Oral fosfomycin therapy for chronic bacterial prostatitis

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BACKGROUND

Chronic bacterial prostatitis (CBP)
- High rates of recurrence[1-2]
- May increase risk of prostate-related complications[1-2]

Treatment of CBP
- Can be difficult since few antibiotics penetrate the prostate well[3-6]
- Antibiotic options often further limited in certain patients (Figure 1)
- Need for additional antibiotic options

Fosfomycin
- FDA-indicated and guideline-recommended for treatment of acute uncomplicated cystitis in women
- Unique mechanism limits cross-resistance[7]
- Effective against resistant organisms such as ESBL–producing GNRs, VRE, and MRSA[7]

Fosfomycin for CBP
- Very limited literature & focused primarily on outpatients
- Previous studies show good prostate penetration and efficacy for CBP
- Only 2 prior trials with N = 44 and N = 15
- Emerging area of interest; most studies published in past 5 years

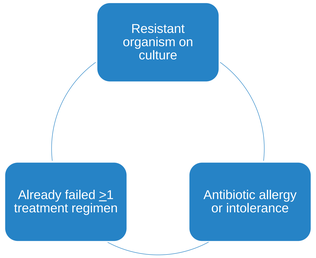

Figure 1. Antibiotic options for CBP are further limited in many patients

METHODS

- Retrospective, single-center, single-group
- Patients were followed for 6 months from completion of fosfomycin therapy

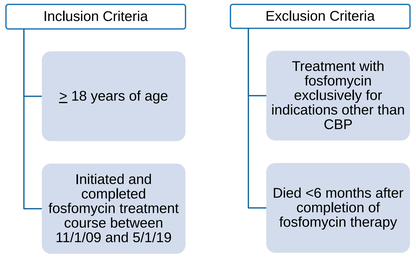

Figure 2. Study inclusion and exclusion criteria

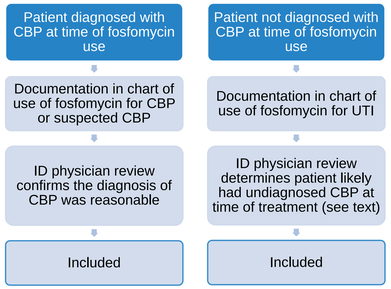

Figure 3. Process for retrospective determination of whether patient was receiving fosfomycin for CBP

- A board-certified infectious diseases physician reviewed all episodes 1. diagnosed with CBP at the time of therapy to confirm the diagnosis was reasonable, and 2. diagnosed with UTI but not CBP at the time of therapy to determine if the UTI may have been undiagnosed CBP (Figure 3)
- At least 2/3 of the following had to be met to apply a retrospective diagnosis of CBP to UTI patients:
  1. History of recurrent urinary tract infection (UTI) without other clear cause
  2. Imaging concerning for prostatitis
  3. Signs and symptoms of CBP such as lower urinary tract symptoms (LUTS), concerning prostate exam, elevated prostate-specific antigen (PSA), and elevated C-reactive protein)

Outcomes
- **Clinical cure:** Lack of repeat presentation with signs and symptoms of CBP at 6 months. Included all episodes
- **Microbiological cure:** Urine cultures that failed to grow the original pathogen between completion of therapy and 6 months later. Excluded episodes without follow up data. Urinalysis results could be substituted when culture data was unavailable, but no included episodes without follow-up cultures had urinalyses
- **Medication-related adverse effects:** All adverse events (AEs) reported to fosfomycin. Patients with multiple episodes were included as single data points and counted as experiencing an AE if one was documented during any of their treatment courses

Post hoc analyses
- **Long vs. short course of therapy:** All patients received either ≥ 28 days or ≤ 14 days of fosfomycin, so we additionally examined if outcomes differed between these two groups. Note that CBP usually requires long courses of therapy
- **Composite of clinical and microbiological cure:** It was difficult to assess clinical cure in patients with LUTS at baseline and microbiological cure in patients chronically colonized by an organism. As CBP patients are often plagued with recurrent UTIs, achievement of either result may be considered meaningful. Included all episodes

Data analysis
- Descriptive statistics

RESULTS

N = 28 episodes (21 unique patients)

Susceptibility testing
- All treated specimens had a fosfomycin susceptibility test documenting susceptibility prior to treatment
- 5 patients (4 short course group / 1 long course group) had follow-up urine cultures growing the same pathogen where fosfomycin susceptibility testing was completed, and all remained susceptible

Table 1. Selected baseline characteristics

Characteristic	Median (range), or number (rate)
Age	70 (42-87)
Race	27 white (96%)
CrCl	61.1 (8.3 - >120)
Initial setting	19 (68%) outpatient
Prior occurrences	
Number of prior occurrences	1 (0-5)
Previously treated with antibiotics	25 (89%)
Most common antibiotics for prior occurrences	
Fluoroquinolones	10 (40%)
Cephalosporins	7 (28%)
Carbapenems	7 (28%)
Fosfomycin	7 (28%)
Penicillins	6 (24%)
Trimethoprim-sulfamethoxazole	4 (16%)
Nitrofurantoin	4 (16%)
When diagnosed	
Diagnosed at the time	14 (50%)
Diagnosed retrospectively	14 (50%)
Pathogen characteristics	
E. coli	22 (76%)
Klebsiella spp.	3 (10%)
Enterococcus spp.	2 (7%)
Pseudomonas spp.	1 (3%)
Serratia spp.	1 (3%)
MDR	25 (86%)
Fosfomycin MIC	1.0 (0.4-64.0)
Length of treatment with fosfomycin	
Long course ≥ 28 days	11 (39%)
Median days of treatment	40 (28-150)
Short course ≤ 14 days	17 (61%)
Median days of treatment	8 (3-14)

