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**KIDNEY DISEASES: DEFINITIONS, DIAGNOSIS AND
APPROACHES TO PREVENTION AND TREATMENT
MODULE # 2**

*The executive task force
for students of medical faculty of 5th year of studying*

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The executive task force is provided to the students of medical institutions of higher education for self-education on some topics in the fields of nephrology incorporated onto discipline of «Internal Medicine». There is information about most important topics regarding diagnosis of renal diseases.

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Index of acronyms

AKIN	Acute Kidney Injury Network
BSA	body surface area
BOO	bladder outlet obstruction
CKD –	chronic kidney disease
CRP	C-reactive protein
CT	computed tomography
CTD	connective tissue disease
FENa	fractional excretion of Na
HPF	high-power field
GFR	glomerular filtration rate
RBC	red blood cells
RIFLE	Risk–Injury–Failure–Loss–Endstage renal disease
SSA	sulfosalicylic acid
NP	nocturnal polyuria
OAB	overactive bladder syndrome

PREFACE

The task force is addressed to students of 5th course of medical university for helping to study of some parts of internal medicine in field of kidney diseases. It includes the use of contemporary tools for identification of glomerular diseases, pyelonephritis, kidney amyloidosis, tubulointerstitial nephritis including objectives, laboratory studies, genetic investigations, biopsy materials, X-ray, multidetector CT, angiography, MRI procedures. Etiology and pathophysiology are discussed also separately for each of kidney disorders. Diagnostic algorithm and procedures choosing are considered obligatory with an elucidation of contemporary management and prevention of kidney diseases. This book has been written in a concise and easy assimilable style to enable rapid understanding of the kidney diseases. Hopefully, in some way, all of the effort and expertise brought together here will help advance this field.

Authors

CHAPTER 1

BASIC SIGNS AND SYMPTOMS OCCURRED IN KIDNEY DISEASES

1.1 Evaluation of the Renal Patient

In patients with renal disorders, symptoms and signs may be nonspecific, absent until the disorder is severe, or both. Findings most often are local (eg, reflecting kidney inflammation or mass), result from the systemic effects of kidney dysfunction, or affect urination (eg, changes in urine itself or in urine production).

History

History plays a limited role because symptoms are nonspecific. Hematuria is relatively specific for a GU disorder, but patients who report red urine may instead have one of the following:

- Myoglobinuria
- Hemoglobinuria
- Porphyrinuria
- Porphobilinuria
- Food-induced urine coloring (some foods, eg, beets, rhubarb, sometimes food coloring, may make urine appear red)
- Drug-induced urine coloring (some drugs, most commonly phenazopyridine, but sometimes cascara, diphenylhydantoin, methyldopa, phenacetin, phenindione, phenolphthalein, phenothiazines, and senna may make urine appear red)

High concentrations of urinary protein cause frothy or sudsy urine. Urinary frequency should be distinguished from polyuria in patients who report excessive urination. Nocturia may be a feature of either but is often the result of excess fluid intake too close to bedtime or of chronic kidney disease. Family history is useful for identifying inheritance patterns and risk of polycystic kidney disease or other hereditary nephropathies (eg, hereditary nephritis, thin basement membrane disease, nail-patella syndrome, cystinuria, hyperoxaluria).

Physical Examination

Patients with moderate or severe chronic kidney disease sometimes appear pale, wasted, or ill. Deep (Kussmaul's) respirations suggest hyperventilation in response to metabolic acidosis with acidemia.

Chest examination

Pericardial and pleuritic friction rubs may be signs of uremia.

Abdominal examination

Visual fullness of the upper abdomen is an unusual, nonspecific finding of polycystic kidney disease. It may also indicate a kidney or abdominal mass or hydronephrosis. A soft, lateralizing bruit is occasionally audible in the epigastrium or the flank in renal artery stenosis; presence of a diastolic component increases the probability of renovascular hypertension. Pain elicited by mild striking of the back, flanks, and angle formed by the 12th rib and lumbar spine with a fist (costovertebral tenderness) may indicate pyelonephritis or urinary tract obstruction (eg, due to calculi). Normal kidneys are not usually palpable. However, in some women, the lower pole of the right kidney can occasionally be felt with palpation during deep inspiration, and large kidneys or masses can sometimes be felt without special maneuvers. In neonates, the kidneys can be felt with the thumbs when the thumbs are placed anterior and the fingers posterior to the costovertebral angle. Transillumination can distinguish solid from cystic renal masses in some children < 1 yr if the kidney and mass are manipulated against the abdominal wall.

Skin examination

Chronic kidney disease can cause any of the following:

- Xerosis due to sebaceous and eccrine sweat gland atrophy
- Pallor due to anemia
- Hyperpigmentation due to melanin deposition
- Sallow or yellow-brown skin due to urochrome deposition
- Petechiae or ecchymoses due to platelet dysfunction

Uremic frost, the deposition of white-to-tan urea crystals on the skin after sweat evaporation, is rare.

Neurologic examination

Patients with acute renal failure may be drowsy, confused, or inattentive; speech may be slurred. Asterixis can be detected in handwriting or by observation of outstretched hands maximally extended at the wrists; after several seconds in this position, a hand flap in the flexor direction is asterixis. Asterixis suggests one of the following:

- Chronic kidney disease
- Chronic liver failure
- CO₂ narcosis

Testing

Urinalysis and measurement of serum creatinine are the initial steps in evaluation of renal disorders. Other urine, blood, and imaging tests (eg, ultrasonography, CT, MRI) are done in specific circumstances. Ideally, after the urethral meatus is cleaned, the urine specimen is collected midstream (clean-catch specimen) during the first void of the morning; the urine should be examined immediately because delays can lead to changes in test results. Bladder catheterization or suprapubic aspiration can be used for collection when urine cannot be obtained by spontaneous voiding or when vaginal material contaminates the urine specimen. However, the trauma of catheterization may falsely increase the number of RBCs in the specimen, so catheterization is usually avoided if the outcome of interest is microscopic hematuria. A specimen from a catheter collection bag is not acceptable for microscopic or bacteriologic tests.

Urinalysis

A complete urinalysis includes the following:

- Inspection for color, appearance, and odor
- Measurement of pH, specific gravity, protein, glucose, RBCs, nitrites, and WBC esterase by dipstick reagents
- Microscopic analysis for casts, crystals, and cells (urine sediment)

Bilirubin and urobilinogen, although standard parts of many dipstick tests, no longer play significant roles in evaluation of renal or hepatic disorders.

Color is the most obvious of urine attributes, and observation of color is an integral part of urinalysis. Urine color may suggest possible causes and help direct additional testing.

