6. TÜRKİYE EKMUD
BİLİMSEL PLATFORMU
"Antimikrobiyal Direnç ve Akılcı Antimikrobiyal Tedavi"
4-8 Nisan 2017 Regnum Carya Kongre Merkezi ANTALYA

Dirençli Kolonizasyonda Mikrobiyotanın Yeri

Prof. Dr. Z. Ceren KARAHAN

Ankara Üniversitesi Tıp Fakültesi

Tıbbi Mikrobiyoloji Anabilim Dalı

Sunum İçeriği

Antibiyotik direnci, direncin kaynağı, yayılımı

Bağırsak mikrobiyotası, rezistomu, içeriği, önemi

Sonuç…

«To my generation of **bacteriologists the inhibition of one microbe by another was commonplace**. We were all taught about these inhibitions and indeed it is seldom that an observant clinical bacteriologist can pass a week without seeing in the course of his ordinary work very definite instances of bacterial antagonism.

…

My only merit is that I did not neglect the observation and that I pursued the subject as a bacteriologist.»

A. Fleming, Nobel Lecture: Penicillin: http://www.nobelprize.org/nobel_prizes/medicine/laureates/1945/fleming-lecture.pdf

No. 3713, DEC. 28, 1940 NATURE 837

LETTERS TO THE EDITORS

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IN THE PRESENT CIRCUMSTANCES, PROOFS OF "LETTERS" WILL NOT BE SUBMITTED TO CORRESPONDENTS OUTSIDE GREAT BRITAIN.

An Enzyme from Bacteria able to Destroy Penicillin

FLEMING[1] noted that the growth of *B. coli* and a number of other bacteria belonging to the coli-typhoid group was not inhibited by penicillin. This observation has been confirmed. Further work has been done to find the cause of the resistance of these organisms to the action of penicillin.

An extract of *B. coli* was made by crushing a suspension of the organisms in the bacterial crushing mill of Booth and Green[2]. This extract was found to contain a substance destroying the growth-inhibiting property of penicillin. The destruction took place on incubating the penicillin preparation with the bacterial extract at 37°, or at room temperature for a longer time. The following is a typical experiment showing the penicillin-destroying effect of *B. coli* extracts. A solution of 1 mgm. penicillin in 0·8 c.c. of water was incubated with 0·2 c.c. of centrifuged and dialysed bacterial extract at 37° for 3 hours, in the presence of ether, and a control solution of penicillin of equal concentration was incubated without enzyme for the same time. [The penicillin used was extracted from cultures of *Penicillium notatum* by a method to be described in detail later. It possessed a degree of purity similar to that of the samples used in the chemotherapeutic experiments recorded in a preliminary report[3].) The growth-inhibiting activity of the solutions was then tested quantitatively on agar plates against *Staphylococcus aureus*. The penicillin solution incubated with the enzyme had entirely lost its growth-inhibiting activity, whereas the control solution had retained its full strength.

The conclusion that the active substance is an enzyme is drawn from the fact that it is destroyed by heating at 90° for 5 minutes and by incubation with papain activated with potassium cyanide at *p*H 6, and that it is non-dialysable through 'Cellophane' membranes. It can be precipitated by 2 volumes of alcohol, but much of its activity is lost during this operation. The activity of the enzyme, which we term penicillinase, is slight at *p*H 5, but increases considerably towards the alkaline range of *p*H. It is very active at *p*H 8 and 9. Higher *p*H's could not be tested as penicillin is unstable above *p*H 9.

The mechanism of the enzymatic inactivation of penicillin is being studied. No oxygen uptake occurs during the reaction, and the inactivation proceeds with equal facility under aerobic and anaerobic conditions. No appearance of acid groups could be detected by *p*H measurement with the hydrogen electrode. Extracts of a number of other micro-organisms, made by crushing the bacteria in the bacterial grinding mill, were tested for penicillinase. The enzyme was absent from extracts of the penicillin-sensitive *Staphylococcus aureus*, of yeast and of *Penicillium notatum*. It was present in a Gram-negative rod, insensitive to penicillin, found as a contaminant of some Penicillium cultures. Unlike *B. coli*, it was not necessary to crush the organism in the bacterial mill in order to obtain the enzyme from it; the latter appeared in the culture fluid. The enzyme was also found in *M. lysodeikticus*, an organism sensitive to the action of penicillin, though less so than *Staphylococcus aureus*. Thus, the presence or absence of the enzyme in a bacterium may not be the sole factor determining its insensitivity or sensitivity to penicillin.

The tissue extracts and tissue autolysates that have been tested were found to be without action on the growth-inhibiting power of penicillin. Prof. A. D. Gardner has found staphylococcal pus to be devoid of inhibiting action, but has demonstrated a slight inhibition by the pus from a case of *B. coli* cystitis. The bacteriostatic action of the sulphonamide drugs is known to be inhibited in the presence of tissue constituents and pus.[4] That the anti-bacterial activity of penicillin is not affected under these conditions gives this substance a definite advantage over the sulphonamide drugs from the chemotherapeutic point of view. The fact that a number of bacteria contain an enzyme acting on penicillin points to the possibility that this substance may have a function in their metabolism.

E. P. ABRAHAM,
E. CHAIN,
Sir William Dunn School of Pathology,
Oxford.
Dec. 5.

[1] Fleming, A., *Brit. J. Exp. Path.*, **10**, 226 (1929).
[2] Booth, V. H., and Green, D. E., *Biochem. J.*, **32**, 855 (1938).
[3] Chain, E., Florey, H. W., Gardner, A. D., Heatley, N. G., Jennings, M. A., Orr-Ewing, J., and Sanders, A. G., *Lancet*, 226 (1940).
[4] MacLeod, C., *J. Exp. Med.*, **72**, 217 (1940).

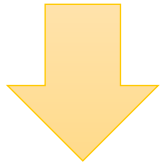
Morphological Effects of Penicillin on Bacteria

WHILE working with Chain, Florey and others on the inhibition of bacterial growth by penicillin[1], I noticed that concentrations of less than full inhibiting power caused a change in the appearance of the growth of *Cl. welchii* in fluid media. The normal uniform turbidity was replaced by a flocculent growth with a heavy deposit. Microscopical examination showed an extreme elongation of the majority of the cells, which took the form of unsegmented filaments ten or more times longer than the average normal cell.

I have now examined a number of bacteria grown in broth or serum broth with penicillin, and I have found similar microscopical changes in all the rod-shaped organisms that have shown any inhibition. These changes may be traceable, in the form of a distinct average lengthening of the cells, to a dilution eight or ten times, and even sometimes thirty times, higher than that which completely inhibits growth.

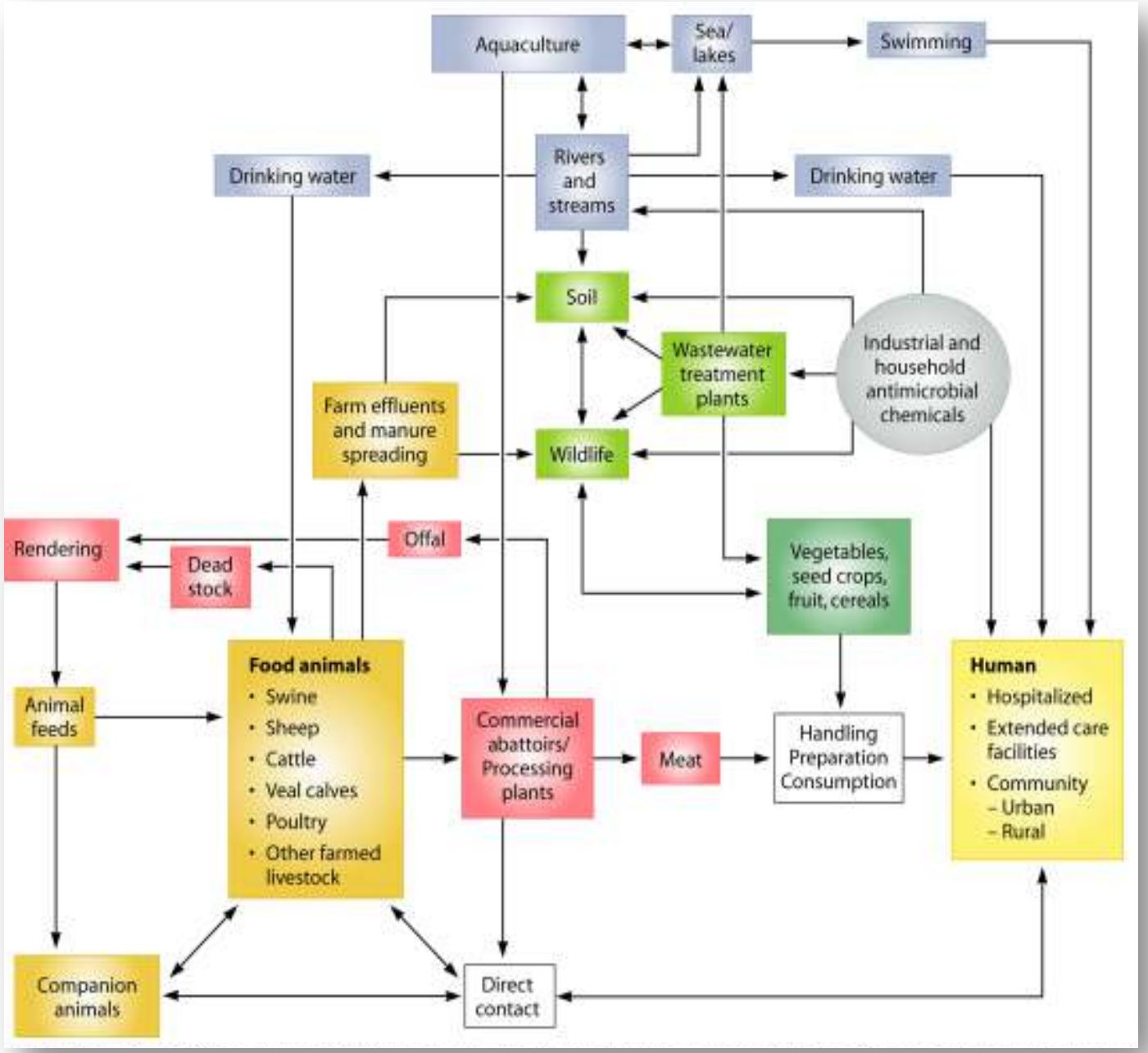
The Gram-negative rods, which are relatively resistant to penicillin, show the effect very well. Thus

