Carbapenems: why, how and what are the risks?

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with many slides borrowed from Françoise Van Bambeke and Magali Dodemont

with the support of Wallonie-Bruxelles International
Why do you wish to use carbapenems?

• Do you really have resistant organisms?

• Can you obtain MICs?

• If you use them can you de-escalate?

• You may better follow an Infection Control Plan…
**β-lactames: pharacochemistry**

- pename (pénicillines)
- clavame (inhibiteurs)
- carbapenems

- cepham (céphalosporines)
- oxacephem
- monobactame

β-lactames: pharmacochemistry
From penicillin to carbapenems

Imipenem

Meropenem
Carbapenems: thienamycin

No "left" lateral chain (but only a methyl) ➔ resist. to β-lactamases

No S atom in the cycle ➔ tight PBP binding ➔ VERY broad spectrum

"Right" lateral chain with a S atom and a terminal amine ➔ tight binding to PBP
BUT ➔ intrinsic instability

"classic" pharmacophore

Thienmycin is too unstable for clinical use
Carbapenems: from thienamycin to imipenem

Addition of a formimidoyl (iminomethylamino) ➔ Improved stability

BUT imipenem is the substrate of a renal DEHYDROPEPTIDASE
➢ rapid degradation of the antibiotic…
➢ liberation of nephrotoxic reaction products…
Carbapenems: imipenem + cilastatine

Imipenem + cilastatine = **TIENAM ®**
Carbapenems: from imipenem to meropenem

Resistance to the dehydropeptidase through steric hindrance

meropenem

doripenem
Carbapenems: from meropenem to ertapenem

**Meropenem**

- Long half-life
- Loss of useful activity against *P. aeruginosa*

**Ertapenem**

- Chemical structure shown
- Notably different from meropenem
Spectrum of activity

• Beta-lactams with the broadest antibacterial spectrum currently available

• Gram positive
  – *S. pneumoniae* (including penicillin-resistant), MSSA, *Streptococci*. *E. faecalis* are moderately susceptible.

• Gram negative: most of them (*)

• Anaerobes:
  – Very active, including *Bacteroides, Fusobacterium*, anaerobic gram-positive cocci

(*) !!! Bacteria resistant: MRSA, *E. faecium*, *Stenotrophomonas maltophilia*
Spectrum of activity

• Similar for all carbapenem except ertapenem
  – Ertapenem has no useful activity against *P. aeruginosa*

• Little difference in the activities of individual agents
  – **Imipenem**: slighter better activity against Gram-positive bacteria than meropenem
  – **Meropenem** is more active against Gram-negative bacteria than imipenem
  – **Doripenem**: slightly improved antipseudomonal activity

• Active against ESBL and AMPc producers
Pharmacokinetic properties

• Unstable in gastric acid → parenteral route

• Half-life: 1 hour for meropenem, imipenem and doripenem (frequent administration)
  BUT 4.5 hours for ertapenem (once daily administration)

• Protein binding: ~10%
  • Protein binding of DHP-I inhibitor cilastatine: 35%

• Distribution: most tissues and fluids, low concentrations occur in CSF

• Elimination: essentially renal

• **Unstable in aqueous solution at room temperature**
  – Degradation 10-20% in less than 3h for imipenem

• Liver failure: no dose adaptation; renal failure: lower doses
Pharmacodynamics…
About efficacy ... and concentration effect relationships

Delta log CFU/mg prot. from time 0

-2 -1 0 1 2

Log extracellular concentration (X MIC)

-4 -2 0 2

E_{min} E_{max}

oxacillin
gentamicin

Introducing pharmacokinetics…

- weak concentration dependence

$C_{\text{min}} - C_{\text{max}}$

- strong concentration-dependence

β-lactams are time-dependent...

but how long do you need them?

various β-lactams

doripenem

various pathogens

Fig. 7. Relationship between the change in log_{10} CFU per thigh or lung for various pathogens following 24 h of therapy with different doses of penicillins (∆), cephalosporins (○), and carbapenems (□).

