CARBAPENEMS
A REVIEW

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PREAMBLE

I’m here to give you “feedback” on your prescribing.
OBJECTIVES

• To review carbapenems as a class and individually
• To summarize the clinical evidence for carbapenems
• To share some recent carbapenem cases
• To answer some common questions about carbapenems
Q1: DO WE HAVE A PROBLEM?

• Globally, yes
  • Carbapenemases have threatened the utility of these drugs
  • Genes often confer resistance to other, non-beta-lactam antibiotics (e.g. NDM-1)
  • Often co-exist with other mutations

• Documented world-wide

• Clinical challenge
  • Limited treatment options
  • Independent RF for mortality
  • Spread
Table 3. Oligonucleotides used for screening of main carbapenemase genes in *Enterobacteriaceae*. *A detailed technique for PCR amplification has been reported by Poirot et al. (34). VIM, Verona integron-encoded metallo-β-lactamase; OXA, oxacillinase; NDM, New Delhi metallo-β-lactamase-1; KPC, Klebsiella pneumoniae carbapenemase.*

<table>
<thead>
<tr>
<th>Primer</th>
<th>Sequence, 5' → 3'</th>
<th>Gene</th>
<th>Product size, bp</th>
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<tbody>
<tr>
<td>IMP-F</td>
<td>GGAATAGAGTGCTTAAYTC</td>
<td><em>bla</em>&lt;sub&gt;IMP&lt;/sub&gt;</td>
<td>232</td>
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<tr>
<td>IMP-R</td>
<td>TCGGTAAAAYAAAAACAACCACC</td>
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<td>VIM-F</td>
<td>GATGGTGTTTGGTCGATA</td>
<td><em>bla</em>&lt;sub&gt;VIM&lt;/sub&gt;</td>
<td>390</td>
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<tr>
<td>VIM-R</td>
<td>CGAATGCGGCACGACCCAG</td>
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<tr>
<td>OXA-48-F</td>
<td>GCGTGTTAAGAGATGAACAC</td>
<td><em>bla</em>&lt;sub&gt;OXA-48&lt;/sub&gt;</td>
<td>438</td>
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<tr>
<td>OXA-48-R</td>
<td>CATCAAGTCCACCAACCAG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NDM-F</td>
<td>GGTTCGCGATCTGGTTTC</td>
<td><em>bla</em>&lt;sub&gt;NDM&lt;/sub&gt;</td>
<td>621</td>
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<tr>
<td>NDM-R</td>
<td>CGGAATGCGTCATCAGGATC</td>
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<td></td>
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<tr>
<td>KPC-Fm</td>
<td>CGTCTAGTCTCTGCTGGTTT</td>
<td><em>bla</em>&lt;sub&gt;KPC&lt;/sub&gt;</td>
<td>798</td>
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<tr>
<td>KPC-Rm</td>
<td>CTTGTCATCATCTGGTTTACG</td>
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<table>
<thead>
<tr>
<th>Ambler class</th>
<th>Enzyme</th>
<th>Function</th>
<th>Known organisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>KPC&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Hydrolyzes all β-lactam antibiotics; inhibited by clavulanate</td>
<td><em>K. pneumoniae</em>, Enterobacteriaceae</td>
</tr>
<tr>
<td>B</td>
<td>MBLs&lt;sup&gt;2&lt;/sup&gt; (NDM, IMP, VIM, GIM, SPM)</td>
<td>Hydrolyze all β-lactams except aztreonam; may be inhibited by clavulanate; require zinc for enzymatic activity; inhibited by EDTA</td>
<td><em>P. aeruginosa</em>, <em>Acinetobacter</em> spp, Enterobacteriaceae</td>
</tr>
<tr>
<td>D</td>
<td>OXA</td>
<td>Oxacillin hydrolyzing; less able to hydrolyze carbapenems</td>
<td><em>P. aeruginosa</em>, <em>A. baumannii</em>, Enterobacteriaceae</td>
</tr>
</tbody>
</table>
Q1: DO WE HAVE A PROBLEM?

• At Island Health, no (not yet)
  • CPO rates are very low
  • Carbapenem prescribing is very low
    • Prevalence at RJH
    • Proportion of followed by ID
    • Most are appropriate

• BUT…
  • CPOs have arrived
  • Challenging to craft therapy against
  • Associated with poor outcomes
DEVELOPMENT

Resistant bacteria on the rise

Antibiotics on the fall


imipenem meropenem doripenem ertapenem
THE CLAN: DIFFERENCES

Imipenem – the original carbapenem heartthrob

Ertapenem – weaker, but still a contender

Meropenem – tries to be better in so many ways, but is it?

