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Are All Quinolones Equal with Regard to Resistance?

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As quinolones have been used increasingly in clinical medicine over the past two decades, resistance has emerged in both gram-positive and gram-negative bacteria. Quinolones differ in the extent to which resistance can be selected in the laboratory, and a number of factors affect the frequency of selection of mutants. One pharmacodynamic factor involves the relationship of drug concentration at the site of infection and the MIC of quinolones for the infecting organism. The mutant prevention concentration (MPC) reflects a drug concentration that is sufficient to kill or inhibit the growth of spontaneous mutants in a large bacterial population, preventing such mutants from being selected. For many organisms and quinolones the MPC is approximately eightfold above the MIC, because single first-step mutations often confer this level of resistance or lower. The MPC is achievable for the most potent quinolones but may not be for others, and when strains with first-step resistance mutations themselves constitute the entire population, prevention of additional mutations through attainment of a higher MPC value may not be possible.

Quinolones also differ in the extent to which they are affected by specific resistance mechanisms. With two quinolone target enzymes, DNA gyrase and topoisomerase IV, the frequency of selection of mutants is reduced for quinolones that have similar inhibitory activities for both enzymes relative to those with differing potencies for the two targets. In former case, this property reflects the lack of a selectable resistance phenotype unless there are mutations in both target enzymes, whereas in the latter case a single mutation in the primary target enzyme confers a potentially selectable increase in MIC. Quinolones also differ in the extent to which they are substrates for a variety of bacterial efflux pumps, but many bacteria have multiple pumps which may expand the number of quinolones to which resistance could occur by selection for mutations that increase the expression of these pumps. Finally, plasmid-mediated resistance mechanisms may also differ in their effects on different quinolones. Although the plasmid-encoded Qnr proteins appear to have broad effects on most quinolones, the plasmid-encoded Aac(6')-Ib-cr variant enzyme is only capable of modifying and reducing the activity of quinolones with an unblocked secondary amine on a piperazinyl substituent, such as found in norfloxacin and ciprofloxacin.

Data on the extent to which differences among quinolones in resistance selection in the laboratory can be correlated with clinical resistance are few and often confounded. But MPC and other pharmacodynamic correlations of the occurrence of resistance in animal models have been consistent with basic laboratory data and are almost certain to operate in natural settings as well as in the laboratory.