Medical Management of Kidney Stones

Warren Kupin, MD FACP
Professor of Medicine
Miami Transplant Institute
University of Miami Miller School of Medicine
What is Your Stone IQ?

- 45 year old Caucasian male
- New onset of right sided flank pain radiating down into the groin associated with gross hematuria
- Plain KUB of the abdomen
- CT of the abdomen

Radio-opaque stones in the right kidney and distal ureter
All stones 5-7 mm
Case Presentation

- Urinalysis showed
  - Specific Gravity: 1.015
  - pH: 6.0
  - Blood: 2+
  - Leukocyte Esterase: trace
  - Crystals
Based on this presentation what can you do for your patient…??

A. Prayer
B. Ask them if they signed their organ donor card
C. Consider Medical Expulsion Therapy with diuretics
D. Consider Medical Expulsion Therapy with α blockers
E. Consider Medical Expulsion Therapy with calcium channel blockers
F. Just IV fluids and call a urologist
G. What in the world is Medical Expulsion Therapy?
Will it pass if we do nothing? The Potential for a Stone to Pass Spontaneously

![Bar charts showing the percentage of stones passing spontaneously based on ureter location and stone size.](image-url)
Time for Stones to Pass Spontaneously

- < 2 mm: 8.2 days
- 2 - 4 mm: 12 days
- > 4 mm: 22 days
American Urologic Association

AUA Guideline

Patients with uncomplicated ureteral stones ≤10 mm should be offered observation, and those with distal stones of similar size should be offered MET with α-blockers. (Index Patient 3) Strong Recommendation; Evidence Level Grade B

In most patients, if observation with or without MET is not successful after four to six weeks and/or the patient/clinician decide to intervene sooner based on a shared decision making approach, clinicians should offer definitive stone treatment. (Index Patients 1-3) Moderate Recommendation; Evidence Level Grade C

Mitigating Factors:
- Obstruction
- Infection
- Intolerance to MET
- Intractable Pain
Medical Expulsive Therapy (MET)
Relaxing Ureteric Contractions and Sphincter Tone

<table>
<thead>
<tr>
<th>Type</th>
<th>Generic name</th>
<th>Trade name</th>
<th>Recommended dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium-channel blocker</td>
<td>Nifedipine</td>
<td>Adalat Adalat CC Procardia Procardia XL</td>
<td>30 mg/day</td>
</tr>
<tr>
<td>α1-Selective α-blocker</td>
<td>Tamsulosin</td>
<td>Flomax Flomaxtra Urimax</td>
<td>0.4 mg/day</td>
</tr>
<tr>
<td>α1-Selective α-blocker</td>
<td>Terazosin</td>
<td>Hytrin</td>
<td>5 mg/day</td>
</tr>
<tr>
<td>α1-Selective α-blocker</td>
<td>Doxazosin</td>
<td>Cardura</td>
<td>4 mg/day</td>
</tr>
<tr>
<td>Corticosteroid</td>
<td>Deflazacort</td>
<td>Calcort Cortex Decortil Deflanil</td>
<td>30 mg/day</td>
</tr>
<tr>
<td>Glucocorticoid</td>
<td>Methylprednisolone</td>
<td>Medrol A-methaPred Depo-Medrol Medrol DosePak Solu-Medrol</td>
<td>16 mg/day</td>
</tr>
</tbody>
</table>
Medical Expulsive Therapy: 
α Blockade For Stones < 10 mm

