

# **ANTİBİYOTİKLERİN KULLANIMINDA ZOR KARARLAR**

Dr. Şıran Keske  
VKV Amerikan Hastanesi  
İnfeksiyon Hastalıkları Bölümü

| Developed indicators                                                               | Number of articles mentioning the indicator / total number of articles | Percentage of articles mentioning the indicator |
|------------------------------------------------------------------------------------|------------------------------------------------------------------------|-------------------------------------------------|
| Prescribe empirical antibiotic therapy according to (local or national) guidelines | 10/14                                                                  | 71                                              |
| Switch from intravenous to oral therapy                                            | 9/14                                                                   | 64                                              |
| Perform at least two sets of blood cultures                                        | 8/14                                                                   | 57                                              |
| Change to pathogen-directed therapy when culture results become available          | 8/14                                                                   | 57                                              |
| Timely initiation of antibiotic therapy                                            | 7/14                                                                   | 50                                              |
| Adapt dose and dosing interval of antibiotics to renal function                    | 7/14                                                                   | 50                                              |
| Documentation of antibiotic plan in medical record                                 | 7/14                                                                   | 50                                              |
| Perform a site culture                                                             | 6/14                                                                   | 43                                              |
| Discontinue antibiotic therapy if infection not confirmed                          | 6/14                                                                   | 43                                              |
| Duration of antibiotic therapy                                                     | 6/14                                                                   | 43                                              |

**PARENTERAL TEDAVİDEN  
ORAL TEDAVİYE NE ZAMAN  
GEÇELİM?**

# **Antibiotic stewardship and early discharge from hospital: impact of a structured approach to antimicrobial management**

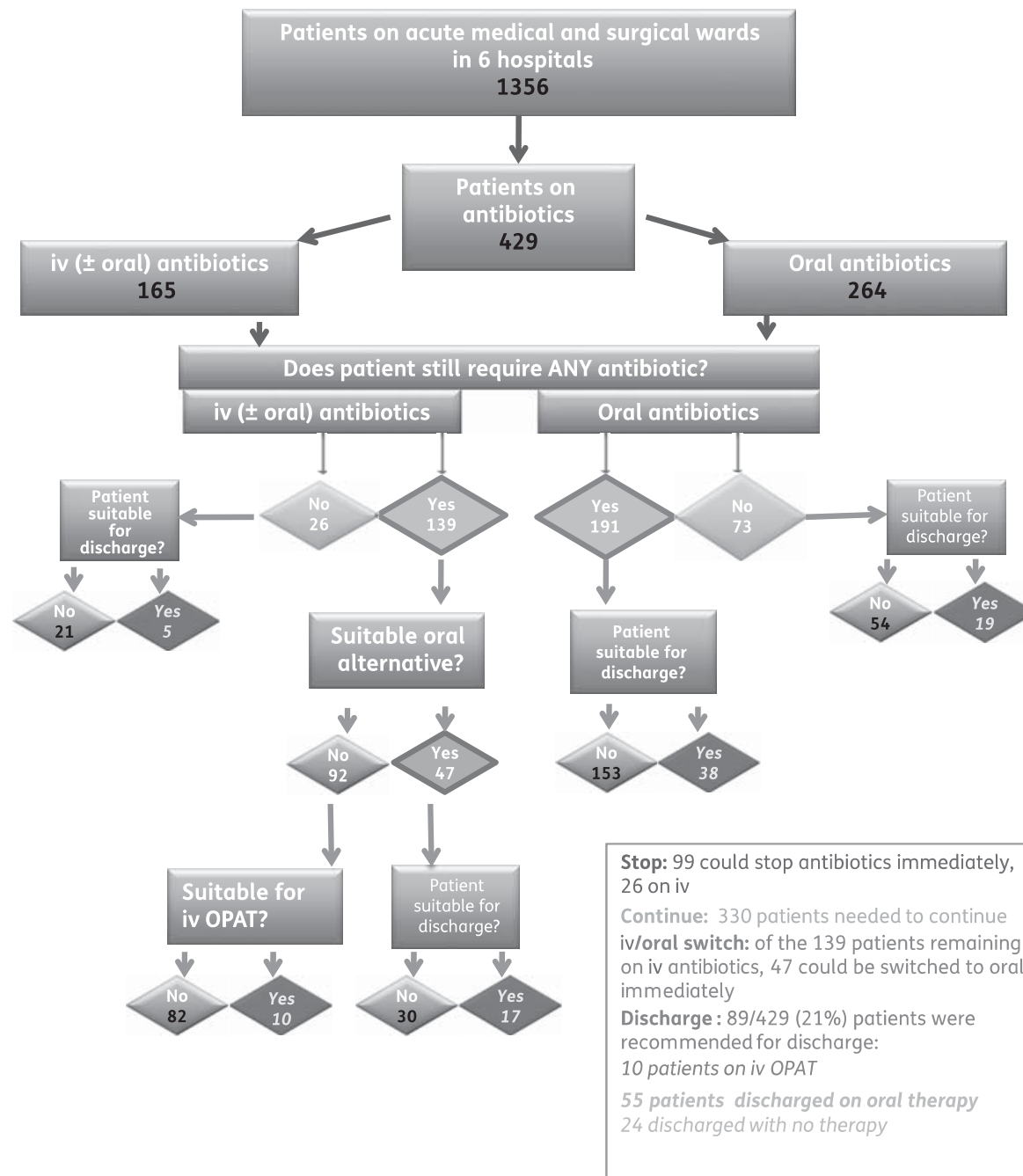
**M. Dryden<sup>1\*</sup>, K. Saeed<sup>1</sup>, R. Townsend<sup>2</sup>, C. Winnard<sup>2</sup>, S. Bourne<sup>1</sup>, N. Parker<sup>1</sup>, J. Coia<sup>3</sup>, B. Jones<sup>3</sup>, W. Lawson<sup>4</sup>,  
P. Wade<sup>5</sup>, P. Howard<sup>6</sup> and S. Marshall<sup>7</sup>**

<sup>1</sup>Royal Hampshire County Hospital, Winchester SO22 5DG, UK; <sup>2</sup>Northern General Hospital, Sheffield S5 7AU, UK; <sup>3</sup>Glasgow Royal Infirmary, Glasgow G31 2ER, UK; <sup>4</sup>Imperial College Healthcare NHS Trust, London, UK; <sup>5</sup>Guys & St Thomas's NHS Foundation Trust, London SE1 7EH, UK; <sup>6</sup>Leeds Teaching Hospitals NHS Trust, Leeds LS1 3BR, UK; <sup>7</sup>pH Associates, Marlow SL7 1PG, UK

\*Corresponding author. Tel: +44-1962-824451; Fax: +44-1962-825431; E-mail: matthew.dryden@hhft.nhs.uk

**Criteria for antibiotic change and early discharge: X – not essential, ☒ - essential**

|                                                                                            | iv/oral switch                      | Stop Abx                            | Early discharge                     |
|--------------------------------------------------------------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|
| Appropriate duration for clinical focus based on guidelines/accepted practice              | ×                                   | <input checked="" type="checkbox"/> | ×                                   |
| Able to tolerate and absorb oral Abx                                                       | <input checked="" type="checkbox"/> | ×                                   | ×                                   |
| Infection is resolving clinically and inflammatory markers (WBC count and CRP) are falling | <input checked="" type="checkbox"/> | <input checked="" type="checkbox"/> | <input checked="" type="checkbox"/> |
| No sepsis syndrome                                                                         | <input checked="" type="checkbox"/> | <input checked="" type="checkbox"/> | <input checked="" type="checkbox"/> |
| Patient has no comorbidities that may preclude them from being sent home                   | ×                                   | ×                                   | <input checked="" type="checkbox"/> |
| Patient is medically fit for discharge                                                     | ×                                   | ×                                   | <input checked="" type="checkbox"/> |
| Post-discharge care plan in place                                                          | ×                                   | ×                                   | <input checked="" type="checkbox"/> |



89 hasta taburcu edilmiş

47 hastada IV'den oral tedaviye geçilmiş.

**Figure 2.** Summary of early discharge and antibiotic management data.

RESEARCH ARTICLE

Open Access

# Is switching to an oral antibiotic regimen safe after 2 weeks of intravenous treatment for primary bacterial vertebral osteomyelitis?

Baharak Babouee Flury<sup>1\*</sup>, Luigia Elzi<sup>1</sup>, Marko Kolbe<sup>2</sup>, Reno Frei<sup>3</sup>, Maja Weisser<sup>1</sup>, Stefan Schären<sup>4</sup>, Andreas F Widmer<sup>1</sup> and Manuel Battegay<sup>1</sup>

## Abstract

**Background:** Vertebral osteomyelitis (VO) may lead to disabling neurologic complications. Little evidence exists on optimal antibiotic management.

**Methods:** All patients with primary, non-implant VO, admitted from 2000–2010 were retrospectively analyzed. Patients with endocarditis, immunodeficiency, vertebral implants and surgical site infection following spine surgery were excluded. Persistence of clinical or laboratory signs of inflammation at 1 year were defined as treatment failure. Logistic regression was used to estimate the odds ratios (OR) of switch to an oral regimen after 2 weeks.

## **Conclusion**

Our results suggest that switching to an oral antibiotic regimen after two weeks of intravenous therapy is safe in immunocompetent patients for primary non-implant vertebral osteomyelitis if epidural or paravertebral abscesses have been drained and if an oral antibiotic therapy with documented susceptibility, high bio-availability and bactericidal activity is available. Our results should be confirmed by a prospective randomized controlled trial.



# Earlier switching from intravenous to oral antibiotics owing to electronic reminders☆☆



Patrick E. Beeler<sup>a</sup>, Stefan P. Kuster<sup>b</sup>, Emmanuel Eschmann<sup>a</sup>, Rainer Weber<sup>b</sup>, Jürg Blaser<sup>a,\*</sup>

<sup>a</sup> Research Center for Medical Informatics, University Hospital Zurich and University of Zurich, Zurich, Switzerland

<sup>b</sup> Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich and University of Zurich, Zurich, Switzerland

IV antibiyotğin 60. saatinde bilgisayar bazlı uyarı sistemi aktive oluyor ve bir algoritma oluşuyor.

