How to improve/decrease carbapenem use

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Conflicts of Interest

• Research grants from Pfizer
• Travel grants from Pfizer, Astellas, Gilead, Novartis, Abbott
Outline of the presentation

1. Introduction
2. How to improve carbapenem use
   1. Pharmakokinetics
   2. Combinations
   3. Strategies to preserve susceptibilities of carbapenems
3. How to decrease carbapenem use
   1. Carbapenem sparing regimens
   2. Alternative strategies
4. Conclusions
Proportion of Carbapenems Resistant (R+I) *Pseudomonas aeruginosa* Isolates in Participating Countries in 2011

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

(C) ECDC/Dundas/TESSy
Proportion of Carbapenems Resistant (R+I) Klebsiella pneumoniae Isolates in Participating Countries in 2011
Carbapenems are valuable

- Appropriate use of carbapenems is a particular concern because they are often used as the last line of defence against increasingly difficult-to-treat Gram-negative pathogens such as *Pseudomonas aeruginosa*

- A large European sepsis study showed that *P. aeruginosa* was associated with worse clinical outcomes in Intensive Care Unit patients, presumably due to enhanced phenotypic resistance

The ultimate goal

Avoiding collateral damage and preserving the effectiveness of the carbapenem class are priorities in the context of widespread resistance to often-used antibiotics.

The optimal strategy

“Rescuing”
Or
“Sparing” ?
Outlook of the presentation

1. Introduction
2. How to improve carbapenem use
   1. Pharmacokinetics
   2. Combinations
   3. Strategies to preserve susceptibilities of carbapenems
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   1. Carbapenem sparing regimens
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Probabilities of attaining 50% T>MIC target for meropenem

- 30 min infusion of 1g, q8 h
  For MIC of 4 mg/l $\rightarrow$ 69%

- 3 h infusion of 2g, q8 h
  - For MIC of 4 mg/l $\rightarrow$ 100%
  - For MIC of 8 mg/l $\rightarrow$ 85%

- Paediatric patients 40 mg/kg tid with a longer infusion duration (4h) is more effective against bacteria with MIC >2 µg/mL.
  - probability of target attainment 97.0%
  - Correlates to the microbiological efficacy rate (97.0%) and also to the clinical efficacy rate (95.9%).

Ertapenem

- Ertapenem is highly albumin bound (85–95%).
- Data from three studies suggest that **hypoalbuminaemia may have a profound effect on ertapenem**.
- Unbound concentrations did not achieve the 40% fT>MIC PD target in half of the critically ill patients with severe sepsis.

**Recommended loading dose in hypoalbuminaemia:**

2 g

**Recommended maintenance dose:**

increase frequency of administration (e.g. 1 g q12h)


Target attainment results for doripenem infused over 1 h and 4 h over a wide range of creatinine clearances observed in phase 1, 2, and 3 studies.

Doripenem 500 mg every 8 h

The failed DORINOS 3008 study

- 233 patients with late-onset VAP
- The non-inferiority of:
  - a fixed 7-day course of doripenem (1 g, q 8 h as a 4 h infusion) compared to
  - a fixed 10-day course of imipenem/cilastatin (1 g q 8 hours as a 1 h infusion). was not demonstrated
New recommendations on dosing, duration and precautions for treatment of pts with NP with doripenem

• The short fixed duration of therapy was a major contributor to the inferior outcome in the doripenem group

• Based on PK/PD modeling and safety data from approximately 500 subjects, 1 g doripenem q 8 h as a 4-h infusion may be considered when treating patients with NP (including VAP), in the following instances:
  - augmented renal clearance
    (particularly those with CrCl ≥150 ml/min)
  - infections by non-fermenting gram-negatives
    treatment duration 10-14 days
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Colistin + Doripenem

• Against MDR *P. aeruginosa*
  

• Against MDR *K. pneumoniae*
  
Time-kill curves for colistin and doripenem combination therapy against a colistin-resistant MDR clinical isolate of *P. aeruginosa*

The combination of Colistin plus Doripenem is synergistic against colistin-resistant MDR *K. pneumoniae* and colistin-resistant *MDR P. aeruginosa*

- One-compartment in vitro PK/PD model was employed, with inocula of $\sim 10^6$ and $\sim 10^8$ CFU/ml

- Against the colistin-resistant isolate, colistin at 2 mg/liter plus doripenem (Cmax, 25 mg/liter) at the low inoculum improved bacterial killing.

