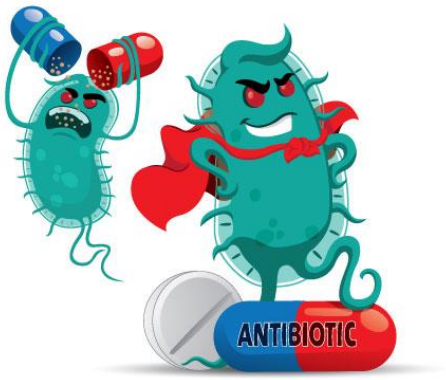
Dirençli Bakterilerde Farklı Kombinasyonlar: Gram-Negatif Enterikler

Dr. Nihal Pişkin

Zonguldak Bülent Ecevit Üniversitesi Tıp Fakültesi

Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji AD

KLİMİK, 14 Mart 2019



Sunum Planı - Öğrenim Hedefleri

- ***Gram negatif bakteri infeksiyonlarının tedavisindeki zorluklar***
- ***Gram negatif enterik bakterilerdeki antibiyotik direncinin boyutu***
- ***Direnç sorunu yaşanan Gram negatif enterik bakteri infeksiyonlarının tedavisinde en etkin kombinasyon tedavileri***

Simpozyum 2

Dirençli Bakterilerde Farklı Kombinasyonlar

Öğrenim Hedefleri

Bu oturumun sonunda katılımcılar:

- GRAM negatif bakteri infeksiyonlarının tedavisindeki zorlukları saptamak,
- GRAM negatif enterik ve nonfermentatif bakterilerdeki antibiyotik direncinin boyutunu belirlemek,
- Direnç sorunu yaşanan GRAM negatif enterik ve nonfermentatif bakteri infeksiyonlarının tedavisinde en etkin kombinasyon tedavilerini saptamak, öğrenim hedefleri olarak belirlenmiştir.

Oturum Başkanları
Yeşim TAŞOVA,
Şebnem EREN-GÖK

Gram-Negatif Enterikler
Nihal PİŞKİN

Gram-Negatif Non Fermantatifler
Dilara İNAN

Gram negatif bakteri infeksiyonlarının tedavisindeki zorluklar

Antibiotic discovery and resistance timeline

Antibiotic class

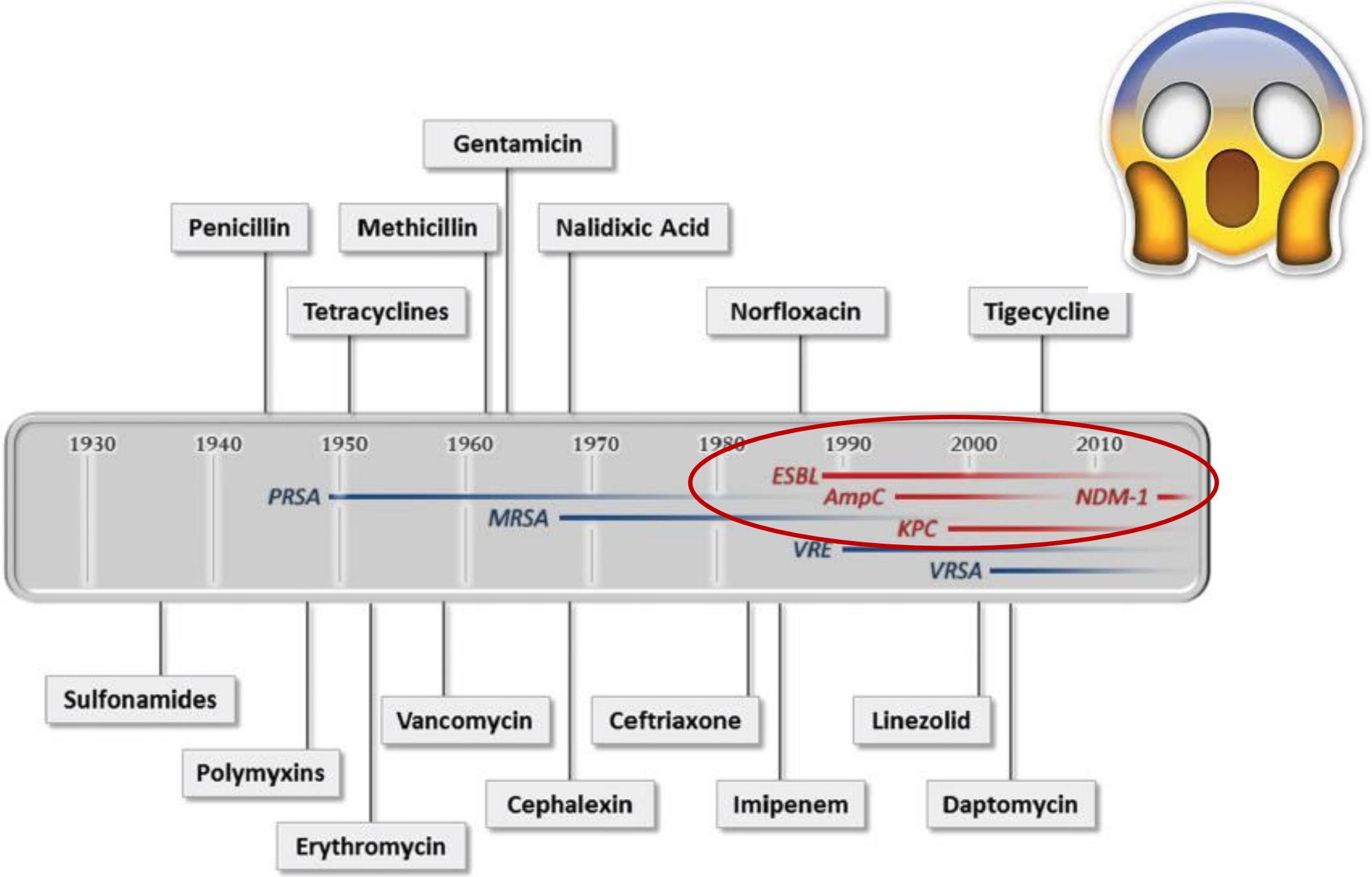
- PENICILLINS
- MACROLIDES
- CARBAPENEMS
- TETRACYCLINES
- FLUOROQUINOLONES

Date of resistance identified: 1940, 1953, 1985, 1993

Date of discovery: 1928, 1948, 1985

Year: 1920 1930 1940 1950 1960 1970 1980 1990 20 010 2020

SON 30 YILDIR YENİ BİR ANTİBİYOTİK SINIFI KULLANIMA GİRMEDİ!!!



Molton J, et al. Clin Infect Dis 2013;56:1310-1318

TABLE 6. Definitions for multidrug-resistant (MDR), extensively drug-resistant (XDR) and pandrug-resistant (PDR) bacteria

Bacterium	MDR	XDR	PDR
Staphylococcus aureus		least 1 agent	The isolate is non-susceptible to [illegible] but 2 or fewer antimicrobial cat[illegible]
Enterococcus spp.		l agent d in Table 2	The isolate is non-susc[illegible] but 2 or fewer antimicrob[illegible]
Enterobacteriace		e to at least 1 agent al categories listed in Table 3	The isolate is non-sus[illegible] but 2 or fewer antimic[illegible]
Pseudomonas aeruginos	The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories listed in Table	The [illegible]te is non-susceptible to [illegible]t 1 agent in all [illegible]r fewer antimicrobial ca[illegible]ories in Table 4.	
Acinetobacter spp.	The isolate is non-susceptible [illegible] in ≥3 antimicrobial categories	[illegible]n-susceptible to at least 1 agent in all [illegible]bial categories in Table 5.	

[a]All MRSA isolates are defined as MDR because res[illegible]lity to all categories of β-lactam antimicrobials listed in this document, with the exception of the anti-MRSA ceph[illegible]ms, β-lactamase inhibitors and carbapenems currently approved up until 25 January 2011).
http://www.ecdc.europa.eu/en/activities/diseaseprog[illegible]ical_m[illegible]ology_infection_article.aspx.

MDR
≥ 3 AB grubuna direnç

PDR
Tüm AB gruplarına karşı direnç

XDR
≤ 2 AB grubu dışında tümüne direnç

Magiorakos AP et al. Clin Microbiol Infect 2012; 18: 268–281

Gram negatif enterik bakterilerdeki antibiyotik direncinin boyutu

Antimicrobial resistance surveillance in Europe

Annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net)

2010

E. coli

Figure 5.14: *Escherichia coli*: proportion of invasive isolates with resistance to third-generation cephalosporins in 2010

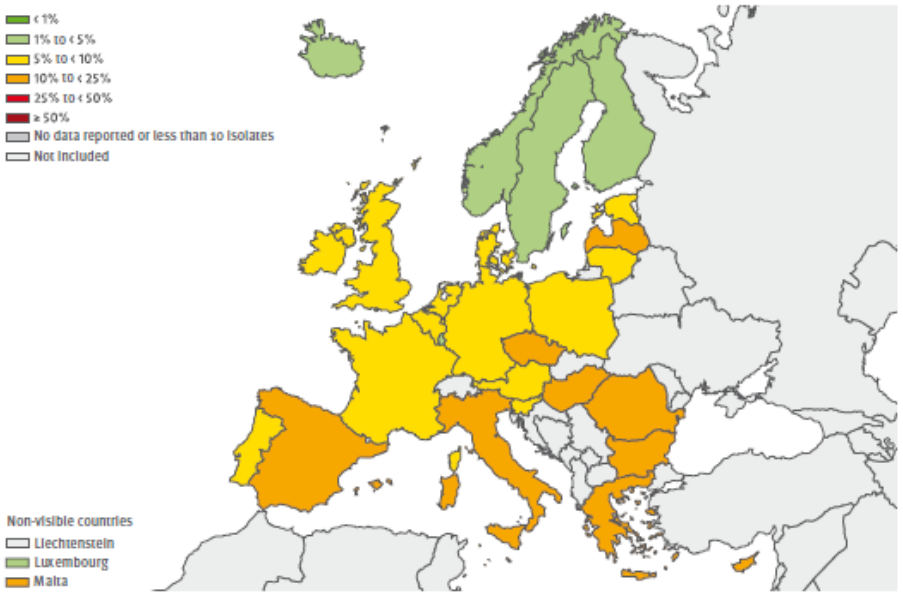


Figure 5.15: *Escherichia coli*: proportion of invasive isolates with resistance to fluoroquinolones in 2010

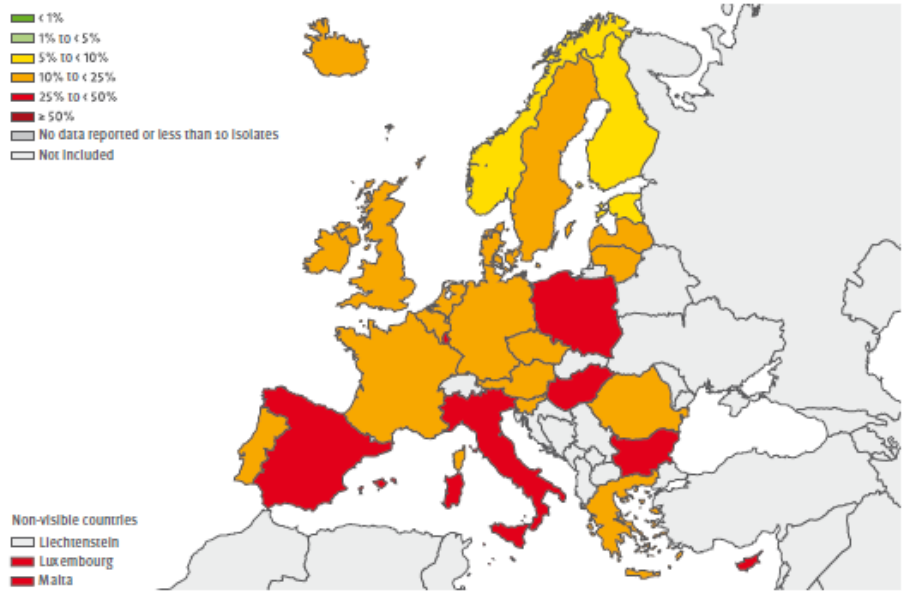
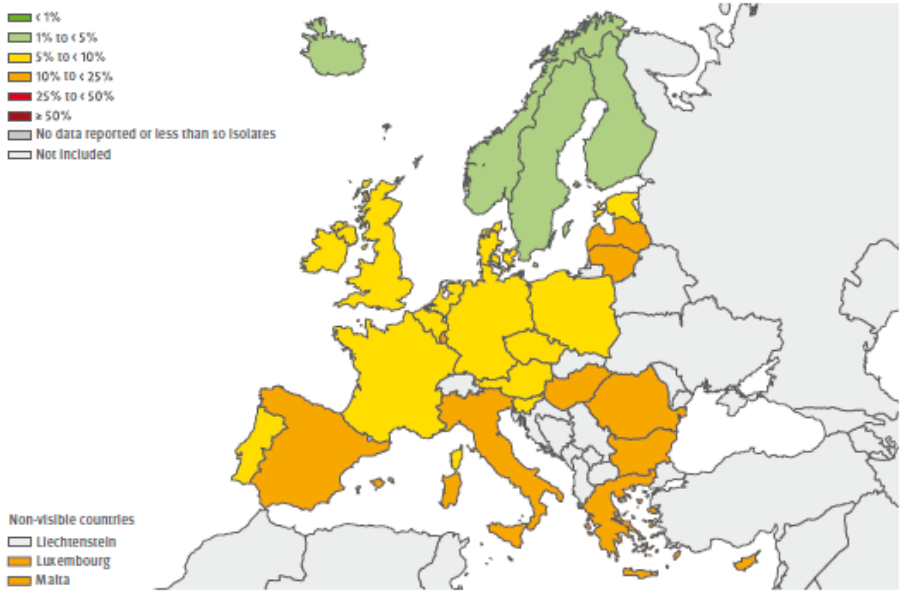


Figure 5.16: *Escherichia coli*: proportion of invasive isolates with resistance to aminoglycosides in 2010



Antimicrobial resistance surveillance in Europe

Annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net)

2010

K. pneumoniae

Figure 5.22: ***Klebsiella pneumoniae*: proportion of invasive isolates resistant to third-generation cephalosporins in 2010**