<table>
<thead>
<tr>
<th>Author-Year</th>
<th>a-Blocker/ event</th>
<th>a-Blocker/ Control</th>
<th>Control/ event</th>
<th>Control/ Control</th>
<th>OR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gurbuz, 1997</td>
<td>52</td>
<td>105</td>
<td>3</td>
<td>38</td>
<td>10.47 (3.38, 33.30)</td>
<td>2.99</td>
</tr>
<tr>
<td>Genrikov, 2002</td>
<td>41</td>
<td>51</td>
<td>32</td>
<td>52</td>
<td>2.69 (1.1, 6.65)</td>
<td>4.12</td>
</tr>
<tr>
<td>Autorino, 2005</td>
<td>28</td>
<td>32</td>
<td>19</td>
<td>32</td>
<td>4.79 (1.33, 16.94)</td>
<td>2.94</td>
</tr>
<tr>
<td>Yilmaz, 2005</td>
<td>67</td>
<td>80</td>
<td>15</td>
<td>28</td>
<td>3.00 (1.24, 7.52)</td>
<td>4.03</td>
</tr>
<tr>
<td>De So, 2006</td>
<td>45</td>
<td>50</td>
<td>27</td>
<td>46</td>
<td>6.33 (2.12, 18.62)</td>
<td>3.42</td>
</tr>
<tr>
<td>Frithan, 2007</td>
<td>22</td>
<td>30</td>
<td>12</td>
<td>30</td>
<td>4.13 (1.39, 12.27)</td>
<td>3.43</td>
</tr>
<tr>
<td>Lojajaput, 2008</td>
<td>27</td>
<td>50</td>
<td>1</td>
<td>26</td>
<td>28.17 (3.32, 224.67)</td>
<td>1.53</td>
</tr>
<tr>
<td>Bardis, 2008</td>
<td>25</td>
<td>34</td>
<td>27</td>
<td>35</td>
<td>0.82 (0.29, 2.46)</td>
<td>3.41</td>
</tr>
<tr>
<td>Sia, 2003</td>
<td>40</td>
<td>45</td>
<td>23</td>
<td>46</td>
<td>7.05 (2.56, 22.65)</td>
<td>3.41</td>
</tr>
<tr>
<td>Vang, 2008</td>
<td>51</td>
<td>64</td>
<td>17</td>
<td>31</td>
<td>3.23 (1.27, 8.22)</td>
<td>3.95</td>
</tr>
<tr>
<td>Agrawal, 2009</td>
<td>52</td>
<td>68</td>
<td>12</td>
<td>34</td>
<td>5.56 (2.42, 14.64)</td>
<td>4.07</td>
</tr>
<tr>
<td>Kurnia, 2009</td>
<td>39</td>
<td>50</td>
<td>40</td>
<td>56</td>
<td>0.89 (0.34, 2.32)</td>
<td>3.84</td>
</tr>
<tr>
<td>Forpilag, 2009</td>
<td>37</td>
<td>46</td>
<td>22</td>
<td>45</td>
<td>4.20 (1.99, 9.04)</td>
<td>3.95</td>
</tr>
<tr>
<td>Salem, 2009</td>
<td>52</td>
<td>58</td>
<td>32</td>
<td>56</td>
<td>6.50 (2.44, 17.62)</td>
<td>3.73</td>
</tr>
<tr>
<td>Abd-El-Meguid, 2010</td>
<td>61</td>
<td>82</td>
<td>42</td>
<td>76</td>
<td>2.56 (1.32, 4.97)</td>
<td>4.58</td>
</tr>
<tr>
<td>Almonte, 2010</td>
<td>48</td>
<td>60</td>
<td>14</td>
<td>36</td>
<td>4.57 (1.79, 11.80)</td>
<td>3.89</td>
</tr>
<tr>
<td>Al-Awardi, 2010</td>
<td>41</td>
<td>50</td>
<td>26</td>
<td>56</td>
<td>3.50 (1.14, 10.09)</td>
<td>4.02</td>
</tr>
<tr>
<td>Vincenzo, 2010</td>
<td>48</td>
<td>66</td>
<td>43</td>
<td>63</td>
<td>1.07 (0.95, 2.26)</td>
<td>4.84</td>
</tr>
<tr>
<td>Zelt, 2010</td>
<td>23</td>
<td>33</td>
<td>12</td>
<td>32</td>
<td>3.83 (1.37, 10.75)</td>
<td>3.62</td>
</tr>
<tr>
<td>Afdah, 2011</td>
<td>25</td>
<td>31</td>
<td>11</td>
<td>26</td>
<td>6.82 (2.13, 21.86)</td>
<td>3.21</td>
</tr>
<tr>
<td>Nair, 2012</td>
<td>37</td>
<td>50</td>
<td>15</td>
<td>56</td>
<td>6.64 (2.77, 15.63)</td>
<td>4.15</td>
</tr>
<tr>
<td>Rahim, 2012</td>
<td>37</td>
<td>45</td>
<td>22</td>
<td>45</td>
<td>4.84 (1.85, 12.65)</td>
<td>3.05</td>
</tr>
<tr>
<td>Woe-Hoon, 2012</td>
<td>82</td>
<td>107</td>
<td>16</td>
<td>34</td>
<td>3.69 (1.44, 8.28)</td>
<td>4.43</td>
</tr>
<tr>
<td>Bajwa, 2013</td>
<td>23</td>
<td>30</td>
<td>11</td>
<td>30</td>
<td>5.08 (1.84, 17.49)</td>
<td>3.32</td>
</tr>
<tr>
<td>Phuihan, 2013</td>
<td>51</td>
<td>60</td>
<td>12</td>
<td>30</td>
<td>8.59 (3.01, 23.62)</td>
<td>3.69</td>
</tr>
<tr>
<td>Lin, 2014</td>
<td>33</td>
<td>35</td>
<td>20</td>
<td>33</td>
<td>10.73 (2.19, 52.54)</td>
<td>2.21</td>
</tr>
<tr>
<td>Foyik, 2015</td>
<td>140</td>
<td>166</td>
<td>127</td>
<td>155</td>
<td>1.19 (0.98, 1.43)</td>
<td>5.27</td>
</tr>
</tbody>
</table>

Overall (I-squared = 57.8%, p = 0.000)

NOTE: Weights are from random effects analysis

Favors control  Favors MET
Tamulosin is Superior to Nifedipine for Overall Expulsion Rate and Time to Expulsion

