Antimicrobial Stewardship: Carbapenem-sparing strategies

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Disclosures

- **Research grants**
  - Astellas, Pfizer, MSD, Gilead

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- **Speaker/chairman**
  - Astra Zeneca, Astellas, Pfizer, MSD, Gilead, Angelini, Vifor, Shionogi, Novartis
Antimicrobial Stewardship

Antibiotic resistance is inevitable.

The rate of spread of resistance is not inevitable.

## Correlation Between Antibiotic Consumption and Resistance in *P. aeruginosa*

Univariate analysis of risk factors for MDR *P. aeruginosa* infection

<table>
<thead>
<tr>
<th>Antibiotic class</th>
<th>Hazard ratio (95% CI)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>2.40 (0.57–9.11)</td>
<td>$P=0.13$</td>
</tr>
<tr>
<td>B-lactam-B-lactamase inhibitors</td>
<td>2.71 (1.25–5.73)</td>
<td>$P=0.003$</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>0.99 (0.39–2.32)</td>
<td>$P=0.99$</td>
</tr>
<tr>
<td>AP- Cephalosporins</td>
<td>4.07 (2.12–7.76)</td>
<td>$P&lt;0.001$</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>7.92 (1.99–45.04)</td>
<td>$P &lt;0.001$</td>
</tr>
</tbody>
</table>

Risk factors for KPC isolation and infection

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KPCKP isolation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2 previous acute-care hospitalizations$^b$</td>
<td>5.92 (4.40–7.98)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Indwelling central venous catheter$^c$</td>
<td>1.66 (1.29–2.12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recent carbapenem therapy$^d$</td>
<td>2.98 (2.19–4.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recent fluoroquinolone therapy$^d$</td>
<td>1.69 (1.29–2.21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous intensive care unit admission$^b$</td>
<td>5.13 (3.49–7.53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Indwelling urinary catheter$^c$</td>
<td>3.89 (3.03–4.99)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hematological cancer</td>
<td>1.90 (1.27–2.83)</td>
<td>0.002</td>
</tr>
<tr>
<td>Surgical drain$^c$</td>
<td>1.62 (1.16–2.45)</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>KPCKP infection</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2 previous acute-care hospitalizations$^b$</td>
<td>4.26 (3.02–6.01)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Indwelling central venous catheter$^c$</td>
<td>2.59 (1.91–3.50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recent carbapenem therapy$^d$</td>
<td>3.59 (2.46–5.23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recent fluoroquinolone therapy$^d$</td>
<td>2.22 (1.59–3.10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Charlson score ≥3$^c$</td>
<td>7.49 (5.46–10.27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recent surgical procedures$^d$</td>
<td>2.03 (1.48–2.76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neutropenia$^c$</td>
<td>3.19 (1.50–6.78)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Percentage of ESBL producers in *E. coli* by country (2011-2014)

Source CDDEP 2015; WHO 2014 and PAHO
Predictors of Mortality in Patients with Bloodstream Infections Caused by Extended-Spectrum-β-Lactamase-Producing *Enterobacteriaceae*: Importance of Inadequate Initial Antimicrobial Treatment

97 ESBL-BSI patients initially treated with potentially active agents

Carbapenems have been widely used as treatment for serious ESBL infections exerting selection pressure on increased MDR enterics (ESBLs).

Increased carbapenem-R strains

Transmission and spread of resistant genes

Select carbapenem-R strains

Rates of Carbapenem Resistance Higher in Pseudomonas aeruginosa infections Compared With Enterobacteriaceae

- 69,475 healthcare-associated infections, US hospitals, 2009-2010

CA-UTI, catheter-associated urinary tract infections; VAP, ventilator-associated pneumonia.

