ZAPORIZHZHYA STATE MEDICAL UNIVERSITY

THE DEPARTMENT OF INTERNAL DISEASES № 3

Casebook

IN NEPHROLOGY

(tutorial for practical exercises for 6-year students of medical faculty)

2015

«RATIFIED»

By Central methodical advice of
Zaporizhzhya state medical university
Protocol № 2 from 26.11.2015

Authors:

1. Dotsenko S.Y. - head of department of internal diseases -3, Zaporizhzhya state medical university, professor, doctor of medical sciences
2. Shehovtseva T. G. - associate professor of department of internal diseases-3 of Zaporizhzhya state medical university, candidate of medical sciences
3. Samura B. B. - associate professor of department of internal diseases -3 of Zaporizhzhya state medical university, candidate of medical sciences
4. Sychov R.A. - associate professor of department of internal diseases -3 of Zaporizhzhya state medical university, candidate of medical sciences
5. Sklyarova N.P. - assistant of department of internal diseases -3 of Zaporizhzhya state medical university, candidate of medical sciences

Учебное пособие “Кклинические задачи по нефрологии)” (на английском языке) предназначено студентам 6-го курса лечебного факультета, которые проходят обучение на английском языке, для самостоятельной подготовки к практическим занятиям по дисциплине “Внутренняя медицина“. В учебное пособие включены клинические задачи, вопросы и ответы к ним, дискуссии по синдромной диагностике, с которыми наиболее часто сталкивается врач в нефрологической клинике.

Reviewers:

- head of the department of Clinical Pharmacology, Pharmacy and Pharmacotherapy with the Course of Cosmetology of Zaporizhzhya state medical university, doctor of medical sciences, professor Kraydashenko O.V.

- professor of the Family Medicine and Therapy Department of FPE of Zaporizhzhya state medical university, doctor of medical sciences Deynega V.G.

Contents:

Preface

Most doctors think that the most memorable way to learn medicine is to see patients. It is easier to recall information based on a real person than a page in a textbook. Another important element in the retention of information is the depth of learning. Learning that seeks to understand problems is more likely to be accessible later than superficial factual accumulation. This is the basis of problem-based learning, where students explore problems with the help of a facilitator. The cases in this book are designed to provide another useful approach, parallel to seeing patients and giving an opportunity for self-directed exploration of clinical problems. They are based on the findings of history taking and examination, together with the need to evaluate initial investigations such as blood investigations, X-rays and ECGs. These cases are no substitute for clinical experience with real patients, but they provide a safe environment for students to explore clinical problems and their own approach to diagnosis and management. Most are common problems that might present to a general practitioner's surgery, a medical outpatients or a session on call in hospital. There are a few more unusual cases to illustrate specific points and to emphasize that rare things do present, even if they are uncommon. The cases are written to try to interest students in clinical problems and to enthuse them to find out more. They try to explore thinking about diagnosis and management of real clinical situations.

Part I: URINARY SYNDROME

CASE 1:

A 21-year-old college student is referred to the renal clinic for further evaluation of microscopic hematuria, which was discovered during a preemployment physical examination. There is no history of recent infections, trauma, or intravenous drug abuse. She denies any history of rashes, arthralgia, myalgias, fevers, or episodes of gross hematuria.

Physical examination reveals a well-developed, well-nourished woman who is in no acute distress. Her blood pressure is 125/85 mm Hg; pulse 72 beats per minute; and respiratory rate 16 breaths per minute. No rashes, lymphadenopathy, or joint tenderness is noted. The remainder of the physical examination findings is within normal limits.

The following laboratory data are reported: serum sodium 135 mEq/L; potassium 4.5 mEq/L; chloride 105 mEq/L; carbon dioxide 25 mEq/L; glucose 98 mg/dL; BUN 12 mg/dL; and creatinine 0.8 mg/dL. Urinalysis shows a specific gravity of 1.015, pH of 5.0, 1+ heme, and 1+ protein on dipstick examination. Microscopic examination of the urine reveals 5 to 10 red blood cells per high-power field, and possibly one red blood cell cast is noted on close scrutiny of the entire slide. The 24-hour urine excretion is of 1.5 L total volume, with 1,200 mg of creatinine and 1,200 mg of protein.

On further laboratory examination, no secondary systemic cause for the nephritic syndrome is identified. Specifically, ANA and antineutrophil cytoplasmic antibody tests are negative, as are tests for hepatitis B and C. Likewise, both the C3 and C4 complement levels are normal. Consequently, a percutaneous renal biopsy is performed. The histologic, immunofluorescence, and electron microscopy findings are all consistent with IgA nephropathy.

- What are the clinical entities that have been associated with prominent mesangial IgA deposits?
- What clinical findings indicate a poor prognosis in IgA nephropathy?
- What is the clinical course of IgA nephropathy?
- What would you advise this patient if she were to contemplate pregnancy?
- What treatment options are available for this patient?

CASE 2:

An 18-year-old man presents with a 2-day history of reddish-brown urine. He was diagnosed with streptococcal pharyngitis 2 weeks ago (treated with amoxicillin). Physical exam is significant for 2+ bilateral peripheral edema. Blood pressure is 160/100. Other vital signs are normal. Urine dipstick detects 3+ blood and 1+ protein. Urine sediment reveals 12 RBCs/HPF, RBC casts, and dysmorphic RBCs.

- What is the syndrome?
- What is the next diagnostic step?
- What is the next step?
- What is the diagnosis?

CASE 3:

A 60-year-old patient reports that he noticed his urine was reddish-brown yesterday and the day before. He is otherwise asymptomatic. He does not take any medications. He has a 30-pack/year history of smoking. Physical exam and vital signs are normal.

- What is the next step in management?
- What is the differential diagnosis of hematuria?

CASE 4:

A 33-year-old man presents to the clinic with gross hematuria. About 5 days ago, he had a fever, runny nose, and sore throat. He is currently asymptomatic. There is no family history of hematuria or renal failure. Physical exam and vital signs are normal. Urinalysis demonstrates dysmorphic RBCs, RBC casts, and trace proteinuria. Serum chemistries are normal. Serum complement and other serologies are normal. Hematuria persists 1 week later.

- What is the most likely diagnosis?
- How is asymptomatic glomerular hematuria managed?

CASE 5:

A 45-year-old man presents with clinical manifestations and urinalysis consistent with acute glomerulonephritis. Past history is significant for 10-lb weight loss due to episodes of diffuse abdominal pain after meals (intestinal angina). There are red, non-blanchable, reticulated lesions on his legs (livedo reticularis). Serum creatinine is 2.8 mg/dL, and BUN is 28 mg/dL. Serum complement is normal. The only significant serology finding is (+) HBsAg.

- What diagnosis should you suspect?
- How can you establish the diagnosis?
- How is PAN treated?

CASE 6:

A 40-year-old man presents with clinical manifestations and urinalysis indicative of acute glomerulonephritis. BUN and serum creatinine are 33 mg/dL and 3.5 mg/dL. Serum complement level is normal. C-ANCA is positive.

- What does positive ANCA indicate?
- What is the next step in management?

CASE 7:

An 18-year-old man presents with a 10-hour history of renal colic. His father and a paternal uncle have a history of nephrolithiasis. Urinalysis is significant for hematuria and hexagonal crystals. CT scan and KUB demonstrate a 2-mm stone in the right upper ureter.

- What is the most likely composition of this stone?
- What is the recommended therapy to prevent recurrence?

CASE 8:

A patient with no past medical history presents with renal colic, hematuria, and urine pH of 4.8. CT scan identifies a 4-mm stone in the upper ureter. KUB is negative. He receives IV fluids

and ketorolac and is discharged home. Twenty-four hours later, he passes a stone. Serum uric acid is elevated, and stone analysis reveals that he had a uric acid stone.

- What are risk factors for uric acid stones?
- How would you prevent recurrent uric acid stones in this patient?

CASE 9:

A 40-year-old woman presents to the clinic with mild flank pain. Past history is significant for UTIs. Urinalysis is significant for hematuria, urine pH of 7.6, positive leukocyte esterase and nitrite, and coffin lid–shaped crystals. Figure 9-1 is the patient's CT scan. Vital signs are normal.

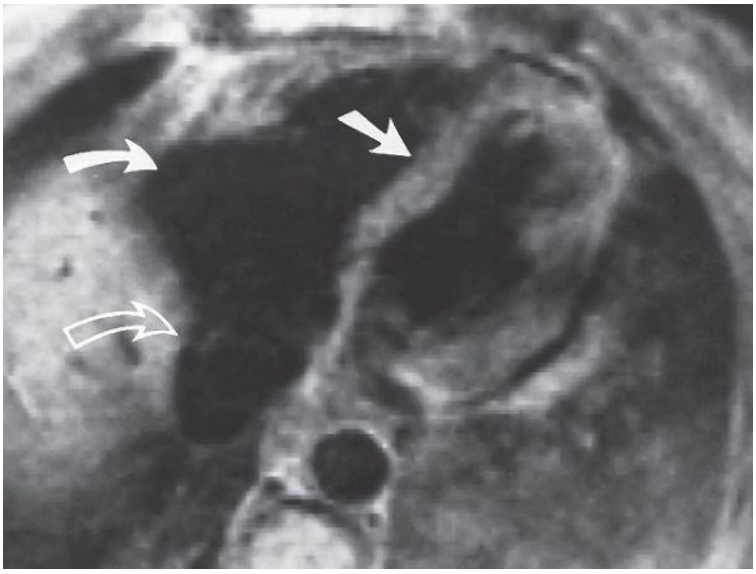

Figure 9–1. CT: Staghorn calculi.

- What do the imaging findings demonstrate?
- What causes struvite stones?
- How are struvite stones managed?

CASE 10:

A 35-year-old woman presents to the clinic with a 2-day history of painful burning urination (dysuria), frequency, and urgency. She does not have any discharge or pain during intercourse (dyspareunia). Physical exam is significant for suprapubic tenderness. There is no CVA tenderness. She has been in a monogamous relationship with her husband for the last 10 years. Vital signs are normal.

- What is the most likely diagnosis?
- What is the next step in management?

CASE 11:

A 50-year-old man undergoes hematopoietic stem cell transplantation for treatment of acute myelogenous leukemia. Before transplantation, he received high-dose cyclophosphamide and busulfan. Two days after the procedure, he presents with dysuria, urgency, frequency, and suprapubic pain. His urine is bright red with blood clots. Vital signs are normal.

- What diagnosis should you suspect?
- What is the next diagnostic step?
- How is hemorrhagic cystitis treated?

CASE 12:

A 35-year-old woman presents to the emergency department with a 2-day history of fever, flank pain, nausea, and vomiting. She also complains of frequency, urgency, dysuria, and suprapubic pain for the last 4 days. She has no other medical conditions. Physical exam is significant for right costovertebral angle (CVA) tenderness. Vital signs are temperature 38.4°C, pulse 115 bpm, respirations 18/min, and blood pressure 118/75.

- What diagnosis should you suspect?
- What is the next step in management?
- Which patients with pyelonephritis require hospitalization?
- What empiric antibiotics are indicated?
- What empiric agents are recommended for hospitalized patients?
- When is imaging indicated for patients with pyelonephritis?

CASE 13:

A 65-year-old man with type 2 diabetes presents with right flank pain and fever. Physical exam is significant for right CVA tenderness. Leukocyte esterase and nitrite are positive. Complete blood count shows leukocytosis with a left shift. CT scan shows a wedge-shaped hypodense collection in the right kidney.

- What is the diagnosis?
- How are renal abscesses treated?
- What are other important complications of pyelonephritis?

CASE 14:

A 45-year-old man presents with an 8-hour history of intense pain in the right flank. The pain waxes and wanes in severity. Over the last hour, the pain has begun to radiate to the right groin. He noticed blood in his urine a couple of hours ago. This is his first such episode. Vital signs are temperature 37.1°C, pulse 110 bpm, respirations 21/min, blood pressure 140/85, and oxygen saturation 100% on room air. Urine dipstick is positive for blood. Urine nitrite and leukocyte esterase are negative.

- What is the most likely diagnosis?
- What is the next diagnostic step?

- What are the next steps in management?
- How would you manage stones that do not pass spontaneously?
- In addition to analysis of the stones, what work-up is recommended?
- How can you prevent stone recurrence?

CASE 15:

A 46-year-old woman presents to the emergency department with a 2-day history of right-sided loin pain and macroscopic haematuria. The pain is continuous and dull in character. Over the past 10 years she has had previous episodes of loin pain which have occurred on both sides and resolved spontaneously over a few days. She has never passed any stones. She was noted to be mildly hypertensive during her three pregnancies. She has no other significant medical history. Her father died of a subarachnoid haemorrhage, aged 48 years. Her father's brother has had a kidney transplant. She has no siblings. Her three children, aged 17, 14 and 10 years, are well. She works as a teacher and neither smokes nor drinks alcohol.

Examination On examination she is afebrile. Her pulse is regular at 76/min and her blood pressure is 135/105 mmHg. Examination of the cardiovascular and respiratory systems is otherwise unremarkable. On palpation of her abdomen, ballottable masses are palpable in each flank. The right-sided mass is tender to palpation. Percussion note is resonant over the masses. Neurological examination is normal. Funduscopy shows arteriovenous nipping and silverwiring of the retinal vessels.

		Normal
Haemoglobin	14.3 g/dL	11.7-15.7 g/dL
White cell count	5.2 X 109/L	3.5-11.0 X 109/L
Platelets	206 X 109/L	150-440 X 109/L
Sodium	138 mmol/L	135-145 mmol/L
Potassium	4.3 mmol/L	3.5-5.0 mmol/L
Urea	10.2 mmol/L	2.5-6.7 mmol/L
Creatinine	146 μ^^^	70-120 μmol/L
Albumin	42 g/L	35-50 g/L

Urinalysis: + protein; + + + blood. Urine microscopy: >200 red cells; 10 white cells; no organisms Abdominal X-ray: no intra-abdominal calcification seen.

- What is the diagnosis?
- How would you proceed to manage and investigate this patient?
-

Part II: EDEMATOUS SYNDROME

CASE 16:

A 27-year-old man presents to the outpatient clinic complaining of days of facial and hand swelling. He first noticed swelling around his eyes 2 days ago, along with difficulty putting on his wedding ring because of swollen fingers. Additionally, he noticed that his urine appears reddish-brown and that he has had less urine output over the last several days. He has no significant medical history. His only medication is ibuprofen that he took 2 weeks ago for fever and a sore throat,

which have since resolved. On examination, he is afebrile, with heart rate 85 bpm and blood pressure 172/110 mm Hg. He has periorbital edema; his funduscopic examination is normal without arteriovenous nicking or papilledema. His chest is clear to auscultation, his heart rhythm is regular with a nondisplaced point of maximal impulse (PMI), and he has no abdominal masses or bruits. He does have edema of his feet, hands, and face. A dipstick urinalysis in the clinic shows specific gravity of 1.025 with 3+ blood and 2+ protein, but it is otherwise negative.

- What is the most likely diagnosis?
- What is your next diagnostic step?

CASE 17:

A 54-year-old man presents with a 3-week history of bilateral pedal edema. He does not have any dyspnea or chest pain. Medical history is significant for poorly controlled type 2 diabetes. He last visited a physician 1 year ago. At that time, urinalysis detected trace protein and serum creatinine was 2.0 mg/dL. He is not compliant with losartan and insulin. He does not smoke or drink alcohol. On physical exam, there is periorbital and bilateral pitting pedal edema. Vital signs are normal.

- What is the most likely cause of this patient's edema?
- What are the causes of nephrotic syndrome?
- What are the next diagnostic steps?

CASE 18:

The patient is a 20-year-old man with clinical manifestations and laboratory evidence of nephrotic syndrome. Blood glucose is normal. Renal biopsy shows minimal changes. There is no history of NSAID use. Physical exam and vital signs are normal.

- What is the next step in management?

CASE 19:

A 67-year-old man with multiple myeloma presents with clinical manifestations of nephrotic syndrome. In addition to edema, physical exam is significant for a thickened, waxy tongue (macroglossia). Blood glucose is normal. When the renal biopsy sample is stained with Congo red stain and examined under polarized light, there is green birefringence.

- What is the diagnosis?
- How is primary amyloidosis treated?

CASE 20:

The patient is a 36-year-old woman with clinical features of nephrotic syndrome. Past history is significant for fatigue and joint pain. Physical examination is significant for areas of alopecia and an erythematous rash across the nose and cheeks (malar rash).

- What is the most likely diagnosis?
- How is lupus nephritis treated?

CASE 21:

A 72-year-old man goes to his general practitioner (GP) complaining of painless swelling of both legs which he first noted approximately 2 months ago. The swelling started at the ankles but now his legs, thighs and genitals are swollen. His face is puffy in the mornings on getting up. His weight is up by about 10 kg over the previous 3 months. He has noticed that his urine appears to be frothy in the toilet. He has noted gradual increasing shortness of breath, but denies any chest pain. He has also developed spontaneous bruising over the past 6 months. He is a retired heavy goods vehicle driver. He had hypertension diagnosed 13 years ago, and a myocardial infarction 4 years previously. He lives with his wife and has no children. He continues to smoke 30 cigarettes a day, and drinks about 30 units of alcohol a week. His medication consists of atenolol 50 mg once a day.

On examination there is pitting edema of the legs which is present to the level of the sacrum. There is also massive edema of the penis and scrotum. There is bruising on the forearms and around the eyes. There are no signs of chronic liver disease. His pulse rate is 72/min and regular. Blood pressure is 166/78 mmHg. His jugular venous pressure is raised at 5 cm. His apex beat is not displaced, and auscultation reveals normal heart sounds and no murmurs. There is dullness to percussion and reduced air entry at both lung bases. The liver, spleen and kidneys are not palpable, but ascites is demonstrated by shifting dullness and fluid thrill. Neurological examination is unremarkable.

		Normal
Haemoglobin	10.7 g/dL	13.3-17.7 g/dL
Mean corpuscular volume (MCV)	95 fL	80-99 fL
White cell count	4.7 X 109/L	3.9-10.6 X 109/L
Platelets	176 X 109/L	150-440 X 109/L
Sodium	138 mmol/L	135-145 mmol/L
Potassium	4.9 mmol/L	3.5-5.0 mmol/L
Urea	7.4 mmol/L	2.5-6.7 mmol
Creatinine	112 μ^^^	70-120 μ^^^
Glucose	4.7 mmol/L	4.0-6.0 mmol/L
Albumin	16 g/L	35-50 g/L
Cholesterol	15.2 mmol/L	3.9-6.0 mmol/L
Triglycerides	2.7 mmol/L	0.55-1.90 mmol/L

Clotting screen: normal Urinalysis: + + + protein; no blood

- What is the cause of this patient's edema?
- What is the likely underlying diagnosis?
- How would you further examine, investigate and manage this patient?

Part III: NEPHROTIC SYNDROME

CASE 22:

A 48-year-old Hispanic woman presents to your office complaining of persistent swelling of her feet and ankles, so much so that she cannot put on her shoes. She first noted mild ankle swelling approximately 2 to 3 months ago. She borrowed a few diuretic pills from a friend; the pills seemed to help, but now she has run out. She also reports that she has gained 20 to 25 lb over the last few months, despite regular exercise and trying to adhere to a healthy diet. Her medical history is significant for type 2 diabetes, for which she takes a sulfonylurea agent. She neither sees a doctor regularly nor monitors her blood glucose at home. She denies dysuria, urinary frequency, or urgency, but she does report that her urine has appeared foamy. She had no fevers, joint pain, skin rashes, or gastrointestinal (GI) symptoms.

Her physical examination is significant for mild periorbital edema, multiple hard exudates, and dot hemorrhages on funduscopic examination, and pitting edema of her hands, feet, and legs. Her chest is clear, her heart rhythm is regular without murmurs, and her abdominal examination is benign. She has diminished sensation to light touch in her feet and legs to mid-calf. A urine dipstick performed in the office shows 2+ glucose, 3+ protein, and negative leukocyte esterase, nitrates, and blood.

> What is the most likely diagnosis?
> What is the best intervention to slow disease progression?

CASE 23:

A 40-year-old woman is referred for evaluation of proteinuria. Apart from occasional arthralgias, she has felt well but is concerned about progressive weight gain and marked swelling of her lower extremities. She has no personal or family history of renal disease, no known chronic systemic illness, nor is she taking any medications. Physical examination findings, including blood pressure, are normal, except for the presence of edema that is most notable in dependent areas. Laboratory evaluation reveals a normal hematocrit, as well as serum glucose, BUN, and creatinine levels, but she has profound hypoalbuminemia (1.9 g/dL) and hypercholesterolemia (490 mg/dL). Urinalysis shows 4+ proteinuria, oval fat bodies, and free fat droplets, but no cellular elements or casts. Her 24-hour urinary excretion of protein is found to be 8.6 g.

> What features of the history and physical examination are important in determining if this patient has a primary (idiopathic) or secondary form of the nephrotic syndrome?
> What additional laboratory tests would you order either to establish or refute a secondary cause of the nephrotic syndrome?
> How should this patient's evaluation proceed?

Part IV: RENAL ARTERIAL HYPERTENSION

Case 24:

A 38-year-old adopted white man is seen by his family physician for the management of hypertension of 2 years' duration. Current medications include amiloride (5 mg) and hydrochlorothiazide (50 mg), with good blood pressure control until now. Review of systems reveals increasing fatigue, headaches, and muscle cramps. Physical examination reveals a blood pressure of 140/100 mm Hg in the left arm and 136/100 mm Hg in the right arm. No disparity in the blood pressure between the arms and the legs is found. The remainder of the examination findings are otherwise unremarkable.

The following laboratory data are reported: sodium 145 mEq/L; potassium 2.7 mEq/L; chloride 109 mEq/L; bicarbonate 29 mEq/L; BUN 10 mEq/L; creatinine 1.2 mg/dL; calcium 9.1 mg/dL; cholesterol 213 mg/dL; triglycerides 163 mg/dL; uric acid 6.1 mg/dL; phosphate 2.1 mg/dL; and glucose 99 mg/dL. Results of urinalysis, including microscopic examination, are normal.

The diuretics are stopped and the patient is placed on potassium supplements. Repeat laboratory work reveals that his sodium level is 147 mEq/L, potassium level is 3 mEq/L, and blood pressure is 146/104 mm Hg.

- What is the differential diagnosis of this patient's hypertension?
- What symptoms are related to the patient's hypokalemia?
- What diagnostic steps would help confirm the diagnosis in this patient?
- What are the treatment options in this patient?

CASE 25:

A 40-year-old woman presents with a 4-week history of flank pain. Past history is significant for UTIs. Her father and paternal grandfather died of kidney disease in their 50s. Blood pressure is 160/100. Other vital signs are normal. Urinalysis is significant for hematuria.

- What diagnosis should you suspect?
- What are the clinical manifestations of APKD?
- What is the next diagnostic step?
- Renal ultrasound confirms the diagnosis. How is APKD managed?

CASE 26:

A 36-year-old woman is referred by her general practitioner (GP) to a hypertension clinic. She was noted to be hypertensive when she joined the practice 2 years previously. Her blood pressure has been difficult to control and she is currently taking four agents (ben- drofluazide, atenolol, amlodipine and doxazosin). She had normal blood pressure and no pre-eclampsia during her only pregnancy 9 years previously. There is no family history of premature hypertension. She smokes 20

cigarettes a day and drinks less than 10 units a week. She is not on the oral contraceptive pill. She works part time as a teaching assistant.

She is not overweight and looks well. Her pulse rate is 68/minute and blood pressure 180/102 mmHg. There is no radiofemoral delay. There are no cafe-au-lait spots or neurofibromas. Examination of the cardiovascular, respiratory and abdominal systems is normal. The fundi show no significant changes of hypertension.

		Normal
Hemoglobin	13.3 g/dL	11.7-15.7 g/dL
White cell count	6.2 X 109/L	11.0 X 109/L
Platelets	266 X 109/L	150-440 X 109/L
Sodium	139 mmol/L	135-145 mmol/L
Potassium	4.4 mmol/L	5.0 mmol/L
Urea	10.7 mmol/L	6.7 mmol/L
Creatinine	136 μmol/L	70-120 μmol/L
Albumin	42 g/L	35-50 g/L

Urinalysis: no protein; no blood. Renal ultrasound: normal size kidneys. Results of a renal angiogram are shown in Fig. 26.1.

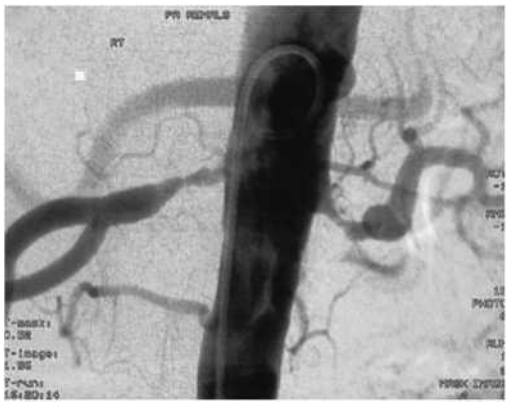

Figure 26.1. Renal angiogram

- What is the diagnosis?
- How would you further manage this patient?

Part V: CHRONIC RENAL FAILURE

CASE 27:

Serum creatinine of a 46-year-old woman is incidentally found to be 3.0 mg/dL. Urinalysis is normal. Review of prior records indicates serum creatinine was 2.8 mg/dL 6 months earlier. She has a history of chronic headaches for which she takes high doses of aspirin and ibuprofen. Physical exam and vital signs are normal. CT scan without contrast is significant for renal papillary necrosis.