- **İnsanların antibiyotikleri kullanım süresi ~80 yıl**
- **Doğada antibiyotik üreten kökenler ve direnç genleri milyonlarca yıldır var**
  - **Beta-laktam, tetrasiklin, vankomisin ve makrolid direnç genleri**



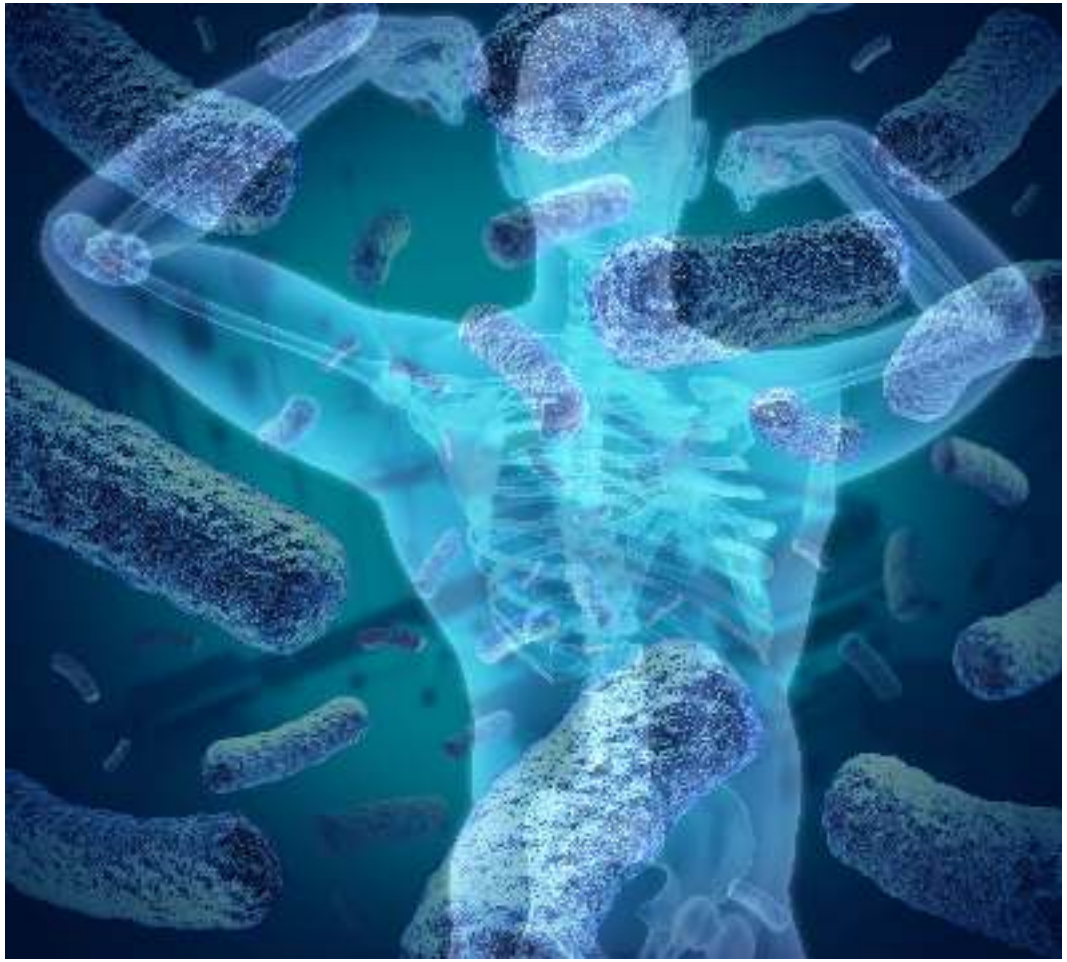
- **Antibiyotik üretimi, mikrobiyal topluluklarda, üreten mikroorganizma için bir avantaj sağlar**
  - **Antibiyotik üreticileri sıklıkla aynı gen kümesi üzerinde dirençten sorumlu genleri taşır**
    - **Eflüks pompaları**
    - **Hedef molekülleri değiştiren enzimler**
- **Öldürmeyen antibiyotik konsantrasyonları**
  - **Bakterilerde fizyolojik ve davranışsal değişiklikler oluşturur**
  - **İletişim molekülleri olarak ortaya çıkmış olmaları muhtemel**
  - **Direnç gelişimine katkıda bulunur…**

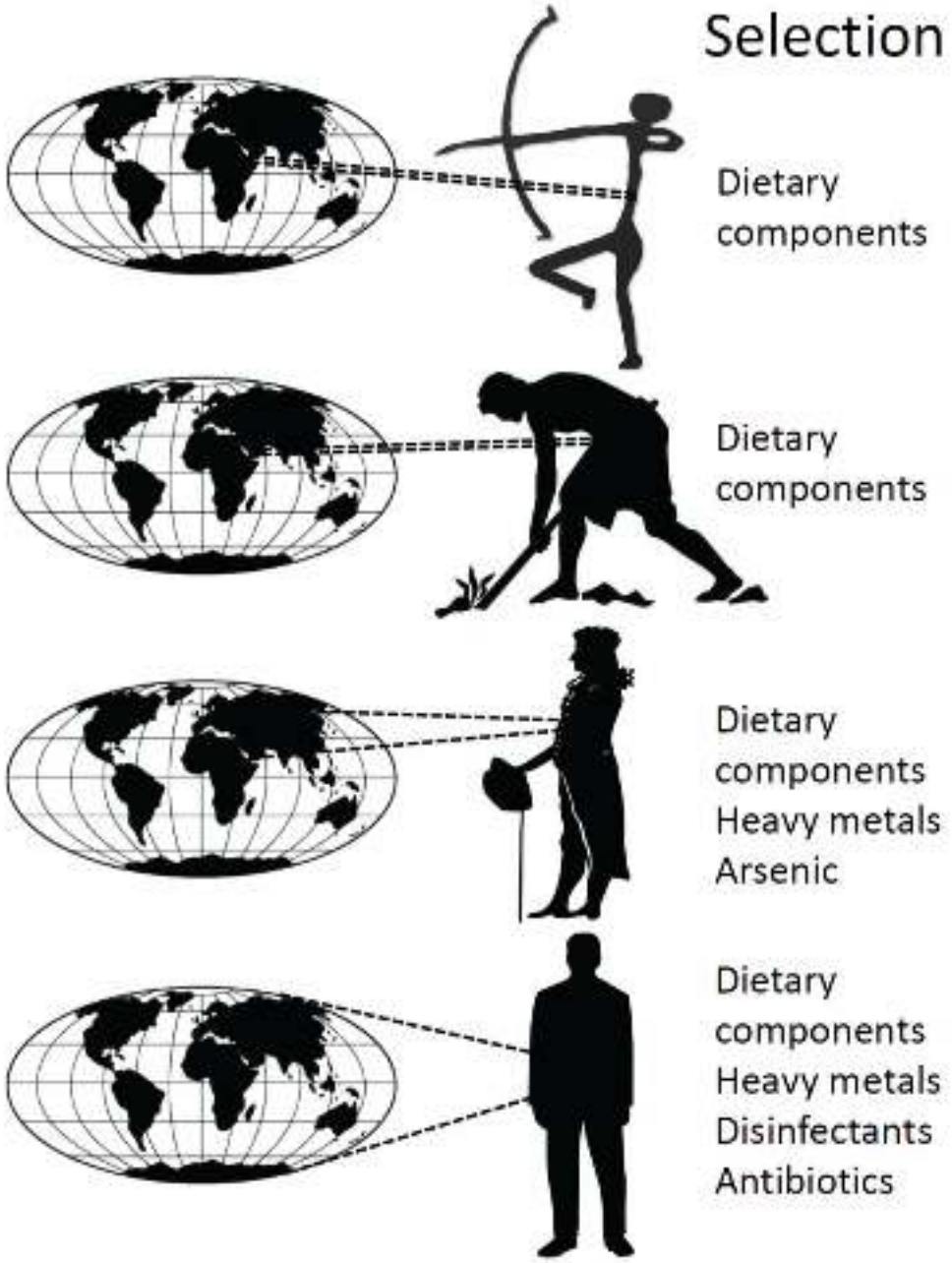
Kaynak???



Davies J, Davies D. Origins and evolution of antibiotic resistance. Microbiol Mol Biol Rev 2010; 74: 417-433.

