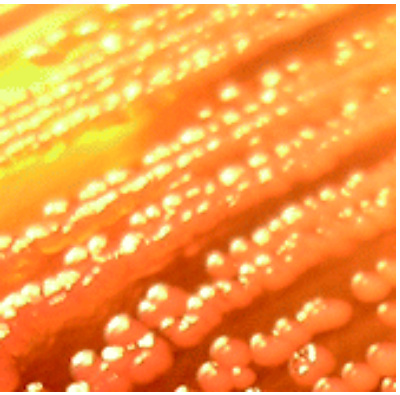
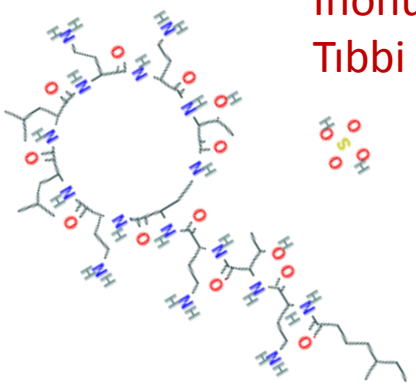


mcr (+) Acinetobacter spp

Barış Otlu
İnönü Üniversitesi Tıp Fakültesi
Tıbbi Mikrobiyoloji Anabilim Dalı, Malatya.



Antibiyotik Direnci

- Yeni bir antibiyotik direnci tespit edildiğinde, klinik ve halk sağlığı üzerine potansiyel etkilerinin değerlendirilmesi gerekir.

BBC Menü

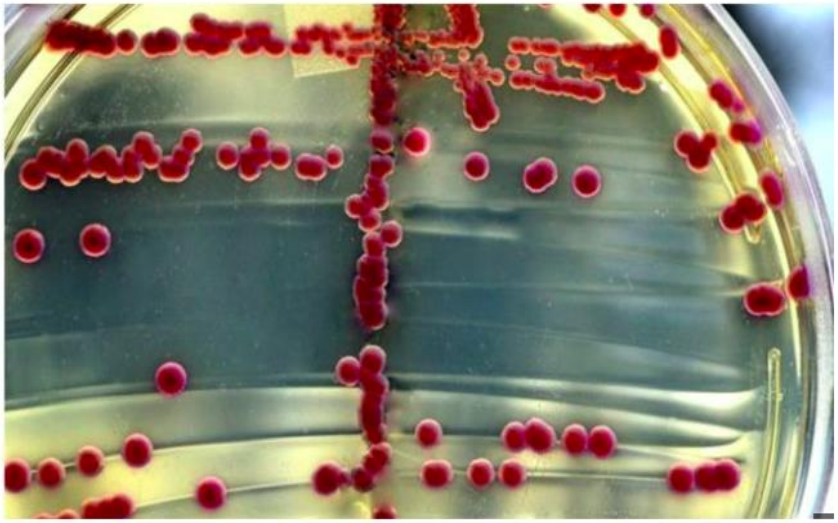
NEWS | TÜRKÇE

Haberler | Video | Fotoğraf | Dergi | Spor | Ekonomi | Bilim | Teknoloji | Sağlık

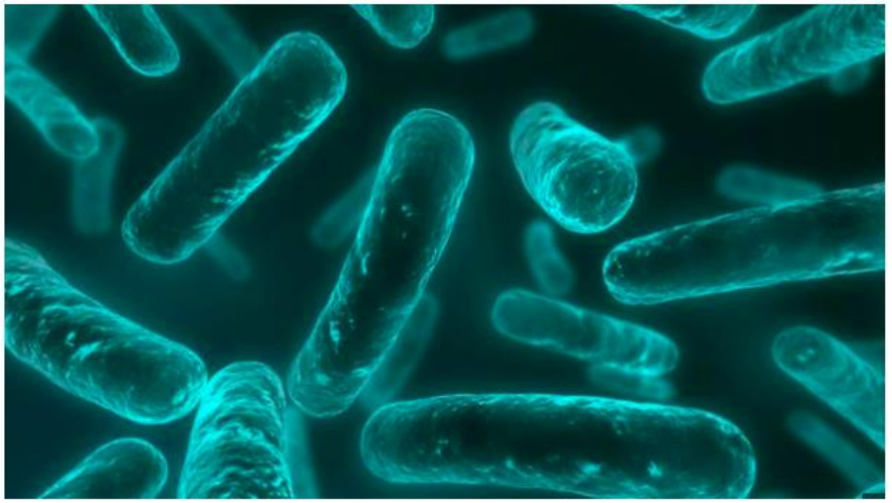
Uzmanlar uyardı: Antibiyotik kıyametin eşiğindeyiz

James Gallagher
BBC Sağlık Editörü

19 Kasım 2015 Paylaş



Çinli bilim insanları MCR-1 adı verilen yeni gen mutasyonunun Colistin'in bakterileri öldürmesini engellediğini tespit etti.

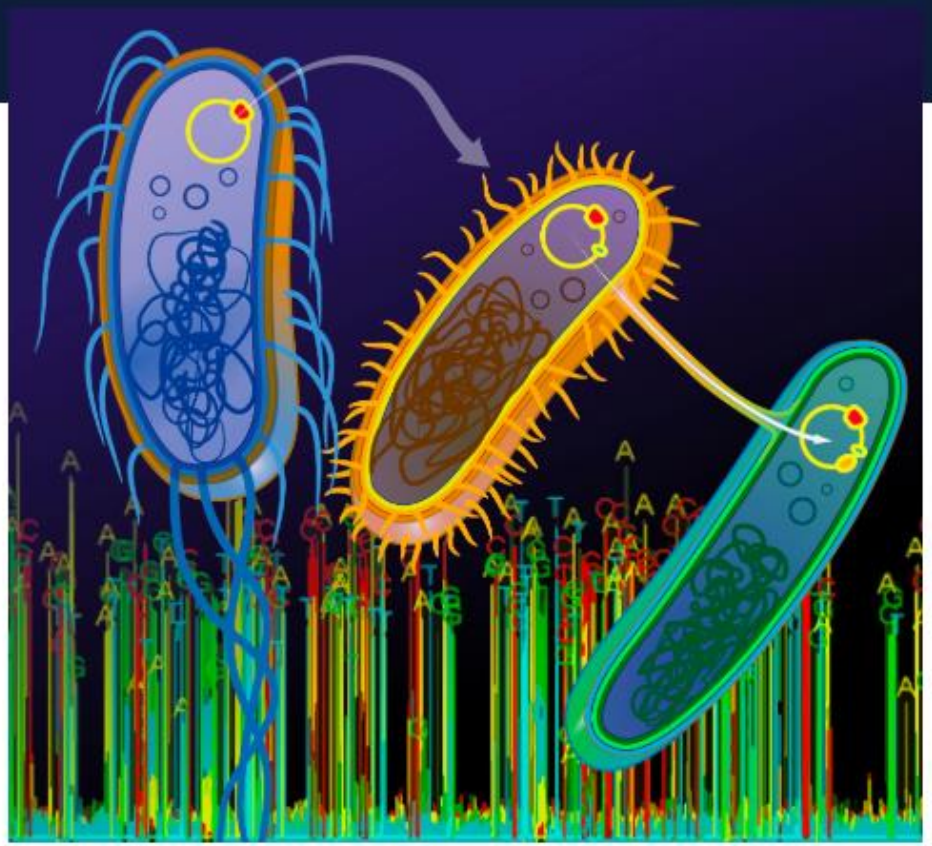


Antibiyotik Direnci

- Kolistin direncine neden olan mcr geni transfer edilebilir bir plazmid üzerine kodlanmış durumdadır.

NEWS

Sex in the Sink: Gene-Swapping Bacteria Are Making New Superbugs



Plasmid transfer between bacterial species can be investigated with single-molecule DNA sequencing technology. Plasmids, small mobile pieces of DNA, carry genes encoding resistance to antibiotics, including carbapenems, a powerful class of antibiotics used to treat serious infections.

Darryl Leja / NHGRI/NIH

Mcr (+) Acinetobecter spp.

- Acinetobacter türlerinin neden olduğu infeksiyonları giderek artıyor.

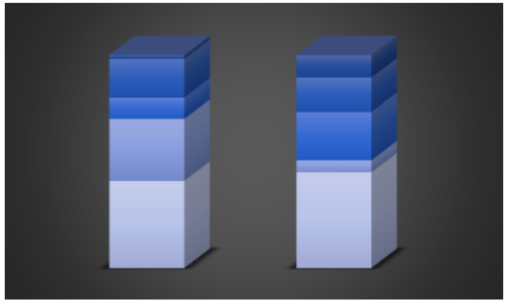
THE NEWSMATES

Home Health Science Technology

Home / News / Business / Acinetobacter Infections Treatment Market 2019 Important Research, Market Trends and Development 2024

Acinetobacter Infections Treatment Market 2019 Important Research, Market Trei Development 2024

William Parker • March 13, 2019 10:27 AM EDT



The Global Acinetobacter Infections Treatment market report 2019 current critical inside data/ information and descriptive data about the Acinetobacter Infections Treatment Industry providing an overall statistical study based on market drivers, market restraints and its future prospects with growth trends, various stakeholders like investors, CEOs, traders, suppliers, SWOT analysis i.e. Strength, Weakness, Opportunities and Threat to the organization. and others. Acinetobacter Infections Treatment Market report covers the industry structure and even landscape, the problems along with business strategies and market effectiveness.

Topmost manufacturers/ Key player/ Economy by Business Leaders Leading Players of Acinetobacter Infections Treatment Market Are: Entasis Therapeutics,Roche,Adenium Biotech,Vaxdyn,Hsiri Therapeutics,Aridis Pharmaceuticals,LegoChem Biosciences,Atterx Biotherapeutics,Achaogen,Peptilogics,Sealife PHARMA,Shionogi,Techulon,Tetraphase Pharmaceuticals.. And More.....

- Son birkaç yılda, Acinetobacter infeksiyonlarının tedavisindeki küresel market %2.96'lık büyüme

Acinetobecter spp. VS Kolistin

- Bir zamanlar çok da önemsenmeyen; bir bakteri ve bir antibiyotiğin hikayesi

Acinetobacter spp.

Martinus Beijerinck 1851-1931

1911, Beijerinck

- *Micrococcus calco-aceticus*
- Topraktan “calcium acetate” ile zenginleştirilmiş besiyerinde üretmiş.

Acinetobacter spp.

- Bu tarihten sonra *Acinetobacter* cins ve türleri en az 15 farklı isim almış.

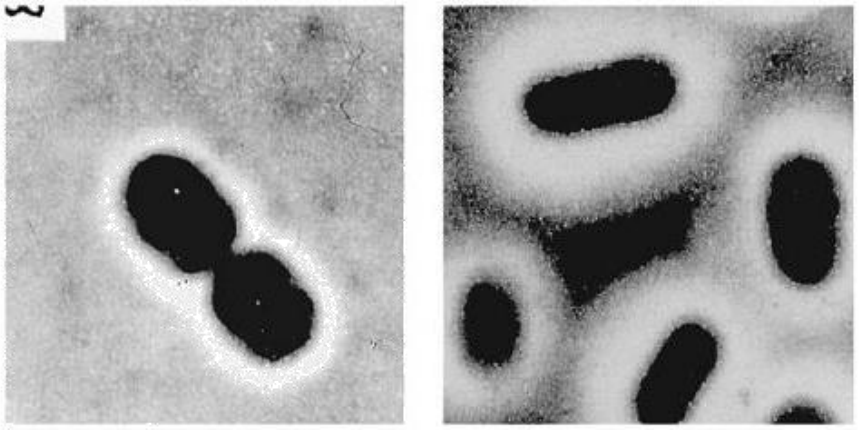


Fig. 1 Morphology of *Acinetobacter* spp
Until the 1980s, the morphology of these bacteria has led to taxonomic confusion: several names were used such as *Mima polymorpha, B. anitratum, Herella vaginicola, Moraxella...* In addition, being isolated from different infection sites, their pathogenicity was misunderstood

Diplococcus mucosus

Micrococcus calcoaceticus

Alcaligenes haemolysans

Mima polymorpha

Moraxella lwoffi

Herellea vaginicola

Bacterium anitratum

Moraxellalwoffi var. *glucidolytica*

Neisseria inogradskyi

Achromobacter anitratus,

Achromobacter mucosus

Acinetobacter spp. Nomenclatur

- Şu an için 32 farklı Acinetobacter türü tanımlanmış durumda

Acinetobacter infeksiyonların 2/3 *A. baumannii*

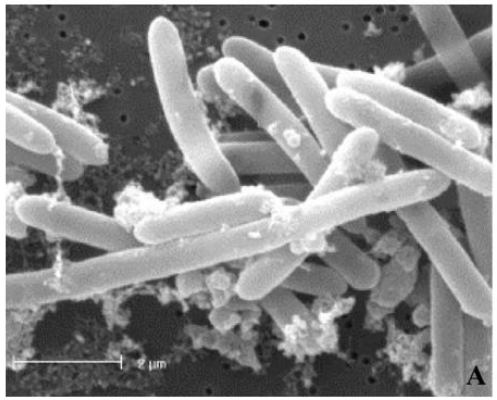
Acinetobacter nectaris
Acinetobacter nosocomialis
Acinetobacter parvus
Acinetobacter pittii
Acinetobacter radioresistens
Acinetobacter rudis
Acinetobacter schindleri
Acinetobacter soli
Acinetobacter tandoii
Acinetobacter tjernbergiae
Acinetobacter towneri
Acinetobacter ursingii
Acinetobacter venetianus

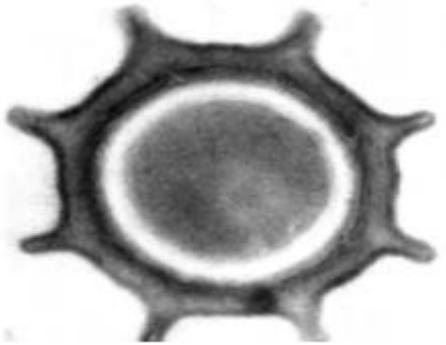
Acinetobacter nectaris
Acinetobacter nosocomialis
Acinetobacter parvus
Acinetobacter pittii
Acinetobacter radioresistens
Acinetobacter rudis
Acinetobacter schindleri
Acinetobacter soli
Acinetobacter tandoii
Acinetobacter tjernbergiae
Acinetobacter towneri
Acinetobacter ursingii
Acinetobacter venetianus

Bacillus aerosporus

- 1889, sinonim; *Bacillus polymyxa*, sporlu, aerob, nitrit fikse eden toprak basili

Mace Eugene
1856-1938





Journal of Plant Pathology (2008), 90 (3), 419-430

Bacillus aerosporus

- 1947, *Bacillus polymyxa*

No. 4060 August 23, 1947 NATURE

'Aerosporin', an Antibiotic Produced by *Bacillus aerosporus* Greer

A BACTERIUM isolated from the soil of a market garden in Surrey during February 1946 and afterwards from a Yorkshire soil and from the air has been found to produce an antibiotic of possible therapeutic importance for which, as it appears to be hitherto undescribed, the name 'Aerosporin'* is proposed. The production and properties of aerosporin are under investigation by a group of workers at the Wellcome Physiological Research Laboratories, and the purpose of the present communication is to direct attention to certain aspects of these studies, the results of which will be published in detail elsewhere.

The organism, a Gram-positive, spore-forming rod, has been identified by Mr. H. Proom with that described by Greer[1] from Chicago tap water as *Bacillus aerosporus*. *B. aerosporus* is considered by some authorities to be synonymous with *B. polymyxa* (Prazm.) Migula, and of three cultures so designated from the National Collection of Type Cultures, two (N.C.T.C. 4747, which originated from the Chicago Board of Health as *B. aerosporus*, and 1380) proved to possess similar antibiotic-producing activity, while one (N.C.T.C. 4745, from the United States and originally designated *B. asterosporus* (Meyer) Migula) did not.

Aerosporin

Aerosporin may be available in the countries listed below.

Ingredient matches for Aerosporin

Polymyxin B

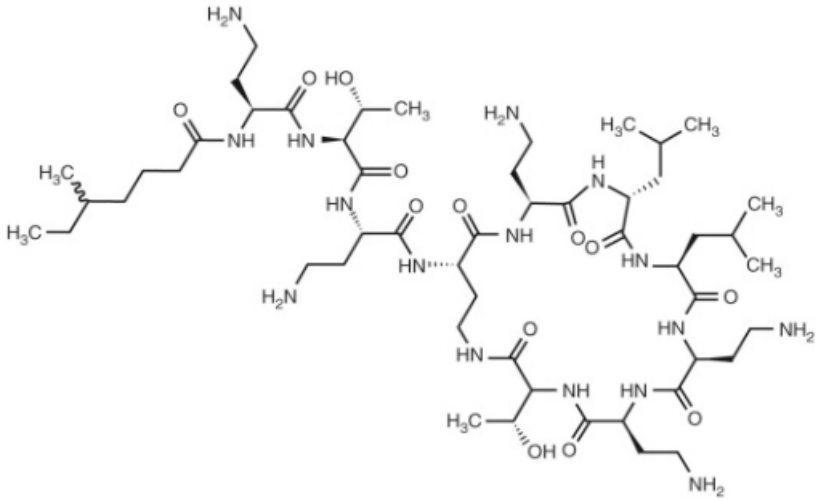
Polymyxin B is reported as an ingredient of Aerosporin in the following countries:

- India

Bacillus aerosporus

- 1950, *Bacillus polymyxa var. colistinus*

Y Koyama, A Kurosasa, A Tsuchiya, K Takakuta (1950).
"A new antibiotic 'colistin' produced by spore-forming soil bacteria". J Antibiot (Tokyo). ***3****.*



polymyxin E

Acinetobacter ile tanışma

Intensive care medicine is 60 years old: the history and future of the intensive care unit

Authors: Fiona E Kelly,[A] Kevin Fong,[B] Nicholas Hirsch[C] and Jerry P Nolan[D]

Intensive care is celebrating its 60th anniversary this year. The concept arose from the devastating Copenhagen polio epidemic of 1952, which resulted in hundreds of victims experiencing respiratory and bulbar failure. Over 300 patients required artificial ventilation for several weeks. This was provided by 1,000 medical and dental students who were employed to hand ventilate the lungs of these patients via tracheostomies. By 1953, Bjorn Ibsen, the anaesthetist who had suggested that positive pressure ventilation should be the treatment of choice during the epidemic, had set up the first intensive care unit (ICU) in Europe, gathering together physicians and physiologists to manage sick patients – many would consider him to be the 'father' of intensive care. Here, we discuss the events surrounding the 1952 polio epidemic, the subsequent development of ICUs throughout the UK, the changes that have occurred in intensive care over the past 10 years and what the future holds for the specialty.

