Preparing the future ESCMID guideline on infections due to MDR Gram-negative bacteria - a case-based discussion

Discussion panel:
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Mical Paul
Pilar Retamar
Evelina Tacconelli
Case 5
03-01-2018

56 year-old men
- 2017: massive rectorragnia requiring urgent colectomy (intestinal lymphoma); secondary peritonitis requiring reintervention (pip-taz; meropenem); CVC-BSI S. epidermidis (vanco); right nephrostomy (urether infiltration)
- 5 chemo cycles (last one 7 days before hospital admission)
- Recurrent UTIs (cipro, amoxi-clav)
- No allergies

**Medical history**

**Hospital admission**

**Empirical treatment:** colistin 3 MU/8h + meropenem 2 g/8h (extended infusion)

- Fever
- Purulent urine (nephrostomy bag)

**Physical examination:**
- T: 38,3°C, BP 76/44, HR 98, RR 14

**Tests:**
- WBC: 1.200 leucocytes/mm3 (960 neutrophils/mm3), lactate 2.8 mmol/L, creatinine 1.3 mg/dL; urine: nitrites (+), leucocytes (+++)
- Urine and blood culture performed
- Rectal swab positive for KPC-producing *Klebsiella pneumoniae*
Case 5
Urine and blood culture

KPC producer

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>S/I/R</th>
<th>MIC (ug/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>R</td>
<td>&gt;16</td>
</tr>
<tr>
<td>Amoxicillin-clavulanic</td>
<td>R</td>
<td>&gt;16/8</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>R</td>
<td>&gt;64/4</td>
</tr>
<tr>
<td>Cepharoquine</td>
<td>R</td>
<td>&gt;16</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>R</td>
<td>&gt;16</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>R</td>
<td>&gt;16</td>
</tr>
<tr>
<td>Ceftazidime-avibactam</td>
<td>S</td>
<td>≤1</td>
</tr>
<tr>
<td>Cefepim</td>
<td>R</td>
<td>&gt;8</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>R</td>
<td>&gt;1</td>
</tr>
<tr>
<td>Meropenem</td>
<td>R</td>
<td>&gt;16</td>
</tr>
<tr>
<td>Amikacin</td>
<td>R</td>
<td>&gt;32</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>R</td>
<td>&gt;4</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>R</td>
<td>&gt;4</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>R</td>
<td>&gt;2</td>
</tr>
<tr>
<td>Tmp/Smx</td>
<td>R</td>
<td>&gt;4/76</td>
</tr>
<tr>
<td>Colistin</td>
<td>S</td>
<td>≤1</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>S</td>
<td>≤1</td>
</tr>
</tbody>
</table>

Fosfomycin susceptible
Question for a smart audience
How would you treat?

1. Colistin
2. Colistin and Meropenem
3. Colistin and Tigecyclin
4. Colistin, Tigecyclin, and Meropenem
5. Ceftazidime-avibactam
6. Ceftazidime-avibactam and Colistin / Meropenem
• Symptoms
• Source of infection
• Comorbidities
• Risk for future infections

Patient

• Sensitivity pattern
• Risk of relapse
• Risk of development of new resistance

Bacteria

• Penetration
• Side effects
• Selection of resistance
• Mono vs combi

Drug

• Ward colonisation pressure
• Risk of resistance in community

Society
- Mild symptomatic
- Urinary tract source of infection
- No allergies
- Not severe neutropenia
- Age < 60 y.o.
- Right nephrostomy
- Intestinal lymphoma
- Recurrent UTIs

**Patient**

- Sensitivity pattern
- Risk of relapse
- Risk of development of new resistance

**Bacteria**

- KPC producer
- Meropenem MIC
- Risk of relapse of KP
- Risk of development of resistance

**Society**

- Ward colonisation pressure
- Risk of resistance in community

- Impact of usage of colistin / cefta-avibactam / tigecycline on selecting ward´s resistance rates
- Risk of spreading resistance in the community (home discharge / LTCF)
1. Monotherapy vs combination therapy