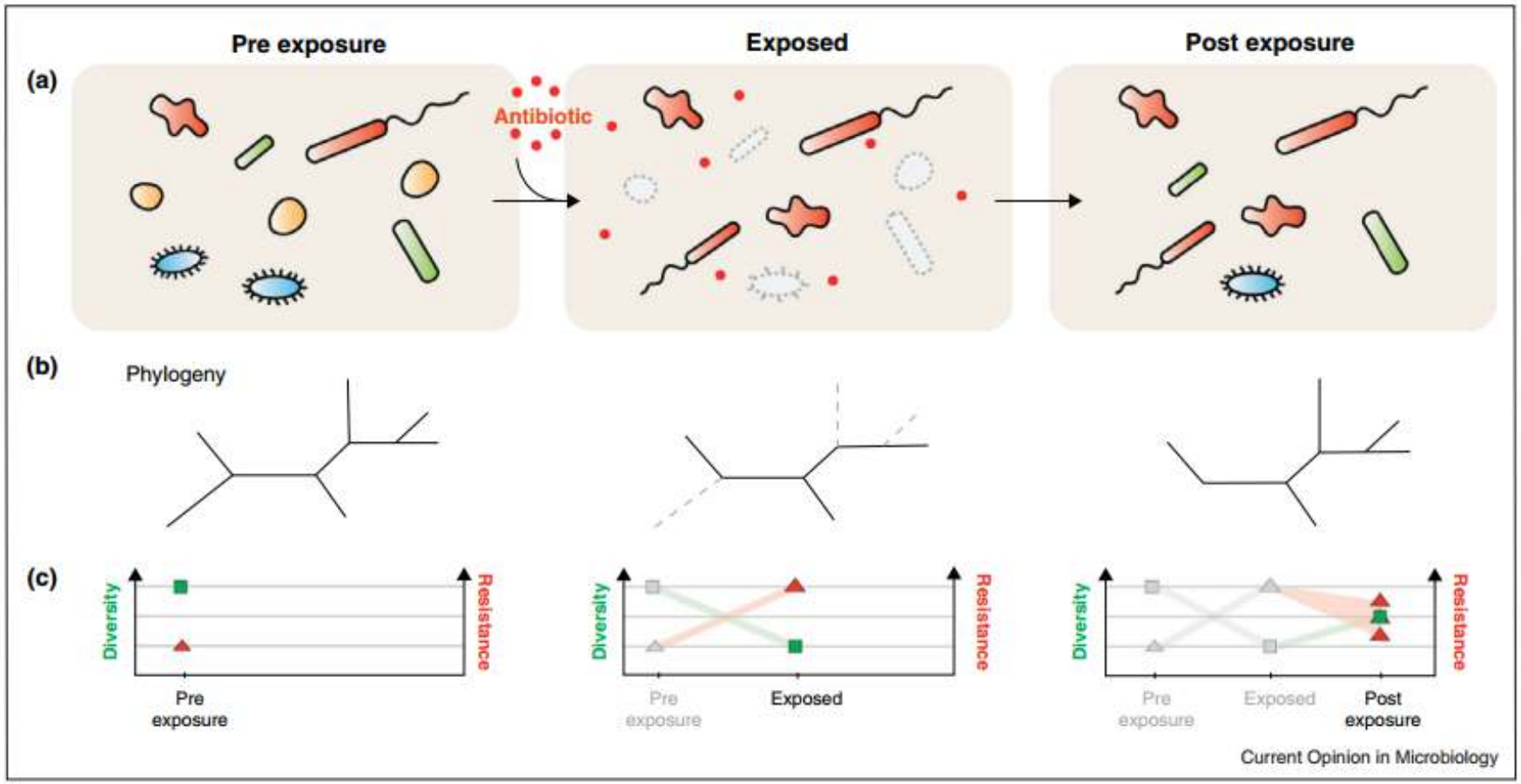
Direncin yayılımı



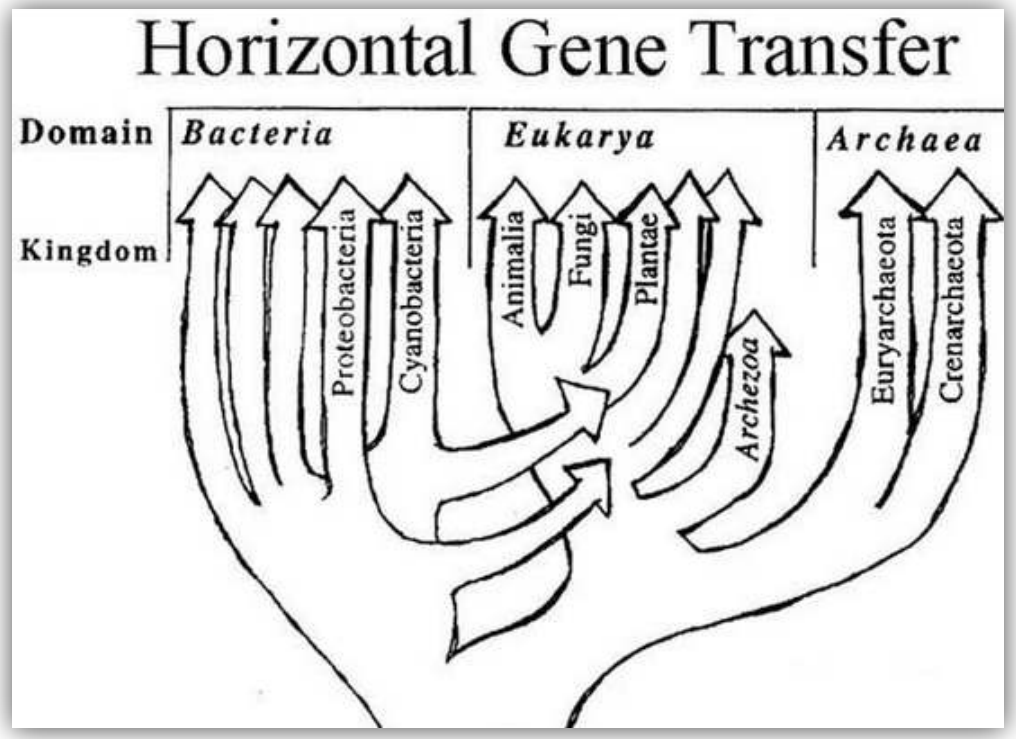


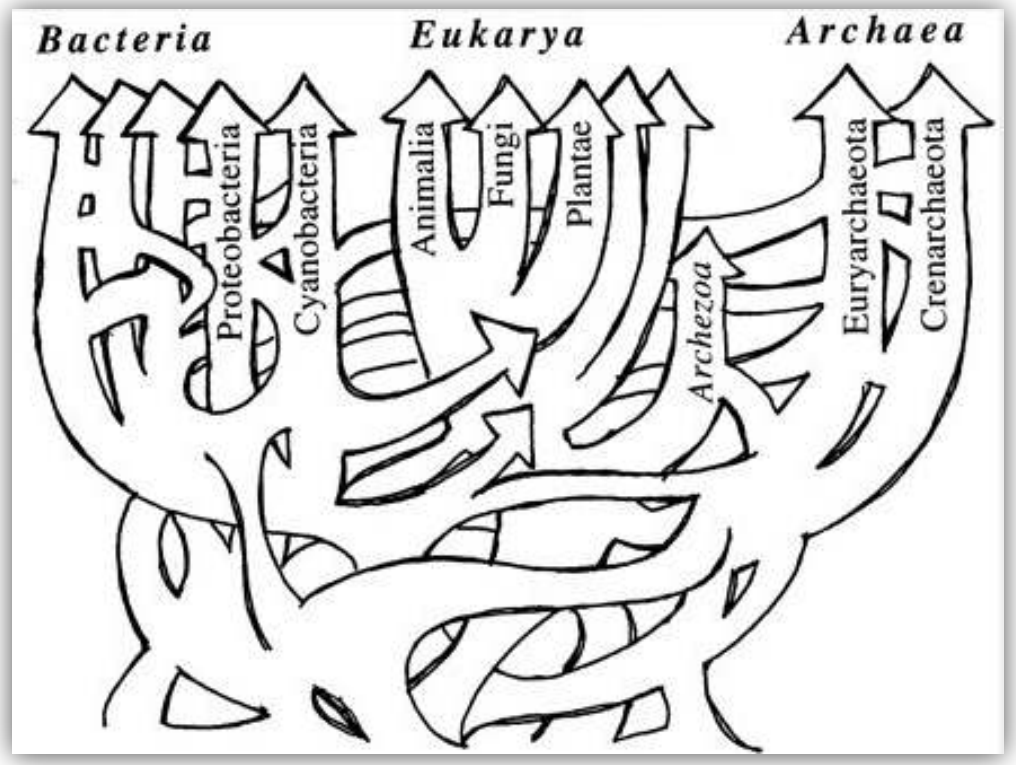
Duyarlı bakterilerde direnç gelişimi

- ***Hedef molekülleri kodlayan genlerde kromozomal mutasyonlar***

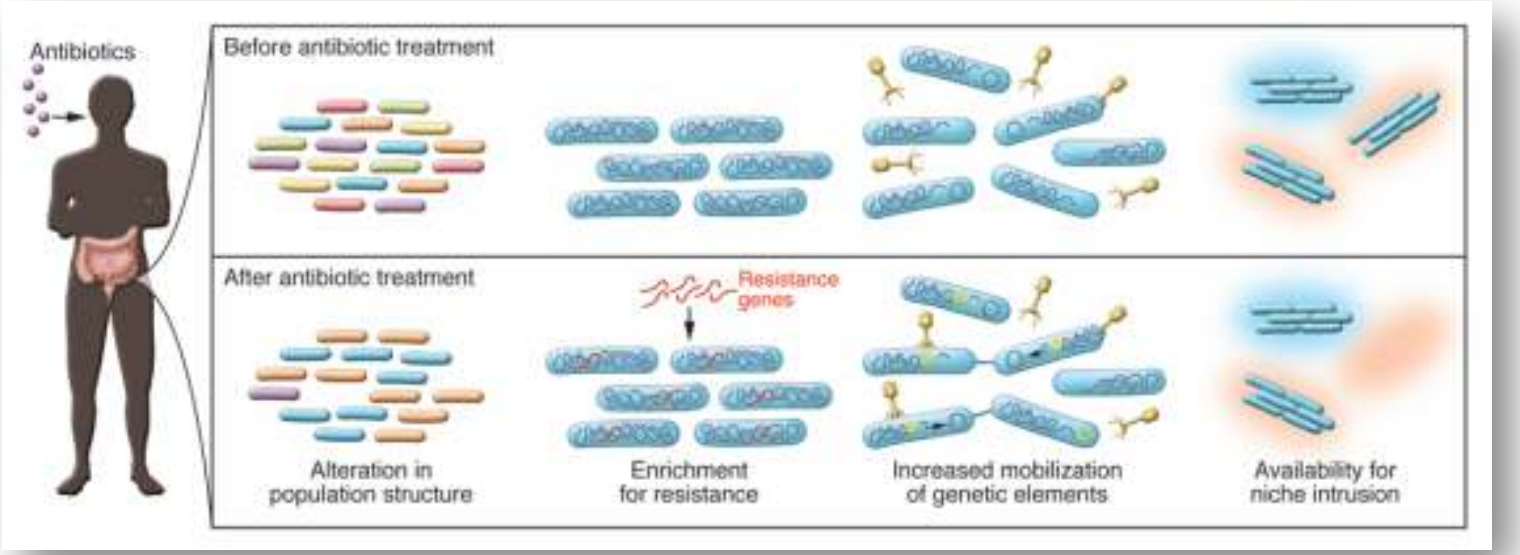


- ***Horizontal gen transferi***
  - **Farklı organizmalar arasında direnç genlerinin aktarımı**





- Topluluğa direnç genleri bir kere girdikten sonra sağladığı avantaj, direnci taşımanın yaratacağı yüke üstün gelirse, ekosistem içinde direnç genleri varlığını sürdürür



High Frequency of Antimicrobial Resistance in Human Fecal Flora

STUART B. LEVY,[1,2]* BONNIE MARSHALL,[1] SUSAN SCHLUEDERBERG,[1] DEBORAH ROWSE,[1] AND JOANNE DAVIS[1]

