Case presentation
Nephrology ED

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Main complaints

- 39-years old woman was reported to the hospital emergency department
- She has flank pain on the left lasting 3 hours
- The pain radiates to the groin
- Nausea, vomiting
- She has taken acetaminophen 2 x 0,5g – no relief
- There is no fever

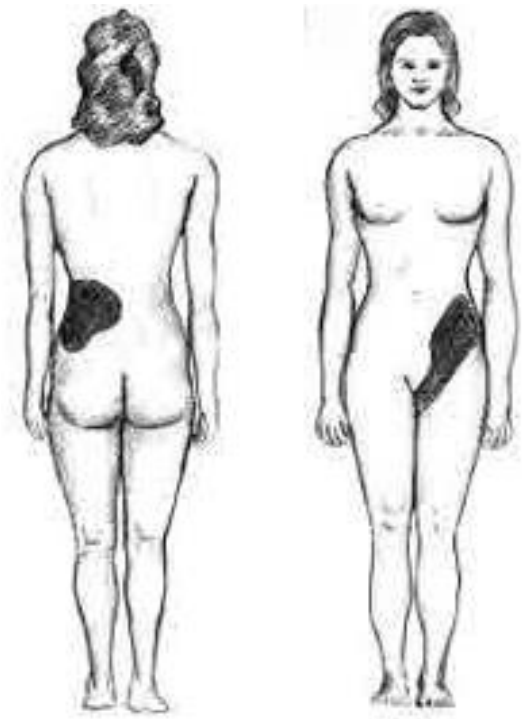
Physical examination

- increased muscle tension of abdomen on the left
- positive test for costophrenic angle tenderness (Goldflam's sign)
- BMI 31kg/m2
- blood pressure 147/95 mmHg
- no other abnormalities

What is the initial diagnosis?

- What lab tests would be done?

- What radiologic examination?



Renal stones differentiation

- **biliary colic**
- **appendicitis**
- **diverticulitis**
- **ulcer disease**
- pancreatitis
- ovarian torsion
- testicular torsion
- tubo-ovarian abscess

- **pyelonephritis**
- renal vein thrombosis
- papillary necrosis
- **renal cell carcinoma**
- tuberculosis of genitourinary tract
- ureterocele
- congenital ureteropelvic junction obstruction
- vesicoureteral reflux

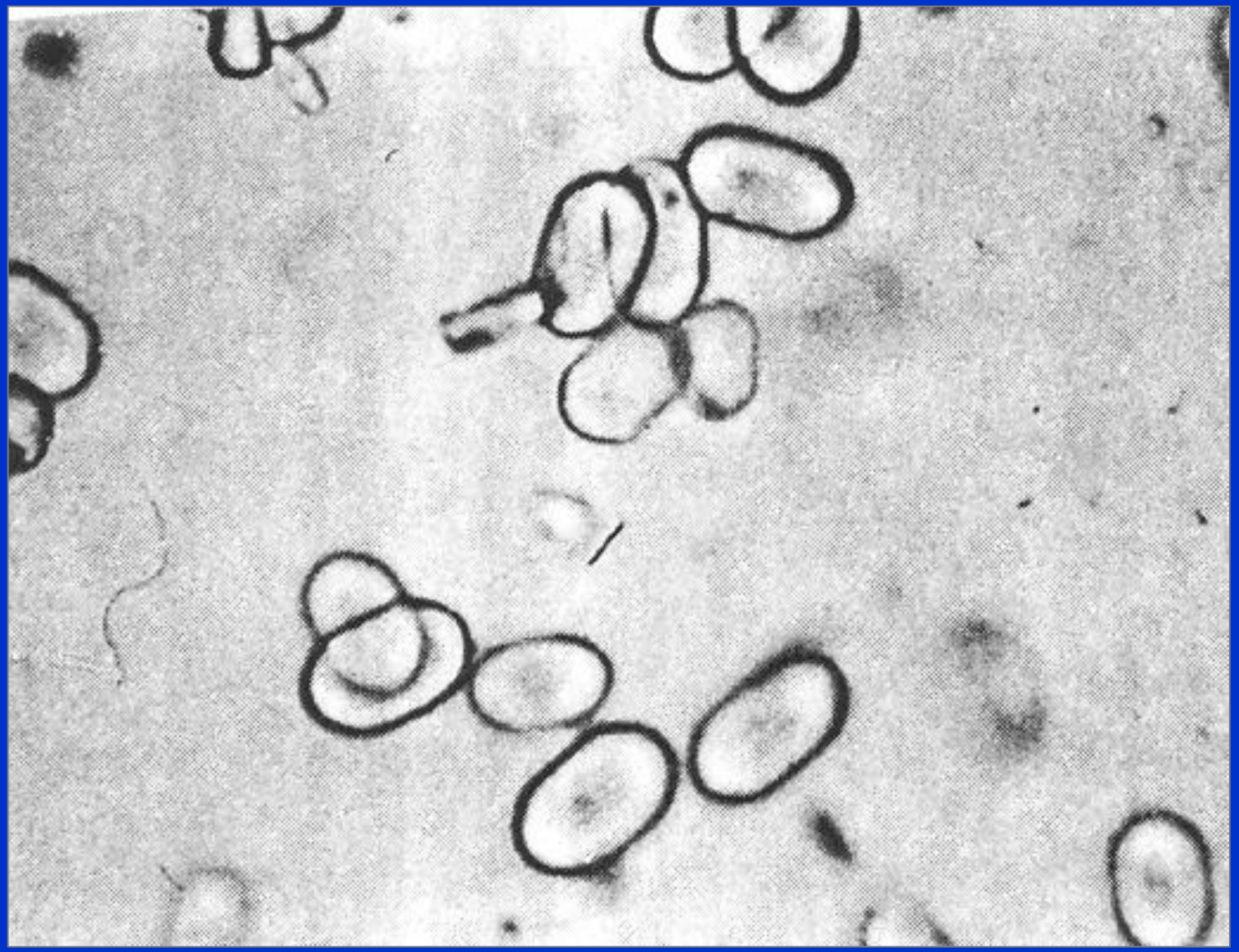
Laboratory tests

- CBC – Hb 14,2g/dl, L 14G/L, PLT 236G/L
- CRP - 7mg/L (N<10)
- Ca – 10,2 mg/dl
- uric acid – 6,7 mg/dl
- PO4, HCO3, Na, K, creatinine, glucose - N
- urynalysis

