REVIEW

# Antibiotic policy and prescribing strategies for therapy of extended-spectrum β-lactamase-producing Enterobacteriaceae: the role of piperacillin–tazobactam

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## ABSTRACT

Therapy of infections caused by extended-spectrum β-lactamase (ESBL)-producing bacteria with an antimicrobial to which they are resistant results in treatment failure, higher cost and increased mortality. The CLSI recommends reporting ESBL-producing strains of *Escherichia coli*, *Klebsiella* spp. and *Proteus* spp. as resistant to all penicillin, true cephalosporin and monobactam antimicrobials, but as susceptible to β-lactam–β-lactamase inhibitor combinations, including piperacillin–tazobactam, when they test as such. Current literature supports the action of piperacillin–tazobactam against susceptible strains of ESBL-producing bacteria based on the structure–activity relationship between inhibitors and the ESBLs, as well as on recent clinical outcome studies.

**Keywords** β-Lactamase inhibitor, *Escherichia coli*, extended-spectrum β-lactamase, *Klebsiella* species, piperacillin–tazobactam, review

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## CURRENT POLICY FOR ESBL-PRODUCING ENTEROBACTERIACEAE

Since the beginning of the 21st century, there has been increasing concern over the optimal therapeutic approach for patients infected with ESBL-producing Enterobacteriaceae [1–5]. One early report, by Paterson *et al*. [1], described a prospective evaluation of ten patients with bacteraemia caused by ESBL-positive *Klebsiella pneumoniae*. Failure was defined as death at 14 days or bacteraemia persisting for ≥2 days under treatment. They found that four of seven patients whose infecting organism required an MIC <8 mg/L for the prescribed cephalosporin responded to therapy, whereas none of three improved when the MIC was 8–16 mg/L [1]. In a review of the literature, they found 26 additional cases of *K. pneumonia* bacteraemia in which the patients had been treated with a non-carbapenem β-lactam antibiotic, with ten of 25 responding when the MIC was <8 mg/L, while in the sole case with a reported MIC of 16 mg/L, therapy failed [1]. At nearly the same time, Lautenbach *et al.* [2] reported a case series of 33 patients with bacteraemia caused by ESBL-producing *K. pneumoniae* and *Escherichia coli* whom they matched with 66 controls. While there was no difference between the mortality of the case and the control patients, the case patients received effective therapy 60 h later than the control patients and stayed in hospital significantly longer, leading to an average hospital cost in excess of $44 000 [2]. These, along with the other subsequent observations [3–6], led to the CLSI recommendation to report ESBL-producing *E. coli* and *Klebsiella* spp. as resistant to all penicillin, true cephalosporin and monobactam antimicrobials, but as susceptible to β-lactam–β-lactamase inhibitor combinations provided that they tested as such in the laboratory [7]. However, there had been only modest experience with the β-lactam–β-lactamase inhibitor agents, and some experts recommend the use of a carbapenem antibiotic for *all* cases of serious infection because of ESBL-producing bacteria [1,4].

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## CLINICAL EXPERIENCE WITH β-LACTAM–β-LACTAMASE INHIBITOR COMBINATIONS

Reports that address the role of β-lactam–β-lactamase inhibitors in the treatment of infections with ESBL-producing bacteria have appeared. The first of these was from Tumbarello and co-workers [8]. They evaluated treatment outcome in 48 cases of infection caused by ESBL-producing bacteria, compared with 99 control cases. The rate of failure in the patients infected with ESBL producers was nearly twice that of the controls (31% vs. 17%), with a 21-day mortality rates of 52% and 29%, respectively [8]. Inadequate initial therapy (based on in-vitro susceptibility) was 50% for the patients infected with ESBL producers vs. 2% for those with infections caused by ESBL-non-producing *K. pneumoniae*. Inadequate treatment was seen for all 17 patients who received a cephalosporin, five of eight who received a fluoroquinolone, and two of eight who received a β-lactam–β-lactamase inhibitor combination [8]. Importantly, definitive therapy leading to a successful outcome was treatment with a carbapenem in 33% of the cases, an aminoglycoside in 22%, a fluoroquinolone in 17%, and a β-lactam–β-lactamase inhibitor combination in 28% [8]. This was the first large series of patients with ESBL-producing Enterobacteriaceae treated with β-lactam–β-lactamase inhibitor agents, and it demonstrated, when the in-vitro testing indicated susceptibility, that a successful outcome could be expected. A recent publication by Gavin *et al.* [9] revealed a similar outcome. They investigated the impact of the use of β-lactam–β-lactamase inhibitor agents on patients infected with ESBL-producing strains of *E. coli* and *Klebsiella* spp. from seven medical centres across North America. In total, 148 patient records were reviewed, with 30% of these patients receiving a fluoroquinolone, 18% a carbapenem, 16% piperacillin–tazobactam, 9% other β-lactams, 7% ampicillin–sulbactam, 6% aminoglycosides, and 6% trimethoprim–sulphamethoxazole [9]. Among these patients, 83% were given monotherapy. Twenty-three patients received piperacillin–tazobactam, and of these, 17 had infections involving sites outside the urinary tract [9]. For infections where the organism required an MIC of piperacillin–tazobactam of ≤16 mg/L (the current susceptibility breakpoint) a successful outcome was reported in 14 of 15 cases, including ten of 11 non-urinary tract infections. Only one of five non-urinary tract infections responded when the piperacillin–tazobactam MIC exceeded 16 mg/L. The authors also included the interesting observation that meropenem therapy was successful in only two of four piperacillin–tazobactam-resistant infections, demonstrating that even the carbapenems are not uniformly effective in the treatment of non-urinary tract infections caused by ESBL-producing bacteria [9]. The most recent series, described by Rodríguez-Baño *et al.* [10], analysed the outcome of 43 episodes of *E. coli* bacteraemia caused by ESBL-producing strains (primarily CTX-M-14). Mortality was lower when patients were given a β-lactam–β-lactamase inhibitor combination or carbapenem, as compared with either a cephalosporin or fluoroquinolone (9% vs. 35%, p 0.05). In this series, the *E. coli* susceptibility was 100% to meropenem, 95% to piperacillin–tazobactam, 26% to ciprofloxacin and 0% to the cephalosporins [10].

