Karbapeneme dirençli *Enterobacterales* Tedavisi:

Neyle, Nasıl?

Dr. Alpay Azap
Ankara Üniversitesi Tıp Fakültesi
Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji AD

Karbapeneme dirençli enterik bakteriler (KDE)

Clinical Infectious Diseases

IDSA FEATURES

Infectious Diseases Society of America Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR-*P. aeruginosa*)

Pranita D. Tamma,[1] Samuel L. Aitken,[2] Robert A. Bonomo,[3] Amy J. Mathers,[4] David van Duin,[5] and Cornelius J. Clancy[6]

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13.000 Nozokomiyal infeksiyon, 1000 ölüm/yıl

KDE:

En az 1 karbapeneme dirençli

veya

Karbapenemaz pozitifliği gösterilmiş

KDE'nin %50'si karbapenemaz (+) (ABD)

CRE account for more than 13 000 nosocomial infections and contribute to more than 1000 deaths annually in the United States [2]. The CDC defines CRE as members of the Enterobacterales order resistant to at least 1 carbapenem antibiotic or producing a carbapenemase enzyme [2]. A CRE isolate may be resistant to some carbapenems (eg, ertapenem) but not others (eg, meropenem). CRE comprise a heterogenous group of pathogens with multiple potential mechanisms of resistance, broadly divided into those that are carbapenemase-producing and those that are not carbapenemase-producing. Carbapenemase-producing isolates account for approximately half of all CRE infections in the United States [44–46]. The most common carbapenemases in the United States are *Klebsiella pneumoniae* carbapenemases (KPCs), which can be produced by any Enterobacterales. Other notable carbapenemases that have been identified in the United States include New Delhi metallo-β-lactamases (NDMs), Verona integron-encoded metallo-β-lactamases (VIMs), imipenem-hydrolyzing metallo-β-lactamases (IMPs), and oxacillinase (eg, OXA-48–like) carbapenemases [47, 48]. Knowledge of whether a CRE clinical isolate is carbapenemase-producing and, if it is, the specific carbapenemase produced are important in guiding treatment decisions.

Clin Infect Dis 2021;72(7):1109-16

Enterik bakterilerde karbapenem direnci

- Karbapenemazlar

- Birleşik mekanizmalar
  - GSBL (ör.CTX-M) + geçirgenlikte azalma
  - Yüksek düzey AmpC + geçirgenlikte azalma

  Bu mekanizmalar ertapenemde meropenem veya imipeneme göre daha sık görülür

- *Proteus, Providencia, Morganella*: IPM-R

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MINIREVIEW

Past and Present Perspectives on β-Lactamases

Karen Bush[a]

[a]Department of Biology, Indiana University Bloomington, Bloomington, Indiana, USA

TABLE 1 Table of Firsts: the dates, organisms, and locations of the first of a series of β-lactamase-producing isolates with long-term clinical significance

Original β-lactamase name (currently recognized name)	Yr of first verified isolation	Organism	Location	First description in literature	Reference(s)
Penicillinase (chromosomal AmpC)	1940	*Bacillus coli* (*Escherichia coli*)	England	1940	1
Penicillinase	1942	*Staphylococcus aureus*	England	1942	65
OXA	1962	*Salmonella enterica* serovar Typhimurium, *Escherichia coli*[a]	England	1965 1967	87, 215
TEM-1	1963	*Escherichia coli*	Greece	1965	85
SHV-1	1972	*Klebsiella pneumoniae*	Unknown	1972	216
Transferable ESBL (SHV-2)	Pre-1983	*K. pneumoniae*	Germany	1983	217
Serine (class A, group 2f) carbapenemase (SME-1)	1982 1985	*Serratia marcescens*	England (London) USA (Minnesota)	1990 1986	148, 150
Plasmid-encoded AmpC (MIR-1)	1988	*K. pneumoniae*	USA (Massachusetts)	1990	141
Plasmid-encoded MBL (IMP-1)	1988	*Pseudomonas aeruginosa*	Japan	1991	151
Inhibitor-resistant TEM (TEM-30)	1991	*E. coli*	France (Paris)	1994	118
KPC-type (KPC-2)	1996	*K. pneumoniae*	USA (North Carolina)	2000	158
NDM-1	2006	*K. pneumoniae*	India (New Delhi)	2009	175, 176

[a]Anderson and Datta described a *Salmonella* Typhimurium isolate from 1962 that later was confirmed to produce the OXA-2 enzyme (215). Egawa et al. described an *E. coli* isolate in 1967 that produced the OXA-1 enzyme (87).

