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
**β-lactames: pharmacochemistry**

- pénicillines
- inhibiteurs
- carbapénème
- céphalosporines
- oxacéphème
- monobactame

**Chemical Structures:**

- Penicillins
- Cephalosporins
- Oxacephems
- Carbapenems
- Monobactams
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

\[
\text{imipenem} + \text{cilastatine} = \text{TIENAM} \, ^\circledR
\]

Inhibitor of the déhydropeptidase
Carbapenems: from imipenem to meropenem

Resistance to the dehydropeptidase through steric hindrance

**Chemical Structures**

- **Meropenem**
  - Molecular formula: C₂₃H₂₉NO₅S
  - Structure includes a thiazolidine ring and dehydropeptidase resistance through steric hindrance.

- **Doripenem**
  - Molecular formula: C₂₅H₃₁NO₇S
  - Similar structure to meropenem but with an additional methyl group in the thiazolidine ring.

- **Imipenem**
  - Molecular formula: C₂₅H₃₁NO₇S
  - Structure includes a lactam ring and is the precursor of doripenem.
Carbapenems: from meropenem to ertapenem

**meropenem**

**ertapenem**

long half-life BUT loss of useful activity against *P. aeruginosa*
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

\[ \Delta \log \text{CFU/mg prot. from time 0} \]

- **Oxacillin**
  - \( E_{\min} \)
  - \( E_{\max} \)

- **Gentamicin**
  - \( E_{\min} \)
  - \( E_{\max} \)

\[ \log \text{extracellular concentration (X MIC)} \]
Introducing pharmacokinetics…

\[ C_{\text{min}} - C_{\text{max}} \]

**weak concentration dependence**

**strong concentration-dependence**
**β-lactams are time-dependent...**

Various β-lactams

Various pathogens

![Graph showing relationship between 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 (□).](image)

**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 (□).

Various pathogens

Doripenem

![Graph showing relationship between doripenem exposure, as measured by % Time > MIC, and response in a neutropenic murine-thigh infection model involving Gram-negative bacteria.](image)

**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% $\rightarrow$ bacteriostatic effects

- $T>MIC$ of 40% $\rightarrow$ 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
  
  o Increase the drug dose (to obtain at least 40% of 4xMIC)
  o 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 → liver → Valproic acid glucuronide

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

Valproic acid $\rightarrow$ reduced serum concentrations of valproic acid

Valproic acid concentration $\rightarrow$ 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
## MDR organisms that may require carbapenems (after documentation)

<table>
<thead>
<tr>
<th>First choice</th>
<th>Comment</th>
<th>Combined with</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acinetobacter baumanii</td>
<td>R to pip-tazo, cephalo III, FQ, AG</td>
<td></td>
</tr>
<tr>
<td>Enterobacter</td>
<td>R to pip-tazo, cephalo III, FQ, AG</td>
<td></td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>ESBL</td>
<td></td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>R to pip-tazo and ceftazidime + ciprofloxacin or aminoglycoside</td>
<td>+ ciprofloxacin or aminoglycoside</td>
</tr>
<tr>
<td></td>
<td>R to pip-tazo, ceftazidime, aminoglycosides</td>
<td>+ ciprofloxacin</td>
</tr>
</tbody>
</table>
Empiric treatments with carbapenems?

Sandford guide (2012-2013)
# CNS Infections

<table>
<thead>
<tr>
<th>Infection</th>
<th>Pathogen/Population</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain abscess</td>
<td>Pseudomonas suspected</td>
<td>(cefepime + metronidazole) or meropenem</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>enterobacteriaceae</td>
<td>Meropenem or cephalo III</td>
</tr>
<tr>
<td></td>
<td>Pseudomonas</td>
<td>Amikacin + (ceftazidime or meropenem)</td>
</tr>
<tr>
<td>Brain abscess or pulmonary infection or cutaneous</td>
<td>Nocardia, disseminated</td>
<td>TMP-SMX + (meropenem or ceftriaxone) + amikacin</td>
</tr>
<tr>
<td>infection in immunocompromised patient</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Respiratory tract infections

