KLİMİK
TÜRK KLİNİK MİKROBİYOLOJİ VE İNFEKSİYON HASTALIKLARI DERNEĞİ

Her Yönüyle Kolistin

Dr. Ceren Atasoy Tahtasakal
Şişli Hamidiye Etfal EAH.
İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji
Dr. Şiran Keske
VKV Amerikan Hastanesi
İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji
31.10.2017

AMERİKAN HASTANESİ

Sunum Planı

- Olgu sunumu
- Olgu akışı içerisinde soru-cevap ve tartışma
  - Karbapeneme dirençli infeksiyonlarda kolistin tedavisi
  - Kolistin dozu
  - Kolistinin yan etkisi ve yönetimi
  - İnhaler-intratekal kolistin kullanımı
  - Kolistinin SSS infeksiyonlarında kullanımı
  - Kolistin dirençli infeksiyonlar ve yönetimi
  - Kolistin dirençli infeksiyon salgınları

Olgu

21.02.2016

- E.T, Erkek, 40 yaş
- 10 gün önce bilinç bulanıklığı ile başvuru

- 8 aydır dış merkezde nörobehçet, SSS lenfoma, multiple skleroz ön tanıları ile ayaktan takipli, bilinç bulanıklığı ortaya çıkması üzerine dış merkez yoğun bakıma yatırılıyor, yangın sonrası merkezimize sevk

- Yoğun bakım ünitesinde (YBÜ) entübe olarak takip

Olgu

- Özgeçmiş

- 8 aydır nöroloji takipli, dış merkezde bir hafta önce beyin biyopsisi
- Tüberküloz geçirme öyküsü

- Soygeçmiş

- Özellik yok

21.02.2016

Fizik muayane;

- A: 36.2 °C TA:132/55mmhg, KTA: 90/dk ritmik
- Genel durumu kötü, bilinç kapalı, ağrıya fleksör yanıt, mekanik ventilasyon desteği altında, IR:+/+,
- Ense sertliği, meningeal irritasyon bulguları yok
- **Sağ frontoparietal bölgede 5cm'lik stapler ile sütüre edilmiş alan mevcut.**
- Kardiyak sesleri doğal, s1,s2 doğal, ek ses, üfürüm yok.
- **Akciğer sesleri bilateral bazallerde azalmış.**
- Bağırsak sesleri normoaktif, NG'den enteral besleniyor

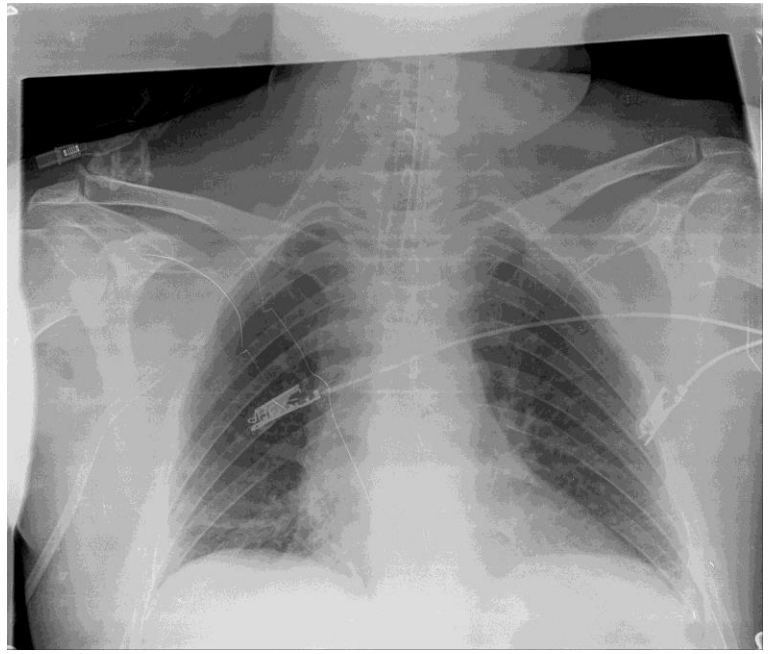
21.02.2016

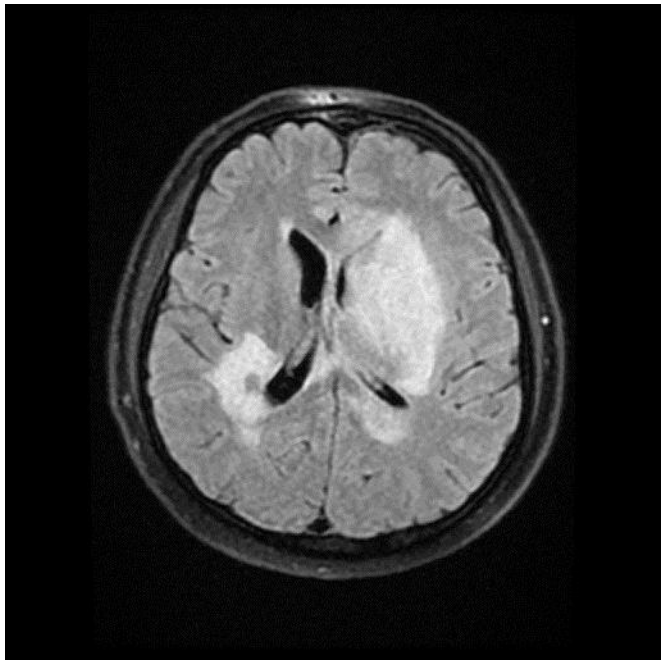
Tetkikler

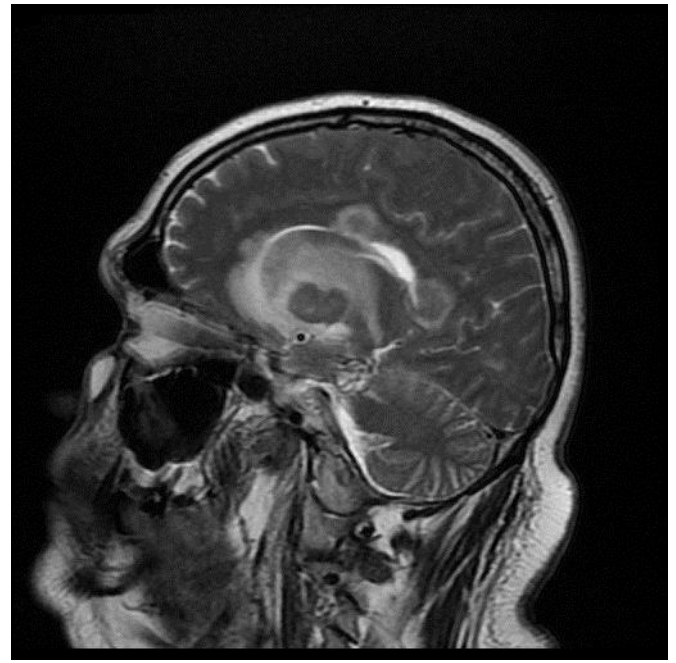
- WBC : 8770
- Nötrofil oranı: 6110/8770
- CRP : **45** mg/L (0-5)
- Pct : 0,1ng/ L
- Kre : 0,55 mg/dl
- AST : 50 U/L
- ALT : 50 U/L
- NA: 140 mmol/l
- K: 3.45 mmol/l

Görüntüleme

- Akciğer grafisinde
- Kranial MR







Tedavi

- Mannitol 6x75mg,
- Deksametazon 4x4mg (10. günü),
- Ranitidin 4x1, Levetiresetam 500mg 2x3, Isolayt 1000cc, Combivent 4x1,
- Ampisilin sulbaktam 4x2gr iv

Yatışının 4. günü

24.02.2016

- Ateş: 38.3°C Nb: 96/dk TA: 140/80 mm/hg
- FM'de nonpürülan sekresyon +, SS kaba, PEEP artış yok.

- İnfeksiyon konsültasyonu; odak? kan, idrar, ETA, kateter kültürü alındı.
- **Meropenem 3*1 gr (olası pnömoni)**

- Cildiye konsültasyon; Behçet ile uyumlu cilt döküntüsü

Yatışının 6. günü

26.02.2016

- Kültürlerde üreme yok!!

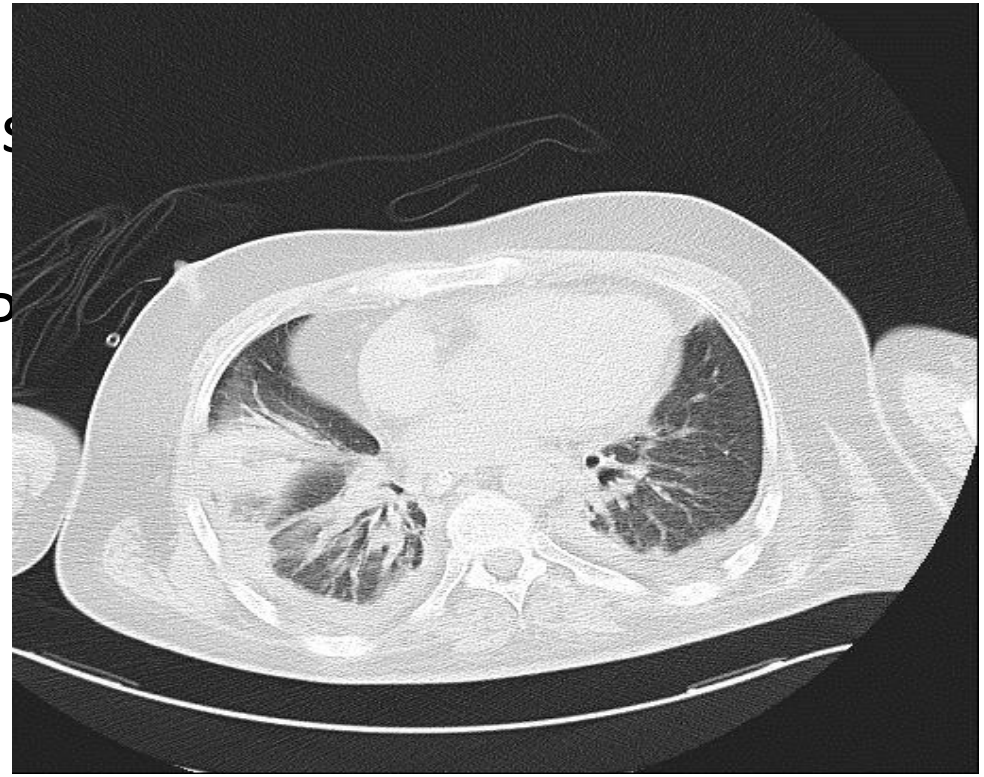
- Ateş devam ediyor.
- Kültürlerin tekrarlanması sonrası ampirik **linezolid 2*600 mg** eklendi.

- Kateter kültürde ; **MRKNS tek şişede→** Etken ? Kontaminasyon?

Yatışının 9. günü

29.02.2016

- Ateş+, pürülan sekresyonda ve infeks
  kötüleşme
- FM'de akciğerde kaba yaygın raller, P
- Kan, kateter, idrar, ETA kültür
- Toraks BT'de infitrasyon +



Linezolid (4. gün) kesildi. **VİP? -**Meropenem (6. gün) devam edildi ve **kolistin 300 mg/gün (yükleme), 2x150 mg (idame) iv**

+linezolid

Meropenem

+ Kolistin

	21.02	26.02	29.02 (9)			
CRP(mg/L)	45	109	294			
Pct (ng/L)	0,1	0,8	1,18			
Wbc	8770	14800	17000			
NE	6110	10100	15900			
Plt						
Kreatinin (mg/dl)	0,55	0,46	0,45			
AST (U/L)	50	90	51			
ALT (U/L)	50	134	92			
Kültürler		MRKNS				

Kolistin Dozu?

Polymyxin E, Colistin

CrCl (mL/min)	PK Study Group div bid (Max daily dose)*	EMA (doses div bid or tid)*	U.S. FDA (Wt - IBW)*
≥90	360 mg/day	300 mg/day	2.5-5 mg/kg/day div 2-4 doses
80 to <90	340 mg/day		
70 to <80	300 mg/day		2.5-3.8 mg/kg/day div 2 doses
60 to <70	275 mg/day		
50 to <60	245 mg/day		
40 to <50	220 mg/day	183-250 mg/day	2.5 mg/kg once daily or div bid
30 to <40	195 mg/day		
20 to <30	175 mg/day	150-183 mg/day	1.5 mg/kg q36h
10 to <20	160 mg/day		
5 to <10	145 mg/day	117 mg/day	N/R
<5	130 mg/day		

* All doses are stated as colistin base activity (CBA) in mg. IBW = ideal body weight

- **Inhalation therapy:** 50-75 mg CBA in 3-4 mL saline via vibrating mesh nebulizer 2-3 times/day: concentration in lung epithelial lining is 100-1000x greater with inhaled dosing vs. IV dosing alone
- **Meningitis** (intraventricular or intrathecal dose): 10 mg/day x several weeks; intrathecal dose often combined with IV dosing

Top

MAJOR ARTICLE

Infectious Diseases Society of America hiv medicine association OXFORD

Dosing Guidance for Intravenous Colistin in Critically Ill Patients

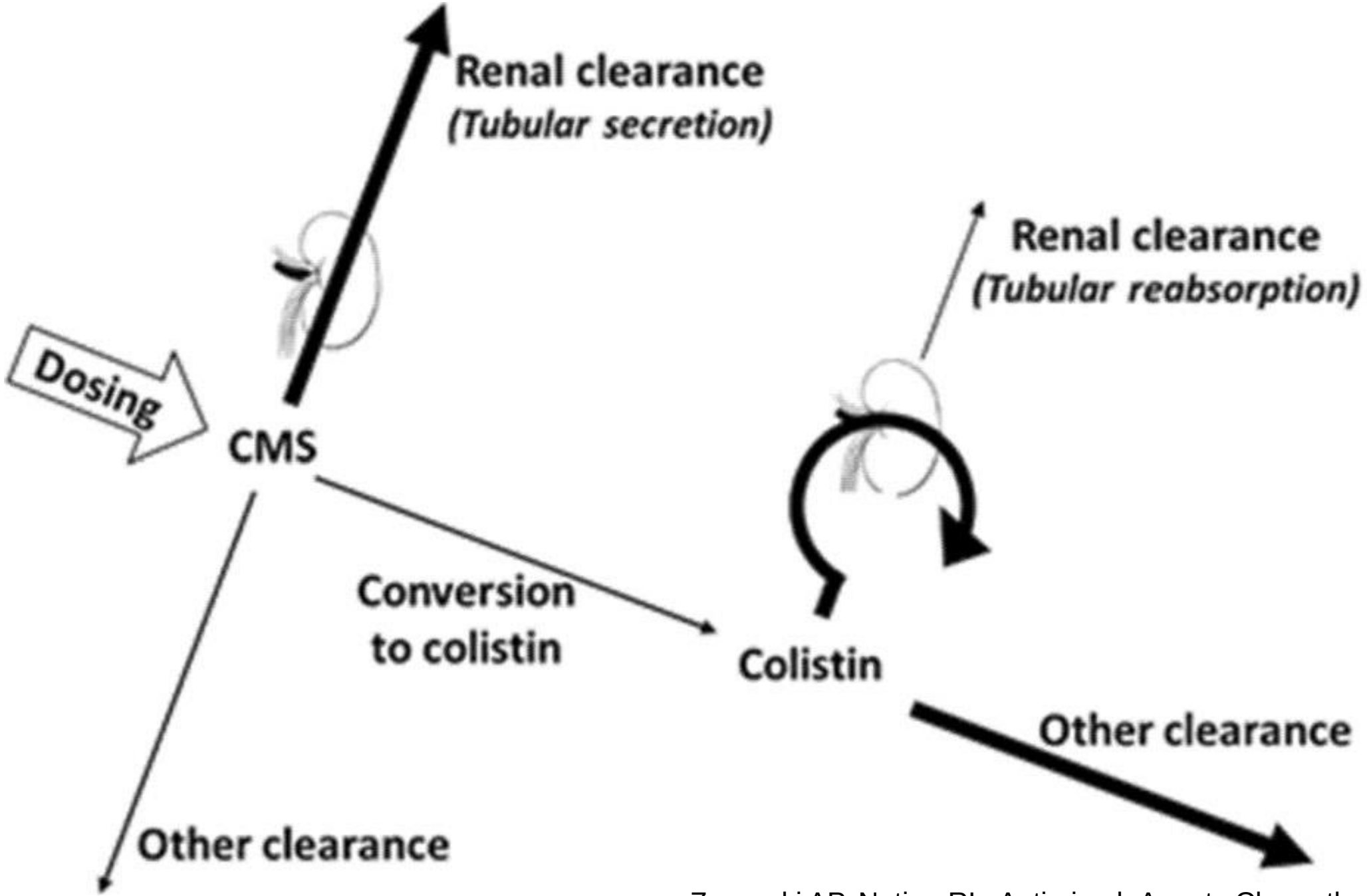
Roger L. Nation,[1] Samira M. Garonzik,[3] Visanu Thamlikitkul,[5] Evangelos J. Giamarellos-Bourboulis,[6] Alan Forrest,[3] David L. Paterson,[2] Jian Li,[1] and Fernanda P. Silveira[4]