**Rate of Expulsion**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Tamsulosin</th>
<th>Nifedipine</th>
<th>Weight (%)</th>
<th>Risk ratio M–H, fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balci et al12</td>
<td>19</td>
<td>25</td>
<td>1.1</td>
<td>1.19 (0.82, 1.71)</td>
</tr>
<tr>
<td>Choi et al14</td>
<td>27</td>
<td>32</td>
<td>1.4</td>
<td>1.25 (0.94, 1.66)</td>
</tr>
<tr>
<td>Dellabella et al10</td>
<td>56</td>
<td>70</td>
<td>3.6</td>
<td>1.26 (1.10, 1.44)</td>
</tr>
<tr>
<td>Gandhi and Agrawal9</td>
<td>51</td>
<td>64</td>
<td>2.1</td>
<td>1.59 (1.21, 2.10)</td>
</tr>
<tr>
<td>Islam et al8</td>
<td>27</td>
<td>33</td>
<td>1.6</td>
<td>1.33 (0.92, 1.94)</td>
</tr>
<tr>
<td>Liao et al17</td>
<td>48</td>
<td>59</td>
<td>1.9</td>
<td>1.53 (1.22, 2.17)</td>
</tr>
<tr>
<td>Lü et al13</td>
<td>48</td>
<td>60</td>
<td>2.9</td>
<td>1.11 (0.82, 1.53)</td>
</tr>
<tr>
<td>Pickard et al11</td>
<td>307</td>
<td>387</td>
<td>0.0</td>
<td>0.99 (0.82, 1.16)</td>
</tr>
<tr>
<td>Porpiglia et al11</td>
<td>24</td>
<td>28</td>
<td>1.5</td>
<td>1.07 (0.85, 1.35)</td>
</tr>
<tr>
<td>Vicentini et al9</td>
<td>23</td>
<td>33</td>
<td>1.2</td>
<td>1.25 (0.81, 1.91)</td>
</tr>
<tr>
<td>Ye et al14</td>
<td>1,530</td>
<td>1,596</td>
<td>78.2</td>
<td>1.30 (1.26, 1.35)</td>
</tr>
<tr>
<td>Zhang et al12</td>
<td>75</td>
<td>102</td>
<td>4.5</td>
<td>1.08 (0.90, 1.29)</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>2,107</strong></td>
<td><strong>2,061</strong></td>
<td><strong>1.29 (1.25, 1.33)</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 1,942
Heterogeneity: $\chi^2=14.16, df=10 (P=0.17)$; $I^2=26%$
Test for overall effect: $Z=17.26 (P<0.0001)$

**Time to Expulsion**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight (%)</th>
<th>Standard mean difference IV, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balci et al10</td>
<td>9</td>
<td>5</td>
<td>25</td>
<td>5</td>
<td>5</td>
<td>25</td>
<td>14.1</td>
<td>-0.02 (-0.57, 0.53)</td>
</tr>
<tr>
<td>Islam et al18</td>
<td>7.9</td>
<td>3.25</td>
<td>33</td>
<td>9.3</td>
<td>4.5</td>
<td>33</td>
<td>15.5</td>
<td>-0.35 (-0.84, 0.13)</td>
</tr>
<tr>
<td>Liao et al17</td>
<td>11</td>
<td>9</td>
<td>59</td>
<td>14</td>
<td>10</td>
<td>53</td>
<td>17.9</td>
<td>-0.31 (-0.69, 0.06)</td>
</tr>
<tr>
<td>Lü et al13</td>
<td>4</td>
<td>4</td>
<td>60</td>
<td>8</td>
<td>4</td>
<td>60</td>
<td>17.7</td>
<td>-0.99 (-1.37, -0.61)</td>
</tr>
<tr>
<td>Pickard et al11</td>
<td>16.5</td>
<td>12.6</td>
<td>79</td>
<td>16.2</td>
<td>14.5</td>
<td>74</td>
<td>10.1</td>
<td>0.02 (-0.30, 0.34)</td>
</tr>
<tr>
<td>Vicentini et al9</td>
<td>15.3</td>
<td>2.1</td>
<td>33</td>
<td>16.7</td>
<td>2.2</td>
<td>35</td>
<td>15.8</td>
<td>-0.64 (-1.12, -0.17)</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>294</strong></td>
<td></td>
<td><strong>280</strong></td>
<td><strong>100</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>-0.39 (-0.72, -0.05)</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: $t^2=0.13, \chi^2=19.15, df=5 (P=0.002); I^2=74%$
Test for overall effect: $Z=2.27 (P=0.026)$

Favors Tamulosin

**Drug Des Devel Ther.** 2016; 10: 1257–1265
Medical Expulsion Therapy: Phosphodiesterase 5 Inhibitors

PDE5 inhibitors may be another option for MET however current guidelines recommend α-1 blockers primarily until further studies are performed.

<table>
<thead>
<tr>
<th>Study</th>
<th>Tamsulosin</th>
<th>Tadalafil</th>
<th>Tamsulosin+Tadalafil</th>
<th>Silodosin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study</td>
<td>61.0%</td>
<td>84.1%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Kumar et al, 2014 [20]</td>
<td>74.2%</td>
<td>-</td>
<td>83.9%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Jayant et al, 2014 [21]</td>
<td>65.5%</td>
<td>-</td>
<td>83.6%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Kumar et al, 2015 [23]</td>
<td>64.4%</td>
<td>66.7%</td>
<td>-</td>
<td>83.3%</td>
<td>-</td>
</tr>
<tr>
<td>Hasan et al, 2011 [22]</td>
<td>-</td>
<td>93%</td>
<td>-</td>
<td>-</td>
<td>67%</td>
</tr>
<tr>
<td>Al-Ansari et al, 2010 [24]</td>
<td>82%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>61%</td>
</tr>
</tbody>
</table>
Based on this presentation what can you do for your patient .............