Antimicrob Agents Chemother 2018 62;10:e01076-18

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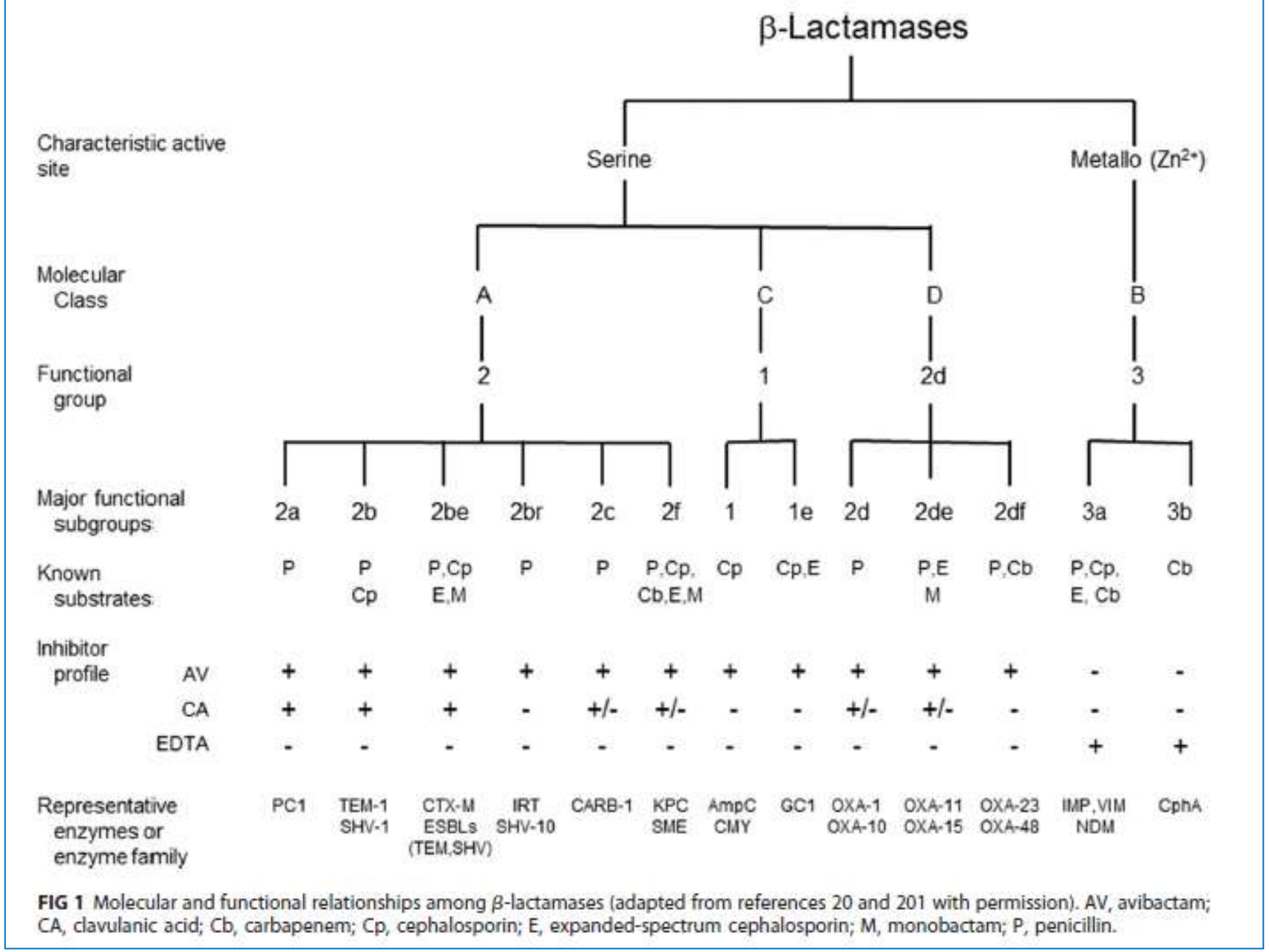

FIG 1 Molecular and functional relationships among β-lactamases (adapted from references 20 and 201 with permission). AV, avibactam; CA, clavulanic acid; Cb, carbapenem; Cp, cephalosporin; E, expanded-spectrum cephalosporin; M, monobactam; P, penicillin.

Antimicrob Agents Chemother 2018 62;10:e01076-18

Karbapenemazlar:

Sınıf	Enzim	En sık görülen tür
Sınıf A	KPC, SME, IMI, NMC, GES **KPC**: **K**lebsiella **P**neumoniae **C**arbapenemase	Enterobacteriaceae *P. aeruginosa* *Acinetobacter spp.*
Sınıf B (metallo-b-laktamaz)	NDM, IMP, VIM, GIM, SPM, IND **NDM**: **N**ew **D**elhi **M**etallobetalactamase	Enterobacteriacea *P. aeruginosa* *Acinetobacter* spp.
Sınıf D	OXA (**Oxa**cillinase)	**Enterobacteriaceae (OXA-48),** *Acinetobacter* spp. (OXA 23, OXA 24…)

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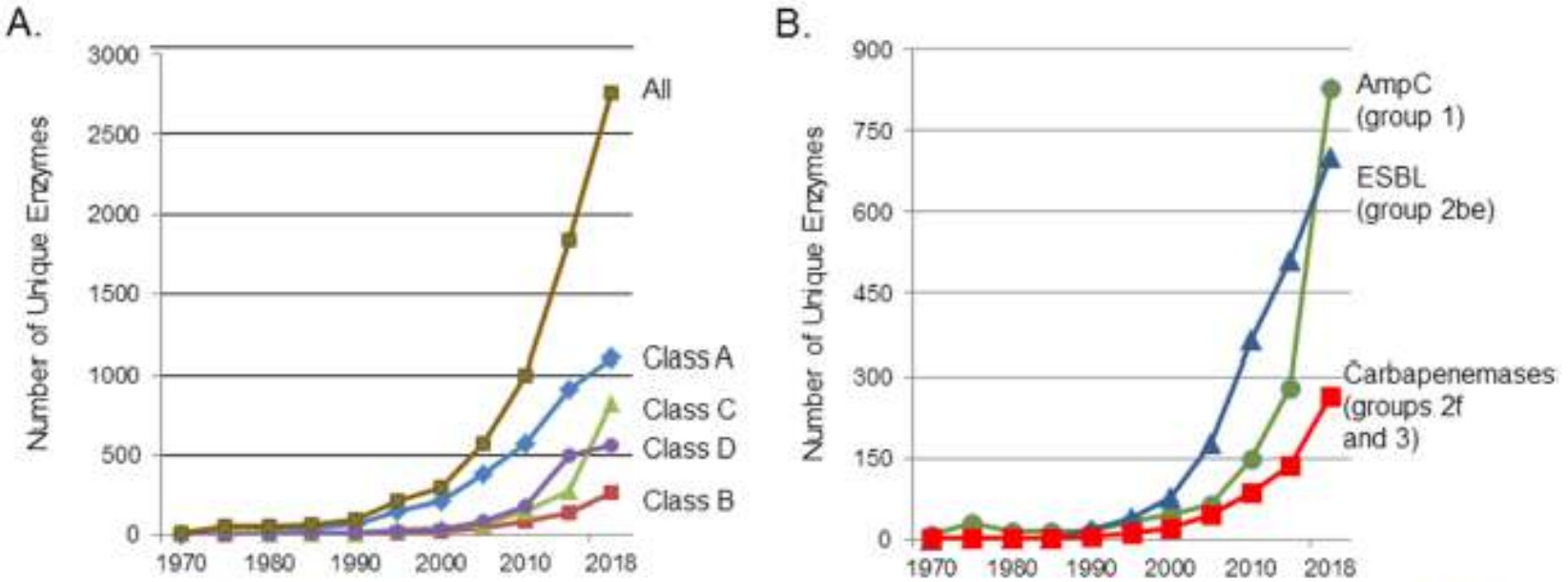


FIG 3 Increase in numbers of unique, naturally occurring β-lactamases (some data from reference 224 as well as from http://www.lahey.org/Studies/ and https://www.ncbi.nlm.nih.gov/bioproject/PRJNA313047). (A) β-Lactamases enumerated according to molecular classes A, B, C, and D, with the total number of enzymes (all) equal to 2,771. (B) β-Lactamases enumerated according to major functional groups with their trivial names, AmpC, group 1; ESBLs, group 2be; and carbapenemases, groups 2f and 3.