Odor, often unintentionally noted during visual inspection, conveys useful information only in rare cases of inherited disorders of amino acid metabolism when urine has a distinctive smell (eg, maple syrup in maple syrup urine disease, sweaty feet in isovaleric acidemia, tomcat urine in multiple carboxylase deficiency)

pH is normally 5.0 to 6.0 (range 4.5 to 8.0). Measuring with a glass pH electrode is recommended when precise values are necessary for decision making, as when diagnosing renal tubular acidosis; in these cases, a layer of mineral oil should be added to the urine specimen to prevent escape of CO₂. Delay in processing a specimen may elevate pH because ammonia is released as bacteria break down urea. Infection with urease-producing pathogens can spuriously increase pH.

Specific gravity provides a rough measure of urine concentration (osmolality). Normal range is 1.001 to 1.035; values may be low in the elderly or in patients with impaired renal function, who are less able to concentrate urine. It is measured by hydrometer or refractometer or estimated with a dipstick. Accuracy of the dipstick test is controversial, but the test may be sufficient for patients who have calculi and are advised to self-monitor urine concentration to maintain dilute urine. Specific gravity by dipstick may be spuriously elevated when urine pH is < 6 or low when pH is > 7. Hydrometer and refractometer measurements may be elevated by high levels of large molecules (eg, radiopaque contrast agent, albumin, glucose, carbenicillin) in the urine.

Protein, detected by standard dipstick tests, reflects mainly urinary albumin concentration, classified as negative (< 10 mg/dL), trace (15 to 30 mg/dL), or 1+ (30 to 100 mg/dL) through 4+ (> 500 mg/dL). Microalbuminuria, an important marker for renal complications in patients with diabetes, is not detected by standard dipsticks, but special microalbumin dipsticks are available. Light-chain proteins (eg, due to multiple myeloma) also are not detected. Significance of proteinuria depends on total protein excretion rather than protein concentration estimated by dipstick;

thus, when proteinuria is detected with dipstick testing, quantitative measures of urinary protein should be done. False-negative results can be caused by dilute urine. False-positive results can be caused by any of the following:

- High pH (> 9)
- Presence of cells
- Radiopaque contrast agents
- Concentrated urine

Glucose usually appears in the urine when serum glucose increases to > 180 mg/dL (> 10.1 mmol/L) and renal function is normal. Threshold for detection by urine dipstick is 50 mg/dL (2.8 mmol/L). Any amount is abnormal. Falsely low or negative results can result from any of the following:

- Ascorbic acid
- Ketones
- Aspirin
- Levodopa
- Tetracycline
- Very high urine pH
- Dilute urine

Hematuria is detected when RBCs lyse on a dipstick test strip, releasing Hb and causing a color change. Range is from negative (0) to 4+. Trace blood (corresponding to 3 to 5 RBCs/high-power field [HPF]) is normal under some circumstances (eg, exercise) in some people. Because the test strip reagent reacts with Hb, free Hb (eg, due to intravascular hemolysis) or myoglobin (eg, due to rhabdomyolysis) causes a positive result. Hemoglobinuria and myoglobinuria can be distinguished from hematuria by the absence of RBCs on microscopic examination and by the pattern of color change on the test strip. RBCs create a dotted or speckled pattern; free Hb and myoglobin create a uniform color change. Povidone iodine causes false-positive results (uniform coloring); ascorbic acid causes false-negative results.

- Nitrites are produced when bacteria reduce urinary nitrates derived from amino acid metabolism. Nitrites are not normally present and signify bacteriuria. The test is either positive or negative. False-negative results may occur with any of the following:

Infection with certain pathogens that cannot convert nitrate to nitrite (eg, *Enterococcus faecalis*, *Neisseria gonorrhoeae*, *Mycobacterium tuberculosis*, *Pseudomonas* sp)

- Urine that has not stayed long enough (< 4 h) in the bladder
- Low urinary excretion of nitrate
- Enzymes (of certain bacteria) that reduce nitrates to nitrogen
- High urine urobilinogen level
- Presence of ascorbic acid
- Urine pH < 6.0

Nitrites are used mainly with WBC esterase testing to monitor patients with recurrent urine infections, particularly children with vesicoureteral reflux, and sometimes to confirm the diagnosis of uncomplicated UTI in women of childbearing age.

WBC esterase is released by lysed neutrophils. Its presence in urine reflects acute inflammation, most commonly due to bacterial infection but sometimes due to interstitial nephritis, nephrolithiasis, or renal TB. Threshold for detection is about 5 WBCs/HPF, and test results range from negative to 4+. The test is not very sensitive for detection of infection. Contamination of a urine specimen with vaginal flora is the most common cause of false-positive results. False-negative results may result from any of the following:

- Very dilute urine
- Glycosuria
- Urobilinogen
- Use of phenazopyridine, nitrofurantoin, rifampin, or large amounts of vitamin C

WBC esterase is used mainly with nitrite testing to monitor patients with recurrent urine infections and sometimes to diagnose uncomplicated UTI in women of childbearing age. If both tests are negative, the likelihood of a positive urine culture is small.

Microscopic analysis

Detection of solid elements (cells, casts, crystals) requires microscopic analysis, ideally done immediately after voiding, and dipstick testing. The specimen is prepared by centrifuging 10 to 15 mL of urine at 1500 to 2500 rpm for 5 min. The supernatant is fully decanted; a small amount of urine remains with the residue at the bottom of the centrifuge tube. The residue can be mixed back into solution by gently agitating the tube or tapping the bottom. A single drop is pipetted onto a slide and covered with a coverslip. For routine microscopic analysis, staining is optional. The specimen is examined under reduced light with the low-power objective and under full-intensity light with the high-power objective; the latter is typically used for semiquantitative estimates (eg, 10 to 15 WBCs/HPF). Polarized light is used to identify some crystals and lipids in the urine. Phase-contrast microscopy enhances identification of cells and casts.

Epithelial cells (renal tubular, transitional, squamous cells) frequently are found in urine; most common are squamous cells lining the end of the urethra and contaminants from the vagina. Only renal tubular cells are diagnostically important; however, except when found in casts, they are difficult to distinguish from transitional cells. A few renal tubular cell casts appear in normal urine, but a large number suggests tubular injury (eg, acute tubular necrosis, tubulointerstitial nephropathy, nephrotoxins, nephrotic syndrome).

RBCs < 3/HPF may be normal (< 5/HPF is sometimes normal, eg, after exercise), and any hematuria should be interpreted in clinical context. On microscopic analysis, glomerular RBCs are dysmorphic, with spicules, folding, and blebs; nonglomerular RBCs retain their normal shape.

WBCs < 5/HPF may be normal; special staining can distinguish eosinophils from neutrophils. Pyuria is defined as > 5 WBCs /HPF in a sample of centrifuged urine.

Lipiduria is most characteristic of the nephrotic syndrome; renal tubular cells absorb filtered lipids, which appear microscopically as oval fat bodies, and cholesterol, which produces a Maltese cross pattern under polarized light. Lipids and cholesterol can also be free floating or incorporated into casts.

