Diminished Susceptibility to Cefoperazone/Subbactam and Piperacillin/Tazobactam in *Enterobacteriaceae* Due to Narrow-Spectrum β-Lactamases as Well as Omp Mutation

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**A b s t r a c t**

Cefoperazone/subbactam (CSL) and piperacillin/tazobactam (TZP) are commonly used in clinical practice in China because of their excellent antimicrobial activity. CSL and TZP-nonsusceptible *Enterobacteriaceae* are typically resistant to extended-spectrum cephalosporins such as ceftriaxone (CRO). However, 11 nonrepetitive *Enterobacteriaceae* strains, which were resistant to CSL and TZP yet susceptible to CRO, were collected from January to December 2020. Antibiotic susceptibility tests and whole-genome sequencing were conducted to elucidate the mechanism for this rare phenotype. Antibiotic susceptibility tests showed that all isolates were amoxicillin/clavulanic acid-resistant and sensitive to ceftazidime, cefepime, cefepime/tazobactam, cefepime/zidebactam, cefotaxime/avibactam, and cefolozane/tazobactam. Whole-genome sequencing revealed three of seven *Klebsiella pneumoniae* strains harbored *bla*<sub>SHV-1</sub> only, and four harbored *bla*<sub>SHV-1</sub> and *bla*<sub>TEM-1B</sub>. Two *Escherichia coli* strains carried *bla*<sub>TEM-1B</sub> only, while two *Klebsiella oxytoca* isolates harbored *bla*<sub>OXY-1-3</sub> and *bla*<sub>OXY-1-1</sub>, respectively. No mutation in the β-lactamase gene and promoter sequence was found. Outer membrane protein (Omp) gene detection revealed that numerous missense mutations of OmpK36 and OmpK37 were found in all strains of *K. pneumoniae*. Numerous missense mutations of OmpK36 and OmpK35 and OmpK37 deficiency were found in one *K. oxytoca* strain, and no OmpK gene was found in the other. No Omp mutations were found in *E. coli* isolates. These results indicated that narrow spectrum β-lactamases, TEM-1, SHV-1, and OXY-1, alone or in combination with Omp mutation, contributed to the resistance to CSL and TZP in CRO-susceptible *Enterobacteriaceae*.

**Key words:** cefoperazone/subbactam, piperacillin/tazobactam, TEM, SHV, OXY

**Introduction**

*Enterobacteriaceae*, such as *Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca*, are responsible for approximately 30% of healthcare-associated infections (Stewart et al. 2021). The antibiotics cefoperazone/subbactam (CSL) and piperacillin/tazobactam (TZP) have broad activity spectra against Gram-positive, Gram-negative, and anaerobic organisms. In China, CSL and TZP are widely used in daily clinical practice (Chen et al. 2021). However, a decreasing rate of susceptibility to CSL and TZP among *Enterobacteriaceae* threatens their continued use. Enzymes such as carbapenemases, AmpC β-lactamase, and some
extended-spectrum β-lactamases (ESBLs) (Stewart et al. 2021), are the leading cause of CSL and TZP-resistant Enterobacteriaceae isolates. Many of these enzymes also hydrolyze third-generation cephalosporins and most CSL and TZP-nonsusceptible Enterobacteriaceae are also resistant to ceftiazidime (CRO). We recently encountered Enterobacteriaceae isolates that were CSL and TZP-resistant (R), but CRO-susceptible (S). Here, antibiotic susceptibility tests and the whole genome-sequencing technique were applied to explore their resistance mechanisms.

**Experimental**

**Materials and Methods**

**Bacterial isolates.** This retrospective study was conducted from January to December 2020 in the Department of Laboratory Medicine, Yantai Yuhuangding Hospital of Shandong Province, a 3,000-bed tertiary teaching hospital located in east China. Enterobacteriaceae strains resistant to CSL and TZP but sensitive to CRO were collected in routine clinical practice. All isolates intentionally collected for this study were cultured in blood agar in a 35°C incubator for 16–24 hours and then stored in skim milk in a deep freezer at –80°C until use. Duplicate isolates collected from the same patient within three months were excluded. The patients’ medical records were retrospectively reviewed, and information on clinical characteristics, including age, sex, and source of infection, was collected. Approval and verbal informed consent were obtained for experimentation with human subjects due to the study’s retrospective nature. The study protocol, including the verbally informed consent procedure, was approved by the Yantai Yuhuangding Hospital Ethics Committee.