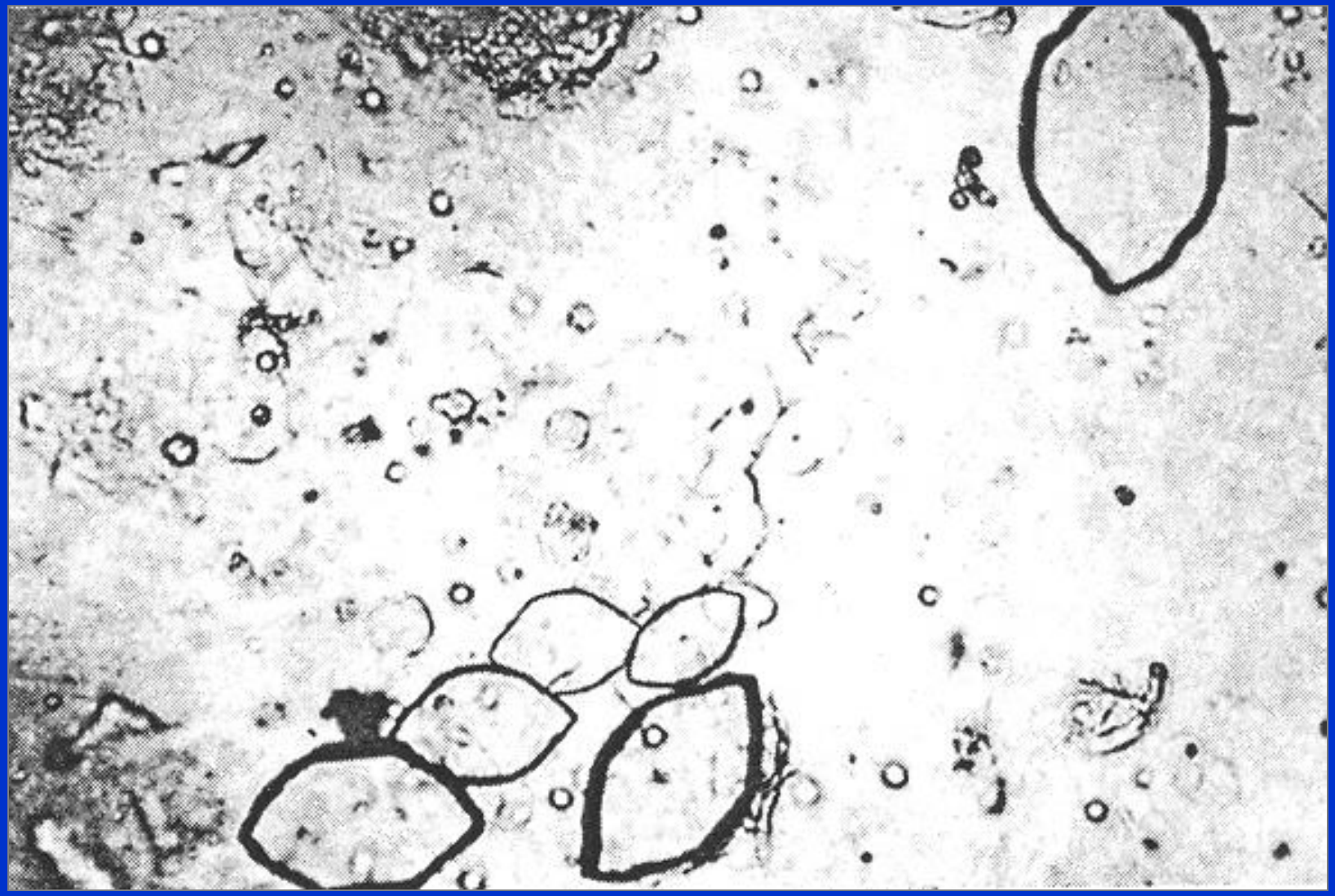
Urynalysis

- specific gravity of urine - 1.022
- pH 6,1
- Prot – neg
- Glu – neg
- **L 7-10ppf**
- **E – whole pf (massive hematuria)**
- Crystals – calcium oxalate