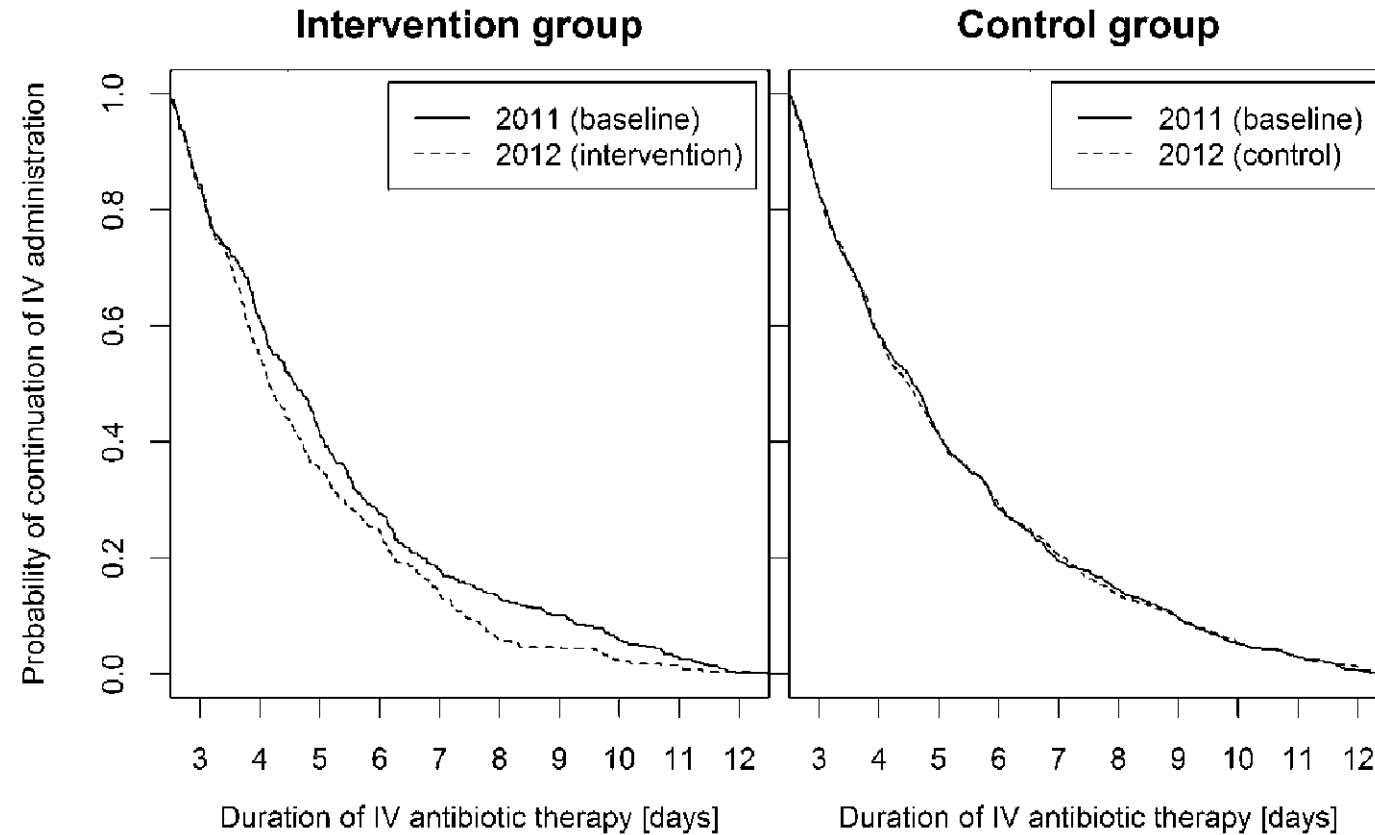


Fig. 1. Kaplan–Meier curves of the duration of intravenous (IV) antibiotic therapies that were switched to oral therapy within the time frame of 60–300 h in the intervention group ( $P=0.0059$ ) and the control group ( $P=0.88$ ).

# Efficacy of early switch from intravenous to oral antimicrobials in patients with aspiration pneumonia: A prospective observational study

**Table 1 – Novel switch criteria for aspiration pneumonia.**

**Vital signs stability\***

Body temperature  $\leq 38^{\circ}\text{C}$

Respiratory rate  $\leq 24$  breaths/min

Pulse rate  $\leq 100$  beats/min

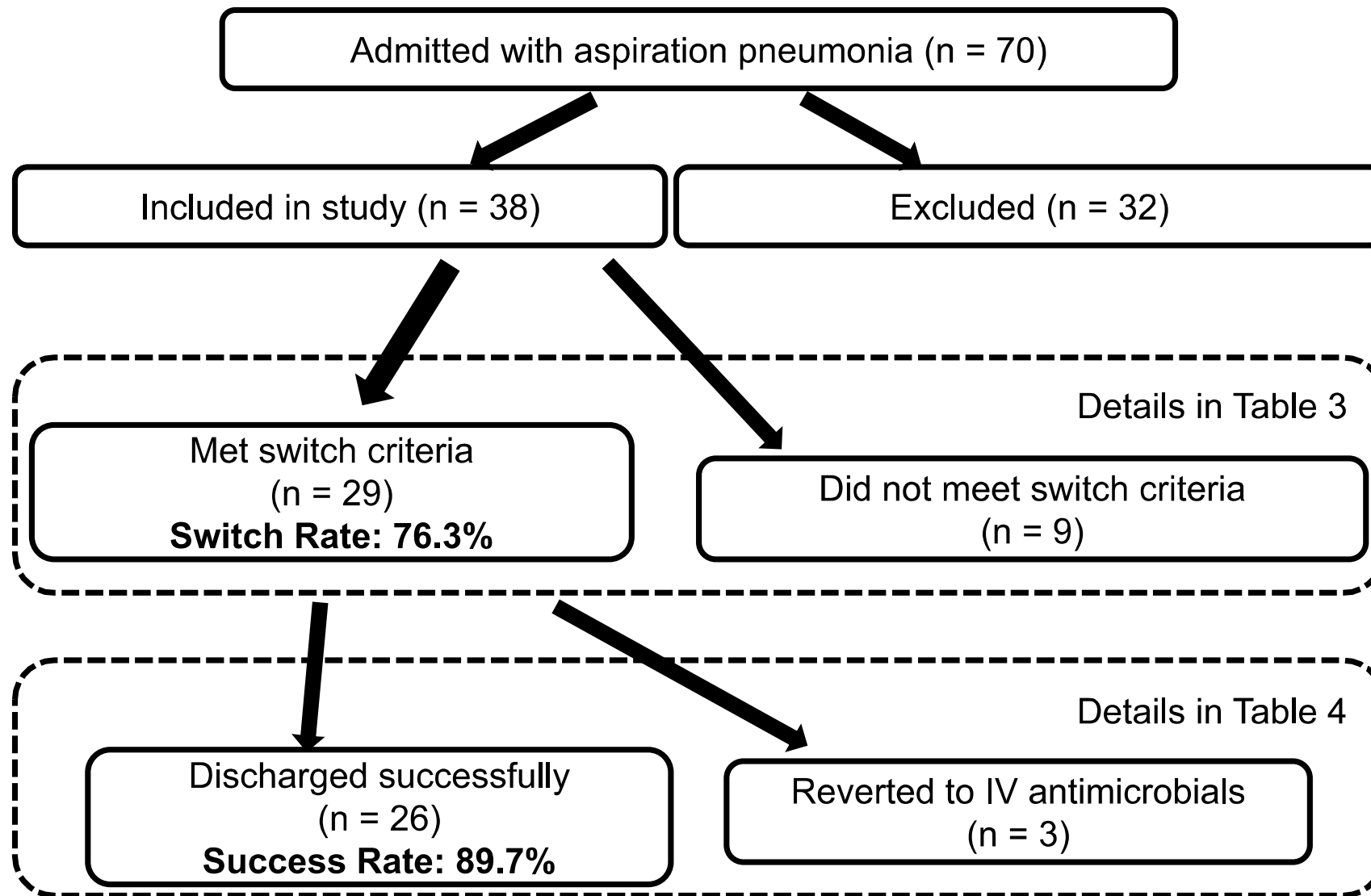
**Swallowing ability**

Repetitive saliva swallowing test  $\geq 2$

Modified water swallow test  $\geq 4$

All the criteria listed above should be met prior to switching to oral antimicrobials.

\* Vital signs stability should be maintained consistently for  $\geq 24$  h.



**Fig. 3 – Summary of results.**

# **KOLİSTİN DOZU**

# Population Pharmacokinetics of Colistin Methanesulfonate and Formed Colistin in Critically Ill Patients from a Multicenter Study Provide Dosing Suggestions for Various Categories of Patients<sup>▽</sup>



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

24 October 2014  
EMA/643444/2014

European Medicines Agency completes review of  
polymyxin-based medicines

Recommendations issued for safe use in patients with serious infections  
resistant to standard antibiotics

| Colistimethate sodium (IU) | Colistimethate sodium (mg) | Colistin-base activity (CBA) (mg) <sup>1</sup> |
|----------------------------|----------------------------|------------------------------------------------|
| 12 500                     | 1                          | 0.4                                            |
| 150 000                    | 12                         | 5                                              |
| 1 000 000                  | 80                         | 34                                             |
| 4 500 000                  | 360                        | 150                                            |
| 9 000 000                  | 720                        | 300                                            |

- Günlük doz 9 milyon IU. 2-3 seferde.
- Ciddi infeksiyonlarda 9 milyon IU yükleme dozu.
- Kan beyin bariyerini geçerek etkin doza ulaşamadığı için intraventriküler uygulanabilir. En fazla 125 bin IU/gün
- İnhalasyon dozu ise 1-2 milyon IU. 2-3 seferde

**TABLE 1.        Suggested Modification of Dosage Schedules of Coly-Mycin M Parenteral for Adults with Impaired Renal Function**

| Renal Function                    | Degree of Impairment |         |          |              |
|-----------------------------------|----------------------|---------|----------|--------------|
|                                   | Normal               | Mild    | Moderate | Considerable |
| Plasma creatinine, mg/100 mL      | 0.7–1.2              | 1.3–1.5 | 1.6–2.5  | 2.6–4.0      |
| Urea clearance,% of normal        | 80–100               | 40–70   | 25–40    | 10–25        |
| <b>Dosage</b>                     |                      |         |          |              |
| Unit dose of Coly-Mycin M, mg     | 100–150              | 75–115  | 66–150   | 100–150      |
| Frequency, times/day              | 4 to 2               | 2       | 2 or 1   | every 36 hr  |
| Total daily dose, mg              | 300                  | 150–230 | 133–150  | 100          |
| Approximate daily dose, mg/kg/day | 5.0                  | 2.5–3.8 | 2.5      | 1.5          |

**Note:** The suggested unit dose is 2.5–5 mg/kg; however, the time INTERVAL between injections should be increased in the presence of impaired renal function.

**Table 1**  
Polymyxin dosing recommendations

| Creatinine clearance | CMS US package insert | CMS EMA package insert | CMS authors' recommendation (US based) | Polymyxin B package insert                   | Polymyxin B authors' recommendation |
|----------------------|-----------------------|------------------------|----------------------------------------|----------------------------------------------|-------------------------------------|
| ≥80 mL/min           | 5 mg/kg/day CBA       | 9 MIU CMS              | 5 mg/kg/day CBA                        | 1.5–2.5 mg/kg/day<br>Dose ‘reduced downward’ | 2.5 mg/kg/day                       |
| 50–79 mL/min         | 3.8 mg/kg/day CBA     |                        |                                        |                                              |                                     |
| 30–49 mL/min         | 2.5 mg/kg/day CBA     | 5.5–7.5 MIU CMS        | 3.5 mg/kg/day CBA                      |                                              |                                     |
| 10–29 mL/min         | 1 mg/kg/day CBA       | 4.5–5.5 MIU CMS        | 2.5 mg/kg/day CBA                      |                                              |                                     |
| <10 mL/min           | 1 mg/kg/day CBA       | 3.5 MIU CMS            | 1.5 mg/kg/day CBA                      |                                              |                                     |

CBA, colistin base activity; CMS, colistin methanesulphonate; EMA, European Medicines Agency; MIU, million international units.  
 \*The US package insert does not specify what dosing weight should be used for determining colistin dose, the authors would recommend using ideal body weight or actual body weight, whichever is lower.



