KLİMİK

Dirençli Gram-negatif İnfeksiyonların Tanı ve Tedavisinde *Kritik Kararlar*

Karbapeneneme Dirençli *Enterobacterales* İnfeksiyonları

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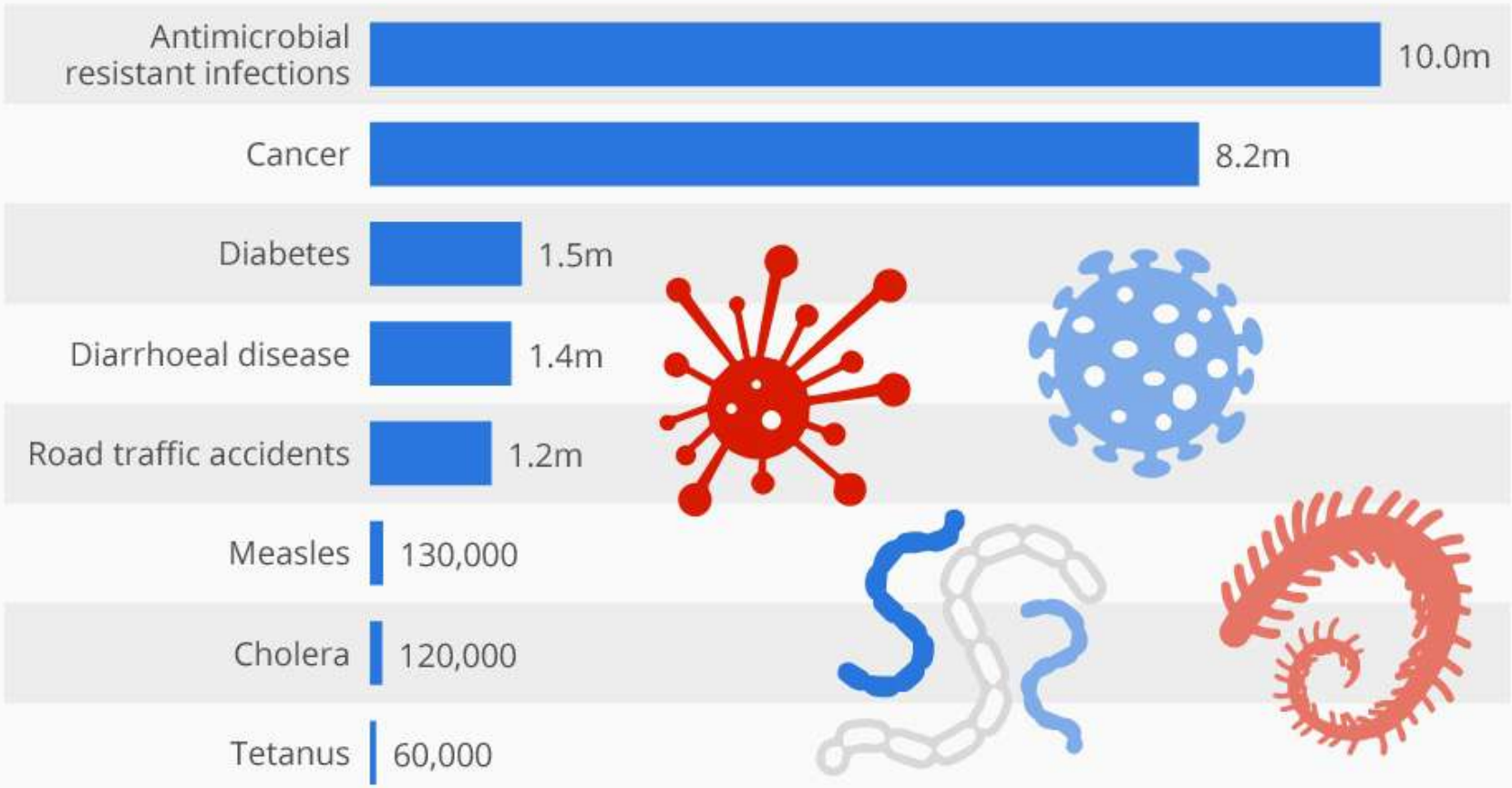
Kartal Dr.Lütfi Kırdar Şehir Hastanesi

31 Ekim 2023

Deaths From Drug-Resistant Infections Set To Skyrocket

Deaths from antimicrobial resistant infections and other causes in 2050



Source: Review on Antimicrobial Resistance

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Antibiotic Resistance Spreads Easily Across the Globe

Resistant bacteria and fungi can spread across countries and continents through people, animals, and goods.

Detect Resistant Threats

Prevent & Contain Resistant Germs

Improve Antibiotic Use

CDC-Antibiotic Resistance Threats in the United States, 2019

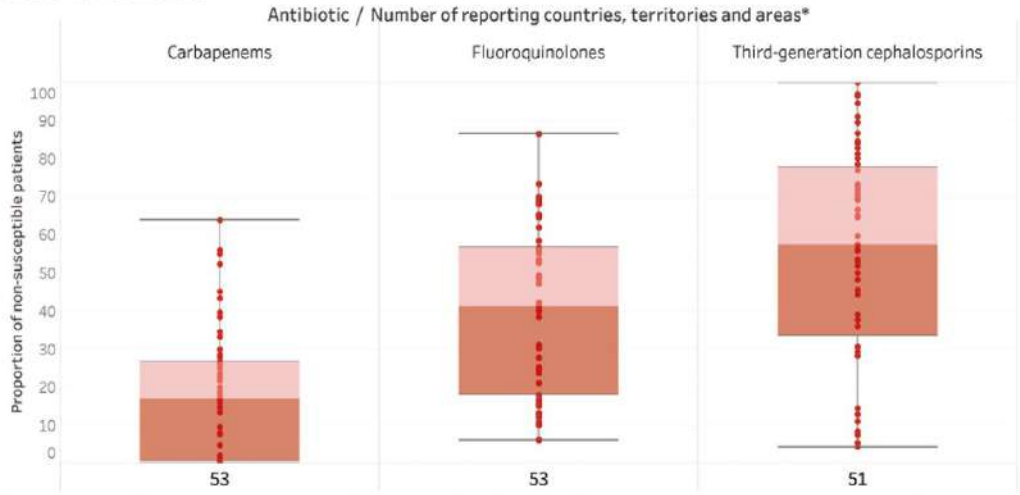
Global Antimicrobial Resistance and Use Surveillance System (GLASS) Report

Early implementation

2020

World Health Organization

Blood - K. Pneumoniae



*Rates are shown only if results were reported for > 10 patients and for pathogen–antibiotic combinations with > 10 AST results and < 30% unknown results. Single antibiotic results are shown only if data were submitted by at least 50% of the countries reporting on the specimen-pathogen combination.

Antibiyotiklere direnç➔maliyeti

- ABD'de yapılan bir araştırma, hastaneler için tek bir vakayı yönetmenin maliyetinin 22.484 ile 66.031 ABD doları arasında olduğunu tahmin ediyor
- Çok ilaca dirençli infeksiyonları (KDE dahil) ortadan kaldırmak için katı önlemlerin uygulanmasının maliyetini değerlendiren bir çalışmada, bunun pozitif hasta başına 285 € ile 57.532 € arasında değiştiğini tahmin etmiştir
- Birleşik Krallık'ta yapılan bir çalışmada, 10 ay boyunca infekte olduğu veya kolonize olduğu belirlenen 40 hastanın bulunduğu KDE salgınının maliyetinin 1 milyon £ olduğu tahmin edilmiştir
- Maliyet, salgını kontrol altına almak için yapılan fiili harcamaların yanı sıra servis kapanması nedeniyle gelir kaybı gibi 'fırsat' maliyetlerini de içeriyordu.

INTERNATIONAL JOURNAL OF
SYSTEMATIC AND EVOLUTIONARY MICROBIOLOGY
Volume 66, Issue 12

Research Article | Free

Genome-based phylogeny and taxonomy of the '*Enterobacteriales*': proposal for *Enterobacterales* ord. nov. divided into the families *Enterobacteriaceae*, *Erwiniaceae* fam. nov., *Pectobacteriaceae* fam. nov., *Yersiniaceae* fam. nov., *Hafniaceae* fam. nov., *Morganellaceae* fam. nov., and *Budviciaceae* fam. nov.

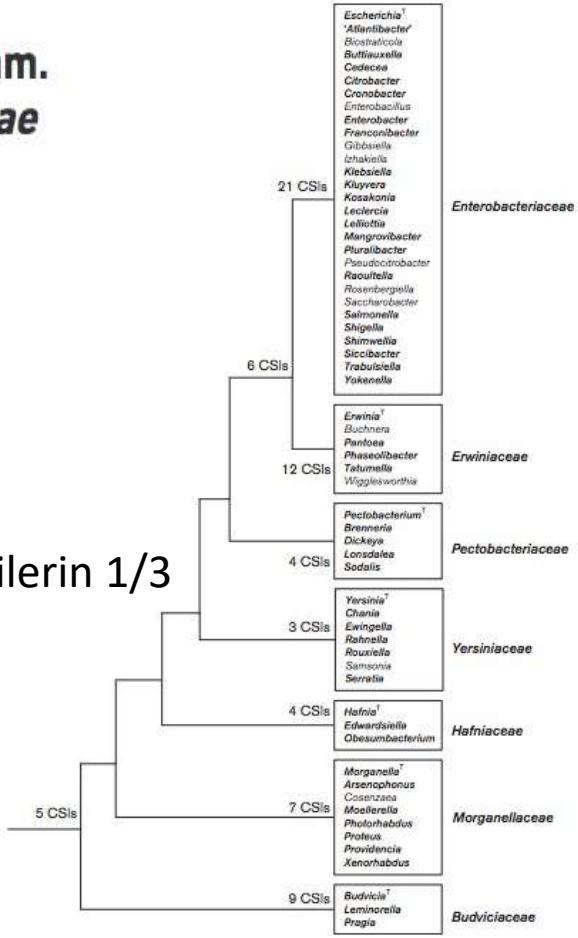
Mobolaji Adeolu[1,†], Seema Alnajar[1,†], Sohail Naushad[1], Radhey S. Gupta[1]
View Affiliations

Published: 01 December 2016 | https://doi.org/10.1099/ijsem.0.001485

- *Enterobacterales* takımı- 7 aileden oluşuyor
- *Enterobacteriaceae* ailesi bu takım içinde tüm bakteriyemilerin 1/3

ve üriner sistem infeksiyonlarının %70'inden sorumlu

E.coli, *Klebsiella* spp., *Enterobacter* spp…….



Dikkatle izlenmesi gereken patojenler!

ESKAPE

- *E. faecium*
- *S. aureus*
- *K. pneumoniae*
- *A. baumannii*
- *P. aeruginosa*
- *Enterobacter* spp.