[1]Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University, Melbourne, and [2]University of Queensland Center for Clinical Research, Royal Brisbane and Women's Hospital, Brisbane, Australia; [3]School of Pharmacy and Pharmaceutical Sciences, State University of New York at Buffalo; [4]Division of Infectious Diseases, University of Pittsburgh Medical Center, Pennsylvania; [5]Division of Infectious Diseases and Tropical Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand; and [6]Fourth Department of Internal Medicine, University of Athens Medical School, Greece

Background. Intravenous colistin is difficult to use because plasma concentrations for antibacterial effect overlap those causing

Table 3. "Look-up" Table of Daily Doses of Colistimethate for a Desired Target colistin $C_{ss,avg}$ of 2 mg/L for Narrow Windows of Creatinine Clearance

Creatinine clearance, mL/min	Dose of Colistimethate for $C_{ss,avg}$ of 2 mg/L[a]	
	CBA, mg/d	Million IU/d
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



Zavascki AP, Nation RL. Antimicrob Agents Chemother. 2017;61(3)

Karbapenem Dirençli Klebsiella İnfeksiyonu ve Yönetimi

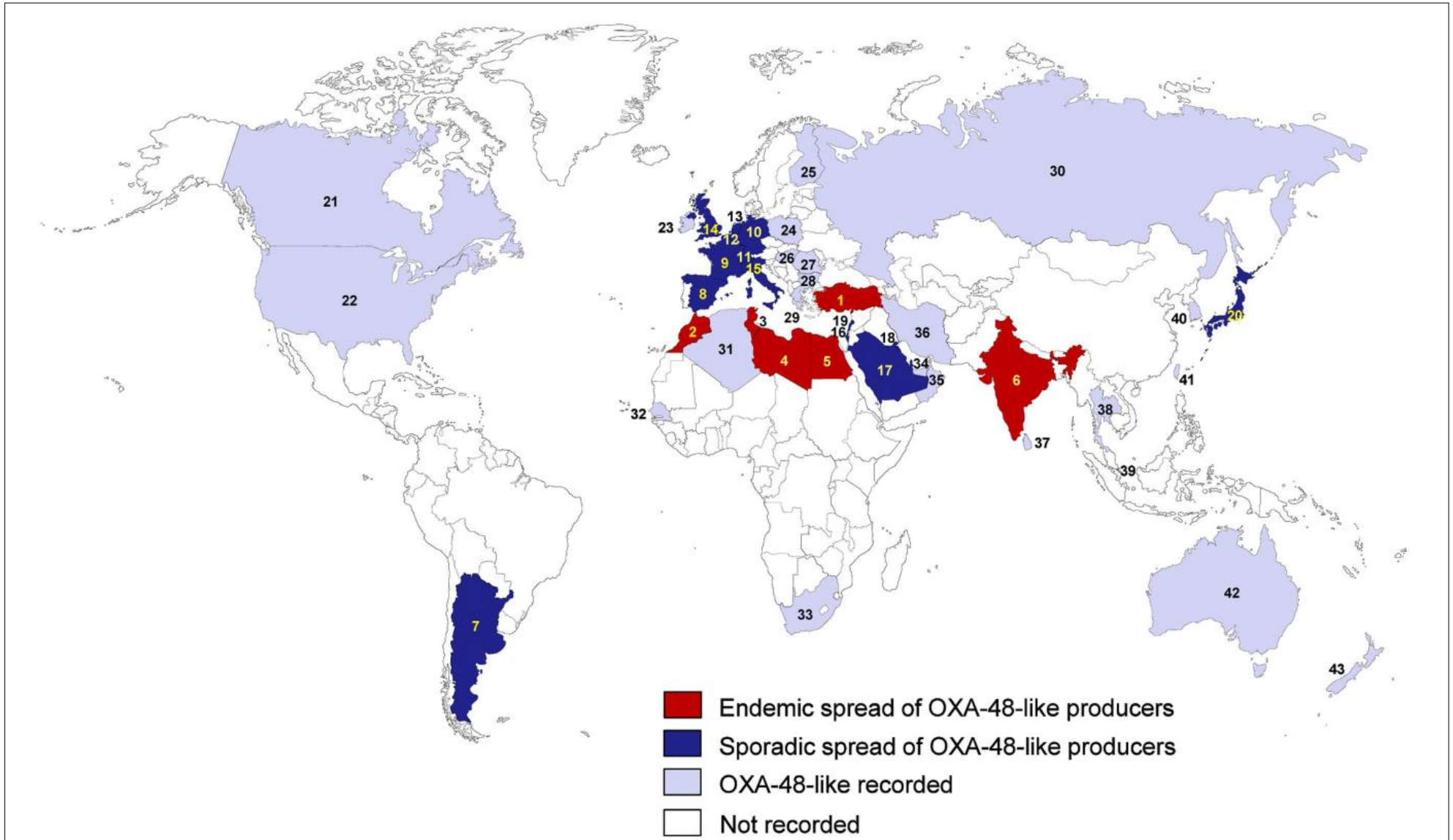


FIGURE 4 | Epidemiological features of OXA-48-like-producing *K. pneumoniae*. (1) Turkey; (2) Morocco; (3) Tunisia; (4) Libya; (5) Egypt; (6) India; (7) Argentina; (8) Spain; (9) France; (10) Germany; (11) Switzerland; (12) Belgium; (13) Netherlands; (14) UK; (15) Italy; (16) Israel; (17) Saudi Arabia; (18) Kuwait; (19) Lebanon; (20) Japan; (21) Canada; (22) USA; (23) Ireland; (24) Poland; (25) Finland; (26) Hungary; (27) Romania; (28) Bulgaria; (29) Greece; (30) Russia; (31) Algeria; (32) Senegal; (33) South Africa; (34) United Arab Emirates; (35) Oman; (36) Iran; (37) Sri Lanka; (38) Thailand; (39) Singapore; (40) South Korea; (41) Taiwan; (42) Australia; (43) New Zealand.

Lee CR, et al. *Front Microbiol.* 2016; 7: 895

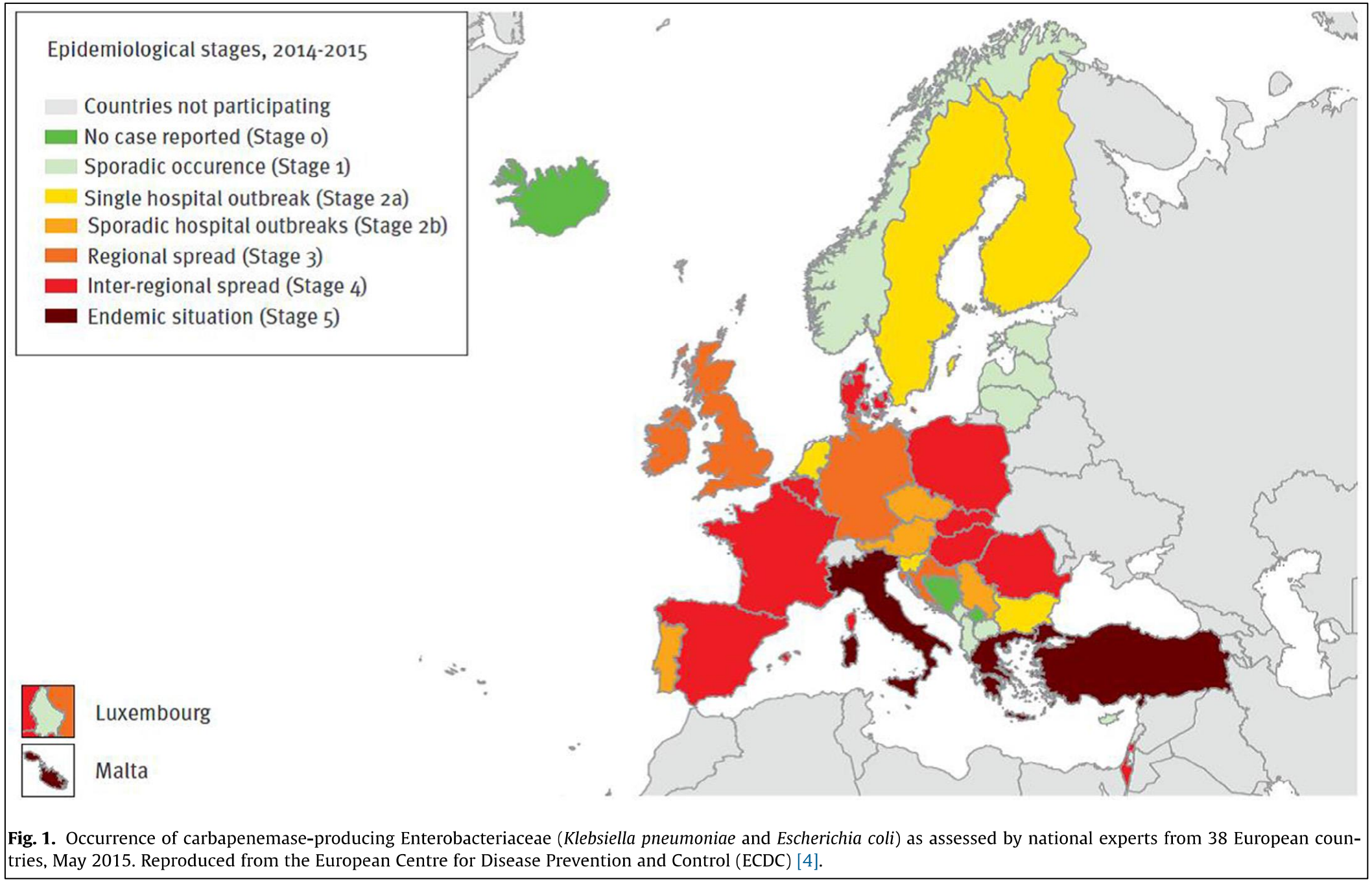
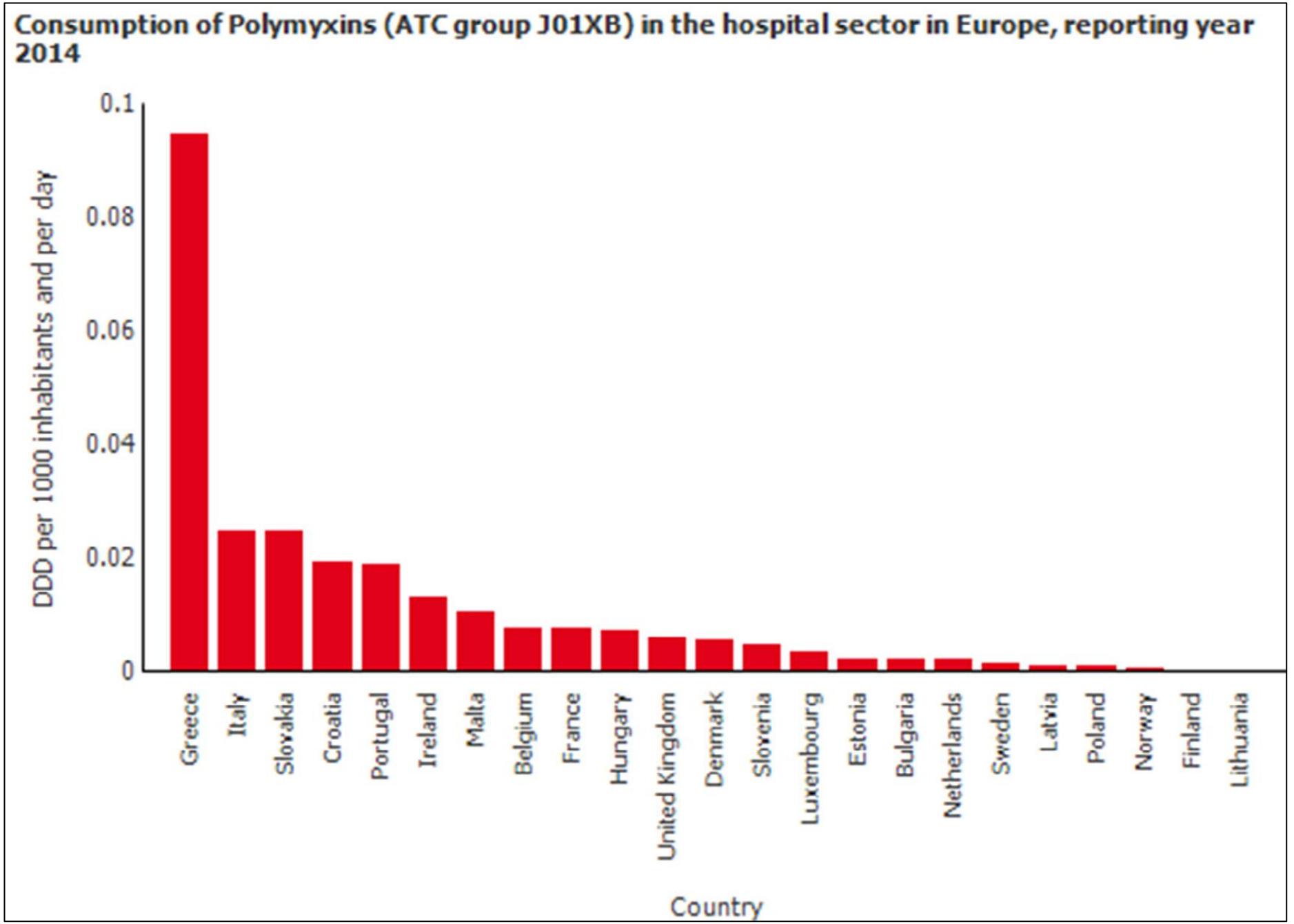


Fig. 1. Occurrence of carbapenemase-producing Enterobacteriaceae (*Klebsiella pneumoniae* and *Escherichia coli*) as assessed by national experts from 38 European countries, May 2015. Reproduced from the European Centre for Disease Prevention and Control (ECDC) [4].

Giamarellou H. Int J Antimicrob Agents. 2016;48(6):614-621.



Giamarellou H. Int J Antimicrob Agents. 2016;48(6):614-621.