Fig. 4. Relationship between doripenem exposure, as measured by % Time > MIC, and response in a neutropenic murine-thigh infection model involving Gram-negative bacteria.


First conclusions (and discussion)....

- Every antibiotic is concentration-dependent (simple pharmacological principle) …

- **BUT**, for β-lactams, activity if already optimal when the concentration exceeds the MIC by 3 to 4-fold, which is what easily happens with conventional administration… and bacteria with low MICs

- **AND**, having no or little post-antibiotic effect, β-lactams need to stay above the MIC (preferably 4-fold…) for the maximum time…

Medical controversies by H. Daumier (1808-1879)
First conclusions (and discussion)....

• The most important PK/PD parameter predicting bacteriological and clinical efficacy is **T>MIC**

• T>MIC of 20% → bacteriostatic effects

• T>MIC of 40% → bactericidal effects

• In severe critically ill septic patients, in impaired renal function patients and in neutropenic patients: imipenem has to exceed 66% of T>MIC to result in good clinical outcome (Mouton et al. Clin Pharmacokinet. 2000;39:185–201)

• Maximum killing effect is reached at concentration of 4 x MIC

• Some post-antibiotic effect against Gram-negative bacteria
  – Most marked with *P. aeruginosa*
Pharmacodynamics in the ICU …

- ICU patients
  - Increased volume of distribution
  - Modified antibiotic clearance
  - Modified protein binding protein caused by hypo-albuminaemia
  - Modified tissue penetration

**Implications for clinical efficacy and correct dosage of AB**

- Potential underdosing
- Risk of development of resistance and/or therapeutic failure
  - Increase the drug dose (to obtain at least 40% of 4xMIC)
  - Prolong the infusion time
Adverse effects

• Rash, nausea, diarrhea, thrombophlebitis
  – Imipenem: higher rate of nausea and vomiting (particularly after rapid infusion)

• Hypersensitivity reaction
  – ! Patient with history of penicillin allergy (cross-reactivity ~50%)

• Seizure activity → with imipenem
  • If underlying CNS problems or decrease renal function

• Risk of developing pseudomembranous colitis, especially with prolonged therapy
Drug-Drug Interactions

- **Valproic acid** → reduced serum concentrations of valproic acid

Valproic acid → Valproic acid glucuronide

Liver

acylpeptide hydrolase (APEH)

acting as **valproic acid glucuronide (VPA-G) hydrolase**

Drug-Drug Interactions

- Valproic acid → reduced serum concentrations of valproic acid

Valproic acid concentration → Valproic acid glucuronide
liver

acylpeptide hydrolase (APEH)
acting as valproic acid glucuronide (VPA-G) hydrolase

INHIBITED BY CARBAPENEMS

Clinical use: microbiological considerations (*)

- Infections due to resistant pathogens
  - Regarded as first-line therapy for serious infections caused by Extended Spectrum β-Lactamase (ESBL)-producing organisms
  - Especially in patients with risk factors of harbouring resistant pathogens
    - Previous hospitalization or antibiotherapy
    - Colonization with MDR organism
    - Late nosocomial infection (> 5 days after administration)
    - Epidemic with MDR Gram-negative bacteria in the unit

- Infections with multiple organisms involved (e.g.: mixed, aerobic/anaerobic bacteria) when more than 1 antibiotic is required

* imipenem and meropenem
Clinical use: approved indications (*)

- Complicated intra abdominal infections
- Obstetric/gynecologic infections
- Respiratory tract infections (Hospital-acquired pneumonia)
- Bacteremia
- Serious skin and soft tissue infections
- Bone and joint
- Complicated UTI
- Febrile neutropenia
- Bronchial exacerbation in the cystic fibrosis patient
  - not in monotherapy → emergence of resistance
- Meningitis (meropenem only)

* imipenem and meropenem (imipenem: children ≥ 12 years only)
Clinical use:
approved indications of doripenem