IDSA-2004

ESCAPE

- *E. faecium*
- *S. aureus*
- *C. difficile (C.aurius)*
- *A. baumannii*
- *P. aeruginosa*
- *Enterobacterales*

DSÖ-2017, CDC-2019

Bacteria and Fungi Listed in the 2019 AR Threats Report

Urgent Threats

- Carbapenem-resistant *Acinetobacter*
- *Candida auris*
- *Clostridioides difficile*
- Carbapenem-resistant Enterobacterales
- Drug-resistant *Neisseria gonorrhoeae*

Serious Threats

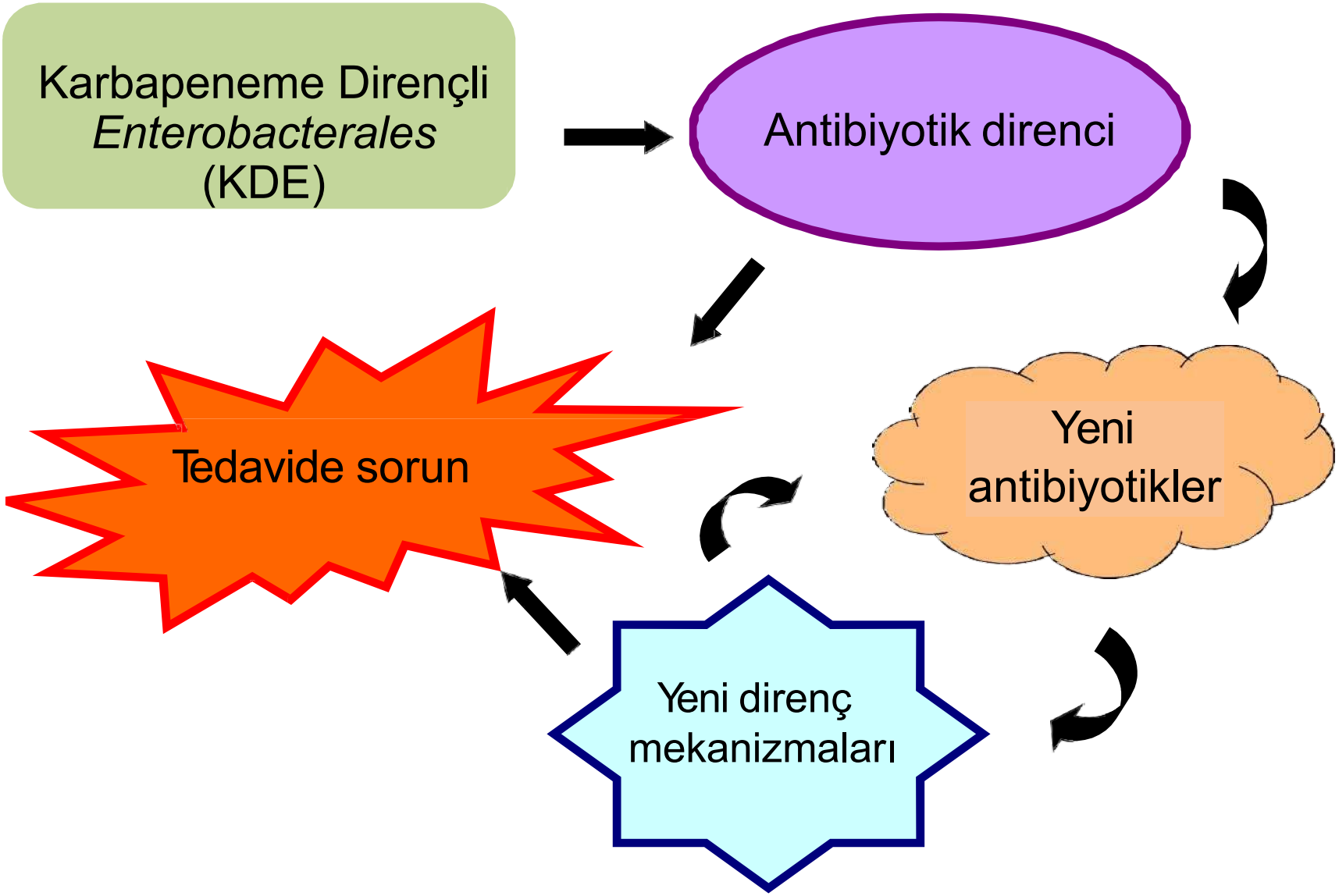
- Drug-resistant *Campylobacter*
- Drug-resistant *Candida*
- ESBL-producing Enterobacterales
- Vancomycin-resistant *Enterococci* (VRE)
- Multidrug-resistant *Pseudomonas aeruginosa*
- Drug-resistant nontyphoidal *Salmonella*
- Drug-resistant *Salmonella* serotype Typhi
- Drug-resistant *Shigella*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Drug-resistant *Streptococcus pneumoniae*
- Drug-resistant Tuberculosis

Concerning Threats

- Erythromycin-Resistant Group A *Streptococcus*
- Clindamycin-resistant Group B *Streptococcus*

Watch List

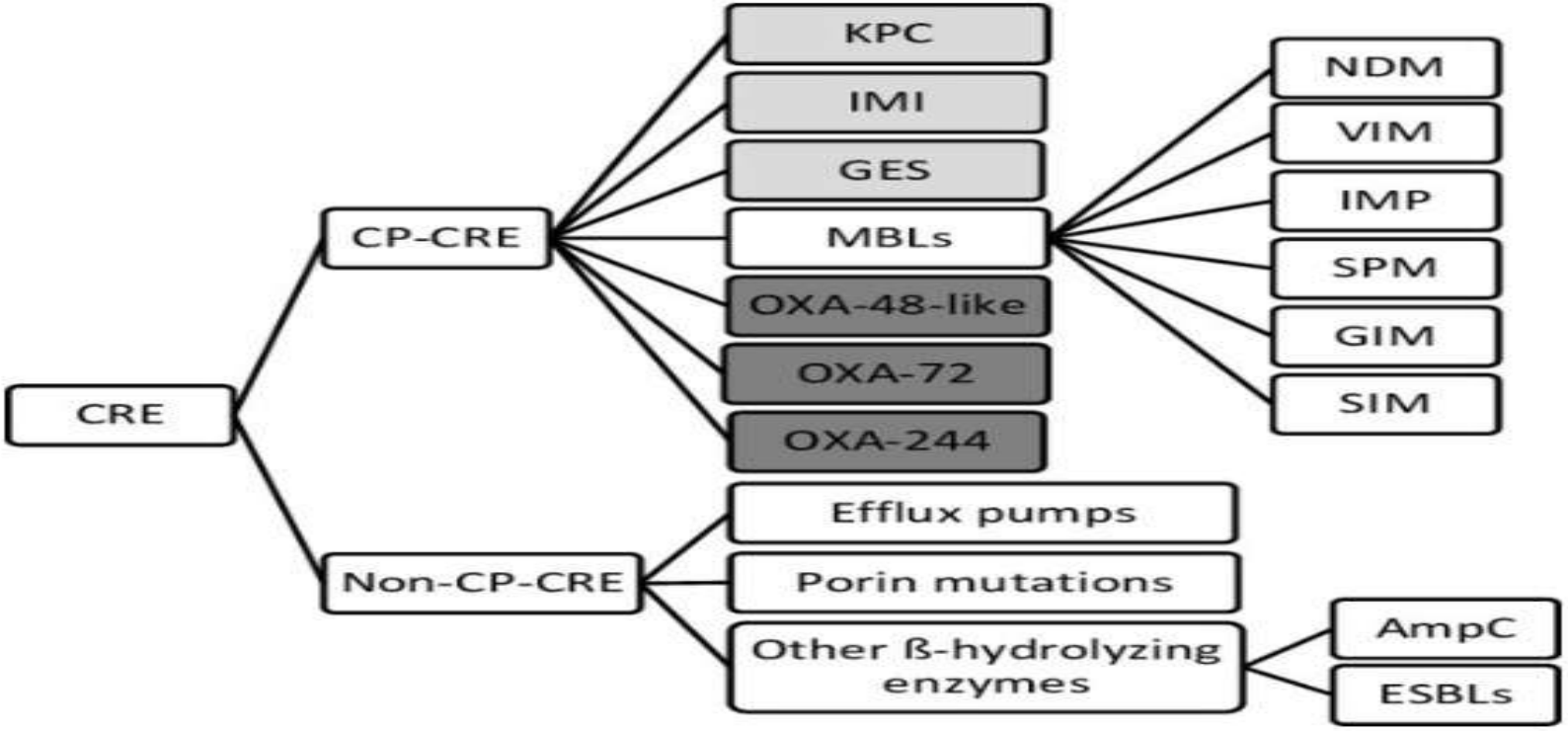
- Azole-resistant *Aspergillus fumigatus*
- Drug-resistant *Mycoplasma genitalium*
- Drug-resistant *Bordetella pertussis*


Karbapeneme Dirençli
Enterobacterales
(KDE)
Antibiyotik direnci
Yeni
antibiyotikler
Yeni direnç
mekanizmaları
Tedavide sorun

Karbapeneneme dirençli *Enterobacterales* (KDE) takımı üyeleri

-En az bir karbapeneneme dirençli (genellikle imipeneme duyarlı olmayan bakteriler (örneğin Proteus spp., Morganella spp., Providencia spp.) için imipenem dışında) (hedef proteinde değişiklikler, efluks pompalarında artış veya membran geçirgenliğinde azalma + bir beta-laktamazın edinilmesi veya up-regülasyonu) veya bir karbapenemaz enzimi üretir (kromozomal olarak ya da plazmid aracılığıyla kazanarak)

- KPC ABD, Kolombiya, Arjantin, Yunanistan ve İtalya'da endemiktir
- MBL NDM-1 Hindistan, Pakistan ve Sri Lanka'da ana karbapenemaz
- OXA-48 Türkiye, Malta, Orta Doğu ve Kuzey Afrika'da endemiktir



Enterobacterales takımının karbapenemlere dirençli hale gelmesinin üç ana mekanizması vardır

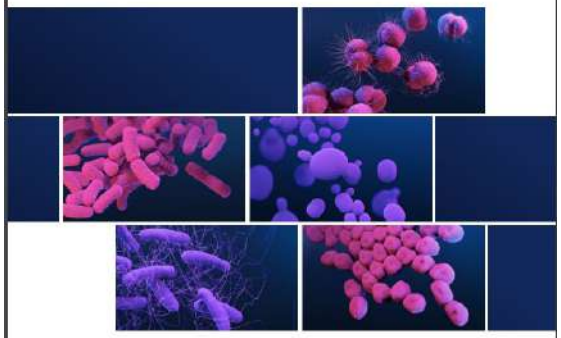
-Enzim üretimi (karbapenamazlar, ESBLs)

-Efluks pompaları

-Porin mutasyonları

ANTIBIOTIC RESISTANCE THREATS
IN THE UNITED STATES

2019



CDC's 2019 AR Threats Report: PREVENTION WORKS.

18% fewer deaths from antibiotic resistance overall since 2013 report

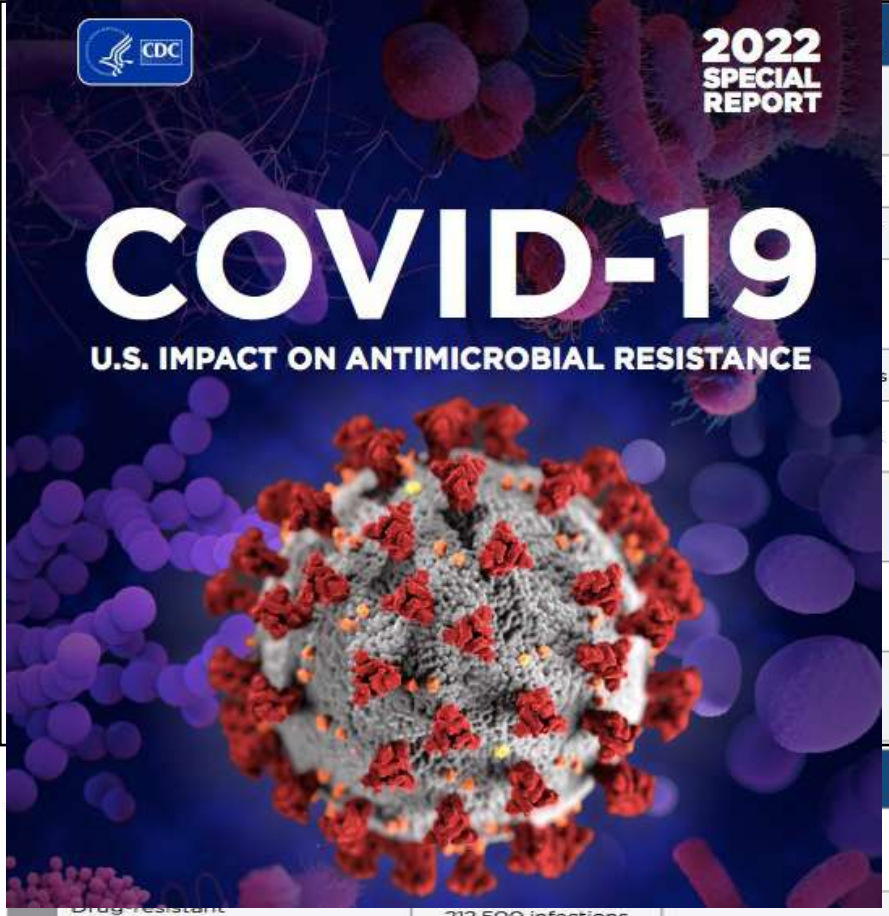
28% fewer deaths from antibiotic resistance in hospitals since 2013 report

AND DECREASES IN INFECTIONS CAUSED BY:

- **41%** Vancomycin-resistant *Enterococcus*
- **33%** Carbapenem-resistant *Acinetobacter*
- **29%** Multidrug-resistant *Pseudomonas aeruginosa*
- **25%** Drug-resistant *Candida*
- **21%** Methicillin-resistant *Staphylococcus aureus* (MRSA)
- **STABLE** Carbapenem-resistant Enterobacteriaceae (CRE) & drug-resistant tuberculosis (TB disease cases)

This following table summarizes the 2019 AR Threats Report estimates, and compares these estimates to the 2013 report when applicable.