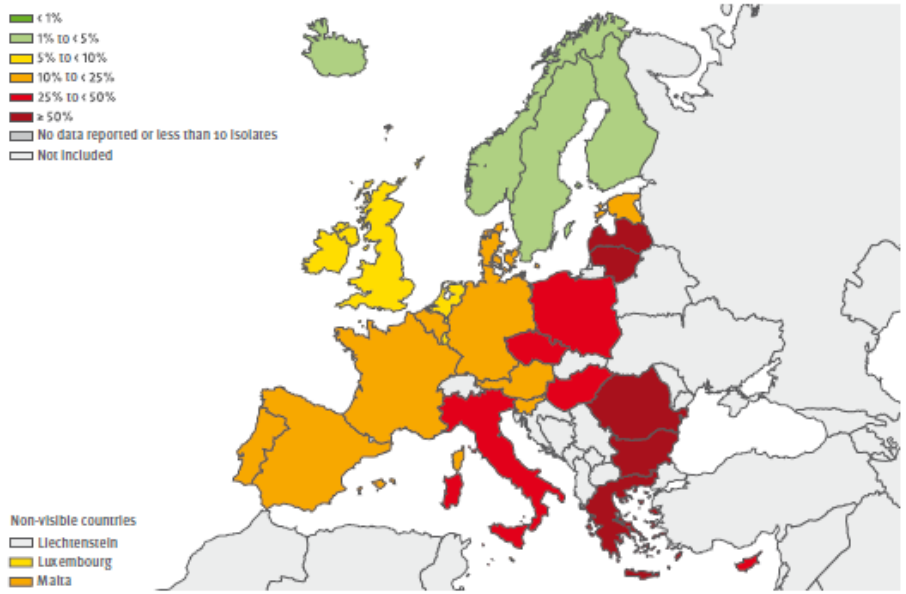


Figure 5.23: ***Klebsiella pneumoniae*: proportion of invasive isolates resistant to fluoroquinolones in 2010**

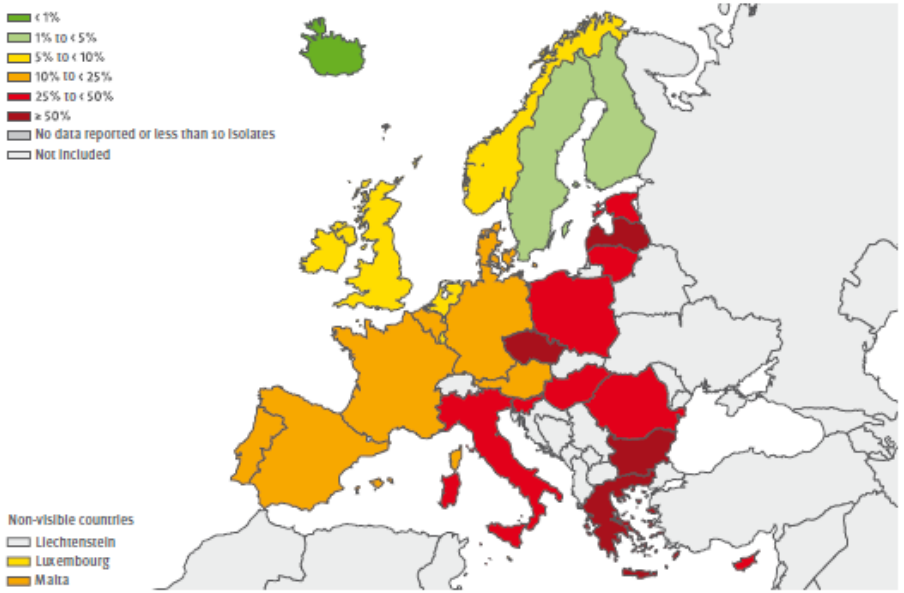
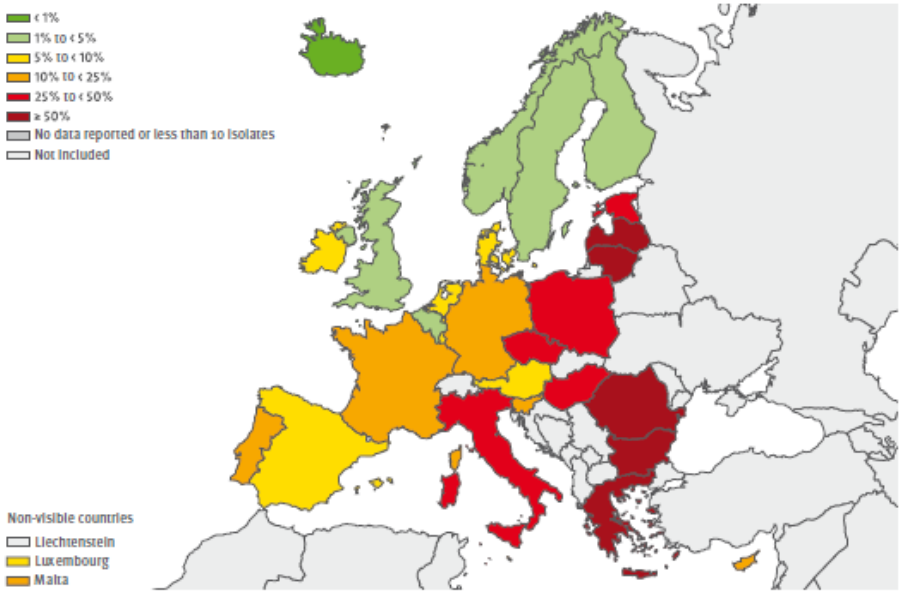
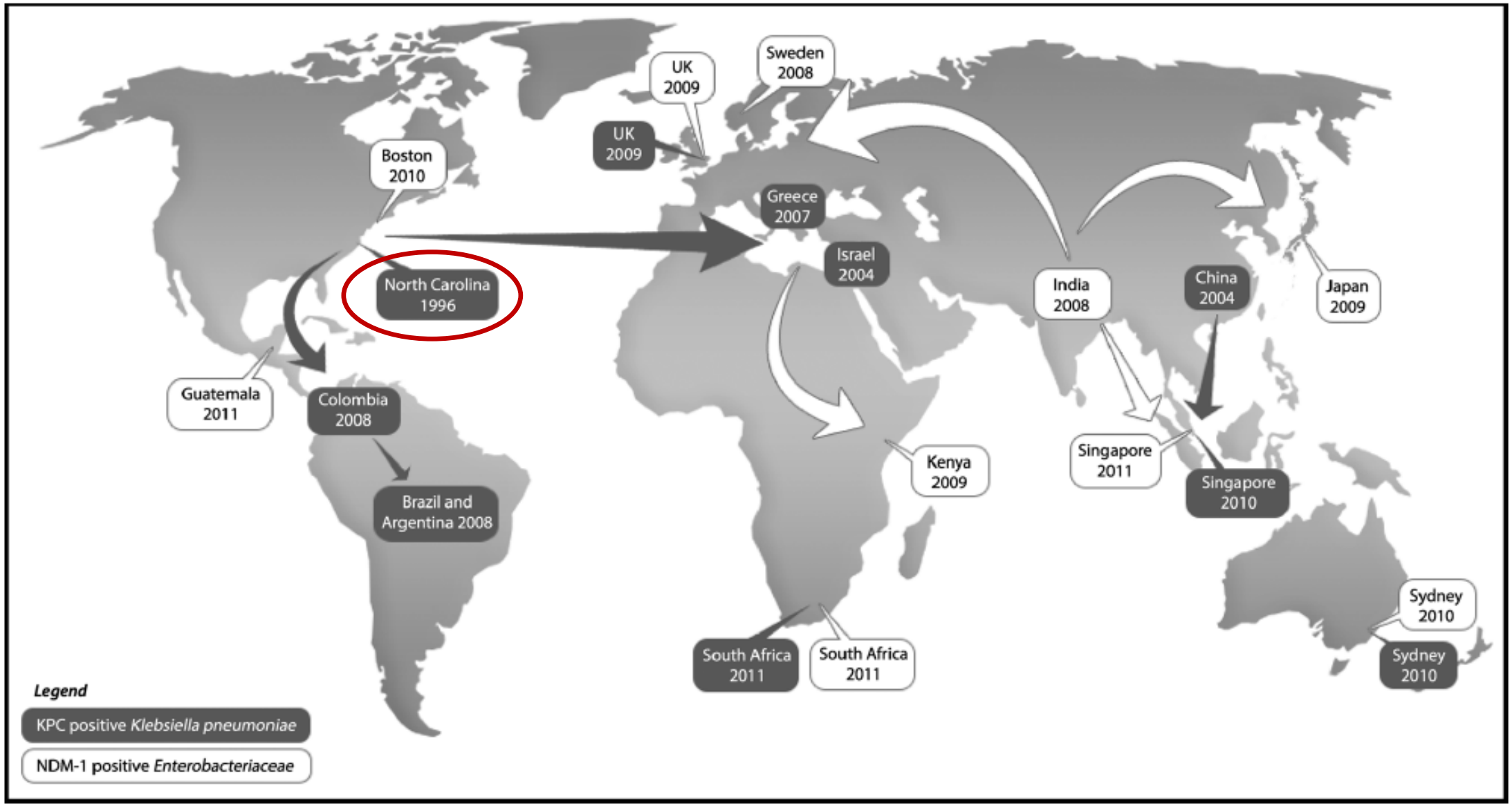


Figure 5.24: ***Klebsiella pneumoniae*: proportion of invasive isolates resistant to aminoglycosides in 2010**





Molton J, et al. Clin Infect Dis 2013;56:1310-1318

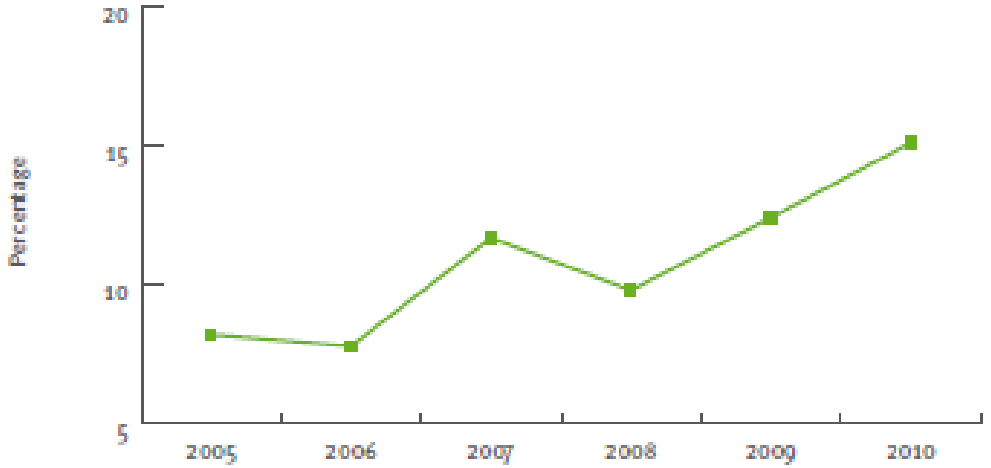
Antimicrobial resistance surveillance in Europe

Annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net)

2010

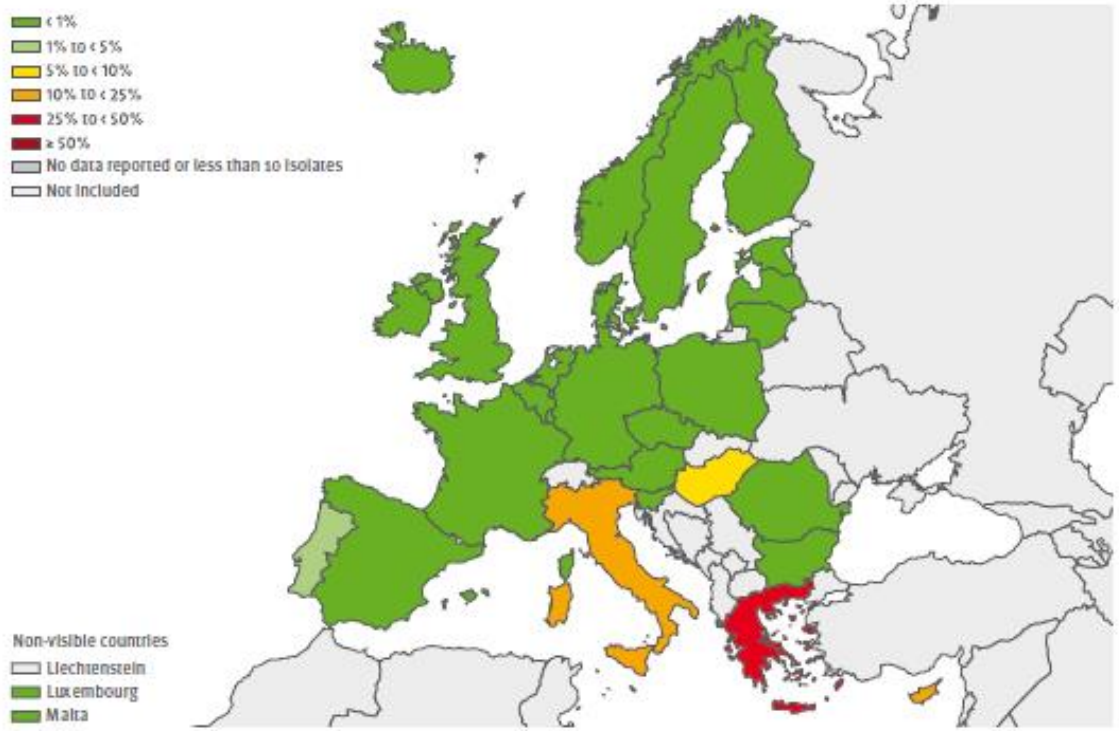
K. pneumoniae

Figure 2.2: *Klebsiella pneumoniae*: Percentage of carbapenem-resistant invasive isolates repo by year, 2005–2010 (18 countries; 140 laboratories)



Only laboratories that continuously reported susceptibility results for carbapenems during the period 2005–2010 are included in th

Figure 5.25: *Klebsiella pneumoniae*: proportion of invasive isolates resistant to carbapenems in 2010



Enzyme	Common genetic platform	Species distribution in Enterobacteriaceae	Geographic distribution
KPC (*Klebsiella pneumoniae* carbapenemase)	*K pneumoniae* sequence type 258, various plasmids types, transposon Tn*4401*x	*K pneumoniae*, *Escherichia coli*, *Enterobacter* species, diverse Enterobacteriaceae	Endemic in the United States, Greece, Israel, Italy, Puerto Rico, China, and South America
NDM (New Delhi metallo-beta-lactamase)	Various plasmid types	*K pneumoniae* and *E coli* predominantly, diverse Enterobacteriaceae	Indian subcontinent and the Balkan region, and around the world
OXA-48 (oxacillinase)	IncI/M-type plasmid	*K pneumoniae* predominantly, diverse Enterobacteriaceae	Southern and Western Europe, Turkey and North Africa; rare in the United States
VIM (Verona integron-encoded metallo-beta-lactamase)	Gene cassettes in class 1 integrons	*K pneumoniae* predominantly	Common in Italy, Greece, and the Far East, sporadic globally
IMP	Gene cassettes in class 1 integrons	*K pneumoniae* predominantly	Common in the Far East and South America, sporadic globally
SME	Chromosome	*Serratia marcescens*	Sporadic in North America and South America

L. S. Tzouvelekis et al. Clinical Microbiology Reviews 2012

Worsening epidemiological situation of carbapenemase-producing Enterobacteriaceae in Europe, assessment by national experts from 37 countries, July 2018

