ *Entamoeba histolytica*
- ▶ Complete blood cell count with differential
- ▶ C-reactive protein and erythrocyte sedimentation rate
- ▶ Albumin
- ▶ Creatinine and electrolytes
- ▶ Aminotransferases, bilirubin, gamma-glutamyltransferase, alkaline phosphatase

BLOOD TESTING IN SPECIFIC SITUATIONS

- ▶ Human T-lymphotropic virus types I and II antibodies
- ▶ *Strongyloides stercoralis*

GENERAL STOOL TESTING

- ▶ Detection of *Clostridium difficile*
- ▶ Detection of enteric pathogens, including *Salmonella*, *Shigella*
- ▶ *Campylobacter*, *Escherichia coli* O157 H7, *Yersinia*, vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus*, Gram-negative multidrug-resistant bacteria
- ▶ Norovirus
- ▶ Antigens and/or acid fast staining for *Giardia lamblia* and *Cryptosporidium parvum*
- ▶ Protozoa (including *Blastocystis hominis*) and helminths
- ▶ Faecal occult blood testing

STOOL TESTING IN SPECIFIC SITUATIONS

- ▶ Detection of *Vibrio cholera* and *Listeria monocytogenes*
- ▶ Antigens and/or acid fast staining for *Isospora* and *Microsporidia*
- ▶ Calprotectin
- ▶ *Helicobacter pylori* faecal antigen
- ▶ Rotavirus

Yoğun Bakım Hastaları

- Sepsiste antibiyotiklerin mikrobiyotaya etkisi
- Hipoksi, barsak motilite değişikliği, nutrisyon solüsyonlar da etkilemektedir.
- SDD nozokomiyal infeksiyonları ve mortaliteyi azaltıyor
- Direnç?

The role of the gut microbiota in sepsis



Bastiaan W Haak, W Joost Wiersinga

For decades, the gut was thought to play an important role in sepsis pathogenesis. Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ failure assessment for sepsis focuses on respiratory, cardiovascular, hepatic, renal, neurological, and haematological systems. Unfortunately, symptoms of organ failure are non-specific and are therefore not assessed. The composition of the intestinal microbiome, however, is