<table>
<thead>
<tr>
<th>Infection</th>
<th>Pathogen/population</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAP/VAP</td>
<td>ESBL producer</td>
<td>meropenem (but see later !)</td>
</tr>
<tr>
<td>Pneumonia in immunocompromised patient</td>
<td></td>
<td>(Cephalo III or Pip-tazo or meropenem) +/− amikacin</td>
</tr>
<tr>
<td>Infection</td>
<td>Pathogen/population</td>
<td>Treatment</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>mastoiditis</td>
<td>Often polymicrobial</td>
<td>Piperacillin-tazobactam or meropenem</td>
</tr>
<tr>
<td>Diabetic foot grade 4</td>
<td>Recent exposure to AB</td>
<td>Piperacillin-tazobactam or meropenem, + vancomycin if Gram(+)</td>
</tr>
<tr>
<td>Established wound infection with sepsis</td>
<td>Staphylococci, streptococci, enterobacteriaceae</td>
<td>(amoxi-clav + cipro or levo or amikacin) or meropenem</td>
</tr>
<tr>
<td></td>
<td>Exposure to fresh water (Pseudomonas)</td>
<td>Ciprofloxacin or levofloxacin or meropenem</td>
</tr>
<tr>
<td>Sepsis in immunocompromised patients</td>
<td></td>
<td>(Ceftazidime or cefepime or Pip-tazo or meropenem) +/- amikacin</td>
</tr>
<tr>
<td>Catheter related infections</td>
<td>Severe or risk factors</td>
<td>vancomycin + (ceftazidime, cefepime, piperacillin-tazobactam or meropenem)</td>
</tr>
<tr>
<td>Hospital acquired pelvic or portal thrombophlebitis</td>
<td></td>
<td>Pip-tazo or meropenem or (cefpem or ceftazidime + metronidazole)</td>
</tr>
</tbody>
</table>
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 $\rightarrow$ emergence of resistance
- Meningitis (meropenem only)

* imipenem and meropenem (imipenem: children $\geq 12$ 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 Endometritis, 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 meningitis** 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.
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>

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

- Penicillinase (TEM-1, SHV-1)
- ESBLs (CTX-M, TEM, SHV, ...)
- Carbapenemases (VIM, NDM, OXA-48, ...)

1940 - 1970 - 1990 - 2010
## 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

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Penicillins</th>
<th>Cephalosporins 1st et 2nd generation</th>
<th>Cephalosporins 3rd/4th generation cefepime cefpirome</th>
<th>β-lactams/Inhibitors of β-lactamases</th>
<th>Carbapenems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambler class</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td></td>
<td>Penicillinases: KPC, IMI, GES..</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td></td>
<td>Metallo-enzymes: VIM, IMP, NDM-1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td></td>
<td>Oxacillinases = OXA-48, OXA-181</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Cephemycins excluded for most class As

From P. Nordman
Carbapenemase producing *Enterobacteriaceae*
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>Mainly found in <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 -“MBLs”)</td>
<td>NMD-1, IMP-1, 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?
High hospital consumption of carbapenems

Carbapenems

2010

“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

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>% Susceptible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imipenem</td>
<td>100</td>
</tr>
<tr>
<td>Pip-tazo</td>
<td>80</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>30</td>
</tr>
<tr>
<td>Cefepime</td>
<td>10</td>
</tr>
<tr>
<td>Cipro</td>
<td>0</td>
</tr>
</tbody>
</table>
Variation of MIC in *Enterobacteriaceae* producing 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>

*KPC, Klebsiella pneumoniae carbapenemase; OXA-48, oxacillinase-48.†Including New Delhi metallo-β-lactamase-1.*

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

### Enterobacteriaceae

#### Penicillins

<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>Ampicillin-sulbactam</td>
<td>8¹,²</td>
<td>8²</td>
<td>10-10</td>
</tr>
<tr>
<td>Amoxicillin-clavulanic acid</td>
<td>8¹,³</td>
<td>8³</td>
<td>20-10</td>
</tr>
<tr>
<td>Amoxicillin-clavulanic acid (uncomplicated UTI only)</td>
<td>32¹,³</td>
<td>32³</td>
<td>20-10</td>
</tr>
<tr>
<td><strong>Piperacillin-tazobactam</strong></td>
<td>8⁴</td>
<td>16⁴</td>
<td>30-6</td>
</tr>
</tbody>
</table>

#### Cephalosporins

<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>Cefepime</td>
<td>1</td>
<td>4</td>
<td>30</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>1</td>
<td>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
Use of EUCAST breakpoints to predict outcome based on MIC determination

