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

Drug	*Strep*. & *Staph*. (included MRSA)	*Enterobacteriaceae*	Non-fermentors
Imipenem	+	+	+
Meropenem	+	+	+
Ertapenem	+	+	Restricted activity
Doripenem	+	+	+

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

*Little, ML; et al. (2012). International Journal of Antimicrobial Agents. **39** (1): 52–57.
Nordmann, Patrice; et al. (2012). Cell Press. **18 (5): 263–272.
*** Pfeifer, Yvonne; et al. (2010). Int J Med Microbiol. **300** (6): 371–9.

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

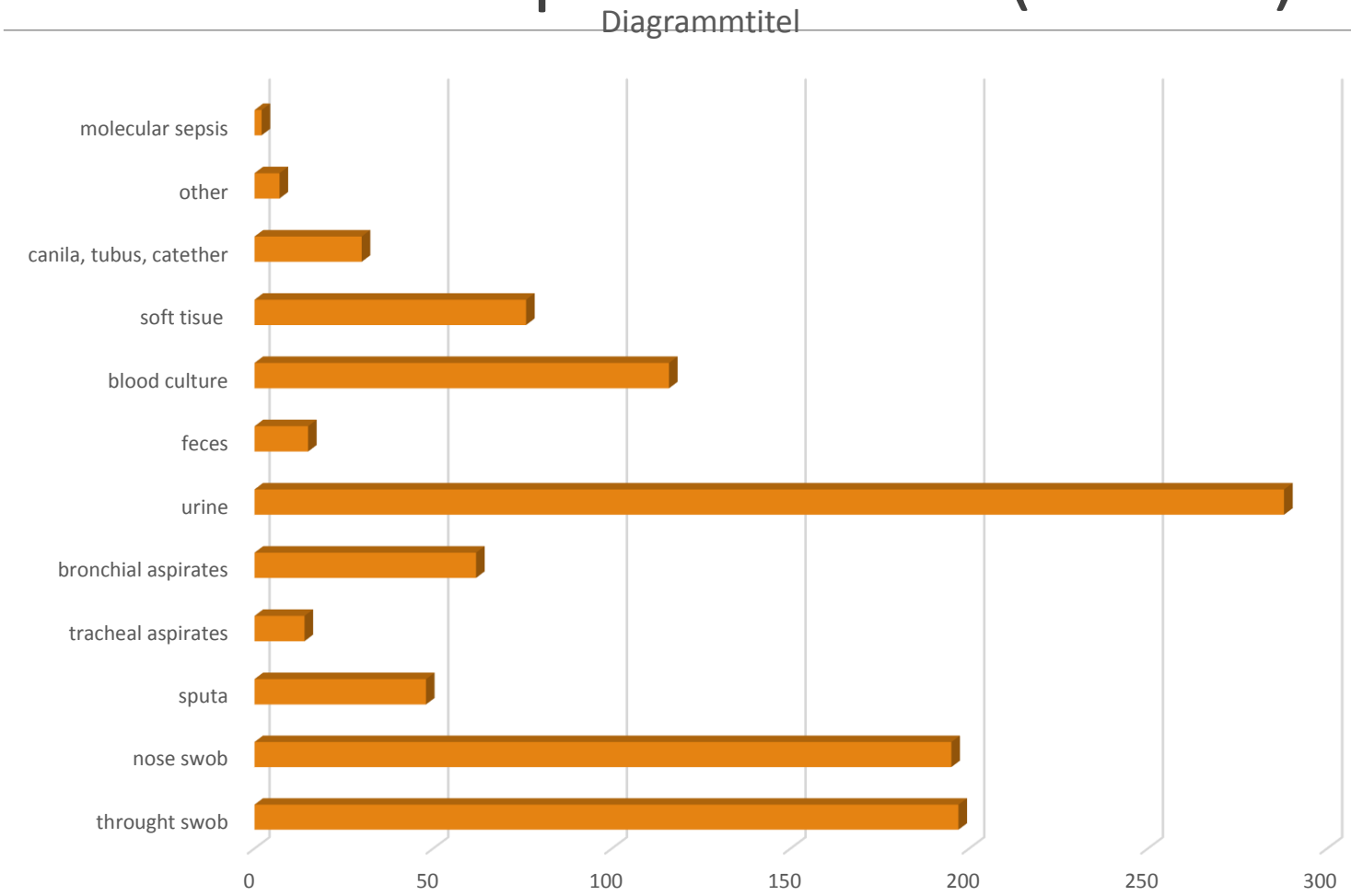
University Clinic for Cardio-surgery

- Established in 2014
- Macedonian and surgeons from abroad

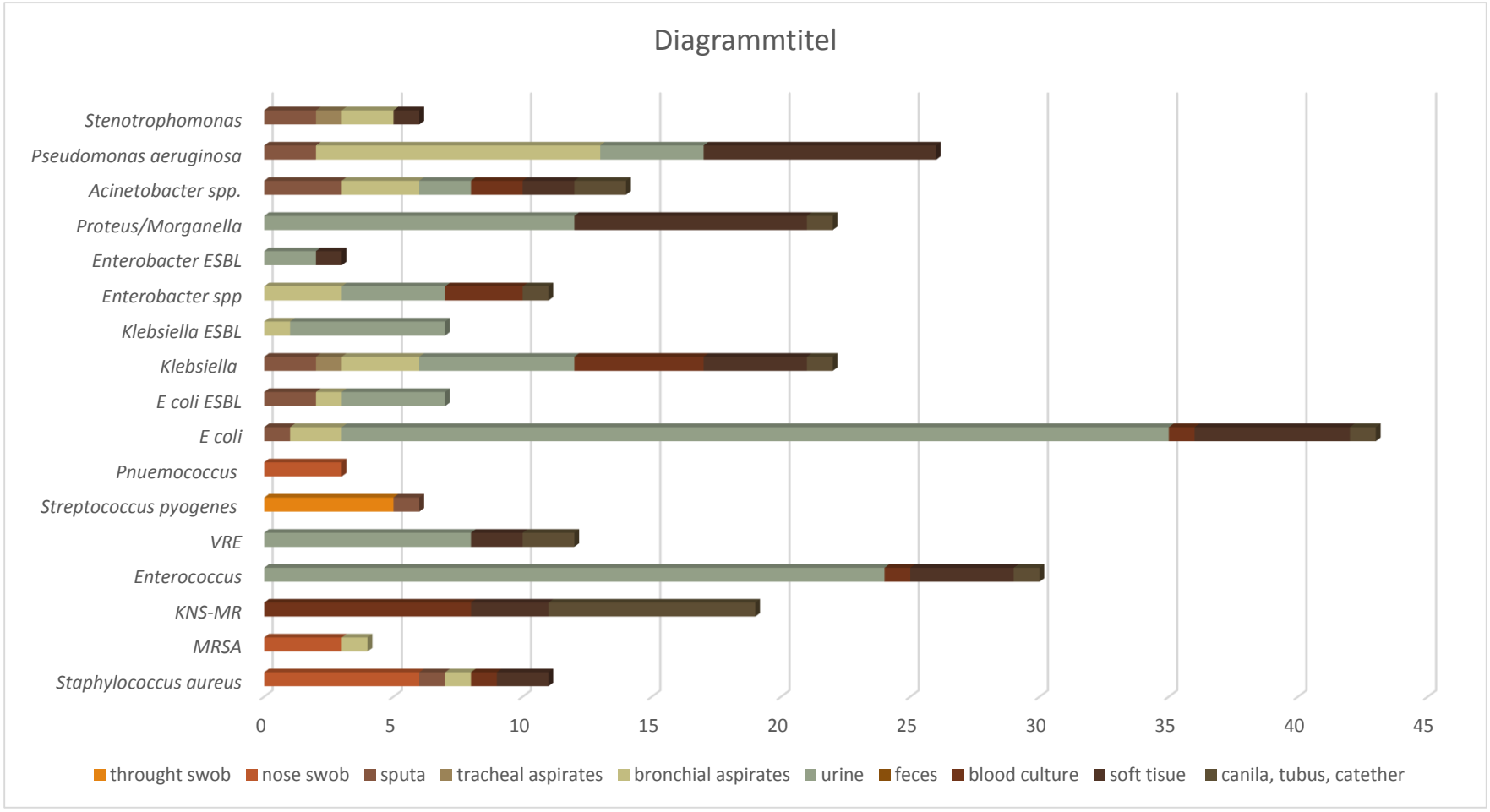
- Total No of beds = 15 in 4 rooms, 6 in ICU
- Total No of patients during 2018 = 411