- Prevented the emergence of colistin-resistant subpopulations

Antimicrobial Combinations for KPC(+) *K. pneumoniae*
Combination Treatment

Recent supportive studies

• 41 bacteremic patients-retrospective study
• 28-day mortality was 13.3% in the combination therapy group compared with 57.8% in the monotherapy group (P = 0.01).
• In the multivariate analysis, definitive therapy with a combination regimen was independently associated with survival (odds ratio, 0.07 P = 0.02)
• The most commonly used combinations were colistin or tigecycline with a carbapenem (mortality 12.5%)
• Despite in vitro susceptibility, patients who received monotherapy with colistin-polymyxin B or tigecycline had a higher mortality of 66.7% (8/12).

Outcomes of 294 patients with infections caused by carbapenemase-producing K. pneumoniae* according to treatment Regimen Bacteremias-HAP/VAP

- **KPC and VIM, ** IMP or MER
- *** COL, TIG, Aminoglycoside

• 125 ICU patients with bloodstream infections (BSIs) caused by KPC-producing Kp isolates

• The overall 30-day mortality rate was 41.6%
  • significantly higher among patients treated with monotherapy (54.3% vs. 34.1% in those who received combined drug therapy, \( P = 0.02 \)).

• Definite treatment with a triple combination of tigecycline, colistin, and meropenem was associated with lower mortality (OR, 0.11; 95% CI, 0.02 to 0.69; \( P = 0.01 \))

Kaplan Meier Curve

Summary of accumulated data from the Greek experience

Carbapenems may be a reasonable treatment option against CPKP, provided that:
(i) the carbapenem MIC for the infecting organism is ≤4 mg/L;
(ii) a high-dose prolonged-infusion regimen is administered
(iii) a second active drug is administered

Exploiting increased *in vitro* affinity of KPC enzymes for ertapenem “a suicide substrate”

*In vitro* chemostat model (doripenem MIC, 4 g/ml).
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Bacteremia due to ESBL(+) bacteria

• Carbapenems are considered the drugs of choice.

• Alternatives to carbapenems are needed because of the emergence of carbapenemase-producing enterobacteria.

• The efficacy of β-lactam/β-lactam inhibitors (BLBLI) in such infections is controversial.
Bacteremia due to ESBL(+) \textit{E. coli} (ESBL-EC)

- Post hoc analysis of patients with BSIs due to ESBL-EC from 6 published prospective cohorts.
- Patients treated with an:
  - \textbf{active BL/BLI} (AMC and P/TZ]) or
  - \textbf{carbapenem}
    were compared regarding mortality and LOS.
- Two cohorts:
  - the empirical therapy cohort (ETC) \textit{and}
  - the definitive therapy cohort (DTC).

Mortality due to bacteremia due to ESBL(+) \textit{E. coli}

After adjustment for confounders, 

no association was found between:

- empirical therapy
  
  \begin{itemize}
  \item \text{HR, 1.14; CI, 0.29–4.40; P=0.84}
  \end{itemize}

- definitive therapy
  
  \begin{itemize}
  \item \text{HR, 0.76; CI, 0.28–2.07; P=0.5}
  \end{itemize}

and increased mortality

Bacteremia due to ESBL(+) \textit{E. coli}

Conclusions
The results suggest that AMC and PTZ are suitable alternatives to carbapenems for treating patients with BSIs due to ESBL-EC if active in vitro and would be particularly useful as definitive therapy.