Lancet Gastroenterol Hepatol
2017; 2: 135–43

Center for Experimental and
Molecular Medicine

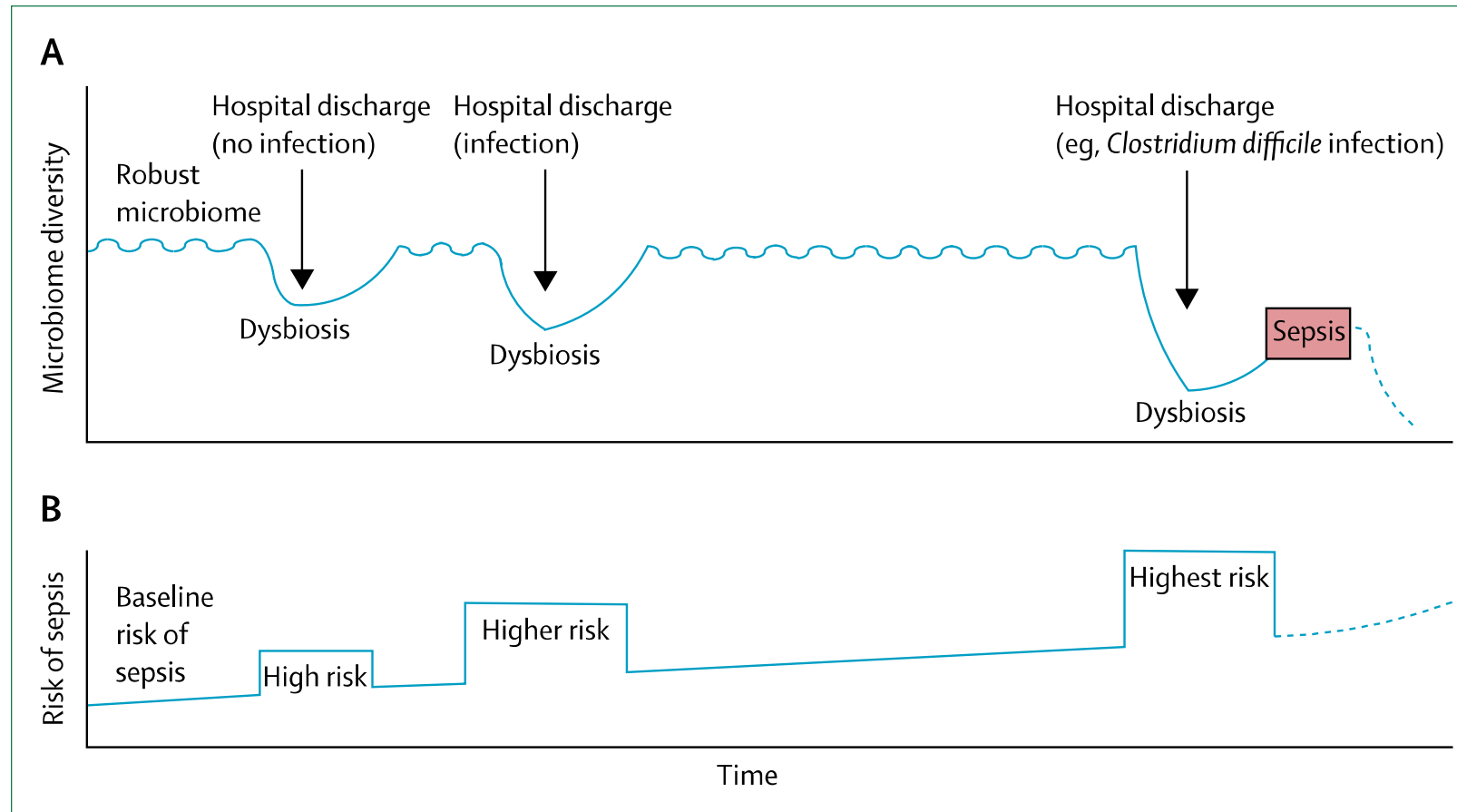


Figure 2: Conceptual diagram of dysbiosis as a potential risk factor for sepsis

(A) Periods of dysbiosis correspond with hospitalisation, with recovery after discharge. (B) Each period of dysbiosis is associated with an increased susceptibility to sepsis. The baseline risk of sepsis increases over time as patients get older. Adapted from Prescott and colleagues,⁴² with permission of the American Thoracic Society.

Hematoloji-Onkoloji

- KT ilişkili GİS hasarı ve antibiyotik etkisi
- Kök hücre engrafman öncesi mikrobiyota çeşitliliği fazla olan kişilerde transplantasyon sonrası enfeksiyona ya da GVHD'ye bağlı mortalite daha az görülmekte (%9 ve %53)
- Anti-anaerobik antibiyotikleri sınırlı kullanmaya çalışın.