**Identification and antibiotic susceptibility tests.** All isolates were initially identified with the VITEK®2 GN card (bioMérieux, France). Then, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (Bruker Daltonics, Germany) was used to confirm the identification. All procedures were performed following the manufacturer’s instructions. According to the Clinical Laboratory Standards Institute (CLSI) guidelines, the minimum inhibitory concentrations (MICs) of TZP (4–128 µg/ml) and ceftazidime (CAZ, 1–64 µg/ml) were determined by VITEK®2 AST-GN09 card (bioMérieux, France). CSL resistance was tested by the disk diffusion method on Mueller-Hinton agar (105 µg, Oxoid, UK) and then confirmed by the broth microdilution method (1–128 µg/ml, Thermo Fisher Scientific, USA). The MICs of CRO (0.5–32 µg/ml), cefepime (FEP, 0.06–128 µg/ml), amoxicillin/clavulanic acid (AMC, 0.06–128 µg/ml), cef-

**Results**

**Identification and clinical characteristics.** According to the inclusion criteria, 11 nonrepetitive strains were enrolled, including seven cases of *K. pneumoniae*, two cases of *E. coli*, and two cases of *K. oxytoca*. Among the 11 strains, five were isolated from sputum, three from urine, and one from bile, pus and blood, respectively. Fifty-five percent (6/11) of the isolates were obtained from an intensive care unit, 18% (2/11) from a teaching hospital, and 38% (4/11) from an intensive care unit. Among the 11 strains, five were isolated from sputum, three from urine, and one from bile, pus and blood, respectively. Fifty-five percent (6/11) of the isolates were obtained from an intensive care unit, 18% (2/11) from a teaching hospital, and 38% (4/11) from an intensive care unit.
a neurosurgery ward, and 9% (1/11) from a stoma-
tological ward, vascular surgery ward, and hepato-
biliary ward, respectively. The age of the patients
ranged from 41 to 91-years-old, with an average of
67.64 ± 15.27-years-old, of which 45% (5/11) were male
and 55% (6/11) were female.

**Antibiotic susceptibility tests.** The results of anti-
biotic susceptibility tests are shown in Table I. In addi-
tion to CRO, CSL, and TZP as inclusion criteria, the
antibacterial activities of CAZ, FEP, and currently avail-
able β-lactam/β-lactamase inhibitors (BL/BLIs), includ-
ing AMC, FPT, FPZ, CZA, and CZT were also assayed.
As shown in Table I, all isolates were susceptible to
CRO, CAZ, and FEP, and MIC90 were 1, 4, and 2 µg/ml,
respectively. All strains were resistant to AMC, CSL,
and TZP with the MIC90 ≥ 128, ≥ 128, and ≥ 256 µg/ml,
respectively. Moreover, these strains showed sensitivity
to FPT, FPZ, CZA, and CZT, and the MIC90 were 2,
0.25, 1, and 2 µg/ml, respectively.

**Genome sequencing.** The results of gene sequenc-
ing are listed in Table II. No dominant ST was found.
ST45 accounted for 42.8% (n = 3) of *K. pneumoniae*
followed by ST2358, ST2854, and ST189. The seven
strains of the three *K. pneumoniae* strains harbored *
bla*<sub>SHV-1</sub> while four carried *
bla*<sub>SHV-1</sub> and *
bla*<sub>TEM-1B</sub>. All strains of *E. coli* had the *
bla*<sub>TEM-1B</sub> gene. One *K. oxytoca* isolate
harbored *
bla*<sub>OXY-1-3</sub>, and the other harbored *
bla*<sub>OXY-1-1</sub>. No mutation in the β-lactamase gene and promoter

| Antibiotics | Breakpoints | Klebsiella pneumoniae | Escherichia coli | Klebsiella oxytoca |
|-------------|-------------|-----------------------|------------------|-------------------|
|             | (µg/ml)     | E1 | E3 | E4 | E7 | E9 | E10 | E11 | E6 | E8 | E2 | E5 |
| CRO         | ≤ 1 ≥ 4     | ≤ 0.5 | ≤ 0.5 | ≤ 0.5 | 1 | ≤ 0.5 | 1 | ≤ 0.5 | 1 | ≤ 0.5 | 1 | 1 | 1 |
| CAZ         | ≤ 2 ≥ 16    | 1 | 2 | 1 | 4 | 4 | 4 | 4 | 2 | 4 | 1 | 1 |
| FEP         | ≤ 2 ≥ 16    | 1 | 1 | 0.25 | 1 | 2 | 2 | 2 | 0.5 | 2 | 1 | 1 |
| AMC         | ≤ 8 ≥ 32    | ≥ 128 | ≥ 128 | ≥ 128 | ≥ 128 | ≥ 128 | ≥ 128 | ≥ 128 | ≥ 128 | ≥ 128 | ≥ 128 | ≥ 128 |
| CSL         | ≤ 16 ≥ 64   | 64 | 64 | 64 | 64 | ≥ 128 | 128 | ≥ 128 | 64 | 128 | 128 | ≥ 128 |
| TZP         | ≤ 16 ≥ 12   | ≥ 256 | ≥ 256 | ≥ 256 | ≥ 256 | ≥ 256 | ≥ 256 | ≥ 256 | ≥ 256 | ≥ 256 | ≥ 256 | ≥ 256 |
| FPT         | ≤ 2 ≥ 16    | 1 | 0.5 | 0.06 | 0.125 | 0.25 | 0.25 | 0.25 | 0.25 | 0.25 | 0.125 | 0.25 |
| FPZ         | ≤ 2 ≥ 16    | 0.25 | 0.25 | 0.06 | 0.125 | 0.25 | 0.25 | 0.25 | 0.25 | 0.25 | 0.125 | 0.125 |
| CZA         | ≤ 8 ≥ 16    | 1 | 0.5 | 0.25 | 0.25 | 0.25 | 0.25 | 0.25 | 0.25 | 0.25 | 0.5 | 0.5 |
| CZT         | ≤ 2 ≤ 8     | 2 | 1 | 0.5 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |

