STONES
Dietary and Medical Therapy
Prevention
Adjuvant

Manoj Monga, MD
The Cleveland Clinic
Incidence and Prevalence

- Worldwide, 1 in 10 people experience a kidney stone in their lifetime
- Recurrence rates are high
  - 30% to 50% chance of developing another stone within 5 years
  - Average rate of new stone formation: 1 stone every 2 to 3 years
- Prevalence has increased
  - Faster rate of increase in women
EMPIRIC DIETARY TX

Conservative treatment plan

- High fluid intake (Ten 10-oz glasses)
- Dietary sodium restriction (1500 mg/day)
- Dietary citrate (4oz concentrated lemon/lime)
- Adequate calcium intake
  - 2 to 3 dairy servings per day
  - 1200 mg daily
Fluids
Target – 2L of urine
5-year follow-up

J Urol 155: 839, 1996

P = .008

P = .016
Type of Soda – what happens when you stop?

Stone recurrence rate (%)

- >160 ml/day
- Abstain

Control
Phosphoric acid
Citric acid

Schuster, 1992
Citrate Effect on Lithogenesis

Supersaturation

Nucleation and growth

Binds ionic Ca

Inhibits spontaneous and heterogeneous Nucleation

Growth and aggregation

Retards agglomeration of preformed CaOx crystals and inhibits crystal growth of CaP

Membrane molecules exposed

Modified:
courtesy of Kris Penniston PhD

Crystal-cell binding

Renal stone
Lemon Juice 4 oz / day

![Graph showing the change in Citrate and Oxalate levels before and after lemon juice consumption. The graph indicates a significant decrease in Citrate levels (P < 0.001) and no significant change in Oxalate levels.]

J Urol 156: 907, 1996
## IMPACT OF FRUITS & VEGGIES

<table>
<thead>
<tr>
<th></th>
<th>Elimination of F&amp;V</th>
<th>Addition of F&amp;V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Subjects</td>
<td></td>
<td>Stone Formers</td>
</tr>
<tr>
<td>Urinary K</td>
<td>-62%</td>
<td>+68%</td>
</tr>
<tr>
<td>Urinary Mg</td>
<td>-26%</td>
<td>+23%</td>
</tr>
<tr>
<td>Urinary Cit</td>
<td>-44%</td>
<td>+68%</td>
</tr>
<tr>
<td>Urinary Ca</td>
<td>+49%</td>
<td>+10%</td>
</tr>
<tr>
<td>Saturation CaOx</td>
<td>+30%</td>
<td>-52%</td>
</tr>
</tbody>
</table>

Borghi, et al, 2005

Courtesy Dr Glenn Preminger, AUA Review Course Content, 2015
Dietary Citrate

- **CITRIC ACID**
  - Lemon
  - Lime
  - Orange
  - Citrate
  - pH
  - K+

- **POTASSIUM CITRATE**
  - Melon
  - Tomato
  - Citrate

J Endourol 26: 1221-6, 2012
Limit Calcium

- Low dietary calcium increases risk of symptomatic kidney stones

  NEJM 328: 833-8, 1993
  Ann Int Med 126: 553-5, 1997
  NEJM 346: 77-84, 2002
Stone Formers Have Lower Ca$^{++}$ Intake

Dietary Calcium Intake (mg/d)

Calcium supplement users: RR 1.20

Curhan GC, NEJM 1993; Annals Int Med 1997; Archives Int Med 2004
Calcium Content

1200 mg / day

- Milk 8 oz: 300 mg
- Yogurt 8 oz: 350 mg
- Cheese 1 oz: 200 mg
- Salmon ½ cup: 250 mg
Salt

- Every 2300 mg of Salt (one teaspoon)
  - 23 mg increase in urinary calcium
    - higher rates of bone resorption
    - effect greater if low dietary calcium
    - decreases urinary citrate 20%
• 77% OF SALT COMES FROM EATING OUT OR EATING PROCESSED FOOD

[Image of Sodium Facts, United States chart]

- Average daily sodium intake age 2 and up: 3,436 mg
- Tolerable Upper Intake Level: 2,300 mg
- Recommended Adequate Intake Level: 1,500 mg
- How much daily sodium our bodies need: 180–500 mg

Decreasing sodium intake could prevent thousands of deaths annually.^^

^^Because nearly 400,000 deaths each year are attributed to high blood pressure.
EFFECT OF LOW SALT DIET ON IDIOPATHIC HYPERCALCIURIA


62% normalized urinary calcium with sodium restriction
# UroRisk Diagnostic Profile

