Kidney Stones: Diagnosis, Treatment, & Future Prevention

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PGY 3

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ARUP LABORATORIES

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Learning Objectives

1. Describe the clinical presentation, laboratory, and radiographic findings of an individual affected by a kidney stone.
2. Compare 3 composition types of kidney stones and their clinical management.
3. Differentiate spontaneous and familial risk factors for kidney stone development.

Outline

- Case-based Approach:
  - Diagnosis of a Kidney Stone
  - Epidemiology
  - Pathogenesis
  - Risk Factors
  - Management
  - Further Work-up
  - Prevention
  - Complications

Case #1: 38 year old male

- Flank pain
  - Acute, colicky
  - Radiating to pelvis and genitalia
- Nausea and vomiting
- Urinary urgency, frequency, and dysuria
- This has happened once before…

http://www.md-health.com/Kidney-Stones.html

Differential Diagnosis

- Urinary tract infection
- Musculoskeletal pain
- Groin hernia
- Acute pyelonephritis
- Prostatitis

- Women:
  - Ectopic Pregnancy
  - Ovarian torsion
  - Ovarian cyst rupture

Indications for testing:

Flank pain, Nausea & vomiting, and/or symptoms of a stone

↓

Order: Urinalysis

↓

Hematuria

↓

Imaging

↓

Strain urine and stone analysis

If second stone, consider 24 hour urine

Emergency Department Work-Up

- Complete blood count
- Comprehensive metabolic panel
- Urinalysis
- Imaging

CBC Normal Values for Adult Male

RBC	4.7-6.4 M/uL
WBC	4.5-11K/uL
Hgb	14-18 g/dL
Hct	40-50%
MCV	78-98 fL
MCH	27-35pg
MCHC	31-37%
Neutrophils	50-81%
Bands	1-5%
Lymphocytes	14-44%
Monocytes	2-6%
Eosinophils	1-5%
Basophils	0-1%

Comprehensive Metabolic Panel	
Glucose	65-100 mg/dL
BUN	8-25 mg/dL
Creatinine	0.6-1.3 mg/dL
EGFR	>60 ml/min/1.73
Sodium	133-146 mmol/L
Potassium	3.5-5.3 mmol/L
Chloride	97-110 mmol/L
Carbon dioxide	18-30 mmol/L
Calcium	8.5-10.5 mg/dL
Protein, total	6.0-8.4 g/dL
Albumin	2.9-5.0 g/dL
Bilirubin, total	0.1-1.3 mg/dL
Alkaline phosphatase	30-132 U/L
AST	5-35 U/L
ALT	7-56 U/L

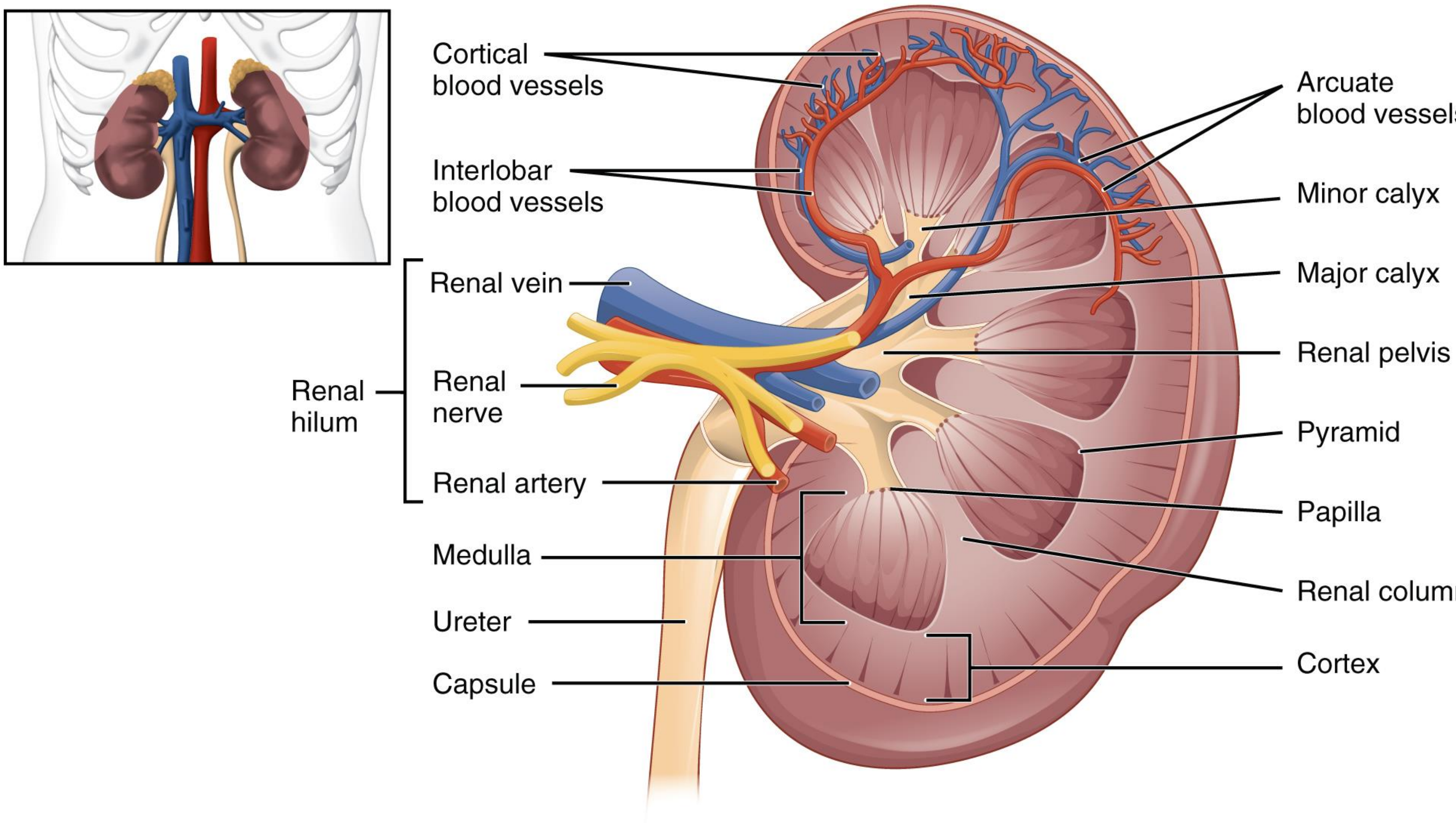
Leukocytes 120s	Neg.			Trace 15	Small 70	Moderate 125	Large 500	cacells/µl
Nitrite 60s	Neg.				Positive (Any degree of uniform pink color)			
Urobilinogen 60s	3.2	Normal	16		32 +	64 ++	128 +++	µmol/l
Protein 60s	Neg.		Trace ±	0.3 +	1.0 ++	3.0 +++	≥20.0 ++++	g/l
pH 60s	5.0	6.0	6.5	7.0	7.5	8.0	8.5	
Blood 60s	Neg.	Non hemolyzed 10 Trace		Hemolyzed 10 Trace	25 Small	80 Moderate	200 Large	cacells/µl
Specific Gravity 45s	1.000	1.005	1.010	1.015	1.020	1.025	1.030	
Ascorbate 40s	0			0.6	1.4	2.8	5.0	mmol/l
Ketone 40s	Neg.		Trace 0.5	Small 1.5	Moderate 4.0	Large 8.0	Large 16	mmol/l
Bilirubin 30s	Neg.				Small 17	Moderate 50	Large 100	µmol/l
Glucose 30s	Neg.		5 Trace	15 +	30 ++	60 +++	110 ++++	mmol/l

https://www.alibaba.com/product-detail/disposable-multi-parameter-urine-strip_60024754250.html

UA Findings

- Hematuria, microscopic
  - Small amount of blood in urine
    - Still yellow in color
  - Single, most discriminating predictor of kidney stone if patient presents with unilateral flank pain
    - Present in 95% of patients on Day #1
    - Present in 65-68% of patients on Day #3 or #4

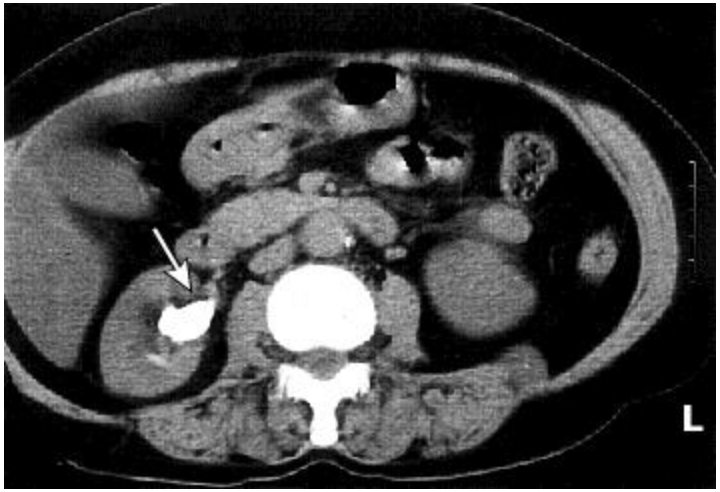
Kidney Anatomy

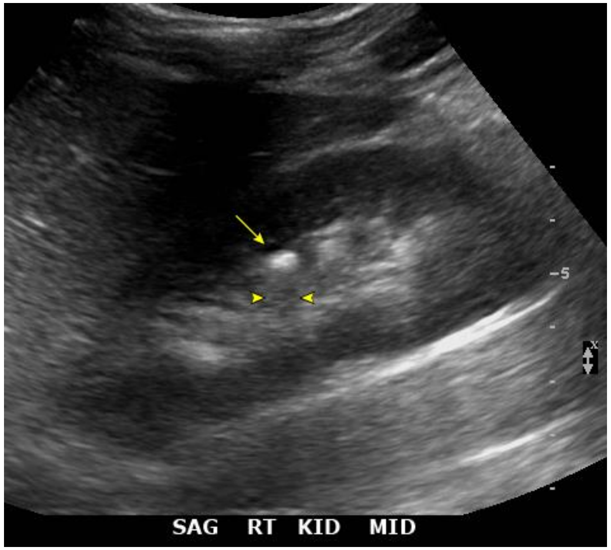


http://philschatz.com/anatomy-book/contents/m46429.html

Imaging

- Non-contrast helical CT
  - More sensitive (88%)
  - Radiation exposure, cumulative
- Ultrasonography
  - At bedside (54-57%)
  - No radiation