Substituting Ertapenem for Group 2 carbapenems and the fear of selection of resistance

- Concern that use of ertapenem will select for resistances to imipenem and meropenem in nosocomial pathogens, notably *Pseudomonas aeruginosa*
- Whilst ertapenem can select for *P. aeruginosa* mutants with cross-resistance to imipenem and ertapenem in vitro, this selectivity should be minimal under clinical conditions.

How to define the best patient candidate

- Ertapenem could be used as either empirical or directed therapy for infections due to aerobic Gram-negative and mixed anaerobic bacteria.
- Typical scenarios might include intra-abdominal infections where the probability of non-fermentative Gram-negatives including *Pseudomonas* is unlikely based on the clinical course and risk factors of the patient.
- Caution! Local epidemiology data are extremely important to guide the use of ertapenem as empiric treatment.
Summary of ertapenem studies

- Appropriate use of ertapenem in the context of local institutional antibiotic policies appears to improve the overall hospital ecology in some studies.
- A 9-year, observational, multicentre analysis indicated that ertapenem did not impact antipseudomonal carbapenem susceptibilities.
- A minority of studies showed increased susceptibility to imipenem amongst *Pseudomonas* spp.

Pires dos Santos R, AAC 2010;54:3076–7
Nikolau D IJAA 2012; 39: 11–15
<table>
<thead>
<tr>
<th>Setting</th>
<th>Group 2 carbapenem use (DDD before/after)</th>
<th>% carbapenem susceptible (pre versus post ertapenem introduction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single centre, USA [Graber, EpidemiolInfect 2011]</td>
<td>37.5 to 21.0/1000 PD</td>
<td>Pseudomonas, 62.2 vs. 70.4 (P = N/S) Enterobacteriaceae, 82.5 vs. 88.6 (P=NS)</td>
</tr>
<tr>
<td>Single centre, USA [Goldstein, AAC 2009]</td>
<td>30 to 25/1000 PD (median)</td>
<td>Pseudomonas, 69 vs. 88 Enterobacteriaceae, no change</td>
</tr>
<tr>
<td>Single centre, USA [Goff, J Infect 2008]</td>
<td>21.5 to 31.1/1000 PD</td>
<td>Pseudomonas, 69 vs. 88 Enterobacteriaceae, no change</td>
</tr>
<tr>
<td>Retrospective, hospital database study of nine medical wards Israel [Carmeli, Diagn Microbiol Infect Dis 2011]</td>
<td>4637</td>
<td>3.8% annual increase in imipenem-resistant Pseudomonas (P = 0.001), associated only with group 2 carbapenem use (P = 0.0014)</td>
</tr>
<tr>
<td>Single-centre study pharmacy and microbiology reports; USA [Crank, IDSA; 2006 Poster 285].</td>
<td>1650 to 2295</td>
<td>Pseudomonas, imipenem P = N/S; meropenem 76.6 vs.71.9 (P = 0.0001)</td>
</tr>
<tr>
<td>Single centre, Brazil [Lima, ICHE 2009 and Braz J Infect Dis 2011]</td>
<td>46.3 to 16.1/1000 PD</td>
<td>Pseudomonas, 20 to 0 (P = N/S)</td>
</tr>
<tr>
<td>Single centre, Brazil [Lima, Braz J Infect Dis 2011]</td>
<td>61.1 to 48.7 DDD/1000 PD</td>
<td>Pseudomonas, Acinetobacter, Enterobacteriaceae, no change</td>
</tr>
<tr>
<td>Multicentre retrospective, data analysis; USA [Eagye, JAC 2010 and 2011]</td>
<td>10.4 to 15.3</td>
<td>Pseudomonas, 85.4 to 81.0 (P = N/S)</td>
</tr>
</tbody>
</table>

