



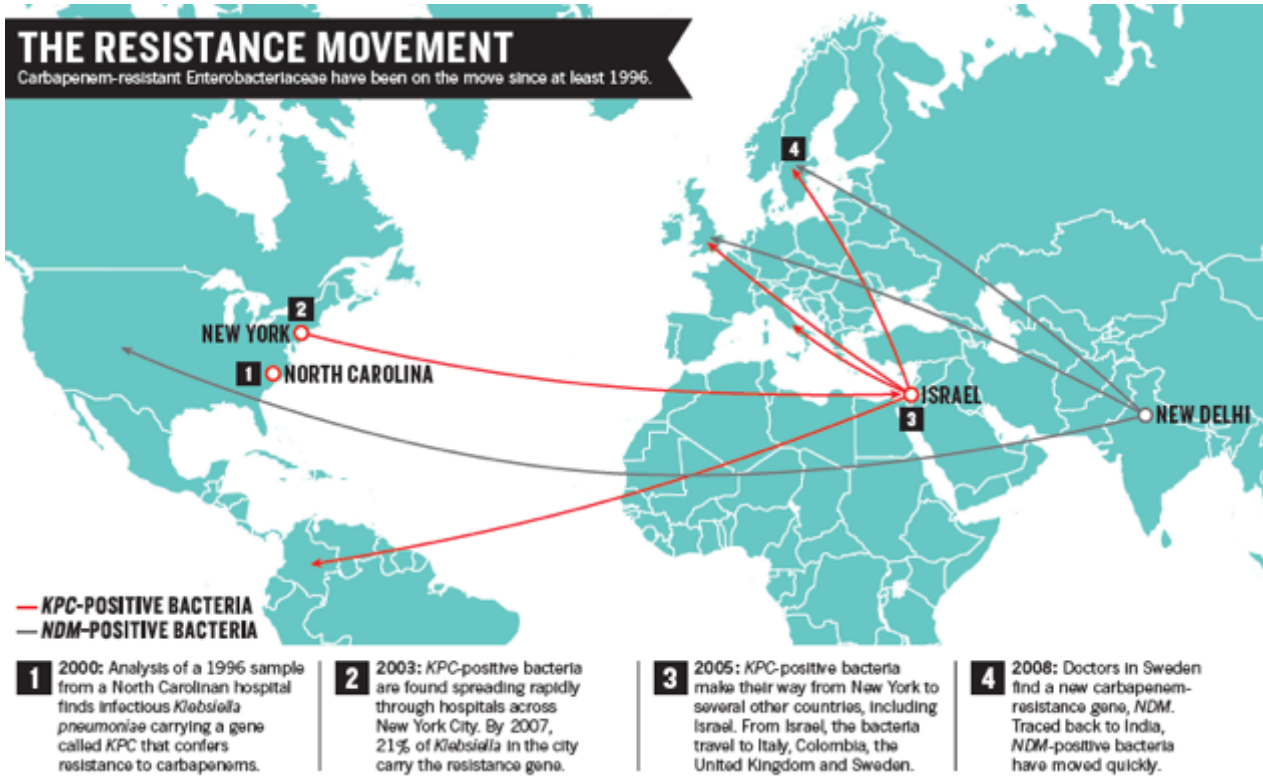
Dünyada ve Türkiye’de Antimikrobiyal Direnç

Prof. Dr. Füsün Can
Koç Üniversitesi Tıp Fakültesi

Hastane Uygulamaları İçin Antimikrobiyal Yönetim Kursu
18-19 Ekim 2019
İstanbul

Antibiyotik Direnci Global Sorun

Antibiyotik Direnci hızla yayılıyor



MacKenna, Nature 2013

Dirençli Enfeksiyonlar artıyor

- Dirençli enfeksiyon oranları
2005: %14
2015: %17
(Türkiye %35)
- 2050 yılında dirençli enfeksiyonlardan beklenen ölüm 10 milyon

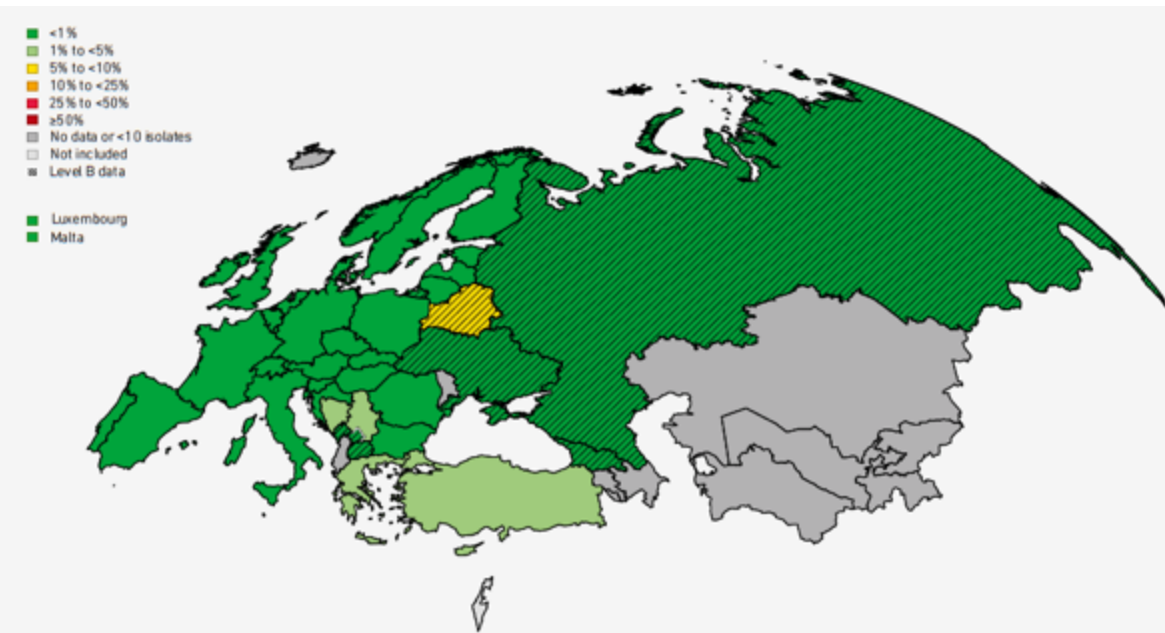
Türkiye verileri

- Gram negatif bakterilerde kinolon, karbapenem ve polimiksin antibiyotik direnci hızla artıyor
- Antibiyotik tüketimi 31 DDD/1000
- Ulusal Akılcı İlaç Kullanımı Eylem Planı
 - Kısa dönem
 - DDD ve maliyetlerde azalma
 - Uzun Dönem
 - Antibiyotik Direnç oranlarında azalma (özellikle gram negatif)