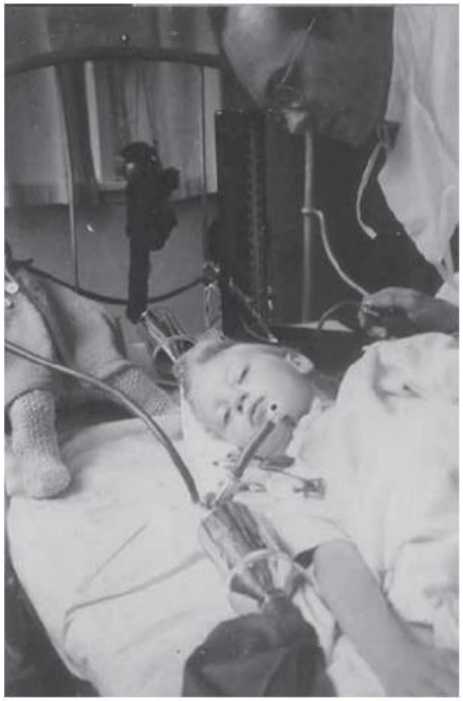


Fig 3. An 8-year-old girl being hand ventilated via a tracheostomy.

Fig 1. Coventry alligator iron lung.

Acinetobacter ile tanışma

Causative organism	No. of infections	Site of infection: Sputum	Tracheostomy	Wound swab	Urine
Coliforms	39	18	6	5	10
Ps. aeruginosa	21	11	7	2	1
Proteus spp.	9	5	1	1	2
H. influenzae	6	5	1	0	0
Strep. pneumoniae	3	3	0	0	0
Staph. aureus	21	10	4	7	0
Strep. faecalis	4	0	1	3	0
Strep. pyogenes	3	0	0	3	0
Candida spp.	14	3	11	0	0
Clostridium welchii	1	0	0	1	0
Totals	121	55	31	22	13

Plan of the Intensive Therapy Unit at the Royal Hospital, Sheffield.

Eski dost yeni düşman !!!

Journal of Hospital Infection (2009) 73, 355–363

Available online at www.sciencedirect.com

ScienceDirect

www.elsevierhealth.com/journals/jhin

REVIEW

Acinetobacter: an old friend, but a new enemy

K.J. Towner*

Department of Clinical Microbiology, Nottingham University Hospitals NHS Trust, Queen's Medical Centre, Nottingham NG7 2UH, UK

Available online 22 August 2009

KEYWORDS
Acinetobacter;
Epidemiology;
Infection control measures;
Nosocomial infection;
Therapeutic options

outbreaks can occur in such units, involving the infection or colonisation of numerous patients by specific epidemic strains of *A. baumannii*. Recently, a particular problem has concerned cross-infection of injured military patients repatriated from combat regions of the world (e.g. Iraq and Afghanistan). Carbapenems have previously been the treatment of choice for infected patients, but increasing reports worldwide now describe *A. baumannii* isolates resistant to all conventional antimicrobial regimens. Data to support therapeutic use of the limited number of new antimicrobial agents (e.g. tigecycline) with in-vitro activity against these pathogens are still very limited. Detailed advice concerning prevention and control of outbreaks caused by multidrug-resistant strains of acinetobacter is available from the UK Health Protection Agency. In addition to antibiotic prescribing policies and audit, these measures focus on reinforcing standard infection control procedures and precautions, with particular attention to thorough cleaning of patient areas to take account of the long-term survival of acinetobacter after drying and inadequate disinfection. Despite these measures, the problem continues to escalate, with many hospitals worldwide now reporting outbreaks caused by multidrug-resistant strains of acinetobacter.

Acinetobacter spp.vs Kolistin

- 1970'ler, ilk karşılaşmalar

Infections Due to Organisms of the Genus Herellea

B5W and B. Anitratum

A. KATHLEEN DALY
BOSKO POSTIC, M.D.
AND
EDWARD H. KASS, M.D., Ph.D.
BOSTON

The common bacterial infections have, until relatively recently, been caused by bacteria that were not indigenous to the host but rather were acquired by the host from external sources. The decline in prevalence of the common communicable infections such as tuberculosis, diphtheria, etc., has occurred steadily during the latter decades of the 19th century and the early decades of the 20th. This decline was perhaps accelerated by the development of specific prophylactic and therapeutic agents, although the evidence that these agents were critical to this declining pattern is far from secure.

However, accompanying the decline in the prevalence of the commonest infections of other decades has been an increase in infections due to bacteria that are indigenous to the host. The latter organisms are from genera that are usually ordinary inhabitants of the host, and, perhaps because of the widespread use of antibacterial agents, these organisms are often already resistant to many therapeutic drugs upon initial isolation. In addition, the aging population, the use of drugs such as nitrogen mustards, corticosteroids, etc., that may depress resistance to infection, and the many surgical and other therapeutic advances of recent years have increased the numbers of individuals whose tissues might be expected to be more readily invaded by bacteria. Whatever the precise explanation, there can be little doubt that bacterial infections in the immediate future will center around autochthonous bacteria that cause infection in hosts that have harbored these bacteria for years.

Bacteria of the genus Herellea [1,2] represent an example of this general problem. These organisms are ordinarily commensals of the gastrointestinal, genital, and respiratory tracts of human beings. They have been

From the Mallory Institute of Pathology, Thorndike Memorial Laboratory, Second and Fourth (Harvard) Medical Services, Boston City Hospital, and Department of Bacteriology and Immunology, Harvard Medical School.

Aided by grants from the National Institutes of Health, United States Public Health Service.

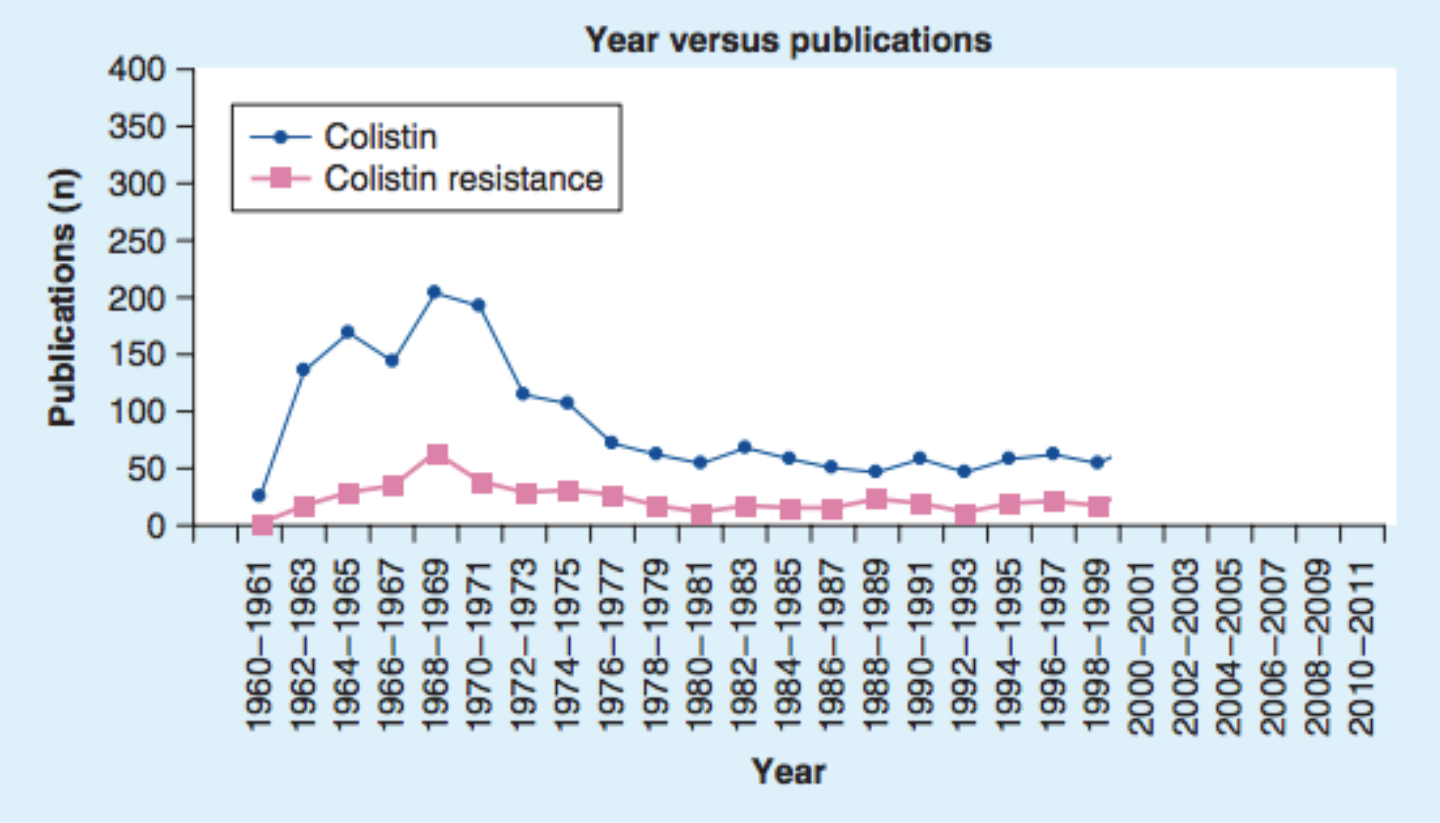
Clinical Data

During the past 3 years, 18 patients have been found to yield organisms of the genus Herellea from blood cultures or other body fluids in association with severe infections. Their case histories are presented briefly:

CASE 1.—A 55-year-old male suffered cervical compression of the spinal cord after a fall. A cervical laminectomy was performed in an attempt to relieve the pressure on the cord, and within 2 days after this procedure the operative wound was found to have become infected. Meningitis developed subsequently. Herellea (Type I) was recovered from the wound on 3 occasions, from the cerebrospinal fluid on 4, and from the urine once. The organisms were uniformly resistant to penicillin, streptomycin, tetracycline, chloramphenicol, and sensitive to polymyxin, colistin sulfate, kanamycin, and neomycin. The patient received polymyxin

Acinetobacter spp.vs Kolistin

- Oldukça etkili olmasına rağmen nefrotoksisitesi ve nöroksisitesi nedeniyle kullanımı sınırlandırıldı.

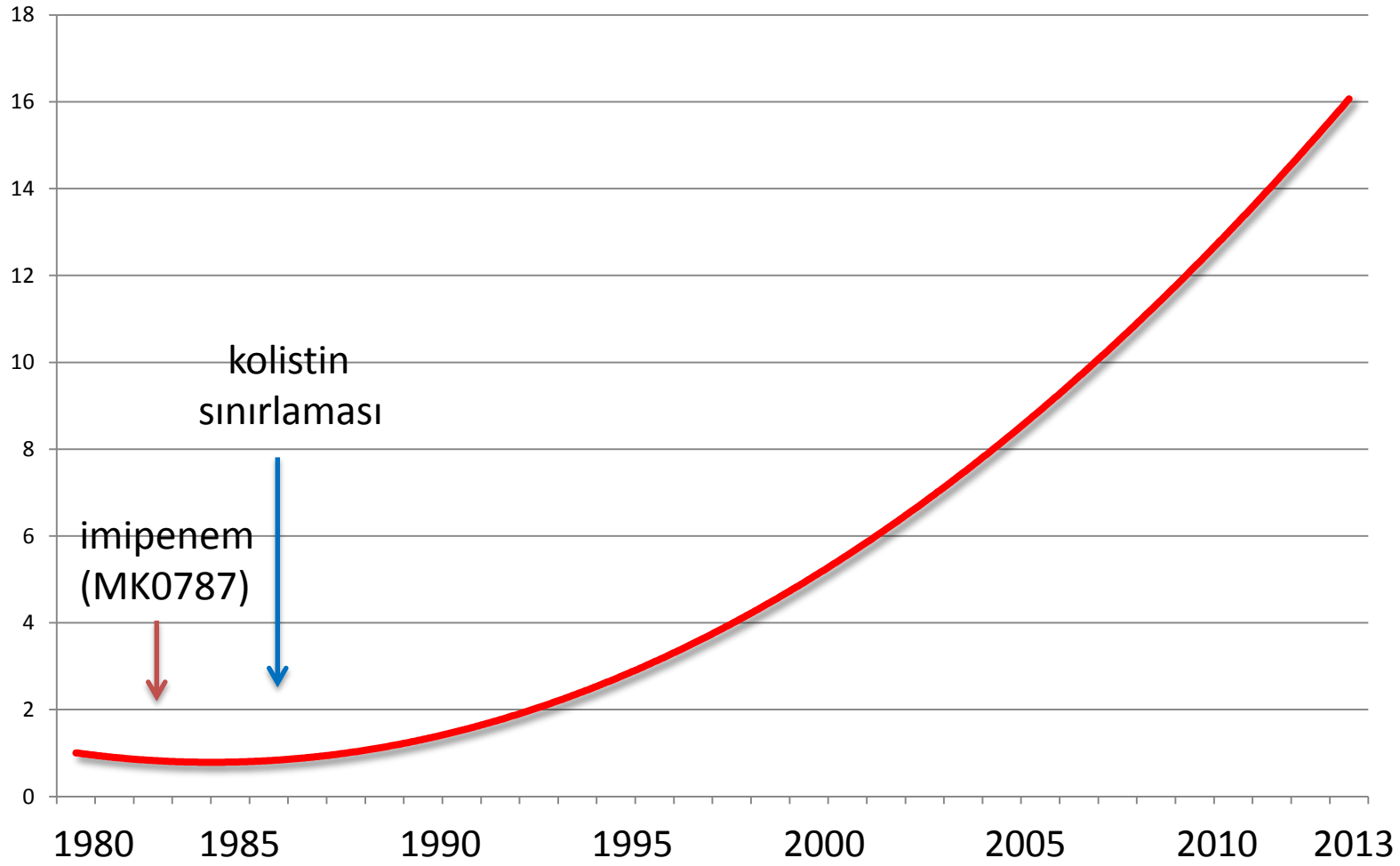


Expert Rev Anti Infect Ther. 2012 Aug;10(8):917-34

Acinetobacter'in yükselişi

- PubMed'de son 40 yılda 500'den fazla

Acinetobacter spp. salgını yayın haline gelmiş !!!



Acinetobacter'in yükselişi

- Özellikle 90'lı yıllardan sonra infeksiyonlarda artış

MDR

Sefalosporinler
B-laktam/b-laktam inhibitors
Aminoglikozitler
Florakinolonlar

XDR

MDR +
Karbapenemler

Acinetobacter'in yükselişi

- CESAR 2016 raporu, MDR *A. baumannii*

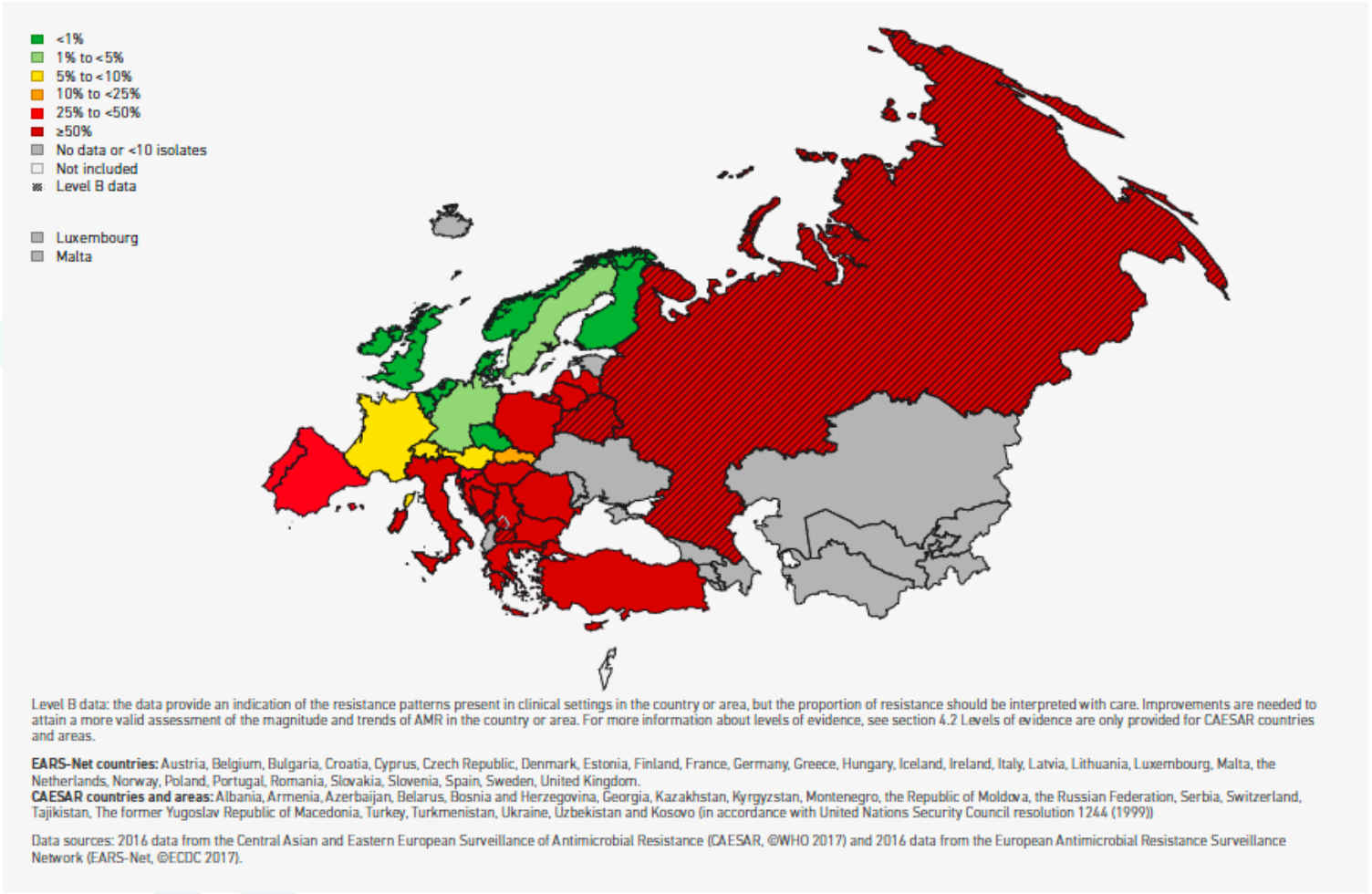


Fig. 7.5 Multidrug-resistant (combined resistance to fluoroquinolones, aminoglycosides and carbapenems) *Acinetobacter* spp. in the European Region (EARS-Net and CAESAR), 2016