Adapted from Nikolau D *IJAA* 39 (2012) 11–15
Ciprofloxacin as promoter of carbapenem resistance

• The use of fluoroquinolones and group-2 carbapenems is a known risk factor for infections with carbapenem-resistant *P. aeruginosa*

*Lautenbach E, Infect Control Hosp Epidemiol 2010;31:47–53*
*Messadi AA, Burns 2008;34:1098–1102*
*JooEJ Microb Drug Resist 2011;17:305–312*
Quinolones and carbapenem resistance

- Quinolone use may lead to cross-resistance to all of the group 2 carbapenems, either by increased efflux (meropenem and doripenem) or by decreased porin entry (imipenem, meropenem, and doripenem).

Ciprofloxacin restriction is beneficial for carbapenems against *Pseudomonas* spp

- Decreased ciprofloxacin usage was associated with a decrease in the resistance of *P. aeruginosa* to group-2 carbapenems and ciprofloxacin
- No changes were observed in the susceptibilities of nosocomial Enterobacteriaceae or *A. baumannii* to carbapenems despite an increase in carbapenem use.
Rate of resistant infections per 10000 patient/days by month

Month 42: introduction of ciprofloxacin restriction policy
Panel A Carbapenem-resistant infections $P=0.0006$
Panel B Ciprofloxacin-resistant infections $P=0.0001$
Panel C Cefepime-resistant infections $P=0.0004$

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Available treatment options

- Colistin (susceptibility variable)
- Tigecycline (susceptibility variable)
- Aminoglycosides (susceptibility variable)
Why colistin performed so badly as monotherapy?
Optimization of colistin PK/PD
Colistin pharmacodynamics

• Concentration-dependent bacterial killing activity.
  \((\text{Li J}, \text{et al. AAC2001; 45:781})\)

• fAUC/MIC ratio is the parameter best associated with its efficacy.
  \((\text{Bergen PJ, et al. JAC 2008; 61:636})\)
Population pharmacokinetic analysis of colistin methanesulfonate and colistin after intravenous administration in critically ill patients with infections caused by gram-negative bacteria


Plasma colistin A and colistin B concentrations were determined by a novel liquid chromatography-tandem mass spectrometry method

Dosage regimen reevaluation: A loading with 9MIU followed by 3MIU q8h was proposed.

Pharmacokinetics of Colistin in Critically ill Patients

New data indicate that

**Sub-therapeutic** concentrations (0.6μg/ml) during the first days (up to 48h) that may lead to:

- Delayed achievement of therapeutic levels
- Treatment failures
- Emergence of resistance

Plachouras D et al. AAC 2009;53:3430
# Suggested Colistin Dosing for Various Patients Categories

<table>
<thead>
<tr>
<th></th>
<th>Loading dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Targeting peak blood level of 2μg/ml in all patient category</td>
<td>Body weight(^a) divided by 7.5 (maximum permitted dose 10 mil iu)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal renal function</strong></td>
</tr>
<tr>
<td>(Cl(_{cr}) divided by 10) + 2 given in 2-3 doses</td>
</tr>
<tr>
<td>The 1(^{st}) dose should be given 24h post loading dose</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>In Hemodialysis</th>
<th>2 million IU in two daily doses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Additional 30% of the daily dose post dialysis</td>
</tr>
</tbody>
</table>

| In continuous hemofiltration | 10-12 mil iu in two or three daily doses\(^b\)                           |

---

\(^a\) Ideal or real body weight in Kg (choose the least)  
\(^b\) For doses >10 mil iu special attention to renal function

Adapted from Garonzik SM, et al. AAC 2011;55:3284
Loading dose of colistin: a simplified formula

Loading dose = Desired colistin plasma concentration at steady state

\[ \times \]

Body weight

\[ \times \]

60.000

Next maintenance dose should be given at 24h after induction dose

Adapted from Garonzik SM, et al. AAC 2011; 55:3284
Loading doses higher than the standard 160 to 240 mg CMS were shown to increase the initial bacterial kill.