- What is the most likely cause of this patient's CRI?
- What are other common causes of chronic interstitial nephritis?

Part VI: ACUTE RENAL FAILURE

Case 28:

A 54-year-old man with a history of type 2 diabetes and coronary artery disease is admitted to the coronary care unit with worsening angina and hypertension. His pain is controlled with intravenous nitroglycerin, and he is treated with aspirin, beta-blockers to lower his heart rate, and angiotensin-converting enzyme (ACE) inhibitors to lower his blood pressure. Cardiac enzymes are normal. He undergoes coronary angiography, which reveals no significant stenosis. By the next day, his urine output has diminished to 200 mL over 24 hours. Examination at that time reveals that he is afebrile, his heart rate is regular at 56 bpm, and his blood pressure is 109/65 mm Hg. His fundus reveals dot hemorrhages and hard exudates, his neck veins are flat, his chest is clear, and his heart rhythm is normal with an S4 gallop and no murmur or friction rub. His abdomen is soft without masses or bruits. He has no peripheral edema or rashes, with normal pulses in all extremities. Current laboratory studies include Na 140 mEq/L, K 5.3 mEq/L, Cl 104 mEq/L, CO2 19 mEq/L, and blood urea nitrogen (BUN) 69 mg/dL. His creatinine (Cr) level has risen to 2.9 mg/dL from 1.6 mg/dL on admission.

- What is the patient's new clinical problem?
- What is your next diagnostic step?

CASE 29:

A 60-year-old woman presents to her primary care physician with chronic knee pain. She has a history of diabetes and hypertension. Medications include insulin and enalapril. Her physician recommends an ice pack. She presents 1 week later for a follow-up appointment. The ice pack was not helpful, so she has been taking increasing amounts of naproxen for pain relief. Physical exam is significant for 2+ lower extremity pitting edema. Vital signs are normal. Abnormal serum chemistries are potassium 5.2 mEq/L, blood urea nitrogen (BUN) 74 mg/dL, and serum creatinine 3.2 mg/dL. Last week, BUN and serum creatinine were 27 mg/dL and 2.0 mg/dL, respectively; 3 months ago, BUN and serum creatinine were 25 mg/dL and 2.0 mg/dL, respectively.

- What is the next diagnostic step?
- What is the cause of ARF?
- What are the indications for urgent dialysis?

CASE 30:

A 57-year-old woman with insulin-dependent type 2 diabetes presents to her primary care physician with acute onset of left lower quadrant pain. She undergoes CT scan with iodinated contrast (an ionic contrast agent) to rule out diverticulitis. Baseline BUN and serum creatinine are 25 mg/dL and 2.0 mg/dL, respectively. BUN and serum creatinine 5 hours later are 30 mg/dL and 3.5 mg/dL. Vital signs are normal. A large volume of urine does not flow upon insertion of a bladder catheter. Complete blood count is normal. Urine osmolality is 200 mOsm/kg, urine sodium is 25 mEq/L, FeNa is 0.6%, and serum BUN/creatinine is 8.5. Urine output is 40 mL/hour. Urine dipstick findings are specific gravity 1.012, trace protein, and no blood. Urine sediment reveals few granular casts. Hansel's stain is negative.

- What is the cause of ARF?
- How is intrinsic renal failure treated?

CASE 31:

A 28-year-old fireman is brought to the hospital after being rescued from the rubble of a collapsed building. On exam, mucous membranes are dry. Vital signs are temperature 37.5°C, blood pressure 98/60, pulse 120 bpm, respirations 25/min. Abnormal serum chemistries are potassium 5.9 mEq/L, BUN 80 mg/dL, creatinine 6.0 mg/dL, bicarbonate 18 mg/dL, and calcium 6.5 mg/dL. A large volume of urine does not flow upon insertion of a bladder catheter. Complete blood count is normal. Urine osmolality is 150 mOsm/kg, urine sodium is 30 mEq/L, FeNa is 3%. Urine output is 6 mL/hour (140 ml/day). Urine is red. Urine dipstick findings are specific gravity 1.013, trace protein, and 2+ blood. Urine sediment and supernatant are clear. Sediment analysis reveals reddish gold as well as muddy brown casts but no red blood cells (RBCs).

- What is the cause of ARF?
- What are the major causes of rhabdomyolysis in adults?
- What fluid and electrolyte abnormalities commonly occur in rhabdomyolysis?
- What are the next steps in management?

CASE 32:

A 48-year-old woman with hypertension and osteoarthritis presents to the clinic with fever and malaise. She recently completed a course of amoxicillin for streptococcal pharyngitis. Two weeks ago, she started taking lisinopril. She also takes ibuprofen off and on to control symptoms of arthritis. Physical exam is significant for a rash. Temperature is 38.4°C, pulse 70 bpm, blood pressure 120/80, respirations 12/min. Abnormal serum chemistries are BUN 26 mg/dL and serum creatinine 2.5 mg/dL. Complete blood count is significant for increased eosinophils. Urine osmolality is 110 mOsm/kg, urine sodium is 40 mEq/L, FeNa is 2%. Urine dipstick findings are specific gravity 1.011, 1+ protein, and 1+ blood. Sediment analysis reveals hyaline casts. Hansel's stain is positive.

- What is the cause of ARF?
- What is the next step in management?

CASE 33:

A 60-year-old, previously healthy man presents with a chief complaint of difficulty with urination. He has not been able to urinate in the last 48 hours. He does not take any medications. On physical exam, the bladder feels distended. Vitals signs are normal. Serum chemistries are significant for BUN 30 mg/dL and serum creatinine 2.7 mg/dL. A large volume of urine flows on insertion of a bladder catheter.

- What is the next step in management?

CASE 34:

The medical team is asked to review a postoperative surgical patient. A 62-year-old lady had been admitted 10 days previously to have a right hemicolectomy performed for a caecal carcinoma. This was discovered on colonoscopy which was performed to investigate an iron-deficiency anaemia and change in bowel habit. She is otherwise fit with no significant medical history. She is a retired teacher. She neither smokes nor drinks alcohol and is on no medication. Her preoperative serum creatinine was 76 μmol/L. The initial surgery was uneventful, and she was given cefuroxime and metronidazole as routine antibiotic prophylaxis. However the patient developed a prolonged ileus associated with abdominal pain. On postoperative day 5, the patient started to spike fevers up to 38.5°C and was commenced on intravenous gentamicin 80 mg 8 hourly in addition to the other antibiotics. Over the next 5 days the patient remained persistently febrile, with negative blood cultures. In the last 24 h, she has also become relatively hypotensive with her systolic blood pressure being about 95 mmHg despite intravenous colloids. Her urine output is now 15mL/h.

She is unwell and sweating profusely. She is jaundiced. Her pulse rate is 110/min regular, blood pressure 95/60 mmHg and jugular venous pressure is not raised. Her heart sounds are normal. Her respiratory rate is 30/min. Her breath sounds are normal. Her abdomen is tender with guarding over the right iliac fossa. Bowel sounds are absent.

		Normal
Haemoglobin	8.2 g/dL	11.7-15.7 g/dL
Mean corpuscular volume (MCV)	83 fL	80-99 fL
White cell count	26.3 X 109/L	3.5-11.0 X 109/L
Platelets	94 X 109/L	150-440 X 109/L
Sodium	126 mmol/L	135-145 mmol/L
Potassium	5.8 mmol/L	3.5-5.0 mmol/L
Bicarbonate	6 mmol/L	24-30 mmol/L
Urea	36.2 mmol/L	2.5-6.7 mmol/L
Creatinine	523 μmol/L	70-120 μmol/L
Glucose	2.6 mmol/L	4.0-6.0 mmol/L
Albumin	31 g/L	35-50 g/L
Bilirubin	95 mmol/L	3-17 mmol/L
Alanine transaminase	63 IU/L	5-35 IU/L
Alkaline phosphatase	363 IU/L	30-300 IU/L
Trough gentamicin level	4.8 mg/mL	<2.0 mg/mL

Urinalysis: + blood; + protein; granular casts and epithelial cells

- What are the causes of this patient's acute renal failure?
- How would you further investigate and manage this patient?

ANSWERS AND DISCUSSION TO CASES

PART I: URINARY SYNDROME

ANSWERS TO CASE 1:

What are the clinical entities that have been associated with prominent mesangial IgA deposits?

Henoch-Schonlein purpura, chronic liver disease, dermatitis herpetiformis, axial arthropathies, and Berger's disease have all been found in the setting of mesangial IgA deposits.

What clinical findings indicate a poor prognosis in IgA nephropathy?

The clinical findings that portend a poor prognosis in IgA nephropathy are persistent proteinuria of greater than 1 g per day, elevated blood pressure, male gender, an elevated serum creatinine level, and the absence of macroscopic hematuria.

What is the clinical course of IgA nephropathy?

Patients with IgA nephropathy may experience intermittent episodes of gross hematuria, and 5% to 10% of the patients may have early nephrotic syndrome. End-stage renal disease develops in approximately 10% of affected patients by 10 years, and by 20 years in 20% of affected patients. In addition, another 20% to 30% may experience some decline in renal function within 20 years.

What would you advise this patient if she were to contemplate pregnancy?

Despite early reports to the contrary, large retrospective surveys reveal no evidence indicating that IgA nephropathy unfavorably alters the course of pregnancy. In addition, the chances for a successful pregnancy are excellent if the patient remains free of hypertension or renal insufficiency.

What treatment options are available for this patient?

There is no proven treatment for IgA nephropathy. The results of some trials of steroids have suggested that they are somewhat effective in patients with persistent proteinuria, when renal function is still well preserved (S_{Cr} <1.4 mg/dL).

CASE DISCUSSION

What is the definition of hematuria?

Hematuria refers to the presence of an abnormally high number of red blood cells (>5 per high-power field) in the urine. This is most commonly detected by a dipstick (Hemastix) method, which identifies the presence of hemoglobin. The hematuria is considered macroscopic when the urine is obviously red due to the presence of blood, and it is deemed microscopic when the urine grossly appears normal. A number of foods (such as beets) and some drugs (such as phenazopyridine hydrochloride) as well as porphyria can turn the urine red. In these circumstances, the dipstick result is negative.

What are the major causes of hematuria?

The causes of hematuria are best approached in terms of their being either extrarenal or renal in origin. Extrarenal bleeding can occur in the ureters due to calculi or carcinoma; in the bladder due to hemorrhagic cystitis stemming from infection (including Schistosoma haematobium in endemic areas), as well as from cyclophosphamide use, carcinoma, catheterization, or calculi; in the prostate due to hypertrophy, carcinoma, or prostatitis; and in the urethra due to urethritis or trauma. Renal causes of hematuria can be classified as either glomerular or nonglomerular and are listed in Table 1-1.

Table 1-1. Glomerular and nonglomerular renal parenchymal causes of hematuria

Glomerular

- Proliferative glomerulonephritis
  - Primary
  - Secondary
- Familial diseases of the glomerulus
  - Alport's syndrome
  - Recurrent benign hematuria (thin basement membrane disease)
- Malignant hypertension

Nonglomerular

- Neoplasms
  - Renal cell carcinoma
  - Wilms' tumor
  - Benign cysts

Vascular

- Renal infarct
- Renal vein thrombosis
- Malignant hypertension
- Arteriovenous malformation
- Capillary necrosis
- Loin pain-hematuria syndrome

Metabolic

- Hypercalciuria
- Hyperuricosuria

Familial

- Polycystic kidney disease
- Medullary sponge kidney

Papillary necrosis

- Analgesic abuse
- Sickle cell disease and trait
- Renal tuberculosis
- Diabetes
- Obstructive uropathy

Drugs

- Anticoagulants (heparin, coumarin)
- Drug-induced acute interstitial nephritis

Trauma

What can help point toward a glomerular origin as the source of the hematuria?

The following findings point toward a glomerular cause as the source of hematuria: (a) the presence of dysmorphic red blood cells on phase-contrast microscopy; (b) the presence of red blood cell casts, which is virtually a diagnostic finding; and (c) proteinuria exceeding 500 mg per day.

What is the definition of the nephritic syndrome?

The nephritic syndrome is defined by a constellation of urinary findings that include the presence of hematuria, proteinuria, and red blood cell casts. These findings indicate the presence of a glomerular lesion and are frequently accompanied by azotemia, hypertension, and edema.

What are the primary diseases of the kidney associated with glomerular hematuria (nephritic syndrome)?

The primary diseases associated with glomerular hematuria are immunoglobulin A (IgA) nephropathy, poststreptococcal glomerulonephritis, membranoproliferative glomerulonephritis, and idiopathic RPGN.

What systemic diseases are associated with glomerular hematuria?

SLE, Henoch-Schonlein purpura, Goodpasture's syndrome, vasculitis (including polyarteritis nodosa and Wegener's granulomatosis), and essential mixed cryoglobulinemia are all associated with glomerular hematuria.

How is rapidly progressing glomerulonephritis (RPGN) defined?

RPGN is primarily defined in clinical terms as a glomerular disease characterized by progression to end-stage renal disease within weeks to months. The pathologic correlate is extensive crescent formation in the glomeruli, as seen in kidney biopsy specimens.

What clinical disorders cause RPGN?

A number of disorders cause RPGN. These are best defined in immunopathologic terms, depending on the absence or presence (and pattern) of immune deposits (Table 1-2).

Table 1-2. Immunopathogenetic classification of rapidly progressive glomerulonephritis (RPGN)

- Anti-GBM antibody (linear immune deposits)
  - With lung hemorrhage (Goodpasture's syndrome)
  - Without lung hemorrhage (idiopathic)
- Immune complex (granular immune deposits)
  - Predominantly IgA
    - IgA nephropathy
    - Henoch-Schonlein purpura
  - Predominantly IgG (others may be present)
    - Postinfectious
    - Visceral abscess
    - Bacterial endocarditis
    - Lupus nephritis
    - Cryoglobulinemia
    - Membranoproliferative glomerulonephritis
- Pauciimmune (no immune deposits)
  - Vasculitis
    - Microscopic polyarteritis
    - Wegener's
    - Hypersensitivity vasculitides (e.g., Churg-Strauss syndrome)
  - Idiopathic

GBM, glomerular basement membrane; IgA, immunoglobulin A; IgG, immunoglobulin G.

ANSWERS TO CASE 2:

What is the syndrome?

Hematuria, proteinuria, dysmorphic RBCs, and RBC casts indicate glomerular injury (glomerulonephropathy). There are two clinical patterns of glomerular injury:

- Nephritic (glomerular inflammation): Inflammation of <50% of glomeruli leads to focal nephritis. More extensive inflammation leads to nephritic syndrome.

- Focal nephritis: gross or microscopic hematuria, RBC casts, dysmorphic RBCs, 1+ proteinuria.
- Nephritic syndrome: focal nephritis plus hypertension, edema, and renal insufficiency; can cause CRI and ARF. Mnemonic is "PHAROH" (Proteinuria, Hematuria, Azotemia, RBCs (RBC casts and dysmorphic RBCs), Oliguria, and Hypertension).

• Nephrotic (increased permeability but no inflammation): Proteinuria and lipiduria but no RBC casts or dysmorphic RBCs. Severe damage leads to nephrotic syndrome.

- Nephrotic syndrome: >3.5 g/day of proteinuria leads to hypoalbuminemia, edema (due to sodium retention), hyperlipidemia (liver's response to decreased oncotic pressure), fatty casts (due to lipiduria), hypercoagulable state (decreased clotting cascade proteins), and increased infections (decreased immunoglobulin proteins). Can cause CRI; infrequently causes ARF.

Urine dipstick protein: trace = 50 to 150 mg/day, 1+ = 150 to 500 mg/day, 2+ = 500 to 2000 mg/day, 3+ = 2 to 5 g/day, 4+ = >5 g/day.

What is the next diagnostic step?

Obtain serum chemistries (to determine if the patient has azotemia) and 24-hour urine collection (to quantify the level of protein excretion).

Renal ultrasound: Consider this test if the patient has azotemia and baseline chemistries are not available. Renal scarring indicates underlying CRI.

BUN and serum creatinine are 28 mg/dL and 2.8 mg/dL, respectively. Protein excretion is 200 mg/day. There is no scarring on renal ultrasound.

What is the next step?

This patient has acute glomerulonephritis with laboratory evidence of ARF. Obtain the following battery of serum tests to rapidly determine the cause of glomerulonephritis: serum complement, antistreptolysin O (ASO) titer, anti-nuclear antibody and anti-dsDNA, anti-neutrophilic cytoplasmic antibodies (ANCA), anti-glomerular basement membrane (anti-GBM), cryoglobulins, hepatitis B and C serologies, and blood cultures if febrile (Table 2-1). If serology is negative or nonspecific, perform renal biopsy.

Table 2–1. Major causes of focal and diffuse glomerulonephritis in adults

	Disorder	Possible Serology Findings
Systemic causes associated with decreased complement	• Type III or IV lupus nephropathy • Cryoglobulinemia a • Endocarditis • Shunt nephritis b	• (+) ANA or anti-dsDNA • (+) HCV serology (90%), increased cryoglobulins • (+) Blood cultures • (+) Blood cultures • (+) ASO titer
Primary renal disorders associated with decreased complement	Postinfectious GN	
Systemic causes associated with normal complement	• Wegener's disease c • Microscopic polyangiitis c • Churg-Strauss syndrome c • Polyarteritis nodosa c	• (+) c-ANCA >>(+) p-ANCA • (+) p-ANCA >>(+) c-ANCA • (+) p-ANCA >>(+) c-ANCA • (+) Hepatitis B serology (occasionally)

	• Goodpasture's syndrome	• (+) Anti-GBM antibodies
Primary renal disorders associated with normal complement (serology negative)		
IgA nephropathy (Berger's disease)		
Benign familial hematuria (thin basement membrane disease)		
Hereditary nephritis (Alport's syndrome)		
Idiopathic RPGN		

***Abbreviations**: ANA, anti-nuclear antibody; ANCA, anti-neutrophilic cytoplasmic antibody; ASO, antistreptolysin O; GBM, glomerular basement membrane; HCV, hepatitis C virus; RPGN, rapidly progressive GN.*

a First-line therapy is to treat underlying HCV infection.

b Shunt nephritis is caused by antibodies that develop in response to chronic infection of a surgically placed shunt (e.g., ventriculoatrial shunt). Treatment is antibiotics and removal of the shunt.

c Vasculitides.

Asymptomatic nephritis and no azotemia: First obtain serum complement (disorders with immune complex deposition cause decreased complement). Then obtain serologies on the basis of complement levels and clinical manifestations. Order renal biopsy if serologies are not diagnostic or the patient develops azotemia.

Complement levels are decreased. ASO titer is positive.

What is the diagnosis?

The patient has postinfectious glomerulonephritis (PIGN). Streptococcus is the most common infection associated with PIGN (occurs approximately 10 days after infection). Most cases are self-limiting, so limit treatment to close monitoring of serum chemistries and correction of fluid and electrolyte abnormalities. Obtain renal biopsy only if the patient's symptoms persist.

ANSWERS TO CASE 3:

What is the next step in management?

Red, brown, or pink urine suggests the patient has increased RBCs in his urine (hematuria). However, myoglobin, hemoglobin, and other pigments can also cause red, brown, or pink urine (Fig. 3-1).

The next step in management is urinalysis. Examine the color of the supernatant and sediment, check the urine dipstick and assess for the presence of RBCs on sediment microscopy.

- Microscopic hematuria: Urine is clear; ≥3 RBCs/high-powered field (HPF) on urinalysis.
- Gross hematuria: Urine is pink, red, or brown. Urinalysis detects ≥3 RBCs/HPF.
- Pseudohematuria: Urine is pink, red, or brown, but sediment is clear with <3 RBCs/HPF.

Urine dipstick: sensitive but not specific for hematuria.

Urine sediment is red and microscopy detects 10 RBCs/HPF.

A thorough diagnostic evaluation is indicated in the following patients with asymptomatic hematuria and no identifiable cause on urinalysis (Fig. 3-2):

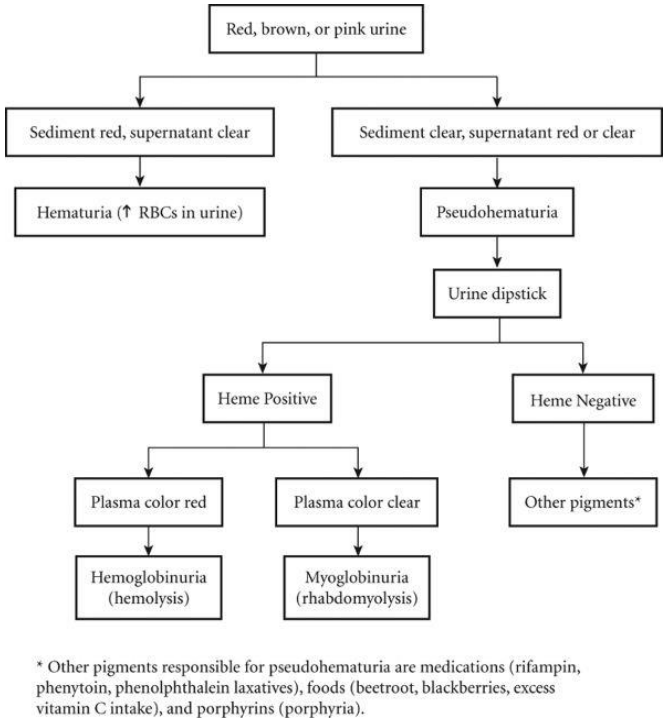

Figure 3–1. Approach to patients with red, brown, or pink urine.

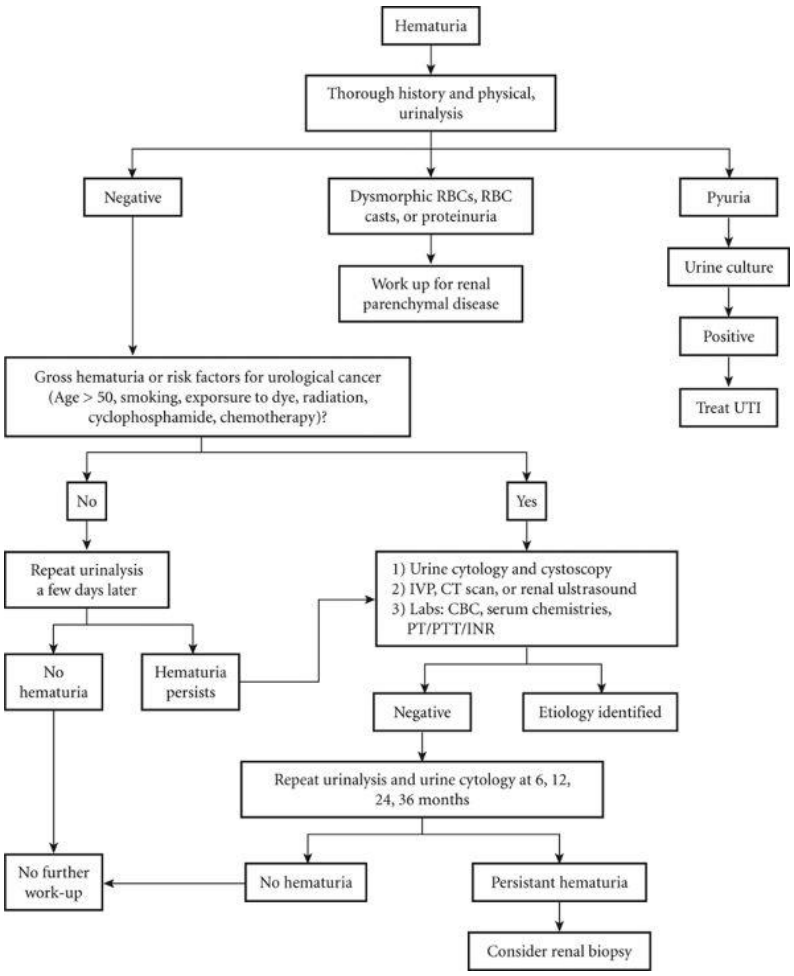

Figure 3–2. Approach to patients with hematuria.

- All patients with gross hematuria
- Gross or microscopic hematuria in patients any risk factor for a urological cancer

Risk factors for urinary tract cancers:

- Age > 50 years
- Cigarette smoking
- Chemicals: exposure to aromatic amines or benzenes (used in dye industry)
- History of radiation therapy or chemotherapy with cyclophosphamide/ifosfamide

What is the differential diagnosis of hematuria?

- Kidneys:
    - Parenchymal disease (glomerulonephropathy or interstitial nephritis): Suspect glomerulonephropathy if urinalysis detects proteinuria, RBC casts, or dysmorphic RBCs; suspect interstitial nephritis if urinalysis detects pyuria and mild proteinuria.
    - Kidney infection (pyelonephritis, renal and perinephric abscess)
    - Kidney stones
    - Kidney cysts
    - Renal papillary necrosis
- Bladder: lower UTI (cystitis) and hemorrhagic cystitis.
- Prostate: prostate cancer (rare), BPH, and prostatitis.
- Urinary tract cancers (kidney or bladder) (Table 3-1)
- Bleeding disorders or anticoagulants (e.g., warfarin)
- Trauma or strenuous exercise are benign, transient causes of hematuria.

Table 3–1. Key features of major urological cancers.