- Complicated intra abdominal infections
- Complicated UTI including pyelonephritis

why so few?
Clinical use:
approved indications of ertapenem

- Complicated Intra-Abdominal Infections

- Complicated Skin and Skin Structure Infections, Including Diabetic Foot Infections without Osteomyelitis

- Community Acquired Pneumonia

- Complicated Urinary Tract Infections Including Pyelonephritis

- Acute Pelvic Infections Including Postpartum Endomyometritis, Septic Abortion and Post Surgical Gynecologic Infections

- Prophylaxis of Surgical Site Infection Following Elective Colorectal Surgery Complicated intra abdominal infection
Clinical use:
approved indications of ertapenem

- Complicated Intra-Abdominal Infections
- Complicated Skin and Skin Structure Infections, Including Diabetic Foot Infections without Osteomyelitis
- Community Acquired Pneumonia
- Complicated Urinary Tract Infections Including Pyelonephritis
- Acute Pelvic Infections Including Postpartum Endomyometritis, Septic Abortion and Post Surgical Gynecologic Infections
- Prophylaxis of Surgical Site Infection Following Elective Colorectal Surgery Complicated intra abdominal infection

You must exclude **P. aeruginosa**
Clinical use: general considerations

- Empiric therapy for nosocomial infections must be initiated as soon as possible and needs to be broad enough.

- BUT, always reevaluate the clinical utility after 48 - 72 hours according to microbiological documentation.
Imipenem: details

• **Absorption:** poor oral absorption

• **Distribution**
  – Urine, sputum, synovial fluid, pleural fluid, bone
  – Variable penetration into the cerebral spinal fluid → 3rd generation cephalosporins are the drugs of choice for meningitis
  – **Imipenem not recommended for therapy of meningitidis** because increase frequency of seizures due to higher doses necessary to achieve adequate CSF concentration of the drug

• **Elimination**
  – Primarily via the kidneys by glomerular filtration
    → specific dosage reductions for various degrees of renal dysfunction
Imipenem: details

Dosage

• EUCAST breakpoints apply to imipenem 500 mg x 4 daily administered intravenously over 30 minutes as the lowest dose. 1g x 4 daily was taken into consideration for severe infections and in setting the I/R breakpoint.

• Pediatric dose: 20 to 50 mg/kg iv (q12h)

• Decreased dosage: renal failure (60 to 100 mg/kg) (div q6h)

• Increased dosage: pregnancy
Imipenem: dosage modifications

Renal impairment

- CrCl $\geq 71$ mL/min/1.73 m²: 250 mg IV q6hr
- CrCl 41-70 mL/min/1.73m²: 250 mg IV q8hr
- CrCl 21-40 mL/min/1.73 m²: 125-250 mg IV q12hr
- CrCl $\leq 20$ mL/min/1.73 m²: 125-250 mg IV q12hr
- CrCl $< 5$ mL/min/1.73 m²: Use IV only if haemodialysis is instituted within 48 hours
- Haemodialysis: Give supplemental dose after each dialysis, then q12hr
Maximising the utility of the carbapenems

• **High dose**
  – Specific population of patient with altered pharmacokinetics (severe sepsis) or infection with bacteria exhibiting higher MICs
    • Meropenem: good CNS tolerability and low incidence of nausea and vomiting

• **Increased frequency of administration**
  – Administer a smaller dose more frequently

• **Extended infusion**
  – Extended infusion (3-5h)

Mode of administration

- Standard regimen: intermittent short-term infusion
- Extended infusion may optimizing $T_{>\text{MIC}}$ particularly in critically ill patients.