A. Prayer
B. Ask them if they signed their organ donor card
C. Consider Medical Expulsion Therapy with diuretics
D. **Consider Medical Expulsion Therapy with α blockers**
E. Consider Medical Expulsion Therapy with calcium channel blockers
F. Just IV fluids and call a urologist
G. What in the world is Medical Expulsion Therapy?
MET was successful and this particle came out – what is it?

A. Calcium phosphate  
B. Calcium oxalate  
C. Uric Acid  
D. Staghorn stone  
E. Cystine  
F. Struvite stone  
G. Parasite  
H. OMG !!! No way anyone passed that thing in the urine – it’s an artifact! Fake News! This patient just wants pain medication.

Hint  
Radio-opaque  
Urine pH 6.0
3. When a stone is available, clinicians should obtain a stone analysis at least once. (Clinical Principle)

AUA Guideline

Worldwide Distribution of Kidney Stones
Kidney Stones in Pets

- Overall 3% of Dogs and Cats
- Mixture of bladder stones and upper tract stones
  - Calcium Oxalate
  - Struvite
- Most common breeds (26 total)
  - shih tzu, miniature schnauzer, bichon frisé, lhasa apso, and Yorkshire terrier
Drug Induced Nephrolithiasis

**Direct**
Drug metabolites form the stone

**Indirect**
Drug creates a favorable metabolic milieu for stone formation
Drug Induced Kidney Stones

Indinavir

Guaifenesin Metabolite

Sulfamethoxazole Metabolite

Iothalamate Metabolite

Oxypurinol

Triamterene and Metabolites

Indinavir

Guaifenesin Metabolite

Ciprofloxacin Metabolite

Sulfamethoxazole Metabolite

Phenytoin Metabolite

Triamterene and Metabolites

Phenazopyridine

Guaifenesin Metabolite

Aminophylline

Sulfamethoxazole Metabolite
Drug Induced Kidney Stones

- Actual Drug Metabolite Stone Composition
  - Triamterene
  - Ciprofloxacin
  - Protease Inhibitors
    - Indinavir
    - Atazanavir
  - Guaifenesin
  - Sulfonamides
    - Bactrim
    - Acyclovir
  - Ephedra

In HIV patient – PI induced stones are very important to keep in mind
Drug Induced Kidney Stones

Represent 1-1.5% of all stones

- Direct Stone from the drug itself (0.95%)
  - Pure drug metabolites
  - Most important recent drugs causing stones are the Protease Inhibitors for HIV treatment
- Altered urine pH (0.65%)
  - Calcium Phosphate Stones
    - Carbonic Anhydride Inhibitors
      - Topamax (Topiramate)
      - Diamox (acetazolamide)
  - Calcium Oxalate
    - Ascorbic acid (RR 1.6, daily use)

ASN 2016
Participants of the Health Professionals Follow-up Study (HPFS) and Nurses' Health Study (NHS) I and II
12% increased risk of stones with PPI and H2 blockers
# Kupin’s Counterfeit Calculi

<table>
<thead>
<tr>
<th>Inorganic</th>
<th># pts.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silicaceous stones (pebbles)</td>
<td>35</td>
</tr>
<tr>
<td>Metallic shot pellets</td>
<td>10</td>
</tr>
<tr>
<td>Calcium carbonate</td>
<td>8</td>
</tr>
<tr>
<td>Unidentified</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Organic</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Plant seeds</td>
<td>6</td>
</tr>
<tr>
<td>Crayon</td>
<td>1</td>
</tr>
<tr>
<td>Fecalith</td>
<td>1</td>
</tr>
<tr>
<td>Bone fragments</td>
<td>1</td>
</tr>
<tr>
<td>Tooth fragments</td>
<td>1</td>
</tr>
<tr>
<td>Unidentified</td>
<td>6</td>
</tr>
</tbody>
</table>
Economic Impact of Nephrolithiasis

- $3 Billion Yearly Cost
- $3,500 cost per stone episode
- 2.4 days missed work per episode
- 2 million ER visits
- 1% admissions
- 40% increase in outpatient visits
- 43% increase in ER visits
- 45% inpatient care
- 30% outpatient care
- 25% ER visits
- 1% admissions
Nephrolithiasis in the U.S.

Incidence
0.1 – 0.3%

Prevalence
8 - 12 %

13% Men

7% Women
Lifetime Risk for Nephrolithiases

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>White Male</td>
<td>13%</td>
</tr>
<tr>
<td>White Female</td>
<td>7.5%</td>
</tr>
<tr>
<td>Hispanic Male</td>
<td>7.1%</td>
</tr>
<tr>
<td>Hispanic Female</td>
<td>5.7%</td>
</tr>
<tr>
<td>Black Male</td>
<td>4.5%</td>
</tr>
<tr>
<td>Black Female</td>
<td>4.2%</td>
</tr>
</tbody>
</table>
Geographic Distribution of Stone Disease
Prevalence (%) of Kidney Stones Among Men by Region
Prevalence of Nephrolithiasis in the U.S.
Effect of Temperature and Sunlight on Calcium Stone Disease

Sunlight Index

Mean Annual Temperature
Predicted “Climate Change” / “Global Warming” and Kidney Stones
Metabolic Syndrome Increases the Risk of Kidney Stones

Obesity is a MAJOR risk factor for kidney stones

Rendina D. J Nephrol April 2014
Scales C. Euro Urol 2102, 62:160
Long Term Impact of Nephrolithiasis: Chronic Kidney Disease