**Table 2.** Recommended Colistin Dosing Regimens Based on Renal Function<sup>21,25,26,a</sup>

| <b>Estimated Renal Function (CL<sub>cr</sub>)</b> | <b>FDA-Approved Labeling</b>                               | <b>EMA-Approved Labeling<sup>b</sup></b>                                                                                                                                                                                                                                                                               | <b>ESCMID Task Force<sup>c</sup></b>                                                                                                                                                                                                            |
|---------------------------------------------------|------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ≥80 mL/min                                        | 2.5–5 mg CBA/kg (divided into 2–4 doses per day)           | 9 MIU of CMS (divided into 2–3 doses per day)                                                                                                                                                                                                                                                                          | 4.5 MIU of CMS every 12 hr                                                                                                                                                                                                                      |
| 50–79 mL/min                                      | 2.5–3.8 mg CBA/kg (divided into 2 doses per day)           | 9 MIU of CMS (divided into 2–3 doses per day)                                                                                                                                                                                                                                                                          | 4.5 MIU of CMS every 12 hr                                                                                                                                                                                                                      |
| 30–49 mL/min                                      | 2.5 mg CBA/kg (once daily or divided into 2 doses per day) | 5.5–7.5 MIU of CMS (divided into 2 doses per day)                                                                                                                                                                                                                                                                      | ... <sup>d</sup>                                                                                                                                                                                                                                |
| 10–29 mL/min                                      | 1.5 mg CBA/kg (every 36 hr)                                | 4.5–5.5 MIU of CMS (divided into 2 doses per day)                                                                                                                                                                                                                                                                      | ...                                                                                                                                                                                                                                             |
| <10 mL/min                                        | ...                                                        | 3.5 MIU of CMS (divided into 2 doses per day)                                                                                                                                                                                                                                                                          | ...                                                                                                                                                                                                                                             |
| Dialysis                                          | ...                                                        | Patients receiving intermittent hemodialysis: on nonhemodialysis days, 2.25 MIU of CMS per day; on hemodialysis days, 3 MIU of CMS per day (divided into 2 doses per day)<br>Patients receiving continuous venovenous hemofiltration: same dose as for those with normal renal function (divided into 3 doses per day) | Patients receiving intermittent hemodialysis: 2 MIU of CMS every 12 hr<br>Patients receiving continuous venovenous hemofiltration: same dose as for those with normal renal function (divided into 2–3 doses per day); higher doses may be used |

<sup>a</sup>CL<sub>cr</sub> = creatinine clearance, FDA = Food and Drug Administration, EMA = European Medicines Agency, ESCMID = European Society of Clinical Microbiology and Infectious Diseases, CBA = colistin base activity, CMS = colistimethate sodium, MIU = million international units.

<sup>b</sup>In critically ill patients, a colistin loading dose of 9 MIU should be given.

<sup>c</sup>A loading dose of 6–9 MIU is recommended in all patients, including those with renal dysfunction.

<sup>d</sup>No specific recommendation.

Kime Şiran Keske

Dear Sanford Guide Customer,

Our editorial board made the decision to remove the Colistin Calculator from the app since recommendations for the dosing of Colistin have changed (see note below). You can find more information about the dosing of Colistin on our Polymyxin E/Colistin page in the app.

**Currently there are colistin (polymyxin E) dosing recommendations from three sources:** 1) an international pharmacokinetics (PK) study group, using creatinine clearance (CrCl)-based dosing, 2) the European Medicines Agency (EMA), also CrCl-based (with broader divisions than the PK study group), and 3) the US FDA, which uses weight- and CrCl-based dosing as found in the official prescribing information. **The Sanford Guide editors favor the approach of the PK study group as published** [\(Clin Infect Dis 2016 Dec 23 \[Epub ahead of print\]\)](#).

In 2011 the PK study group published complex colistin dosing recommendations derived from an interim analysis of 105 critically ill patients [\(Antimicrob Agents Chemother 55:3284, 2011\)](#). The group has now updated these recommendations based on their final analysis of data from 214 patients. **The result is a more clinician-friendly dosing approach** designed to achieve an average steady-state colistin plasma concentration of 2 µg/mL. Patients are administered a loading dose (expressed as mg of colistin base activity) of 4 x body weight (using the lower of actual or ideal body weight) followed by a maintenance regimen beginning 12 hours later using a "look-up" table of daily dose based on CrCl (divided in 10 mL/min increments). The maintenance dose should be administered in two divided doses 12 hours apart. The group also provides dosing recommendations for patients receiving intermittent hemodialysis, SLED, and CRRT. Full details are provided on our colistin page. Colistin dosing remains a challenge. We recommend use of polymyxin B rather than colistin with one importance exception: polymyxin B does not achieve adequate urine concentrations. Hence, colistin is required to treat multidrug-resistant gram-negative infections of the urinary tract.

Scott Kelly

**Antimicrobial Therapy Inc.**

*Publisher of The Sanford Guides*

<http://www.sanfordguide.com/>

**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,<br>mL/min | Dose of Colistimethate<br>for $C_{ss,avg}$ of 2 mg/L <sup>a</sup> |              |
|---------------------------------|-------------------------------------------------------------------|--------------|
|                                 | 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         |

Abbreviations: CBA, colistin base activity;  $C_{ss,avg}$ , average steady-state plasma concentrations of colistin.

**KARBAPENEM/KOLİSTİN**  
**DİRENÇLİ KLEBSIELLA**  
**TEDAVİSİ**

A vertical timeline diagram with a central grey line. At the top is a dark blue circle. At the bottom is a larger dark blue circle containing the year '2017'. Three colored rectangular boxes are positioned along the timeline: an orange box pointing left for 1983, an orange box pointing right for 1993, and a dark red box pointing left for 2007. Each box contains a year and a description of antibiotic resistance in *Klebsiella pneumoniae*.

**1993**  
Karbapenem dirençli *Klebsiella pneumoniae*

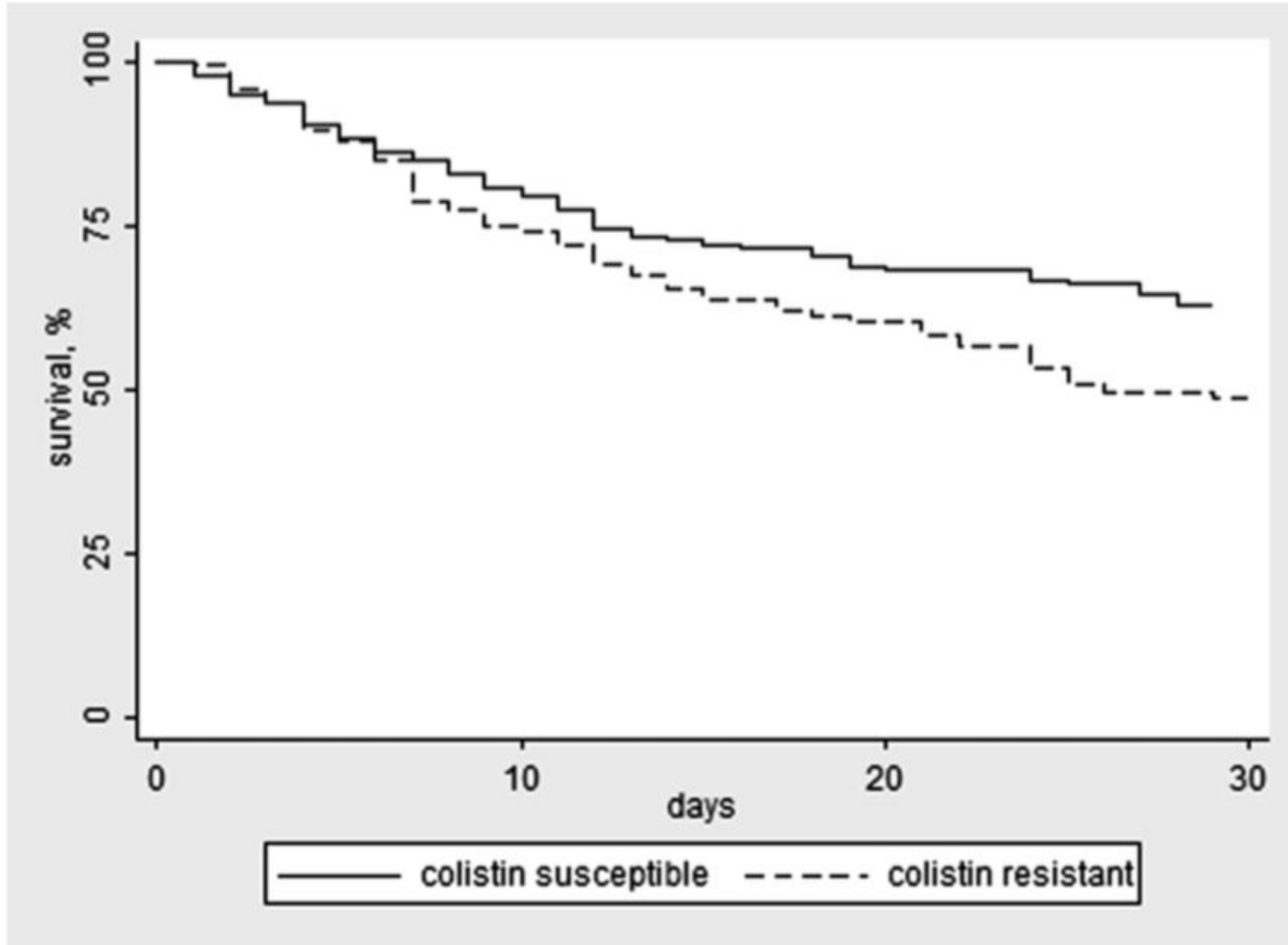
**1983**  
ESBL pozitif *Klebsiella pneumoniae*

**2007**  
Kolistin dirençli *Klebsiella pneumoniae*

**2017**

Knothe H, et al. *Infection*. 1983; 11: 315-7  
Antoniadou A, et al. *J Antimicrob Chemother*. 2007; 59(4): 769-90

Naas T, Nordmann P. *Proc Natl Acad Sci*. 1994; 91: 7693-7.



**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.

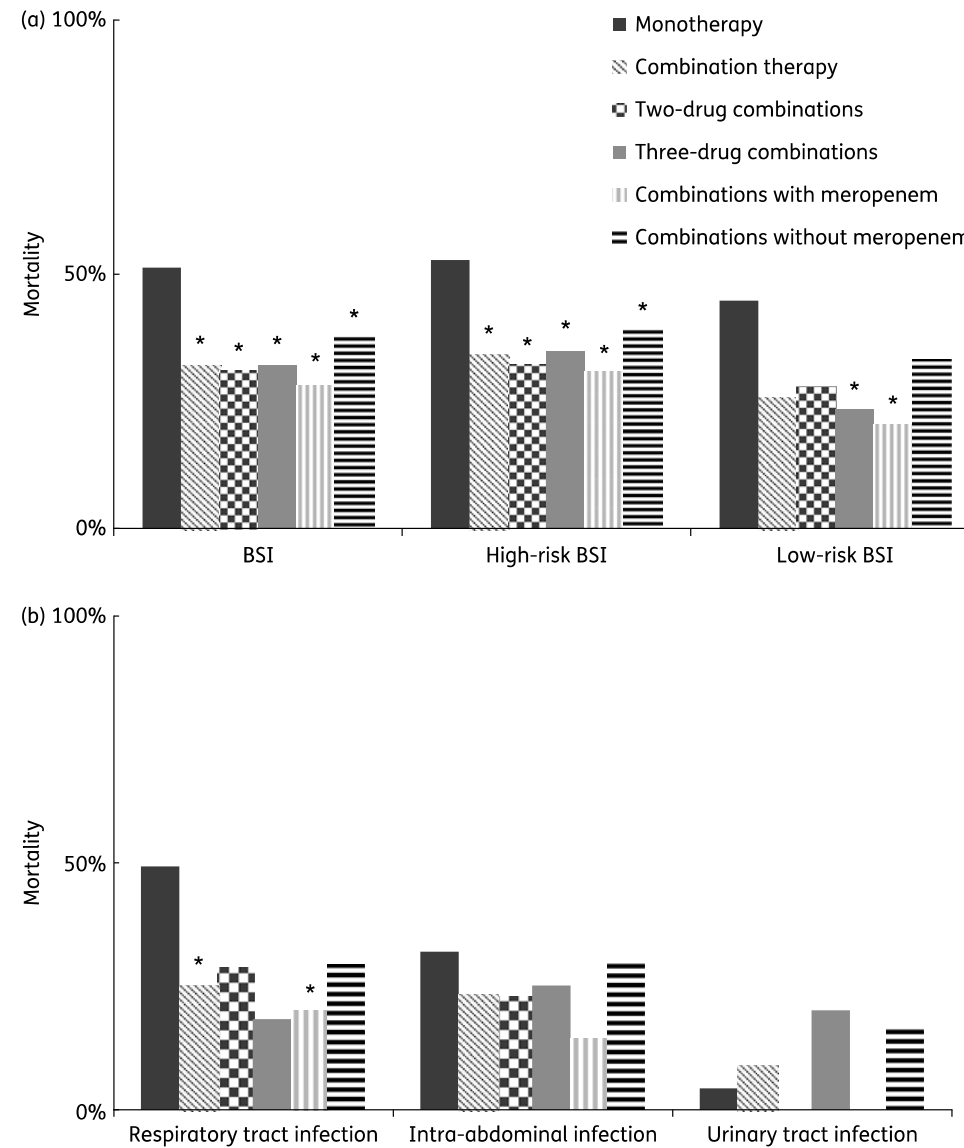
## **Infections caused by KPC-producing *Klebsiella pneumoniae*: differences in therapy and mortality in a multicentre study**

