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Carbapenemases-Threat of the Next Decade?

Szabados Florian*

Department of Medical Microbiology, Institute for Hygiene and Microbiology, University of Bochum, Germany

Increased cost in hospitals due to nosocomial infections is an important socioeconomic topic. Some gram-positive organisms such as Methicillin-Resistant *S. aureus* (MRSA) and Vancomycin Resistant *Enterococci* (VRE) and their implication to hygiene have been described. MRSA is widely accepted as an increasing burden in nosocomial infections. Especially the prevalence of MRSA is increasing since years in many countries. In contrast MRSA-infections, where usually therapeutic options are left, in gram-negatives the development of resistance is different. Especially *Klebsiella pneumonia* but also other gram-negatives became an important nosocomial pathogen since the early 1970s. Firstly, resistance to aminoglycosides, later then Extended-Spectrum ß-lactamase (ESBL) -producing strains, mostly TEM and SHV's active against cephalosporin's often combined with a variety of genes conferring resistance to antibiotics other than ß-lactam drugs have been described. ESBL-producing *Enterobacteriaceae*, especially *Escherichia coli* and *K. pneumonia* are the most important pathogens in community and hospital settings in a variety of countries. In other species of *Enterobacteriaceae*, ESBL's and acquired AmpC are also emerging since several years. Meanwhile, ESBL-harbouring strains have been described to be resistant to all antibiotics including the carbapenem-class. Carbapenemases- Producing *Enterobacteriaceae* (CPE) are dramatically emerging in distinct countries [1], but were also present and emerging in Europe and USA. Carbapenem like imipenem or meropenem are the most important antibiotic drugs to treat seriously ill patients usually in an intensive-care setting. Most of these CPE-strains harbour also an ESBL, therefore resistance to all ß-lactams and other drugs are very common in CPE, independent of the type of Carbapenemases. In addition, isolates have been described harbouring several types of Carbapenemases. Therapeutic options in CPE are often limited to tigecycline and colistin and also "pan"-resistant strains have been described. In contrast to gram-positive bacteria new drugs for gram-negatives are very limited. Therefore the threat of CPE is different from that of gram-positive bacteria. Carbapenemases have been described in three molecular classes, class A, B and D. The most frequent types and variants in class A Carbapenemases in CPE is the KPC-group (KPC2-2 to -13), which have been firstly described in *K. pneumonia*, but were also detected in *E. coli*, *Klebsiella oxytoca*, *Serratia marcescens*, *Enterobacter* species, *Citrobacter freundii*, *Salmonella. enterica* and *Raoutella* species [2]. In class B Carbapenemases, also called metallo-ß-lactamase, VIM, IMP and NDM are the most prevalent types in CPE. A variety of VIM-variants have been described in *K. pneumonia*, *E. coli*, *K. oxytoca*, *S. marcescens* and *S. liquefaciens*, *Enterobacter* species, *C. freundii*, *Morganella morganii*, *Providencia stuartii* and *Proteus mirabilis* [2]. IMP-type Carbapenemases in CPE have been described for *K. pneumonia*, *E. coli*, *K. oxytoca*, *S. marcescens* and *Enterobacter* species, *C. freundii*, *Proteus mirabilis*. *Providencia rettgeri*, *Shigella flexneri* and *M. Morganii* [2]. In *Enterobacteriaceae*, NDM have been detected in *K. pneumonia*, *E. coli*, *Enterobacter* species, *C. freundii*, *K. oxytoca*, *M. morganii* and *Providencia* species [2]. In addition, detection of NDM-harbouring strains is more difficult, compared to other Carbapenemases, since there aredf some diagnostic pitfalls [3]. In *Enterobacteriaceae*, the OXA-type Carbapenemases (class D) were found in *K. pneumonia*, *E. coli*, *C. freundii* and *P. Mirabilis* [2]. Especially the OXA-48 is in Europe one of the most prevalent OXA-type Carbapenemases in *Enterobacteriaceae*. Several phenotypic screening tests have been established for the screening of suspected Carbapenemases- harbouring, carbapenem-resistant *Enterobacteriaceae* [3,4]. An increased Minimal Inhibitory Concentration (MIC) in carbapenem could be also mediated by mechanism independent of the presence of a Carbapenemases. Porin-loss in addition to the presence of AmpC or ESBL is the most important alternative to the presence of a Carbapenemases in carbapenem-resistant isolates. Molecular methods are therefore necessary in addition to phenotypic tests to validate suspected Carbapenemases [5]. A Matrix-Assisted Laser Desorption/Ionisation Time-Of-Flight Mass-Spectrometry (MALDI TOF MS)-based detection of ß-lactamase [6] and Carbapenemases-activity in *Enterobacteriaceae* [7,8] have been recently described. The introduction of these fast methods that directly identify underlying resistance mechanisms could be of eminent importance in the near future for the determination of resistance. This is especially due to a very fast testing in combination with a high accuracy. MALDI-TOF MS-based antimicrobial resistance testing of resistance-mechanisms other than ß-lactamase, such as the detection of methicillin-resistance in *S. aureus* (PBP2a) have been described, but were yet controversially discussed in literature [9,10]. Even though, the MALDI-TOF-based approach to detect ß-lactamase and Carbapenemases is sufficient, alternative fast and accurate methods are highly desirable for the detection of resistance mechanisms other than degradation of ß-lactam drugs.

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***Corresponding author:** Szabados Florian, Department for Medical Microbiology, Institute for Hygiene and Microbiology, University of Bochum, Bochum, Germany, Tel : +49-234-32-26467; Fax: +49-234-32-14197; E-mail: Florian.szabados@rub.de

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