Antimicrob Agents Chemother 2018 62;10:e01076-18

Karbapenemaz üreten enterik bakterilerde

direnç mekanizmasının saptanmasının önemi?

Direnç mekanizması saptanması:	
Antimikrobiyal duyarlılık belirlenmesi için gereklidir	**Hayır**
Enfeksiyon kontrolü	**Evet**

Gene sahip olması Karbapenem dirençli olduğu anlamına gelmez !

Karbapenemaz negatif olması duyarlı olduğu anlamına gelmez !

Table 1. Activity and Indications of New Agents Against Carbapenem-resistant Gram-negative Pathogens

	Activity							
	Enterobacteriaceae							
Agent	Class A Carbapenemase (eg, KPC)	Class B Carbapenemase (eg, NDM)	Class D Carbapenemase (eg, OXA-48)	*P. aeruginosa*	*A. baumannii*	*S. maltophilia*	Indications (Including Expected)	Pathogen-directed Trial (Including Expected)
Ceftazidime-avibactam	Yes	No	Yes	Yes	No	No	cUTI/AP, cIAI, HABP/VABP	No
Ceftolozane-tazobactam	No	No	No	Yes	No	No	cUTI/AP, cIAI, NP	No
Meropenem-vaborbactam	Yes	No	No	No[a]	No	No	cUTI/AP	Yes
Imipenem-cilastatin-relebactam	Yes	No	No	Yes	No	No	cUTI/AP, cIAI, HABP/VABP	Yes
Cefiderocol	Yes	Yes	Yes	Yes	Yes	Yes	cUTI/AP, HABP/VABP	Yes
Plazomicin	Yes	Variable[b]	Yes	Variable	No	No	cUTI/AP	Yes
Eravacycline	Yes	Yes	Yes	No	Yes	Yes	cIAI	No
Fosfomycin	Yes	Yes	Yes	Variable	No	No	cUTI/AP	No

Clinical Infectious Diseases 2019;69(S7):S565–75

Empiric Therapy

Empiric treatment recommendations are not provided in this guidance document since a given host at risk for infection by 1 of the pathogen groups is usually at risk of infection by other antimicrobial-resistant pathogens. Empiric treatment decisions should be guided by local susceptibility patterns for the most likely pathogens. When determining empiric treatment for a given patient, clinicians should consider previous organisms and associated antibiotic susceptibility data in the past 6 months and antibiotic exposures in the past 30 days (eg, if a treatment course of piperacillin-tazobactam was recently completed, consider empiric coverage with a gram-negative agent from a different class that offers a comparable spectrum of activity, such as meropenem). Empiric decisions should be refined based on the severity of the patient's illness, whether the patient is immunocompromised, and the likely source of the infection (eg, presumed ventilator-associated pneumonia typically warrants broader empiric coverage than presumed cystitis).

Ampirik tedavi önerisi yok:

Farklı bakteriler için aynı riskler geçerli

Belli risk faktörü ⇢ spesifik morg. ✗

Ampirik tdv. başlarken;

- ✓ Son 6 ayda ünitedeki duyarlılık
- ✓ Daha önce üretilen bakteriler
- ✓ Son 30 gündeki antibiyotik kullanımı
- ✓ Hastanın altta yatan durumları
- ✓ Hastalığın ciddiyeti
- ✓ Enfeksiyon bölgesi

Duration of Therapy

Recommendations on durations of therapy are not provided, but clinicians are advised that prolonged treatment courses are not necessary against infections by antimicrobial-resistant pathogens per se, compared with infections caused by the same bacterial species with a more susceptible phenotype. After antibiotic susceptibility results are available, it may become apparent that inactive antibiotic therapy was initiated empirically. This may impact the duration of therapy. For example, cystitis is typically a mild infection. If an antibiotic not active against the causative organism was administered empirically for cystitis but clinical improvement nonetheless occurred, it is generally not necessary to repeat a urine culture, change the antibiotic regimen, or extend the planned treatment course [11]. However, for all other

infections included in this document, if antibiotic susceptibility data indicate a potentially inactive agent was initiated empirically, a change to an active regimen for a full treatment course (dated from the start of active therapy) is recommended. Additionally, important host factors related to immune status, ability to attain source control, and general response to therapy should be considered when determining treatment durations for antimicrobial-resistant infections, as with the treatment of any bacterial infection.

Tedavi süresi önerisi yok:

Dirençli bakteriyi duyarlı bakteriye kıyasla daha uzun süre tedavi etmeye gerek yok

Ampirik tedaviye klinik yanıt varsa ADT sonucunda dirençli olsa dahi sistitte tedaviyi değiştirmeye veya süreyi uzatmaya gerek yok

Diğer infeksiyonlarda ampirik tedaviye direnç tespit edilirse duyarlı antibiyotiğe geçilmeli
Tedavi süresi duyarlı antibiyotiğe göre ayarlanmalı
Hastaya ilişkin faktörler ve odak kontrolü göz önüne alınmalı

Karbapenem Dirençli Enterobacterales

Question 1: What are preferred antibiotics for the treatment of uncomplicated cystitis caused by CRE?

Recommendation: Ciprofloxacin, levofloxacin, trimethoprim-sulfamethoxazole, nitrofurantoin, or a single dose of an aminoglycoside are preferred treatment options for uncomplicated cystitis caused by CRE. Standard infusion meropenem is a preferred treatment option for cystitis caused by CRE resistant to ertapenem but susceptible to meropenem when carbapenemase testing results are either not available or negative.

Komplike olmamış sistit:

CİP, LEV, NF, SXT, AGA

EPM R MEM D ⇢ sd MEM

Question 2: What are preferred antibiotics for the treatment of pyelonephritis and complicated urinary tract infections (cUTIs) caused by CRE?

