AIM
To determine whether medical therapy with α-blockers and calcium-channel blockers (medical expulsive therapy) is effective in hastening passage of ureteral calculi.

METHODS
A systematic review and meta-analysis of 211 studies yielded 22 randomized trials involving nearly 2000 adult patients with radiographically confirmed ureteral calculi, to evaluate the benefit of α-antagonists (tamsulosin) and/or calcium-channel blockers (nifedipine) compared with standard therapy.

RESULTS
While none of the included studies met all the criteria for a well-done, randomized control trial, the authors used the techniques of influence analysis to assure that no single study unduly influenced the results. For the α-antagonist, tamsulosin, benefit was found in terms of likelihood of stone expulsion at 4 weeks (RR 1.59 [95% CI, 1.44 to 1.75]), with a number needed to treat of 3.3 (CI, 2.1 to 4.5). For the trials that reported time to expulsion, a 2- to 6-day average improvement was found. For the calcium-channel blocker nifedipine, stone expulsion rates were superior to standard therapy (RR 1.50 [CI, 1.35 to 1.68]) with an number needed to treat of 3.9 (CI, 3.2 to 4.6). Time to expulsion was improved in 7 of the 9 nifedipine trials. Minimal or no adverse side effects of either the tamsulosin (0.4 mg/day) or nifedipine (30 mg/day) were observed.

CONCLUSIONS
The results of this study were concordant with another recent meta-analysis and suggest benefit from medical expulsion of ureteral stone > 5mm (but < 10mm), both in terms of likelihood and time to passage. The implication is that patients treated with medical expulsive therapy experience fewer days of renal colic and are less likely to require intercentions, such as lithotripsy or ureteroscopic procedures.

IMPLICATIONS FOR INTERNAL MEDICINE
The lifetime risk for urolithiasis in the United States is estimated at 13% for men and 7% for women, with a recurrence rate of 50% within 5 years. This accounts for 2 million office visits nationwide. Most ureteral calculi that are smaller than 5 mm in diameter pass spontaneously within 4 weeks of symptom onset.

Persistent ureteral stones are associated with stricture and renal damage. For the most part, open surgery to remove stone has given way to less invasive methods, including shock wave lithotripsy, ureteroscopy, and percutaneous nephrolithotomy; however, these procedures are expensive and have side effects of their own.

Insofar as ureteral contraction is driven by an increase in intercellular calcium and is modulated by the autonomic nervous system and both α-antagonist and calcium-channel blockers have been shown to inhibit ureteral spasm, it makes sense that these agents promote antegrade stone passage. Even more important is that this meta-analysis suggests that the benefits of these well-tolerated drugs outweigh the risks.

Recognizing the caveats associated with treatment decisions based on meta-analyses for patients with ureteral stone between 5 and 10 mm that are not passing quickly, it makes sense to use treatment with α-adrenergic or calcium-channel blockers for a period of about 4 weeks to promote stone passage and to avoid more uncomfortable and costly procedures.

RELATED REFERENCE

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CERVICAL CANCER AND HPV VACCINATION
Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions: the FUTURE II study group

AIM
To determine whether a quadrivalent human papillomavirus (HPV) vaccine will reduce cervical cancer and its precursor lesions (CIN 2 and 3).

METHODS
This was a randomized, placebo-controlled, double-blind study done in 90 centers in 16 countries worldwide.
Over 12,000 women ages 15-26 were enrolled in the study and received either the vaccine (quadrivalent, against HPV 6,11, 16 and 18) or placebo, given on day 1, month 2, and month 6 of the study. Subjects could not be pregnant or have a history of abnormal Pap smears prior to the study. Subjects had cervical Pap smear testing and viral HPV DNA testing done on various anogenital sites at baseline, and these were repeated periodically over 4 years. Pap smear and viral DNA analysis were done in double-blind fashion and WHO reporting criteria were used. The primary endpoint was occurrence of CIN 2, CIN 3, or adenocarcinoma of the cervix (in situ or invasive).

RESULTS
Over 6,000 subjects were enrolled in each group, with a mean age of 20 years, most of who were from Europe (7% from North America). Approximately 11% in each group had baseline abnormalities on Pap smear, and 10% had detectable HPV 16 or 18 on polymerase chain reaction testing. Most were sexually active. Vaccination was highly effective in reducing HPV 16 and 18 infections and related high-grade cervical lesions as compared with placebo.