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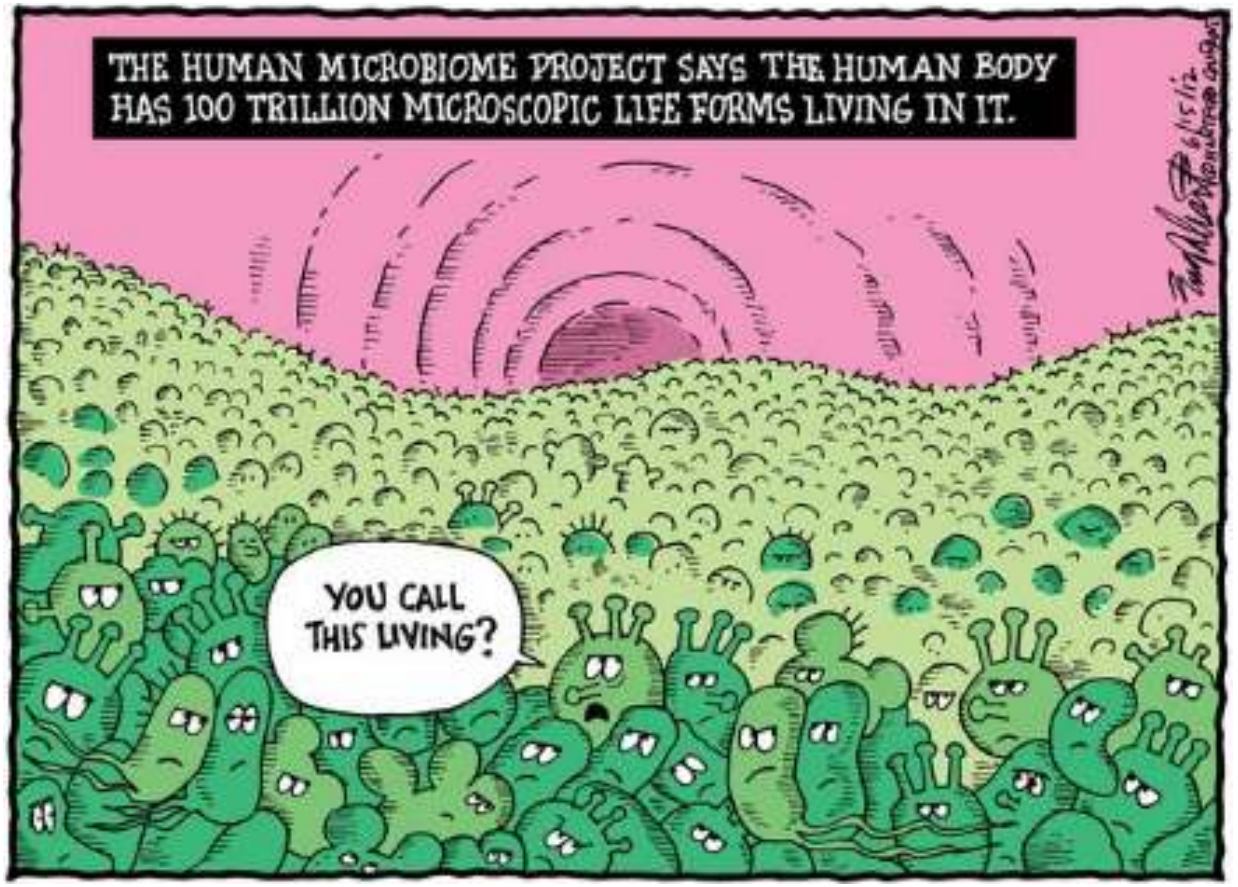
Received 25 April 1988/Accepted 9 September 1988

The frequency of resistance to seven different antimicrobial agents was examined in the aerobic gram-negative gut flora of over 600 individuals from hospitals, from laboratories where antibiotics were used, and from urban and rural communities. In a majority (62.5%) of fecal samples from people without a recent history of taking antibiotics, 10% or more of the total organisms were resistant to at least one of the antibiotics. In about 40% of the samples, resistance to more than one drug was present at this level. More than one-third of the samples contained resistant organisms comprising 50% or more of the total flora examined. Organisms with coresistance to multiple drugs were found frequently. Individuals taking antibiotics produced more samples with a higher proportion (>50%) of resistant bacteria, and these samples also had a significantly greater number of different resistance determinants. This extensive study revealed a high prevalence of resistant bacteria in the gut flora of ambulatory and hospitalized individuals whether or not they were taking antibiotics.

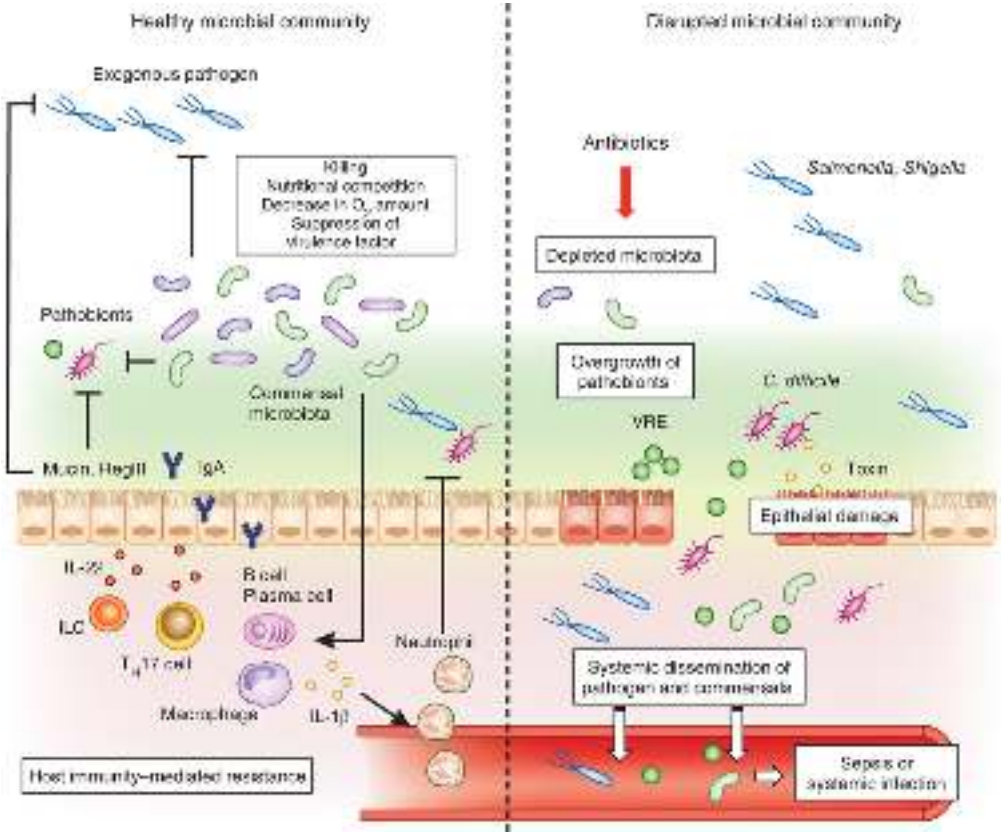
İnsan bağırsak mikrobiyotası

- 200-1000 farklı bakteri türü
- 100 trilyon bakteri
- 3,3 milyon farklı bakteri geni
  - İnsan genomunun 150 katı!
- Firmicutes
- Bacteroidetes
  - Actinobacteria
    - Proteobacteria (<%1)
    - Verrucomicrobiae
    - Fusobacteria



Önemli bir görev: Kolonizasyon direnci

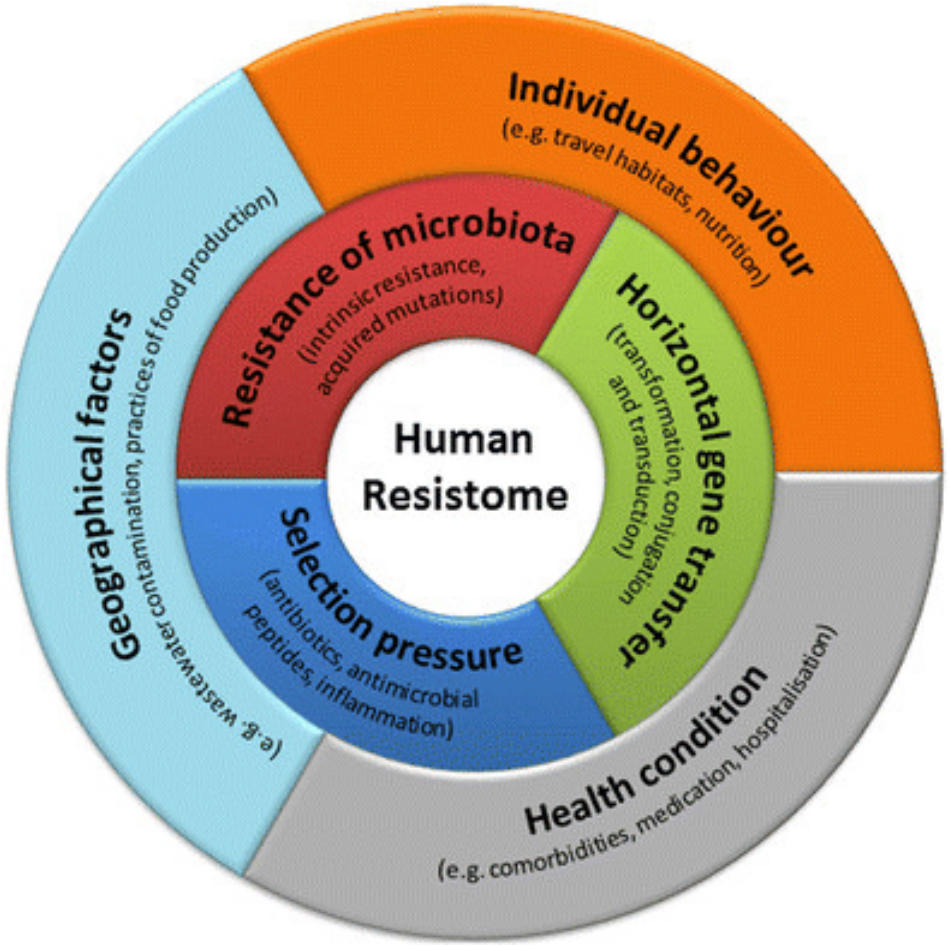
- Patojen mikroorganizmaların yerleşmesini engeller
- Direncin kaybı:
  - Bağırsak ortamı/denge bozulur
  - Patojenler ve bağırsak florası arasında horizontal gen transferi hızı artar
  - Fırsatçı dirençli patojenler için bir rezervuar halini alabilir
- Özellikle immün yetmezlikli hastalar ve yoğun bakım ünitelerinde yatanlarda ciddi enfeksiyonlara yol açabilir



