

TITLE: EVALUATION OF THE *IN VITRO* SUSCEPTIBILITY OF β -LACTAM-RESISTANT GRAM-NEGATIVE BACILLI TO CEFTOLOZANE-TAZOBACTAM

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ABSTRACT:

Healthcare-Associated Infections (HAIs) caused by multidrug-resistant microorganisms are associated with high morbidity and mortality rates and higher hospital costs. The spread of carbapenemases and extended-spectrum β -lactamase (ESBL)-producing Gram-negative bacilli (GNB) represents a global public health threat by limiting therapeutic options in hospitalized patients. Ceftolozane-tazobactam (C/T) is a combination of a fifth-generation cephalosporin and a known β -lactamase inhibitor approved for the treatment of hospital-acquired and mechanical ventilation-associated bacterial pneumonia. This study aimed to evaluate the *in vitro* susceptibility of β -lactam-resistant GNB to C/T and to investigate the molecular determinants of resistance. One hundred and one clinical isolates of Enterobacterales and *Pseudomonas aeruginosa* collected in a general hospital in Southern Brazil were analyzed. The antimicrobial susceptibility was evaluated by an automated method and the minimum inhibitory concentrations of C/T were determined by the Etest[®]. The β -lactamase-encoding genes were investigated by the polymerase chain reaction. High susceptibility to C/T was observed among ESBL-producing Enterobacterales (97.3% - CLSI or 83.8% - BRCAS) and carbapenem-resistant *P. aeruginosa* (87.2%). However, carbapenemase-producing *Klebsiella pneumoniae* (KPC) exhibited high resistance to C/T (80% - CLSI or 100% - BRCAS). C/T was inactive against metallo- β -lactamase-producing *K. pneumoniae* isolates and carbapenem-resistant CESP-group (*Citrobacter freundii*, *Enterobacter* spp., *Serratia* spp., *Providencia* spp., *Morganella morganii* and *Hafnia alvei*). The *bla*_{CTX-M}, *bla*_{SHV} and *bla*_{KPC} genes were the most frequent genes in C/T-resistant isolates. Most C/T resistant isolates concomitantly carried two or more β -lactamase-encoding genes (77.4%). C/T is a therapeutic option against microorganisms with β -lactam resistance phenotypes, except when resistance is mediated by metallo- β -lactamases.

Keywords: Gram-negative bacilli, ceftolozane-tazobactam, *in vitro* activity, genetic marker

Development Agency: Foundation for Research and Innovation Support of the State of Santa Catarina (FAPESC) and the Research Support Fund of the University of the Region of Joinville (FAP/Univille).