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CON: Carbapenems are NOT necessary for all infections caused by ceftriaxone-resistant Enterobacterales

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Carbapenems are considered the drugs of choice for the treatment of serious infections caused by ceftriaxone-resistant Enterobacterales. However, because of the dramatic increase in carbapenem-resistant organisms worldwide, finding alternatives to carbapenems is a must. The potential options include β-lactam/β-lactamase inhibitor combinations, temocillin, cephamycins and some non-β-lactam drugs. The most controversial is piperacillin/tazobactam; the results of the MERINO trial are challenged because the isolates of patients with worse outcomes were frequently not susceptible to piperacillin/tazobactam when studied by reference methods, and also because the drug was not administered in extended infusion. Other potential options are briefly discussed. We conclude that carbapenems are not necessary for all patients with infections caused by ceftriaxone-resistant Enterobacterales.

There is little doubt that carbapenems are the reference drugs for the treatment of invasive infections caused by ceftriaxone-resistant Enterobacterales. So, the first question to discuss is whether considering alternatives to carbapenems is needed at all. Let's review some facts: ceftriaxone-resistant Enterobacterales are frequent; carbapenem consumption has increased very significantly;[1] and carbapenem-resistance among Gram-negative bacteria is booming.[2] The extent to which the spread of carbapenem-resistant organisms is caused by the increase in carbapenem consumption is arguable, but there is little doubt that there is at least a partially causal effect. In fact, 'squeezing the balloon' in the use of antibiotics has long known to be a bad idea,[3] and this is probably what is happening with ceftriaxone-resistant Enterobacterales and carbapenems. So yes, we do think that alternatives to carbapenems for ceftriaxone-resistant Enterobacterales are needed.

A critical aspect to consider is which infection we are talking about. On one extreme, we may consider patients with septic shock and patients with difficult-to-treat infections such as ventilator-associated pneumonia or meningitis. In these infections, maximizing an early exposure to a fully active drug in the site of infection is critical. In the other extreme, we have patients with mild urinary or biliary tract infections, for which some antibiotics are expected to provide high concentrations at the source of infection, or infections without sepsis in which the source is readily removed. In the era of individualized medicine, treating all these patients equally is unjustified. For this reason, we have suggested that alternatives to carbapenems must be considered according to the features of the patient and the type of infection.[4]

The list of potential alternatives includes drugs which are active against some/most ceftriaxone-resistant Enterobacterales. These include some β-lactams (namely, old and new β-lactam/β-lactamase inhibitor combinations [BL/BLI], temocillin, cephamycins for ESBL producers and cefepime for AmpC producers) and non β-lactams (tigecycline, aminoglycosides, fosfomycin, trimethoprim/sulfamethoxazole and fluroquinolones). Whether any of these drugs can be used to treat some patients with ceftriaxone-resistant Enterobacterales infections is controversial, and this is the reason for this debate.

The controversy is particularly important for BL/BLI, mostly because of the results of the MERINO trial, which concluded that, among patients with *Escherichia coli* or *Klebsiella pneumoniae* bloodstream infection and ceftriaxone resistance, 'definitive treatment with piperacillin-tazobactam compared with meropenem did not result in a noninferior 30-day mortality. These findings do not support use of piperacillin-tazobactam in this setting.'[5] The MERINO trial is very important for many reasons. It is an investigator-driven, well-designed trial, which was transparently and appropriately reported. However, such a thing as perfect study that can be applied to all patients does not exist, and of course MERINO has some limitations.[6] It was an open-labelled trial; piperacillin/tazobactam was administered at 4.5 g/8 h in 30 min, while most data available today suggest that for MICs around 16 mg/L extended infusion is needed;[7] it was prematurely stopped, and the imbalance of groups for some variables might

not have been corrected in the analysis; and mortality was mostly unrelated to the infection but occurred mostly in patients with advanced cancer. Beyond that, the most important problem in MERINO is that a significant proportion of the isolates were found to be non-susceptible to piperacillin/tazobactam when using broth microdilution[8] despite having been classified as susceptible by the local laboratories, in which MIC strip tests were used.[5] In fact, when patients with isolates showing piperacillin/tazobactam MICs >16 mg/L or >8 mg/L by broth microdilution were excluded, the differences in mortality were reduced from 9% in the initial analysis (95% CI 3%–15%) to 5% (95% CI −1%–11%) and 4% (95% CI −2%–11%), respectively; Also, piperacillin/tazobactam MIC >16 mg/L was found to be independently associated with increased risk of mortality.[8] Why did it happen? Because isolates co-producing an ESBL and OXA-1 may show false susceptibility to piperacillin/tazobactam when studied by automatic methods[9] or strip-gradient tests.

The problem of false susceptibility to piperacillin/tazobactam when using the above methods is critical since it reinforces the efficacy of piperacillin/tazobactam for truly susceptible strains. It also explains the discrepancy between some observational studies and MERINO, as some of the former included a high proportion of infections caused by *E. coli* not co-producing OXA-1,[10,11] for which piperacillin/tazobactam MICs are around 2–4 mg/L. On the contrary, a biphasic distribution in MICs was shown in MERINO, with an important proportion of isolates showing MIC ≥8 mg/L,[8] which is the EUCAST breakpoint for resistance. However, if automated or MIC strip methods are unreliable, the problem is now transferred to the microbiologists. Research is being done to find accurate tests for piperacillin/tazobactam susceptibility that can be used in routine practice; meanwhile, ceftriaxone-resistant Enterobacterales isolates showing susceptibility to both amoxicillin/clavulanate and piperacillin/tazobactam (using EUCAST breakpoints) can be safely considered as not co-producing OXA-1.