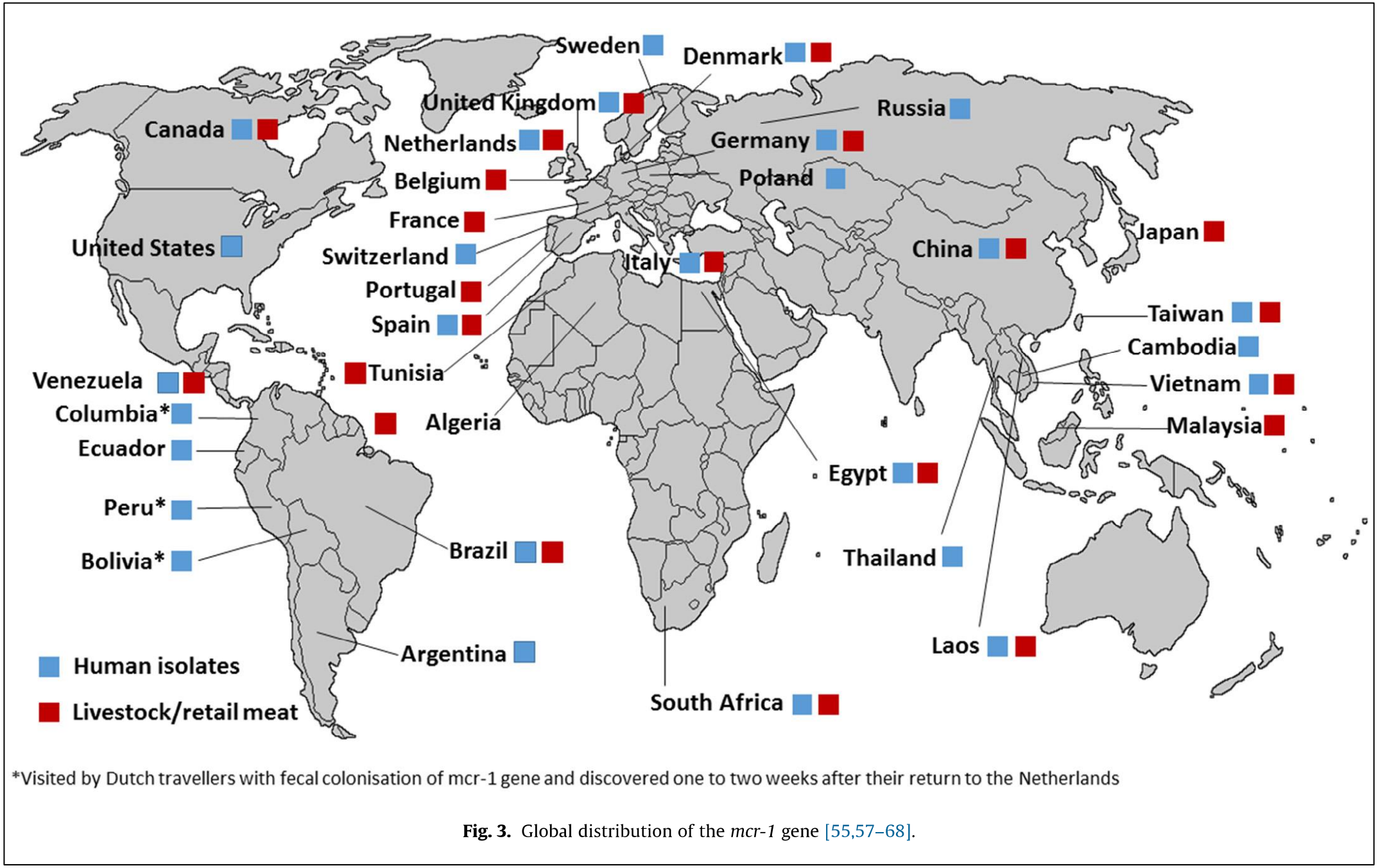


Fig. 3. Global distribution of the *mcr-1* gene [55,57–68].

RESEARCH ARTICLE

AJH

Bloodstream infections caused by *Klebsiella pneumoniae* in onco-hematological patients: clinical impact of carbapenem resistance in a multicentre prospective survey

Enrico Maria Trecarichi,[1]* Livio Pagano,[2] Bruno Martino,[3] Anna Candoni,[4] Roberta Di Blasi,[2] Gianpaolo Nadali,[5] Luana Fianchi,[2] Mario Delia,[6] Simona Sica,[2] Vincenzo Perriello,[7] Alessandro Busca,[8] Franco Aversa,[9] Rosa Fanci,[10] Lorella Melillo,[11] Federica Lessi,[12] Maria Ilaria Del Principe,[13] Chiara Cattaneo,[14] and Mario Tumbarello,[1] for the HaematologicMalignancies Associated Bloodstream Infections Surveillance (HEMABIS) registry – Sorveglianza Epidemiologica Infezioni Funginein Emopatie Maligne(SEIFEM) group, Italy

The aim of this study was to identify risk factors for mortality in patients suffering from hematological malignancies (HMs) with bloodstream infections (BSIs) caused by Klebsiella pneumoniae (KP). We conducted a prospective cohort study on KP BSI in 13 Italian hematological units participating in the HEMABIS registry–

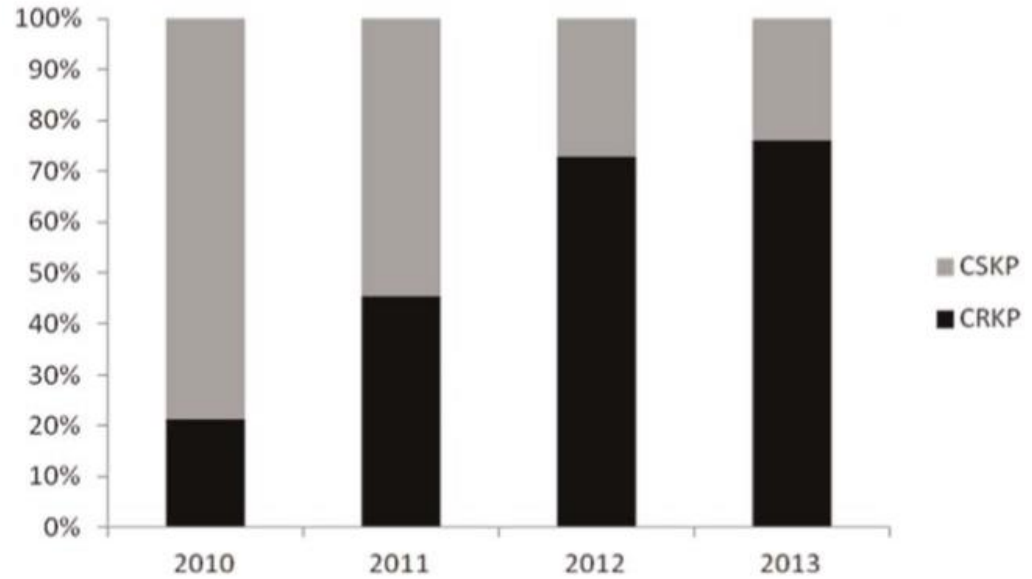


Figure 1. Percentages of resistance to carbapenems among Klebsiella pneumoniae isolates throughout the study period.

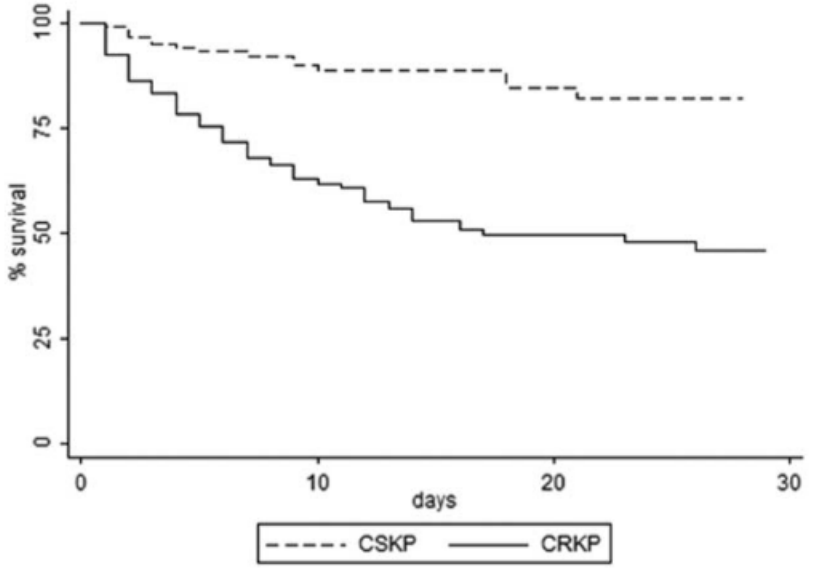


Figure 2. Kaplan-Meier survival estimates among patients with BSI caused by carbapenem resistant (CR) and carbapenem susceptible (CS) *Klebsiella pneumoniae* (KP).

Trecarichi EM, et al. *Am J Hematol.* 2016 Jul 18.

Tedavi
Monoterapi & Kombine Tedavi?

J Antimicrob Chemother 2015; 70: 2133 – 2143
doi:10.1093/jac/dkv086 Advance Access publication 21 April 2015

Journal of Antimicrobial Chemotherapy

Infections caused by KPC-producing *Klebsiella pneumoniae*: differences in therapy and mortality in a multicentre study

Mario Tumbarello[1*], Enrico Maria Trecarichi[1], Francesco Giuseppe De Rosa[2,3], Maddalena Giannella[4], Daniele Roberto Giacobbe[5], Matteo Bassetti[6], Angela Raffaella Losito[1], Michele Bartoletti[4], Valerio Del Bono[5], Silvia Corcione[2,3], Giuseppe Maiuro[1], Sara Tedeschi[4], Luigi Celani[1], Chiara Simona Cardellino[2,3], Teresa Spanu[7], Anna Marchese[8], Simone Ambretti[9], Roberto Cauda[1], Claudio Viscoli[5] and Pierluigi Viale[4] on behalf of ISGRI-SITA (Italian Study Group on Resistant Infections of the Società Italiana Terapia Antinfettiva)

2010-2014
5 akademik merkez
661 KPC Klebsiella infeksiyonu

Table 5. Multivariate analysis of risk factors for 14 day mortality in patients with infections caused by KPC-Kp

Variable	*P* value	OR (95% CI)
Combination therapy	0.001	0.52 (0.35–0.77)
BSI	<0.001	2.09 (1.34–3.29)
Septic shock at infection onset	0.001	2.45 (1.47–4.08)
APACHE III score	<0.001	1.05 (1.04–1.07)
Chronic renal failure	<0.001	2.27 (1.44–3.58)
Colistin-resistant isolate	0.001	2.18 (1.37–3.46)
Inadequate empirical antimicrobial therapy	0.04	1.48 (1.01–2.18)

Tumbarello M, et al. *J Antimicrob Chemother* 2015; 70: 2133–43

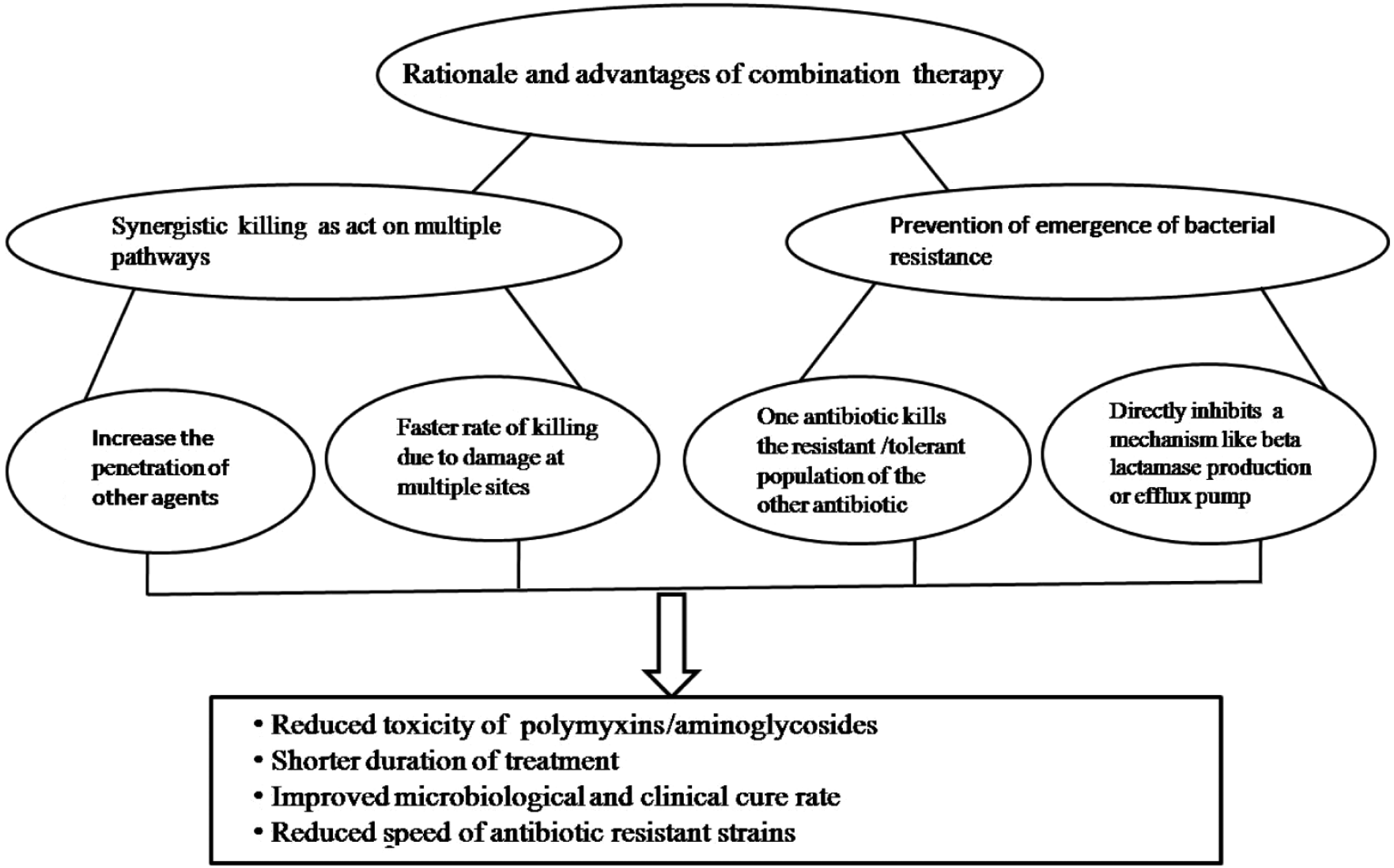


Figure 1. Rationale and advantages of combination therapy.

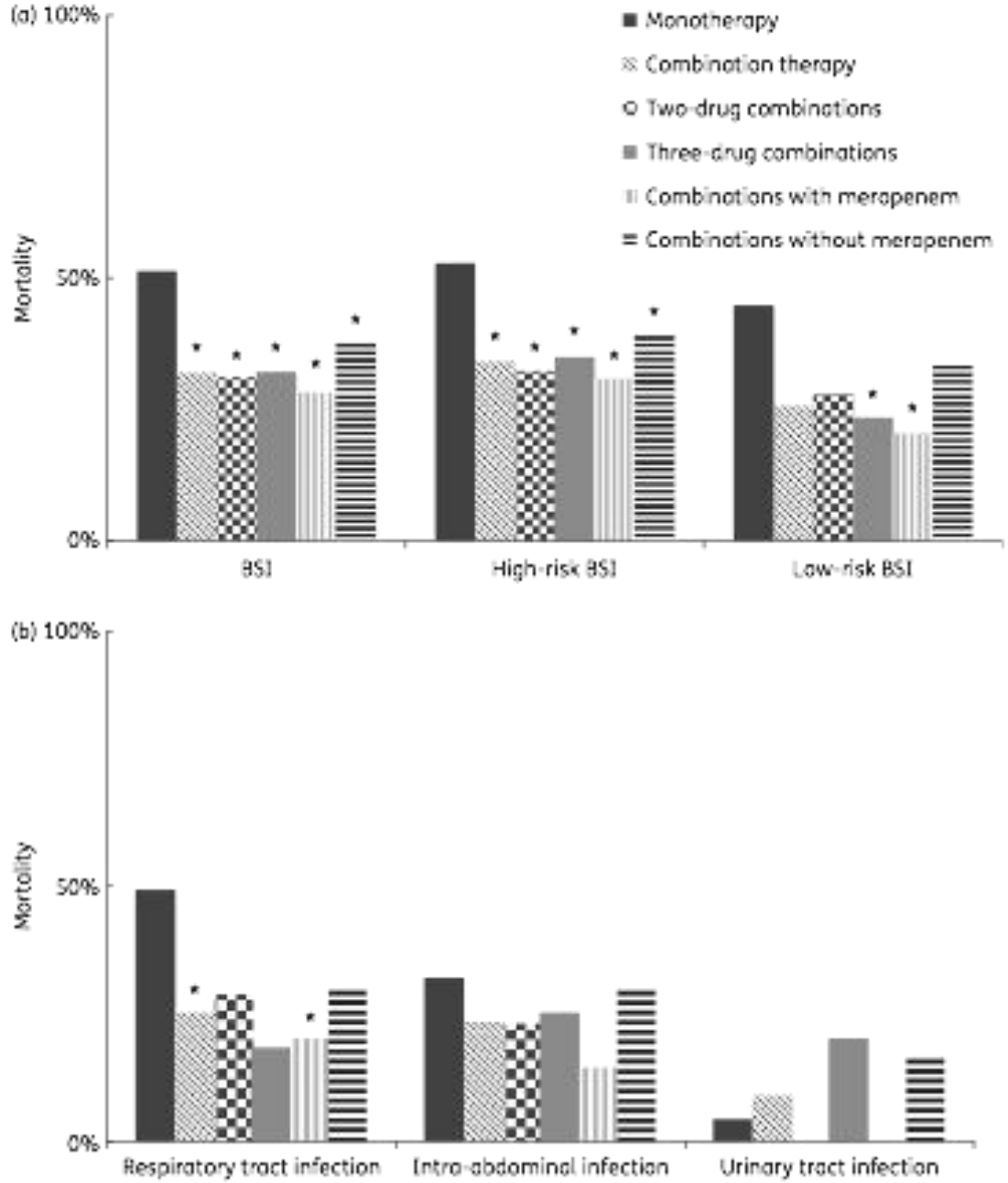


Figure 2. Mortality rates associated with different antimicrobial drug regimen categories in patients with BSIs (a) or non-bacteraemic infections (b).
*Statistically significant differences ($P < 0.05$) among different types of combination therapy and monotherapy.

