Treatment of XDR Gram negatives

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Universidad de Sevilla
Spanish Network for Research in Infectious Diseases
Hospital de Sangre (5 Llagas), XVIc → Hospital Univ. V. Macarena

Plague outbreak, XVII century

A. baumannii
(AJIC 2009)

MRSA
(ICHE 2010)

ESBL-Kp
(JHI 2009)
70 yo male. Fever, right flank pain, dysuria (48h)

COPD. Admission 4 months ago because of respiratory tract infection treated with levofloxacin.

Tª 39ºC, BP: 110/65, pulse 88 bpm, rest unremarkable.

15.000 leucocytes (95% PMN), creatinine 1.9 mg/dL (calculated Cr Cl 40 mL/min), lactate normal, CRP 85 mg/L. Urine: leucocytes+++ 

Urine and blood cultures performed

Echography; mild right hydronephrosis due to ureter stone

Nephrostomy planned for next morning
Would you empirically cover...

- Fluorquinolone-resistant isolates
- Cephalosporin-resistant isolates (e.g., ESBL)
- Carbapenem-resistant isolates
- FQ and ceph-resistant isolates
- None of the above
Effects of confounders and intermediates on the association of bacteraemia caused by extended-spectrum β-lactamase-producing Enterobacteriaceae and patient outcome: a meta-analysis

Wouter C. Rottier¹*, Heidi S. M. Ammerlaan¹,² and Marc J. M. Bonten¹,³

<table>
<thead>
<tr>
<th>Study name</th>
<th>OR</th>
<th>Lower limit</th>
<th>Upper limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cordery</td>
<td>2.55</td>
<td>0.64</td>
<td>10.15</td>
</tr>
<tr>
<td>Daikos</td>
<td>1.00</td>
<td>0.31</td>
<td>3.18</td>
</tr>
<tr>
<td>Gudiol</td>
<td>1.00</td>
<td>0.33</td>
<td>3.00</td>
</tr>
<tr>
<td>Kang</td>
<td>2.99</td>
<td>1.01</td>
<td>8.83</td>
</tr>
<tr>
<td>Marchalm</td>
<td>2.30</td>
<td>1.09</td>
<td>4.87</td>
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<tr>
<td>Marra</td>
<td>1.00</td>
<td>0.39</td>
<td>2.56</td>
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<td>Meizer</td>
<td>1.81</td>
<td>0.83</td>
<td>3.52</td>
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<tr>
<td>Mendhe</td>
<td>1.00</td>
<td>0.34</td>
<td>2.94</td>
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<tr>
<td>Ortega</td>
<td>1.00</td>
<td>0.68</td>
<td>1.48</td>
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<tr>
<td>Pena</td>
<td>1.00</td>
<td>0.41</td>
<td>2.46</td>
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<td>Rodríguez-Bañó</td>
<td>1.08</td>
<td>0.43</td>
<td>2.69</td>
</tr>
<tr>
<td>Schwaber</td>
<td>3.60</td>
<td>1.38</td>
<td>9.38</td>
</tr>
<tr>
<td>Szillágyi</td>
<td>2.47</td>
<td>1.13</td>
<td>5.40</td>
</tr>
<tr>
<td>Trecarichi</td>
<td>8.84</td>
<td>1.48</td>
<td>52.86</td>
</tr>
<tr>
<td>Tsai</td>
<td>1.00</td>
<td>0.42</td>
<td>2.37</td>
</tr>
<tr>
<td></td>
<td>1.52</td>
<td>1.15</td>
<td>2.01</td>
</tr>
</tbody>
</table>

*OR and 95% CI

[Graph showing OR and 95% CI for lower and higher mortality]
Mortality and delay in effective therapy associated with extended-spectrum β-lactamase production in Enterobacteriaceae bacteraemia: a systematic review and meta-analysis

Mitchell J. Schwaber1* and Yehuda Carmeli1,2

ESBL producers: risk of appropriate treatment delay
Figure 3.2. *Escherichia coli*. Percentage (%) of invasive isolates with resistance to third-generation cephalosporins, by country, EU/EEA countries, 2014.

- < 1%
- 1% to < 5%
- 5% to < 10%
- 10% to < 25%
- 25% to < 50%
- ≥ 50%
- No data reported or less than 10 isolates
- Not included

Non-visible countries:
- Liechtenstein
- Luxembourg
- Malta
Coming from abroad?
Prevalence of ESBL producers in other areas

Data from EARS-Net, SMART, SENTRY, MYSTIC, EARSS...
Local prevalence at the time: 10-15%

### TABLE 2. Multivariate logistic regression analysis of risk factors for ESBL-producing *Enterobacteriaceae* isolation within 48 h of hospital admission in the derivation set, with corresponding point values