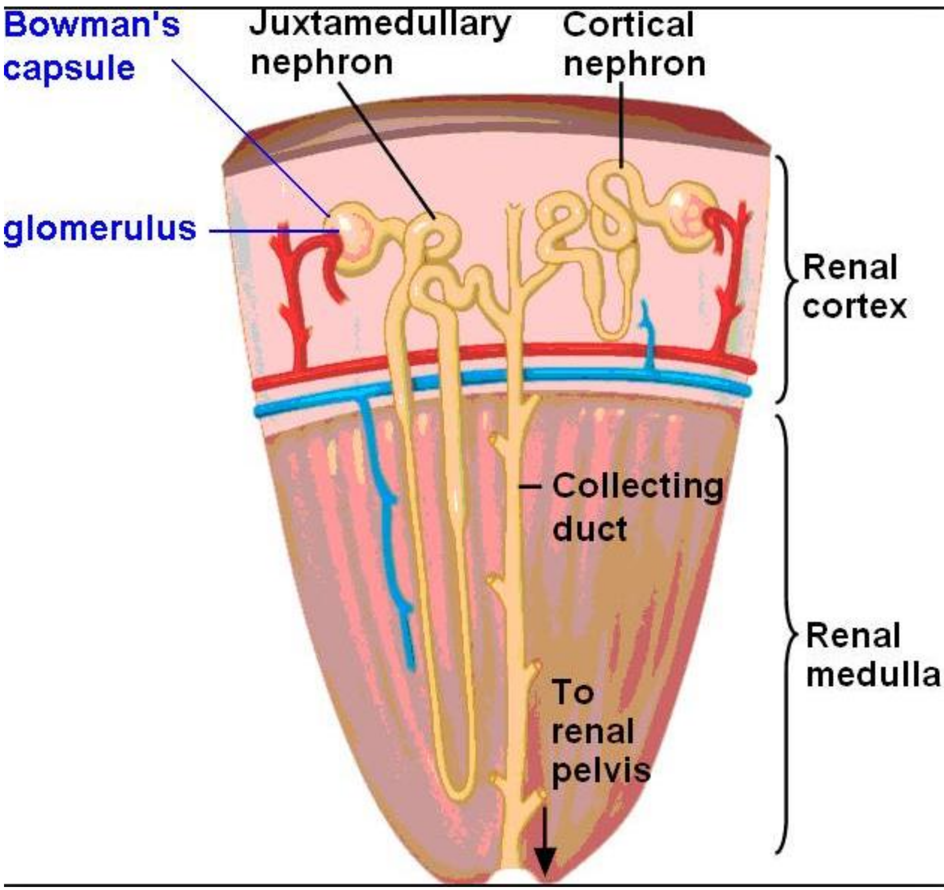
UpToDate.com

Epidemiology

- 1-5/1000 incidence
  - Approximately 1/11 affected in lifetime
  - Increased from 3.8% in 1970s to 8.8% in 2000s
- Peak incidence in 20s
  - Caucasian men
- Male > Female (2-3:1)
- Geography:
  - Hotter and drier climates

Pathogenesis Theory #1

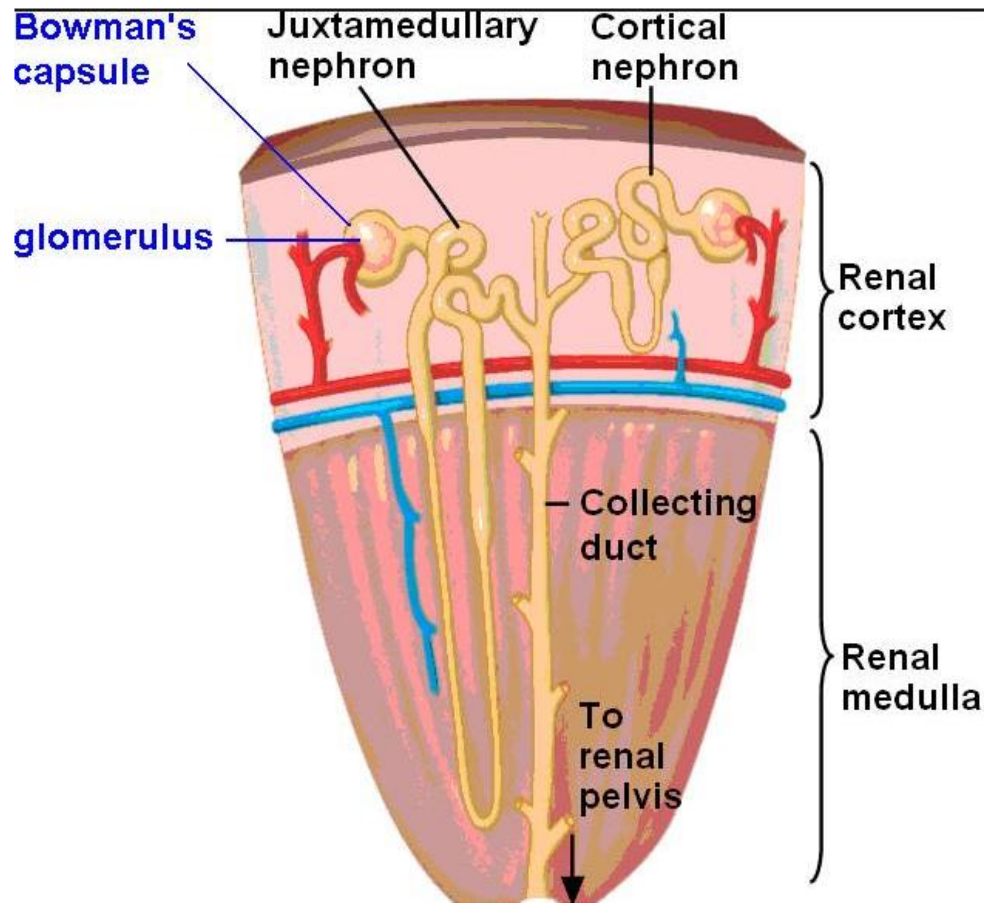
- Normally soluble material supersaturates within the urine and begins process of crystal formation.
- Becomes anchored at damaged epithelial cells.



http://bio1152.nicerweb.com/Locked/media/ch44/nephron.html

Pathogenesis Theory #2

- Initiated in renal medullary then extruded into renal papilla.
- Acts as a nidus for further deposition.



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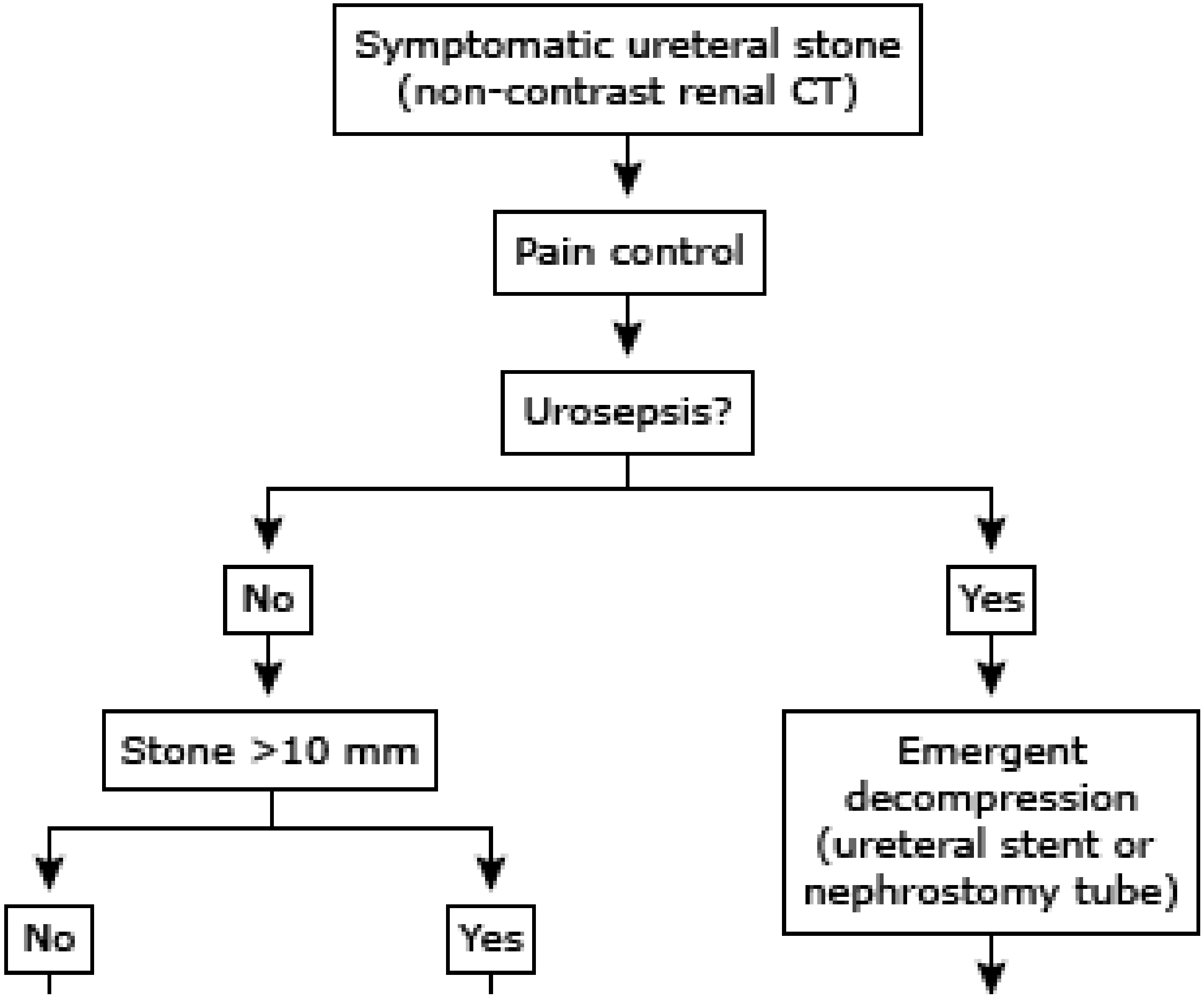
Risk Factors