Crystals in urine are common and usually clinically insignificant. Crystal formation depends on all of the following:

- Urine concentration of crystal constituents
- pH
- Absence of crystallization inhibitors

Drugs are an underrecognized cause of crystals.

Casts are made up of glycoprotein of unknown function (Tamm-Horsfall protein) secreted from the thick ascending loop of Henle. They are cylindrical and have regular margins. Their presence indicates renal origin, which may be helpful diagnostically. Types of casts differ in constituents and appearance.

Other urine tests

Other tests are useful in specific instances.

Total protein excretion can be measured in a 24-h collection or can be estimated by the protein/creatinine ratio, which, in a random urine sample, correlates well with values in g/1.73 m² BSA from a 24-h collection (eg, 400 mg/dL protein and 100 mg/dL creatinine in a random sample equal 4 g/1.73 m² in a 24-h collection). The protein/creatinine ratio is less accurate when creatinine excretion is significantly increased (eg, in muscular athletes) or decreased (eg, in cachexia).

Microalbuminuria is albumin excretion persistently between 30 and 300 mg/day (20 to 200 µg/min); lesser amounts are considered within the range of normal, and amounts > 300 mg/day (> 200 µg/min) are considered overt proteinuria. Use of the urine albumin/urine creatinine ratio is a reliable and more convenient screening test because it avoids timed urine specimens and correlates well with 24-h

values. A value $> 30 \text{ mg/g}$ ($> 0.03 \text{ mg/mg}$) suggests microalbuminuria. The reliability of the test is best when a midmorning specimen is used, vigorous exercise is avoided before the test, and unusual creatinine production (in cachectic or very muscular patients) is not present. Microalbuminuria can occur in all of the following:

- Diabetes mellitus
- Hypertension
- Renal allograft dysfunction
- Preeclampsia
- UTI

Microalbuminuria is highly predictive of subsequent nephropathy in type 1 but not type 2 diabetes. Microalbuminuria is a risk factor for cardiovascular disorders and early cardiovascular mortality independent of diabetes or hypertension.

Sulfosalicylic acid (SSA) test strips can be used to detect protein other than albumin (eg, Igs in multiple myeloma) when dipstick urine tests are negative; urine supernatant mixed with SSA becomes turbid if protein is present. The test is semiquantitative with a scale of 0 (no turbidity) to 4+ (flocculent precipitates). Readings are falsely elevated by radiopaque contrast agents.

Ketones spill into urine with ketonemia, but use of test strips to measure urinary ketones is no longer widely recommended because they measure only acetoacetic acid and acetone, not β -hydroxybutyric acid. Thus, a false-negative result is possible even without an exogenous cause (eg, vitamin C, phenazopyridine, N-acetylcysteine); direct measurement of serum ketones is more accurate. Ketonuria is caused by endocrine and metabolic disorders and does not reflect renal dysfunction.

Osmolality, the total number of solute particles per unit mass (mOsm/kg [mmol/kg]), can be measured directly by osmometer. Normally, osmolality is 50 to 1200 mOsm/kg. Measurement is most useful for evaluating hypernatremia, hyponatremia, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and diabetes insipidus.

Electrolyte measurements help diagnose specific disorders. Na level can help distinguish whether volume depletion (urine Na $< 10 \text{ mEq/L}$) or acute tubular

necrosis (urine Na > 40 mEq/L) is the cause of acute renal insufficiency or failure. The fractional excretion of Na (FENa) is the percentage of filtered Na that is excreted. It is calculated as the ratio of excreted to filtered Na, which can be simplified to the following:

$$FE_{Na} = \frac{(U_{Na})(P_{Cr})}{(P_{Na})(U_{Cr})} \times 100\%$$

where UNa is urine Na, PNa is plasma Na, PCr is plasma creatinine, and UCr is urine creatinine.

This ratio is a more reliable measure than UNa alone because UNa levels between 10 and 40 mEq/L are nonspecific. FENa < 1% suggests prerenal causes, such as volume depletion; however, acute glomerulonephritis or certain types of acute tubular necrosis (eg, rhabdomyolysis, radiocontrast-induced renal failure) can result in FENa < 1%. A value > 1% suggests acute tubular necrosis or acute interstitial nephritis.

Other useful measurements include the following:

- Fractional excretion of HCO₃ in evaluation of renal tubular acidosis
- Cl levels and urine anion gap for diagnosis of metabolic alkalosis and nonanion gap metabolic acidosis
- K levels in determining the cause of hypokalemia or hyperkalemia
- Levels of Ca, Mg, uric acid, oxalate, citrate, and cystine in evaluation of calculi

Eosinophils, cells that stain bright red or pink-white with Wright's or Hansel staining, most commonly indicate one of the following:

- Acute interstitial nephritis
- Rapidly progressive glomerulonephritis
- Acute prostatitis
- Renal atheroembolism

Cytology is used for the following:

- To screen for cancer in high-risk populations (eg, petrochemical workers)
- To evaluate painless hematuria in the absence of glomerular disease (suggested by the absence of dysmorphic RBCs, proteinuria, and renal failure)
- To check for recurrence after bladder tumor resection.

Sensitivity is about 90% for carcinoma in situ; however, sensitivity is considerably lower for low-grade transitional cell carcinomas. Inflammatory or reactive hyperplastic lesions or cytotoxic drugs for carcinoma may produce false-positive results. Accuracy for detecting bladder tumors may be increased by vigorous bladder lavage with a small volume of 0.9% saline solution (50 mL pushed in and then aspirated by syringe through a catheter). Cells collected in the saline are concentrated and examined. Gram stain and cultures with susceptibility testing are indicated when GU tract infections are suspected; a positive result must be interpreted in the clinical context.

Amino acids are normally filtered and reabsorbed by the proximal tubules. They may appear in urine when a hereditary or acquired tubular transport defect (eg, Fanconi syndrome, cystinuria) is present. Measuring type and amount of amino acids may help in the diagnosis of certain types of calculi, renal tubular acidosis, and inherited disorders of metabolism.

Blood tests

Blood tests are useful in evaluation of renal disorders.

Serum creatinine values > 1.3 mg/dL (> 114 $\mu\text{mol/L}$) in men and > 1 mg/dL (> 90 $\mu\text{mol/L}$) in women are usually abnormal. Serum creatinine depends on creatinine generation as well as renal creatinine excretion. Because creatinine turnover increases with higher muscle mass, muscular people have higher serum creatinine levels and elderly and undernourished people have lower levels.

Serum creatinine may also be increased in the following conditions:

- Use of ACE inhibitors and angiotensin II receptor blockers
- Consumption of large amounts of meat
- Use of some drugs (cimetidin, cefoxim, trimetoprim)

ACE inhibitors and angiotensin II receptor blockers reversibly decrease GFR and increase serum creatinine because they vasodilate efferent more than afferent glomerular arterioles, mainly in people who are dehydrated or are receiving diuretics. In general, serum creatinine alone is not a good indicator of kidney function. The Cockcroft and Gault formula and the Modification of Diet in Renal Disease formula estimate GFR based on serum creatinine and other parameters and more reliably evaluate kidney function.