**Important message for the clinicians!**

<table>
<thead>
<tr>
<th>Enterobacteriaceae</th>
<th>MIC breakpoint (mg/L)</th>
<th>Disk content (μg)</th>
<th>Zone diameter breakpoint (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillins¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ampicillin-sulbactam</td>
<td>20-10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin-clavulanic acid</td>
<td>16&lt;sup&gt;AB&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin-clavulanic acid (uncomplicated UTI only)</td>
<td>32&lt;sup&gt;1,3&lt;/sup&gt;</td>
<td>32&lt;sup&gt;3&lt;/sup&gt;</td>
<td>20-10</td>
</tr>
<tr>
<td><strong>Piperacillin-tazobactam</strong></td>
<td>8&lt;sup&gt;4&lt;/sup&gt;</td>
<td>16&lt;sup&gt;4&lt;/sup&gt;</td>
<td>30-6</td>
</tr>
<tr>
<td>Cephalosporins¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefepime</td>
<td>1</td>
<td>4</td>
<td>30</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>1</td>
<td>4</td>
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[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*

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Carbapenems Events</th>
<th>Carbapenems Total</th>
<th>BL/BLIs Events</th>
<th>BL/BLIs Total</th>
<th>RR M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apsisarnthanarak et al. (2008)</td>
<td>0</td>
<td>5</td>
<td>1</td>
<td>10</td>
<td>1.9%</td>
</tr>
<tr>
<td>Bin et al. (2006)</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>7</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Chaubey et al. (2010)</td>
<td>0</td>
<td>10</td>
<td>6</td>
<td>16</td>
<td>9.0%</td>
</tr>
<tr>
<td>De Rosa et al. (2011)</td>
<td>8</td>
<td>57</td>
<td>2</td>
<td>8</td>
<td>6.2%</td>
</tr>
<tr>
<td>Ferrandez et al. (2011)</td>
<td>2</td>
<td>6</td>
<td>6</td>
<td>13</td>
<td>6.7%</td>
</tr>
<tr>
<td>Gudiel et al. (2010)</td>
<td>2</td>
<td>5</td>
<td>3</td>
<td>6</td>
<td>4.8%</td>
</tr>
<tr>
<td>Kang et al. (2012)</td>
<td>21</td>
<td>78</td>
<td>8</td>
<td>36</td>
<td>19.3%</td>
</tr>
<tr>
<td>Lee et al. (2010)</td>
<td>4</td>
<td>24</td>
<td>1</td>
<td>13</td>
<td>2.3%</td>
</tr>
<tr>
<td>Metan et al. (2009)</td>
<td>7</td>
<td>22</td>
<td>5</td>
<td>7</td>
<td>13.4%</td>
</tr>
<tr>
<td>Qureshi et al. (2011)</td>
<td>0</td>
<td>8</td>
<td>1</td>
<td>4</td>
<td>3.4%</td>
</tr>
<tr>
<td>Rodriguez-Bano et al. (2012)</td>
<td>6</td>
<td>31</td>
<td>7</td>
<td>72</td>
<td>7.4%</td>
</tr>
<tr>
<td>Tumbarello et al. (2007)</td>
<td>1</td>
<td>28</td>
<td>4</td>
<td>33</td>
<td>6.5%</td>
</tr>
<tr>
<td>Velaphi et al. (2009)</td>
<td>13</td>
<td>40</td>
<td>12</td>
<td>48</td>
<td>19.2%</td>
</tr>
</tbody>
</table>

**Total (95% CI)**

Total events 64 56

Heterogeneity: $\chi^2 = 12.95; df= 11 (P = 0.30); I^2 = 15$

Test for overall effect: $Z = 0.58 (P = 0.56)$

**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


**FIG 1** Kaplan-Meier survival estimates of patients with carbapenemase-producing *K. pneumoniae* bloodstream infections according to treatment regimen: combination therapy (continuous line) versus monotherapy (dotted line). $P = 0.003$ (log rank test).
Combination therapies

- Aminoglycoside, ampicillin/sulbactam, carbapenem, colistin, rifampicin → *Acinetobacter* spp

- Aminoglycosides, ampicillin/sulbactam, carbapenem, colistin, rifampicin, tigecycline, fosfomycin → *Enterobacteriaceae*

- Combination including carbapenem if MIC is ≤ 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

Tängden T. Journal of Medical Sciences 2014;119:149-153
In case of carbapenem-resistance: other options