Country	Epidemiological stage for the spread of carbapenemase-producing Enterobacteriaceae				Change in epidemiological stage 2015–18
	2010 [11]	2013 [9]	2014–15 [8]	2018	
Albania	NA	2a	1	1	→
Austria	0	2b	2b	2b	→
Belgium	2b	3	4	4	→
Bosnia and Herzegovina[a]	1	1	0	2b	↑
Bulgaria	0	2a	2a	2b	→
Croatia	1	3	3	4	↑
Cyprus	2a	2a	1	2a	↑
Czech Republic	1	2b	2b	3	↑
Denmark	1	2a	4	4	→
Estonia	0	2a	1	1	→
Finland	1	2a	2a	3	↑
France	3	3	4	4	→
Germany	3	3	3	3	→
Greece	5	5	5	5	→
Hungary	3	4	4	4	→
Iceland	0	0	0	1	↑
Ireland	1	4	3	4	↑
Italy	4	5	5	5	→
Kosovo[b]	NA	2b	0	1	↑
Latvia	1	1	1	1	→
Lithuania	1	1	1	1	→
Luxembourg	NA	1	1	1	→
Malta	1	5	5	5	→
Montenegro	NA	0	1	1	→
The Netherlands	2a	2b	2a	2b	→
North Macedonia	NA	0	1	2a	↑
Norway	2a	2a	1	1	→
Poland	4	3	4	4	→
Portugal	1	1	2b	3	↑
Romania	1	1	4	4	→
Serbia	1	1	2b	4	↑
Slovak Republic	NA	2a	4	4	→
Slovenia	0	1	2a	1	↓
Spain	2b	3	4	4	→
Sweden	2a	2b	2a	2b	→
Turkey	NA	2a	5	5	→
United Kingdom[c]	2b	3	3	3	→

↑: Increase in the epidemiological stage between 2015 and 2018
→: unchanged epidemiological stage between 2015 and 2018
↓: decreased epidemiological stage between 2015 and 2018

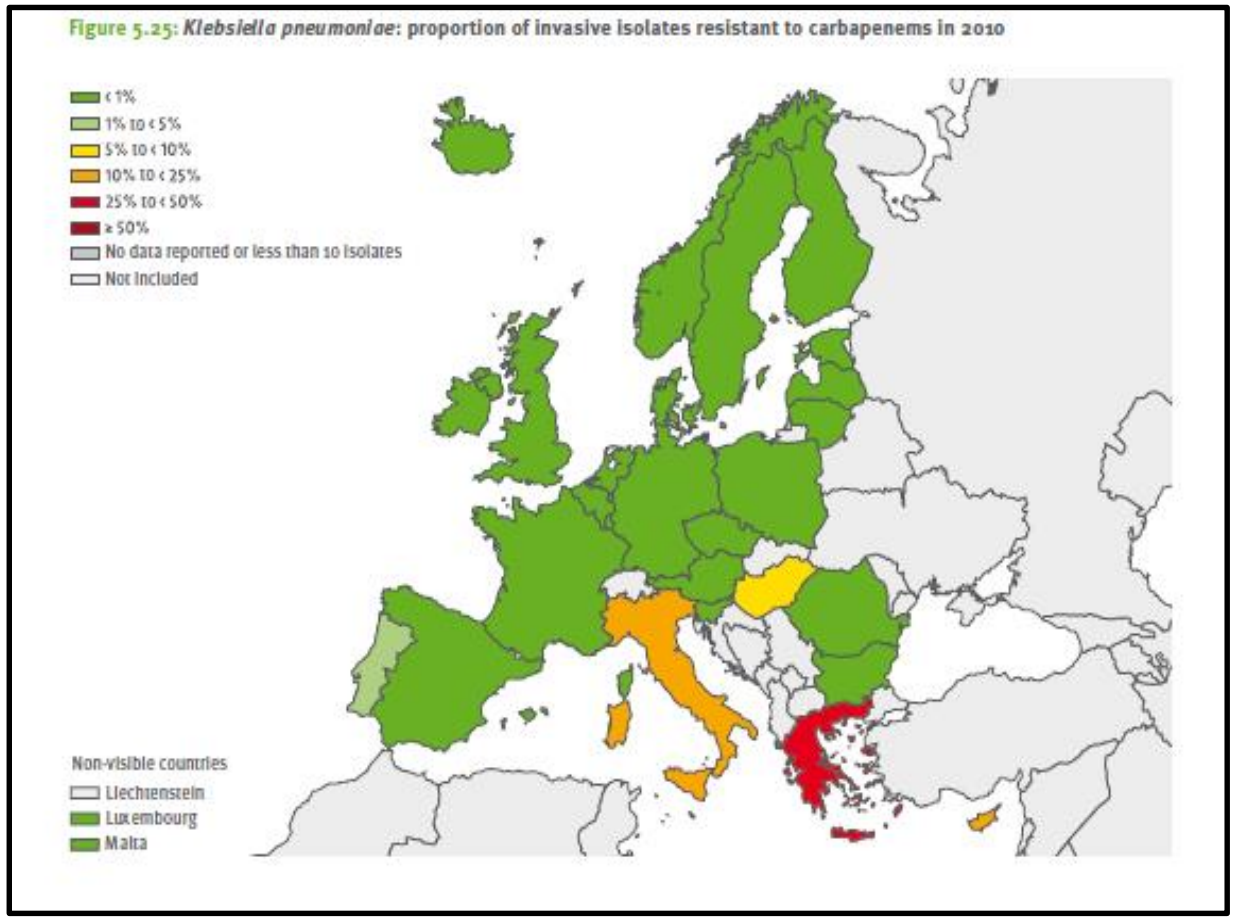
- 2018 yılı itibari ile verilerini paylaşan 37 ülkenin hepsinde CPE vakaları bildirilmiş…
- 2015 yılına kıyasla 2018 yılında CPE oranları;
  - 11 ülkede artmış
  - 25 ülkede benzer oranlar var
  - Sadece 1 ülkede bir salgın sonrası alınan önlemlerle oranlar azalmış.

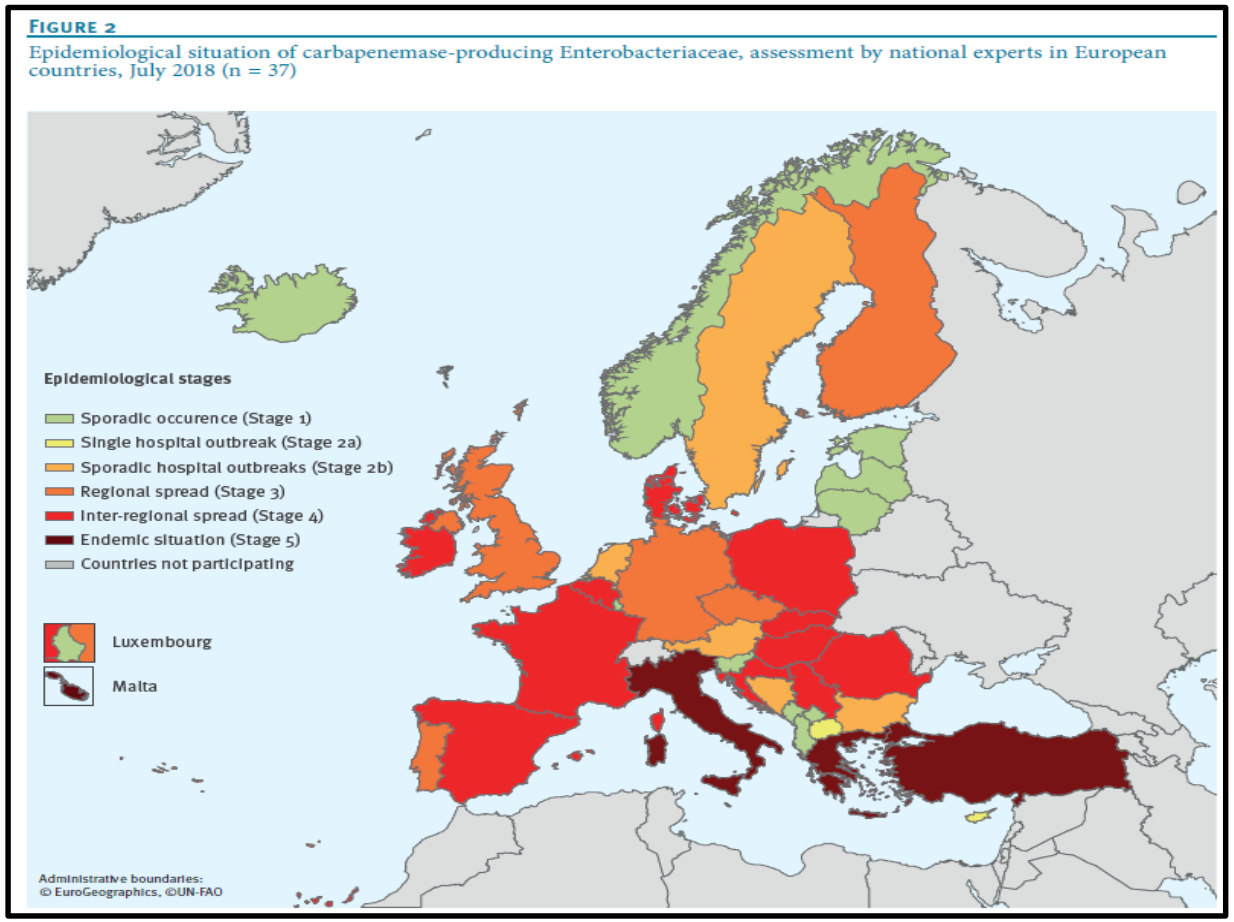
Epidemiological stages

- **Stage 0:** no case reported
- **Stage 1:** sporadic occurrence (epidemiologically unrelated single cases)
- **Stage 2a:** single hospital outbreak (two or more epidemiologically associated cases with indistinguishable geno- or phenotype in a single institution)
- **Stage 2b:** sporadic hospital outbreaks (unrelated hospital outbreaks with epidemiologically unrelated introduction or different strains, no autochthonous inter-institutional transmission reported)
- **Stage 3:** regional spread (more than one epidemiologically related hospital outbreak confined to hospitals that are part of the same region or health district, indicating regional autochthonous inter-institutional transmission)
- **Stage 4:** inter-regional spread (multiple epidemiologically related outbreaks occurring in different health districts, indicating inter-regional autochthonous inter-institutional transmission)
- **Stage 5:** endemic situation (most hospitals in a country are repeatedly seeing cases admitted from autochthonous sources)