KIDNEY CANCERS	
Epidemiology	Major kidney cancers are RCC (80%–85%) and renal transitional cell carcinoma (10%).
Origin	• RCC originates in the renal cortex • Renal transitional cell carcinoma originates in renal pelvis
Clinical presentation	• Most common initial presentation is painless hematuria (transient or persistent). • <10% of patients present with the classic triad (hematuria, flank pain, palpable abdominal or flank mass). • Advanced disease can present with fever, weight loss, anemia of chronic disease, and paraneoplastic syndromes (hypercalcemia (ectopic PTH), polycythemia (ectopic EPO), Cushing syndrome (ectopic cortisol)).
Diagnostic tests	First test is renal ultrasound or CT scan of the abdomen. If imaging suggests RCC or renal transitional cell carcinoma, perform nephrectomy or partial nephrectomy to confirm the diagnosis histologically.
Screening for RCC	Screening ultrasound or CT scan is recommended only for the following: • Patients with Von Hippel Lindau syndrome or tuberous sclerosis. • Young patients with end-stage renal disease on dialysis for >3 years. • Patients with family history of RCC or personal history of radiation.
BLADDER CANCER	
Epidemiology	Bladder cancer is more common than kidney cancer. 90% of bladder cancer cases are transitional cell carcinomas; 10% of cases are squamous cell carcinoma and adenocarcinoma.
Clinical presentation	• Most common initial presentation is painless hematuria (transient or persistent). • Second most frequent finding is chronic urinary frequency, urgency, and dysuria.

	• Advanced disease can present with abdominal or flank pain and constitutional symptoms (fever, weight loss, etc.).
Diagnostic tests	Key diagnostic test is cystoscopy with biopsy.

Abbreviations*: CT, computed tomography; EPO, erythropoietin; PTH, parathyroid hormone; RCC, renal cell carcinoma.*

Note*: Patients with renal and bladder cancer tend to present at a late stage so overall prognosis is poor.*

Patients on chronic anticoagulation: Do not assume hematuria is due to warfarin without excluding other causes first.

Urine dipstick is negative for protein. No RBC casts, dysmorphic RBCs, or WBCs are evident on urine microscopy.

ANSWERS TO CASE 4:

What is the most likely diagnosis?

The most common glomerulonephropathies associated with persistent asymptomatic hematuria in adults are IgA nephropathy, benign familial hematuria, and Alport's syndrome. This patient with negative family history and gross hematuria 5 days after an upper respiratory infection most likely has IgA nephropathy.

- Benign familial hematuria: Suspect if microscopic hematuria and 50% of first-degree relatives have microscopic hematuria (autosomal dominant condition).
- Alport's syndrome: Suspect if family history of renal failure with or without deafness.

IgA nephropathy versus PIGN: IgA nephropathy occurs approximately 5 days after upper respiratory infection, and PIGN occurs approximately 10 days after upper respiratory infection. Serum complement and ASO are normal in IgA nephropathy.

How is asymptomatic glomerular hematuria managed?

IgA nephropathy and benign familial hematuria are typically benign (focal nephritis), so limit management of these conditions to close monitoring of blood pressure, serum chemistries, and urine protein. Obtain renal biopsy only if the patient develops signs of nephritic syndrome.

Alport's syndrome: Obtain skin biopsy if the patient has suggestive features.

ANSWERS TO CASE 5:

What diagnosis should you suspect?

Suspect polyarteritis nodosa (PAN) in this patient with acute glomerulonephritis and (+) HBsAg. This ANCA-negative vasculitis can affect a number of organ systems besides the kidney including the abdomen (microaneurysms cause intestinal angina), skin (purpura, tender nodules, livedo reticularis), eyes (scleritis), and peripheral nerves (peripheral neuropathy). PAN does not usually affect the lungs though.

Hepatitis B: responsible for only small percentage of PAN (most cases are idiopathic).

How can you establish the diagnosis?

First obtain a mesenteric angiogram to screen for microaneurysms. If there are no microaneurysms, confirm the diagnosis with renal biopsy. If angiography detects aneurysms, consider biopsy of another affected organ to confirm the diagnosis (because renal biopsy can cause aneurysm rupture).

Mesenteric angiography demonstrates microaneurysms. Colorectal biopsy confirms the diagnosis.

How is PAN treated?

First-line treatment is prednisone. Add cyclophosphamide if prednisone does not induce remission.

All forms of vasculitis often present initially with nonspecific constitutional symptoms (fever, weight loss, etc.) and increased ESR (nonspecific marker of inflammation).

ANSWERS TO CASE 6:

What does positive ANCA indicate?

A number of conditions can cause positive ANCA, such as:

- Vasculitides (Wegener's disease, Churg-Strauss syndrome, microscopic polyangiitis)
- Connective tissue disorders (systemic lupus erythematosus (SLE), Sjögren's, rheumatoid arthritis, etc.)
- Inflammatory bowel disease
- Wegener's disease: Among ANCA-positive patients, 90% are c-ANCA (10% are p-ANCA).
- Other disorders: Among ANCA-positive patients, the majority are p-ANCA.

What is the next step in management?

Obtain renal biopsy in ANCA-positive patients to determine the cause of acute glomerulonephritis. Renal biopsy also helps assess disease severity.

Negative ANCA does not rule out vasculitis (need biopsy if vasculitis suspected).

Renal biopsy demonstrates vasculitis, granulomas, and areas of necrosis, which is diagnostic of Wegener's disease. The biopsy also notes numerous “crescents.”

What is the next step in management?

The presence of glomerular crescents indicates rapidly progressing glomerulonephritis (RPGN). RPGN typically occurs in normal complement disorders. Systemic causes like Wegener's pose a much higher risk for RPGN than renal-limited causes like IgA nephropathy (see Table 1-1). Patients with RPGN progress to end-stage renal failure and death within weeks to months if left untreated.

- <50% crescents: Prognosis is good with treatment.
- >80% crescents: Prognosis is poor even with treatment.

CASE DISCUSSION

How is Wegener's disease treated?

Treat ANCA-positive vasculitides (Wegener's, microscopic polyangitis, Churg-Strauss syndrome) with prednisone and cyclophosphamide. Untreated, these disorders are fatal (particularly when associated with crescents).

What other organ systems can Wegener's disease affect?

Wegener's disease most commonly affects the kidneys and respiratory tract. Respiratory manifestations include dyspnea (due to subglottic stenosis), saddle-nose deformity (due to nasal cartilage inflammation), and hemoptysis (due to vascular lung granulomas). Other frequently affected organ systems include the eye (proptosis and double-vision due to retro-orbital pseudotumor), skin (ulcers and purpura), and peripheral nerves (mononeuritis multiplex).

Disorders associated with glomerulonephritis and lung infiltrates:

- Wegener's disease
- Churg-Strauss syndrome
- Goodpasture's syndrome: Classic presentation is glomerulonephritis and pulmonary hemorrhage. Associated with (+) anti-GBM and not (+) ANCA. Treat with prednisone, cyclophosphamide, and plasmapheresis.

ANSWERS TO CASE 7:

What is the most likely composition of this stone?

Positive family history and hexagonal crystals indicate that this patient has a cystine stone (Table 7-1). Cystine stones form in patients with a rare autosomal recessive disorder called hereditary cystinuria.

Table 7–1: Comparison of different types of renal stones

	Calcium	Uric Acid	Cystine	Struvite
Gender	Male > Female	Male > Female	Male > Female	Female > Male
Causes a	Increased urine calcium and oxalic acid, decreased urine citrate, and medullary sponge kidney	Gout Can Create Most Dreadful Colic	Hereditary cystinuria (autosomal recessive)	Urinary tract infection with urease-producing bacteria
Urine pH b	5.5–7.0	<5.5	5.5–7.0	>7.0
Urine crystals	Calcium oxalate stones are needle-shaped or square envelope shape	Yellow-brown diamond or barrel shape	Hexagonal	Coffin-lid shape
KUB	Radiopaque	Radiolucent	Radiopaque	Radiopaque
Treatment	Fluids and analgesics; ESWL or intracorporeal lithotripsy if persistent.	Fluids and analgesics; ESWL or intracorporeal lithotripsy if persistent.	Fluids and analgesics; intracorporeal lithotripsy if persistent (not ESWL).	Percutaneous nephrolithotomy; antibiotics and potassium citrate if fragments persist.
Prophylaxis to prevent recurrences a	Thiazides (if increased urine calcium)	Allopurinol (if refractory to increased fluid intake and alkali)	Tiopronin or penicillamine (if refractory to increased fluid intake and alkali)	Treat urinary tract infections aggressively

Abbreviations: *ESWL, extracorporeal shock wave lithotripsy; KUB, kidneys, ureter, bladder radiograph.*

a Decreased fluid intake is a risk factor for all four types of stones, so increased fluid intake is recommended in all patients to prevent recurrences.

b In normal subjects, urine pH is usually 5.5–6.5.

The patient receives fluids and ketorolac and is discharged home. He passes the stone 36 hours later. Stone analysis confirms the presence of a cystine stone. A 24-hour urine collection reveals increased urinary cystine.

What is the recommended therapy to prevent recurrence?

First-line therapy is increased fluid intake and urine alkalinization with potassium citrate or potassium bicarbonate. If the patient continues to have recurrent stones, consider cystine-binding drugs like tiopronin or penicillamine.

Treat persistent cystine stones with intracorporeal lithotripsy and not ESWL.

ANSWERS TO CASE 8:

What are risk factors for uric acid stones?

Remember risk factors for uric acid stones with the mnemonic "Gout Can Create Most Dreadful Colic":

- Gout: This is a risk factor because of increased uric acid production or decreased excretion.
- Cancer: Dying cells release uric acid.
- Chemotherapy: Dying cells release uric acid.
- Myeloproliferative disorders: Dying cells release uric acid.
- Diabetes: This is a risk factor because it predisposes to acidic urine.
- Chronic diarrhea: This is a risk factor because it predisposes to acidic urine.

Excess uric acid also predisposes to calcium stones.

Most uric acid stones occur in patients with no known risk factors, although metabolic evaluation often demonstrates abnormalities similar to primary gout such as elevated serum uric acid, decreased uric acid excretion, and low urine pH (<5.5).

How would you prevent recurrent uric acid stones in this patient?

Prevent recurrent stones with increased fluid intake (decreases urine uric acid concentration) and potassium citrate or potassium bicarbonate (maintains alkaline urine). If the patient has recurrent uric acid stones despite fluids and alkali, add allopurinol (prevents uric acid production) to the regimen.

ANSWERS TO CASE 9:

What do the imaging findings demonstrate?

The CT scan and KUB demonstrate staghorn calculi (i.e., the calculi (stone) has an appearance like the horns of a deer. These large stones involve the renal pelvis and at least two calyces and usually contain magnesium ammonium phosphate (struvite). Occasionally, staghorn calculi arise from calcium oxalate or calcium phosphate stones.

What causes struvite stones?

Struvite stones result from UTI due to urease-producing bacteria such as proteus (number one cause), klebsiella, and Ureaplasma urealyticum but not E. coli (do not produce urease). Urease breaks down urea to form ammonium; ammonium leads to an alkaline urine (pH > 7.0) and combines with magnesium phosphate to form struvite stones (also called infection stones, urease stones, or triple phosphate stones). Struvite stones tend to grow rapidly (weeks to months) into staghorn calculi.

How are struvite stones managed?

Medical management is usually insufficient. First-line treatment is percutaneous nephrolithotomy. If stone fragments persist 8 weeks later, administer antibiotics and potassium citrate (see Table 7-1).

Percutaneous nephrolithotomy is recommended even for asymptomatic patients because untreated staghorn calculi can progress to septic shock and chronic renal failure.

ANSWERS TO CASE 10:

What is the most likely diagnosis?

Dysuria, frequency, urgency, and suprapubic tenderness are the characteristic clinical manifestations of bladder inflammation (cystitis) due to a urinary tract infection (UTI). UTIs are more common in women because they have a shorter urethra than men. They occur when fecal flora colonize the vagina and spread upward into the urinary tract.

- Uncomplicated patients: young, healthy, non-pregnant females.
- Complicated patients: all others (males, elderly, pregnant, comorbidities, etc.).

What are the risk factors for UTIs in adults?

Remember risk factors for UTIs with the mnemonic "Sex, Sperm, & Sugar make Stacy & Betsy PP Constantly":

- Sex: Intercourse pushes vaginal contents upward into the urinary tract.
- Spermicide-containing contraceptives.
- Sugar (diabetes) weakens immune system and predisposes to neurogenic bladder.
- Urinary Stasis: Causes include incomplete voiding, neurogenic bladder, and obstruction (due to nephrolithiasis, benign prostatic hypertrophy (BPH), etc.).
- Bedridden (Immobility) and Bowel incontinence.
- Pregnancy.
- Past episodes.
- Catheter (indwelling urinary catheter).

Specific risk factors in men: anal intercourse and lack of circumcision.

What is the next step in management?

Empiric therapy without further diagnostic work-up is indicated for this uncomplicated patient with all of the characteristic symptoms. First-line treatment is a 3-day course of trimethroprim/sulfamethoxazole (TMP-SMX). If the patient's symptoms are severe (affects daily routine) or she lives in an area with high TMP/SMX resistance, consider a 3-day course of an oral fluoroquinolone. Also prescribe phenazopyridine (urinary analgesic) if the patient reports severe dysuria. If symptoms persist despite antibiotics, treat her as a complicated patient.

Uncomplicated UTI microbiology:

- Gram-positive cocci: Staphylococcus saprophyticus (number two cause), enterococcus.
- Gram-negative rods: Enterobacteriaceae such as Escherichia coli (number one cause), klebsiella, and proteus.

Note: E. coli accounts for 80% to 85% of UTIs, whereas S. saprophyticus accounts for 10% to 15% of UTIs.

A 7-day course of nitrofurantoin is an alternative to a 3-day course of oral fluoroquinolone.

CASE DISCUSSION

What would have been the next steps in management if the patient did not have characteristic symptoms?

Confirm the diagnosis using urinalysis (Table 10-1) prior to initiating antibiotics. First, evaluate the urine dipstick. Positive leukocyte esterase (indicates pyuria) ± positive nitrite (detects enterobacteriaceae) is diagnostic. If leukocyte esterase is negative but the patient has symptoms suggestive of a UTI, evaluate the unspun urine sample for white blood cells (WBCs); >10 WBCs per high-powered field indicates pyuria and is diagnostic. Treatment is as described earlier.

Table 10–1. Urinalysis and normal values

Collection	
Obtain a mid-stream specimen. Within 30 minutes, centrifuge the specimen to obtain supernatant and sediment. Perform gross inspection and chemical analysis of the supernatant and microscopic analysis of the sediment.	
GROSS INSPECTION OF SUPERNATANT (color and clarity):Normally light yellow and clear. CHEMICAL ANALYSIS (urine dipstick)	
pH	Can range from 4.5–8, but typically between 5.5 and 6.5
Specific gravity	1.002–1.03
Protein	Negative to trace
Glucose	Negative
Blood	Negative
Ketones	Negative
Nitrite	Negative
Leukocyte esterase	Negative
Microscopic analysis of sediment	
Red blood cells	0–2/HPF
White blood cells	0–2/HPF
Red blood cell casts	0/HPF

***Abbreviation**: HPF, high-powered field.*

Urethritis due to a sexually transmitted disease can cause dysuria. Patients with UTI often have hematuria, whereas those with sexually transmitted disease generally do not. Include pelvic exam in the diagnostic evaluation if the patient reports any of the 4Ds:

- Dyspareunia
- Dysuria in her partner
- Vaginal Discharge, odor, or pruritus
- Duration: Symptom onset is gradual (weeks)

What would have been the next steps in management if the patient was complicated?

- First, obtain urinalysis and urine culture (with Gram stain and antibiotic susceptibility pattern).
- If urinalysis indicates the patient has a UTI, treat with a 7-day course of an oral fluoroquinolone; tailor antibiotics if urine culture detects an organism resistant to fluoroquinolones.
- If symptoms do not resolve despite 24 to 48 hours of treatment with appropriate antibiotics (culture and susceptibility confirmed), repeat urine culture. Also, consider renal ultrasound or computed tomography (CT) scan to identify any urinary tract abnormalities that would predispose the patient to UTIs.
- Interstitial cystitis: Consider this diagnosis if a patient has recurrent UTI symptoms but laboratory tests do not show any evidence of infection.
- Positive culture (bacteriuria): Traditional criterion is $\geq 10^5$ colony forming units (CFU)/mL; however, some patients may have as low as 10^2 CFU/mL.

• Asymptomatic bacteriuria: Do not treat unless the patient is pregnant or the patient will soon undergo a urological surgery/procedure.

• Pregnant patients: Treat symptomatic and asymptomatic bacteriuria with a 3 to 7 day course of oral nitrofurantoin, amoxicillin, or cephalexin; avoid fluoroquinolones, which can cause fetal arthropathy.

The patient's symptoms improve with a 3-day course of TMP/SMX. Over the next 2 years, she has six more UTIs, all of which respond to TMP/SMX. What strategies are generally recommended to prevent recurrences?

Remember strategies to decrease UTI recurrences with the mnemonic "Taking Juice Can Avoid Infections":

• Topical estrogen: Prevents recurrences in post-menopausal women.

• Cranberry Juice

• Contraceptives: Avoid spermicides and diaphragms.

• Antibiotics: Consider continuous or postcoital antibiotics if the patient has two or more UTIs every 6 months or three or more UTIs every 12 months that markedly alter daily routine.

• Decreased Intercourse: Abstinence decreases the frequency of UTIs; many physicians also recommend urinating soon after intercourse (unclear benefit).

Classification of recurrent UTIs:

• Relapse: Symptoms recur within 2 weeks of treatment, and urine culture identifies the same strain.

• Re-infection: Symptoms recur within 2 weeks, but urine culture identifies a different strain OR symptoms recur after 2 weeks (same or different strain on urine culture).

Men with recurrent UTIs: Evaluate the patient for prostatitis.

ANSWERS TO CASE 11:

What diagnosis should you suspect?

Suspect a severe type of cystitis called hemorrhagic cystitis when a patient with one of the following risk factors presents with symptoms of cystitis, hematuria, and/or blood clots:

• Immunocompromised (increased risk of infections such as BK polyoma virus, etc.)

• Pelvic radiation

• Chemotherapy with cyclophosphamide, ifosfamide, or busulfan (bladder toxins)

Bone marrow transplantation poses a very high risk because patients are immunosuppressed, and they usually receive high dose cyclophosphamide and busulfan.

What is the next diagnostic step?

In addition to urinalysis and urine culture, order viral cultures and a complete blood count. Also, perform cystoscopy with biopsy to confirm the diagnosis.

Urinalysis demonstrates pyuria and hematuria. Cultures are negative. Complete blood count shows pancytopenia. Cystoscopy with biopsy confirms the diagnosis.

How is hemorrhagic cystitis treated?

Initial therapy for stable patients is to increase fluid intake. If symptoms do not resolve, options include:

• Administer hyperbaric oxygen (only in stable patients).

• Perform cystoscopy with clot extraction and/or intravesical administration of agents such as alum, formalin, prostaglandin, or estrogen.

• Surgery is indicated if there are signs of hypovolemic shock due to severe hemorrhage.

Note: No method is superior to any other in this list.

Use one of the following to prevent hemorrhagic cystitis when using a bladder toxin such as cyclophosphamide:

- Mesna: An additional benefit is decreased future risk of bladder cancer due to cyclophosphamide.
- Suprahydration: Normal saline plus furosemide maintains increased urine output.
- Continuous bladder irrigation

ANSWERS TO CASE 12:

What diagnosis should you suspect?

Fever, flank pain, and CVA tenderness are highly suggestive of acute upper UTI (acute pyelonephritis). The source of infection is usually ascending infection from the lower urinary tract, so patients often report symptoms of cystitis as well (frequency, urgency, dysuria, and suprapubic pain).

- Uncomplicated patients: young, healthy, non-pregnant females.
- Complicated patients: anyone else.

What is the next step in management?

The most important initial test is urinalysis and urine culture. Positive leukocyte esterase and/or nitrite tests are an indication for empiric antibiotics. Urinalysis may also demonstrate white cell casts (localizes infection to the kidney if present) and hematuria. If urinalysis is positive, obtain complete blood count (typically shows leukocytosis with a left shift) and a pregnancy test (if the patient is a premenopausal woman).

Leukocyte esterase and nitrite are positive. β-hCG (pregnancy test) is negative. Complete blood count is significant for leukocytosis with a left shift.

Which patients with pyelonephritis require hospitalization?

Outpatient therapy is indicated only for uncomplicated patients who are likely to be compliant and do not appear extremely ill (able to tolerate oral intake, fever <39°C, pain not very severe, and no signs of septic shock). All other patients require hospitalization.

Order blood culture if you decide to hospitalize the patient.

This young, non-pregnant female with no other medical conditions appears to have good social support at home. She is able to tolerate oral intake. The physician decides to treat the patient as an outpatient.

What empiric antibiotics are indicated?

Initiate a 10- to 14-day course of an oral fluoroquinolone. Tailor antibiotics later on the basis of Gram stain and culture results. For instance, if the Gram stain shows Gram-negative bacilli susceptible to TMP-SMX, you can switch to this agent. If Gram stain shows Gram-positive cocci, add amoxicillin to the regimen to cover enterococcus.

Microbiology of pyelonephritis is similar to cystitis.

What empiric agents are recommended for hospitalized patients?

Initially, treat the patient with IV antibiotics. First-line therapy for uncomplicated patients is ceftriaxone. If the Gram stain shows Gram-positive cocci, switch to ampicillin and gentamycin or piperacillin-tazobactam to cover enterococcus. When the patient improves clinically and can tolerate oral intake (should occur within 24 to 48 hours), switch to oral antibiotics (oral fluoroquinolone or TMP/SMX depending on susceptibility pattern). As with outpatients, total duration of therapy is usually 10 to 14 days.

When is imaging indicated for patients with pyelonephritis?

Most uncomplicated patients with pyelonephritis do not require any imaging tests. Remember indications for CT scan or renal ultrasound (perform ultrasound first; obtain CT if ultrasound shows renal enlargement) with the mnemonic "Complicated Pyelonephritis Requires Cat Scan":

- Complicated patients (anyone who is not a young, healthy, non-pregnant female)
- Persistent fever despite 72 hours of antibiotics
- Recurrence of symptoms in <2 weeks
- Culture demonstrates pseudomonas
- Stones (paroxysmal flank pain or stones identified incidentally on radiographs)

The goal of imaging is to rule out "AOA":

- Abscess (perinephric or intrarenal)
- Obstruction (e.g., renal stones, tumors)
- Anatomic abnormality that predisposes to pyelonephritis (e.g., vesicoureteral reflux, neurogenic bladder, polycystic kidney disease (PKD)

What is the diagnosis?

The CT scan shows a collection in the right kidney consistent with renal abscess. Most cases occur as a complication of pyelonephritis in patients with a predisposing condition (obstruction, an anatomic abnormality, or diabetes). Occasionally, patients develop renal abscess through hematogenous spread. Clinical presentation is similar to pyelonephritis.

- Ascending infection causes renal abscess in medulla.
- Hematogenous spread causes renal abscess in cortex.

How are renal abscesses treated?

- Drainage: If the patient has an identifiable obstruction or anatomic abnormality, drain surgically. Otherwise, percutaneous drainage under CT or ultrasound guidance is sufficient. This patient with diabetes is likely to have neurogenic bladder, so surgical drainage is preferable.
- Antibiotics: If you identify the abscess during initial presentation (as is the case with this patient), treat empirically with an IV aminoglycoside for 10 to 14 days plus a fluoroquinolone for a few weeks. If you identify the abscess later, continue antibiotics initiated for treatment of pyelonephritis. Tailor antibiotics on the basis of blood and abscess fluid culture.

What are other important complications of pyelonephritis?

- Perinephric abscess: This infection of fat surrounding the kidney has a clinical presentation similar to uncomplicated pyelonephritis, except that patients can have flank erythema and a palpable flank mass. Risk factors, diagnosis and treatment are similar to renal abscess.
- Emphysematous pyelonephritis: This severe infection of the renal parenchyma is caused by gas-producing organisms. Approximately 90% of cases occur in diabetics. Clinical presentation is similar to uncomplicated pyelonephritis, but CT scan shows gas bubbles. Treat with antibiotics and percutaneous drainage. Patients with perirenal extension or bilateral infection require surgery (partial nephrectomy).
- Urosepsis: This is an infection that spreads to the bloodstream. In some patients, urosepsis can progress to septic shock.

ANSWERS TO CASE 14:

What is the most likely diagnosis?

Renal colic (acute paroxysms of flank pain) and hematuria (gross or microscopic) is the classic description for ureteral obstruction by a kidney stone (nephrolithiasis). Upper ureter obstruction causes flank pain. As the stone migrates down to the lower ureter, the pain radiates to

the ipsilateral groin. When the stone enters the bladder and urethra, the patient may report dysuria and urgency. Patients may also report nausea and vomiting.

Some patients report mild discomfort and not renal colic; 10% of patients do not have hematuria.

Types of kidney stones: calcium stones (80% to 85%), uric acid stones (10%), struvite stones (5% to 10%), cystine stones (<1%).

What is the next diagnostic step?

The test of choice to confirm suspected nephrolithiasis is helical (spiral) CT scan of the abdomen without contrast. Many institutions also perform KUB (abdominal radiograph that includes the kidney, ureter, and bladder). KUB detects calcium, struvite, and cystine stones because they are radiopaque.

Note: KUB does not detect Uric acid stones because they are radiolucent.

