UK guidelines for GNB infections

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Joint Working Party on Multi resistant Gram-negative infection: Treatment

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Peter R Wilson         And on behalf of the patient
                        representative panel

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DEFINITION-MDRGNB

- Original “resistant to multiple agents”

- ECDC “resistant to 3 or more classes”- problem of sul & amp resistance. Availability of agents and differences in breakpoints

- We have adopted “sensitive to only one or no readily available drugs”
5.4 What is the scope of the guidelines?

Two sets of guidelines have been developed. We examine the background information on mechanisms and global spread, UK prevalence of resistance and prescribing, and then discuss treatment both in hospitals with intravenous antibiotics and in primary care with oral agents, ending with a consideration of antibiotic stewardship.
“The difficult is what takes a little time, the impossible is what takes a little longer”

F. Nansen (1861-1930) Polar explorer
Proportions and country distributions of CTX-M ESBL genotypes

Faecal isolates
a Lebanon, b Israel, c Kuwait

Hawkey & Jones 2009 JAC 64 Suppl 1 i3-i10
ESBL carriage rates in the community

## Distribution of CTX-M genotypes according to global origin

<table>
<thead>
<tr>
<th>Global origin</th>
<th>$bla_{\text{CTX-M}}$</th>
<th>$bla_{\text{CTX-M 9/14}}$</th>
<th>$bla_{\text{CTX-M 15}}$</th>
<th>ST131/Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe n=571</td>
<td>46 (8.1%)$^a$</td>
<td>15 (2.5%)</td>
<td>31 (5.4%)$^a$</td>
<td>8/23</td>
</tr>
<tr>
<td>MESA n=152</td>
<td>34 (22.4%)$^a$</td>
<td>7 (4.5%)</td>
<td>27 (17.8%)$^a$</td>
<td>6/21</td>
</tr>
</tbody>
</table>

$^a$ p < 0.0002

Patients failing cephalosporin treatment for serious infections caused by ESBL-producers

Paterson et al, 2001
Antibacterial resistance rates of genetically diverse cephalosporin-resistant *E. coli* from 3 geographically distinct centres in India

No and % resistant

<table>
<thead>
<tr>
<th>Antibacterial agent</th>
<th>CTX-M positive (n = 72)</th>
<th>CTX-M negative (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>63</td>
<td>88</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>65</td>
<td>90</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>68</td>
<td>94</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>32</td>
<td>44</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>66</td>
<td>92</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>31</td>
<td>43</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>70</td>
<td>97</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>72</td>
<td>100</td>
</tr>
<tr>
<td>Cefpodoxime</td>
<td>72</td>
<td>100</td>
</tr>
<tr>
<td>Cefepime</td>
<td>61</td>
<td>85</td>
</tr>
<tr>
<td>Meropenem</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Agents for treating infections caused by ESBL producers

**Intravenous**
- Carbapenems
- Gentamicin or amikicin (if susceptible)
- Temocillin
- Tigecycline
- Colistin
- Fosfomycin
- Ceftolozane/tazobactam

**Oral agents**
- Nitrofurantoin
- Fosfomycin
- Cefixime or Pivmecillinan with Co-amoxiclav
Structure Activity Relationship

Ceftolozane
- Aminothiadiazole ring 7-position side chain provides enhanced activity against Gram-negative bacilli
- Dimethylacetic acid moiety provides improved antipseudomonal activity
- Pyrazole ring on the 3-position side-chain confers stability against AmpC β-lactamases

Tazobactam
- Sulfone group at position 1 facilitates bond formation with β-lactamases, leading to inhibition

Hard-Hitting Empiric Monotherapy You Can Trust

Carbapenem Power¹, Cephalosporin Tolerability²
The Flexible Carbapenem¹
Proportion of Carbapenems Resistant (R) *Klebsiella pneumoniae* Isolates in Participating Countries

2009

2011

TESSy, The European Surveillance System, European Centre for Disease Prevention and Control 2012
Carbapenemase-producing CRE in the US confirmed by CDC

*Other CPE genes

This map was last updated on February 2014
Patients with KPC-producing Carbapenem-resistant Enterobacteriaceae (CRE) reported to the Centers for Disease Control and Prevention (CDC) as of January 2017, by state
Patients with NDM-producing Carbapenem-resistant Enterobacteriaceae (CRE) reported to the Centers for Disease Control and Prevention (CDC) as of January 6, 2017, by state
Carbapenamase producing Enterobacteriaceae in West Midlands 2007-14

- 60% submitted in 2013/14 – 119 unique isolates
- 69/119 NDM; 26/119 KPC; 16/119 OXA-48 like 7/119 VIM; 1/119 NDM + OXA
- Isolates mainly *Klebsiella* (89/139 submitted), many different ST’s only four ST 258
- 25/139 *E. coli*, mainly NDM, only two ST131

Findlay et al 2017 JAC
Agents for treating infections caused by carbapenemase producers

**Intravenous**
- Gentamicin/amikacin, ciprofloxacin (if susceptible)
- Tigecycline
- Colistin
- Temocillin if KPC in urine
- Fosfomycin
- Ceftazidime/avibactam

**Oral agents**
- Fosfomycin
Inhibitors of serine β-lactamases

avibactam
RPX7009

relebactam
RG6080

Ceftazidime-Avibactam and Carbapenem-Resistant Enterobacteriaceae: “We’re Gonna Need a Bigger Boat”

Brad Spellberg,1,2 and Robert A. Bonomo3
Mutations in KPC-3 giving resistance to ceftazidime-avibactam (cazavi)

- 10/37 patients with CPE had microbiologic failure
- 3/10 failing had KPC-3 mutant strains cazavi MIC 32->256
- Impact of mutations on cazavi MICS:
  179 tyr/thr 243 met > asp 179 tyr>val 240 gly
- Affected Ω loop binding of caz to site enhancing hydrolysis and/or reducing avibactam binding