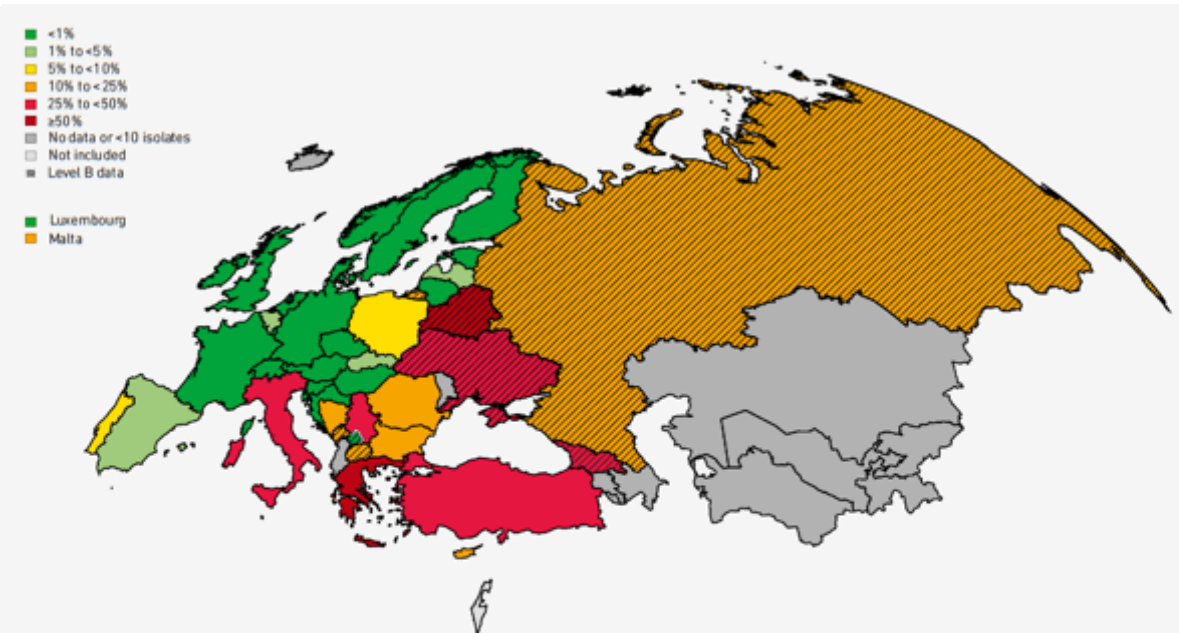
Akıcı A, et al. National Drug Consumption Surveillance-2011, Ministry of Health-2015

Karbapenem direnci (EARS-Net ve CAESAR 2017)

E.coli



K. pneumoniae



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. See section 4.2 for more information about levels of evidence, which 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 and the 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)).

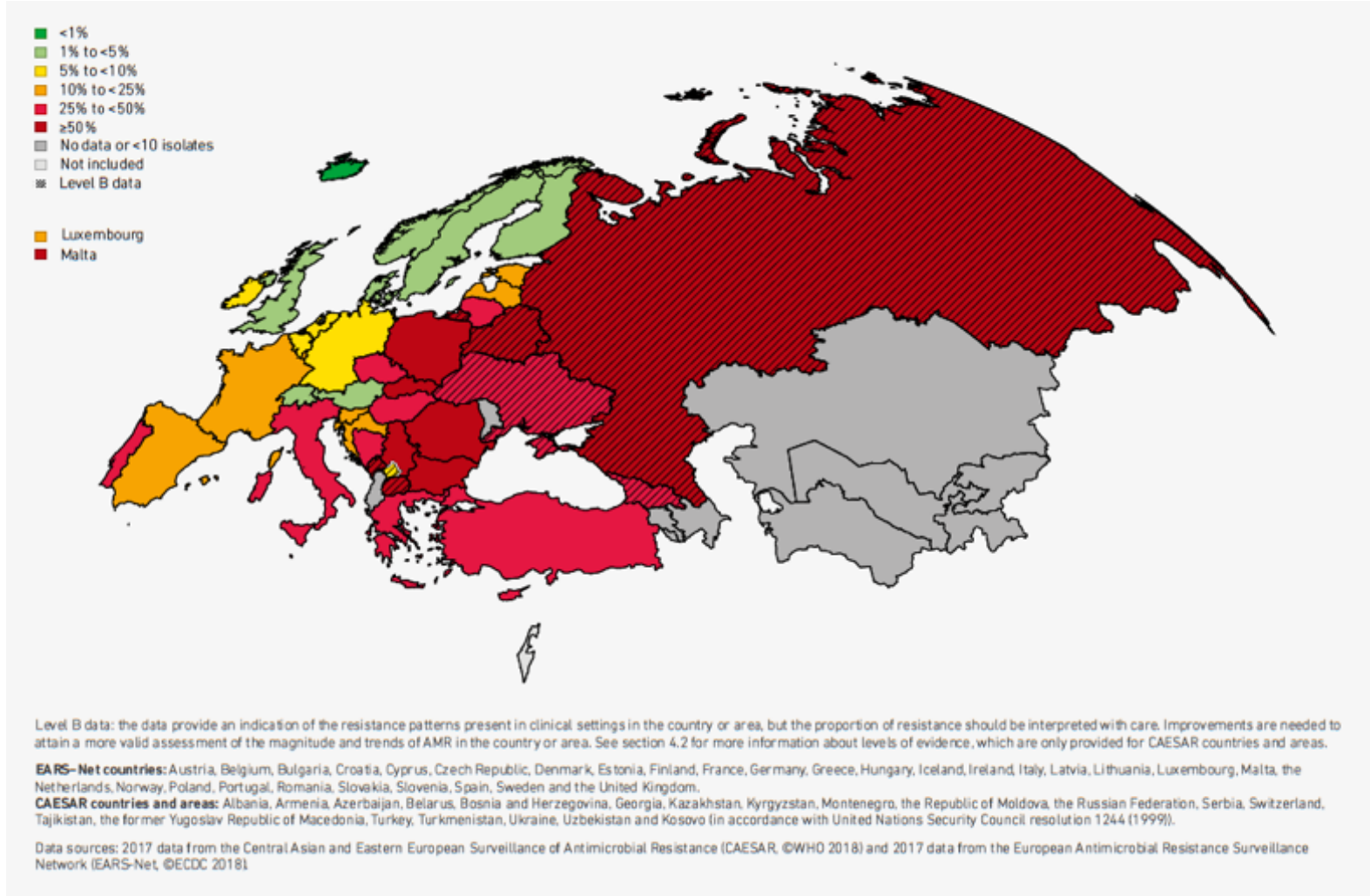
Data sources: 2017 data from the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR, ©WHO 2018) and 2017 data from the European Antimicrobial Resistance Surveillance Network (EARS-Net, ©ECDC 2018).

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. See section 4.2 for more information about levels of evidence, which are only provided for CAESAR countries and areas.