- Intravenous pyelogram (IVP): Inject IV contrast and obtain KUB. This test is more sensitive and specific than KUB alone, and it can detect all four types of stones. CT scan is usually preferred to IVP because CT is more accurate and does not use contrast.
- Pregnant patients: Avoid CT scan because of radiation exposure. The first diagnostic test is renal and pelvic ultrasound. If initial tests are negative, order transvaginal ultrasound. If ultrasound tests are negative but the patient has persistent suspicious symptoms, order IVP.

CT scan confirms the presence of two to three stones in the lower ureter, all <3 mm. KUB detects the stones as well (radiopaque).

What are the next steps in management?

Most stones <5 mm pass spontaneously, so initial therapy is conservative. Administer IV fluids and analgesics (opiates or IV nonsteroidal anti-inflammatory drugs (NSAIDs) such as ketorolac). Then discharge the patient and instruct him to drink plenty of fluids at home. Also ask him to strain his urine and bring any stones and gravel that pass for analysis.

Indications for hospitalization and urgent urology consult in patients with nephrolithiasis (mnemonic: “Stones Are Inside, Ouch!”):

- Severe pain unresponsive to analgesics
- Acute postrenal failure/Anuria (due to obstruction)
- Infection of the urinary tract (fever, positive leukocyte esterase and nitrite)
- Oral intake not tolerated

How would you manage stones that do not pass spontaneously?

If the stone does not pass within a few days (more common if size >5 mm), refer the patient to an urologist. The surgeon's first-line management of persistent stones depends on the size and location:

- Proximal ureter stones: Extracorporeal shock wave lithotripsy (ESWL) if stone <10 mm, intracorporeal lithotripsy (with laser) if stone >10 mm.
- Mid-ureter stones: intracorporeal lithotripsy (with laser).
- Distal ureter stones: ESWL or intracorporeal lithotripsy.
- ESWL: Locate stone using ultrasound. Then pass shock waves from outside the body to break the stone. This method is not indicated for cystine stones.
- Intracorporeal lithotripsy: Pass ureteroscope close to the stone. Then use laser, basket with grasper, pneumatic, or electrical device at the tip of the scope to break/remove the stone.
- Percutaneous nephrolithotomy: This is usually second-line treatment if ESWL and/or intracorporeal lithotripsy is unsuccessful (exception: this is the first-line treatment for struvite stones).

The patient spontaneously passes three stones.

In addition to analysis of the stones, what work-up is recommended?

Patients with a family history of nephrolithiasis, multiple stones, or recurrent stones should undergo a complete evaluation to search for risk factors. Order the following tests in this patient with multiple stones:

- Serum chemistries and serum uric acid
- Urinalysis
- Obtain 24-hour urine collection 2 to 3 months after the acute episode (measure urine volume, pH, and excretion of calcium, uric acid, citrate, oxalate, sodium, and creatinine).

Single uncomplicated kidney stone: Follow-up recommendations are less clear; some physicians advocate a complete evaluation, whereas others recommend a limited evaluation.

Urine calcium/creatinine: Ratio >0.3 indicates hypercalciuria. This measure is less accurate but more convenient than 24-hour urine collection.

Analysis of the stones indicates he had calcium phosphate stones.

What are the risk factors for calcium stones?

Risk factors for calcium stones are elevated urine calcium and oxalic acid, decreased urine citrate, and medullary sponge kidney:

- Causes of increased urine calcium (hypercalciuria):
    - Hypercalcemia: causes secondary hypercalciuria (Chapter 8: Endocrinology)
    - Idiopathic hypercalciuria (stable serum Ca, increased urine Ca excretion)
- Causes of increased urine oxalic acid (increased risk of calcium oxalate stones):
    - Severe malabsorption (Crohn's, bowel resection)
    - Excessive vitamin C
- Causes of decreased urine citrate:
    - Chronic metabolic acidosis (diarrhea, carbonic anhydrase inhibitors)
    - Type 1 RTA (stable anion gap metabolic acidosis yet urine pH >5.5)
- Medullary sponge kidney: Cystic dilation of collecting tubules is an idiopathic, asymptomatic condition usually detected incidentally on imaging. Patients have increased risk of calcium stones and UTIs, but otherwise the condition is benign.

Citrate in urine normally binds calcium and prevents stone formation. Metabolic acidosis promotes citrate reabsorption.

Metabolic work-up is significant for elevated urine calcium. Serum calcium and all other labs are normal.

How can you prevent stone recurrence?

The evaluation indicates that the patient has idiopathic hypercalciuria. Prevent recurrent calcium stones in patients with increased urine calcium by prescribing thiazide diuretics and increased fluid intake.

Increased fluid intake helps prevent recurrence of all four types of kidney stones.

Preventing recurrent calcium stones in patients with other 24-hour urine abnormalities:

- Increased uric acid: Decreased protein (purine) intake and weight loss only if urine pH <6.0.
- Decreased citrate: Consider potassium citrate or potassium bicarbonate only if urine pH <6.0.
- Increased oxalate: Increased calcium (binds oxalate) and decreased oxalate intake only if urine calcium is not elevated.

ANSWERS TO CASE 15:

What is the diagnosis?

This patient has autosomal dominant polycystic kidney disease (ADPKD). She has macroscopic haematuria, hypertension and impaired renal function. The palpable abdominal masses in both flanks have the characteristic features of enlarged kidneys. They are ballot- table and resonant to percussion because of overlying bowel. The other principal causes for palpable kidneys are renal cell carcinoma and massive hydronephrosis. Rest is the best management for cyst bleeding. Gross haematuria rarely lasts for more than a week.

ADPKD is the most common inherited renal disease, occurring in approximately 1:600 to 1:1000 individuals. Although the name 'ADPKD' is derived from renal manifestations of cyst growth leading to enlarged kidneys and renal failure, this is a systemic disorder manifested by the presence of hepatic cysts, diverticular disease, inguinal hernias, mitral valve prolapse, intracranial aneurysms and hypertension. Flank pain is the most common symptom, and may be caused by cyst rupture, cyst infection or renal calculi. Macroscopic haematuria due to cyst haemorrhage occurs commonly and usually resolves spontaneously. Renal calculi occur in approximately 20 per cent of ADPKD patients (most commonly uric acid stones). Hypertension occurs early in the course of this disease affecting 60 per cent of patients with normal renal function. Approximately 50 per cent of ADPKD patients will develop end-stage renal failure.

Although it is not known if this patient's father had renal disease, it is highly likely that he had ADPKD and an associated ruptured berry aneurysm as the cause for his subarachnoid haemorrhage. The patient's uncle required a renal transplant. The pattern of inheritance in this family is consistent with an autosomal dominant trait.

How would you proceed to manage and investigate this patient?

Ultrasound is the preferred initial screening technique as it is cheap, non-invasive and rapid. It detects cysts as small as 0.5 cm. For a certain diagnosis, there should be at least three renal cysts with at least one cyst in each kidney. Computed tomography (CT) and magnetic resonance imaging (MRI) are more sensitive techniques for detecting smaller cysts. Ultrasound in this patient shows the typical appearance of multiple cysts (black areas) surrounded by thickened walls (Fig. 15.1). She should be referred to a nephrologist for long-term follow-up of her renal failure, and plans should be made for renal replacement therapy. She needs to have effective blood pressure control with diastolic pressure <85 mmHg to retard the progression of her renal failure. Clinical trials are starting of vasopressin receptor antagonists which show promise at inhibiting cyst growth.

She should have MRI angiography to exclude an intracranial aneurysm. This is not advocated for all ADPKD patients, but is indicated for those patients with a positive family history of aneurysm rupture. The patient's children should have their blood pressure checked and later be screened by ultrasound. By age 30 years, 90 per cent of ADPKD patients will have cysts detectable by ultrasound.

Ninety per cent of ADPKD patients have mutations in the *ADPKD1* gene. This gene encodes for the protein polycystin which is a membrane glycoprotein that probably mediates cell-cell and/or cell-matrix interactions. Most remaining patients have mutations in the *ADPKD2* gene which codes for polycystin-2, which has structural homology to polycystin and to calcium channels. ADPKD1 patients generally have an earlier age of onset of hypertension and development of renal failure as compared to ADPKD2 patients.

Patients with ADPKD are often asymptomatic. ADPKD patients may present with loin pain or haematuria. ADPKD is the commonest familial cause of renal failure. ADPKD is the most likely cause of bilateral renal masses. Family members who may have ADPKD should be advised to have their blood pressure measured and a renal ultrasound.

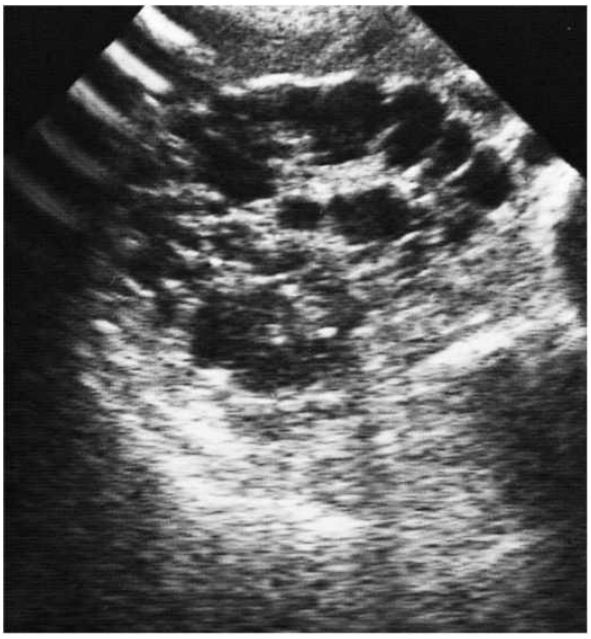

Figure 15.1 Renal ultrasound demonstrating multiple cysts.

PART II: EDEMATOUS SYNDROME

ANSWERS TO CASE 16:

A 27-year-old man complains of several days of facial and hand swelling, decreased urine output, and reddish-brown urine. He took ibuprofen for fever and a sore throat 2 weeks ago. He is afebrile, hypertensive with a blood pressure of 172/110 mm Hg, and has periorbital edema but a normal funduscopic examination. His cardiac, pulmonary, and abdominal examinations are normal, but he does have edema of his feet, hands, and face. A dipstick urinalysis in the clinic shows specific gravity of 1.025 with 3+ blood and 2+ protein.

- Most likely diagnosis: Acute glomerulonephritis (GN).
- Next diagnostic step: Examine a fresh spun urine specimen to look for red blood cell (RBC) casts or dysmorphic red blood cells.

ANALYSIS

Considerations

A young man without a significant medical history now presents with new onset of hypertension, edema, and hematuria following an upper respiratory tract infection. He has no history of renal disease, does not have manifestations of chronic hypertension, and has not received any nephrotoxins. He does not have symptoms of systemic diseases such as systemic lupus erythematosus. The presentation of acute renal failure, hypertension, edema, and hematuria in a young man with no significant medical history is highly suggestive of glomerular injury (GN). He likely has acute GN, either postinfectious (streptococcal) or immunoglobulin (Ig)A nephropathy. The reddish-brown appearance of the urine could represent hematuria, which was later suggested by dipstick urinalysis (3+ blood); hence, microscopic examination of the urine for RBCs is very important. Together, the history and the examination suggest that the patient likely has acute GN, either primary GN of unknown etiology (no concomitant systemic disease is mentioned) or

secondary GN as a result of recent upper respiratory infection (postinfectious GN). The next logical step in diagnosing GN should be to examine the precipitate of a freshly spun urine sample for

If present, these are signs of inflammation and establish the diagnosis of acute GN. Although likely to be present, these markers do not distinguish among the distinct immune-mediated causes of GN; they merely allow us to make the diagnosis of acute GN (primary or secondary). Further evaluation with serologic markers, such as complement levels and antistreptolysin- O (ASO) titers (Table 16-1), may help to further classify the GN.

Table 16-1. Serologic markers of glomerulonephritis

Complement levels (C3,C4): low in complement-mediated GN (SLE, MPGN, infective endocarditis, poststreptococcal/postinfectious GN, cryoglobulin-induced GN)

Antineutrophil cytoplasmic antibody levels (p-ANCA and c-ANCA): positive in Wegener, microscopic polyangiitis, Churg-Strauss

ANA: positive in SLE (anti-dsDNA, anti-Smith)

Antiglomerular basement membrane (anti-GBM) antibody levels : positive in anti-GBM GN and Goodpasture

ASO titers: elevated in poststreptococcal GN (postinfectious GN)

Blood cultures: positive in infective endocarditis

Cryoglobulin titers: positive in cryoglobulin-induced GN

Hepatitis serologies: hepatitis C and hepatitis B associated with cryoinduced GN active sediment (cellular components, red cell cast, dysmorphic red cells).

APPROACH TO SUSPECTED GLOMERULONEPHRITIS

Definitions

HEMATURIA: Presence of blood in the urine

GROSS HEMATURIA: Blood in the urine visible to the eye

MICROSCOPIC HEMATURIA: Red blood cells in the urine that require microscopy for diagnosis

Clinical approach

The term *hematuria* describes the presence of blood in the urine. Although direct visualization of a urine sample (gross hematuria) or dipstick examination (positive blood) can be helpful, the diagnosis of hematuria is made by microscopic confirmation of the presence of red blood cells (microscopic hematuria). The first step in evaluating a patient who complains of red-dark urine is to differentiate between true hematuria (presence of RBCs in urine) and pigmented urine (red-dark urine). The breakdown products of muscle cells and red blood cells (myoglobin and hemoglobin, respectively) are heme- containing compounds capable of turning the color of urine dark red or brown in the absence of true hematuria (red blood cells). A dipstick urinalysis positive for blood without the presence of RBCs (negative microscopic cellular sediment) is suggestive of hemoglobinuria or myoglobinuria.

After confirmation, the etiology of the hematuria should be determined. Hematuria can be classified into two broad categories: intrarenal and extrarenal (Table 16-2). The history and physical examination are very helpful in the evaluation (age, fever, pain, family history). Laboratory analysis and imaging studies often are necessary, and considering the potential clinical implications, the etiology of hematuria should be pursued in all cases of hematuria. First, examination of the cellular urine sediment can help to differentiate glomerular from nonglomerular hematuria. The presence of dysmorphic/ fragmented RBCs or red cell casts is indicative of glomerular origin (GN); renal biopsy may offer further confirmation if indicated. Second, the urine Gram stain and culture can aid in the diagnosis of infectious hematuria. Third, the urine sample

should be sent for cytologic evaluation when the diagnosis of malignancy is suspected. Finally, renal imaging via ultrasound or intravenous pyelogram (IVP) can help in the visualization of the renal parenchyma and vascular structures. Cystoscopy can be used to assess the bladder; and abdominal CT (computed tomography) or MRI (magnetic resonance imaging) can be performed to assess mass effect and surrounding structures.

Table 16-2. Common causes of hematuria

Intrarenal hematuria
. Kidney trauma
. Renal stones and crystals
. Glomerulonephritis
. Infection (pyelonephritis)
. Neoplasia (renal cell carcinoma)
. Vascular injury (vasculitis, renal thrombosis)
Extrarenal hematuria
. Trauma (eg, Foley placement)
. Infections (urethritis, prostatitis, cystitis)
. Nephrolithiasis (ureteral stones)
. Neoplasia (prostate, bladder)

However, a complete workup for hematuria is rarely needed because the initial evaluation of the patient and urinalysis often lead to the appropriate diagnosis.

Glomerular Disease

Rarely do patients with glomerular disease present according to the description in textbooks. In clinical medicine, glomerulopathies are encountered mainly in the form of two distinct syndromes: nephritic or nephrotic (or, more often, as an overlap of the two syndromes). Nephritis (nephritic syndrome) is defined as an inflammatory renal syndrome that presents as hematuria, edema, hypertension, and a low degree of proteinuria (<3.5 g over 24 hours). Nephrosis (or the nephrotic syndrome) is a noninflammatory (no active sediment in the urine) glomerulopathy. Glomerular injury may result from a variety of insults and presents either as the sole clinical finding in a patient (primary renal disease) or as part of a complex syndrome of a systemic disorder (secondary glomerular disease). Although all glomerular disorders are often given the all-encompassing name of *glomerulonephritis*, this term specifically describes an inflammatory intraglomerular process associated with cellular proliferation that results in hematuria and renal failure *(nephritis* or nephritic syndrome) and excludes the nonproliferative, noninflammatory glomerulopathies (ie, *nephrosis* or nephrotic syndrome). For the purpose of this discussion, *glomerulonephritis* (GN) includes only the inflammatory glomerulopathies.

Nephritic Syndrome

The presentation of acute renal failure with associated hypertension, hematuria, and edema is consistent with acute GN. Acute renal failure, as manifested by a decrease in urine output and azotemia, results from impaired urine production and ineffective filtration of nitrogenous waste by the glomerulus, respectively. The glomerular apparatus (endothelial and epithelial components) is responsible for the ultrafiltration of blood in the kidney and the initial formation of what will later become the urine. Glomerular injury leads to impaired/ineffective filtration of sodium, glucose, nitrogenous products, and amino acids/proteins and its consequent clinical manifestations. Common signs suggesting an inflammatory glomerular cause of renal failure (ie, acute GN) include hematuria (caused by ruptured capillaries in the glomerulus), proteinuria (caused by altered permeability of the capillary walls), edema (caused by salt and water retention), and hypertension

(caused by fluid retention and disturbed renal homeostasis of blood pressure). The presence of this constellation of signs in a patient makes the diagnosis of glomerulonephritis very likely. However, it is important to note that often patients present with an overlap syndrome, sharing signs of both nephritis and nephrosis. Moreover, the presence of hematuria in itself is not pathognomonic for GN because there are multiple causes of hematuria of nonglomerular origin. Therefore, confirmation of the presumptive diagnosis of acute glomerulonephritis requires microscopic examination of a urine sample from the suspected patient. The presence of red cell casts (inflammatory cast) or dysmorphic RBCs (caused by filtration through damaged glomeruli) in a sample of spun urine establishes the diagnosis of GN.

Acute GN is a condition characterized by an inflammatory attack of the glomerular apparatus. The different types of GN have a variety of causes, outcomes, and responses to treatment. Once the presumptive diagnosis of acute GN is made, they can be broadly classified as either *primary*(present clinically as a renal disorder) or *secondary*(renal injury caused by a systemic disease). In the case of primary glomerular disorders, the inciting cause is rarely known (no associated systemic disease), and the pathophysiology is often poorly understood (eg, IgA nephropathy or membranoproliferative glomerulonephritis [MPGN]). In general, primary GN is named by the histopathologic appearance and clinical manifestation of the injured kidney (mesangioproliferative GN, MPGN, fibrillary GN, crescentic GN, rapidly progressive GN; Table 16-3). In the case of secondary GN, the inflammatory systemic disorder causes glomerular injury and presents with the clinical manifestations of acute GN (eg, SLE, hepatitis C, HIV, and a variety of vasculitis; Table 15-3). Secondary GN may be classified further by their histopathologic appearance. Because the etiology of inflammation and the degree of cellular proliferation vary widely among the different GNs, alternatively GN can be classified by the mechanism of immune- mediated injury to the glomeruli. In this classification, the injury patterns of all GNs generally fall under three categories: (1) complement-mediated GN, (2) antibody-mediated GN, or (3) non-antibody and complement-mediated (ANCA-mediated) GN, also known as pauci-immune GN. Glomerular injury occurs via circulating immune complexes (antibody and complement-mediated) that precipitate on the glomeruli or by direct attack on the glomerular. This injury pattern can be visualized via immunofluorescence for specific staining patterns (IgG, IgA) and under electron microscopy of the injured glomeruli for characteristic deposit patterns (linear, granular, pauci-immune, etc).

Table 16-3. Classification of glomerulonephritis

Primary renal disorders (based on histopathology)
Membranoproliferative glomerulonephritis (MPGN, types I and II)
Mesangioproliferative glomerulonephritis (MSGN)
Crescentic glomerulonephritis
. Immune deposit (anti-GBM)
. Pauci-immune (ANCA)
Fibrillary glomerulonephritis
Proliferative glomerulonephritis (IgA nephropathy)
Secondary renal disorders (based on clinical presentation)
Lupus nephritis
Postinfectious glomerulonephritis (poststreptococcal GN)
Hepatitis C/hepatitis B-related glomerulonephritis (cryo-GN)
Vasculitis-related glomerulonephritis (Wegener, Churg-Strauss, polyarteritis nodosa, microscopic polyangiitis, Henoch-Schonlein purpura)
Infective endocarditis-related glomerulonephritis membranes (antibody-, complement-, and ANCA-mediated).

Therefore, it is easy to see that although the diagnosis of primary versus secondary GN can be made simply by obtaining a detailed medical history, physical examination, and routine laboratory tests, the classification of a specific GN into a given immune-mediated category requires further microscopic analysis, blood tests, and sometimes a kidney biopsy.

Diagnostic Approach to Glomerulonephritis

The approach to the patient with glomerular disease should be systematic and undertaken in a stepwise fashion. The history should be approached meticulously, looking for evidence of preexisting renal disease, systemic disease, and exposure to nephrotoxins. Likewise, the physical examination should assess for blood pressure, evidence of hypertension, presence of edema, renal and vascular bruits, and evidence of systemic disease. The urine should be analyzed for hematuria and sediment. Proteinuria should be categorized as nephrotic (>3.5 g over 24 hours) versus nephritic range (<3.5 g over 24 hours). When erythrocyte casts or dysmorphic red cells are seen in the urine, a diagnosis of GN can be made. Although likely to be present, these markers do not distinguish among the distinct immune-mediated causes of GN; they merely allow us to make the diagnosis of acute GN (primary or secondary). Serologic markers of systemic diseases should be obtained, if indicated (Figure 16-1) in order to further classify the GN. The serologic workup of GN should be guided by the history and physical examination and the clinical suspicion for an individual entity to exist.

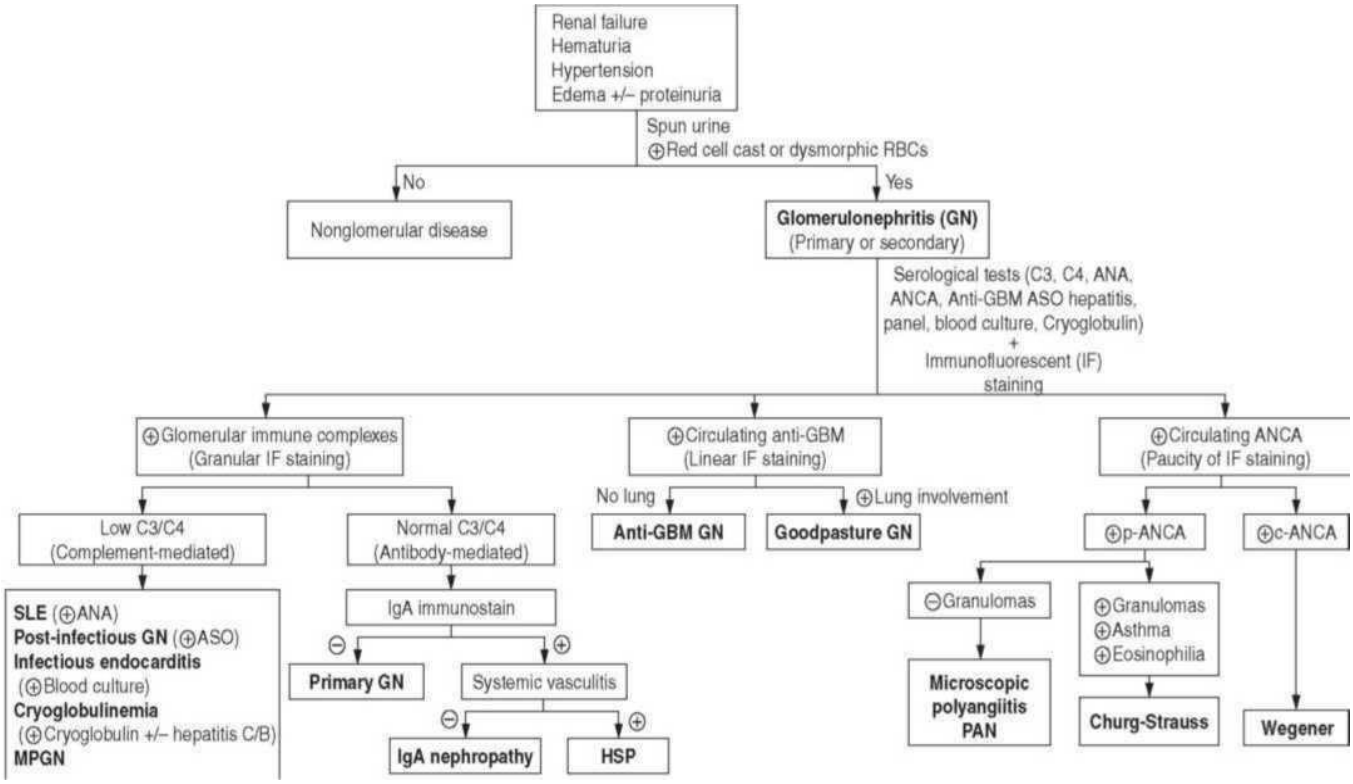

Figure 16-1. Algorithm of approach to the patient with acute glomerulonephritis.