Doripenem – it’s meropenem on steroids
Q2: IS DORIPENEM IN CANADA YET?

- NoC issued by Health Canada in 2010
  - Approved for pneumonia, cIAI and cUTIs/pylonephritis
- In 2012, an RCT showed increased mortality in VAP
- FDA asked JnJ for more evidence to determine indications
- JnJ plans to re-submit evidence to Health Canada*

*Source: questionably reliable JnJ rep from Wisconsin
SIMILARITIES

- Mechanism of action
- Bactericidal
  - If T>MIC is 40% or above; bacteristatic otherwise
- Absorption
  - Ertapenem can be given IM
- Distribution
  - CSF distribution varies most
- Metabolism
  - Meropenem is hepatically metabolized
- Excretion
  - Renally

**SPECTRUM OF ACTIVITY - GPC**

- Q3: Do carbapenems cover “everything”? 

<table>
<thead>
<tr>
<th>Gram Positive Bacteria</th>
<th>Imi</th>
<th>Mero</th>
<th>Ertal</th>
<th>Dori</th>
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<tbody>
<tr>
<td>MSSA/CONS</td>
<td></td>
<td></td>
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<td>Sensitive</td>
</tr>
<tr>
<td>MRSA/CONS</td>
<td></td>
<td></td>
<td></td>
<td>Resistant</td>
</tr>
<tr>
<td>Strep</td>
<td></td>
<td></td>
<td></td>
<td>Sensitive</td>
</tr>
<tr>
<td><em>E. faecalis</em></td>
<td>S</td>
<td>I</td>
<td>R</td>
<td>I</td>
</tr>
<tr>
<td><em>E. faecium</em></td>
<td></td>
<td></td>
<td></td>
<td>Resistant</td>
</tr>
</tbody>
</table>

- Doripenem “tried” to be superior for GPC but isn’t
Case 1 – PC is a 58 y/o male sent to the ED by his GP for a poorly healing diabetic L foot infection

- Amox-Clav x 7 days
- MHx: Uncontrolled DM, HTN and gout, eGFR ~ 50ml/min
- Plain X-ray: consistent with osteomyelitis of the 5th toe
- CT angio: PVD
- Switched to piptazo + vanco
- Underwent initial debridement with goal to save the leg
CASE 1 CONT.

• Surgical cultures were sent

• Switched to meropenem when sensitivities returned

• What’s going on?
SPECTRUM OF ACTIVITY – GNB

- Carbapenems are famously effective against “SPICE” organisms which produce AmpC
  - *Serratia*
  - *Pseudomonas*
  - *Indole-positive protae* (P. vulgaris, morganella, providencia)
  - *Citrobacter*
  - *Enterobacter cloacae*
- Imipenem has the weakest activity against indole-positive protae – our case, and some pseudomonas also have higher MICs
- Ertapenem also differs; does not cover pseudomonas
- Meropenem and doripenem win for their GN coverage
- GO AC!
CARBAPENEMS AND ESBLS

- Carbapenems are also well known for their activity against ESBLs – raison d’être

- **Case 2:** GC is an 81 y/o male re-admitted to hospital secondary to development of fever, flank pain and malaise. He was discharged home 7 days ago on cipro following cystoscopy and removal of a large renal stone
  - He is started on cipro and ceftriaxone
  - 2 days later, blood and urine cultures are positive with an ESBL *E. coli*
  - The bacteria is sensitive only to pip/tazo, carbapenems and aminoglycosides
- Q4: MRP is wondering if he should use a carbapenem over pip/tazo
ESBLS: TWO VIEWS

• BL/BLIs are **not** recommended even if tested susceptible by the lab
  • Increasing rate of CTX-M-15 and OXA-1 producers
  • “Inoculum effect”
  • PK/PD studies (monte-carlo simulations): lower frequency of MIC attainment at standard doses
  • Anecdotal clinical failures
  • Problems with detection in some automated systems
ESBLS CONT.

