Several antimicrobial agents are being investigated as alternatives to carbapenems in the treatment of infections caused by ESBL-producing Enterobacteriaceae, which may be useful in avoiding overuse of carbapenems in the context of recent global spread of carbapenem-resistant Enterobacteriaceae. The most promising candidates for invasive infections so far are β-lactam/β-lactamase inhibitor combinations and cephemycins.

Extended-spectrum-β-lactamase (ESBL)-producing members of the Enterobacteriaceae are frequent causes of community- and health care-associated infections (1); carbapenems are considered the drugs of choice for serious infections due to ESBL producers (2); the consumption of carbapenems is increasing dramatically (3); and carbapenemase-producing organisms are now widespread and rampant in many countries (4). While it is obvious that the spread of carbapenemases is a multifactorial phenomenon, a correlation between these facts looks like a rational hypothesis.

Therefore, finding alternatives to carbapenems for treatment of infections caused by ESBL-producing Enterobacteriaceae is an urgent medical need. Because ESBL producers are frequently also resistant to fluoroquinolones and trimethoprim-sulfamethoxazole, the options are scarce. While there are also some noncarbapenem β-lactam agents that retain activity against many ESBL-producing organisms, they were not investigated further for potential clinical use when carbapenem resistance was not a major problem for the medical community. They must be re-evaluated now.

ESBLs are inhibited by β-lactamase inhibitors, and therefore, a substantial proportion of ESBL producers are susceptible to amoxicillin-clavulanic acid (AMC) or piperacillin-tazobactam (PTZ), although with significant regional variations (5, 6). If we can rely on β-lactam/β-lactamase inhibitor combinations (BLBLIs) for treatment of infections caused by Enterobacteriaceae producing non-ESBL β-lactamases (such as TEM-1 and SHV-1), then why not also treat those caused by ESBL-producing Enterobacteriaceae with BLBLIs? The results from the biggest observational studies published so far are contradictory (6, 7), which may be partly due to differences in PTZ dosing (susceptible ESBL producers frequently show borderline MICs, so high doses of PTZ are probably needed). The preliminary results of the INCREMENT project, an international cohort study, favor the concept that BLBLIs are as effective as carbapenems (8). The results of the MERINO trial, which is comparing PTZ and meropenem as definitive therapy for ceftriaxone-resistant Escherichia coli and Klebsiella sp. bacteremic infections (9), are eagerly awaited.

In addition to BLBLIs, cephemycins, which include ceftoxitin, cefotetan, cefmetazole, moxalactam, and flomoxef, are stable against hydrolysis by ESBLs (2). However, because of some anecdotal failures with ceftoxitin related to induction of porin loss during therapy leading to resistance, cephemycins were largely proscribed from this indication (2). In this issue of Antimicrobial Agents and Chemotherapy, Matsumura et al. provide data from a retrospective multicenter cohort study in Japan comparing cefmetazole and flomoxef with carbapenems for the treatment of bacteremia due to ESBL-producing E. coli (10). After using a propensity score to control for confounding by indication, they could not find that treatment with cephemycins was associated with increased short-term mortality. Following the methods used in previous studies (5), appropriate specific criteria were used to include the patients in the treatment arms, and separate analyses were performed for empirical and definitive therapy. They also included an external group for comparison composed by bacteamic episodes caused by non-ESBL-producing E. coli treated with cephemycins. The authors are commended for conducting this study, which is by far the largest to date investigating the use of cephemycins for this indication. Unfortunately, the statistical power was still insufficient to definitively detect clinically relevant differences in mortality. Importantly, only E. coli episodes were studied, and hematologic or neutropenic patients were excluded from the adjusted analysis. Furthermore, cephemycins were used more frequently in urinary tract infections and in patients with lower acute severity of illness. The use of a propensity score likely helped in mitigating this imbalance but was probably not enough to control for the effects of all potential confounders, and interactions could not be investigated. Therefore, more studies are needed to assess whether cephemycins are as effective as carbapenems, particularly in patients with “high-risk” infections, such as pneumonia or nonbiliary intra-abdominal infections, or in patients with septic shock. Nevertheless, this is an important contribution, as it brings cephemycins back to the list of potential alternatives for treatment of infections due to ESBL producers.
Other potential treatment options include temocillin, a β-lactam which is stable to hydrolysis by ESBLs and AmpC β-lactamases but available in only a few countries. Available data from extended-spectrum β-lactamases (ESBL)-producing Enterobacteriaceae is stable to hydrolysis by ESBLs and AmpC β-lactamases (13). Whether these can be used in the treatment of serious infection is a subject of intense debate (14). Finally, many ESBL producers are susceptible to fosfomycin; however, an intravenous formulation, which is more appropriate for invasive infections, such as bacteremia, is available in only a few countries. The FOREST trial, now recruiting, will compare the efficacy of fosfomycin and meropenem or ceftriaxone in the definitive treatment of bacteremic urinary tract infections due to cephalosporin or fluoroquinolone-resistant E. coli (15).

In conclusion, there are several promising alternatives to carbapenems for the treatment of ESBL producers. While more high-quality observational studies and randomized trials are needed, the available data suggest that BLBLS and cephamycins are potential alternatives in some frequently encountered clinical scenarios, such as infections with ESBL-producing E. coli in the urinary and biliary tracts. On the other hand, carbapenems are still preferred for patients with severe sepsis or shock and pneumonia due to ESBL producers until more definitive data become available on this issue. However, the emerging evidence suggests that “infection due to ESBL producer” must no longer be followed by “therapy with a carbapenem” without some consideration of alternative approaches.

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