## Metabolic

<table>
<thead>
<tr>
<th>Ca</th>
<th>Ox</th>
<th>UA</th>
<th>Cit</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>283</td>
<td>28</td>
<td>419</td>
<td>845</td>
<td>5.91</td>
</tr>
<tr>
<td>mg/day</td>
<td>mg/day</td>
<td>mg/day</td>
<td>mg/day</td>
<td></td>
</tr>
</tbody>
</table>

## Environmental

<table>
<thead>
<tr>
<th>TV</th>
<th>Na</th>
<th>P</th>
<th>Mg</th>
<th>CaOx</th>
<th>Br</th>
<th>NaU</th>
<th>UA</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.84</td>
<td>130</td>
<td>921</td>
<td>71</td>
<td>1.17</td>
<td>0.73</td>
<td>0.50</td>
<td>0.74</td>
</tr>
<tr>
<td>l/day</td>
<td>mcg/day</td>
<td>mg/day</td>
<td>mg/day</td>
<td>CaOx</td>
<td>Br</td>
<td>NaU</td>
<td>UA</td>
</tr>
</tbody>
</table>

## Other Values

- **K**: 57 meq/day
- **Creatinine**: 1104 mg/day

---

**Increased Risk**

**Reduced Risk**
Fish Oil

- Cold water fish
- Eicosapentanoic acid (n-3 fatty acid)
- Competes with arachidonic acid (n-6)
- **LESS PGE2**
  - Less renal CA excretion
  - Activation of Na/K/Ca – more CA reabsorption
  - Decreased 1,25 Vitamin D levels
  - Decreased bone resorption
  - ? Impact on ureteral contractility in obstruction
Hypercalciuria: Omega 3 Fatty Acids

- salmon, tuna, mackerel
- sardines, walnuts, flax seeds, canola oil
EPA 1800 mg for 18 months

Urinary CA
Yasui et al

Urinary Citrate
Ito et al
Thiazides

• Decrease urinary CA 20-30%
  – Distal Renal Tubule
  – Inhibit NA reabsorption, Increase CA reabsorption
• Increase Bone Mineral Density
• Ten randomized controlled studies
• *** monitor CA, K, UA, GLU***
• *** limit dietary sodium***
Indapamide
Urinary CA

J Cardiovasc Pharm 22 (Suppl 6: S78-S86, 1993)
Indapamide
Stone-free at 3 years

J Cardiovasc Pharm 22 (Suppl 6: S78-S86, 1993)
Thiazides and stone recurrence

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Thiazide</th>
<th>Control</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ettinger 1988</td>
<td>6</td>
<td>14</td>
<td>0.32 [0.14, 0.73]</td>
</tr>
<tr>
<td>Borghi 1993</td>
<td>6</td>
<td>9</td>
<td>0.33 [0.13, 0.79]</td>
</tr>
<tr>
<td>Lauerum 1984</td>
<td>5</td>
<td>12</td>
<td>0.45 [0.19, 1.09]</td>
</tr>
<tr>
<td>Fernández-Rodriguez 2006</td>
<td>31</td>
<td>28</td>
<td>0.55 [0.38, 0.81]</td>
</tr>
<tr>
<td>Ahlstrand 1996</td>
<td>9</td>
<td>19</td>
<td>0.61 [0.38, 0.99]</td>
</tr>
<tr>
<td>Ala-Opas 1987</td>
<td>6</td>
<td>12</td>
<td>0.80 [0.34, 1.90]</td>
</tr>
<tr>
<td>Scholz 1982</td>
<td>6</td>
<td>6</td>
<td>1.04 [0.39, 2.80]</td>
</tr>
</tbody>
</table>

Total (95% CI) 278/220 100.0% 0.55 [0.43, 0.70]

Heterogeneity: Tau² = 0.00; Chi² = 5.76, df = 6 (P = 0.45); I² = 0%
Test for overall effect: Z = 4.93 (P < 0.00001)

N=565
Mean duration 34 months
Cumulative incidence of vertebral fractures among Rochester, Minnesota, residents following the initial episode of symptomatic urolithiasis, 1950 to 1974.

Observed (solid line) and expected (dashed line)

Women’s Health Initiative
Risk of Stones in Ca/Vit D vs placebo

Risk of kidney stones 17% higher in Ca + D group
(HR 1.17, 95% CI 1.02 to 1.34)

Although rate of hip fx was 12% lower with Ca + D, the difference was not significant
(95% CI 0.72-1.08)
Effect of Potassium Citrate on Bone Density, Microarchitecture, and Fracture Risk in Healthy Older Adults without Osteoporosis: A Randomized Controlled Trial

K citrate 60 meq qd with calcium and vitamin D

Jehle S et al, JCEM epub 11/15/2012
Effect of thiazide/indapamide and K-Cit on BMD of the L2–L4 spine, femoral neck, and radial shaft of hypercalciuric kidney stone formers.

