Abstract

Ceftolozane-tazobactam is approved for the treatment of patients with complicated skin and skin structure infections and community-acquired pneumonia caused by designated susceptible bacteria (1, 2). Ceftazidime (CPT), the active metabolite of ceftolozane-tazobactam, is a cephalosporin possessing in vitro activity against Gram-positive bacteria and common Gram-negative pathogens excluding those producing serine- and metallo-β-lactamases. A small number (7.5%) of Gram-negative bacteria excluding those producing serine- and metallo-β-lactamases, are resistant to CPT (2). An understanding of CPT resistance mechanisms is critical for future development of cephalosporins containing CPT.


ESBL (n): SHV-2 (1); CTX-M-2 (2); CTX-M-63 (1); CTX-M-65 (1); TEM-52 + CTX-M-14 (1).

OSBL (n): TEM-OSBL (1).

ESBL + OSBL (n): SHV-2 + TEM-OSBL (1); CTX-M-3 (5), CTX-M-9 (1), CTX-M-14 (9) + SHV-OSBL, original-spectrum β-lactamase; ESBL, extended-spectrum β-lactamase; No β-lactamase identified, no plasmid-encoded β-lactamase was identified in 27.2% (57) of the isolates – 150 medical centers in Europe (EUR), Asia-Pacific (AP), Latin America (LA), and Middle East-Africa (MEA). Susceptibility testing was performed using CLSI broth microdilution in all regions (Table 1).

Results

• Isolates with CAZ MIC ≤1 mg/L and CPT MIC >0.5 mg/L (ESBL screen-negative and CPT non-susceptible) comprised 7.5% of isolates collected globally in 2013 and were detected in all regions (Table 1).

• Production of plasmid-encoded β-lactamases was most likely responsible for ceftaroline resistance in 72.6% (150) of isolates characterized to contain 98.0–99.4% of E. coli (Fig. 1), 98.3% of K. pneumoniae (Fig. 3), 100% of P. mirabilis (Fig. 2), and 10.0% of K. oxytoca (Fig. 4).

• Identified β-lactamases included ESβLs, serine carbapenemases, and metallo-β-lactamases that are known to hydrolyze ceftazidime, as well as AmpC β-lactamases and OSβLs that confer ceftazidime resistance when hyper-produced (7, 8). The CPT-M enzymes identified possess higher activity against ceftaroline than ceftazidime in this study. Similarly, the majority of these enzymes are reported to possess higher activity against ceftazolin than ceftazidime (9).

• No plasmid-encoded β-lactamase was identified in 27.2% (57) of the isolates. The stability of ceftaroline to form a complex with E. coli was more likely to account for ceftaroline resistance in 51 and 7 isolates, respectively (Fig. 2). The CAZ screen-negative isolates (Ceftaroline Non-Susceptible) comprised 2.2% of the isolates (9173), which comprised 150 medical centers in Europe (EUR), Asia-Pacific (AP), Latin America (LA), and Middle East-Africa (MEA).

Materials & Methods

• Non-duplicate clinical strains and isolates, from respiratory tract, intra-abdominal, and urinary tract infections were collected from 150 medical centers in Europe (EUR), Asia-Pacific (AP), Latin America (LA), and Middle East-Africa (MEA).

• Susceptibility testing was performed using CLSI broth microdilution in all regions (Table 1).

• 217 randomly selected isolates inhibited by ≤1 mg/L of ceftazidime (CAZ) and ceftaroline (CPT) were screened for β-lactamase genes encoding ESβLs (SHV, TEM, CTX-M, VEB, PER, GES), cephalosporinases (KPC, OXA-48, IMP, VIM, NDM, SPM), and plasmid-encoded AmpC β-lactamases (ACC, ACP, ACT, CMY, FOX, DHA, MOX) by multiplex polymerase chain reaction (PCR) (8).

• Detected genes were sequenced and enzyme variants were identified based on comparison to the NCBI database (www.ncbi.nlm.nih.gov) and the LabNet Clinic website (www.labsnet.org.Unsupported).

• Expression levels of chromosomally-encoded ESβLs and AmpC β-lactamases were determined by real-time PCR.

Conclusions

• The ceftazidime screen-negative indicator (CAZ MIC ≤1 mg/L) alone cannot be used to call isolates ESβL-negative.

• The stability of ceftolozane-tazobactam and ceftaroline to hydrolysis by assorted plasmid- and chromosomally-encoded β-lactamases is different. For this reason, ceftaroline cannot be used as a surrogate marker for ceftazidime.

• Additional resistance mechanisms may be at play in isolates that produce only original spectrum β-lactamases, e.g. changes in efflux or porin production that reduce susceptibility to ceftazidime.