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P2498 Bactericidal and synergistic activity of ceftobiprole combined with different antibiotics against selected Gram-positive isolates

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Background: Ceftobiprole is an advanced cephalosporin that binds to multiple penicillin-binding proteins (PBPs) including PBP2a, approved in the EU for the treatment of hospital-acquired and community-acquired pneumonia sustained by Gram-positive and Gram-negative pathogens. We investigated the *in vitro* susceptibility of ceftobiprole and its synergistic activity in combination with other antimicrobials against selected Gram-positive pathogens belonging to different antibiotic-resistance classes.

Materials/methods: 46 clinical Gram-positive isolates collected from a recent Italian survey were analysed for their antibiotic susceptibility and synergy testing by gradient-cross method. The combination analysed were: ceftobiprole *plus* daptomycin, levofloxacin, linezolid, rifampicin and piperacillin/tazobactam. Time-kill curves were performed to assess bactericidal activity and quantify the degree of synergy for seven representative isolates: 4 *Staphylococcus aureus* (MSSA, MRSA/VSSA, MRSA/hVISA, MRSA with PBP2a mutation); 1 *S. epidermidis* MDR-linezolid-resistant (LNZ-R); 1 VRE *Enterococcus faecium* β-lactamase producer and 1 VRE E. *faecalis*.

Results: Ceftobiprole $MIC_{50/90}$ for *Staphylococcus aureus* isolates were 0.5/2 mg/L; 0.75/2 mg/L for CoNS; 2/≥32 mg/L for *E. faecalis*, and ≥32/≥32 mg/L for *E. faecium*. There was good agreement between gradient test and broth microdilution methods. Daptomycin, linezolid and piperacillin-tazobactam represented the most efficient combinations (50-54% synergistic and additivity effect). Most of the synergistic interactions were observed for MSSA, *S. epidermidis* and LNZ-R staphylococci. *E. faecium* showed indifference in almost all combinations, while *E. faecalis* showed largely synergistic effect in combination with linezolid, rifampicin and piperacillin-tazobactam.

Time-kill curve analysis demonstrated the potent ceftobiprole bactericidal activity, higher than that of the comparator drugs. Ceftobiprole *plus* daptomycin represented the most potent combination, with synergy against all isolates at the MIC concentration and enhanced killing at concentrations 2 and 4 times above the MIC. Ceftobiprole *plus* linezolid was synergistic against four isolates belonging to different species (MRSA/VSSA, *S. epidermidis*-LNZ-R, *E. faecium; E. faecalis*). Against enterococci, the association with levofloxacin was synergistic at the MIC concentration. Ceftobiprole *plus* piperacillin-tazobactam, and rifampicin produced less reliable activity.

Conclusions: Ceftobiprole exhibited a potent *in vitro* antibacterial activity and synergism with daptomycin against all Gram-positive isolates, despite their MDR phenotypes. The use of ceftobiprole

in combination may provide a promising alternative therapy for the treatment of Gram-positive infections.