Resistant germ	Threat Estimate, 2019 report	What CDC Counted, 2019 report	What CDC Did Not Count, 2019 report	Threat Estimate, 2013 report	New 2013 Threat Estimate, 2019 report	Can Data be Compared? 2013 vs 2019 reports	Year-to-Year Comparison Provided, 2019 report	Resistant Infection Increase/ Decrease, 2019 report
Drug-resistant *Neisseria gonorrhoeae*	550,000 infections	All infections	N/A	246,000 infections & <5 deaths	N/A	Yes	Resistance over time from 2000-2017	↑ Increase
Candida auris	323 clinical cases	Clinical cases	Colonization/ screening cases	N/A—was not listed in 2013 report	N/A	N/A	Cases over time from 2015-2018	↑ Increase
ESBL-producing Enterobacteriaceae	197,400 cases & 9,100 deaths	Incident hospitalized positive clinical cultures, including hospital- & community-onset	Non-hospitalized cases	26,000 healthcare associated infections & 1,700 deaths	131,900 cases & 6,300 deaths (2012 estimates)	No	Cases over time from 2012-2017	↑ Increase
Erythromycin-resistant group A *Streptococcus*	5,400 infections & 450 deaths	Invasive infections	Non-invasive infections including common upper-respiratory infections like strep throat	1,300 infections & 160 deaths	N/A	Yes	Invasive infection rates over time from 2010-2017	↑ Increase
Carbapenem-resistant Enterobacteriaceae	13,100 cases & 1,100 deaths	Incident hospitalized positive clinical cultures, including hospital- & community-onset	Non-hospitalized cases	9,300 healthcare associated infections & 600 deaths	11,800 cases & 1,000 deaths (2012 estimates)	No	Cases over time from 2012-2017	Stable



			2019 Threat Estimate	2017-2019 Change	2020 Threat Estimate and 2019-2020 Change
			6,000 cases 500 deaths	Stable*	7,500 cases 700 deaths **Overall: 35% increase*** **Hospital-onset: 78% increase***
			466 clinical cases	Increase	754 cases **Overall: 60% increase**
			202,600 infections 11,500 deaths	Decrease	Data delayed due to COVID-19 pandemic
			11,900 cases 1,000 deaths	Decrease*	12,700 cases 1,100 deaths Overall: Stable* **Hospital-onset: 35% increase***
			942,000 infections	Increase	Data unavailable due to COVID-19 pandemic
			725,210 infections	Increase	Data delayed due to COVID-19 pandemic‡ 26% of infections were resistant, a 10% decrease
			26,600 cases 1,300 deaths	Decrease*	28,100 cases 1,400 deaths **Overall: 12% increase*** **Hospital-onset: 26% increase***
			194,400 cases 9,000 deaths	Increase*	197,500 cases 9,300 deaths **Overall: 10% increase*** **Hospital-onset: 32% increase***
			47,000 cases 4,700 deaths	Stable*	50,300 cases 5,000 deaths **Overall: 16% increase*** **Hospital-onset: 14% increase***

				2019 Threat Estimate	2017-2019 Change	2020 Threat Estimate and 2019-2020 Change
			28,200 cases 2,400 deaths	Decrease*	28,800 cases 2,500 deaths Overall: Stable* **Hospital-onset: 32% increase***
SERIOUS	Drug-resistant nontyphoidal *Salmonella*	212,500 infections 70 deaths	228,290 infections	254,810 infections	Increase	Data delayed due to COVID-19 pandemic‡ 14% of infections were resistant, a 3% decrease
	Drug-resistant *Salmonella* serotype Typhi	4,100 infections <5 deaths	4,640 infections	6,130 infections	Increase	Data delayed due to COVID-19 pandemic‡ 85% of infections were resistant, a 10% increase
	Drug-resistant *Shigella*	77,000 infections <5 deaths	215,850 infections	242,020 infections	Increase	Data delayed due to COVID-19 pandemic‡ 46% of infections were resistant, a 2% increase
	Methicillin-resistant *Staphylococcus aureus*	323,700 cases 10,600 deaths	298,700 cases 10,000 deaths	306,600 cases 10,200 deaths	Stable*	279,300 cases 9,800 deaths Overall: Stable* **Hospital-onset: 13% increase***
	Drug-resistant *Streptococcus pneumoniae*	12,100 invasive infections 1,500 deaths†	See pathogen page if comparing data over time	12,000 invasive infections 1,200 deaths	Stable	Data delayed due to COVID-19 pandemic
	Drug-resistant Tuberculosis (TB)	888 cases 73 deaths†	962 cases 102 deaths	919 cases	Stable	661 cases Decrease‡
CONCERNING	Erythromycin-resistant group A *Streptococcus*	5,400 infections 450 deaths†	See pathogen page if comparing data over time	6,200 infections 560 deaths	Increase	Data delayed due to COVID-19 pandemic
	Clindamycin-resistant group B *Streptococcus*	13,000 infections 720 deaths†	See pathogen page if comparing data over time	15,300 cases 940 deaths	Increase	Data delayed due to COVID-19 pandemic

> Acta Microbiol Immunol Hung. 2021 Jul 29. doi: 10.1556/030.2021.01525. Online ahead of print.

Ceftazidime – Avibactam susceptibility among carbapenem-resistant Enterobacterales in a pilot study in Turkey

Hasan Selcuk Ozger [1], Ebru Evren [2], Serap Suzuk Yildiz [3], Cigdem Erol [4], Fatma Bayrakdar [3], Ozlem Azap [4], Alpay Azap [5], Esin Senol [1]

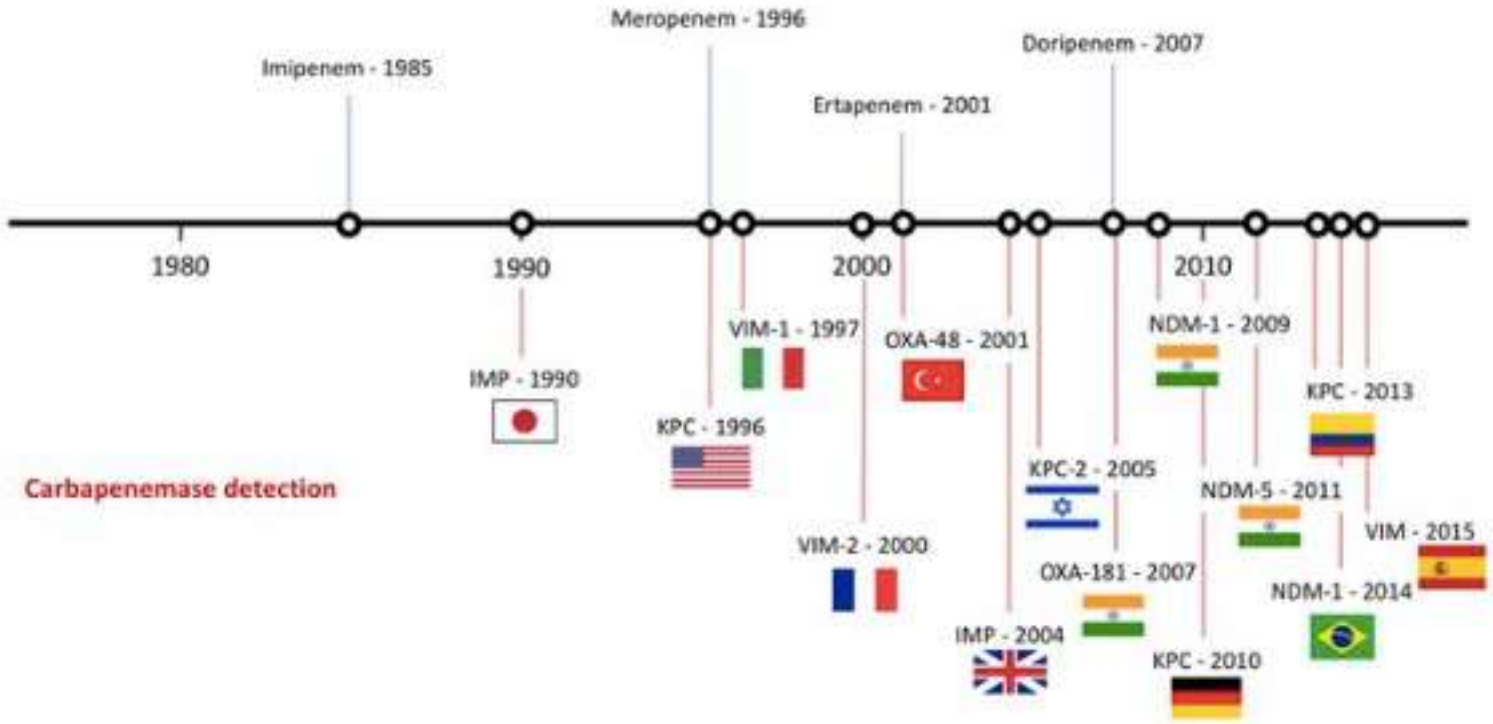
- Toplam 318 karbapeneme dirençli *Enterobacterales* izolatı
- Karbapenemaz genlerini saptamada PCR
- Seftazidim-Avibaktam (CZA) in vitro duyarlılığı broth mikrodilüsyon (BMD) ve disk difüzyon yöntemleri ile değerlendirilmiş
- n = 290, %91,2 *K.pneumoniae*
- En yaygın karbapenemaz OXA-48 (n=82) ve 2 adet KPC karbapenemaz
- 84 izolatta hem broth mikrodilüsyon hem de disk difüzyon yöntemleri ile CZA çalışılmış ve 4 izolat CZA'a dirençli

> Lab Med. 2020 Nov 2;51(6):601-605. doi: 10.1093/labmed/lmaa017.