BUN/creatinine ratio is used to distinguish prerenal from renal or postrenal (obstructive) azotemia; a value > 15 is considered abnormal and may occur in prerenal and postrenal azotemia. However, BUN is affected by protein intake and by several nonrenal processes (eg, trauma, infection, GI bleeding, corticosteroids) and, although suggestive, is generally inconclusive as evidence of renal dysfunction.

Cystatin C, a serine proteinase inhibitor that is produced by all nucleated cells and filtered by the kidneys, can also be used to evaluate kidney function. Its plasma concentration is independent of sex, age, and body weight. Testing is not always available, and values are not standardized across laboratories.

Serum electrolytes (eg, Na, K, HCO_3) may become abnormal and the anion gap ($\text{Na} - [\text{Cl} + \text{HCO}_3]$) may increase in acute kidney injury and chronic kidney disease. Serum electrolytes should be monitored periodically.

CBC may detect anemia in chronic kidney disease or, rarely, polycythemia in renal cell carcinoma or polycystic kidney disease. Anemia is often multifactorial (mainly due to erythropoietin deficiency and sometimes worsened or caused by blood loss in dialysis circuits or the GI tract); it may be microcytic or normocytic, and may be hypochromic or normochromic.

Renin, a proteolytic enzyme, is stored in the juxtaglomerular cells of the kidneys. Renin secretion is stimulated by reduced blood volume and renal blood flow and is inhibited by Na and water retention. Plasma renin is assayed by measuring renin activity as the amount of angiotensin I generated per hour. Specimens should be drawn from well-hydrated, Na- and K-replete patients. Plasma renin, aldosterone, cortisol, and ACTH should be measured in evaluation of all of the following:

- Adrenal insufficiency
- Hyperaldosteronism
- Refractory hypertension

The plasma aldosterone/renin ratio calculated from measurements obtained with the patient in an upright posture is the best screening test for hyperaldosteronism, provided that plasma renin activity is > 0.5 ng/mL/h and aldosterone is > 12 to 15 ng/dL.

Evaluating Kidney Function

Kidney function is evaluated using values calculated from formulas based on results of blood and urine tests.

GFR

Glomerular filtration rate (GFR), the volume of blood filtered through the kidney per minute, is the best overall measure of kidney function; it is expressed in mL/min. Because normal GFR increases with increasing body size, a correction factor using body surface area (BSA) typically is applied. This correction is necessary to compare a patient's GFR to normal and to define different stages of chronic kidney disease. Given the mean normal BSA of 1.73 m², the correction factor is $1.73/\text{patient BSA}$; adjusted GFR results are then expressed as mL/min/ 1.73 m².

Normal GFR in young, healthy adults is about 120 to 130 mL/min/ 1.73 m² and declines with age to about 75 mL/min/ 1.73 m² at age 70 . Chronic kidney disease is defined by a GFR < 60 mL/min/ 1.73 m² for > 3 months. The gold standard for GFR measurement is inulin clearance. Inulin is neither absorbed nor secreted by the renal tubule and therefore it is the ideal marker for evaluation of kidney function. However, its measurement is cumbersome and therefore it is mostly used in research settings.

Creatinine clearance

Creatinine is produced at a constant rate by muscle metabolism and is freely filtered by the glomeruli and also is secreted by the renal tubules. Because creatinine is secreted, creatinine clearance (CrCl) overestimates GFR by about 10 to 20% in people with normal kidney function and by up to 50% in patients with advanced renal failure; thus, use of CrCl to estimate GFR in chronic kidney disease is discouraged.

Using a timed (usually 24-h) urine collection, CrCl can be calculated as

$$\text{CrCl} = \text{UCr} \times \frac{\text{UVol}}{\text{Pcr}}$$

where UCr is urine creatinine in mg/mL, UVol is urine volume in mL/min of collection (1440 min for a full 24-h collection), and PCr is plasma creatinine in mg/mL.

Estimating creatinine clearance: Because serum creatinine by itself is inadequate for evaluation of kidney function, several formulas have been devised to estimate CrCl using serum creatinine and other factors.

The Cockcroft and Gault formula can be used to estimate CrCl. It uses age, lean body weight, and serum creatinine level. It is based on the premise that daily creatinine production is 28 mg/kg/day with a decrease of 0.2 mg/yr of age.

$$\text{CrCl}_{(\text{est})} = \frac{(140 - \text{age}[\text{yr}])(\text{lean body wt}[\text{kg}])}{(72)(\text{serum creatinine}[\text{mg/dL}])} \times 0.85 (\text{if female})$$

The Modification of diet in renal disease (MDRD) study formula (current 4-factor formula) can also be used, although it requires a calculator or computer:

$$\text{CrCl}_{(\text{est})} = 186 \times (\text{serum Cr})^{-1.154} \times (\text{age})^{-0.203} \times 0.742 (\text{if female}) \\ \times 1.210 (\text{if African American})$$

1.2 Urinary frequency and volume changes

1.2.1 Dysuria

Dysuria is painful or uncomfortable urination, typically a sharp, burning sensation. Some disorders cause a painful ache over the bladder or perineum. Dysuria is an extremely common symptom in women, but it can affect men and can occur at any age.

Pathophysiology

Dysuria results from irritation of the bladder trigone or urethra. Inflammation or stricture of the urethra causes difficulty in starting urination and burning on

urination. Irritation of the trigone causes bladder contraction, leading to frequent and painful urination. Dysuria most frequently results from an infection in the lower urinary tract, but it could also be associated with an upper UTI. Impaired renal concentrating ability is the main reason for frequent urination in upper UTIs.

Etiology

Dysuria is typically caused by urethral or bladder inflammation, although perineal lesions in women (eg, from vulvovaginitis or herpes simplex virus infection) can be painful when exposed to urine. Most cases are caused by infection, but sometimes noninfectious inflammatory disorders are responsible. Overall, the most common causes of dysuria are

- Cystitis
- Urethritis from a sexually transmitted disease (STD)

Evaluation

History

History of present illness should cover duration of symptoms and whether they have occurred in the past. Important accompanying symptoms include fever, flank pain, urethral or vaginal discharge, and symptoms of bladder irritation (frequency, urgency) or obstruction (hesitancy, dribbling). Patients should be asked whether the urine is bloody, cloudy, or malodorous and the nature of any discharge (eg, thin and watery or thick and purulent). Clinicians should also ask whether patients have recently engaged in unprotected intercourse, have applied potential irritants to the perineum, have had recent urinary instrumentation (eg, cystoscopy, catheterization, surgery), or might be pregnant. Review of systems should seek symptoms of a possible cause, including back or joint pain and eye irritation (connective tissue disorder) and GI symptoms, such as diarrhea (reactive arthritis). Past medical history should note prior urinary infections (including those during childhood) and any known abnormality of the urinary tract. As with any potentially infectious illness, a history of immune compromise or recent hospitalization is important.