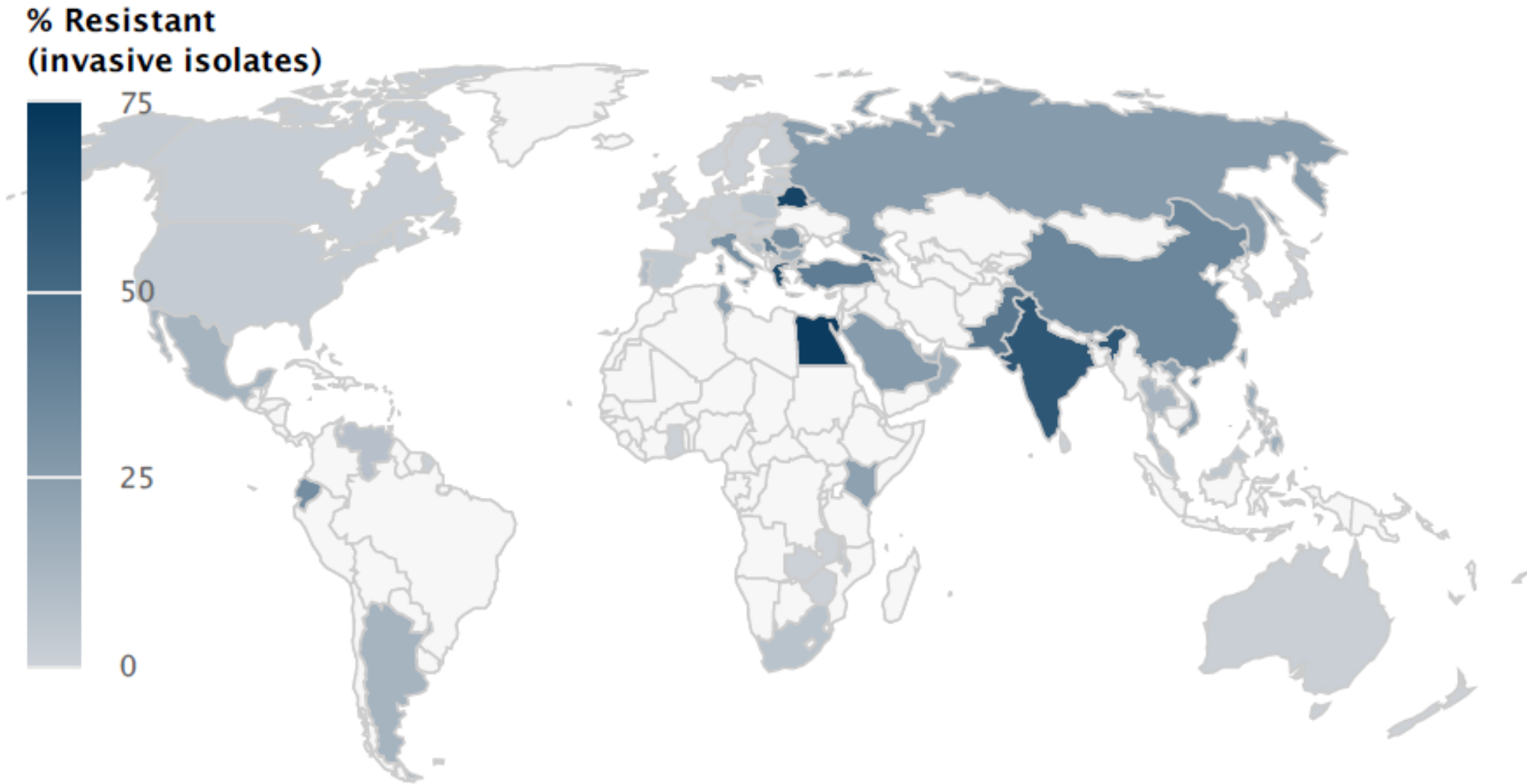
www.eurosurveillance.org

Karbapenem Direnci 2010 vs 2018



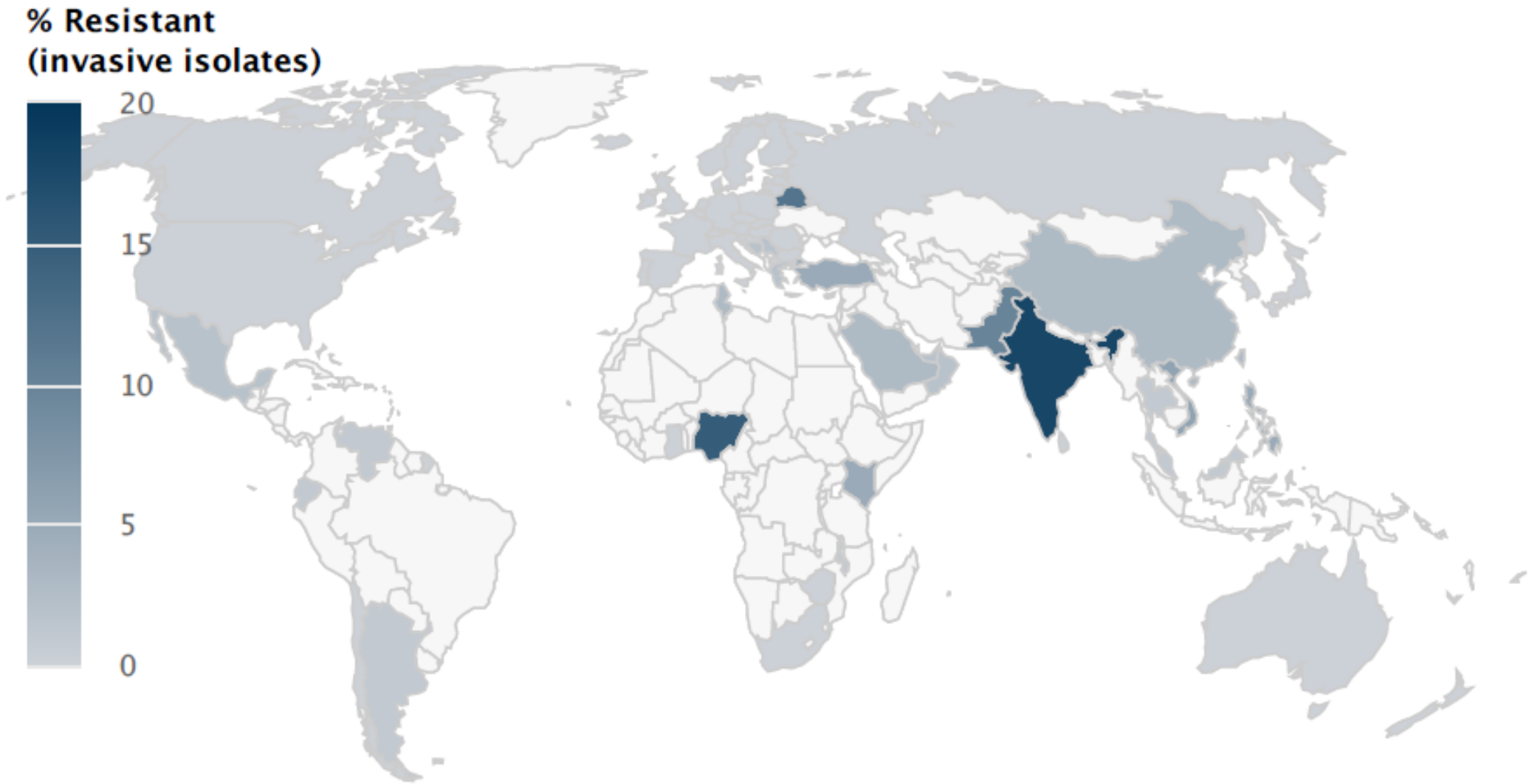


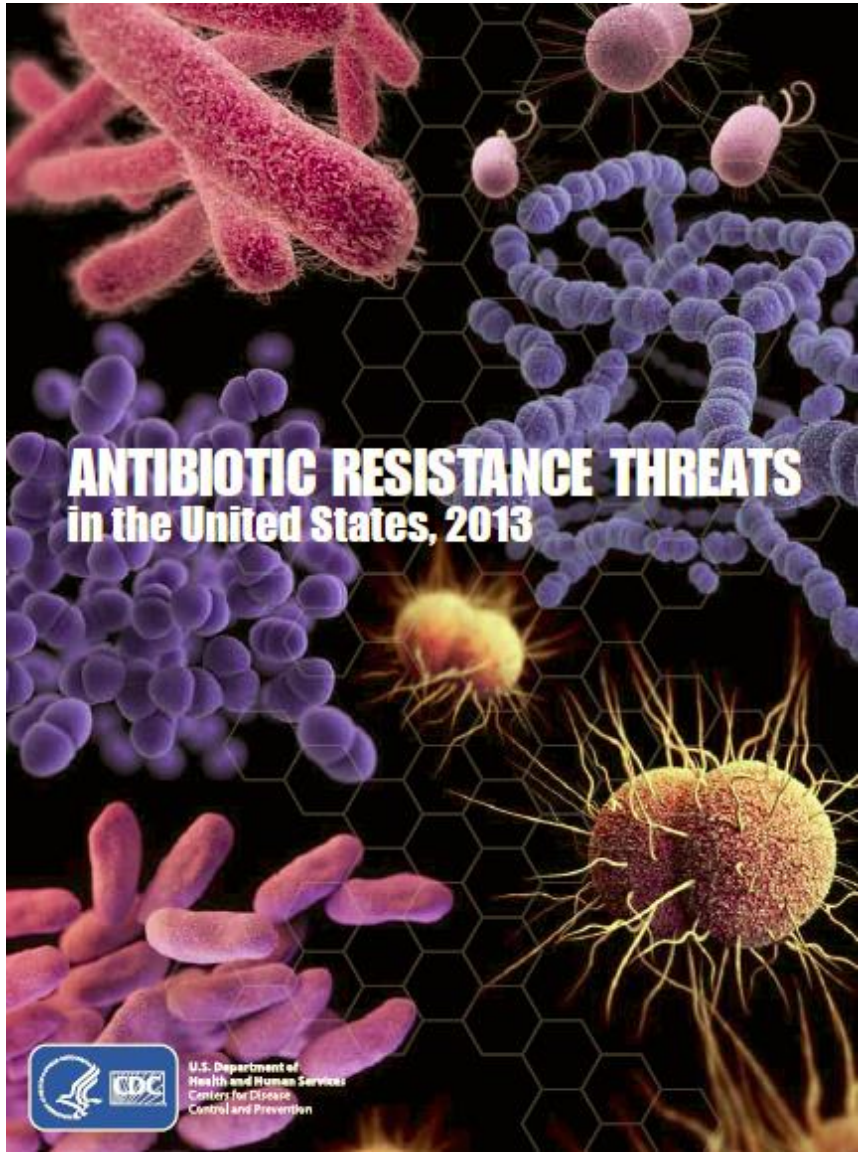
Resistance of *Klebsiella pneumoniae* to Carbapenems



Center for Disease Dynamics, Economics & Policy (cddep.org) © Natural Earth

Resistance of *Escherichia coli* to Carbapenems





THREAT LEVEL **URGENT**

These bacteria are immediate public health threats that require urgent and aggressive action.

MICROORGANISMS WITH A THREAT LEVEL OF URGENT

Clostridium difficile

Carbapenem-resistant **Enterobacteriaceae**

Drug-resistant ***Neisseria gonorrhoeae***

THREAT LEVEL **SERIOUS**

These bacteria are a serious concern and require prompt and sustained action to ensure the problem does not grow.

MICROORGANISMS WITH A THREAT LEVEL OF SERIOUS

Multidrug-resistant ***Acinetobacter***

Drug-resistant ***Campylobacter***

Fluconazole-resistant ***Candida*** (a fungus)

Extended spectrum β-lactamase producing **Enterobacteriaceae (ESBLs)**

Vancomycin-resistant ***Enterococcus*** **(VRE)**

Multidrug-resistant ***Pseudomonas aeruginosa***

Drug-resistant **non-typhoidal *Salmonella***

Drug-resistant ***Salmonella* Typhi**

Drug-resistant ***Shigella***

Methicillin-resistant ***Staphylococcus aureus*** **(MRSA)**

Drug-resistant ***Streptococcus pneumoniae***

Drug-resistant **tuberculosis**

THREAT LEVEL **CONCERNING**

These bacteria are concerning, and careful monitoring and prevention action are needed.

MICROORGANISMS WITH A THREAT LEVEL OF CONCERNING

Vancomycin-resistant ***Staphylococcus aureus*** **(VRSA)**

Erythromycin-resistant **Group A *Streptococcus***

Clindamycin-resistant **Group B *Streptococcus***

WHO PRIORITY PATHOGENS LIST FOR R&D OF NEW ANTIBIOTICS

Priority 1: CRITICAL#

Acinetobacter baumannii, carbapenem-resistant

Pseudomonas aeruginosa, carbapenem-resistant

*Enterobacteriaceae**, carbapenem-resistant, 3rd generation cephalosporin-resistant

Priority 2: HIGH

Enterococcus faecium, vancomycin-resistant

Staphylococcus aureus, methicillin-resistant, vancomycin intermediate and resistant

Helicobacter pylori, clarithromycin-resistant

Campylobacter, fluoroquinolone-resistant

Salmonella spp., fluoroquinolone-resistant

Neisseria gonorrhoeae, 3rd generation cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: MEDIUM

Streptococcus pneumoniae, penicillin-non-susceptible

Haemophilus influenzae, ampicillin-resistant

Shigella spp., fluoroquinolone-resistant

Şubat 2017

TACKLING DRUG-RESISTANT INFECTIONS GLOBALLY: FINAL REPORT AND RECOMMENDATIONS

THE REVIEW ON ANTIMICROBIAL RESISTANCE

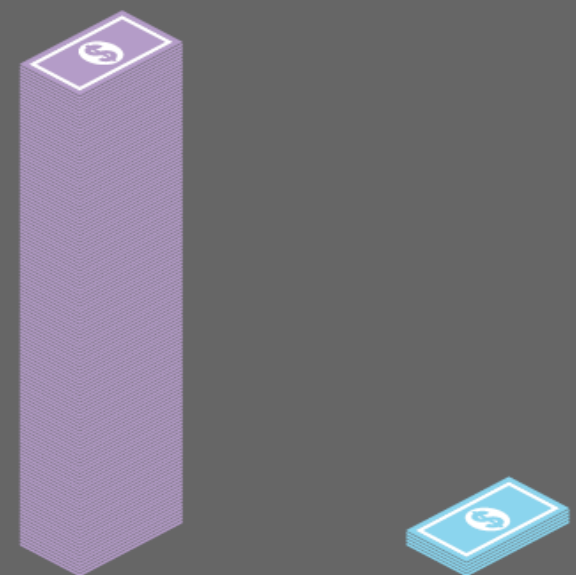
CHAIRED BY JIM O'NEILL

MAY 2016

ANTIMICROBIAL R&D IS NOT ATTRACTIVE TO VENTURE CAPITALISTS

Less than 5%

of venture capital investment in pharmaceutical R&D between 2003 and 2013 was for antimicrobial development.



Total venture capital investment

$38bn

Antimicrobial venture capital investment

$1.8bn

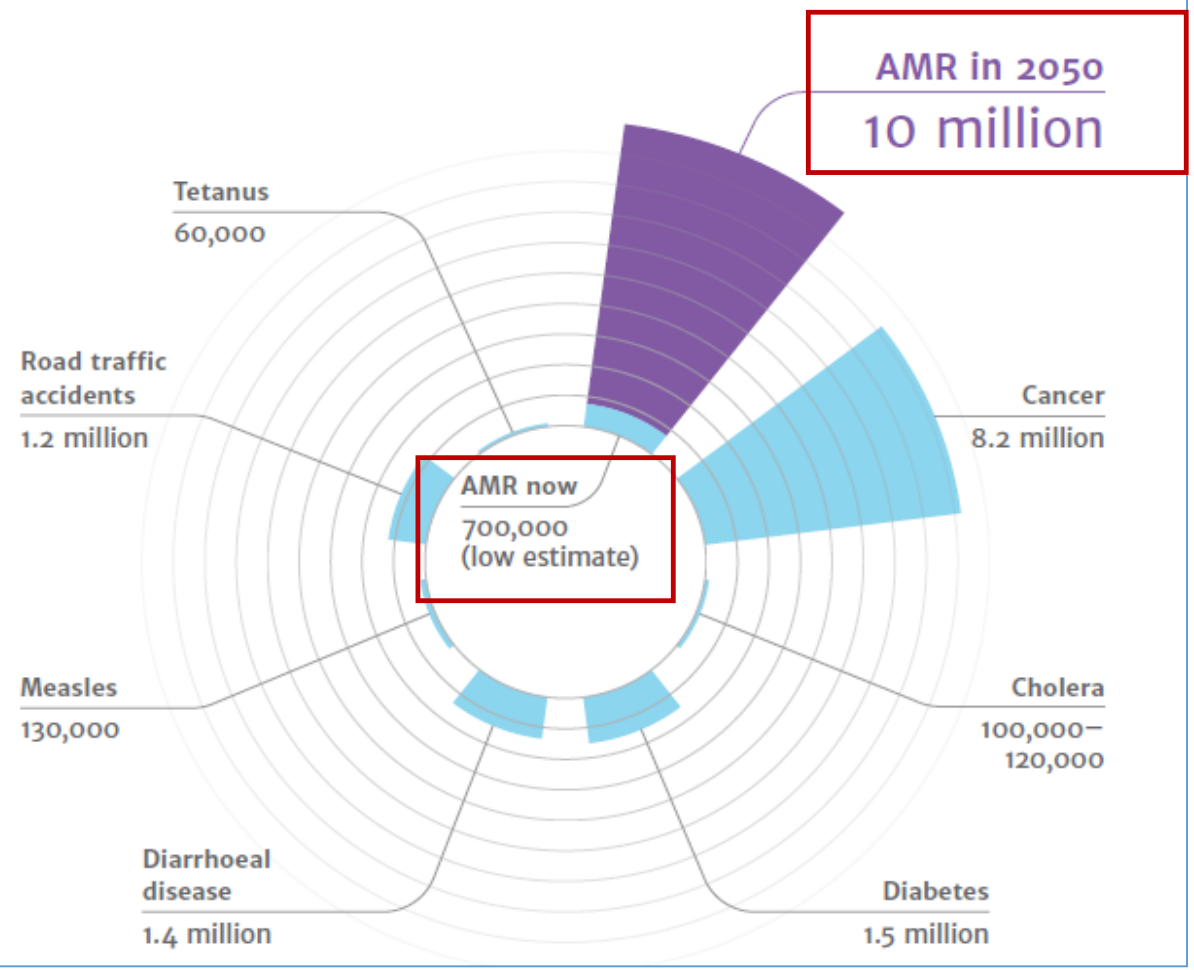
TACKLING DRUG-RESISTANT INFECTIONS GLOBALLY:
FINAL REPORT AND RECOMMENDATIONS

THE REVIEW ON ANTIMICROBIAL RESISTANCE

CHAIRED BY JIM O'NEILL

MAY 2016

DEATHS ATTRIBUTABLE TO AMR EVERY YEAR



Tedavi seçenekleri?

ESBL üreten Enterobacteriaceae

- ESBL salgılayan patojenlerle meydana gelen enfeksiyonlarda ***karbapenemler hala ilk seçenek***

- Bu mo larda **fluorokinolon direnci çok yaygın**

- **Aminoglikozid direnci çok yaygın**

- **Tigesiklin ESBL üreten enterobakterilerin tümüne etkin**
  - Fakat **zayıf penetrasyon**undan dolayı üriner sistem enfeksiyonunda kullanımıyla ilgili yeterli veri yok
  - Tigesiklin kullanıldığında özellikle VİP'de tedavi başarısızlığı riski yüksek; **artmış mortalite ve tedavi başarısızlığı ile ilişkili** bulunmuş

Karbapenemaz üreten Enterobacteriaceae

Günümüz bilgisiyle **optimal CPE tedavisi konusunda fikir birliği yok…**

Enterobacteriaceae Karbapenemazları

Ambler Sınıfı	Enzim	Bakteri
Sınıf A	KPC	K. pneumoniae, E. coli, Enterobacter spp.
Sınıf B (metallobetalaktamaz)	NDM, VIM, IMP	NDM: K. pneumoniae, E. coli VIM:K. pneumoniae IMP: K. pneumoniae
Sınıf D	OXA-48	K. pneumoniae

KPC, Klebsiella pneumoniae carbapenemase; NDM, New Delhi metallo--lactamase; VIM, Verona integrin-encoded metallo—lactamase; IMP, imipenemase; OXA, oxacillinase.