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

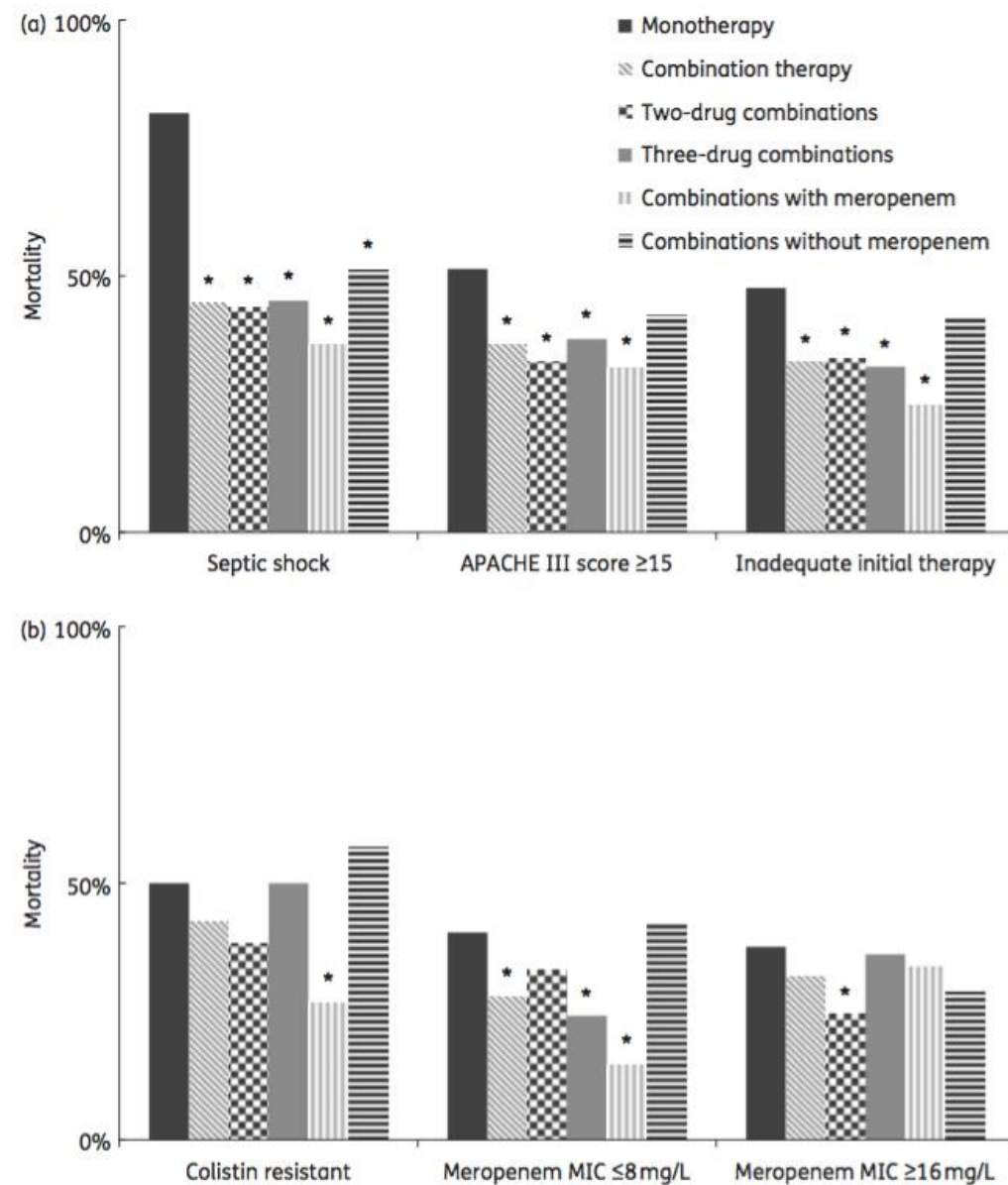
**Table 5.** Multivariate analysis of risk factors for 14 day mortality in patients with infections caused by KPC-Kp

| 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) |





**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.



**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.

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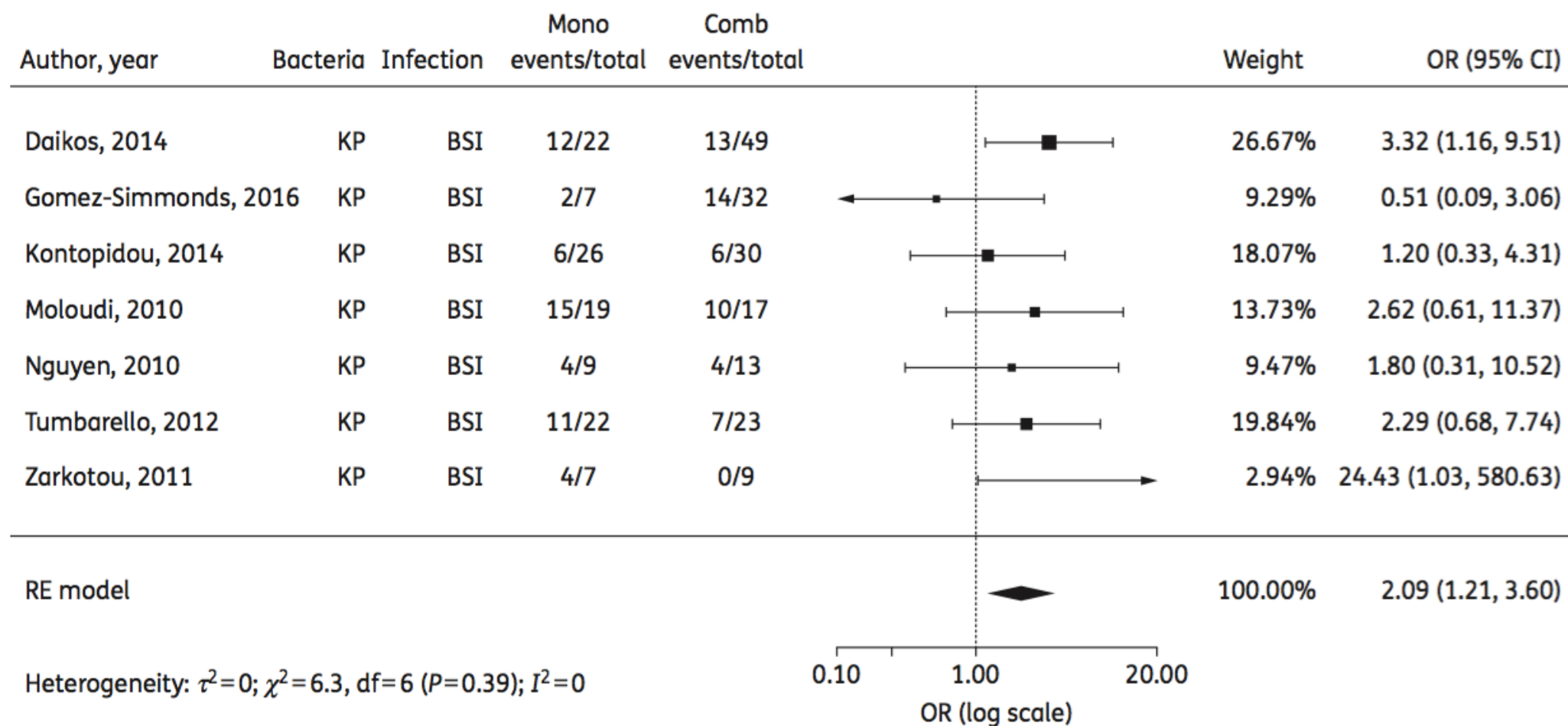
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# **Polymyxin monotherapy or in combination against carbapenem-resistant bacteria: systematic review and meta-analysis**

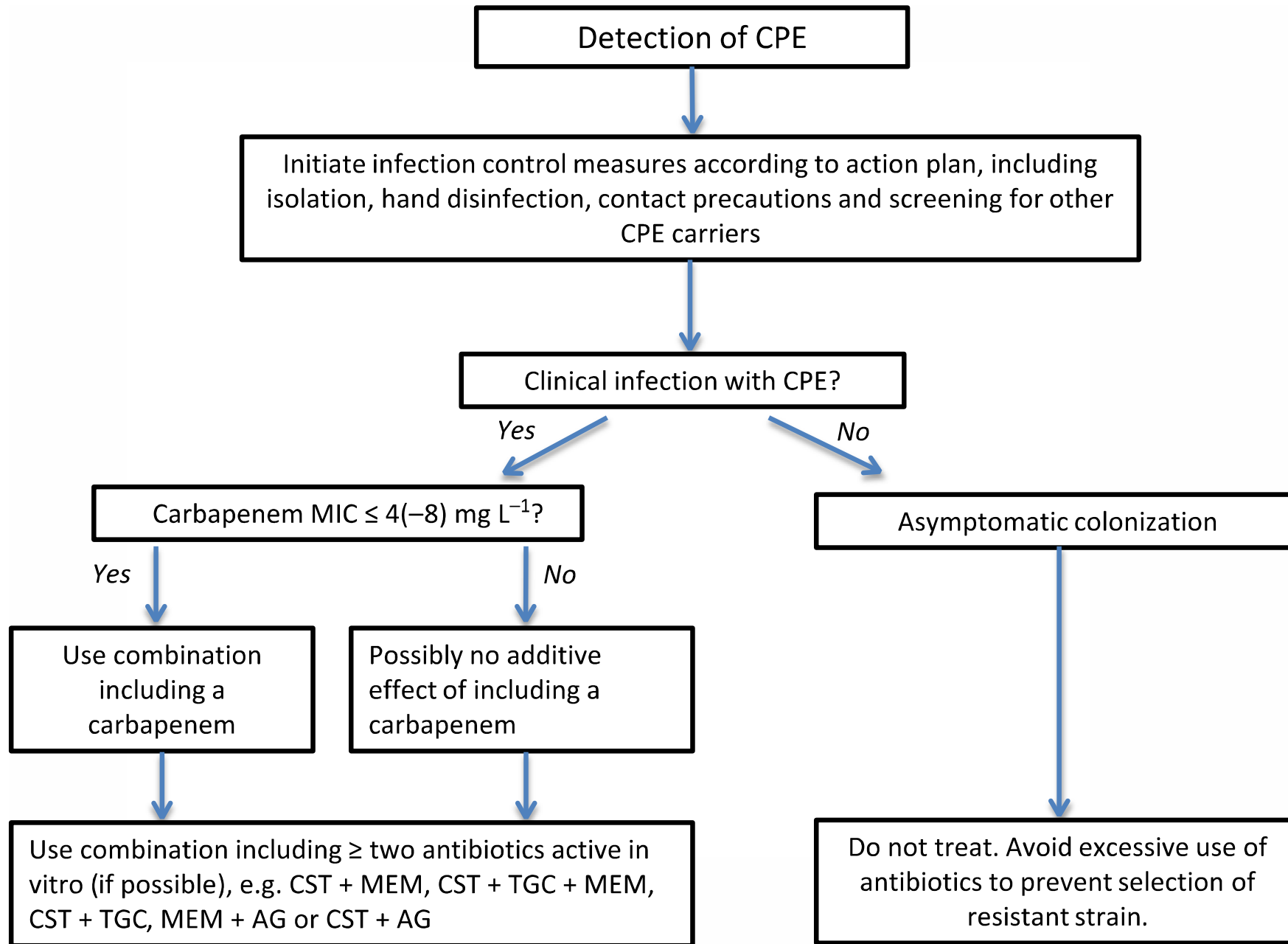
**Oren Zusman<sup>1\*</sup>, Sergey Altunin<sup>2,3†</sup>, Fidi Koppel<sup>2</sup>, Yael Dishon Benattar<sup>2,4</sup>, Habip Gedik<sup>5</sup> and Mical Paul<sup>2,3</sup>**

<sup>1</sup>*Department of Medicine E, Rabin Medical Center, Petah-Tiqva, Israel;* <sup>2</sup>*Infectious Diseases Unit, Rambam Medical Center, Haifa, Israel;*

<sup>3</sup>*The Ruth and Bruce Rappaport Faculty of Medicine, Technion, Israel Institute of Technology, Haifa, Israel;* <sup>4</sup>*The Cheryl Spencer Department of Nursing, University of Haifa, Haifa, Israel;* <sup>5</sup>*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.