| Number | Accession | Strain | ST | β-Lactamase gene | Promoter sequence mutation | Omp mutation |
|--------|-----------|--------|----|------------------|-----------------------------|--------------|
| E1     | JAKQY10000000000 | Kpn | 45 | bla<sub>SHV-1</sub>, bla<sub>TEM-1B</sub> | none | OmpK36, OmpK37 |
| E3     | JAKOEX00000000000 | Kpn | 45 | bla<sub>SHV-1</sub>, bla<sub>TEM-1B</sub> | none | OmpK36, OmpK37 |
| E4     | JAKOEY00000000000 | Kpn | 2854 | bla<sub>SHV-1</sub> | none | OmpK36, OmpK37 |
| E7     | JAKOGA00000000000 | Kpn | 2358 | bla<sub>SHV-1</sub>, bla<sub>TEM-1B</sub> | none | OmpK36, OmpK37 |
| E9     | JAKOGC00000000000 | Kpn | 2358 | bla<sub>SHV-1</sub>, bla<sub>TEM-1B</sub> | none | OmpK36, OmpK37 |
| E10    | JAKOGD00000000000 | Kpn | 189 | bla<sub>SHV-1</sub> | none | OmpK36, OmpK37 |
| E11    | JAKOPO00000000000 | Kpn | 45 | bla<sub>SHV-1</sub> | none | OmpK36, OmpK37 |
| E6     | JAKOEZ00000000000 | Eco | 88 | bla<sub>TEM-1B</sub> | none | none |
| E8     | JAKOGB00000000000 | Eco | 409 | bla<sub>TEM-1B</sub> | none | none |
| E2     | JAKPCO00000000000 | Kox | 194 | bla<sub>OXY-1-3</sub> | none | OmpK36 mutations, OmpK35 and OmpK37 deficiency |
| E5     | JAKPCD00000000000 | Kox | 11 | bla<sub>OXY-1-1</sub> | none | no OmpK (OmpK35, OmpK36 and OmpK37) gene found |

Kpn – Klebsiella pneumoniae, Eco – Escherichia coli, Kox – Klebsiella oxytoca
sequence was found. None of the isolates possessed an ESBL enzyme, AmpC β-lactamase, or carbapenemase. Numerous missense mutations of OmpK36 and OmpK37 were found in all strains of K. pneumoniae, while no OmpK35 mutation was found. Numerous missense mutations of OmpK36 and OmpK35 and OmpK37 genes deficiency were found in one K. oxytoca strain, and no OmpK gene was found in the other. No Omp (OmpC or OmpF) point mutation was found in E. coli isolates.

Discussion

In recent years, the global research on β-lactamases has been focused mainly on ESBLs, AmpC β-lactamase, and carbapenemase, while some narrow-spectrum β-lactamases have been ignored. It has resulted in clinical treatment failures. In this study, none of these isolates harbored an ESBL, AmpC β-lactamase, or carbapenemase. There have been few published analyses of Enterobacteriaceae displaying a CSL-R/TZP-R/CRO-S resistance phenotype. It is increasingly urgent to understand the CSL/TZP-resistance due to the emergence of a CSL/TZP-resistant but 3rd generation cephalosporin-susceptible Enterobacteriaceae phenotype, as well as the increasing reliance on CSL and TZP as empirical treatments in daily clinical practice in China.