Physical examination

Examination begins with review of vital signs, particularly to note the presence of fever. Skin, mucosa, and joints are examined for lesions suggesting reactive arthritis (eg, conjunctivitis, oral ulcers, vesicular or crusting lesions of palms, soles, and around nails, joint tenderness). The flank is percussed for tenderness over the kidneys. The abdomen is palpated for tenderness over the bladder. Women should have a pelvic examination to detect perineal inflammation or lesions and vaginal or cervical discharge. Swabs for STD testing and wet mount should be obtained at this time rather than doing a 2nd examination. Men should undergo external inspection to detect penile lesions and discharge; the area under the foreskin should be examined. Testes and epididymis are palpated to detect tenderness or swelling. Rectal examination is done to palpate the prostate for size, consistency, and tenderness.

The following findings are of particular concern:

- Fever
- Flank pain or tenderness
- Recent instrumentation
- Immunocompromised patient
- Recurrent episodes (including frequent childhood infections)
- Known urinary tract abnormality

Interpretation of findings

Some findings are highly suggestive. In young, healthy women with dysuria and significant symptoms of bladder irritation, cystitis is the most likely cause. Visible urethral or cervical discharge suggests an STD. Thick purulent material is usually gonococcal; thin or watery discharge is nongonococcal. Vaginitis and the ulcerative lesions of herpes simplex virus infection are typically apparent on inspection. In men, a very tender prostate suggests prostatitis, and a tender, swollen epididymis suggests epididymitis. Other findings also are helpful but may not be diagnostic; eg, women with findings of vulvovaginitis may also have a UTI or another cause of dysuria. Findings suggestive of infection are more concerning in patients with red flag findings. Fever, flank pain, or both suggest an accompanying

pyelonephritis. History of frequent UTIs should raise concern for an underlying anatomic abnormality or compromised immune status. Infections following hospitalization or instrumentation may indicate an atypical or resistant pathogen.

Testing

No single approach is uniformly accepted. Many clinicians presumptively give antibiotics for cystitis without any testing (sometimes not even urinalysis) in young, otherwise healthy women presenting with classic dysuria, frequency, and urgency and without red flag findings. Others evaluate everyone with a clean-catch midstream urine sample for urinalysis and culture. Some clinicians defer culture unless dipstick testing detects WBCs. In women of childbearing age, a pregnancy test is done (UTI during pregnancy is of concern because it may increase the risk of preterm labor or premature rupture of the membranes). Vaginal discharge warrants a wet mount. Many clinicians routinely obtain samples of cervical (women) or urethral (men) exudate for STD testing (gonococcus and chlamydia culture or PCR) because many infected patients do not have a typical presentation. A finding of $> 10^5$ bacteria colony-forming (CFU) units/mL suggests infection. In symptomatic patients, sometimes counts as low as 10^2 or 10^3 CFUs indicate UTI. WBCs detected with urinalysis in patients with sterile cultures are nonspecific and may occur with an STD, vulvovaginitis, prostatitis, TB, tumor, or other causes. RBCs detected with urinalysis in patients with no WBCs and sterile cultures may be due to cancer, calculus, foreign body, glomerular abnormalities, or recent instrumentation of the urinary tract. Cystoscopy and imaging of the urinary tract may be indicated to check for obstruction, anatomic abnormalities, cancer, or other problems in patients who have no response to antibiotics, recurrent symptoms, or hematuria without infection. Pregnant patients, older patients, and patients with prolonged or recurrent dysuria need closer attention and a more thorough investigation.

Treatment

Treatment is directed at the cause. Many clinicians do not treat dysuria in women without red flag findings if no cause is apparent from examination and the results of a urinalysis. If treatment is decided upon, a 3-day course of

trimethoprim/sulfamethoxazole, trimethoprim alone, or a fluoroquinolone is recommended. Some clinicians give presumptive treatment for an STD in men with similarly unremarkable findings; other clinicians await STD test results, particularly in reliable patients. Acute, intolerable dysuria due to cystitis can be relieved somewhat by phenazopyridine 100 to 200 mg po tid for the first 24 to 48 h. This drug turns urine red-orange; patients should be cautioned not to confuse this effect with progression of infection or hematuria. Upper UTI requires 10 to 14 days of treatment with an antibiotic that is effective against gram-negative organisms, particularly *Escherichia coli*.

Prognosis

Prognosis is usually depended on cause of dysuria.

1.2.2 Nicturia

Nocturia, a common symptom, is defined as waking at night to void, where each micturition is preceded and followed by sleep. Although by definition even a single episode of awakening to urinate is nocturia, epidemiological evidence and expert clinical opinion both suggest nocturia is likely clinically meaningful if a patient voids two or more times nightly. Patients themselves are more likely to consult a provider about nocturia if they have three or more episodes. Nocturnal urinary incontinence or nighttime bed-wetting (enuresis) is distinct from nocturia. However, nocturnal polyuria (NP) is common in older men and can lead to nocturia.

Causes.

The causes for nocturia may be non-urological:

- non-pathological (e.g. waking up at night because of disturbance, then voiding for convenience and going back to sleep)

- pathological (e.g. congestive cardiac failure, untreated diabetes mellitus).

Urological causes can be classified into four broad types based on bladder function and urine production

- Abnormal bladder function + Normal urine production
- Abnormal bladder function + Excessive urine production
- Normal bladder function + Normal urine production

- Normal bladder function + Excessive urine production

Abnormal bladder function may result from a variety of causes such as detrusor overactivity (neurogenic or idiopathic) and bladder outlet obstruction (BOO) (e.g. due to benign prostatic enlargement). Excessive urine production may be due to causes such as (a) nocturnal polyuria (abnormal night/day ratio >0.25) and (b) 24-hour (global) polyuria (normal night/day ratio ≤ 0.25 but urine output $>40\text{ml/kg/day}$). Global polyuria is caused by either (i) water diuresis, or (ii) solute diuresis. Water diuresis (urine osmolality $<300\text{mOsm/L}$; specific gravity <1.010) is caused by low basal vasopressin (antidiuretic hormone; ADH) resulting in high urinary volume. Low ADH may be due to either (1) extra-renal (pituitary diabetes insipidus; primary polydipsia) or (2) renal (renal resistance to ADH due to nephrogenic diabetes insipidus). Solute diuresis (urine osmolality $\geq 300\text{mOsm/L}$; specific gravity ≥ 1.010) is caused by the increased delivery to the renal collecting tubules of any solute such as glucose, sodium and chloride, urea, mannitol or radio-contrast.

Diagnosis.

History. A thorough medical and surgical history should include enquiry into the presence and severity of LUTS (including urinary tract infections, haematuria); fluid intake (type, timing and volumes); medications (type, timing); co-morbidities (congestive cardiac failure, diabetes); and sleep disturbances (snoring partner, occupation, sleep disorders).