Tumbarello M, et al. *J Antimicrob Chemother* 2015; 70: 2133–43

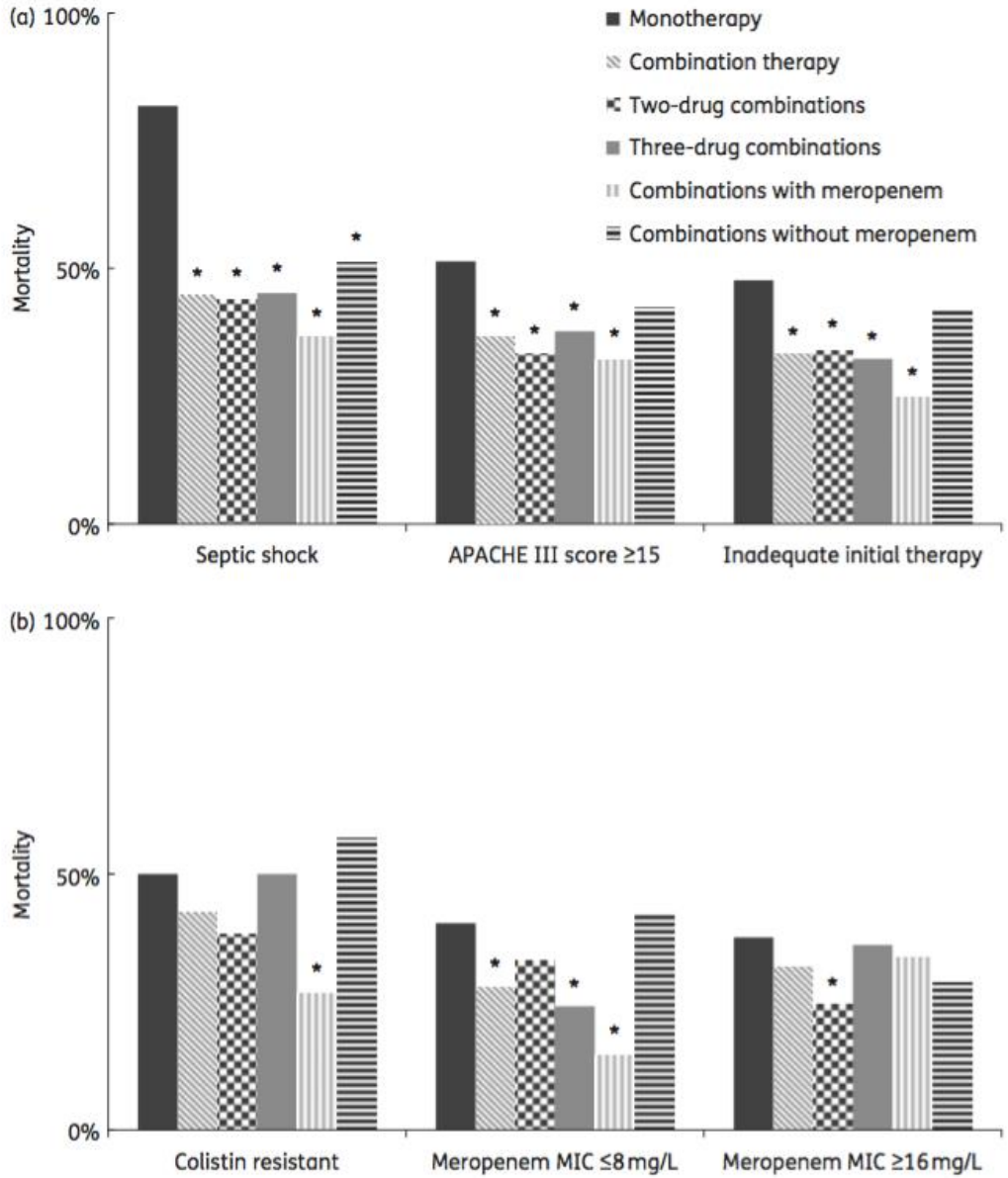


Figure 3. Mortality rates associated with different antimicrobial drug regimen categories in patients with different presenting features (a) or in patients with different KPC-Kp isolate characteristics (b). *Statistically significant differences ($P < 0.05$) among different types of combination therapy and monotherapy.

Tumbarello M, et al. *J Antimicrob Chemother* 2015; 70: 2133–43

Journal of Antimicrobial Chemotherapy Advance Access published September 13, 2016

J Antimicrob Chemother
doi:10.1093/jac/dkw377

Journal of Antimicrobial Chemotherapy

Polymyxin monotherapy or in combination against carbapenem-resistant bacteria: systematic review and meta-analysis

Oren Zusman[1]*, Sergey Altunin[2,3]†, Fidi Koppel[2], Yael Dishon Benattar[2,4], Habip Gedik[5] and Mical Paul[2,3]

[1]Department of Medicine E, Rabin Medical Center, Petah-Tiqva, Israel; [2]Infectious Diseases Unit, Rambam Medical Center, Haifa, Israel; [3]The Ruth and Bruce Rappaport Faculty of Medicine, Technion, Israel Institute of Technology, Haifa, Israel; [4]The Cheryl Spencer Department of Nursing, University of Haifa, Haifa, Israel; [5]Department of Infectious Diseases and Clinical Microbiology, MoH Bakirkoy Sadi Konuk Training and Research Hospital, Istanbul, Turkey

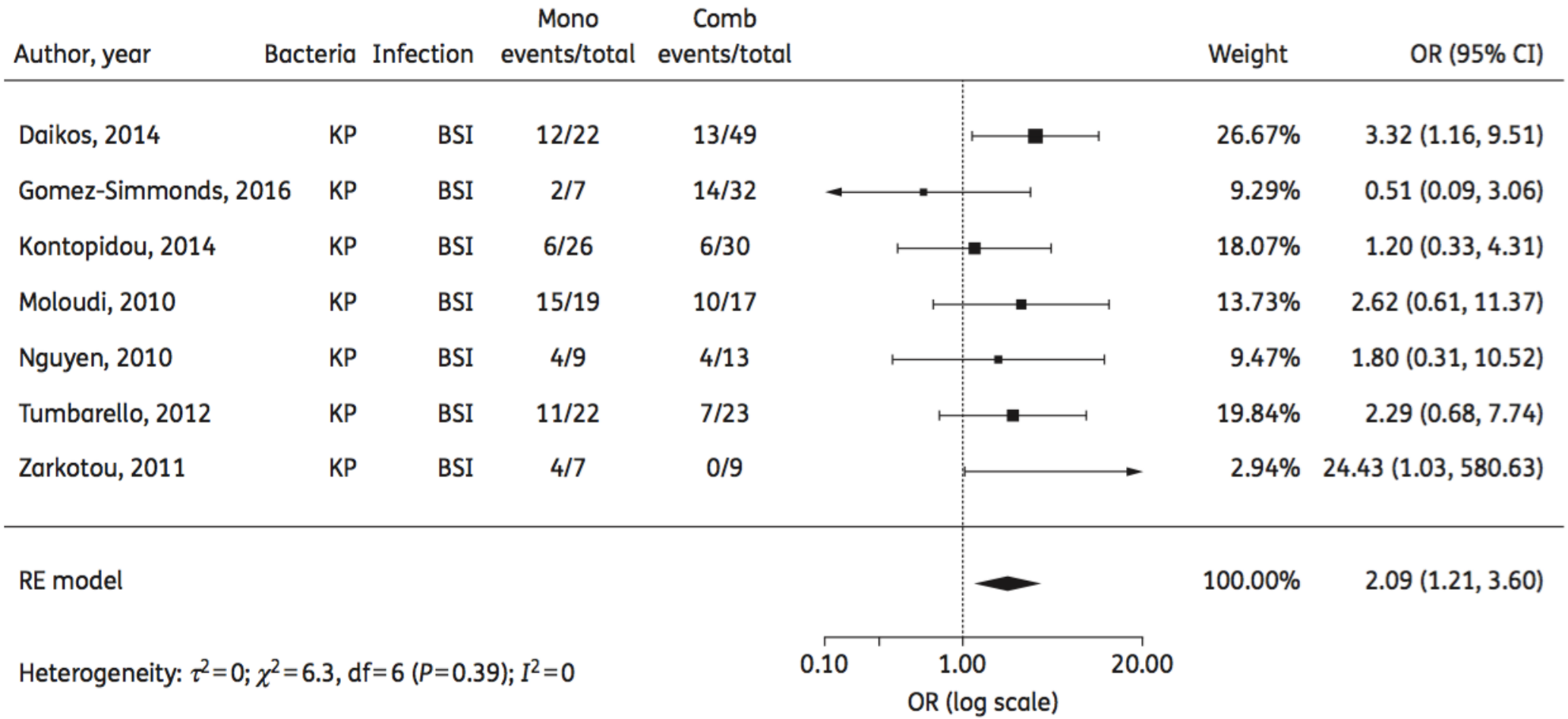


Figure 6. Polymyxin monotherapy versus combination with tigecycline or aminoglycoside in KP BSI, all-cause mortality.

Karbapenem R veya karbapenemaz pozitif KP'lerde tedavi karşılaştırılmış

Zusman O. *J Antimicrob Chemother.* 2016 Sep 13

Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae (INCREMENT): a retrospective cohort study

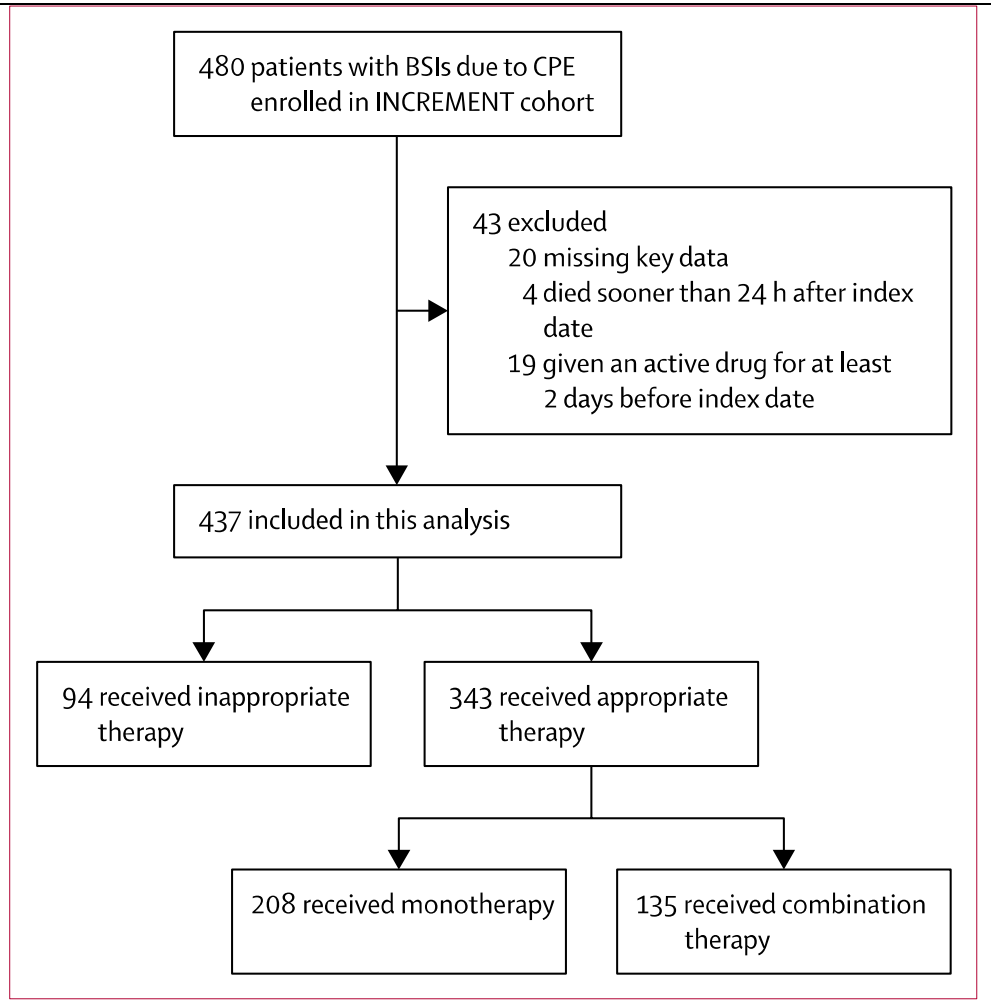
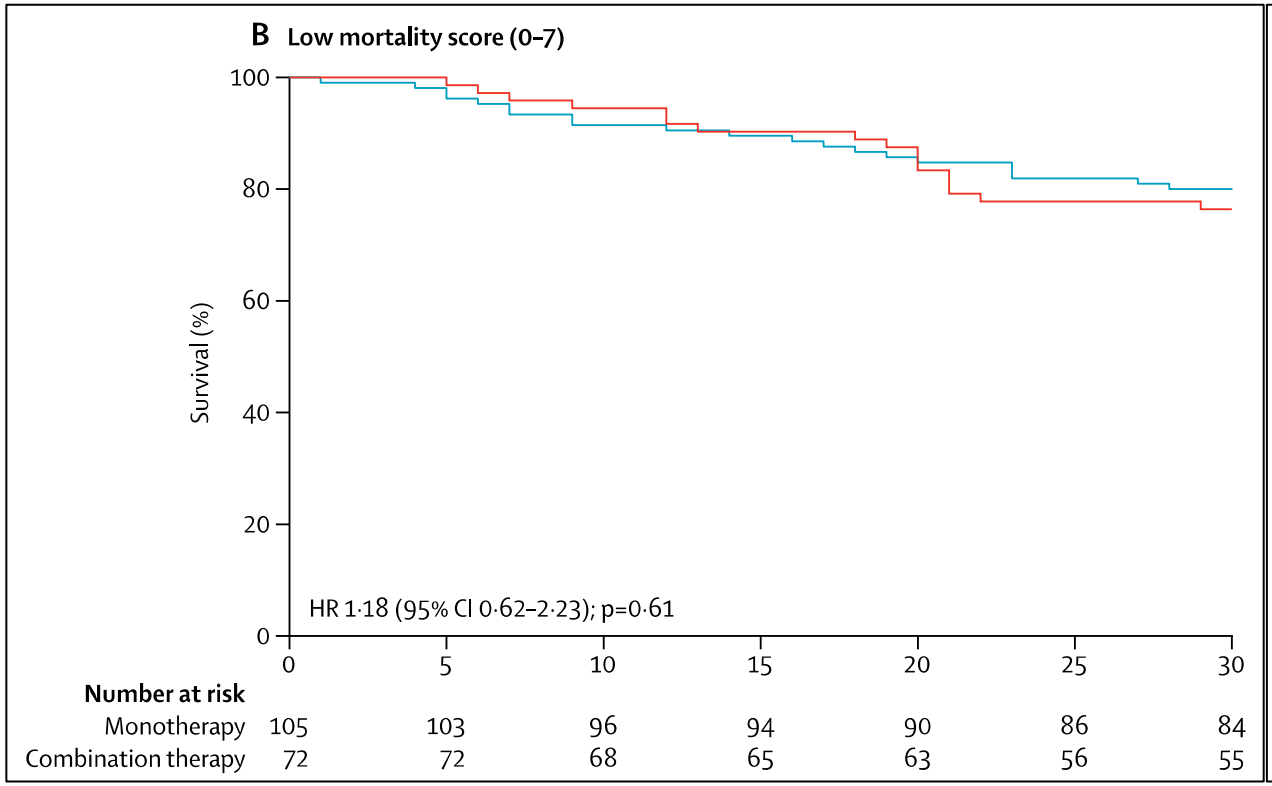
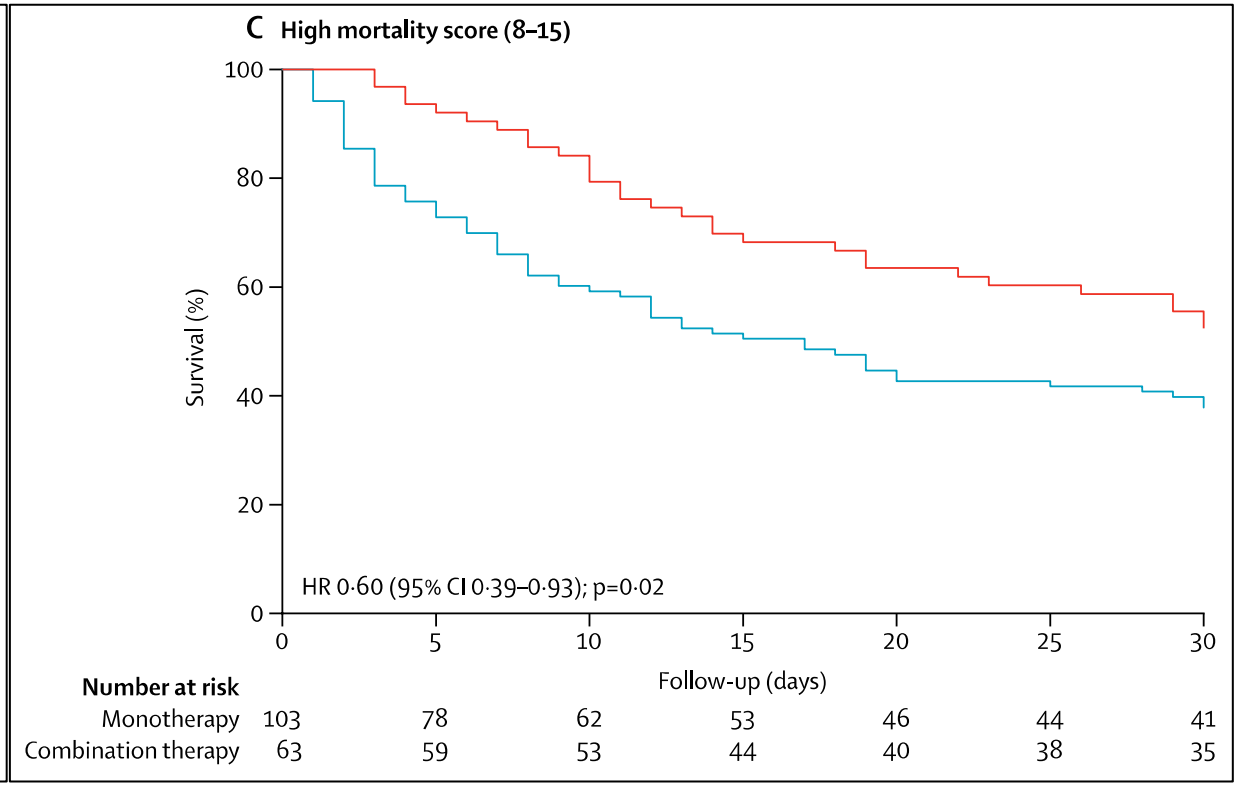