Najy Alsayed
Resistance and Carbapenems use

European Centre for Disease Prevention and Control. Point prevalence survey of healthcare associated infections and antimicrobial use in European acute care hospitals. Stockholm: ECDC; 2012-2013
### Use of carbapenems in ESBL-carriers in ICU

<table>
<thead>
<tr>
<th>Antimicrobial class</th>
<th>non-ESBL-PE carriers</th>
<th>ESBL-PE carriers without ESBL-PE infection</th>
<th>ESBL-PE carriers with ≥1 ESBL-PE infection</th>
<th>P value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbapenems</td>
<td>69</td>
<td>241</td>
<td>627</td>
<td>&lt;0.0001&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>BL BLI combinations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>amoxicillin/ clavulanic acid</td>
<td>220</td>
<td>103</td>
<td>123</td>
<td>&lt;0.0001&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>ticarcillin/ clavulanic acid</td>
<td>122</td>
<td>54</td>
<td>26</td>
<td>&lt;0.0001&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>piperacillin/ tazobactam</td>
<td>99</td>
<td>49</td>
<td>97</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>114</td>
<td>87</td>
<td>108</td>
<td>0.89</td>
</tr>
</tbody>
</table>

<sup>a</sup>See the Patients and methods section for details.

<sup>b</sup>Global comparison.

<sup>c</sup>P<0.05 for the comparison between non-carriers and carriers (either infected or not).
What is Antimicrobial Stewardship?

- Antimicrobial stewardship is an organizational or healthcare system-wide approach to promoting and monitoring judicious use of antimicrobials to preserve their future effectiveness\(^1,2\)

- Promote **timely and optimal selection, dose and duration** of an antimicrobial with minimal toxicity to the patient and **minimal impact on resistance**\(^3\)

- Benefits:
  - Improved patient outcomes
  - Reduction in antimicrobial resistance
  - Decreased spread of infections caused by multidrug-resistant organisms\(^1,4-7\)

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Improving patient outcomes

Clinical outcomes: comparing a stewardship program* to usual practice¹

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Stewardship program (n=96)</th>
<th>Usual practice (n=95)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appropriate antimicrobial</td>
<td>90%</td>
<td>32%</td>
<td>2.8 (2.1–3.8)</td>
</tr>
<tr>
<td>Cure</td>
<td>91%</td>
<td>55%</td>
<td>1.7 (1.3–2.1)</td>
</tr>
<tr>
<td>Failure</td>
<td>5%</td>
<td>31%</td>
<td>0.2 (0.1–0.4)</td>
</tr>
<tr>
<td>Resistance</td>
<td>1%</td>
<td>9%</td>
<td>0.13 (0.02–1.0)</td>
</tr>
</tbody>
</table>

AMS programs have shown that appropriate initial antibiotic use leads to decreased mortality,² improved infection cure rates, reduced resistance³ and surgical infection rates¹

*AMS program at the Hospital of the University of Pennsylvania, Philadelphia, PA, USA
AMS, antimicrobial stewardship; CI, confidence interval
Example of a Reduction of Carbapenem Use Associated with Decreased Drug-resistant *Pseudomonas aeruginosa*

- Hospitals that restricted carbapenems (*n* = 8; 36%) reported lower rates of carbapenem-resistant *P. aeruginosa* (*P* = 0.01) for all study years

CR-PA = carbapenem-resistant *P. aeruginosa*; DOT = days of therapy.

Antibiotic Prescribing

What do we Know About Effective Practice, and What is the Evidence?
Are Cycling and Mixing the Same?

- **Cycling (Rotation)**\(^1,^2\)
  - Antibiotics are withdrawn from use for a period of time, to be reintroduced later
  - One antibiotic is replaced by one from another class\(^2\)
  - Purpose is to limit resistance to the cycled agent\(^1\)

- **Mixing**
  - Simultaneous, mixed use of different antimicrobial classes for different patients in a unit\(^3,^4\)
  - Allows for greater antibiotic heterogeneity than cycling\(^4\)

- **Models have shown that heterogeneous [diverse] antibiotic use is a potential way of reducing the selection pressure that leads to antibiotic resistance\(^3-^6\)**

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The Environment of a Bacterial Clone...
...from bed to bed to bed...