- Urine composition
- Prior kidney stones
- Family history of kidney stones
- Enhanced enteric oxalate absorption
- Frequent upper urinary tract infections
- Hypertension
- Low fluid intake
- Acidic urine

Management and Treatment

Management of acute symptomatic nephrolithiasis



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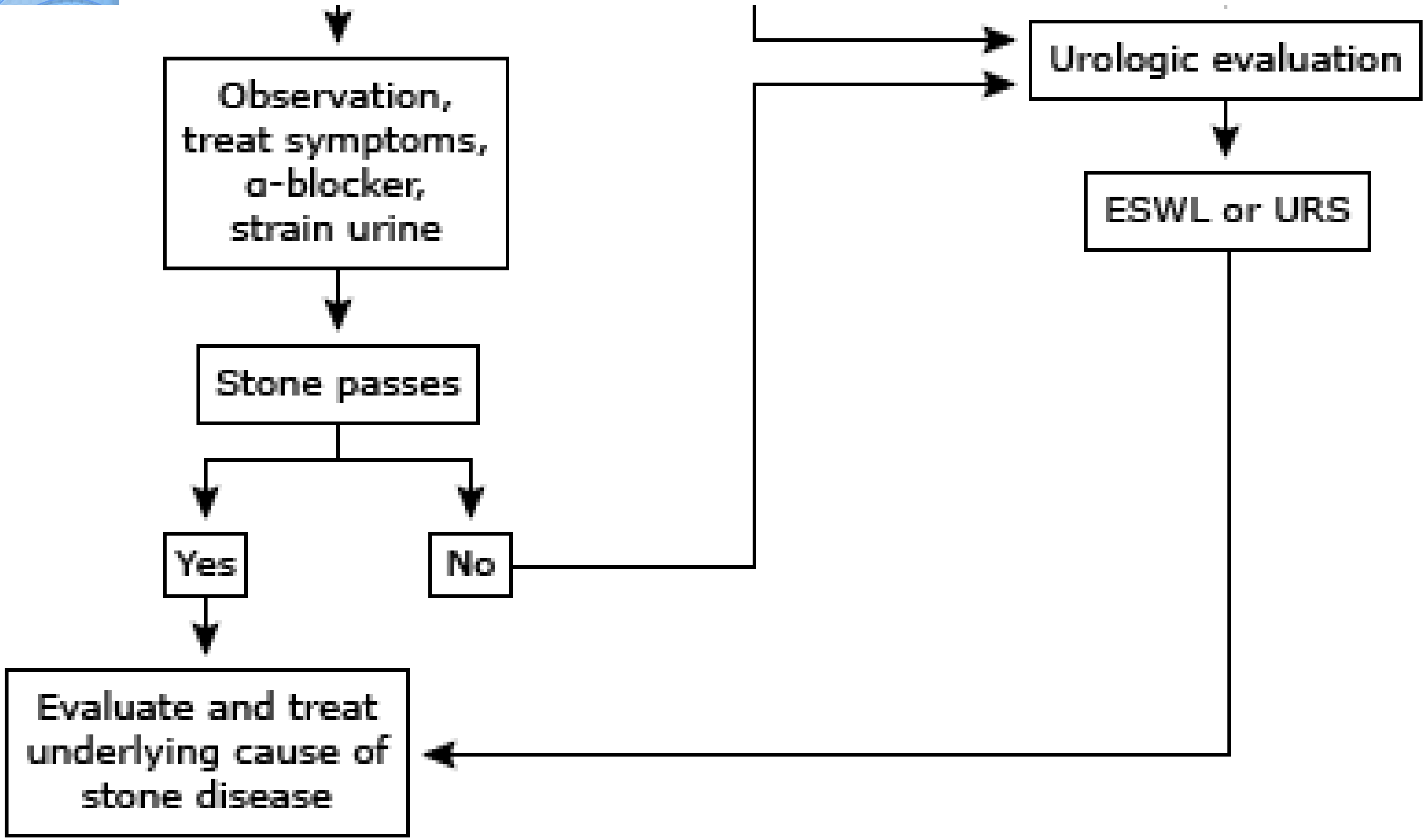

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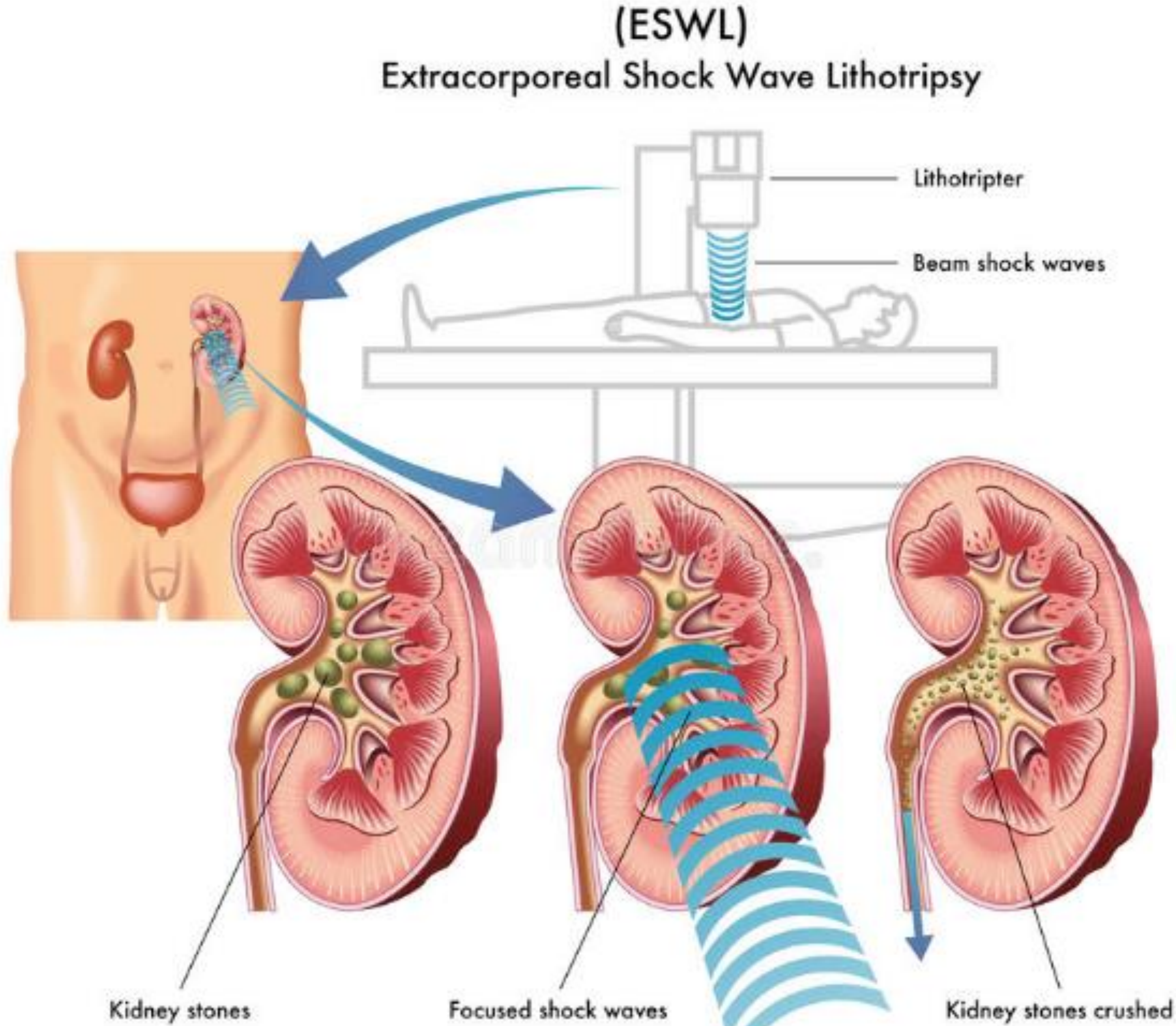
Conservative Management

- Hydration
- Pain management
- Alpha blockers
- Strain/filter urine

Aggressive Management

- Extracorpreal shock wave lithotripsy
- Ureterorendoscopic manipulation
- Open or laparoscopic surgery
- Decompression
    - Ureteral stent
    - Nephrostomy tube

Aggressive Management



https://www.dreamstime.com/stock-photo-extracorporeal-shock-wave-lithotripsy-medical-illustration-treatment-kidney-stones-image46835340

Further Work-up

- Chemistry panel
  - If serum calcium high-normal, then test parathyroid hormone concentration
- Stone analysis
- 24 hour urine
  - Measured 2-3 times
  - Wait 1-3 months after acute episode

Stone analysis

- Collect information from the stone to establish cause(s) of stone formation and growth
- Identify possible underlying metabolic disorders
- Guide preventative therapy