May be related to lifestyle / Diet / HTN / Diabetes
Radiologic Appearance of Nephrolithiasis

Radio-opaque
- Calcium Oxalate
- Cystine
- Triple Phosphate
- Calcium Phosphate

Radio-lucent
- Uric Acid
- Xanthine
- Triamterene
- Ephedrine
- PI
Urine pH and Nephrolithiasis

5.0                                           6.5                                        8.0

Uric Acid                                      Triple Phosphate

Cystine                                        Calcium Phosphate

Calcium Oxalate (pH independent)
Urinary Crystals and Nephrolithiasis

Calcium Oxalate Monohydrate

Calcium Oxalate Dihydrate
Calcium Oxalate Crystals and Nephrolithiasis
Urinary Crystals and Nephrolithiasis

Uric Acid
Urinary Crystals and Nephrolithiasis

Uric Acid
Urinary Crystals and Nephrolithiasis

Cystine
Urinary Crystals and Nephrolithiasis

Triple Phosphate – Struvite
Urinary Crystals and Nephrolithiasis

Calcium Phosphate
Calcium Oxalate Stones

Calcium Oxalate Dihydrate
WHEDDELLITE

Calcium Oxalate Monohydrate
WHEWELITTE
Uric Acid
Cystine
Struvite - Triple Phosphate
Staghorn Stones: Differential Diagnosis

• **Definition**
  – Branched calculi greater than 5 cm in overall width involving 2 or more calyces

• **Types of Stones in order of frequency**
  – **Triple Phosphate (Struvite)**
    • Urease producing infection (Proteus)
  – **Cystine**
Staghorn Stones
Staghorn Stones
MET was successful and this particle came out – what is it?

A. Calcium phosphate
B. Calcium oxalate
C. Uric Acid
D. Staghorn stone
E. Cystine
F. Struvite stone
G. OMG !!! No way anyone passed that thing in the urine – it’s an artifact!

Hint
Radio-opaque
Urine pH 6.0
This is the first time this patient has ever had a kidney stone—what type of workup do you do for a first time calcium oxalate stone former?

A. No workup at all for a first time stone former
B. Basic labs – urinalysis
C. Basic labs – PTH - urinalysis
D. Basic labs – PTH – urinalysis – One 24 hour urine for mineral analysis
E. Basic labs – PTH – urinalysis – Two 24 hour urine for mineral analysis
F. Basic labs – urinalysis – One 24 hour urine for mineral analysis
G. Basic labs – urinalysis – Two 24 hour urines for mineral analysis
Workup of a First Time Calcium Oxalate Stone Former

1. A clinician should perform a screening evaluation consisting of a detailed medical and dietary history, serum chemistries and urinalysis on a patient newly diagnosed with kidney or ureteral stones. (Clinical Principle)

2. Clinicians should obtain serum intact parathyroid hormone (PTH) level as part of the screening evaluation if primary hyperparathyroidism is suspected. (Clinical Principle)

A PTH level IS NOT a routine test for calcium stone formers

Indications
1) Calcium phosphate stone NOT calcium oxalate
2) Hypercalcemia
Capt. Charles Martell

1918
22 yrs old
6’1”

First established case of Hyperparathyroidism causing kidney stones in the U.S.

Underwent 7 operations before an ectopic gland was found under the sternum

1926
30 yrs old
5’6”
Primary Hyperparathyroidism (PHPT) and Calcium Stone Disease

- Accounts for only 5 – 7% of all cases of calcium stones
- Only 5 – 10% of patients with PHPT develop stones during long term followup
- **Metabolic abnormalities**
  - Hypercalciuria
  - Hyperphosphaturia
  - Alkaline urine (Type II RTA)
- **Stone Composition**
  - *Calcium phosphate* >> *Calcium oxalate*
Calcium Phosphate Stones

Primary Hyperparathyroidism

Renal Tubular Acidosis (Carbonic Anhydrase Inhibitors Topamax / Diamox)
Calcium Oxalate Nephrolithiasis

• Most common type of stone disease worldwide

• Stone demographics
  – Solitary
  – < 1 cm in size
    • 3 mm – 7 mm
  – pH independent
  – Radio-opaque
  – Unilateral
  – Male predominance
    • Age range 30-40 years old
Cumulative Incidence of Recurrence for Calcium Oxalate Stones

50% recurrence at 5 years
Time Interval of Recurrence For Calcium Stone Formers

- First Recurrence: 5 yrs
- Second Recurrence: 3 yrs
- Third Recurrence: 2 yrs
- Fourth Recurrence: 1.7 yrs
5. Clinicians should perform additional metabolic testing in high-risk or interested first-time stone formers and recurrent stone formers. (Standard; Evidence Strength: Grade B)

6. Metabolic testing should consist of one or two 24-hour urine collections obtained on a random diet and analyzed at minimum for total volume, pH, calcium, oxalate, uric acid, citrate, sodium, potassium and creatinine. (Expert Opinion)
Nephrolithiasis:
Indication for 24 hour Urine Analysis

- Residual calculi after surgical treatment
- Initial presentation with multiple calculi
- Renal failure
- Solitary kidney / Renal transplantation
- Immunocompromised patients
- Family history of calculi
- More than 1 stone in the past year
- Patients younger than 25 years
- High risk occupation
- Short bowel syndromes
- Anatomic abnormalities of the urinary tract
Anatomic Abnormalities Causing Stone Disease

- Medullary Sponge Kidney
- Horseshoe Kidney
- Ureteral Stricture
- UPJ Obstruction
- Reflux
- Calyceal Diverticulum
 Syndromes Associated with Hyperoxaluria and Nephrolithiasis

Normally a moderate amount of calcium and oxalate bind each other in the diet and precipitate in the intestines and are both eliminated in the stool.