![Graph showing concentration over time with different infusion durations.](Bhavnani et al., AAC (2005) 49:3944-47)
Prolonged infusion

• useful to prolong the T > MIC
• can be the only solution for antibiotics that cannot be administered by continuous infusion (discussed later)
• the following slides are an example with doripenem that may also apply to meropenem
• be careful for imipenem as it may be much less stable than the two other penems
## Comparative PK profile

### Bolus vs Prolonged infusion

<table>
<thead>
<tr>
<th>parameter</th>
<th>DOR (500 mg)</th>
<th>MEM (1g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Bol)</td>
<td>(Prol)</td>
</tr>
<tr>
<td>Cmax (mg/L)</td>
<td>23</td>
<td>8</td>
</tr>
<tr>
<td>AUC (mg.h/L) – 8 h</td>
<td>36</td>
<td>17</td>
</tr>
<tr>
<td>T &gt; CMI 1</td>
<td>55</td>
<td>80</td>
</tr>
<tr>
<td>T &gt; CMI 4</td>
<td>27.5</td>
<td>55</td>
</tr>
<tr>
<td>T &gt; CMI 8</td>
<td>17.5</td>
<td>-</td>
</tr>
</tbody>
</table>

*Kim et al., AAC (2008) 52:2497-2502*

*Jaruratnasirikul et al., AAC (2005) 49:1337-39*
Meropenem: PK/PD modeling

Probability of target attainment rate based on Monte Carlo simulation

## Possible advantages and disadvantages of continuous/long infusion vs bolus

<table>
<thead>
<tr>
<th>Administration method</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extended infusion</td>
<td>Predictable PK</td>
<td>Requires education</td>
</tr>
<tr>
<td></td>
<td>Lower daily dose may be effective</td>
<td>Requires infusion pumps</td>
</tr>
<tr>
<td></td>
<td>Less time consuming for nurses</td>
<td>Issues of stability</td>
</tr>
<tr>
<td>Bolus</td>
<td>Simple</td>
<td>Unpredictable PK</td>
</tr>
<tr>
<td></td>
<td>Less likely failure/error</td>
<td>Neurological side-effects probably more common</td>
</tr>
</tbody>
</table>

Modified from Abdul-Aziz MH Ann Intensive care 2012;2:37
Resistance

The hospital staff did this to you?

No, the hospital staph.
Mechanisms of resistance

GRAM negative rods

• **Membrane impermeability:** Loss of an outer membrane protein (Opr D porin) which is necessary for imipenem to reach its PBP target site (*P. aeruginosa*)

• **Efflux mechanisms:** overexpression of the MexA-MexB-oprM pump system (*P. aeruginosa*)

• **Destruction by beta-lactamases = CARBAPENEMASE**
  – associated with mechanisms of resistance to other antibiotic classes -> highly multidrug resistant organisms
Mechanisms of resistance

Gram positive

• Mutation of PBPs
• Acquisition of a new carbapenem-resistant PBP

All carbapenems are inactive against MRSA or MRSE ...
Escalating antimicrobial resistance to $\beta$-lactams

- **$\beta$-lactam agents**: have been used widely for treatment of infection caused by *Enterobacteriaceae* since the 70-80’s

- **Worldwide emergence of community-acquire ESBL+** strains since the early 2000’s

- **Carbapenems**: last resort antimicrobial agents for the treatment of ESBL + infection

- **Since 1993**: emergence of first carbapenem-R isolates due to production of carbapenemases

- **Therapeutic dead-end** (almost no reserve/new drugs in the pipelines)
Rapid evolving resistance in Enterobacteriaceae

1940-1970:
- Wild type

1970-1990:
- Penicillinase (TEM-1, SHV-1)

1990-2010:
- ESBLs (CTX-M, TEM, SHV, ..)
- Carbapenemases (VIM, NDM, OXA-48, ..)
# Carbapenem resistance mechanisms

<table>
<thead>
<tr>
<th>Pathogens</th>
<th>Mechanisms of resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Enterobacteriaceae</em></td>
<td>Cephalosporinase/ESBL + porin loss</td>
</tr>
<tr>
<td></td>
<td><strong>Carbapenemase</strong></td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>Porin loss</td>
</tr>
<tr>
<td></td>
<td>Up-regulated efflux</td>
</tr>
<tr>
<td></td>
<td><strong>Carbapenemase</strong></td>
</tr>
<tr>
<td><em>Acinetobacter spp.</em></td>
<td>Cephalosporinase + porin loss</td>
</tr>
<tr>
<td></td>
<td><strong>Carbapenemase</strong></td>
</tr>
</tbody>
</table>
Classification of the different carbapenemases in Enterobacteriaceae

From P. Nordman
Carbapenemase producing- *Enterobacteriaceae*

From P. Nordman
NDM-producers…

FIG. 2. Geographical distribution of NDM producers.