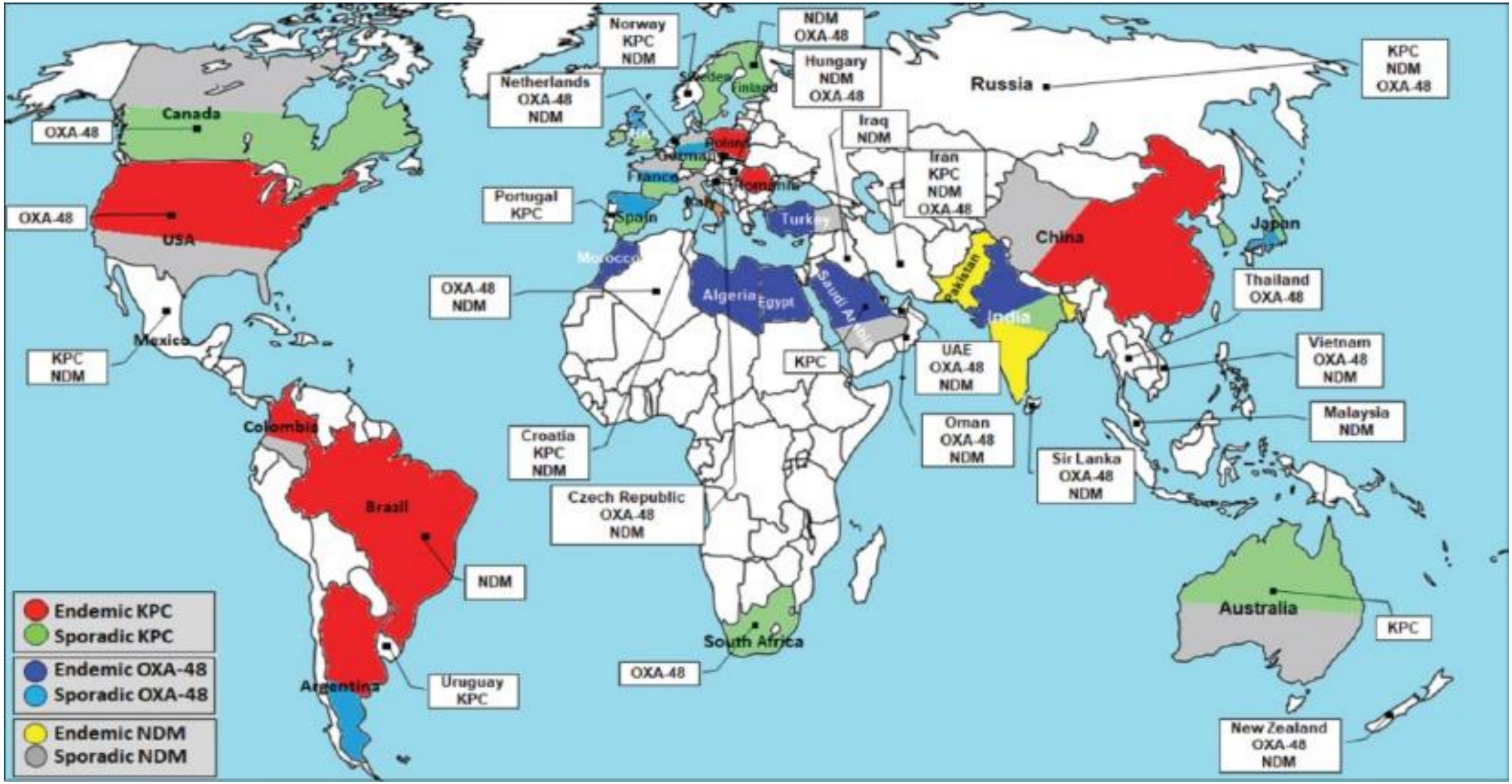
Enterobacteriaceae Karbapenemazlar

TABLE 1 | Classification and characteristics of major carbapenemases in *Enterobacteriaceae*.

Carbapenemase	KPC	MBLs (NDM, VIM, IMP)	OXA-48
Ambler molecular class	A	B	D
Substrates of hydrolysis	All β-lactams	All β-lactams except for aztreonam	Penicillins and carbapenems
Inhibited by classic β-lactamase inhibitors	Minimally	No	No
Inhibited by avibactam	Yes	No	Yes
Inhibited by vaborbactam	Yes	No	No
Inhibited by relebactam	Yes	No	No
Common species in *Enterobacteriaceae*	*K. pneumoniae*, *E. coli*, *Enterobacter* spp.	NDM: *K. pneumoniae*, *E. coli* VIM: *K. pneumoniae* IMP: *K. pneumoniae*	*K. pneumoniae*

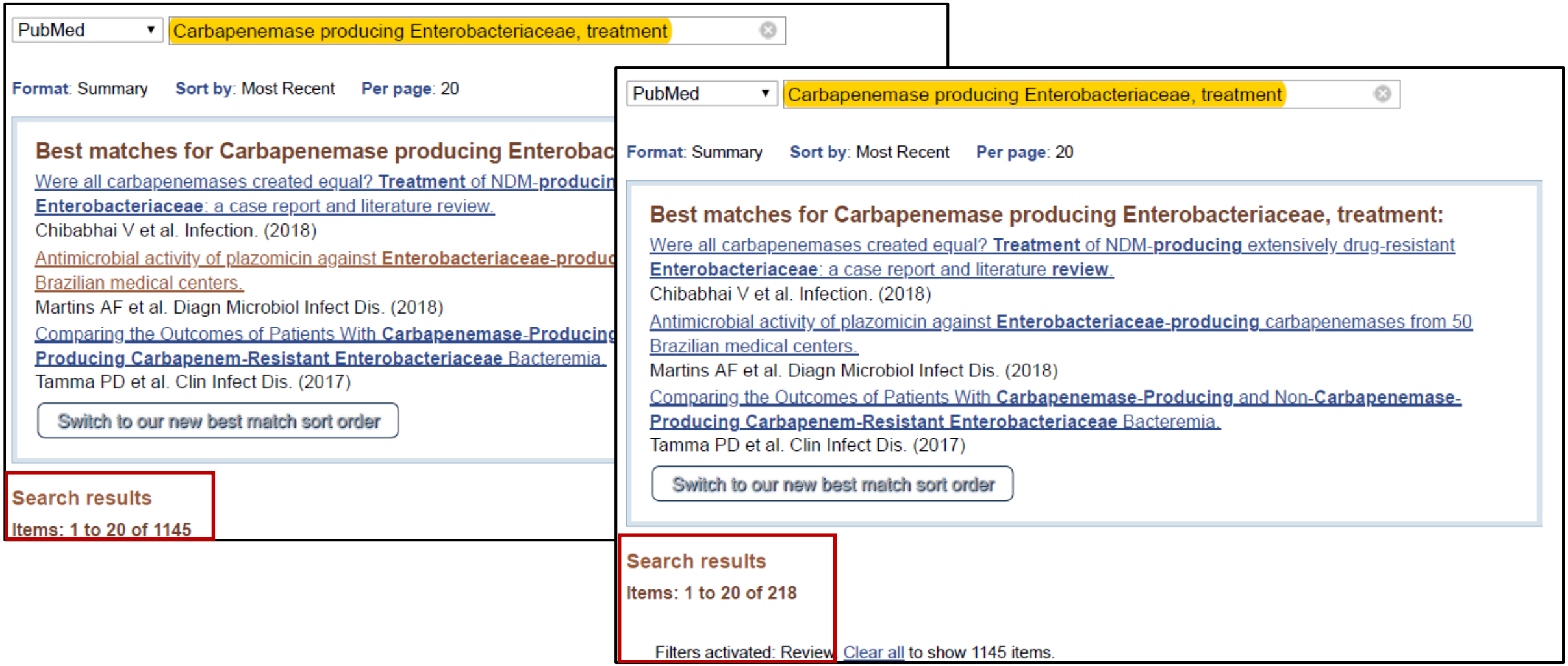
KPC, Klebsiella pneumoniae carbapenemase; MBL, metallo-β-lactamase; NDM, New Delhi metallo-β-lactamase; VIM, Verona integrin-encoded metallo-β-lactamase; IMP, imipenemase; OXA, oxacillinase.

Sheu CC et al. Frontiers in Microbiology 2019; 10.80



Zahrani IA. Saudi Med J 2018; Vol. 39 (9): 861-872

Karbapenemaz üreten Enterobacteriaceae



CRE’de etkili olduğu bilinen ajanlar

- Kolistin
- Polimiksin B
- Tigesiklin
- Fosfomisin
- Aminoglikozidler

«FARKLI»

CRE tedavisinde alternatif arayışlar

- Yüksek doz tigesiklin
- Yüksek doz / uzamış infüzyon karbapenem
- Çift karbapenem

CRE tedavisinde yeni ajanlar

- Seftazidim avibaktam
- Plazomisin
- Meropenem vaborbaktam
- Eravasiklin
- İmipenem relebaktam*
- Sefiderokol*

KOMBİNASYON?

Çalışma dizaynlarında ve direnç mekanizmalarındaki çeşitlilik nedeniyle optimal öneri ???

Kombinasyon vs Monoterapi

Antibiotic Treatment of Infections Due to Carbapenem-Resistant *Enterobacteriaceae*: Systematic Evaluation of the Available Evidence

Matthew E. Falagas,[a,b,c] Panagiota Lourida,[a] Panagiotis Poulikakos,[a,b] Petros I. Rafailidis,[a] Giannoula S. Tansarli[a]

TABLE 1 Mortality of infections caused by carbapenemase-producing *Enterobacteriaceae* or CRE among different antibiotic treatment regimens

Organisms	First author, yr of study (reference)	Study design: period, country	Population characteristics: most common underlying diseases	Site of infection (% of total population)	No. of infected patients who received definitive antibiotic treatment	Causative pathogen(s)	Susceptibility breakpoints used (agent), yr[f]	Mortality assessed	Antibiotic treatment administered, no. of patients (% mortality)	
									Combination therapy	Monotherapy
KPC-producing *Klebsiella* spp.	Capone, 2013 (11)	MC prospective cohort: 2010–2011, Italy	Inpatients (48.4% were ICU patients): DM, COPD, chronic kidney or liver disease, malignancy	BSI (37.4), UTI (31.9), septic shock (16.5), LRTI (15.4), SSTI (12.1)[b]	67 (appropriate antibiotic treatment was known for 56)	KPC-producing *Klebsiella pneumoniae*	EUCAST, NR	In hospital	Coll-Tige, 16 (25) Tige-Fos, 6 (33) Coll-Fos, 5 (0) Coll-Gen, 5 (40)	Gen, 16 (6.3) Colt, 10 (40)
	Alexander, 2012 (9)	SC retrospective cohort: 2006–2008, USA	Inpatients	UTI, 2 patients developed bacteremia	14	KPC-producing *K. pneumoniae* and *Citrobacter freundii*	CLSI, 2006 FDA (Tige)[c]	In hospital	NR[d]	Gen, 5 (40) Cipro, 4 (0) Dox, 1 (0) Ntr, 1 (0)
	Bergamasco, 2012 (10)	SC retrospective cohort: 2009–2010, Brazil	Solid-organ transplant recipients: DM, cardiovascular disease, liver disease, renal disease	BSI (33.3), UTI (33.3), SSI (16.7), pneumonia (16.7)	12	KPC-producing *K. pneumoniae*	CLSI, 2009 FDA (Tige)[c]	At 30 days	Carba-PolB, 3 (67) Tige-PolB, 3 (0) Carba-Tige, 1 (0)	Carba, 2 (100) PolB, 3 (33)
	Qureshi, 2012 (19)	SC retrospective cohort: 2005–2009, USA	Inpatients (53.7% were ICU patients at enrollment): DM, cardiovascular disease, CRF, renal dialysis, COPD, malignancy (51.2% had an Apache II score of ≥20)	Bacteremia, the sources for which were pneumonia (24.4), line related (31.7), UTI (17.1), primary (14.6)	34	KPC-producing *K. pneumoniae*	CLSI, 2011	At 28 days	Coll-Carba, 5 (20) Coll-Tige, 1 (0) Coll-FQ, 1 (0) Tige-Carba, 3 (0) Tige-AG, 2 (0) Carba-FQ, 1 (100) Azt-FQ, 1 (0) Cipm-Gen, 1 (0)	Colt, 7 (57) Tige, 5 (80) Carba, 4 (50) Gen, 1 (0) A-S, 1 (0) Tzp, 1 (100)
	Tumbarello, 2012 (25)	MC retrospective cohort: 2010–2011, Italy	Inpatients (13.6% were in shock): DM, heart failure, CRF, malignancy	BSI, the sources for which were LRTI, CVC, UTI, other, and unknown	125	KPC-producing *K. pneumoniae*	CLSI, 2011 FDA (Tige)[c]	At 30 days	Tige-Coll, 23 (30) Tige-Gen, 12 (50) Coll-Gen, 7 (57) Other 2-drug combinations, 14 (43) Tige-Coll-Carba, 16 (13) Tige-Gen-Carba, 6 (17) Coll-Gen-Carba, 1 (100)	Tige, 19 (53) Colt, 22 (50) Gen, 5 (80)
	Zarkotou, 2011 (28)	SC prospective cohort: 2008–2010, Greece	Inpatients (71.7% were in the ICU at admission)	BSI, the sources for which were primary (43.4) and catheter related (22.6)	35	KPC-producing *K. pneumoniae*	CLSI, 2010 EUCAST, 2010 (Coli)	Infection related	Tige-Coll, 9 (0) Tige-Gen, 3 (0) Tige-Coll-Carba, 2 (0) Tige-Coll-Gen, 1 (0) Tige-Carba, 1 (0) Tige-Amk, 1 (0) Coll-Gen, 2 (0) Carba-Gen, 1 (0)	Coll, 7 (57) Tige, 5 (40) Gen, 2 (0) Carba, 1 (100)
	Souli, 2010 (22)	SC retrospective cohort: 2007–2008, Greece	Inpatients (61% were ICU patients): DM, cardiovascular disease, COPD, renal failure, malignancy	BSI (77.8), SSI (11), UTI (5.6), HAP (5.6)	17	KPC-producing *K. pneumoniae*	CLSI, 2009 EUCAST, 2009 (Fos, Coli) FDA (Tige)[c]	Overall	Carba-Coll, 6 (67) Coll-Tige, 2 (0) Carba-Coll-Gen, 1 (100) Carba-Coll-Cipro, 1 (0) Carba-Coll-Tige, 1 (100) Carba-Coll-Tige-Amk, 1 (100) Coll-Tige-Amk-Tzp, 1 (100) Tzp-Cipro-Coli-Gen and then Tige-Amk, 1 (100) Tzp-Amk and then Tige, 1 (100)	Carba, 1 (0) Tzp and then Tige, 1 (0)
	Weisenberg, 2009 (26)	SC retrospective cohort: 2006, USA	Inpatients	Bacteremia (19), pneumonia (23.8), UTI (9.5), urosepsis (15.3), other RTIs (19), CSF infection (4.8), wound infection (4.8), line-related infection (4.8)	21	KPC-producing *K. pneumoniae*	NR	Undetermined	Tige-Gen, 1 (0) Tige-Carba, 1 (100)	Carba, 11 (9) Tige, 5 (0) Gen, 2 (0) Amk, 1 (0)

Falagas M et al. Antimicrob. Agents Chemother 2014; 58: 654–663.