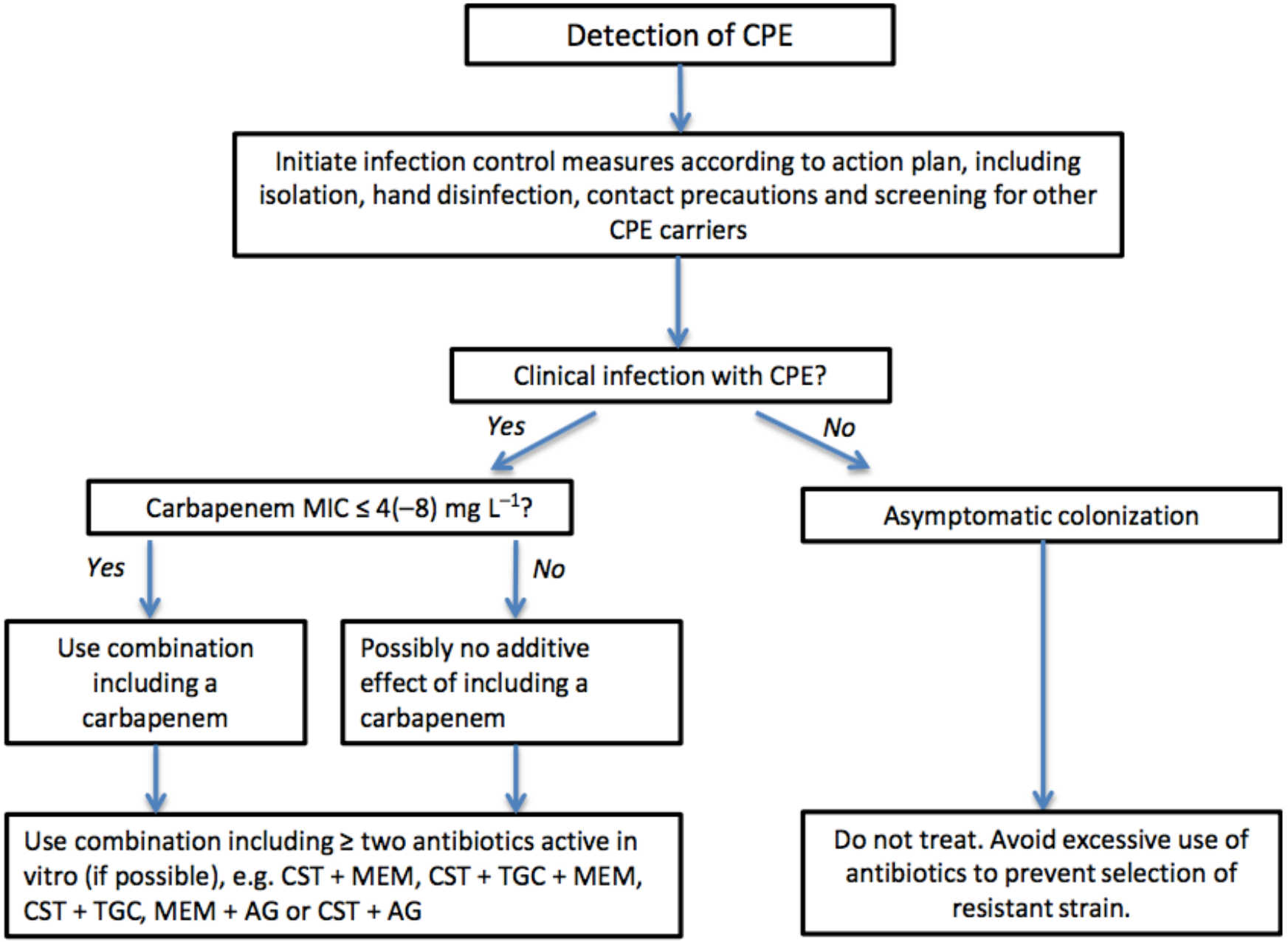
Figure 1: **Flow chart of included patients with BSIs due to CPE**

Gutiérrez-Gutiérrez B. Lancet Infect Dis. 2017;17(7):726-734.





Gutiérrez-Gutiérrez B. Lancet Infect Dis. 2017;17(7):726-734.

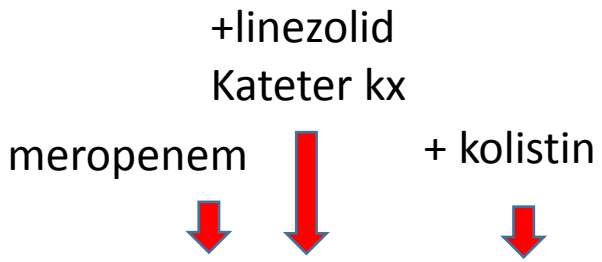


Tängdén T, Giske CG. *J Intern Med.* 2015; 277(5): 501-12.

Yatışının 14. günü

03.03.2016

- Ateş ve bilinç kapalılığı devam ediyor…
- Kültürlerde üreme yok.
- Meropenem,kolistin devam



	21.02	26.02	29.02 (9)	01.03	03.03 (14)
CRP	45	109	294	232-272	231
Pct	0,1	0,8	1,18	0,9	0.61
Wbc	8770	14800	17000	12400	10700
NE	6110	10100	15900	10300	8010
Plt					
Kre	0,55	0,46	0,45	0,42	0,40
AST	50	90	51	44	67
ALT	50	134	92	82	93
Kültürler		MRKNS			

Yatışının 14. günü

03.03.2016

- BOS örneği subaraknoid aralıktan alındı. (shift)

- BOS incelemesi:
  - Mikroskobisi lökosit, eritrosit yok.
  - Biyokimya; glukoz 72 mg/dl (kan glukozu: 160) protein; 70 mg/dl, pandy (+)

- BOS standart kültür, mikobakteri ve mantar kültürü

Yatışının 18. günü

07.03.2017;

- Nöroşirurji tarafından beyin biyopsisi
- **BOS kültüründe üreme yok, ARB negatif**

18-29. günler arasında seyir

- Genel durumu kötü, bilinç kapalı, IR-/-

- Ateş ara ara subfebril, sekresyonlarında azalma mevcut, diğer sistem muayanelerinde infeksiyon bulgusu yok.

- Meropenem + kolistin tedavisi devam
- Antiödem tedavisi tekrar başlandı. (deksametazon 12 mg/gün)

Patoloji

- CD 20 (+) atipik lenfositlerden oluşan neoplastik infiltrasyon

- Olguda öncelikle CD 20(+) , **büyük b hücreli lenfoma** düşünüldü.

Yatışının 29. günü

16.03.2016

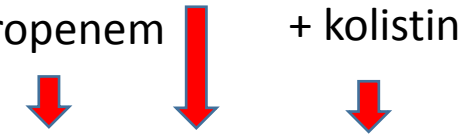
- Ateşi subfebril, AFR gerileme eğiliminde
- Meropenem (24)+ **kolistin** 18. günü

- Kreatininde artış !!!
- Kolistin dozu GFR'ye göre 2x150 mg olarak devam edildi.

(GFR: 105$_{ml/min/1.73m2}$)

+linezolid
Kateter kx

meropenem + kolistin



	21.02	26.02	29.02	01.03	03.03 (14)	16.03 (29)	
CRP (mg/L)	45	109	294	232-272	231	126	
Pct (ng/L)	0,1	0,8	1,18	0,9	0.61	0.18	
Wbc	8770	14800	17000	12400	10700	8200	
NE	6110	10100	15900	10300	8010	5400	
Plt	264000	281000	388000	336000	473000		
Kreatinin (mg/dl)	0,55	0,46	0,45	0,42	0,40	1.14	
AST (U/L)	50	90	51	44	67	54	
ALT (U/L)	50	134	92	82	93	44	
Kültürler		MRKNS					

Yatışının 32. günü

19.03.2016

- **<u>Kolistin (21. gün)</u>**, meropenem (27.gün) kesildi. (kreatinin: 2.06 mg/dl)

- CRP: 124 mg/L , prokalsitonin: 0.2 ng/L
- Ateşi yok, sekresyonları devam ediyor

+linezolid
Kateter kx
MRKNS

Meropenem + Kolistin

Ab stop

	21.02	26.02	29.02	01.03 (12)	03.03 (14)	16.03 (29)	19.03 (32)		
CRP(mg/L)	45	109	294	232-272	231	126	124		
Pct (ng/L)	0,1	0,8	1,18	0,9	0.61	0.18	0.20		
Wbc	8770	14800	17000	12400	10700	8200	10200		
NE	6110	10100	15900	10300	8010	5400	8200		
Plt	264000	281000	388000	336000	473000				
Kreatinin (mg/dl)	0,55	0,46	0,45	0,42	0,40	1.14	2.06		
AST (U/L)	50	90	51	44	67	54	36		
ALT (U/L)	50	134	92	82	93	44	10		
Kültürler		MRKNS							

Kolistin Yan Etki Gelişimi ve Yönetimi

Nefrotoksisite

- %14-19'dan %48-49'a kadar görülebilir.
- C_{col}>2.5 mg/L
- Doz bağımlı ve reversible
- 5-7. günlerde görülür.
- Risk faktörleri
  - Yüksek doz,
  - Tedavi süresi
  - Septik şok
  - Hipoalbuminemi
  - Hiperbilirubinemi
  - Obesite
  - Nefrotoksik başka ajanların kullanımı (Aminoglikozit, vankomisin)

Tran TB. Int J Antimicrob Agents. 2016;48(6):592-597.

Fiaccadori E, et al. Am J **Kidney** Dis. 2016;68(2):296-306

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

Acute kidney injury during colistin therapy: a prospective study in patients with extensively-drug resistant *Acinetobacter baumannii* infections

E. Durante-Mangoni [1], R. Andini [1], S. Signoriello [2], G. Cavezza [1], P. Murino [3], S. Buono [3], M. De Cristofaro [4], C. Taglialatela [4], M. Bassetti [5], P. Malacarne [6], N. Petrosillo [7], A. Corcione [3], C. Viscoli [8], R. Utili [1,*], C. Gallo [2]

166 hasta prospektif izlenmiş

ABY %50.6 görülmüş.

7. günde %30.6

14. günde %58.8

Yaş ve kronik böbrek hastalığı risk faktörü

Nefrotoksisite geliştikten sonra:

- Kolistinin kesilmesi
- Kesilemiyorsa doz düzenlenmesi(!!),
- Serum kolistin düzeyi bakılması
- Diğer nefrotoksiklerin kesilmesi
- Anti-oksidan kullanımı (Oksidatif stres nedeniyle) ???

Fiaccadori E, et al. Am J **Kidney** Dis. 2016;68(2):296-306

Nörotoksisite

%7 civarında görülmektedir.

Doz bağımlı ve geri dönüşlü (reversible)

- Parestezi,
- nöbet,
- görme bozuklukları,
- ataksi,
- vertigo,
- deliryum,
- nöromüsküler bozukluklar,
- apne

Fiaccadori E, et al. Am J **Kidney** Dis. 2016;68(2):296-306

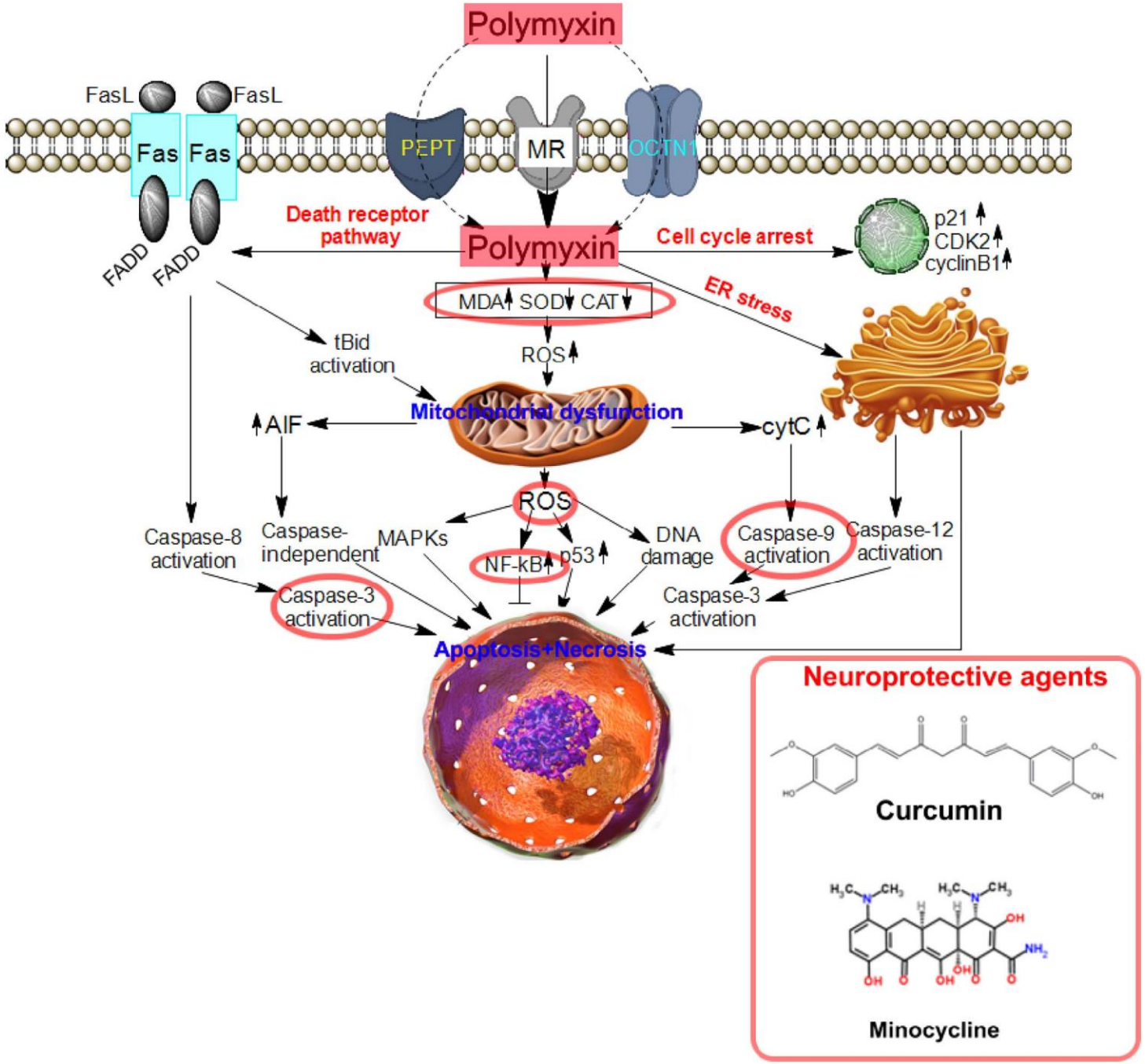


Fig. 2. Pathways of polymyxin-induced neurotoxicity and potential neuroprotective mechanism of minocycline and curcumin.