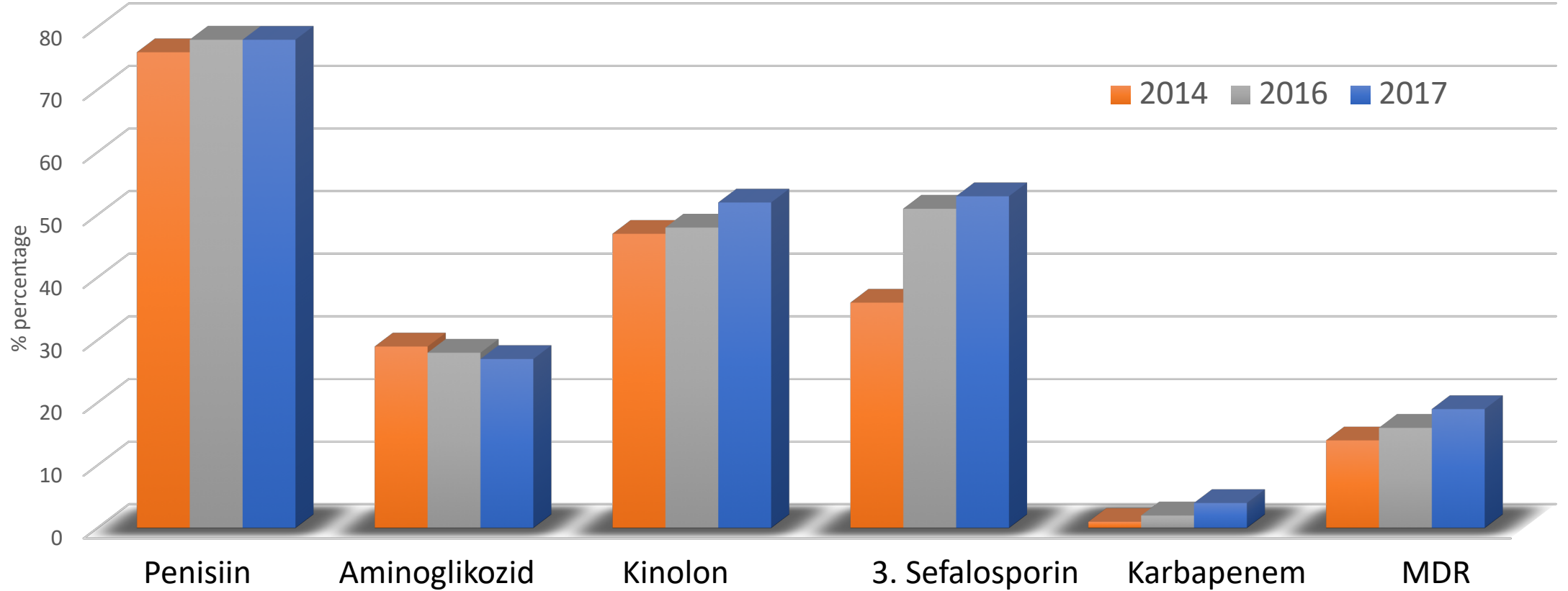
EARS-Net countries: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and the United 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: 2017 data from the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR, ©WHO 2018) and 2017 data from the European Antimicrobial Resistance Surveillance Network (EARS-Net, ©ECDC 2018).