Based on these results, a loading dose of 480 to 720 mg (6 to 9 MU) is recommended in critically ill patients.
High-Dose, Extended-Interval Colistin Administration in Critically Ill Patients: Is This the Right Dosing Strategy? A Preliminary Study

- Prospective study 28 septic episodes in ICU patients
- $\text{Cr}_\text{cl} > 50 \text{ mL/min}$ loading CMS dose of 9 MU, maintenance dose of 4.5 MU every 12 hours.
  - $\text{Cr}_\text{cl} < 50 \text{ mL/min}$, loading dose of 9 MU, maintenance doses of 4.5 MU/24 hours for $\text{Cr}_\text{cl} 20–50 \text{ mL/min}$, or 4.5 MU/48 hours for $\text{Cr}_\text{cl}$ of <20 mL/min
- 50% of episodes received colistin monotherapy
- Bloodstream infection (64.3%) and ventilator-associated pneumonia (35.7%), *K. pneumoniae* (46.4%),
- Clinical cure was observed in 23 cases (82.1%)
  - 40% microbiological eradication in VAP episodes

*Dalfino L et al, CID 2012:54*
Association Between Colistin Dose and Microbiologic Outcomes in Patients With Multidrug-Resistant Gram-Negative Bacteremia

Giulia Vicari, Seth R. Bauer, Elizabeth A. Neuner, and Simon W. Lam

Department of Pharmacy, Community Hospital North, Indianapolis, Indiana; and Department of Pharmacy, Cleveland Clinic, Ohio

- A **retrospective cohort study**
- All patients at a large, academic, tertiary care medical center who received
Results

- 76 pts adult were included
- 80% were critically ill in an ICU
- The most common source of infection was CR-BSIs, with catheter removal rates approaching or achieving 100%.
- The median colistin MIC was 2.0 mg/L

Colistin dose

The median colistin dose was significantly higher in patients who achieved microbiological success (87.000 vs 45.000 IU/kg/day; P = 0.011).

Colistin dose

• The median colistin dose was also significantly higher among survivors at day 7.

  \(81.000 \text{ vs } 45.000 \text{ IU/kg/day; } P = 0.007\)

• However, no difference was observed in colistin dose when comparing survivors and non-survivors at day 28.

Independent risk factors associated with day-7 microbiological success in patients treated with Colistin for Carbapenem-resistant Gram (-) BSIs

In multivariate logistic regression model:

• increased colistin dose was independently associated with microbiologic success (OR: 1.74, p=0.015)

  whereas

• increased Pitt bacteremia score (OR: 0.64, p=0.001)
  and

• tigecycline use (OR: 0.23, p=0.019)
  were associated with microbiologic failure.

Colistin PKs in critically ill patients receiving CVVH

Colistin PKs in critically ill patients receiving CVVH

- 5 ICU patients receiving CVVHD
- Colistin concentrations (mean = 0.92 mg/l) were below the current MIC breakpoints.
- The fAUC/MIC was lower than recommended,
- Suggesting that a dosage regimen of 160mg CMS (2 x 10^6 IU) every 8 h is inadequate.

Colistin PKs in critically ill patients receiving CVVHD

• 2 ICU patients receiving CVVHD

• Conclusions:
  The recommended polymyxin B doses should not be reduced for pts on CVVHD.

Carbapenem-sparing regimens

• 22 polytrauma ICU pts without co-morbidities.
• 26 KPC (+) *K. pneumoniae* infectious episodes.
• A carbapenem-sparing regimen of: *tigecycline* plus *gentamicin or colistin*
  was effective for treating 24 (92%) of the pts.
• The 30-day crude mortality rate was 14%.
• Regimens were considered appropriate in 12% (Vitek 2 System) and in 100% (E-test) of episodes.