Examination: A directed physical exam should involve abdominal examination to exclude masses compressing the bladder, a digital rectal examination in men and vaginal examination in women to assess oestrogen status and exclude prolapse. Anal tone, sensation and lower limb examination may help exclude neurological causes. A cardio-respiratory examination may help detect signs of cardiac failure such as pitting oedema and pulmonary basal crepitations.

Investigations: Dipstick urinalysis helps to detect diabetes, infections and haematuria. Flow-rate and post-void residuals may help to ascertain causes of abnormal bladder function or outflow obstruction. Depending on the causes, further investigations may include renal biochemistry, urinary tract imaging, cystoscopy or

urodynamics. Frequency-volume charts (FVC) are very useful and, depending on the information required, their completion can vary from 1 to 14 days. The ICS recommendation is 2 days for nocturia.

Quality of life (QoL): Assessment of the impact of nocturia on the patients' QoL is important as it can help evaluate the need for intervention. The ICIQ-N (Fig 1.2.2.1) is a simple and useful 2-symptom questioning tool which can be expanded to an additional tool (with 13 questions) if further questioning is required. NP is determined with frequency-volume charts. Two definitions of NP were used: (1) a nocturnal urine production (NUP) of >90ml/h (NUP90) and (2) the nocturnal voided volume plus first morning void being >33% of the 24-h voided volume (NUV33). Nocturia was defined as two or more voids per night.

Epidemiology

The prevalence of nocturia is higher with increasing age. Occasional nocturia is present in 50 percent of men and women aged 50 to 59 years. Among 18 to 49 year olds, more women than men have nocturia; the sex ratio reverses after 60 years of age, with prevalence greater in men than women. The prevalence of twice nightly or greater nocturia among men between 70 and 79 is nearly 50 percent.

Frequency

NUP90 prevalents in 27.7% of men with nocturia and in 8.0% of those without nocturia. At baseline, NUV33 prevalents in 91.9% of men with nocturia and in 70.1% of men without nocturia. Due to the fluctuation of NP, it is advisable to first determine its chronicity and cause before starting treatment. Because of the high prevalence of NP in men without nocturia, NUV33 should be reconsidered as a discriminative definition of NP. Male sex, high BMI, deterioration of voiding symptoms, and metabolic syndrome were independent factors associated with the incidence of nocturia. Male sex, sum of voiding symptoms, age and metabolic syndrome were independent negative factors associated with remission of nocturia.

Nocturia

Many people experience urinary symptoms some of the time. We are trying to find out how many people experience urinary symptoms, and how much they bother them. We would be grateful if you could answer the following questions, thinking about how you have been, on average, over the PAST FOUR WEEKS.

1. Please write in your date of birth:
DAY MONTH YEAR

2. Are you (tick one): Female Male

3a. How often do you pass urine during the day?

hourly 3
every two hours 2
every three hours 1
every four hours or more 0

3b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all a great deal

4a. During the night, how many times do you have to get up to urinate, on average?

none 0
one 1
two 2
three 3
four or more 4

4b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all a great deal

Fig 1.2.2.1. Quality of life questionnaire.

Clinical

Clinically significant nocturia is prevalent in patients with chronic kidney disease, and the severity increased with chronic kidney disease stage and patient age. Contrary to previous reports, the metabolic syndrome did not increase the risk of clinically significant nocturia in patients with chronic kidney disease. Improvements in lower urinary tract symptoms correlate with changes in sleeping abilities with time in men with benign prostatic hyperplasia. While nocturia is significantly associated with sleep disturbance, other changes in overall lower urinary tract symptoms are better predictors of changes in sleep dysfunction. Nocturia is also associated with increased rates of depression, work absenteeism, lower self-rated physical and mental health, congestive heart failure, and increased all cause mortality. In the very old, nocturia is associated with higher rates of accidental falls and fractures.

Treatment

Conservative: As there are many non-medical and non-urological causes, simple modifications to lifestyle may improve nocturia and QoL significantly.

Measure such as reducing fluid intake and avoiding caffeine or alcohol prior to sleep, having dinner earlier, addressing noise disturbances and voiding prior to sleep may help reduce nocturia. Medical causes such as diabetes and cardiac failure may warrant medical optimisation. Sleep disorders and psychological disturbances may benefit from psychological or psychiatric input.

Medical: Nocturia is reported to be as high as 87% in those with overactive bladder syndrome (OAB). Nocturnal polyuria and nocturia relief in patients treated with solifenacin for overactive bladder symptoms and nocturnal polyuria is reported to account for around 76% of cases of nocturia. Treatment with antimuscarinics, such as solifenacin, is generally ineffective. Similarly, in men with BOO, nocturnal polyuria is the cause of nocturia in around 70%; the use of alpha-blockers, such as tamsulosin, is also likely to be ineffective. Therefore, nocturnal polyuria needs to be ruled out in those with OAB or BOO as the standard treatments, with antimuscarinics or alpha- blockers, are likely to fail.

Desmopressin is a synthetic analogue of 8-arginine vasopressin (AVP) and can be delivered via the oral or sublingual routes. Several double-blind, placebo-controlled randomised trials have demonstrated its efficacy and safety in treating nocturia. It is licensed for use in those aged <65 years; caution must be employed when treating those >65 years by ensuring that baseline serum sodium is >135mmol/L and that baseline urine output is <30ml/kg/day. Amongst a variety of other treatments which have been investigated, there appears to be some benefit in trying loop diuretics such as furosemide 40mg. A novel therapy for nocturnal polyuria] and bumetanide 1mg, six hours prior to bedtime.

Patients suffering with nocturia are often referred to urologists for assessment of their LUTS. However, LUTS are associated with many risk factors and comorbidity. Risk factors and comorbid factors associated with lower urinary tract symptoms. Furthermore, nocturia itself has multi-factorial aetiology. Analysis of nocturia with a 24-h urine volume, nocturnal urine volume, nocturnal bladder capacity and length of sleep duration: concept for effective treatment modality and

treatment has to be aimed at all the possible causative factors and may need a multi-disciplinary approach with health-care professionals from other specialities.

In conclusion, patients with nocturia are often referred to urologists, but the underlying cause most often lies outside the urinary tract. Nocturia should be considered a systemic disorder and investigated and treated as such. Comprehensive assessment of the symptoms, optimally including a frequency volume chart, can help to determine the potential underlying cause and help to direct the patient to the most suitable medical professional for further management.

1.2.3 Hypostenuria

Hypostenuria is referred to as a secretion of urine of low specific gravity due to inability of the kidney to concentrate the urine normally less than 1016. If specific gravity is totally less than 1010 hypostenuria is present.