Shields AAC, 2017 E02097  Shields CID, 2016 63, 1615
Suggested algorithm for the treatment of MDR Gram negative bacteria admitted to UK hospitals

1. Gram negative infection suspected
2. Local policy
3. Multiresistant strain suspected/known
4. Avoid cephalosporins trimethoprim quinolones
5. No past carbapenem-resistance
6. Resistance to carbapenem in past or past healthcare in high risk country according to local/national policy for resistance

Joint Working Party on MDRGNB infection: Treatment
Suggested algorithm for the treatment of MDR Gram negative bacteria admitted to UK hospitals

No past carbapenem-resistance

KPC-carbapenemase
- Colistin & meropenem (if unknown/S in past)
- Consider addition of tigecycline to above or ceftazidime-avibactam to meropenem

Resistance to carbapenem in past or past healthcare in high risk country according to local/national policy for resistance

OXA-48
- Aztreonam or Ceftazidime
- Ceftazidime-avibactam if R or unknown

Metallo-B-carbapenemase
- Fosfomycin and colistin
- Consider tigecycline
- Use cotrimoxazole if Stenotrophomonas

Joint Working Party on MDRGNB infection: Treatment
Suggested algorithm for the treatment of MDR Gram negative bacteria admitted to UK hospitals

Susceptibility known of past or current infection

N or systemic Infection

Yes and urinary infection

Outpatient
Ertapenem

Inpatient
Meropenem or
Meropenem-sparing:
Temocillin (if urinary)
Ceftazolone-tazobactam

Parenteral
Coamoxiclav or
Piperacillin-tazobactam or
Gentamicin or Amikacin
Oral follow on
Fosfomycin or
Nitrofurantoin or
Pivmecillinam with oral coamoxiclav

Joint Working Party on MDRGNB infection: Treatment
Fosfomycin trometamol

- Licenced in UK 1994-6, now available for uncomplicated cystitis
- Only 4 observational studies for lower UTI caused by MDRGNB
- Has been used for prophylaxis of pyelonephritis in ASB of pregnancy
- PK recently reviewed, need for studies in upper UTI
- Little published experience with parenteral, but successful in 9/15 pandrug res Klebs
- Will resistance rise with greater use, China 60% of KPC producers resistant with fosA

References:

Pivmecillinam

- Inactive ester converted to active mecillinam
- Against ESBL only case series available, variable results when used alone poorer against CTX-M 15, but stable to AmpC
- Combination with co-amoxiclav reduces MICs and trials needed in ESBL
- Stability to most carbapenemases, particularly KPC is poor.
- Resistance in clinical isolates is due to mutations in cysB resulting in reduced fitness
- A single old good RCT suggested that i.v. mecillinam with ampicillin performed well in pyelonephritis¹

¹Cromberg S 1995 Scan J.I.D. 27,463
Nitrofurantoin

- Now recommend above trimethoprim for lower UTI
- Low rates of resistance (1-4%), but higher in ESBLs although resistant strains have reduced fitness
- V. Low tissue concentrations, common ESBL *E. coli* clones have pathogenicity factors for upper tract disease (e.g. ST131, ST9 etc)
- Do not use in renal impairment, rare pulmonary AE’s
- Urgent need for good comparative studies in ESBLs with other agents
Suggested algorithm for the treatment of UTI in the UK community likely to be due to MDR GNB

Any of: Recurrent UTI, Persistent symptoms after initial prescription, >7 days hospital admission in last 6/12, Residence in a care home, Recent travel/healthcare in high risk countries. Previous UTI due to Coamox or quinolone or cephalosporins R GNB or recent treatment with these

Yes

Previous trimethoprim resistance or treatment failure on trimethoprim

No

Previous nitrofurantoin resistance or treatment failure on nitrofurantoin

Joint Working Party on MDRGNB infection: Treatment
Suggested algorithm for the treatment of UTI in the UK community likely to be due to MDR GNB

Joint Working Party on MDRGNB infection: Treatment
Suggested algorithm for the treatment of UTI in the UK community likely to be due to MDR GNB

- **ESBL-producing bacteria likely. Pyelonephritis?**
  - Yes: Patient requires hospital admission
  - No: eGFR >45ml/min/1.73 m²
    - Yes: Iv Meropenem or meropenem-sparing antibiotics as IP
    - No: iv Ertapenem as OPAT
  - No: Nitrofurantoin² Fosfomycin Pivmecillinam
  - Fosfomycin Pivmecillinam

1. Not nitrofurantoin if pyelonephritis or eGFR <45ml/min.
2. Caution re prolonged/frequently repeated courses
3. Not fosfomycin if pyelonephritis
Conclusions - 1

• We found licencing trials contribute little to the understanding of the use of agents against MDRGNB often have very low numbers of resistant bacteria.

• Very few quality in use studies with outcomes – particularly for older agents-need for new studies/registers.

• VAP and cIAI with CPE difficult and relies on combinations with colistin, tigecycline, meropenem (if MIC low) and new agents e.g. BLI’s
• The increase in nitrofurantoin use may increase pyelonephritis as trimethoprim provided cover. Lack of oral agents with activity against very resistant GNB-probably only fosfomycin.

• Empirical treatment is dictated by local and imported epidemiology.

• Risk factors other than hospital treatment abroad lacking.

• Rapid changes in epidemiology in some countries e.g. Italy, USA, China, South Asia will impact success of new & old agents. As resistance genes become integrated into community faecal flora empirical treatment of community presenting patients will be difficult. Asia current biggest risk reservoir.

• Rapid diagnostics to target susceptibilities of MDRGNB critical to better management.