Tigecycline in the treatment of CPKP

(-)
- FDA warning
- Tigecycline is bacteriostatic against Gram-negative organisms
- The attainable drug concentrations at several anatomic sites such as blood, urine and epithelial lining fluid are suboptimal
- The trial of VAP produced disappointing results

(+) 
- In vitro Synergy with Meropenem and colistin
- Dose escalation is possible to achieve PK/PD targets
- Data in real life senaria are encouraging when tigecycline is used in combinations

Fosfomycin combinations

Efficacy of Fosfomycin in infections caused by XDR and PDR Gram-negative pathogens in ICU critically ill patients:
A multi-center observational study
ECCMID Berlin 2013, accepted
Combinations of fosfomycin
Extracted data: non-carbapenem combinations

**26 isolates of K. pneumoniae**
- 50% XDR
- 38.5% PDR
  - 100% carbapenem resistance
  - 78.3% Colistin resistance
  - 33.3% tigecycline resistance
  - 26.1% gentamicin resistance

**26 isolates of P. aeruginosa**
- 30.8% XDR
- 3.8% PDR
  - 100% carbapenem resistance
  - 11.1% colistin resistance
  - 77.8% gentamicin resistance

<table>
<thead>
<tr>
<th>Primary Bacteremia</th>
<th>CRBSI</th>
<th>VAP</th>
<th>IAI</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>34.6%</td>
<td>11.5%</td>
<td>30.8%</td>
<td>19.2%</td>
<td>11.5%</td>
</tr>
</tbody>
</table>

Courtesy of Prof H. Giamarellou and Dr K. Pontikis
Combinations of fosfomycin
Preliminary data from a Greek study

26 patients
Various combinations of fosfomycin 24 g/d with colistin (69%),
tigecycline (42%), aminoglycoside (30%)
Mean age (SD) : 56.6 yrs (17.3)
Mean ICU stay duration (SD) before fosfomycin initiation: 35.5 (22) days
Mean APACHE II (SD) at fosfomycin initiation: 21.4 (8.05)
Mean duration (SD) of sepsis at fosfomycin initiation: 3.6 (4.4)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Improvement</th>
<th>Failure</th>
<th>Indeterminate</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>65.4%</td>
<td>26.9%</td>
<td>3.8%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Microbiological</td>
<td>69.2%</td>
<td>23.1%</td>
<td>7.7%</td>
<td>-</td>
</tr>
</tbody>
</table>

28 Day Mortality | 34.6%
Future options

- B-lactamase inhibitors: avibactam (NXL104) combination seems promising with Aztreonam or Ceftazidime or Ceftaroline
  
  *Endimiani A et al, AAC 2011*
  
  *Livermore D et al, AAC 2011*

- Plazomicin, a novel aminoglycoside: ACHN-490 (neoglycoside)
  
  *Endimiani A et al, AAC 2009*
Plazomicin (ACHN-490)  
Achaogen  

• A new aminoglycoside (neoglycoside) with in vitro antibacterial activity against many MDR Gram-negative bacteria including carbapenem-resistant Enterobacteriaceae  
• Activity against *P. aeruginosa* and *Acinetobacter* spp. was lower with an MIC50 of 8-64 mg/ml.  
• Vulnerable to certain methylases found in most NDM-1-producing Enterobacteriaceae

*Aggen JB, AAC 2010; 54:4636-4642*  
*Tenover FC, IJAA 2011, 38:352-354,*  
Plazomicin retains activity against all isolates of *K. pneumoniae*, *E. coli* and *Enterobacter* spp tested, including those with ESBL, KPC and MBL resistance mechanisms

Plazomicin PK and Safety

• Two randomized, double-blind, placebo-controlled clinical studies investigated the pharmacokinetics (PK), safety, and tolerability of ACHN-490 injection in healthy subjects.