• “The inoculum effect” - ESBLs
Another issue: PK/PD breakpoints differ than those set by CLSI/EUCAST

Determined by Monte-Carlo simulations

- Computer modeling process
- Considers achievable PK parameters and natural MIC distribution within a population

<table>
<thead>
<tr>
<th></th>
<th>CLSI</th>
<th>EUCAST</th>
<th>PK/PD</th>
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<tbody>
<tr>
<td>Piptazo</td>
<td>8</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>Imipenem</td>
<td>2</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Meropenem</td>
<td>2</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>
ESBLs: SECOND VIEW

• BL/BLIs can be used if tested susceptible in the lab
  • Very little CTX-M-15 and OXA-1 producers locally
  • MICs at IH are low (4 or below for most isolates)
  • 89% sensitive
    • (?cut-off for empiric treatment)
  • “Inoculum effect” is arbitrary
    • Often not known
    • Source control
    • Drug levels (e.g. kidney or urine)
• Better data now exist to support clinical efficacy
MEET MATTHEW FALAGAS

• Has conducted over a dozen meta-analyses on carbapenems
• 21 studies of 1600 patients
• Primary outcome is mortality


Carbapenems versus alternative antibiotics for the treatment of bacteraemia due to Enterobacteriaceae producing extended-spectrum β-lactamases: a systematic review and meta-analysis

Konstantinos Z. Vardakas1,2, Giannoula S. Tansarli1, Petros I. Rafailidis1,2 and Matthew E. Falagas1-3*

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Directed therapy – similar forest plot but larger CI
ESBLS: PERSONAL VIEW

• Would consider pip/tazo appropriate for empiric or definitive therapy with ESBL
  • Resistance is low
  • MICs are low
• Prefer a carbapenem for serious infections
  • High suspicion of resistance
  • High grade infection, poor source control
  • ICU
• Consider higher doses of pip/tazo
Carbapenems have excellent activity against anaerobic bacteria
  • Oral and below-the-waist
  • I=M=E=D in this regard
• Cover some weirdo bugs (nocardia, mycobacteria)
• Carbapenems also do not cover:
  • Atypical organisms
  • Stenotrophomonas
SAFETY
Q5: ARE CARBAPENEMS SAFER THAN OTHER BETA-LACTAMS?

• Beta-lactams remain one of the safest antibiotic groups

• Common beta-lactam ADRs:
  • Hypersensitivity reactions
    • Type I – anaphylaxis
    • Type II – antibody mediated (haemolytic anemia, neutropenia)
    • Type III – immune-complex (DRESS, drug fever, AIN)
    • Type IV – T-cell mediated (exanthems, inc. SJS)
  • GI side effects, including C. difficile
  • Neurological ADRs
ARE CARBAPENEMS LESS ALLERGENIC?

• Yes, probably
• Enough experience already
• Anaphylaxis
  • SR: 854 patients with penicillin allergy history – 4.3% cross reactivity
  • 0.3% cross-reactivity in those with a positive skin test
  • Various studies confirming low reactivity, incl. in children
• Type II reactions
  • Several case reports, but very confounded (e.g. pip/tazo, vanco)
• AIN – Case 3: Pt on dialysis with AIN from cefazolin
  • 2 case reports only; 1 due to cross-reactivity
• Type IV rashes – lower than with other beta-lactams
  • 2 studies: one 0%, one 5.5% for cross-reactivity

Q6: DO CARBAPENEMES REALLY CAUSE MORE SEIZURES?

- Neurological ADRs with penicillins have been well described
  - >20MU of penicillin → encephalopathy and seizures
  - RF include underlying CNS disorder and renal dysfunction
- Imipenem has been historically seen as being more epileptogenic
  - Early observational studies noted higher seizure risk in children on imipenem for meningitis
  - Retrospective studies also noted ↑ risk
    - Doses of 4g/day
    - Renal dysfunction
  - Newer evidence refutes significant epileptogenicity over other carbapenems at doses of 2g/day or if renally adjusted
- Not evaluated formally until this year
The risk of seizures among the carbapenems: a meta-analysis

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Objectives: A consensus exists among clinicians that imipenem/cilastatin is the most epileptogenic carbapenem, despite inconsistencies in the literature.

- 169 RCTs of carbapenems vs. non-carbapenems
  - 25 were vs. penicillins
- OR for seizures was calculated for all carbapenems and of direct comparisons of imi vs. meropenem
Bottom line: NNH:142; driven by imipenem

40 extra seizures /6000
Based on these rates, you need **9500** patients to detect a two-fold increase in the OR at these described rates.