TEM-1, SHV-1, and OXY-1 β-lactamases are narrow-spectrum β-lactamases, which belong to group 2be in the Bush-Jacoby classification scheme (Paterson and Bonomo 2005; Kashefieh et al. 2021; Rehman et al. 2021). Enterobacteriaceae with TEM-1, SHV-1, or OXY-1 β-lactamase are usually susceptible to CSL and TZP. However, Enterobacteriaceae strains resistant to CSL and TZP yet susceptible to CRO were observed in this study. It is reported that the gene mutation-induced single amino acid substitutions at Ambler positions Met69, Ser130, Arg244, Arg275, and Asp276 in TEM and SHV β-lactamases may result in enzymes with reduced affinity for β-lactamase inhibitors (Ramdani-Bouguessa et al. 2011; Winkler et al. 2015). Another possible mechanism is that resistance to BL/BLIs may result from gene amplification, and subsequent hyperproduction of β-lactamase (Sun et al. 2013; Noguchi et al. 2019; Zhou et al. 2019; Hubbard et al. 2020). Mutations in the promoters have been shown to be responsible for bla_{OXY-1} and bla_{SHV-1} amplification (Fournier et al. 1999; Han et al. 2020). Moreover, a strong promoter, such as the Pa/Pb promoter or IS26-mediated excision and repeated insertion can also lead to the TEM-1 hyperproduction (Noguchi et al. 2019; Hubbard et al. 2020). Exposure to BL/BLIs such as TZP has been shown to induce the excision and repeated insertion of bla_{TEM-1}, increase the bla_{TEM-1} copy number and then lead to the TEM-1 hyperproduction (Schechter et al. 2018). No mutation in the β-lactamase gene and promoter sequence was found in this study. It is speculated that the possible mechanism of resistance to CSL and TZP is the gene amplification caused by gene excision and repeated insertion. The emergence of multiple β-lactamase gene copies in genome sequence and the wide application of CSL and TZP in China support this hypothesis.

Omp is necessary for drug transport across cell membranes. A deficiency of Omp has been shown to contribute to the increase in the MIC for Enterobacteriaceae (Aihara et al. 2021). The current research on Omp focuses mainly on carbapenem-resistant Enterobacteriaceae (Tian et al. 2020), and few studies on Enterobacteriaceae with bla_{TEM-1}, bla_{SHV-1}, or bla_{OXY-1} appear to have examined the prevalence of the Omp deficiency. OmpK is expressed in Klebsiella, and OmpK35 defects are common in isolates carrying genes encoding ESBL, while defects in OmpK36 may be more critical for carbapenem resistance (Martinez-Martinez 2008). The importance of the minor porin, OmpK37, is less clear. Except for one strain with the OmpK gene deficiency, numerous missense mutations in the porin genes OmpK36 and OmpK37 were found in almost all Klebsiella strains in our study. It may lead to non-functional porins and be associated with CSL and TZP resistance. OmpF and OmpC constitute the main Omps in E. coli (Bafna et al. 2020). No Omp mutation suggests that Omp is unnecessary for resistance against CSL and TZP in E. coli.

Another finding was that, although this collection of Enterobacteriaceae was resistant to AMC, CSL, or TZP, the newer BL/BLI combinations, FPT, FPZ, CZA, and CZT, were much more active. Previous studies have confirmed that the newer BL/BLI combinations exhibit excellent antibacterial activity against Enterobacteriaceae, consistent with this study (Joshi et al. 2021; Kuo et al. 2021). In addition, simultaneous analysis of the MICs of FEP, FPT, and FPZ delineated tazobactam as a distinctly less active inhibitor than zidebactam against strains producing TEM-1, SHV-1, and OXY-1 β-lactamases. It may be attributed to the dual activity against strains producing TEM-1, SHV-1, and OXY-1 β-lactamases that were previously thought to be adequately inhibited by sulbactam and tazobactam. The high frequency of bla_{TEM-1}, bla_{SHV-1}, and bla_{OXY-1} in the CSL and TZP-resistant isolates supported the notion that bla_{TEM-1}, bla_{SHV-1}, and bla_{OXY-1} alone or in combination with Omp mutations, were important contributors.
to CSL and TZP resistance. However, some limitations existed in this study. We sequenced the whole genome of the collected strains, but we did not determine the activities of β-lactamases and the Omp expression. The transferability of β-lactamase genes was not confirmed. Other characteristics, such as efflux pumps or the permeation of CSL and TZP, were not evaluated. Thus, much more work is needed to clarify the resistance mechanisms of CSL/TZP-R but CRO-S Enterobacteriaceae.

Conclusion

In China, the CSL/TZP-R but CRO-S phenotype of Enterobacteriaceae is prevalent and threatens the optimal use of CSL and TZP. TEM-1, SHV-1, and OXY-1, the most common β-lactamases, alone or in combination with Omp mutations, contribute to the resistance of CSL and TZP. Continuous monitoring and investigation of CSL/TZP-R but CRO-S isolates are needed in the current era of high CSL and TZP administration.

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Conflict of interest

The authors do not report any financial or personal connections with other persons or organizations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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