Table 2. Fosfomycin dosing regimen used to treat CBP

Fosfomycin dosing regimen	All episodes	Long course	Short course
3g q24h	5 (18%)	1 (9%)	4 (18%)
3g q48h	20 (71%)	8 (73%)	12 (75%)
3g three times weekly	1 (4%)	1 (9%)	0 (0 %)
3g q72h	2 (7%)	1 (9%)	1 (6%)

Table 3. Number of episodes included in each outcome group

Outcome	All episodes	Long course	Short course
Clinical cure & efficacy composite	28	11	17
Microbiological cure	26	9	17
Adverse effects	21	10	11

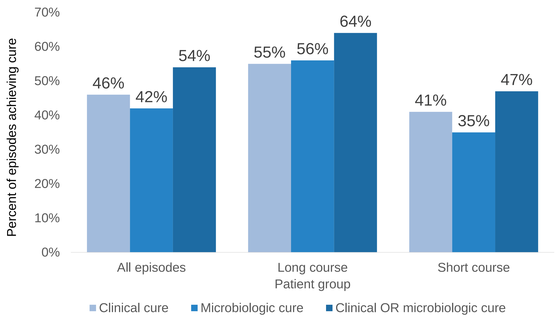

Figure 4. Cure rates

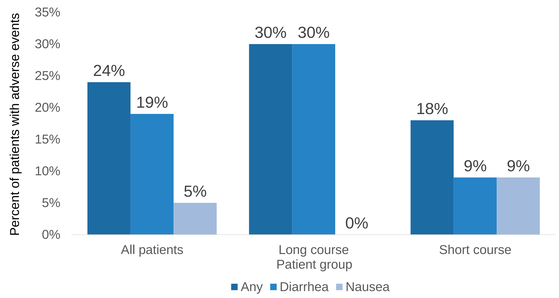

Figure 5. Adverse events reported to fosfomycin

DISCUSSION

Population
- Almost a third (32%) of patients in this study were initially treated in an inpatient setting, a different population than in prior trials[8,9]. This provides support for the use of fosfomycin in this population
- Treatment durations in the two prior fosfomycin-for-CBP trials (usually 6 weeks) were more comparable to those of our long course group, which received a median of 40 days of therapy

Efficacy
- Overall cure rates, especially in the long course group, were similar to those reported in the one prior retrospective trial[8] (N=15, 47% clinical and 53% microbiological cure)
- The one prior prospective trial[9] had higher cure rates (N=44, 73% clinical and 77% microbiological cure)
- Patients that received a short course of therapy had lower rates of both clinical cure (41%) and microbiological cure (35%) than the long course group (55% and 56%, respectively). This supports the well-established use of long treatment courses in CBP

Safety
- All adverse events were mild in severity (diarrhea, nausea) and resolved with treatment adjustment or completion of therapy in agreement with prior literature
- While the long course group appears to have experienced a greater rate of adverse events (AEs), rates are inflated by the small number of unique patients, with 2/11 short course and 3/10 long course patients experiencing AEs
- Overall, adverse event rates were higher in our study than in the two prior trials, perhaps because of a higher median age in our population (70 years vs. 54 and 53 years) and the inclusion of inpatients, who may have been sicker and thus more susceptible to adverse events (for example, due to reduced renal function)

Susceptibility
- Though data was limited, maintained susceptibility after fosfomycin exposure mirrors findings in the two prior trials, though it is noteworthy most of our patients with repeat susceptibility testing received short courses

Further practical application
- All 14 patients not diagnosed with CBP at the time and 3 patients diagnosed at the time inappropriately received short courses
  - Provider education on assessing for CBP and appropriate duration of treatment could increase cure rates
- Despite higher cure rates in the long course group, the short course group had appreciable cure rates
  - It may be reasonable to attempt a shorter course of fosfomycin therapy initially with close follow up in cases where CBP diagnosis is truly uncertain or the patient tolerates fosfomycin poorly. In the case of failure, a longer course could be attempted as pathogens may retain fosfomycin susceptibility

CONCLUSION

- Fosfomycin may be safe and effective for the treatment of CBP
- Treatment courses longer than 4 weeks may be more effective than courses shorter than 2 weeks, with potentially comparable risk of minor adverse events that resolve with discontinuation of fosfomycin
- In microbiological failure, testing isolates on follow-up culture for fosfomycin susceptibility may be worthwhile as pathogens may remain susceptible, which may suggest treatment can be repeated with a longer course
- However, large randomized controlled trials are still needed to define the primary efficacy of fosfomycin and the utility of retreatment

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