Velkov T, et al. Pharmacol Ther. 2017;S0163-7258(17)30192-4

şiran keske <sirankeske@yahoo.com> Eyl 9 saat 11:27 PM

Kime roger.nation@monash.edu

Dear Roger Nation,
First of all, thank you for your recent colistin dosing schedule that changed our practice about colistin dosing.
We have a patient with acute renal failure due to colistin use. He is 32 years old and taking chemotherapy for acute lymphocytic leukemia. His neutrophil level is "0" and he has carbapenem resistant Klebsiella pneumoniae bacteremia in his recent consecutive blood culture. His creatinin level is 3.8 and creating clearance is estimated to be about 20 mL/min. He is 80 kg weight. We are giving colistin 2x90 mg IV (18. day) plus meropenem 2x1 g IV plus amikacin 600 mg/36 h IV. Today he developed neurological signs and we think that colistin might have caused these neurological problems. Our nephrologist thinks that colistin dose is high and these neurological problems may be resulted due to high dose colistin use and should be decreased. We don't have opportunity to follow up blood colistin level. I become happy if you comment on colistin dose for our patient. What can we do now and can you help us for blood colistin dose monitoring? I look forward to hearing from you.

Best wishes,

Şiran Keske, MD
VKV American Hospital, Istanbul
Department of Infectious Diseases and Clinical Microbiology
+90 505 4657075

Roger Nation <roger.nation@monash.edu> Eyl 10 saat 3:39 AM
Kime şiran keske

Dear Şiran

Thank you for your email. It sounds like you have a difficult case to deal with.

From the information you have provided, it seems that there are several possible drug-related causes for neurological changes in such a patient. These are:

- colistin
- the other two classes of antibiotics you mentioned
- the chemotherapy (you didn't mention which agents he is receiving but as you know neurotoxicity is a potential adverse effect with some chemotherapeutic agents)
- a combination of some or all of the above

Similarly, I guess AKI is not necessarliy due solely to colistin, as some of the other agents you mention can also decrease renal function, or it could be the result of effects of a combination of drugs.
Having said that, it may well be that your nephrologist is correct in suggesting that for this patient the dose you mention (I assume it is 90 mg colistin base activity twice daily) is somewhat too high. Things to consider in deciding on a possible reduction in daily dose of IV colistin are:

- you mention that the creatinine clearance is estimated to be about 20 mL/min. If the patient is in the evolving onset stage of AKI, the increase in the serum creatinine concentration will lag behind the actual decrease in creatinine clearance (because the time to approach a new steady-state value of serum creatinine is determined by the half-life of creatinine). That is, your point-in-time estimate of creatinine clearance in a patient with evolving AKI may over-estimate the actual creatinine clearance at that point in time
- it is important to recognise that the suggested daily doses provided in Table 3 of the attached article are to achieve a plasma average steady-state colistin concentration of 2 mg/L in the 'typical' patient (as mentioned in the paper, a target of 2 mg/L was chosen to cover MICs up to the EUCAST 'breakpoint'). You haven't mentioned the colistin MIC against the isolate. If the MIC is relatively low, you may not need to be targeting 2 mg/L.
- it is very important to recognise that there is very wide inter-patient variability in the dose requirements, even for a given creatinine clearance (as shown in Figure 2 of the same paper and this is also discussed in the text of the paper). In other words, among patients with a certain creatinine clearance some will achieve the target value of 2 mg/L with a daily dose lower than that listed in Table 3.

So, as mentioned above, a reduction in daily dose may be very appropriate.

Concerning measurement of plasma colistin concentration, it is obviously not possible to get samples to Australia in a timely manner and in any case this would not be financially feasible. You could consider contacting William Couet in France (william.couet@univ-poitiers.fr) as I believe that he offers a therapeutic drug monitoring service for colistin in Europe.

I hope that this information is helpful and I especially hope for a good outcome for your patient.

Best wishes

Roger

Yatışının 34. günü

21.03.2016

- Ateş 38 °C, kültürleri tekrarlandı.

➢TPN

➢Kateter

➢Uzun süreli antibiyotik

Üreme olmadı !

- **Kaspofungin** 50 mg/gün (70mg yükleme) iv başlandı.

Yatışının 38. günü

25.03.2017

- Trakeotomi, PEG
- Kranial RT ilk seans

- Kreatinin yüksekliği için hidrasyon arttırıldı, nefrotoksik ajanlar kesildi.
- Ateşi yok, sekresyonları ve AFR geriledi, antifungal tedavisi kesildi.

Yatışının 48. günü

04.04.2016

- Antibiyoterapisiz 17. gün,
- Ateş 38.3 °C CRP:14→189 mg/L WBC: 16 bin →56 bin

YBÜ'de karbapenamaz üreten *Klebsiella pneumoniae* salgını !!!

- **Kan kültürü alındı.**
- **Meropenem 3*2 gr** 4 saatlik infüzyon (kreatinin: 1.36, GFR: 85$_{ml/min/1.73m2}$)

+ kolistin doz 3x150 mg (300 mg yükleme)

06.04.2016

Yatışının 50. günü

- **06.04.2016**: Kan ve kateter kx'de; ***K.pneumoniae***

  İdrar: ***Klebsiella pneumoniae***

Meropenem ve kolistin tedavisine devam

Santral kateter çekildi.

	16.03 (29)	19.03 (32)	04.04 (48)	06.04 (50)
CRP	126	67-14	189	290
Pct	0.18	0.20	82	18
Wbc	8200	10200	56000	32200
NE	5400	8200	52000	31100
Kre	1.14	2.06	1.36	1.38
AST	54	36	41	41
ALT	44	10	79	79

KAN KÜLTÜRÜ

İstem Zamanı 04/04/2016 13:18 | Barkod Zamanı 04/04/2016 13:16 | Örne 04/04

Kan Kültürü Kol 1.Şişe

Materyal : **KAN**

Boyama :

Gram Boyama: Gr (-) çomak,

Açıklama : imipenem mık >32 ug/ml
meropenem mık >32 ug/ml
ertapenem mık >32 ug/ml
kolistin mık 4 ug/ml

Bakteri 1 : Escherichia coli

Bakteri 2 : Klebsiella pneumoniae

	Organizma
Antibiyogram	Klebsiella pneumoniae
AMIKACIN	Duyarlı
AMOXİCİLLİN-CLAVULANATE (F)	Dirençli
AMPICILLIN	Dirençli
AZTREONAM	Dirençli
CEFEPIME	Dirençli
CEFTAZIDIME	Dirençli
CEFTRIAXONE	Dirençli
CEFUROXİME	Dirençli
CIPROFLOXACIN	Dirençli
ERTAPENEM	
GENTAMICIN	
KOLİSTİN	
MEROPENEM	
NETILMICIN	
PIPERACILLIN	
PIPERACILLIN-TAZOBA	
TMP / SXT	
TİGESİKLİN	Duyarlı
İMİPENEM	Dirençli

MİKROBİYOLOJİ

İstem Zamanı 07/04/2016 15:43 | Barkod Zamanı 07/04/2016 15:41 | Örnek Alma Za 07/04/2016 15:4

KATATER (Santralvenöz)

Materyal : **KATETER**

Bakteri 1 : Klebsiella pneumoniae

Direnç Belirteci: *Isolate tested res. to one or more carbapenems*

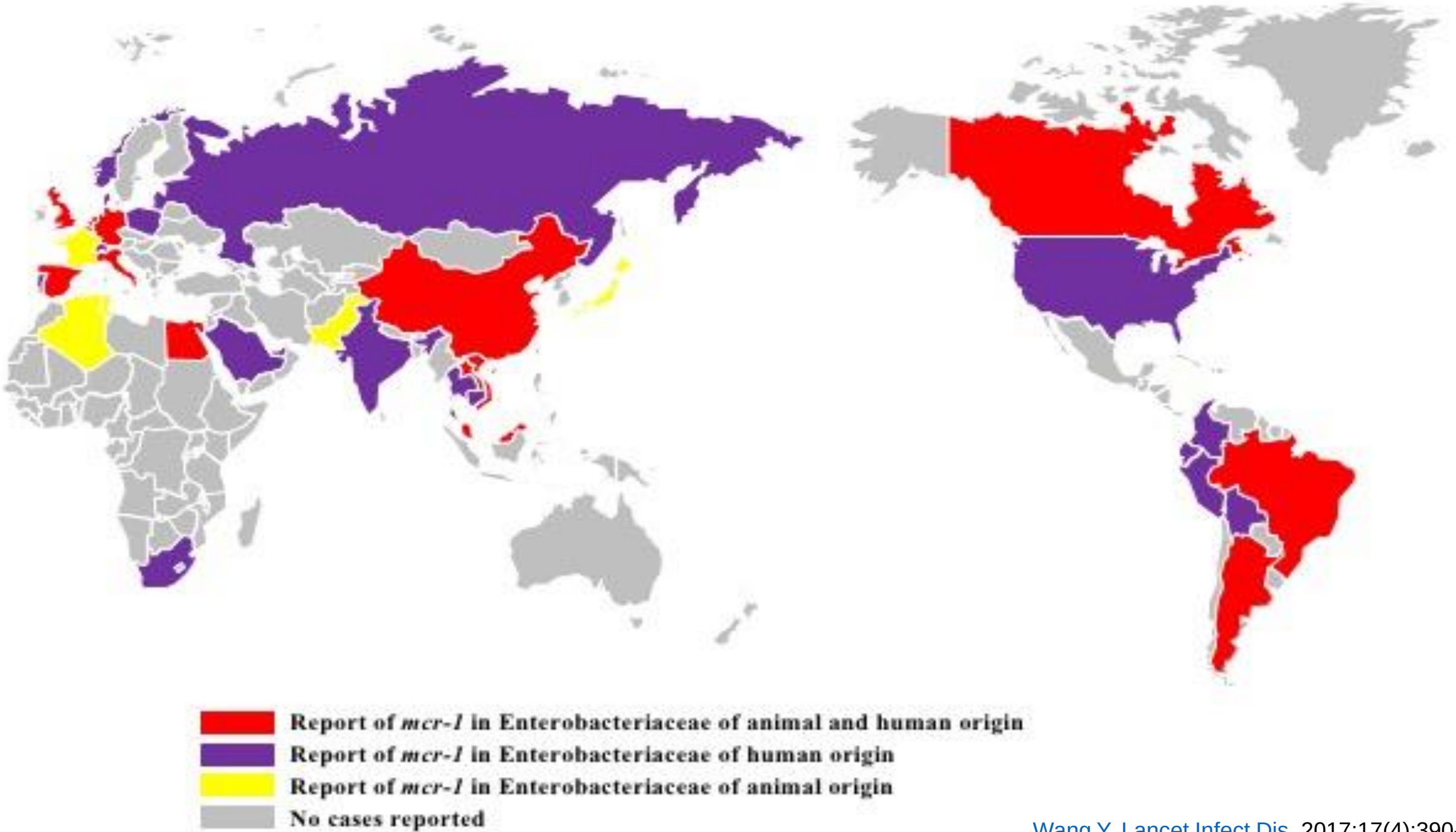
	Organizma
Antibiyogram	Klebsiella pneumoniae
AMIKACIN	Duyarlı
AMOXİCİLLİN-CLAVULANATE (F)	Dirençli
AMPICILLIN	Dirençli
AMPICILLIN/ SULBACTAM	Dirençli
AZTREONAM	Dirençli
CEFEPIME	Dirençli
CEFOXITIN	Dirençli
CEFTAZIDIME	Dirençli
CEFTRIAXONE	Dirençli
CEFUROXİME	Dirençli
CIPROFLOXACIN	Dirençli
TİGESİKLİN	Orta Duyarlı
İMİPENEM	Dirençli

imipenem mık >32 ug/ml
meropenem mık >32 ug/ml
ertapenem mık >32 ug/ml
kolistin mık 4 ug/ml

Siz olsanız ne yapardınız?

Kolistin duyarlığı doğru bakılıyor mu?

Kolistin Dirençli Klebsiella İnfeksiyonları ve Yönetimi



Wang Y. Lancet Infect Dis. 2017;17(4):390-9.

Risk factors for bloodstream infections due to colistin-resistant KPC-producing *Klebsiella pneumoniae*: results from a multicenter case–control–control study

D. R. Giacobbe[1], V. Del Bono[1], E. M. Trecarichi[2], F. G. De Rosa[3], M. Giannella[4], M. Bassetti[5], A. Bartoloni[6], A. R. Losito[2], S. Corcione[3], M. Bartoletti[4], E. Mantengoli[6], C. Saffioti[1], N. Pagani[3], S. Tedeschi[4], T. Spanu[7], G. M. Rossolini[8,9,10], A. Marchese[11], S. Ambretti[11], R. Cauda[2], P. Viale[4], C. Viscoli[1] and M. Tumbarello[2], for ISGRI-SITA (Italian Study Group on Resistant Infections of the Società Italiana Terapia Antinfettiva)

1) *Infectious Diseases Division, University of Genoa (DISSAL) and IRCCS San Martino-IST, Genoa,* 2) *Institute of Infectious Diseases, Catholic University of the Sacred Heart, A. Gemelli Hospital, Rome,* 3) *Department of Infectious Diseases, Amedeo di Savoia Hospital, University of Turin, Turin,* 4) *Clinic of Infectious Diseases, University of Bologna, S. Orsola-Malpighi Hospital, Bologna,* 5) *Infectious Disease Division, Santa Maria Misericordia University Hospital, Udine,* 6) *Infectious and Tropical Diseases Unit, Careggi Hospital, Department of Experimental and Clinical Medicine, University of Florence, Florence,* 7) *Institute of Microbiology, Catholic University of the Sacred Heart, A. Gemelli Hospital, Rome,* 8) *Department of Medical Biotechnologies, University of Siena,*