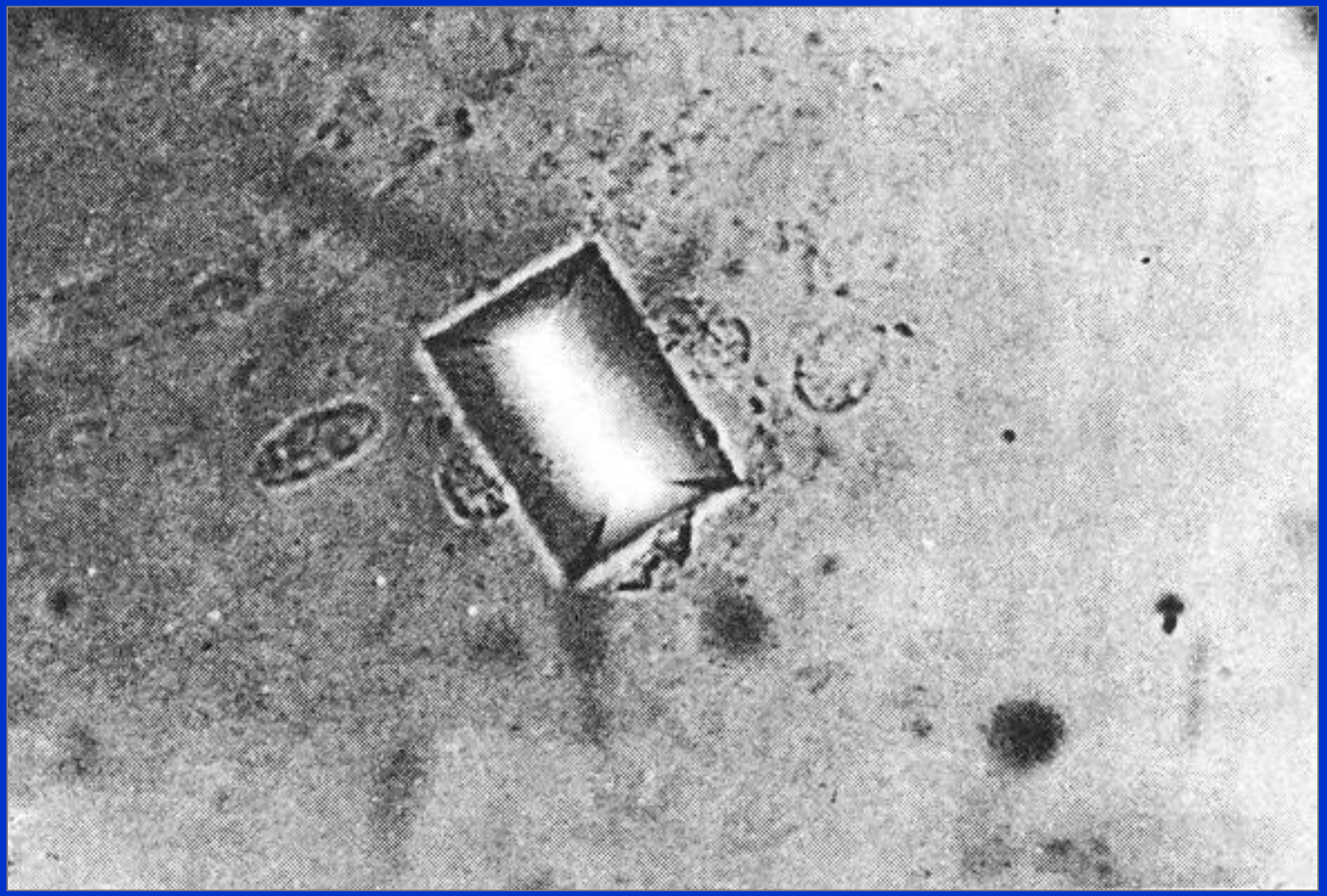
Calcium oxalate



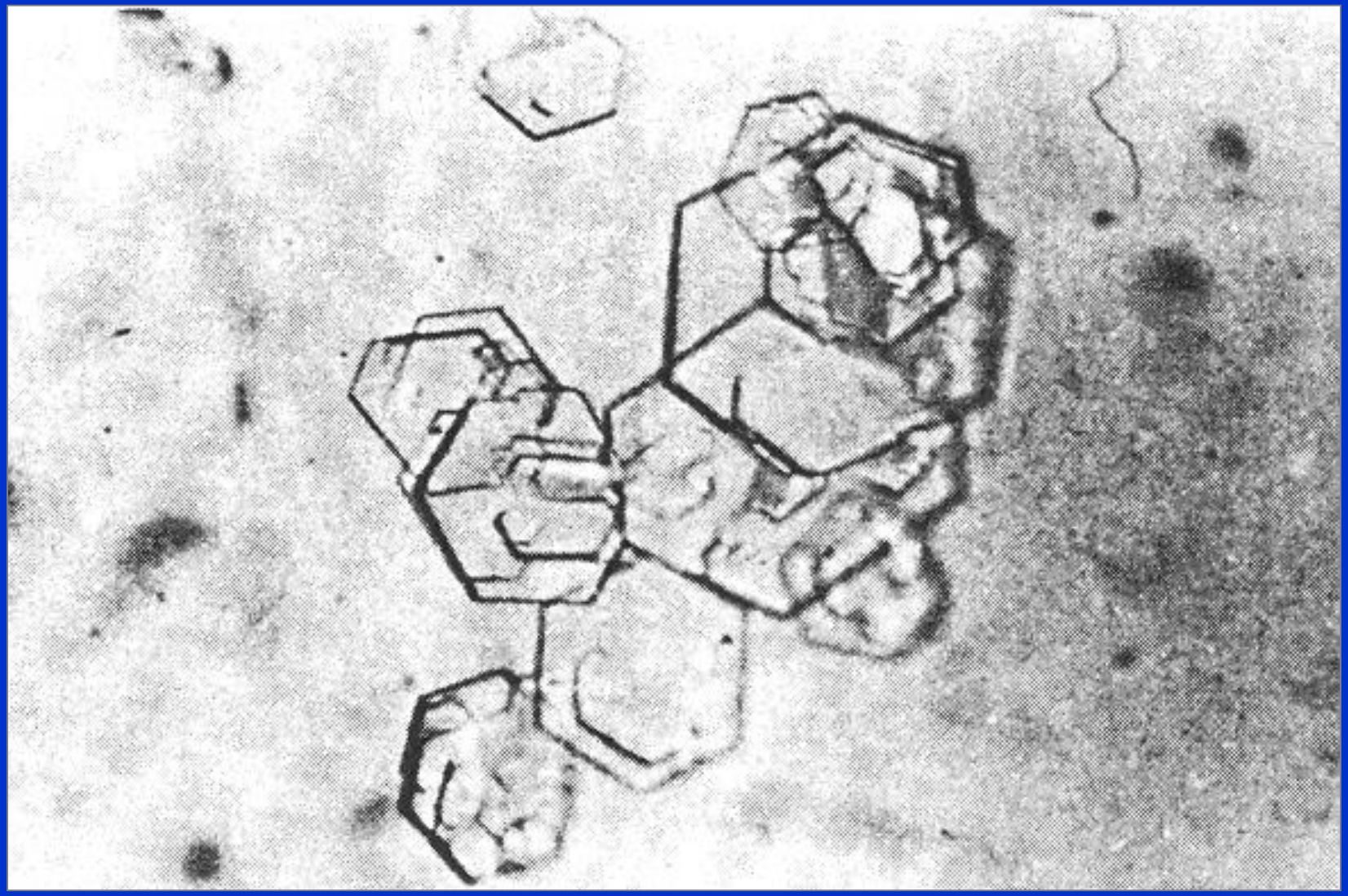
Uric acid



Struvite



Cystine crystals – indicative of stone formation



Type of urinary stone

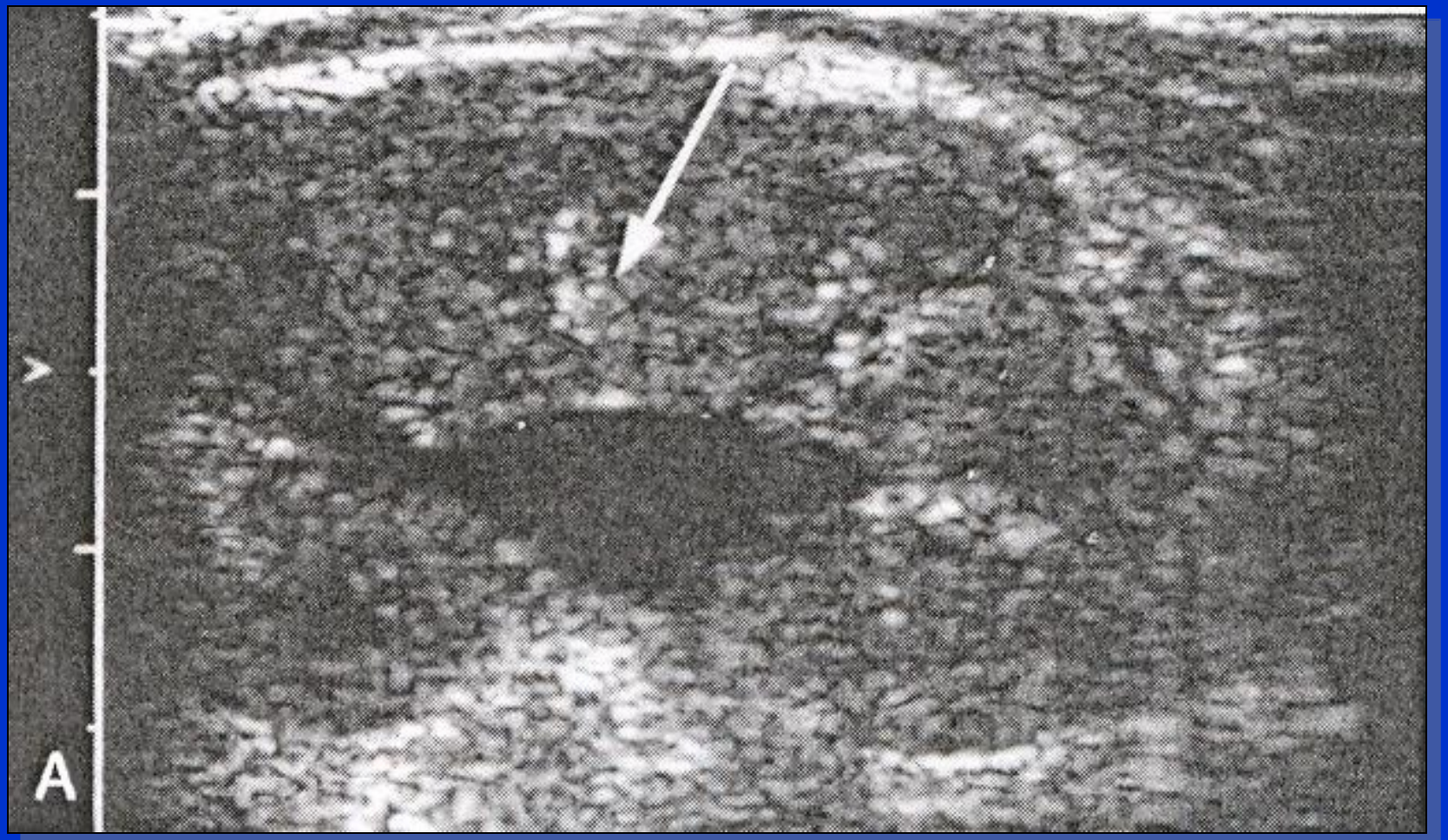
- calcium oxalate – 70-80%
- calcium phosphate – 5-10%