Types of Stones

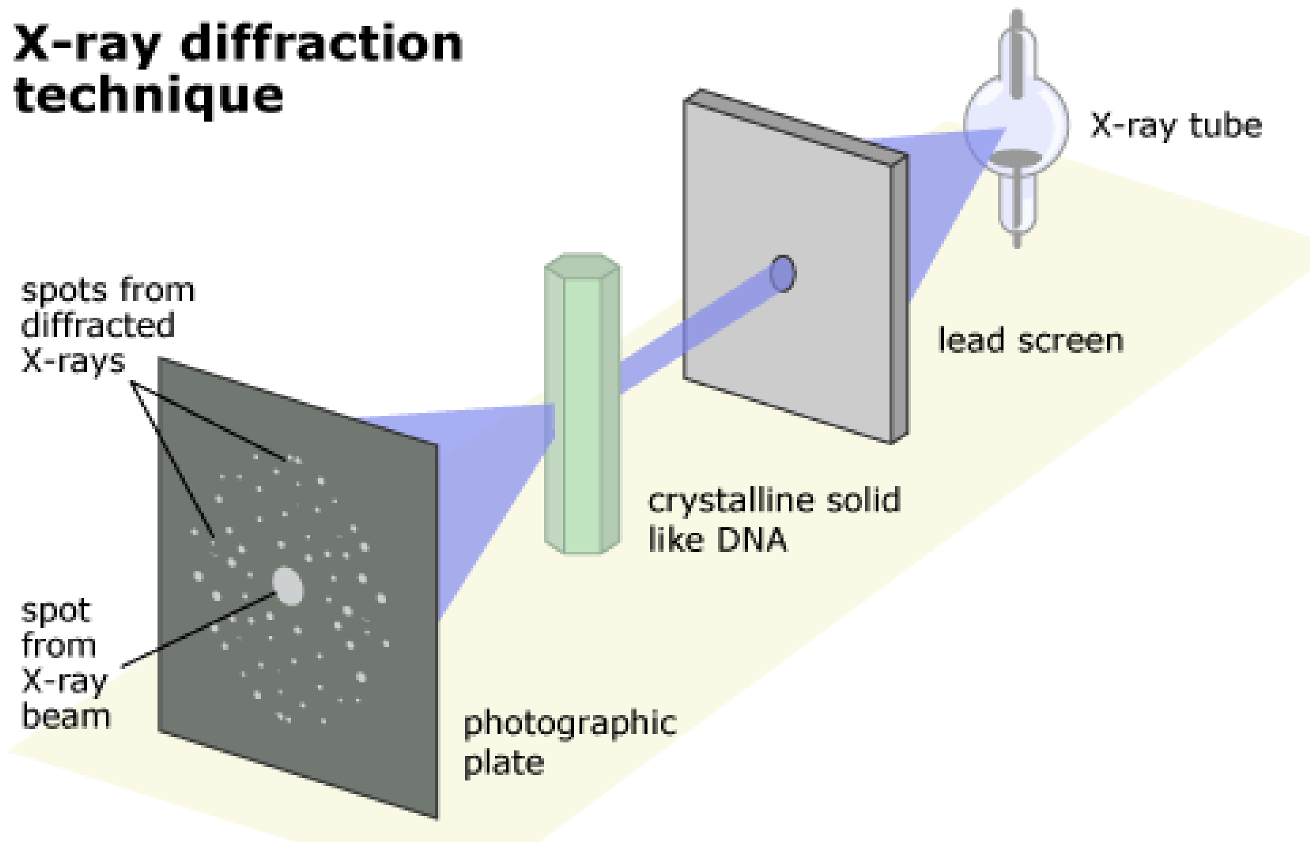
- Calcium stones
  - Calcium oxalate (~80%)
  - Calcium phosphate (~5-10%)
- Struvite stones (~10-15%)
  - Magnesium ammonium phosphate hexahydrate
- Uric acid stones (~5-10%)
- Cystine stones (~1-2%)
- Combination

Stone Analysis Testing Methods

- Chemical methods
  - Destructive and need several mg of sample
  - Cannot distinguish mineral constituents (with similar chemical composition)
- Physical methods
  - Need less sample
  - Distinguish different minerals within one stone

Physical methods

- X-ray diffraction (XRD)
- Fourier transform infrared spectroscopy



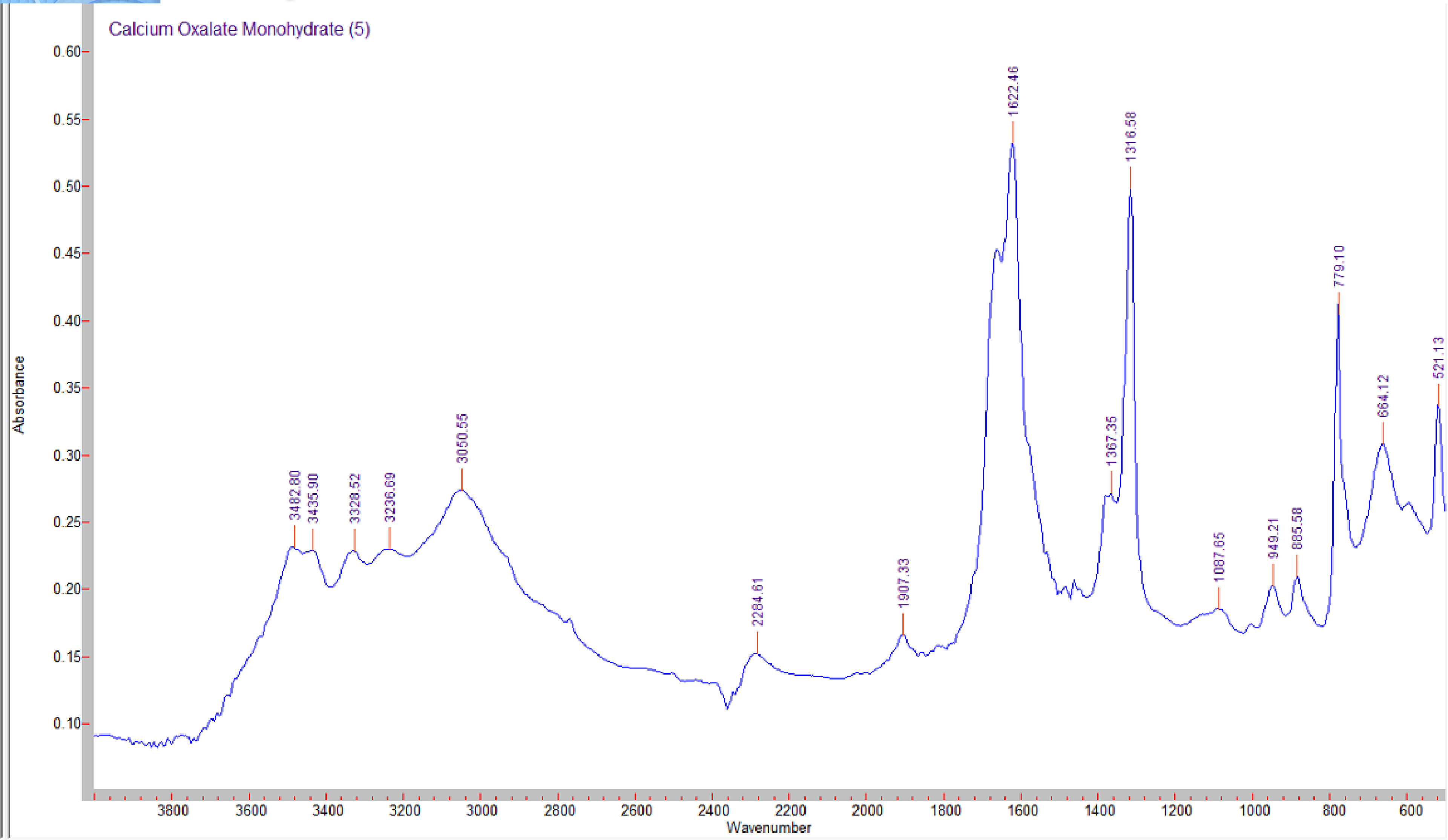
http://undsci.berkeley.edu/article/0_0_0/dna_04

Fourier Transform Infrared Spectroscopy

1. Crush into a powder
2. Infrared beam passes through powder
3. Molecular bonds within powder absorb portion of radiation giving a unique spectra

http://www.kwipped.com/rentals/laboratory/infrared-spectrometers/479

Spectrum



Calcium Oxalate Monohydrate (5)
Absorbance
Wavenumber
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
3482.80
3435.90
3328.52
3236.69
3050.55
2284.61
1907.33
1622.46
1367.35
1316.58
1087.65
949.21
885.58
779.10
664.12
521.13

Stone Analysis

- Calcium oxalate monohydrate
  - $Ca(COO)_2 \cdot H_2O$ (Whewellite)

ARUP

24 Hour urine collection

- Measure:
  - Volume
  - pH
  - Calcium
  - Uric acid
  - Citrate
  - Oxalate
  - Sodium
  - Creatinine

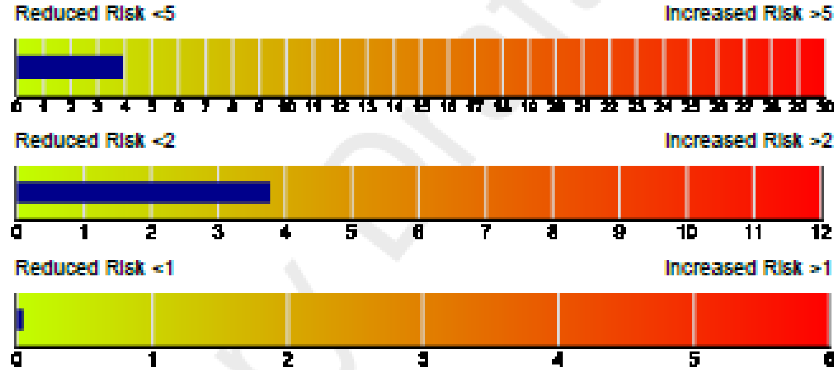
https://www.youtube.com/watch?v=BLq5NibwV5g

What is a supersaturation profile?

- Urine frequently supersaturated, favoring precipitation of crystals
  - Balanced by crystallization inhibitors: ions (citrate) and macromolecules
- Measure ion concentration
- Computer program can calculate theoretical supersaturation risk with respect to specific crystalline phases

Calculus	Calculated Risk
Calcium Oxalate	**3.93**
Calcium Hydrogen Phosphate	**3.78**
Uric Acid	**0.05**

Relative Supersaturation



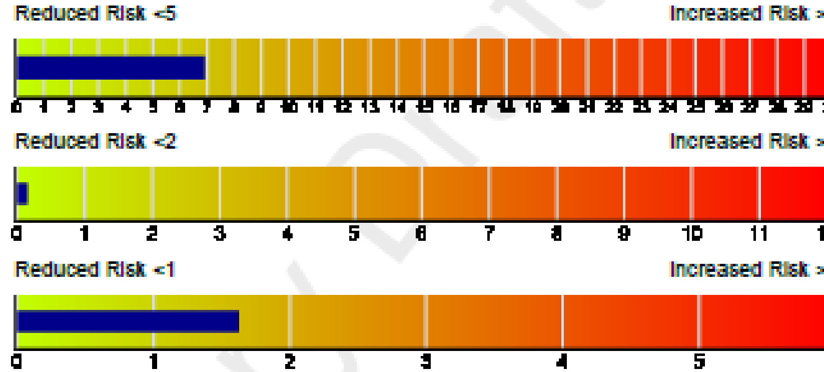
Calculated risk is derived by a computer program that models the thermodynamics of calculi formation using measured urine components.