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Regression coefficient</th>
<th>p</th>
<th>OR (95% CI)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent hospitalization&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.73</td>
<td>&lt;0.001</td>
<td>5.69 (2.94–10.99)</td>
<td>3</td>
</tr>
<tr>
<td>Admission from another healthcare facility</td>
<td>1.72</td>
<td>0.006</td>
<td>5.61 (1.65–19.08)</td>
<td>3</td>
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<tr>
<td>Charlson comorbidity index ≥ 4</td>
<td>1.33</td>
<td>&lt;0.001</td>
<td>3.80 (1.90–7.59)</td>
<td>2</td>
</tr>
<tr>
<td>Previous therapy with β-lactams and/or fluoroquinolones&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.30</td>
<td>&lt;0.001</td>
<td>3.68 (1.96–6.91)</td>
<td>2</td>
</tr>
<tr>
<td>History of urinary catheterization&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.25</td>
<td>&lt;0.001</td>
<td>3.52 (1.96–6.91)</td>
<td>2</td>
</tr>
<tr>
<td>Age ≥70 years</td>
<td>1.16</td>
<td>&lt;0.001</td>
<td>3.20 (1.79–5.70)</td>
<td>2</td>
</tr>
</tbody>
</table>

Score 7 → 80% PPV

Tumbarello et al, AAC 2011
Back to our case…

- Empirical therapy: amoxicillin/clavulanic acid (2 g/8h) + amikacin (one dose, adjusted to renal function)

- Day 1: Nephrostomy catheter placed. Purulent urine obtained. Urine + blood cultures: Gram negative, *E. coli* (MALDI-TOF)

- Day 2. $T^\circ = 37.7^\circ C$. Normal WBC count. Creatinine 1.3 mg/dl. CRP 15 g/L. Blood and urine cultures...
Urine and blood cultures:
- Carbapenem-susceptible ESBL-producing *E. coli*

Treatment?
- A carbapenem
- I would like to see the antibiogram
## ESBL-producing *E. coli*

- **Ampicillin** | R
- **Amoxicillin/clavulante** | S (MIC=4 mg/L)
- **Piperacillin/tazobactam** | S (MIC=2 mg/L)
- **Ceftazidime** | S (MIC=1 mg/L)
- **Cefotaxime** | R
- **Cefoxitin** | S (MIC=1 mg/L)
- **Temocillin** | S
- **Meropenem** | S
- **Ertapenem** | S
- **Ciprofloxacin** | R
- **Co-trimoxazole** | R
- **Gentamicin** | R
- **Amikacin** | S
- **Tigecycline** | S (but UTI)
- **Fosfomycin** | S
Your choice for definitive therapy,..

- Amox/clav
- Pip/taz
- Ceftazidime
- Cefoxitin
- Ertapenem
- Imipenem or meropenem
- Amikacin
- Fosfomycin (IV)
Antibiotic resistance—the need for global solutions

Carbapenems sales

Figure 1: Trends in retail sales of carbapenem antibiotics for Gram-negative bacteria

Lancet Infect Dis 2013
Meta-analysis for AG in monotherapy, compared to other drugs (mostly beta-lactams and quinolones)
- Higher failure rate except in UTI
- Higher rate of adverse events
  - Vidal et al, JAC 2007
Fosfomycin disodium (IV)

- **Dosing**: 4 g/6h - 8 g/8h
  - Parker, IJAA 2013, Docobo JAC 2016
- **Well tolerated** (hypokaliemia; sodium overload)
- **Risk of resistance development**: probably lower for *E. coli*
  - Karageorgopoulos, JAC 2012
- **Limited clinical expedience and always in combination**
- **Ongoing RCT**
  - FOREST: fosfomycin vs meropenem in bacteraemic UTI due to ESBL-producing *E. coli*
Temocillin

Lack of comparative data
N=91 (43 UTI, 42 BSI, 8 HAP); 53 ESBL/AmpC producers

CURE RATES:

![Bar chart showing cure rates for different conditions and antibiotic dosages.

Balakrishnan et al, JAC 2011C

© by author
Oxy-imino-cephalosporins

- Cefotaxime, ceftriaxone, ceftazidime, cefepime
- Stochastic modelling suggests breakpoint MIC ≤1 mg/L
  - MacGowan, CMI 2008, Nguyen, JAC 2014
- BUT: inoculum effect, expression of beta-lactamases
- Scarce clinical data
  - Good results: Goethaert, CMI 2006 (n=21); Bin, DMID 2006 (n=7)
  - Not so good: Rodríguez-Baño, CMI 2012; Chopra, AAC 2012, Lee, CID 2013

- Interpretation
  - Probably safe for UTI if MIC ≤1 mg/L
  - Doubts for septic shock/non-UTI...
Beta-lactam/beta-lactam inhibitors

- Resistance due to ESBL overproduction, additional mechanisms (AmpC-type, OXA-1, porin loss, etc.)
- Inoculum effect: pit/taz but not amox/clav
  - López-Cerero, CMI 2010
- Animal models: exposure-dependent efficacy
BLBLI vs carbapenems

<table>
<thead>
<tr>
<th></th>
<th>Empirical therapy cohort</th>
<th>Definitive therapy cohort</th>
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</thead>
<tbody>
<tr>
<td>Death (HR, adjusted)*</td>
<td>0.93 (0.25-3.51)</td>
<td>0.76 (0.28-2.07)</td>
</tr>
<tr>
<td>Hospital stay (HR, adjusted)*</td>
<td>1.07 (0.3-3.0)</td>
<td>1.32 (0.91-1.90)</td>
</tr>
</tbody>
</table>