→ CALCIUM stones – 75-90%!!!

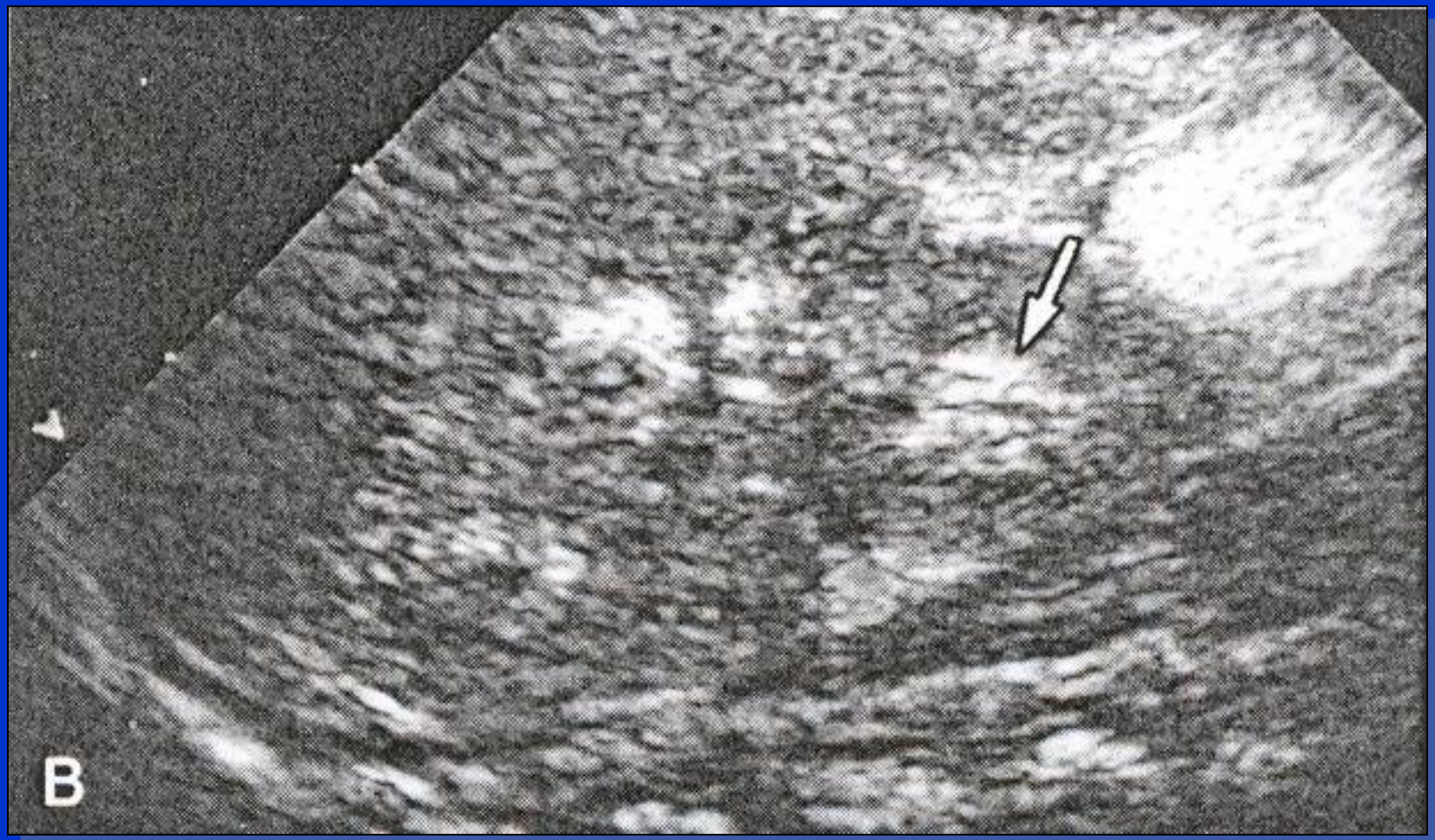
- uric acid – 5-10%
- struvit – 5-10%
- cystine – 1%
- rare: xanthine, 2,6-dihydroxyadenine, stones composed of drugs (triamterene), inspissation of indanavir (antiretroviral protease inhibitor), sulfasalazine

Renal calculi (nephrolithiasis)

- **calculi in the urinary collecting system (urolithiasis)**
- cortical calcification
  - tuberculosis
  - acute cortical necrosis
- medullary calcifications (nephrocalcinosis)



Mild nephrocalcinosis



Moderate nephrocalcinosis

Nephrocalcinosis

- Primary hyperparathyroidism
- Medullary sponge kidney
- Renal tubular acidosis (RTA)

OUR PATIENT
Futher examination?

Examination

- conventional radiography – plain film of the abdomen (but: bowel gas, vessel calcifications)
- excretory urography (IVU) – degree of obstruction
- ultrasonography – useful in young or pregnant patients
- **nonenhanced CT scanning – the examination of choice for the detection and localization of urinary stones**
- → conventional or digital radiography is used to **monitor the passage of stones** if the stone is visible on conventional radiographs

CT findings

- renal and ureter stones
- enlarged kidneys
- hydronephrosis
- perinephric fluid
- ureteral dillatation
- soft tissue around the rim of a calculus

CT

- sensitivity: 94-97%, specificity: 96-100%
- frequently depict non-obstructing stones that are missed on IVU
- **differentiates between stones and blood clots or tumors**
- better than IVU in detecting other causes of abdominal pain
- contrast-enhanced CT differentiates between phleboliths and urinary stones

Limitations of CT

- costs
- false negative finding:
  - protease-inhibitor (indinavir) CT-lucent stone
  - pure matrix CT-lucent stone
- **false-positive results:**
  - phleboliths adjacent to the ureter (inravenous contrast material is needed to opacify the ureter)
- the radiation dose is greater than that of IVU
- **Contraindications**: pregnancy (in contrast-enhanced CT: allergy to contrast material, renal insufficiency)