Treatment Options for Carbapenem-Resistant Enterobacteriaceae Infections

Haley J. Morrill,1,2 Jason M. Pogue,3 Keith S. Kaye,4 and Kerry L. LaPlante1,2,5
1Veterans Affairs Medical Center, Infectious Diseases Research Program, Providence, Rhode Island; 2College of Pharmacy, Department of Pharmacy Practice, University of Rhode Island, Kingston; 3Department of Pharmacy Services; 4Division of Infectious Diseases, Detroit Medical Center, Wayne State University, Michigan; and 5Division of Infectious Diseases, Warren Alpert Medical School of Brown University, Providence, Rhode Island

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>
<tbody>
<tr>
<td>Bloodstream</td>
<td>• High-dose meropenem or doripenem</td>
<td>• Aminoglycoside</td>
<td>Meropenem/doripenem:</td>
</tr>
<tr>
<td></td>
<td>• And polymyxin B</td>
<td>• Tigecycline</td>
<td>• MIC ≤16 µg/mL continue high-dose meropenem/doripenem</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Fosfomycin</td>
<td>• MIC &gt;16 µg/mL consider alternative in vitro active antimicrobial</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Rifampin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Polymyxin B/colicin:</td>
</tr>
<tr>
<td>Lung</td>
<td>• High-dose meropenem or doripenem</td>
<td>• Tigecycline</td>
<td>• MIC ≤2 µg/mL continue polymyxin B/colicin</td>
</tr>
<tr>
<td></td>
<td>• And polymyxin B</td>
<td>• Aminoglycoside</td>
<td>• MIC &gt;2 µg/mL consider alternative in vitro active antimicrobial</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Fosfomycin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Rifampin</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal/biliary tract</td>
<td>• High-dose meropenem or doripenem</td>
<td>• Fosfomycin</td>
<td>If both meropenem/doripenem MIC (&gt;16 µg/mL) and polymyxin B/colicin MIC (&gt;2 µg/mL), then consider a high-dose Tigecycline-based regimen or a dual dual carbapenem-based regimen</td>
</tr>
<tr>
<td></td>
<td>• And polymyxin B</td>
<td>• Rifampin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• And high-dose tigecycline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine</td>
<td>• High-dose meropenem or doripenem</td>
<td>• Colistin</td>
<td>If pan-drug-resistant infection, select case-reports support dual carbapenem-based regimen</td>
</tr>
<tr>
<td></td>
<td>• And fosfomycin</td>
<td>• Aminoglycoside</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Or aminoglycoside</td>
<td></td>
<td>Tigecycline:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• MIC ≤1 µg/mL consider tigecycline</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• MIC &gt;1 µg/mL consider alternative in vitro active antimicrobial</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fosfomycin:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• MIC ≤32 µg/mL consider fosfomycin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• MIC &gt;32 µg/mL consider alternative in vitro active antimicrobial</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Amioglycoside:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• MIC ≤2 µg/mL (Gentamicin/ Tobramycin) or ≤4 µg/mL (Amikacin) consider aminoglycoside</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• MIC &gt;2 (Gentamicin/ Tobramycin) or &gt;4 µg/mL (Amikacin) consider alternative in vitro active antimicrobial</td>
</tr>
</tbody>
</table>
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
Combating the spread of carbapenemases in *Enterobacteriaceae*: a battle that infection prevention should not lose

P. Savard¹,² and T. M. Perl³,⁴
1) Department of Microbiology, Infectiology and Immunology, Université de Montréal, 2) Medical Microbiology and Infectious Diseases Department, Centre Hospitalier Universitaire de Montréal, Hôpital St-Luc, Montréal, QC, Canada, 3) Division of Infectious Diseases, Department of Medicine, Johns Hopkins University School of Medicine and 4) Epidemiology and Infection Prevention, The Johns Hopkins Health System and Johns Hopkins Medicine, Baltimore, MD, USA

First general conclusions for carbapenems: do NOT loose the battle!

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
First general conclusions for carbapenems: do NOT loose the battle!

**TABLE 1. Infection prevention and control recommendations for carbapenem-resistant Enterobacteriaceae**

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

<table>
<thead>
<tr>
<th>Suggested enhanced infection prevention measures</th>
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</thead>
<tbody>
<tr>
<td>Limit patient transfers</td>
</tr>
<tr>
<td>One-to-one nursing</td>
</tr>
<tr>
<td>Decolonize patients with chlorhexidine gluconate baths</td>
</tr>
</tbody>
</table>
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?