Association Between Carbapenem Resistance and Mortality Among Adult, Hospitalized Patients With Serious Infections Due to *Enterobacteriaceae*: Results of a Systematic Literature Review and Meta-analysis

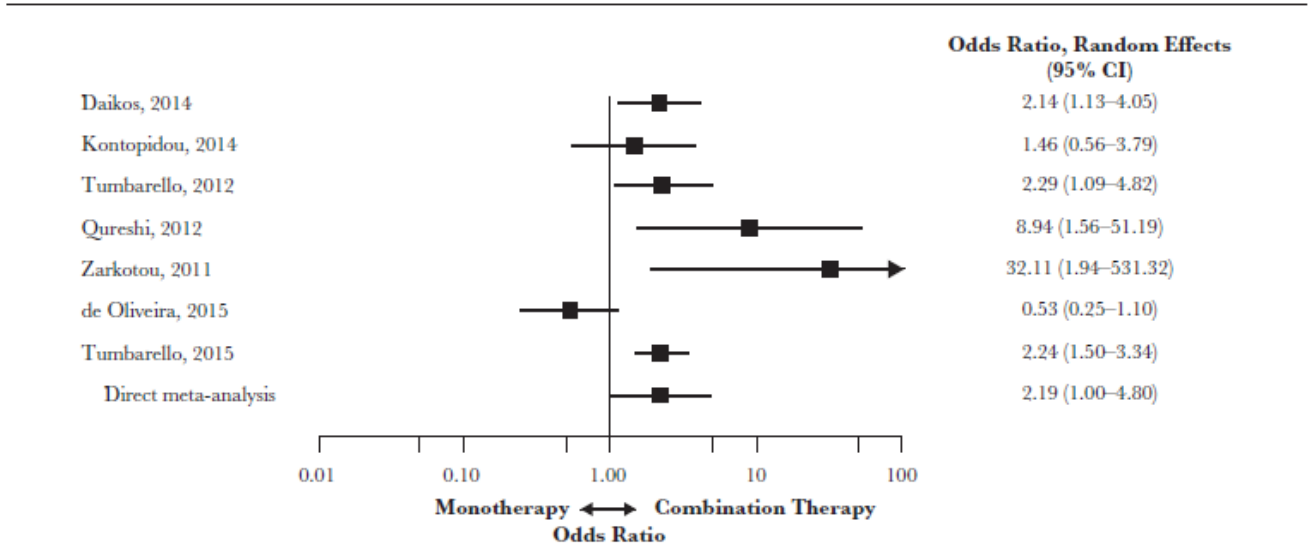


Figure 6. Mortality in patients with CRE infections treated with monotherapy vs combination therapy. Abbreviations: CI, confidence interval; CRE, carbapenem-resistant Enterobacteriaceae.

- **22 çalışma alınmış**
- **7 çalışmada kombinasyon vs monoterapi**
- **4 BSI, 3 miks enfeksiyon**
- **Monoterapi ile mortalite belirgin yüksek (OR= 2.19)**
- **Ancak heterojenite çok yüksek (I^2= % 84.2)**

Martin A et al. *Open Forum Infect. Dis. 2018*

CRE'de optimal öneriyi belirlemek neden zor?

- Çalışmalar non-RCT; çoğu retrospektif dizaynda…

- Farklı enfeksiyon bölgelerinde
- Farklı ciddiyetteki hasta gruplarında
- En önemlisi küçük hasta gruplarında ya

RCT'lerden daha etkin sonuçlar alınıncaya kadar ***ciddi enfeksiyonu olan kritik hastalarda KOMBİNASYON*** tercih!!!

- Farklı genotipteki patojenlerle (KPC, OXA, VIM)
- Farklı mortalite değerlendirmeleri
- Farklı doz ve sürede uygulanan AB değerlendirilmeleri kullanılmış…

Falagas M et al. Antimicrob. Agents Chemother 2014; 58: 654–663.

Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial

- **Yayınlanmış ilk prospektif RCT**
- **Kolistin monoterapi vs kolistin + meropenem**
- **Enterobacteriaceae hastaların % 18'i (73/406)**
- **Enterobacteriaceae infeksiyonlarının % 77'si KDİ ve K. pneumoniae (%89) majör patojen**
- **Enterobacteriaceae ile ilgili subgrup analizlerinde;**
  - **Klinik sonuçta fark yok**
  - **Klinik başarısızlık ve 28 gün mortalite kombinasyon grubunda daha az ama istatistiksel anlamlı değil….**

	Colistin	Colistin and meropenem	Risk ratio (95% CI) for outcome with combination	p value
Per protocol population*				
n	169	185	..	..
Clinical failure	129 (76%)	131 (71%)	0·92 (0·82–1·05)	0·220
28-day mortality	69 (41%)	75 (41%)	0·97 (0·76–1·25)	0·840
14-day mortality	48 (28%)	53 (29%)	1·00 (0·72–1·39)	0·992
Inappropriate empirical antibiotic treatment†				
n	92	105	..	..
Clinical failure	74 (80%)	76 (72%)	0·91 (0·78–1·07)	0·254
28-day mortality	40 (43%)	44 (42%)	0·98 (0·71–1·36)	0·910
14-day mortality	34 (37%)	28 (27%)	0·74 (0·49–1·13)	0·166
Bloodstream infection, ventilator-associated pneumonia, or hospital-acquired pneumonia				
n	173	182	..	..
Clinical failure	141 (82%)	133 (73%)	0·9 (0·8–1·004)	0·059
28-day mortality	77 (45%)	81 (45%)	0·99 (0·79–1·25)	0·931
14-day mortality	55 (328%)	60 (33%)	1·04 (0·78–1·38)	0·804
Main pathogen				
n	198	208	..	..
Clinical failure				
Acinetobacter baumannii	125 (83%), n=151	130 (81%), n=161	0·97 (0·87–1·09)	0·643
Enterobacteriaceae‡	23 (68%), n=34	18 (46%), n=39	0·78 (0·54–1·13)	0·185
Pseudomonas or others§	8 (62%), n=13	4 (50%), n=8	0·81 (0·36–1·84)	0·673
28-day mortality				
A baumannii	70 (46%), n=151	84 (52%), n=161	1·11 (0·87–1·41)	0·404
Enterobacteriaceae	12 (35%), n=34	8 (21%), n=39	0·62 (0·29–1·36)	0·235
Pseudomonas or others	4 (31), n=13	2 (25%), n=8	0·81 (0·19–3·47)	1·0
14-day mortality				
A baumannii	54 (36%), n=151	62 (39%), n=161	1·11 (0·82–1·52)	0·495
Enterobacteriaceae	6 (18%), n=34	6 (15%), n=39	0·90 (0·32–2·51)	0·838
Pseudomonas or others	4 (31%), n=13	2 (25%), n=8	0·81 (0·19–3·47)	1·0

Paul M et al. Lancet Infect Dis 2018;18: 391–400

CRE tedavisinde alternatif arayışlar

Yüksek doz Tigesiklin

200 mg yükleme dozu sonrası 2x 100 mg

- Yüksek doz tigesiklinin etkinliğini değerlendiren çalışmalarda sonuçlar çelişkili…
- Seçilmiş hasta gruplarında (travma hastaları veya post-op abdominal cerrahi hastalarında gelişen CRE enfeksiyonlarında)düşünülebilir…
- Ancak plazmada geniş dağılımı ve dokularda konsantre olması nedeniyle KDİ'larında kullanılmamalı…

Sheu CC et al. Frontiers in Microbiology 2019;10:80

Tigecycline Treatment for Carbapenem-Resistant *Enterobacteriaceae* Infections

A Systematic Review and Meta-Analysis

Wentao Ni, MD, Yuliang Han, MD, Jie Liu, MD, Chuanqi Wei, MD, Jin Zhao, MD, Junchang Cui, MD, Rui Wang, PhD, and Youning Liu, MD

TABLE 4. Subgroup Analysis of Mortality Using Different Tigecycline Regimens to Treat Carbapenem-Producing *Enterobacteriaceae* and Carbapenem-Resistant *Enterobacteriaceae* Infections

Variables	Mortality Type	Studies, No. (Patients, No.)	Mortality Difference OR (95% CI); *P*	Heterogeneity of Studies Included
Monotherapy vs combination	30-day	9 (317)	1.83 (1.07–3.12); $P=0.03$	$I^2=0\%$; $Q=7.81$; $P=0.45$
	Infection-related	3 (59)	1.75 (0.33–9.27); $P=0.51$	$I^2=46.34\%$; $Q=3.73$; $P=0.16$
	14-day	2 (42)	1.00 (0.34–2.99); $P=1.00$	$I^2=0\%$; $Q=0.65$; $P=0.42$
	ICU	2 (62)	1.10 (0.11–10.67); $P=0.94$	$I^2=46.29\%$; $Q=1.86$; $P=0.17$
Double combination* vs triple combination†	30-day	8 (205)	2.18 (1.03–4.63); $P=0.04$	$I^2=4.31\%$; $Q=6.27$; $P=0.39$
	Infection-related	4 (58)	0.63 (0.16–2.54); $P=0.51$	$I^2=0\%$; $Q=1.05$; $P=0.59$
High dose vs standard dose‡	30-day	2 (47)	2.25 (0.55–9.24); $P=0.26$	$I^2=0\%$; $Q=0.02$; $P=0.90$
	ICU	2 (62)	12.48 (2.06–75.43); $P=0.006$	$I^2=0\%$; $Q=0.22$; $P=0.64$

- Tigesiklinin CRE enfeksiyonlarındaki etkinliğini değerlendiren 25 çalışma
- Subgrup analizlerinde yüksek doz tigesiklin ile daha düşük YBÜ mortalitesi (OR= 12.48)

Ni W et al. Medicine 2016;95(11):e3126

Carbapenemase-producing *Klebsiella pneumoniae*: (when) might we still consider treating with carbapenems?

G. L. Daikos[1] and A. Markogiannakis[2]

TABLE I. Clinical studies, antimicrobial therapies and outcomes of patients infected with carbapenemase-producing *Klebsiella pneumoniae*

References	First author (year of publication)	Study design	No. of patients	Carbapenemase (no. of isolates)	Treatment (no. of patients)	Outcome (no. of successes/ no. of failures)
42 22 43 17 52 41 53 14 54	Villegas (2004) Lomaestro (2006) Wei (2007) Daly (2007) Mendes (2008) Endimiani (2008) Marschall (2009) Mathers (2009) Benenson (2009)	Case reports	11	KPC (11) IMP (1)	Carbapenem (4) Carbapenem combined with another agent (1) Other treatment (6)	5/6
11	Yan (2001)	Case series	16	IMP (16)	Carbapenem (3) Other treatment (13)	9/7
39	Lee (2004)	Case series	3	IMP (3)	Carbapenem (3)	3/0
55	Bradford (2004)	Case series	4	KPC (4)	Carbapenem combined with another therapy (3) Other treatment (1)	3/1
10	Bratu (2005)	Retrospective	58	KPC (29)	No precise information on treatment (58)	9/20
24	Daikos (2007)	Retrospective	28	VIM (28)	Carbapenem (11) Carbapenem combined with another agent (13) Other treatment (4)	9/19
18	Souli (2008)	Case series	17	VIM (17)	Carbapenem combined with another agent (9) Other treatment (8)	14/3
23	Weisenberg (2009)	Case series	21	KPC (21)	Carbapenem (11) Carbapenem combined with another agent (1) Other treatment (9)	8/13
56	Maltezou (2010)	Case series	22	KPC (22)	Carbapenem combined with another agent (1) Other treatment (13) No information on treatment (8)	11/3
57	Endimiani (2009)	Case series	7	KPC (7)	Carbapenem combined with another agent (1) Other treatment (1) No information on treatment (5)	4/3
58	Nadkarni (2009)	Case series	6	KPC (6)	Other treatment	2/4
25	Daikos (2009)	Prospective observational	67	VIM (67)	Carbapenem (14) Carbapenem combined with another agent (12) Other treatment (41)	16/51
59	Souli (2010)	Case series	18	KPC (18)	Carbapenem (1) Carbapenem combined with another agent (11) Other treatment (6)	11/7
15	Mouloudi (2010)	Case control	37	VIM (18) KPC (19)	Other treatment (37)	21/16

- **22 çalışma (çoğu olgu serisi)**
- **Karbapenemlerin teröpatik etkinliği;**
  - **MIC >8 mg/L olan izolatlarda % 29**
  - **MIC ≤ 4 mg/L olan izolatlarda % 69'a yükselmekte ki bu oran CPE olmayan izolatlarla benzer (% 73)!**
- **Mortalite karbapenem içeren rejimlerde ve MIC≤4 mg/L olan izolatlarda en düşük (OR=5.3)**

Daikos GL. Clin Microbiol Infect 2011; 17: 1135–1141

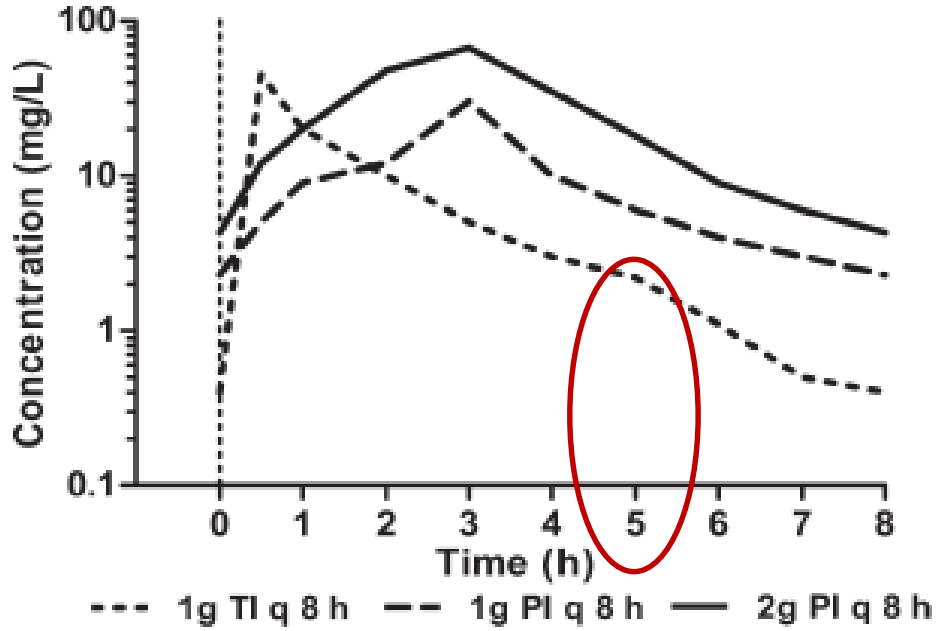


FIG. 1. Simulated concentration–time profiles of three different dosing regimens of meropenem. TI, traditional 30-min infusion; PI, prolonged 3-h infusion. Adapted from [35,45,47].