Component Results

Analyte	Result	Units	Reference Interval	Effect
Total Volume	3600	mL		Low urine volume (<1L/24h) promotes calculi formation.
pH	6.94		5.00-7.50	Acidic urine (pH<5.5) promotes precipitation of UrA. Alkaline urine (pH>7.2) promotes formation of CaHPO4 stones.
Calcium	457	mg/d		Hypercalciuria (>200 mg/d) promotes formation of CaOx and CaHPO4 stones.
Oxalate	43	mg/d	16-49	Hyperoxaluria (>40 mg/d) promotes formation of CaOx stones.
Phosphorus	1152	mg/d	400-1300	Forms insoluble complexes with calcium.
Sodium	306	mmol/d	51-286	Increased sodium promotes formation of CaOx and CaHPO4 stones.
Sulfate	32	mmol/d	6-30	Normal to high sulfate promotes precipitation of CaOx and CaHPO4 stones.
Urate	839	mg/d	250-750	Hyperuricosuria (>600 mg/d) promotes formation of UrA stones.
Citrate	1109	mg/d	320-1240	High citrate inhibits formation of CaOx and CaHPO4 stones.
Magnesium	238	mg/d	12-199	High magnesium inhibits fomation of CaOx and CaHPO4 stones.
Potassium	140	mmol/d	25-125	Forms soluble complexes and inhibits stone formation.
Chloride	238	mmol/d	140-250	Forms soluble complexes and inhibits stone formation.
Creatinine	1548	mg/d	800-2100	Excretion provides a measure of completeness of 24h urine collection.

Calculus	Calculated Risk
Calcium Oxalate	**6.93**
Calcium Hydrogen Phosphate	**0.16**
Uric Acid	**1.63**

Relative Supersaturation



Calculated risk is derived by a computer program that models the thermodynamics of calculi formation using measured urine components.

Component Results

Analyte	Result	Units	Reference Interval	Effect
Total Volume	881	mL		Low urine volume (<1L/24h) promotes calculi formation.
pH	5.17		5.00-7.50	Acidic urine (pH<5.5) promotes precipitation of UrA. Alkaline urine (pH>7.2) promotes formation of CaHPO4 stones.
Calcium	67	mg/d		Hypercalciuria (>200 mg/d) promotes formation of CaOx and CaHPO4 stones.
Oxalate	27	mg/d	16-49	Hyperoxaluria (>40 mg/d) promotes formation of CaOx stones.
Phosphorus	335	mg/d	400-1300	Forms insoluble complexes with calcium.
Sodium	59	mmol/d	51-286	Increased sodium promotes formation of CaOx and CaHPO4 stones.
Sulfate	7	mmol/d	6-30	Normal to high sulfate promotes precipitation of CaOx and CaHPO4 stones.
Urate	263	mg/d	250-750	Hyperuricosuria (>600 mg/d) promotes formation of UrA stones.
Citrate	309	mg/d	320-1240	High citrate inhibits formation of CaOx and CaHPO4 stones.
Magnesium	50	mg/d	12-199	High magnesium inhibits fomation of CaOx and CaHPO4 stones.
Potassium	22	mmol/d	25-125	Forms soluble complexes and inhibits stone formation.
Chloride	51	mmol/d	140-250	Forms soluble complexes and inhibits stone formation.
Creatinine	722	mg/d	800-2100	Excretion provides a measure of completeness of 24h urine collection.

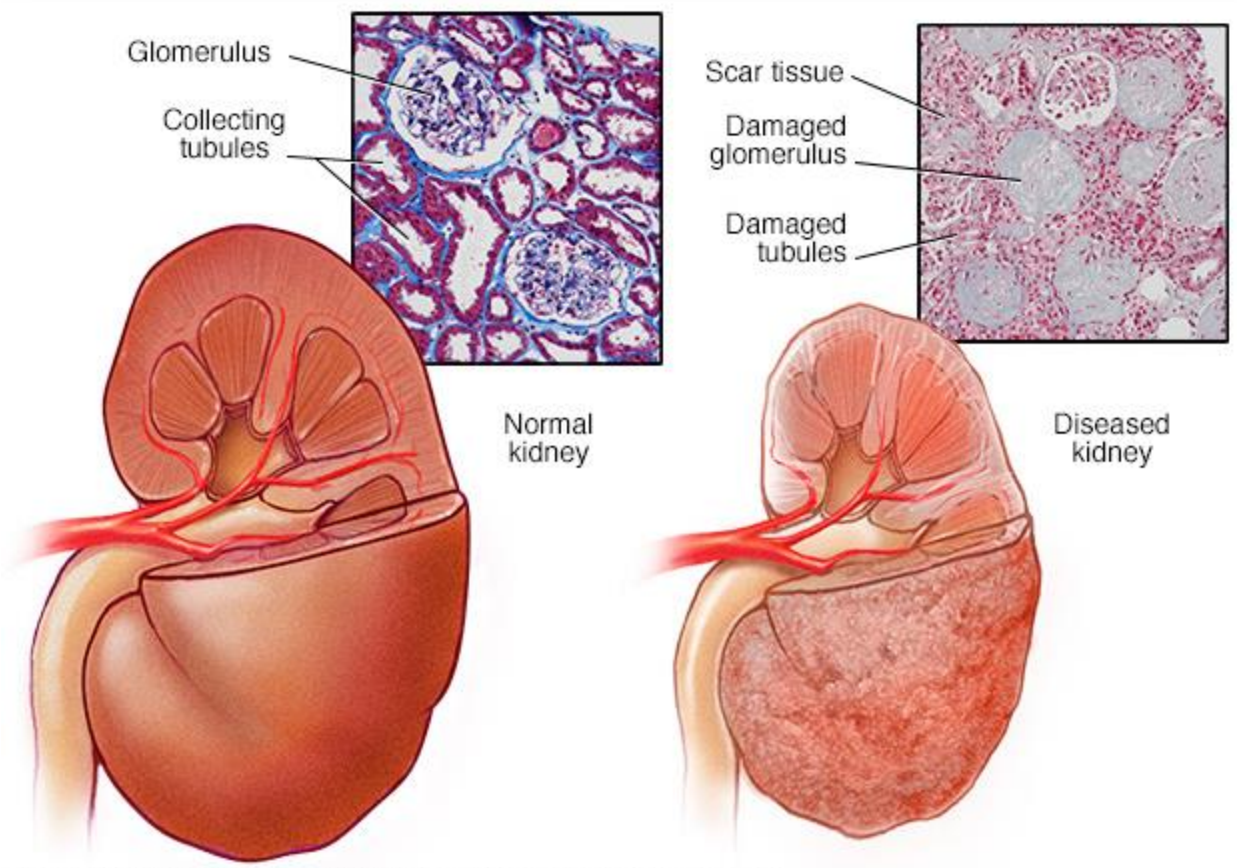
Case Wrap-Up and Prevention

- All stones: maintain urine volume >2.5L/day

- Our patient had a calcium oxalate stone
- Recommendations:
  - Reduce soft drink intake
  - Thiazide diuretics
  - Citrate pharmacotherapy (lower urinary citrate)
  - Reduce sodium and animal protein
  - Limit oxalate and eat more dairy (if oxalate high)

Complications

- Can lead to persistent renal obstruction
  - Permanent renal damage or renal failure



Case #2: 27 year old female

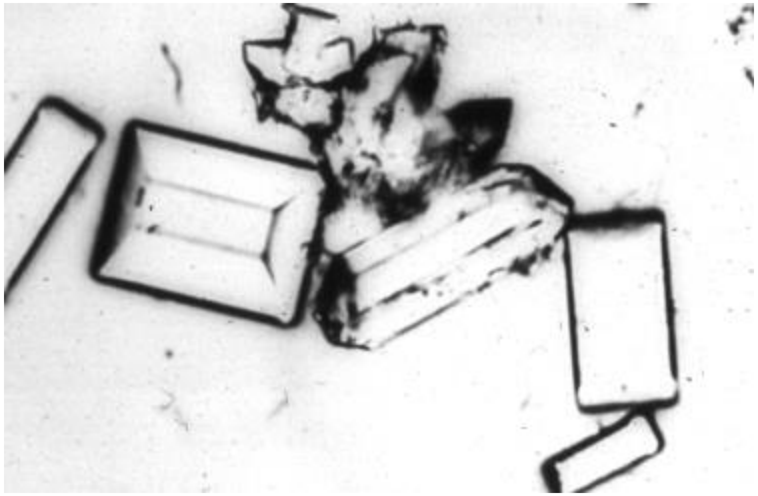
- Mild dysuria for a few weeks
- Mild flank pain, which has intensified over the last 24 hours

- Emergency Department Work-up:
  - Complete Blood Count
  - Complete Metabolic Panel
  - Urinalysis with Culture
  - Imaging

Female Complete Blood Count	
RBC	4.2-5.7 M/uL
WBC	4.5-11K/uL
Hgb	12-16 g/dL
Hct	37-47%
MCV	78-98 fL
MCH	27-35pg
MCHC	31-37%
Neutrophils	50-81%
Bands	1-5%
Lymphocytes	14-44%
Monocytes	2-6%
Eosinophils	1-5%
Basophils	0-1%

