Recent outbreak in the Hospital for Cardio-surgery

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Scope

Outbreak of HAI with carbapenem-resistant *Klebsiella pneumoniae* happened during August – September 2018 at the University Clinic for Cardio surgery in Skopje.

Imported strain from other clinic was spread to 7 patients and successfully cured in 4 of them as well as eradicated from the Cardio surgery clinic in the next month.
Importance of carbapenem resistant bacteria

- Severe problem in hospitalized patients
- Global distribution (39 countries in 2013 in EU)
- High mortality (40-50%)
- Genes coding different groups of antimicrobials (no new antibiotics)
- Reservoirs – community!
- High transmission rate in bacterial population
  - Clonal expansion
  - Plasmid transmission
- Not specially virulent bacteria – harder to treat
Carbapenem Resistant *Enterobacteriaceae* (CRE) highly drug resistant pathogens from over 70 different genera

CRE definition - non-susceptible to carbapenems, AND resistant to all third generation cephalosporins

- CRE infections - usually not affect healthy people; happened to hospitalized patients, nursing homes, and other healthcare settings.

- Associated with devices and antibiotics use:
  ◦ breathing machines,
  ◦ urinary catheters,
  ◦ intravenous catheters,
  ◦ long courses of carbapenem exposure

- One case of CRE infection in heath care facility – many other infected / colonized patients
Family of beta lactam agents

- Penicilines
- Cephalosporins
- Monobactams
- Carbapenems - last line of defense in treating Enterobacteriaceae

Mechanism of action
- Enter periplasmic space through PORINS
- Inhibit transpeptidases - PBPs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Strep. &amp; Staph. (included MRSA)</th>
<th>Enterobacteriaceae</th>
<th>Non-fermentors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imipenem</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Meropenem</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>+</td>
<td>+</td>
<td>Restricted activity</td>
</tr>
<tr>
<td>Doripenem</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
Carbapenem resistance - mechanisms

- **EFFLUX** - active transport of drug out of the cell

- **OMP (Outer Membrane Porins)** - mutation OR loss*
  - *Klebsiella pneumoniae* – lack of OMPP (OmpK35 and OmpK36 = high level R, both MIC >32mg/L

- **Carbapenemases production**
  - Different classes

**Classes of carbapenemases ***,***

- **Class A** (serine CP, encoded via chromosomes and plasmids genes)
  - SME (associated with *Serratia marcescens*)
  - IMI (in *Enterobacter cloacae* and other)
  - GES (in *Pseudomonas aeruginosa* as well as *Kl. pneumoniae* and *E. coli*)
  - KPC (in *Klebsiella pneumoniae*)

- **Class B** (MBLs) (metalo-beta lactamases – Zn on active sites)
  - Subclasses B1, B2 and B3

- **Class D** (OXA) - hydrolyze oxacillin (serine CP, plasmid encoded)
  - $bla_{OXA}$ genes, chromosomal and plasmide

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Carbapenemase producing *Enterobacteriaceae* in Republic of North Macedonia

– sporadic occurrence till 2013
- In 2017
  ◦ 48 specimens, 40 patients
    ◦ 44 *Klebsiella pneumoniae*, 4 *Enterobacter cloacae*
  ◦ Blood culture
  ◦ Urine
  ◦ Wound
  ◦ Tubus / canila
  ◦ Sputa / Tracheal aspirates
University Clinic for Cardio-surgery

- Established in 2014
- Macedonian and surgeons from abroad

- Total No of beds = 15 in 4 rooms, 6 in ICU
- Total No of patients during 2018 = 411

- Total No microbiology specimens = 1050
- Total No of isolates = 263
Examined specimens (2018)

molecular sepsis
other
canila, tubus, catether
soft tissue
blood culture
feces
urine
bronchial aspirates
tracheal aspirates
sputa
nose swob
throught swob

Diagrammtitel
Isolates / specimens (2018)

Diagrammstitel

- *Stenotrophomonas*
- *Pseudomonas aeruginosa*
- *Acinetobacter spp.*
- *Proteus/Morganella*
- *Enterobacter ESBL*
- *Enterobacter spp*
- *Klebsiella ESBL*
- *Klebsiella*
- *E coli ESBL*
- *E coli*
- *Pneumococcus*
- *Streptococcus pyogenes*
- *VRE*
- *Enterococcus*
- *KNS-MR*
- *MRSA*
- *Staphylococcus aureus*