# Synergistic Activity of Colistin plus Rifampin against Colistin-Resistant KPC-Producing *Klebsiella pneumoniae*

**Carlo Tascini,<sup>a</sup> Enrico Tagliaferri,<sup>a</sup> Tommaso Giani,<sup>c</sup> Alessandro Leonildi,<sup>a</sup> Sarah Flammini,<sup>a</sup> Beatrice Casini,<sup>b</sup> Russell Lewis,<sup>e</sup> Simone Ferranti,<sup>a</sup> Gian Maria Rossolini,<sup>c,d,f</sup> Francesco Menichetti<sup>a</sup>**

U.O. Malattie Infettive, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy<sup>a</sup>; Dipartimento di Ricerca Traslationale, Università di Pisa, Pisa, Italy<sup>b</sup>; Dipartimento di Biotecnologie Mediche, Università di Siena, Siena, Italy<sup>c</sup>; Dipartimento di Medicina Sperimentale e Clinica, Sezione di Medicina Critica e Medicine Specialistiche, Università di Firenze, Florence, Italy<sup>d</sup>; U.O. Malattie Infettive, Policlinico S'Orsola-Malpighi, Università di Bologna, Bologna, Italy<sup>e</sup>; S.O.D. Microbiologia e Virologia, Azienda Ospedaliera Universitaria Careggi, Florence, Italy<sup>f</sup>

| No. of isolates | Method (inoculum, CFU/mL)                                                   | Drug 1 (concentration in µg/mL)        | Drug 2 (concentration in µg/mL)            | Bactericidal [N (%)] | Synergy [N (%)]       | Antagonism [N (%)] | Reference |
|-----------------|-----------------------------------------------------------------------------|----------------------------------------|--------------------------------------------|----------------------|-----------------------|--------------------|-----------|
| 18              | Time–kill assay <sup>a</sup> (N/A)                                          | Colistin (5)                           | Imipenem (10)                              | 2 (11)               | 2 (11)                | 10 (56)            | [62]      |
| 3 <sup>b</sup>  | Time–kill assay <sup>c</sup> (ca. 10 <sup>6</sup> and ca. 10 <sup>8</sup> ) | Colistin (0.5)                         | Doripenem (2.5)                            | N/A                  | 2 (67) <sup>d</sup>   | N/A                | [41]      |
|                 |                                                                             | Colistin (0.5)                         | Doripenem (25)                             | N/A                  | 3 (100) <sup>d</sup>  | N/A                |           |
|                 |                                                                             | Colistin (2)                           | Doripenem (2.5)                            | N/A                  | 3 (100) <sup>d</sup>  | N/A                |           |
|                 |                                                                             | Colistin (2)                           | Doripenem (25)                             | N/A                  | 3 (100) <sup>d</sup>  | N/A                |           |
| 10              | Time–kill assay <sup>a</sup> (1 × 10 <sup>6</sup> )                         | Colistin (1)                           | Doripenem (8)                              | 7 (70)               | 6 (60)                | 0 (0)              | [61]      |
|                 |                                                                             | Colistin (1)                           | Gentamicin (2)                             | 5 (50)               | 2 (20)                | 0 (0)              |           |
|                 |                                                                             | Colistin (1)                           | Doxycycline (2)                            | 0 (0)                | 1 (10)                | 3 (30)             |           |
|                 |                                                                             | Doripenem (8)                          | Gentamicin (2)                             | 2 (20)               | 1 (10)                | 2 (20)             |           |
|                 |                                                                             | Doripenem (8)                          | Doxycycline (2)                            | 1 (10)               | 3 (30)                | 2 (20)             |           |
|                 |                                                                             | Gentamicin (2)                         | Doxycycline (2)                            | 2 (10)               | 4 (40)                | 2 (20)             |           |
| 1               | Time–kill assay <sup>a</sup> (ca. 10 <sup>5</sup> –10 <sup>6</sup> )        | Colistin (0.25–0.5 × MIC) <sup>e</sup> | Vancomycin(0.25–0.5 × MIC) <sup>e</sup>    | 1 (100)              | 1 (100)               | 0 (0)              | [65]      |
|                 |                                                                             | Colistin (0.25–0.5 × MIC) <sup>e</sup> | Trimethoprim (0.25–0.5 × MIC) <sup>e</sup> | 1 (100)              | 1 (100)               | 0 (0)              |           |
|                 |                                                                             | Colistin (0.25–0.5 × MIC) <sup>e</sup> | SXT (0.25–0.5 × MIC) <sup>e</sup>          | 1 (100)              | 1 (100)               | 0 (0)              |           |
| 14              | Etest                                                                       | Colistin                               | Fosfomycin                                 | N/A                  | 5 (35.7) <sup>f</sup> | 0 (0)              | [22]      |
| 8               | Time–kill assay <sup>a</sup> (N/A)                                          | Fosfomycin (100)                       | Meropenem (10)                             | N/A <sup>g</sup>     | 5 (62.5)              | N/A                | [63]      |
|                 |                                                                             | Fosfomycin (100)                       | Colistin (5)                               | N/A <sup>h</sup>     | 2 (25)                | N/A                |           |
|                 |                                                                             | Fosfomycin (100)                       | Gentamicin (5)                             | N/A                  | 0 (0)                 | N/A                |           |
| 13              | Checkerboard assay (2.5 × 10 <sup>5</sup> )                                 | Colistin                               | Rifampicin                                 | N/A <sup>i</sup>     | 13 (100)              | 0 (0)              | [64]      |
|                 |                                                                             | Colistin                               | Imipenem                                   | N/A                  | 5 (38.5)              | 0 (0)              |           |
|                 |                                                                             | Colistin                               | Meropenem                                  | N/A                  | 5 (38.5)              | 0 (0)              |           |
|                 |                                                                             | Colistin                               | Tigecycline                                | N/A                  | 5 (38.5)              | 0 (0)              |           |
|                 |                                                                             | Colistin                               | Gentamicin                                 | N/A                  | 5 (38.5)              | 0 (0)              |           |
|                 |                                                                             | Tigecycline                            | Imipenem                                   | N/A                  | 0 (0)                 | 0 (0)              |           |
|                 |                                                                             | Tigecycline                            | Meropenem                                  | N/A                  | 0 (0)                 | 0 (0)              |           |
|                 |                                                                             | Tigecycline                            | Gentamicin                                 | N/A                  | 0 (0)                 | 0 (0)              |           |
|                 |                                                                             | Imipenem                               | Gentamicin                                 | N/A                  | 3 (23.1)              | 0 (0)              |           |
|                 |                                                                             | Meropenem                              | Gentamicin                                 | N/A                  | 5 (38.5)              | 0 (0)              |           |

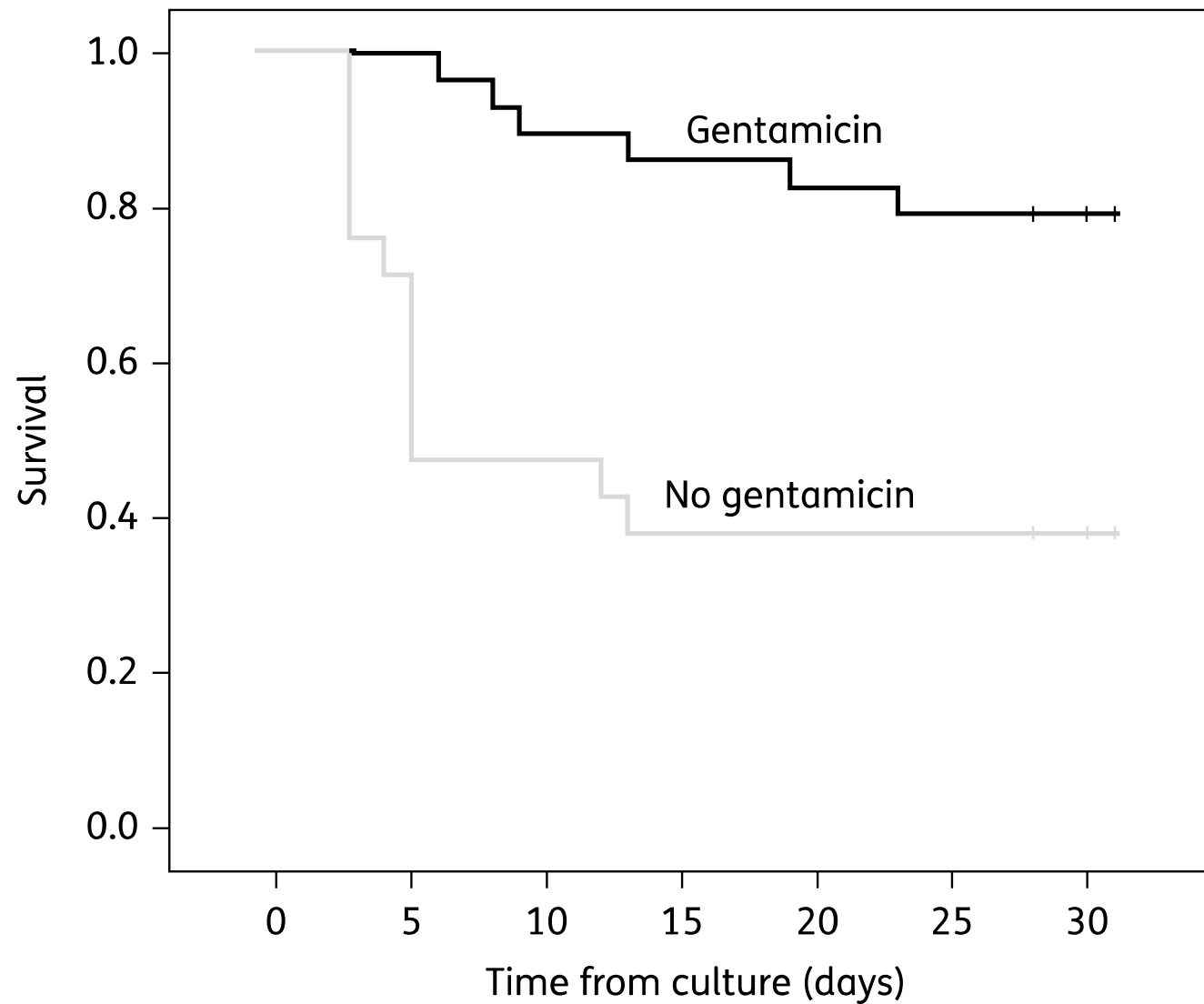
In the checkerboard and Etest assays, synergy was defined as a fractional inhibitory concentration index (FICI) of ≤0.5 and antagonism as a FICI of >4. In time–kill assay a bactericidal effect was defined as a ≥3 log<sub>10</sub> decrease from the starting inoculum. Synergy means a ≥2 log<sub>10</sub> greater reduction for the combination treatments than th