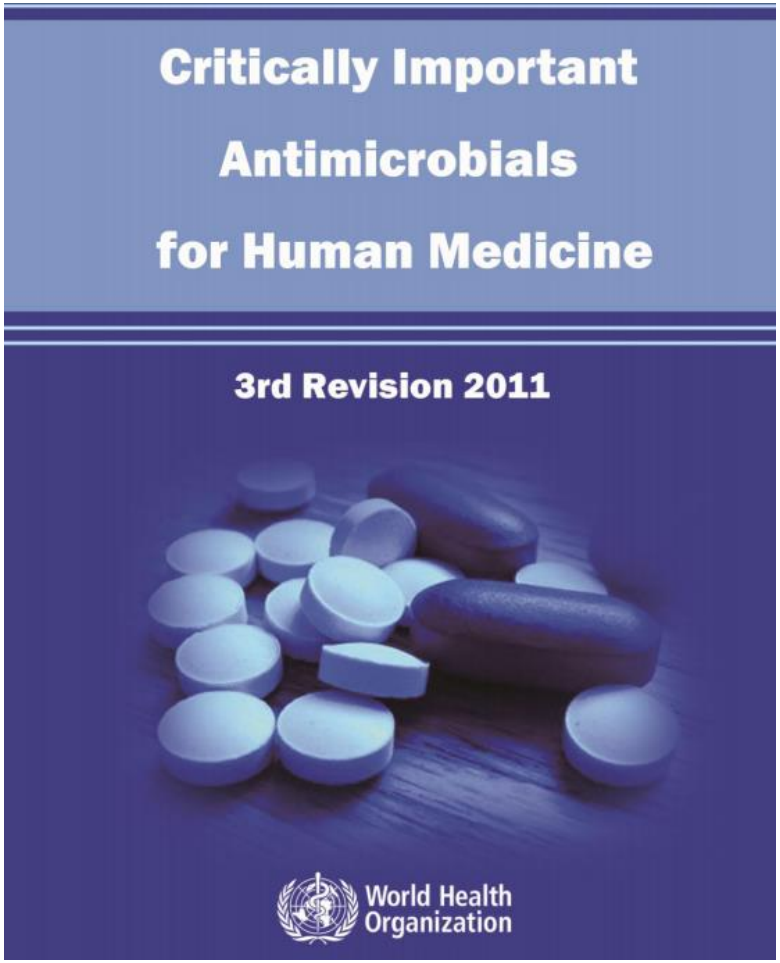
Level B data: the data provide an indication of the resistance patterns present in clinical settings in the country or area, but the proportion of resistance should be interpreted with care. Improvements are needed to attain a more valid assessment of the magnitude and trends of AMR in the country or area. For more information about levels of evidence, see section 4.2 Levels of evidence are only provided for CAESAR countries and areas.

EARS-Net countries: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, United Kingdom.
CAESAR countries and areas: Albania, Armenia, Azerbaijan, Belarus, Bosnia and Herzegovina, Georgia, Kazakhstan, Kyrgyzstan, Montenegro, the Republic of Moldova, the Russian Federation, Serbia, Switzerland, Tajikistan, The former Yugoslav Republic of Macedonia, Turkey, Turkmenistan, Ukraine, Uzbekistan and Kosovo (in accordance with United Nations Security Council resolution 1244 (1999))

Data sources: 2016 data from the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR, ©WHO 2017) and 2016 data from the European Antimicrobial Resistance Surveillance Network (EARS-Net, ©ECDC 2017).

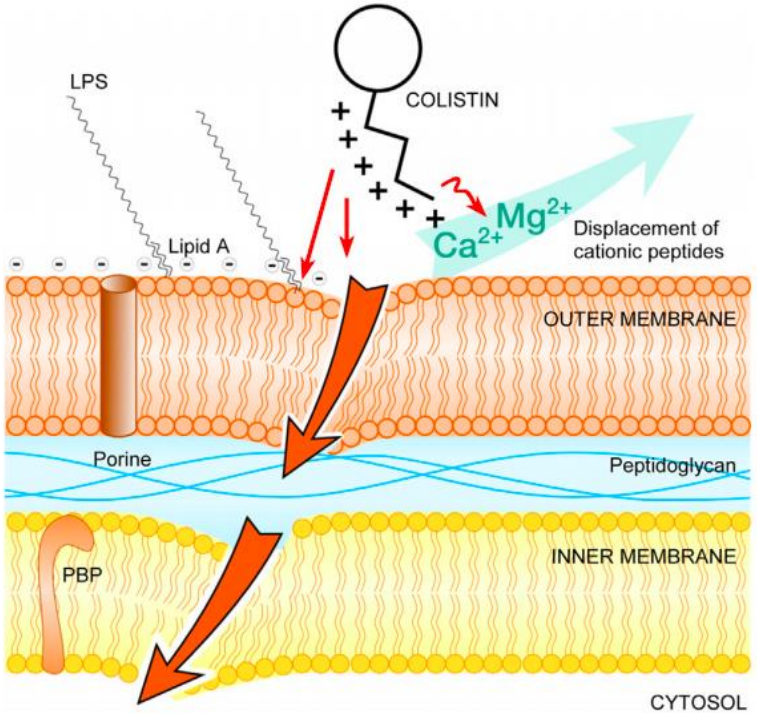
Kolistinin yükselişi

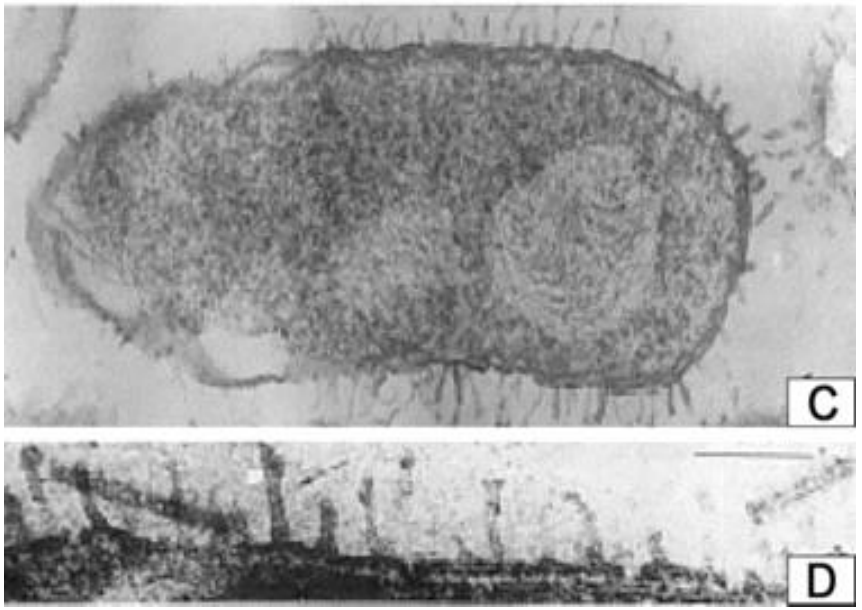
- 2011, yılında WHO tarafından kritik önemi olan antibiyotikler arasında sınıflandırıldı.



Acinetobacter spp VS Kolistin

- Hücrenin Mg^{+2} ve Ca^{+2} ile yer değiştirir.
- Hidrofilik zincirin de katkısıyla membran geçirgenliği bozulur, hücre içeriği dışarı boşalır ve bakteri ölür.





Journal of Infection (2014) 69, 1e12
Clin Infect Dis. 2005 May 1;40(9):1333-41. Epub

Acinetobacter spp VS Kolistin

- 1999, İlk kolistin dirençli *A. baumannii* Çek Cumhuriyetinden bildirildi.

Acta Univ Palacki Olomuc Fac Med. 1999;142:73-7.

Characteristics of Acinetobacter strains (phenotype classification, antibiotic susceptibility and production of beta-lactamases) isolated from haemocultures from patients at the Teaching Hospital in Olomouc.

Hejnar P[1], Kolár M, Hájek V.

Author information

Abstract

A total of 85 strains of the genus Acinetobacter were isolated from haemocultures at the Institute of Microbiology of the Teaching Hospital in Olomouc over the period January 1993 to June 1997. Sixty-two (73.0%) strains of the Acinetobacter calcoaceticus-baumannii complex (Acb complex) were the most frequent. In 3 (3.5%) strains it was impossible to decide whether they belonged to the Acb complex. Other acinetobacter species were represented by 20 (23.5%) strains. The greatest amount (28.2%) of these strains was collected from the Clinic of Internal Medicine. Leukemias, lymphomas and myelodysplastic syndromes were the most frequent clinical diagnoses (20.0%) of the patients with a positive haemoculture. The most effective antimicrobial preparations tested were as follows: meropenem (98.8% of susceptible strains), colistin (94.1%), quinolones (90.6-94.1% according to the type of agent) and amikacin (91.8%). The Acb complex strains were less susceptible to antimicrobial agents than other acinetobacters. Production of inductive chromosomal beta-lactamases AmpC was proved in 42 (49.4%) strains whilst no occurrence of extended-spectrum beta-lactamases (ESBL) in the isolated organisms was recorded.

Acinetobacter spp VS Kolistin

- 1999, İk kolistin dirençli *A. baumannii* Çek Cumhuriyetinden bildirildi

MDR
Sefalosporinler
B-laktam/b-laktam inhibitors
Aminoglikozitler
Florakinolonlar

XDR
MDR +
Karbapenmeler

PDR
XDR +
Kolistin

Acinetobacter spp VS Kolistin

- Tüm dünyadan kolistin direnci bildirilmeye başlandı

Journal of Hospital Infection 98 (2018) 260–263

Available online at www.sciencedirect.com

Journal of Hospital Infection

journal homepage: www.elsevier.com/locate/jhin

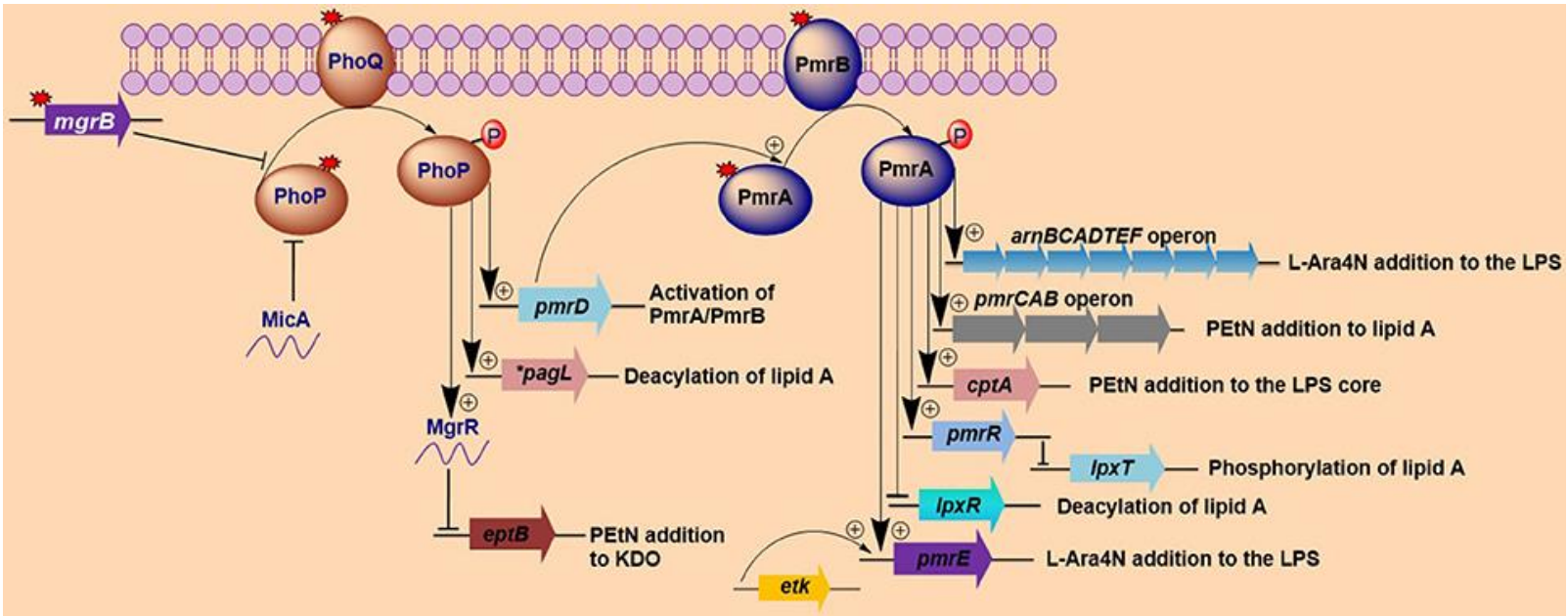
Table I

Antibiotic resistance rates in 1556 episodes of healthcare-associated Gram-negative bacteraemia

Species	*N* (%) of isolates that were resistant to:				
	Carbapenems	Fluoroquinolones	Third-generation cephalosporins	Aminoglycosides	Colistin
Acinetobacter baumannii N = 437	401 (91.8)	389 (89.0)	410 (93.8)	310 (70.9)	9 (2.1)
Klebsiella pneumoniae N = 416	216 (51.9)	266 (63.9)	320 (76.9)	200 (48.1)	67 (16.1)
Escherichia coli N = 339	34 (10.0)	189 (55.8)	203 (59.9)	103 (30.4)	3 (0.9)
Pseudomonas aeruginosa N = 205	88 (42.9)	102 (49.8)	103 (50.2)	65 (31.7)	18 (8.8)
Enterobacter cloacae N = 159	37 (23.3)	46 (28.9)	59 (37.1)	51 (32.1)	9 (5.7)

Acinetobacter spp VS Kolistin

- *A. baumannii*'de 4 ana kolistin direnç mekanizması tanımlanmıştır
  - Lipit A yapısına fosfoetonolamin eklenmesi
  - Lipit A sentezinden sorumlu gen bölgesinin mutasyonu ile LPS'nin tamamen kaybı,
  - LPS sentezinde rolü olan kofaktörlerin ekspresyonunun azaltılması
  - LPS'nin dış membrana taşınmasında görev alan proteinlerin ekspresyonunun azaltılması



Clin Infect Dis. 2005 May 1;40(9):1333-41. Epub

A. baumannii'nin kolistin bağımlılığı

- *A. baumannii*'nin kolistin bağımlı hale gelebiliyor.

J Antimicrob Chemother 2016
doi:10.1093/jac/dkw121
Advance Access publication 13 April 2016

High rate of colistin dependence in *Acinetobacter baumannii*

Yoon-Kyoung Hong[1], Ji-Young Lee[1], Yu Mi Wi[2] and Kwan Soo Ko[1]*

[1]*Department of Molecular Cell Biology, Sungkyunkwan University School of Medicine, Suwon, South Korea;* [2]*Division of Infectious Diseases, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon, South Korea*

*Corresponding author. Tel: +82-31-299-6223; Fax: +82-31-299-6229; E-mail: ksko@skku.edu

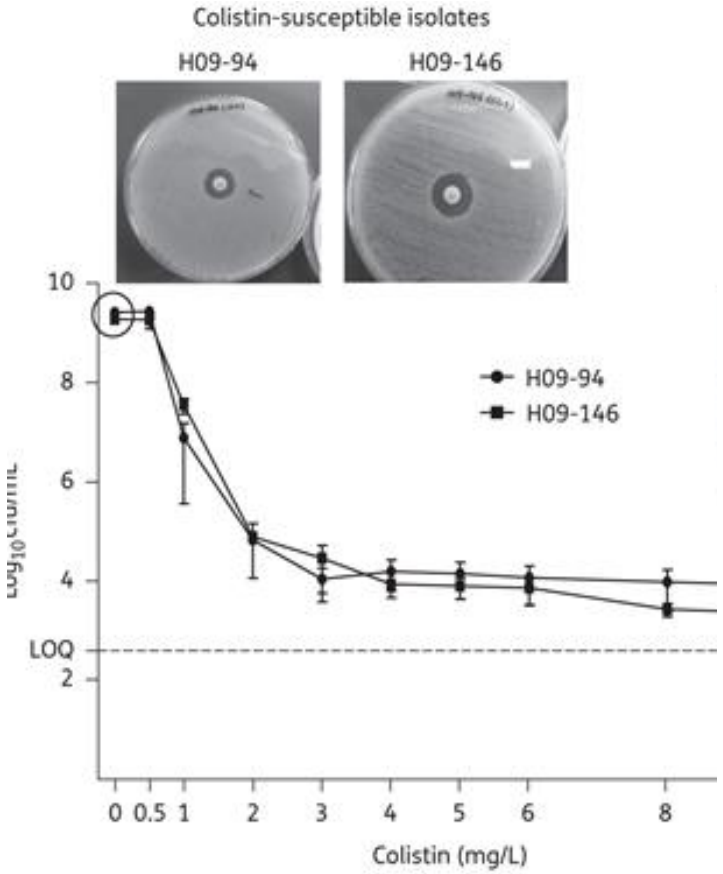
Sir,

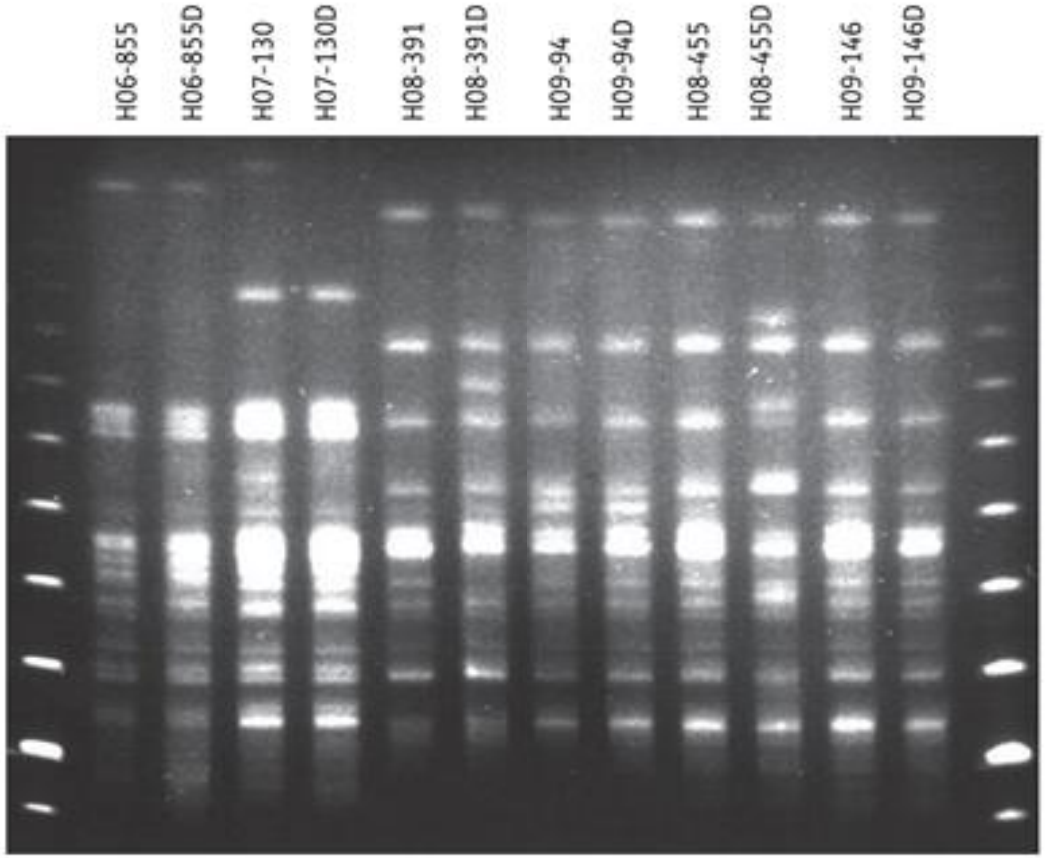
Colistin is currently considered the last treatment option for MDR *Acinetobacter* infections. Although the current resistance rates to colistin are relatively low, they are increasing and threaten to become a serious problem worldwide.[1] In this study, we report the *in vitro* development of colistin dependence in many colistin-susceptible *Acinetobacter baumannii* isolates after exposure to colistin.