- Short Bowel Syndrome
  - Gastric bypass procedure
  - Short small bowel

Fat malabsorption ➔ Precipitation with oral calcium in the bowel lumen and fecal excretion ➔ Increased oxalate absorption in the colon
High risk stone formation occupation: Astronaut!!

Space: “The Final Frontier”
Kidney Stones and Space Travel

• 11 astronauts / cosmonauts have developed renal stones disease
  – 10 episodes within the first year after the flight
  – 1 episode occurred during the flight

• Missions included
  – Apollo
  – Gemini
  – Shuttle
  – Space Lab
  – Mir space station
Calcium Stone Disease and Space Flight

The graph shows the % change in Urine Volume, Urinary Calcium, and Urinary Citrate. The % change values are -57, 30, and -28 respectively.
Metabolic Workup for Calcium Oxalate Stones

- **When to initiate evaluation?**
  - Do not obtain 24 hour urine collections while the patient is hospitalized for their stone episode

  - Dietary intake and fluid intake will not reflect the milieu that allowed the stone to form

  - Must wait a minimum of 8-12 weeks before obtaining the 24 hour urine

    - Patients need time to revert back to their daily routine that may have led to the stone formation

  - Obtain 1-2 collections separated by a week or more to determine the most accurate risk
It takes 2-3 months for a person to return to their typical pre-stone fluid intake after a stone episode.
Number of 24 Urine Collections and Detection of Metabolic Abnormalities

All collections > 3 months after the initial stone episode

![Bar chart showing the number of abnormalities detected in one collection versus two collections.](chart.png)
As an Example:

Litholink (LabCorp) Order Sheet

Diagnosis:

- N20.0 Kidney Stones
- Other

Diagnosis/Signs/Symptoms in ICD-CM format in effect at Date of Service (Highest Specificity Required)

Kidney Stone Urine Panels:

- One, 24-hour collection
- Two, 24-hour collections

Cystine Urine Panels: (for patients with known cystinuria)

- One, 24-hour collection
- Two, 24-hour collections

All tests will be performed on each 24-hour urine collection.

Serum/Blood Collection

Location:

- LabCorp Patient Service Center
- Physician’s Office or Hospital

All tests will be performed per blood draw.
This is the first time this patient has ever had a kidney stone—what type of workup do you do for a first time calcium oxalate stone former?

A. No workup at all for a first time stone former
B. Basic labs – urinalysis
C. Basic labs – PTH - urinalysis
D. Basic labs – PTH – urinalysis – One 24 hour urine for mineral analysis
E. Basic labs – PTH – urinalysis – Two 24 hour urine for mineral analysis
F. Basic labs – urinalysis – One 24 hour urine for mineral analysis
G. Basic labs – urinalysis – Two 24 hour urines for mineral analysis
The two 24 hour urine collections indicate the following:

1) urine volume 2 liters

What would you think of this result?

A. Urine volume is fine
B. Urine volume is low – drink more water
C. Urine volume is low – drink more soda
D. Urine volume is low – drink more tea
E. Urine volume is low – drink more fruit juice
F. Urine volume is low – drink more alcohol
G. It doesn’t matter what you drink as long as the urine volume is > 3 liters a day
Urine Volume and Prevention of Nephrolithiasis

Diet Therapies

Guideline Statement 8.

Clinicians should recommend to all stone formers a fluid intake that will achieve a **urine volume of at least 2.5 liters daily**. (Standard; Evidence Strength: Grade B)

If insensible losses are approximately 500 cc – then most patients need to **drink a minimum of 3 liters a day** to get a **URINE VOLUME of 2.5 L / Day**
Urinary Volume and Calcium Stone Disease

RR

< 1200: 1
1200-1600: 1.05
1601-2000: 0.95
2001-2500: 0.89
>2501: 0.71
Citrus Products and Stone Disease

- Exerts a protective effect on the formation of calcium oxalate stones
  - Citrate converts into bicarbonate after ingestion
    - Urinary alkalinization
    - Increased urinary citrate levels
    - Decreased urinary calcium
- Citrus products contain only small amounts of potential lithogenic compounds
  - Vitamin C (< 500 mg)
  - Oxalate (<20 mg)
**Citrate Concentration of Various Products**

- **Orange**: 140 mg
- **Grapefruit**: 130 mg
- **Lemon**: 280 mg
- **Pineapple**: 170 mg
- **Cranberry**: 95 mg

**Completely avoid Cola with phosphoric Acid**
The 2 - 24 hour urine collections indicate the following
1) urine volume 2 liters

What would you think of this result?