Urinalysis findings: Struvite

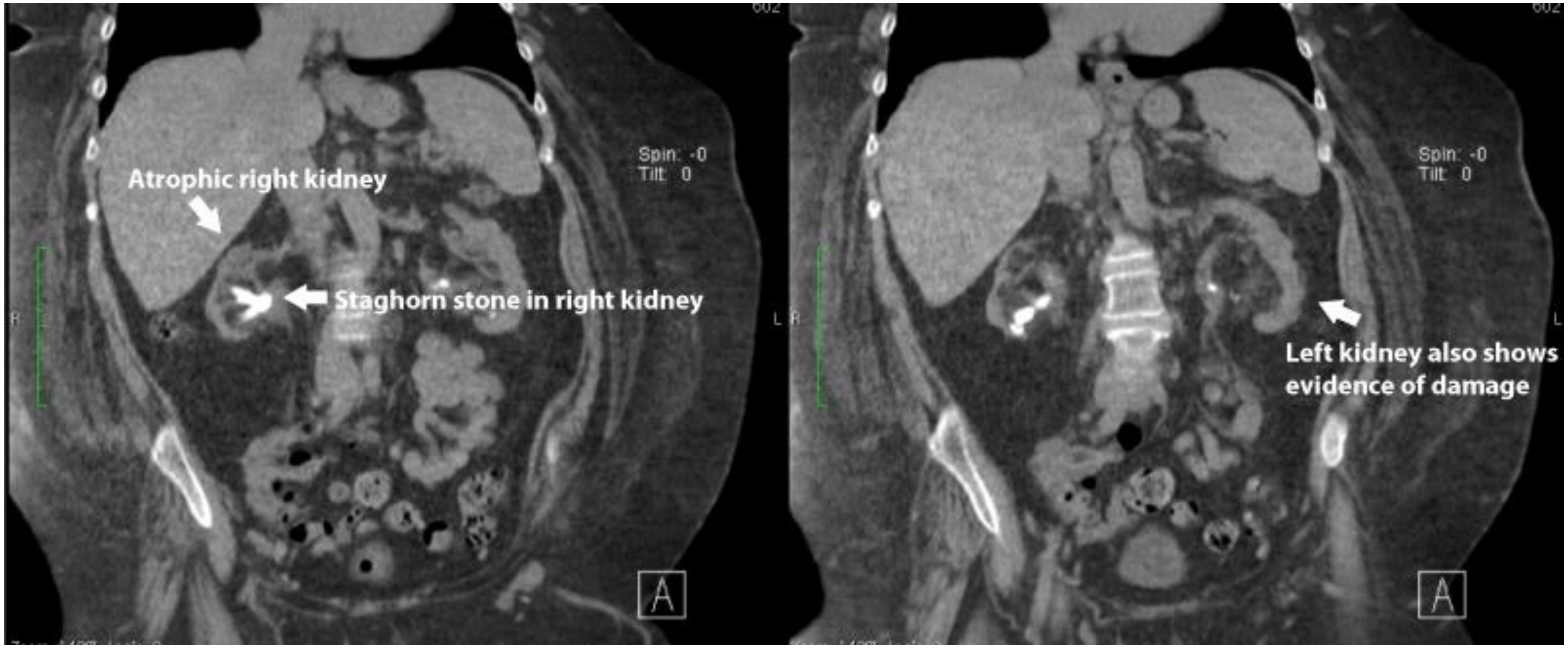
- Microscopic hematuria
- Elevated:
  - Leukocyte esterase
  - White blood cells
  - Bacteria
- Crystals
  - Coffin lid appearance
  - Typically in alkaline urine



UpToDate.com
https://www.123rf.com/photo_3667641_coffin-with-waving-hand--vector-illustration.html

Imaging

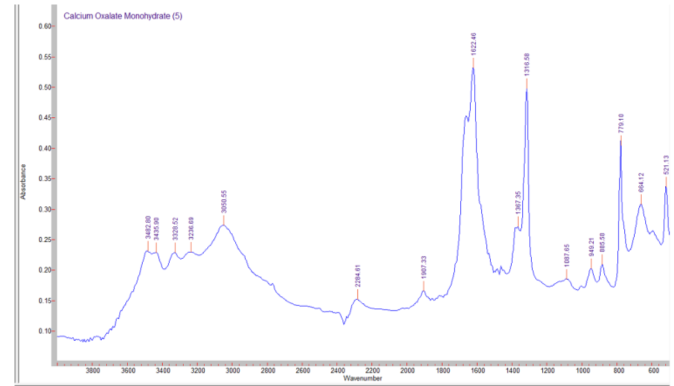
- Very dramatic
- Can block entire renal calyces

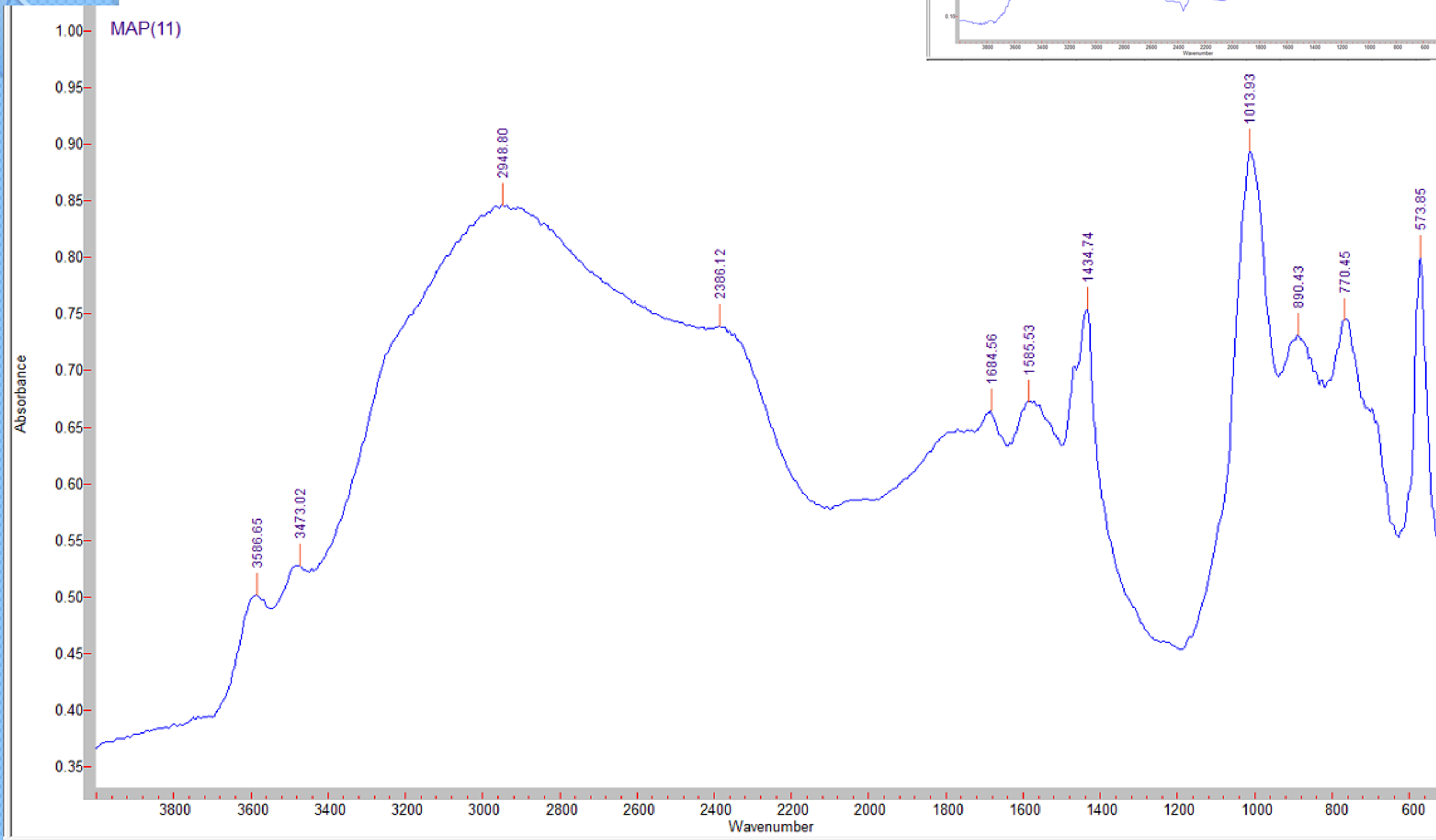


UpToDate.com

https://www.dreamstime.com/stock-photo-extracorporeal-shock-wave-lithotripsy-medical-illustration-treatment-kidney-stones-image46835340