Initially, we performed population analysis for some colistin-susceptible isolates collected from two different hospitals, Samsung Medical Center (Seoul, Korea) and Samsung Changwon Hospital (Changwon, Korea). We plated 50 μL of bacterial cell suspension (~10^9 cfu/mL) and its serial dilutions on Mueller–Hinton agar containing 0, 0.5, 1, 2, 3, 4, 5, 6, 8 and 10 mg/L colistin sulphate. Surviving colonies at 10 mg/L were plated on Mueller–Hinton agar with discs of 10 mg colistin. We found that the bacteria grew only near the disc (Figure 1a), which indicated colistin dependence. Next, we performed colistin susceptibility testing for 170 *A. baumannii* isolates collected from ICUs of Korean hospitals in 2015 and examined colistin-susceptible isolates for colistin dependence by using population analysis and the colistin disc method.

A. baumannii'nin kolistin bağımlılığı

- İki farklı hastaneden kolistine duyarlı izolatlar için popülasyon analizi.
- 0, 0.5, 1, 2, 3, 4, 5, 6, 8 ve 10 mg / L kolistin sülfat içeren Mueller-Hinton agar üzerine





A. baumannii'nin kolistin bağımlılığı

- Kolistin bağımlılığı daha önce *A. baumannii-Acinetobacter calcoaceticus* kompleksi izolatında rapor edildi. Bu çalışmada, 19 izolattan sadece 1'i kolistin bağımlılığı geliştirmiştir.

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 2007, p. 4529–4530 Vol. 51, No. 12
0066-4804/07/$08.00+0 doi:10.1128/AAC.01115-07

Letters to the Editor

Development of Colistin-Dependent *Acinetobacter baumannii-Acinetobacter calcoaceticus* Complex

The phenomenon of antimicrobial agent dependence has been infrequently described, with vancomycin-dependent *Enterococcus faecalis* first reported in 1994 (3) and then occasionally thereafter (7, 9). Although heteroresistance of the *Acinetobacter baumannii-Acinetobacter calcoaceticus* complex (ABC) to colistin has been described, the dependence of the ABC on antimicrobial agents has not been reported (5). We describe the isolation of a colistin-dependent subpopulation of the ABC from a clinical isolate.

A 77-year-old diabetic male was admitted with calcaneal osteomyelitis and bacteremia due to multidrug-resistant ABC. He was treated with colistin (colistimethate sodium, 125 mg) intravenously every 12 h for 9 days. A calcaneus bone specimen was submitted for culture during a below-the-knee amputation on the fifth day of colistin therapy. The ABC was isolated and identified using the Vitek system (bioMerieux, Inc., Durham, NC) and was stored frozen in the clinical laboratory. This patient isolate and 18 other ABC clinical isolates were subsequently subcultured twice on sheep blood agar, and colistin susceptibility was confirmed by broth microdilution (BMD) MIC testing using in-lab-prepared frozen panels. The panels contained colistin, polymyxin B, and 10 other drugs (Table 1). BMD was performed according to the Clinical and Laboratory Standards Institute method with cation-adjusted Mueller-Hinton broth, a standard inoculum density of 5×10^5 CFU/ml, and incubation at 35°C for 20 to 24 h (1). Quality control organisms *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 were tested simultaneously, and results were within acceptable limits (2).

For population analysis studies, colistin sulfate (Sigma, St. Louis, MO) was added to molten Mueller-Hinton agar (Difco, BD, Sparks, MD) to produce plates containing 8 μg/ml colistin. A suspension of each patient isolate was prepared in 0.9% saline to a 5 McFarland standard, and 100-μl aliquots were used to inoculate each of two colistin plates. The plates were

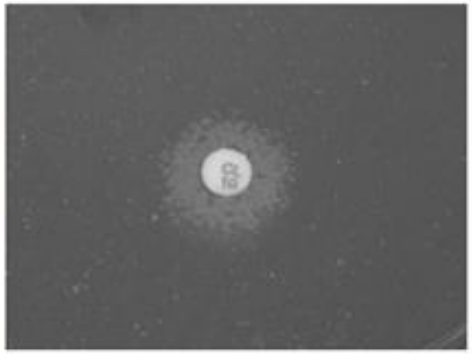
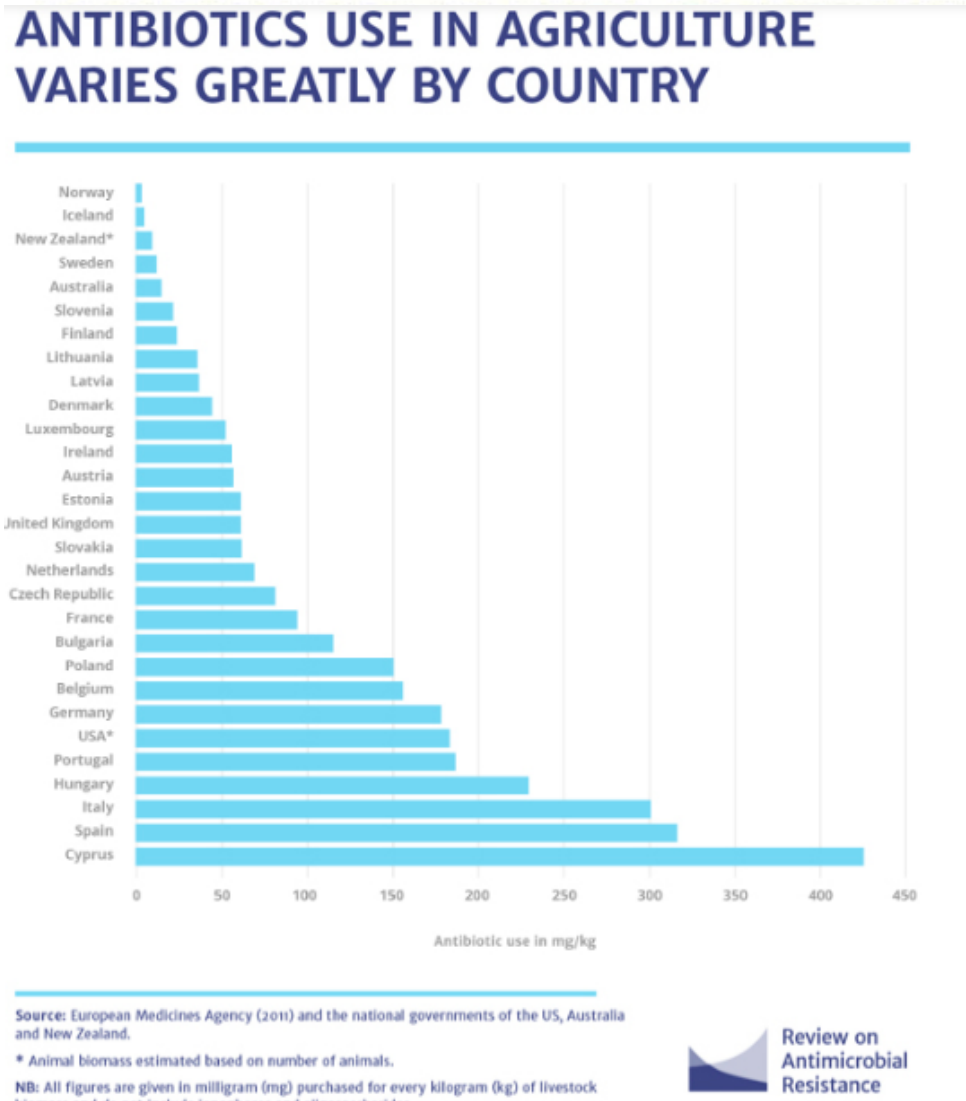


FIG. 1. Kirby-Bauer plate demonstrating colistin-dependent growth pattern. The diameter of the zone of growth is 16 mm.

- lpxA , lpxC ve lpxD'deki mutasyonlara sahip bazı LPS-eksikliği bulunan suşlarda tanımlandı

Kolistinin Aşırı Tüketimi

- Hayvanlar için antibiyotikler daha fazla kullanılıyor.



Plazmit Aracılı Aktarılabilir Kolistin Direncii

- 2015, ilk kez Çin'den plazmit aracılı mcr-1 geni bildirildi.

Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study

Yi-Yun Liu, Yang Wang*, Timothy R Walsh, Ling-Xian Yi, Rong Zhang, James Spencer, Yohei Doi, Guobao Tian, Baolei Dong, Xianhui Huang, Lin-Feng Yu, Danxia Gu, Hongwei Ren, Xiaojie Chen, Luchao Lv, Dandan He, Hongwei Zhou, Zisen Liang, Jian-Hua Liu, Jianzhong Shen*

Summary

Background Until now, polymyxin resistance has involved chromosomal mutations but has never been reported via horizontal gene transfer. During a routine surveillance project on antimicrobial resistance in commensal *Escherichia coli* from food animals in China, a major increase of colistin resistance was observed. When an *E coli* strain, SHP45, possessing colistin resistance that could be transferred to another strain, was isolated from a pig, we conducted further analysis of possible plasmid-mediated polymyxin resistance. Herein, we report the emergence of the first plasmid-mediated polymyxin resistance mechanism, MCR-1, in Enterobacteriaceae.

Methods The *mcr-1* gene in *E coli* strain SHP45 was identified by whole plasmid sequencing and subcloning. MCR-1 mechanistic studies were done with sequence comparisons, homology modelling, and electrospray ionisation mass spectrometry. The prevalence of *mcr-1* was investigated in *E coli* and *Klebsiella pneumoniae* strains collected from five provinces between April, 2011, and November, 2014. The ability of MCR-1 to confer polymyxin resistance in vivo was examined in a murine thigh model.

Findings Polymyxin resistance was shown to be singularly due to the plasmid-mediated *mcr-1* gene. The plasmid carrying *mcr-1* was mobilised to an *E coli* recipient at a frequency of 10^{-1} to 10^{-3} cells per recipient cell by conjugation, and maintained in *K pneumoniae* and *Pseudomonas aeruginosa*. In an in-vivo model, production of MCR-1 negated the efficacy of colistin. MCR-1 is a member of the phosphoethanolamine transferase enzyme family, with expression in *E coli* resulting in the addition of phosphoethanolamine to lipid A. We observed *mcr-1* carriage in *E coli* isolates collected from 78 (15%) of 523 samples of raw meat and 166 (21%) of 804 animals during 2011–14, and 16 (1%) of 1322 samples from inpatients with infection.

Interpretation The emergence of MCR-1 heralds the breach of the last group of antibiotics, polymyxins, by plasmid-mediated resistance. Although currently confined to China, MCR-1 is likely to emulate other global resistance mechanisms such as NDM-1. Our findings emphasise the urgent need for coordinated global action in the fight against pan-drug-resistant Gram-negative bacteria.

Funding Ministry of Science and Technology of China, National Natural Science Foundation of China.

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See Comment page 132

*Contributed equally

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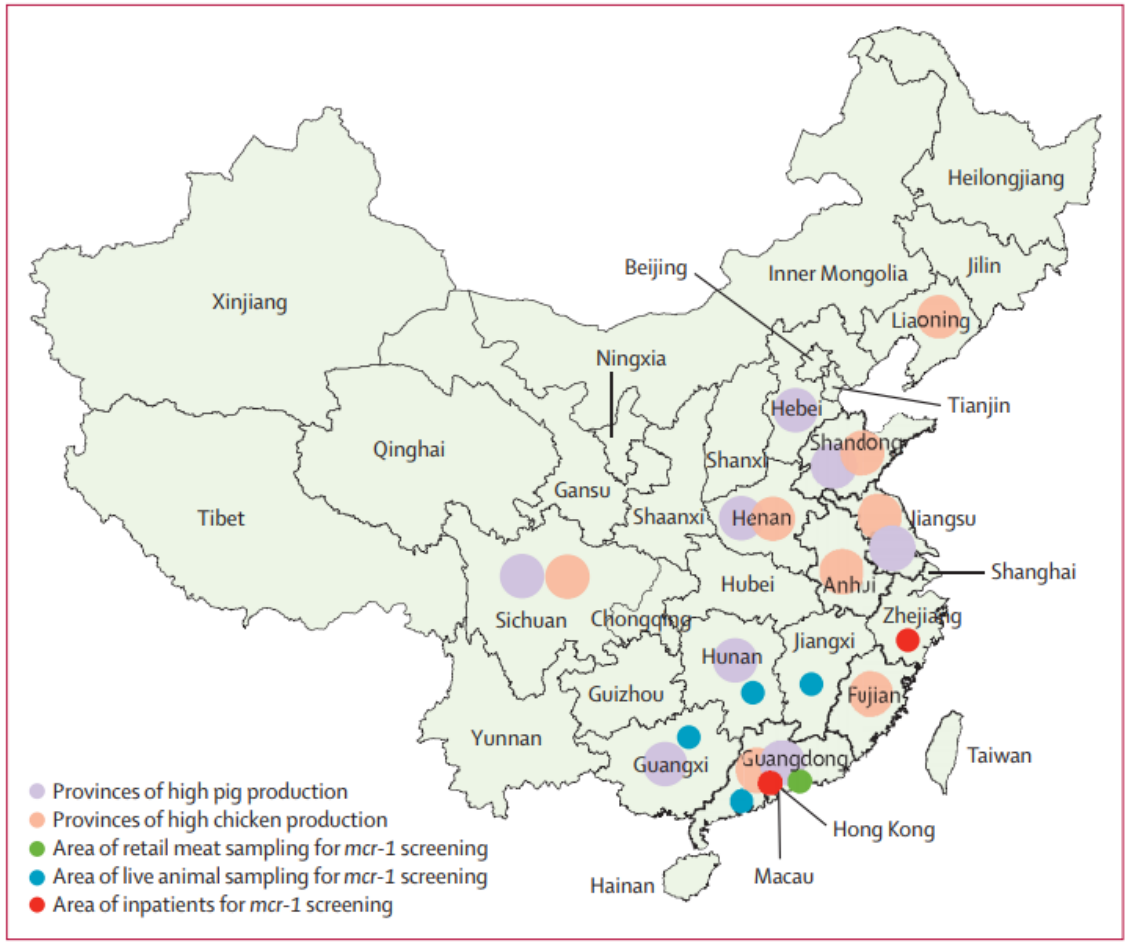
Plazmit Aracılı Aktarılabilir Kolistin Direnci

- Örnekler 2011-2014 yılları arasında toplanmış,
  - 523 çiğ et örneğinden 78'inde (% 15),
  - 804 hayvan izolatının 166'sında (% 21)
  - 1322 insan izolatının 15'inde (% 1) mcr-1 tespit edilmiş



Plazmit Aracılı Aktarılabilir Kolistin Direnci

- Mcr-1 genini taşıyan pHNHSP45 plazmidi
- Konjugatif ve yüksek sıklıkla konjugasyon yapabilen bir plazmid

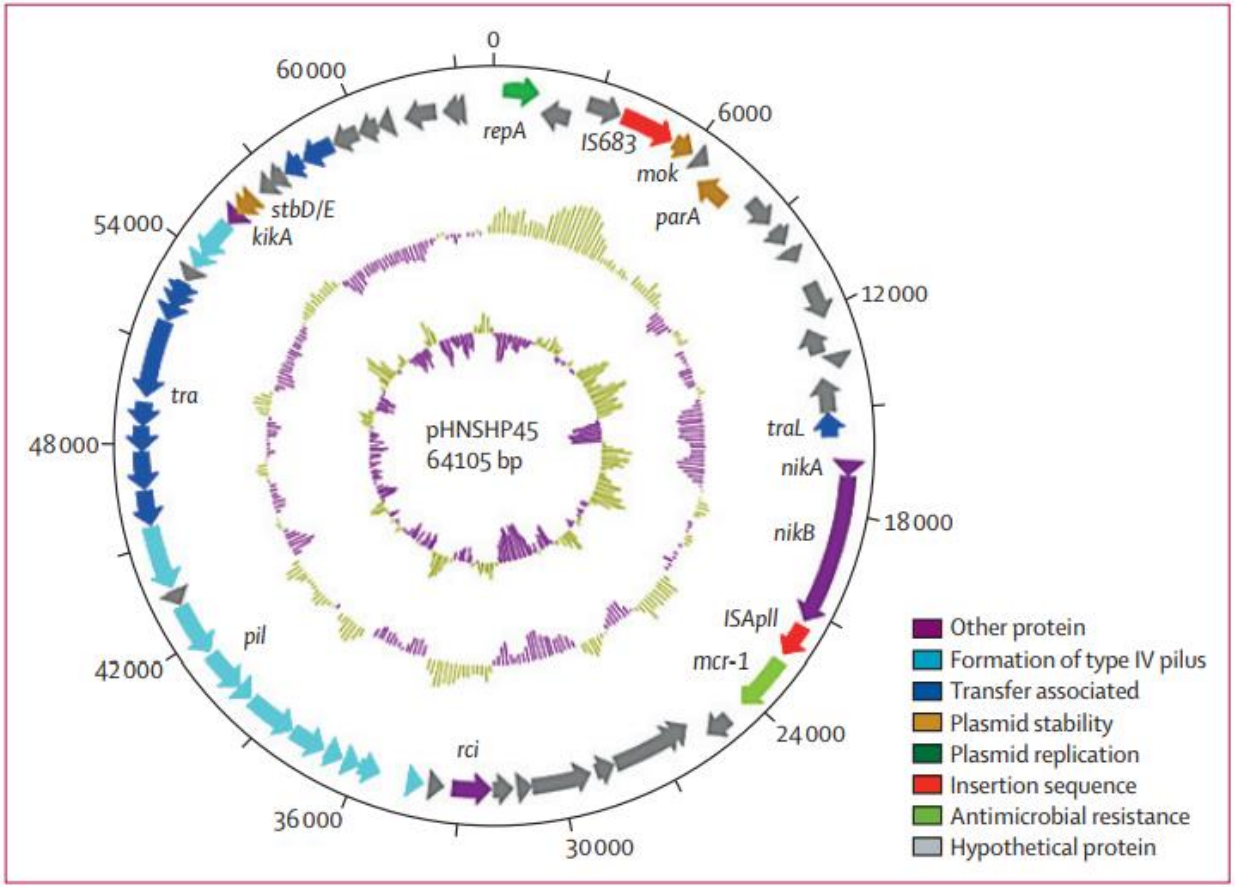


Figure 2: **Structure of plasmid pHNSHP45 carrying *mcr-1* from *Escherichia coli* strain SHP45**

Plazmit Aracılı Aktarılabilir Kolistin Direnci

- *Mcr-1* taşıyan plazmidler;

  ESBL ve karbapenemaz genlerini de içerebildiği tespit edilmiş.