Çok ilaca Dirençli *Klebsiella pneumoniae*

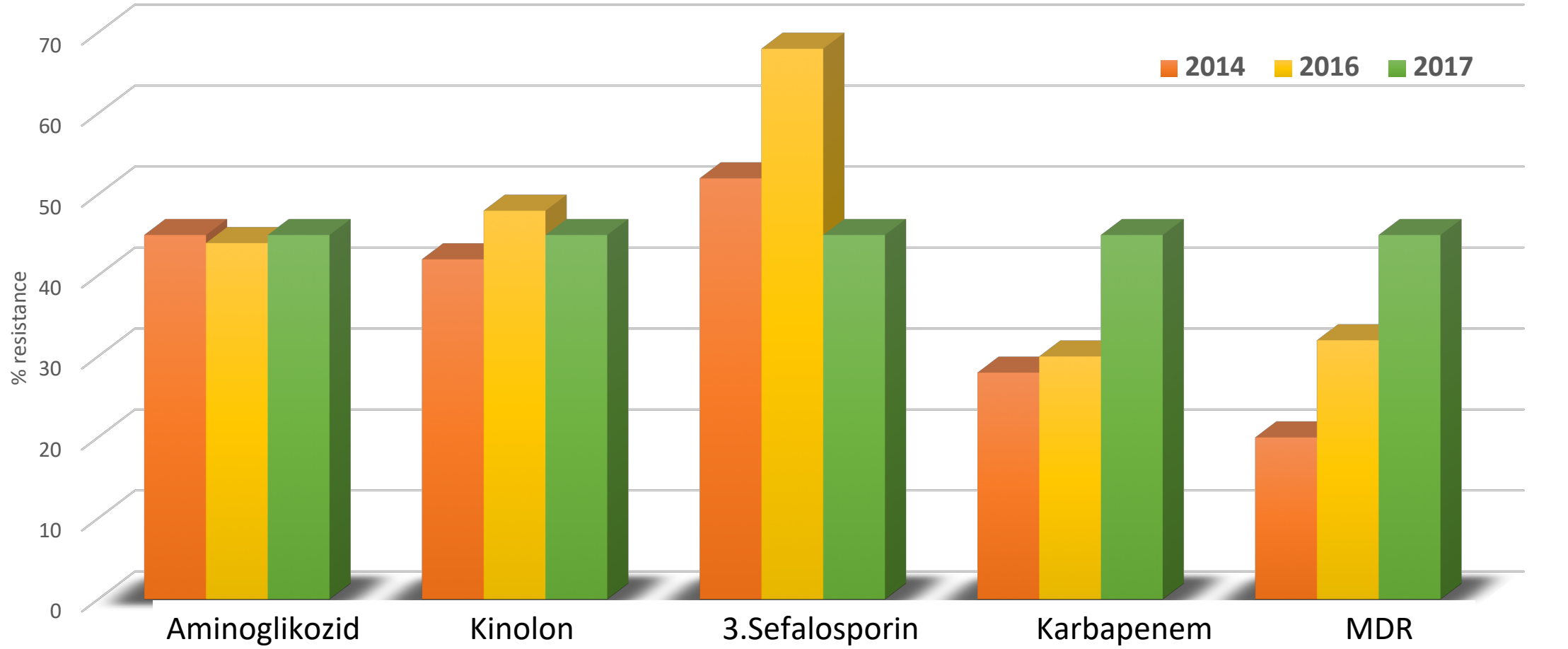


Kan ve BOS E.coli izolatlarında direnç oranları Türkiye verileri 2014-2017



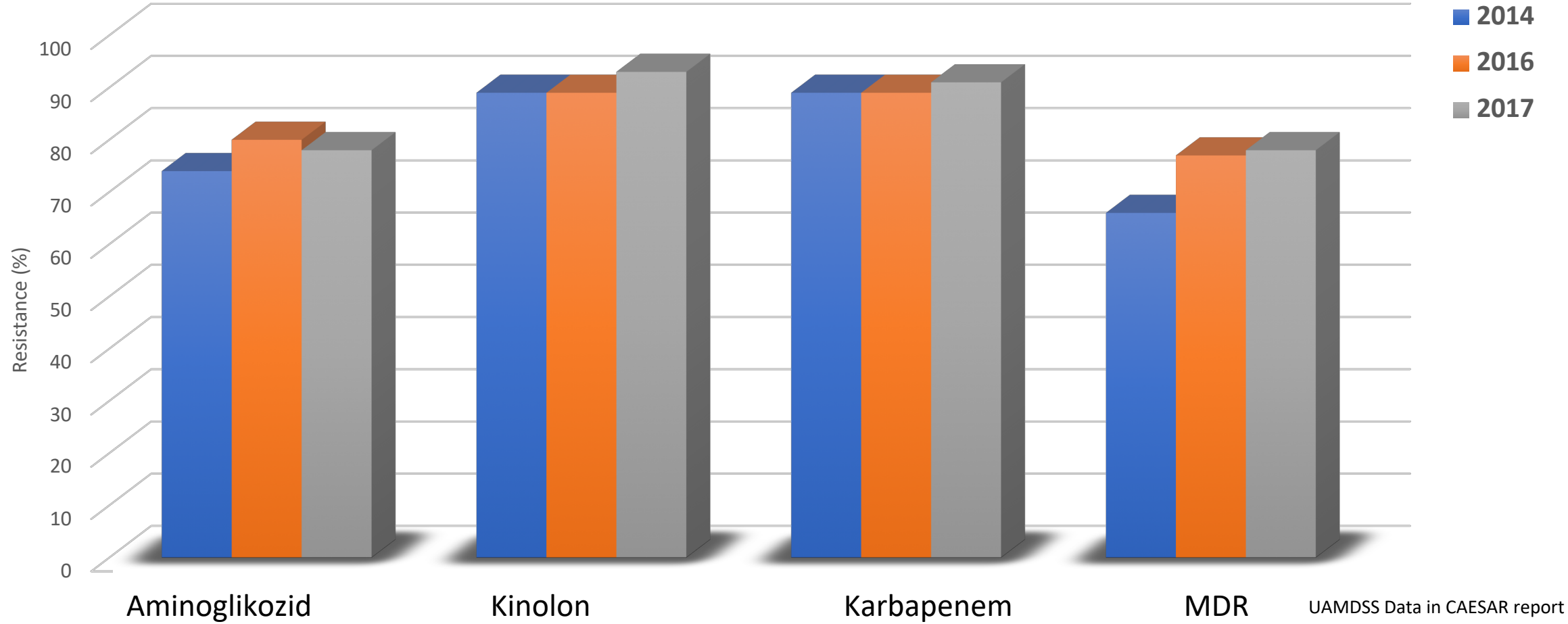
UAMDDSS Data in CAESAR report

Kan ve BOS *K.pneumoniae* izolatlarında direnç oranları Türkiye verileri 2014-2017



UAMDSS Data in CAESAR report

Kan ve BOS *A.baumannii* izolatlarında direnç oranları Türkiye verileri 2014-2017





Short report

Healthcare-associated Gram-negative bloodstream infections: antibiotic resistance and predictors of mortality

Ö. Ergönül^{a,*}, M. Aydın^b, A. Azap^c, S. Başaran^d, S. Tekin^a, Ş. Kaya^e, S. Gülsün^e, G. Yörük^f, E. Kurşun^g, A. Yeşilkaya^h, F. Şimşekⁱ, E. Yılmaz^j, H. Bilgin^k, Ç. Hatipoğlu^l, H. Cabadak^m, Y. Tezer^m, T. Toganⁿ, İ. Karaoğlu^o, A. İnan^p, A. Engin^q, H.E. Alışkan^g, S.Ş. Yavuz^d, Ş. Erdiñç^l, L. Mulazimoglu^k, Ö. Azap^h, F. Can^a, H. Akalın^j, F. Timurkaynak^b, Turkish Society of Clinical Microbiology and Infectious Diseases, Healthcare-Related Infections Study Group

Table III

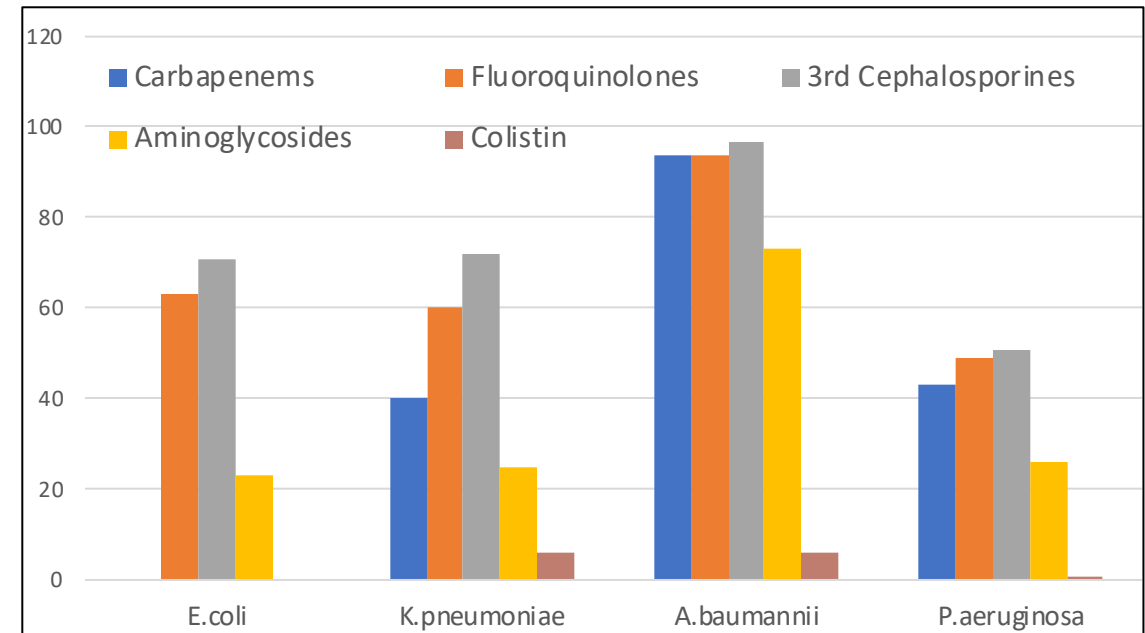
Multi-variate analysis of risk factors for mortality in patients with healthcare-associated Gram-negative bloodstream infections

Variable	Odds ratio	95% CI	P-value
Age >70 years	2	1.22–3.51	0.006
Central venous catheter	2.1	1.09–4.07	0.025
Ventilator-associated pneumonia	1.9	1.1–3.16	0.02
Carbapenem resistance	1.8	1.11–2.95	0.016
APACHE II score	1.1	1.07–1.13	<0.001

CI, confidence interval.

2013-2015 izolaatları

- Karbapenem direnci *A.baumannii*
K.pneumoniae
P.aeruginosa
- Gram negatif bakteriyemilerde karbapenem direnci mortalite ile ilişkili



Gram negatif kan izolatlarında antibiyotik direnci



The effect of colistin resistance and other predictors on fatality among patients with bloodstream infections due to *Klebsiella pneumoniae* in an OXA-48 dominant region

Şirin Menekşe^{a,*}, Yasemin Çağ^b, Mehmet Emirhan Işık^a, Suzan Şahin^c,
Demet Haciseyitoğlu^d, Fusun Can^e, Onder Ergonul^e

^a Infectious Diseases and Clinical Microbiology Department, Kartal Kocuyolu Training and Research Hospital, Istanbul, Turkey

^b Infectious Diseases and Clinical Microbiology Department, School of Medicine, Medeniyet University, Istanbul, Turkey

^c Infectious Diseases and Clinical Microbiology Department, Lütfü Kırdar Training and Research Hospital, Istanbul, Turkey

^d Clinical Microbiology Department, Lütfü Kırdar Training and Research Hospital, Istanbul, Turkey

^e Infectious Diseases and Clinical Microbiology Department, Koç University School of Medicine, Istanbul, Turkey

2016-2017 :
210 K.pneumoniae Kan Enfeksiyonu

Table 2

Multivariate analysis for 30-day mortality among patients with *Klebsiella pneumoniae* blood stream infections.