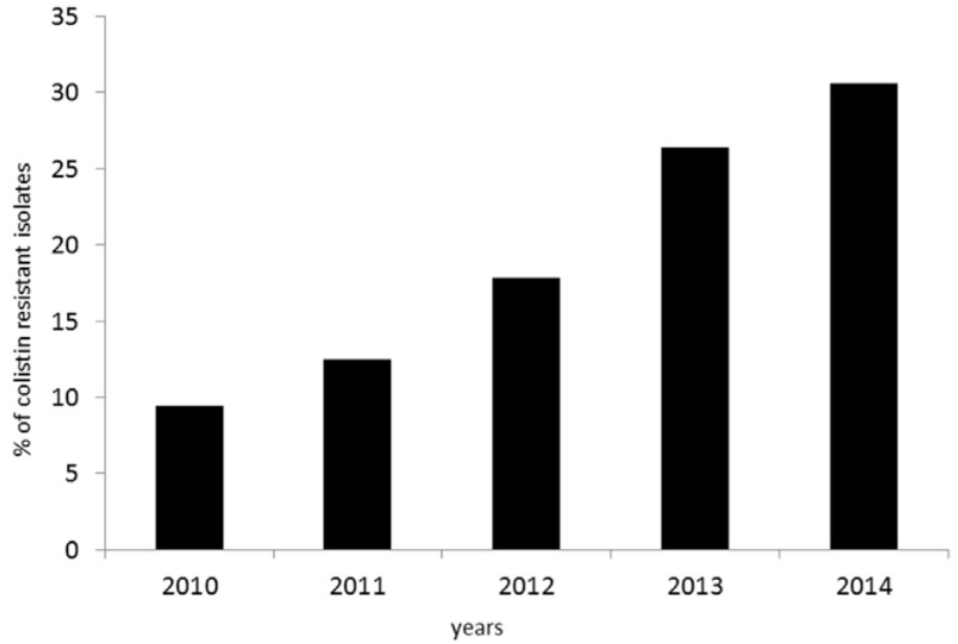


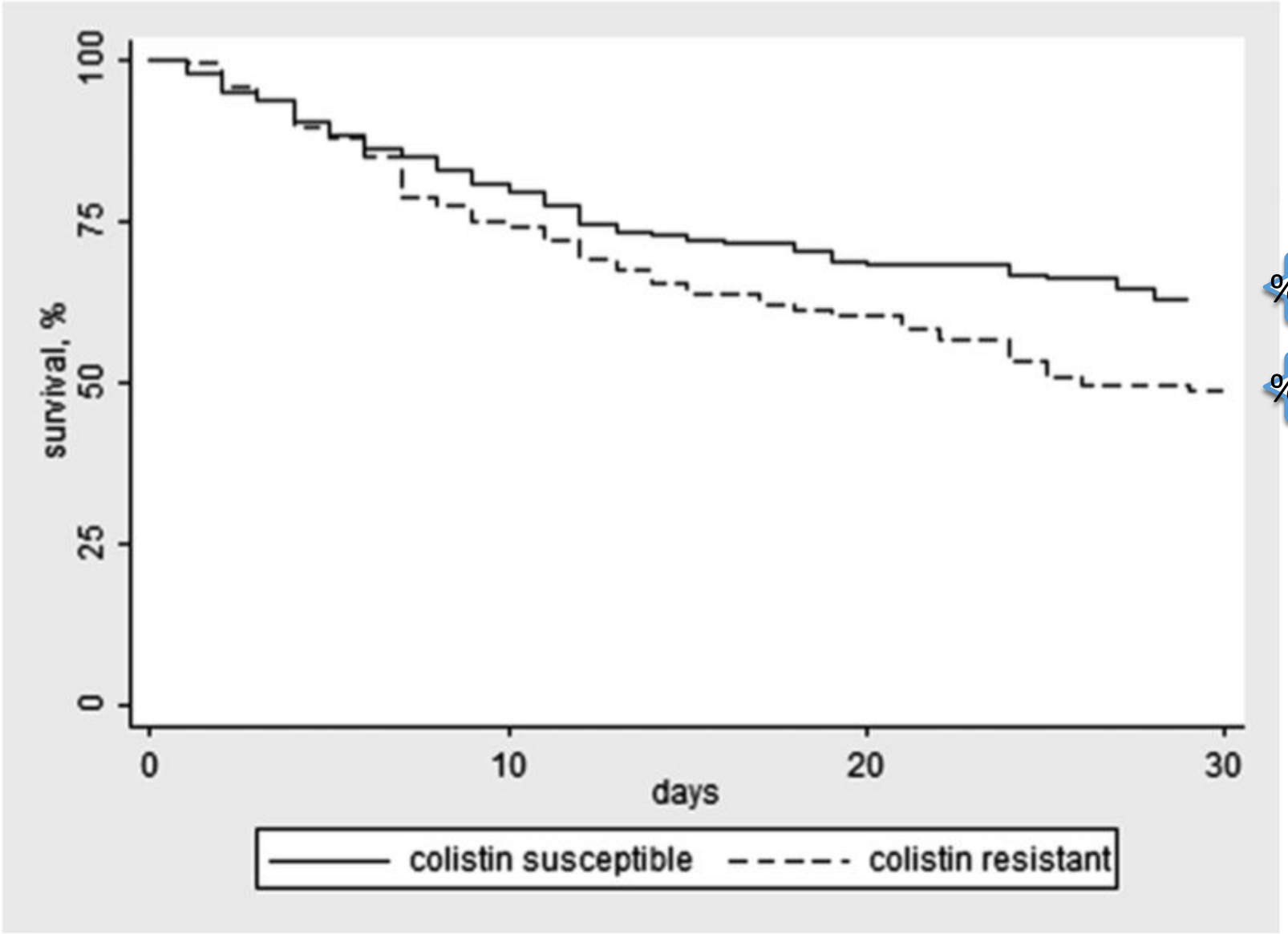
FIG. 1. Increase in colistin resistance (ColR) among blood *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* isolates during the study period (χ^2 for trend, p <0.001).

İtalyada 6 eğitim hastanesinde yapılmış.

TABLE 2. Multivariate analysis of risk factors for BSI caused by colistin-resistant KPC-Kp[a]

Control group and risk factors	OR (95% CI)	p
Control group A (patients without KPC-Kp infection)[b]		
Previous colistin administration	24.51 (8.75–68.67)	<0.001
Previous colonization with KPC-Kp	18.71 (8.05–43.51)	<0.001
Previous ≥3 hospitalization	5.32 (2.48–11.38)	<0.001
Charlson score ≥3	2.84 (1.52–5.29)	0.001
Neutropenia	2.72 (1.02–7.23)	0.04
Control group B (patients with BSI due to colistin-susceptible KPC-Kp)[c]		
Previous colistin administration	6.88 (3.55–13.34)	<0.001
Previous colonization with KPC-Kp	2.40 (1.46–3.97)	0.001
Charlson score ≥3	2.97 (1.74–5.06)	<0.001

Giacobbe DR, et al. *Clin Microbiol Infect* 2015; 21: 1106.e1–8



%61

%49

p= 0.02

FIG. 2. Kaplan-Meier survival curves of patients with bloodstream infection due to *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* according to colistin resistance or susceptibility of isolates.

Giacobbe DR, et al. *Clin Microbiol Infect* 2015; 21: 1106.e1–8

J Antimicrob Chemother 2015; 70: 905 – 913
doi:10.1093/jac/dku432 Advance Access publication 25 October 2014

Journal of Antimicrobial Chemotherapy

Gentamicin therapy for sepsis due to carbapenem-resistant and colistin-resistant *Klebsiella pneumoniae*

Marcelino Gonzalez-Padilla[1]†, Julián Torre-Cisneros[1,2]*†, Francisco Rivera-Espinar[3], Antonio Pontes-Moreno[3], Lorena López-Cerero[2,4,5], Alvaro Pascual[2,4,5], Clara Natera[1], Marina Rodríguez[3], Inmaculada Salcedo[6], Fernando Rodríguez-López[2,7], Antonio Rivero[1] and Jesús Rodríguez-Baño[2,4,5]

İspanya
2012 Haziran-2013 Şubat
K. pneumoniae, 50 olgu

Table 2. Antibiotics used in 50 patients with severe infection caused by carbapenem-resistant and colistin-resistant *K. pneumoniae*

	Number (%) of patients					
	optimal	mortality	suboptimal	mortality	total	mortality
Empirical treatment	6 (8.0)	2 (33.3)	44 (92.0)	17 (38.6)	50	19 (38.0)
tigecycline	4 (66.6)	2 (50.0)	0	0	4 (8.0)	2 (50.0)
tigecycline + gentamicin	2 (33.3)	0	0	0	2 (4.0)	0
fosfomycin	0	0	1 (2.2)	0	1 (2.0)	0
meropenem	0	0	18 (40.9)	8 (44.4)	18 (36.0)	8 (44.4)
piperacillin/tazobactam	0	0	7 (15.9)	0	7 (14.0)	0
amoxicillin/clavulanic acid	0	0	2 (4.5)	0	2 (4.0)	0
others	0	0	16 (36.4)	9 (56.2)	16 (32.0)	9 (56.2)
Targeted treatment	37 (74.0)	9 (24.3)	13 (26.0)	10 (76.9)	50	19 (38.0)
monotherapy	16 (43.2)	4 (25.0)	6 (46.2)	5 (83.3)	22 (44.0)	9 (40.9)
tigecycline	8 (21.6)	3 (37.5)	1 (7.7)	0	9 (18.0)	3 (33.0)
high-dose tigecycline	3 (8.1)	0	0	0	3 (6.0)	0
gentamicin	8 (21.6)	1 (12.5)	0	0	8 (16.0)	1 (12.5)
meropenem	0	0	5 (38.5)	5 (100)	5 (10.0)	5 (100)
combination therapy	21 (56.7)	5 (23.8)	7 (53.8)	5 (71.4)	28 (56.0)	10 (35.7)
tigecycline + gentamicin	21 (56.7)	5 (23.8)	0	0	21 (42.0)	5 (23.8)
high-dose tigecycline	7 (18.9)	1 (14.3)	0	0	7 (14.0)	1 (14.3)
meropenem + fosfomycin	0	0	1 (7.7)	1 (100)	1 (2.0)	1 (100)
tigecycline + colistin	0	0	1 (7.7)	1 (100)	1 (2.0)	1 (100)
high-dose tigecycline	0	0	1 (7.7)	1 (100)	1 (2.0)	1 (100)
meropenem + colistin ± fosfomycin	0	0	5 (38.5)	3 (60.0)	5 (10.0)	3 (60.0)

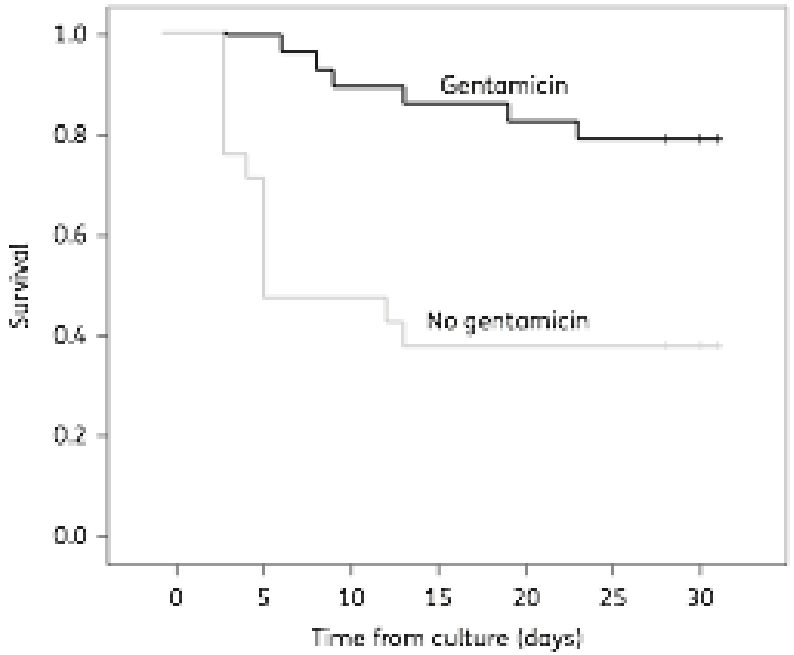
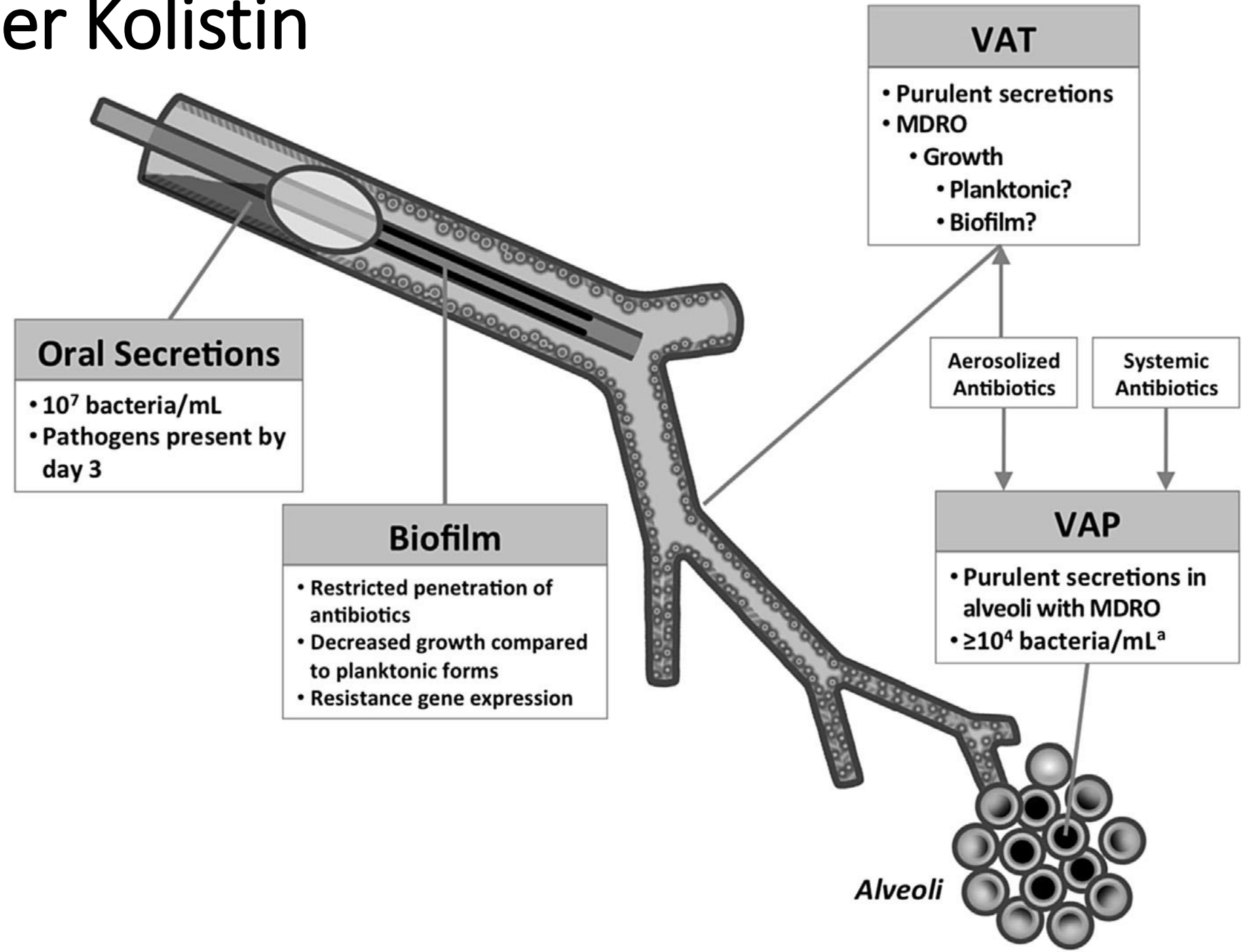


Figure 1. Kaplan–Meier curves showing the impact of targeted treatment with gentamicin on survival at 30 days in patients with severe infection caused by carbapenem-resistant and colistin-resistant *K. pneumoniae* (log-rank test 11.9, $P=0.001$).

Akciğer odak olsaydı inhaler antibiyotik kullanır mıydınız?

İnhaler Kolistin



Box 1
Inhaled antibiotics used in mechanically ventilated patients for respiratory infection: off-label use and Food and Drug Administration approved

Amikacin

Amikacin proprietary preparation[a]

Amikacin/fosfomycin proprietary preparation[b]

Colistin

Colistin methanesulfonate[c]

Ceftazidime

Gentamicin

Tobramycin

Tobramycin proprietary preparation[d]

Sisomicin

Vancomycin

[a] Phase 3 enrolling patients. Delivered by Bayer Healthcare with proprietary pulmonary drug delivery system.

[b] Phase 1 completed. Delivered with Pari investigational eFlow inline nebulizer.

[c] Prodrug of colistin polymyxin E.

[d] FDA approved for spontaneous breathing patients with cystic fibrosis known to be colonized with *P aeruginosa*.

From Palmer LB. Ventilator-associated infection: the role for inhaled antibiotics. Curr Opin Pulm Med 2015;21:239–49.