Personal opinion – imipenem is probably worse.
IMIPENEM AND RENAL DYSFUNCTION

• Q7: Is imipenem nephrotoxic? Should it not be used in renal insufficiency?

• PK of imipenem
  • $T_{1/2} = 15$ minutes; prolonged by cilastatin to 1hr
  • $T_{1/2}$ of cilastatin is also 1h
    • In severe renal dysfunction, $T_{1/2}$ is affected to a different extent
    • E.g. eGFR 10-20ml/min; $T_{1/2}$ C = 2.5-4.5h; $T_{1/2}$ I = 2-3h
  • At the same time, imipenem was linked to seizures, esp. in patients with renal dysfunction \(\rightarrow\) older data said: not to use, hard to dose!

• Much recent work has been done to characterize PK in renal dysfunction
  • Cmax and AUC are stable over time when properly adjusted
  • Imipenem dose adjustment does yield predictable levels

• Imipenem is NOT nephrotoxic
  • Cilastatin has been found to be nephroprotective
Q8: DO CARBAPENEMS CAUSE MORE GI ADRS?

- Nausea: YES
  - Imipenem consistently causes nausea in 2% of people
  - Higher than other IV beta-lactams (e.g. ceftriaxone)
- Antibiotic-associated diarrhea is about the same
- *C difficile*: YES
  - Carbapenems are broad-spectrum antibiotics
  - Recent studies
    - Carbapenem: OR 1.66 compared to other cIAI antibiotics (SS)
    - Population-based study in California: OR = 2.77 (vs. 1.88 FQ; 1.49 ceftriaxone; SS)

JSTOR 2008; 29 (1)
Q9: ARE CARBAPENEMS INTERCHANGEABLE?

- Based on spectrum of activity, ertapenem is not interchangeable
- Imipenem and meropenem have historically been interchanged
  - Various hospitals have one or the other as their workhorse carbapenem
  - Slight differences in activity
- Historically, price drove decision making
  - Imipenem became generic first at a significant cost difference ($6.40/500mg vs. $25/500mg for meropenem)
  - Meropenem became generic this year ($8.95/500mg)
  - Ertapenem remains brand name only ($42/1g)
- Meropenem is still restricted to ID/Med Micro but cost is no longer a barrier, and this restriction may change
Q11: ARE CARBEPENEMS INDICATED FOR EVERYTHING?

- Process for approval of new drugs
  - Non-inferiority RCT against standard therapy
  - Done for each indication in a well-characterized population

- Over 150 RCTs with a carbapenem
  - SSTI
  - Pneumonia (doripenem no longer approved)
  - IAI
  - CNS infections (meropenem approved only)
  - Diabetic foot infections
  - Febrile neutropenia
  - Bacteremia/Sepsis

- Hard for older drugs to compete
  - Can look at this evidence for comparator arm as well
Q12: ARE CARBAPENEMS BETTER?

• Thus far, there have been 44 MA published of carbapenems vs. other antibiotics

• Thank you Matthew Falakas!
  • Very little convincing evidence that carbapenems are superior in any way
    • Especially vs. piptazo or current standard of treatment

• Carbapenems are better than:
  • Cefipime in FN
  • Clinda/gent regimens for cIAI
  • Tigecycline in general
  • Non BL/BLIs for ESBL bacteremia
  • Placebo in necrotizing pancreatitis
APPROPRIATE USES SUMMARY

• 1. Documented/suspected MDR pathogen
  • Chose meropenem if bug is a morganella, proteus or providencia
  • Don’t use ertapenem for pseudomonas or enterococcus

• 2. Patient deteriorating on current broad-spectrum therapy

• 3. Serious ESBL infection where inoculum is high/poor source control

• 4. Severe allergy to first-line antibiotics
SUMMARY

• You’re doing well!
• Carbapenems are very broad but don’t cover everything
  • MRSA, CONS, VRE, atypicals, steno
  • Watch enterococcus, psuedomonas and protae
• Carbapenems are safe
  • Less allergenic
  • Do increase odds for seizures
  • Imipenem can be used in renal dysfuncion
  • Cause more GI ADRs
• Imi and mero can be interchanged, not erta
• No great evidence to suggest they are better
CONTINUE TO SAVE (BY THE BELL) OUR CARBAPENEMS!

THANK YOU!