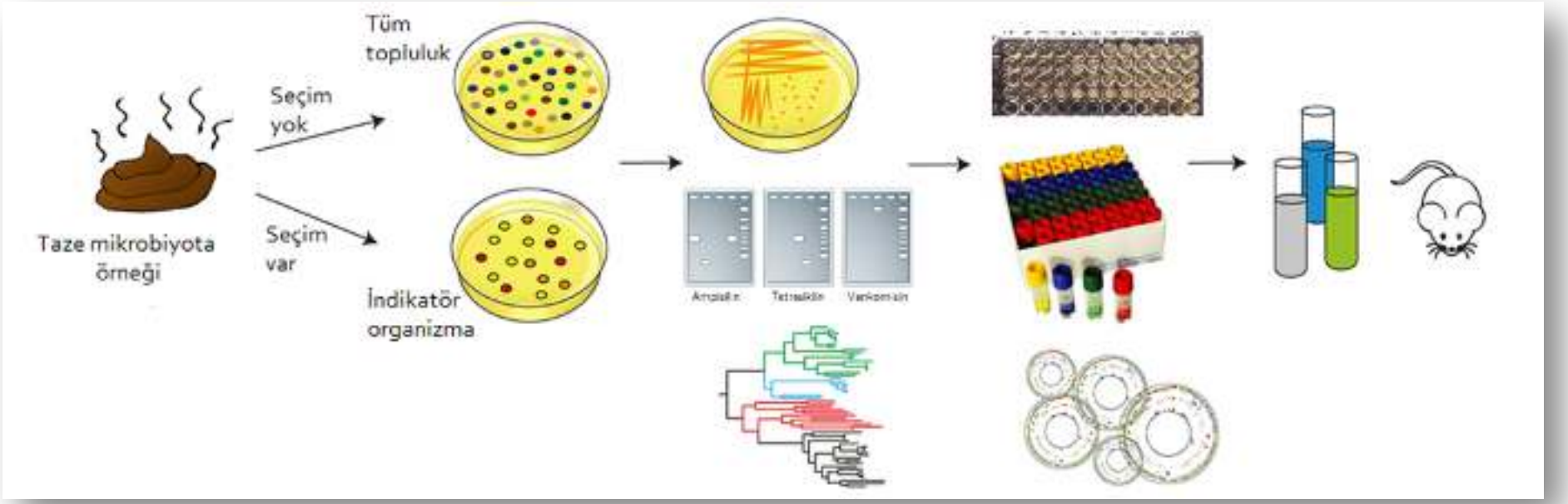
Buffie CG, Pamer EG. Microbiota-mediated colonization resistance against intestinal pathogens. Nature Rev Immunol 2013;13: 790–801.

Rezistom

- Mikrobiyotada bulunan direnç genleri topluluğu
  - Rezistomu oluşturan direnç genleri?
  - Direnç genlerinin kaynağı?
  - Direnç genlerinin bağırsak bakterileri arasında aktarımı?
  - Direnç genlerinin bağırsak bakterileri ile patojenler arasında aktarım oranı?
  - Direnç genlerinin akıbeti?
    - Varlığını sürdürme süresi?
    - Yok eden faktörler?



Rezistom analizi-Kültüre dayalı yöntemler



- **Ucuz**
- **Tekrarlanabilir**

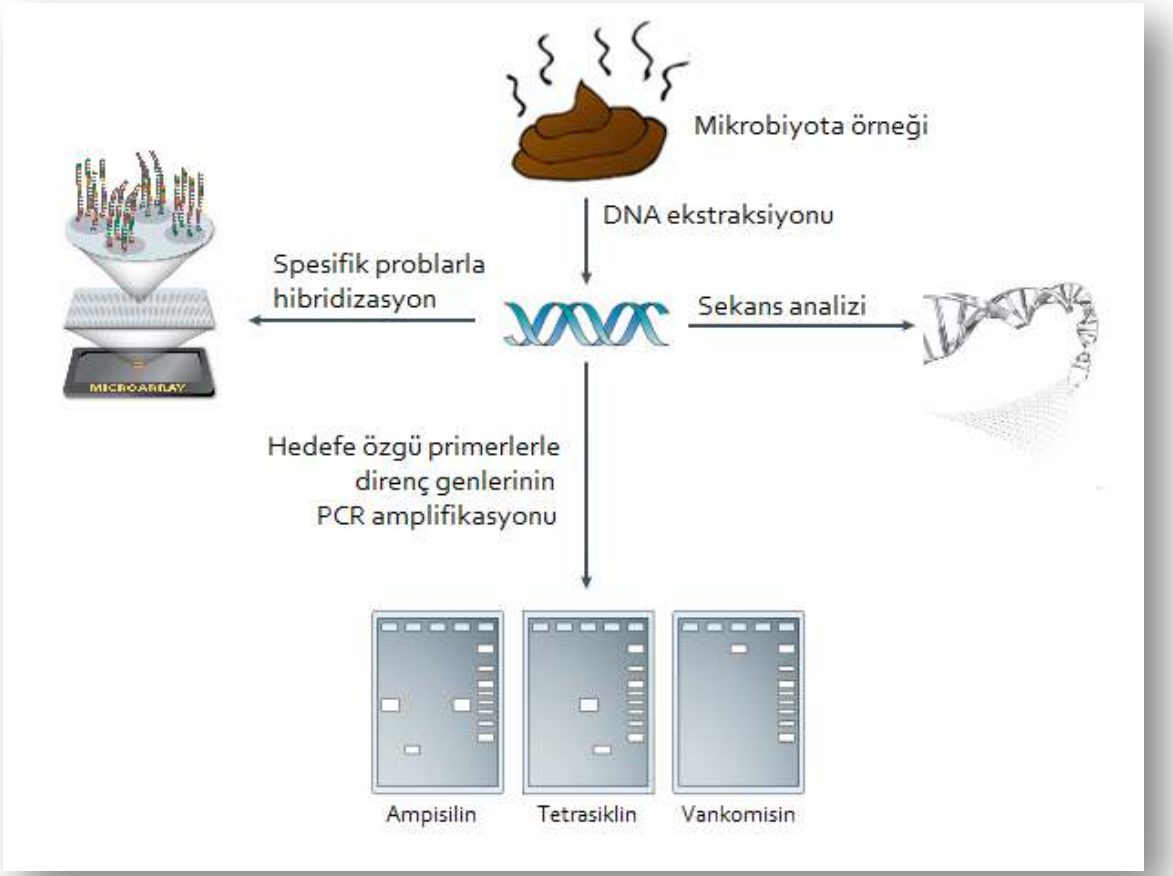
- **Değerli bir veri kaynağı**
  - **Coğrafik farklılıklar**
  - **Zamana bağlı değişiklikler**
  - **Hastaneye yatış ile ilişki**
  - **Hayvan ve çevresel kökenlerle ilişki**
  - **Direncin fenotipik/genotipik karakteri**

İnsan bağırsak mikrobiyotasının %80'ini kültürü yapılamayan bakteriler oluşturuyor!

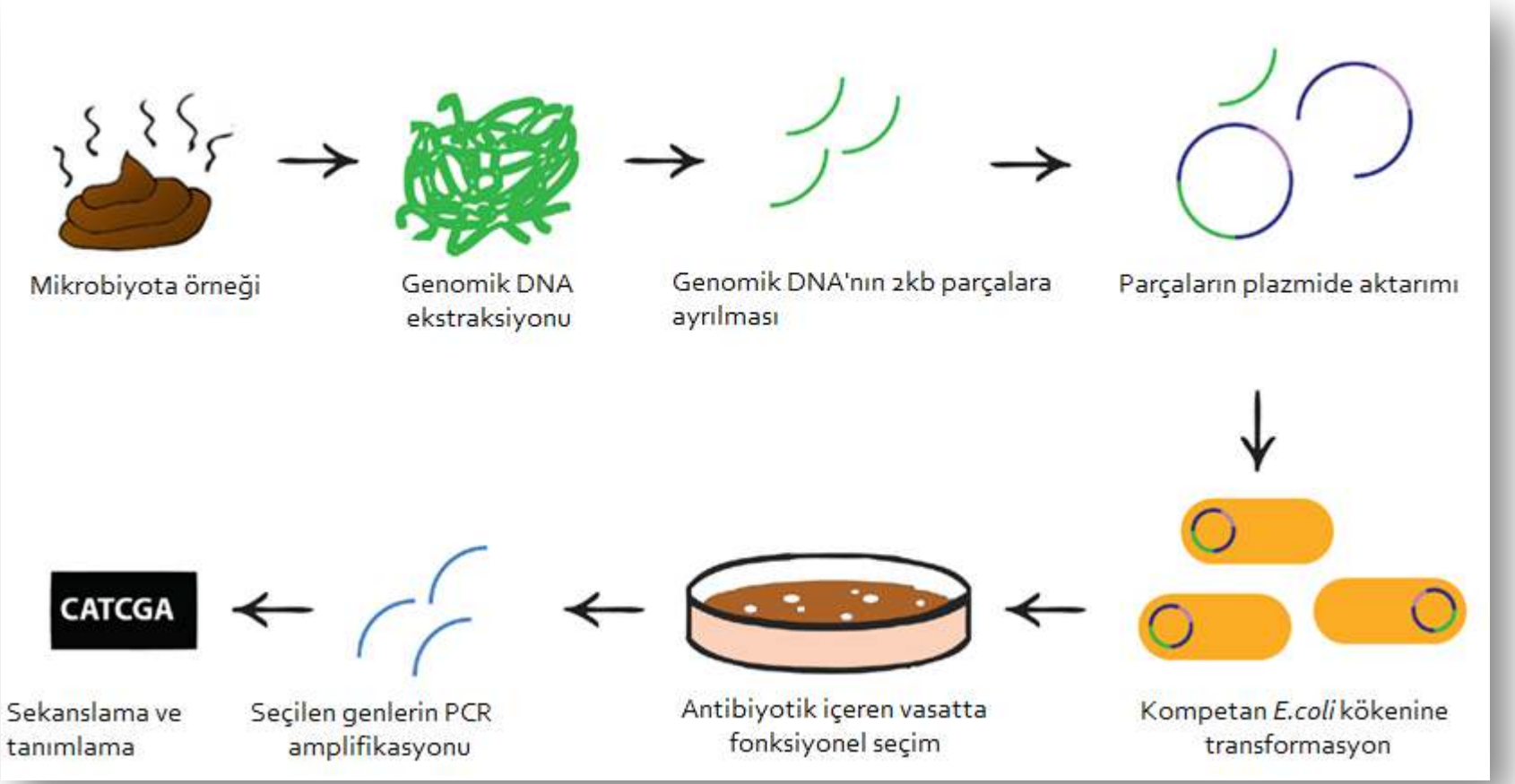
Rezistom Analizi-Moleküler yöntemler

- Bilinen direnç genlerinin araştırılması
- Doğrudan biyolojik materyalden çalışılabilir
  - Metagenomik yaklaşımlar!
- Değerli veri kaynağı
  - Direnç genlerinin yayılımı
  - İntegronların keşfi
  - Plazmidlerle direnç yayılımı takibi…

Bilinmeyen genler???