Hypostenuria is presented as present non-specific symptoms for tubular disorders due to wide spectrum reasons from acute kidney injury to end stage of chronic kidney disease. In acute presentation this symptom may be infection- or drug-induced or it may occur without a known cause. Other forms of tubular dysfunction, such as Bartter's syndrome and Gitelman's syndrome can appear as retardation in growth, pitressin-resistant hypostenuria in association with hypokalemic alkalosis, high activity of the juxta-angiotensin-renin-aldosterone system with normal blood pressure; vascular insensitivity to angiotensin and hypertrophy and hyperplasia of the juxtaglomerular apparatus.

Acute tubulointerstitial nephritis is an leading important cause of hypostenuria. Sometimes this sign reflects chronic tubular dysfunction and unexplained renal failure. Occasionally, polyuria, arterial hypertension and glycosuria were found also. The diagnosis can be verified at renal biopsy. Early recognition of the disease is important to remove possible aetiological agents and to treat them before chronic lesions are present to avoid long-term renal damage.

Treatment is depended on a main reason.

1.2.4 Polyuria

Polyuria is urine output of > 3 L/day; it must be distinguished from urinary frequency, which is the need to urinate many times during the day or night but in normal or less-than-normal volumes. Either problem can include nocturia.

Pathophysiology

Water homeostasis is controlled by a complex balance of water intake (itself a matter of complex regulation), renal perfusion, glomerular filtration and tubular reabsorption of solutes, and reabsorption of water from the renal collecting ducts. When water intake increases, blood volume increases and thus renal perfusion and GFR increase, resulting in increased urine volume. However, the increased water intake lowers blood osmolality, decreasing release of ADH (also referred to as arginine vasopressin) from the hypothalamic-pituitary system. Because ADH promotes water reabsorption in the renal collecting ducts, decreased levels of ADH increase urine volume, allowing body water to return to normal. Additionally, high amounts of solutes within the renal tubule cause a passive osmotic diuresis (solute diuresis) and thus an increase in urine volume. The classic example of this process is the glucose-induced osmotic diuresis in uncontrolled diabetes mellitus, when high urinary glucose levels (> 250 mg/dL) exceed tubular reabsorption capacity, leading to high glucose levels in the renal tubules; water follows passively, resulting in glucosuria and increased urine volume.

Therefore, polyuria results from any process that involves

- Sustained increase in water intake (polydipsia)
- Decreased ADH secretion (central diabetes insipidus)
- Decreased peripheral ADH sensitivity (nephrogenic diabetes insipidus)
- Solute diuresis

Etiology

The most common causes of polyuria are:

- Diabetic nephropathy
- Primary polydipsia
- Central diabetes insipidus
- Nephrogenic diabetes insipidus

- Primary polydipsia
- Chronic kidney disorders
- Polyuric phase of acute kidney insufficiency
- Tubular disorders

Evaluation

History

History of present illness should include the amounts of fluid consumed and voided to distinguish between polyuria and urinary frequency. If polyuria is present, patients should be asked about the age at onset, rate of onset (eg, abrupt vs gradual), and any recent clinical factors that may cause polyuria (eg, IV fluids, tube feedings, resolution of urinary obstruction, stroke, head trauma, surgery). Review of systems should seek symptoms suggesting possible causes, including dry eyes and dry mouth (Sjögren's syndrome) and weight loss and night sweats (cancer).

Past medical history should be reviewed for conditions associated with polyuria, including diabetes mellitus, psychiatric disorders, sickle cell disease, sarcoidosis, amyloidosis, and hyperparathyroidism. A family history of polyuria should be noted. Drug history should note use of any drugs associated with nephrogenic diabetes insipidus and agents that increase urine output (eg, diuretics, alcohol, caffeinated beverages).

Physical examination

The general examination should note signs of obesity (as a risk factor for type 2 diabetes mellitus) or undernutrition or cachexia that might reflect an underlying cancer or an eating disorder with surreptitious diuretic use. The head and neck examination should note dry eyes or dry mouth (Sjögren's syndrome). Skin examination should note the presence of any hyperpigmented or hypopigmented lesions, ulcers, or subcutaneous nodules that may suggest sarcoidosis. Comprehensive neurologic examination should note any focal deficits that suggest an underlying neurologic insult and assess mental status for indications of a thought disorder.

The following findings are of particular concern:

- Abrupt onset or onset during the first few years of life
- Night sweats, cough, and weight loss, especially when there is an extensive smoking history
- Psychiatric disorder

Interpretation of findings

History can often distinguish polyuria from frequency, but rarely a 24-h urine collection may be needed.

Clinical evaluation may suggest a cause, but testing is usually necessary. Diabetes insipidus is suggested by a history of cancer or chronic granulomatous disease (due to hypercalcemia), use of certain drugs (lithium, cidofovir, ifosfamide), and less common conditions (eg, sickle cell disease, renal amyloidosis, sarcoidosis, Sjögren's syndrome) that have manifestations that are often more prominent than and precede the polyuria.

Abrupt onset of polyuria at a precise time suggests central diabetes insipidus, as does preference for extremely cold or iced water. Onset during the first few years of life is typically related to inherited central or nephrogenic diabetes insipidus or uncontrolled type 1 diabetes mellitus. Polyuria caused by diuresis is suggested by a history of diuretic use or diabetes mellitus. Psychogenic polydipsia is more common in patients with a history of a psychiatric disorder (primarily bipolar disorder, or schizophrenia) rather than as an initial manifestation.

Testing

Once excess urine output has been verified by history or measurements, serum or fingerstick glucose determination should be done to rule out uncontrolled diabetes.

If hyperglycemia is not present, then testing is required:

- Serum and urine chemistries (electrolytes, Ca)
- Serum and urine osmolality and sometimes plasma ADH level

These tests look for hypercalcemia, hypokalemia (due to surreptitious diuretic use), and hypernatremia or hyponatremia:

- Hypernatremia (Na > 142 mEq/L) suggests excess free water loss due to central or nephrogenic diabetes insipidus.

- Hyponatremia ($\text{Na} < 137 \text{ mEq/L}$) suggests excess free water intake secondary to polydipsia.
- Urine osmolality is typically $< 300 \text{ mOsm/kg}$ with water diuresis and $> 300 \text{ mOsm/kg}$ with solute diuresis.

If the diagnosis remains unclear, then measurement of serum and urine Na and osmolality in response to a water deprivation test and exogenous ADH administration should be done. Because serious dehydration may result from this testing, the test should be done only while patients are under constant supervision; hospitalization is usually required. Additionally, patients in whom psychogenic polydipsia is suspected must be observed to prevent surreptitious drinking.

The test is started in the morning by weighing the patient, obtaining venous blood to determine serum electrolyte concentrations and osmolality, and measuring urine osmolality. Voided urine is collected hourly, and its osmolality is measured. Dehydration is continued until orthostatic hypotension and postural tachycardia appear, $\geq 5\%$ of the initial body weight has been lost, or the urinary concentration does not increase $> 30 \text{ mOsm/kg}$ in sequentially voided specimens. Serum electrolytes and osmolality are again determined, and 5 units of aqueous vasopressin are injected sc. Urine for osmolality measurement is collected one final time 60 min postinjection, and the test is terminated.