Molecular Epidemiology of Carbapenem-Resistant Enterobacterales Strains Isolated from Blood Cultures in Antalya, Turkey

Harun Reşid Su [1], Özge Turhan [2], Cemile Aylin Erman Daloğlu [3], Meral Dilara Öğünç [3], Betil Özhak [3], Gözde Öngüt [3], Mert Ahmet Kuşkucu [4], Kenan Midilli [4], Latife Mamıkoğlu [2]

- 2010-2015 yılları arasında 330 en az 1 karbapeneme duyarlılığı azalmış *Enterobacterales* kan kültürü izolatı
- Karbapenemaz ve CTX-M genleri araştırılmış
- Karbapeneme dirençli 152 izolatın 113'ünde (%74,3) en az 1 karbapenemaz geni saptanmış
- OXA-48 (%69,7) en yaygın karbapenemaz (VIM, NDM ve IMP saptanan diğer karbapenemazlar)
- Hiçbir izolat KPC-pozitif değildi
- Seksen altı izolatta (%56,6) CTX-M ve 65'inde hem OXA-48 hem de CTX-M vardı


Carbapenem introduction
Imipenem - 1985
Meropenem - 1996
Doripenem - 2007
Ertapenem - 2001
1980
1990
2000
2010
IMP - 1990
VIM-1 - 1997
OXA-48 - 2001
NDM-1 - 2009
KPC - 2013
KPC - 1996
KPC-2 - 2005
NDM-5 - 2011
VIM - 2015
VIM-2 - 2000
OXA-181 - 2007
NDM-1 - 2014
IMP - 2004
KPC - 2010
Carbapenemase detection

UK Health Security Agency

Framework of actions to contain carbapenemase-producing Enterobacterales

September 2022

Enterobacterales	A group of bacteria that usually live harmlessly in the gut of humans (and animals). They include *Escherichia coli* (*E. coli*), *Klebsiella* spp., *Enterobacter* spp.
high-risk for colonisation and or infection with CPE	• patients with a history of an overnight stay in hospital within the last 12 months, including abroad • patients who were previously identified as CPE positive • patients who have multiple hospital admissions or treatments for example are dialysis dependent or have had cancer chemotherapy in last 12 months • epidemiological link to a known carrier of CPE • patients who are admitted into augmented care or high risk units

- Yurt dışı dahil son 12 ay içinde bir gece hastanede kalma öyküsü olan hastalar
- Öncesinde KÜE pozitif olduğu belirlenen hastalar
- Birden fazla hastaneye başvuran veya tedavi gören hastalar, örneğin diyalize bağımlı olanlar veya son 12 ay içinde KT görmüş olanlar
- Bilinen bir KÜE taşıyıcısıyla epidemiyolojik bağlantı
- Artırılmış bakıma veya yüksek riskli birimlere kabul edilen hastalar

UK Health Security Agency

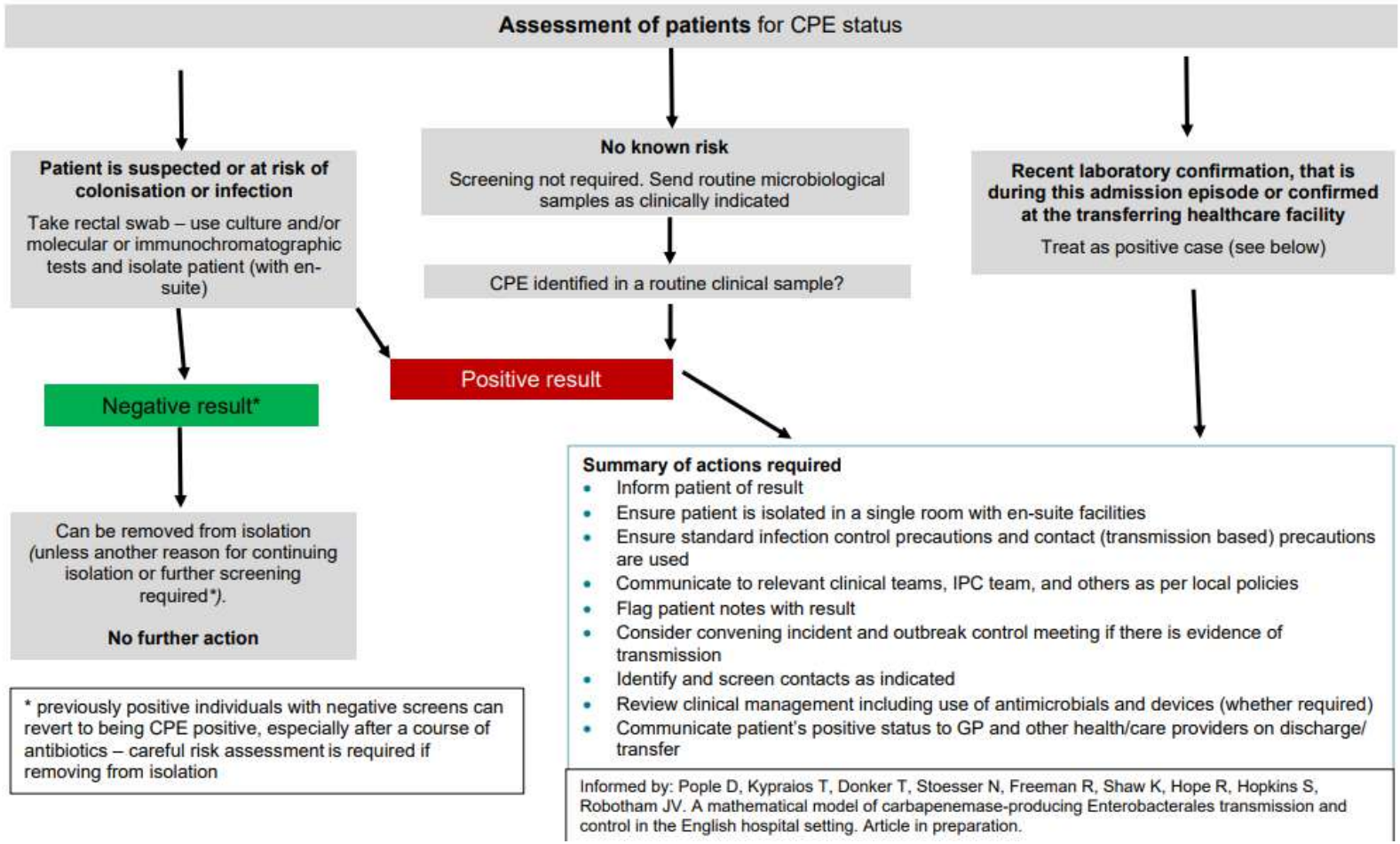
RISK

R – Recent exposure to antibiotics	Patients that have received the following antibiotics in the previous month are at increased risk of CPE carriage: • Cephalosporins • Piperacillin and tazobactam • Fluoroquinolones • Carbapenems
I – In the last 12 months	Screen if a patient: • previously been identified as CPE positive • was admitted to any hospital in the UK or overseas • has had multiple hospital treatments for example haemodialysis or receiving cancer chemotherapy

S – Specialty	Patients admitted to the following specialties should be screened:
	• augmented care
	• high risk settings –
	  • immunosuppression
	  • transplant
	  • haematology and oncology
	  • organ support
	  • extensive care needs for example liver
	  • burns unit
	• Long Term Care Facilities where higher levels of interventional care are provided for example long term ventilation

K – Knowledge of local CPE transmission	Screen if patient has been in contact with a known case of CPE

UK Health Security Agency

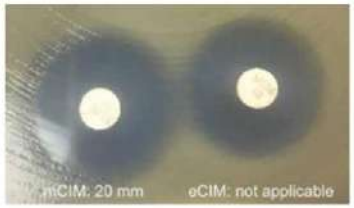


Enterobacterales ve *P. aeruginosa* izolatlarında karbapenemazları tespit eden fenotipik testler

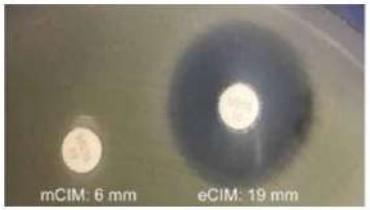
	Organisms	Strengths	Limitations	Regulatory Status
mCIM and/or eCIM (see Fig 5a)	Enterobacterales *P. aeruginosa*	• Detects KPC, IMP, VIM, NDM andOXA-48 like carbapenemases with high sensitivity and specificity of >90% • High sensitivity (>90%) and specificity (>90%) with class A (KPC), class B (IMP, VIM, NDM), and class D (OXA-48 like) carbapenemases • eCIM is capable of detecting class B enzymes.	• Long turn-around time (18–24 h) • When class B and class A/D carbapenemases are co-expressed, eCIM is unable to detect class B enzymes.	CLSI recommended
Carba NP® (see Fig 5b)	Enterobacterales *P. aeruginosa*	• Detects class A and class B carbapenemases with the sensitivity and specificity of >90% • Rapid turn-around time (5 min-2 h)	• Class D carbapenemases and mucoid isolates yielded false negatives Doesn't differentiate the class of carbapenemase	CLSI recommended
RAPIDEC carba NP® (see Fig 5b)	Enterobacterales *P. aeruginosa*	As mentioned in carba NP®	As mentioned in carba NP®	FDA
NG-Test CARBA 5® (Multiplex lateral flow immunoassay) (see Fig 5c)	Enterobacterales	• High sensitivity (100%) and specificity (100%) for carbapenemases of classes A, B, and DRapid turn-around time (<15 min) • Differentiate the classes of carbapenemase	• Fails to detect carbapenemases such as GES, SME, IMI, and NMC, which are rare carbapenemases.	FDA
Accelerate 8Pheno® system (In development)	Enterobacterales *P. aeruginosa* *A. baumannii*	-	-	-

*mCIM – Modified carbapenem inactivation; Ecim – EDTA modified carbapenem inactivation; TAT – turnaround time; CLSI – Clinical and Laboratory Standards Institute; FDA – Food and Drug Administration

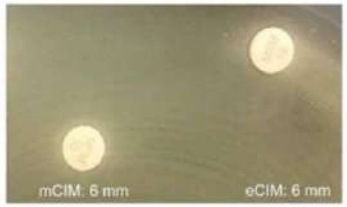
A. Modified carbapenem inactivation method (mCIM) and EDTA mCIM (eCIM)



Carbapenemase not detected

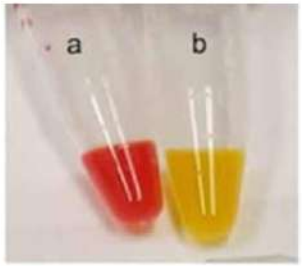


Metallo beta-lactamases detected

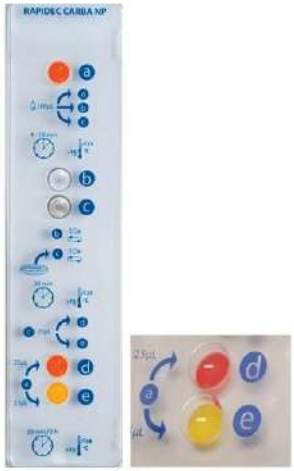


Serine carbapenemase detected

B. Carba NP and variant



Manual carba NP - CLSI



Rapidec carba NP

C. Multiplex lateral flow immunoassay

NG test carba 5

MİK değeri önemli mi??

