Karolinska Institutet

Institutionen för mikrobiologi, tumör- och cellbiologi – MTC

Enheten för klinisk mikrobiologi

Extended-spectrum β-lactamase-producing Enterobacteriaceae

Epidemiology and dynamics of fecal carriage

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Rolf Luft auditorium, L1:00, Karolinska Universitetssjukhuset Solna

Fredagen den 18 oktober 2013, kl 13.30

av

Emilia Titelman
Leg. Läkare

Huvudhandledare:
Docent Christian Giske
Karolinska Institutet – MTC
Enheten för klinisk mikrobiologi

Bihandledare:
PhD Aina Iversen
Karolinska Institutet - MTC
Enheten för klinisk mikrobiologi

Professor Mats Kalin
Karolinska Institutet
Institutionen för medicin, Solna
Enheten för infektionssjukdomar

Fakultetsopponent:
Professor Pentti Houvinen
University of Turku
National Institute of Health and Welfare
Finland

Betygsnämnd:
Professor Andrej Weintraub
Karolinska Institutet
Institutionen för laboratoriemedicin

Docent Christina Åhrén
Göteborgs universitet
Institutionen för biomedicin

Docent Anders Johansson
Umeå universitet
Institutionen för klinisk mikrobiologi

Stockholm 2013

ABSTRACT

ESBL-producing Enterobacteriaceae (EPE) has become a major cause of community acquired urinary tract infection (UTI), and fecal carriage of EPE is emerging worldwide. The aims of this thesis were to study the molecular epidemiology of ESBL-enzymes in Stockholm (**I**) to evaluate treatment alternatives to the carbapenems for EPE (**I-III**), and to study the duration of fecal carriage and identify factors associated with prolonged carriage (**IV**).

Paper I describes a consecutive collection of EPE (n=169). The distribution of ESBL-enzymes and clonal relatedness of the isolates was determined with PCR, DNA sequencing and pulsed-field gel electrophoresis (PFGE). Antimicrobial activity was evaluated using gradient test, broth microdilution and disk diffusion, and the susceptibility test methods were compared for parenteral β-lactams. We found that CTX-M-15 (75%) and CTX-M-14 (23%) were the dominating genotypes, that the collection was largely polyclonal and that 41% of *E. coli* belonged to the international clone sequence type (ST) 131. We concluded that there are several oral (mecillinam, nitrofurantoin, fosfomycin) and parenteral (piperacillin-tazobactam, tigecycline, temocillin) treatment alternatives for *E. coli* but few for *K. pneumoniae*. We also showed that susceptibility rates obtained with Etest and disk diffusion (DD) were not in agreement with the reference method broth microdilution for piperacillin-tazobactam (TZP), and Etest and DD are therefore not reliable to detect resistance to TZP, with the breakpoints used at the time of the study.

In **paper II** the novel cephalosporin CXA-101 (later known as ceftolozane) in combination with tazobactam (CXA-201) was evaluated against the same collection of isolates as in paper **I**, and compared to other β-lactam/β-lactamase inhibitors. MICs were determined with broth microdilution and susceptibility to CXA-201 was 88-98%, depending on the concentration of tazobactam and the tentative breakpoint used. All ACL-resistant and 94% of the TZP-resistant isolates were CXA-201 susceptible. We concluded that ceftolozane-tazobactam (CXA-201) is a potential future therapeutic option against EPE, especially for TZP-resistant isolates.

Paper III evaluates the clinical and bacteriological activity of pivmecillinam for patients treated for lower UTI caused by an EPE (n=8). The clinical cure (resolved UTI symptoms after completed treatment) was high (8/8) but bacteriological cure (< 10^3 CFU/ml at follow-up after 30 days) was low (2/8), although none of the patients with persisting bacteriuria relapsed within 6 months.

In **paper IV** we studied the duration and dynamics of ESBL-carriage. A cohort of patients (n=61) were followed with fecal samples and questionnaires about antimicrobial treatment and risk factors for EPE, 1, 3, 6 and 12 months after EPE infection. EPE strains were subjected to PFGE, PCR for phylogrouping, detection of CTX-M phylogroup, *pabB* (ST131) and virulence genes and PCR based replicon typing. Patient and strain related variables were compared for carriers and non-carriers at 12 months. We concluded that EPE carriage is common 12 months after infection (43%) and that persisting carriage may be associated with *E. coli* phylogroup B2 and CTX-M-9. The strain background frequently changes throughout the carriage and negative samples do not imply eliminated carriage.

This knowledge will hopefully contribute to providing better medical care of patients with infection caused by EPE. It may also prove important for defining patients that require prolonged isolation in ingle rooms or cohorts. Thereby the spread of EPE in hospitals and long term care facilities can be limited.

ISBN 978-91-7549-279-7