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

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

<sup>1</sup>Clinic Unit of Infectious Diseases, Hospital Universitario Reina Sofía-IMIBIC-Universidad de Córdoba, Córdoba, Spain; <sup>2</sup>Spanish Network for Research in Infectious Diseases (REIPI RD12/0015), Instituto de Salud Carlos III, Madrid, Spain; <sup>3</sup>Intensive Care Unit, Hospital Universitario Reina Sofía, Córdoba, Spain; <sup>4</sup>Clinic Unit of Infectious Diseases, Microbiology and Preventive Medicine, Hospitales Universitarios Virgen Macarena y Virgen del Rocío, Seville, Spain; <sup>5</sup>Departamento de Medicina, Universidad de Sevilla, Seville, Spain; <sup>6</sup>Clinic Unit of Preventive Medicine, Hospital Universitario Reina Sofía, Córdoba, Spain; <sup>7</sup>Clinic Unit of Microbiology, Hospital Universitario Reina Sofía, Universidad de Córdoba, Córdoba, Spain



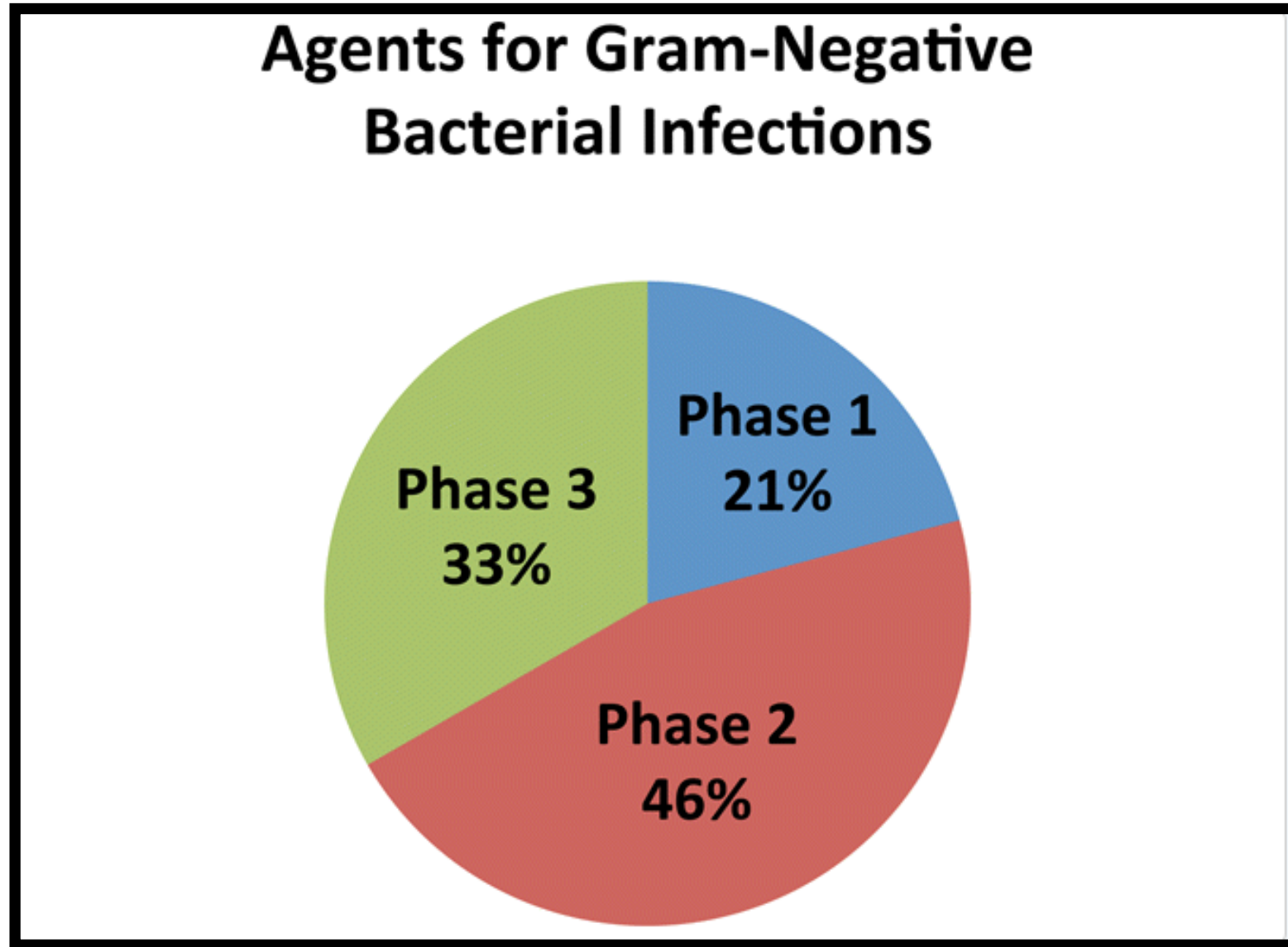


**Figure 1.** Kaplan–Meier curves showing the impact of targeted treatment with gentamicin on survival at 30 days in patients with severe infection caused by carbapenem-resistant and colistin-resistant *K. pneumoniae* (log-rank test 11.9,  $P=0.001$ ).

# CRE'de YENİ ANTİBİYOTİK SEÇENEKLERİ

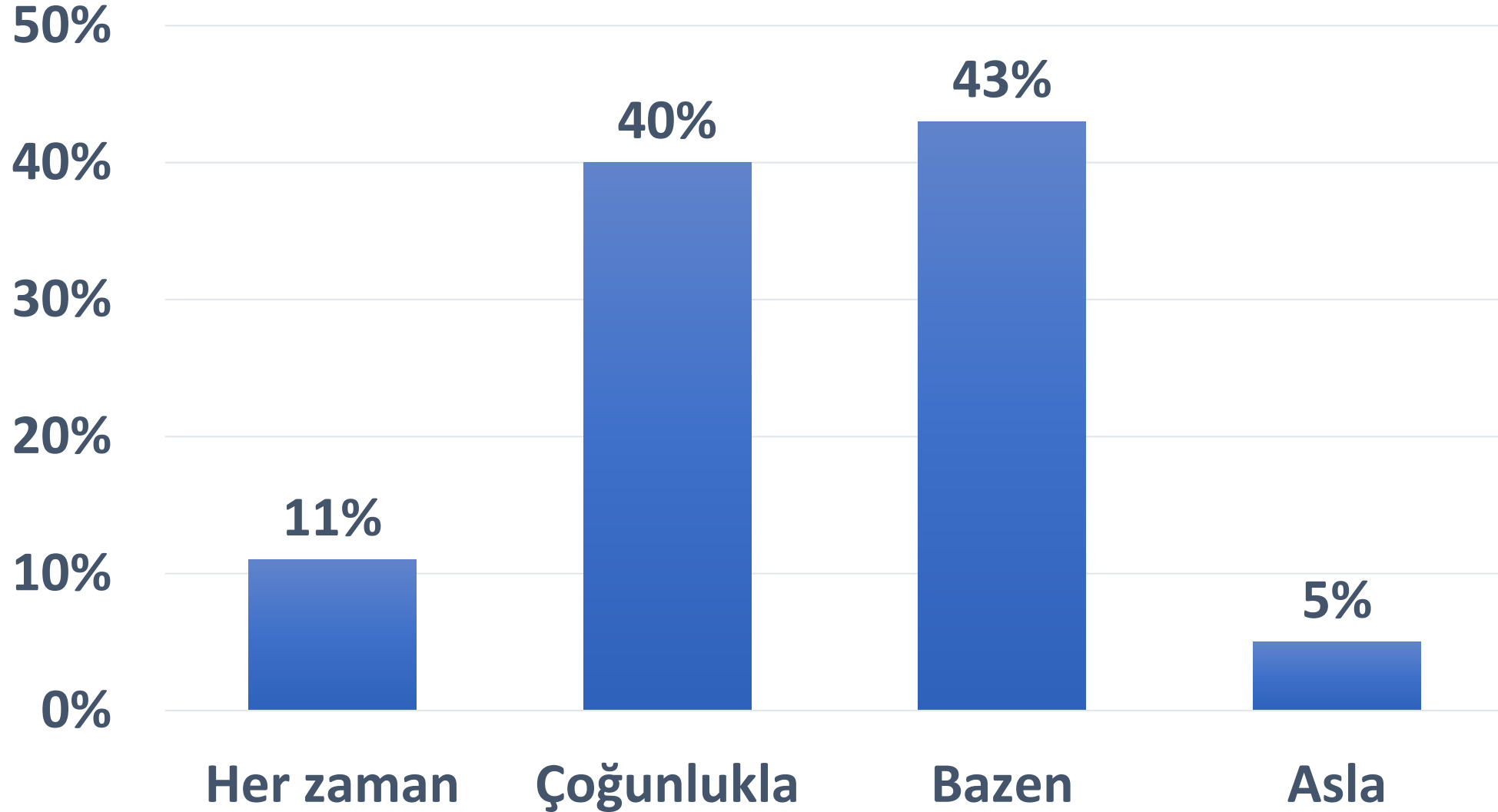
| Antibiyotik           | Etki Mekanizması                                                                                                          | Endikasyon                                                                           | Diğer özellikler                                                                                                                        |
|-----------------------|---------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| Seftazidim-avibaktam  | Ambler A, C ve D 'yi inhibe etmektedir<br>CRE'li suşların %98'ine in vitro etkili.                                        | Komplike Üriner sistem<br>enfeksiyonu ve intra-<br>abdominal enfeksiyon              | Class B (NDM-1 ve IMP) ve bazı class D (OXA-23) direnç                                                                                  |
| Fosfomisin            | NDM-1 suşlarının %94'üne in vitro etkili                                                                                  |                                                                                      | IV yol belirsizlikler (4x4 g)<br>Tedavi sırasında direnç<br>Mükemmel doku penetrasyonu<br>Kombine tedavide                              |
| Tigesiklin            | CRE suşlarının %88-96'sına in vitro etkili                                                                                | Komplike intra-abdominal inf<br>CYDE<br>Toplum kökenli pnömoni                       | Monoterapide mortalite yüksek. Önerilmez<br>Kombine tedavide oldukça etkin<br>Yüksek dozda etkinlik artmakta                            |
| Meropenem-vaborbaktam | siklik boronik asit inh.<br>Class A ve C'ye etkili.<br>In vitro olarak KPC içeren<br>Enterobacteriaceae etkinliği yüksek. |                                                                                      | Akciğer dokusuna penetrasyonu iyi<br>Faz 3 çalışma tamamlandı yayın aşamasında                                                          |
| Imipenem-relebaktam   | serin beta-laktamaz inh.<br>Class A ve C'ye etkili.                                                                       |                                                                                      | Imipenem ile karşılaştırıldığında MİK değerlerini düşürüyor.<br>Karbapenem R suşlarda çalışmalar devam ediyor                           |
| Plazomisin            | CRE'ye in vitro olarak oldukça etkili                                                                                     | 346 ESBL/AmpC suşunda çok<br>etkili                                                  | Nefrotoksitesi diğer AG'lere göre düşük. Faz 2 çalışmada<br>%5.                                                                         |
| Eravasiklin           | CRE'de tigesikline göre in vitro olarak<br>2-4 kat daha etkin                                                             | Ertapenemle karşılaştırmalı<br>çalışmalarda intraabdominal<br>enfeksiyonlarda etkin. | In vitro aktivitesine bakılırsa tigesiklinden daha etkili olduğu<br>düşünülmemekte.<br>CRE'deki etkinliği ile ilgili çalışmalar sürüyor |