*Including propensity score

BUT
Community-onset BSI due to ESBL-E. coli
60% urinary or biliary tract
**Carbapenems versus alternative antibiotics for the treatment of bacteraemia due to Enterobacteriaceae producing extended-spectrum β-lactamases: a systematic review and meta-analysis**

Konstantinos Z. Vardakas¹,², Giannoula S. Tansarlí¹, Petros I. Rafailidis¹,² and Matthew E. Falagas¹–³*

<table>
<thead>
<tr>
<th>Carbapenems</th>
<th>Pooled RR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>vs. non-BLBI</td>
<td></td>
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<tr>
<td>Empirical</td>
<td>0.50 (0.33-0.77)</td>
</tr>
<tr>
<td>Definitive</td>
<td>0.65 (0.47-0.91)</td>
</tr>
<tr>
<td>vs. BLBLI</td>
<td></td>
</tr>
<tr>
<td>Empirical</td>
<td>0.91 (0.66-1.25)</td>
</tr>
<tr>
<td>Definitive</td>
<td>0.52 (0.23-1.13)</td>
</tr>
</tbody>
</table>

JAC 2013

© by author
Mosty *Klebsiella* spp; lower dose of piptaz
INCREMENT Project
BLBLI vs carbapenems

Sensitivity tests
Anecdotal report of development of R during therapy

**PRO**

- Retrospective, multicenter. Bacteremia due to ESBL-producing *E. coli*. Cefmetazole or flomoxef vs carbapenems.
  - Matsumura et al. AAC 2015
  - Lee et al, JAC 2016

**CON**

- Retrospective cohort, ESBL Kleb or *E. coli*. Flomoxef.
  - Lee et al, IJAA 2015
Back to our case...

- Definitive therapy: amoxicillin/clavulanic acid (2 g/8h), switched to oral after 4 days
- Discharged day 8
- Follow-up culture negative on day 4 and thereafter
- 10 days total duration of therapy
- Lithotripsy performed 2 weeks later, nephrostomy catheter removed
this issue. However, the emerging evidence suggests that “infection due to ESBL producer” must no longer be followed by “therapy with a carbapenem” without some consideration of alternative approaches.
78 yo female, admitted because of stroke. Urinary catheter because of urinary retention.

Day 5: UTI due to *Proteus mirabilis*, ciprofloxacin.

Day 10: new fever, cough, dyspnoea. Aspiration 2 days before.

Tª 39ºC, BP 95/65 mmHg, heart rate 90/min, rest unremarkable.

17.000 WBC (85% leucocytes), creatinine 0.9 mg/dl, lactate 2.5 mmol/L. O₂ sat 94%. Chest X-ray: new infiltrate

Urine and blood cultures performed

Oxygen, IV fluids and piperacillin/tazobactam (4/0.5 g bid, prolonged infusion) + amikacin (15 mg/Kg) administered.

Blood cultures...
ESBL-producing *K. pneumoniae*

- Ampicillin: R
- Amoxicillin/clavulante: R
- Piperacillin/tazobactam: R
- Ceftazidime: R
- Cefotaxime: R
- Cefoxitin: R
- Temocillin: R
- **Meropenem**: S (≤0.125 mg/L)
- Ertapenem: S (0.5 mg/L)
- Ciprofloxacin: R
- Co-trimoxazole: R
- Gentamicin: R
- **Amikacin**: S
- Tigecycline: S (1 mg/L)
- Fosfomycin: S (8 mg/L)
- Colistin: S (1 mg/L)
Your choice for definitive therapy...

- Ertapenem
- Imipenem or meropenem
- Amikacin
- Tigecycline
- Fosfomycin
- Colistin
- Combination therapy
Your choice for definitive therapy...

- Ertapenem
- Imipenem or meropenem
- Amikacin
- Tigecycline
- Fosfomycin
- Colistin
- Combination therapy

Lower efficacy in non-UTI infections
Paul et al, JAC 2007
Your choice for definitive therapy...

- Ertapenem
- Imipenem or meropenem
- Amikacin
- Tigecycline
- Fosfomycin
- Colistin
- Combination therapy

Lower efficacy in meta-analysis
Tasina et al, Lancet ID 2011
Yahav et al, JAC 2011
Prased et al CID 2012
Your choice for definitive therapy...

- Ertapenem
- Imipenem or meropenem
- Amikacin
- Tigecycline
- Fosfomycin
- Colistin
- Combination therapy

Scarce experience, combination
Your choice for definitive therapy...

- Ertapenem
- Imipenem or meropenem
- Amikacin
- Tigecycline
- Fosfomycin
- Colistin
- Combination therapy

Reserve for carba-R?
Your choice for definitive therapy...