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Impact of a Hospital-Wide Program of Heterogeneous Antibiotic Use on the Development of Antibiotic-resistant Gram-negative Bacteria

- **12-month** period prior to establishment of Department of Infection Control and Prevention (baseline)
- **6-month** preparation period during which some forms of intervention occurred (based on historical use patterns)
- **18 months** of Periodic Antibiotic Monitoring and Supervision (PAMS) divided into **three 6-month periods**

Impact of a Hospital-Wide Program of Heterogeneous Antibiotic Use

Relative antibiotic usage density (%AUD) is defined as the cumulative use in defined daily doses of 1 supervised class divided by the cumulative use of all 6 classes.

AUD = antibiotic usage density (cumulative DDD of 1 class/all classes)
The incidence of patients from whom resistant GNR were isolated decreased significantly ($p<0.001$). The isolation of multidrug resistant GNR decreased from 1.7% to 0.5% ($p<0.001$).
Resistence Rates of *P. aeruginosa*

Percent (%) Pseudomonal resistance rates (one isolate per patient)

- Resistance Rates:
  - Imipenem
  - Ciprofloxacin
  - Pip/tazo
  - Cefepime
  - Gentamicin

Pre-establishment and preparation period

PAMS

What Does This Suggest?

- A new approach to antibiotic choice that is patient-specific, with a focus on using a variety of agents appropriately, can lead to prescribing diversity.

- Structured programs of restriction or prioritization can lead to high use of a limited number of drugs that help drive the development and spread of resistance.
Antibiotic Use and the Risk of CRKP

Scatter plot with fitted regression lines presenting the interaction effect of carbapenems and fluoroquinolones on the risk of ESBL-CRKP infection.

Principal components of strategies for stewardship and antimicrobial use in the era of increasing antimicrobial resistance

- **Leadership Commitment:**
  - Implementing antibiotic stewardship programs
  - Implementing infection control practices
  - Improve communication between laboratory and clinical staff
  - Implement local resistance data for developing local antibiotic guidelines

- **Multidisciplinary approach**
  - A multidisciplinary team including infectious diseases specialists, microbiologists, pharmacist and ICU physician and nurses should be in charge of developing a specific ICU antibiotic stewardship.
  - Weekly round for cases discussion

- **Implementation of modern antimicrobial use approach:**
  - Aggressive good quality microbiological sampling (blood-cultures; distal airway sampling; urine culture; systematic sampling of wound, drain discharge and any collection suspect of infection)
  - Selection of empirical antimicrobials according to the clinical conditions, the presence of risk factors for resistant microorganisms and to the local epidemiology
  - Achievement of adequate pharmacokinetic/pharmacodynamic parameters of the antimicrobial agents used (Extended/continuous infusion, TDM)
  - Systematic de-escalation
  - **Limit use of carbapenems, cephalosporins and quinolones**

Are you prepared to face the horror?

ESBLs
A true story!

Starring: the deadly Extended Spectrum Beta-Lactamase
Produced by: Klebsiella spp.,
E. coli and others
Support cast: Cephalosporins, Penicillins and Aztreonam

Now showing at a hospital near you.
A retrospective study of monomicrobial bacteremia caused by ESBL producers at 2 medical centers between May 2002 and August 2007 was performed (n=178)

The patients definitively treated with *in vitro* active cefepime (cases) were compared with those treated with a carbapenem (controls) in a propensity score–matched analysis to assess therapeutic effectiveness. The 30-day crude mortality was the primary endpoint.

Multivariate regression revealed that a critical illness with a Pitt bacteremia score ≥4 points (OR 5.4; 95% CI, 1.4–20.9; *P* = .016), a rapidly fatal underlying disease (OR 4.4; 95% CI, 1.5–12.6; *P* = .006), and definitive cefepime therapy (OR 9.9; 95% CI, 2.8–31.9; *P* < .001) were independently associated with 30-day crude mortality.
Based on the current CLSI susceptible breakpoint of cefepime (MIC $\leq 8\ \mu g/mL$), cefepime definitive/directed therapy is inferior to carbapenem therapy in treating patients with so-called cefepime-susceptible ESBL-producer bacteremia (except if MIC $\leq 1\ mg/L$).

