Effect of Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for Patients with E coli or Klebsiella pneumoniae Bloodstream Infection and Ceftriaxone Resistance

BACKGROUND:

- Gram-negative bacteria that produce extended spectrum b-lactamases (ESBL) are causing issues globally due to resistance to oxyiminocephalosporins, in addition to penicillins
- ESBL producers accounted for at least 26,000 infections and 1,700 deaths annually
- Carbapenems are the standard of treatment in these serious infections with extended spectrum b-lactamase producers but with increased use there is increased resistance to carbapenems.
- Observational studies have suggested that β-Lactam/β-lactamase inhibitor (BLBLI) may be clinically effective for treating infections caused by ESBL producers, but conflicting results have been reported

HYPOTHESIS

- Piperacillin/tazobactam (a carbapenem-sparing regimen) is non-inferior to meropenem (a widely used carbapenem) for the definitive treatment of bloodstream infections due to third-generation cephalosporin non-susceptible *E. coli* or *Klebsiella* spp.

METHODS

- **Type of study design:** International, multicenter, open-label, parallel, randomized controlled experimental, noninferiority clinical trial
- **Study duration**: Minimum of 4 calendar days after randomization and up to 14 days
- **Inclusion criteria**: Bloodstream infection with *E. coli* or *Klebsiella* spp,; non-susceptible to 3rd generation cephalosporins and susceptible to meropenem and piperacillin-tazobactam from at least one blood culture draw**;** ≥ 21 years old, (non-pregnant in females); no more than 72 hours elapsed since the first positive blood culture collection
- **Exclusion criteria**: Life expectancy <4 days; patient allergy to either medication; significant polymicrobial bacteraemia; use of concomitant antimicrobials in the first 4 days after enrolment with known activity against Gram-negative bacilli; treatment is not with the intent to cure the infection
- **Patient Screening**: 1646 screened for eligibility
    - 391 randomized: 196 to piperacillin/tazobactam, 195 to meropenem
    - Primary analysis: 187 to piperacillin-tazobactam; 191 to meropenem
    - Per-protocol analysis: 170 to piperacillin/tazobactam, 186 to meropenem
- **Primary Outcom**e: All-cause mortality at 30 days after randomization: noninferiority established if upper bound of the 1-sided 97.5% CI did not cross the margin of 5%
- **Secondary Outcome(s)**: 1) time to clinical and microbiologic resolution of infection; (2) clinical and microbiologic success at day 4; (3) microbiologic resolution of infection; (4) relapsed bloodstream infection; (5) secondary infection with a meropenem- or piperacillin/tazobactam–resistant organism or *Clostridium difficile* infection
- **Data handling method**: Modified intent to treat and per-protocol
- **Power**: 454 patients were needed in total to achieve 80% power with a 1-sided α level of .025, allowing for 10% dropout

RESULTS

- **Primary outcome for all-cause mortality at 30 days**
    - **Primary analysis**: 23 of 187 (12.3%) in the piperacillin-tazobactam group vs. 7 of 191 (3.7%) in the meropenem group
        - Risk difference, 8.6% [1-sided 97.5% CI, −∞ to 14.5%]; P = .90 for noninferiority)
    - **Per-protocol analysis**: 18 of 170 (10.6%) in the piperacillin-tazobactam group vs. 7 of 186 (3.8%) in the meropenem group
        - risk difference, 6.8% [one-sided 97.5% CI, −∞ to 12.8%]; *P* = .76 for noninferiority
- **Secondary outcomes**

    - Clinical and microbiological resolution by day 4
        - 121 of 177 patients (68.4%) in the piperacillin-tazobactam group compared with 138 of 185 (74.6%) with meropenem (risk difference, −6.2% [95% CI, −15.5 to 3.1%]; *P* = .19)
    - Median day of resolution of signs of infection after randomization
        - 3 (interquartile range [IQR], 1,5) in the piperacillin-tazobactam group, and 2 (IQR, 1,5) in the meropenem group, but this difference was not significant (*P* = .18)
    - Microbiological resolution by day 4 or rates of microbiological relapse
        - 9 of 187 (4.8%) in piperacillin-tazobactam group compared with 4 of 191 (2.1%) in meropenem group (risk difference, 2.7% [95% CI, −1.1 to 7.1%]
    - Secondary infection with another multiresistant organism, or *C difficile*
        - 15 of 187 (8%) in piperacillin-tazobactam group compared with 8 of 191 (4.2%) in meropenem group (risk difference, 3.8% [95% CI, −1.1 to 7.1%]
- **Adverse effects**
    - Nonfatal serious adverse events occurred in 5 of 188 patients (2.7%) in the piperacillin-tazobactam group compared with 3 of 191 (1.6%) in the meropenem group
- **Author's conclusions**
    - Among patients with E coli or K pneumoniae bloodstream infection and ceftriaxone resistance, definitive treatment with piperacillin-tazobactam compared with meropenem did not result in noninferior 30-day mortality. These findings do not support use of piperacillin-tazobactam in this setting.

STRENGTHS

- Active control is treatment of choice
- Randomization stratified to comparable treatment groups
- Appropriate treatment dosing
- Individual sub categories and analysis completed and shown
- Conclusion consistent with results
- Reasonable noninferiority margin choses (5%)

LIMITATIONS

- Sample size not sufficient for power of 80%
- No data on compliance outside of hospital treatment
- Empirical therapy not in control of study team, could lead to complication in analysis
- Step down therapy after day 5 allowed for treatment to be switched
- Only two patients from North America, limits extrapolation to United States
- Unblinded → potential bias and early cessation of piperacillin-tazobactam if physician perceived clinical failure.

CONCLUSIONS

- Piperacillin-tazobactam did not result in noninferiority compared with meropenem when looking a all-cause mortality at 30 days.
    - The evidence and results were unable to show noninferiorty in primary or any secondary outcomes
- Piperacillin-tazobactam has many uses in therapy of infections, but in the case of E coli or K pneumoniae infections with extended spectrum b-lactamase producers, it should not be the treatment of choice.
- Further research needs to be conducted to determine alternative methods of treatment to spare the use of carbapenems and avoid resistance.

Harris PNA, Tambyah PA, Lye DC, et al. Effect of Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for Patients with E coli or Klebsiella pneumoniae Bloodstream Infection and Ceftriaxone Resistance. JAMA. 2018 Sep 11;320(10):984-994.

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September 2018