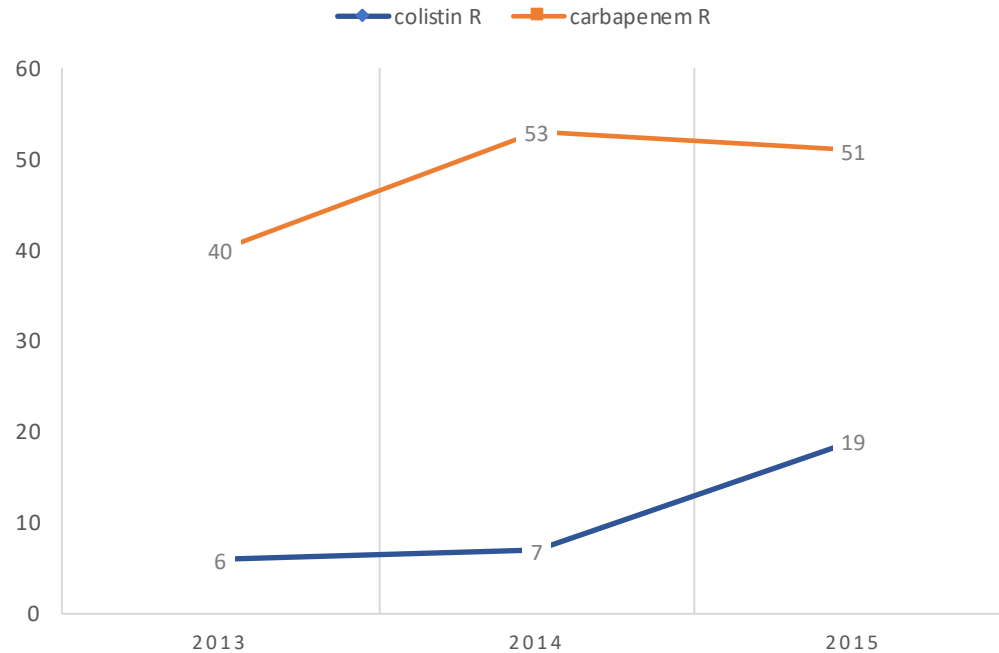
	Crude analysis			Adjusted analysis (with backward selection)		
	OR	95% CI	p-Value	OR	95% CI	p-Value
Carbapenem resistance	2.8	1.6–4.98	<0.001	5.2	2.47–10.9	<0.001
Colistin resistance	1.7	0.89–3.14	0.105	–	–	–
APACHE score	1.19	1.13–1.25	<0.001	1.19	1.12–1.26	<0.001
Adding of amikacin to the regimen	0.16	0.04–0.59	0.006	0.05	0.01–0.23	<0.001
Lung as the source of infection	2.7	1.32–5.4	0.025	–	–	–

OR, odds ratio; CI, confidence interval; APACHE, Acute Physiology and Chronic Health Evaluation.



Rapid emergence of colistin resistance and its impact on fatality among healthcare-associated infections

M. Aydın ^{a,*}, Ö. Ergönül ^b, A. Azap ^c, H. Bilgin ^d, G. Aydın ^{c,e}, S.A. Çavuş ^f, Y.Z. Demiroğlu ^g, H.E. Alışkan ^h, O. Memikoğlu ^c, Ş. Menekşe ⁱ, Ş. Kaya ^j, N.A. Demir ^k, İ. Karaoğlu ^l, S. Başaran ^m, Ç. Hatipoğlu ⁿ, Ş. Erdinç ⁿ, E. Yılmaz ^o, A. Tümtürk ^p, Y. Tezer ^p, H. Demirkaya ^q, Ş.E. Çakar ^r, Ş. Keske ^b, S. Tekin ^b, C. Yardımcı ^s, Ç. Karakoç ^t, P. Ergen ^u, Ö. Azap ^q, L. Mülazımoğlu ^d, O. Ural ^k, F. Can ^v, H. Akalın ^o, Turkish Society of Clinical Microbiology and Infectious Diseases, Healthcare-related Infections Study Group, Turkey



2014-2015

Gram negatif kan dolaşımı enfeksiyonları 1556 vaka

Etken

Kolistin direnci

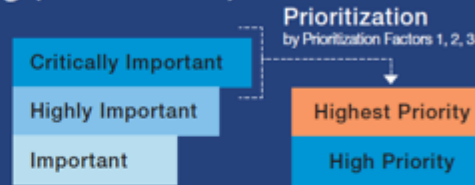
- %28 *Acinetobacter baumannii* %2
- %27 *Klebsiella pneumoniae* %19
- %22 *Escherichia coli*
- %13 *Pseudomonas aeruginosa*
- %10 *Enterobacteriaceae* spp

K.pneumoniae kolistin direnci artıyor

Kolistin MİK değerleri ile fatalite arasında anlamlı ilişki

WHO list of Critically Important Antimicrobials for Human Medicine (WHO CIA list)

WHO CIA list categorizes all antimicrobials used in human medicine into 3 groups based on their importance to human medicine. The current scope is limited to antibacterial drugs of which most are also used in veterinary medicine. The list assists in managing antimicrobial resistance, ensuring that all, especially critically important antimicrobials, are used prudently both in human and veterinary medicine.



Categorization
by Criterion 1, 2



WHO supports optimization of the use of antimicrobial medicines in human and animal to preserve their effectiveness by taking a One Health approach

WHO Critically Important Antimicrobials for Human Medicine 6th revision Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR) November 2018

Summary of categorization and prioritization of antimicrobials categorized as Critically important, Highly important and Important

	Antimicrobial class	Criterion / Prioritization factor (Yes=●)				
		C1	C2	P1	P2	P3
Critically Important	CRITICALLY IMPORTANT ANTIMICROBIALS					
	<i>HIGHEST PRIORITY</i>					
	Cephalosporins (3 rd , 4 th and 5 th generation)	●	●	●	●	●
	Glycopeptides	●	●	●	●	●
	Macrolides and ketolides	●	●	●	●	●
	Polymyxins	●	●	●	●	●
	Quinolones	●	●	●	●	●
	<i>LOW PRIORITY</i>					
	Aminoglycosides	●	●	●	●	●
	Ansamycins	●	●	●	●	●
Medically Important Antimicrobials	CRITICALLY IMPORTANT					
	Carbapenems and other penems	●	●	●	●	●
	Glycylcyclines	●	●	●	●	●
	Lipopeptides	●	●	●	●	●
	Monobactams	●	●	●	●	●
	Oxazolidinones	●	●	●	●	●
	Penicillins (antipseudomonas)	●	●	●	●	●
	Penicillins (aminopenicillins)	●	●	●	●	●
	Penicillins (aminopenicillins with β-lactamase inhibitors)	●	●	●	●	●
	Phosphonic acid derivatives	●	●	●	●	●
Medically Important Antimicrobials	HIGHLY IMPORTANT ANTIMICROBIALS					
	Amphenicols	●	●	●	●	●
	Cephalosporins (1 st and 2 nd generation) and cephamycins	●	●	●	●	●
	Lincosamides	●	●	●	●	●
	Penicillins (amidopenicillins)	●	●	●	●	●
	Penicillins (anti-staphylococcal)	●	●	●	●	●
	Penicillins (narrow spectrum)	●	●	●	●	●
	Pseudomonas acids	●	●	●	●	●
	Riminolesazines	●	●	●	●	●
	Steroid antibacterials	●	●	●	●	●
Medically Important Antimicrobials	IMPORTANT ANTIMICROBIALS					
	Sulfonamides, dihydrofolate reductase inhibitors and combinations	●	●	●	●	●
	Sulfones	●	●	●	●	●
	Tetracyclines	●	●	●	●	●
	Aminocyclitols	●	●	●	●	●
	Cyclic polypeptides	●	●	●	●	●
	Nitrofurans derivatives	●	●	●	●	●
	Nitroimidazoles	●	●	●	●	●
	Pleuromutins	●	●	●	●	●
	Streptogramins	●	●	●	●	●

C1 Criterion 1
The antimicrobial class is the sole, or one of limited available therapies, to treat serious bacterial infections in people.