Antibiyotik Direnci ve Mikrobiyota

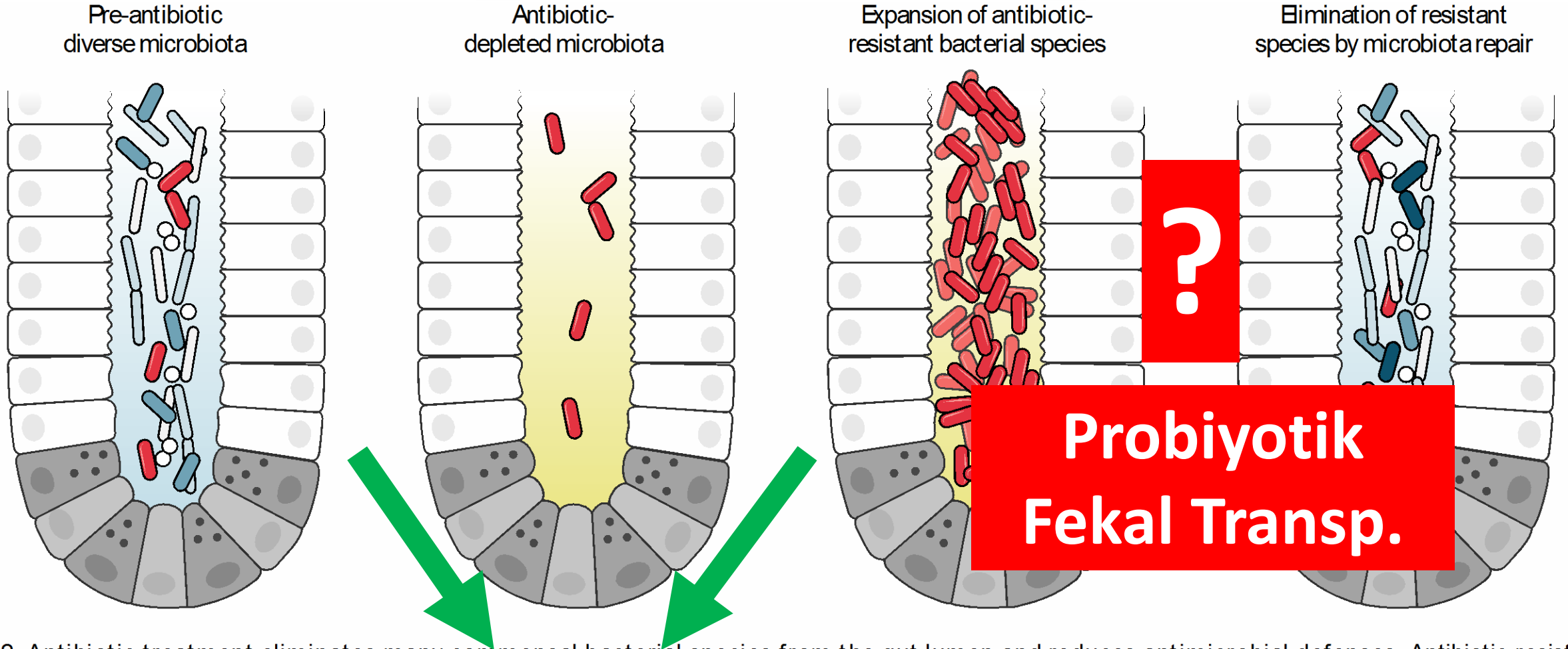
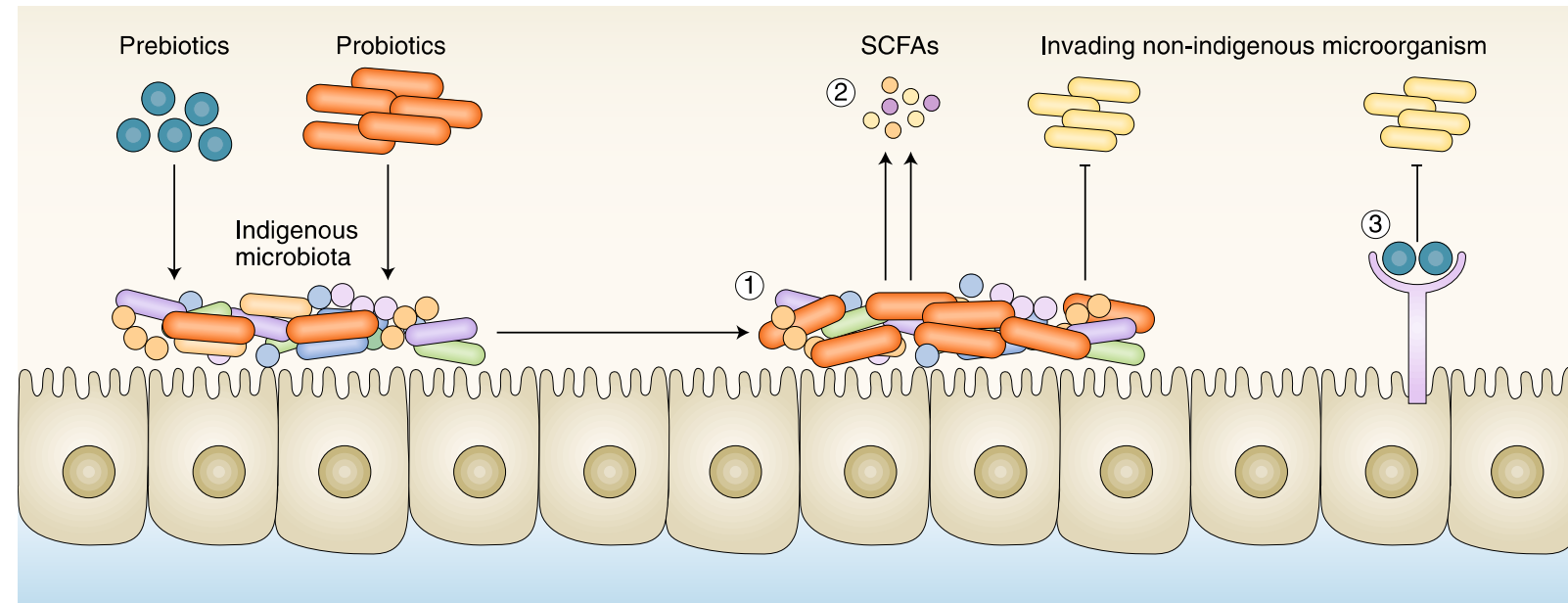