Aerosolized plus Intravenous Colistin versus Intravenous Colistin Alone for the Treatment of Ventilator-Associated Pneumonia: A Matched Case-Control Study

Diamantis P. Kofteridis,[1] Christina Alexopoulou,[2] Antonios Valachis,[1] Sofia Maraki,[3] Dimitra Dimopoulou,[1] Dimitrios Georgopoulos,[2] and George Samonis[1]

Departments of [1]Internal Medicine, [2]Intensive Care Unit, [3]Clinical Microbiology, University Hospital of Heraklion, Crete, Greece

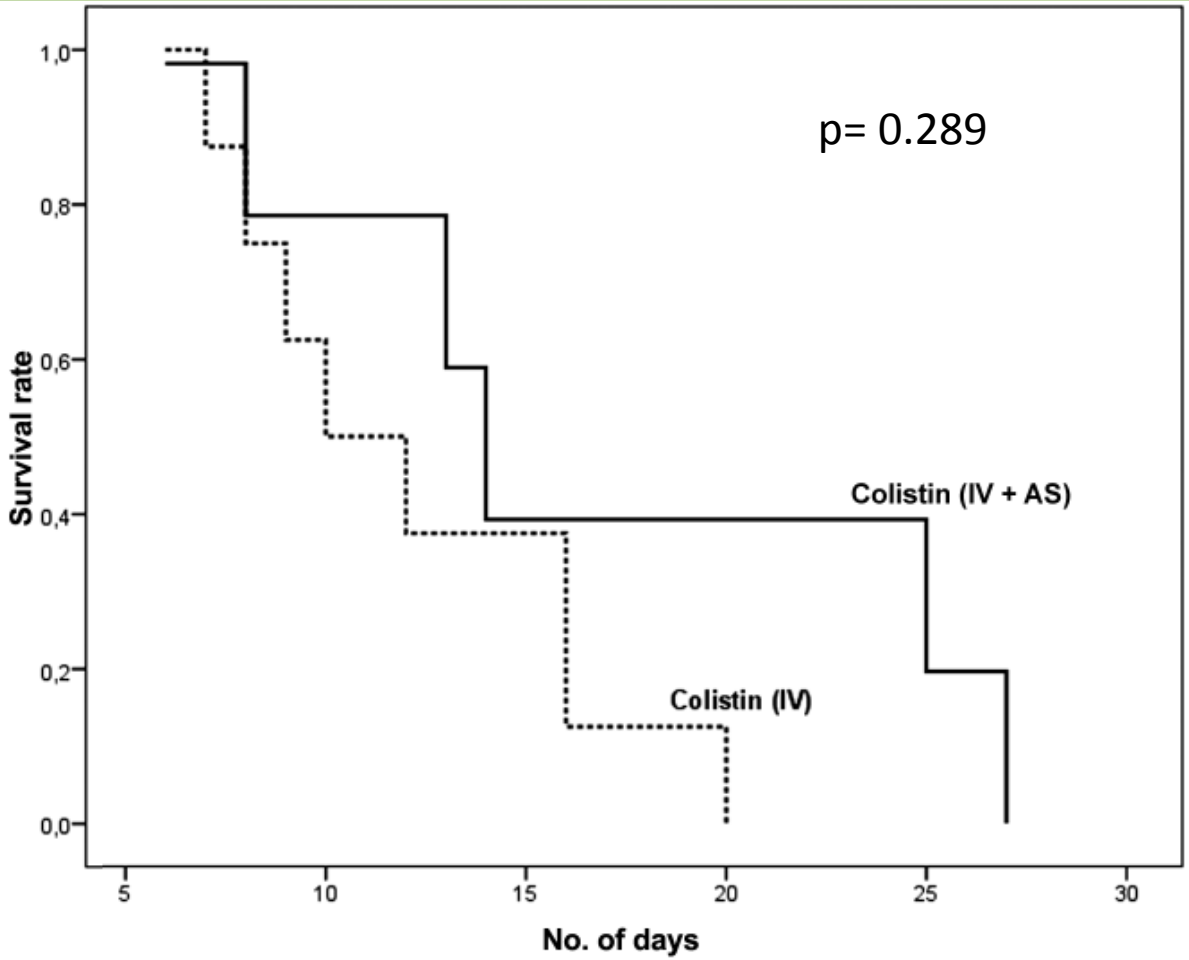


Figure 2. Ventilator-associated pneumonia–related mortality in the 2 treatment groups. AS, aerosolized; IV,

Kofteridis DP, et al Clin Infect Dis. 2010 ;51(11):1238-44.

The Role of Aerosolized Colistin in the Treatment of Ventilator-Associated Pneumonia: A Systematic Review and Metaanalysis*

Valachis, Antonis MD, PhD[1]; Samonis, George MD, PhD[2]; Kofteridis, Diamantis P. MD, PhD[2]

Critical Care Medicine: March 2015 - Volume 43 - Issue 3 - p 527–533

- İnhaler kolistin
- Mikrobiyolojik eradikasyon arttı
- Enfeksiyona bağlı mortalite azaldı
- Kaba mortalite hızı değişmedi
- İnhaler kolistin verilebilir.

Valachis A. Crit Care Med. 2015;43(3):527-33.

Clinical Infectious Diseases

IDSA GUIDELINE

Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society

IV kolistin’e inhaler kolistin eklenebilir (Zayıf kanıt düzeyi).

Table 1
Toxicity related to aerosolized antibiotics

Drug	Adverse Events
Aminoglycosides	Bronchial Constriction Renal toxicity[a] Tinnitus, vestibular Toxicity, hoarseness
Colistin	Nephrotoxicity[b] Bronchospasm[b] Neurologic toxicity
Aztreonam lysine	Cough, bronchoconstriction
Vancomycin	Not well described
Cefotaxime/ceftazidime	Not well described

İntratekal kolistin kullanımı

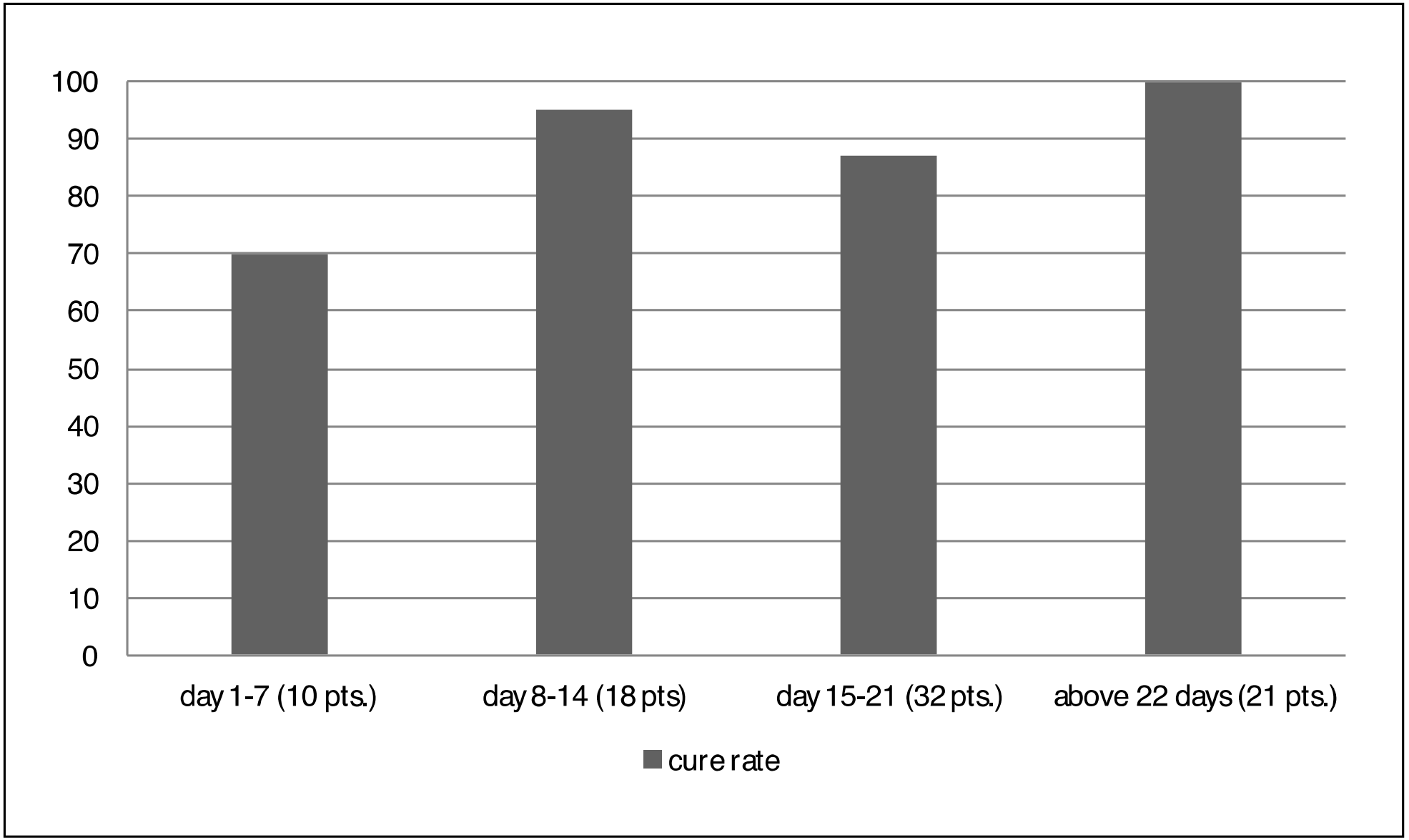
- IV kolistin ile SSS'de etkin tedavi düzeyine ulaşmak mümkün değil.
- Intratekal/intraventriküler uygulama önerilir.
- Doz: 10 mg/gün

Tran TB. Int J Antimicrob Agents. 2016;48(6):592-7.

Tunkel AR, et al. *Clin. Infect. Dis*. 2004;39:1267-84 (IDSA)

Velkov T, et al. Pharmacol Ther. 2017;S0163-7258(17)30192-4

Intratekal kolistin kullanım süresine göre tedavi başarısı

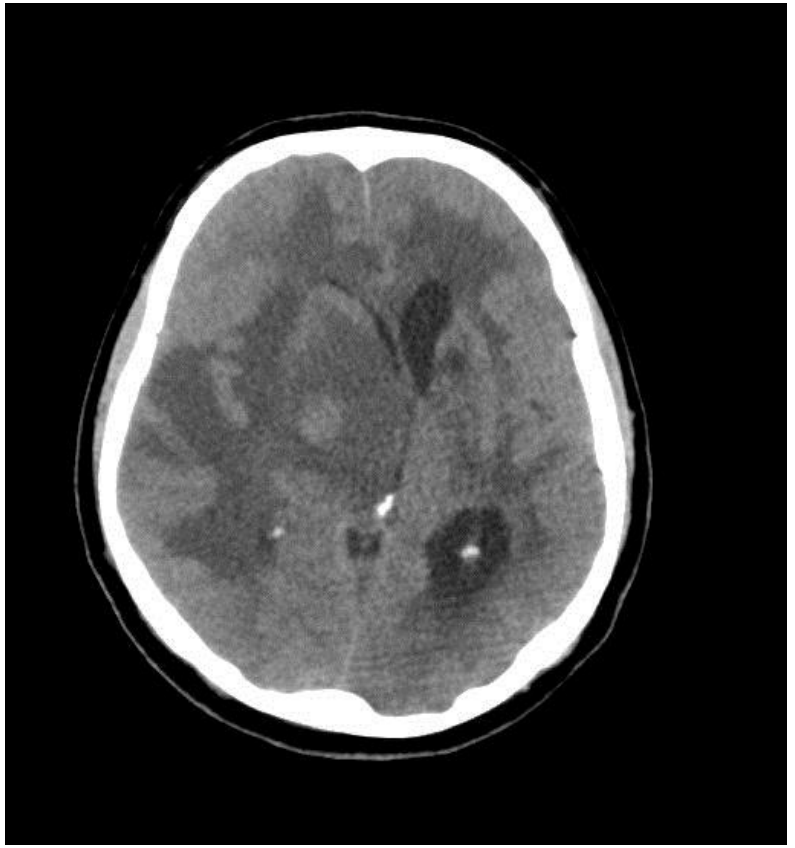


Bargiacchi O, De Rosa FG. Infez Med. 2016;24(1):3-11

Yatışının 58. günü

14.04.2016

- Hasta infeksiyon açısından kontrol altında
- Kontrol kan- kateter kültüründe üreme olmadı
- Kan- kateter kültüründe *K.pneumoniae* üremesinin 10. günü
- İntrakranial shift nedeniyle exitus!



+linezolid
Kateter kx

Meronem+
kolistin

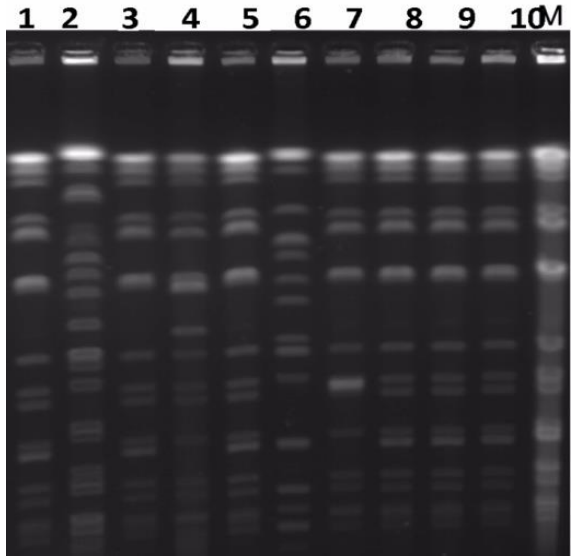
Kan-kateter kx;
K.pneumoniae

Meropenem + kolistin Ab stop ex

	21.02	26.02	29.02	01.03	03.03 (14)	16.03 (29)	19.03 (32)	04.04 (48)	06.04 (50)	10.04 (54)	14.04 (58)
CRP(mg/L)	45	109	294	232-272	231	126	67-14	189	290	13	7.8
Pct (ng/L)	0,1	0,8	1,18	0,9	0.61	0.18	0.20	82	18	1.18	0.6
Wbc	8770	14800	17000	12400	10700	8200	10200	56000	32200	8750	7800
NE	6110	10100	15900	10300	8010	5400	8200	52000	31100	7200	6100
Plt	264000	281000	388000	336000	473000						
Kreatinin (mg/dl)	0,55	0,46	0,45	0,42	0,40	1.14	2.06	1.36	1.38	1.16	1.02
AST (U/L)	50	90	51	44	67	54	36	41	41	23	25
ALT (U/L)	50	134	92	82	93	44	10	79	79	62	45
Kültürler		MRKNS							***K.pneumoniae***		

- **Beş ay içinde YBÜ'de yatan 21 hasta**
- **Mikrobiyolojik örneklerinde karbapenem ve kolistine dirençli *K. Pneumoniae* (KKDK)**
- **SALGIN !!!**
- **Rektal sürüntü ve ortam kültürleri**

Salgın yönetimi



PFGE ile oluşan bantlar (1,3-5,7-10; temsili EYBÜ ilişkili salgın izolatları, 2,6; salgınla ilişkisiz hasta ve kolonizasyon izolatları)

- **‘Pulse field’ jel elektroforez (PFGE)**
- **İnfüzyon pompası, aynı suş (dış merkezden gelen 2 hasta hariç)**
- **8/14 rektal kolonizasyon, 3/8 enfekte**
- **OXA-48 geni pozitif, NDM geni negatif**

İnfeksiyon kaynağının bulunması ve kontrolü? Ortam kültürü, tarama kültürü alınmalı mı?

World Health Organization

Table 6.72 Percentage of resistance for *E. coli* and *K. pneumoniae* among blood and CSF isolates in Turkey in 2015

	E. coli		*K. pneumoniae*	
	n	Resistance (%)	*n*	Resistance (%)
Aminopenicillins (R)	2730	78	NA	NA
Aminoglycosides (R)	4108	28	2550	44
Fluoroquinolones (R)	3996	48	2518	48
Fluoroquinolones (I+R)	3996	49	2518	52
Third-generation cephalosporins (R)	3852	51	2489	68
Third-generation cephalosporins (I+R)	3852	53	2489	70
Carbapenems (R)	3914	2	2533	30
Carbapenems (I+R)	3914	5	2533	35
Multidrug resistance (R)	4054	16	2510	32

Teşekkürler…