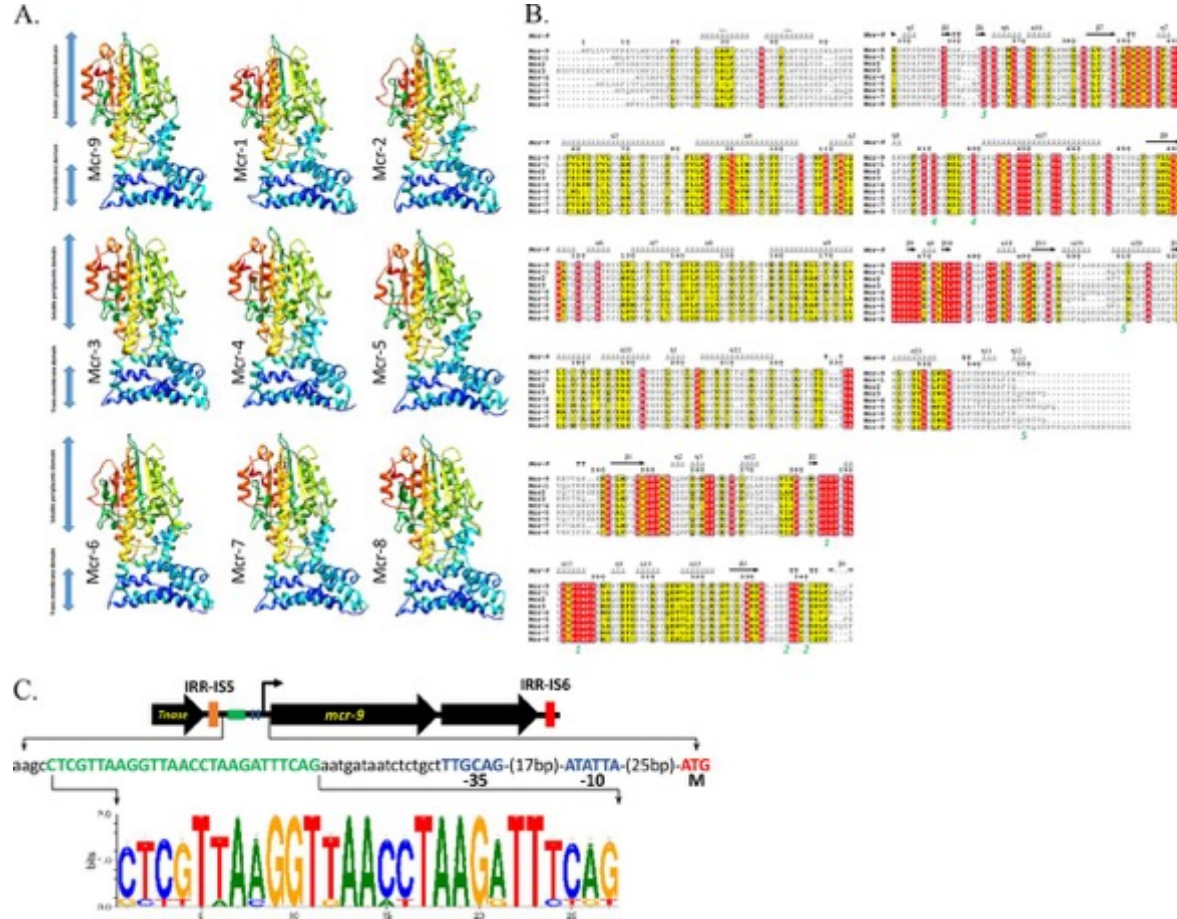
C2 Criterion 2
The antimicrobial class is used to treat infections in people caused by either: (1) bacteria that may be transmitted to humans from nonhuman sources, or (2) bacteria that may acquire resistance genes from nonhuman sources.

P1 Prioritization factor 1
Large number of people in the community or in certain high-risk populations (e.g. patients with serious infections in health care settings), who are affected by diseases for which there are very limited antimicrobial choices.

P2 Prioritization factor 2
High frequency of use of the antimicrobial class for any indication in human medicine or in certain high-risk groups (e.g. patients with serious infections in health care settings), since use may favour selection of resistance.

P3 Prioritization factor 3
The antimicrobial class is used to treat infections in people for which there is already extensive evidence of transmission of resistant bacteria (e.g. non-typhoidal Salmonella spp. and Campylobacter spp.) or resistance genes (high for E. coli and Enterococcus spp.) from non-human sources.

Plazmid Kaynaklı Kolistin Direnci



- Düşük düzey kolistin direnci
- Özellikle E.coli ve Salmonella spp.
- Klebsiella taşıyıcılığı düşük %0.2

Quan J, *The Lancet Infectious Diseases* , 2017

Laura M. Carroll et al. *mBio* 2019

Structural models of all published Mcr proteins (Mcr-1 to -8) and Mcr-9, based on lipooligosaccharide phosphoethanolamine transferase EptA.

Türkiye’de mcr-1 kaynaklı kolistin Direnci

Journal of Global Antimicrobial Resistance 15 (2018) 169–170



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Journal of Global Antimicrobial Resistance

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



Letter to the Editor

First report of *Escherichia coli* carrying the mobile colistin resistance gene *mcr-1* in Turkey



Sir,

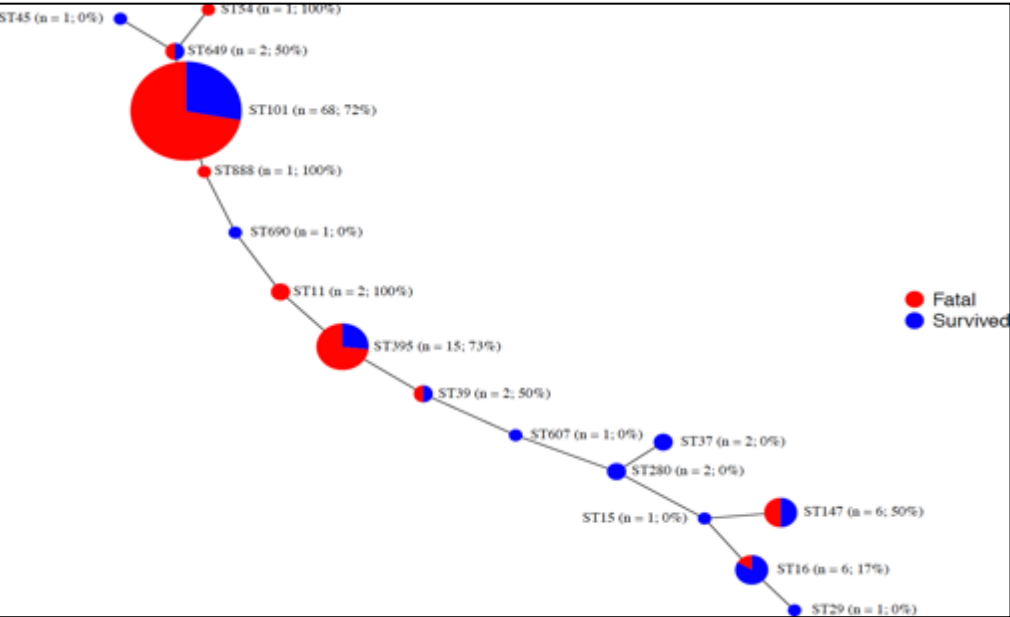
Colistin has recently regained great attention as a last-resort antimicrobial drug playing a vital role in the treatment of certain

in all three strains and showed 100% nucleotide similarity with the previously annotated *mcr-1* gene [2]. Plasmid sequencing of three strains (A1, A5 and A9) resulted in long contigs of multiple plasmids in each strain. For strain A9, a 31 203-bp plasmid sequence (plasmid replicon type IncX4) was found to be almost completely covering plasmid pICBEC171Smcr harbouring the *mcr-1* gene that was previously isolated in Brazil (accession no. CP021418.1). For strains A1 and A5, *mcr-1*-carrying contigs were