**BSI** (285 patients)  
**OR 2.09, 95%CI 1.21–3.6**

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Bacteria</th>
<th>Infection</th>
<th>Mono events/total</th>
<th>Comb events/total</th>
<th>Weight</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daikos, 2014</td>
<td>KP</td>
<td>BSI</td>
<td>12/22</td>
<td>13/49</td>
<td>26.67%</td>
<td>3.32 (1.16, 9.51)</td>
</tr>
<tr>
<td>Gomez-Simmonds, 2016</td>
<td>KP</td>
<td>BSI</td>
<td>2/7</td>
<td>14/32</td>
<td>9.29%</td>
<td>0.51 (0.09, 3.06)</td>
</tr>
<tr>
<td>Kontopidou, 2014</td>
<td>KP</td>
<td>BSI</td>
<td>6/26</td>
<td>6/30</td>
<td>18.07%</td>
<td>1.20 (0.33, 4.31)</td>
</tr>
<tr>
<td>Moloudi, 2010</td>
<td>KP</td>
<td>BSI</td>
<td>15/19</td>
<td>10/17</td>
<td>13.73%</td>
<td>2.62 (0.61, 11.37)</td>
</tr>
<tr>
<td>Nguyen, 2010</td>
<td>KP</td>
<td>BSI</td>
<td>4/9</td>
<td>4/13</td>
<td>9.47%</td>
<td>1.80 (0.31, 10.52)</td>
</tr>
<tr>
<td>Turnbarello, 2012</td>
<td>KP</td>
<td>BSI</td>
<td>11/22</td>
<td>7/23</td>
<td>19.84%</td>
<td>2.29 (0.68, 7.74)</td>
</tr>
<tr>
<td>Zarkotou, 2011</td>
<td>KP</td>
<td>BSI</td>
<td>4/7</td>
<td>0/9</td>
<td>2.94%</td>
<td>24.43 (1.03, 580.63)</td>
</tr>
</tbody>
</table>

**Zusman O, 2017: 7 retrospective cohort studies**  
- Mortality was significantly higher with polymyxin mono vs combi (tige/ amino/ fosfo); 285 patients, no heterogeneity; very low quality

**BSAC guidelines 2018** (SR 2012, Medline up to 2014, some references added Oct 2016-June 2017)

Recommendation by antibiotic and bacteria  
- **Severe infections use combination**
2017-2018 evidence

1.44 (1.03 – 2.00) in favour of combination (low risk of bias)

1.59 (1.06 – 2.39) in favour of combination (BSI)

Carrara E, ESCMID GL (28 studies) 2018
Monotherapy vs combination therapy
Combination with carbapenems

- Penetration
- Side effects
- Selection of resistance
- Mono vs combi

**Drug**

**MIC < 16!**

High-dose carbapenem in combination only if MIC lower or equal than 8 mg/l

<table>
<thead>
<tr>
<th>Author, year</th>
<th>CARBA</th>
<th>MIC</th>
<th>OR (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.511)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>TIG-CAR</td>
<td></td>
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</tbody>
</table>

2 uncontrolled, retrospective study on carba MIC > 8 (Pea F 2017, Giannella 2018)

Not enough evidence to use continuous infusion of carbapenem with MIC of .8 and .64 mg/L

**Research recommendation**: optimal dosages and infusion for MIC 8-64 mg/L

Carrara E, ESCMID GL (14 studies) 2018
12 OBSERVATIONAL STUDIES ON MIXED INFECTIONS
2 OBSERVATIONAL STUDIES ON UTI

1. Colistin could be considered in combination therapy in BSI-KPC-CR-KP (possible combination in this patient tigecycline, fosfomycin, and ceftazidime-avibactam)

2. Dosing: evidence incomplete for a recommendation (SHEA polymyxin consensus under development)

Research recommendation: loading doses, high dosages and combination, and serum level monitoring
<table>
<thead>
<tr>
<th>Drug</th>
<th>Colistin</th>
<th>Ceftazidime avibactam</th>
<th>Tygeciclin</th>
<th>Fosfomicin</th>
</tr>
</thead>
</table>