Recommendation: Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol are preferred treatment options for pyelonephritis and cUTIs caused by CRE resistant to both ertapenem and meropenem. Extended-infusion meropenem is a preferred treatment option for pyelonephritis and cUTIs caused by CRE resistant to ertapenem but susceptible to meropenem when carbapenemase testing results are either not available or negative.

Piyelonefrit ve komplike ÜSİ:

CAZ-AVI, IMI-rel, MEM-vab, CDRL

EPM R MEM D ⇢ ydui MEM

Question 3: What are preferred antibiotics for the treatment of infections outside of the urinary tract caused by CRE resistant to ertapenem but susceptible to meropenem when carbapenemase testing results are either not available or negative?

ÜSİ dışındaki infeksiyonlar:

EPM R MEM D ⇢ ydui MEM

Question 4: What are the preferred antibiotics for the treatment of infections outside of the urinary tract caused by CRE resistant to both ertapenem and meropenem when carbapenemase testing results are either not available or negative?

Recommendation: Ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam are the preferred treatment options for infections outside of the urinary tract caused by CRE resistant to both ertapenem and meropenem when carbapenemase testing results are either not available or negative.

ÜSİ dışındaki infeksiyonlar:

EPM R MEM R ➞

CAZ-AVI, IMI-rel, MEM-vab,

Question 5: What are the preferred antibiotics for the treatment of infections outside of the urinary tract caused by CRE if carbapenemase production is present?

Recommendation: Ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam are the preferred treatment options for KPC-producing infections outside of the urinary tract. Ceftazidime-avibactam in combination with aztreonam or cefiderocol as monotherapy are preferred treatment options for NDM and other metallo-β-lactamase–producing CRE infections. Ceftazidime-avibactam is the preferred treatment for OXA-48-like–producing CRE infections.

ÜSİ dışındaki infeksiyonlar:

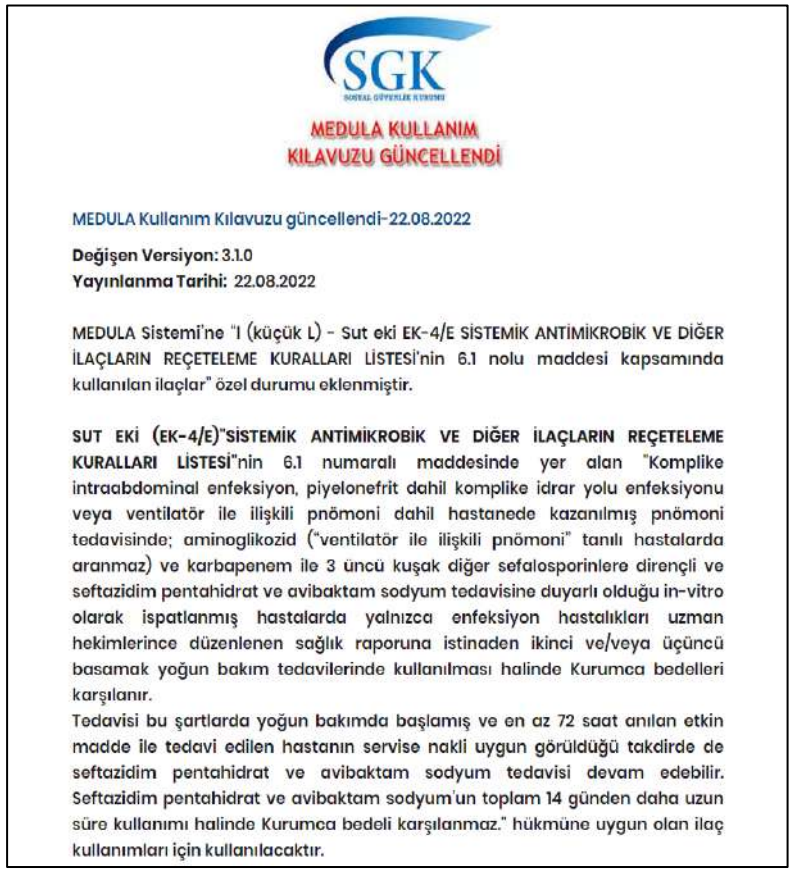
Karbapenemaz (+) ➞

KPC: CAZ-AVI, IMI-rel, MEM-vab,

NDM: CAZ-AVI+ Aztreonam, CDRL

OXA-48: CAZ-AVI

Seftazidim Avibaktam Kullanım Koşulları



SGK

MEDULA KULLANIM KILAVUZU GÜNCELLENDİ

MEDULA Kullanım Kılavuzu güncellendi-22.08.2022

Değişen Versiyon: 3.1.0
Yayınlanma Tarihi: 22.08.2022

MEDULA Sistemi'ne "I (küçük L) - Sut eki EK-4/E SİSTEMİK ANTİMİKROBİK VE DİĞER İLAÇLARIN REÇETELEME KURALLARI LİSTESİ'nin 6.1 nolu maddesi kapsamında kullanılan ilaçlar" özel durumu eklenmiştir.

SUT EKİ (EK-4/E)"SİSTEMİK ANTİMİKROBİK VE DİĞER İLAÇLARIN REÇETELEME KURALLARI LİSTESİ"nin 6.1 numaralı maddesinde yer alan "Komplike intraabdominal enfeksiyon, piyelonefrit dahil komplike idrar yolu enfeksiyonu veya ventilatör ile ilişkili pnömoni dahil hastanede kazanılmış pnömoni tedavisinde; aminoglikozid ("ventilatör ile ilişkili pnömoni" tanılı hastalarda aranmaz) ve karbapenem ile 3 üncü kuşak diğer sefalosporinlere dirençli ve seftazidim pentahidrat ve avibaktam sodyum tedavisine duyarlı olduğu in-vitro olarak ispatlanmış hastalarda yalnızca enfeksiyon hastalıkları uzman hekimlerince düzenlenen sağlık raporuna istinaden ikinci ve/veya üçüncü basamak yoğun bakım tedavilerinde kullanılması halinde Kurumca bedelleri karşılanır.
Tedavisi bu şartlarda yoğun bakımda başlamış ve en az 72 saat anılan etkin madde ile tedavi edilen hastanın servise nakli uygun görüldüğü takdirde de seftazidim pentahidrat ve avibaktam sodyum tedavisi devam edebilir. Seftazidim pentahidrat ve avibaktam sodyum'un toplam 14 günden daha uzun süre kullanımı halinde Kurumca bedeli karşılanmaz." hükmüne uygun olan ilaç kullanımları için kullanılacaktır.