Nephrolithiasis – conventional radiography

- opaque stones (90%):
  - calcium oxalate
  - calcium phosphate
  - cystine
  - struvit with calcium phosphate complexes
- nonopaque stones:
  - **uric acid**
  - struvit (without complexes with calcium phosphate)

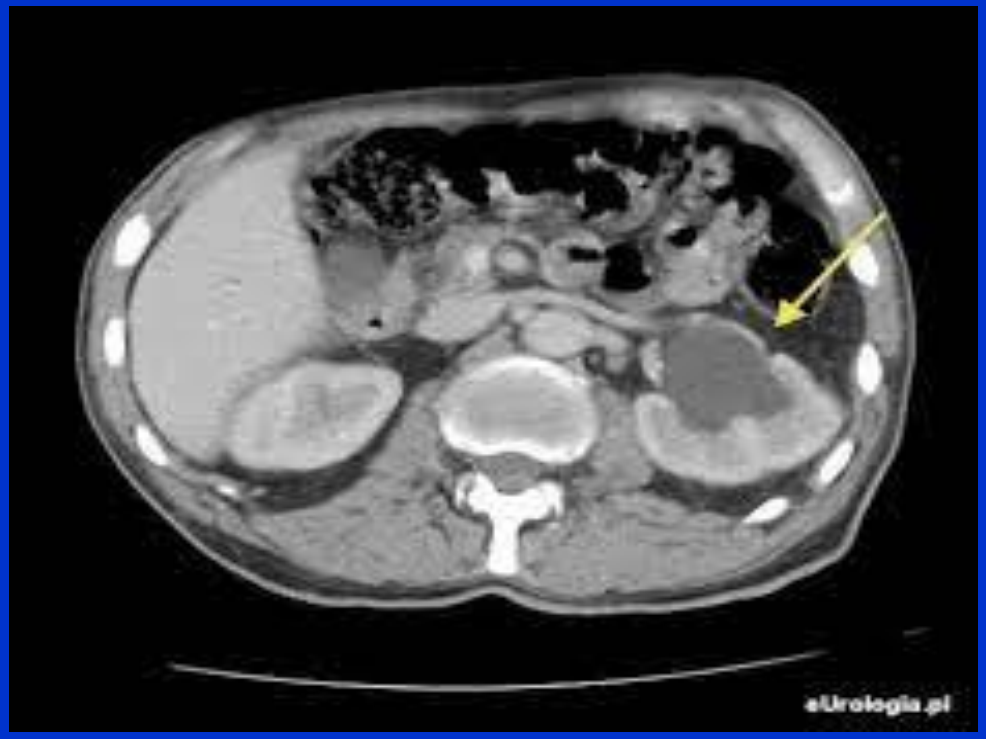
US , IVU

- US
  - **has limited sensitivity for smaller stones**
  - **does not depict the ureters well**
  - good in pregnancy, uric acid stones, monitoring of obstruction
- IVU
  - **intravenous contrast is required (allergic reaction, nephrotoxicity)**
  - **less sensitive (50-60%) and less specific (70%) than CT,** especially for small or non-obstructing stones
  - 10% of stones are radiolucent
  - lucent stones = filling deffects (like transitional cell carcinoma or blood clots)

OUR PATIENT
Nonenhanced CT scanning

- Hydronephrosis of the left kidney
- Calculus 8 mm diameter in the medium part of the left ureter
- No other ubnormalities

Nonenhanced CT scanning - hydronephrosis



Our patient is suffering…

- What is the treatment of renal colic?

Treatment of renal colic

- analgesia:
  - nonsteroid antiinflammatory drugs: diclofenac 75mg, ketoprofen 100 mg
  - acetaminophen 1,0 i.v.
  - opioids: morphine 2-5 mg i.v. or 10 mg i.m., s.c.
- drotaverine, hioscine
- tamsulosin 0,4 mg, doxazosin 4 mg for distal ureteric stones (>5mm, <10mm)
- glucocorticosteroids
- intravenous fluids

Prognosis

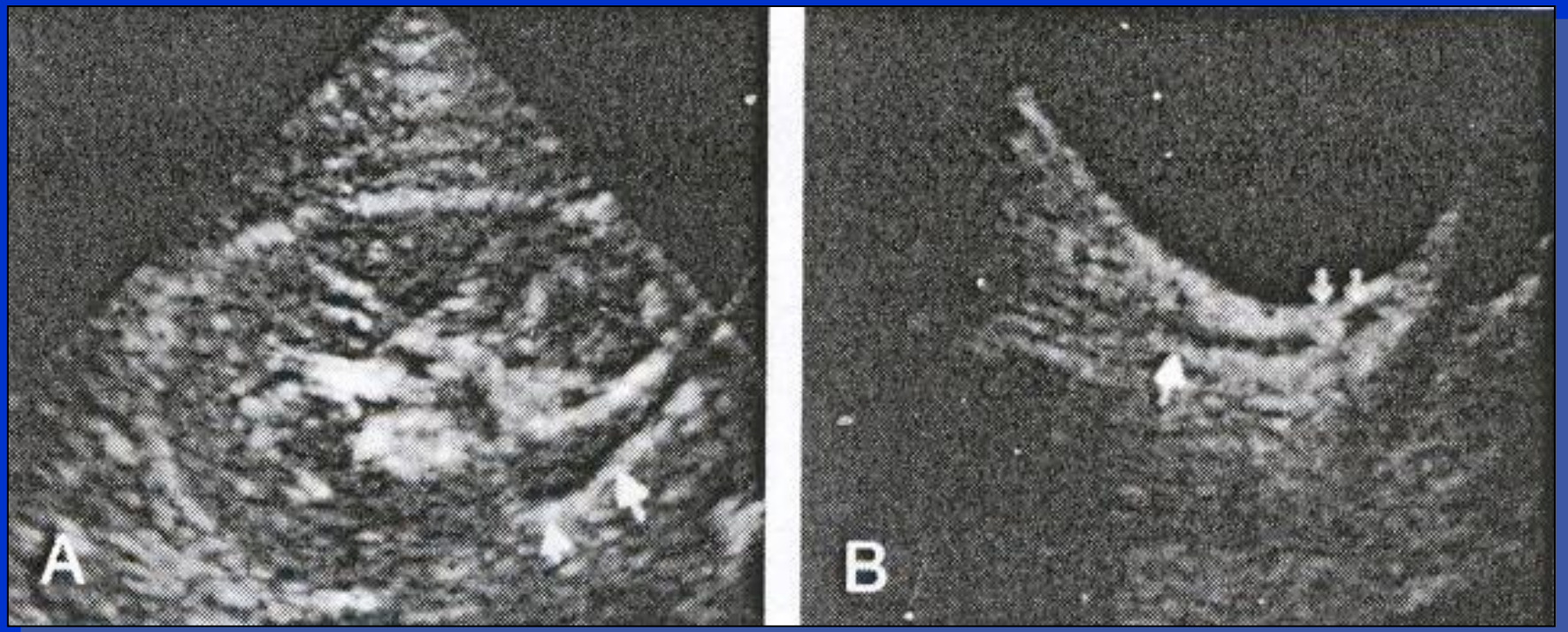
- **spontaneus passing of stones:**
- < 4mm – 80% of patients
- 4-6 mm – 50%
- > 8 mm – 20%
- > 10 mm - unlikely
- **hospitalization:**
- fever, sepsis
- complete urinary tract obstruction, anuria
- vomiting, AKI,
- uncontrolled pain