- Ertapenem
- Imipenem or meropenem
- Amikacin
- Tigecycline
- Fosfomycin
- Colistin
- Combination therapy

No evidence for superiority
Ertapenem

- Lower ecologic (or not higher) impact on *P. aeruginosa* than imipenem/meropenem
  - Sousa, JAC 2013; Carmeli, DMID 2011; Eagye, JAC 2011; Cook, AAC 2011; Nicoalu, IJAA 2012

- Evidence of efficacy in ESBL: cohorts, case-series
  - OPAT: Bazaz, JAC 2010

- Anecdotal reports of development of R
Ertapenem in critically ill patients with early-onset ventilator-associated pneumonia: pharmacokinetics with special consideration of free-drug concentration

Olaf Burkhardt¹⁻³, Vipul Kumar¹, Denise Katterwe³, Jolanta Majcher-Peszynska⁴, Bernd Drewelow⁴, Hartmut Derendorf¹ and Tobias Welte²,³


Time after start of infusion (h)

0.5 mg
Ertapenem for the treatment of bloodstream infections due to ESBL-producing Enterobacteriaceae: a multinational pre-registered cohort study

Belén Gutiérrez-Gutiérrez1, Robert A. Bonomo2,3, Yehuda Carmeli4, David L. Paterson5, Benito Almirante6, Luis Martinez-Martinez7, Antonio Oliver8, Esther Calbo9, Carmen Peña10, Murat Akava11, Johann Pitout12, Julio Orögén13, Vicente Pintado14, Elisa García-Vázquez15, Oriol Gasch16, Axel Hamprecht17, Nuria Prim18, Mario Tumbarello19, German Bou20, Pierluigi Viale21, Evelina Tacconelli22, Manel Almela23, Federico Pérez24, Helen GiamarelloZúñiga24, José Miguel Clisneros25, Mitchell J. Schwaber24, Mario Venditti26, Warren Lowman26, Joaquín Bermejo27, Po-Ren Hsueh28, Marta Mora-Rillo29, Irene Gracia-Ahulguera29, Álvaro Pasquali30 and Jesús Rodríguez-Baño31,32 on behalf of the REIPI/ESGBIS/INCREMENT Group†

J Antimicrob Chemother 2016
Back to our case...

- Contact precautions
- Day 3, definitive therapy:
  - Discussion AMS team: ertapenem 1 gr/day, ertapenem 2 gr/day or meropenem 1 gr/8h??
  - Meropenem 1 g/8h was started
- Early response. Negative follow-up blood cultures
- Day 6: switched to ertapenem 1 gr/day and discharged (OPAT)
- Day 10: stop antibiotics (7 days, total duration with carbapenems)
• 57 y, male, stroke
• Nosocomial pneumonia, severe sepsis, bacteraemic
• *K. pneumoniae*  MIC (mg/L)  Report
  - Ceftazidime  >32  R
  - Meropenem  8  R
  - Gentamicin  >32  R
  - Cipro  >2  R
  - Tigecycline  4  R
  - Colistin  1  S
  - Fosfomycin  16  S
Select your choice...

- Meropenem (optimised)
- Colistin (optimised)
- Combination: meropenem + colistin
- Combination: meropenem + colistin + fosfomycin
- Meropenem + ertapenem
- 57 y female, kidney stones
- Low grade fever, urinary complains. Urine + blood cultures. Dicharged with oral amox/clav → ID outpatient clinic
- Urine and blood:
- **K. pneumoniae**
  - Ceftazidime: >32 R
  - Meropenem: 0.5 S
  - Ertapenem: 2 R
  - Gentamicin: 0.5 S
  - Cipro: >2 R
  - Tigecycline: 0.5 S
  - Colistin: 1 S
  - Fosfomycin: 16 S
Select your choice...

- Meropenem
- Colistin
- Combination: meropenem + colistin
- Combination: meropenem + colistin + fosfomycin
- Combination: colistin + fosfomycin
- Any other
Carbapenem resistance in Enterobacteriaceae

• ESBL or AmpC + porin loss
• Carbapenemases (heterogeneous carba MIC)
  – Class A: KPC
  – Class B: MBL (VIM, IMP, NDM...)
    • No active against aztreonam
  – Class D: OXA-48
    • No active against cephalosporins (but ESBL frequent)
Carbapenemase-producing *Klebsiella pneumoniae*: (when) might we still consider treating with carbapenems?

G. L. Daikos¹ and A. Markogiannakis²

**FIG. 2.** Simulated target attainment probabilities for 50% time above the MIC (50% T > MIC) of three different regimens of meropenem. TI, traditional 30-min infusion; PI, prolonged 3-h infusion. Adapted from [36].
TABLE 5 Results of carbapenem monotherapy in 50 CPE-infected patients from 15 studies

<table>
<thead>
<tr>
<th>MIC of carbapenem (µg/ml)</th>
<th>No. of patients</th>
<th>No. of successes</th>
<th>No. of failures</th>
<th>% Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1</td>
<td>12</td>
<td>12</td>
<td>5</td>
<td>29.4</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>9</td>
<td>3</td>
<td>25.0</td>
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<td>4</td>
<td>6</td>
<td>5</td>
<td>2</td>
<td>28.6</td>
</tr>
<tr>
<td>8</td>
<td>8</td>
<td>2</td>
<td>6</td>
<td>33.3</td>
</tr>
</tbody>
</table>