**Figure 1.** Mortality rates of 3 subgroups of patients who receive cefepime therapy ($n = 33$) by the cefepime minimum inhibitory concentration (MIC)
Recently, a post hoc analysis of patients with bloodstream infections due to ESBL-producing *E. coli* from 6 published prospective cohorts, provided insight into the potential role of βL/βL-inhibitors.

- Amoxicillin-clavulanic acid [AMC] and piperacillin-tazobactam [PTZ]) or carbapenem were compared in 2 cohorts: the empirical therapy cohort (ETC, n=103) and the definitive therapy cohort (DTC, n=174).

- Mortality rates at day 30 for those treated with BLBLI versus carbapenems were 9.7% versus 19.4% for the ETC and 9.3% versus 16.7% for the DTC, respectively (P > 0.2, log-rank test).

Rodriquez-Bano et al.. *Clin Infect Dis* 2012:54:167-74
After adjustment for confounders, no association was found between either empirical therapy with BLBLI (adjusted hazard ratio [HR], 1.14; 95% confidence interval [CI], 0.29–4.40; P = .84) or definitive therapy (adjusted HR, 0.76; 95% CI, 0.28–2.07; P = .5) and increased mortality.

The results suggest that AMC and PTZ are suitable alternatives to carbapenems for treating patients with BSIs due to ESBL-producing E. coli and Klebsiella spp. bacteremia. This was confirmed by Peralta et al., in a multicentre cohort study evaluating the impact of empirical treatment in ESBL-producing E. coli and Klebsiella spp. bacteremia.

Such results need to be confirmed by further clinical outcome studies.
The differences between the studies by Rodriguez-Baño and colleagues and Tamma and colleagues are informative and help to explain their conflicting conclusions:

1. In the study of Rodriguez-Baño and colleagues, > 90% of patients who received piperacillin-tazobactam were administered a dose of 4.5 g intravenously every 6 hours. In contrast, only 39% of the patients receiving piperacillin-tazobactam in the study of Tamma and colleagues were given such a high dose.

2. In the Spanish cohort, about half of the isolates had a piperacillin-tazobactam MIC ≤ 2 µg/mL, which was associated with improved 30-day mortality. In the Johns Hopkins cohort, 99% of isolates had a piperacillin-tazobactam MIC ≥ 4 µg/mL.

3. Rodriguez-Baño and colleagues found a higher proportion of urinary and biliary infections: 72% vs 26% found by Tamma and colleagues.

4. Finally, Rodriguez-Baño and colleagues exclusively included *E coli* isolates, whereas Tamma and colleagues also included *Klebsiella* species and *Proteus mirabilis*. 

**β-lactam/β-lactamase inhibitors: Treatment of serious ESBL infections**
Meropenem versus piperacillin-tazobactam for definitive treatment of bloodstream infections due to ceftriaxone non-susceptible *Escherichia coli* and *Klebsiella* spp (the MERINO trial): study protocol for a randomised controlled trial

Patrick NA Harris¹, Anton Y Peleg², Jon Iredell³, Paul R Ingram⁴,⁵, Spiros Miyakis⁶, Andrew J Stewardson⁷, Benjamin A Rogers⁸, Emma S McBryde⁹, Jason A Roberts¹⁰, Jeff Lipman¹⁰, Eugene Athan¹¹, Sanjoy K Paul¹², Peter Baker¹³, Tiffany Harris-Brown¹ and David L Paterson¹
Tigecycline in monotherapy for ESBL infections

Role of tigecycline

- Tigecycline as a tool to save carbapenems, either as a primary treatment or de-escalation
- Tigecycline to avoid «collateral damage»
Fosfomycin