A. Urine volume is fine
B. Urine volume is low – drink more water
C. Urine volume is low – drink more soda
D. Urine volume is low – drink more tea
E. **Urine volume is low – drink more fruit juice**
F. Urine volume is low – drink more alcohol
G. It doesn’t matter what you drink as long as the urine volume is > 3 liters a day
Treatment of Calcium Oxalate Stone Disease
Maximizing Urinary Inhibitors

Guideline Statement 11.
Clinicians should encourage patients with calcium stones and relatively low urinary citrate to increase their intake of fruits and vegetables and limit non-dairy animal protein. (Expert Opinion)

Guideline Statement 15.
Clinicians should offer potassium citrate therapy to patients with recurrent calcium stones and low or relatively low urinary citrate. (Standard; Evidence Strength Grade B)

Pharmacologic Supplementation
- Potassium Citrate
- Potassium Magnesium Citrate

Avoid sodium salts of citrate as they will increase urinary calcium
The 2-24 hour urine collections also indicate the following
1) urine calcium 375 mg (normal < 300 mg)

What would you do with this result?

A. Ignore it
B. Decrease dietary calcium
C. Add a calcium channel blocker
D. Add a thiazide diuretic
E. Add a loop diuretic
F. Add allopurinol
G. Check dietary sodium
Calcium Intake and Nephrolithiasis

Guideline Statement 9.
Clinicians should counsel patients with calcium stones and relatively high urinary calcium to limit sodium intake and consume 1,000-1,200 mg per day of dietary calcium. (Standard; Evidence Strength Grade: B)

Guideline Statement 14.
Clinicians should offer thiazide diuretics to patients with high or relatively high urine calcium and recurrent calcium stones. (Standard; Evidence Strength Grade B)
Etiologies of Calcium Oxalate Stones

Both Hypercalciuria and Hyperuricosuria: 12
No abnormality: 10
Hypocitraturia: 25
RTA: 4
Primary HPTH: 7
Hyperuricosuria: 15
Hyperoxaluria: 25
Hypercalciuria: 35
Hypercalciuria and Kidney Stones

Absorptive
- Increased Vitamin D receptor activity

Renal Leak
- TALH tubular loss

Most of these cases are “Idiopathic”
No clear genetic / exogenous / endogenous etiology
**Idiopathic Hypercalciuria**

- **Prevalence**
  - Incidence of stone disease in the general population
    - 0.1 – 0.5%
  - Prevalence of Hypercalciuria
    - General population
      - 2 – 4%
    - Stone formers
      - 30 – 40%
  - Caveat
    - Hypercalciuria is clinically silent without stone disease in 80 – 90% of the population
    - Hypercalciuria is not a predictor of stone disease in a person with no prior history of stones
Effect of Sodium Intake on Hypercalciuria

Na excretion / day (meq)

- <100 meq: 1
- 100-149 meq: 3
- 150-199 meq: 20
- >200 meq: 24

% increase
Impact of Dietary Sodium on Hypercalciuria

- Sodium and calcium are handled in the TALH and DCT
- Increased sodium intake will lead to
  - Hypercalciuria
  - Volume expansion
- Caveat
  - Sodium restriction to less than 150 meq / day is essential to determine whether or not true Hypercalciuria is present
Calcium Oxalate Stones: Treatment

• Hypercalciuria
  – Decrease sodium intake (< 150 meq/day)
  – **Do not decrease dietary calcium !!!**

• Increased risk of stone disease with reduced calcium intake
• Dietary calcium supplements decreased stone formation

**Rationale**

– Calcium is necessary to bind dietary oxalate in the intestines which prevents its absorption
– Reduced intestinal calcium allows enhanced oxalate absorption
Stone Disease and Dietary Calcium Intake

The diagram shows the relative risk (RR) of stone disease associated with different levels of dietary calcium intake (mg/day). The x-axis represents calcium intake ranges, and the y-axis represents the RR. The ranges and their corresponding RR values are as follows:

- < 605 mg/day: 1
- 605-722 mg/day: 0.74
- 723-848 mg/day: 0.68
- 849-1049 mg/day: 0.68
- > 1050 mg/day: 0.66
Hypercalciuria

- **Diuretics**
  - Thiazide diuretics reduce urinary calcium
    - Mild volume depletion
    - Enhanced urinary sodium and calcium absorption
  - Do not use loop diuretics
    - Increase urinary calcium
- **Side effects**
  - Hypokalemia
  - Glucose Intolerance
  - Cramps
The 2-24 hour urine collections also indicate the following
1) urine calcium 375 mg (normal < 300 mg)

What would you do with this result?

A. Ignore it
B. Decrease dietary calcium
C. Add a calcium channel blocker
D. Add a thiazide diuretic
E. Add a loop diuretic
F. Add allopurinol
G. Check dietary sodium
Calcium Oxalate Stones : Treatment

- Hyperoxaluria
  - Avoid Vitamin C compounds
  - Avoid food rich in oxalate
  - Ensure adequate calcium intake

Guideline Statement 10.
Clinicians should counsel patients with calcium oxalate stones and relatively high urinary oxalate to limit intake of oxalate-rich foods and maintain normal calcium consumption. (Expert Opinion)
## Oxalate Containing Food