# CRE'de YENİ ANTİBİYOTİK SEÇENEKLERİ

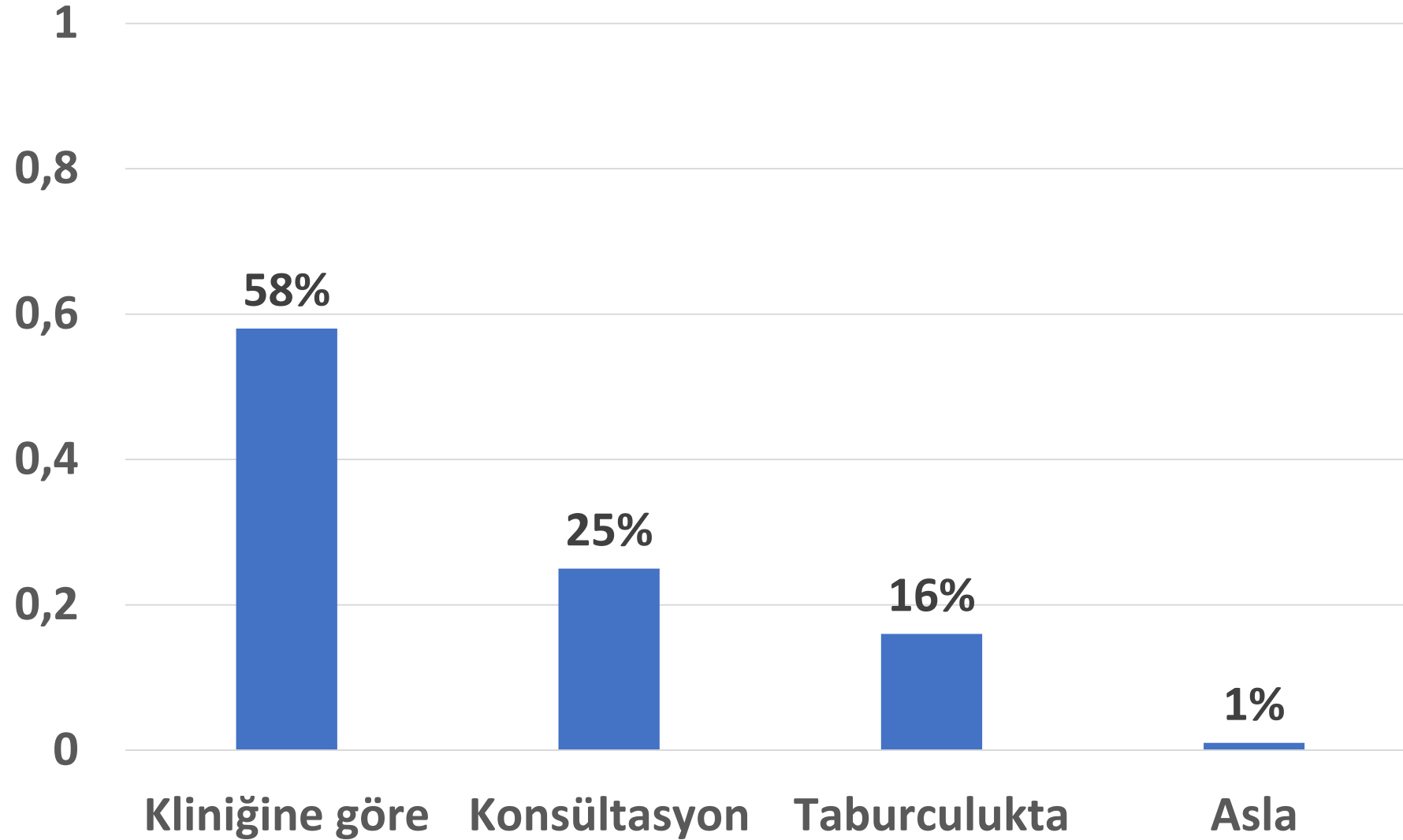


| Developed indicators                                                               | Number of articles mentioning the indicator / total number of articles | Percentage of articles mentioning the indicator |
|------------------------------------------------------------------------------------|------------------------------------------------------------------------|-------------------------------------------------|
| Prescribe empirical antibiotic therapy according to (local or national) guidelines | 10/14                                                                  | 71                                              |
| Switch from intravenous to oral therapy                                            | 9/14                                                                   | 64                                              |
| Perform at least two sets of blood cultures                                        | 8/14                                                                   | 57                                              |
| Change to pathogen-directed therapy when culture results become available          | 8/14                                                                   | 57                                              |
| Timely initiation of antibiotic therapy                                            | 7/14                                                                   | 50                                              |
| Adapt dose and dosing interval of antibiotics to renal function                    | 7/14                                                                   | 50                                              |
| Documentation of antibiotic plan in medical record                                 | 7/14                                                                   | 50                                              |
| Perform a site culture                                                             | 6/14                                                                   | 43                                              |
| Discontinue antibiotic therapy if infection not confirmed                          | 6/14                                                                   | 43                                              |
| Duration of antibiotic therapy                                                     | 6/14                                                                   | 43                                              |

## Parenteral Tedaviden oral tedaviye ne sıklıkla geçersiniz?



# Parenteral tedaviden oral tedaviye geçme kararını neye göre verirsiniz?



# **BİLGİSAYAR BAZLI SİSTEMLER**

- Cerrahi profilaksi
- Antibiyotik kullanım süreleri
- İlaç etkileşimleri
- Dirençli mikroorganizmaları hatırlatma
- Yan etki ile ilgili uyarılar
- Doz aşımı ile ilgili uyarılar

| Developed indicators                                                               | Number of articles mentioning the indicator / total number of articles | Percentage of articles mentioning the indicator |
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| Prescribe empirical antibiotic therapy according to (local or national) guidelines | 10/14                                                                  | 71                                              |
| Switch from intravenous to oral therapy                                            | 9/14                                                                   | 64                                              |
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| Discontinue antibiotic therapy if infection not confirmed                          | 6/14                                                                   | 43                                              |
| Duration of antibiotic therapy                                                     | 6/14                                                                   | 43                                              |



ERİŞKİN HASTALARDA ÜST SOLUNUM  
YOLU ENFEKSİYONLARIN KLİNİK YOLU

HASTA BARKODU: .....

AKUT  
TONSİLLİT/FARENJİT

Gripisiz olan hastaya aşağıdaki koruyucu uygulanır.

| Kriterler                          | Puan  |
|------------------------------------|-------|
| Öksürük olmaması                   | 1     |
| Hassas ve şişmiş tonsil nodlar     | 1     |
| Ateş $\geq 38^{\circ}\text{C}$     | 1     |
| Kriptik/Hipertrofik tonsil varlığı | 1     |
| Yaş $\geq 45$ yaş ve üstü          | -1    |
| <b>Toplam Puan:</b>                | ..... |

Puan  $\geq 1$ Puan  $\geq 2$ Puan  $\geq 3$ Puan  $\geq 4$ Puan  $\geq 5$ AGBHS  
\*  
Farenjit  
RiskiAGBHS  
Farenjit  
Riski %5-10AGBHS  
Farenjit  
Riski %11-17AGBHS  
Farenjit  
Riski %28-35AGBHS  
Farenjit  
Riski %51-53

Seçenek

İleri tetkike gerek  
yok ve antibiyotik  
ENDİKASYONU YOKBoğaz kültürü ya da hızlı  
Antijen (Streptokok)  
Tarama testi\*\*Negatif  
Antibiyotik  
ENDİKASYONU  
YOK.Pozitif  
Antibiyotik  
tedavi

**Antibiyotik başla;**

☐ Amoksisilin-klavulonik asit  
[2x1g/gün (10gün)]

☐ Benzatin penisilin  
[1,2x10<sup>6</sup> ü/tek doz (10gün)]

☐ Makrolidler

☐ Azitromisin  
[1x500mg/gün (5gün)]

☐ Klaritromisin  
[2x500mg/gün (10gün)]

☐ Klindamisin  
[3x300mg/gün (10gün)]

☐ Sefuroksim  
[2x500mg/gün (5gün)]

☐ Diğer Antibiyotik;

Nedeni;

Antibiyotik Başlandı ise;  
Nedeni: .....

Hastada viral etken düşünülüyorsa veya hasta grip benzeri hastalık semptomları taşıyorsa hastanın klinik durumu orta/ciddi olarak değerlendiriliyorsa hastadan influenza hızlı test/SYVP\*\* istenebilir.

\*AGBHS: A Grubu Beta Hemolitik Streptokoklar  
\*\*SYVP: Solunum Yolları Virüs Paneli (Multiplex PCR)Hastayı  
Değerlendiren  
Hekim : .....ERİŞKİN HASTALARDA ÜST SOLUNUM  
YOLU ENFEKSİYONLARIN KLİNİK YOLU

## AKUT RİNOSİNÜZİT

SOĞUK ALGINLIĞI VE  
SPESİFİK OLMAYAN ÜSYEKOMPLİKE OLMAYAN  
BRONŞİT

%98 viraldir

Etkenlerin tamamı virustur

En sık hastalanan semptom öksürüktür

Aşağıdaki durumlardan en az birinin varlığı bakteriyel enfeksiyonu düşündürür.

\*Ateş  $\geq 4$  gün ve  $\geq 39^{\circ}\text{C}$  ve/veya üretilen akıntı veya yüzde hassasiyet

\*10 günün ötesinde burun akıntısı veya ağrı boyu süren öksürük

\*Viral üst solunum yolu enfeksiyonu ile birlikte sonraki 5-6 gün içinde ateş, öksürük ve burun akıntısının yeniden başlaması/artması

Not: Rutin olarak virüs

Semptomlar: .....

\*Ateş .....

\*Öksürük .....

\*Burun akıntısı .....

\*Nazal konjesyon .....

\*Postnazal akıntı .....

\*Boğaz ağrısı .....

\*Baş ağrısı .....

\*Kas ağrısı .....

Öncelikle akciğer inleme bulgusu yok ise pnömoni dışlanmalıdır.

Semptomlar: .....

\*Kalp ritmi  $\geq 100/\text{dk}$

\*Solunum sayısı  $\geq 24/\text{dk}$

\*Ateş  $\geq 38$

Renkli balgam, karmak bakteriyel enfeksiyonu GÖSTERMEZ.

Not: Öğunluk akciğer grafisi endikasyonu YOKTUR.

TANI

TEDAVİ

Bakteriyel enfeksiyon düşünülüyorsa;

**İlk tercih:**

☐ Amoksisilin-klavulonik asit  
[2x1g/gün (10gün)]

**Penisilin alerjisi varsa;**

☐ Doksisiklin  
[2x100mg/gün (7gün)] veya

☐ Levofloksasin  
[1x500mg/gün (7gün)] veya

☐ Moksifloksasin  
[1x400mg/gün (7gün)] önerilir.

Azitromisin ÖNERİLMEZ.

☐ Diğer Antibiyotik;

Nedeni: .....

Antibiyotik kullanımı ÖNERİLMEZ.

➢ Dekonjestan (pseudoefedrin ve fenilefrin) ve birinci kuşak antihistaminik kullanılabilir.

➢ Non-steroidal antiinflamatuvarlar kullanılabilir.

➢ Tek başına antihistaminik, opioid kullanımı, intranasal kortikosteroid, burun tuzlu solüsyon kullanımı ÖNERİLMEZ.

Antibiyotik kullanımı ÖNERİLMEZ.

Semptomatik tedavi yeterlidir.

