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 regimes 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

Results:

• 24 RCTs on 5637 participants (93 and 5544), publication years 1977-2009
• No statistical difference in clinical cure (TABLE 1)
• The bacteriological cure comparisons showed a trend in favor of high dosage treatment (TABLE 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).

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.

FIG 1: Network meta-analysis scheme

TABLE 1: Meta-analysis: Results for clinical cure

<table>
<thead>
<tr>
<th>Comparison</th>
<th># of Studies</th>
<th>Participants Total</th>
<th>Statistical Method</th>
<th>Effect Estimate</th>
<th>95% CI</th>
<th>p</th>
<th>Direction Favor</th>
</tr>
</thead>
<tbody>
<tr>
<td>High PIV vs. moderate PIV</td>
<td>2</td>
<td>691</td>
<td>RR (M-H, FEM, 95% CI)</td>
<td>1.05 [0.99; 1.10], p = 0.0550</td>
<td>0%</td>
<td>High PIV</td>
<td></td>
</tr>
<tr>
<td>High PIV vs. low PIV</td>
<td>2</td>
<td>124</td>
<td>RR (M-H, FEM, 95% CI)</td>
<td>1.02 [0.89; 1.16], p = 0.7589</td>
<td>35%</td>
<td>High PIV</td>
<td></td>
</tr>
<tr>
<td>Moderate vs. low PIV</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

TABLE 2: Meta-analysis: Results for clinical cure

<table>
<thead>
<tr>
<th>Comparison</th>
<th># of Studies</th>
<th>Participants Total</th>
<th>Statistical Method</th>
<th>Effect Estimate</th>
<th>95% CI</th>
<th>p</th>
<th>Direction Favor</th>
</tr>
</thead>
<tbody>
<tr>
<td>High PIV vs. moderate PIV</td>
<td>1</td>
<td>523</td>
<td>RR (M-H, 95% CI)</td>
<td>1.05 [0.88; 1.23], p = 0.1314</td>
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<td>High PIV</td>
<td></td>
</tr>
<tr>
<td>High PIV vs. low PIV</td>
<td>1</td>
<td>53</td>
<td>RR (M-H, 95% CI)</td>
<td>1.13 [0.91; 1.44], p = 0.2472</td>
<td>0%</td>
<td>High PIV</td>
<td></td>
</tr>
<tr>
<td>Moderate vs. low PIV</td>
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<td></td>
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