The use of piperacillin-tazobactam to treat ESBL infections

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OBJECTIVE: To review literature that evaluates the use of piperacillin-tazobactam in treating infections caused by organisms that produce extended-spectrum beta-lactamases.

DATA SOURCES: PubMed was used to search for literature that addressed the use of piperacillin-tazobactam with ESBL-producing organisms. The terms piperacillin tazobactam and ESBL were used as search criteria. In addition, references cited within the articles obtained from the PubMed search were consulted.

CONCLUSIONS: Piperacillin-tazobactam may have a place in the treatment of infections caused by ESBL-producing organisms when the isolate has an MIC of ≤8 mg/L. It may be a reasonable carbapenem-sparing alternative once susceptibilities are known, but probably is not a safe empiric treatment option for serious infections where there is a suspicion for ESBL's.

KEYWORDS: piperacillin tazobactam, zosyn, ESBL

REQUEST

What data is there for the use of piperacillin-tazobactam in treating infections caused by ESBL-producing organisms?

RESPONSE

Background

Beta-lactamases are enzymes produced by bacteria that cleave the beta-lactam ring of beta-lactam antibiotics through hydrolysis, thus inactivating the antibiotic. A review article published in 2010 indicated there were close to 900 different types of beta-lactamases.[1]

The advent of third-generation cephalosporins in the early 1980's introduced antimicrobials that remained stable to the beta-lactamases known at the time.[2] However, bacteria were quick to develop beta lactamases that could cleave even these new "extended spectrum" 3rd generation cephalosporins. Bacteria did this through a single nucleotide mutation. The first incidence of this was reported in 1983, and others were discovered soon after.[2] These new types of beta-lactamases were termed "extended-spectrum beta lactamases" (ESBL's). There are now more than 400 different types of ESBL enzyme types that have been identified.[3]

ESBL's are most commonly produced by members of the *Enterobacteriaceae* family (*E. coli, Klebsiella, Proteus*, etc.). They can hydrolyze the following beta-lactam / monobactam antibiotics: penicillins; 1st, 2nd, and 3rd generation cephalosporins; and aztreonam. Beta lactamase inhibitors such as clavulanic acid can generally inhibit ESBL enzymes.[2]

Carbapenems are usually stable to ESBL's and have historically been the treatment of choice for infections caused by ESBL-producing organisms, although newer beta-lactamases that can hydrolyze carbapenems are emerging.[2] These beta-lactamases are referred to as carbapenamases. Carbapenem-sparing alternatives are needed because of these emerging resistance patterns.

In the United States, 8% of *E. coli* and 12% of *Klebsiella* strains produce ESBL's.[3] Carbapenems maintain low MICs to these organisms. However, there has been recent interest in whether beta-lactam/beta-lactamase inhibitor (BLBLI) combinations can be used as carbapenem-sparing alternatives due to their in vivo stability conferred by the beta-lactamase inhibitor component.

As mentioned, there are numerous types of ESBL enzymes that have been identified. The ESBL labeled CTX-M is becoming one of the most predominant.[3] Tazobactam is a potent CTX-M inhibitor, but sulbactam is not. Unfortunately, CTX-M is often co-expressed with OXA-1, another beta lactamase, which is resistant to inhibition by beta-lactamase inhibitors.[3] AmpC, yet another type of beta-lactamase generally produced by *Enterbacter chloaecae, Serratia* spp., and *Citrobacter* spp., is resistant to inhibition by tazobactam and other beta-lactamase inhibitors.[3]

The reasons why BLBLI's have been avoided in the past to treat ESBL infections are four-fold: 1) BLBLI MICs rise as bacterial innocula rise (to 10^7CFU for piperacillin-tazobactam); 2) the presence of concurrent mechanisms of resistance in these ESBL-producing bacteria to which the BLBLI would not be stable (porin loss in the bacterial cell membrane, AmpC enzyme production, and hyper-production of non-ESBL beta-lactamase enzymes; 3) higher doses than conventionally used may be required according to pharmacokinetic / pharmacodynamic studies; and 4) the paucity of published data.[2, 4]