Clinical Microbiology and Infection ©2014 European Society of Clinical Microbiology and Infectious Diseases, CMI, 20, 821–830
Carbapenemase producing- *Enterobacteriaceae*

### Table 1. Overview of Carbapenemase Enzyme Types in *Enterobacteriaceae*

<table>
<thead>
<tr>
<th>Ambler Class (Active Site)</th>
<th>Example Enzymes</th>
<th>Host Organisms</th>
<th>Carbapenems</th>
<th>Inhibition by Currently Available β-Lactamase Inhibitors (Clavulanic Acid, Tazobactam, and Sulbactam)</th>
<th>Region Mostly Found In</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (serine)</td>
<td>KPC-2 to 22</td>
<td><em>Klebsiella pneumoniae</em> (have been identified in other <em>Enterobacteriaceae</em> and nonfermenters)</td>
<td>Yes</td>
<td>Variable&lt;sup&gt;a&lt;/sup&gt;</td>
<td>United States and worldwide</td>
</tr>
<tr>
<td>B (Zinc binding thiol − &quot;MBLs&quot;)</td>
<td>NMD-1, IMP-I, VIM-1</td>
<td><em>Enterobacteriaceae</em> and nonfermenters</td>
<td>Yes</td>
<td>No</td>
<td>Southern Asia</td>
</tr>
<tr>
<td>D (serine)</td>
<td>OXA-48</td>
<td><em>Enterobacteriaceae</em> (other types of OXA carbapenemases mainly found in <em>Acinetobacter</em> spp.)</td>
<td>Minimal Hydrolysis&lt;sup&gt;b&lt;/sup&gt;</td>
<td>No</td>
<td>Southern Europe</td>
</tr>
</tbody>
</table>

Abbreviations: KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamase; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase.

<sup>a</sup> Some KPC enzyme types, such as KPC-2, can hydrolyze clavulanic acid, tazobactam, and sulbactam. However, this ability to hydrolyze these β-Lactamase Inhibitors is uncommon in Class A enzymes [8, 9].

<sup>b</sup> OXA-48 is weakly active against extended spectrum cephalosporins and hydrolyzes carbapenems only minimally [10].

Resistance to carbapenems: why?

- Carbapenems resistance is promoted by the widespread use of these antibiotics, creating a continuous selective pressure on bacteria.

- Rational use of carbapenems is vital to control and prevent both the clinical impact and the development of resistance.
  - Limit the duration of therapy (most infections: 5-7 days).
  - Use of therapeutic alternatives for the treatment of infections caused by ESBL.
    - β-lactam (amoxicillin) + inhibitor of β-lactamase (clavulanic acid).
    - Fosfomycin.
    - Cotrimoxazole.
    - Tigecycline.
    - Piperacillin-tazobactam.
Rational use of carbapenems

• Algorithm to limit excessive and inappropriate use of carbapenems
  – 1. Appropriate indication for a carbapenem?
  – 2. Other alternatives?
    • Narrower spectrum or lower ecological impact on bacterial flora
  – 3. Duration of treatment appropriate?
  – 4. Adequate dose?

F. jary at al. Médecine et maladies infectieuses 42(2012) 510-516
  – 99 carbapenem prescriptions were evaluated
  → 66.7% of all prescriptions were considered inappropriate
  → An alternative was available in 16% of cases
  → Need for guidelines and local best practices recommendations
Can we avoid carbapenems?
“In 2012, consumption of carbapenems varied by a factor of 14, from 0.01 (Bulgaria) to 0.14 DDD per 1,000 inhabitants and per day (Portugal).”

“The proportion of consumption of carbapenems out of antibacterials for systemic use ranged from 0.8% (Latvia) to 9.8% (Portugal) with an EU/EEA population-weighted mean of 2.9%.”