• Good penetration to ELF

• No evidence of treatment-related side effects or effects on renal, cochlear, or vestibular functions or QTc prolongation

• Has completed a Phase 2 clinical trial for the treatment of complicated urinary tract infections (cUTI)

• Now enters phase 3 studies for cUTI

_Cass RT, Antimicrob Agents Chemother 2011_  
[http://clinicaltrials.gov](http://clinicaltrials.gov)
Avibactam (NXL104) Cerexa

- Avibactam is a β-lactamase inhibitor with higher affinity with class A and class C β-lactamases compared to its ancestors.
- It has demonstrated synergistic activity in vitro and in vivo with ceftaroline against ESBL- and KPC-producing enteric bacteria.

Aztreonam+avibactam
Ceftazidime+ avibactam (Astra Zeneca/Forrest Labs)

**In vitro data against carbapenem-resistant Enterobacteriaceae**

- Ceftazidime-NXL104 was active against strains with carbapenem- inactivating mechanisms except metallo-β-lactamase producers
- Aztreonam-NXL104 was active against all carbapenemase producers, including those with metallo-β-lactamases

Avibactam combinations in clinical studies (www.clinicaltrials.gov)

- Aztreonam+avibactam
  - phase 1- safety
- Ceftaroline+ avibactam
  - phase 1 renal impairment dose
- Ceftazidime+avibactam
  - phase 1- safety
  - Phase 3 UTIs
  - Phase 3 cUTIs vs doripenem
  - Phase 3 cIAI vs meropenem
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Unorthodox combinations
Synergy of telavancin with colistin against Gram-negative pathogens demonstrated by various in vitro methods

<table>
<thead>
<tr>
<th>Species</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt; (µg/ml)</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; (µg/ml)</th>
<th>Mean fold reduction</th>
<th>% susceptible&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. baumannii (35)</td>
<td>2</td>
<td>16</td>
<td>&gt;4.5</td>
<td>20</td>
</tr>
<tr>
<td>S. maltophilia (8)</td>
<td>2</td>
<td>2</td>
<td>&gt;5</td>
<td>12.5</td>
</tr>
<tr>
<td>Enterobacteriaceae (23)</td>
<td>0.5</td>
<td>4</td>
<td>&gt;6</td>
<td>65</td>
</tr>
<tr>
<td>All isolates (66)</td>
<td>2</td>
<td>12</td>
<td>&gt;5</td>
<td>35</td>
</tr>
</tbody>
</table>

<sup>a</sup> Data were obtained using the highest concentration of COL (0.25 to 0.75 µg/ml) able to support semiconfluent growth on Iso-Sensitest agar for each isolate.

<sup>b</sup> Based on the FDA/EUCAST breakpoint for staphylococci of ≤1 µg/ml.

Unorthodox combinations
Synergy of telavancin with colistin against Gram negative pathogens

• *In vitro* TLV was highly active when combined with colistin against *A. baumannii*, *E. coli*, *K. pneumoniae*, *Enterobacter* spp., and *S. maltophilia* type strains and clinical isolates

• When used together, the drugs were not only synergistic but also bactericidal with the exception of *S. maltophilia* NCTC 10258

By use of nebulized antibiotics we can achieve better concentrations in the site of infection

- Aminoglycosides
  - Gentamicin: 12% ELF penetration
  - Tobramycin: 32% ELF penetration
  - Peak values well below the 10xMIC of pathogens
- Colistin
  - After iv administration of 2 MU CMS, no detectable concentrations in the BAL

Imberti et al, Chest 2010
Nebulized amikacin in BAL

- Phase II study
- 28 patients with VAP
- Nebulized amikacin
  - 400 mg bid
  - PDDS nebulizer (vibrating mesh)
  - Amikacin sulphate for inhalation
- 30 min after inhalation of day 3 (steady state) BAL

**Results**

- High concentrations in the lung parenchyma, >10MIC
- Low plasma concentrations
- One episode of renal failure (shock)
- One patient with bronchospasm