Subtotal                   | 42             | 30              | 12             | 28.6b     |

Total                      | 50             | 32              | 18             | 36        |
Carbapenemases in Klebsiella pneumoniae and Other Enterobacteriaceae: an Evolving Crisis of Global Dimensions

L. S. Tzouvelekis, A. Markogiannakis, M. Psychogiou, P. T. Tassios, and G. L. Daikos

Clin Microbiol Rev 2012
## Clinical studies analysing combination therapy for CPE

<table>
<thead>
<tr>
<th>Ref</th>
<th>Design</th>
<th>Patients</th>
<th>N</th>
<th>Lower mortality (adjusted)</th>
<th>Limitations</th>
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<tbody>
<tr>
<td>Zarcotou</td>
<td>Retrospective cohort</td>
<td>Bacteraemia KPC Kp</td>
<td>53</td>
<td>No¹ (adequate therapy)</td>
<td>+++</td>
</tr>
<tr>
<td>CMI 2011</td>
<td></td>
<td></td>
<td></td>
<td>(infection-related)</td>
<td></td>
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<tr>
<td>Tumbarello</td>
<td>Retrospective cohort</td>
<td>Bacteraemia KPC Kp</td>
<td>124</td>
<td>Yes¹ (MER + COL + TIG)</td>
<td>++</td>
</tr>
<tr>
<td>CID 2013</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Qureshi</td>
<td>Retrospective cohort</td>
<td>Bacteraemia KPC Kp</td>
<td>41</td>
<td>Yes²</td>
<td>+++</td>
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<td>AAC 2013</td>
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<td>Daikos</td>
<td>Retrospective cohort</td>
<td>Bacteraemia KPC or VIM Kp</td>
<td>205</td>
<td>Yes¹</td>
<td>++</td>
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<td>AAC 2014</td>
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</table>

1. In vitro active (EUCAST)
2. With activity against gram negatives
Carbapenemase-Producing *Klebsiella pneumoniae* Bloodstream Infections: Lowering Mortality by Antibiotic Combination Schemes and the Role of Carbapenems

A

<table>
<thead>
<tr>
<th></th>
<th>Mortality (%)</th>
<th>N=49</th>
<th>N=73</th>
<th>N=14</th>
<th>N=16</th>
<th>p=0.045</th>
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<tbody>
<tr>
<td>Sepsis</td>
<td></td>
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<tr>
<td>Severe sepsis</td>
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<td></td>
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<td></td>
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<td>p=0.746</td>
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<tr>
<td>Septic shock</td>
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B

<table>
<thead>
<tr>
<th></th>
<th>Mortality (%)</th>
<th>N=54</th>
<th>N=86</th>
<th>N=18</th>
<th>N=17</th>
<th>p=0.001</th>
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<tbody>
<tr>
<td>Non-rapidly fatal</td>
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<tr>
<td>Rapidly fatal</td>
<td></td>
<td></td>
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</table>

p=0.547

Combined therapy

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

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![Bar chart showing mortality rates for different types of infections](chart.png)

J Antimicrob Chemother 2015
Survivor bias
Higher probability of receiving combination therapy in survivors?

BSI
Isolation of MDR *K. pneumoniae*
Not clearly improving

Meropenem
Colistin
Tigecycline

BSI
Death

Meropenem
## Bacteraemia due to OXA-48-carbapenemase-producing Enterobacteriaceae: a major clinical challenge

C. Navarro-San Francisco¹, M. Mora-Rillo¹, M. P. Romero-Gómez², F. Moreno-Ramos³, A. Rico-Nieto¹, G. Ruiz-Carrascoso², R. Gómez-Gil², J. R. Arribas-López¹, J. Mingorance² and J. R. Paño-Pardo¹

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### Table: Treatment Outcomes

<table>
<thead>
<tr>
<th>Treatment</th>
<th>All patients (n = 34)</th>
<th>Patients alive at day 30 after onset of BSI (n = 19) (%)</th>
<th>Patients dead at day 30 after onset of BSI (n = 15) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monotherapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colistin</td>
<td>1</td>
<td>1 (5.2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>2</td>
<td>2 (10.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Amikacin</td>
<td>3</td>
<td>2 (10.5)</td>
<td>1 (6.6)</td>
</tr>
<tr>
<td>Carbapenem</td>
<td>1</td>
<td>0 (0)</td>
<td>1 (6.6)</td>
</tr>
<tr>
<td><strong>Total monotherapy</strong></td>
<td>7</td>
<td>5 (26.3)</td>
<td>2 (13.3)</td>
</tr>
<tr>
<td><strong>Combined therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Two or more active drugs (carbapenem not included)</td>
<td>21</td>
<td>10 (52.6)</td>
<td>11 (73.3)</td>
</tr>
<tr>
<td>Two or more active drugs (carbapenem included)</td>
<td>6</td>
<td>4 (21.1)</td>
<td>2 (13.3)</td>
</tr>
<tr>
<td><strong>Total combined therapy</strong></td>
<td>27</td>
<td>14 (73.7)</td>
<td>13 (86.6)</td>
</tr>
</tbody>
</table>