- Total No microbiology specimens = 1050
- Total No of isolates = 263

Examined specimens (2018)



Isolates / specimens (2018)



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

Carbapenems*	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Ertapenem	0.5	0.5	10	25	5
Imipenem**	2	4	10	22	7
Meropenem	2	8	10	22	16

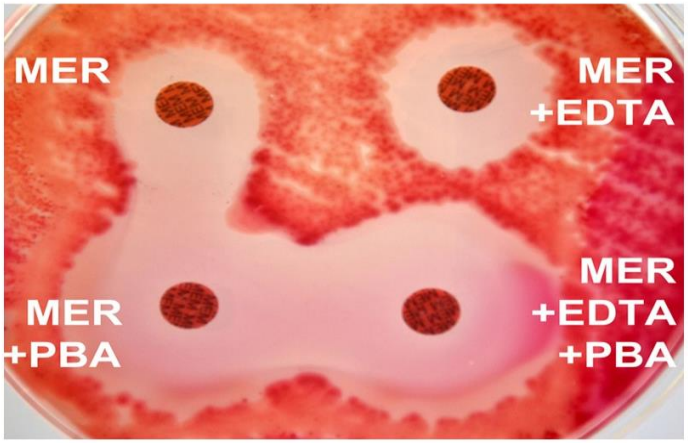
Breakpoint table used for above values:
http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_9.0_Breakpoint_Tables.pdf.
**: Certain isolates that produce carbapenemase are categorised as susceptible with these breakpoints and should be reported as tested, i.e. the presence 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)

Increase in inhibition zone diameters compared to disk A (meropenem)			Interpretation
Disk B (meropenem+ DPA)	Disk C (meropenem+A PBA)	Disk D (meropenem+cloxac illin)	
< 5 mm	< 5 mm	< 5 mm	Non-carbapenemase producer
≥ 5 mm	< 5 mm	< 5 mm	MBL producer
< 5 mm	≥ 5 mm	< 5 mm	KPC producer
< 5 mm	≥ 5 mm	≥ 5 mm	AmpC + porin loss

PMC full text: J Clin Microbiol. 2013 Sep; 51(9): 2986–2990.
doi: 10.1128/JCM.00901-13

Fig 1



Appearance of a CDT positive for KPC-producing CPE. Inhibition zone diameters were 19 mm for the meropenem (MER) disk, 20 mm for the MER disk + EDTA, 29 mm for the MER disk + phenyl boronic acid (PBA), and 31 mm for the MER disk + PBA + EDTA. MEM, meropenem 10 mg.

Outbreak of CR *Klebsiella pneumoniae*

patient No.ID	date	specimen	date	specimen	date	specimen	date	specimen	date	specimen
1.BI - MBL	27.8.	blood culture	5.9.	bronchial asp.	7.9.	blood culture	12.9.	blood culture	12.10.	urine
2.AJ - MBL	30.8.	blood culture								
3.ER - MBL	4.9.	sputum								
4.SS - MBL E coli	6.9.	blood culture	12.9.	bronchial asp.	20.9.	blood culture	22.9.	urina	25.9.	blood culture
5.JA - non carbapenemase producer ??	7.9.	urine	11.9.	urine						
6. VI - MBL	12.10.	blood culture	12.10.	urine						
7.RU - MBL	8.11.	soft tissue	15.12.	soft tissue						

Outbreak of CR *Klebsiella pneumoniae*

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

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 (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 *E.coli* and *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 multydrug 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