- throught swob
- nose swob
- sputa
- tracheal aspirates
- bronchial aspirates
- urine
- feces
- blood culture
- soft tissue
- canila, tubus, catheter
Identification of CPE recommendations

Carbapenem Inactivation Method (CIM)
  ◦ Screening media – incorporated imipenem (1-2 or 0.5-1mg/L) / meropenem (0.5mg/L)

Disc-diffusion methods
  ◦ Combination disks test (mast Diagnostic, D70C)

MIC detection –
  ◦ VITEK 2 compact
  ◦ E-test

PCR gene detection

MALDI-TOF MS
  ◦ First screen for admitted patient at the hospital
Disc-diffusion test
MIC breakpoints

### Table 1. EUCAST breakpoints for carbapenems

<table>
<thead>
<tr>
<th>Carbapenems*</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></td>
</tr>
<tr>
<td>Ertapenem</td>
<td>0.5</td>
<td>0.5</td>
<td>10</td>
</tr>
<tr>
<td>Imipenem**</td>
<td>2</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Meropenem</td>
<td>2</td>
<td>8</td>
<td>10</td>
</tr>
</tbody>
</table>

Breakpoint table used for above values:

*: Certain isolates that produce carbapenemase are categorised as susceptible with these breakpoints and should be reported as tested, i.e. the presence or absence of a carbapenemase does not in itself influence the categorisation of susceptibility. Carbapenemase detection and characterisation are recommended for public health and infection control purposes. For carbapenemase screening, a meropenem screening cut-off of >0.125 mg/L (zone diameter <28 mm) is recommended.

**: Low-level resistance is common in Morganella spp., Proteus spp. and Providencia spp.
Interpretation of the combination disc test (CDT)

<table>
<thead>
<tr>
<th>Increase in inhibition zone diameters compared to disk A (meropenem)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disk B (meropenem+DPA)</td>
<td>Non-carbapenemase producer</td>
</tr>
<tr>
<td>&lt; 5 mm</td>
<td>&lt; 5 mm</td>
</tr>
<tr>
<td>≥ 5 mm</td>
<td>≥ 5 mm</td>
</tr>
<tr>
<td>Disk C (meropenem+A PBA)</td>
<td>MBL producer</td>
</tr>
<tr>
<td>&lt; 5 mm</td>
<td>&lt; 5 mm</td>
</tr>
<tr>
<td>≥ 5 mm</td>
<td>≥ 5 mm</td>
</tr>
<tr>
<td>Disk D (meropenem+cloxacillin)</td>
<td>KPC producer</td>
</tr>
<tr>
<td>&lt; 5 mm</td>
<td>&lt; 5 mm</td>
</tr>
<tr>
<td>≥ 5 mm</td>
<td>≥ 5 mm</td>
</tr>
<tr>
<td>&lt; 5 mm</td>
<td>AmpC + porin loss</td>
</tr>
<tr>
<td>≥ 5 mm</td>
<td>≥ 5 mm</td>
</tr>
</tbody>
</table>

Appearance of a CDT positive for KPC producing CPE. Inhibition zone diameters were 19 mm for meropenem (MER) disk, 20 mm for the MER disk + EDTA, 20 mm for the MER disk + phenylboronic acid (PBA), and 31 mm for the MER disk + PBA + EDTA. MDM, meropenem 10 μg.
# Outbreak of CR *Klebsiella pneumoniae*

<table>
<thead>
<tr>
<th>patient No.ID</th>
<th>date</th>
<th>specimen</th>
<th>date</th>
<th>specimen</th>
<th>date</th>
<th>specimen</th>
<th>date</th>
<th>specimen</th>
<th>date</th>
<th>specimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.BI - MBL</td>
<td>27.8</td>
<td>blood culture</td>
<td>5.9</td>
<td>bronchial asp.</td>
<td>7.9</td>
<td>blood culture</td>
<td>12.9</td>
<td>blood culture</td>
<td>12.1</td>
<td>urine</td>
</tr>
<tr>
<td>2.AJ - MBL</td>
<td>30.8</td>
<td>blood culture</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.ER - MBL</td>
<td>4.9</td>
<td>sputum</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.SS - MBL E coli</td>
<td>6.9</td>
<td>blood culture</td>
<td>12.9</td>
<td>bronchial asp.</td>
<td>20.9</td>
<td>blood culture</td>
<td>22.9</td>
<td>urina</td>
<td>25.9</td>
<td>blood culture</td>
</tr>
<tr>
<td>5.JA - non carbapenemase producer ??</td>
<td>7.9</td>
<td>urine</td>
<td>11.9</td>
<td>urine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. VI - MBL</td>
<td>12.10</td>
<td>blood culture</td>
<td>12.10</td>
<td>urine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.RU - MBL</td>
<td>8.11</td>
<td>soft tissue</td>
<td>15.12</td>
<td>soft tissue</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Outbreak of CR *Klebsiella pneumoniae*