ECDC; ESAC Net 2012
Non-Carbapenem Therapy for Bacteremia Caused by Extended-Spectrum β-Lactamase-Producing *Enterobacteriaceae*

- Presence of ESBL does not necessarily confer bacterial resistance to all β-lactams… (viz. piperacillin/tazobactam …)
- **MIC is a better predictor of outcome** than simple detection of enzyme (genomic) or mechanism-based categorization

Figure 4. In vitro susceptibility of *E. coli* in North America (2009-2010) using 2012 CLSI breakpoints"
Variation of MIC in *Enterobacteriaceae* producing carbapenemases

Table 1. MIC range of carbapenems for *Enterobacteriaceae* that produce several types of carbapenemases

<table>
<thead>
<tr>
<th>Carbapenemase</th>
<th>Imipenem</th>
<th>Meropenem</th>
<th>Ertapenem</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPC</td>
<td>0.5–&gt;64</td>
<td>1–&gt;64</td>
<td>0.5–&gt;64</td>
</tr>
<tr>
<td>Metallo β-lactamases†</td>
<td>0.5–&gt;64</td>
<td>0.25–&gt;64</td>
<td>0.5–&gt;64</td>
</tr>
<tr>
<td>OXA-48 type</td>
<td>1–&gt;64</td>
<td>0.5–&gt;64</td>
<td>0.25–&gt;64</td>
</tr>
</tbody>
</table>


Nordmann P et al. EID 2011; 17:1791
Use of EUCAST breakpoints to predict outcome based on MIC determination

## Enterobacteriaceae

<table>
<thead>
<tr>
<th></th>
<th>MIC breakpoint (mg/L)</th>
<th>Disk content (µg)</th>
<th>Zone diameter breakpoint (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S ≤</td>
<td>R &gt;</td>
<td>S ≥</td>
</tr>
<tr>
<td><strong>Penicillins</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ampicillin-sulbactam</td>
<td>$8^1,2$</td>
<td>$8^2$</td>
<td>10-10</td>
</tr>
<tr>
<td>Amoxicillin-clavulanic acid</td>
<td>$8^1,3$</td>
<td>$8^3$</td>
<td>20-10</td>
</tr>
<tr>
<td>Amoxicillin-clavulanic acid (uncomplicated UTI only)</td>
<td>$32^1,3$</td>
<td>$32^3$</td>
<td>20-10</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>$8^4$</td>
<td>$16^4$</td>
<td>30-6</td>
</tr>
<tr>
<td><strong>Cephalosporins</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefepime</td>
<td>$1$</td>
<td>$\geq 4$</td>
<td>30</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>$1$</td>
<td>$\geq 4$</td>
<td>10</td>
</tr>
</tbody>
</table>

1. The cephalosporin breakpoints for Enterobacteriaceae will detect all clinically important resistance mechanisms (including ESBL and plasmid mediated AmpC). Some isolates that produce beta-lactamases are susceptible or intermediate to 3rd or 4th generation cephalosporins with these breakpoints and should be reported as tested, *i.e.* the presence or absence of an ESBL does not in itself influence the categorisation of susceptibility. In many areas, ESBL detection and characterisation is recommended or mandatory for infection control purposes.

[http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_5.0_Breakpoint_Table_01.pdf](http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_5.0_Breakpoint_Table_01.pdf)
**Use of EUCAST breakpoints to predict outcome based on MIC determination**

### Important message for the clinicians!

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>MIC breakpoint (mg/L)</th>
<th>Disk content (µg)</th>
<th>Zone diameter breakpoint (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piperacillin-tazobactam</td>
<td>8(^4) 16(^4)</td>
<td>30-6</td>
<td>20 17</td>
</tr>
<tr>
<td>Cephalosporins (^1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefepime</td>
<td>1 4</td>
<td>30</td>
<td>24 21</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>1 4</td>
<td>10</td>
<td>22 19</td>
</tr>
</tbody>
</table>

1. The cephalosporin breakpoints for Enterobacteriaceae will detect all clinically important resistance mechanisms (including ESBL and plasmid mediated AmpC). Some isolates that produce beta-lactamases are susceptible or intermediate to 3rd or 4th generation cephalosporins with these breakpoints and should be reported as tested, *i.e.* the presence or absence of an ESBL does not in itself influence the categorisation of susceptibility. In many areas, ESBL detection and characterisation is recommended or mandatory for infection control purposes.