Important

- The patient instructed to sieve the urine
- The stone is examined with crystalography or spectroscopy or X-ray diffraction

After 3 days

- Fever 39 C
- Moderate relief of pain
- → hospitalization
- Plain X-ray – stone in lower part of ureter
- US - left hydronephrosis
- CRP – 120mg/L, PCT – 0,1ng/L
- creatinine - 1.1 mg/dl, eGFR 89ml/min
- urinalysis – hematuria, pyuria
- urine culture - E.coli



Acute obstruction caused by a calculus

Intervention

- Indication:
  - significant urinary tract obstruction
  - stone associated with UTI
  - hematuria
- Lithotripsy: shock-wave, laser
- SWL, URS, PCNL (PCN)
- retrograde pyeloureterography
- antegrade pyeloureterography
- stent placement: retrograde, antegrade
- nephrostomy

Extracorporeal shock wave lithotripsy (ESWL, SWL)

- 5-10- 20mm stones
- Effectiveness:
- medium and upper part of ureter – 75%
- lower part of ureter – 20%
- contraindication:
  - bleeding diathesis
  - obstructing lesion that might prevent the passage of stone fragments
  - pregnancy
- Complications: hematoma, bleeding, hematuria, abdominal pain, dyzuria

Uretherorenoscopic lithotripsy URSL (URS)

- Indication:
  - Stone >10 mm, lower or middle part of ureter
  - Rigid stones: cystine, calcium oxalate stone
- Uretherorenoscopy in short general anaesthesia
- Contraindication: sepsis
- Complications: haematuria, ureter laesion, infection, pain

Percutaneous nephrolithotripsy PCNL

- Indication:
  - Stone >20 mm or difficult for ESWL, localized in kidney or in upper ureter

- Nephroscopy, whole stone or lithotripsy

Intervention in ureteral stones

- Ureteral stone
- < 10 mm –URS, SWL
- > 10 mm – URS (or SWL)

- **URS** prefered if cystine, uric acid stones, rigid stones, skin to stone>10cm, obesity

Intervention in renal stones

- <10 mm - SWL
- 10-20 mm - URS, SWL
- >20 mm – PCNL
- If PCNL contraindicated – RIRS (retrograde intrarenal surgeries) or SWL and consider ureteral stent

- <5 mm asymptomatic – watchfull waiting

Treatment

- Ceftriakson 2,0 i.v.
- Ketoprofen
- Tamsulosin
- URS (lower part of ureter, obesity)
- Next day after URS- serum sodium, potassium

- Stone analysis – calcium oxalate 60%, calcium phosphate 40%

Polyuria after removing obstruction

- The reasons:
  - Increased volemia
  - Osmotic diuresis
  - Increased ANP
  - Acquired diabetes insipidus (decreased vasopressine sensitivity)
- Control volemia and Na, K balance!

2-3 months after colic pain

- The patient in stable condition
- Why did the colic pain happen?
- What to do to prevent reccurence?

Recurrence

- in untreated patient the probability of the second stone formation is:
  - 15% at 1-3 years
  - **50% at 10 years**
- high risk of recurrence:
  - cistine, uric acid, struvite
  - high stone activity (passage of a newly formed stones, rapid growth, the passage of gravel)

Pathogenesis of nephrolithiasis

- an **increase in excretion** of calcium, oxalate, phosphate, uric acid, cystine
- an increase in concentration of these substances due to a **low urine volume**
- a reduction in excretion of **inhibitors** of crystal and stone formation (hypocitraturia)
- secondary crystal growth: the presence of **uric acid crystals**, which can act as nidus for calcium stone formation
- urine pH is the determinant of uric acid (low pH) and struvite ora calcium phosphate (high pH) stone formation
- urinary tract obstruction, alteration in uroepithelial surface

Inhibitors of crystallization

- **magnesium** (form soluble complexes with oxalate)
- **citrate** (calcium)
- **nephrocalcin** (glycoprotein inhibitor of calcium oxalte crystal growth, contains γ-carboxyglutamic acid)
- Tamm-Horsfall protein
- uropontin
- urinary prothrombin fragment-1
- bikunin
- calgranulin
- glycosaminoglycans

Hereditary anatomic factors contributing to the development of stone disease

- ureteropelvic junction (UPJ) obstruction
- horeshoe or ectopic kidney
- autosomal dominant polycystic kidney disease (ADPKD)
- vesicoureteral reflux
- medullary sponge kidney

Normal limits for daily urine excretion

Substance excreted	Men	Women
calcium, mg	< 300	< 250
calcium, mg/kg	< 4	< 4
uric acid, mg	< 800	< 750
oxalate, mg	< 50	< 50
citrate, mg	> 450-600	> 650-800

Urine collection (2 x 24hs)

- Calcium 354 mg
- Oxalate 35 mg
- Uric acid 602 mg
- Citrate 731 mg

Calcium-containing stones

HYPERCALCIURIA:

- secondary to hypercalcemia (primary hyperparathyroidism, vit.D excess, sarcoidosis, skeletal release, neoplasms, multiple myeloma)

- secondary to reduction in tubular Ca reabsorption (high dietary sodium, loop diuretic)

- type 1 renal tubular acidosis

- **idiopathic hypercalciuria – 85%**

Idiopathic hypercalciuria (IH)

- inherited
- serum Ca - normal
- the most common cause of calcium oxalate stones!
- 50-60% of men and 70-80% of women with calcium stones have elevated Ca excretion
- **exclude other causes of hypercalciuria**

The role of high-sodium intake in hypercalciuria

- Ca reabsorption passively follows that of sodium in the proximal tubule and the loop of Henle
- high-sodium intake → hypercalciuria

- NB: volume depletion at the time of urine collection → may obscure hypercalciuria

The role of high-protein intake in stone formation

- protein → enhanced GFR
- **high acid load**
  - → reduces excretion of citrate (inhibitor of crystallization)
  - → increases Ca excretion
  - → chronic bone resorption
- **high metabolism of purines** → high uric acid excretion

Approach to the patient - initial stone passage

- crystallographic analysis: calcium oxalate
- exclude hypercalcemia - serum Ca
- diet recommendation:
  - high fluid intake
  - restriction intake of protein and sodium while not limiting calcium intake
  - avoiding excess vit. C or D intake
- diet high in fruits and vegetables
- treat UTI
- correct urinary obstruction
- monitor the subject yearly

Therapy of active calcium stone disease -1

- idiopathic hypercalciuria:

- **DIET:** dietary calcium 1000-800mg/day (avoid excessive dietary calcium restriction, which elevates the calcitriol and increases oxalate absorption!!)

