Fluoroquinolone resistance in urinary pathogens

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Urinary tract infections are a major cause of morbidity and mortality, both in the community and in healthcare settings. In most UTIs, E. coli is the predominating urinary pathogen while other Enterobacteriaceae, staphylococci and enterococci are occasionally involved. While fluoroquinolones are established therapeutic options in UTIs, the usefulness of this class of agents is undermined by increasing fluoroquinolone resistance among the uropathogens, especially among *E. coli* in the community. Consequently, the clinical guidelines have been updated to address the clinical challenges from increasing antimicrobial resistance. According to the updated guidelines, fluoroquinolones are not recommended as empirical therapy in regions where the resistance rate of community uropathogens is above 10%. This threshold is exceeded in many countries, particular in the Asia-Pacific region where the fluoroquinolone resistance rates were reported to above 20-30%. Risk factors which are often associated with fluoroquinolone resistance in community-acquired UTIs include elderly patients, previous exposure, and ESBL production. In addition, the new guidelines have emphasized that agents, such as fluoroquinolones and cephalopsorins with a high propensity to cause collateral damage (i.e. by selecting for resistant bacteria in the gut or other body sites) be avoided as the first line agents in empirical therapy of UTIs. Instead, nitrofurantoin and fosfomycin, due to the low prevalence of resistance among common uropathogens and minimal propensity to select resistance development are now recommended as first-line agents for empirical therapy of uncomplicated cystitis. However, adverse effect, patient compliance, drug cost and availability have to be considered. In Enterobacteriaceae, resistance to fluoroquinolone primarily results from accumulation of mutations in DNA gyrase (GryA), then in topoisomerase IV (ParC) genes in the chromosome. In addition, fluoroquinolone resistance could also be mediated by plasmid-mediated quinolone resistance (PMQR) mechanisms: Qnr quinolone resistance proteins (QnrA, QnrB, QnrC, QnrD, QnrS), the AAC(6')-Ib-cr aminoglycoside acetyltransferase and efflux

(QepA and OqxAB). The PMQR genes do not cause MICs of the fluoroquinolones to rise to levels that could be detected by the clinical breakpoints but only a degree of reduced susceptibility. A series of experiments have showed that the PMQR mechanisms might allow the organisms to survive low level of quinolones, allowing resistance mutations in GyrA and ParC to develop sequentially. Surveillance have showed that the PMQR determinants, especially the qnr genes occur widely in many different enterobacterial species but mostly in E. coli and Klebsiella pneumoniae. High prevalence of qnr genes have been reported in some surveillance of fluoroquinolone-resistant uropathogens. The qnr genes have been reported to occur in plasmids which often harbor other genes encoding resistance to beta-lactams, aminoglycosides, sulphonamides and trimethoprim. This partly explains the multidrug-resistant phenotypes in enterobacterial species positive for the qnr genes.