MIC breakpoints for piperacillin-tazobactam as set by the Clinical and Laboratory Standards Institute (CLSI) are currently as follows for the piperacillin component: ≤16 mg/L (susceptible), 32-64 mg/L (intermediate), and >128 (resistant).[3] The tazobactam component has an MIC of 4mg/L for each category. ESBL-producing isolates with MICs in the 8-16 range are classified as "high susceptible" and may be associated with poorer outcomes when piperacillin-tazobactam is used.[3] Pharmacokinetic studies

ESBL, Extended Spectrum Beta Lactamase; BLBLI, beta lactam/beta lactamase inhibitor; CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial and Susceptibility Testing; ESBL-EC, ESBL-E. coli; ESBL-K, ESBL-Klebsiella spp.

have reported that piperacillin-tazobactam 3.375 g given as a prolonged infusion over 4 hours, dosed every 8hr, is needed for isolates having MICs ≤16 mg/L.[3]

Data Sources

A PubMed search was performed using the terms piperacillin tazobactam and ESBL. Both clinical trials and review articles were selected, the latter being used to provide background as well as additional clinical trials commonly referenced by multiple authors on this topic.

Clinical Trials

As pointed out in a review article, randomized controlled trials do not exist for this issue.[3] Post-hoc analyses, retrospective reviews, and meta analyses comprise the body of data that is currently available.

A review article published in 2014 looked at three surveillance databases that collected data from medical centers all across the world from 1998 to 2008. They found that for piperacillin-tazobactam, there was a 28-75% susceptibility rate for ESBL-producing isolates from the USA (compared to 94-100% for imipenem). They also noted that ESBL-E. coli was generally more susceptible to piperacillin-tazobactam than was ESBL-Klebsiella (62-75% vs 28-62% susceptibility, respectively).[3]

In a post-hoc analysis conducted by Rodriguez-Bano and colleagues published in *Clinical Infectious Diseases* in 2012, patients with ESBL-EC bacteremia were evaluated for mortality and length of hospital stay when treated with amoxicillin-clavulanate, piperacillin-tazobactam, or a carbapenem.[5] Patients were included in the analysis if they met the following inclusion criteria: had monomicrobial ESBL-EC bacteremia (confirmed by blood culture), met sepsis criteria, and received therapy with a BLBLI or carbapenem for ≥48 hrs. Two different cohorts were analyzed: 1) the empirical therapy cohort (ETC, n=103) were those patients who had received their first dose of drug (either amox-clav, n=37; pip-tazo, n=35; or carbapenem, n=31) within 24 hours after the blood culture was drawn and the isolate later proved to be susceptible to this empiric drug initially chosen for treatment; 2) the definitive therapy cohort (DTC, n=174) were those patients who received a drug susceptible to their isolate for at ≥50% of total duration of treatment (amox-clav, n=36; pip-tazo, n=18; or carbapenem, n=120). Patient data was analyzed out to day 30. The number of patients treated with a BLBLI in the ETC cohort was 72 (70%) and 54 (30%) in the DTC. CTX-M was the most common type of ESBL produced by the isolates.[5]

The following dosing regimens were received by the majority (>90%) of the patients (all IV): piperacillin-tazobactam 4500 mg q6h, amoxicillin-clavulanate 1200 mg q8h, imipenem 500 mg q6h, meropenem 1 g q8h, or ertapenem 1g q24h.

The two cohorts were analyzed separately. Mortality rates between BLBLI and carbapenem users were compared utilizing Kaplan-Meir curves and log-rank tests. Confounding was controlled using Cox regression multivariate analysis.[5]

In the ETC cohort, the hazard ratio for mortality associated with BLBLI use compared to carbapenem use was 1.14 (95% CI 0.29-4.40, p=0.84). The hazard ratio for increased length of hospital stay with BLBLI compared to carbapenem use was 1.07 (95% CI 0.35-3.02, p=0.9). Thus, neither mortality nor hospital stay appeared to differ when a BLBLI agent was used in the setting of ESBL-EC bacteremia compared to a carbapenem.