Fig. 2. Antibiotic treatment disrupts the microbiota, which in turn reduces antimicrobial defenses. Antibiotic-resistant bacterial species can thrive, and colonization resistance can be lost. **ANTİBİYOTİK YÖNETİMİ**

a Prebiotic and probiotics



b Faecal microbiota transplantation

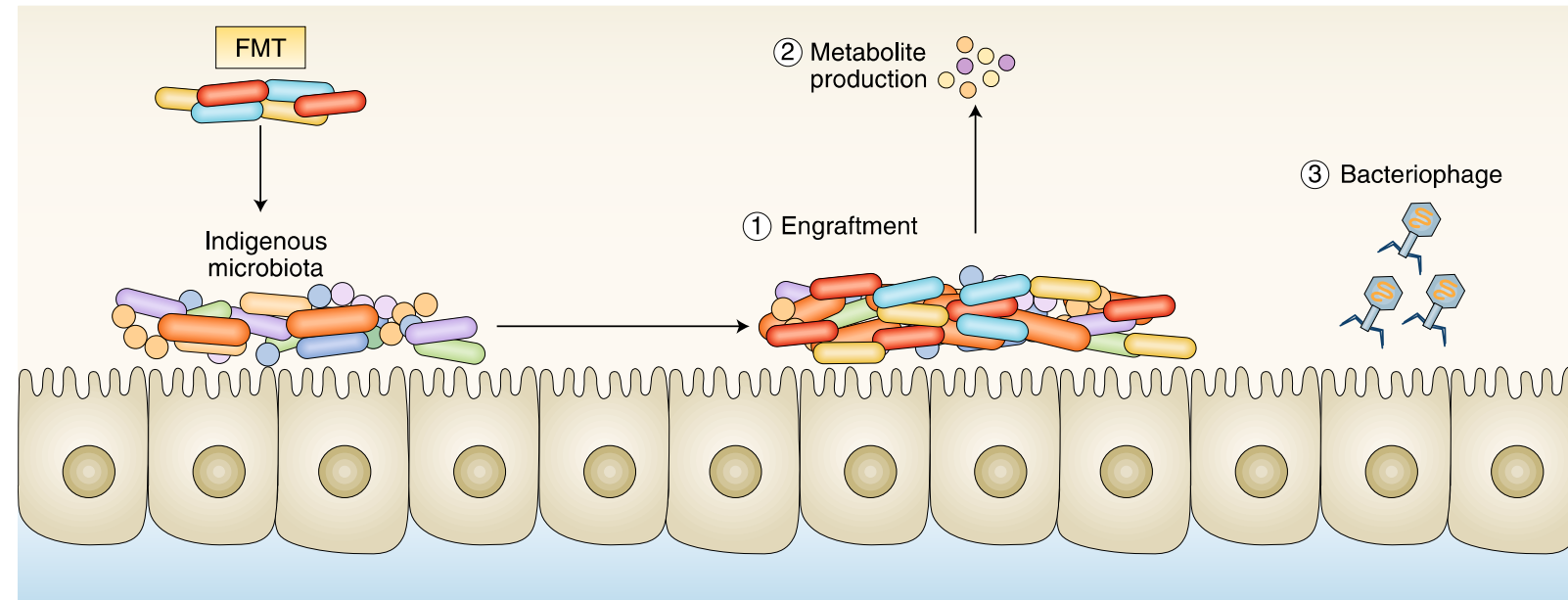


Table 4. Overview of the Infectious Diseases or Patient Groups With Risk of Infectious Disease in Which the Microbiome Has Been Targeted for Prevention or Treatment and Tested in Human Clinical Trials