<table>
<thead>
<tr>
<th>&gt; 1% Oxalate</th>
<th>0.2 – 1.0% Oxalate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beets</td>
<td>Green Beans</td>
</tr>
<tr>
<td>Chocolate</td>
<td>Celery</td>
</tr>
<tr>
<td>Cocoa</td>
<td>Coffee</td>
</tr>
<tr>
<td>Figs</td>
<td>Oranges</td>
</tr>
<tr>
<td>Rhubarb</td>
<td>Strawberries</td>
</tr>
<tr>
<td>Spinach</td>
<td>Tomatoes</td>
</tr>
<tr>
<td>Tea</td>
<td>Sweet Potato</td>
</tr>
<tr>
<td>Poppy seeds</td>
<td>Endive</td>
</tr>
<tr>
<td>Pepper</td>
<td>Raspberries</td>
</tr>
</tbody>
</table>
Vitamin C and Urinary Oxalate

Increase Urinary Oxalate (mg)

Oral Ascorbic Acid (gm)

- 4 gm: 12 mg
- 8 gm: 45 mg
- 10 gm: 68 mg
Vitamin C Supplements and Stone Disease

Vitamin C intake (mg/day)

RR

0
0.25
0.5
0.75
1
1.25

None 90-249 250-499 500-999 > 1000

Vitamin C C intake (mg/day)
Calcium Oxalate Stones: Hyperuricosuria

Guideline Statement 12.
Clinicians should counsel patients with uric acid stones or calcium stones and relatively high urinary uric acid that limitation of intake of non-dairy animal protein may help reduce stone recurrence. (Expert Opinion)

Guideline Statement 16.
Clinicians should offer allopurinol to patients with recurrent calcium oxalate stones who have hyperuricosuria and normal urinary calcium. (Standard; Evidence Strength Grade B)

- Decrease dietary purine (meat) intake
- Add Allopurinol if urinary uric acid remains high
  - It is not required to have hyperuricemia or a history of gout
Case Presentation

The stone is not passing spontaneously with medical management and prayer! What is the next choice for removing renal / ureteral stones?

A. SWL
B. PNL
C. URS
D. FBI
E. ESPN
F. Do Jumping Jacks
G. Ride a Roller Coaster

SWL = Shock wave Lithotripsy
PNL = Percutaneous Nephrolithotomy
URS = Ureteroscopy
FBI = Federal Bureau of Investigation
ESPN – you know that!
**Ureteroscopy (URS) : Flexible or Rigid**

- **Indications**
  - Stones in the lower to middle ureter
  - Can be used for proximal stones depending on degree of visualization
  - Stone removal achieved
    - **Forceps**
    - Ultrasonic / pneumatic / laser / electrohydraulic fragmentation (intracorporeal lithotripsy)
Ureteroscopy

Holmium Laser fragmentation With URS
Shock Wave Lithotripsy

- Ideal for calcium based stones < 1 cm in diameter in the renal pelvis or ureter
  - Proximal ureteric stones can be pushed back into the renal pelvis to allow for better visualization and targeting:
  - “Push-Bang” technique
SWL : Potential Renal Complications

- Incomplete Stone Fragmentation - Obstruction
- Renal Parenchymal Injury
- Decrease GFR
- HTN

SWL
10. Clinicians should inform patients that SWL is the procedure with the least morbidity and lowest complication rate, but URS has a greater stone-free rate in a single procedure. **Strong Recommendation; Evidence Level Grade B**

11. In patients with mid or distal ureteral stones who require intervention (who were not candidates for or who failed MET), clinicians should recommend URS as first-line therapy. For patients who decline URS, clinicians should offer SWL. **Strong Recommendation; Evidence Level Grade B**

12. URS is recommended for patients with suspected cystine or uric acid ureteral stones.

13. In patients with total renal stone burden >20 mm, clinicians should not offer SWL as first-line therapy.
Over several years, a notable number of our patients reported passing renal calculi spontaneously after riding the Big Thunder Mountain Railroad roller coaster at Walt Disney World’s Magic Kingdom theme park in Orlando, Florida. The number of stone passages was sufficient to raise suspicions of a possible link between riding a roller coaster and passing renal calculi.
Kidney stones were placed in the upper – mid and lower poles and analysis was based on how many ended up in the lower (bladder) at the end of the ride.
Where is the Best Place to Sit on a Roller Coaster if you have a Stone??

The Back Seats!!

<table>
<thead>
<tr>
<th>Pass</th>
<th>Front</th>
<th>Back</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>67</td>
<td>58</td>
</tr>
</tbody>
</table>

- 4 mm
- 13 mm

Case Presentation

The stone is not passing spontaneously with medical management and prayer! What is the next choice for removing renal / ureteral stones?

A. SWL
B. PNL
C. URS
D. FBI
E. CIA
F. Do Jumping Jacks
G. Ride a Roller Coaster
Followup

Guideline Statement 23.

After the initial follow-up, clinicians should obtain a single 24-hour urine specimen annually or with greater frequency, depending on stone activity, to assess patient adherence and metabolic response. (Expert Opinion)

Guideline Statement 27.

Clinicians should periodically obtain follow-up imaging studies to assess for stone growth or new stone formation based on stone activity (plain abdominal imaging, renal ultrasonography or low dose computed tomography [CT]). (Expert Opinion)

1 year followup with plain KUB or ultrasound if the stone is made of uric acid (radiolucent)
True – Grit Theory of Stone Formation

• “The longer we tend to live the more we begin to harden: First to calcify, then to ossify, and finally, like the forests and the plants of the sea to petrify. One may view all of history as the slow migration of the human species from one Stone Age to another.”

Richard Selzer Esquire 1985
The Kidney Rocks !!!