In the DTC cohort, the hazard ratio for increased length of hospital stay when a BLBLI was used compared to a carbapenem was 1.32 (95% CI 0.91-1.90, p=0.13). Here again, no statistically significant difference in mortality between BLBLI users and carbapenem users was shown.

The authors of this study concluded that if a BLBLI is susceptible in vitro to the ESBL-EC isolate from a bacteremic patient, it can be a reasonable alternative to a carbapenem, as no difference in mortality or length of hospital stay was shown between the two treatments.[5] They also add that the use of a BLBLI would be most appropriate once the susceptibility results are known, and would be a viable de-escalation treatment option after the patient is dosed empirically with a carbapenem. The authors point to susceptibility trends for this argument and that less favorable outcomes would be expected if the patient had a severe infection caused by ESBL-EC that was not susceptible to a BLBLI where treatment with a carbapenem was delayed.[5]

In a post-hoc analysis conducted by Retamar and colleagues, 39 patients with ESBL-EC bacteremia who had received empiric therapy with piperacillin-tazobactam were analyzed for the MIC of their isolates. Of note is that these patients were drawn from the same pool as the post-hoc study previously described by Rodriguez-Bano and colleagues, so the same inclusion criteria (monomicrobial , sepsis criteria, etc.) applied here. The primary endpoint was all-cause mortality at 30-days.[6]

The goal of the study was to determine a correlation between MICs of piperacillin-tazobactam and the outcome of patients presenting with bacteremia caused by ESBL-EC who began empiric therapy with piperacillin-tazobactam instead of a carbapenem.[6]

Isolates were classified according to their MICs with piperacillin-tazobactam: low MIC (≤ 2 mg/L; n=18

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isolates), intermediate MIC (4-8 mg/L; n=10 isolates), and high MIC (>8 mg/L; n=11 isolates). All-cause 30-day mortality was significantly higher for patients who had received empiric piperacillin-tazobactam and had a high MIC isolate than for patients who had low and intermediate MIC isolates (Relative Risk=0.21, 95% CI 0.06-0.75, p=0.01). Higher rates of mortality were also seen in the combined intermediate-high MIC group compared to the low MIC group (Relative Risk 0.13, 95% CI 0.01-0.98, p=0.002). In contrast, no patient with a low MIC isolate died. Their conclusion was that patients had better survival rates when their ESBL-EC isolate exhibited a low MIC to piperacillin-tazobactam.[6]

In a retrospective review of laboratory databases, Gavin and colleagues analyzed 23 patients treated with piperacillin-tazobactam (alone or in combination with other antimicrobials) that had ESBL-producing isolates.[7] MICs for the isolates of these 23 patients ranged from <0.5 to >128 mg/L.[7] Piperacillin-tazobactam treatment was successful in 91% of patients with an ESBL-organism when the MIC was ≤16m but the success rate dropped to 20% when MICs reached >16 (p = 0.027).[6] This suggests that infections caused by ESBL-producing bacteria could be successfully treated with piperacillin-tazobactam, provided that the MIC of the isolate to pip-tazo is no more than 16 mg/L.

Evidence Comparison

The post-hoc analysis conducted by Rodriguez-Bano and colleagues had the largest number of patients (n=103 and n=174). The post-hoc analysis performed by Retamar and colleagues was much smaller (n=39) and the retrospective review by Gavin and colleagues even smaller still (n=23). The Rodriguez-Bano study group went into the most amount of detail about how they attempted to control for potential confounders; the other articles did not report this information.

The studies by both Retamar and Gavin had similar sample sizes and reported similar information about how MIC relates to success rates of piperacillin-tazobactam use in ESBL infections.