KDE infeksiyonlarını tedavi etmek için kullanılan antimikrobiyal ajanlar için mümkünse MİK'ler belirlenmelidir

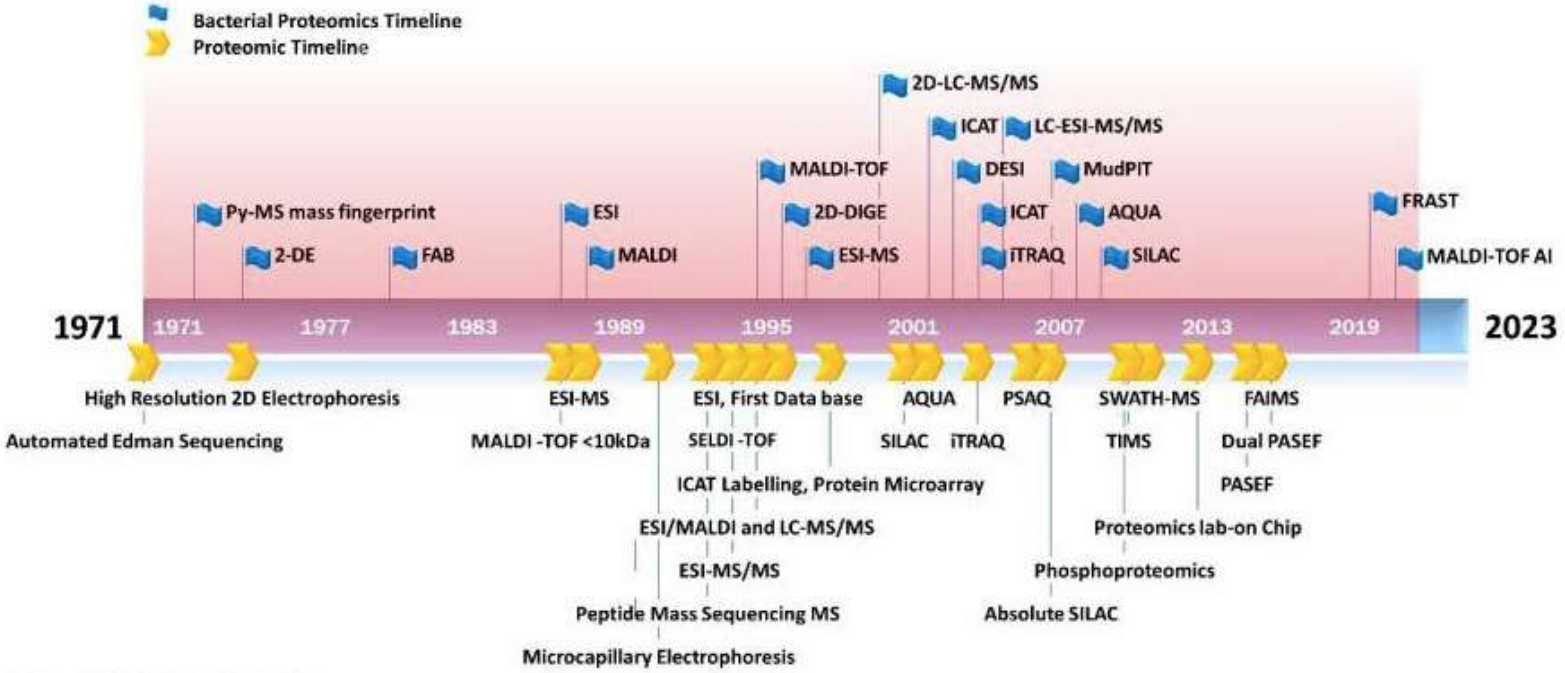
EUCAST ve CLSI önerileri dikkate alınarak testler uygulanmalı

- Sıvı mikrodilüsyon standart yöntem
- Agar dilüsyon yöntemi veya E-test yöntemi
- Otomatik antimikrobiyal duyarlılık test sistemleri de göreceli olarak düşük doğruluğa rağmen kullanılabilir

- ✓ Kolistin (sıvı mikrodilüsyon, modifiye disk elisyon)
- ✓ Fosfomisin (agar dilüsyon, sıvı mikrodilüsyon)

KDE izolatlarında karbapenemazların tespiti için onaylanmış moleküler yöntemler

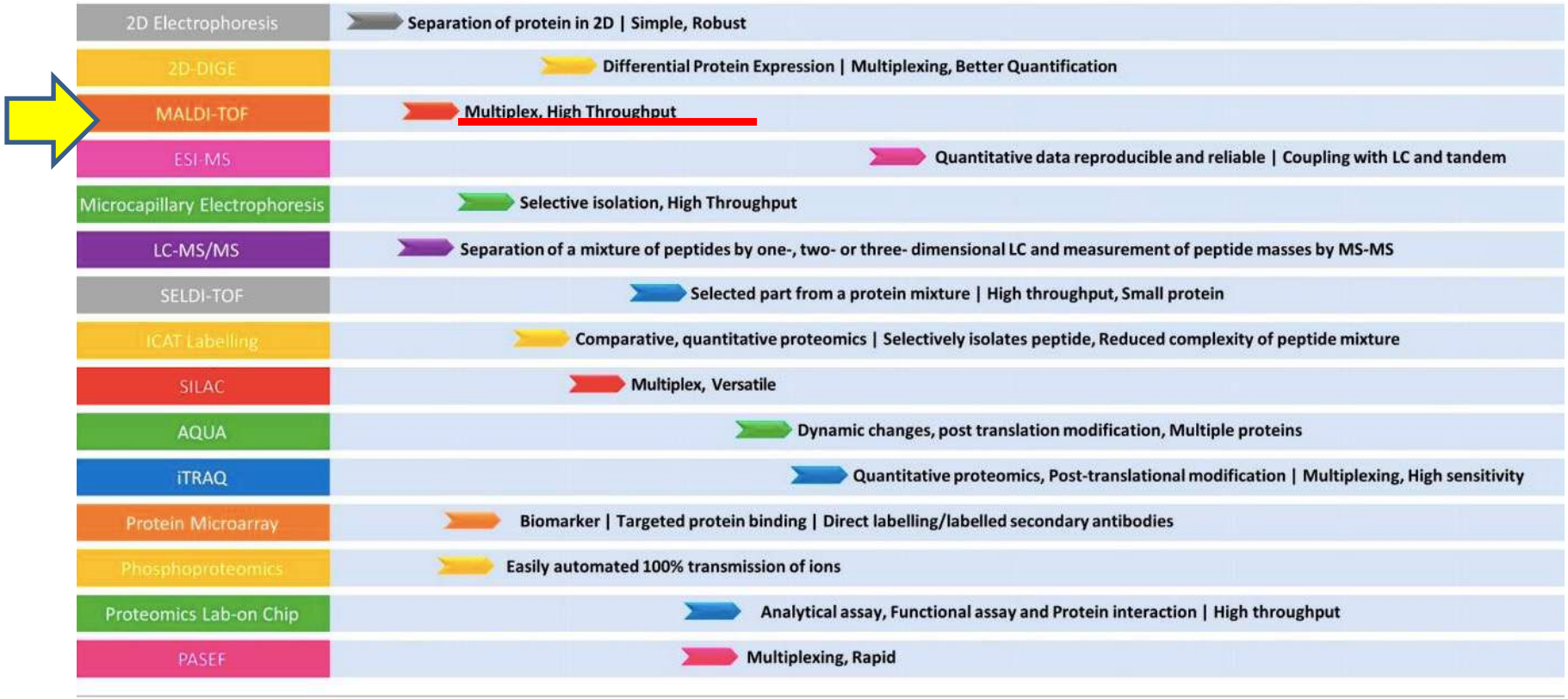
Assay	Method	Time of results	Source	Detection of carbapenemases gene	Sensitivity (%)	Specificity (%)	Approval
Xpert Carba-R®	Real time multiplex PCR	2 hrs	Isolate	KPC, IMP, VIM, NDM, OXA-48 like	1[illegible]0	100	CE-IVD FDA IVD
BioFire film Array®	Real-time PCR	1-2 h	Positive blood culture	KPC	NA	NA	CE-IVD FDA IVD
Nanosphere Verigene BC-GN®	Microarray	2 h	Positive blood culture	KPC, NDM, VIM, IMP, OXA	NA	NA	CE-IVD FDA IVD
EntericBio CPE® assay	Real time multiplex PCR	2 h	Isolate, swabs	KPC, IMP, VIM, NDM, OXA-48 like, GES-5, IMI, OXA-23	100	100	RUO
Check- Direct CPE® assay	Real time multiplex PCR	3.5 h	Rectal swab/ Isolate	KPC, OXA-48 including OXA-181, VIM and NDM	100	94%	RUO
AID® line probe assay	Multiplex PCR and reverse hybridization with carbapenemases probes	5 h	Various clinical specimens	KPC, IMP, VIM, NDM, OXA-48, SIM, SPM, AIM, BIC, DIM, GIM, IMI, NMC-A	97.7	NA	RUO
Hyplex MBL ID® system	Multiplex PCR and reverse hybridization with carbapenemases probes	5 h	Various clinical specimens	VIM and IMP	98	98.6	RUO
BB MAX™ CRE Assay®	Real-time PCR	2 h	Rectal swab/ Isolate	KPC, NDM, oxa-48	93.1	97.3	RUO
Check-MDR 103 XL	PCR followed by microarray	6.5 h	Isolate	KPC, OXA-48, VIM, NDM, GES, GIM, SPM, OXA-23 like, Oxa-24 like	100	100	RUO
Eazyplex® SuperBug CRE®	Loop mediated	15 min	Positive blood	KPC, NDM, VIM	100	100	RUO



Py- MS : Pyrolysis Mass Spectrometry
2-DE :Two Dimensional Electrophoresis
FAB : Fast Atom Bombardment
ESI : Electrospray ionization
MALDI : matrix-assisted laser desorption ionization
MALDI – TOF: matrix-assisted laser desorption ionization-time of flight
2D-DIGE: Two dimensional differential gel electrophoresis

DESI : Desorption electrospray ionization
LC–MS : Liquid chromatography – mass spectrometry
ICAT : Isotope-coded affinity tag
iTRAQ : Isobaric tag for relative and absolute quantitation
MudPIT : multidimensional protein identification technology
SILAC : stable isotope labeling by amino acids in cell culture
AQUA: absolute quantification
PSAQ: protein standard absolute quantification

TIMS :Trapped ion mobility spectrometry
FAIMS: High-Field Asymmetric Waveform Ion Mobility Spectrometry
SWATH–MS : Sequential window acquisition of all theoretical fragment-ion spectra mass spectrometry
PASEF :Parallel Accumulation Serial Fragmentation
FRAST : Fast Raman-Assisted Antibiotic Susceptibility Test
MALDI–TOF/AI: matrix-assisted laser desorption ionization-time of flight / Artificial Intelligence