- Yoğun bakım ünitesinde başlanabiliyor
- Serviste verilebilmesi için en az 72 saattir YBÜ'de veriliyor olmalı
- Sefalosporinlere, karpapenemlere ve aminoglikozitlere DİRENÇLİ olduğuna ilişkin rapor olmalı
- Etken olan bakterinin seftazidim avibaktama duyarlı olduğuna ilişkin rapor olmalı
- En fazla 14 gün kullanılabilir

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],

Clinical Microbiology and Infection 28 (2022) 521e547

Carbapenem-resistant Enterobacterales (CRE)

Recommendations on the choice of antibiotic treatment for CRE

For patients with severe infections du… ceftazidime-avibactam if active *in v…*	Conditional	Moderate/low
For patients with severe infections due to CRE carrying metallo-β-lactamases and/or resistant to all other antibiotics, including ceftazidime-avibactam and meropenem-vaborbactam, we conditionally recommend treatment with cefiderocol.	Conditional	Low
…on an individual basis and according to the source of infection, as good clinical practice. For patients with cUTI, we suggest aminoglycosides, including plazomicin, over tigecycline.	Good practice statement/conditional	Expert opinion/low
W… …nts with pneumonia, clinicians may use high dose tigecycline.	Conditional	Low
There is no evidence to recommend for or against the use of imipenem-relebactam and fo…	No recommendation	

Ağır infeksiyonda duyarlı ise CAZ-AVI

Ağır olmayan infeksiyonlarda duyarlı eski antibiyotik: AGA, SXT vb.

Tigesiklin bakteremi ve HİP/VİP yüksek dozda kullanılmalı

Tek başına Fosfomisin kullanımını destekleyen bir veri yok

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],

Clinical Microbiology and Infection 28 (2022) 521e547

Recommendations on combination therapy for CRE

For patients with C…with ceftazidime-avibactam, meropenem-vab…mmend combination therapy.	Strong	Low
For patients with severe infections caused by CRE carrying metallo-β-lactamases and/or resi…idime-avibactam con…	Conditional	Moderate
For patients with severe infections caused by CRE susceptible *in vitro* only to polymyxins, …l, we …ainst specific combinations can be provided	Conditional	Moderate
We sugge…for CRE infections, unless …usion meropenem may be used as part of combination therapy if the new BLBLI are not used.	Conditional	Low
In patients with non-severe infections or among patients with low-risk infections, under the con…from am…e of infection as good clinical practice	Good practice statement	Expert opinion

Duyarlı ise tek başına CAZ-AVI

Metallo-betalaktamaz (+) ise Aztreonam + CAZ-AVI

Polimiksin/AGA/Tgcy/Fos duyarlı ciddi infeksiyonlarda kombinasyon

Karbapenem dirençli ise tedavide kullanmamalı (MİK≤8 µg ise yduiMEM olabilir)

Ağır olmayan infeksiyonlarda duyarlı bir eski AB ile tekli tedavi

Clinical Infectious Diseases
IDSA FEATURES

Infectious Diseases Society of America Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR-*P. aeruginosa*)

Pranita D. Tamma,[1] Samuel L. Aitken,[2] Robert A. Bonomo,[3] Amy J. Mathers,[4] David van Duin,[5] and Cornelius J. Clancy[6]

Question 7: What is the role of combination antibiotic therapy for the treatment of infections caused by CRE?

Recommendation: Combination antibiotic therapy (ie, the use of a β-lactam agent in combination with an aminoglycoside, fluoroquinolone, or polymyxin) is not routinely recommended for the treatment of infections caused by CRE.

Kombinasyon rutin olarak önerilmez

Clinical Microbiology and Infection 28 (2022) 66–72

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

Clinical management of severe infections caused by carbapenem-resistant gram-negative bacteria: a worldwide cross-sectional survey addressing the use of antibiotic combinations

Elena Carrara [1,*,†], Alessia Savoldi [1,†], Laura J.V. Piddock [2], Francois Franceschi [2],

Clinical Microbiology and Infection 28 (2022) 66-72

- ✓ 95 ülkeden 1012 yanıtlayan,
- ✓ %30'unda lokal tedavi rehberleri var
- ✓ %71'i enfeksiyon hastalıkları konsültasyonuna ulaşabiliyor

  Yüksek gelirli ülkelerde %85, orta-üst gelirli: %59, Düşük-orta gelirli %30

- ✓ Hedefe yönelik tedavi rejimi sayısı: CRAB: 40 CRE: 100
- ✓ Patojen ve enfeksiyon odağından bağımsız olarak en çok : Polimiksin + Karbapenem tercih ediliyor

- ✓ Yanıt verenler kombinasyon tanımında anlaşamamış:

  %20'si Abx'lerin bir arada kullanılması

  %42 etkili ajanların bir arada kullanılması

  %38'i invitro sinerjik etkili ajanların kullanılması

İkili karbapenem?

Karbapenemazların ertapeneme afinitesi daha yüksek: Oyalama taktiği !???