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Complete Sequences of *mcr-1*-Harboring Plasmids from Extended-Spectrum-β-Lactamase- and Carbapenemase-Producing *Enterobacteriaceae*

Aiqing Li,[a] Yong Yang,[a] Minhui Miao,[a] Kalyan D. Chavda,[b] José R. Mediavilla,[b] Xiaofang Xie,[a] Ping Feng,[a] Yi-Wei Tang,[c] Barry N. Kreiswirth,[b] Liang Chen,[b] Hong Du[a]

Department of Clinical Laboratory, The Second Affiliated Hospital of Soochow University, Suzhou, Jiangsu, China[a]; Public Health Research Institute Tuberculosis Center, New Jersey Medical School, Rutgers University, Newark, New Jersey, USA[b]; Department of Laboratory Medicine, Memorial Sloan Kettering Cancer Center, New York, New York, USA[c]

Here we completely sequenced four *mcr-1*-haboring plasmids, isolated from two extended-spectrum-β-lactamase (ESBL)-producing *Escherichia coli* and two carbapenemase-producing *Klebsiella pneumoniae* clinical isolates. The *mcr-1*-harboring plasmids from an *E. coli* sequence type 2448 (ST2448) isolate and two *K. pneumoniae* ST25 isolates were identical (all pMCR1-IncX4), belonging to the IncX4 incompatibility group, while the plasmid from an *E. coli* ST2085 isolate (pMCR1-IncI2) belongs to the IncI2 group. A nearly identical 2.6-kb *mcr-1-pap2* element was found to be shared by all *mcr-1*-carrying plasmids.

Plazmit Aracılı Aktarılabilir Kolistin Direnci

- *Mcr-1 ;* phosphoethanolamine transferase enzim ailesinden

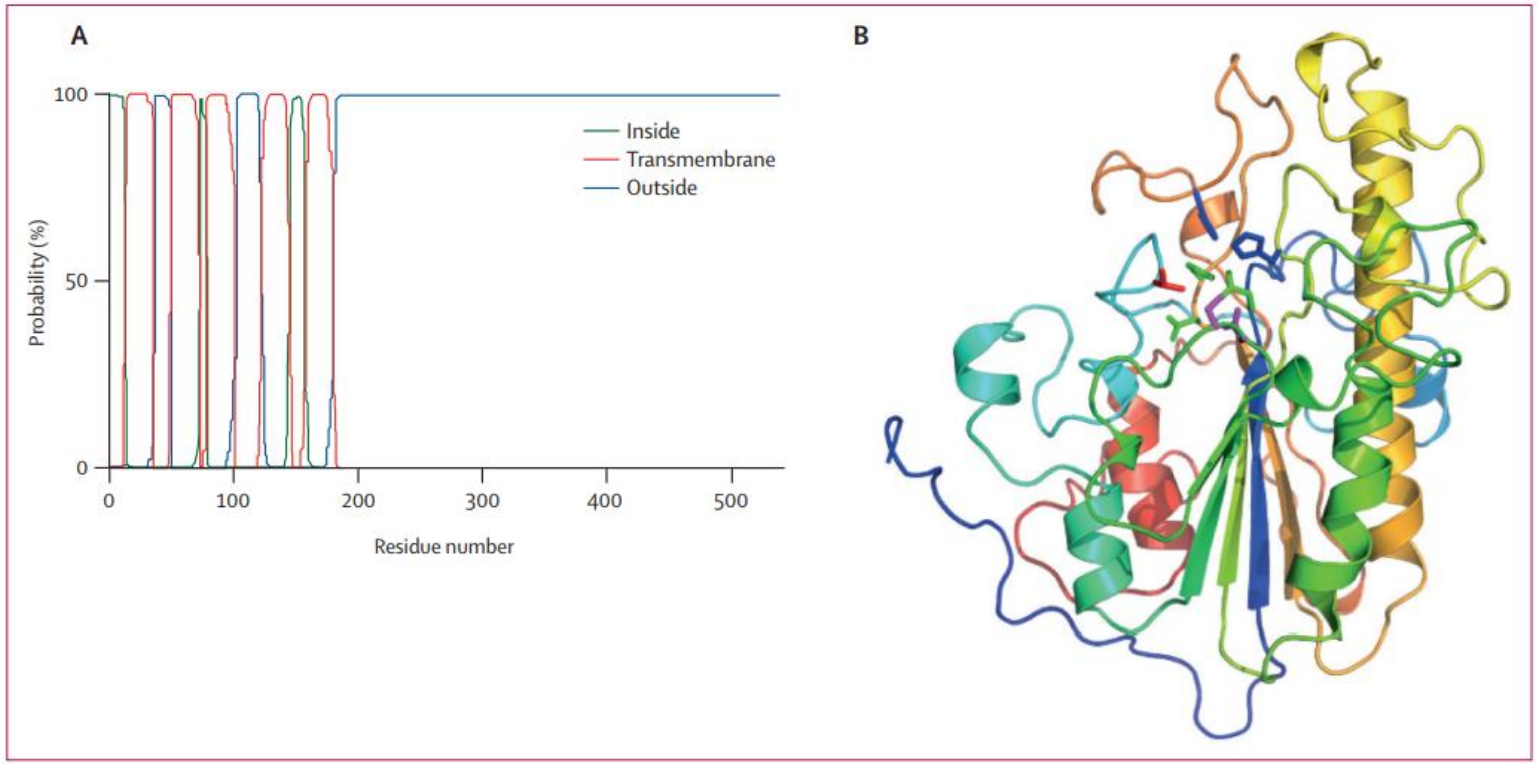


Figure 3: Hydropathy plot predicting five transmembrane α-helices in the N-terminal 200 aminoacids of MCR-1 (A) and i-Tasser homology modelling analysis of MCR-1 based on models from LptA (*Neisseria meningitidis*; Protein Data Bank ID 4KAY) and EptC (*Campylobacter jejuni*; Protein Data Bank ID 4TNO; B)

Mcr-1

- Muhtemelen *phosphatidylethanolamine transferase*

UniProt

UniProtKB | Advanced | Search

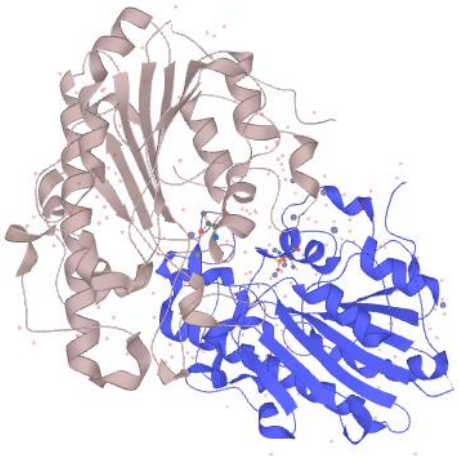
BLAST | Align | Retrieve/ID mapping | Peptide search | Help | Contact

UniProtKB - A0A0R6L508 (MCR1_ECOLX)

Basket

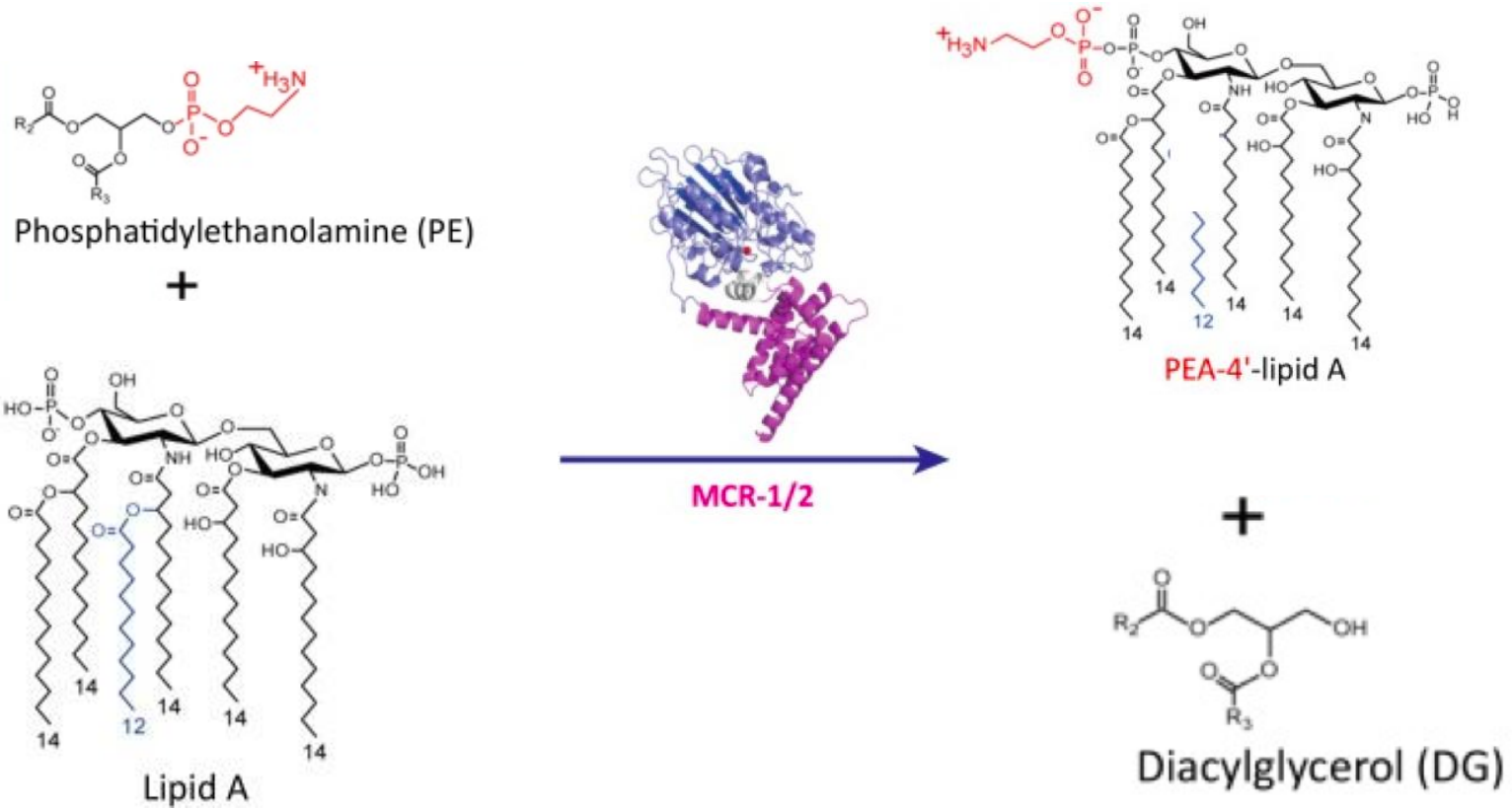
Names & Taxonomy

Protein names	*Recommended name:* **Probable phosphatidylethanolamine transferase Mcr-1** (EC:2.7.-.-) *Alternative name(s):* • Polymyxin resistance protein MCR-1 (1 Publication)
Gene names	*Name:***mcr1** Synonyms:mcr-1 (1 Publication) ORF Names:APZ14_31440
Encoded on	Plasmid pHNSHP45 (0 Publication)
Organism	Escherichia coli
Taxonomic identifier	562 [NCBI]
Taxonomic lineage	Bacteria › Proteobacteria › Gammaproteobacteria › Enterobacterales › Enterobacteriaceae › Escherichia
Proteomes	UP000054864 Component: Unassembled WGS sequence



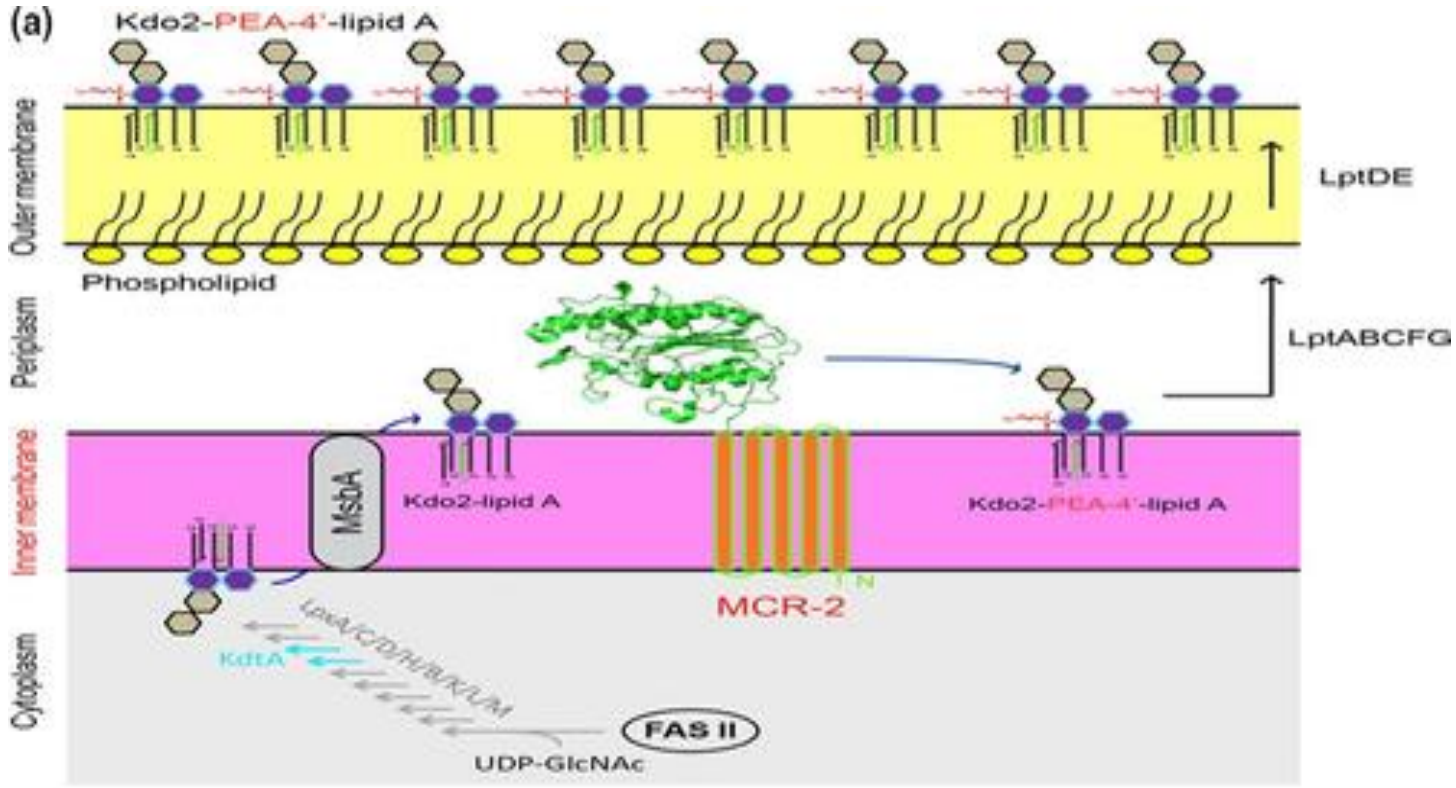
Mcr-1

- Mcr-1/2; enzimi hangi reaksiyonu katalizliyor?



Mcr-1

- Mcr-1/2 enzimi LPS/LipidA'yı nerede buluyor ?