Average dose
Kcitrate 35 meq/d

Mean f/u = 3.7 yr

Data are expressed as percentage of normal, matched for age and gender (Z-score). **Indicates P=0.001, †indicates P<0.001. Bars above the blocks represent mean±s.d.


Urine Ca (mg/d):
Pre Rx - 346 ± 85
On Rx - 248 ± 79

Stone formation rate/year:
Pre Rx – 2.9 ± 9.3
On Rx – 0.05 ± 0.3
Hypercalciuria

- Indapamide 1.25 to 2.5 mg/day
- Chlorthalidone 25 mg/day
- HCTZ 25mg BID
- $+ K_3$Cit (eg, Urocit®-K)
  - 15 mEq daily
Alkaline therapy

- INCREASE PH
  - Decrease supersaturation of CAOX and CAPH
  - Decrease stone growth and aggregation
Stone-Free Rate at 3 years

- J Urol 150: 1761, 1993
- Br J Urol 73: 362, 1994
- J Urol 158: 2069, 1997
Stone Formation Rate
Preminger 3 year followup

$P < 0.0001$

Citrates and stone recurrence

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Citrate</th>
<th>Control</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Soygur 2002</td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>28</td>
<td>8</td>
</tr>
<tr>
<td>Ettinger 1997</td>
<td>4</td>
<td>31</td>
<td>21</td>
</tr>
<tr>
<td>Barcelo 1993</td>
<td>5</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>Hofbauer 1994</td>
<td>11</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>93</td>
<td>103</td>
<td>100.0%</td>
</tr>
<tr>
<td>Total events</td>
<td>20</td>
<td>61</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 1.05; Chi² = 20.62, df = 3 (P = 0.0001); I² = 85%
Test for overall effect: Z = 1.83 (P = 0.07)

N=479
Mean Duration 29 months

# UroRisk®
## Diagnostic Profile

<table>
<thead>
<tr>
<th>Metabolic</th>
<th>Environmental</th>
<th>Relative Supersaturation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca</td>
<td>pH</td>
<td>TV</td>
</tr>
<tr>
<td>Ox</td>
<td>Na</td>
<td>NaU</td>
</tr>
<tr>
<td>UA</td>
<td>P</td>
<td>Mg</td>
</tr>
<tr>
<td>Cit</td>
<td>Mg</td>
<td>CaOx</td>
</tr>
</tbody>
</table>

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<thead>
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<th>Environmental</th>
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<td>Na</td>
<td>NaU</td>
</tr>
<tr>
<td>UA</td>
<td>P</td>
<td>Mg</td>
</tr>
<tr>
<td>Cit</td>
<td>Mg</td>
<td>CaOx</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ca</th>
<th>Ox</th>
<th>UA</th>
<th>179</th>
<th>57</th>
<th>805</th>
<th>1859</th>
<th>5.57</th>
<th>1.83</th>
<th>225</th>
<th>794</th>
<th>176</th>
<th>1.54</th>
<th>0.26</th>
<th>2.83</th>
<th>3.68</th>
</tr>
</thead>
<tbody>
<tr>
<td>mg/day</td>
<td>mg/day</td>
<td>mg/day</td>
<td>mg/day</td>
<td>l/day</td>
<td>meq/day</td>
<td>mg/day</td>
<td>mg/day</td>
<td>mg/day</td>
<td>mg/day</td>
<td>mg/day</td>
<td>mg/day</td>
<td>mg/day</td>
<td>mg/day</td>
<td>mg/day</td>
<td></td>
</tr>
</tbody>
</table>

**Other Values**

- **K**: 75 meq/day
- **Creatinine**: 2311 mg/day
<table>
<thead>
<tr>
<th>Oxalate-rich foods</th>
<th>Food item</th>
<th>1 serving</th>
<th>Oxalate content (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinach, cooked</td>
<td>½ cup</td>
<td>755</td>
<td></td>
</tr>
<tr>
<td>Rhubarb</td>
<td>½ cup</td>
<td>541</td>
<td></td>
</tr>
<tr>
<td>Almonds</td>
<td>1 oz</td>
<td>122</td>
<td></td>
</tr>
<tr>
<td>Beets</td>
<td>½ cup</td>
<td>76</td>
<td></td>
</tr>
</tbody>
</table>
Simplified oxalate diet