J Antimicrob Chemother
https://doi.org/10.1093/jac/dkac292

Journal of Antimicrobial Chemotherapy

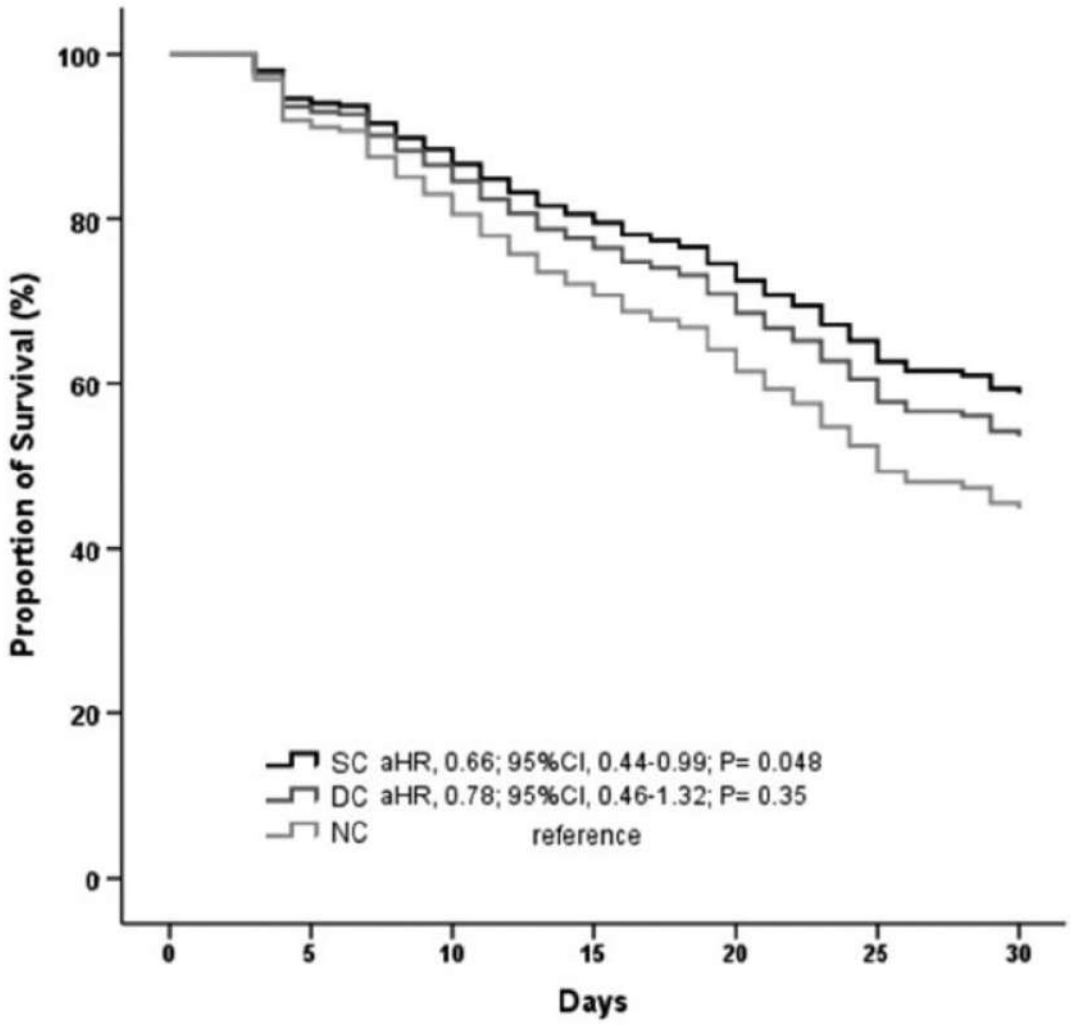
Double-, single- and none-carbapenem-containing regimens for the treatment of carbapenem-resistant Enterobacterales (CRE) bloodstream infections: a retrospective cohort

Maria Helena Rigatto[1,2,3]*†, Fabiano Ramos[1,4]†, Andressa Barros[1], Silvia Pedroso[4], Isabelli Guasso[4],

Brezilya, 2013-2020 retrospektif

Grup A Karbapenemaz ile gelişen 279 KDİ

%17 ikili, %53.4 tek kbpnm, %29.6 kbpnm içermeyen tdv



International Journal of Antimicrobial Agents 57 (2021) 106344

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

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

Review

Systematic review and meta-analysis of in vitro efficacy of antibiotic combination therapy against carbapenem-resistant Gram-negative bacilli

Luigia Scudeller[a,1], Elda Righi[b,1,*], Margherita Chiamenti[b], Damiano Bragantini[b],

Table 3
In vitro synergy of antibiotic combinations against *Klebsiella pneumoniae* assessed by pharmacokinetic/pharmacodynamic (PK/PD) and time–kill (TK) studies

Antibiotic regimen	Assay	No. of strains	No. of studies	No. of tests	ES	95% CI	Synergy rate
Ceftazidime/avibactam + amikacin	PK/PD	3	1	1	0.33	0.06–0.79	Low
Ceftazidime/avibactam + aztreonam	PK/PD	1	1	1	1.00	0.21–1.00	High
Colistin + doripenem	PK/PD	1	1	4	0.50	0.00–1.00	Positive trend
Colistin + fosfomycin	PK/PD	8	3	5	0.58	0.28–0.86	Moderate
Polymyxin B + fosfomycin	PK/PD	4	2	4	1.00	0.66–1.00	High
Meropenem + tigecycline	PK/PD	5	1	1	0.40	0.12–0.77	Moderate
Ceftazidime/avibactam + colistin	TK	16	1	1	0.25	0.10–0.49	Low
Colistin + doripenem	TK	62	5	6	0.50	0.28–0.71	Moderate
Colistin + ertapenem	TK	9	1	2	0.38	0.10–0.70	Moderate
Colistin + fosfomycin	TK	2	1	21	0.60	0.41–0.78	Moderate
Colistin + gentamicin	TK	26	2	2	0.31	0.14–0.50	Low
Colistin + meropenem	TK	9	2	2	0.12	0.00–0.46	No synergy
Colistin + meropenem + tigecycline	TK	6	1	1	0.00	0.00–0.39	No synergy
Colistin + rifampicin	TK	25	2	2	1.00	0.95–1.00	High
Colistin + tigecycline	TK	10	2	3	0.42	0.00–0.98	Positive trend
Colistin + tobramycin	TK	4	1	2	0.37	0.05–0.76	Moderate
Doripenem + ertapenem	TK	12	1	1	0.00	0.00–0.24	No synergy
Doripenem + gentamicin	TK	26	2	2	0.15	0.03–0.32	Low
Imipenem + amikacin	TK	4	1	1	1.00	0.51–1.00	High
Meropenem + amikacin	TK	4	1	1	1.00	0.51–1.00	High
Meropenem + ertapenem	TK	21	1	1	0.43	0.24–0.63	Moderate
Meropenem + gentamicin	TK	13	1	1	0.00	0.00–0.23	No synergy
Meropenem + tigecycline	TK	13	1	1	0.00	0.00–0.23	No synergy
Meropenem + tigecycline + gentamicin	TK	13	1	1	0.00	0.00–0.23	No synergy
Polymyxin B+ doripenem	TK	1	1	4	1.00	0.51–1.00	High
Polymyxin B + imipenem	TK	2	1	3	1.00	0.67–1.00	High
Polymyxin B + meropenem	TK	25	6	50	0.45	0.36–0.53	Moderate

ES, effect size; CI, confidence interval.

