Prospects for expanding the use of \(\beta\)-lactamase inhibitors

Since the introduction of antibiotics there has been a constant battle to develop new antimicrobial agents to combat increasing resistance to the older drugs. This has been particularly so for the \(\beta\)-lactam agents, which are among the most widely used antimicrobial agents worldwide. Resistance varies geographically but is generally much higher in the developing world. The most important mechanism by which bacteria become resistant to these agents is the production of \(\beta\)-lactamases which catalyse the hydrolysis of the \(\beta\)-lactam ring. Of the \(\beta\)-lactamases encountered in gram-negative bacilli the TEM-1 enzyme is probably the most important clinically; it can be present in up to 50% of *Escherichia coli* isolates and up to 85% of ampicillin-resistant *E. coli*.\(^{3,4}\) Recently the TEM-1 enzyme was detected in 42% of commensal *E. coli* isolates from the faeces of healthy volunteers in Scotland (Philippa Shanahan, personal communication).

Two strategies have been employed to overcome resistance mediated by \(\beta\)-lactamases. Firstly, the development of new \(\beta\)-lactam antibiotics which, as a result of modifications in structure, are not hydrolysed by most \(\beta\)-lactamases found amongst clinical isolates. Secondly, the use of \(\beta\)-lactamase inhibitors which when co-administered prevent inactivation by \(\beta\)-lactamases.\(^{3,4}\)

The first strategy has yielded successive generations of \(\beta\)-lactams, in particular the penicillilln-resistant penicillins and the cephalosporins. To overcome resistance in gram-negative bacilli, the \(\beta\)-lactamase-stable “second generation” and extended-spectrum “third generation” cephalosporins were developed.\(^8\) However, shortly after the introduction of these agents, plasmid-mediated resistance arose as a result of simple mutations of the already prevalent plasmid \(\beta\)-lactamases, especially TEM-1.\(^{4,6}\) More than 30 extended-spectrum \(\beta\)-lactamases have been identified worldwide although it is by no means certain that all are distinct.\(^6\) Reassuringly, even when these enzymes appear during treatment they rarely persist and they have not yet displaced TEM-1 as the most prevalent \(\beta\)-lactamase.\(^6\) There have been occasional reports of extended-spectrum \(\beta\)-lactamases, in particular TEM-3, appearing with high frequency but these have been local outbreaks probably related to spread of the host strain.\(^7\) Why these \(\beta\)-lactamases have not spread further is unclear but the mutation allowing hydrolysis of the extended-spectrum cephalosporins may render the enzymes less efficient against simple penicillins which remain the major selective pressure—a situation which may change with the recent introduction of oral preparations of extended-spectrum cephalosporins.

The problem of extended-spectrum \(\beta\)-lactamases has led to a renewed interest in \(\beta\)-lactamase inhibitors, particularly as all the TEM-derived and SHV-derived extended-spectrum \(\beta\)-lactamases identified to date are inhibited by clavulanic acid, sulbactam and tazobactam.\(^8,9\) There have been two recent reports of resistance to expanded-spectrum cephalosporins caused by plasmid-mediated \(\beta\)-lactamases that were not inhibited by clavulanic acid; these enzymes, designated BIL-1 and MIR-1, are not related to TEM but appear to be chromosomal \(\beta\)-lactamases which have migrated on to plasmids.\(^{10,11}\)

Despite widespread use within hospitals and in general practice, resistance to co-amoxiclav (amoxycillin plus clavulanic acid) remains low\(^{12}\) although there have been reports of resistance resulting from hyperproduction of the TEM-1 \(\beta\)-lactamase.\(^{13,14}\) The exact mechanism is unclear but several possibilities have been proposed, including plasmid rearrangement to give small multicyclic plasmids and gene duplication.\(^{13,14}\) It is not known whether such strains arose as a result of use of co-amoxiclav or already existed in the bacterial population before the introduction of inhibitor combinations.\(^{2,17}\) Although strains producing higher levels of TEM-1 require more clavulanic acid to potentiate amoxycillin, there has been no increase in the frequency of such strains in clinical isolates between 1982 and 1989.\(^8\)

It has been argued that mutation to clavulanic acid resistance in the TEM-1 \(\beta\)-lactamase would deprive the enzyme of its catalytic ability to hydrolyse \(\beta\)-lactam antibiotics. However, such enzymes have been selected *in vitro* and have recently been detected in clinical isolates.\(^{18-20}\) They have a lower PI than TEM-1 and require a higher concentration of clavulanic acid to inhibit their activity. The plasmid-encoded \(\beta\)-lactamase TRC-1, isolated from a clinical source, increases the MIC of co-amoxiclav for a standard *E. coli* recipient from 4 to 32 mg/L, but results in an MIC of amoxycillin alone of only 256 mg/L; the MIC of amoxycillin for TEM-1 producing strains is normally 1024 mg/L. Mutant forms of the TEM-1 \(\beta\)-lactamase selected *in vitro* with co-amoxiclav have the same PI as TRC-1 and a similarly raised resistance to inhibition by clavulanic acid; the MIC of amoxycillin for strains harbouring this enzyme are reduced from 1024 to 128 mg/L (Thomson and Amyes, unpublished results). It is unclear if such enzymes will have any significant clinical impact, but after ten years of use of...
inhibitor combinations they still appear to be rare. Furthermore, the increased resistance to clavulanic acid may not compensate for the reduced activity against amoxycillin.

The most commonly prescribed β-lactamase inhibitor has been clavulanic acid in combination with ticarcillin or amoxycillin. Sulbactam, a penicillanic acid sulphone, is now available in combination with ampicillin or, in some countries, with cefoperazone. The related sulphone, tazobactam, shows in-vitro activity comparable with that of clavulanic acid. If new β-lactamase inhibitors are developed, how will they be used? At present they are available only in fixed combination with β-lactam agents in the UK, but if the newer expanded-spectrum β-lactamases become a clinical problem, there may be a case for using them in combination with aminothiazole cephalosporins, or making them available as individual agents, leaving the final choice of antibiotic partner to the clinician, as currently occurs in some countries.

The use of β-lactamase inhibitors is an important strategy in the fight against resistance to β-lactam antibiotics. Increased use may lead to resistance, but the fact that the inhibitor binds to the active site of the β-lactamase suggests that β-lactamase-mediated resistance may be of lesser importance.

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References