- University of Wisconsin
  - focus on spinach, nuts & seeds, and potatoes;
    - 44% of oxalate intake
    - lowest calcium:oxalate ratios….high bioavailability
    - teas, fruits and leafy green vegetables other than spinach accounted for <10% of total oxalate consumed
      - (Abstract 2060)
CHOCOLATE
Calcium and Oxalate

<table>
<thead>
<tr>
<th></th>
<th>Urinary Oxalate</th>
</tr>
</thead>
<tbody>
<tr>
<td>DARK</td>
<td>5</td>
</tr>
<tr>
<td>MILK</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Oxalate (mg)</th>
<th>Calcium (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DARK</td>
<td>94</td>
<td>26</td>
</tr>
<tr>
<td>MILK</td>
<td>94</td>
<td>430</td>
</tr>
</tbody>
</table>
Vitamin B-6

• ↑ oxalate excretion with B-6 deficient diet
• ↓ stone risk with ↑ B-6 intake
• Co-factor in AGT conversion of glyoxylate to glycine
Hyperoxaluria: Vitamin B6

- bananas, avocados, soybeans, halibut, mangos, oatmeal
  - fortified ready-to-eat cereals, select breads

Supplements:
50mg ....100mg.....200mg
Vit B6 and Hyperoxaluria

57 pts
15 month follow-up
72% of pts responded

P<0.0001

P<0.001
URIC ACID STONES

- Radiolucent on KUB
- Hounsfield units <320
- Urine pH <5.5
- Gout
- DISSOLVE – Alkalinize
- PREVENT – Alkalinize and Allopurinol
Sources of Uric Acid

• End product of purine metabolism
  – Endogenous
    • de novo synthesis / catabolism of nucleic acid
    • 300-400 mg/day
  – Exogenous
    • dependent on dietary intake
    • Average 200-300 mg/day
High animal protein diet

• Increases urinary calcium, uric acid
• Decrease citrate and urinary pH
• Increase bone resorption due to increased acid-ash content

Br J Urol 56: 263, 1984
Am J Kid Dis 40: 265, 2002
PROTEIN

• Not a low protein recommendation but rather adequate protein
• 0.8-1.0 grams/kilogram
• Plant protein less likely to make urine acidic
pH Dependence of Uric Acid Solubility

- Solubility of Uric Acid (pKa = 5.57)
  - pH 5.0  60 mg per L
  - pH 6.0  200 mg per L
  - pH 7.0  1600 mg per L

K-Cit 15 mEq qD and titrate up if needed

pH 6.5
BODY WEIGHT AND URINARY PH

Mechanism is independent of diet

 Courtesy Dr Glenn Preminger, AUA Review Course Content, 2015 Sakhaee, Coe, Pak 2004
IMPACT OF OBESITY

% PREVALENCE OF URIC ACID STONES

Obese Patients: 63%
Control Group: 11%

Courtesy Dr Glenn Preminger, AUA Review Course Content, 2015  Ekeruo, et al, 2004
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male 175 (57) 134 (43)</td>
<td>101 (44) 128 (56)</td>
<td>.004</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>&lt;50 220 (71) 89 (29)</td>
<td>122 (53) 107 (46)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td></td>
<td>≥50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>N &lt;25 129 (41) 112 (36)</td>
<td>83 (36) 65 (28)</td>
<td>.003</td>
</tr>
<tr>
<td></td>
<td>Overweight 68 (22)</td>
<td>81 (35)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Obese (≥30)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

What’s changing in the 24 hour urine?
What's changing in the 24 hour urine?

<table>
<thead>
<tr>
<th>Condition</th>
<th>Risk Factors</th>
<th>Group 1</th>
<th>Group 2</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypocitraturia</td>
<td>All Patients</td>
<td>142 (46)</td>
<td>137 (60)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Obese (BMI ≥ 30)</td>
<td>27 (40)</td>
<td>51 (63)</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>N (BMI &lt; 25)</td>
<td>68 (53)</td>
<td>48 (58)</td>
<td>.465</td>
</tr>
<tr>
<td>Hyperoxaluria</td>
<td>All Patients</td>
<td>72 (23)</td>
<td>69 (30)</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>Males</td>
<td>56 (32)</td>
<td>53 (53)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Females</td>
<td>16 (12)</td>
<td>16 (13)</td>
<td>.89</td>
</tr>
</tbody>
</table>
MP01-16: Metabolic syndrome increases the risk for calcium oxalate stone formation: results from a Nationwide Survey on Urolithiasis in Japan
Akinori Iba et al, Wakayama, Japan