[http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_5.0_Breakpoint_Table_01.pdf](http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_5.0_Breakpoint_Table_01.pdf)
Systematic review and meta-analysis of carbapenems vs alternatives in ESBL Enterobacteriaceae

Figure 3. Forest plot depicting the RRs of all-cause mortality of patients with ESBL-positive bacteraemia treated empirically with carbapenems versus BL/BLIs. Vertical line='no difference' point between the two regimens. Squares=RRs. Diamond=pooled RR for all studies. Horizontal lines=95% CIs.

Systematic review and meta-analysis of carbapenems vs alternatives in ESBL Enterobacteriaceae

Non-Carbapenem Therapy for Bacteremia Caused by Extended-Spectrum β-Lactamase-Producing Enterobacteriaceae

such as K. pneumoniae. Moreover, our data extend to AMC and PTZ but not to other BLBLIs. In conclusion, our results suggest that AMC or PTZ, if used at adequate dosages, are suitable options for the definitive therapy of susceptible ESBL-EC strains causing BSI, mainly in the urinary and biliary tracts, which could help prevent overuse of carbapenems.

Radriguez-Bano et al. CIS 2012:54
Treatment of MDR bacteria

Combination therapy

- Monotherapy is associated with higher mortality rates than combination in case of MDR

Combination therapies

- Aminoglycoside, ampicillin/sulbactam, carbapenem, colistin, rifampicin $\rightarrow$ *Acinetobacter* spp
- Aminoglycosides, ampicillin/sulbactam, carbapenem, colistin, rifampicin, tigecycline, fosfomycin $\rightarrow$ *Enterobacteriaceae*
- Combination including carbapenem if MIC is $\leq$ 8 mg/L
  - Carbapenem-containing combinations resulted in significantly lower mortality rates (18.8%) than the carbapenem-sparing combinations (30.7%)
- Colistin: increases the permeability of other AB through the bacterial outer membrane by a detergent mechanism

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In case of carbapenem-resistance: other options

Treatment Options for Carbapenem-Resistant *Enterobacteriaceae* Infections

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This article provides a comprehensive review of currently available treatment options for infections due to carbapenem-resistant *Enterobacteriaceae* (CRE). Antimicrobial resistance in Gram-negative bacteria is an emerging and serious global public health threat. Carbapenems have been used as the “last-line” treatment for infections caused by resistant *Enterobacteriaceae*, including those producing extended spectrum β-lactamases. However, *Enterobacteriaceae* that produce carbapenemases, which are enzymes that deactivate carbapenems and most other β-lactam antibiotics, have emerged and are increasingly being reported worldwide. Despite this increasing burden, the most optimal treatment for CRE infections is largely unknown. For the few remaining available treatment options, there are limited efficacy data to support their role in therapy. Nevertheless, current treatment options include the use of older agents, such as polymyxins, fosfomycin, and aminoglycosides, which have been rarely used due to efficacy and/or toxicity concerns. Optimization of dosing regimens and combination therapy are additional treatment strategies being explored. Carbapenem-resistant *Enterobacteriaceae* infections are associated with poor outcomes and high mortality. Continued research is critically needed to determine the most appropriate treatment.

*Keywords.* carbapenemases; carbapenem-resistant *Enterobacteriaceae*; carbapenems; resistant infections; treatment.