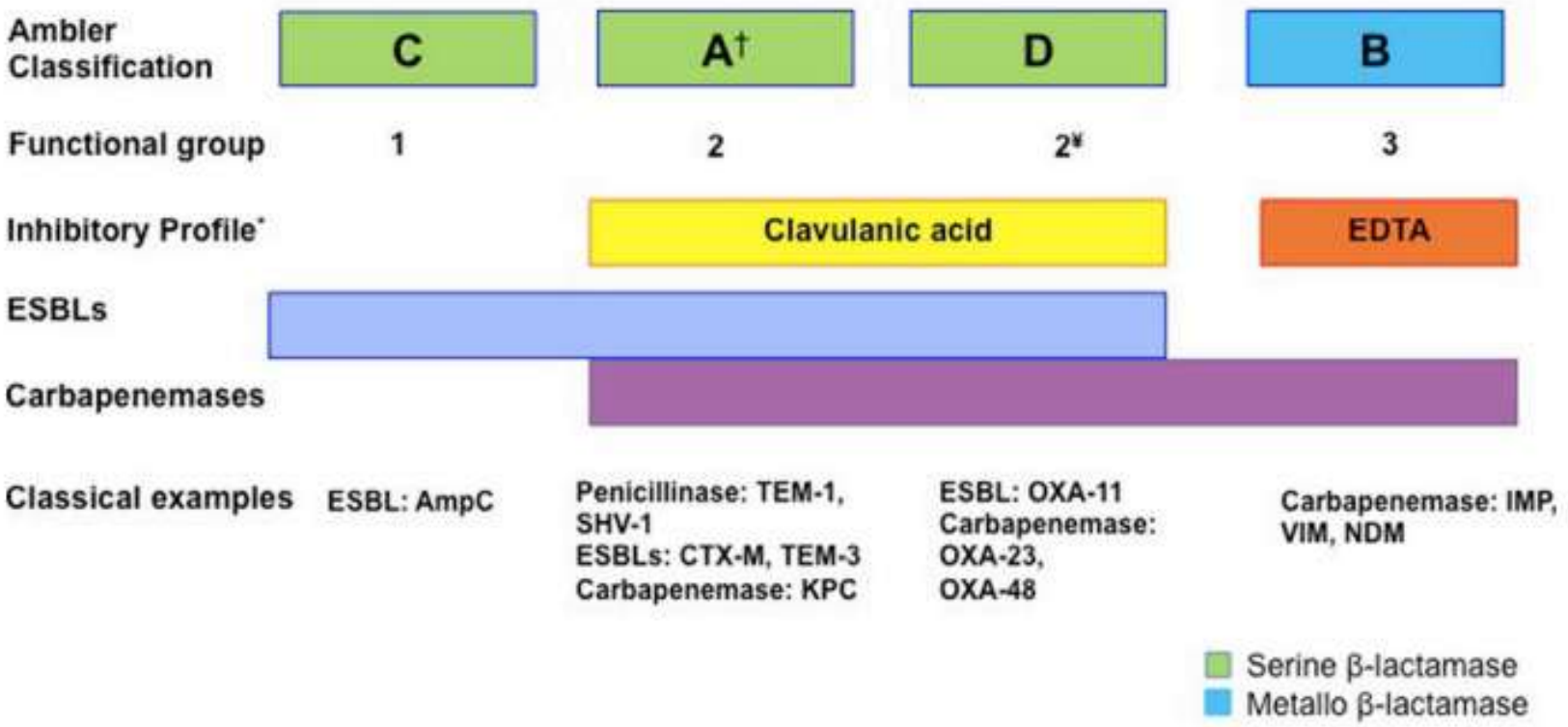

2D Electrophoresis
Separation of protein in 2D | Simple, Robust
2D-DIGE
Differential Protein Expression | Multiplexing, Better Quantification
MALDI-TOF
Multiplex, High Throughput
ESI-MS
Quantitative data reproducible and reliable | Coupling with LC and tandem
Microcapillary Electrophoresis
Selective isolation, High Throughput
LC-MS/MS
Separation of a mixture of peptides by one-, two- or three- dimensional LC and measurement of peptide masses by MS-MS
SELDI-TOF
Selected part from a protein mixture | High throughput, Small protein
ICAT Labelling
Comparative, quantitative proteomics | Selectively isolates peptide, Reduced complexity of peptide mixture
SILAC
Multiplex, Versatile
AQUA
Dynamic changes, post translation modification, Multiple proteins
iTRAQ
Quantitative proteomics, Post-translational modification | Multiplexing, High sensitivity
Protein Microarray
Biomarker | Targeted protein binding | Direct labelling/labelled secondary antibodies
Phosphoproteomics
Easily automated 100% transmission of ions
Proteomics Lab-on Chip
Analytical assay, Functional assay and Protein interaction | High throughput
PASEF
Multiplexing, Rapid

- Karbapenemaz üreten izolatlar, ABD’de KDE vakalarının yaklaşık %35-%59'unu oluşturmaktadır
- ABD'nde en yaygın karbapenemazlar, *K. pneumoniae* izolatlarıyla sınırlı olmayan *K. pneumoniae* karbapenemazlarıdır (KPC'ler).
- Ayrıca New Delhi metallo-β-laktamazları (NDM'ler), Verona integron-encoded metallo-β-laktamazları (VIM'ler), imipenem-hidrolize metallo-β-laktamazları (IMP'ler) ve oksasilinazlar (örn. OXA-48 like)
- Bir KDE izolatının karbapenemaz üretip-üretmediğinin ve eğer üretiyorsa, üretilen spesifik karbapenemazın bilinmesi tedavi kararlarının yönlendirilmesinde önemlidir.

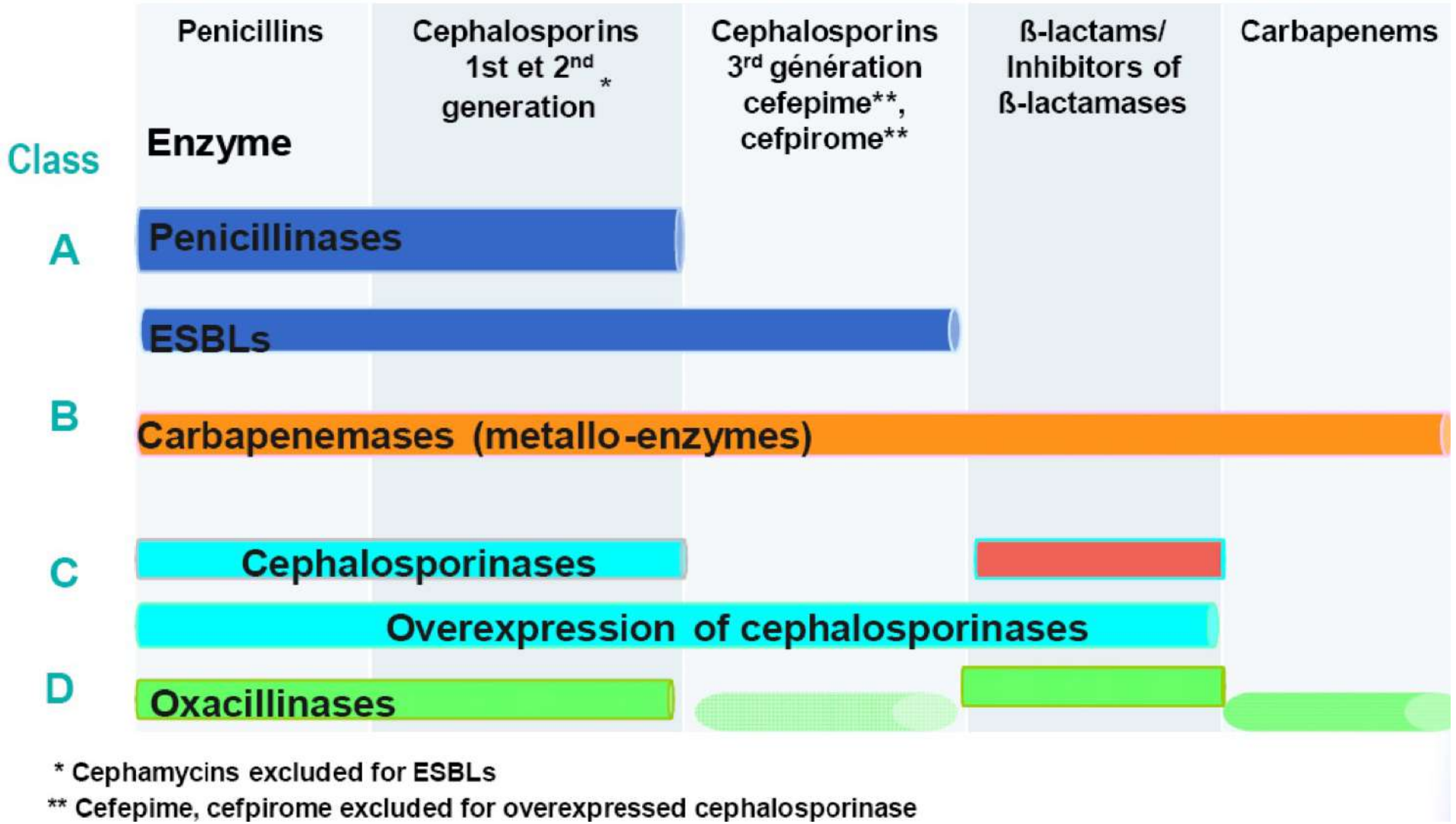
- Modifiye karbapenem inaktivasyon yöntemi gibi fenotipik testler, karbapenemaz ve karbapenemaz üretmeyen KDE'yi ayırt eder
- Moleküler testler spesifik karbapenemaz gen ailelerini tanımlayabilir (örneğin, blaKPC'yi blaOXA-48 benzeri genlerden ayırmak)
- Klinik mikrobiyoloji laboratuvarlarını optimal tedavi kararları için karbapenemaz testlerini takip etmeye önerisi mevcut

	Enterobacterales		
	Class A Carbapenemase (*e.g.* KPC)	**Class B Carbapenemase (*e.g.* NDM)**	**Class D Carbapenemase (*e.g.* OXA-48)**
Ceftobiprole			
Ceftolozane-tazobactam			
Ceftazidime-avibactam			
Cefiderecol			
Meropenem-vaborbactam			
Imipenem-relebactam			
Aztreonam-avibactam			
Plazomicin			
Eravacycline			

New antibiotics for Gram-negative pneumonia. European Respiratory Review 2022 31: 220119; DOI: 10.1183/16000617.0119-2022

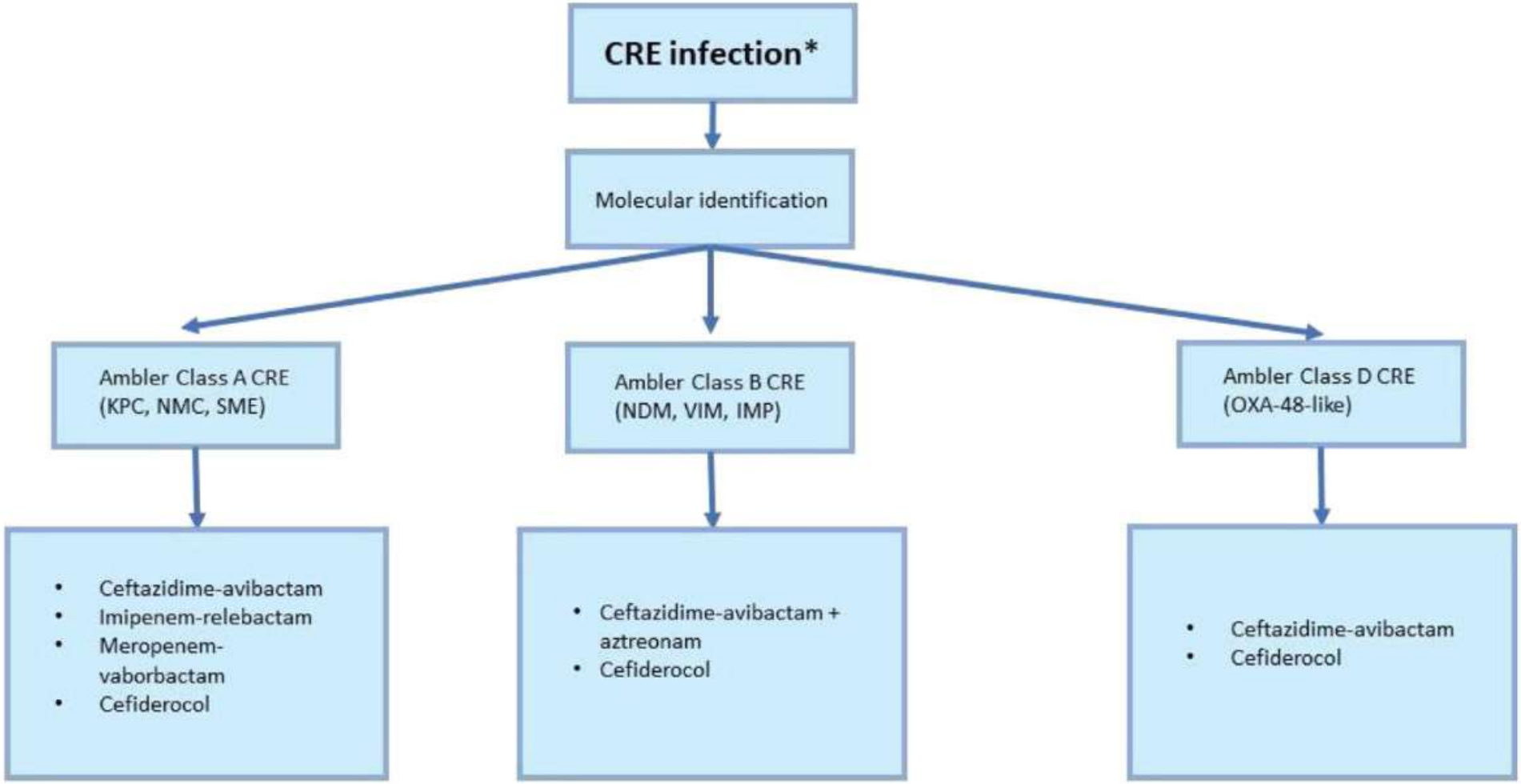

Ambler Classification
C
A†
D
B
Functional group
1
2
2¥
3
Inhibitory Profile*
Clavulanic acid
EDTA
ESBLs
Carbapenemases
Classical examples
ESBL: AmpC
Penicillinase: TEM-1, SHV-1
ESBLs: CTX-M, TEM-3
Carbapenemase: KPC
ESBL: OXA-11
Carbapenemase: OXA-23, OXA-48
Carbapenemase: IMP, VIM, NDM
Serine β-lactamase
Metallo β-lactamase