Impact of the ST101 clone on fatality among patients with colistin-resistant *Klebsiella pneumoniae* infection

Fusun Can^{1*}, Sirin Menekse², Pelin Ispir¹, Nazlı Atac¹, Ozgur Albayrak¹, Tuana Demir³, Doruk Can Karaaslan³, Salih Nafiz Karahan³, Mahir Kapmaz⁴, Ozlem Kurt Azap⁵, Funda Timurkaynak⁶, Serap Simsek Yavuz⁷, Seniha Basaran⁷, Fugen Yoruk⁸, Alpay Azap⁸, Safiye Koculu⁹, Nur Benzonana¹⁰, Nathan A. Lack^{11,12}, Mehmet Gönen^{3,13} and Onder Ergonul¹⁴

2014-2016 Sağlık Bakımı ile ilişkili *K.pneumoniae*



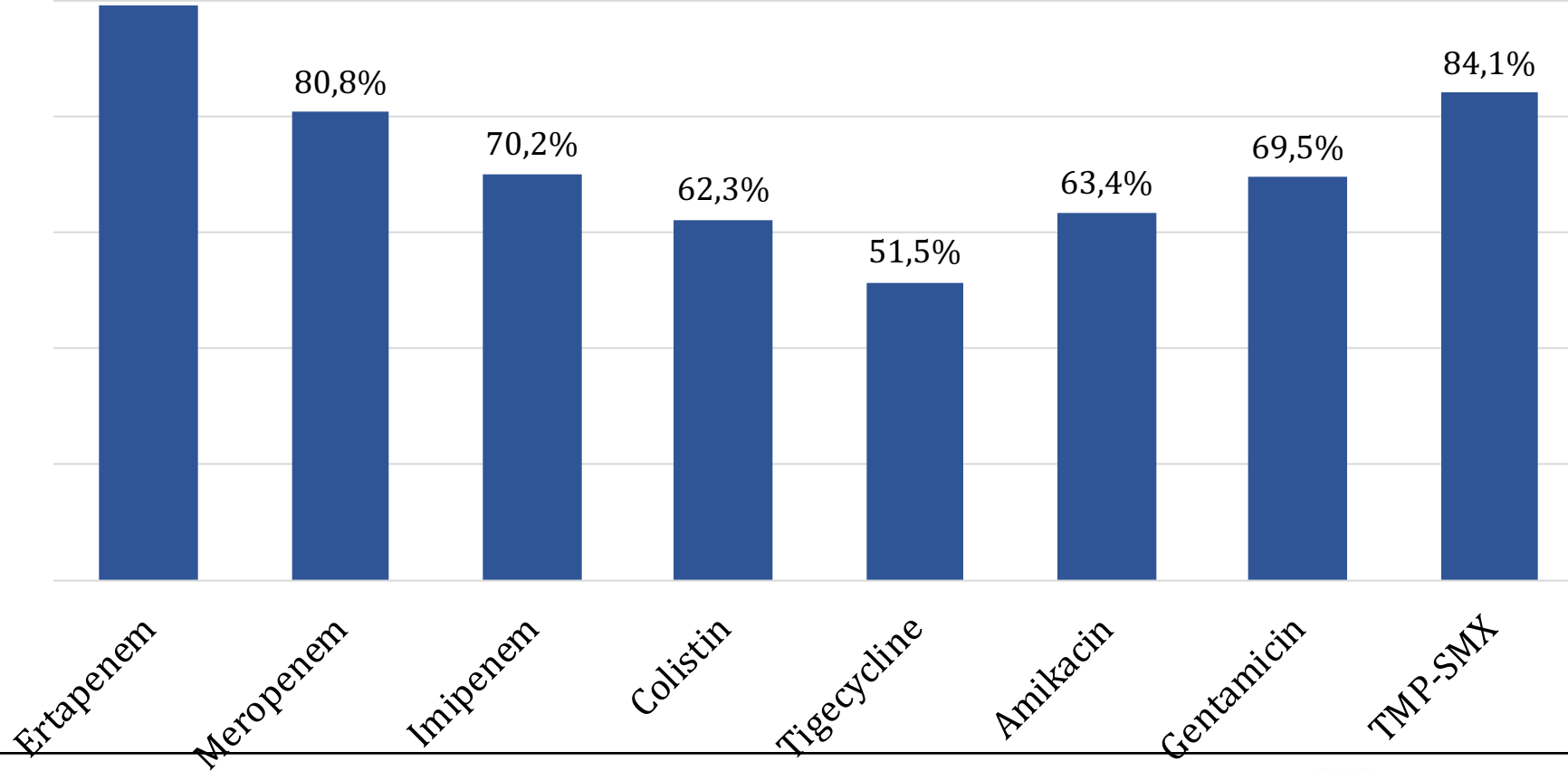
Minimum spanning tree of colistin resistant *K.pneumoniae* by MLST type and gene allele profiles.

Predictors for 30-day fatality among the patients infected with colistin resistant *K.pneumoniae*

	Univariate analysis			Adjusted analysis*		
	OR	CI	p	OR	CI	p
Female gender	0.7	0.3-1.54	0.341	-	-	-
Being in ICU	6.6	1.85-29.97	<0.001	7.4	2.23-29.61	0.002
Bacteremia	0.9	0.4-2.1	0.848	-	-	-
Pneumonia	2.3	0.99-5.33	0.038	1.6	0.71-3.86	0.249
Colistin exposure	0.6	0.27-1.41	0.252	-	-	-
Carbapenem resistance	2.2	0.35-15.53	0.43	-	-	-
NDM-1	0.9	0.32-2.69	>0.999	-	-	-
OXA-48	1.4	0.48-3.9	0.628	-	-	-
ST101	3.2	1.36-7.52	0.004	3.4	1.46-8.15	0.005

Turkish Prospective Cohort Study on Carbapenem Resistant *Klebsiella Pneumoniae* Bacteraemia (THREAT)-13 merkez

- Burcu Isler¹, Güle Çınar², Abdullah Aslan³, Funda Şimşek⁴, Necla Tülek⁵, Hamiyet Demirkaya⁶, Mehtap Aydın⁷, İlker İnanç Balkan⁸, Şirin Menekşe⁹, Mahir Kapmaz¹⁰, Elif Tigen¹¹, Safiye Koçulu¹², Şiran Keske¹³, Cansel Vatansever¹⁴, Berna Özer¹⁴, Özlem Doğan¹⁴, Çiğdem Arabacı¹⁵, Serap Yağcı¹⁶, Gülşen Hazırolan¹⁷, Veli Oğuzalp Bakır¹⁰, Mehmet Gönen¹⁰, Neşe Saltoğlu⁸, Alpay Azap², Özlem Azap⁶, Murat Akova³, Füsun Can¹⁴ and Önder Ergönül¹⁰