Patient Category	Disease	Target and Known Effects	Key Refs.
Critically ill, adult	VAP	SDD for the prevention of respiratory tract infections. Probiotics for the prevention of VAP. Moderate evidence supports the indication.	[1, 2]
	Mortality	SDD and probiotics for the prevention of mortality. Strong evidence for SDD. No conclusions possible based on limited evidence for probiotics.	[2–5]
Critically ill, neonatal	Necrotizing enterocolitis	Probiotics for the prevention of NEC. Strong evidence supporting derived from meta-analyses supporting probiotics for prevention of NEC severity and mortality. However, recent RCT, not included in the meta-analysis, showed no benefit of probiotic in NEC.	[6, 7, 39]
	Candidemia	Probiotics tested for prevention of candidemia, <i>Candida</i> colonization, and candiduria. No conclusions possible based on limited evidence	[8]
	Late-onset sepsis	Probiotics for the prevention of late-onset sepsis in preterm infants. Moderate evidence supporting probiotics for the prevention of late-onset mortality.	[7, 9]
Surgical	Trauma	Probiotics for the prevention of “infectious complications” and mortality. SDD for prevention of “infectious complications and mortality”. Heterogeneous studies, with some support for use, no conclusions possible based on limited evidence.	[10, 11]
	Post-GI surgery	Probiotics for the prevention of infectious complications and mortality. Heterogenous studies, with some support for use. No conclusions possible based on limited evidence.	[12, 13]
Oncology and hematology	HSCT and chemotherapy complications	Microbiome composition and diversity can act as a predictor for the risk of blood stream and other infections. FMT (study ongoing) and probiotics to decrease infectious complications and GvHD—no conclusions possible based on limited evidence to date.	[14–16]
	Mucositis	Probiotics for the prevention and treatment of chemotherapy and radiation-induced mucositis and diarrhea. Few studies, significant heterogeneity, no conclusions possible based on limited evidence.	[17, 18]

Table 4. Overview of the Infectious Diseases or Patient Groups With Risk of Infectious Disease in Which the Microbiome Has Been Targeted for Prevention or Treatment and Tested in Human Clinical Trials

Patient Category	Disease	Target and Known Effects	Key Refs.
HIV	Disease progression	Probiotics and synbiotics for improvement of immune function. Small, heterogeneous studies, no conclusions possible based on limited evidence.	[19]
	Diarrhea	Probiotics to decrease diarrhea in HIV patients. Small, heterogeneous studies, no conclusions possible based on limited evidence.	[20]
Upper respiratory	Upper respiratory tract infection	Probiotics for prevention of URTI in children. Small, heterogeneous studies, some support of use, no conclusions possible based on limited evidence.	[21, 22]
Gastrointestinal	<i>Clostridium difficile</i> and antibiotic-associated diarrhea	FMT effective as treatment for refractory <i>C difficile</i> . Bacteriotherapy for prevention. Probiotics for prevention. Moderate quality evidence suggests probiotics are safe and effective.	[23–25]
	Acute infectious gastroenteritis	Probiotics for the prevention and treatment of infectious gastroenteritis. Evidence supports probiotics use in the treatment of persistent diarrhea in pediatric patients and shortening and reducing stool frequency in adults and infants.	[26, 27]
	Traveler’s diarrhea	Probiotics for the prevention of traveler’s diarrhea. Limited and inconclusive evidence that probiotics prevent traveler’s diarrhea.	[28, 29]
	Amebiasis	Probiotics for the treatment of amebiasis in children. No conclusions possible based on limited evidence.	[30]
	<i>Helicobacter pylori</i>	Probiotics for the adjunctive treatment of <i>H pylori</i> . No evidence probiotics improve eradication.	[31]
	Spontaneous bacterial peritonitis	Probiotics for the prevention of SBP in patients with ascites. No evidence that probiotics prevent SBP.	[32]
Urogenital	Urinary tract infection	Probiotics for the prevention of (recurrent) UTI. No significant benefit, no conclusions possible based on limited evidence.	[33]
Antimicrobial resistance	Multiresistant infections or colonization	FMT for treatment of multidrug-resistant colonization and AMR genes. FMT can reduce antibiotic-resistant organisms and genes, but evidence to date of clinical consequences only in case series and reports.	[34–36]

SORULAR

- ÇİD bakterilerin eliminasyonu?
 - Probiyotikler (İçerik)
 - Fekal Transp.
- ÇİD bakterisi olan ve cerrahiye gidecek hastalar, immunsupresif tedavi alacak hastalar??
- Seyahatlerin ÇİD bakteri kolonizasyonuna etkisi
- *C. difficile* için fekal transplantasyon