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2/5 (40%)  13/27 (48%)
Carbapenem-Sparing Antibiotic Regimens for Infections Caused by *Klebsiella pneumoniae* Carbapenemase–Producing *K. pneumoniae* in Intensive Care Unit

Francesco Sbrana,1 Paolo Malacarne,2 Bruno Viaggi,2 Sergio Costanzo, Piero Leonetti,3 Alessandro Leonildi,4 Beatrice Casini,5 Carlo Tascini,4 and Francesco Menichetti

Clin Infect Dis 2013

26 infections in 22 patients
18 polytrauma

TIG + GEN: 16 (+ FOS 8)
TIG + COL 11 (+ FOS 5, GEN 5)
COS + GEN 1
TIG 1

<table>
<thead>
<tr>
<th>Site of Infection</th>
<th>Appropriate Therapy by Vitek 2 System</th>
<th>Appropriate Therapy by E-test&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Response to Therapy</th>
<th>Survival at 30 Days After Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAP with bacteremia</td>
<td>0/5</td>
<td>5/5</td>
<td>4/5</td>
<td>3/5&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bloodstream infection</td>
<td>1/7</td>
<td>7/7</td>
<td>7/7</td>
<td>7/7</td>
</tr>
<tr>
<td>Others&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1/3</td>
<td>3/3</td>
<td>2/3</td>
<td>2/3&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> E-test: 23/26

<sup>b</sup> Others: 23/26
Back to our first CPE case...

- KPC producer
- *K. pneumoniae*  
<table>
<thead>
<tr>
<th>MIC (mg/L)</th>
<th>Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftazidime</td>
<td>&gt;32</td>
</tr>
<tr>
<td>Meropenem</td>
<td>8</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>&gt;32</td>
</tr>
<tr>
<td>Cipro</td>
<td>&gt;2</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>4</td>
</tr>
<tr>
<td>Colistin</td>
<td>1</td>
</tr>
<tr>
<td>Fosfomycin</td>
<td>16</td>
</tr>
</tbody>
</table>

- My choice would be meropenem 2 g/8h (extended infusion) + colistin 4.5 million IU/12h (loading dose, 6 M)
- May consider adding fosfomycin 4 gr/6h if no early response (48 h)
Back to our second CRP case...

- OXA-48 + ESBL producer
- *K. pneumoniae* MIC (mg/L) Report
  - Ceftazidime >32 R
  - Meropenem 0.5 S
  - Ertapenem 2 R
  - Gentamicin 0.5 S
  - Cipro >2 R
  - Tigecycline 0.5 S
  - Colistin 1 S
  - Fosfomycin 16 S

- Urologic work-up
- Gentamicin 5 mg/kg/day 5 days
- Follow-up cultures negative day 3
- Switched to oral fosfomycin tromethamine, 3 g /48h to complete 14 days
Diagnosis and antimicrobial treatment of invasive infections due to multidrug-resistant Enterobacteriaceae. Guidelines of the Spanish Society of Infectious Diseases and Clinical Microbiology

Jesús Rodríguez-Baño\textsuperscript{a,b,\*}, José Miguel Cisneros\textsuperscript{a,c}, Nazaret Cobos-Trigueros\textsuperscript{d}, Gema Fresco\textsuperscript{e}, Carolina Navarro-San Francisco\textsuperscript{f}, Carlota Gudiel\textsuperscript{g}, Juan Pablo Horcajada\textsuperscript{h}, Lorena López-Cerero\textsuperscript{a}, José Antonio Martínez\textsuperscript{d}, José Molina\textsuperscript{a}, Milagro Montero\textsuperscript{h}, José R. Paño-Pardo\textsuperscript{f}, Alvaro Pascual\textsuperscript{a,i}, Carmen Peña\textsuperscript{g}, Vicente Pintado\textsuperscript{e}, Pilar Retamar\textsuperscript{a}, María Tomás\textsuperscript{j}, Marcio Borges-Sa\textsuperscript{k}, José Garnacho-Montero\textsuperscript{c,l}, Germán Bou\textsuperscript{j}, for the Study Group of Nosocomial Infections (GEIH) of the Spanish Society of Infectious Diseases, Infectious Diseases (SEIMC)

