Multi-drug Resistant Gram-negative Infections
Treatment Options and Challenges

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Infected with Gram-negative Bacilli
E. coli, Klebsiella, Enterobacter, Serratia, Citrobacter, Pseudomonas, Acinetobacter

Asymptomatic colonisation
Wound infection / Diabetic foot
Lower urinary tract infection
Upper urinary tract infection
Nosocomial pneumonia / VAP
Intra-abdominal / pelvic infection
Bacteraemia / septicemia
Neurosurgical meningitis

Problem Organisms
• Cephalosporin resistant and ESBL producing Enterobacteriaceae
  – E. coli, K. pneumoniae
• Virulent epidemic clones – E. coli ST131, K. pneumoniae ST 258
• De-repressed chromosomal or plasmidic AmpC producers
• Carbapenem resistant Gram-negatives
  – E. coli, K. pneumoniae – KPC, OXA-48, NDM +/- ESBLs
  – P. aeruginosa, A. baumannii - IMP, VIM
• “XDR” and “Pan-drug” – resistant Gram-negatives
  – P. aeruginosa – MBLs +/- permeability and efflux lesions
  – A. baumannii – OXA-23/24/58 +/- MLBLs, ESBLs, permeability and efflux lesions
  – P. aeruginosa – MBLs +/- permeability and efflux lesions

Treatment of ESBL Producing Enterobacteriaceae
Severe infections – Bacteraemia / Sepsis
Carbapenems v anything else if susceptible?
Other β-lactams (BLI) - Cephalosporins / β-lactam/ inhibitor combinations (BLICs)
Others - Quinolones / aminoglycosides / tigecycline / colistin

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

Can we trust the meta-analysis?
Heterogeneity in studies……
Different regions of the world……
Different complement of ESBLs……
Differing MICs and dosing regimens……
BLICs probably still have a role.
Do we overuse Carbapenems?

- Initiatives to improve the treatment of sepsis
- Highly active antimicrobial therapy saves lives¹

- But de-escalation also important
- Only 20% of Gram-negative bacteremias de-escalated²

- Generic carbapenems remove financial considerations

- 'Workhorse' antibiotics
- Used earlier and wider

- Antimicrobial Stewardship....

¹Nurmi et al Crit Care Med 2006, ²Phee & Wareham (ISICEM 2011)

ESBL Producers: Other Options?

Prevalence and mechanisms of colistin resistance in Enterobacteriaceae in London and South East England

Nicolae A. C., Paul E. A., Ronald Hoppe, Monica Nunn, Steve R. Johnson, and David M. Livermore

on behalf of the London and South East ESBL Project Group

<table>
<thead>
<tr>
<th>Percentage resistant (n=96)</th>
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<tbody>
<tr>
<td>In Vitro</td>
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<tr>
<td>ESBL Producers: Other Options</td>
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</tbody>
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- Treatment of Carbapenemase Producers

What impact against carbapenem resistant Enterobacteriaceae? Evaluation of chloramphenicol, ampicillin, ticarcillin, temocillin, and amoxicillin

<table>
<thead>
<tr>
<th>MIC (mg/L)</th>
<th>TEM OC</th>
<th>TEM OC-amp</th>
<th>TEM OC-amp-amp</th>
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</tr>
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<tr>
<td>≤ 0.5</td>
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- Temocillin for ESBLs?

  - Ticarcillin derivative
    - Stable to ESBLs and AmpC
      - No activity versus Pseudomonas or Gram positives
  - Rodriguez-Villalobos 2006
    - Breakpoints ≤ 32 mg/L – 92% of isolates susceptible
  - Livermore 2006
    - Good activity versus UK ESBL and AmpC hyperproducing Enterobacteriaceae
    - Modal MIC 8 mg/L

- Retrospective outcome study

  - n=92

  - 42 BSIs, 42 UTIs, 8 VAP

  - Clinical cure rate
    - Overall efficacy 86%
    - No difference in efficacy v AmpC producers
    - Significantly more effective at higher dose (2 mg 12 hourly)

- Treatment of Carbapenemase Producers

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- Can We Use Carbapenems?