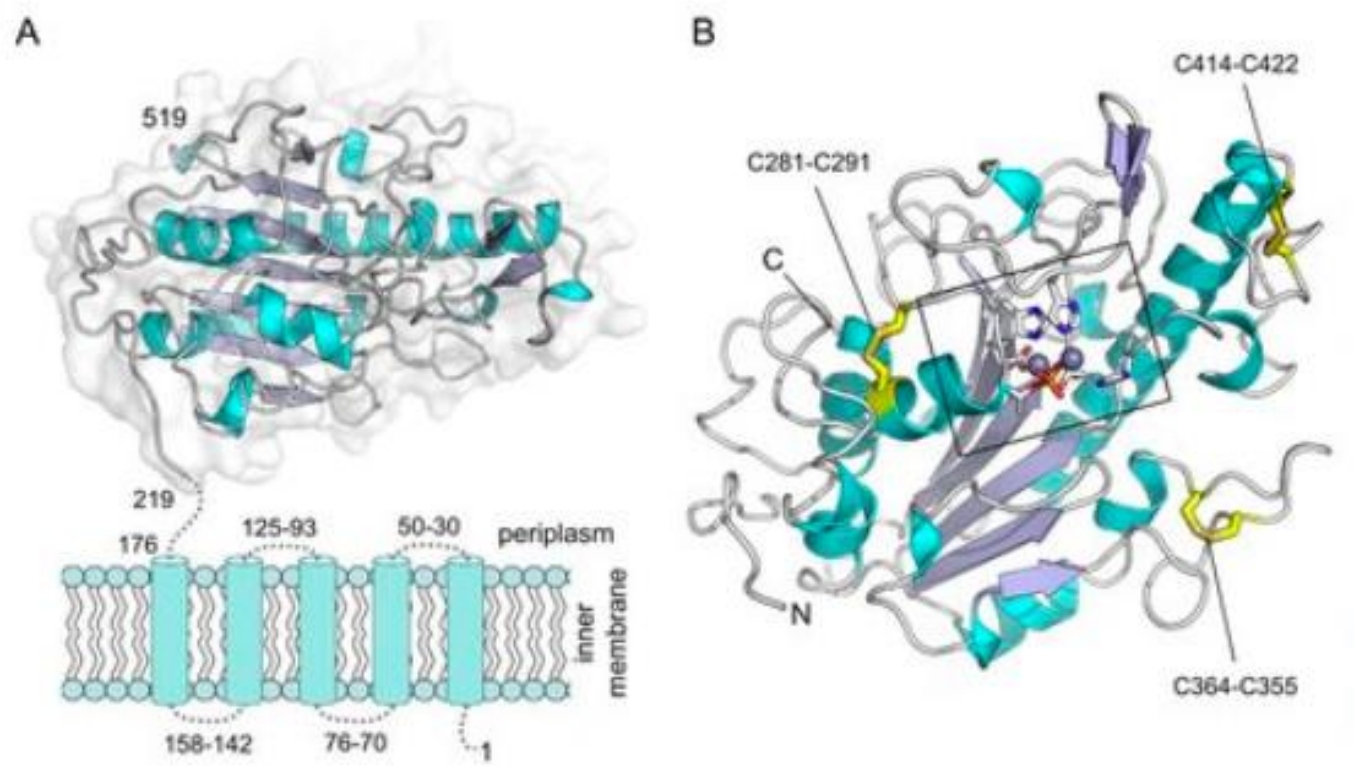


MicrobiologyOpen. 2018;e682. https://doi.org/10.1002/mbo3.682

Mcr-1

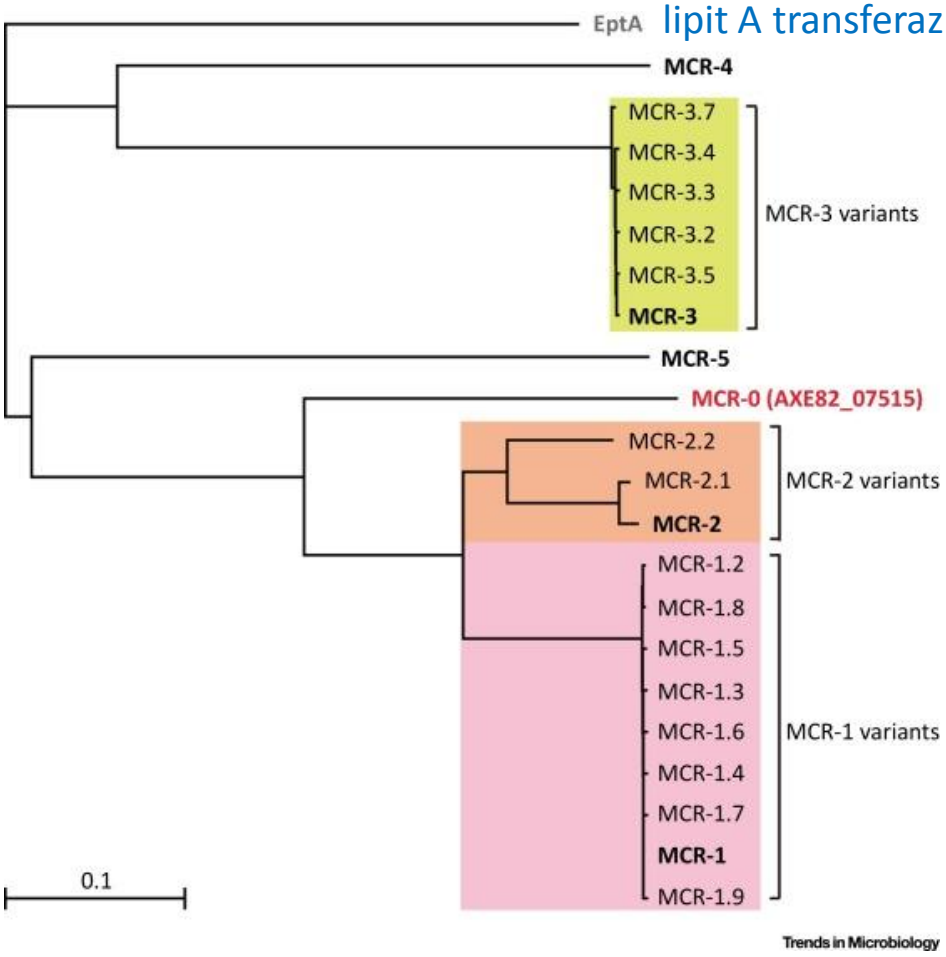
- Mcr-1 enzimi periplasmik alana nasıl yerleşiyor?

www.nature.com/scientificreports



*Mcr g*eni varyantları

- MCR Benzeri Enzimlerin Filogenisi; AXE82_07515 *Moraxella osloensis* (koyu ve kırmızı olarak MCR-0 olarak belirtilen), MCR-1/2 için olası bir progenitör olarak önerilmiştir.



Mcr-1

- Mcr-1 ne düzeyde kolistin direncine neden oluyor?

GLASS
Global AMR Surveillance System

European Committee on Antimicrobial Susceptibility Testing

Breakpoint tables for interpretation of MICs and zone diameters

Version 9.0, valid from 2019-01-01

This document should be cited as "The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 9.0, 2019. http://www.eucast.org."

Miscellaneous agents	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)			Notes
	S ≤	R >	ATU		S ≥	R <	ATU	Numbered notes relate to general comments and/or MIC breakpoints. Lettered notes relate to the disk diffusion method.
Chloramphenicol	-	-			-	-		1. Colistin MIC determination should be performed with broth microdilution. Quality control must be performed with both a susceptible QC strain (*E. coli* ATCC 25922 or *P. aeruginosa* ATCC 27853) and the colistin resistant *E. coli* NCTC 13846 (*mcr-1* positive).
Colistin[1]	2	2			Note[A]	Note[A]		
Daptomycin	-	-			-	-		
Fosfomycin iv	-	-			-	-		2. Trimethoprim:sulfamethoxazole in the ratio 1:19. Breakpoints are expressed as the trimethoprim concentration.
Fosfomycin oral	-	-			-	-		
Fusidic acid	-	-			-	-		A. Use an MIC method (broth microdilution only).
Metronidazole	-	-			-	-		
Nitrofurantoin (uncomplicated UTI only)	-	-			-	-		
Nitroxoline (uncomplicated UTI only)	-	-			-	-		
Rifampicin	-	-			-	-		
Spectinomycin	-	-			-	-		
Trimethoprim (uncomplicated UTI only)	-	-			-	-		
Trimethoprim-sulfamethoxazole[2]	2	4		1.25-23.75	14	11		

*Mcr g*eni taşıyan plazmid türleri

- Bir çok farklı plazmid türünde mcr geni tespit edildi.
- Şu ana kadar 10 farklı plazmid; mcr tipine, mikroorganizma türü ve coğrafik olarak değişiyor

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Novel Plasmid-Mediated Colistin Resistance Gene *mcr-3* in *Escherichia coli*

Wenjuan Yin,[a] Hui Li,[a] Yingbo Shen,[a] Zhihai Liu,[a] Shaolin Wang,[a] Zhangqi Shen,[a] Rong Zhang,[b] Timothy R. Walsh,[c] Jianzhong Shen,[a] Yang Wang[a]

Beijing Advanced Innovation Center for Food Nutrition and Human Health, College of Veterinary Medicine, China Agricultural University, Beijing, China[a]; The Second Affiliated Hospital of Zhejiang University, Zhejiang University, Hangzhou, China[b]; Department of Medical Microbiology and Infectious Disease, Institute of Infection and Immunity, Heath Park Hospital, Cardiff, United Kingdom[c]

ABSTRACT The mobile colistin resistance gene *mcr-1* has attracted global attention, as it heralds the breach of polymyxins, one of the last-resort antibiotics for the treatment of severe clinical infections caused by multidrug-resistant Gram-negative bacteria. To date, six slightly different variants of *mcr-1*, and a second mobile colistin resistance gene, *mcr-2*, have been reported or annotated in the GenBank database. Here, we characterized a third mobile colistin resistance gene, *mcr-3*. The gene coexisted with 18 additional resistance determinants in the 261-kb IncHI2-type plasmid pWJ1 from porcine *Escherichia coli*. *mcr-3* showed 45.0% and 47.0% nucleotide sequence identity to *mcr-1* and *mcr-2*, respectively, while the deduced amino acid sequence of MCR-3 showed 99.8 to 100% and 75.6 to 94.8% identity to phosphoethanolamine transferases found in other *Enterobacteriaceae* species and in 10 *Aeromonas* species, respectively. pWJ1 was mobilized to an *E. coli* recipient by conjugation and contained a plasmid backbone similar to those of other *mcr-1*-carrying plasmids, such as pHNSHP45-2 from the original *mcr-1*-harboring *E. coli* strain. Moreover, a truncated transposon element, Tn*As2*, which was characterized only in *Aeromonas salmonicida*, was located upstream of *mcr-3* in pWJ1. This ΔTn*As2-mcr-3* element was also identified in a shotgun genome sequence of a porcine *E. coli* isolate from Malaysia, a human *Klebsiella pneumoniae* isolate from Thailand, and a human *Salmonella enterica* serovar Typhimurium isolate from the United States. These results suggest the likelihood of a wide dissemination of the novel mobile colistin resistance gene *mcr-3* among *Enterobacteriaceae* and aeromonads; the latter may act as a potential reservoir for *mcr-3*.

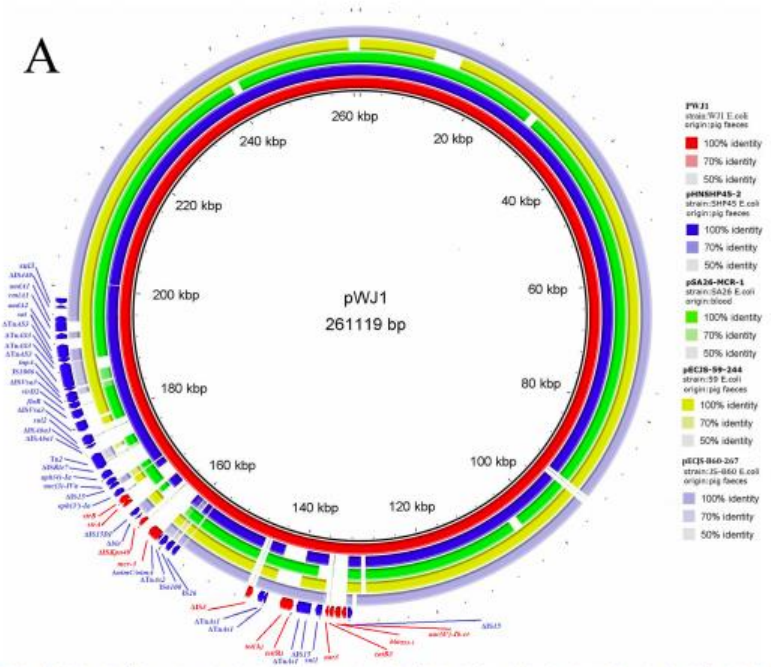

FIG 1 (A) BRIG analysis of the *mcr-3*-carrying plasmid pWJ1. Comparative analysis of pWJ1 with four closely related *mcr-1*-harboring plasmids from *E. coli* isolates using the BLAST Ring Image Generator (10). The concentric rings display similarity between the reference sequence in the inner ring and the other sequences in the outer rings. The various color levels indicate a BLAST result with a matched degree of shared regions, as shown to the right of the ring. (B) Comparison of the genetic environments of *mcr-3* genes in different plasmids and shotgun sequences extracted from the GenBank database. Arrows indicate the positions and directions of the genes; Δ indicates the truncated gene. Regions with >99% homology are indicated in gray shadow, with homology of >85% shown by a lighter gray shadow. (C) Structure prediction for the *mcr-3* gene product, MCR-3. Domain 1 was predicted to be a transmembrane domain, while domain 2 was predicted to be phosphoethanolamine transferase. (D) The five transmembrane α-helices predicted by the Philius transmembrane prediction server (type confidence, 0.99; topology confidence, 0.88).

İlk çalışmalar Çin'den

- Mcr geni aynı hücrede hem kromozomal hem de plazmid üzerinde taşınabiliyor.

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Occurrence of Plasmid- and Chromosome-Carried *mcr-1* in Waterborne *Enterobacteriaceae* in China

Hong-Wei Zhou,[a] Ting Zhang,[b] Ji-Hua Ma,[c] Ying Fang,[a] Han-Yu Wang,[d] Zi-Xian Huang,[e] Yang Wang,[f] Congming Wu,[f] Gong-Xiang Chen[a]

Second Affiliated Hospital of Zhejiang University, School of Medicine, Zhejiang University, Hangzhou, China[a]; The First Affiliated Hospital of Zhejiang University, School of Medicine, Zhejiang University, Hangzhou, China[b]; The Children's Hospital, School of Medicine, Zhejiang University, Hangzhou, China[c]; University of Connecticut, Mansfield, Connecticut, USA[d]; The Affiliated High School to Hangzhou Normal University, Hangzhou, China[e]; College of Veterinary Medicine, China Agricultural University, Beijing, China[f]

ABSTRACT The aim of this study was to investigate the prevalence of the polymyxin resistance gene *mcr-1* in *Enterobacteriaceae* from environmental water sources in Hangzhou, China. Colistin-resistant bacteria were isolated from environmental water samples using an enrichment broth culture method, were screened for *mcr-1*, and then were analyzed for the location and transferability of *mcr-1*. Isolates positive for *mcr-1* were further examined to determine their susceptibility profiles and were screened for the presence of additional resistance genes. Twenty-three *mcr-1*-positive isolates (16 *Escherichia coli*, two *Citrobacter freundii*, two *Klebsiella oxytoca*, two *Citrobacter braakii*, and one *Enterobacter cloacae*) were isolated from 7/9 sampling locations; of those, eight *mcr-1*-positive isolates also contained β-lactamase-resistance genes, eight contained *qnrS*, and 10 contained *oqx*. No *mcr-2*-positive isolates were identified. The majority of isolates demonstrated a low to moderate level of colistin resistance. Transconjugation was successfully conducted from 14 of the 23 *mcr-1*-positive isolates, and *mcr-1* was identified on plasmids ranging from 60 to 220 kb in these isolates. Conjugation and hybridization experiments revealed that *mcr-1* was chromosome-borne in only three isolates. Pulsed-field gel electrophoresis showed that the majority of *E. coli* isolates belonged to different clonal lineages. Multilocus sequence typing analysis revealed that sequence type 10 (ST10) was the most prevalent, followed by ST181 and ST206. This study demonstrates the utility of enrichment broth culture for identifying environmental *mcr-1*-positive isolates. Furthermore, it highlights the importance of responsible agriculture and clinical use of polymyxins to prevent further widespread dissemination of polymyxin-resistant pathogens.

Çalışmaların Çoğu Çin'den

- Çin'deki sağlıklı çocukların dışkı örneklerinin yaklaşık %10'nunda mcr geni

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Short Communication

Colistin resistance gene *mcr-1* in gut flora of children

Yan-yan Hu [a], Yue-ling Wang [b], Qiao-ling Sun [a], Zi-Xian Huang [c], Han-Yu Wang [d], Rong Zhang [a], Gong-xiang Chen [a,*]

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[b] Department of Clinical Laboratory, Shandong Provincial Hospital Affiliated to Shandong University, Jinan, China
[c] The Affiliated High School to Hangzhou Normal University, Hangzhou, China
[d] University of Connecticut, Storrs, CT, USA

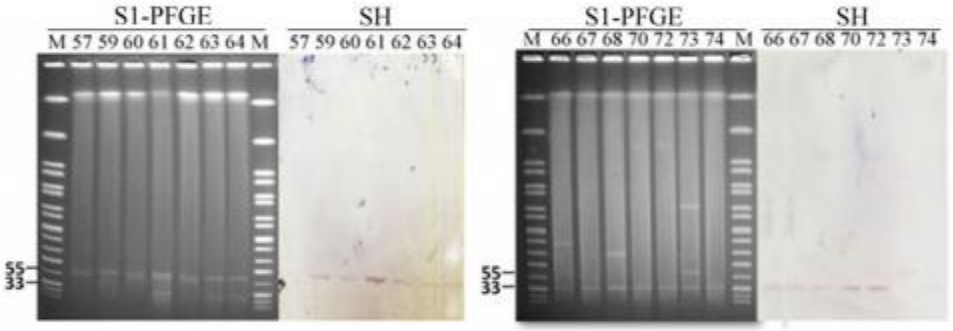

Fig. 1. S1 nuclease pulsed-field gel electrophoresis (S1-PFGE) and Southern hybridisation analysis of 14 *mcr-1*-positive conjugative plasmids harboured by strains of *Escherichia coli*.

Çalışmaların Çoğu Çin'den

- mcr-1 pozitif kolistin dirençli bir Klebsiella pneumonaie salgınını bildirilmiş.
- iki aylık sürede lösemik çocuklarda sapatanan beş (mcr-1 pozitif) *K. pneumoniae*

MCR-1-producing *Klebsiella pneumoniae* outbreak in China

In January, 2017, *The Lancet Infectious Diseases* published our finding[1] that Enterobacteriaceae carrying *mcr-1*, a plasmid-mediated colistin resistance gene, are highly heterogenous in sequence type (ST) grouping and plasmid types indicating the diversity of *mcr-1*-carrying bacteria in China, and *mcr-1*-positive Enterobacteriaceae infections were associated with male sex, immunosuppression and antibiotics use before hospitalisation. Here we report a hospital outbreak of the MCR-1-producing *Klebsiella pneumoniae*.

Six clinical isolates including one *Escherichia coli* and five *K pneumoniae* were identified from six patients with pneumonia admitted to a paediatric leukaemia ward at a hospital in Guangzhou, China, during 2 months between December, 2015, and January, 2016. These patients were treated with different combinations of vancomycin, *K pneumonia* were clonally related. Colistin resistance was successfully transferred to *E coli* C600 with high conjugation frequencies (10^{-1} to 10^{-2}) in all isolates, suggesting that *mcr-1* was located on transferable plasmids. The results of S1-PFGE and plasmid replicon typing for *mcr-1*-carrying plasmid in the transconjugants showed that *mcr-1* was located at IncX4 plasmids of approximately 50 kb in size in all six isolates, which harboured bla_{TEM-1} and $bla_{CTX-M-3}$ (appendix).