Mikrobiyota Analizi-Fonksiyonel Metagenomik Yaklaşımlar



✓Kompetan bakteri olmalı ✓Konakta eksprese olmalı

Functional Characterization of the Antibiotic Resistance Reservoir in the Human Microflora

Science 2009; 325: 1128-1131.

Morten O. A. Sommer,*† Gautam Dantas,*†‡ George M. Church

To understand the process by which antibiotic resistance genes are acquired by human pathogens, we functionally characterized the resistance reservoir in the microbial flora of healthy individuals. Most of the resistance genes we identified using culture-independent sampling have not been previously identified and are evolutionarily distant from known resistance genes. By contrast, nearly half of the resistance genes we identified in cultured aerobic gut isolates (a small subset of the gut microbiome) are identical to resistance genes harbored by major pathogens. The immense diversity of resistance genes in the human microbiome could contribute to future emergence of antibiotic resistance in human pathogens.

Beta-lactamase family	Enzyme name	Gene ID	GenBank ID	Source	Amino acid identity to NCBI (%)
AmpC	AmpC-EcoK12	AX_iG2_08	GQ343010	Aerobic gut isolate	100.0
	AmpC-EC6	PE_iG1_02	GQ343155	Aerobic gut isolate	100.0
	AmpC-EC31	PE_iG2_05	GQ343162	Aerobic gut isolate	100.0
	AmpC-HG1	AX_iG2_21	GQ343018	Aerobic gut isolate	99.7
	AmpC-HG2	CA_iG2_12	GQ343059	Aerobic gut isolate	99.5
	AmpC-HG3	CF_iG2_01	GQ343071	Aerobic gut isolate	90.0
	AmpC-HG4	CF_iG2_06	GQ343073	Aerobic gut isolate	97.4
	AmpC-HG5	CA_iG1_06	GQ343055	Aerobic gut isolate	99.2
TEM	TEM-1b	AX_iG1_01	GQ343004	Aerobic gut isolate	100.0
	TEM-168	PE_iG2_13	GQ343167	Aerobic gut isolate	99.7
	TEM-169	PI_iG2_05	GQ343173	Aerobic gut isolate	99.1
CTX-M	CTX-M-15	AX_iG1_04	GQ343005	Aerobic gut isolate and metagenomic gut sample	100.0
CblA	CblA-1	AX_iG2_02	GQ343019	Aerobic gut isolate and metagenomic gut sample	100.0
	CblA-2	AX_mG2_03	GQ342999	Metagenomic gut sample	99.7
	CblA-3	PE_mG2_02	GQ343154	Metagenomic gut sample	99.0
CfxA	CfxA6	AX_mG2_01	GQ342996	Metagenomic gut sample	87.2
HGA	HGA-1	CA_mG1_02	GQ343038	Metagenomic gut sample	61.4
HGB	HGB-1	AX_mG2_05	GQ343000	Metagenomic gut sample	58.5
HOA	HOA-1	AX_mO1_01	GQ343035	Metagenomic saliva sample	49.5
HGC	HGC-1	CA_mG1_01	GQ343037	Metagenomic gut sample	48.1
	HGC-2	CA_mG1_04	GQ343039	Metagenomic gut sample	51.0
HGD	HGD-1	CA_mG2_04	GQ343044	Metagenomic gut sample	52.9
HGE	HGE-1	AX_mG2_11	GQ343003	Metagenomic gut sample	37.1
HGF	HGF-1	AX_mG2_09	GQ343002	Metagenomic gut sample	43.3
HGG	HGG-1	PI_mG1_01	GQ343151	Metagenomic gut sample	38.8
HGH	HGH-1	PI_mG1_01	GQ343170	Metagenomic gut sample	34.5
HGI	HGI-1	CA_mG2_07	GQ343045	Metagenomic gut sample	42.6

- İnsan mikrobiyomu patojenik bakterilerin antibiyotik direnç genlerine ulaşabileceği bir rezervuar oluşturabilir.
- Kültürü yapılabilen aerobik izolatlar insan mikrobiyomunun uyuyan patojenleri olabilir.
- Kommensaller arasında lateral gen transferini önleyen bir bariyer bulunabilir.

Application of Microarray and Functional-Based Screening Methods for the Detection of Antimicrobial Resistance Genes in the Microbiomes of Healthy Humans

Roderick M. Card[1], Philip J. Warburton[2¤], Nikki MacLaren[1], Peter Mullany[2], Elaine Allan[2], Muna F. Anjum[1*]

1 Department of Bacteriology, Animal Health and Veterinary Laboratories Agency, Addlestone, Surrey, United Kingdom, 2 Department of Microbial Diseases, Eastman Dental Institute, University College London, London, United Kingdom

Abstract

The aim of this study was to screen for the presence of antimicrobial resistance genes within the saliva and faecal microbiomes of healthy adult human volunteers from five European countries. Two non-culture based approaches were employed to obviate potential bias associated with difficult to culture members of the microbiota. In a gene target-based approach, a microarray was employed to screen for the presence of over 70 clinically important resistance genes in the saliva and faecal microbiomes. A total of 14 different resistance genes were detected encoding resistances to six antibiotic classes (aminoglycosides, β-lactams, macrolides, sulphonamides, tetracyclines and trimethoprim). The most commonly detected genes were *erm*(B), bla_{TEM}, and *sul2*. In a functional-based approach, DNA prepared from pooled saliva samples was cloned into *Escherichia coli* and screened for expression of resistance to ampicillin or sulphonamide, two of the most common resistances found by array. The functional ampicillin resistance screen recovered genes encoding components of a predicted AcrRAB efflux pump. In the functional sulphonamide resistance screen, *folP* genes were recovered encoding mutant dihydropteroate synthase, the target of sulphonamide action. The genes recovered from the functional screens were from the chromosomes of commensal species that are opportunistically pathogenic and capable of exchanging DNA with related pathogenic species. Genes identified by microarray were not recovered in the activity-based screen, indicating that these two methods can be complementary in facilitating the identification of a range of resistance mechanisms present

Table 2. Summary of BAC clones made from human Saliva DNA recovered from functional-based screens.

Clone ID[1]	Antibiotic employed in screen	Best match taxonomic classification of cloned DNA (Accession number)	Nucleotide Identity (%)	Size of Cloned DNA (bp)	Predicted number of ORFs in cloned DNA[2]	Antibiotic Susceptibilities[3]	Gene(s) responsible for resistance phenotype
AMP4	Ampicillin	*Haemophilus parainfluenzae* (NC_015964)	96	9,476	7	Amp^{I}	*acrRAB*
AMP5	Ampicillin	*Haemophilus parainfluenzae* (NC_015964)	95	12,200	10	Amp^{I}	*acrRAB*
AMP7	Ampicillin	*Haemophilus parainfluenzae* (NC_015964)	93	16,716	13	Amp^{I}	*acrRAB*
SUL6	Sulphonamide	*Neisseria subflava* (ACEO02000001)	96	13,526	16	Sul^{RS}/Sxt^{R}	*folP*
SUL8	Sulphonamide	*Neisseria subflava* (ACEO02000001)	95	14,125	18	Sul^{RS}/Sxt^{R}	*folP*
SUL9	Sulphonamide	*Neisseria subflava* (ACEO02000001)	96	10,250	11	Sul^{RS}/Sxt^{R}	*folP*
SUL15	Sulphonamide	*Neisseria subflava* (ACEO02000001)	96	11,916	13	Sul^{RS}/Sxt^{R}	*folP*
SUL11	Sulphonamide	*Streptococcus infantis* (NZ_AEDY01000064)	94	13,436	16	Sul^{RS}/Sxt^{R}	*folP*
SUL3	Sulphonamide	*Veillonella parvula* (CP001820)	88	17,734	18	Sul^{R}/Sxt^{RS}	*folP*
SUL5	Sulphonamide	*Veillonella parvula* (CP001820)	87	21,161	20	Sul^{R}/Sxt^{RS}	*folP*
SUL10	Sulphonamide	*Veillonella parvula* (CP001820)	86	15,616	16	Sul^{RS}/Sxt^{R}	*folP*
SUL20	Sulphonamide	*Veillonella parvula* (CP001820)	86	15,605	16	Sul^{RS}/Sxt^{R}	*folP*

[1]Accession numbers for the clone sequences are: AMP4 (KF982313), AMP5 (KF982314), AMP7 (KF982315), SUL3 (KF982316), SUL5 (KF982317), SUL6 (KF982318), SUL8 (KF982319), SUL9 (KF982320), SUL10 (KF982321), SUL11 (KF982322), SUL15 (KF982323), and SUL20 (KF982324).

[2]ORF prediction by RAST server [27].

[3]Amp^{I} = intermediate ampicillin resistance; Sul^{R} = resistant to sulphonamide compounds; Sul^{RS} = reduced susceptibility to sulphonamide compounds compared to EPI300; Sxt^{R} = resistant to trimethoprim/sulphamethoxazole 1:19; Sxt^{RS} = reduced susceptibility to trimethoprim/sulphamethoxazole 1:19 compounds compared to *E. coli* EPI300.