Luyt et al, Critical Care 2009
Efficacy of High-dose Nebulized Colistin in Ventilator-associated Pneumonia Caused by Multidrug-resistant 
*Pseudomonas aeruginosa* and *Acinetobacter baumannii*

Lu et al, Anesthesiology 2012

- 1/1/2006 to 31/12/2010
- Multivalent ICU (La Pitié-Salpêtrière, Paris)
- VAP από Pseudomonas- Acinetobacter
  - Pathogens β-lactam susceptible (122 pts)
  - Pathogens β-lactam resistant (43 pts)
  - Empiric coverage at the discretion of treating physicians
- Hypothesis: monotherapy with nebulized colistin is non-inferior to standard iv treatment with a β-lactam with aminoglycoside or a quinolone in the treatment of VAP caused by *Pseudomonas* spp and *Acinetobacter* spp (non-inferiority margin 16%)
- **Dosage of inhaled CMS 5MU every 8 hours**

Lu et al, Anesthesiology 2012
Summary of the study

• Nebulized colistin is effective to treat VAP caused by multidrug-resistant *P. aeruginosa* and *A. baumannii*; the clinical cure rate is noninferior to that obtained in VAP caused by susceptible *P. aeruginosa* and *A. baumannii*;

• The risk of developing colistin resistance after nebulization is low

• Nebulized colistin does not increase the risk of kidney failure, although repeated nebulization induces systemic accumulation.

Lu Q et al, Anesthesiology 2012
Selective digestive decontamination for eradication of carbapenem-resistant *K. pneumoniae* carriage?

- Oral gentamicin 80 mg q.i.d. was administered in 15 CRKP carriers of a hematology unit until eradication (median duration 29 days)-no side effects
- The eradication rate was 66%; discontinuation of persistent bacteremia occurred in 62.5% and 5 underwent allo-SCT

  *Zuckerman T, Bone Marrow Transplantation* (2011) 46, 1226–1230

- Randomised controlled SDD trial: 40 patients, oral gentamicin and polymyxin E gel and oral solutions of gentamicin and polymyxin E
- Eradication from throat in the SDD arm after 3 days (P < .0001).
- Positive rectal cultures were significantly reduced at 2 weeks.
- Groin colonization prevalence did not change in either arm

  *Saidel-Odes L, Infect Control Hosp Epidemiol. 2012;33:14-9*
Future alternative pathways...

• Advances in biomarkers such as procalcitonin in order to determine the real need of antibiotic administration and for how long

• Rapid diagnostics aimed at determining which antibiotics should be prescribed in order to tailor appropriate therapy and de-escalate unnecessary therapy

• A thinking out-of-the box approach: vaccines and monoclonal antibodies targeting the prevention of infections caused by antibiotic-resistant pathogens

Kollef and Micek Critical Care 2012; 16:179
Lodes U, Langenbecks Arch Surg 2012;397:447-455
The enhanced permeability retention (EPR) effect

A new paradigm for drug targeting in infection


An example of thinking out of the box...
Enhanced permeability retention (EPR) effect in infection

Enhanced permeability predominantly occurs at the post-capillary venule level.

Infection causes outflow obstruction and increased interstitial pressure, hindering drainage.

Outline of the presentation

1. Introduction
2. How to improve carbapenem use
   1. Pharmakokinetics
   2. Combinations
   3. Strategies to preserve susceptibilities of carbapenems
3. How to decrease carbapenem use
   1. Carbapenem sparing regimens
   2. Alternative strategies
4. Conclusions
Conclusions

• In order to improve carbapenem use we need to rationalize their use
• Ertapenem could be used in carefully selected patients with ESBL producing bacteria
• Ciprofloxacin restriction could have an indirect beneficial effect on resistance to carbapenems
• Optimization of PK/PDs of carbapenems and of combinations with other agents could provide protection against development of resistance
• Combinations of non-carbapenem options against MDR pathogens should be tested in randomized controlled studies