Spectrum





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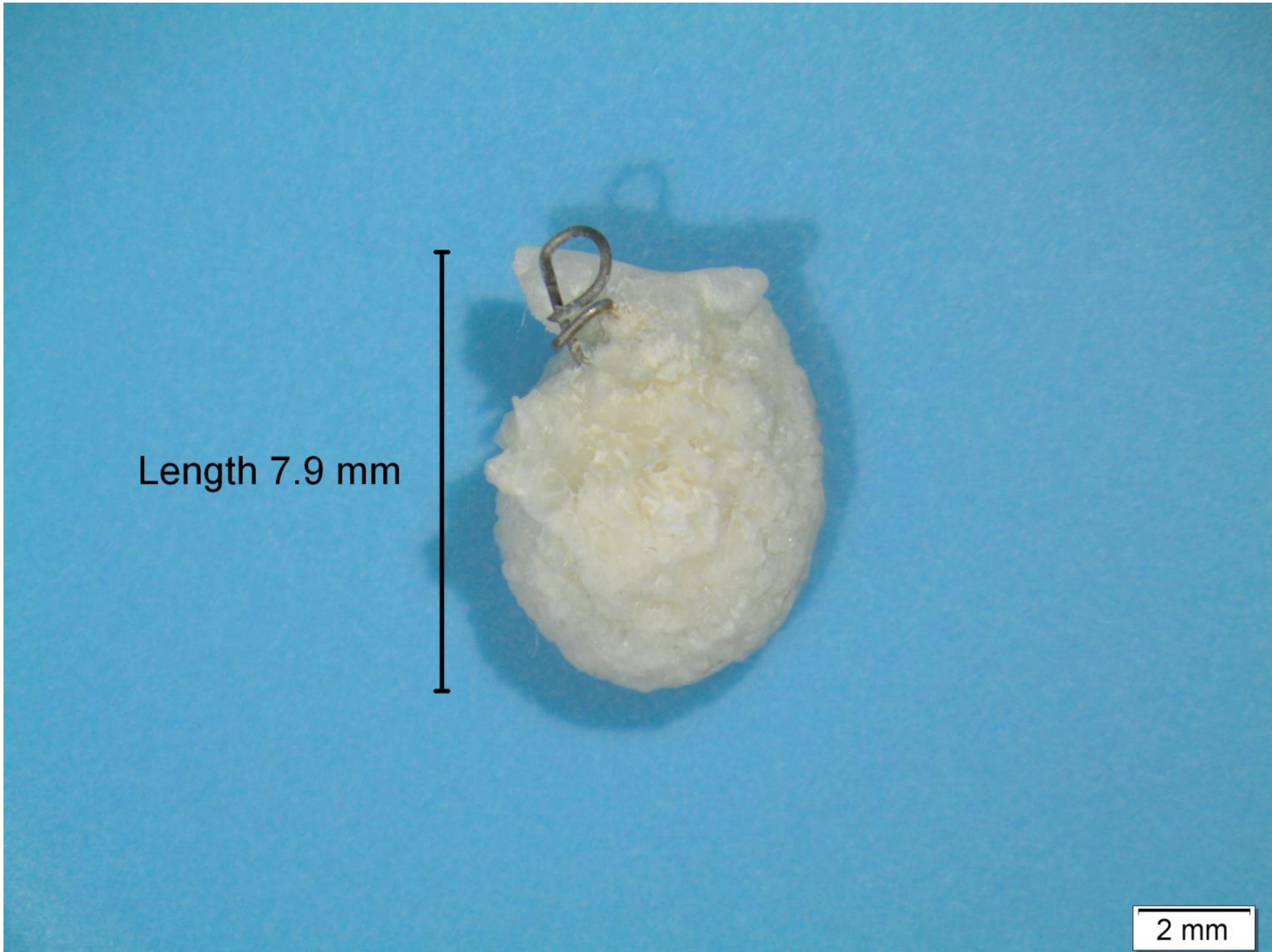
Struvite



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Epidemiology

- Approximately 10-15% of kidney stones
- Typically women (3:1)
  - Higher rates of urinary tract infections

Pathogenesis

- Formation occurs only when ammonia production increased and urine pH is elevated, i.e. by urease-producing organisms:
  - Proteus or Klebsiella

Risk Factors

- Urinary tract infections
  - Female
  - Neurogenic bladder
  - Urinary diversion

Management

- Most large staghorn calculi require surgical treatment
- Options:
  - Medical therapy alone
  - Open or laparoscopic surgery
  - Percutaneous nephrolithotomy
  - Shock-wave lithotripsy

Prevention

- Metabolic evaluation
  - Similar to other types of kidney stone formers
- Treat underlying medical issue
  - Urinary tract and/or kidney infection

Case #3: 7 year old girl

- Flank pain
- Abdominal pain

- Preliminary Work-up:
  - Complete Blood Count
  - Complete Metabolic Panel
  - Urinalysis with culture
  - Imaging

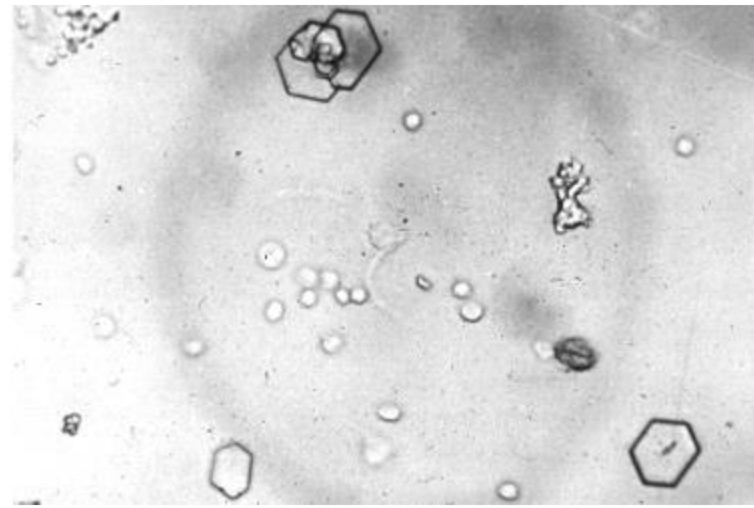
http://www.sheknows.com/health-and-wellness/articles/814344/kids-kidney-stones-cases-on-the-rise-1

Child Complete Blood Count

RBC	3.5-5.0 M/uL
WBC	4.5-11K/uL
Hgb	10-14 g/dL
Hct	30-42%
MCV	78-98 fL
MCH	27-35pg
MCHC	31-37%
Neutrophils	50-81%
Bands	1-5%
Lymphocytes	14-44%
Monocytes	2-6%
Eosinophils	1-5%
Basophils	0-1%

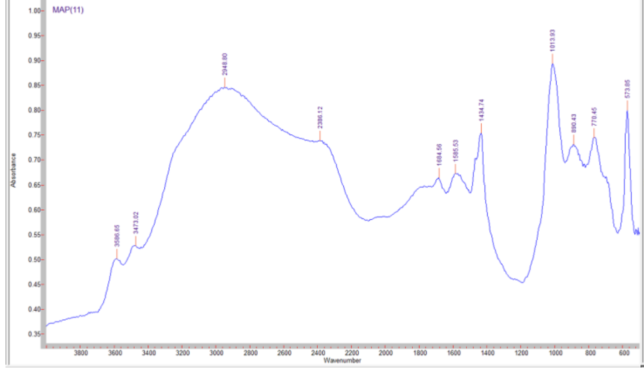
UA Findings

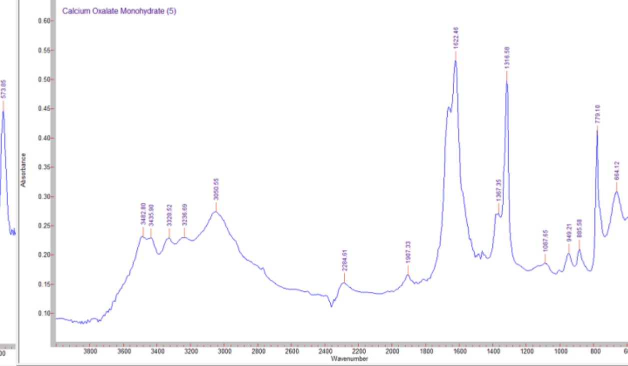
- Microscopic hematuria
- Crystals
  - Hexagonal crystals

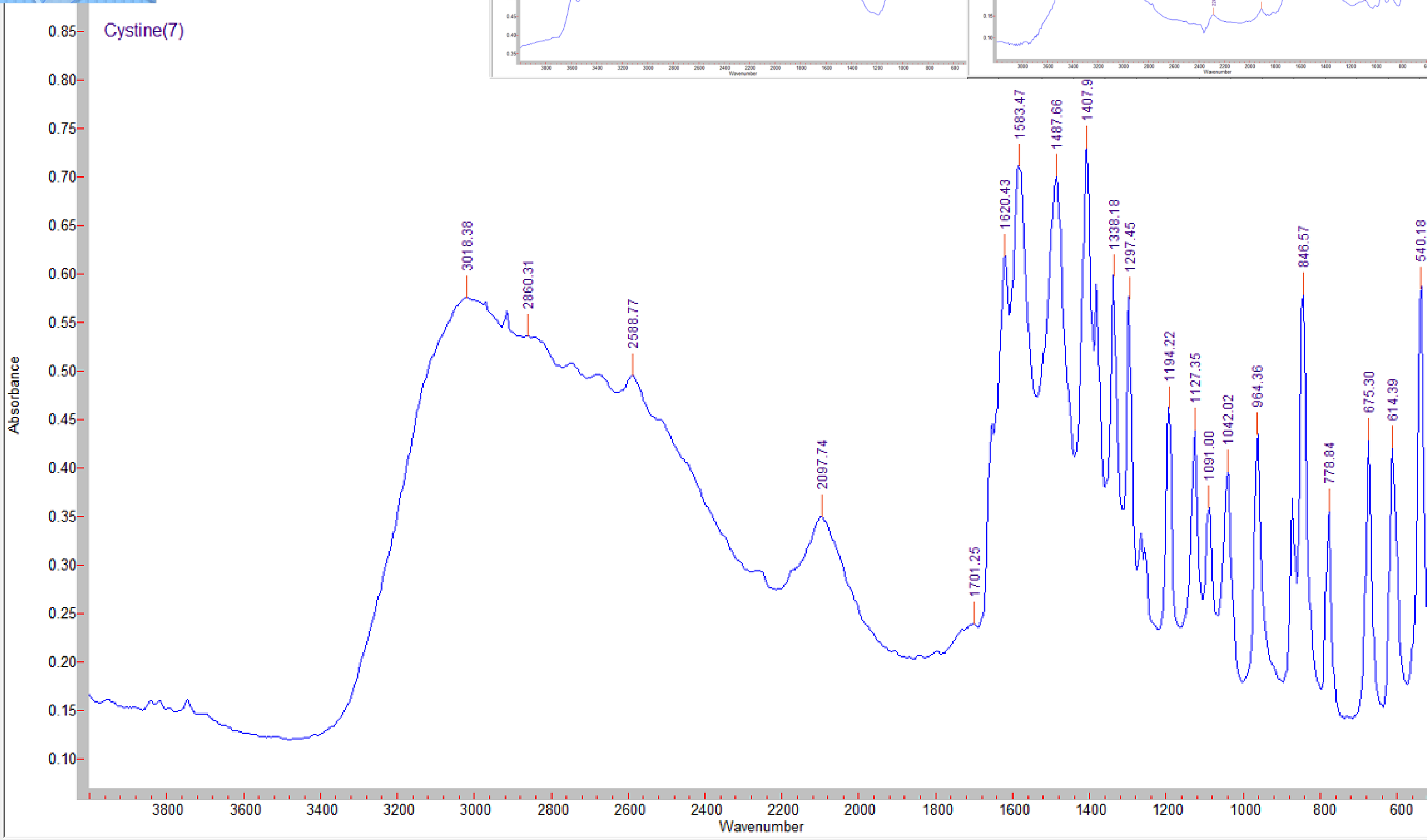


UpToDate.com

Spectra


MAP(11)
Absorbance
Wavenumber


Calcium Oxalate Monohydrate (5)
Absorbance
Wavenumber


Cystine(7)
Absorbance
Wavenumber
3018.38
2860.31
2588.77
2097.74
1701.25
1620.43
1583.47
1487.66
1407.9
1338.18
1297.45
1194.22
1127.35
1091.00
1042.02
964.36
846.57
778.84
675.30
614.39
540.18