GNB Betalaktamazlar



* Cephamycins excluded for ESBLs

** Cefepime, cefpirome excluded for overexpressed cephalosporinase


CRE infection*
Molecular identification
Ambler Class A CRE (KPC, NMC, SME)
Ambler Class B CRE (NDM, VIM, IMP)
Ambler Class D CRE (OXA-48-like)
• Ceftazidime-avibactam
• Imipenem-relebactam
• Meropenem-vaborbactam
• Cefiderocol
• Ceftazidime-avibactam + aztreonam
• Cefiderocol
• Ceftazidime-avibactam
• Cefiderocol

IDSA 2023 Guidance on the Treatment of Antimicrobial Resistan Gram-Negative Infections

Published by IDSA on 6/7/2023. Document is current as of 12/01/22, 7/1/2023

Guidelines

European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine)

Mical Paul [1, 2, §], Elena Carrara [3, §], Pilar Retamar [4, 5], Thomas Tängdén [6], Roni Bitterman [1, 2], Robert A. Bonomo [7, 8, 9], Jan de Waele [10], George L. Daikos [11], Murat Akova [12], Stephan Harbarth [13], Celine Pulcini [14, 15], José Garnacho-Montero [16], Katja Seme [17], Mario Tumbarello [18], Paul Christoffer Lindemann [19], Sumanth Gandra [20], Yunsong Yu [21, 22, 23], Matteo Bassetti [24, 25], Johan W. Mouton [26, †], Evelina Tacconelli [3, 27, 28, *, §], Jesús Rodríguez-Baño [4, 5, §]

Dirençli patojenlere özel bir tedavi süresi önerisi yok

Duyarlı suşlar için tedavi süresi = dirençli suşlar için tedavi süresi

Kültür sonuçları elde edildiğinde

-Sistit dışındaki tüm infeksiyon hastalıklarında klinik iyileşme gözlense bile tedavinin kültür sonucuna göre duyarlı bir ajanla değiştirilmesi ve tedavi süresinin başlangıç tarihi için aktif ajanın başlandığı günün esas alınması önerilir

IDSA Infectious Diseases Society of America

ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

Kombinasyon tedavileri (Beta laktam antibiyotik+aminoglikozit, florokinolon veya polimiksin kombinasyonu) KDE infeksiyonlarının tedavisinde rutin olarak önerilmemekte

Tedavilerinde önerilen ajanların yan etki profilleri göz önüne alındığında, yeni kuşak beta laktam antibiyotiğe karşı duyarlılık gösterilmişse tedaviye yalnızca yeni beta laktam antibiyotik ile devam edilmesi önerilmekte

→ NDM ve diğer metallo-β-laktamaz üreten infeksiyonlar için seftazidime-avibaktam tercih edilecekse aztreonam ile kombine edilmelidir

Tigesiklin veya eravasiklin, kan dolaşımı veya idrar yolunu içermeyen KDE infeksiyonlarının tedavisi için alternatif seçeneklerdir

IDSA
Infectious Diseases Society of America

ESCMID
EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

- Meropenem MİK değeri > 8 mg/L → KDE infeksiyonları için karbapenem bazlı kombinasyon tedavisinden kaçınmalıdır

- Yeni betalaktam antibiyotikler kullanılmıyorsa, kombinasyon tedavisinin bir parçası olarak yüksek doz uzatılmış infüzyon meropenem (MİK≤8 mg/L ise) kullanılabilir ***

ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

KRE'nin neden olduğu ciddi infeksiyonların tedavisinde yüksek doz, uzatılmış infüzyon meropenem+polimiksin kombinasyon tedavisinin polimiksin monoterapisine göre avantajlı olduğuna dair düşük kesinlikte kanıt

Çift karbapenem kullanımı için çelişkili invitro veri mevcut

Gözlemsel çalışmalar yeterince standardize değil, daha fazla değerlendirme gerektirdiği sonucuna varılmış yetersiz kanıt

ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

- Hızlı testler ile karbapenemaz türünün belirlenmesi ve tedavinin bu doğrultuda şekillenmesi önerisi var
- KPC enzimine sahip suşların infeksiyonlarında seftazidim-avibaktam veya meropenem-vaborbaktam
- OXA-48-benzeri enzime sahip suşların infeksiyonlarında seftazidim-avibaktam

ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

- Yeni antibiyotikler temin edilemiyorsa, eski antibiyotiklerin (polimiksin, tigesiklin, fosfomisin, aminoglikozid, meropenem) kombinasyonu (in vitro etkili 2 antibiyotik kombinasyonu) önerilmektedir
- Meropenem MİK ≤8 mg/L olmadıkça kombinasyonda yer alması önerilmemektedir

IDSA kılavuzu eski antibiyotiklerle yapılan kombinasyon tedavilerini önermemekte

- ✓ Yeni antibiyotiklerin olması
- ✓ Klinik çalışmalarda özellikle seftazidim avibaktam ve meropenem vaborbaktamın polimiksin içeren kombinasyonlardan daha etkili olması
- ✓ Karbapenem kullanımından kaçınarak karbapeneme direncin önlenmesi
- ✓ Polimiksinlere bağlı nefrotoksisiteden kaçınmak

Yeni antibiyotiklerle tedavi yaklaşımları

	İlk tercih*	Alternatif
Komplike olmayan sistit	Siprofloksasin	Seftazidim-avibaktam
	Levofloksasin	Meropenem-vaborbaktam
	TMP-SXT	İmipenem-silastatin-relebaktam
	Nitrofurantoin	Sefiderokol
	Aminoglikozid	
Ertapenem dirençli Meropenem duyarlı (karbapenmaz test sonucu bilinmiyor ya da negatif)	Meropenem SD, Sİ	Kolistin**
Piyelonefrit/Komplike ÜSİ	Siprofloksasin	Aminoglikozid*
	Levofloksasin	
	TMP-SXT	
	Meropenem-vaborbaktam	
	İmipenem-silastatin-relebaktam	
	Sefiderokol	
Ertapenem dirençli Meropenem duyarlı (karbapenmaz test sonucu bilinmiyor ya da negatif)	Meropenem YD, Uİ	
Üriner Sistem Dışındaki İnfeksiyonlar		
Ertapenem dirençli-Meropenem duyarlı-(Karbapenemaz testi sonucu bilinmiyor ya da negatif)	Meropenem YD, Uİ	
Ertapenem dirençli-Meropenem dirençli-(Karbapenemaz testi sonucu bilinmiyor ya da negatif veya karbapenemaz pozitif fakat türü bilinmiyor)	Seftazidim-avibaktam	
	Meropenem-vaborbaktam	
	İmipenem-silastatin-relebaktam	
Enzim türü biliniyorsa	MBL(+) ise seftazidim-avibaktam + aztreonam veya sefiderokol monoterapisi	
	OXA-48(+) ise seftazidim-avibaktam	
	KPC(+) ise seftazidim-avibaktam veya meropenem-vaborbaktam	

Maruziyet sonrası direnç oranları

seftazidim-avibaktam %20

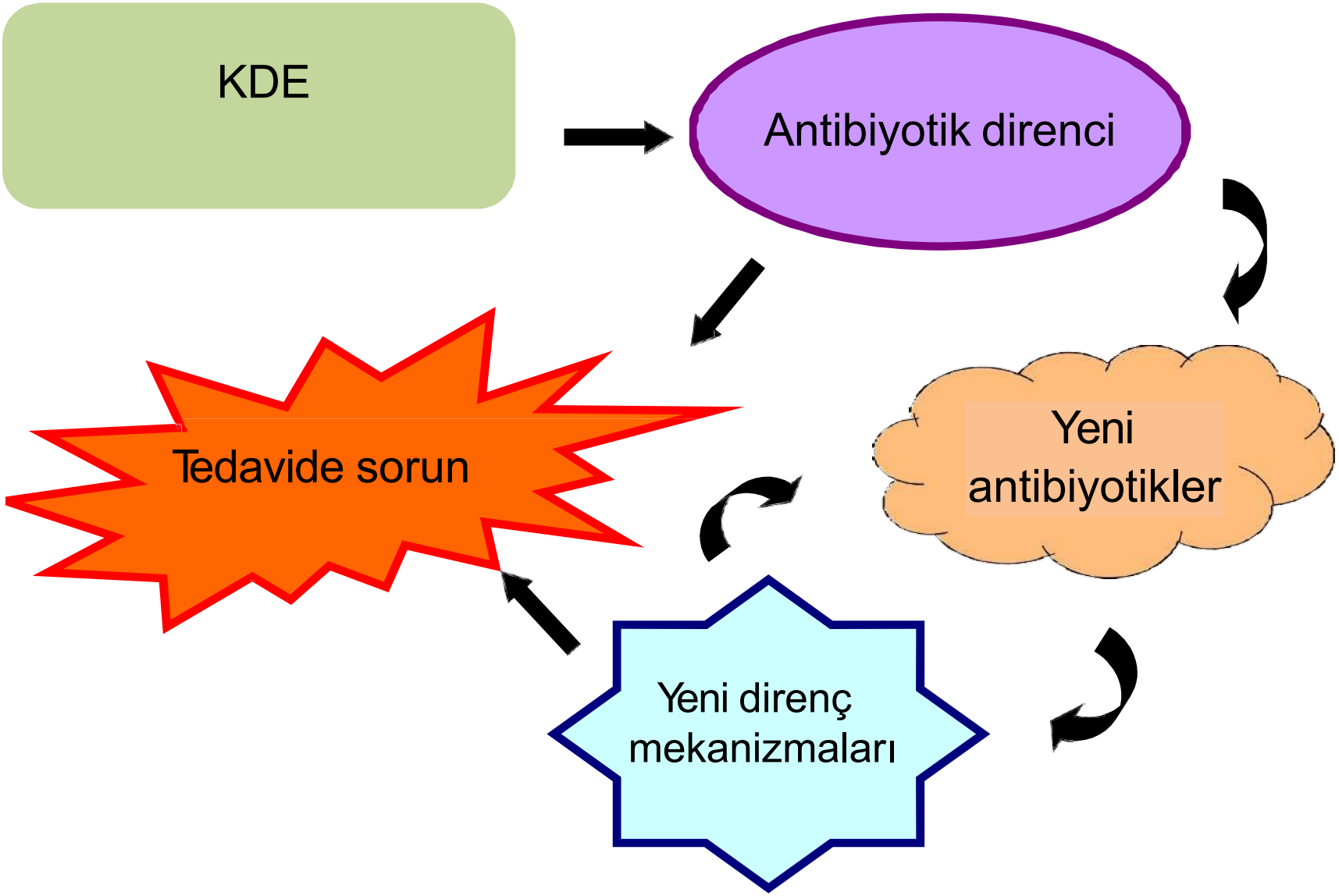
meropenem-vaborbaktam %3

Çalışmalar sınırlı olsa da seftazidim-avibaktamın monoterapi ya da kombinasyon rejiminin parçası olmasını dirençle ilişkilendirmemiş