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- Isolates with a meropenem MIC of ≥ 4 mg/L may be treatable with high dose prolonged infusions of meropenem

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MDRGN – Treatment Options and Challenges
Dr David Wareham, Queen Mary Universitys, UK
Broadcast live from the HIS/FIS conjoint conference www.hisconference.org.uk

Possible Treatment Options From the Antibiogram

- Most KPC producers sensitive to aminoglycosides
  - ST258 usually susceptible to gent – others only amikacin
  - 16S methylases rare in these strains
- Some MBL (IMP / VIM) producers sensitive to aminoglycosides
- Mostly non-fermenters – Enterobacteriaceae usually have co-resident ESBL ?
- OXA-48 producers may be susceptible to cephalosporins
- Mostly Enterobacteria and usually have co-resident ESBL ?
- Most Enterobacteria and Acinetobacter ‘sensitive’ to tigecycline
- About all ‘sensitive’ to polymyxins
- Some NDM-1 producers resistant to all...
  - Tigecycline or Colistin ?

Experience with Tigecycline (TGC)

- Good in-vitro activity v most Carbapenem R Enterobacteria and MDRAB
- Bacteriostatic - Very low serum levels: 0.8 mg/l.
  - A review of clinical and microbiological outcomes following treatment of infections involving multiresistant Acinetobacter baumannii
  - with tigecycline
  - A. C. Goodden1 and E. N. W. Rowland2

  1Division of Medicine, Barts and The London NHS Trust, London, UK. 2Centre for Infections Disease, Department of Cell and Molecular Science, Barts and The London, Queen Mary’s School of Medicine and Dentistry, London, UK.

- Case series of infections involving MDRAB treated with tigecycline:
  - 78 % clinical response rate
  - 41 % overall mortality
  - Recurrent episodes of bacteremia with development of frank resistance in 3 cases

Emergence of TGC resistance during TGC therapy

AdeABC-mediated efflux and tigecycline MICs for epidemic clones of A. baumannii

Rapid emergence of resistance due to overexpression of efflux pumps

Efficacy and safety of tigecycline: a systematic review and meta-analysis

Jehana Haque1,2, Addy Lander1, Wei Hu1,2 and Gerard Lodge1,2

Conclusions: In the light of the increased mortality, probability explained by decreased clinical and microbiological effect, clinicians should avoid tigecycline monotherapy in the treatment of severe infections and warrant its use if deemed effective.

The Rebirth of Colistin ?

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Colistin / Polymyxins

Unique Mode of Action

- "How to carry out susceptibility testing?"
- "Is colistin effective?"
- "Is colistin safe?"
- "How should it be administered?"

Colistin MIC breakpoints and Susceptibility Testing

- MIC determination highly method dependent
  - Poor diffusion in agar – compromises discs / Etests
  - Poor reproducibility in broth – adhesion to glass / plastic?
  - Not evaluated with automated systems – Vitek, Phoenix, Microscan
- Breakpoints: CLSI: ≤ 2 mg/L, EUCAST: < 4 mg
- No molecular target for PCR gold standard
- Time Kill methodology as gold standard?

Colistin MICs and Breakpoints

Colistin is not sufficiently bactericidal versus many GNRs

Regrowth after 24 – 48 hrs in time kill assays at up to 32 x MIC1

1Li, AAC 2006

Heteroresistance to Colistin in Multidrug-Resistant Acinetobacter baumannii

Run Li, Craig K. Harewood, Roger E. Nunn, Patricia J. O’connor, Denis Spremulli, Run Fang Tan, and Eric Lipton

Faculty for Antimicrobial Drug Development and Innovation, Victorian College of Pharmacy, Melbourne University, Victoria, Australia, and Department of Microbiology and Infectious Diseases, St Vincent’s, St Vincent’s Hospital, Melbourne, Victoria, Australia

- A sub-population of bacteria recovered from growth of a ‘susceptible’ strain at colistin concentrations above breakpoint of 2mg/L;
- Also reported in K. pneumoniae, P. aeruginosa and Enterobacter

Colistin heteroresistance in carbapenem-producing Klebsiella pneumoniae

Does Colistin work?