➢ Öksürük baskılayıcı (Kodein, dekstrometorfan)

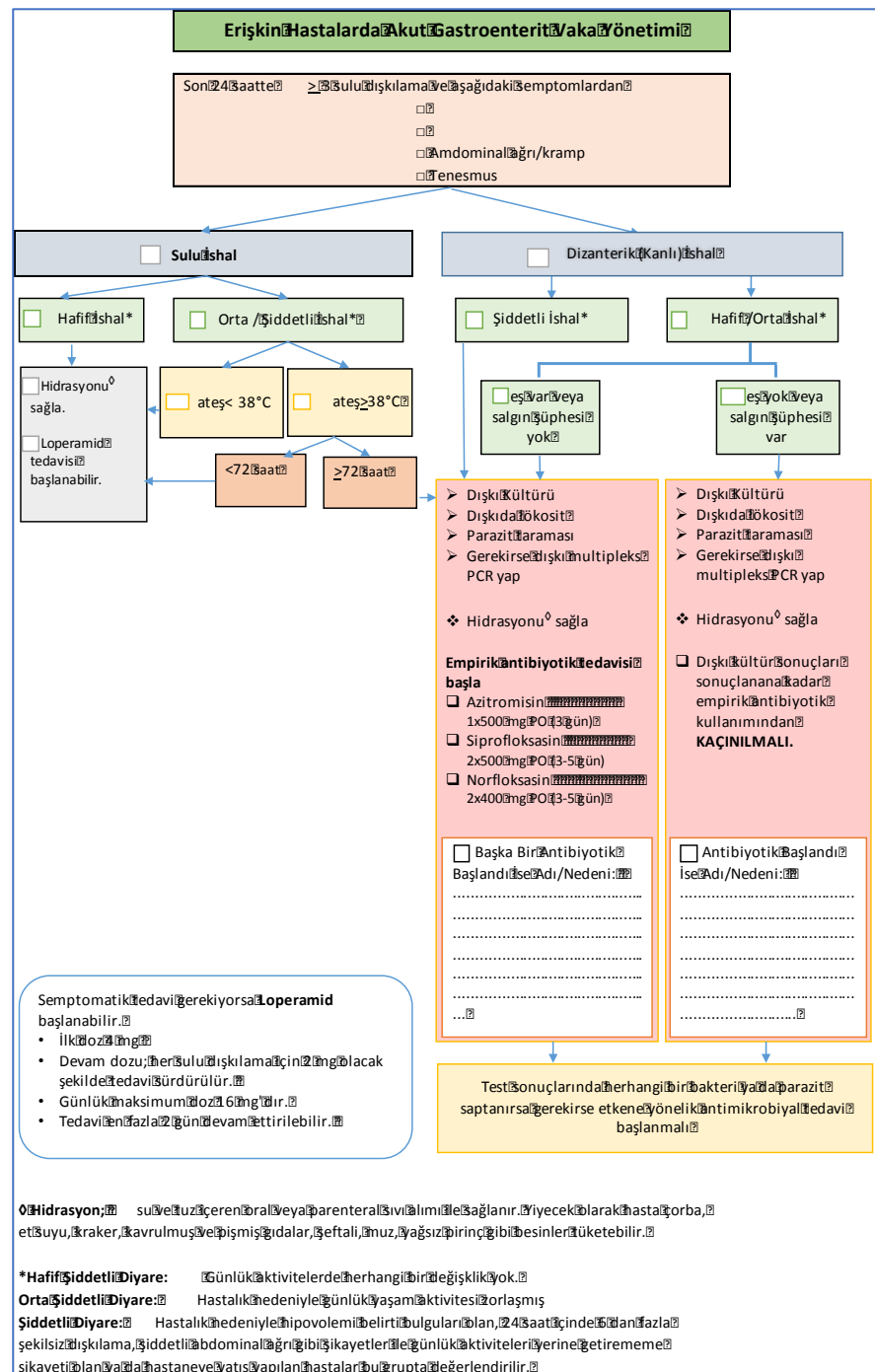
➢ Birinci kuşak antihistaminikler (Difenhidramin)

➢ Dekonjestan (Fenilefrin)

➢ Beta2 agonistler (albuterol)

Antibiyotik Başlandı ise;  
Nedeni: .....

Not: Hastada viral etken düşünülüyorsa veya hasta grip benzeri hastalık semptomları taşıyorsa ve klinik durumu orta/ciddi olarak değerlendiriliyorsa hastadan influenza hızlı test/Solunum Yolları Virüs Paneli (Multiplex PCR) istenebilir.



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Hastayı aşağıdaki tanımlanan SIRS ve qSOFA Kriterlerine göre değerlendiriniz. Mutlaka her iki değerlendirme de yapılmalıdır.

**SIRS\*** kriterlerinden **en az 2'sini** ve **qSOFA\*\*** kriterlerinden **en az 2'sini** pozitif olması durumunda hastada sepsis olasılığı ortaya çıkar.

| SIRS (Sistemik İnflamatuvar Yanıt Sendromu) Kriterleri                                                                                                                                                                                                                                                                                           | qSOFA** Kriterleri                                                                                                                                                              |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <input type="checkbox"/> Ateş > 38.0 °C veya < 36.0 °C<br><input type="checkbox"/> Kalp atım hızı > 90/dk<br><input type="checkbox"/> Solunum sayısı ≥ 22/dakika veya arteriyel karbondioksit basıncı (PaCO <sub>2</sub> ) < 32 mmHg<br><input type="checkbox"/> Kanda beyaz küre sayısı > 12.000/mcL veya < 4000/mcL veya > %10 band formasyonu | <input type="checkbox"/> Solunum sayısı ≥ 22/dakika<br><input type="checkbox"/> Hastanın bilinç durumunda kötüleşme<br><input type="checkbox"/> Sistolik kan basıncı ≤ 100 mmHg |

**EVET** **HAYIR** **HAYIR** **EVET**

Hastanın klinik durumunu takip et. Gerekirse kriterleri tekrar gözden geçir.

**SEPSİS ŞÜPHESİ**

**PRİMER DOKTORU / KAT DOKTORUNA haber ver!** **Saat:**

**Doktor değerlendirme:** Bulgular enfeksiyonla ilgili olabilir mi?  
Öksürük, Balgam, Karın ağrısı, Batında gerginlik, Diyare, İdrar yapma güçlüğü, Ense sertliği ve Baş ağrısı, Yumuşak doku enfeksiyonu, Kateter enfeksiyonu, Endokardit.

Primer Doktor ve / veya Enfeksiyon Hastalıkları Doktorunu ara!

**Sepsis şüphesi var.** **Sepsis şüphesi yok.** **Takip**

**SEPSİS İ**

**Kan kültürü al, Prokalsitonin bakılmasını sağla** **Saat:** ☐ UD ☐

**İlk doz antibiotiği şimdi başla**(Enfeksiyon Hastalıkları) **Saat:** ☐ UD ☐

**O<sub>2</sub> desteği sağla** ☐ UD ☐

**IV sıvı desteği** ☐ UD ☐

**Kan gazı al** ☐ UD ☐

**Aldığı - çıkardığı sıvı takibi** ☐ UD ☐

Not: **Sepsis 6** Uygulamaları doktor direktifi ile uygulanır.

**Sepsis Düşünüldü** ☐

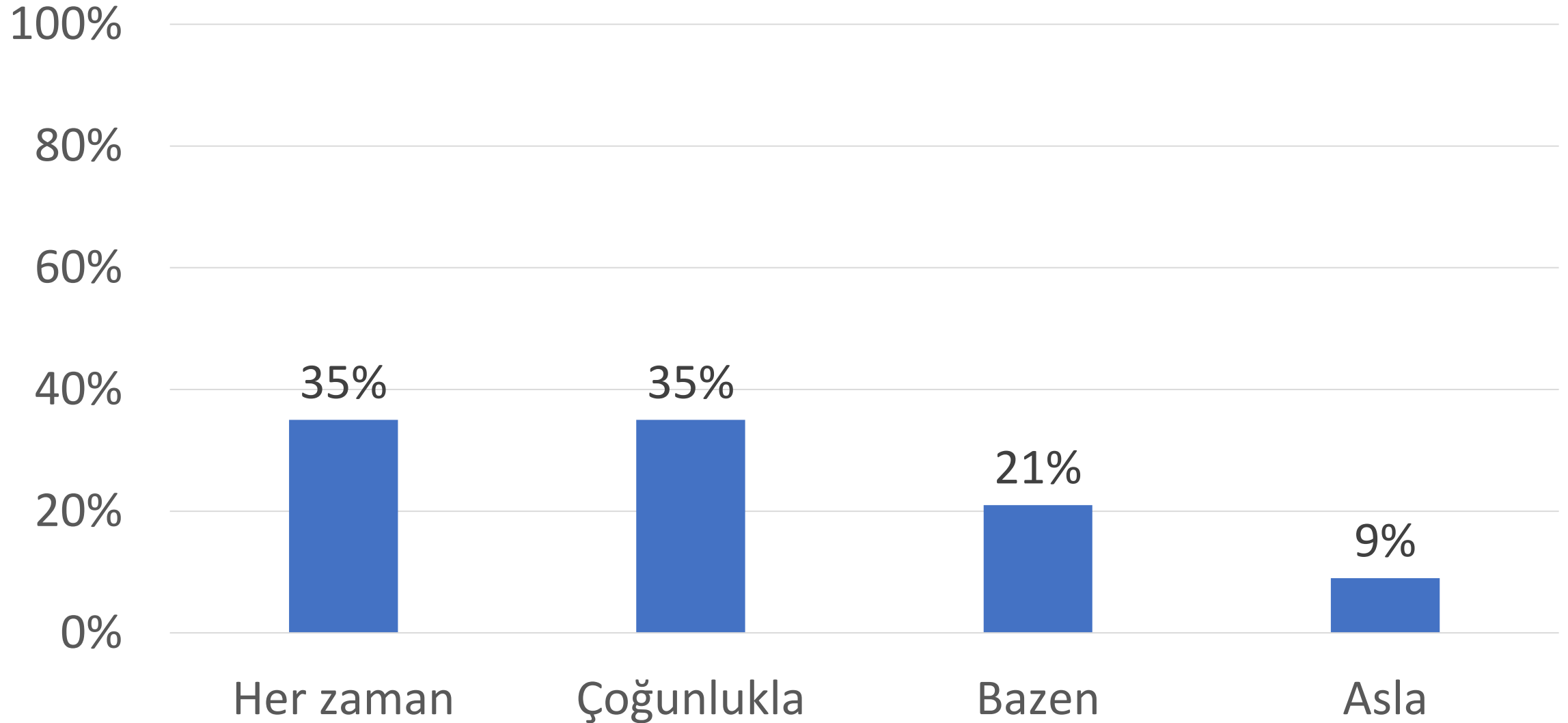
**Kültür ile Doğrulanmış Sepsis** ☐

**Klinik Tanı Sepsis** ☐

| Hemşire | Hekim | Hasta Kimlik Etiketi |
|---------|-------|----------------------|
| Tarih:  |       |                      |
| İmza:   |       |                      |

\* Systemic Inflammatory Response Syndrome \*\* Quick Sepsis-related Organ Failure Assessment  
1. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, Rubenfeld G, Kahn JM, Shankar-Hari M, Singer M, Deutschman CS, Escobar GJ, Angus DC. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315:865-874.  
2. Shankar-Hari M, Phillips GS, Levy ML, Seymour CW, Liu VX, Deutschman CS, Angus DC, Rubenfeld GD, Singer M; Sepsis Definitions Task Force. Developing a New Definition and Assessing New Clinical Criteria for Septic Shock: For the Third International Consensus Definitions for Sepsis and Septic Shock. Crit Care Med. 2017;45:e131-137.  
UD: Uygun değil

# Cerrahi profilaksi rehberini ne sıklıkla kullanıyorsunuz?



**Profilaksi rehberini kullanmıyorsanız neye göre prof. antibiyotik başlıyorsunuz?**