The only article that provided information about dosing was the Rodriguez-Bano trial. No article provided information about whether the BLBLI was given as extended infusion, which administration technique was suggested in the review by Nguyen and colleagues as proven to provide a better kill than intermittent dosing.[3]

Although post-hoc analyses are inherently weak due to confounders that cannot always be controlled, the Rodriguez-Bano study did attempt to control for a number of them.

One of the weaknesses of the Rodriguez-Bano trial was that it did not breakdown hazard ratios for piperacillin-tazobactam by itself; it was just grouped together with amoxicillin-clavulanate as BLBLI's. Of note is that amoxicillin-clavulanate is not available as IV in the United States, the dosage form that was utilized in this study. Since IV dosing is almost always required in the setting of serious infections such as bacteremia, this may limit the external validity for patients in the United States. Also of note is that the application of the results of this study would be limited to only ESBL-EC bacteremia because they did not look at other types of infections that could be caused by ESBL's.

Weaknesses of the Retamar and Gavin studies were the small number of patients and limited information provided in the articles about how potential confounders were controlled. Gavin's study indicated that patients were identified based on treatment with piperacillin-tazobactam, alone or in combination with other antimicrobials, but never specified or analyzed which other antimicrobials these were. This is definitely a potential confounder and limits how much we can extrapolate this data to other patients.

DISCUSSION

None of the trials currently available are randomized controlled trials, which limits the confidence one can place in the conclusions. It is also acknowledged that two of the trials cited (Rodriguez-Bano and Retamar) obtained data from the same patient population, which should be kept in mind when extrapolating their data to other patient populations.

The fact that piperacillin-tazobactam was statistically similar to carbapenems with respect to mortality and length of hospital stay, even when most of the ESBL isolates were of the CTX-M type, is worth noting. Recall that Nguyen and colleagues pointed out that in their review that CTX-M is often co-expressed with OXA-1, the latter being resistant to beta lactamase inhibitors. This may be promising information in favor of piperacillin-tazobactam use.

Piperacillin-tazobactam may be a safe option for treating ESBL's with lower MICs, as suggested in the studies by Retamar and Gavin, thus sparing the carbapenems for higher MICs where piperacillin-tazobactam had worse outcomes. Using piperacillin-tazobactam for ESBL's with lower MICs and carbapenems for higher MICs could be a more responsible way to use carbapenems because it would save them for when it is really necessary.

The conclusions of the studies cited seem to be in support of one another. Piperacillin-tazobactam may be a good alternative to carbapenems to treat ESBL infections, but

only when susceptibilities are known. It is probably not a safe *empiric* option due to poorer outcomes associated with higher MICs of ESBLs to piperacillin-tazobactam, information that would only be known after a susceptibility test is performed.

CONCLUSION

The study by Rodriguez-Bano showed that piperacillin-tazobactam was similar to carbapenems with respect to mortality and length of hospital stay. The Retamar study demonstrated how piperacillin-tazobactam had worse survival rates when ESBL isolates have an MIC above 8, and possibly above 4 mg/L, but that MICs of 2 or lower have safe outcomes (zero mortality in their patient population). Gavin and colleagues showed how piperacillin-tazobactam had much higher success rates when MIC stayed below 16 mg/L.

Although more studies are needed to validate these findings, the conclusions seem to be consistent with one another. Piperacillin-tazobactam may be a useful alternative to treating ESBL infections, once susceptibilities are known, and provided that the MIC is definitely below 16, or possibly even below 8 or 4 mg/L. Piperacillin-tazobactam should not be used empirically to treat bacteremia where ESBL is suspected, as an increase in mortality is suggested. Carbapenems should be used empirically and also when MICs for piperacillin-tazobactam are higher than 16 mg/L.

ESBL, Extended Spectrum Beta Lactamase; BLBLI, beta lactam/beta lactamase inhibitor; CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial and Susceptibility Testing; ESBL-EC, ESBL-E. coli; ESBL-K, ESBL-Klebsiella spp.

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