APPLIED AND ENVIRONMENTAL MICROBIOLOGY, Feb. 2001, p. 561–568 Vol. 67, No. 2
0099-2240/01/$04.00+0 DOI: 10.1128/AEM.67.2.561–568.2001

Evidence for Extensive Resist… spp. and among *Bacteroides* a…

N. B. SHOEM…
Department…

Transfer of antibiotic resista… resistance. Yet virtually no info… in natural settings. In this pa… increased antibiotic resistance… bacteria. Over the past 3 decad… 30% to more than 80% of strain… 100% identical at the DNA seq… spread. Southern blot analyses… (CTn) of the CTnDOT type. Ca… 23% and accounted for about 7… genes was the same in isolates t… obtained from patients with *Ba*… in the community and not just i… resistance genes in people who… these resistance genes are stabl… carried *ermB* genes. Two were i… one to three mismatches. The… identical to the *ermG* of *Bacillu*… bacteria, including bacteria tha… Our results support the hypoth… both within the genus *Bacteroid*…

LETTER
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The Human Gut Microbiome as a Transporter of Antibiotic Resistance Genes between Continents

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Previous studies of antibiotic resistance dissemination by travel have, by targeting only a select number of cultivable bacterial species, omitted most of the human microbiome. Here, we used explorative shotgun metagenomic sequencing to address the abundance of >300 antibiotic resistance genes in fecal specimens from 35 Swedish students taken before and after exchange programs on the Indian peninsula or in Central Africa. All specimens were additionally cultured for extended-spectrum beta-lactamase (ESBL)-producing enterobacteria, and the isolates obtained were genome sequenced. The overall taxonomic diversity and composition of the gut microbiome remained stable before and after travel, but there was an increasing abundance of *Proteobacteria* in 25/35 students. The relative abundance of antibiotic resistance genes increased, most prominently for genes encoding resistance to sulfonamide (2.6-fold increase), trimethoprim (7.7-fold), and beta-lactams (2.6-fold). Importantly, the increase observed occurred without any antibiotic intake. Of 18 students visiting the Indian peninsula, 12 acquired ESBL-producing *Escherichia coli*, while none returning from Africa were positive. Despite deep sequencing efforts, the sensitivity of metagenomics was not sufficient to detect acquisition of the low-abundant genes responsible for the observed ESBL phenotype. In conclusion, metagenomic sequencing of the intestinal microbiome of Swedish students returning from exchange programs in Central Africa or the Indian peninsula showed increased abundance of genes encoding resistance to widely used antibiotics.

Belki de rezistomumuzla doğuyoruz?

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Acquired Antibiotic Resistance: Are We Born with It?▽

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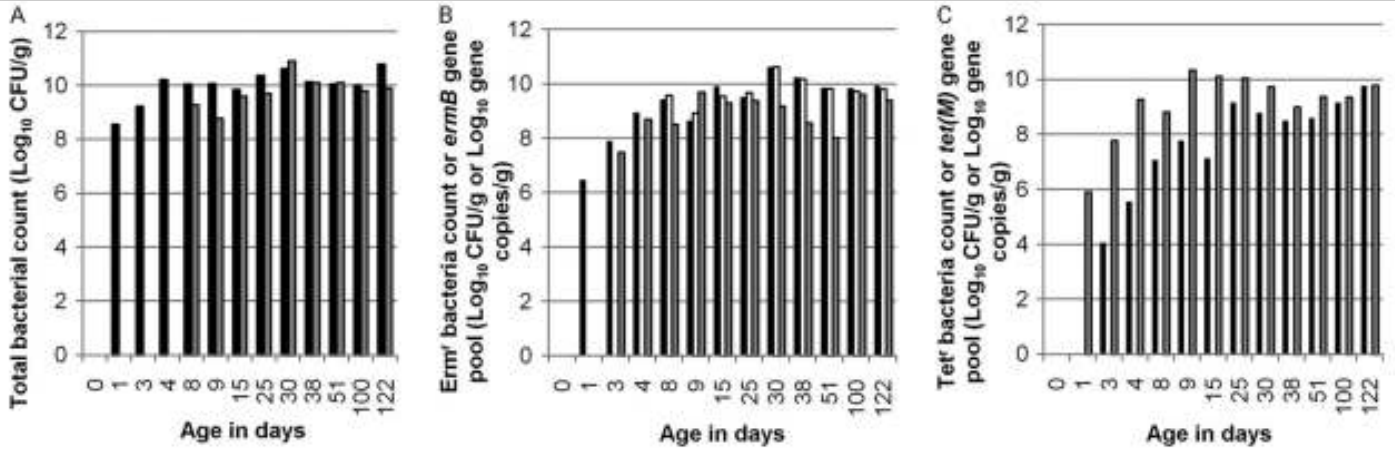
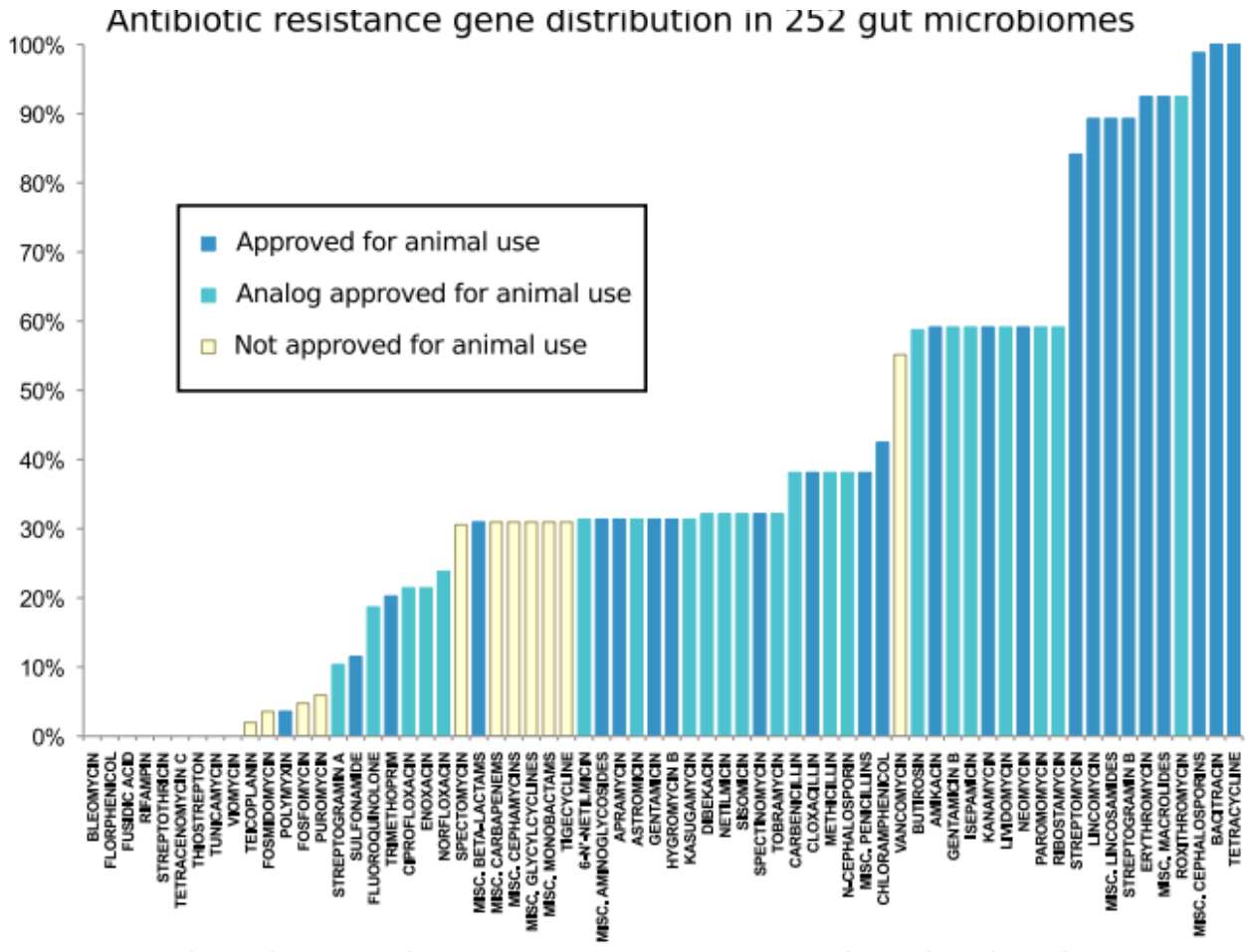


TABLE 2. Prevalence of AR genes and identified carriers in infant fecal samples

AR gene	Prevalence (%) (no. of positive results/total no. of samples)		AR gene carriers (no. of specific genera/total no. of AR gene carries)
	Infant subjects	Corresponding ART population	
tet(M)	100 (14/14)	58 (651/1,130)	*Enterococcus* spp. (114/153), *Escherichia coli*/*Shigella* spp. (3/153), *Providencia* sp. (1/153), *Veillonella* sp. (1/153), *Streptococcus* spp. (17/153), *Staphylococcus* spp. (17/153)
ermB	100 (4/4)	34 (86/250)	*Enterococcus* spp. (14/30), *Streptococcus* spp. (10/30), *Klebsiella* spp. (5/30), *Staphylococcus* sp. (1/30)
sul2	100 (4/4)	54 (85/157)	*Escherichia coli*/*Shigella* spp. (36/36)

- İnsan bağırsak mikrobiyotası, önemli bir direnç geni kaynağıdır*
- Direnç genlerinin çeşitliliği ve miktarı, ülkeden ülkeye değişir**



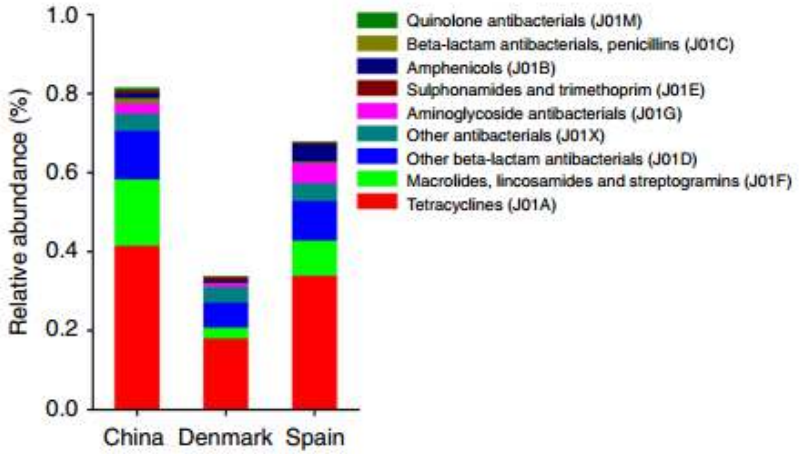
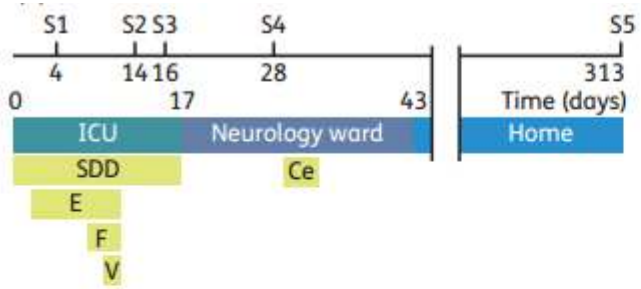


Figure 5 | The relative abundance of antibiotic resistance gene types assigned to each major antibiotic class in the different populations. Resistance gene types were mapped to antibiotics according to the ARDB, and the classification of antibiotics was based on WHO ATC code J01. The average abundance for each gene type among individuals was used for mapping (excluding outliers). Resistances determined by more than one gene are not included, for example, by the vancomycin resistance operon. China: $n = 37$; Denmark: $n = 80$; Spain: $n = 36$.