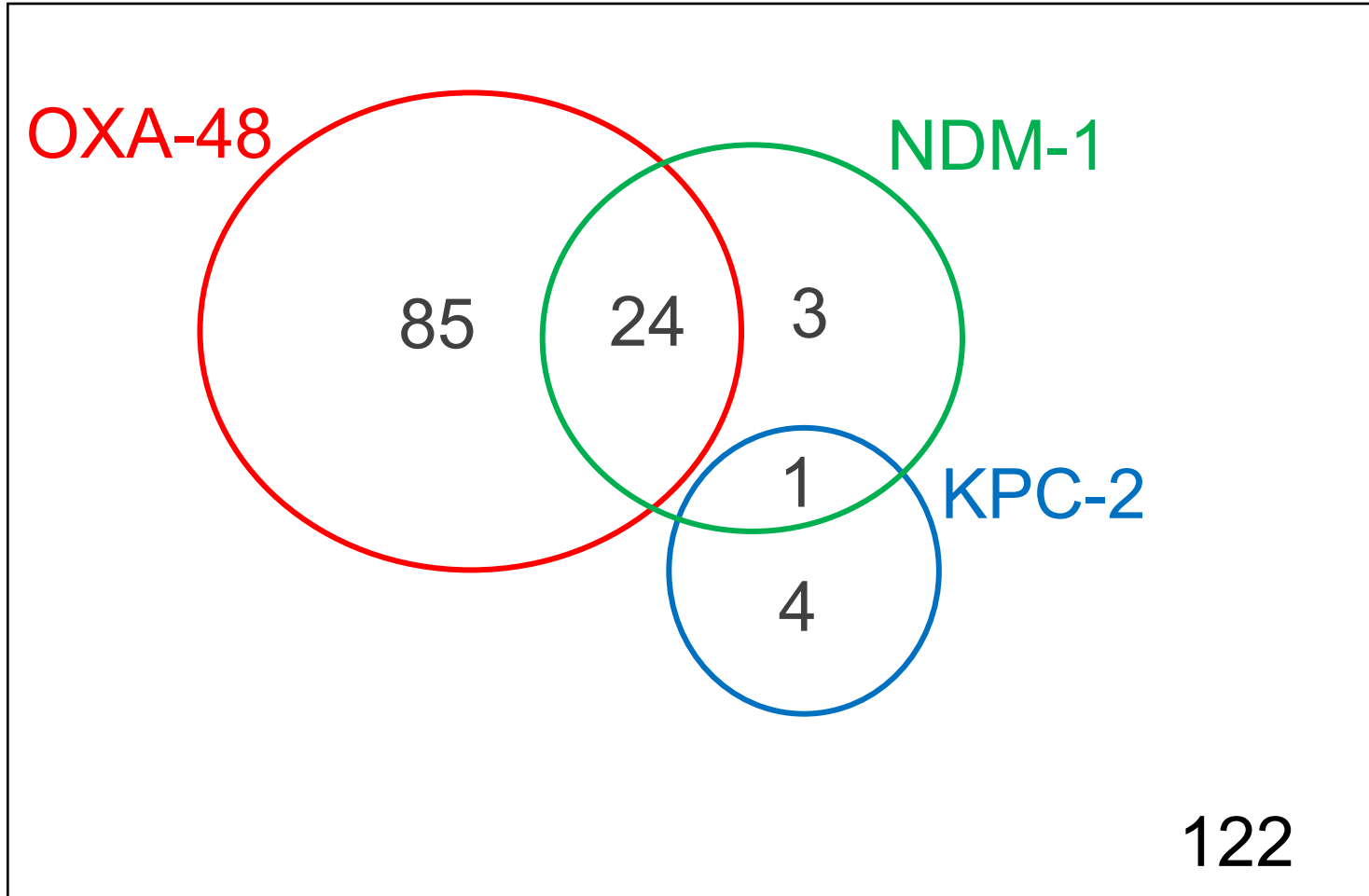
Mortalite

30-gün: 70/143 (49%)

14-gün: 56/143 (39.2%)

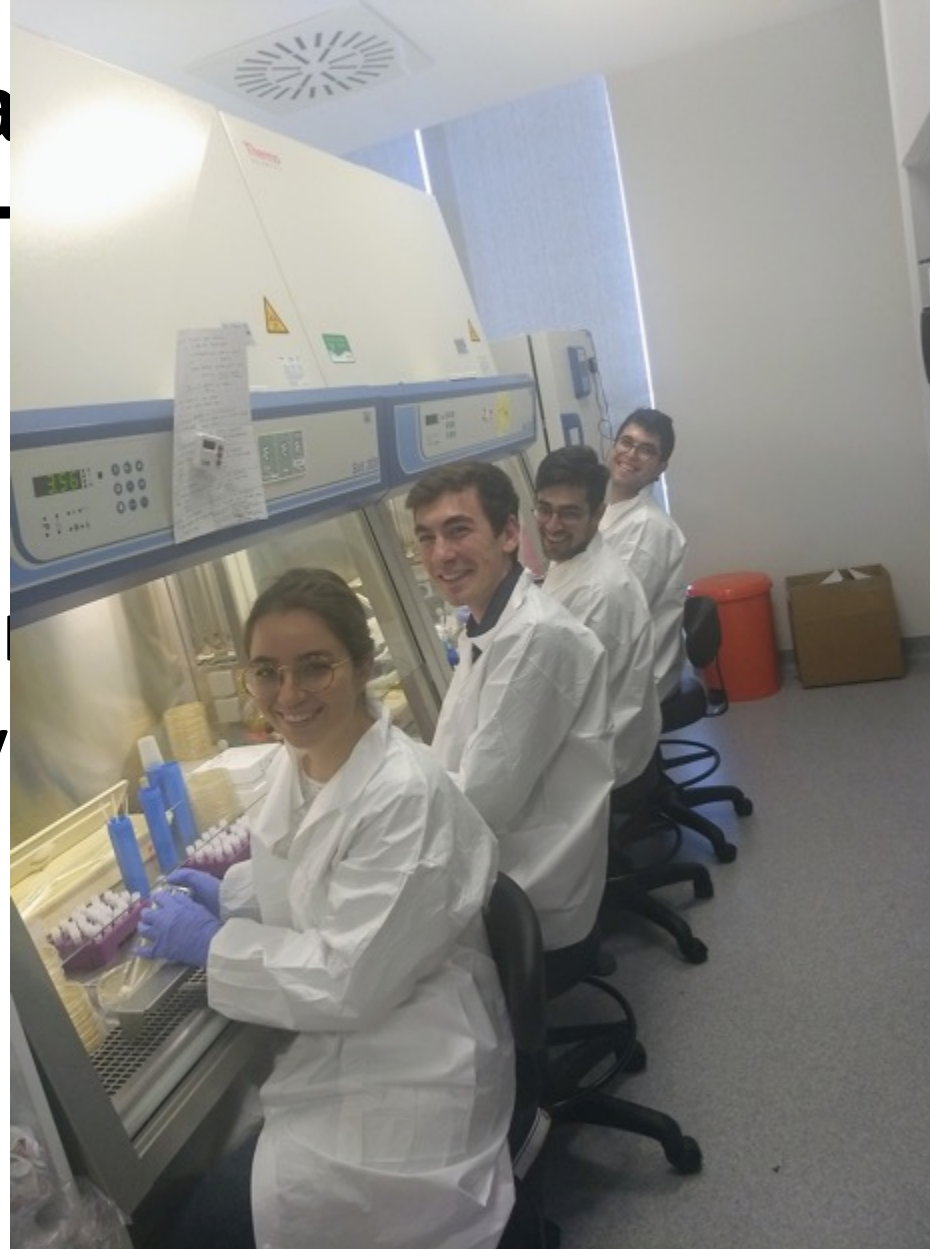
7-gün: 33/143 (23%)

Karbapenemaz tipleri



Ne yapılmalı

- Çok merkezli
- Karbapenem
- polimiksin di
- Antimikrobiy



arın artırılması
u bölgelerde