Our conclusion is that piperacillin/tazobactam should be considered an alternative for bacteraemic infections caused by truly susceptible strains, particularly urinary tract infections (UTI) and in patients without severe sepsis or shock. We recommend using 4.5 g every 6–8 h in 3–4 h extended infusion. However, in the case of patients with pneumonia or septic shock, a carbapenem is recommended.

There are fewer data for other BL/BLI. Amoxicillin/clavulanate does not suffer from the inoculum effect[12] and is useful for cystitis caused by susceptible ESBL producers,[13] allowing avoidance of the use of IV carbapenems in these infections; however, the proportion of susceptible isolates is lower than for piperacillin/tazobactam. Available data suggest that ceftazidime/avibactam and ceftolozane/tazobactam, which are active against most ceftriaxone-resistant Enterobacterales, would have comparable efficacy to carbapenems,[14,15] but we suggest having them in reserve for carbapenemase producers or MDR *Pseudomonas aeruginosa*, respectively.

Some observational studies have compared the efficacy of cephamycins with carbapenems for ESBL producers (they are not active against AmpC producers):[16] their results are not consistent, and well-designed randomized trials are needed; they might be an option for mild cases of UTI. Temocillin is a very interesting drug as it is stable against ESBL and AmpC producers, and is not active against *P. aeruginosa*, making it attractive from the perspective of antibiotic stewardship. However, we could not find comparative studies published; the ASTARTÉ trial will compare temocillin and meropenem for bacteraemia infections due to ceftriaxone-resistant Enterobacterales (https://clinicaltrials.gov/ct2/show/NCT04478721). Cefepime is not a good substrate for AmpC enzymes and therefore is frequently active against isolates producing these β-lactamases; so far, available data from observational studies do not provide evidence to suggest that cefepime is inferior to carbapenems.[17] The FOREST trial compared fosfomycin with meropenem or ceftriaxone for MDR bacteraemic UTI caused by MDR *E. coli* infections; the definite results will be available soon. Anyhow, fosfomycin would not be a drug to consider in other types of infection. Tigecycline is active against many ceftriaxone-resistant Enterobacterales, but meta-analyses showed it was associated with worse outcomes than comparators, particularly in respiratory tract infections,[18] and is not recommended unless other alternatives are not available. Finally, not many ceftriaxone-resistant Enterobacterales are susceptible to fluoroquinolones or trimethoprim/sulfamethoxazole; if they are, we cannot see any reason for not using them with similar considerations as we do for other pathogens or infections, as is suggested by some observational studies.[19,20] In addition, they might provide the option of completing the treatment course orally.

The above considerations are mostly relevant for definitive therapy. However, empirical therapy is important from antibiotic stewardship purposes. The use of aminoglycosides, to which a significant proportion of ceftriaxone-resistant Enterobacterales isolates are susceptible, is a possibility. For example, in our area, most ESBL or AmpC producers are susceptible to amikacin. Aminoglycosides showed similar efficacy to comparators for UTI in a meta-analysis,[21] but toxicity is a concern. Therefore, in order to avoid the overuse of empirical carbapenems, administration of an aminoglycoside (alone or in combination with a lower spectrum β-lactam) might be an option in the empirical treatment of febrile UTI for patients at risk of ceftriaxone-resistant Enterobacterales. In fact, in an observational study of bacteraemic infections due to ESBL producers, we found similar adjusted outcomes in patients who empirically received an active aminoglycoside or a carbapenem,[19] and the administration of one dose of gentamicin in the emergency department has been shown to be safe.[22] After 1–2 doses, the microbiology results should always be reviewed in order to stop the aminoglycoside and avoid toxicity.

Overall, the above data support considering drugs other than carbapenem in selected patients with ceftriaxone-resistant Enterobacterales; the conditions to consider are summarized in Table 1. In all other situations, it seems prudent to use a carbapenem.

In summary, we think that overinterpreting MERINO results may cause an overuse of carbapenems, which will not help in controlling the dramatic increase of carbapenem-resistant organisms; we agree that patients with severe or difficult-to-treat ceftriaxone-resistant Enterobacterales infections should be treated with carbapenems. However, many others, if well selected, can be safely treated with other options. To do that, a careful clinical evaluation and a good microbiology support are needed.

Table 1. Considerations for the use of non-carbapenem drugs in infections caused by ceftriaxone-resistant Enterobacterales—all conditions must be fulfilled

Condition	Comments
The isolate is susceptible to a suitable drug	To be checked in all cases using appropriate methods. For piperacillin/tazobactam, OXA-1 production can be reasonably discarded if susceptible to amoxicillin/clavulanate.
Absence of septic shock or severe neutropenia	Data on patients with these conditions are scarce.
Low risk source of infection	Examples: urinary tract infection without obstruction or if obstruction is released; intraabdominal infection with appropriate surgical drainage; catheter-related bloodstream infection with catheter withdrawal. Evidence for the efficacy of each drug for the specific source of infection must be considered.
Appropriate dosing	For β-lactams, high doses are recommended; for piperacillin/tazobactam, 4.5 g every 6–8 h in extended infusion.

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Transparency declarations

None to declare.

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