Retrospective cohort study of 399 Acinetobacter spp bacteremia (MDRAB n=78)

Impact of carbapenem R, colistin Rx (1 mu 8 hrs)
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Is Colistin safe?

- Nephrotoxicity?
  - Colistin has been shown to cause kidney injury more frequently than previously reported. The observation of increased incidence of nephrotoxicity under conditions of renal insufficiency, used as a surrogate for delayed elimination of colistin in the absence of renal function, has meant that the incidence of colistin-induced nephrotoxicity may be overestimated in settings with impaired renal function. However, the incidence of significant renal impairment associated with colistin varied widely between different studies, with the highest incidence of significant nephrotoxicity being observed in patients with end-stage renal disease.
  - Nephrotoxicity associated with Intravenous Colistin
    - Colistin dosage
    - Precautions
    - Rare to non-existent with modern use

How should we administer colistin?

- Colistin Methanesulfonate Sodium: 1-2 million units per 8 hours

Combination Treatments for MDR, XDR and PDR strains?

- Numerous in-vitro studies of colistin containing combinations
  - Polymyxin B + imipenem + rifampin – Synergy
  - Colistin + minocycline + Synergy
  - Colistin + cefazolin = Synergy
  - Polymyxin B + meropenem + rifampicin = Synergy

- In-vivo studies of colistin containing combinations
  - Colistin + rifampin = effective in mouse pneumonia and rat model

- Case reports
  - Colistin + rifampin = ‘favorable response’

Colistin Dosage Recommendations

<table>
<thead>
<tr>
<th>Patient category</th>
<th>Dose (mIU) to target atCss, avg mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loading dose</td>
<td>BW* (kg) / 7.5 (max 10)</td>
</tr>
<tr>
<td>Maintenance dose</td>
<td>Not on renal replacement</td>
</tr>
<tr>
<td></td>
<td>1st dose 24h after loading dose</td>
</tr>
<tr>
<td></td>
<td>2nd dose (in two doses)</td>
</tr>
<tr>
<td></td>
<td>Hemodialysis = 30% on the day of hemod, after session</td>
</tr>
<tr>
<td></td>
<td>Continuous renal replacement</td>
</tr>
<tr>
<td></td>
<td>12 in 2-3 doses</td>
</tr>
</tbody>
</table>

*1 million IU of CMS = ~ 30 mg of CBA = ~ 80 mg of CMS
**Lower of ideal or actual body weight in kg

Garnzik SM et al. AAC 2011 (modified)

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In-vitro ‘Synergy’

- Multiple methods
  - checkerboards / eTest / time kill
  - ‘synergy’ by established criteria
    - fractional inhibitory concentration index ≤ 0.5
      (MIC of A in combination with B / MIC of A alone)
      (MIC of B in combination with A / MIC of B alone)
- Susceptible breakpoint index (SBPI) as a better parameter?
  - (Susceptible breakpoint of A / MIC of A in combination with B)
  - (Susceptible breakpoint of B / MIC of B in combination with A)
- SBPI > 2 = clinically relevant synergy

1 Milne and Gould, JAC 2010

Colistin Combined with Vancomycin

- Potent synergy when colistin is combined with vancomycin
- Vancomycin combined with colistin prevents re-growth of A. baumannii in time-kill assays

Colistin / Glycopeptide combinations in-vivo

Galleria mellonella infection model
‘Treated’ with human mg/kg doses

Time kill kinetics of vancomycin 20 mg/l and colistin 1 mg/l + MDRAB

Effective with other glycopeptides

- Telavancin, daptomycin, ….. But very species dependent – lack of target?

