Optimal dosage and duration of Pivmecillinam treatment for uncomplicated lower urinary tract infections: a systematic review and meta-analysis

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Background:

Pivmecillinam (PIV) is recommended in several clinical guidelines for the treatment of lower urinary tract infections (UTIs). However, the optimal dosage, duration and frequency of PIV therapy remains unknown.

Aim: To compare the efficacy and safety of different PIV regimes in the management of UTIs.

Methods:

Medline, Embase and the Cochrane Central Register of Controlled Trials were searched (last search in April 2016). Data were screened and extracted independently by two authors

Inclusion criteria:

RCTs involving adults/children with symptoms suggestive for uncomplicated UTI comparing different PIV regimes or PIV versus other antibiotics.

Outcome assessment:

Short- and long clinical as well as bacteriological cure, adverse events, reinfection, relapse and failure.

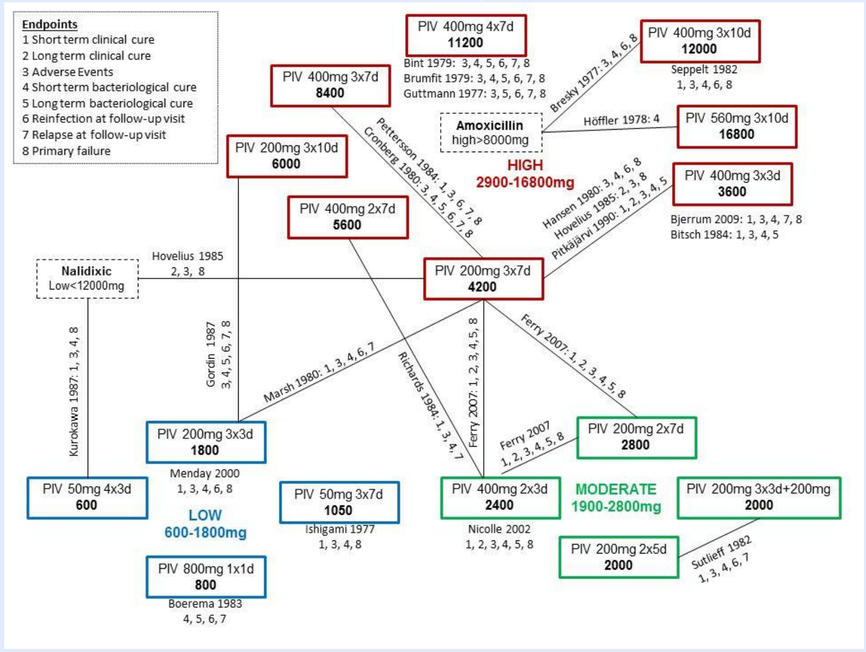
Risk of bias assessment: Cochrane RCT Tool

Statistical analysis:

PIV regimens were categorized into high (2900-16800 mg), moderate (1900-2800 mg) and low dosages (600-1800 mg) (**FIG 1**). Meta-analyses were conducted to obtain direct and indirect efficacy estimated:

- For a positive outcome (cure): RR>1 favors a higher PIV total dosage
- For a negative outcome (adverse events, re-infection, relapse, failure): RR >1 favors a lower PIV total dosage

FIG 1: Network meta-analysis scheme



Results:

- 24 RCTs on 5637 participants (♂93 and ♀5544), publication years 1977-2009
- No statistical difference in clinical cure (**TAB 1**)
- The bacteriological cure comparisons showed a trend in favor of high dosage treatment (**TAB 2**)
- Results for relapse, reinfection and failure were inconclusive and statistically not significant (data not shown here).
- Higher dosages lead to 40% (p=0.062) and 44% (p=0.293) more mild to moderate adverse events (data not shown here).

TAB 1: Meta-analysis: Results for clinical cure

Comparison	# of Studies	Participants total	Statistical Method	Effect Estimate	I^2	Direction Favors
Short term clinical cure						
High PIV vs. moderate PIV	2	818	RR (M-H, FEM, 95% CI)	1.01 [0.90; 1.14], p = 0.8127	0%	--
High PIV vs. low PIV	1	125	Mean Difference* (95% CI)	0 [-0.44; 0.45], p = 1		--
Moderate vs. low PIV	0					
Long-term clinical cure						
High PIV vs. moderate PIV	1	487	RR (95%CI)	1.09 [0.96; 1.23], p = 0.1744		High PIV
High PIV vs. low PIV	0					
Moderate vs. low PIV	0					

RR: Risk Ratio; M-H: Mantel-Haenszel; FEM: fixed-effect model; CI confidence interval

TAB 2: Meta-analysis: Results for clinical cure

Short term bacteriological cure						
High PIV vs. moderate PIV	2	691	RR (M-H, FEM, 95% CI)	1.05 [0.99; 1.10], p = 0.0560	0%	High PIV
High PIV vs. low PIV	2	124	RR (M-H, FEM, 95% CI)	1.02 [0.89; 1.18], p = 0.7589	35%	High PIV
Moderate vs. low PIV	0					
Long-term bacteriological cure						
High PIV vs. moderate PIV	1	523	RR (95%CI)	1.05 [0.98; 1.13], p = 0.1314		High PIV
High PIV vs. low PIV	1	53	RR (95%CI)	1.13 [0.91; 1.40], p = 0.2472		High PIV
Moderate vs. low PIV	0					

RR: Risk Ratio; M-H: Mantel-Haenszel; FEM: fixed-effect model; CI confidence interval

Conclusions

- There is insufficient evidence to support the use of an optimal combination of dosage, frequency and duration of PIV therapy for the treatment of uncomplicated lower UTIs.
- Evidence is limited due to high risk of bias, poor reporting and heterogeneous study data.
- No difference in efficacy between the different total dosage categories, with somewhat higher adverse events in high dosage groups.
- In order to give guidance on patient care for clinicians, who are in need of definitive recommendations in clinical practice, data suggest that 3-days treatment durations of 400 mg three times daily can safely be recommended
- This dosage is in line with current antimicrobial stewardship strategies.

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