### CEFTAZIDIME-AVIBACTAM

**Risk of bias**
- Very serious
- Not serious
- Not serious
- Not serious
- None

**Other considerations**
- Very low

### 4 uncontrolled studies on CR-KP

Shields, 2016: 31 patients; overall clinical success rate: 59%
- Microbiological failure: 32%
- Resistance emerged in three cases (KPC-3 enzymes)

Shields, 2017: 13 patients
- Comparison: 96 carbapenem combination (median MIC 32 mcg/ml)
- 30-day mortality: 7% vs 31%
- 5 patients received ceftazidime-avibactam plus gentamicin

Caston, 2017: 8 patients
- Clinical cure: 86% vs. 35% (other drugs)

Van Duin, 2018: 38 patients
- Comparison: 99 colistin (46% BSI)
- 30-day mortality: 9% vs 32%
- Most patients received additional anti-CRE agents

1. **Cefta-avibactam could be considered in combination (mono)-therapy in BSI-KPC-CR-KP.**
   - Very limited quality of evidence

2. **Resistance emerging in 10% of treated patients.** KPC-3-producing Klebsiella spp. are vulnerable to mutations in the blaKPC-3 gene causing resistance

Comparison: 99 colistin (46% BSI)
- 30-day mortality: 9% vs 32%
<table>
<thead>
<tr>
<th>Drug</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIGECYCLIN</td>
<td></td>
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</tbody>
</table>

BSI and mortality

- Observational studies 5,6,9,10: very serious
- Not serious
- Not serious
- Not serious
- None

**Colistin**
- Ceftazidime avabactam

**Tygeciclin**
- Fosfomicin

**KPC-CR-KP-BSI**

4 small retrospective cohorts
No advantage in combination
High mortality rate in CR-KP BSI

Balandin-Moreno, 2014 (16 patients, mixed infections): no difference

De Pascale, 2014 (100 patients, mixed aetiology / infections): HD performed better in VAP subgroup

Verdakas, 2015 (22 patients): no difference

- **High Dosage (HD): not enough data for a recommendation**
- **Research recommendation**: high dosages in selected populations
4 observational studies (combination)

Michalopoulos, 2010: 11 critically ill patients / mixed KPC infections
- 30-day mortality 9%

Pontikis, 2014: 23 ICU patients / mixed infections
- Overall mortality: 44%

Karageorgopoulos, 2012: 3 patients KPC-BSI
- All 3 developed resistance to fosfomycin during treatment

- **Not enough data for a recommendation**
  Could be considered for a salvage therapy for susceptible KPC-CR-KP
- **Research recommendation**: optimal dosages and indications
Question for the smart audience after a (hopefully) smart presentation

How would you treat?

1. Colistin
2. Tigecycline
3. Colistin and Tigecyclin
4. Tigecyclin and meropenem
5. Ceftazidime-avibactam
6. Ceftazidime-avibactam and colistin / meropenem

KPC-CR-KP-BSI
Final selection

How long can we discuss in case of low / very low evidence? How much we are influenced by personal experience, working setting and availability of diagnostic and budget?

1. Ceftazidime-avibactam and Colistin
2. Ceftazidime-avibactam
3. Tigecycline and Colistin

KPC-CR-KP-BSI (genta-R)
Take home message

Summary of evidence

- 28 studies: 1 RCT and 27 observational studies (23 retrospective, 4 prospective)
- Certainty of assessment for all outcomes: Very low
- Heterogeneity of setting, population, dosages, and combination

What else?

- Enhanced infection control essential! (EUCIC decolonisation GL, Tuesday 13:30 Hall A)
- Clinical studies on loading dosages, dosages, duration, and combined effect of specific drugs are urgently needed
- Networking for research among high endemic countries and within the same country could make a difference