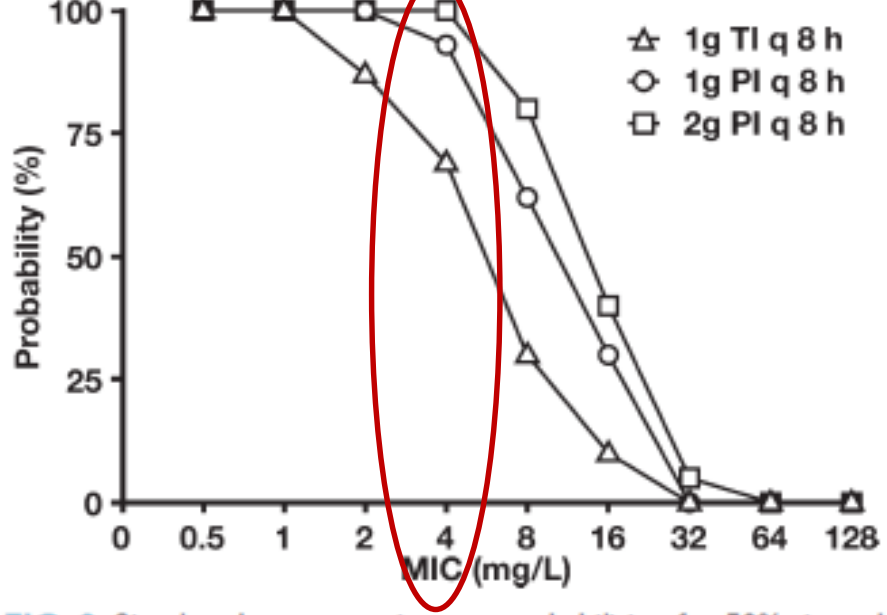


FIG. 2. Simulated target attainment probabilities for 50% time above the MIC (50% T > MIC) of three different regiments of meropenem. TI, traditional 30-min infusion; PI, prolonged 3-h infusion. Adapted from [36].

- **PK verilere bakıldığında;**
  - **1g TI q 8h ile 5 saat sonra EUCAST MIC sınır değer olan 2 mg/L'nin altına düşmekte..**
  - **1 g PI q 8H ile; dozlar arası sürenin tamamında 2mg/L'nin üzerinde olmakta…**
  - **2 g PI q 8H ile; konsantrasyon 4 mg/L'ye çıkmakta…**

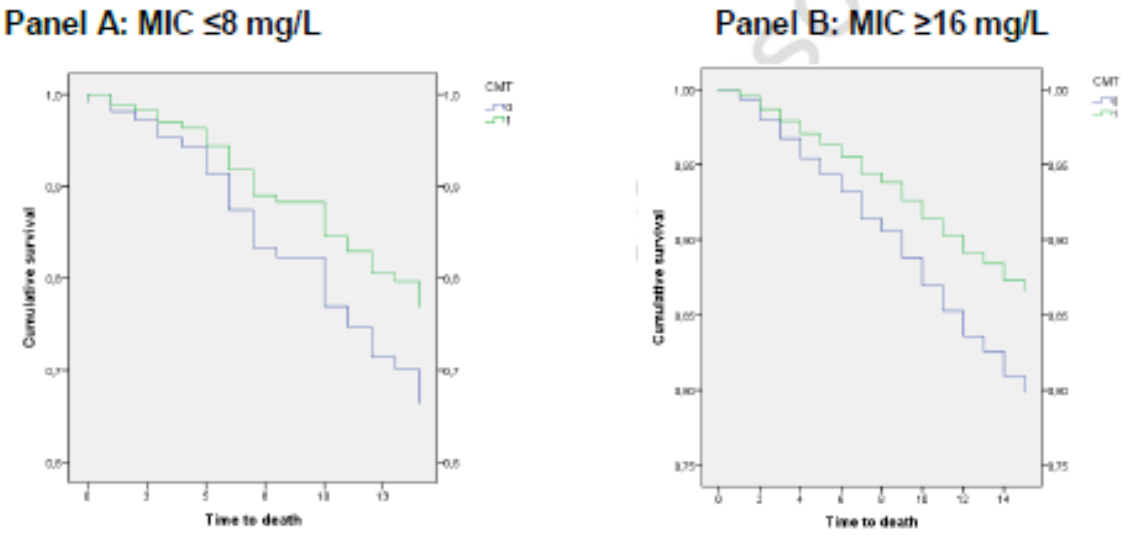
- **Farklı doz şemaları ile Monte-Carlo simulasyonu yapıldığında MIC 4 mg/L için %50T>MIC hedefine ulaşma olasılığı**
  - **1g TI q 8h ile % 69**
  - **1 g PI q 8H ile % 93**
  - **2 g PI q 8H ile; % 100**

Daikos GL. Clin Microbiol Infect 2011; 17: 1135–1141

Short Communication

Effect of combination therapy containing a high-dose carbapenem on mortality in patients with carbapenem-resistant *Klebsiella pneumoniae* bloodstream infection

Figure 1. Cox regression analysis of survival stratified for carbapenem MIC



CMT: combination with meropenem treatment: 0 no, 1 yes.

Panel A and Panel B show cumulative survival at 14 days from CR-KP BSI onset for patients receiving or not carbapenem combination therapy, it was adjusted for all the covariates included into the Cox regression model and the propensity score. The model was further stratified according with the meropenem MIC ≤8 mg/L (Panel A), MIC ≥16 mg/L (Panel B), the overall aHR for the variable carbapenem combination therapy (CMT) was: 0.63, 95%CI 0.41-0.96, p=0.03.

- **595 CRKP etkenli KDİ olan hasta**
- **İzolatların % 77'sinde meropenem MIC ≥16 mg/L**
- **Yüksek doz ve uzamış infüzyon karbapenem tedavisi MIC ≥16 mg/L olan izolatlarda bile etkili**

Giannella M et al. Int J of Antimicrob Agents 2018;51:244-248.

VIRULENCE
2017, VOL. 8, NO. 1, 66–73
http://dx.doi.org/10.1080/21505594.2016.1213476

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RESEARCH PAPER

Meropenem for treating KPC-producing *Klebsiella pneumoniae* bloodstream infections: Should we get to the PK/PD root of the paradox?

ABSTRACT

The objective of this study was to assess the achievement of pharmacokinetic/pharmacodynamic (PK/PD) targets of meropenem (MEM) in critically-ill patients with bloodstream infections (BSI) due to *Klebsiella pneumoniae*-carbapenemase-producing *Klebsiella pneumoniae* (KPC-Kp) with MEM minimum inhibitory concentrations (MICs) ≥16 mg/L. Nineteen critically-ill patients with KPC-Kp BSI were given combination therapy including MEM, tigecycline, plus colistin or gentamicin (according to susceptibility testing). MEM was administered as an extended 3-hour infusion of 2 g every 8 hours, or adjusted according to renal function. MEM plasma concentrations were determined by high-performance liquid chromatography. PK/PD targets for MEM were defined as T > 40% 1×MIC and T > 40% 4×MIC. Possible synergisms between MEM and coadministered agents were assessed by time-kill assays based on plasma levels for MEM and on fixed plasma concentrations for the other agents. In none of 19 patients MEM reached any PK/PD target. The actual MEM MICs were 256, 512, and 1024 mg/L in 1, 3, and 15 isolates, respectively. However, theoretically, the PK/PD target of T > 40% 1×MIC could have been achieved in 95%, 68%, 32% and 0% of the isolates for MIC equal to 8, 16, 32, and 64 mg/L, respectively. No synergisms were observed between MEM and coadministered agents. In conclusion, high-dose MEM failed to reach PK/PD targets in 19 patients with BSI due to KPC-Kp with very high MEM MICs. On a theoretical basis, our results suggest a possible usefulness of MEM against resistant blood isolates with MICs up to 32 mg/L.

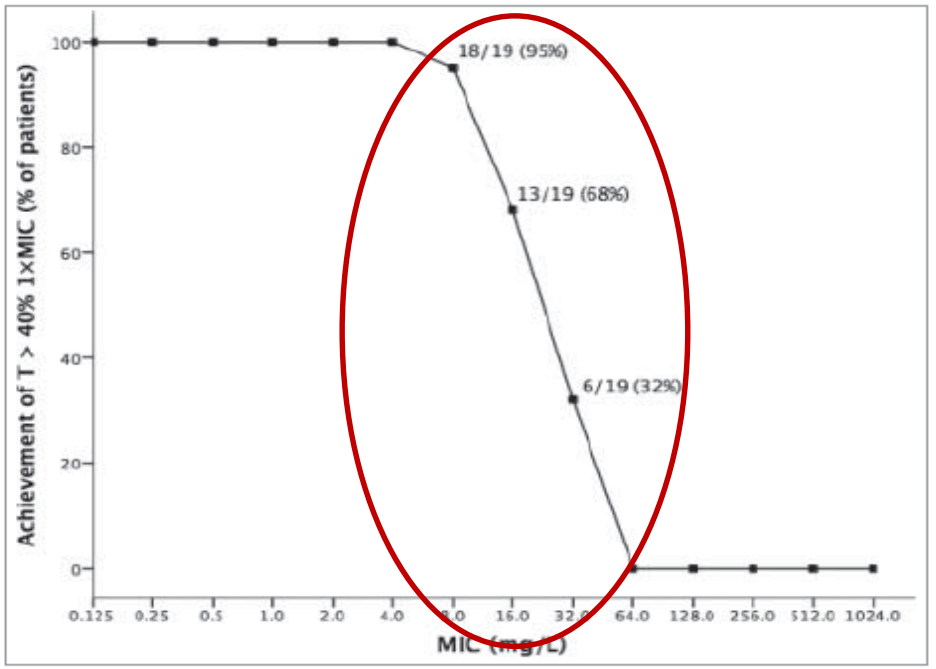


Figure 1. Achievement of T > 40% 1×MIC by measured meropenem levels in 19 critically-ill patients with BSI due to KPC-Kp, according to different hypothetical meropenem MICs. Actual meropenem MICs of all 19 isolates turned out to be far higher than those compatible with the achievement of such a PK/PD target, ranging from 256 to 1024 mg/L.

Del Bono V et al. Virulence 2017;8:66-73.

Karbapenemlerin CRE enfeksiyonlarında kullanımı

- **Karbapenem MIC ≤ 8 (32??) mcg/mL ise kullanılabilir…**
- **Yüksek doz uzun süreli infüzyon uygulanmalıdır…**
  - **3x2 g/gün dozunda > 3 saat infüzyon!!!**
- **Eğer varsa, in vitro aktif başka bir ajanla kombine edilmelidir…**

Sheu CC et al. Frontiers in Microbiology 2019;10:80

Çift karbapenem tedavisi

Ertapenem 1 g
30-60 dakika
infüzyon

1 saat sonra

Meropenem 3x2 g
> 3 saat infüzyon

Mashni O et al. Annals of Pharmacotherapy 2018;1–12

Çift karbapenem tedavisi

- **Ertapenem yüksek afinitesi nedeniyle karbapenemaz türü hidrolitik enzimlere bağlanır (*Suisid İnhibitör Etki / «kurban molekül»)***
- **Diğer karbapenemin daha yüksek konsantrasyonlara ulaşarak bakterisidal aktivitesine izin verir..**

- **Bu kombinasyonun sinerjistik etkisi, yüksek karbapenem direncinde bile gözlenmiş…**

- **Ancak çalışmalar KPC karbapenemazlarda yoğunlaşmış, diğer genotiplerle ilgili ileri çalışmalara ihtiyaç var…**

Critical Review of Double-Carbapenem Therapy for the Treatment of Carbapenemase-Producing *Klebsiella pneumoniae*

Annals of Pharmacotherapy
1–12

DOI: 10.1177/1060028018790573
journals.sagepub.com/home/aop
SAGE

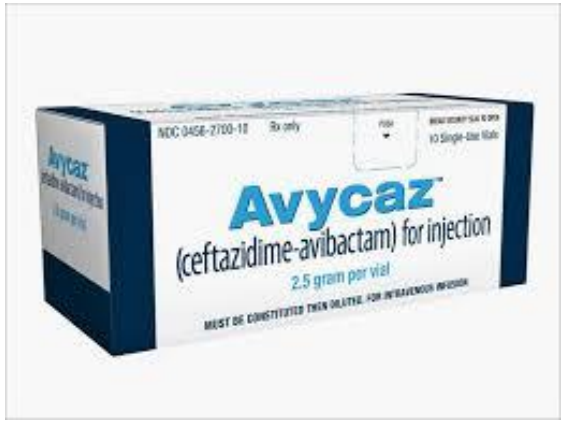
Table 2. (continued)

	Reference					
	De Pascale et al,[29] 2017	Venugopalan et al,[30] 2017	Oliva et al,[31] 2017	Souli et al,[32] 2017	Cprek and Gallagher,[33] 2015	Oliva et al,[34] 2016
Type of infection,[d] n (%)						
Bacteremia	37 (77.1%)	9 (50%)	18 (56.3%)	13 (48.1%)	7 (38.9%)	5 (33.3%)
Pneumonia	25 (52.1%)	3 (16.7%)	9 (28.1%)	1 (3.7%)	5 (27.8%)	1 (6.7%)
Urinary tract	3 (6.3%)	6 (33.3%)	9 (28.1%)	12 (44.4%)	3 (16.7%)	8 (53.3%)
Intra-abdominal	9 (18.8%)	0 (0)	0 (0)	0 (0)	2 (11.1%)	0 (0)
Others	1 (2.1%)	1 (5.6%)	9 (28.1%)	1 (3.7%)	1 (5.6%)	4 (26.7%)
Multiple sites	4 (8.3%)					2 (13.3%)
Sepsis/septic shock, n (%)	• Sepsis: NR • Septic shock: 36 (75%)	NR	• Sepsis: 18 (56.3%) • Septic shock: 8 (25%)	• Sepsis: 21 (77.8%) • Septic shock: 6 (22.2%)	NR	• Sepsis: 7 (46.7%) • Septic shock: 1 (6.7%)
Type of carbapenemase enzyme	• Class A carbapenemase (>90%) • Class B metallo-β-lactamase (<10%) • Class D carbapenemase (<10%)	NR	NR	KPC-2	NR	KPC-3
Outcomes						
Clinical success/cure, n (%)	30 (62.5%)	13 (72.2%)	24 (75%)	21 (77.8%)	7 (38.9%)	12 (80%)
Microbiological success, n (%)	22 (50%), Analyzed in 44 patients	15 (93.8%), Analyzed in 16 patients	NR	20 (74.1%)	11 (78.6%), Analyzed in 14 patients	12 (80%)
Adverse events related to DCT, n (%)	None reported	Seizure, 1 (5.5%)	• Seizure, 2 (6.3%) • Sodium disorder, 1 (3.1%) • Vomiting, 1 (3.1%) • Leukopenia, 2 (6.3%)	• Rash, 1 (3.7%) • Eosinophilia, 1 (3.7%) Meningitis, 2 (7.4 %)	Seizure, 2 (11.1%)	• Seizure, 1 (6.7%) • Nausea, 1 (6.7%) • Hypernatremia, 1 (6.7%)
Mortality (%)	28-Day mortality: 29.2%	30-Day mortality: 31.3%	60-Day mortality: 18.8%	Crude mortality: 29.6%	30-Day mortality: 27.8%	60-Day mortality: 6.7%

CRE tedavisinde yeni ajanlar

Seftazidim-avibaktam

- **FDA onayı;**
- Şubat 2015’de;
  - Komplike intra-abdominal enfeksiyonlar **(cIAI)**
  - Komplike üriner sistem enfeksiyonları **(cUTI)**
- Şubat 2018’de;
  - Hastanede kaynaklı pnömoni **(HAP)** ve ventilatör ilişkili pnömoni **(VAP)**



Avibaktam

- Diğer β-laktamaz inhibitörlerinin aksine **bir β-laktam değil!!!** (*Diazabicyclooctane*)

- Etki spektrumu geniş:
  - Ambler **sınıf A** β-laktamazlar; (GEM, SHV, CTX-M ve **KPC**)
  - Ambler **sınıf C** β-laktamazlara (Amp C)
  - Bazı **sınıf D** (**OXA-48**) β-laktamazlara da **ETKİLİ…**

  - Ambler sınıf B **MBLs** **(IMP, VIM, NDM) ETKİLİ DEĞİL…**

- ***CAZ-AVI pekçok invitro çalışmada CRE izolatlarına karşı etkili, ciddi enfeksiyonlardaki etkinliği ile ilgili klinik çalışma az ancak sonuçlar umut vaat edici…***

Seftazidim-avibaktam

TABLE 4 | Efficacy of ceftazidime/avibactam for treatment of carbapenem-resistant *Enterobacteriaceae* infections.