Abbreviations*: ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; ASO, antistreptolysin -O; c-ANCA, cytoplasmic antineutrophil cytoplasmic antibody; GBM, glomerular basement membrane; HSP, Henoch-Schonlein purpura; MPGN, membranoproliferative glomerulonephritis; PAN, periarteritis nodosa; p-ANCA, perinuclear antineutrophil cytoplasmic antibody; SLE,systemic lupus erythematosus.*

Once the appropriate serologic tests have been reviewed, a kidney biopsy may be required. A

biopsy sample can be examined under the light microscope in order to determine the primary histopathologic injury to the nephron (MPGN, crescentic GN, etc). Further examination of an immunofluorescent stained sample for immune recognition (IgG, IgA, IgM, C3, C4, or pauci-immune staining) of the affected glomerular membrane (capillary, epithelial, etc.) and under electron microscopy for characteristic patterns of immune deposition (granular, linear GN) may provide a definitive diagnosis of the immune- mediated injury to the glomeruli. Figure 16-1 shows an algorithmic approach to the patient with acute GN.

Treatment of Glomerulonephritis

It is difficult to predict the prognosis and outcome of most GNs. Whereas some are self-limiting and largely asymptomatic (eg, IgA-associated), others may progress to end-stage renal failure (ANCA-mediated GN) without treatment. Unfortunately, as is the case with a number of immune-mediated disorders, treatment currently is limited to supportive therapy (hemodialysis for renal failure, antihypertensive medications and diuretics for edema) with or without immunosuppressive drugs. When appropriate, the underlying disease should be treated (infective endocarditis, hepatitis, SLE, or vasculitis). The use of steroids and cyclophosphamide has been advocated in the treatment of ANCA-induced GN, while other antibody-mediated GNs might require plasmapheresis in order to eliminate the inciting antibody-immune complex. Although the diagnosis of acute GN may be straightforward, the ensuing therapy often is frustrating and ineffective and leaves the clinician at the mercy of supportive measures.

Comprehension questions

1. An 18-year-old marathon runner has been training during the summer. He is brought to the emergency room disoriented after collapsing on the track. His temperature is 102°F. A Foley catheter is placed and reveals reddish urine with 3+ blood on dipstick and no cells seen microscopically. Which of the following is the most likely explanation for his urine?

A. Underlying renal disease
B. Prerenal azotemia
C. Myoglobinuria
D. Glomerulonephritis

2. Which of the following laboratory findings is most consistent with poststreptococcal glomerulonephritis?

A. Elevated serum complement levels
B. Positive antinuclear antibody titers
C. Elevated ASO titers
D. Positive blood cultures
E. Positive cryoglobulin titers

3. A 22-year-old man complains of acute hemoptysis over the past week. He denies smoking or pulmonary disease. His blood pressure is 130/70 mm Hg, and his physical examination is normal. His urinalysis also shows microscopic hematuria and red blood cell casts. Which of the following is the most likely etiology?

A. Metastatic renal cell carcinoma to the lungs
B. Acute tuberculosis of the kidneys and lungs
C. Systemic lupus erythematosus
D. Goodpasture disease (antiglomerular basement membrane)

Answers

1. C. This individual is suffering from heat exhaustion, which can lead to rhabdomyolysis and release of myoglobin. Myoglobinuria leads to a reddish appearance and positive urine dipstick reaction for blood, but microscopic analysis of the urine likely will demonstrate no red cells.

2. C. The antistreptolysin-O titers typically are elevated and serum complement levels are decreased in poststreptococcal GN.

3. D. Goodpasture (antiglomerular basement membrane) disease typically affects young males, who present with hemoptysis and hematuria. Antibody against type IV collagen, expressed in the pulmonary alveolar and glomerular basement membrane, leads to the pulmonary and renal manifestations. Hypertension typically is absent. After the initial clinical signs, renal insufficiency usually progresses rapidly. Anti-GBM antibodies almost always are present; the gold standard for diagnosis is renal biopsy.

Clinical Pearls

- Finding red blood cell casts or dysmorphic red blood cells on urinalysis differentiates glomerular bleeding (eg, glomerulonephritis) from non- glomerular bleeding (eg, kidney stones).
- Glomerulonephritis is characterized by hematuria, edema, and hypertension caused by volume retention.
- G ross hematuria following an upper respiratory illness suggests either immunoglobulin A nephropathy or poststreptococcal glomerulonephritis.
- Patients with nonglomerular hematuria and no evidence of infection shoul d undergo investigation with imaging (ultrasound or intravenous pyelogram) or cystoscopy to evaluate for stones or malignancy.

CASE 17:

What is the most likely cause of this patient's edema?

The major causes of bilateral pitting edema are heart failure, cirrhosis, drugs, and nephrotic syndrome. This patient with diabetes and periorbital edema most likely has nephrotic syndrome. Lack of dyspnea or abnormal lung findings makes heart failure unlikely. Cirrhosis is less likely in this non-drinker with no ascites. He does not take any drugs associated with pedal edema (e.g., calcium channel blockers).

Non-pitting edema: Suspect lymphatic obstruction or hypothyroidism.

What are the causes of nephrotic syndrome?

Diabetes mellitus is the number one cause of nephrotic syndrome among adults in the United States. Other important causes include SLE, HIV, neoplasms (such as multiple myeloma), drugs (most commonly NSAIDs), and amyloidosis. Many cases are idiopathic (Table 17-1).

TABLE 17–1. Major causes of nephrotic syndrome in adults.

Renal Biopsy	Differential Diagnosis
Minimal change	1. Idiopathic minimal change disease 2. NSAIDs 3. Hodgkin's disease
Kimmelstein-Wilson nodules	Pathognomic for diabetes mellitus
FSGS	1. Idiopathic FSGS 2. HIV 3. Intravenous heroin 4. Type II lupus nephropathy
MN	1. Idiopathic MN 2. Infections (syphilis, malaria) 3. Drugs: Penicillamine, Probenecid, gold

	4. Type V lupus nephropathy
MPGN	1. Idiopathic MPGN 2. Hepatitis C virus
Green birefringence with Congo red stain	Amyloidosis
Immunoglobulin light chains	Multiple myeloma

***Abbreviations**: FSGS, focal segmental glomerulosclerosis; MN, membranous glomerulonephritis; MPGN, membranoproliferative glomerulonephritis.*

***Note:** The majority of minimal change, FSGS, MN, MPGN are idiopathic.*

Serum lipid, serum albumin, and 24-hour urine protein are obtained, which confirm the diagnosis of nephrotic syndrome.

What are the next diagnostic steps?

Obtain serum chemistry (to assess BUN, serum creatinine, and glucose), HbA1c (to measure glucose control), and an ophthalmology evaluation (to evaluate for diabetic retinopathy). If the evaluation indicates stable CRI and poorly controlled diabetes, no further diagnostic work-up is necessary. If diabetes appears well controlled (no retinopathy, HbA1c <7) or if the patient has signs of ARF, obtain renal biopsy to rule out other causes.

Random urine protein/creatinine: Ratio >0.15 indicates proteinuria. This ratio is an accurate and less cumbersome alternative to 24-hour urine collection (Fig. 17-1).

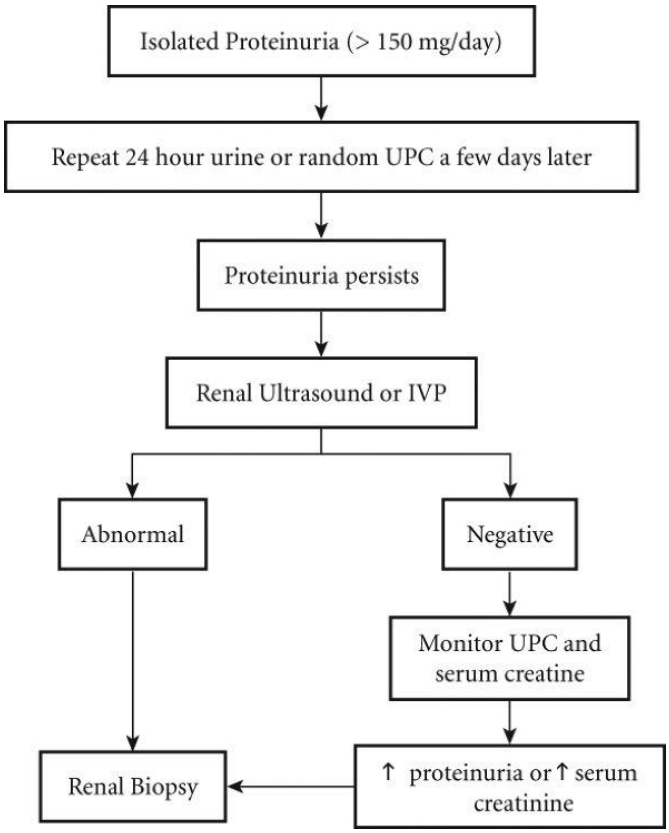

Figure 17–1. Work-up of isolated proteinuria.

Serum creatinine is 2.3 g/dl. HbA1c is 9%. Ophthalmology evaluation shows evidence of diabetic retinopathy.

CASE DISCUSSION

In addition to treating the underlying diabetes, what management strategies are recommended for all patients with CKD?

- Monitor GFR and nutritional status: Monitor GFR using serum creatinine, Cockcroft-Gault equation, and Modification of Diet in Renal Disease (MDRD) equation (equations take into account age, weight, race, and gender). Monitor nutritional status using anthropometric measurements and plasma proteins (serum albumin, pre-albumin, and transferrin).
- Blood pressure: Maintain pressure <130/80. First-line antihypertensives are ACE inhibitors/ARBs. If these are insufficient, add loop diuretics to the regimen.
- Lipids: Treat hyperlipidemia with a statin drug if low-density lipoprotein cholesterol >100 mg/dL.
- Diet: Restrict protein intake to 0.7 to 0.8 g/kg. Restrict dietary potassium, phosphate, and magnesium. Take calcium and vitamin D supplements to prevent renal osteodystrophy.
- Treat symptoms and laboratory abnormalities associated with CRI/uremia:
    - Fluids and electrolytes: Correct hypovolemia with normal saline. Correct volume overload (edema) with loop diuretics and sodium restriction. Correct electrolyte and acid–base abnormalities (hyperkalemia, hyperphosphatemia, hypocalcemia, and metabolic acidosis).
    - Anemia: Maintain hemoglobin between 11 to 13 mg/dL using erythropoietin or darbapoietin.

Major causes of ESRD in the United States: diabetes (28%), hypertension (24%), glomerulonephritis (21%), idiopathic (20%).

When are dialysis/renal transplant indicated for patients with CRI?

Refer patients for renal transplant evaluation when GFR <30 mL/min. Because the demand for organs exceeds supply, many patients require maintenance dialysis while on the transplant wait list. AEIOU are absolute indications for urgent dialysis. Relative indications for maintenance dialysis are:

- Serum creatinine >10 mg/dL and BUN >100 mg/dL
- GFR <15 to 20 mL/min
- Chronic malnutrition

Over the next 2 years, the patient's GFR continues to decline. The nephrologist decides to place the patient on the transplant wait list and institute maintenance dialysis.

What are the different types of dialysis?

- Traditional hemodialysis: Tubes deliver the patient's blood to a machine (dialyzer) outside the body. The dialyzer has two compartments separated by a semipermeable membrane. One compartment contains the patient's blood, and the other contains dialysate fluid. Waste products and excess free water in the blood diffuse across the membrane into the dialysate (ultrafiltration). Tubes return the purified blood to the body. The dialysate is discarded. Typically performed three times a week in 3- to 4-hour sessions.
- Peritoneal dialysis: Dialysate is instilled into the peritoneum. The peritoneal membrane acts as a natural semipermeable membrane. Either the patient or a machine removes the old dialysate and instills fresh dialysate at least once a day. Peritoneal dialysis is more convenient than hemodialysis but carries a risk of complications like peritonitis and abdominal or inguinal hernia.
- Hemofiltration: Tubes deliver blood to a machine with a highly porous semipermeable membrane, so lots of water and solutes enter the other compartment (there is no dialysate). Desired solutes and water are added to the remaining blood, which is returned to the body. Performed slowly and continuously for 12 to 24 hours daily. Main use is for ARF patients in the intensive care unit setting.

- Hemodiafiltration: hemodialysis + hemofiltration.
- Hemodialysis/hemofiltration access: Initially, obtain blood through a central venous catheter (temporary access). In the long term, first-line access is a surgically created arteriovenous fistula in the nondominant arm. If the fistula fails or cannot be created, second-line access is an arteriovenous graft (Gore-Tex connects artery and vein).
- Peritoneal dialysis access: surgically placed catheter (runs from peritoneum to navel).

Thirty minutes after the first hemodialysis session begins, the patient complains of chest pain, back pain, nausea, and vomiting. Vital signs are normal.

What is the most likely cause of his symptoms? What is the next step in management?

The patient has "first use syndrome (type B)," a complement-mediated reaction to the semipermeable membrane that can occur 15 to 30 minutes after the first hemodialysis session begins. Chest pain, back pain, nausea, vomiting, and hypotension are the most common symptoms. Continue hemodialysis unless the patient is hemodynamically unstable or develops signs of anaphylaxis (rare). Use the same dialyzer for subsequent hemodialysis sessions. Symptoms recur less frequently during subsequent sessions.

First use syndrome (type A): Occurs <5 minutes after the first session begins. This type is more severe but far less common than type B. Stop the session immediately and treat symptoms. Pretreat with antihistamines and/or steroids during subsequent sessions.

ANSWERS TO CASE 18:

What is the next step in management?

The patient has idiopathic minimal change disease, which accounts for 10% to 15% of nephrotic syndrome in adults. Treat with a course of high-dose oral steroids. Most patients recover fully without any complications.

Minimal change disease accounts for 90% of nephrotic syndrome in children.

ANSWERS TO CASE 19:

What is the diagnosis?

The patient has amyloidosis. In this condition, low molecular weight proteins deposit on the tissues of multiple organs. There are two main categories of amyloidosis:

- Primary amyloidosis: Plasma cell dyscrasia that often occurs with multiple myeloma (this patient). Tissue deposits are light-chain immunoglobulins.
- Secondary amyloidosis: Secondary to chronic inflammatory diseases like rheumatoid arthritis. Tissue deposits are serum amyloid A (acute phase reactant).

Minor categories of amyloidosis:

- Familial amyloidosis: Many different mutations can cause amyloidosis.
- Hemodialysis-related amyloidosis: β-2 microglobulin deposits in bones and joints.
- Senile amyloidosis: Transthyretin deposits in myocardium, etc., but not the kidney.

Primary amyloidosis and secondary amyloidosis can affect any organ system. Most common are heart (restrictive cardiomyopathy) and skin (waxy thickening, ecchymoses, and periorbital purpura).

How is primary amyloidosis treated?

Treat the underlying plasma cell dyscrasia (refer to Chapter 10: Hematology). In the case of secondary amyloidosis, treat the underlying inflammatory disorder. Most patients with renal amyloidosis progress to ESRD and require dialysis/kidney transplant.

ANSWERS TO CASE 20:

What is the most likely diagnosis?

The clinical picture is consistent with SLE. Renal biopsy is always indicated to determine the class of lupus nephropathy (Table 20-1).

Table 20–1. Types of renal disease in systemic lupus erythematosus

	Renal Biopsy	Clinical Manifestations
Class I	Minimal mesangial deposits	Asymptomatic
Class II	Focal segmental mesangial deposits	Isolated microscopic hematuria, proteinuria
Class III	Focal glomerulonephritis	Variable
Class IV	Diffuse glomerulonephritis	Nephritic ± nephrotic syndrome and ARF (most common and most severe form)
Class V	Membranous GN	Nephrotic syndrome but no azotemia
Class VI	Advanced sclerosis	End-stage renal disease

Renal biopsy indicates the patient has stage III disease.

How is lupus nephritis treated?

- Class I and II disease: No specific treatment.
- Other classes: Optimal therapy uncertain (usually includes corticosteroids + another immunosuppressant); also, treat CKD as described earlier.

Repeat renal biopsy: Obtain if serum creatinine rises, proteinuria does not decrease, or active sediment persists (RBC casts, dysmorphic RBCs).

ANSWERS TO CASE 21:

What is the cause of this patient's oedema?

Peripheral edema may occur due to local obstruction of lymphatic or venous outflow, or because of cardiac, renal, pulmonary or liver disease. Unilateral edema is most likely to be due to a local problem, whereas bilateral leg edema is usually due to one of the medical conditions listed above. Pitting edema needs to be distinguished from lymphedema which is characteristically non-pitting. This is tested by firm pressure with the thumb for approximately 10 s. If the edema is pitting, an indentation will be present after pressure is removed. This man has a subacute onset of massive pitting edema . The major differential diagnoses are cardiac failure, renal failure, nephrotic syndrome, right heart failure (cor pulmonale) secondary to chronic obstructive airways disease or decompensated chronic liver disease. The frothy urine is a clue to the diagnosis of nephrotic syndrome and is commonly noted by patients with heavy proteinuria.

On examination there were no clinical signs to suggest chronic liver disease. The jugular venous pressure would be expected to be more raised, and there should have been signs of tricuspid regurgitation (prominent 'v' wave, pansystolic murmur loudest on inspiration) and cardiomegaly if the patient had cor pulmonale or biventricular cardiac failure. The patient has signs of bilateral pleural effusions which may occur in nephrotic syndrome, if there is sufficient fluid retention. The bruising and peri-orbital purpura is classically seen in patients with nephrotic syndrome secondary to amyloidosis.

The investigations are consistent with the diagnosis of nephrotic syndrome. Nephrotic syndrome is defined by the triad of hypoalbuminaemia (<30g/L), proteinuria (>3 g/24h), and

hypercholesterolaemia. The normochromic, normocytic anaemia is typical of chronic disease and is a clue to the underlying diagnosis of amyloidosis. Patients with amyloidosis may have raised serum transaminase levels due to liver infiltration by amyloid.

What is the likely underlying diagnosis?

The patient should have a renal biopsy to delineate the cause of the nephrotic syndrome. The principal causes of nephrotic syndrome are listed below. Adults presenting with nephrotic syndrome should have a renal biopsy. The exception is the patient with long-standing diabetes mellitus, with concomitant retinopathy and neuropathy, who almost certainly has diabetic nephropathy.

Causes of nephrotic syndrome

- Diabetes mellitus
- Minimal change disease
- Focal and segmental glomerulosclerosis
- Membranous nephropathy
- Systemic lupus erythematosus
- HIV infection
- Amyloidosis/myeloma

In this case renal biopsy confirmed the diagnosis of amyloidosis, and staining was positive for lambda light chains. Immunofixation confirmed the presence of a IgGX paraprotein in the blood. A bone marrow aspirate showed the presence of an excessive number of plasma cells, consistent with an underlying plasma cell dyscrasia. Patients with amyloidosis should have an echocardiogram to screen for cardiac infiltration, and if the facilities are available a serum amyloid P scan should be arranged which assesses the distribution and total body burden of amyloid. An amyloid P scan is shown in Fig. 21.1.

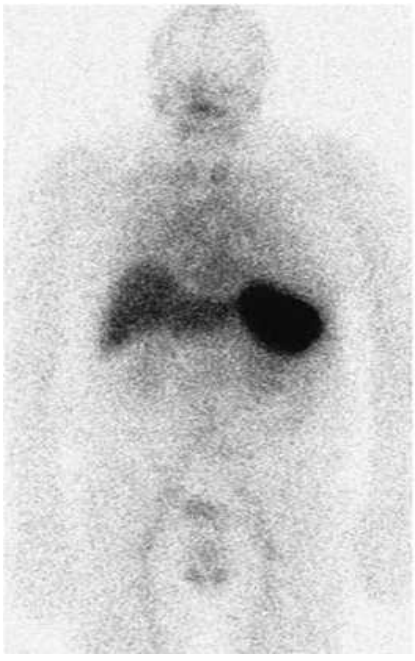

Figure 21.1 Serum amyloid P scan showing uptake predominantly in the spleen.

How would you further examine, investigate and manage this patient?

The initial treatment of this patient involves fluid and salt restriction, and diuretics to reduce the edema . He should be anticoagulated to reduce the risk of deep vein thrombosis or pulmonary embolus. His hyperlipidaemia should be treated with a statin. Definitive treatment is by chemotherapy supervised by the haematologists to suppress the amyloidogenic plasma cell clone. In younger patients, bone marrow transplantation may be considered. Patients with nephrotic

syndrome secondary to amyloidosis usually progress to end-stage renal failure relatively quickly. Death is most commonly due to cardiac involvement.

Clinical pearls

- Bilateral edema may be due to cardiac, liver or renal disease.
- All patients presenting with new-onset edema should have a urinalysis.
- Patients with nephrotic syndrome are at increased risk of pulmonary embolism.

PART III: NEPHROTIC SYNDROME

ANSWERS TO CASE 22:

A 48-year-old woman with long-standing diabetes now presents with edema and significant proteinuria on a urine dipstick. She has diabetic retinopathy, some peripheral neuropathy, and no other findings suggestive of any other systemic disease.

- Most likely diagnosis: Nephrotic syndrome as a consequence of diabetic nephropathy.
- Best intervention: Angiotensin-converting enzyme (ACE) inhibitors.

CASE DISCUSSION

Considerations

Patients develop significant proteinuria as a result of glomerular damage, which can result from many systemic diseases. It is important to screen for diseases such as human immunodeficiency virus (HIV), autoimmune diseases, and malignancy by history, physical examination, and sometimes laboratory investigation to determine the underlying cause and appropriate treatment of the renal manifestations.

Approach to nephrotic syndrome

Definition

NEPHROTIC SYNDROME: Urine protein excretion more than 3.5 g over 24 hours, serum hypoalbuminemia (<3 g/dL), and edema.

Clinical approach

Normally, the kidneys do not excrete appreciable amounts of protein (<150 mg/d) because serum proteins are excluded from the urine by the glomerular filter both by their large size and their net negative charge. Thus, the appearance of significant proteinuria heralds glomerular disease, with disruption of its normal barrier function. Proteinuria in excess of to 3.5 g of protein per 1.73 m^2body surface area (normal adult male body surface area) per day is considered to be in the nephrotic range. The key feature of nephrotic syndrome is the heavy proteinuria, which leads to loss of albumin and other serum proteins. The hypoal- buminemia and hypoproteinemia result in decreased intravascular oncotic pressure, leading to tissue edema that usually starts in dependent areas such as the feet but may progress to involve the face, hands, and ultimately the whole body (anasarca). The decreased oncotic pressure also triggers the liver to start lipoprotein synthesis, thus leading to hyperlipidemia.

Patients typically present to the doctor complaining of the edema and have the laboratory features described earlier. Urinalysis usually shows few or no cellular elements and may show waxy casts and oval fat bodies (which look similar to maltese crosses under polarized light) if hyperlipidemia is present.

In adults, one-third of patients with nephrotic syndrome have a systemic disease that involves the kidneys, such as diabetes or lupus; the rest have a primary renal disease, with one of four pathologic lesions: minimal change disease, membranous nephropathy, focal segmental

glomerulosclerosis (FSGS), or membra- noproliferative glomerulonephritis (MPGN). Thus, a new diagnosis of nephrotic syndrome warrants further investigation into an underlying systemic disease. Common tests include serum glucose and glycosylated hemoglobin levels to evaluate for diabetes, antinuclear antibody (ANA) to screen for systemic lupus erythematosus, serum and urine protein electrophoresis to look for multiple myeloma or amyloidosis, and viral serologies, because HIV and viral hepatitis can cause nephrosis. Less common causes include various cancers, medications such as nonsteroidal anti-inflammatory drugs (NSAIDs), heavy metals such as mercury, and hereditary renal conditions. Of these causes, diabetes mellitus is by far the most common, as in the patient presented in this scenario.

Adults with nephrotic syndrome usually undergo renal biopsy, especially if the underlying diagnosis is unclear, or if there is a possibility of a treatable or reversible condition. Patients with advanced diabetes who have heavy proteinuria and microvascular disease, such as retinopathy, but no active (cellular components) on a urinary sediment are generally presumed to have diabetic nephropathy. These patients typically do not undergo renal biopsy because the nephrotic proteinuria represents irreversible glomerular damage.

Treatment of nephrotic syndrome consists of treatment of the underlying disease, if present, as well as management of the edema and attempts to limit the progression of the renal disease. For edema, all patients require strict salt restriction, but most patients will also need diuretics. Because both thiazide and loop diuretics are highly protein bound, there is reduced delivery to the kidney, and often very large doses are required to manage the edema. Counter intuitively for a patient with hypoproteinemia, dietary protein restriction usually is recommended. It is thought that high-protein intake only causes heavier proteinuria, which can have an adverse effect on renal function. Additionally, use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) reduces proteinuria and slows the progression of renal disease in diabetics with proteinuria.

Besides the edema, patients with nephrotic syndrome have other consequences of renal protein wasting. They have decreased levels of antithrombin III and proteins C and S, and often are hypercoagulable, with formation of venous thromboembolism, including renal vein thrombosis. Patients with evidence of thrombus formation require anticoagulation, often for life. Other complications include hypogammaglobulinemia with increased infection risk (especially pneumococcal infection), iron deficiency anemia caused by hypotransferrinemia, and vitamin D deficiency because of loss of vitamin D-binding protein.

In the progression of diabetic nephropathy, initially the glomerular filtration rate (GFR) is elevated and then declines over time. Prior to the decline in GFR, the earliest stages of diabetic nephropathy can be detected as microalbuminuria. This is defined as a urine albumin excretion between 30 and 300 mg/d. It is possible to measure this in a random urine sample rather than a timed collection, because a ratio of albumin (in milligrams) to creatinine (in grams) of 30 to 300 usually correlates with the total excretion described. When albuminuria exceeds 300 mg/d, it is detectable on ordinary urine dipsticks, and the patient is said to have overt nephropathy.