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Standard dose</th>
<th>Recommended dose in case of severe infection and borderline susceptibility</th>
<th>Strength and quality of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meropenem</td>
<td>1–2 g/8 h</td>
<td>2 g/8 h (EI)</td>
<td>BII</td>
</tr>
<tr>
<td>Imipenem</td>
<td>0.5 g/6 h–1 g/8 h</td>
<td>1 g/8 h</td>
<td>CIII</td>
</tr>
<tr>
<td>Doripenem</td>
<td>0.5 g/8 h</td>
<td>1 g/8 h&lt;sup&gt;b&lt;/sup&gt;</td>
<td>CIII</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>1 g/24 h</td>
<td>1 g/12 h&lt;sup&gt;b&lt;/sup&gt;</td>
<td>CIII</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>1 g/8 h</td>
<td>2 g/8 h (EI)</td>
<td>CIII</td>
</tr>
<tr>
<td>Amoxicillin–clavulanic acid</td>
<td>1 g/0.2 g/8 h</td>
<td>1.2 g/6 h or 2.2 g/8 h</td>
<td>BIII</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>4/0.5 g/8 h</td>
<td>4/0.05 g/8 h or 4/0.5 g/6 h in critically ill patients (EI)</td>
<td>BIII</td>
</tr>
<tr>
<td>Colistin</td>
<td>1–2 MU/8 h</td>
<td>LD: 6–9 MU, MD: 4.5 MU/12 h</td>
<td>BIII</td>
</tr>
<tr>
<td>Amikacin&lt;sup&gt;c&lt;/sup&gt;</td>
<td>15 mg/kg/day</td>
<td>LD: 100 mg, MD: 50 mg/12 h</td>
<td>CIII</td>
</tr>
<tr>
<td>Tigecycline</td>
<td></td>
<td>LD: 20 mg/kg/day, MD: 150–200 mg</td>
<td>BIII</td>
</tr>
<tr>
<td>Fosfomycin disodium</td>
<td>4–6 g/6 h</td>
<td>Not defined</td>
<td>CIII</td>
</tr>
<tr>
<td></td>
<td>or 8 g/8 h</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Colistin resistance

• Different mechanism

• Recent description of plasmid-mediated (MCR-1)
  – China/East Asia: Liu et al, Lancet Infect Dis 2016; Yu et al, AAC 2016; etc
  – USA: McGann, AAC 2016;
  – South America: Fernandes et al, EurSurv 2016
  – South Africa: Coetzee et al, SAMJ 2016
Gentamicin therapy for sepsis due to carbapenem-resistant and colistin-resistant Klebsiella pneumoniae

Marcelino Gonzalez-Padilla, Julián Torre-Cisneros, Francisco Rivera-Espinar, Antonio Pontes-Moreno, Lorena López-Cerero, Alvaro Pascual, Clara Natera, Marina Rodríguez, Inmaculada Salceda, Fernando Rodríguez-López, Antonio Rivero and Jesús Rodríguez-Baño.

Table 5. Multivariate models of risk factors for 30 day crude mortality in patients with carbapenem-resistant and colistin-resistant K. pneumoniae sepsis.

<table>
<thead>
<tr>
<th>Model</th>
<th>Risk Factor</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>Optimal targeted treatment with gentamicin</td>
<td>0.14 (0.03-0.62)</td>
<td>0.010</td>
</tr>
<tr>
<td>Model 1</td>
<td>Optimal targeted treatment</td>
<td>1.19 (0.31-4.53)</td>
<td>0.725</td>
</tr>
<tr>
<td>Model 1</td>
<td>Age</td>
<td>1.04 (1.00-1.07)</td>
<td>0.010</td>
</tr>
<tr>
<td>Model 1</td>
<td>Severe sepsis or septic shock diagnosis</td>
<td>21.2 (2.70-165.9)</td>
<td>0.004</td>
</tr>
<tr>
<td>Model 2</td>
<td>Optimal targeted treatment with gentamicin</td>
<td>0.76 (0.09-0.72)</td>
<td>0.010</td>
</tr>
<tr>
<td>Model 2</td>
<td>Optimal empirical treatment</td>
<td>0.56 (0.12-2.54)</td>
<td>0.455</td>
</tr>
<tr>
<td>Model 2</td>
<td>CLCR</td>
<td>0.99 (0.98-0.99)</td>
<td>0.017</td>
</tr>
<tr>
<td>Model 3</td>
<td>Optimal targeted treatment with gentamicin</td>
<td>0.23 (0.08-0.63)</td>
<td>0.005</td>
</tr>
<tr>
<td>Model 3</td>
<td>Severe sepsis or septic shock diagnosis</td>
<td>15.3 (1.99-117.5)</td>
<td>0.009</td>
</tr>
<tr>
<td>Model 3</td>
<td>CLCR</td>
<td>0.99 (0.98-1.004)</td>
<td>0.15</td>
</tr>
<tr>
<td>Model 4</td>
<td>Optimal targeted treatment with gentamicin</td>
<td>0.19 (0.07-0.54)</td>
<td>0.002</td>
</tr>
<tr>
<td>Model 4</td>
<td>Age</td>
<td>1.03 (1.00-1.05)</td>
<td>0.012</td>
</tr>
<tr>
<td>Model 4</td>
<td>CLCR</td>
<td>0.98 (0.97-0.99)</td>
<td>0.02</td>
</tr>
<tr>
<td>Model 5</td>
<td>Optimal targeted treatment with gentamicin</td>
<td>0.24 (0.08-0.67)</td>
<td>0.007</td>
</tr>
<tr>
<td>Model 5</td>
<td>Urinary tract infection as site of infection</td>
<td>0.39 (0.55-4.43)</td>
<td>0.39</td>
</tr>
<tr>
<td>Model 5</td>
<td>CLCR</td>
<td>0.99 (0.98-0.99)</td>
<td>0.03</td>
</tr>
<tr>
<td>Model 6</td>
<td>Optimal targeted treatment with gentamicin</td>
<td>0.29 (0.09-0.89)</td>
<td>0.03</td>
</tr>
<tr>
<td>Model 6</td>
<td>Neoplasia</td>
<td>4.56 (1.59-13.0)</td>
<td>0.005</td>
</tr>
<tr>
<td>Model 6</td>
<td>CLCR</td>
<td>0.98 (0.98-0.99)</td>
<td>0.024</td>
</tr>
<tr>
<td>Model 7</td>
<td>Optimal targeted treatment with gentamicin</td>
<td>0.30 (0.11-0.84)</td>
<td>0.02</td>
</tr>
<tr>
<td>Model 7</td>
<td>Optimal targeted treatment with tigecycline</td>
<td>0.51 (0.19-1.32)</td>
<td>0.16</td>
</tr>
<tr>
<td>Model 7</td>
<td>CLCR</td>
<td>0.98 (0.98-0.99)</td>
<td>0.02</td>
</tr>
<tr>
<td>Model 8</td>
<td>Optimal targeted treatment with gentamicin</td>
<td>0.28 (0.10-0.82)</td>
<td>0.02</td>
</tr>
<tr>
<td>Model 8</td>
<td>Hospitalization in previous 3 months</td>
<td>1.44 (0.54-3.86)</td>
<td>0.46</td>
</tr>
<tr>
<td>Model 8</td>
<td>CLCR</td>
<td>0.99 (0.98-0.99)</td>
<td>0.039</td>
</tr>
</tbody>
</table>