‘How to Use Colistin Combinations: A Case…?’

- 66yr M admitted ITU with acute renal failure following failed TURP
  - Obstructive nephropathy due to BPH – dialysis dependent
- 44 days in ICU
  - 3 courses of antibiotics – aug / taz / imp
  - Colonised with MDRAB day 27
- Discharged with ureteric MemoKath and JJ stent –
  - Urine sample cultured MDRAB
- Gradual decline in renal function over 18 months
  - Urine persistently cultures MDRAB
  - MemoKath changed twice – colistin 1 MU given as prophylaxis
  - Dialysis dependent – MDRAB cultured X 4

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Urine samples 2 x week for 3 weeks – negative for MDRAB

Time kill with Col 2 mg/L / Teic 20 mg/L

Teicoplanin trough levels – 15 – 22 mg/L
Pre-dialysis colistin trough levels – 1.3 – 3.1 mg/L
Treatment continued for 9 days

'XDR' and 'Pan-drug' – resistant Gram-negatives

Carbapenem resistant Gram-negatives

Aminoglycosides if susceptible
Colistin – (correctly dosed) +/- rifampicin
High dose carbapenems +/- colistin

XDR and Pan-drug – resistant Gram-negatives
Cocktails based on MIC and in-vitro synergy studies?
Colistin +/- rifampicin / carbapenems / tigecycline / glycopeptides?

Summary

Cephalosporin resistant and ESBL producing Enterobacteriaceae

- Severe infections – bacteraemia / sepsis / VAP
  - Carbapenems
  - Possibly BLCs or temocillin
- Other infections – based on antibiotic
  - BLCs
  - Nitrofurantoin
  - Trimethoprim
  - Carbapenem resistant Gram-negatives
  - Aminoglycosides if susceptible
  - Colistin – (correctly dosed) +/- rifampicin
  - High dose carbapenems +/- colistin

XDR and Pan-drug – resistant Gram-negatives
Cocktails based on MIC and in-vitro synergy studies?
Colistin +/- rifampicin / carbapenems / tigecycline / glycopeptides?

Any New Coming?

- New β-lactam inhibitors
  - Avibactam (NXL 104) – Astra Zeneca
  - MK-7655 – Merck +/- imipenem
- Siderophore monobactams – subvert efflux and porin lesions?
  - BAL30072 – Basilea +/- meropenem
  - MC-1 – Pfizer
- Neoglycosides
  - ‘next generation’ aminoglycosides but not v 16s methylases...
  - Plazomcin (ACHN-490) – Achaogen
- ‘next generation’ polymyxins
- NAB 739 – Northern Antibiotics
- Lpx inhibitors – LPS biosynthesis inhibitors
  - Lpx-C1 – Pfizer
  - To be used alone or in combinations?

Col / Teic FICI = 0.062 SBPI = 4.1
Col / Vanc FICI = 0.78 SBPI = 2.5
Dosing regimen optimised according to Garonzik protocol

Antibiotic

<table>
<thead>
<tr>
<th>Staphylococcus</th>
<th>Day 1 (Loading)</th>
<th>Day 2</th>
<th>Day 3</th>
<th>With each dialysis session (3x/week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colistin</td>
<td>750 iu</td>
<td>1.5 mg</td>
<td>1.5 mg</td>
<td>1.5 mg</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>900mg BD</td>
<td>450mg OD</td>
<td>450mg OD</td>
<td>450mg OD</td>
</tr>
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β-lactam inhibitors

- Cefuroxime
- COVA-Clav
- Co-Amoxiclav

Siderophore monobactams – subvert efflux and porin lesions?

- BAL30072 – Basilea +/- meropenem
- MC-1 – Pfizer

'next generation’ aminoglycosides but not v 16s methylases...

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