*Forslund K, Sunagawa S, Kultima JR, et al. Country specific antibiotic use practices impact the human gut resistome. Genome Res 2013; 23: 1163-1169.

**Hu Y, Yang X, Qin J. Metagenome-wide analysis of antibiotic resistance genes in a large cohort of human gut microbiota. Nat Commun 2013; 4:2151

Kısa süreli antibiyotik tedavileri, yoğun bakım ünitesinde yatış bile dirençli bakteri topluluğunun sayısını arttırır ve floranın eski haline dönmesi aylar hatta yıllar alır



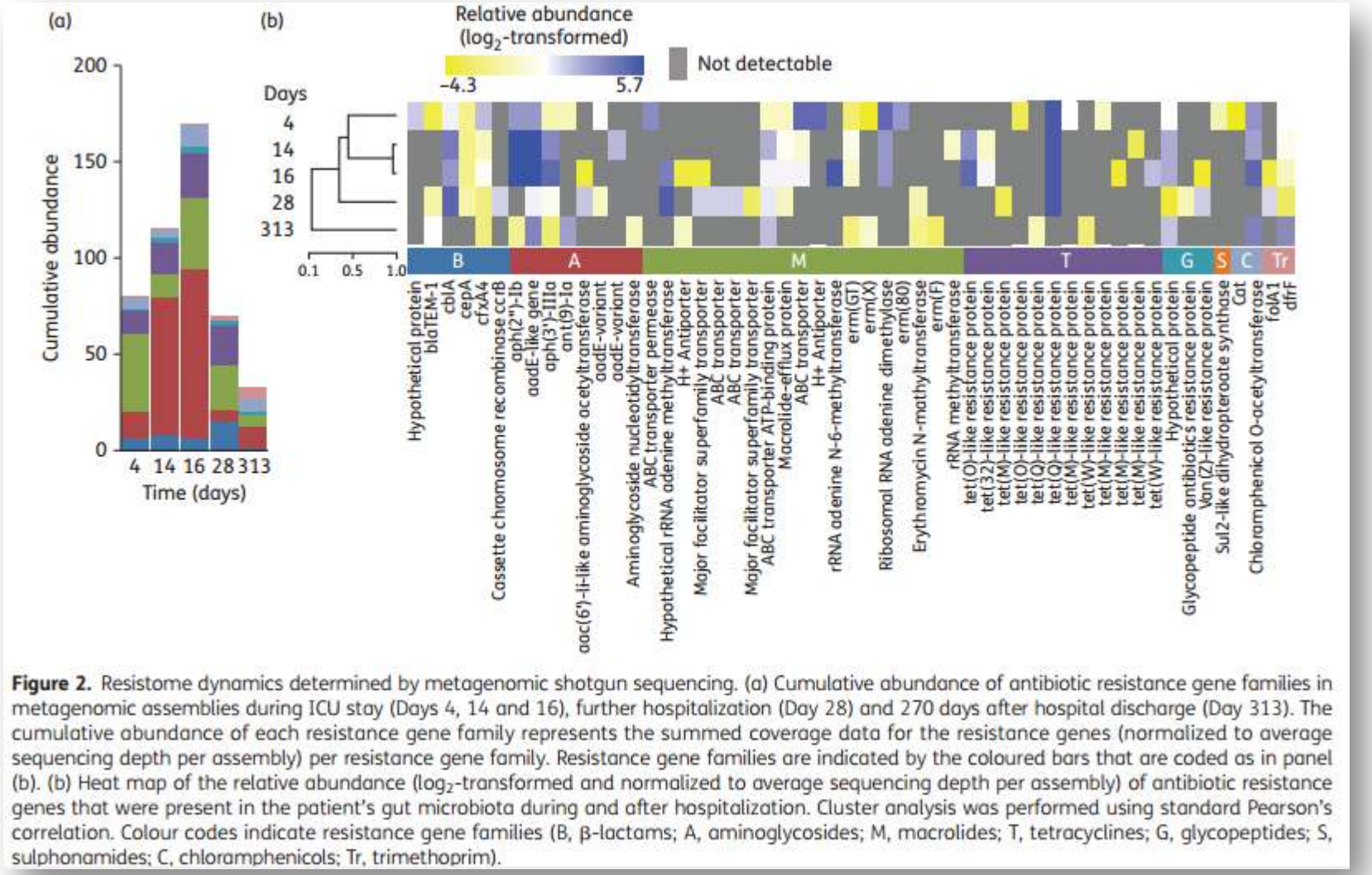
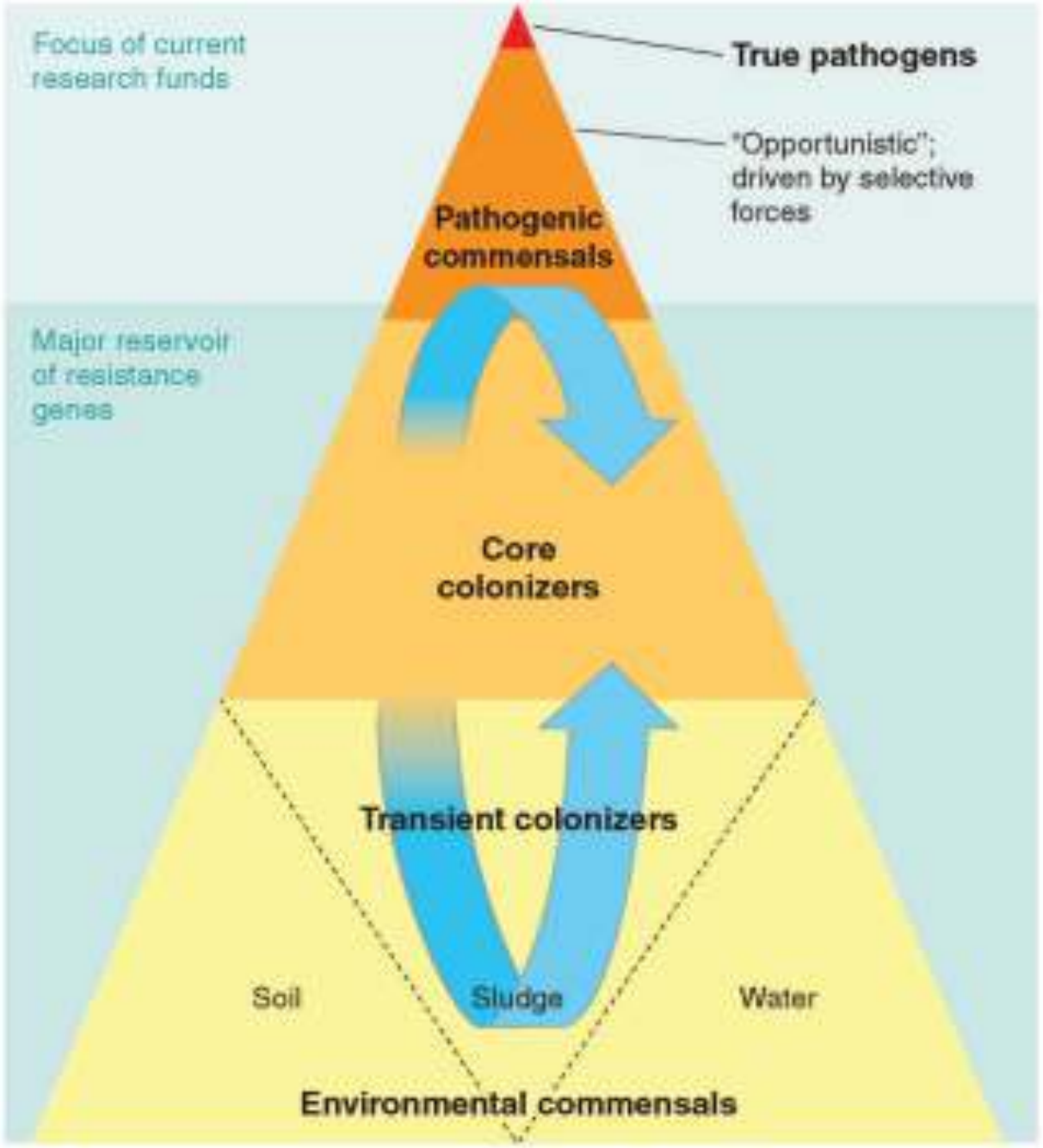


Figure 2. Resistome dynamics determined by metagenomic shotgun sequencing. (a) Cumulative abundance of antibiotic resistance gene families in metagenomic assemblies during ICU stay (Days 4, 14 and 16), further hospitalization (Day 28) and 270 days after hospital discharge (Day 313). The cumulative abundance of each resistance gene family represents the summed coverage data for the resistance genes (normalized to average sequencing depth per assembly) per resistance gene family. Resistance gene families are indicated by the coloured bars that are coded as in panel (b). (b) Heat map of the relative abundance (log_2-transformed and normalized to average sequencing depth per assembly) of antibiotic resistance genes that were present in the patient's gut microbiota during and after hospitalization. Cluster analysis was performed using standard Pearson's correlation. Colour codes indicate resistance gene families (B, β-lactams; A, aminoglycosides; M, macrolides; T, tetracyclines; G, glycopeptides; S, sulphonamides; C, chloramphenicols; Tr, trimethoprim).

Buelow E, Gonzalez TB, Veersluis D, et al. Effects of selective digestive decontamination (SDD) on the gut resistome. J Antimicrob Chemother 2014; 69:2215-2223

Rezistomumuzda taşıdığımız bilinmeyen direnç determinantları yeni direnç mekanizmalarının habercisi olabilir.



Teşekkürler…