- 4,440 pts
- # MetS traits correlated with severity of CaOx stone disease
  - 3-4 MetS traits, 1.8x risk for recurrent/multiple stones
- MetS traits associated with ↑ odds hypercalciuria
MP01-12: THE ASSOCIATION OF HEMOGLOBIN A1C AND URINARY OXALATE IN STONE FORMERS

Kyle Wood, Birmingham, AL, Marc Colaco, Winston-Salem, NC, John Knight, Ross Holmes, Dean Assimos, Birmingham, AL

- 1,428 Patients
- ↑ BMI correlated with ↑ Uox
- ↑ A1C correlated with ↑ Uox
Allopurinol

• End product of purine metabolism
  – Endogenous
    • xanthine – uric acid

Allopurinol if:
  • fails to correct with dietary measures
  • Urinary uric acid >900 mg/day
  • Start at 100mg and titrate to 300mg if needed
NO RCTs evaluating impact on stone recurrence

- Uric acid stones
  - Allopurinol
  - Alkalinization
Responders to Diet

137 pts
10 months f/u
Percentage of patients responding to Medical Therapy

127 pts

Average follow up 14.39±17.36 months
MEDICARE
65 YEARS OR OLDER

PRIVATE
18-64 YEARS OLD

UROLOGIC DISEASES IN AMERICA (NIH-JOHNS HOPKINS)

(COURTESY BRIAN MATLAGA)
MP16-19  Adherence rates for selective medical kidney stone prevention

Claims data – 22102 patients
MORE COMPLIANT:
Men, Midwest, Salaried, Multiple drugs

The Journal of Urology 2015 193, DOI: (10.1016/j.juro.2015.02.1632)
MP41-04 CONSEQUENCES OF NON-ADHERENCE TO SELECTIVE MEDICAL THERAPY AMONG PATIENTS WITH KIDNEY STONES

COMPLIANT PATIENTS HAVE LESS ADMISSIONS 30% ED VISITS 25% ED SURGERY 13%

Claims data – 8590 patients 57% adherent to preventive medications
EXERCISE AND STONES

• National Health and Nutrition Examination Survey database from 2010-2011
  ‘Have you ever had a kidney stone.’ 8.3% YES

Q1: *moderate intensity sports* for at least 10 minutes continuously?
  RR 0.739

Q2: *vigorous intensity sports* for at least 10 minutes continuously
  RR 0.842

Q3: *For the usual way you travel* do you walk / bicycle for at least 10 minutes
  RR 0.854

Q4: *Does your work involve vigorous-intensity activity* for at least 10 minutes continuously.
  RR 1.334
Can a simplified 12-hour nighttime urine collection predict urinary stone risk?

Bryan D. Hinck, Vishnu Ganesan, Sarah Tarplin, John Asplin, Ignacio Granja, Juan Calle, Sri Sivalingam, Manoj Monga

- Can we do better?....Hypothesis
  - A 12-hour, nighttime urine collection will be as sensitive as a 24-hour urine collection
- May be a BETTER predictor of stone risk:
  - more concentrated: may reveal more abnormalities\(^4,5\)
- Potential Significance:
  - Increased compliance
  - Decreased patient burden
  - Decreased dependence on weekend collections

Can a simplified 12-hour nighttime urine collection predict urinary stone risk?

Bryan D. Hinck, Vishnu Ganesan, Sarah Tarplin, John Asplin, Ignacio Granja, Juan Calle, Sri Sivalingam, Manoj Monga
Night vs. 24 hr urine Supersaturations

- detected 5 of 5
- 2 additional cases

- detected 7 of 8
- 4 additional cases

- detected 8 of 9
- 1 additional case
Is Night-time collection adequate for clinical decision making?

• Night-time values identified:
  – > Ox = 14/14 pts
  – < Cit = 21/21 pts
    • Also an additional pt (F with 266 mg/12hr)
  – > UA = 6/6 pts
    • Also an additional pt (M with 436.2 mg/12hr)
  – > Na = 29/30 pts
Is Night-time collection adequate for clinical decision making?

• **Night-time values identified:**
  – > Ca = 14/16 pts
  • Pts “missed”
    – 258.81 mg/d (F) vs 81.05 mg/12hr (F)
    – 255.58 mg/d (M) vs 105.48 mg/12hr (M)
    – **NOTE:** These two pts had elevated night-time NA so would have received appropriate dietary counseling
  • Additional pt identified
    – 177.58 mg/d (F) vs 115.07 mg/12hr (F)
Conclusions

• Strong correlation between 12-hr night collection and 24-hr collection
• BETTER detection of stone risk factors
• Potential benefits:
  • Improved compliance
  • Decrease patient burden
  • Allow for increased weekday collection