In conclusion, we identified a hospital outbreak of an MCR-1-producing *K pneumoniae* ST11 strain among children with acute leukaemia. Our finding suggests that *mcr-1* can spread in the hospital environment in the absence of colistin use.

We declare no competing interests. This work was supported by the National Key Basic Research Program of China (number 2016YFC1200100).

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50 kb lık IncX4 plazmidi olduğu ve ayrıca TEM-1 ve CTX-M-3 genlerini de beraberinde taşıdığı saptanmıştır

Plazmit Aracılı Aktarılabilir Kolistin Direnci

- Plazmid aracılı kolistin direnci tamamen Çin fenomeni midir?

Neredeyse tüm dünyadan bildirildi

- Bugüne kadar beş kıtada, 40'tan fazla ülkede tespit edildi.

Bakteriler	Konak	Ülke	İzolasyon yılı
E. coli	tavuk eti, domuz eti, domuzlar, insanlar	Çin	2011-14
K. pneumoniae	insan	Çin	2014
Bilinmeyen	insan mikrobiyomu	Çin	2011'den önce
E. coli , *K. pneumoniae*	insanlar	Çin	2014-15
E. coli	tavuk eti	Çin	2014
Bilinmeyen	insan mikrobiyomu	Çin	2011'den önce
E. coli	insanlar	Çin	2015
E. coli	tavuklar	Çin	1980–89, 2004, 2006, 2009–14
E. aerogenes , *E. cloacae*	insanlar	Çin	2014
E. coli	insanlar	Çin	2015
E. coli	insan	Çin	2015
E. coli	köpekler, kediler	Çin	2016
E. coli	insanlar	Çin	2015
E. coli	insan	Kamboçya	2012
E. coli	sığır, domuz	Japonya	2012-13
E. coli	insanlar, domuzlar	Laos	2012
E. coli	domuzlar, tavuklar	Malezya	2013
E. coli	tavuklar, domuz, su	Malezya	2013

Ülkemizde Mcr pozitifliği

- Ülekimizden literatüre yansımış mcr geni henüz bildirilmemiştir..

Editöre Mektup/Letter to Editor *Mikrobiyol Bul 2017; 51(3): 299-303*

doi: 10.5578/mb.57515

Ülkemizde Klinik *Enterobacteriaceae* İzolatlarında Plazmit Aracılı Kolistin Direnç Genlerini (*mcr-1* ve *mcr-2*) Araştıran Çok Merkezli Çalışmaya Ait Sonuçlar

Kolistin, son yıllarda çoklu ilaç direnci ve karbapenem direncine sahip gram-negatif bakterilere bağlı enfeksiyonların tedavisinde son seçenek olarak kullanılan polimiksin grubu bir antibiyotiktir. Günümüzde bildirilen kolistin direnç mekanizmaları çoğunlukla kromozomal olup, genellikle özgül iki bileşenli düzenleyici sistemlerini kodlayan genlerde mutasyonlara neden olan mekanizmalardır. İlk kez 2015 yılında plazmit aracılı kolistin direncine yol açan MCR-1 proteini, *Escherichia coli* ve *Klebsiella pneumoniae* izolatlarında tanımlanmıştır ve bunu 2016 yılında MCR-2 proteininin tanımlanması takip etmiştir. Plazmit aracılı direnç mekanizmalarının yatay gen transferi ile hızlı bir şekilde türler arasında yayılım göstermesi, kolistine dirençli kökenlerin sıklığının hızlı artışına ve bu kökenlerin yayılarak salgınlar oluşturma potansiyeli taşımasına bağlı olarak, bu direnç özelliğini klinik ve epidemiyolojik açılardan önemli kılmaktadır. Günümüze kadar birçok farklı ülkeden plazmit kaynaklı *mcr-1/mcr-2* geni taşıyan *Enterobacteriaceae* izolatları bildirilmiş olup ülkemize ait bir bildiri henüz bulunmamaktadır. Bu çalışmanın amacı, ülkemizin farklı bölgelerine ait klinik *Enterobacteriaceae* izolatlarında *mcr-1/mcr-2* varlığının araştırılmasıdır. Bu amaçla, toplam 22 merkeze ait 329 *Enterobacteriaceae* izolatında *mcr-1* ve *mcr-2* gen varlığı polimeraz zincir reaksiyonu (PCR) yöntemi ile araştırılmıştır. Tüm izolatların 217 (%66)'si *Klebsiella pneumoniae*, 75 (%22.8)'i *Salmonella* spp., 31 (%9.4)'i *E.coli*, 3 (%0.9)'ü *Enterobacter cloacae*, 2 (%0.6)'si *Klebsiella oxytoca* ve 1 (%0.3)'i *Enterobacter aerogenes*'tir. Yapılan tüm PCR çalışmalarına ait agaroz jel elektroforezi görüntülerinde pozitif kontrol izolatlarında *mcr-1* gen bölgesi için 309 bp ve *mcr-2* gen bölgesi için 567 bp beklenen bant büyüklüğü elde edilmiştir. Ancak, çalışmaya alınan izolatların hiçbirinde *mcr-1* veya *mcr-2* gen bölgesi saptanmamıştır. Çok merkezli çalışma bulgularımız bu direnç mekanizmalarının ülkemizde henüz bulunmadığını işaret etmektedir. Kolistinin çoklu ilaç direncine sahip ya da karbapenem dirençli gram-negatif bakterilere bağlı enfeksiyonların tedavisinde son seçenek olarak kullanıldığı göz önüne alındığında direnç yayılım mekanizmasının anlaşılması ve dirençli izolatların takibi büyük önem

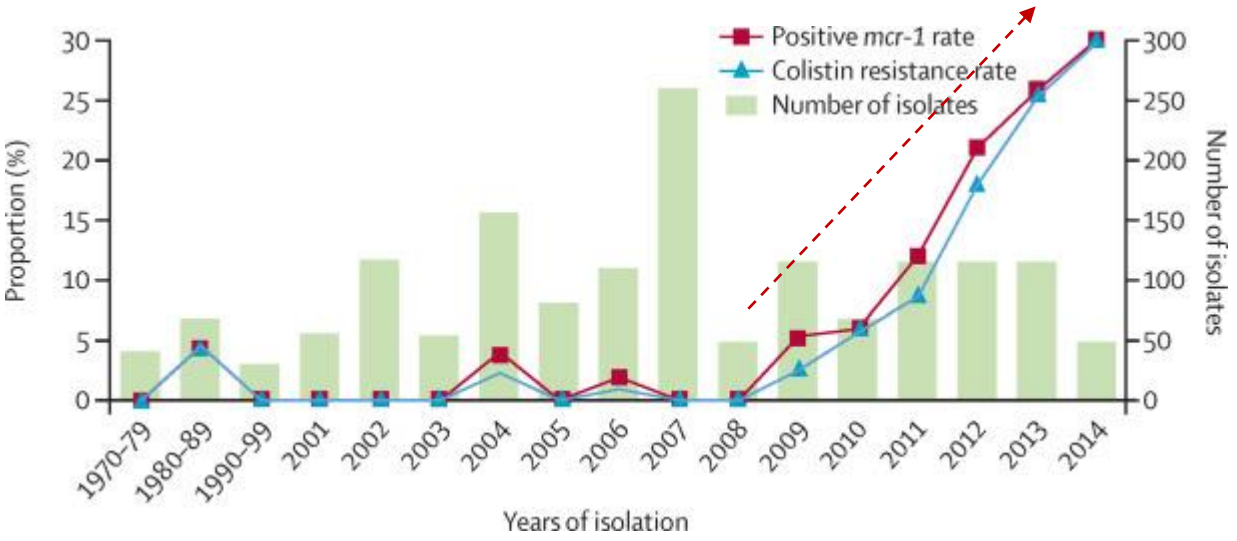
Mcr geni ilk kez ne zaman?

- Ne zamandan beri var?
- 1611 hayvansal *E. coli* kolleksiyonu taranmış
- 1980'li yıllarda izole edilen üç *E. coli* izolatında tespit edildi.

Early emergence of *mcr-1* in *Escherichia coli* from food-producing animals

Our research group and collaborators reported the transferable colistin resistance mechanism caused by the *mcr-1* gene in Enterobacteriaceae.[1] Shortly after, researchers from different regions of the world showed that the *mcr-1* gene has been disseminated to many countries of at least four continents.[2–5] Colistin has long been used in animals as a therapeutic drug or feed additive. Evidence suggests that the spread of *mcr-1* is from animals to human beings.[1–5] Thus, we did a retrospective study to examine the approximate time of emergence of the *mcr-1* gene in food-producing animals.

Our laboratory has 1611 *Escherichia coli* isolates of chicken origin, derived

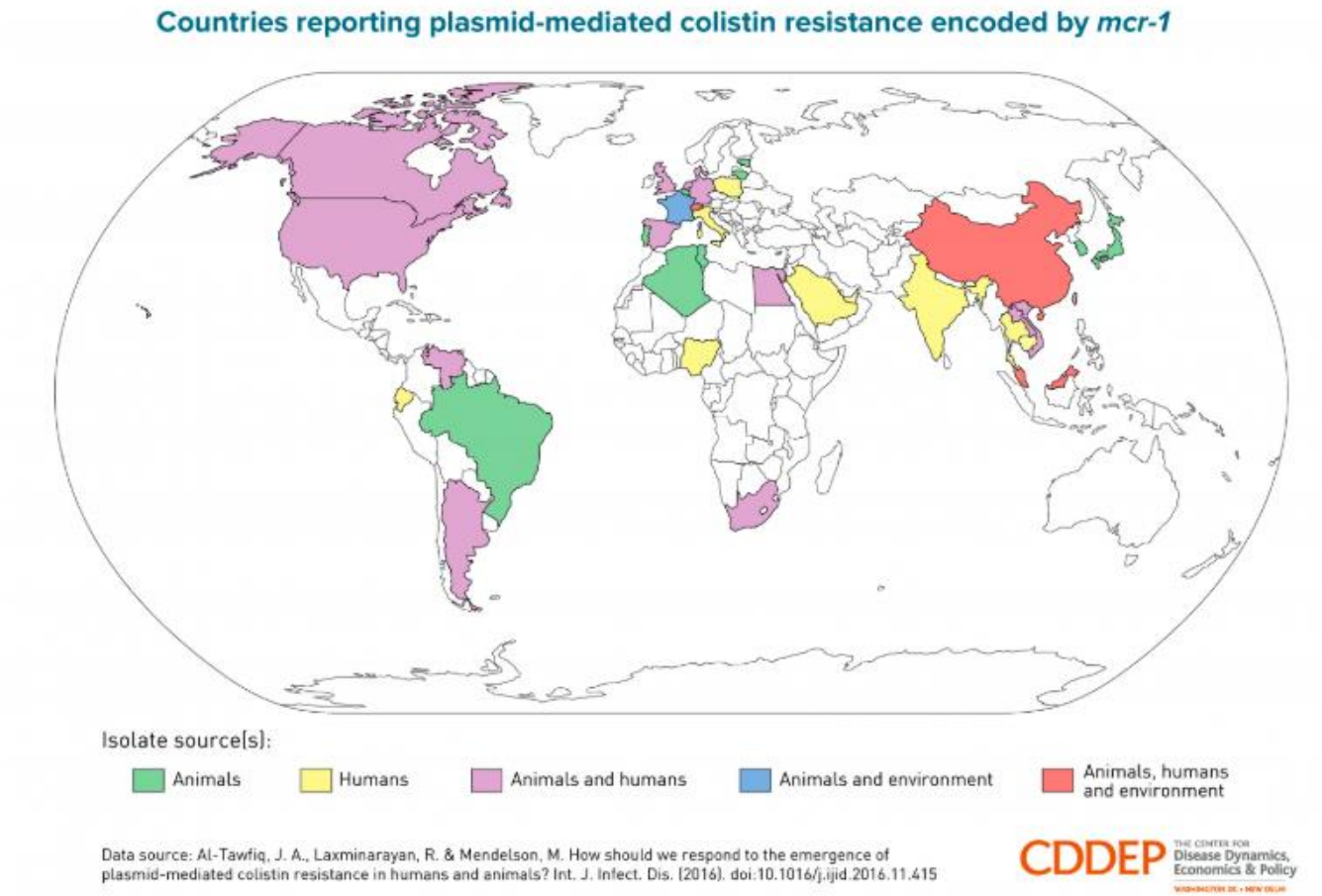


Mcr geni ve moleküler epidemiyoloji

- Kolistin direncinin yarattığı tehdide ve yayılmasına karşı bir direniş mücadelesi olarak görülmeli ve epidemiyolojik çalışmalara yoğunlaşmak gerekir.

OFFICES IN
Washington D.C. & New Delhi

CDDEP
The Center For Disease Dynamics, Economics & Policy



Acinetobacter ve Mcr genleri

- 2018; Acinetobacter türleri plasmid aracılı mcr geni bulundurmuyorlar.
- Ancak Acinetobacter'in plasmid aracılı mcr geni edinmesi sadece bir zaman meselesi.

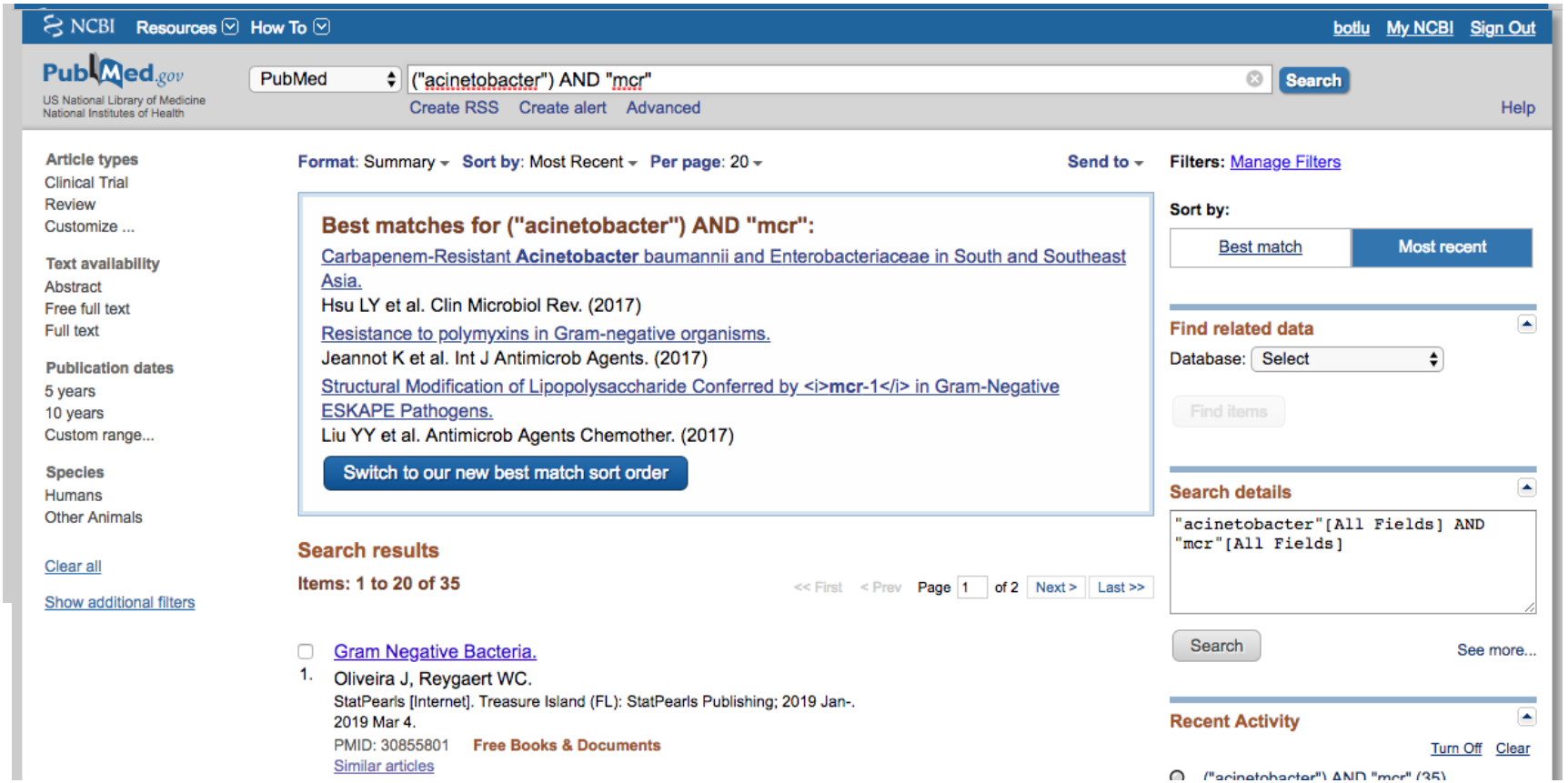
European Journal of Clinical Microbiology & Infectious Diseases (2018) 37:1009–1019
https://doi.org/10.1007/s10096-018-3223-9

REVIEW

The diversity of plasmids harboring *mcr* described in Enterobacteriaceae on different continents shows high potential for dissemination of this gene [30]. By the time of this review, *mcr* has been identified in *E. coli*, *K. pneumoniae*, *Salmonella* spp., *Shigella sonnei*, *Klebsiella* (anteriorly *Enterobacter*) *aerogenes*, *Enterobacter cloacae*, *Cronobacter sakazakii*, *Kluyvera ascorbata*, *Citrobacter freundii*, and *Moraxella* spp. [96–99], but in vitro studies also revealed the possibility of gene acquisition from *K. pneumoniae* to *P. aeruginosa* by transformation [100]. In *A. baumannii*, there is still no report of *mcr*-positive isolates but, the rapid dissemination of this gene as well as the real possibility of non-glucose-fermenting Gram-negative bacilli (e.g., *P. aeruginosa*) to acquire *mcr* from Enterobacteriaceae suggest that this is only a matter of time [33]. Thus, the intensification of surveillance studies is imperative for control of the dissemination of *mcr* and for protection of the class of polymyxins, which are still an important therapeutic option for the treatment of *A. baumannii* extremely-drug-resistant (XDR) infections [15].

Acinetobacter ve Mcr genleri

- PubMed; «Acinetobacter» AND «mcr»



Acinetobacter ve Mcr genleri

- 2018, Mcr-1 taşıyan *Acinetobacter Iwoffii* İtalya'da çevre örneklerinden bildirildi.