<table>
<thead>
<tr>
<th></th>
<th>Vaccine group (n = 5305 negative HPV baseline)</th>
<th>Placebo (n = 5250 negative HPV baseline)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN 2 or 3 (related to HPV 16 or 18)</td>
<td>1 (&lt;0.1%)</td>
<td>57 (1.1%)</td>
<td>91</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>0</td>
<td>1 (not significant)</td>
<td></td>
</tr>
<tr>
<td>New HPV 16 or 18</td>
<td>3 (&lt;0.1%)</td>
<td>67 (1.3%)</td>
<td>83</td>
</tr>
<tr>
<td>CIN 2 or 3 (related to any HPV)</td>
<td>95 (2%)</td>
<td>130 (2.7%)</td>
<td>142</td>
</tr>
</tbody>
</table>

HPV = human papillomavirus; NNT = number needed to treat.

However, the authors also did an intention-to-treat analysis, which included all patients who were enrolled and randomized, including those with baseline cervical abnormalities or HPV infection. The overall risk for HPV 16 or 18 infection and cervical changes in patients receiving the vaccine was still reduced, but less so (1.6% developed vaccine type HPV related CIN 2 or 3 or adenocarcinoma, vs. 3.2% in placebo, or about 50% effective). In addition, the risk for CIN (2 or 3) or adenocarcinoma, irrespective of HPV subtype, was 4.6% for the vaccinated group vs. 5.7% in the placebo group, or about 17% effective. Only the incidence of CIN 2 was significantly reduced in the treatment group; there was no difference in risk for CIN 3 or adenocarcinoma in situ.

For patients who had baseline cervical changes or were HPV 16- or 18-positive, the vaccine was ineffective: there were no differences in subsequent cervical lesions between vaccination and placebo groups. In patients who became pregnant during the study, there were no differences in birth outcomes, although the study was not designed or powered to carefully study this issue.

CONCLUSIONS
Vaccination with a quadrivalent HPV vaccine, when properly administered to women who do not have HPV infections or cervical changes at baseline, is highly effective (99%) at reducing future HPV infections and significant cervical changes (CIN 2 or 3) associated with those specific HPV subtypes. For the mean 3 years of follow-up, there was no difference in the risk for adenocarcinoma, although this period is probably too brief to detect such a difference. The HPV vaccination was only moderately effective (about 17%) at HPV vaccination is helpful in patients already infected with HPV 16 or 18. Vaccination with quadrivalent HPV apperas to be safe, and no pregnancy risks are noted.

IMPLICATIONS FOR INTERNAL MEDICINE
This article shows definitively that vaccination with an HPV quadrivalent vaccine prevents infections and the cervical changes associated with them for those virus subtypes included in the vaccine. The effectiveness is nearly 100% in preventing new HPV 16 or 18 infections, which have been associated in more than 50% of cases of cervical cancer. However, there was only a modest reduction in rates of cervical dysplasia, presumably because of other viral subtypes, or perhaps infection with the virus prior to vaccine effect, since most of these women were sexually active prior to and after vaccination. The research that remains to be done is a study looking at younger females, who are not yet sexually active, although such a study would take many years to complete. This study did not show that the vaccine reduces adenocarcinoma of the cervix, which is the primary goal of the vaccine. However, it is well-known that high-grade dysplasia of the cervix is a precursors risk factor for adenocarcinoma, and most experts in the field consider this to be an acceptable surrogate endpoint. Thus, it follows that reducing these precursor lesions will prevent adenocarcinoma. At this time, the vaccine seems to be safe and to offer at least 5 years of immunity, based on immunologic testing. It is reasonable, therefore, to recommend the vaccine, although careful studies are needed to guide further implementation in specific populations.
RELATED REFERENCES


This study in the same journal issue studied the same HPV vaccine and found similar reductions in CIN 2/3 but no reduction in adenocarcinoma. This study also showed a reduction in noncervical HPV-related diseases, such as warts.


This study compared traditional pap smears to HPV PCR techniques in the detection of high-grade cervical neoplasia. HPV testing was substantially more sensitive than traditional cytologic Pap smear testing, although specificity was slightly lower. This adds to our information; however, most U.S. physicians use liquid Pap technology, which has been shown to be superior to standard cytologic analysis. Further study is required before we can consider switching to HPV screening instead of Pap tests.

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