After the development of microalbuminuria, most patients will remain asymptomatic, but the glomerulopathy will continue to progress over the subsequent 5 to 10 years until overt nephropathy develops. At this point, many patients have some edema, and nearly all patients have developed hypertension. The presence of hypertension will markedly accelerate the decline of renal function. If left untreated, patients then progress to end- stage renal disease (ESRD), requiring dialysis or transplant, within a 5- to 15-year period.

The development of nephropathy and proteinuria is very significant because they are associated with a much higher risk for cardiovascular disease, which is the leading cause of death in

patients with diabetes. By the time patients with diabetes develop ESRD and require dialysis, the average life expectancy is less than 2 years.

Thus, the development of microalbuminuria in diabetic patients is extremely important because of the progressive disease it heralds and because it is potentially reversible, or at least its progression to overt proteinuria can be slowed via medications. The ACE inhibitors slow the progression of renal disease and should be initiated even when patients are normotensive. Tight glycemic control with a goal hemoglobin A1c less than 6.5 to 7.0 has also been shown to slow or prevent the progression of microvascular complications of diabetes, such as retinopathy and nephropathy. If overt nephropathy and hypertension have developed, blood pressure control with a goal less than 130/80 mm Hg (or <125/75 mm Hg if heavy proteinuria >1 g/d) is essential to slow progression.

In addition, because cardiovascular disease is the major killer of patients with diabetes, aggressive risk factor reduction should be attempted, including smoking cessation and reduction of hypercholesterolemia. In the newest recommendations regarding management of cholesterol, patients with diabetes now are regarded as the highest risk category, along with patients who already have established coronary artery or other atherosclerotic vascular disease; they should be treated with diet and statins with a goal of low-density lipoprotein (LDL) cholesterol less than 100 mg/dL.

Comprehension Questions

1. A 49-year-old woman with type 2 diabetes presents to your office for new onset swelling in her legs and face. She has no other medical problems and says that at her last ophthalmologic appointment she was told that the diabetes had started to affect her eyes. She takes glyburide daily for her diabetes. Physical examination is normal except for pitting edema of bilateral upper and lower extremities, hard exudates and dot hemorrhages on funduscopic examination, and diminished sensation to the mid-shin bilaterally. Urine analysis shows 3 + protein and 2+ glucose (otherwise negative). Which of the following is the best treatment for this patient?

A. Have the patient return in 6 weeks and check a repeat urine analysis at that time.
B. Start metoprolol.
C. Change the glyburide to glipizide and have the patient return for follow-up in 6 weeks.
D. Start lisinopril.
E. Refer the patient to a cardiologist.

2. A 19-year-old man was seen at the university student health clinic a week ago complaining of pharyngitis, and now returns because he has noted discoloration of his urine. He is noted to have elevated blood pressure (178/110 mm Hg) and urinalysis reveals RBC casts, dysmorphic RBCs, and 1+ proteinuria. Which of the following is the most likely diagnosis?

A. Systemic lupus erythematosus (SLE)
B. Amyloidosis
C. Post-streptococcal glomerulonephritis
D. HIV nephropathy
E. Diabetic nephropathy

3. Which of the following is the best screening test for early diabetic nephropathy?

A. Urine microalbuminuria
B. Dipstick urinalysis
C. Renal biopsy
D. Fasting blood glucose
E. 24-Hour urine collection for creatinine clearance

4. A 58-year-old man with type 2 diabetes is normotensive but has a persistent urine

albumin/creatinine ratio of 100, but no proteinuria on urine dipstick. Which of the following is the best management for this patient?

A. Start ACE inhibitor.
B. Start high-protein diet.
C. Switch from oral agent to insulin.
D. Refer to ophthalmologist for examination.

Answers

1. D. Beta-blockers are a good first-choice agent for a patient with hypertension and no comorbidities. However, for the patient with diabetes and nephropathy described in the clinical vignette, the benefit of an ACE inhibitor for decreasing proteinuria makes this the best choice for initial treatment. Changing from one sulfonylurea to another is of no benefit because all are equally efficacious. There is no indication for referral to a cardiologist based on the information provided in the vignette.

2. C. The patient has hypertension, and a urinary sediment consistent with a nephritic rather than nephrotic syndrome (RBC casts, mild degree of proteinuria). Given his recent episode of pharyngitis, the most likely cause would be post-infectious, probably due to streptococcal infection. SLE can produce a variety of renal diseases, including both nephritic and nephrotic manifestations, but it would be unlikely in a male patient, especially without other clinical manifestations of lupus such as arthritis. Amyloidosis, diabetes, and HIV all cause renal disease, but usually produce the nephrotic syndrome (heavy proteinuria >3gm/day, edema, hypoalbuminemia).

3. A. Although a 24-hour urine collection for creatinine may be useful in assessing declining GFR, it is not the best screening test for the diagnosis of early diabetic nephropathy. In the outpatient setting, a dipstick urinalysis is readily available but will detect only patients with overt nephropathy (proteinuria >300 mg/d). Thus, a random urinary albumin/creatinine ratio of 30/300 is the best test to screen for early diabetic nephropathy. A fasting blood glucose may aid in the diagnosis of diabetes but not nephropathy. Finally, although most patients with nephrotic syndrome require a renal biopsy for diagnosis, a patient with worsening renal function who has had long-standing diabetes is assumed to have renal disease secondary to diabetic nephropathy, and the majority of these patients do not undergo a renal biopsy.

4. A. The albumin/creatinine ratio of 100 is indicative of microalbuminuria.

Screening for microalbuminuria is very important because it is the one aspect of the disease that is reversible and to which physicians can target therapy to blunt the progression to overt renal failure. Disease progression is slowed with ACE inhibitors, blood pressure control, limited dietary protein intake, weight loss, and improved glycemic control.

Clinical Pearls

- Nephrotic syndrome is characterized by more than 3.5 g proteinuria over 24 hours, hypoalbuminemia, and edema. Often, hypercoagulability and hyperlipidemia are present.
- Nephrotic syndrome can be a result of a primary renal disease but is often a manifestation of a systemic disease such as diabetes, HIV infection, an autoimmune disease,or a malignancy.
- Patients with diabetes should be screened for microalbuminuria (albumin excretion 30-300 mg/d); if present, treatment should be initiated with an angiotensin- converting enzyme inhibitor, even if the patient is normotensive.
- Patients with diabetic nephropathy and proteinuria are at very high risk for cardiovascular disease, so aggressive risk factor reduction, such as use of statins, is important.

ANSWERS TO CASE 23:

What features of the history and physical examination are important in determining if this patient has a primary (idiopathic) or secondary form of the nephrotic syndrome?

Differentiating between the primary and secondary forms of the nephrotic syndrome depends on a careful review of the patient's history and physical examination findings and the performance of selected laboratory tests that can identify underlying disease states. It is imperative to determine if there is a family or personal history of diabetes mellitus or connective tissue disease, hereditary conditions such as sickle cell disease or Alport's syndrome, allergen exposure, and so forth. A complete medication list must be obtained, including the use of nonprescription medicines such as NSAIDs. A history of illicit drug use is equally important because heroin nephropathy is not rare in drug abusers. In addition, a travel history is a crucial part of the history taking because, for example, malaria is a well-known cause of the nephrotic syndrome and should be considered in those patients who have traveled to endemic areas. Risk factors for hepatitis and human immunodeficiency virus (HIV) infection must also be sought because high-risk populations should be screened for these disorders. In this particular patient (a young woman), the history of occasional arthralgias brings up the possibility of a multisystem disease as the source of the nephrotic syndrome.

What additional laboratory tests would you order either to establish or refute a secondary cause of the nephrotic syndrome?

Laboratory tests that are useful in establishing a secondary cause of the nephrotic syndrome include the serum glucose level, an antinuclear antibody (ANA) determination, complement levels, hepatitis screening, venereal disease research laboratory test, HIV test, sickle cell preparation, an antistreptolysin titer, throat culture, and serum and urinary protein electrophoresis. The findings yielded by the history and physical examination dictate which of these tests should be performed in a particular patient. In this patient, the ANA test is positive and the complement levels are low, indicating that she may have systemic lupus erythematosus (SLE) as the cause of her nephrotic syndrome.

How should this patient's evaluation proceed?

In the setting of SLE, a kidney biopsy should be performed in an effort to establish the nature of the underlying disorder responsible for the nephrotic syndrome. This patient most likely has either diffuse proliferative glomerulonephritis or membranous nephropathy with SLE. The therapy for the former calls for treatment with steroids and cytotoxic agents, although the latter does not.

CASE DISCUSSION

What is the most common cause of the secondary nephrotic syndrome in adults? In patients with this disorder, which early finding serves as a harbinger for the subsequent development of nephrotic syndrome and renal insufficiency?

Diabetes mellitus is the most common cause of secondary nephrotic syndrome in adults. In patients with either type 1 or type 2 diabetes, the onset of microalbuminuria (albumin excretion of 20 to 200 Bμg per minute or 30 to 300 mg/g Cr per day) predicts the subsequent development of nephrotic syndrome and renal insufficiency. These patients should begin treatment with an ACE inhibitor or ARBs.

What is the definition of nephrotic syndrome?

Nephrotic syndrome is a clinical entity characterized by (a) proteinuria in excess of 3.5 g/1.73 m^2 of body surface area (or 50 mg/kg of body weight) per day; (b) hypoalbuminemia (<3 g/dL), which is a consequence of the renal losses coupled with inadequate hepatic compensatory synthesis; (c) edema, which is a consequence of both the hypoalbuminemia and the sodium retention; (d)

hyperlipidemia, which is probably due to the increased hepatic synthesis of very “low-density lipoproteins which are converted to cholesterol-carrying low-density lipoproteins; and (e) presence of lipiduria. Impaired removal plays an important but probably secondary role in this setting.

What are the causes of nephrotic syndrome?

The causes of nephrotic syndrome can be easily divided into two broad categories. The primary, or idiopathic, forms of nephrotic syndrome are those for which a specific cause cannot be identified despite a reasonably thorough evaluation. The five major histologic subtypes of primary nephrotic syndrome include minimal-change disease (also called lipoid nephrosis or nil disease), membranous glomerulonephritis, membranoproliferative glomerulonephritis (also called mesangiocapillary glomerulonephritis), focal segmental glomerular sclerosis (FSGS), and proliferative glomerulonephritis. The clinical and histologic characteristics of primary nephrotic syndrome are listed in Table 23-1.

Table 23-1. The clinical and histologic features of the primary (idiopathic) nephrotic syndrome

Minimal-change disease	Most common cause in children (75%); 20% of adults; steroid- or cyclophosphamide-sensitive (80%); nonprogressive; normal renal function; scant hematuria	LM: normal IF: negative EM: podocyte effacement; no immune deposits
Focal segmental glomerulosclerosis	Most common cause in adults (40%-50%); microscopic hematuria; progressive renal failure (75%)	LM: early ”segmental sclerosis in some glomeruli with tubular atrophy; late” sclerosis of most glomeruli
Membranous nephropathy	Peak incidence, fourth and sixth decades; male-female, 2-3:1; early hypertension (30%); spontaneous remission (20%); progressive renal failure (30%-40%)	LM: early ”normal; late ”GBM thickening IF: granular IgG and C3 EM: subepithelial deposits and GBM expansion
Membranoproliferative glomerulonephritis	Peak incidence, second through third decades; mixed nephrotic-nephritic features; slowly progressive in most, rapid in some; hypocomplementemia	LM: hypercellular glomeruli with duplicated GBM EM: type I ”subendothelial immune deposits; type II” dense deposit GBM
Proliferative		

LM, light microscopy; IF, immunofluorescence; IgG, immu noglobulin G; EM, electron microscopy; GBM, glomerular basement membrane.

The secondary forms of the nephrotic syndrome are those associated with specific etiologic events or in which glomerular disease arises as a complication of another disease or systemic process. These may be broadly categorized into those stemming from infections, neoplasia, medications, allergens, multisystem diseases, and heredofamilial diseases, and also include various miscellaneous causes (Table 23-2). Secondary nephrotic syndrome may be associated with any of the major histologic subtypes found in idiopathic nephrotic syndrome. The idiopathic nephrotic syndrome is more common than the secondary form.

What are the possible complications of nephrotic syndrome?

The complications of nephrotic syndrome include accelerated atherosclerosis, increased susceptibility to infections, osteomalacia, and an increased incidence of thromboembolic events.

What are the treatment options for nephrotic syndrome?

The treatment of nephrotic syndrome depends on its cause. Certainly, in the case of the secondary nephrotic syndrome, if the primary disorder is treated effectively, the nephrotic syndrome tends to resolve as well. In the case of the primary nephrotic syndrome, certain histologic subtypes (i.e., minimal-change disease and possibly membranous nephropathy) respond to treatment with steroids, with or without cytotoxic agents. Discussion of the potential role for other agents such as cyclosporine or mycophenolate is beyond the scope of this book. Other lesions may be refractory to any type of therapy. Drugs such as the ACE inhibitors or ARBs may be useful in reducing the proteinuria by affecting intrarenal hemodynamics, but they cannot in any way alter the primary glomerular abnormality involved.

Table 23-2. Disorders Associated with Secondary Nephrotic Syndrome

- Infectious diseases
  - Bacterial: poststreptococcal glomerulonephritis, infective endocarditis, nephritis, shunt syphilis, leprosy
  - Viral: hepatitis B and C, cytomegalovirus, Epstein-Barr virus, herpes zoster, human immunodeficiency virus infections
  - Protozoal: malaria, toxoplasmosis
  - Helminthic: schistosomiasis, trypanosomiasis, filariasis
- Neoplastic diseases
  - Solid tumors (carcinoma and sarcoma): colon, lung, breast, stomach, kidney
  - Hematologic malignancies (leukemias and lymphomas)
- Medications
  - Nonsteroidal antiinflammatory agents
  - Organic, inorganic, elemental mercury
  - Organic gold
  - Penicillamine
  - Street heroin
  - Probenecid
  - Bismuth
  - Captopril
- Multisystem diseases
  - Systemic lupus erythematosus
  - Mixed connective tissue disease
  - Dermatomyositis
  - Dermatitis herpetiformis
  - Sarcoidosis
  - Henoch-Schonlein purpura
  - Goodpasture's syndrome
  - Rheumatoid arthritis
  - Amyloidosis
  - Polyarteritis
- Allergic reactions
  - Bee sting

- Pollens
- Poison ivy and poison oak
- Serum sickness (antitoxins)

- Metabolic diseases
  - Diabetes mellitus
  - Myxedema
  - Hyperthyroidism
- Heredofamilial diseases
  - Alport's syndrome
  - Fabry's disease
  - Nail-patella syndrome
  - Sickle cell disease
  - a1-Antitrypsin deficiency
  - Congenital nephrotic syndrome (Finnish type)
  - Hereditary amyloidosis (familial Mediterranean fever)
- Miscellaneous
  - Chronic renal allograft rejection
  - Pregnancy-associated (preeclampsia, recurrent or transient)
  - Vesicoureteric reflex

PART IV: RENAL ARTERIAL HYPERTENSION

CASE 24:

What is the differential diagnosis of this patient's hypertension?

The differential diagnosis includes essential hypertension, primary hyperaldosteronism, pheochromocytoma, Cushing's syndrome, a renin-producing tumor, and renal artery stenosis. Renal parenchymal disease and coarctation of the aorta can be largely excluded as a cause of this patient's hypertension because the serum creatinine level and urinalysis findings are normal, as are the physical examination findings. The striking feature of this patient's hypertension is the hypokalemia despite treatment with a potassium-sparing diuretic plus potassium supplementation. Hypokalemia may be a feature of primary hyperaldosteronism, Cushing's syndrome, renal artery stenosis, and renin-producing tumors. Pheochromocytoma is considered a possibility because of the patient's complaints of headache and fatigue, although the clinical suspicion for this is low. Although hypokalemia occurs in Cushing's syndrome, the other clinical features of the disorder appear to be lacking. Renal artery stenosis is also unlikely unless the patient has fibromuscular dysplasia. Because the patient's family history is unknown, his genetic propensity for atherosclerosis is not known, but he does not appear to have other evidence of arteriosclerotic disease (e.g., bruits, angina, and claudication). Therefore, the most likely causes include primary aldosteronism and a renin-producing tumor. Essential hypertension can be diagnosed only after the most likely secondary causes have been excluded.

What symptoms are related to the patient's hypokalemia?

Hypokalemia could explain this patient's headaches, muscle cramps, and fatigue. Additional symptoms may include muscle weakness, polyuria, and paresthesias.

What diagnostic steps would help confirm the diagnosis in this patient?

Patients with a history of spontaneous hypokalemia, marked sensitivity to potassium-wasting diuretics, and refractory hypertension should be evaluated for primary hyperaldosteronism. The

initial screening test is to determine the status of aldosterone excretion during prolonged salt loading. To perform this, 10 to 12 g of NaCl is added to the patient's daily intake. After 5 to 7 days of increased salt intake, the serum potassium concentrations and a 24-hour urine excretion of sodium, potassium, and aldosterone are measured. The serum and urine potassium values indicate whether there is inappropriate kaliuresis (a serum potassium level of <3 mEq/L with a urine potassium level >30 mEq/24 hours). The 24-hour urine sodium level verifies compliance with the prescribed salt intake (250 mEq per day). If, under these conditions, the patient's rate of aldosterone excretion fails to show suppression below 14 Bμg per 24 hours, this makes him a prime candidate for additional studies. The presence of hypokalemia and suppressed plasma renin activity further supports the diagnosis of primary hyperaldosteronism. This can be further confirmed by high aldosterone/renin ratio of greater than 100. If a renin-producing tumor were the cause of this patient's hypertension, the plasma renin activity would be elevated. If primary hyperaldosteronism is suspected, adrenal CT scanning should be performed. The finding of an adrenal mass would establish the diagnosis. Adrenal scintigraphy should be done if the CT findings are inconclusive. If the results of scintigraphy are also ambiguous, then adrenal vein sampling should be performed to measure the aldosterone levels. Adrenal vein sampling is still the most accurate test to localize aldosterone-producing tumors.

What are the treatment options in this patient?

The hypertension associated with primary hyperaldosteronism can be managed adequately in most cases by means of salt and water depletion. The combination of spironolactone with hydrochlorothiazide or furosemide has been used successfully. However, if the adrenal adenoma is confined to one gland and there are no contraindications, the tumor should be removed. Only approximately half of patients are normotensive 5 years after surgery, but normal potassium homeostasis is restored permanently. If primary hyperaldosteronism stems from bilateral hyperplasia of the adrenal gland, this is best managed medically because surgical removal of too much of the adrenal gland can result in adrenal insufficiency.

CASE DISCUSSION

What are the major causes of hypertension, and what is the nature of the pathophysiologic mechanism, or mechanisms, responsible for causing the elevation in blood pressure?

Essential hypertension is the most common cause of hypertension and accounts for approximately 90% of all cases. It is usually asymptomatic. The usual age of onset is between 30 and 50 years and patients usually have a genetic predisposition for acquiring it. Other forms of hypertension must be ruled out by an initial screening evaluation before this diagnosis is confidently assigned. The regulation of arterial pressure involves a complex, and as yet not fully understood, interaction among neurohumoral mechanisms, sodium excretion, and baroreceptor reflexes. There is evidence to suggest that the mechanism responsible for the elevation of blood pressure in essential hypertension may involve inherited abnormalities in sodium excretion. This limitation in the ability to excrete sodium may amplify the mechanisms that cause a rise in arterial pressure, thereby producing an abnormal response. These mechanisms include (a) an increment in the extracellular fluid volume and cardiac output, with secondary autoregulation causing an increment in peripheral vascular resistance; (b) an increase in the vascular response to vasoconstriction and (c) an increase in a putative circulating Na+/K+-adenosine triphosphatase inhibitor, which elevates the intracellular sodium and calcium levels, thereby also augmenting peripheral vascular resistance.

The major secondary causes of hypertension are listed in Table 24-1.

Table 24-1. Identifiable causes of hypertension

- Metabolic syndrome (obesity, insulin resistance, impaired glucose tolerance, dyslipidemia, hypertension)
- Obstructive sleep apnea
- Drug-induced hypertension
    - Decongestants
    - Adrenergic agents
    - Calcineurin inhibitors
    - NSAIDs
- Chronic kidney disease
- Primary hyperaldosteronism
- Renovascular disease
- Chronic steroid use or Cushing's
- Pheochromocytoma
- Coarctation of the aorta
- Thyroid or parathyroid disease
- NSAIDs, nonsteroidal anti-inflammatory drugs.

The exact prevalence of renal artery stenosis is not known, but it probably accounts for approximately 5% of the general hypertensive population. It is an important diagnosis to make because it is the most common treatable form of secondary hypertension at any age, and it is one of the few potentially reversible causes of chronic renal failure. The diagnosis must be considered in any patient with severe hypertension refractory to therapy or in any patient who experiences the onset of hypertension either when very young or very old. Atherosclerotic plaques on the renal arteries are the cause in most cases, particularly in patients older than 50 years. Fibromuscular dysplasia, an entity seen in younger patients, particularly women, is the second most common cause of renovascular hypertension. There is evidence to suggest that both renin- and volume-dependent mechanisms play a role in the pathophysiology of renovascular hypertension in humans. The following evidence supports the interplay of both mechanisms: (a) the plasma renin activity is usually normal or high in patients with renal artery stenosis, but never low; (b) there is unilateral hypersecretion of renin from the affected kidney with contralateral suppression; (c) in patients with unilateral renal artery stenosis, removal of the constriction or treatment with an inhibitor of the renin-angiotensin system usually restores the blood pressure to normal or near-normal values; and (d) the effect of angiotensin blockade and salt restriction on blood pressure in patients with bilateral renal artery stenosis is frequently additive.

Primary hyperaldosteronism is an uncommon cause of secondary hypertension, with a prevalence of approximately 1% in the hypertensive population. This disease can occur at any age. The classic form (Conn's syndrome) results from a unilateral adrenocortical adenoma, and accounts for approximately half the cases of hyperaldosteronism. The other half of the patients have bilateral adrenal hyperplasia. A small percentage has overproduction that can be suppressed with glucocorticoids. As in other forms of hypertension, the exact pathogenesis is unclear. The findings from early studies suggested that the expected salt and water retention secondary to the aldosterone excess raises the intravascular volume and subsequently cardiac output, thereby raising the blood pressure. However, hypervolemia is not a universal finding in patients with primary hyperaldosteronism. The results of studies in animals have suggested that the more important mechanism is an increase in sodium stores and total peripheral vascular resistance. The mechanism responsible for this is uncertain, but some study findings suggest that excess mineralocorticoids induce membrane changes in vascular smooth muscle, leading to abnormal cation turnover

(possibly sodium and calcium), which, in turn, augments vasoconstriction and increases peripheral vascular resistance.

Pheochromocytoma is also a rare cause of hypertension. It is estimated to affect 0.1% of patients with hypertension. Pheochromocytoma can occur at any age, but it arises most frequently in the fourth and fifth decades. In adults, most pheochromocytomas affect women. Pheochromocytomas are tumors of neuroectodermal origin. If they go undiagnosed, they carry a high risk of causing morbidity and mortality secondary to hypertensive crisis, shock, arrhythmias, cardiac arrest, and stroke. The hypertension of pheochromocytoma is a function of the norepinephrine released into the synaptic cleft. Circulating levels of norepinephrine have little direct involvement in the cause or maintenance of the hypertension.

Hypertension complicates both acute and chronic renal parenchymal diseases, and affects approximately 80% to 90% of patients on dialysis. There are several mechanisms that may be involved in producing the hypertension in this setting, and these include (a) a markedly impaired ability of the diseased kidney to excrete salt and water; (b) the production of an unidentified vasopressor substance by the kidney; (c) absent production of a necessary humoral vasodilator substance by the kidney; (d) failure of the kidneys to inactivate circulating vasopressor substances; and (e) activation of the renin-angiotensin system.

The blood pressure in the upper extremities is elevated in 80% of children and adults with coarctation of the aorta. The mechanism responsible for this hypertension is an inappropriate activation of the renin-angiotensin system in the presence of an expanded body fluid volume.

Hypertension affects 80% of patients with idiopathic Cushing's syndrome. Other clinical features of the disorder include glucose intolerance, menstrual disorders, sterility, loss of libido, acne, striae, osteoporosis, muscle weakness and wasting, edema, polyuria, and renal stones. However, the mechanism whereby adrenocorticotropic hormone and cortisol raise blood pressure in humans has not been elucidated, although there is evidence to suggest that glucocorticoids possess a hypertensinogenic action that is separate from their glucocorticoid activity.

In the setting of renin-producing tumors, hypertension results from the excess secretion of renin by either a juxtaglomerular cell tumor or nephroblastoma. This causes the peripheral renin levels to be elevated, which mediates the hypertension.

What should the initial evaluation of a patient who presents with an elevation in blood pressure consist of, and, based on the evaluation findings, what specific clinical features would point toward a particular secondary cause of hypertension?

The initial evaluation of patients with hypertension should include history taking, physical examination, and laboratory tests directed toward uncovering a correctable form of secondary hypertension.

In terms of the history, a strong family history, as well as past observations of intermittent blood pressure elevations, suggest essential hypertension. Secondary hypertension often develops either before 30 or after 55 years of age. Other pertinent general questions should elicit information about steroid use, use of drugs, including oral contraceptives, and whether there have been recurrent urinary tract infections or a history of proteinuria, nocturia, trauma, or weight gain or loss.

