Randomized controlled trial of piperacillin-tazobactam, cefepime and ertapenem for the treatment of urinary tract infection caused by extended-spectrum beta-lactamase-producing *Escherichia coli*.

Background:

- ESBLs have seen an increase in hospitals and LTCFs, and the limited number of therapeutic options that cover them make the rise a public health concern.
- While carbapenems are considered the drug of choice for treating ESBLs, current alternatives include ß-lactamase/ß-lactamase inhibitors, cefepime, and aminoglycosides.
- Carbapenem-resistant organisms are emerging, but recent studies bring to question the efficacy of agents like PTZ and cefepime against ESBLs.

Objective:

- To determine the efficacy of PTZ and cefepime against ertapenem for the treatment of UTI caused by ESBL-producing E.coli.

Methods:

- Randomized, prospective, open-label, per-protocol, multicenter
- Hospitalized adult patients with fever due to healthcare-associated UTI from ESBL-producing E.coli
    - Inclusion: HA-UTI defined by the CDC/NHSN recommendations
    - Exclusion: suspicious/confirmed infectious foci other than HA-UTI, antibiotic use within 7 days for any reason, complicating urinary factors not effectively treatable during the trial (obstruction, prostatitis, epididymitis), indwelling urinary catheter expected to remain after completion of therapy, need for RRT
- 72 patients enrolled for 10-14 days of PTZ, ertapenem, and cefepime
    - After 6 patients, cefepime recruitment terminated due to high treatment failure (with no baseline differences)
        - PTZ 4.5g Q6° (CLcr >40mL/min), 2.25g Q6° (CLcr 20-40mL/min), 8g Q8° (CLcr <20mL/min)
        - Cefepime 2g Q12° (CLcr >60mL/min), 2g Q24° (CLcr 30-60mL/min), 1g Q24° (CLcr <30mL/min)
        - Ertapenem 1g Q24° (CLcr >30mL/min), 500mg QD (CLcr ≤30mL/min)
- Primary Outcomes:
    - Clinical Efficacy – resolution of fever and presenting UTI symptoms with no new symptom developed
    - Microbiological Efficacy – elimination of ESBL-E.coli on a urine culture on day 10-14
- Secondary Outcomes:
    - 28-day mortality, E.coli new resistance to study antibiotics, relapse, reinfection

Results:

- 66 patients completed the study
- Results:
    - Clinical Success
        - PTZ 93.9% (31/33) vs. Ertapenem 97% (32/33), P = 0.5
        - PTZ and Ertapenem vs. Cefepime 33.3% (2/6), P < 0.001
    - Microbiological Success

        - PTZ 97% (32/33) vs. Ertapenem 97% (32/33) vs. Cefepime 33.3% (2/6)
    - 28-Day Mortality
        - PTZ and Ertapenem 6.1% (2/33) vs. Cefepime 33% (2/6), P = 0.108
    - No new E.coli resistance, relapse, or reinfection
- PTZ has similar efficacy to ertapenem in the treatment of UTI caused by ESBL-E.coli when the in-vitro test indicates susceptibility. Cefepime should not be used as an alternative treatment for UTI caused by ESBL-E.coli.

Strengths:

- First randomized study comparing the efficacy of PTZ, cefepime, and ertapenem
- Provided new insight for conflicting data regarding ß-Lactam/ß-Lactamase inhibitors vs. carbapenems

Limitations:

- Treatment failure may be closely related to baseline conditions irrespective of MICs, but lack of significant differences in groups makes evaluation of the role of these conditions difficult
- Small sample size with associated low power
- Results cannot be generalized to other MDR pathogens or even other ESBL pathogens outside of ESBL-producing E.coli
- The assumption that carbapenems are the drug of choice in UTIs, even those caused by ESBLs, might have been inappropriate
- Unfortunately, they did not analyze the results based on gender and, given the assumed nature of male UTIs, this made it difficult to determine if treatment failures (particularly in the cefepime group) were entirely due to the drug or if other factors like gender played a larger role

Conclusions:

- Piperacillin-tazobactam could be considered as an alternative to ertapenem for treatment of a suspected ESBL-E.coli UTI, but caution should be used due to the specific nature of the efficacy data surrounding its utility.
- Should carbapenemase activity be high in a given hospital or ESBL-producing E.coli presence be particularly great, PZT is a viable option to treat patients. Cultures should still be obtained and sensitivities followed.

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