Reference	Study place, year	Study design	Patients, number	Infection foci	Organism(s)/ β-lactamase types	Antibiotic(s)	Clinical outcomes	Remarks
van Duin et al., 2018	United States, 8 sites, 2011–2015	Prospective	137	BSI (n = 63; 46%) and pneumonia (n = 30, 22%)	97% (133/137) were *K. pneumoniae*	CAZ/AVI (n = 38) vs. colistin (n = 99)	Adjusted all-cause mortality was significantly lower in the CAZ/AVI group (9% vs. 32%, P = 0.001)	Prospective, observational study on the use of CAZ/AVI compared to colistin specifically for infections due to CRE, including 30 (22%) patients with pneumonia
Castón et al., 2017	Spain, Israel, multicenter, 2012–2016	Retrospective	31, all with hematologic malignancy	Primary BSI (n = 14, 45.2%)	80.6% (25/31) were *K. pneumoniae*	CAZ/AVI (n = 8) vs. others (n = 23)	14-day clinical cure rate was higher in the CAZ/AVI group (85.7% [6/8] vs. 34.8% [8/23], P = 0.031)	Small case numbers; no difference in crude mortality
Shields et al., 2017b	United States, single site, 2009-2017	Retrospective	109	Secondary bacteremia resulted from abdominal (46%, 50/109)	97% (106/109) of *K. pneumoniae* harbored bla_{KPC}	CAZ/AVI (n = 13) vs. others (n = 96)	CAZ/AVI group had higher clinical success rates (85% [11/13] vs. 40.6% [39/96], P = 0.003)	Small case numbers with CAZ/AVI treatment; bias in selection of therapy

CAZ/AVI, ceftazidime/avibactam; BSI, bloodstream infection.

Sheu CC et al. Frontiers in Microbiology 2019; 10.80

Seftazidim-avibaktam direnç

Clinical Infectious Diseases

BRIEF REPORT

Clinical Outcomes, Drug Toxicity, and Emergence of Ceftazidime-Avibactam Resistance Among Patients Treated for Carbapenem-Resistant Enterobacteriaceae Infections

Ryan K. Shields,[1,3,4,a] Brian A. Potoski,[1,2,3,a] Ghady Haidar,[1] Binghua Hao,[4] Yohei Doi,[1] Liang Chen,[6] Ellen G. Press,[1] Barry N. Kreiswirth,[6] Cornelius J. Clancy,[1,4,5] and M. Hong Nguyen[1,3,4]

Thirty-seven carbapenem-resistant Enterobacteriaceae (CRE)-infected patients were treated with ceftazidime-avibactam. Clinical success and survival rates at 30 days were 59% (22/37) and 76% (28/37), respectively. In 23% (5/22) of clinical successes, CRE infections recurred within 90 days. Microbiologic failure rate was 27% (10/37). Ceftazidime-avibactam resistance was detected in 30% (3/10) of microbiologic failures.

Emergence of Ceftazidime-Avibactam Resistance and Restoration of Carbapenem Susceptibility in *Klebsiella pneumoniae* Carbapenemase-Producing *K pneumoniae*: A Case Report and Review of Literature

Ryan K. Shields,[1,2] M. Hong Nguyen,[1,2] Ellen G. Press,[1] Liang Chen,[3] Barry N. Kreiswirth,[3] and Cornelius J. Clancy[1,2,4]

Mikrobiyolojik başarısızlık saptananların % 30'unda (3/10) CAZ-AVI direnci…..

CAZ-AVI ile 10-19 gün tedavi sonrası «*bla* rmKPC-3» genindeki mutasyonlara bağlı direnç!!

Shields RK et al. CID 2016;63(12):1615–8
Shields RK et al. Open Forum Infect Dis 2017

Seftazidim-avibaktam + Aztreonam

- **In vitro çalışmalarda MBL(+) izolatlarda CAZ-AVI + ATM kombinasyonu etkin…**
- **Klinik çalışma yok…**

AMERICAN SOCIETY FOR MICROBIOLOGY | Antim… and …

Can Ceftazidime-Avibactam and Aztreonam Overcome β-Lactam Resistance Conferred by Metallo-β-Lactamases in *Enterobacteriaceae*?

Steven Marshall,[a] Andrea M. Hujer,[a,b] Laura J. Rojas,[a,b,c] Krisztina M. Papp-Wallace,[a] Romney M. Humphries,[d] Brad Spellberg,[e] Kristine M. Hujer,[a,b] Emma K. Marshall,[a] Susan D. Rudin,[a,b] Federico Perez,[a,b] Brigid M. Wilson,[a] Ronald B. Wasserman,[f] Linda Chikowski,[g] David L. Paterson,[h] Alejandro J. Vila,[i] David van Duin,[j] Barry N. Kreiswirth,[k] Henry F. Chambers,[l] Vance G. Fowler, Jr.,[m] Michael R. Jacobs,[n] Mark E. Pulse,[o] William J. Weiss,[o] Robert A. Bonomo[a,b,c,p]

ABSTRACT Based upon knowledge of the hydrolytic profile of major β-lactamases found in Gram-negative bacteria, we tested the efficacy of the combination of … says were conducted, and the *in vivo* efficacy of this combination was assessed in a murine neutropenic thigh infection model. By disk diffusion assay, all 21 isolates were resistant to CAZ-AVI alone, and 19/21 were resistant to ATM. The *in vitro* activity of CAZ-AVI in combination with ATM against diverse *Enterobacteriaceae* possessing MBLs was demonstrated in 17/21 isolates, where the zone of inhibition was ≥21 mm. All isolates demonstrated a reduction in CAZ-AVI agar dilution MICs with the addition of ATM. At 2 h, time-kill assays demonstrated a ≥4-$\log_{10}$-CFU decrease for all groups that had CAZ-AVI with ATM (8 μg/ml) added, compared to the group treated with CAZ-AVI alone. In the murine neutropenic thigh infection model, an almost 4-$\log_{10}$-CFU reduction was noted at 24 h for CAZ-AVI (32 mg/kg every 8 h [q8h]) plus ATM (32 mg/kg q8h) versus CAZ-AVI (32 mg/kg q8h) alone. The data presented herein require us to carefully consider this new therapeutic combination to treat infections caused by MBL-producing *Enterobacteriaceae*.

Marshall S et al. Antimicrobial Agents and Chemotherapy 2017: 61:e02243-16

Meropenem-vaborbaktam

- Ağustos 2017’de komplike üriner sistem enfeksiyonlar **(cUTI)** için FDA onayı…

Vaborbaktam

- Boron içeren β-laktamaz inhibitörü!!!

- Etki spektrumu:
  - Ambler **sınıf A** β-laktamazlar; (GEM, SHV, CTX-M ve **KPC**)
  - Ambler **sınıf C** β-laktamazlar (Amp C) de **ETKİLİ….**

  - Ambler **sınıf B MBLs (IMP, VIM, NDM)** ve **sınıf D** (**OXA-48**) β-laktamazlara **ETKİLİ DEĞİL…**

- ***MER-VAB pekçok invitro çalışmada CRE izolatlarına karşı etkili ancak ciddi enfeksiyonlardaki etkinliği ile ilgili klinik çalışma az…***

Infect Dis Ther (2018) 7:439–455
https://doi.org/10.1007/s40121-018-0214-1

ORIGINAL RESEARCH

Effect and Safety of Meropenem versus Best-Available Therapy in with Carbapenem-Resistant Ent Infections: The TANGO II Rand

- Çok merkezli RCT
- MER/VAB vs BAT(best available therapy)
- 77 hastanın 47'si konfirme CRE
- 22 BSI, 16 cUTI, 5 HAP/VAP, 4 cIAI
- Klinik kür ve 28-gün mortalitede MER/VAB üstün…
- Nefrotoksisite daha az….

Table 2 Efficacy endpoints among all patients with confirmed CRE infections (

	M–V (*n* = 32) *n* (%)	BAT (*n* = 15) *n* (%)
Efficacy endpoints		
Clinical cure at EOT	21 (65.6)	5 (33.3)
Clinical cure at TOC	19 (59.4)	4 (26.7)
Microbiologic cure[c] at EOT	21 (65.6)	6 (40.0)
Microbiologic cure[c] at TOC	17 (53.1)	5 (33.3)
Day-28 mortality	5 (15.6)	5 (33.3)

	M–V (*n* = 23) *n* (%)	BAT (*n* = 15) *n* (%)	Difference[a] (95% CI)	*P* value	Relative difference[b]
Sensitivity analysis of clinical cure at TOC and all-cause mortality at day 28 across all infection types (mCRE-MITT) excluding prior antibiotic failure[d]					
Clinical cure at TOC	16 (69.6)	4 (26.7)	42.9 (13.7–72.1)	0.004	160.7
Day-28 all-cause mortality	1 (4.3)	5 (33.3)	− 29.0 (− 54.3 to -3.7)	0.02	− 87.1

	M–V (*n* = 32) *n* (%)	BAT (*n* = 15) *n* (%)	Difference[a] (95% CI)	*P* value	Relative Difference[b]
Exploratory analysis of risk–benefit profile of meropenem–vaborbactam compared to best available therapy					
Day-28 all-cause mortality or nephrotoxicity[e]	8 (25.0)	6 (40.0)	− 15.0 (− 44.0 to 14.0)	0.31	− 37.5
Clinical failure or nephrotoxicity[f]	10 (31.3)	12 (80.0)	− 48.7 (− 74.6 to − 22.9)	< 0.001	− 60.9
Day-28 all-cause mortality or renal AEs[g]	6 (18.8)	9 (60.0)	− 41.2 (− 69.5 to − 13.0)	0.004	− 68.7
Clinical failure or renal AEs[h]	9 (28.1)	12 (80.0)	− 51.9 (− 77.4 to − 26.3)	< 0.001	− 64.9

AE adverse event, *BAT* best available therapy, *CI* confidence interval, *cUTI/AP* complicated urinary tract infection/acute pyelonephritis, *EOT* end of treatment, *mCRE-MITT* microbiologic carbapenem-resistant Enterobacteriaceae modified intent to treat, *M–V* meropenem–vaborbactam, *TOC* test of cure

Plazomisin

- Sisomisin sentetik derivesi yeni jenerasyon bir aminoglikozid…
- Temmuz 2018'de komplike üriner sistem enfeksiyonları **(cUTI)** için FDA onayı…
- İn vitro çalışmalarda meropenem ve/veya tigesiklin ile kombinasyonunda CRE izolatlarında artmış etkinlik….
- CRE infeksiyonları için klinik çalışma yok…

Sheu CC et al. Frontiers in Microbiology 2019; 10.80

Eravasiklin

- Tetrasiklin sınıfından sentetik «fluorocyclin» antibiyotik…
- Ağustos 2018'de komplike intraabdominal infeksiyonlar (cIAI) için FDA onayı…
- In vitro çalışmalarda CRE'ye karşı tigesiklinden 2 kat etkili!!!
- CRE infeksiyonlarında klinik kullanımı ile ilgili çalışma yok.

Sheu CC et al. Frontiers in Microbiology 2019; 10.80

İmipenem/Silastatin-Relebaktam

- Relebaktamın kimyasal yapısı avibaktama benzer (*Diazabicyclooctane*)

- Henüz FDA onayı yok…
  - Komplike intra-abdominal enfeksiyonlar **(cIAI)**
  - Komplike üriner sistem enfeksiyonları **(cUTI)** için başvurusu var.

- Sınıf A &C karbapenemazlara in vitro etkili.
- Avibaktamdan farklı olarak sınıf D OXA-48 etkinliği yok…

Sefiderocol

- İlk siderofor sefalosporin…
- Henüz FDA onayı yok.
- CRE izolatlarında potent in vitro aktiviteye sahip…
- CRE infeksiyonlarında klinik kullanımı ile ilgili çalışma yok.

Yeni CRE etkili ajanlar- maliyet

- CAZ/AVI 2.5 g (2 g/0.5 g) q 8h
  - 1 kutu=359 $
  - Günlük maliyet=1077 $ (3 kutu)
  - 7-14 gün toplam tedavi süresi= 7539- 15.078 $

- MER/VAB 2 g (1g/1g) q 8h
  - 1 kutu= 173 $
  - Günlük maliyet= 1038 $ (6 kutu)
  - 7-14 gün toplam tedavi süresi= 7266 - 14532 $

Sonuç

Gram-negatif enterik bakterilerde direnç giderek artmakta…

ESBL (+) patojenlerle meydana gelen enfeksiyonlarda karbapenemler hala ilk seçenek…

CRE enfeksiyonlarında kolistin, tigesiklin, aminoglikozidler in vitro duyarlılık testlerine göre kullanılabilecek ajanlar…

Kombinasyon tedavisi ağır hastalarda daha başarılı!!!

Karbapenemler MIC değerlerine göre hala bir seçenek: Ama yüksek doz ve uzamış infüzyon uygulanmalı + çift karbapenem tedavisi de uygun olabilecek bir diğer alternatif…

Yeni antibiyotikler umut vadediyor, ancak OXA-48 etkinlikleri < KPC!!!


@Zonguldak