Many authors have reported ancillary or ecological supporting evidence for the activity of β-lactam–β-lactamase inhibitor combinations against ESBL-producing bacteria, i.e., use of these agents as a replacement for extended-spectrum cephalosporin drugs as part of a formulary strategy to lower the prevalence of ESBL-producing Gram-negative bacilli in healthcare settings [11–16]. The capacity to change antimicrobial agent prescribing habits to include the use of more β-lactam–β-lactamase inhibitor compounds that then lead to a significant reduction of infections due to ESBL-producing Gram-negative bacteria strongly suggests that these compounds have a useful antibacterial impact on this group of resistant bacteria.

## LABORATORY RATIONALE AS TO THE UTILITY OF β-LACTAM–β-LACTAMASE INHIBITOR COMPOUNDS

It is always useful when scientific reports support clinical observations concerning the action of antimicrobial compounds. Such evidence is available for the β-lactamase inhibitor drugs. The sulphone inhibitors, tazobactam and sulbactam, as well as clavulanate, are all small molecules compared with the larger extended-spectrum cephalosporins [17]. Thus, they are able to fit into

the binding pocket of both the typical β-lactamases and the ESBL enzymes, the latter having a structural rearrangement of amino-acid residues leading to an altered configuration of the binding pocket that is opened to accommodate the bulky side chain of third- and fourth-generation cephalosporin antibiotics [18]. Therefore, it is not surprising that the inhibitor compounds should have an impact on the traditional β-lactamases as well as the emerging ESBL enzymes; they are able to reach the binding pocket in β-lactamases of both groups. An expanded use of these inhibitor compounds against susceptible ESBL-producing bacteria would be a welcome addition to our dwindling antibiotic armentarium [19].

One additional, and little appreciated, action of the β-lactamase inhibitor agents is their effect on accessory penicillin-binding protein targets in both Gram-positive and Gram-negative bacteria. They have been shown to enhance cephalosporin action against non-β-lactamase-producing *Staphylococcus aureus*, as well as ampicillin action against *E. coli* and *Proteus* spp., through their capacity to bind secondary penicillin-binding proteins, which augments the bactericidal effect when combined with β-lactam drugs, even in penicillin- and ampicillin-sensitive strains [20,21].

## IMPLICATIONS FOR PATIENT CARE

We live in an era of increasing resistance to antimicrobial agents, with the emergence and global dissemination of new resistance phenotypes, such as ESBL-producing bacteria. Carpin *et al.* [22] have demonstrated that patients can acquire ESBL-producing bacteria from contact with healthcare personnel and then carry them for many years. Piperacillin–tazobactam has retained excellent activity against *E. coli* and *Klebsiella* species in general. Among strains recovered from patients in 25 intensive care units across North America, *c.* 95% of the *E. coli* and 90% of the *Klebsiella* spp. isolates were fully susceptible [23]. In a European collection of isolates from 14 centres, 93% of the *E. coli* isolates showed susceptibility. However, the *Klebsiella* isolates showed more resistance, with only 72% fully susceptible, demonstrating the need to know local susceptibility patterns as well as to have reliable laboratory testing readily available [24]. Increasing resistance within ESBL-producing Enterobacteriaceae is a concern that must be followed to permit clinicians to properly select initial therapy before patient-specific susceptibility results are reported. This is highlighted by the newest report from Sader *et al.* [25], who published their worldwide data on the susceptibility of proven ESBL producers. They found that for *E. coli* isolates with a confirmed ESBL phenotype recovered between 1998 and 2004, the susceptibility rate to piperacillin–tazobactam in North America was 83%, whereas in the remainder of the world it was 74% [25].

Laboratories must critically look for ESBL-producing pathogens, as indicated by a recent study by Gavin *et al.* [26], who found that the majority of physicians changed therapy after a report of an ESBL-producing pathogen from the laboratory; 40% altered the regimen to appropriate monotherapy; and another 23% substituted an active for the initially used inactive antibiotic. After the microbiology report was generated, 54% of the patients were treated with piperacillin–tazobactam, 20% with a carbapenem, and 11% with a fluoroquinolone.

## CONCLUSION

Appropriate therapy for infections caused by ESBL-producing Enterobacteriaceae is an increasing global problem. Current laboratory and clinical evidence indicates: (i) that practicing physicians understand the implications of these infections when they receive a report from the laboratory; (ii) that β-lactam–β-lactamase inhibitor compounds can be successfully used in the treatment of these infections when the causative pathogens test as susceptible in the laboratory and that current CLSI guidelines are appropriate for this group of antibiotics; and (iii) that piperacillin–tazobactam is clinically reliable for the treatment of serious infection caused by susceptible strains of ESBL-producing *E. coli* and *Klebsiella* spp.

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