Prospective cohort study with 116 Patients (83 ICU)
Indications: Pneumonia (33), bone/joint infection (32), UTI (16), Bacteraemia (9), abdominal infection (7), endocarditis (7), CNS-Infektion (7), skin infection (2), ocular infection (2)
Outcome with respect to indication

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Cure rate (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>P. aeruginosa</td>
<td>86,7%</td>
<td>(26/30)</td>
</tr>
<tr>
<td>E. coli</td>
<td>85,7%</td>
<td>(6/7)</td>
</tr>
<tr>
<td>MRSA</td>
<td>50%</td>
<td>(4/8)</td>
</tr>
<tr>
<td>MRCNS</td>
<td>86,7%</td>
<td>(13/15)</td>
</tr>
<tr>
<td>MDR pathogens</td>
<td>78,1%</td>
<td>(43/55)</td>
</tr>
<tr>
<td>ESBL forming pathogens</td>
<td>86,1%</td>
<td>(31/36)</td>
</tr>
<tr>
<td>Panresistant pathogens</td>
<td>89,4%</td>
<td>(17/19)</td>
</tr>
</tbody>
</table>

Ceftolozane/Tazobactam Activity vs Comparators (EU Hospitals 2011-2012)

- Percent inhibited at ≤8 mg/L. Interpretive criteria for comparator compounds as published by EUCAST (2014).
- Program to Assess Ceftolozane/Tazobactam Susceptibility (PACTS).
Activity of Ceftolozane Versus Piperacillin in Combination With Tazobactam Against ESBL-producing *E. coli* and *K. pneumoniae*

**Activity against ESBL-producing E. coli and K. pneumoniae**

*Escherichia coli* (n = 149) and *Klebsiella pneumoniae* (n = 20) strains (most were CTX-M-14 or M-15)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt; (mg/L)</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; (mg/L)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftolozane</td>
<td>64</td>
<td>&gt;64</td>
<td>&lt;0.25 - &gt;64</td>
</tr>
<tr>
<td>Ceftolozane/tazobactam</td>
<td>&lt;0.25</td>
<td>2</td>
<td>&lt;0.25 - &gt;64</td>
</tr>
<tr>
<td>Piperacillin</td>
<td>&gt;128</td>
<td>&gt;128</td>
<td>&lt;0.5 - &gt;128</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>8</td>
<td>64</td>
<td>&lt;1 - &gt;128</td>
</tr>
</tbody>
</table>

Ceftolozane/tazobactam 4 mg/L; preliminary breakpoint S ≤ 2 mg/L.
Pseudomonas aeruginosa Italian countrywide surveillance (20 hospitals, 2013-14)
Ceftolozane/tazobactam patients profile

**clinical entities:**
1. Severe sepsis related to UTI, IAI or pneumonia
2. cUTI
3. Tertiary peritonitis
4. Pneumonia

**Associated Comorbidities:**
- Diabetes
- COPD
- Moderate/severe renal/liver disease
- Immunosuppression/neutropenia
- Elderly
- Solid tumor
- Structural lung disease

**Risk factors for P. aeruginosa + ESBL Enterobacteriaceae**
- Receipt of broad-spectrum antimicrobial therapy in last 90 days (ceph/quin)
- History of long hospitalization and/or LTCFs
- Invasive devices
- Advanced age
- Immunosuppression
- ICU admissions

**Critically ill Patients**

**Consider local epidemiological data**
- P. aeruginosa
  - R to cefta 0-25%
  - R to pip/tazo 0-25%
  - R to carba 0-25%
  - ESBL
    - 0-20% in E. coli and/or Klebsiella
- P. aeruginosa
  - R to cefta > 25%
  - R to pip/tazo > 25%
  - R to carba > 25%
  - ESBL
  - > 20% in E. coli and/or Klebsiella
Ceftolozane/tazobactam

**Pro**
- Predictable PK
- Rapid tissue distribution - Lung
- Renal excretion
- Safely
- High activity against ESBLs & PSA
- Carbapenem- sparing

**Cons**
- Avoid if beta lactam allergy
- No oral formulation to allow for step-down therapy
- Two dosages (1.5 vs 3 g)
- No KPC activity