Figure 2. Kaplan–Meier curves showing the impact of treatment with suboptimal targeted treatment, optimal targeted treatment without gentamicin and optimal 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 17.3, P<0.001).
Successful Ertapenem-Doripenem Combination Treatment of Bacteremic Ventilator-Associated Pneumonia Due to Colistin-Resistant KPC-Producing *Klebsiella pneumoniae*

Giancarlo Ceccarelli, Marco Falcone, Alessandra Giordano, Maria Lina Mezzatesta, Carla Caio, Stefania Stefani, Mario Venditti

Effectiveness of a Double-Carbapenem Regimen for Infections in Humans Due to Carbapenemase-Producing Pandrug-Resistant *Klebsiella pneumoniae*

Helen Giamarello, Lambrini Galani, Fotini Baziko, Ilias Karraskos

Synergistic activity and effectiveness of a double-carbapenem regimen in pandrug-resistant *Klebsiella pneumoniae* bloodstream infections

Alessandra Oliva, Alessandra D’Abramo, Claudia D’Agostino, Marco Iannetta, Maria T. Mascellino, Carmela Gallinelli, Claudio M. Mastroianni and Vincenzo Vullo

Ertapenem-Containing Double-Carbapenem Therapy for Treatment of Infections Caused by Carbapenem-Resistant *Klebsiella pneumoniae*

Jessica B. Cryes, Jason C. Gallagher

Severe Bloodstream Infection due to KPC-Producer *E. coli* in a Renal Transplant Recipient Treated With the Double-Carbapenem Regimen and Analysis of In Vitro Synergy Testing

A Case Report

Alessandra Oliva, MD, PhD, Alessia Cipolla, MS, Francesca Gizzi, MD, Alessandra D’Abramo, MD, PhD, Marco Favaro, PhD, Massimiliano De Angelis, MS, Giancarlo Ferretti, MD, Gianluca Russo, MD, PhD, Marco Iannetta, MD, PhD, Claudio M. Mastroianni, MD, PhD, Maria T. Mascellino, BCMP, and Vincenzo Vullo, MD, PhD
Pipeline

- Ceftazidima-avibactam
  - In vitro active against ESBL-producers, KPC-producers, OXA-48
  - Not active against MBLs
  - Preliminary approval EMA (cUTI, cIAI, NP, GN with limited options)
- Aztreonam-avibactam
  - Add activity against MBLs
- Ceftolozane-tazobactam
  - Active against ESBLs and enhanced activity against *P. aeruginosa*
  - Approved EMA/FDA (cUTI, cIAI)
- Imipenem-relebactam, meropenem-RPX7009
  - Active against KPC
- Plazomycin, everacycline

- Resistance - how long will it takes?
2,000/500 mg/8h
Only 5% bacteraemia
Most BAT: carbapenems
Conclusions

• Empirical treatment
  – Consider severity, local epi, individual risk factors

• Individualisation
  – Severity, source, antibiogram, dosing

• ESBL
  – Not only carbapenems

• CPE
  – Severe infections, possibly combination incluing meropenem if MIC <16 mg/L
  – Combination probably not be needed in other situations
  – CAZ-AVI recently approved
Sevilla
ESCMID Course on Research Methodology (October 26-28)