Utility of Cefoxitin for the Treatment of ESBL-producing *E. Coli* Urinary Tract Infections

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Background

- The incidence of ESBL Enterobacteriaceae (ESBL-E) identified in bacterial cultures in the United States has increased by 53% from 2012 to 2017, in large part due to increased community-acquired infections (1). ESBL E. coli and other enterobacteriaceaes usually remain susceptible to Carbapenems. However, carbapenem overutilization stimulates various resistance pathways including outer membrane protein (OMP) mutations and the selection of β-lactamases capable of hydrolyzing carbapenems (2). Unpublished data by the primary author suggests that it is not well known that ESBL's do not inactivate non-beta lactam agents. Therefore, carbapenems are viewed as the drug of choice for ESBL-E, regardless of the clinical scenario.
- Cephamycins demonstrate consistent in vitro activity against ESBL-producing Enterobacteriaceae isolates, distinguishing them from AmpC cephalosporinases (3). In an excellent review, Tamma et al also posit favorable scenarios where noncarbapenem beta-lactams could be considered in the treatment of ESBL-E, including if noncarbapenem beta-lactam minimum inhibitory concentrations are low and if extended infusion noncarbapenem beta lactams are administered (4).
- Cephamycins such as Cefoxitin and Cefotetan are widely available and have been utilized widely for decades, but there is a paucity of data evaluating cephamycins for treatment of ESBL-E infections. Only 5 studies exist, and many are single-center experiences; additionally, none of these studies occurred in the United States. However, available data do suggest that cephamycins may be an alternative to carbapenems for some non-severe infections, particularly UTIs, and should be administrated at high dose and continuous infusion (5)

Research Objective

Primary Outcomes

- Negative Urine Culture (Ucx) or Urine Analysis (UA)

Secondary Outcomes

- Absence of fever: T < 38 degree 2 days after beginning of study treatment
- Resolution of clinical signs: abscess of flank pain, dysuria, gross hematuria, and abdominal pain
- Readmission within 30 days

Methods

Prospective observational study:

- **Inclusion criteria**
  - ≥ 18 years of age
  - ESBL E. coli in Urine culture that is susceptible to Cefoxitin (MIC ≤ 8)
  - Hemodynamically stable.
- **Exclusion criteria**
  - Pregnancy
  - Bacteremia
  - Hemodynamically unstable
  - Immunocompromised
  - Cephalosporin allergy
  - Urine culture with multiple bacteria other than ESBL E. coli
- **Treatment plan**: Patients were started on empiric therapy per the physician's discretion. If urine cultures demonstrated ESBL E. coli sensitive to Cefoxitin, physicians were contacted to change therapy to Cefoxitin 2gm q 6hr extended infusion (renally adjusted if needed) x 7 days, and obtain a repeat Ucx/ UA in 2-3 days to check for microbial clearance. Monitoring of symptoms was also performed

Results

Patient Selection and Demographic

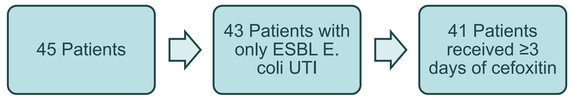

Figure 1: Patient Selection Process

Demographic:
Total patients: 41
Median Age: 79 (19-101)
Gender: 12 M / 29 F
Admitting Diagnosis: UTI (26); non UTI (17)
Mean Creatinine Clearance: 32 ±43
Median Length of Stay: 10 (5-30)

Table 1: Patients demographic and baseline characteristics

Treatment Course

- **Mean Empiric therapy**: 2.7 days ± 0.8 days
- **Empiric Antibiotic Covered ESBL**: 12 patients (29%)
- **Average Cefoxitin MIC**: 4.5 ± 1.4
- **Average daily dose**: 6.4 gm ± 2.1 gm
- **Average duration of therapy**: 5.5 days +/- 1.6 days

Primary Outcomes

Primary Outcomes
Negative UA/Ucx: 27
Positive UA/Ucx: 4
UA/Ucx not collected: 10

Table 2: Results of Repeated UA/ Ucx

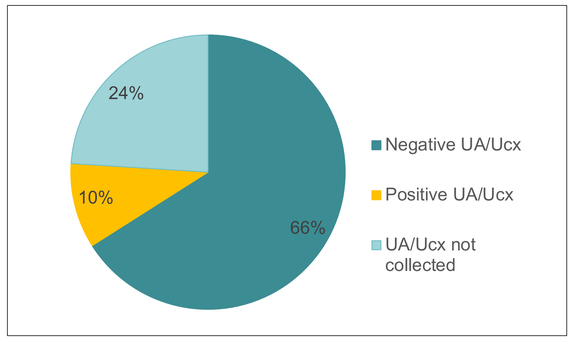

Figure 2: Results of Repeated UA/Ucx

Secondary Outcomes

- **All patients were afebrile 48 hours post treatment**
- **10 Patients did not have a repeat UA/Ucx, as all symptoms resolved**
- **2 patients with persistent symptoms**
- 1 discharged on Ertapenem, 1 changed to Meropenem
- **5 patients readmitted within 30 days**
  - 3 due to NON –UTI diagnoses
  - 1 due to recurrent UTI requiring cystoscopy with urethral dilation, and 1 with obstructed stone requiring stent placement
- **4 patients with positive repeated Urine culture/ Urine Analysis**
  - 1 with reduced bacterial load from 100,000 to 30,000 colonies
  - 1 presented to outpatient clinic for dysuria 2 weeks later and repeated urine culture there grew ESBL E.coli 100,000 colonies
  - 1 went on comfort care
  - 1 with multiple recurrent ESBL E.coli due to obstructed stone

Conclusions

- Cefoxitin is a useful agent for the treatment of ESBL E.coli urinary tract infections. The optimal dose appears to be 2 g intravenously every 6 hours, via extended infusion, in patients with normal creatinine clearance. Further larger studies, involving patients with pyelonephritis, are needed to validate the findings

Clinical Impact

- Strategies to reduce the use of carbapenems are urgently needed
- This study adds to the body of evidence that Cephamycins can be used as a carbapenem-sparing agent for specific patients with ESBL producing E. coli

Limitations

- Prospective cohort observational study with no control group
- Small sample size
- Limited to non bacteremic patients with ESBL E. coli only

References

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