- If hypercalcuria on diet:
  - **thiazide diuretic**
  - **potassium citrate**

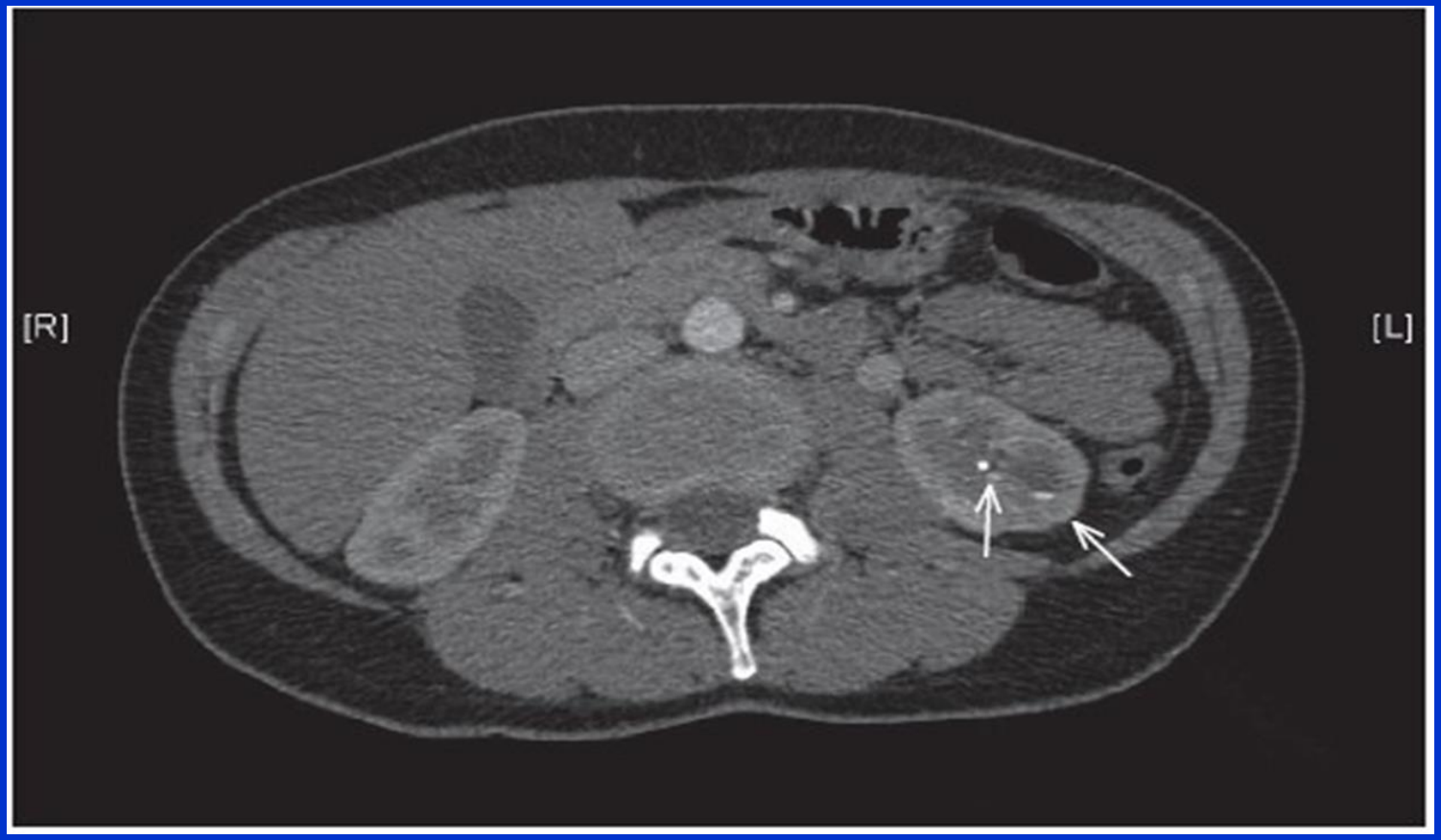
Approach to the patient – initial stone passage 2

- if calcium oxalate and phosphate stone excluded or no possibility for crystallographic analysis:
  - **screening test for cystinuria**
  - **consider uric acid stones**

After 6 months

- Pain in upper abdomen
- Esophagoscopy: gastritis, H. pylori negative
- Calcium – 11,1 mg/dl
- Creatinine – 0,9 mg/dl
- CRP – N
- Phosphate – 1,9 mg/dl
- CBC – N
- Urynalysis – hematuria
- CT

CT - calculi in the left renal calyx



Other abnormalities

- PTH – 1265pg/ml
- Neck US – parathyroid adenoma

Primary hyperparathyroidism

- adenoma or hyperplasia
- hypercalcemia + hypercalciuria
- hyperphosphaturia → hypophosphatemia
- women > men
- multiple measurements of plasma Ca !!!

- Therapy of primary hyperparathyroidism:
- surgery

Other causes of renal stones

Hypocitraturia

all states of chronic acidosis:

- citrate is reabsorbed in the proximal tubule and is metabolized in the liver to bicarbonate via the Krebs cycle → hypocitraturia

Type 1 renal tubular acidosis

- hypocitraturia (because chronic acidosis)
- increased urine excretion of Ca and phoshorus
  - release of these ions from bone during buffering of the excess acid
  - direct inhibition of tubular calcium and phosphorus reabsorption by acidemia
- elevated urine pH promotes **calcium phosphate** precipitation

Therapy of active calcium stone disease - 2

- type 1 renal tubular acidosis: (calcium phosphate stones):
  - potassium citrate
  - thiazide diuretic if also hypercalciuric
  - L-methionine if urinary pH is high
- hypocitraturia: potassium citrate

Hyperoxaluria

- **normal subject** absorbs 10% dietary oxalate due to formation of **insoluble calcium oxalate** within the intestinal lumen
- enteric hyperoxaluria
  - small-bowel injury (inflammatory, surgical) → impaired intestinal absorption of fatty acids and bile salts → they bind to Ca, rising the quantity of free oxalte, → they increase intestinal permeability → they may cause diarrhea → increased oxalate reabsorption across the colon
- vit. C overdose
- primary hyperoxaluria: autosomal recessive disease, enzymatic abnormalities in oxalate metabolism, renal failure in childhood due to nephrolithiasis

Enteric hyperoxaluria

- inflammatory bowel disease
- short gut syndrome
- bowel resection
- gastrointestinal bypass surgery

Treatment of oxalate stones

- enteric hyperoxaluria:
  - low-fat, low-oxalate diet
  - potassium citrate, if metabolic acidosis
  - calcium carbonate (binds oxalate)
  - cholestyramine (binds bile acids and oxalate)
  - in patients with intestinal bypass: restoration of small bowell continuity
- primary hyperoxaluria: magnesium, pyridoxine, KTx + LTx
- avoid: oxalate-rich foods: rhubarb, spinach, cashews, almonds, strong tea, bear, vit.C

Uric acid nephrolithiasis

- markedly acid urine
- hyperuricosuria
- **primary gout (20% of patients)**
- myeloproliferative disorders, acute leukemia
- cell lysis
- dehydration
- chronic diarrhea (volume depletion, metabolic acidosis)
- idiopathic