In case of carbapenem-resistance: other options

<table>
<thead>
<tr>
<th>Infection Source</th>
<th>Empiric Treatment: Core Drugs</th>
<th>Empiric Treatment: Possible Adjunct Drugs</th>
<th>Antimicrobial Susceptibility Directed Treatment Considerations</th>
</tr>
</thead>
</table>
| **Bloodstream**                   | • High-dose meropenem or doripenem  
And polymyxin B | • Aminoglycoside  
Tigecycline  
Fosfomycin  
Rifampin | Meropenem/doripenem:  
MIC $\leq$16 $\mu$g/mL continue high-dose meropenem/doripenem  
MIC $>16$ $\mu$g/mL consider alternative in vitro active antimicrobial$^a$ |
| **Lung**                          | • High-dose meropenem or doripenem  
And polymyxin B | • Tigecycline  
Aminoglycoside  
Fosfomycin  
Rifampin | Polymyxin B/colistin:  
MIC $\leq$ 2 $\mu$g/mL continue polymyxin B/colistin$^{b,c}$  
MIC $>2$ $\mu$g/mL consider alternative in vitro active antimicrobial |
| **Gastrointestinal/ biliary tract** | • High-dose meropenem or doripenem  
And polymyxin B  
And high-dose tigecycline | • Fosfomycin  
Rifampin | If both meropenem/doripenem MIC ($>16$ $\mu$g/mL) and polymyxin B/colistin MIC ($>2$ $\mu$g/mL), then consider a high-dose tigecycline-based regimen or a dual dual carbapenem-based regimen$^{d,e}$ |
| **Urine**                         | • High-dose meropenem or doripenem  
And fosfomycin$^g$  
Or aminoglycoside$^g$ | • Colistin  
Aminoglycoside | If pan-drug-resistant infection, select case-reports support dual carbapenem-based regimen$^e$ |

Tigecycline:  
• MIC $\leq$1 $\mu$g/mL consider tigecycline$^d$  
• MIC $>1$ $\mu$g/mL consider alternative in vitro active antimicrobial

Fosfomycin$^f$:  
• MIC $\leq$32 $\mu$g/mL consider fosfomycin  
• MIC $>32$ $\mu$g/mL consider alternative in vitro active antimicrobial

Aminoglycoside:  
• MIC $\leq$2 $\mu$g/mL (Gentamicin/ Tobramycin) or $\leq 4$ $\mu$g/mL (Amikacin) consider aminoglycoside  
• MIC $>2$ (Gentamicin/ Tobramycin) or $>4$ $\mu$g/mL (Amikacin) consider alternative in vitro active antimicrobial

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General conclusion for combinations

• The hospital MUST have specific rules for proper use:
  – Prescription only in case of multidrug-resistant gram-negative bacilli in hospital
  – When there is no alternative
  – If empirical treatment for 48 hours revaluation in order to de-escalate promoting therapeutic alternative
First general conclusions for carbapenems: do NOT lose the battle!

Combating the spread of carbapenemases in Enterobacteriaceae: a battle that infection prevention should not lose

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Table 1. Infection prevention and antimicrobial stewardship recommendations published to prevent the spread of carbapenem-resistant Enterobacteriaceae

Required infection prevention measures

- Implement a surveillance programme to identify potential carriers (screening)
- Use contact isolation precautions for colonized and infected patients
- Cohort colonized and infected patients
- Enhance hand hygiene and support with audits
- Increase the frequency of environmental cleaning
- Limit the use of devices and remove unnecessary devices
- Implement antimicrobial stewardship, including a programme
- Educate healthcare workers about critical prevention measures

Suggested enhanced infection prevention measures

- Limit patient transfers
- One-to-one nursing
- Decolonize patients with chlorhexidine gluconate baths
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What could Uong Bi do?

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Second general conclusions for carbapenems: Use them appropriately

These antibiotics must be used only

- under supervision of ID specialists
- maintained ONLY after adequate microbiological investigations
- according to rules set forth by the Antibiotic Management Team
- and with surveillance from the Infection control Team
But why do you wish to use carbapenems?

- Do you have resistant organisms that you cannot "treat" with other antibiotics?
- Can you obtain MICs and provide interpretation?
- If used empirically, do you have plans for de-escalation?
- Do you have an Infection Control Plan working?