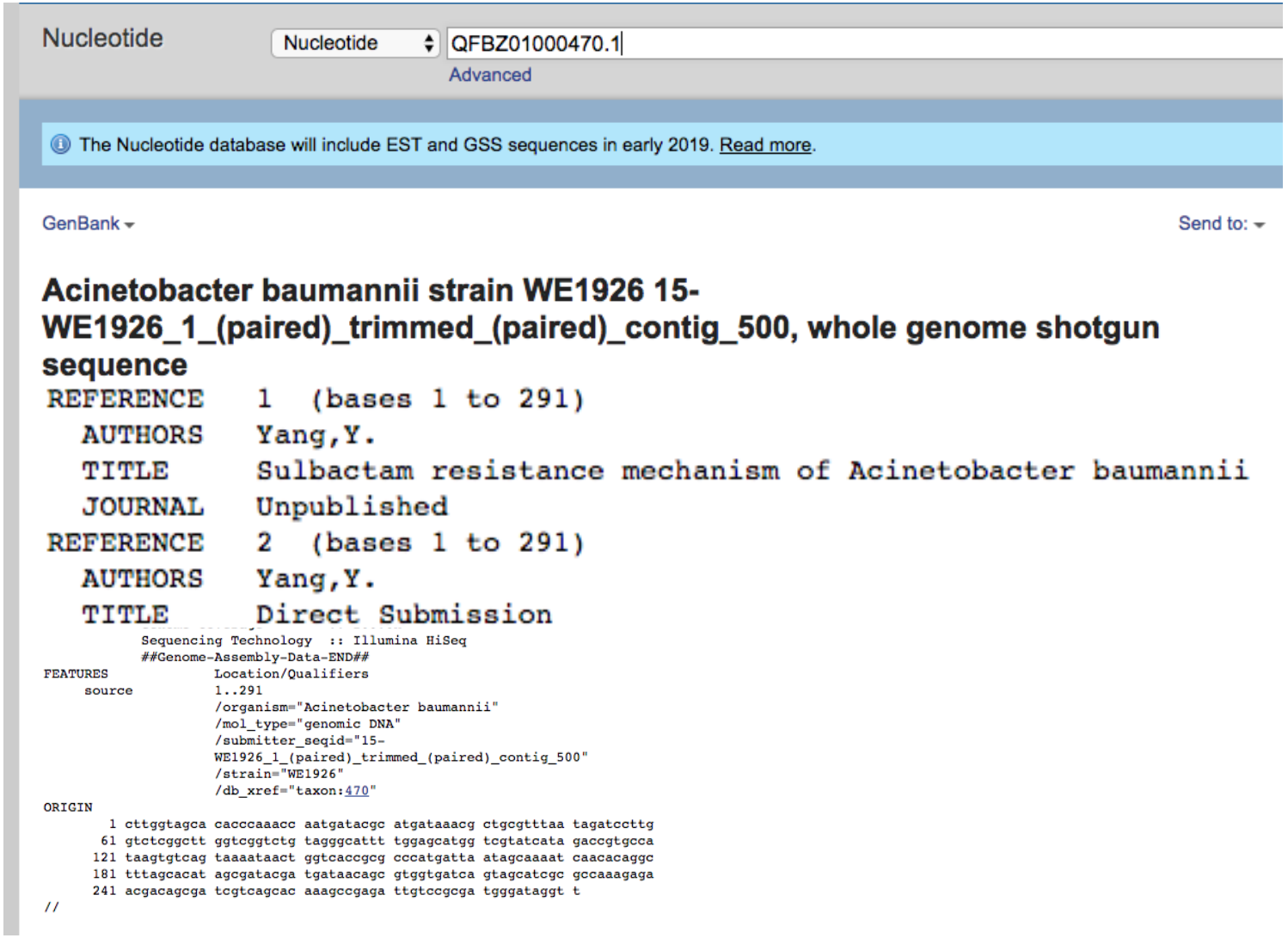
Spread of *mcr-1*–Driven Colistin Resistance on Hospital Surfaces, Italy

Elisabetta Caselli, Maria D'Accolti, Irene Soffritti, Micol Piffanelli, Sante Mazzacane

Identification results indicated that different species harbored the *mcr-1* gene, including *K. pneumoniae*, *K. oxytoca*, *E. coli*, *Acinetobacter Iwoffii*, *Enterobacter cloacae*, *E. agglomerans*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, and *P. putida* (Table). These results suggest that this gene is silently spreading to many gram-negative bacteria responsible for infections in clinical settings.

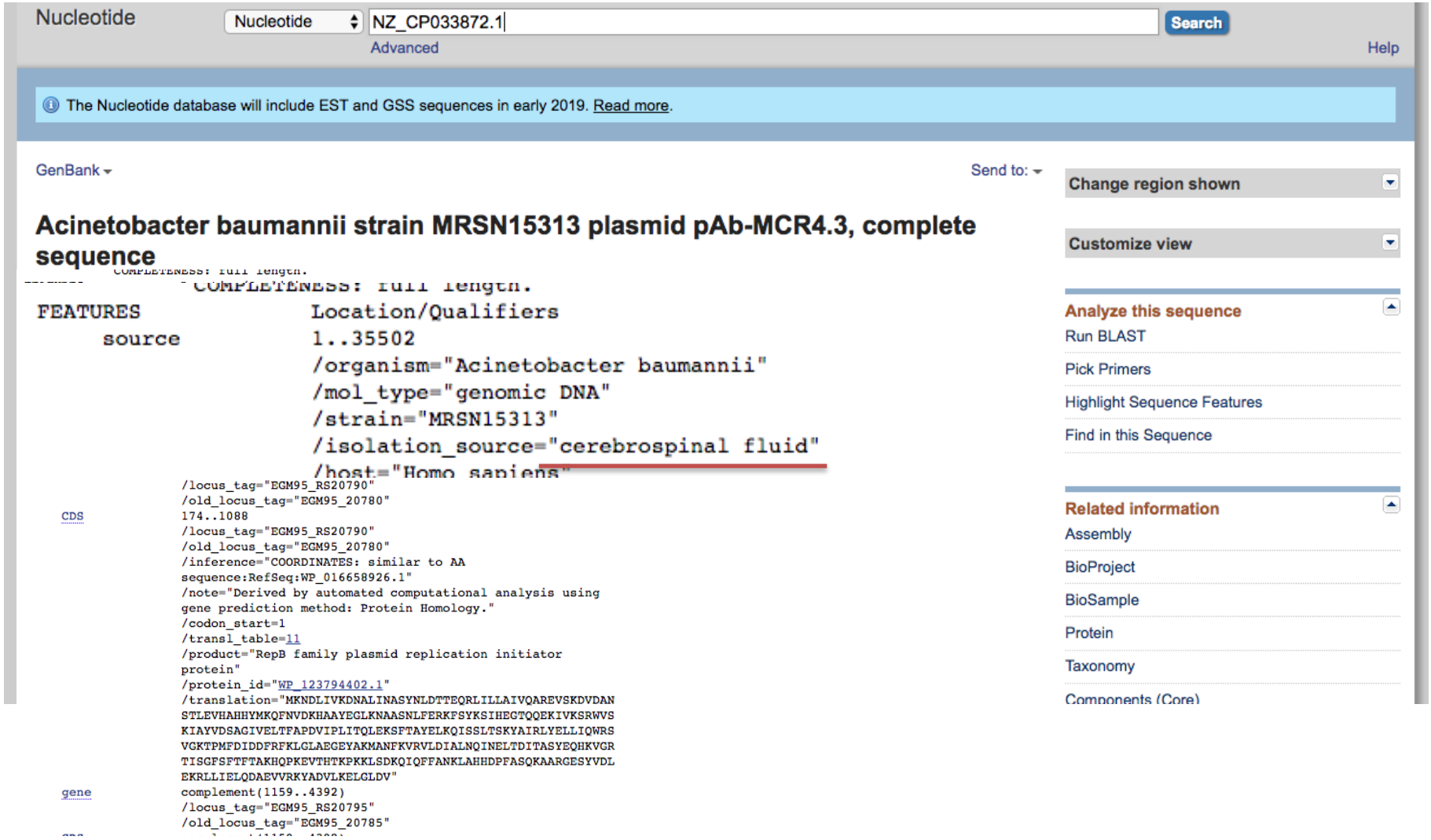
Acinetobacter ve Mcr genleri

- CARD, The Comprehensive Antibiotic Resistance Database



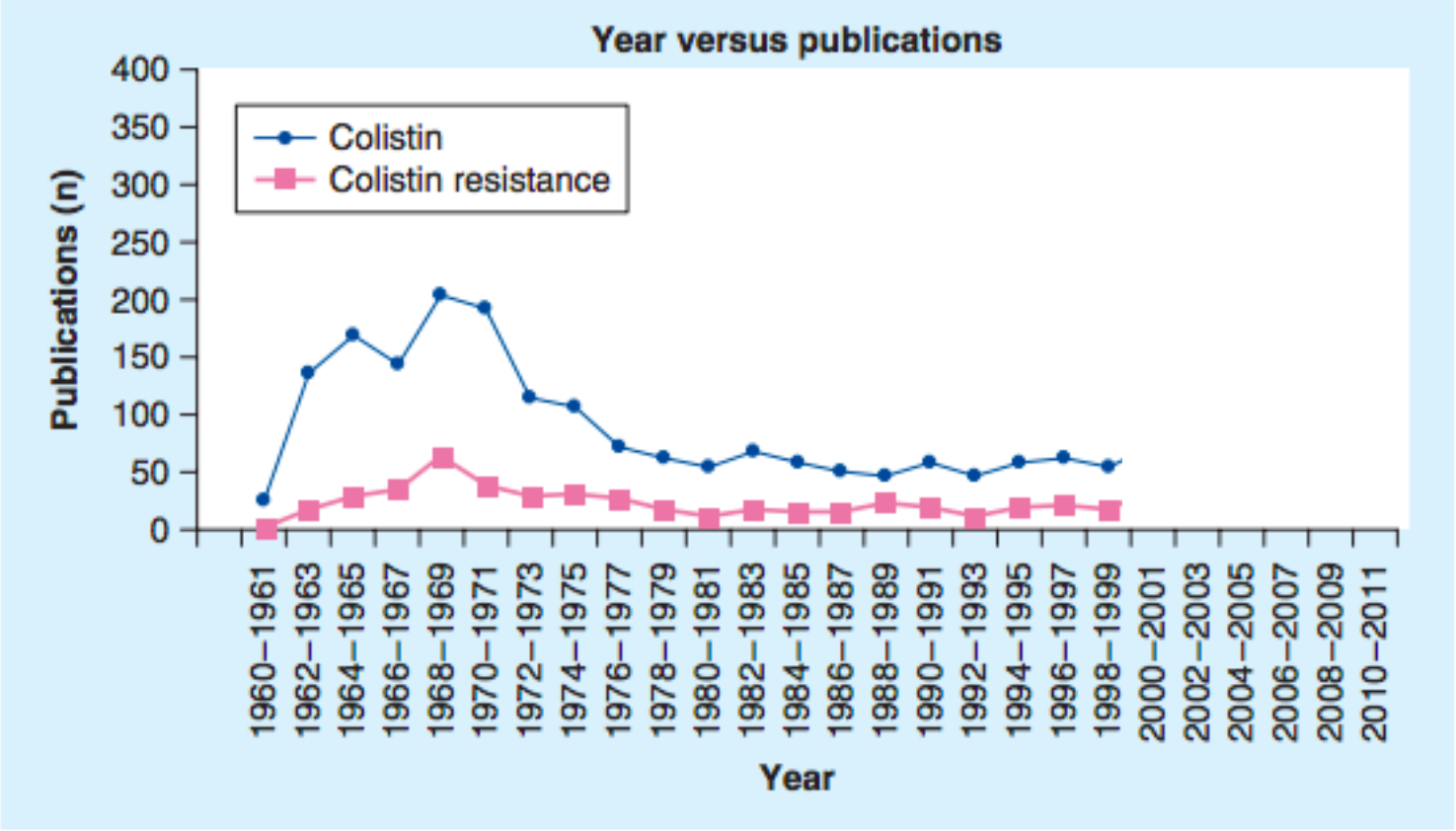
Acinetobacter ve Mcr genleri

- CARD, The Comprehensive Antibiotic Resistance Database



Korkulan oldu!!!

- Acinetobacter türleri mcr taşıyan plazmidler ile buluştu.



Expert Rev Anti Infect Ther. 2012 Aug;10(8):917-34

Dirençle Mücadele

- Polimiksinlerin kullanımını azaltmaya yönelik daha önce çağrı yapıldı.

EPASG ESCMID PK/PD OF ANTI-INFECTIVES STUDY GROUP
European Society of Clinical Microbiology and Infectious Diseases

ESCMID MANAGING INFECTIONS PROMOTING SCIENCE

Framework for optimisation of the clinical use of colistin and polymyxin B: the Prato polymyxin consensus

Roger L Nation, Jian Li, Otto Cars, William Couet, Michael N Dudley, Keith S Kaye, Johan W Mouton, David L Paterson, Vincent H Tam, Ursula Theuretzbacher, Brian T Tsuji, John D Turnidge

In the face of diminishing therapeutic options for the treatment of infections caused by multidrug-resistant, Gram-negative bacteria, clinicians are increasingly using colistin and polymyxin B. These antibiotics became available clinically in the 1950s, when understanding of antimicrobial pharmacology and regulatory requirements for approval of drugs was substantially less than today. At the 1st International Conference on Polymyxins in Prato, Italy, 2013, participants discussed a set of key objectives that were developed to explore the factors affecting the safe and effective use of polymyxins, identify the gaps in knowledge, and set priorities for future research. Participants identified several factors that affect the optimum use of polymyxins, including: confusion caused by several different conventions used to describe doses of colistin; an absence of appropriate pharmacopoeial standards for polymyxins; outdated and diverse product information; and uncertainties about susceptibility testing and breakpoints. High-priority areas for research included: better definition of the effectiveness of polymyxin-based combination therapy compared with monotherapy via well designed, randomised controlled trials; examination of the relative merits of colistin versus polymyxin B for various types of infection; investigation of pharmacokinetics in special patient populations; and definition of the role of nebulised polymyxins alone or in combination with intravenous polymyxins for the treatment of pneumonia. The key areas identified provide a roadmap for action regarding the continued use of polymyxins, and are intended to help with the effective and safe use of these important, last-line antibiotics.

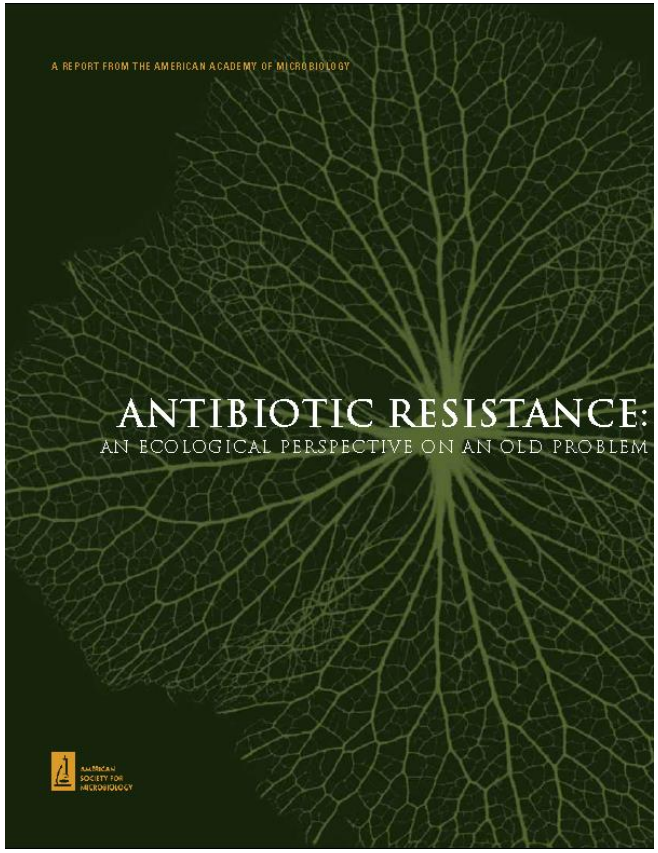
Lancet Infect Dis 2015; 15: 225-34

Published Online October 21, 2014 http://dx.doi.org/10.1016/S1473-3099(14)70850-3

Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University, Melbourne, VIC, Australia (Prof R L Nation PhD, Prof J Li PhD); **Department of Medical Sciences, Section of Infectious Diseases, Uppsala University, Uppsala, Sweden** (Prof Ö Cars MD); **Faculté de Médecine et de**

Dirençle Mücadele

- Antibiyotik direnci ile mücadele bir savaştır ve biz asla kazanamayacağız



INTRODUCTION

" The strength of trillions upon trillions of microorganisms, combined with the ancient force of evolution by constant, unrelenting variation, will inevitably overpower our drugs"

- American Academy of Microbiology

quires lengthy and expensive regimens of chemotherapy—something many patients, particularly those in developing countries, cannot afford. Strains resistant to the two most powerful anti-TB drugs and multidrug-resistant TB have become more common. Now, extensively drug-resistant (XDR) TB strains, which are resistant to all major TB drugs, have arrived on the scene. TB is finding a way around all of the best antibiotics, and, at the present time, the World Health Organization (WHO) estimates that 30% of the world's population is infected with the tuberculosis bacterium. This is an impressive statistic for a disease that should be treatable with antibiotics.

A WAR WE WILL NEVER WIN.

The specific meaning of "antibiotic resistance" depends entirely on context. The clinical definition used in this document refers to the ability of a microorganism—a bacterium, virus, fungus, or parasite—to survive concentrations of antibiotics that kill sensitive cells of the same strain. It is important to note that for every antibiotic, there are sensitive strains, which are killed or inhibited by the drug, and naturally resistant strains. When a sensitive strain gains the ability to withstand an antibiotic, it is "antibiotic resistant."

In bioclinical terms, antibiotic resistance simply means that a pathogen is less susceptible than its counterparts and may not respond to the antibiotic administered. In genomics, organisms that possess a resistance gene are resistant. Like all other living things, the evolution of microorganisms is Darwinian: in the face of change, the fittest survive. Antibiotics represent an evolutionary challenge that microorganisms must surmount or perish.

Resistance is commonly considered simplistically—either an organism is resistant or it's not. In reality, resistance exists as a gradient that reflects phenotypic and

Dirençle Mücadele

- Kolistin direncinin gelecekti yayılımını azaltmak, hatta durdurabilmek için rasyonel yaklaşımlara ihtiyaç var.
- Antibiyotik direnci ile mücadelede tek sağlık yaklaşımı şart!