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BMC Infectious Diseases

RESEARCH ARTICLE Open Access

The role of combination therapy in the treatment of severe infections caused by carbapenem resistant gram-negatives: a systematic review of clinical studies

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11546 hasta içeren 134 çalışma (52'si Enterobacterales)

9 (%7) çalışma RKÇ,

19 (%14) prospektif,

89 (%66) retrospektif,

17 (%13) olgu serisi.

41 çalışma (%31) çok merkezli

92 farklı tedavi rejimi uygulanmış

Patients	Total	Acinetobacter	Enterobacteriaceae	Mixed Gram Negative	Pseudomonas
Undefined	5,863	1,364	2,585	1,806	108
Single-antibiotic regimen					
Aminoglycoside	174	39	96		39
BLBLIs	46				46
Carbapenem	97		97		
Cefepime	88				88
Ceftazidime/avibactam	120		107	13	
Ceftolozane/tazobactam	12				12
Fosfomycin	8		8		
Meropenem/Vaborbactam	50		50		
Polymyxin	2,383	1,066	252	976	89
Sulbactam	142	142			
TMP-SMX	12		12		
Tetracycline	21	21			
Tigecycline	416	221	179	16	

Patients

	Total	Acinetobacter	Enterobacteriaceae	Mixed Gram Negative	Pseudomonas
Undefined	5,863	1,364	2,585	1,806	108
Dual-antibiotic regimen					
Aminoglycoside + Carbapenem	37		37		
Aminoglycoside + Fosfomycin	11		11		
Aminoglycoside + Polymyxin	42		42		
Aminoglycoside + Sulbactam	8	8			
Aminoglycoside + Tetracycline	20	20			
Aminoglycoside + Tigecycline	73	13	60		
BLBLIs + Polymyxin	27	17			10
BLBLIs + Cefepime	24		24		
Carbapenem + Ertapenem	73		73		
Carbapenem + Fosfomycin	41		16		25
Carbapenem + Polymyxin	608	388	134	50	36
Carbapenem + Rifampin	20	20			
Carbapenem + Sulbactam	180	180			
Carbapenem + Tigecycline	48	28	20		
Fosfomycin + Polymyxin	5		5		
Fosfomycin + Tigecycline	22		22		
Glycopeptide + Polymyxin	71	29		42	
Polymyxin + Rifampin	246	246			
Polymyxin + Sulbactam	153	153			
Polymyxin + Tetracycline	7			7	
Polymyxin + Tigecycline	210	88	103	19	

Patients

	Total	Acinetobacter	Enterobacteriaceae	Mixed Gram Neg	Pseudo
Undefined	5,863	1,364	2,585	1,806	108
Triple-antibiotic regimen					
Aminoglycoside + Carbapenem + Tigecycline	9		9		
Aminoglycoside + Fosfomycin + Tigecycline	32		32		
Aminoglycoside + Polymyxin + Tigecycline	6		6		
Carbapenem + Ertapenem + Polymyxin	14		14		
Carbapenem + Fosfomycin + Polymyxin	24				24
Carbapenem + Fosfomycin + Tigecycline	8		8		
Carbapenem + Glycopeptide + Polymyxin	4	4			
Carbapenem + Polymyxin + Rifampin	24			24	
Carbapenem + Polymyxin + Tigecycline	33		33		
Carbapenem + Polymyxin + Tigecycline	15	15			
Polymyxin + Rifampin + Tigecycline	19	19			

Antibiyotik duyarlılıkları?

- **Kolistin:** Kolistin duyarlılığı buyyon mikrodilüsyon ile çalışılmalı.

Otomatize sistem/Disk difüzyon/E-test ile «duyarlı» sonuç elde edilemez

- **Polimiksin B**: Duyarlılık sonucu rutin testlerden elde edilemiyor! **EUCAST'da sınır değer yok !**

- **Tigesiklin**: Buyyon mikrodilüsyon ile çalışılmalı (Besiyeri çalışma günü taze hazırlanmalı)

Otomatize sistemden sadece MİK değeri elde edilebilir. E test ile sonuç verilemez
Disk diffüzyon ile sonuç sadece *E.coli* ve *Citrobacter koseri* suşları için verilebilir

- **Fosfomisin**: Glukoz-6-fosfat varlığında agar dilüsyon ile çalışılmalı.

E-test/otomatize sistem sonuç veremez
Disk difüzyon ile sonuç sadece idrar + *E.coli* izolatlarında mümkün

- **Caz-Avi:** Disk difüzyon yapılabilir

Clinical Infectious Diseases
IDSA FEATURES

Infectious Diseases Society of America Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR-*P. aeruginosa*)

Pranita D. Tamma,[1] Samuel L. Aitken,[2] Robert A. Bonomo,[3] Amy J. Mathers,[4] David van Duin,[5] and Cornelius J. Clancy[6]

Question 6: What is the role of polymyxins for the treatment of infections caused by CRE?

Recommendation: Polymyxin B and colistin should be avoided for the treatment of infections caused by CRE. Colistin can be considered as a last resort for uncomplicated CRE cystitis.

Polimiksinlerden kaçınılmalı (PK/PD sorunları)

Kolistin komplike olmamış sistitte son seçenek

tdv. olabilir

Kolistin :
Sub-optimal konsantrasyondan kaçınmak için doz hesabını dikkatli yapmak gerek

PHARMACOTHERAPY

SPECIAL ARTICLE

International Consensus Guidelines for the Optimal Use of the Polymyxins:

Endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP)†

Pharmacotherapy 2019;39(1):10–39

III. Should I Preferentially Use One Polymyxin Over the Other?

Recommendations. **R5:** We recommend that clinicians have access to parenteral products of both CMS and polymyxin B, so they can choose between the two in particular circumstances.