Empiric choice for P.aeruginosa/ESBL in UTI/cIAI/HAP/VAP
First and second line treatment for ESBL infections

<table>
<thead>
<tr>
<th>ESBL Enterobacteriaceae PTZ MIC ≤ 16/4 mg/l</th>
<th>Primary bloodstream infection</th>
<th>Pneumonia</th>
<th>Abdominal infection</th>
<th>Urinary tract infection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piperacillin–tazobactam 16/2 g every 24 h i.v. (a)</td>
<td>As for bloodstream infections</td>
<td>Piperacillin–tazobactam 16/2 g every 24 h i.v. (a)</td>
<td>As for bloodstream infections</td>
<td></td>
</tr>
<tr>
<td>Meropenem 1 g every 6 h i.v. (b) or ertapenem 500 mg every 6 h i.v. (c) or imipenem 0.5 g every 6 h i.v. (d) or imipenem 1 g every 8 h i.v. (d)</td>
<td>Meropenem 1 g every 6 h i.v. (b) or ertapenem 500 mg every 6 h i.v. (c) or imipenem 0.5 g every 6 h i.v. (d) or imipenem 1 g every 8 h i.v. (d)</td>
<td>Tigecycline 50 mg every 12 h i.v. (e)</td>
<td>Ceftolozane/tazobactam 1.5 g every 8 h i.v. + metronidazole 500 mg every 8 h i.v.</td>
<td></td>
</tr>
<tr>
<td>Ceftolozane/tazobactam 1.5 g every 8 h i.v.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Second-line therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbapenems i.v. + amikacin 15–20 mg/kg/day every 24 h i.v. or tigecycline 50 mg every 12 h i.v. (e)</td>
<td>As for bloodstream infections</td>
<td>As for bloodstream infections</td>
<td>Carbapenems i.v. + amikacin 15–20 mg/kg/day every 24 h i.v. or fosfomycin 4 g every 6 h i.v.</td>
<td></td>
</tr>
<tr>
<td><strong>Enterobacteriaceae PTZ MIC &gt; 16/4 mg/l and/or severe infection</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meropenem 1 g every 6 h i.v. (b) or ertapenem 500 mg every 6 h i.v. (c) or imipenem 0.5 g every 6 h i.v. (d) or imipenem 1 g every 8 h i.v. (d)</td>
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<td>As for bloodstream infections</td>
<td></td>
</tr>
<tr>
<td>Ceftolozane/tazobactam 1.5 g every 8 h i.v.</td>
<td>Ceftolozane/tazobactam 1.5 g every 8 h i.v. + metronidazole 500 mg every 8 h i.v.</td>
<td>Ceftazidime–avibactam 2.5 g every 8 h i.v. + metronidazole 500 mg every 8 h i.v.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftazidime–avibactam 2.5 g every 8 h i.v.</td>
<td>Ceftazidime–avibactam 2.5 g every 8 h i.v. + metronidazole 500 mg every 8 h i.v.</td>
<td>Ceftazidime–avibactam 2.5 g every 8 h i.v. + metronidazole 500 mg every 8 h i.v.</td>
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</table>
Treatment of severe Enterobacteriaceae infection

Enterobacteriaceae infection suspected

Severe infection + local outbreak/epidemiology or risk factors

ESBL suspected

- Piperacillin-tazobactam +/- amikacin/gentamicin
- Carbapenem
- Ceftolozane/tazobactam
- Ceftazidime/avibactam

CRE suspected

- Carbapenem + tigecycline
  - colistin or fosfomycin or gentamicin

Ceftazidime/avibactam

**P.aeruginosa empiric combination options**

**Backbone**
- Ceftolozane/tazobactam
- Piperacillin/tazobactam
- Meropenem
- Imipenem
- Ceftazidime

**2° agent**
- Ciprofloxacin
- Levofloxacin
- Gentamicin
- Amikacin
- Colistin
- Fosfomycin
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