Eski antibiyotiklerle tedavi yaklaşımları

Klinik Tablo	Ağır enfeksiyonlar**	Ağır olmayan enfeksiyonlar
Piyelonefrit veya Komplike ÜSİ		
Ertapenem dirençli-Meropenem dirençli ve Meropenem MİK ≤8 mg/L ise	Meropenem (YD,Uİ) + Kolistin Meropenem (YD,Uİ) + Aminoglikozid veya Fosfomisin veya Tigesiklin	Aminoglikozidler Kolistin Tigesiklin
Meropenem MİK >8 mg/L ise	Fosfomisin + Aminoglikozid Tigesiklin + Kolistin veya Gentamisin	
Seçenekler çok sınırlı ise	Çift karbapenem	
Kan Dolaşımı Enfeksiyonları		
Meropenem MİK ≤8 mg/L ise	Meropenem (YD, Uİ) + Polimiksin Meropenem (YD,Uİ) + Fosfomisin veya Tigesiklin	
Meropenem MİK >8 mg/L ise	Polimiksin+ Tigesiklin Polimiksin + Fosfomisin Tigesiklin + Aminoglikozid	
İntraabdominal Enfeksiyonlar		
Meropenem MİK ≤8 mg/L ise	Meropenem(YD,Uİ) + Tigesiklin	Tigesiklin
Meropenem MİK >8 mg/L ise	Polimiksin + Tigesiklin Fosfomisin + Tigesiklin Polimiksin + Fosfomisin Tigesiklin + Aminoglikozid	
Hastanede Gelişen Pnömoni veya Ventilatörle İlişkili Pnömoni		
Meropenem MİK ≤8 mg/L ise	Meropenem (YD,Uİ) + Polimiksin Meropenem + Fosfomisin	
Meropenem MİK >8 mg/L ise	Meropenem + Fosfomisin Fosfomisin + Tigesiklin (YD) Polimiksin + Tigesiklin (YD)	

Akalın H. Karbapenem Dirençli Enterobacteriaceae Enfeksiyonlarının Tedavisi. Türkiye Klinikleri


KDE
Antibiyotik direnci
Yeni antibiyotikler
Yeni direnç mekanizmaları
Tedavide sorun


İmkansıza ulaşmanın tek yolu, onun mümkün olduğuna inanmaktır.
Lewis Carrol

CRE Carbapenem-resistant Enterobacterales

An Urgent Public Health Threat

Information for Facilities

Carbapenem-Resistant Enterobacterales (CRE)

Enterobacterales is an order of gram-negative bacteria that includes some organisms commonly identified in clinical microbiology laboratories, like *Escherichia coli* and *Klebsiella pneumoniae*.

Carbapenems are last-line antibiotics used to treat serious multidrug-resistant infections. In the United States, about 2-3% of Enterobacterales associated with healthcare-associated infections are resistant to carbapenems.

CRE infections **don't respond to common antibiotics** and invasive infections are associated with high mortality rates. Some CRE are resistant to all available antibiotics.

COMMON ENTEROBACTERALES SPECIES:

- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Enterobacter cloacae*
- *Citrobacter freundii*
- *Serratia marcescens*

Carbapenemase-Producing CRE

A subset of CRE, called **carbapenemase-producing CRE, are primarily responsible for the rapid global spread of CRE,** including in U.S. healthcare settings. Carbapenemases are enzymes that inactivate carbapenems and other β-lactam antibiotics. Carbapenemase-producing CRE can share the genetic code for carbapenemases with other bacteria, rapidly spreading resistance.

CARBAPENEMASES MOST COMMONLY IDENTIFIED IN U.S. CRE

- KPC
- OXA-48-type
- NDM
- IMP
- VIM

How is CRE Transmitted?

CRE spreads through direct or indirect contact with patients infected or colonized with CRE or contaminated environment and surfaces. In healthcare, transmission is usually person to person, and CRE is often carried on the hands of health care personnel or on contaminated shared medical equipment (e.g., portable X-ray machines). Some environmental sources, such as sink drains and toilets, can be important reservoirs contributing to CRE transmission.

Who is at risk?

Hospital patients and long-term care facility residents, especially those who

- Receive complex medical care, including intensive care unit admission or having invasive devices
- Have taken certain antibiotics
- Need help with activities like toileting, bathing, and dressing

Anyone who had medical procedures or was admitted to a hospital outside the United States in the past 6 months.

Colonization

Colonization means that an organism is found in or on the body, but it is not causing any symptoms or disease. CRE primarily colonizes the digestive tract, but can also colonize other body sites. Patients may remain colonized with CRE for months to years.

Why is colonization important?

Infections represent only a fraction of the burden of CRE. Many more patients are colonized. Patients colonized with CRE can be a source of spread to other patients. They are also at higher risk of developing CRE infection than patients who are not colonized. Because patients colonized with CRE don't have signs or symptoms of illness, CRE colonization can go undetected and contribute to silent spread of resistant bacteria.

How can we identify colonized patients to stop spread?

Screening tests identify patients colonized with carbapenemase-producing CRE to prevent transmission to other patients through targeted interventions, like Transmission-Based Precautions. **Screening tests for patients and residents at risk of CRE colonization are available at no cost through CDC's Antimicrobial Resistance (AR) Lab Network.**

CRE Carbapenem-resistant Enterobacterales
Information For Healthcare Facilities

CRE Carbapenem-resistant Enterobacterales
Information For Healthcare Facilities

How Your Facility Can Prevent the Spread of CRE

Timely and Accurate Identification of Patients with CRE

- Ensure your clinical laboratory can identify CRE.
- Ask your health department about the availability of specialized testing through CDC's AR Lab Network to identify carbapenemase-producing CRE from clinical cultures and to screen for CRE colonization.
- Follow public health recommendations for CRE colonization screening.
- When transferring a patient colonized or infected with CRE, notify accepting facilities and units of the patient's CRE history.
- Work with your health department to understand local CRE epidemiology.

Perform Hand Hygiene

- Clean your hands immediately before touching a patient, before performing an aseptic task (e.g., placing an indwelling device), before handling invasive medical devices, and before moving from work on a soiled body site to a clean body site on the same patient.
- Clean your hands after touching a patient or the patient's immediate environment; after contact with blood, body fluids, or contaminated surfaces; and immediately after glove removal.

Did you know?

Alcohol-based hand sanitizers are the preferred method for cleaning your hands in most clinical situations.

Wash your hands with soap and water whenever they are visibly dirty, before eating, and after using the restroom.

Wear Gown & Gloves When Caring for Patients with CRE

CRE can contaminate your hands and clothes while you care for a patient with CRE or work in their environment. This puts the patients who you care for afterward at risk of getting CRE.

- Protect your patients by wearing a gown and gloves for patient care according to the guidelines for your setting (i.e., Contact Precautions in acute care, Enhanced Barrier Precautions in long-term care).
- Don and doff your personal protective equipment (PPE) in the right order and take care not to self-contaminate during doffing.
- Always change your PPE between patients or residents.

Clean and Disinfect the Patient Environment and Medical Equipment

- Follow your facility's cleaning and disinfection protocols.
- Ensure high-touch surfaces (e.g., bed rails, light switches, call buttons) are cleaned frequently.
- Dedicate non-critical medical equipment (e.g., stethoscopes, blood pressure cuffs) to CRE patients whenever possible and always clean and disinfect between patients.
- Ensure shared medical equipment (e.g., portable X-ray machine) is cleaned and disinfected between each patient.

Prevent Transmission from Sinks, Toilets, and Other Wastewater Plumbing

CRE can contaminate wastewater plumbing, especially sink drains, toilets, and hoppers. Splashes from these sources are associated with outbreaks of carbapenemase-producing organisms.

- Clean and disinfect countertops, handles, faucets, and sink basins at least daily.
- Keep patient care items at least three feet away from sinks, toilets, and hoppers.
- Do not discard patient waste in sinks.
- Avoid discarding beverages or other sources of nutrients in sinks or toilets.

Resources

Learn more about CRE: www.cdc.gov/hai/organisms/cre/index.html
Contact your HAI Prevention Program: www.cdc.gov/hai/state-based/index.html
Preventing water-associated infections: www.cdc.gov/hai/prevent/environment/water.html
About CDC's AR Lab Network: www.cdc.gov/drugresistance/ar-lab-networks/domestic.html
Track carbapenemase-producing CRE: https://arpsp.cdc.gov/profile/arln/cre

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

SHİ, KDE kişiden kişiye

- Sağlık personelinin elleri
- Kontamine tıbbi ekipman yoluyla
- Tuvaletler sonrası hijyene uyulmaması* durumlarında bulaşı söz konusu

➢ El hijyeni

➢ Temas önlemleri veya geliştirilmiş bariyer önlemlerinin kullanılması

➢ Çevre temizliği

➢ Lavabo ve tuvalet hijyeni kurallarına uyulması önlenmesinde alınması gereken önlemlerdir

- ABD'de KDE edinimi için ana risk faktörler:

- Sağlık hizmetlerine maruz kalma
  - Tuvalet ve banyo gibi günlük yaşam aktivitelerinin çoğunda yardıma ihtiyaç duyma
  - YBÜ'de kalma
  - MV gereksinimi olması

- Antibiyotiklere maruz kalma
  - Karbapenemler
  - Sefalosporinler
  - Florokinolonlar
  - Vankomisin

https://www.cdc.gov/hai/organisms/cre/technical-info.html#Difference

World Health Organization

Guidelines for the prevention and control of carbapenem-resistant Enterobacteriaceae, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* in health care facilities

Formal recommendation	Key remarks from the GDG*	Strength of recommendation and quality of evidence**
Recommendation 1: Implementation of multimodal IPC strategies		
The panel recommends that multimodal IPC strategies should be implemented to prevent and control CRE-CRAB-CRPsA infection or colonization and that these should consist of at least the following: • hand hygiene • surveillance (in particular, for CRE) • contact precautions • patient isolation (single room isolation or cohorting) • environmental cleaning	• The evidence supporting this recommendation showed that multimodal strategies comprised of several elements implemented in an integrated way were used as the intervention in most studies. The use of multimodal strategies is also strongly recommended as the most effective approach to successfully implement IPC interventions in the 2016 *WHO guidelines on core components of infection prevention and control programmes at the national and acute health care facility level*. • Most studies were from settings with a high prevalence of CRE-CRAB-CRPsA. Nevertheless, the GDG considered that the IPC principles outlined in this recommendation w… all prevalence settings. • While the control of large outbreaks wa… costly, these studies were all conducted… countries. Thus, there are concerns rega… and the affordability of outbreak contro… resources. • Although the scope of the evidence revi… recommendation address acute care fac… that all types of health care facilities ap… for the control of CRE-CRAB-CRPsA. • Implementing this recommendation may … systems as it requires a multidisciplinary … executive leadership, stakeholder commit… possible modifications to workforce stru… cases. Facility leadership should clearly su… aimed at preventing the spread of CRE-CRAB… materials and organizational and administrative support through the allocation of a protected and dedicated budget, according	*Strong recommendation, very low to low quality of evidence*

-El hijyeni
-Sürveyans (özellikle KDE)
-Temas izolasyonu
-Hastaların izolasyonu (tek kişilik oda ya da kohortlanması)
-Çevre temizliği

07 FEBRUARY 2023 | REPORT

Bracing for Superbugs: Strengthening environmental action in the One Health response to antimicrobial resistance

•Antimikrobiyal dirence karşı "Tek Sağlık" müdahalesinde çevresel eylemin güçlendirilmesi, çevrenin antimikrobiyal direnç gelişimi, bulaşması ve yayılmasında kilit bir rol oynadığına dair kanıtlar sunmaktadır

•Önleme, eylemin merkezinde yer almaktadır ve çevre, çözümün önemli bir parçasıdır

Teşekkürler