Cystine

ARUP

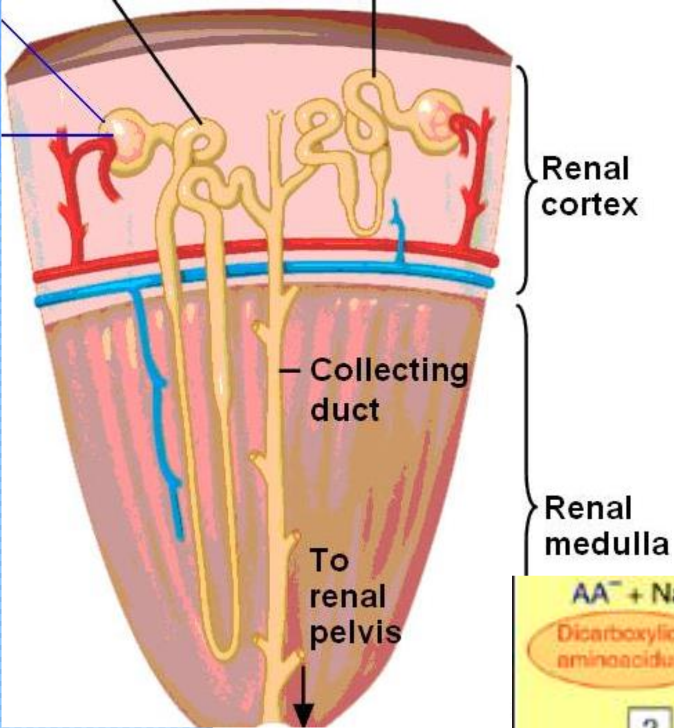
Pediatric Kidney Stones

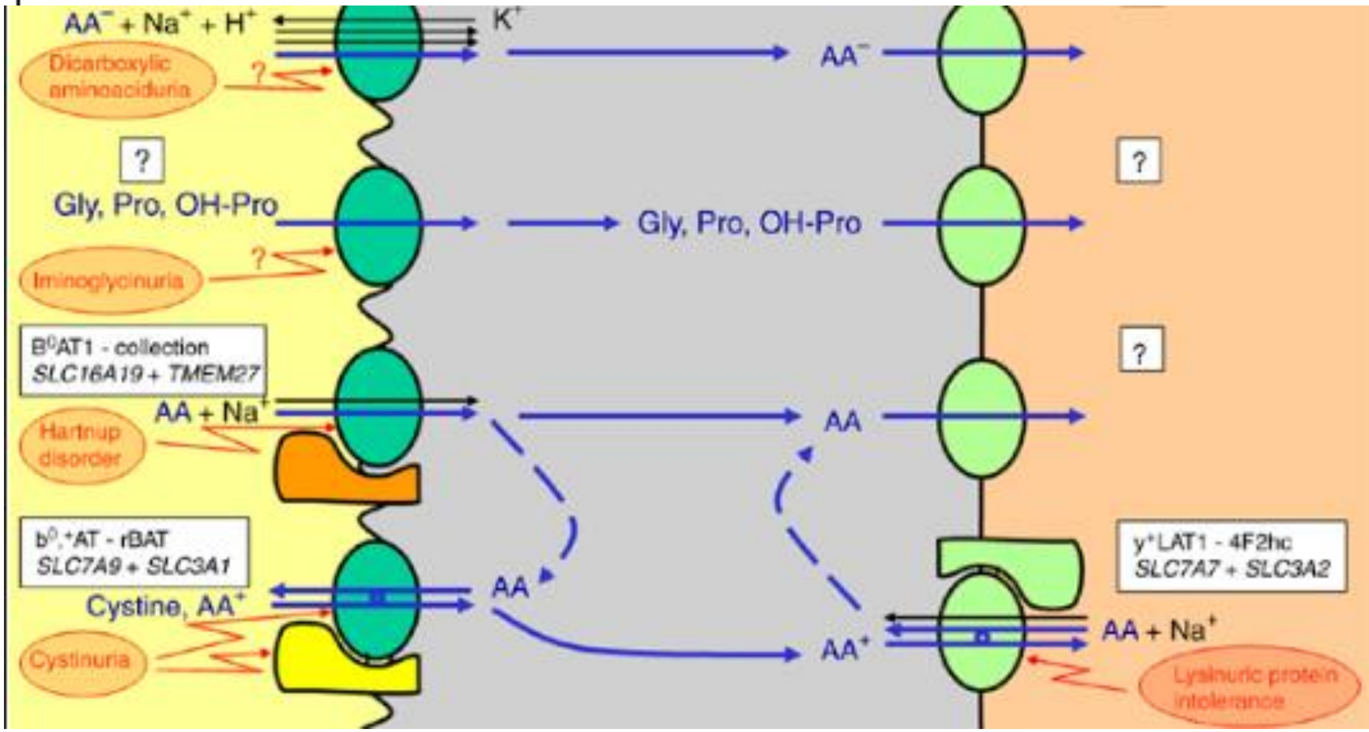
- In a child or adolescent (<12 years old) with first stone, clinician should suspect cystinuria

Epidemiology of Cystinuria

- Cystine stones represent 1-2% of total kidney stones
  - In children, up to 5% of total kidney stones
- Cystinuria:
  - Autosomal recessive
  - Due to an inherited impairment of renal cystine transport
  - Males more severely affected than females

Pathogenesis





http://bio1152.nicerweb.com/Locked/media/ch44/nephron.html

https://www.researchgate.net/publication/5651534_Aminoacidurias_Clinical_and_molecular_aspects

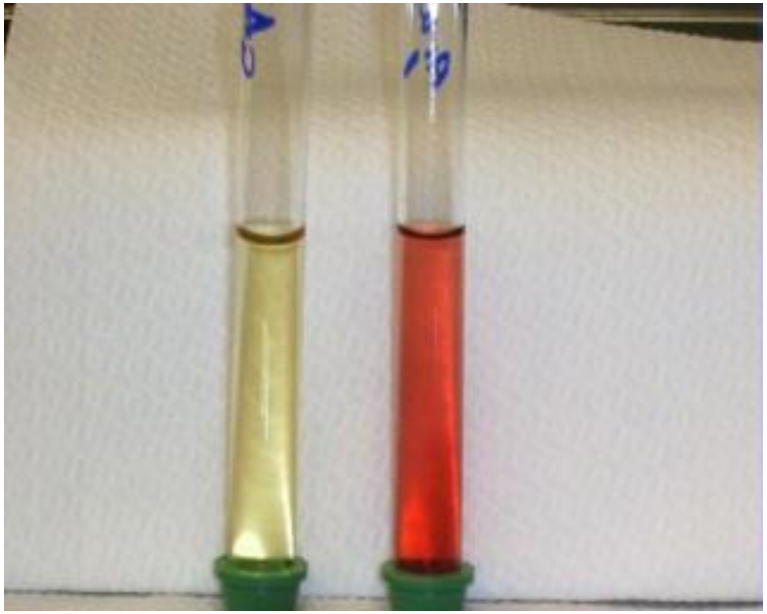
Diagnosis

One or more of the following are required to diagnosis cystinuria:

1. Stone analysis showing cystine
2. Positive family history of cystinuria
3. Hexagonal cystine crystals on urinalysis (about 25% of patients)

Further Work-up

- Cyanide-nitroprusside screen
- Urinary cystine excretion (amino acid panel)



http://slideplayer.com/slide/3167672/

Management & Prevention

- Acute management
- Prevention:
  - Increase fluid intake
  - Reduce sodium and protein intake
  - Urinary alkalization
  - Medications

Management Monitoring

- 24 hour urine evaluation
  - Assess response (and adherence) to treatment
  - Measure urine volume, cystine, pH, creatinine, sodium, and calcium
  - Measure supersaturation risk of cystine

Retention Questions

1. Which type of kidney stone is the most common?
   a) Calcium ★
   b) Uric acid
   c) Cystine
   d) Cholesterol

2. Which of the following options outline conservative prevention strategies?
   a) Surgery
   b) Alpha blocker medication
   ★ c) Increase fluid intake
   d) Increase sodium and animal protein intake

3. Which of the following is *true*?

a) All adults should have a full metabolic work-up with their first kidney stone.

★ b) All children should have a full metabolic work-up with their first kidney stone.

c) Struvite stone formers do not need antibiotic treatment.

d) Kidney stones larger than 10mm usually pass spontaneously.

References

- ARUPConsult.com
- UpToDate.com
- Coe F, Parks J, Asplin J. The pathogenesis and treatment of kidney stones. *New Eng J Med* 1992;327:1141-1151
- Daudon M, Marfisi C, Lacour B, Bader C. Investigation of urinary crystals by Fourier Transform Infrared Microscopy. *Clin Chem* 1991; 37:83.87.
- Jager P. Genetic versus environmental factors in renal stone disease. *Curr opinn Nephrol Hyperten.* 1996: 5342-46.
- Modlin M, Davies PJ. The composition of renal stones analyzed by infrared spectroscopy. *S Afr Med J* 1981; 7:337.341.
- Pichette V, Bonnardeaux A, Cardinal J, Houde M, Nolin L, Boucher A, Ouimet D. Ammonium Acid Urate Crystal Formation in Adult North American Stone-Formers. *American Journal of Kidney Diseases* 1997; 30, 2: 237-242.
- Vergauwe DA, Verbeeck RM, Oosterlinck W. Analysis of urinary calculi. Acta Urol Belg. 1994 Jun; 62(2):5-13.
- UpToDate.com. Accessed June 20, 2017. Topics: Nephrolithiasis, Staghorn Calculi Management, Cystinuria.