Physical examination should divulge further diagnostic clues as to the possible cause of the hypertension. The examination should focus on the patient's general appearance, muscular development, blood pressure and pulses in both upper extremities and a lower extremity, the supine and standing blood pressure, funduscopy, palpation and auscultation of the carotid arteries, cardiac and pulmonary examination, auscultation of the abdomen for bruits and palpation for an abdominal aneurysm and enlarged kidneys, and examination of the lower extremities for edema.

Laboratory evaluation at the initial workup should include urinalysis for the presence of protein, blood, and glucose, together with a microscopic examination; the serum creatinine and BUN levels; hematocrit; the serum potassium level; the white blood cell count; the serum glucose, cholesterol, triglyceride, calcium, phosphate, and uric acid levels; electrocardiography; and a chest radiographic study.

The clinical features that suggest renal vascular hypertension are listed in Table 24-2. The clinical features suggesting other secondary causes of hypertension are listed in Table 24-3.

Table 24-2. Clinical features suggestive of renal vascular hypertension

- Epidemiologic features
  - Hypertension in the absence of family history
  - Age <25 y or >55 y
  - Cigarette smoking
  - White race
- Features of the hypertension
  - Abrupt onset of moderate to severe hypertension
  - Sudden onset of hypertension after abdominal trauma
  - Recent acceleration of severity of hypertension
  - Headaches
  - Resistance or failure of blood pressure control with usual therapy
  - Development of severe or malignant hypertension
  - Retinopathy out of proportion to severity of blood pressure
  - Excellent antihypertensive response to angiotensin-converting enzyme inhibitor
  - Deterioration in renal function in response to angiotensin-converting enzyme inhibitor
  - Blood pressure unaffected or increased with diuretic therapy
- Associated features
  - Unprovoked hypokalemia
  - Hypokalemia in response to a thiazide diuretic
  - Abdominal or flank systolic-diastolic bruits
  - Carotid bruits or other evidence of large-vessel disease
  - Elevated peripheral plasma renin activity in absence of alternative explanation

Table 24-3. Clinical features of other secondary causes of hypertension

- Primary hyperaldosteronism
  - History
  - Proximal muscle weakness, polyuria, nocturia, polydipsia, paresthesia, tetany, muscle paralysis, frontal headaches
  - Laboratory features
  - The diagnostic hallmark of this disease is hypokalemic metabolic alkalosis
  - Hyperglycemia may also be present
- Pheochromocytoma
  - Symptoms
  - Patients may present in a wide variety of clinical settings, including transient ischemic attacks, stroke, headache (usually pounding and severe), palpitations with or without tachycardia, and excessive sweating; less common symptoms include tremor, pallor, nausea, weakness, fatigue, weight loss, and chest or abdominal pain
  - Physical examination

- Postural hypotension occurs in 50%-75% of patients; paroxysmal episodes of hypertension occur in approximately one third of patients; sweating and muscular weakness may be evident
- Laboratory features
- Hyperglycemia or hypercalcemia may be present

- Coarctation of the aorta
  - Symptoms
  - Epistaxis, throbbing headache, leg fatigue, cold extremities, and occasional claudication
  - Physical examination
  - Disparity in the pulsations and blood pressure between the arms and legs the pulsations in the upper extremities are pounding; those in the lower extremities are weak, delayed, or absent; the blood pressure in the arms exceeds that in the legs; there is collateral arterial circulation; murmurs are usually present but vary in location
  - Laboratory features
  - Chest radiograph may show prominence of the left ventricle, notching of the inferior border of the ribs from collateral vessels, and poststenotic dilatation of the aorta
- Cushing's syndrome
  - Symptoms
  - Menstrual disorders, loss of libido, hirsutism, acne, striae, muscle weakness, easy bruising, edema, polyuria
  - Physical examination
  - Hirsutism, acne, striae, muscle weakness and wasting, purpura, bruising, edema, and poor wound healing
  - Laboratory features
  - Hyperglycemia, impaired glucose tolerance, neutrophilia, lymphopenia, and hypokalemia
- Renal parenchymal disease
  - Symptoms
  - Uremia and anemia; associated with renal failure
  - Physical examination
  - If any findings, those associated with renal failure
  - Laboratory features
  - Several laboratory abnormalities may be present these include elevation of the BUN and creatinine levels, anemia, hypocalcemia, hyperphosphatemia, hyperkalemia, metabolic acidosis, proteinuria, and hematuria BUN, blood urea nitrogen.

- Echocardiography can visualize the area of aortic coarctation, but this is best confirmed by cardiac catheterization.

If a secondary cause of hypertension is suspected, what would the further diagnostic evaluation comprise, and what would be the likely findings for each cause?

A number of tests have evolved to assess the likelihood of renal vascular hypertension. Magnetic resonance angiography (MRA) or Doppler ultrasonography of the renal arteries have been used for the evaluation of renal artery stenosis. However, these tests have variable degrees of sensitivity and specificity, largely due to varying degrees of expertise with these techniques at

different centers. Therefore, conventional renal arteriography remains the gold standard. It must be recognized, however, that the finding of renal artery stenosis provides no information concerning the pathophysiology of the vascular lesion. A postcaptopril (25 mg) elevation in plasma renin activity or a decrease in renal perfusion postcaptopril as assessed by scintillation techniques or renal vein renins can provide pathophysiologic information.

If there are clinical features highly suggestive of a pheochromocytoma, the evaluation should begin with an assay of the total plasma catecholamine level, as measured through an indwelling 21-gauge butterfly needle in a patient who has been resting supine for 30 minutes. Values more than 2,000 pg/mL warrant performance of abdominal computed tomography (CT). Values between 1,000 and 2,000 pg/mL require performance of the clonidine suppression test to determine whether a pheochromocytoma is present. Clonidine does not suppress the release of catecholamines in patients with a pheochromocytoma, as it does in patients with essential hypertension. If the plasma catecholamine values are below 1,000 pg/mL, and the patient is hypertensive, the clonidine suppression test should be performed, but, if the patient is normotensive, the glucagon stimulation test may be helpful. For the glucagon test to be positive, the plasma catecholamine level must increase by threefold, or to greater than 2,000 pg/mL, 1 to 3 minutes after administration of the drug. If any of these test results are positive, abdominal CT should be performed. In patients whose clinical presentation suggests a pheochromocytoma but who have only a slight or moderate rise in the catecholamine level (<1,000 pg/mL), repeat testing, including measurement of the urinary catecholamine levels, should be performed.

Historically, Cushing's syndrome has been diagnosed on the basis of the following findings: elevated levels of urinary 17-hydroxycorticosteroids and urinary-free cortisol, loss of diurnal rhythm in the plasma cortisol concentrations, and failure of plasma cortisol levels to suppress overnight after a single 1-mg dose of dexamethasone. Because the overnight dexamethasone suppression test may not elicit suppression in obese and acromegalic patients, the low-dose dexamethasone suppression test (0.5 mg every 6 hours for 2 days) should be done to distinguish patients with Cushing's syndrome from healthy subjects. The high-dose dexamethasone suppression test (2 mg every 6 hours for 2 days) can distinguish Cushing's disease from an adrenal tumor, which does not suppress.

If the cause of renal parenchymal disease cannot be identified with certainty on the basis of the history, physical examination, and laboratory findings, renal biopsy may be indicated. The biopsy results may shed light on whether the process is reversible, and thereby point toward treatment options, if any.

In the setting of renin-producing tumors, determination of the plasma renin activity by renal vein sampling usually shows a unilateral increase in the absence of a renal artery lesion.

What are the respective treatment options for renal artery stenosis, pheochromocytoma, Cushing's syndrome, and primary hyperaldosteronism?

The treatment options for renal artery stenosis are either surgical or medical, and the choice depends on the patient involved. The surgical options include revascularization of the affected kidney using saphenous vein, autogenous artery, or synthetic (Dacron or polytetrafluoroethylene) grafts. A renal artery endarterectomy may be performed in patients with ostial atheromatous lesions. The most popular method of treatment, at least initially, is percutaneous transluminal balloon angioplasty with placement of stents. If these procedures are either unsuccessful or cannot be undertaken, medical management must be instituted.

Cure of a pheochromocytoma consists of surgical removal of the tumor, and proper preoperative preparation helps reduce the attendant morbidity and mortality. In the presence of hypertension, administration of an adrenergic-blocking agent such as phenoxybenzamine (10 to 20

mg twice per day, increasing to 100 mg per day if tolerated) is recommended. Prazosin is not as effective. However, if the location of the tumor is in doubt or if multiple tumors are suspected, it is best not to administer O±-adrenergic blocking agents before surgery. The intravascular volume should be expanded both before and after surgery. In patients with inoperable malignant pheochromocytomas, drug therapy is needed. O±- and OI-Blockers may be used to control arrhythmias, or methyltyrosine may be prescribed to inhibit catecholamine synthesis.

The best surgical approach in a patient with Cushing's disease is selected excision of the pituitary adenoma through a transsphenoidal approach. Surgical removal is sometimes followed by pituitary irradiation to prevent recurrence. A variety of drugs have also been used to treat patients with Cushing's disease. Adrenal tumors are best treated surgically.

Hyperaldosteronism can be treated by either medical or surgical means. Mild aldosterone excess due to an adenoma, and all cases of bilateral hyperplasia, should be managed with aldosterone antagonists such as spironolactone because this disorder is not amenable to surgical treatment. Aldosterone-producing adenomas can be removed to effect cure once they have been appropriately localized by radiologic (CT) techniques.

ANSWERS TO CASE 25:

What diagnosis should you suspect?

Suspect adult polycystic kidney disease (PKD) (APKD) in this patient with chronic flank pain, hypertension, and a family history of renal failure in late adulthood. This autosomal dominant condition results from a mutation in the PKD-1 or PKD-2 gene.

- Autosomal recessive PKD: more severe than APKD; presents at birth or infancy.
- Acquired PKD: develops secondary to scarring in patients with end-stage renal disease (ESRD).

What are the clinical manifestations of APKD?

Patients are typically asymptomatic until adulthood. As cysts grow in size, they can cause any of the following renal manifestations:

- Hematuria: Due to rupture of a cyst into urinary tract.
- Acute flank pain: Results from cyst infection or hemorrhage into a cyst. APKD also predisposes to uric acid stones and pyelonephritis, which cause acute flank pain.
- Chronic flank/abdominal pain: Enlarged kidney stretches renal capsule.
- Hypertension: Enlarged cysts cause areas of renal ischemia. Renal ischemia activates increased renin release, which leads to hypertension.
- Renal insufficiency: Most patients develop ESRD in their 50s or 60s.

APKD can also cause a number of extrarenal manifestations:

- Cerebral aneurysms: May be asymptomatic or cause focal neurological deficits. The most dreaded risk is rupture with subsequent subarachnoid or intracerebral hemorrhage.
- Heart valve abnormalities: Usually not clinically significant.
- Liver cysts: Typically asymptomatic; sometimes, liver cysts can get infected.
- Diverticulosis

What is the next diagnostic step?

The next step is to perform renal ultrasound or CT scan. The presence of multiple kidney cysts (bilateral or unilateral) confirms the diagnosis. Imaging may also detect enlarged kidneys.

Renal ultrasound confirms the diagnosis. How is APKD managed?

There is currently no specific therapy for APKD. Management involves prevention and treatment of complications:

- Intractable flank/abdominal pain: Consider surgical drainage for patients with severe pain unresponsive to opioid analgesics.
- Nephrolithiasis and pyelonephritis: Refer to Cases 6-2 and 6-3.
- Hypertension: Attempt to maintain blood pressure ≤120/80. Angiotensin-converting enzyme (ACE) inhibitors are the first-line antihypertensives in patients with APKD.
- Cerebral aneurysm: Perform CT angiography or magnetic resonance angiography to screen for cerebral aneurysms in the following patients:
    - All symptomatic patients (focal neurological deficits)
    - Asymptomatic patients with family history of ruptured aneurysm
    - Asymptomatic patients who require anticoagulation
- Infected liver/kidney cysts: Suspect if a patient develops fever and flank pain or RUQ pain. Diagnose with CT scan. Treat with surgical drainage and antimicrobial drugs.
- Renal insufficiency: Refer to Case 6-5.

APKD does not increase the risk of polycystic ovarian syndrome.

Flank pain results from a SICC kidney (kidney Stones, Infection, Cysts, or Cancer).

CASE 26:

What is the diagnosis?

This woman has hypertension due to renovascular disease. The vast majority of cases of hypertension are due to essential hypertension. Risk factors for essential hypertension include a family history of hypertension, obesity and lack of exercise. She does not have paroxysmal symptoms of sweating, palpitations and anxiety to suggest a phaeochromocytoma. There are no clinical features to suggest coarctation of the aorta (radiofemoral delay) or neurofibromatosis (cafe-au-lait spots/neurofibromas). Serum potassium is not low making Conn's syndrome or Cushing's syndrome unlikely. The principal abnormality is the modestly raised creatinine suggesting mildly impaired renal function. The absence of hematuria and proteinuria excludes glomerulonephritis. Therefore renovascular disease needs to be considered. The absence of a renal bruit does not exclude the possibility of renovascular disease. The renal angiogram shows bilateral fibromuscular dysplasia (FMD).

How would you further manage this patient?

The commonest cause of renovascular disease is atherosclerotic renal artery stenosis (ARAS). This is common in elderly patients with evidence of generalized atherosclerosis (peripheral vascular disease and coronary artery disease). Ultrasound will often show small kidneys, and renal impairment is common. ARAS is a common cause of end-stage renal failure in the elderly.

At this woman's age atherosclerotic renovascular disease is very unlikely. FMD is the second most common cause of renovascular disease. The commonest form is medial fibroplasia with thinning of the intima and media leading to formation of aneurysms alternating with stenosis, leading to the classic 'string of beads' appearances on angiography. It predominantly affects young and middle-aged women with a peak incidence in the fourth decade of life. Cigarette smoking is a risk factor. FMD usually presents with hypertension, but can rarely present with 'flash' pulmonary oedema. FMD can also affect the carotid arteries causing a variety of neurological symptoms.

Treatment is with percutaneous transluminal renal angioplasty. Unlike atheromatous reno-vascular disease, the hypertension in FMD cases is often cured leading to complete cessation of blood pressure medication. Restenosis is rare.

Clinical pearls

- FMD is an important cause of hypertension in young and middle-aged women.
- Renal artery angioplasty will improve or even cure hypertension in many patients with

> FMD is a very rare cause of end-stage renal failure

PART V: CHRONIC RENAL FAILURE

CASE 27:

What is the most likely cause of this patient's CRI?

The most likely diagnosis is chronic interstitial nephritis due to chronic NSAID use (analgesic nephropathy). Chronic interstitial nephritis leads to CRI with nonspecific urinalysis (normal, mild pyuria, or mild proteinuria) ± renal papillary necrosis. Treatment is to discontinue NSAIDs to prevent progression to ESRD.

What are other common causes of chronic interstitial nephritis?

- Chronic urinary tract obstruction (ruled out by CT scan or ultrasound)
- APKD (ruled out by CT scan or ultrasound)
- Hypertensive nephrosclerosis (ruled out if normotensive and no history of hypertension)

Renal papillary necrosis: Differential diagnosis includes NSAIDs, diabetes, urinary tract obstruction, and sickle cell anemia/trait.

PART VI: ACUTE RENAL FAILURE

CASE 28:

A 54-year-old diabetic male is receiving medical therapy consisting of oral aspirin, beta-blockers, ACE inhibitor, and intravenous nitroglycerin for treatment of his angina and hypertension. He undergoes coronary angiography, which reveals no significant stenosis. He is normotensive. His fundus- copic examination shows dot hemorrhages and hard exudates, evidence of diabetic retinopathy. In this setting, the baseline elevated creatinine level on admission likely represents diabetic nephropathy as well. His creatinine level has risen to 2.9 mg/dL from 1.6 mg/dL on admission. By the next day, he has become oliguric.

> New clinical problem: Acute renal failure (ARF).

> Next step: Urinalysis and urine chemistries to determine whether the process is prerenal or renal, or less likely postrenal.

CASE DISCUSSION

Considerations

A 54-year-old man with diabetes, retinopathy, and some preexisting kidney disease develops ARF in the hospital, as indicated by the elevated serum creatinine level to 2.9 mg/dL and BUN of 69 mg/dL. He has undergone several medical therapies and procedures, all of which might be potentially contributory: acute lowering of his blood pressure, an ACE inhibitor, radiocontrast media, and arterial catheterization with possible atheroemboli. The mortality rate associated with critically ill patients who develop ARF is high; thus, identifying and treating the underlying etiology of this patient's kidney failure and taking measures to protect the kidneys from further damage are essential.

APPROACH TO ACUTE RENAL FAILURE

Definitions

ACUTE RENAL FAILURE (ARF): Abrupt decline in glomerular filtration rate (GFR). True GFR is difficult to measure, so we rely on increases in serum creatinine levels to indicate a fall in

GFR. Because creatinine is both filtered and secreted by the kidneys, changes in serum creatinine concentrations always lag behind and underestimate the decline in the GFR. In other words, by the time the serum creatinine level rises, the GFR has already fallen significantly. ANURIA: Less than 50 mL of urine output in 24 hours. Acute obstruction, cortical necrosis, and vascular catastrophes such as aortic dissection should be considered in the differential diagnosis.

OLIGURIA: Less than 400 mL of urine output in 24 hours. Physiologically, it is the lowest amount of urine a person on a normal diet can make if he or she is severely dehydrated and does not retain uremic waste products. Oliguria is a poor prognostic sign in ARF. Patients with oliguric renal failure have higher mortality rates and less renal recovery than do patients who are nonoliguric. UREMIA: Nonspecific symptoms of fatigue, weakness, nausea and early morning vomiting, itchiness, confusion, pericarditis, and coma attributed to the retention of waste products in renal failure but do not always correlate with the BUN level. A highly malnourished patient with renal failure may have a modestly elevated BUN and be uremic. Another patient may have a highly elevated BUN and be asymptomatic. Elevated BUN without symptoms is called azotemia.

Clinical approach

The differential diagnosis of ARF proceeds from consideration of three basic pathophysiologic mechanisms: prerenal failure, postrenal failure, and intrinsic renal failure. Individuals with prerenal failure experience diminished GFR as a result of a marked decreased renal blood perfusion so that less glomerular filtrate is formed. Sometimes, the clinical presentation is straightforward, such as volume depletion from gastrointestinal fluid loss or hemorrhage; at other times, the presentation of patients with prerenal failure can be more confusing. For example, a patient with severe nephrotic syndrome may appear to be volume overloaded because of the massive peripheral edema present, while the effective arterial blood volume may be very low as a consequence of the severe hypoalbuminemia. Yet the mechanism of this individual's ARF is prerenal. Similarly, a patient with severe congestive heart failure may have prerenal failure because of a low cardiac ejection fraction, yet be fluid overloaded with peripheral and pulmonary edema. The key is to assess "what the kidneys see" versus the remainder of the body. Typically, the BUN:Cr ratio is more than 20 in prerenal failure. Medications such as aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), and ACE inhibitors can alter intrarenal blood flow and result in prerenal failure. Table 29-1 provides an abbreviated listing of the etiologies of prerenal failure.

Postrenal failure, also referred to as obstructive nephropathy, implies blockage of urinary flow. The site of obstruction can be anywhere along the urinary system, including the intratubular region (crystals), ureters (stones, extrinsic compression by tumor), bladder, or urethra. By far, the most common causes of obstructive nephropathy are ureteral obstruction due to malignancy, or prostatic obstruction due to benign or malignant hypertrophy. The patient's symptoms depend on whether or not both kidneys are involved, the degree of obstruction, and the time course of the blockage. This is usually diagnosed by seeing hydronephrosis on renal ultrasound.

Intrinsic renal failure is caused by disorders that injure the renal glomeruli or tubules directly. These include glomerulonephritis, tubulointerstitial nephritis, and acute tubular necrosis (ATN) from either ischemia or nephrotoxic drugs. Table 28-2 lists major causes of intrinsic ARF.

Table 28-1. Causes of prerenal acute renal failure

True volume depletion	**Reduced effective arterial blood volume**
. Gastrointestinal losses	. Nephrotic syndrome
. Renal losses (diuretics)	. Cirrhosis with portal hypertension
	. Severe burns
	. Sepsis
	Systemic inflammatory response syndrome (SIRS)

Medications	Decreased cardiac output
. ACE inhibitors . NSAIDs	. Congestive heart failure . Pericardial tamponade

Table 28-2. Causes of intrinsic acute renal failure

Acute tubular necrosis	Glomerulonephritis	Tubulointerstitial nephritis
Nephrotoxic agents . Aminoglycosides . Radiocontrast . Chemotherapy **Ischemic** . Hypotension . Vascular catastrophe	. Postinfectious . Vasculitis immune complex diseases (lupus, MPGN [mesangioproliferative glomerulonephritis] cryoglobulinemia) cholesterol emboli syndrome . Hemolytic uremic syndrome/thrombotic thrombocytopenic purpura	. Medications (cephalosporins, methicillin, rifampin) . Infection (pyelonephritis, HIV)

Evaluation of a patient with ARF starts with a detailed history and physical examination. Does the patient have signs or symptoms of a systemic disease, such as heart failure or cirrhosis, that could cause prerenal failure? Does the patient have symptoms of a disease, such as lupus, that could cause a glomerulonephritis? Did the patient receive something in the hospital that could cause ATN, such as intravenous contrast or an aminoglycoside? While in the operating room did the patient become hypotensive from sepsis or from hemorrhage that caused ischemic ATN? Is the patient receiving an antibiotic and now has allergic interstitial nephritis? In addition to the history and physical examination, urinalysis and measurement of urinary electrolytes are helpful in making the diagnosis.

Urinalysis

The urine findings based on testing with reagent paper and microscopic examination help with the diagnosis of ARF (Table 28-3). In prerenal failure, urinalysis usually reveals a high specific gravity and normal microscopic findings. Individuals with postrenal failure typically are unable to concentrate the urine, so the urine osmolality is equal to the serum osmolality (isosthenuria) and the specific gravity is 1.010. The microscopic findings vary depending on the cause of the obstruction: hematuria (crystals or stones), leukocytes (prostatic hypertrophy), or normal (extrinsic ureteral compression from a tumor). Urinalysis of various intrinsic renal disorders may be helpful. Ischemic and nephrotoxic ATN usually is associated with urine that is isosthenuric, often with proteinuria, and containing "muddy brown" granular casts on microscopy. In glomerulonephritis, the urine generally reveals moderate to severe proteinuria, sometimes in the nephrotic range, and microscopic hematuria and red blood cell (RBC) casts. Tubulointerstitial nephritis classically produces urine that is isosthenuric (the tubules are unable to concentrate the urine), with mild proteinuria, and on microscopy, reveals leukocytes, white cell casts, and urinary eosinophils.

Urinary electrolytes

Measurement of urinary electrolytes and calculation of the fractional excretion of sodium (FENa) were devised to differentiate oliguric prerenal failure from oliguric ATN; they are of little use in other circumstances. FENa represents the amount of sodium filtered by the kidneys that is not reabsorbed. The kidneys of a healthy person on a normal diet usually reabsorb more than 99% of the sodium that is filtered, with a corresponding FENa less than 1%. Normally, the excreted sodium represents the dietary intake of sodium, maintaining sodium homeostasis. In prerenal failure, decreased renal perfusion leads to a diminished GFR; if the renal tubular function is intact,

FENa remains less than 1%. Furthermore, because the patient has either true volume depletion or "effective" volume depletion, serum aldosterone will stimulate the kidneys to retain sodium, and the urinary sodium will be low (<20 mEq/L). On the other hand, in oliguric ATN, the renal failure is caused by tubular injury. Hence, there is tubular dysfunction with an associated inability to reabsorb sodium, leading to an FENa more than 2% and a urinary sodium more than 20 mEq/L.

Table 28-2. Urine findings based on testing with reagent paper and microscopic examination

Etiology of renal failure	Urinalysis		U_{Na}
Prerenal failure	Concentrated (high specific gravity) with normal sediment	<1%	<20 mEq/L
ATN	Isosthenuric with muddy brown granular casts	>1%	>20 mEq/L
Glomerulonephritis	Moderate to severe proteinuria with red blood cells and red blood cell casts	<1%	Variable
Interstitial nephritis	Mild to moderate proteinuria with red and white blood cells and white blood cell casts	>1%	>20 mEq/L
Postrenal failure	Variable depending on cause	<1% (early) >1% (later)	<20 mEq/L (early) >20 mEq/L (later)

***Abbreviation**: U_{Na}, Urinary concentration of sodium*

Measurements of FENa and urinary sodium are less helpful in other circumstances. For example, in nonoliguric ATN, the injury usually is less severe, so the kidneys still may maintain sodium reabsorption and be able to produce an FE less than 1%. Diuretic medications, which interfere with sodium reabsorption, are often used in congestive heart failure or nephrotic syndrome. Although these patients may have prerenal failure, the use of diuretics will increase the urinary sodium and FENa. In acute glomerulonephritis, the kidneys often avidly resorb sodium, leading to very low urinary sodium levels and

FENa. Early in the course of postobstructive renal failure caused by ureteral obstruction, the afferent arteriole typically undergoes intense vasoconstriction, with consequent, low urinary sodium levels.