<table>
<thead>
<tr>
<th>Patient</th>
<th>No.ID/age (years)</th>
<th>Combination disk test</th>
<th>Imipenem MIC &lt;2 &gt;4</th>
<th>Meropenem MIC &lt;2 &gt;8</th>
<th>Output</th>
<th>Clinical Dg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.BI (67)</td>
<td>MBL</td>
<td>8 - R</td>
<td>12 - R</td>
<td>survive</td>
<td>Sepsis; CAD, CABG</td>
<td></td>
</tr>
<tr>
<td>2.AJ (61)</td>
<td>MBL</td>
<td>&gt;32</td>
<td>&gt;32</td>
<td>exits</td>
<td>Sepsis; ASD, VECA</td>
<td></td>
</tr>
<tr>
<td>3.ER (47)</td>
<td>MBL</td>
<td>16 - R</td>
<td>12 - R</td>
<td>survive</td>
<td>Colonization; endocarditis, AVR</td>
<td></td>
</tr>
<tr>
<td>4.SS (55)</td>
<td>MBL</td>
<td>12 - R</td>
<td>6 - I</td>
<td>exits</td>
<td>Sepsis; CABG</td>
<td></td>
</tr>
<tr>
<td>5.JA (55)</td>
<td>non carbapenemase producer ??</td>
<td>3 - I</td>
<td>12 - R</td>
<td>survive</td>
<td>UTI; ASD closure</td>
<td></td>
</tr>
<tr>
<td>6.VI (52)</td>
<td>MBL</td>
<td>3 - I</td>
<td>4 - I</td>
<td>survive</td>
<td>Sepsis; AAS</td>
<td></td>
</tr>
<tr>
<td>7.RU (77)</td>
<td>MBL</td>
<td>8 - R</td>
<td>6 - I</td>
<td>exits</td>
<td>STI co-morbidities; AAS, AVR</td>
<td></td>
</tr>
</tbody>
</table>

CAD – Coronary Artery Disease  
CABG - Coronary Artery Bypass Grafting  
AAS – Aortic Aneurysm Surgery  
ASD - Atrial Septal Defect  
AVR - Aortic Valve Replacement  
De Vega – Tricuspid annuloplasty using De Vega modified technique
Therapy

Meropenem = 3 pats \((\text{MIC}<8)\)
Tazobactam = 5 pats
Colistin = 4 pats
Aminoglicozides = 3 pats
Fluorocinolones = 1 pat

- **Tigecycline** –
  - higher binding affinity with ribosomes;
  - kill almost all ESBL and MDR \textit{E.coli} and \textit{K.pneumoniae};
  - negative clinical outcome in UTI and primary sepsis = limited penetration and rapid tissue diffusion
  - not registered in RNM

- **Aztreonam** – not registered in RNM
Co-morbidities of the patients

Heart disease - all

Diabetes – 3 pats
Renal insufficiency – 1 pats
Age – 47 to 77
Multidrug-resistant organisms - interventions required in healthcare settings to prevent transmission

Recommendations from the Commission for HAI and microbiologist:
- Isolation of the infected or colonized patients in a separate room
- Refreshing the knowledge for
  ◦ Hand hygiene
  ◦ Hospital hygiene - cleaning, disinfection, chlorhexidine bathing
- Active surveillance - screening of the contacts (indwelling devices = 29, feces = 16)
- Review of lab records
Understand CRE prevalence

“Carbapenemase producing Enterobacteriaceae – current problem in the clinical practice”

national scientific project

Main investigator Prof Dr Ana Kaftandzieva

Institute of Microbiology and Parasitology, Faculty of Medicine,
University Ss Cyril and Methodius, Skopje

March, 2018
Conclusions

- Awareness for CRE and other multi-drug resistant (MDR) bacteria and understanding the importance

- Knowing the distribution of MDR in the country and in the entire institutions

- Control of hospital environmental

- Active surveillance testing of the incoming patients and asymptomatic ones (rectal swabs, not only URT)

- Refreshing the knowledge of the staff for hand and hospital hygiene

- Minimize the use of devices

- Appropriate antimicrobial use – indication / duration; narrowest spectrum of antibiotics