R6: We recommend polymyxin B as the preferred agent for routine systemic use in invasive infections. The rationale for this recommendation is that polymyxin B has superior PK characteristics in humans as well as a decreased potential to cause nephrotoxicity.

R7: We recommend colistin as the preferred polymyxin for the treatment of lower urinary tract infections given renal clearance of the prodrug CMS that then converts to the active moiety colistin in the urinary tract.

PK/PD ve yan etki avantajı nedeniyle Polimiksin B

Üriner sistem infeksiyonlarında: Kolistin

V. Do I Need to Administer an Intravenous Loading Dose When I Initiate Therapy with CMS?

Recommendation. **R9:** We recommend initiating IV therapy with a CMS loading dose of 300 mg CBA (~9 million IU) infused over 0.5–1 hours and to administer the first maintenance dose 12–24 hours later.

Yükleme dozu (300mg, ~ 9 MÜ)

12-24 saat sonra idame dozu

VI. What Should My Initial Daily Maintenance Dose of CMS Be in Patients with Normal Renal Function?

Recommendation. **R10:** We recommend that for a patient with normal renal function, administer a daily dose of 300–360 mg CBA (~9–10.9 million IU), divided into two and infused over 0.5–1 hour at 12-hour intervals. Monitor renal function and adjust the daily dose accordingly using the recommendations in Table 2.

Normal renal fonksiyonu olanlara:

Günlük 300-360 mg, 2'ye bölünerek

0.5 - 1 saat infüzyonla

Table 2. Look-up Table of Daily Doses of CMS[a]

Creatinine clearance, mL/minute[b]	Daily dose of CMS for plasma colistin $C_{ss,avg}$ of 2 mg/L[c]	
	mg CBA/day	Million IU/day
0	130	3.95
5 to < 10	145	4.40
10 to < 20	160	4.85
20 to < 30	175	5.30
30 to < 40	195	5.90
40 to < 50	220	6.65
50 to < 60	245	7.40
60 to < 70	275	8.35
70 to < 80	300	9.00
80 to < 90	340	10.3
≥ 90	360	10.9

VIII. Does Renal Replacement Therapy Have Implications for Selection of Intravenous CMS Dosage Regimens?

patient on *intermittent hemodialysis* (IHD), the following dosing schedule be utilized: On a nondialysis day, administer a CMS dose of 130 mg CBA/day (~3.95 million IU/day). On a dialysis day, administer a supplemental dose of CMS 40 mg CBA (~1.2 million IU) or 50 mg CBA (~1.6 million IU) for a 3- or 4-hour IHD session, respectively. If possible, the supplement to the baseline (nondialysis) daily dose should be administered with the next regular dose, after the dialysis session has ended. Conduct IHD sessions as late as possible within a CMS dosage interval to minimize the amount of CMS and formed colistin lost to the extracorporeal system.

R13: We recommend that to target a plasma colistin $C_{ss,avg}$ of 2 mg/L in patients prescribed *sustained low-efficiency dialysis* (SLED) that 10% of the CMS dose be added to the baseline daily dose per 1 hour of SLED.

R14: We recommend that for patients prescribed continuous renal replacement therapy (CRRT), for a plasma colistin $C_{ss,avg}$ of 2 mg/L, to administer CBA 440 mg/day (~13.3 million IU/day). This equates to 220 mg CBA every 12 hours (~6.65 million IU every 12 hours).

Polimiksin B: Kullanım kolaylığı, düşük yan etki
Akciğer/ELF geçişi az, idrara geçişi yok
Sub-optimal konsantrasyon sorunu var

Polymyxin B Intravenous Dosing

IX. Do I Need to Administer an Intravenous Loading Dose When I Initiate Therapy with Polymyxin B?

Recommendation. **R15:** We recommend a loading dose of 2.0–2.5 mg/kg for polymyxin B, based on total body weight (TBW) (equivalent to 20,000–25,000 IU/kg) over 1 hour.

2-2.5 mg/kg TVA (20-25bin IU/kg)
Yükleme, 1 saat infüzyon

X. What Is the Recommended Initial Daily Maintenance Dose for Polymyxin B in Patients with Normal Renal Function?

Recommendation. R16: We recommend that for patients with severe infections, a polymyxin B dose of 1.25–1.5 mg/kg (equivalent to 12,500–15,000 IU/kg TBW) every 12 hours is infused over 1 hour.

2 x 1.25-5.5 mg/kg TVA (12.5-15bin IU/kg)
Yükleme, 1 saat infüzyon

Fosfomisin: Akciğer dokusu, ELF geçişi çok iyi

Kan düzeyi yüksek

Uygulama zorluğu (Hipernatremi, hipopotasemi)

Acinetobactere etkisi yok

Tigesiklin: Akciğer dokusu/ELF geçişi orta-az

Kan düzeyi düşük

Yüksek dozda kullanılması öneriliyor: Yan etki artıyor

Pseudomonas spp'ye etkili değil

Aminoglikozit: Akciğer dokusu/ELF geçiş orta-az

Abse varlığında etkinlik düşük

Beta-laktamlarla sinerji

Nefrotoksisite

Seftazidim-Avibaktam:

Duyarlılığın gösterilmesi gerekli (NDM?)

YBÜ dışında başlanamıyor

Sonuç;

KRE tedavisinde kombinasyonların daha etkili olduğuna dair net veri YOK

Ağır olmayan infeksiyonlarda kombinasyon kullanılmamalı

Sadece polimiksin/AGA/Tigesiklin/Fosfomisin duyarlı KRE'nin neden olduğu ağır infeksiyonlarda kombinasyon tercih edilebilir (orta düzeyde kanıtlar)

Hangi kombinasyonun daha etkili olduğunu gösteren klinik çalışma çok sınırlı;

- ✓ İkili karbapenem başarılı değil
- ✓ Kolistin + meropenem tedavisi tek başına kolistin den daha etkili değil (MİK ≤ 8 mg/L)
- ✓ Kolistin + Fosfomisin
- ✓ Kolistin + Rifampisin
- ✓ Meropenem + AGA

TİD bakterilerde;
MİK değerine ve infeksiyon bölgesine göre kombinasyon seçilebilir (kurtarma tedavisi)

Teşekkürler….