The indications for dialysis in ARF include fluid overload, such as pulmonary edema, metabolic acidosis, hyperkalemia, uremic pericarditis, severe hyperphosphatemia, and uremic symptoms. Because of the risk of fatal cardiac arrhythmias, severe hyperkalemia is considered an emergency, best treated acutely medically and not with dialysis. An urgent electrocardiogram (ECG) should be performed on any patient with suspected hyperkalemia; if the classic peaked or "tented" T waves are present, intravenous calcium should be administered immediately. Although it will not lower the serum potassium level, the calcium will oppose the membrane effects of the high potassium concentration on the heart, allowing time for other methods to lower the potassium level. One of the most effective methods for treating hyperkalemia is administration of intravenous insulin (usually 10 units), along with 50 to 100 mL of 50% glucose solution to prevent hypoglycemia. Insulin drives potassium into cells, lowering levels within 30 minutes. Potassium also can be driven intracellularly with a beta-agonist, such as albuterol by nebulizer. In the presence of a severe metabolic acidosis, administration of intravenous sodium bicarbonate also promotes intracellular diffusion of potassium, albeit less effectively. All three therapies have only a transient effect on serum potassium levels, because the total body potassium balance is unchanged, and the potassium eventually leaks back out of the cells. Definitive treatment of hyperkalemia, removal of

potassium from the body, is accomplished by one of three methods: (1) administration of a loop diuretic such as furosemide to increase urinary flow and excretion of potassium, or, if the patient does not make sufficient urine, (2) administration of sodium polystyrene sulfonate (Kayexalate), a cationic exchange resin that lowers potassium by exchanging sodium for potassium in the colon, or, finally, (3) emergency dialysis.

Comprehension questions

1.A 63-year-old woman with a history of cervical cancer treated with hysterectomy and pelvic irradiation now presents with acute oliguric renal failure. On physical examination, she has normal jugular venous pressure, is normotensive without orthostasis, and has a benign abdominal examination. Her urinalysis shows a specific gravity of 1.010, with no cells or casts on microscopy. Urinary FENa is 2%, and the Na level is 35 mEq/L. Which of the following is the best next step?

A. Bolus of intravenous fluids
B. Renal ultrasound
C. Computed tomographic (CT) scan of the abdomen with intravenous contrast
D. D. Administration of furosemide to increase her urine output

2.A 49-year-old man with a long-standing history of chronic renal failure as a consequence of diabetic nephropathy is brought to the emergency room for nausea, lethargy, and confusion. His physical examination is significant for an elevated jugular venous pressure, clear lung fields, and harsh systolic and diastolic sounds heard over the precordium. Serum chemistries reveal K 5.1 mEq/L, CO217 mEq/L, BUN 145 mg/dL, and creatinine 9.8 mg/dL. Which of the following is the most appropriate therapy?

A. Administer IV insulin and glucose.
B. Administer IV sodium bicarbonate.
C. Administer IV furosemide.
D. Urgent hemodialysis.

3.A 62-year-old diabetic man underwent an abdominal aortic aneurysm repair 2 days ago. He is being treated with gentamicin for a urinary tract infection. His urine output has fallen to 300 mL over 24 hours, and his serum creatinine has risen from 1.1 mg/dL on admission to 1.9 mg/dL. Which of the following laboratory values would be most consistent with a prerenal etiology of his renal insufficiency?

A. FENa of 3%
B. Urinary sodium level of 10 mEq/L
C. Central venous pressure reading of 10 mm Hg
D. Gentamicin trough level of 4 pg/mL

Answers

1.B. Renal ultrasound is the next appropriate step to assess for hydronephrosis and to evaluate for bilateral ureteral obstructions, which are common sites of metastases of cervical cancer. Her physical examination and urine studies (showing a FE > 1%) are inconsistent with hypovolemia, so intravenous infusion is unlikely to improve her renal function. Use of loop diuretics may increase her urine output somewhat but does not help to diagnose the cause of her renal failure or to improve her outcome. Further imaging may be necessary after the ultrasound, but use of intravenous contrast at this point may actually worsen her renal failure.

2.D. The patient has uremia, hyperkalemia, and (likely) uremic pericarditis, which may progress to life-threatening cardiac tamponade unless the underlying renal failure is treated with dialysis. As for the other treatments, insulin plus glucose would treat hyperkalemia, and bicarbonate would help with both metabolic acidosis and hyperkalemia, but in this patient, his potassium and bicarbonate levels are only mildly abnormal and are not immediately life-threatening. Furosemide

will not help because he does not have pulmonary edema.

3.B. Prerenal insufficiency connotes insufficient blood volume, typically with FENa less than 1% and urinary sodium less than 20 mEq/L. Supporting information would be a low central venous pressure reading (normal central venous pressure is 4-8 mm Hg). The gentamicin level of 4 pg/mL is elevated (normal <2 pg/mL) and may predispose to kidney damage.

Clinical pearls

- The two main causes of renal failure in hospitalized patients are prerenal azotemia and acute tubular necrosis.
- In the anuric patient, one must quickly determine if the kidneys are obstructed or if the vascular supply is interrupted.
- Treatment of prerenal renal failure is volume replacement; treatment of postrenal failure is relief of the obstruction.
- The main causes of postrenal failure are obstruction caused by prostatic hypertrophy in men and bilateral ureteral obstruction caused by abdominal or pelvic malignancy in either gender.
- Uremic pericarditis is an indication for urgent hemodialysis. Other indications include hyperkalemia, metabolic acidosis, severe hyperphosphatemia, and volume overload when refractory to medical management.
- Treatment of hyperkalemia: C BIG K (calcium, bicarbonate/beta-agonist, insulin, glucose, Kayexalate).
- Hyperkalemia is treated initially with calcium to stabilize cardiac membranes; insulin and beta-agonists to redistribute potassium intracellularly (sodium bicarbonate if there is a severe metabolic acidosis); and then loop diuretics, a potassium exchange resin, or hemodialysis to remove excess potassium from the body.
- Indications for dialysis: AEIOU (acidosis, electrolyte disturbances, ingestions, overload, uremia).

ANSWERS TO CASE 29:

What are the next steps in management?

General measures in all types of ARF are as follows:

- Fluids and electrolytes: Correct any imbalances if present.
- Nephrotoxins: Discontinue nephrotoxic agents.
- Nutrition: Provide adequate calories; restrict protein and potassium.
- Infection: Minimize indwelling lines and catheters to decrease infection risk.

This patient with pitting edema and oliguria should receive loop diuretics. Also, administer Kayexalate to treat hyperkalemia. Eliminate the offending agent, which in this case is the recently initiated NSAID. Do not discontinue the ACE inhibitor at this time because it improves mortality in patients with hypertension and diabetes, and renal function was stable on the ACE inhibitor prior to initiating ibuprofen.

Fluid imbalances:

- Volume depletion: Suspect if the patient has hypotension/orthostatic hypotension, tachycardia, dry mucous membranes, and weight loss. Treat with normal saline.
- Volume overload: Suspect if the patient has weight gain, peripheral/pulmonary edema, or urine output <1mL/kg per hour. Treat with loop diuretics such as furosemide (lasix).

Electrolyte imbalances in ARF:

- Hyperkalemia and metabolic acidosis: Most common electrolyte abnormalities.
- Hypo- or hypernatremia: Also common abnormalities.

What is the cause of ARF?

The laboratory findings indicate that the patient has prerenal ARF (see Table 6-5). The kidneys reabsorb sodium and water as if in response to volume depletion, so urine osmolality and specific gravity are high while FeNa and urine sodium are low. Also, BUN is reabsorbed out of proportion to decrease in GFR, so the ratio is high (>20).

What are the indications for urgent dialysis?

Urgent dialysis is indicated in the following settings ("AEIOU"):

- Acidosis (metabolic): pH remains <7.1 despite treatment.
- Electrolytes: Hyperkalemia or sodium imbalances persist despite treatment.
- Intoxication with a dialyzable toxin (lithium, methanol, or ethylene glycol).
- Overload of volume (peripheral or pulmonary edema) refractory to diuretics.
- Uremic pericarditis, encephalopathy, or bleeding.

CASE DISCUSSION

What do elevated BUN and serum creatinine indicate?

Elevated serum creatinine and BUN indicate reduced glomerular filtration rate (GFR). Of the two, serum creatinine is more helpful because BUN can increase independent of GFR in patients with increased dietary protein intake and increased catabolism (steroids, surgery, infection, etc.). A slow increase in serum creatinine over months or years indicates chronic renal insufficiency (CRI), also called chronic kidney disease (CKD). A rapid increase in serum creatinine ≥0.5 mg/dL in ≤2 weeks indicates acute renal failure (ARF). This patient has ARF superimposed on underlying CKD.

Research criteria for ARF:

- All patients: Serum creatinine increases by ≥0.5 mg/dL in ≤2 weeks.
- Baseline creatinine >2.5 mg/dL: Serum creatinine increases by ≥20% in ≤2 weeks.

Increased serum creatinine occurs after >50% of nephrons are destroyed.

What are the clinical manifestations of acute and chronic renal failure?

Many patients present with asymptomatic azotemia. Others may present with any of the signs, symptoms, or laboratory abnormalities of uremia (Table 29-1).

What are the causes of ARF?

There are three broad categories of ARF:

- Prerenal failure (60% to 70%): caused by decreased blood flow to the kidney.
- Intrinsic renal failure (25% to 40%): caused by damage to the renal parenchyma.
- Postrenal failure (5% to 10%): caused by obstruction of the urinary outflow tract.

What is the next diagnostic step?

Order the following tests to determine the category of renal failure (Table 27-3):

- Blood: complete blood count, culture, and chemistries.
- Urine: urinalysis, osmolality, sodium, fractional sodium excretion (FeNa), and creatinine.
- Bladder catheterization: Suspect postrenal obstruction if a large volume of urine flows on inserting the catheter. This maneuver is also therapeutic.

A large volume of urine does not flow upon insertion of the bladder catheter. Complete blood count is within normal limits. Urine osmolality is 700 mOsm/kg, urine sodium is 12 mEq/L, FeNa is 0.6%, serum BUN/creatinine is 23. Urine output is 10 mL/hour (240 mL/day). Urine dipstick findings are specific gravity 1.025 and no protein or blood. Urine sediment reveals few hyaline casts. Hansel's stain is negative.

FeNa is 0.6%, serum BUN/creatinine is 23. Urine output is 10 mL/hour (240 mL/day). Urine dipstick findings are specific gravity 1.025 and no protein or blood. Urine sediment reveals few hyaline casts. Hansel's stain is negative.

TABLE 29–1. Clinical manifestations of uremia

General	**Fatigue**: A major cause of fatigue is *anemia*. Renal failure leads to anemia because the kidney cannot produce sufficient erythropoietin. **Uremic fetor**: Toxic metabolites give breath ammonia-like smell.
Neuro	**Encephalopathy**: Toxic metabolites enter the central nervous system and lead to asterixis and altered mental status. **Peripheral neuropathy**: Pain and paresthesia in lower extremities; mechanism is unclear.
ENT	**Red eye**: Mechanism is unclear. **Nosebleeds**: Uremia leads to thrombocytopenia.
CV	**Uremic pericarditis**: Signs and symptoms of pericarditis are present but there is no characteristic diffuse ST elevation on EKG; cause is unclear. **Arrhythmias**: Because of electrolyte and acid–base disturbances. **Pre-existing heart failure and hypertension worsen**: The kidney cannot excrete sufficient fluid.
Lungs	**Pulmonary edema**: The kidney cannot excrete sufficient fluid.
Gastrointestinal	**Nausea, vomiting, anorexia**: Cause is unclear but symptoms can lead to malnutrition (hypoalbuminemia). **Occult gastrointestinal bleeding**: Another cause of anemia in renal failure, toxic metabolites cause erosive gastritis and colitis; uremia also leads to thrombocytopenia (increased risk of mucosal bleeding).
Skin	**Uremic frost**: Sweat contains excess urea; when sweat evaporates, a powdery white residue remains on skin. **Pruritis**: The kidney cannot remove excess calcium phosphate, which deposits on skin and leads to itching. Hyperpigmentation and velvety skin
Extremities	**Peripheral edema**: The kidney cannot excrete sufficient fluid
MSK pain	**Muscle cramps**: The kidney cannot excrete normal potassium load, which leads to *hyperkalemia* (responsible for muscle cramps). **Renal osteodystrophy**: The kidney cannot hydroxylate vitamin D. Decreased hydroxylated vitamin D leads to decreased calcium absorption from the gastrointestinal tract. *Hypocalcemia* activates secondary hyperparathyroidism, which leads to bone resorption and *hyperphosphatemia*.
Endocrine	**Impotence and infertility**: Production of sex hormone is decreased. **Glucose control**: Kidney clearance of insulin is decreased, so hyperglycemia normalizes in diabetics; however, diabetics have increased risk of hypoglycemic episodes.
Acid–base	***Anion gap metabolic acidosis*** : The kidney cannot regulate metabolic acid–base balance so lactic acid, phosphate, etc., accumulate.

Abbreviation*: MSK, musculoskeletal.*

Note*: Laboratory abnormalities are italicized (anemia, hypoalbuminemia, thrombocytopenia, hyperkalemia, hypocalcemia, hyperphosphatemia, anion gap metabolic acidosis).*

TABLE 29–2. Major causes of acute renal failure

Prerenal failure	
Hypovolemia	Hemorrhage, third spacing (pancreatitis, burns, etc.), vomiting, diarrhea, or decreased fluid intake
Systemic vasodilation	Septic shock, general anesthesia
Decreased cardiac output	Congestive heart failure
Renal vasoconstriction	Hepatorenal syndrome and contrast dyes
Macrovascular disease	RAS, malignant hypertension, emboli (from atherosclerosis, cholesterol, endocarditis)
Drugs	• NSAIDs: prostaglandin (a vasodilator) inhibition • ACE inhibitors/ARBs: angiotensin II (a vasoconstrictor) inhibition. • Vasodilation in the setting of hypovolemia or RAS can decrease renal perfusion. • Tacrolimus, Cyclosporine: cause renal vasoconstriction • Diuretics: cause hypovolemia
Acute tubular necrosis	
Ischemia	Progression of prerenal disease
Toxins	• Pigments: myoglobinuria (secondary to rhabdomyolysis), hemoglobinuria (secondary to hemolysis) • Drugs: Aminoglycosides, Cisplatin, Amphotericin Contrast dyes • Proteins (e.g., light-chain proteins in multiple myeloma) • Crystals (most commonly uric acid crystals)
Acute interstitial nephritis (acronym to remember causes is A(a)I(i)N)	
Allergy to drug	Most common drugs are Penicillins, Allopurinol, Cephalosporins, Ciprofloxacin, Rifampin, Sulfonamides such as TMP/SMX, NSAIDs.
Autoimmune disorders	Systemic lupus erythematosus, etc.
Infection	Bacterial or viral
Infiltration	Sarcoidosis, etc.
Neoplasms	
Microvascular ARF: TTP/HUS, HELLP syndrome, vasculitis	
Acute glomerulonephritis	
Postrenal failure: BPH, prostate and cervical cancers, neurogenic bladder (bladder nerve damage due to diabetes, spinal cord injury, etc., causes loss of voluntary voiding)	

Abbreviations: *ACE, angiotensin-converting enzyme; AIN, acute interstitial nephritis; ARB, angiotensin receptor blocker; ARF, acute renal failure; ATN, acute tubular necrosis; BPH, benign prostatic hyperplasia; HELLP, obstetric complication (hemolytic anemia, elevated liver enzymes, and low platelet count); HUS, hemolytic uremic syndrome; NSAID, nonsteroidal anti-inflammatory drug; RAS, renal artery stenosis; TMP/SMX, trimethroprim/sulfamethoxazole; TTP, thrombotic thrombocytopenic purpura.*

Notes:

1. *Contrast dyes can cause prerenal failure or ATN.*
2. *NSAIDs can cause prerenal failure or AIN.*
3. *Cephalosporins, TMP/SMX can cause AIN or false-positive increased serum creatinine.*

4. Drug mnemonics:

- *Prerenal failure: " NAT Cole Died PREmaturely."*
- *ATN: " Aminoglycosides Cause ATN."*
- *AIN: " Penicillin Allergies Can Cause Really Severe Nephritis."*

Intrinsic renal failure is categorized on the basis of primary site of injury:

- *Acute tubular necrosis (85%): renal tubule damage.*
- *Acute interstitial nephritis (10%): immune-mediated renal interstitial damage.*
- *Acute glomerulonephritis (5%): glomerular damage*
- *Microvascular ARF (uncommon)*

Table 29–3. Laboratory findings in ARF

Urine and serum labs			
	Prerenal ARF	**Intrinsic ARF**	**Postrenal ARF**
Urine osmolality	>500 mOsm/kg	<500 mOsm/kg	<500 mOsm/kg
FeNa	<1%	>1%	<1% (early)
			>1% (few days)
Urine sodium	<20 mEq/L	>20 mEq/L	<20 mEq/L (early)
			>20 mEq/L (few days)
Urine volume	Oliguria	Oliguria or normal	Oliguria or anuria
Serum BUN/creatinine	>20	<20	<20

Urine dipstick

Type of ARF	**Dipstick Protein**	**Dipstick Blood**	**Specific Gravity**
Prerenal	-	-	>1.02
ATN a	Trace	-	1.01-1.02
AIN	+	+	1.01-1.02
Glomerulonephritis	++	++	1.01-1.02
Postrenal	-	-	

Urine sediment

Benign sediment: Normal patients; prerenal and postrenal ARF.
Hyaline casts: Nonspecific, clear, cylindrical casts made up of Tamm-Horsfall protein.
Granular casts: Nonspecific marker of kidney damage.
Muddy brown casts: Coarse, granular, pigmented, cigar-shaped casts indicate ATN.
Broad or waxy casts: Wide casts with cracked edges indicate advanced ATN.
Pigment casts: Reddish gold casts indicate myoglobinuria or hemoglobinuria.
Fatty casts: Hyaline casts with yellow fat globules that appear as a "Maltese cross" under polarized light indicate nephrotic syndrome.
WBC casts: Casts with WBCs indicate inflammation (pyelonephritis, AIN, GN).
RBC casts: Casts with RBCs indicate glomerulonephritis.
Dysmorphic RBCs: Indicate glomerulonephritis; also seen in TTP/HUS.
Hansel's stain: Stains eosinophils bright red; positive stain indicates AIN.

Abbreviations: *GN, glomerulonephritis; RBC, red blood cells; WBC, white blood cells, BUN, blood urea nitrogen; FeNa, fractional sodium excretion.*

1. Urine volume: Normal, 400 mL/day; oliguria, 100–400 mL/day; anuria, <100 mL/day.

2. Complete blood count: Thrombocytopenia and hemolytic anemia are seen in TTP/HUS and HELLP syndrome, and increased eosinophils are seen in AIN.

3. Acute glomerulonephritis, contrast-induced ATN: FeNa is often <1%.

a ATN due to rhabdomyolysis: Urine may be red, but supernatant and sediment are clear. Urine dipstick is positive for blood in 50% of cases, but no RBCs are found on sediment analysis. Key laboratory finding is increased creatinine kinase. ATN due to hemolysis: Urine may be red and supernatant is red, but sediment is clear. Urine dipstick is positive for blood, but no RBCs are found on sediment analysis.

ANSWERS TO CASE 30:

What is the cause of ARF?

This patient has intrinsic ARF. The most likely cause is ATN from the contrast agent. Contrast nephropathy can cause nonoliguric ARF within 12 to 24 hours of administration, particularly in patients with underlying chronic renal failure like this patient.

How is intrinsic renal failure treated?

As with other types of ARF, monitor for and treat any fluid and electrolyte imbalances, discontinue nephrotoxins, provide adequate nutrition, and minimize infection risk. Most patients with contrast nephropathy recover in 3 to 5 days.

Measures to prevent contrast nephropathy if baseline creatinine is ≥1.5:

- IV normal saline and N-acetylcysteine before and after contrast administration.
- Avoid high osmolality ionic contrast (use nonionic agents such as gadolinium instead).

ANSWERS TO CASE 31:

What is the cause of ARF?

The patient has intrinsic renal failure due to ATN. The cause of ATN is rhabdomyolysis (see Table 6-5). Crush injuries cause skeletal muscle breakdown (rhabdomyolysis). Muscle breakdown leads to release of myoglobin, potassium, uric acid, and phosphate from cells. Myoglobin spills into urine and causes ATN.

- Not all cases of rhabdomyolysis result in ARF.
- Patients with advanced ARF due to rhabdomyolysis may not have myoglobinuria.

What are the major causes of rhabdomyolysis in adults?

- Trauma: crush injuries, burns, electrical shock, surgery, excessive physical exertion, and coma (local muscle compression).
- High fever: malignant hyperthermia, neuroleptic malignant syndrome.
- Toxins/drugs: alcohol, lovastatin, etc.

What fluid and electrolyte abnormalities commonly occur in rhabdomyolysis?

- Hyperkalemia, hyperphosphatemia, hyperuricemia
- Metabolic acidosis: because cells release phosphate and uric acid.
- Hypocalcemia: because phosphate binds to calcium.
- Hypovolemia: because plasma water gets sequestered in injured myocytes.

What are the next steps in management?

- Order creatinine kinase: increased creatinine kinase confirms the diagnosis.

- Fluids: Administer normal saline to all patients with rhabdomyolysis (even if normovolemic) to stimulate diuresis. Patients often require a large volume of fluids. If urine output is not sufficient, consider mannitol to stimulate diuresis.
- Correct any electrolyte imbalances, particularly hyperkalemia. Provide adequate nutrition and minimize infection risk. Remember indications for urgent dialysis.

Hypercalcemia: may develop after ARF resolves because the kidney produces increased vitamin D.

ANSWERS TO CASE 32:

What is the cause of ARF?

This patient has a number of risk factors for ARF. Lisinopril and ibuprofen can cause prerenal failure. Streptococcal infection, amoxicillin, and ibuprofen can cause acute interstitial nephritis (AIN). Fever, rash, and laboratory findings indicate that the cause of ARF is AIN.

Classic triad of AIN: Fever, rash, and eosinophilia/eosinophiluria. Only 10% of AIN presents with classic triad. Triad is most common in penicillin-induced AIN.

What is the next step in management?

This patient does not appear to have any fluid and electrolyte imbalances, so the next step is to discontinue offending medications (amoxicillin and ibuprofen). Most patients will recover in 3 to 5 days.

Amoxicillin and ibuprofen are discontinued. Three days later, creatinine is 2.8 mg/dL.

If azotemia persists or increases after 3 to 5 days in patients with suspected AIN, perform renal biopsy to confirm the diagnosis. If biopsy confirms AIN, consider treatment with oral or IV steroids.

NSAID-induced AIN: Studies have not shown any benefit from steroids.

ANSWERS TO CASE 33:

What is the next step in management?

ARF is most likely caused by postrenal obstruction in this patient with anuria, distended bladder, and withdrawal of copious urine on bladder catheterization. The next step is to confirm the diagnosis with renal ultrasound, which should demonstrate hydronephrosis. If ultrasound confirms the diagnosis, identify and treat the underlying cause. If ultrasound is not diagnostic, obtain urine and serum labs to rule out prerenal and intrinsic ARF. As with all other types of ARF, correct any fluid or electrolyte imbalances, discontinue nephrotoxins, provide adequate nutrition, and minimize infection risk. Remember the indications for urgent dialysis (“AEIOU”).

ANSWERS TO CASE 34:

What are the causes of this patient’s acute renal failure?

This patient has postoperative acute renal failure due to a combination of intra-abdominal sepsis and aminoglycoside nephrotoxicity. Her sepsis is due to an anastomotic leak with a localized peritonitis which has been partially controlled with antibiotics. Her sepsis syndrome is manifested by fever, tachycardia, hypotension, hypoglycaemia, metabolic acidosis (low bicarbonate) and oliguria. The low sodium and high potassium are common in this condition as cell membrane function becomes less effective. The elevated white count is a marker for bacterial infection and the low platelet count is part of the picture of disseminated intravascular coagulation. Jaundice and

abnormal liver function tests are common features of intraabdominal sepsis. Aminoglycosides (gentamicin, streptomycin, amikacin) cause auditory and vestibular dysfunction, as well as acute renal failure. Risk factors for aminoglycoside nephrotoxicity are higher doses and duration of treatment, increased age, pre-existing renal insufficiency, hepatic failure and volume depletion. Aminoglycoside nephrotoxicity usually occurs 7-10 days after starting treatment. Monitoring of trough levels is important although an increase in the trough level generally indicates decreased excretion of the drug caused by a fall in the glomerular flow rate. Thus, nephrotoxicity is already established by the time the trough level rises.

How would you further investigate and manage this patient?

This patient needs urgent resuscitation. She requires transfer to the intensive care unit where she will need invasive circulatory monitoring with an arterial line and central venous pressure line to allow accurate assessment of her colloid and inotrope requirements. She also needs urgent renal replacement therapy to correct her acidosis and hyperkalaemia. In a haemodynamically unstable patient like this, continuous haemofiltration is the preferred method. The patient also needs urgent surgical review. The abdomen should be imaged with either ultrasound or computed tomography (CT) scanning to try to identify any collection of pus. Once haemodynamically stable, the patient should have a laparotomy to drain any collection and form a temporary colostomy.

Clinical pearls

- Postoperative acute renal failure is often multifactorial due to hypotension, sepsis and the use of nephrotoxic drugs such as aminoglycosides and non-steroidal anti-inflammatory drugs (NSAIDs).
- Aminoglycoside drugs are extremely valuable for treating Gram-negative infections, but levels must be monitored to avoid toxicity.
- Sepsis syndrome must be recognized early and treated aggressively to reduce the morbidity and mortality of this condition.