Treatment of uric acid nephrolithiasis

- high fluid-low purine intake
- urine volume 2l/day
- urinary alkalinization with potassium citrate (pH > 6-6,5)
- allopurinol

Hyperuricosuria-induced calcium stone disease

- uric acid crystals provide an initial surface on which calcium oxalate can deposit
- occurrence: middle-aged men
- treatment: allopurinol and thiazide

Struvite = magnesium ammonium phosphate (+ calcium carbonate) stones

Pathogenesis

- infection: urea splitting bacteria: Proteus, Providencia, Klebsiella, Pseudomonas sp.
  - ammonia production:
    - bacterial urease:
      - urea → $H_2O + 2NH_3 + CO_2$
  - urine pH elevated

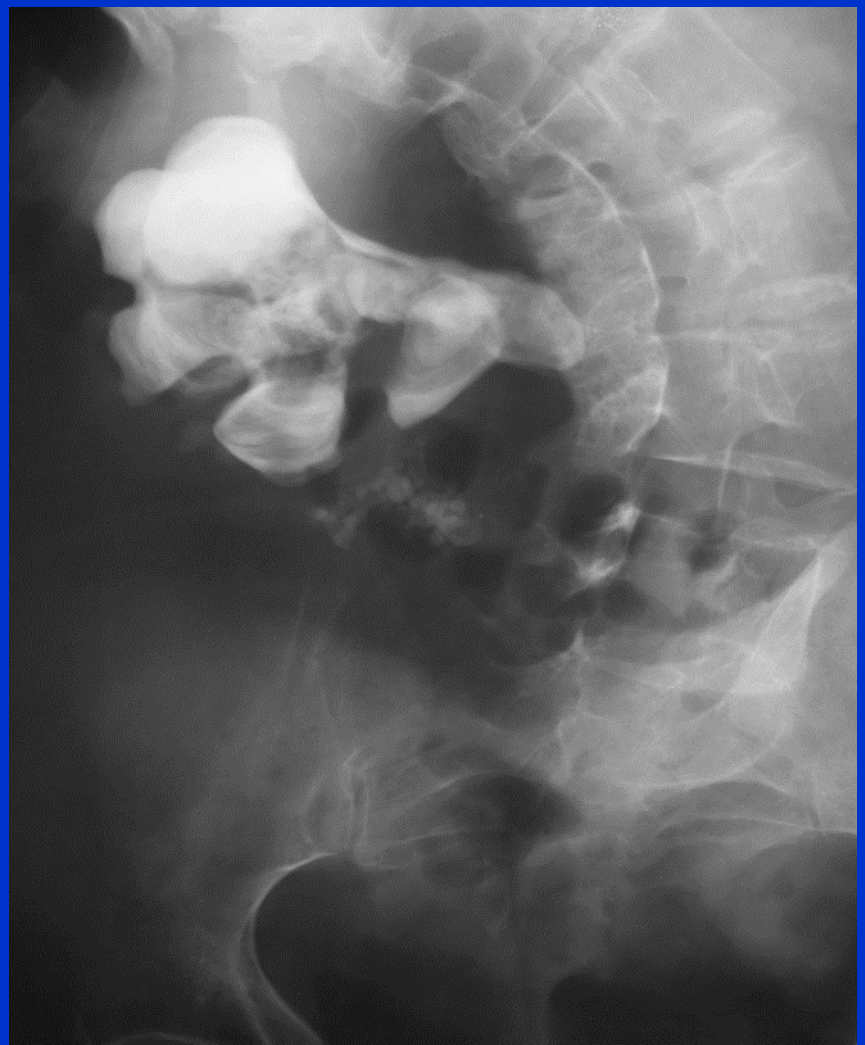
Symptoms:

- UTI, flank pain
- hematuria
- urine pH > 7,0
- multiple magnesium ammonium phosphate crystals in urine

Struvite = magnesium ammonium phosphate stones

- stones form in the renal pelvis and calices
- they fill renal collecting systems and assume a staghorn configuration
- focal parenchymal scarring
- lucent but complex with calcium phosphate → radiopaque
- large size of the stones, rapid growth, frequent growth back after surgical removement
- infection + metabolic cause for stone disease
- infection + obstruction → the kidney damage
- stones grow silently!!!

Struvite stones (plain film)



Treatment of struvite stones

- **clear the urinary tract of stone and sterilize the urine, eliminate urinary obstruction**
- staghorn stones
  - open surgical removal followed by lavage of the renal pelvis with hemiacidrin
  - percutaneus nephrolithotomy (PCN)
  - ESWL with ureteral stenting
  - PCN + ESWL
  - retrograde ureteroscopy with disruption of stones (URS)
- antibacterial
- urease inhibitors – acetohydroxamic acid (AHA) – side effects: headache, tremulousness, anemia

NB: 1.untreated staghorn stones require nephrectomy in 50% of cases! 2.oral acidifying agents are not effective!

Cystine stones

- **cystinuria:**
  - autosomal recessive disease, **defective renal transport** of cystine, ornithine, lysine, arginine→ nephrolithiasis
  - stone disease may begin at any age (>10-20 years)
  - renal colic, hematuria
  - urine sample – hexagonal crystals
  - cystine excretion in urine (> 75ug cystine/mg creatinine)
  - large pelvic staghorn calculi
  - radiopaque stones

Cystine stones treatment

1. **avoid high-protein, high-sodium diet**
2. **maintain diuresis 4l/day**
3. **urine alkalinization (pH 7-7,5) - potassium citrate, potassium bicarbonate (the patient checks the urine pH at voiding)**
4. acetazolamid 250 mg at bedtime (--> nocturnal alkaline diuresis)
5. penicillamine - skin rush, fever, arthralgias, medullary aplasia, proteinuria, membranous nephropathy
6. mercaptoproprionylglicine (tiopronine) -skin rush, fever, nausea, proteinuria, membranous nephropathy
7. captopril
8. SWL, PCNL, URS

Do not mistake cystinuria for cystinosis:

- CYSTINOSIS: autosomal recessive disease: defective **transport of cystine across the lysosomal membrane**, renal Fanconi syndrome, cellular accumulation of cystine → destroys tissue→
  - renal insufficiency
  - hypothyroidism
  - blindness
- treatment: cysteine-leting drug **cysteamine**

Recurrent stones

- 24-hour urine: Ca, phosphate, uric acid, citrate, oxalate, cystine, creatinine, volume
- serum: Ca, phosphate, creatinine, uric acid, bicarbonate, PTH
- urinalysis
- fasting urinary pH > 6 in the absence of UTI → exclude renal tubular acidosis (ammonium chloride acid-loading test: pH does not fall to less than 5,4 in distal RTA)
- Urine culture

Complications of stone disease

- infection, pyelonephritis, abscess
- sepsis, multi-organ failure
- renal scarring, damage
- renal failure – end stage renal disease (struvit stones, bilateral stones)
- death

Frequency of urolithiasis

- **in the general population: 2-3%**
- in less developed countries: lower prevalence (low-protein diet)
- the peak age: 40-60 years
- American population: at least 1 symptomatic episode by the age of 70:
  - men – 10%
  - women – 5%