



## The use of beta-lactamase inhibitors to reconquer resistance

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Beta-lactamases have been present since the early days of antimicrobial therapy and even before. Soon after the introduction of penicillin, *Staphylococcus aureus* strains that contained a beta-lactamase rapidly emerged and at present around 90% of strains are beta-lactamase positive and resistant to penicillin and amoxicillin. In Gram-negatives, various beta-lactamases have been found; some of these as a natural enzyme and strains or species are therefore naturally resistant, in others beta-lactamases have been discovered only recently. It is worrisome that the prevalence of strains with extended-spectrum beta-lactamases (ESBLs) is rapidly increasing, and that beta-lactamases that are able to destroy carbapenems are now frequently observed. In some countries the frequency of carbapenemase producing strains has reached alarming rates, in particular on intensive care units.

Two major strategies have been developed over the years to counter emergence of resistance due to beta-lactamases. The first was the design of antimicrobials that are resistant to specific beta-lactamases, and the development of several drug classes, and the use there-of in clinical practice, shows that this was successful. The second strategy to overcome resistance due to beta-lactamases is to inactivate them by inhibitors of beta-lactamases and by that let the parent compound return its activity. One of the major successes was the introduction of clavulanic acid added to amoxicillin and ticarcillin. Amoxicillin-clavulanic acid is still widely used and active against beta-lactamase producing methicillin susceptible staphylococci as well as *Haemophilus* spp, *Moraxella* spp and many others. Tazobactam as an addition to piperacillin is another widely used combination. Both clavulanic acid and tazobactam, as well as sulbactam, another beta-lactamase inhibitor, have been available for almost two decades or more and no new inhibitors were developed until recently. The advent of carbapenemases, ESBLs as well as the increase of resistance in general has lead to a resurgence of interest in these compounds, and a significant number of beta-lactamase inhibitors – beta lactams combinations are now in development, in particular directed at gram-negative microorganisms. In some of these combinations,

established and active beta-lactams are combined with a new inhibitor (for instance imipenem with MK7655, in development by Merck Inc. and ceftazidime with NXL-104, developed by Astra-Zeneca) or a new beta-lactam with an established inhibitor (CXA101 and tazobactam in development by Cubist) or two new compounds (ceftaroline with NXL-104, developed by Forest). There are a number of challenges in the clinical development of these combinations. The first is the dose that is needed to result in an exposure that overcomes activity of beta-lactamase in clinical use. This will depend on the pharmacokinetic and pharmacodynamic properties of the inhibitors. How to optimize the dosing regimens of these inhibitors however is still a matter of debate. The second challenge is how to measure the activity of the inhibitors in vitro. Virtually all inhibitors display a concentration effect - relationship that is maximized (i.e full inhibition) at relatively high concentrations, in many cases at concentrations that are not attainable in vivo. Yet, (slightly) less than full inhibition may suffice for sufficient activity in vivo to return enough activity to the parent compound to render the micro-organism susceptible. A relationship therefore has to be determined for beta-lactamase activity in vitro and in vivo, and the concentration of inhibitor that is used in measurements of the MICs that is predictive for activity in vivo. While it is now established that this needs to be performed using fixed concentrations of inhibitor it is less clear what the exact concentration should be. Finally, the use of inhibitors raises the question which clinical breakpoints to use for the combination. In principle, it seems logical and justified to use similar breakpoints as for the parent compound, since the efficacy of the parent compound has been established. The requirement for the inhibitor then is that the concentrations in the MIC determinations as well as the in vitro – in vivo relationship of the inhibitor in combination with the parent compound is clearly established. A final challenge here is that the dosing regimen of the parent compound in the new formulation may be different (for instance higher doses) and that would warrant other breakpoints for the combination. For each of the combinations mentioned and under study these issues should be carefully considered. The development of these new beta-lactamase inhibitor combinations will provide a significant addition to the current available antimicrobials.