A normal response produces maximum urine osmolality after dehydration ($> 700 \text{ mOsm/kg}$), and osmolality does not increase more than an additional 5% after injection of vasopressin.

In central diabetes insipidus, patients are typically unable to concentrate urine to greater than the plasma osmolality but are able to increase their urine osmolality after vasopressin administration. The increase in urine osmolality is 50 to 100% in central diabetes insipidus vs 15 to 45% with partial central diabetes insipidus.

In nephrogenic diabetes insipidus, patients are unable to concentrate urine to greater than the plasma osmolality and show no additional response to vasopressin administration. Occasionally in partial nephrogenic diabetes insipidus, the increase in

urine osmolality can be up to 45%, but overall these numbers are much lower than those that occur in partial central diabetes insipidus (usually < 300 mOsm/kg).

In psychogenic polydipsia, urine osmolality is < 100 mOsm/kg. Decreasing water intake will lead to decreasing urine output, increasing plasma osmolality and serum Na concentration.

Measurement of circulating ADH is the most direct method of diagnosing central diabetes insipidus. Levels at the end of the water deprivation test (before the vasopressin injection) are low in central diabetes insipidus and appropriately elevated in nephrogenic diabetes insipidus. However, ADH levels are not routinely available. In addition, water deprivation is so accurate that direct measurement of ADH is rarely necessary. Plasma ADH levels are diagnostic after either dehydration or infusion of hypertonic saline.

Treatment

Treatment varies by cause.

1.2.5 Oliguria / Anuria

Oliguria is defined as a urine output that is less than 1 mL/kg/h in infants, less than 0.5 mL/kg/h in children, and less than 400 mL or 500 mL per 24h in adults - this equals 17 or 21 mL/hour. For example, in an adult weighing 70 kg it equals 0.24 or 0.3 ml/hour/kg. Alternatively, however, the value of 0.5 mL/kg/h is commonly used to define oliguria in adults as well. Anuria is defined as less than 50mL urine output per day. However, oliguria and azotaemia may represent not only intrinsic kidney disease (ischaemic acute tubular necrosis [ATN]) but also a normal response of the kidney to extracellular volume depletion ('pre-renal' state).

Oliguria should be presumed to be reversible and a prompt, active and analytical response is needed to prevent AKI progression. Initial resuscitation is followed quickly by an informed sequence of diagnostic and therapeutic interventions.

Pathophysiology

There are three forms of oligoanuria / anuria:

- Prerenal: in response to hypoperfusion of the kidney (e.g. as a result of dehydration by poor oral intake, cardiogenic shock, diarrhea, massive bleeding or sepsis)
- Renal: due to kidney damage (severe hypoperfusion, rhabdomyolysis, medication)
- Postrenal: as a consequence of obstruction of the urine flow (e.g. enlarged prostate, tumour compression urinary outflow, expanding hematoma or fluid collection)

However, oliguria and anuria usually reflect acute kidney injury irregardless etiology reason (Fig. 1.2.5.1). Acute kidney injury does not invariably present with oliguria: non-oliguric AKI occurs in 28–45% of the general ICU population but may be up to 50% of cases depending on the definition of AKI used, severity of illness and local practice patterns. Non-oliguric AKI in ICU patients is generally portrayed as having a better prognosis when compared with oliguric AKI, and thus, may lead to withholding renal replacement therapy in anticipation of recovery. However, in one study by Liangos et al., non-oliguric AKI was associated with a higher in-hospital mortality. It is therefore important to identify non-oliguric AKI patients who might require early dialytic therapy and not to delay this important intervention.

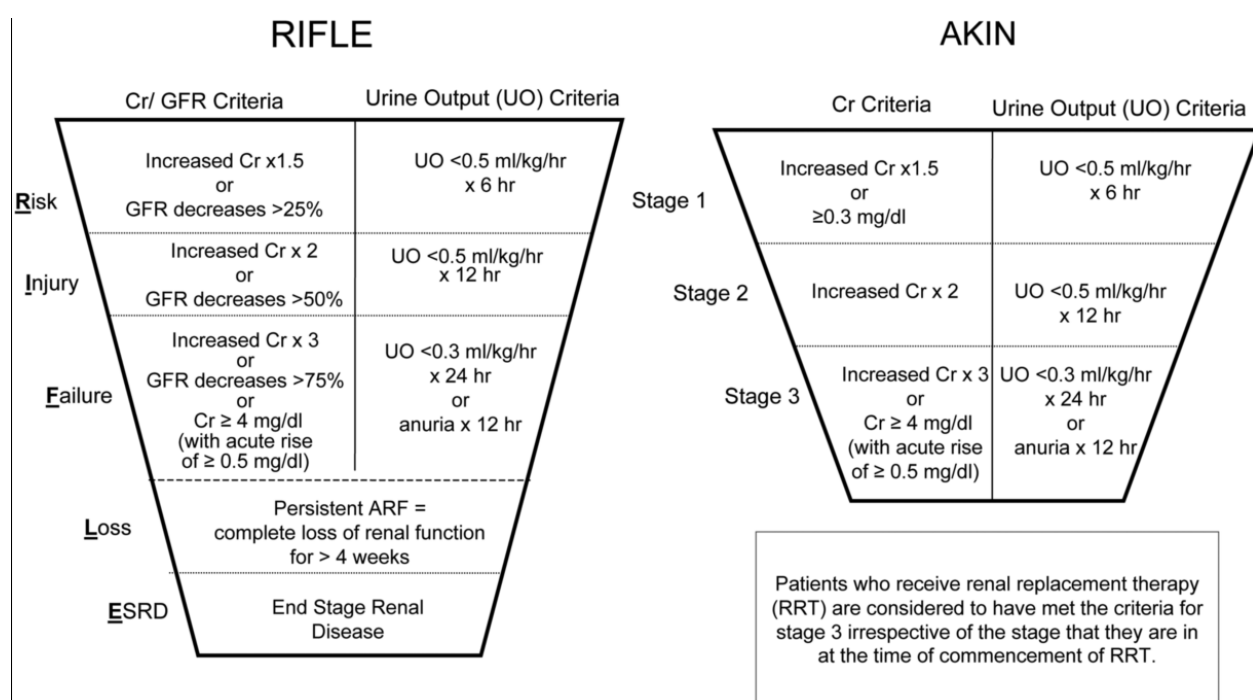


Fig. 1.2.5.1 RIFLE and AKIN classifications for acute kidney injury. Risk–Injury–Failure–Loss–Endstage renal disease (RIFLE) and Acute Kidney Injury Network (AKIN) classifications for acute kidney injury.

Note: ARF - acute renal failure; Cr - creatinine; GFR - glomerular filtration rate.

As mentioned, early clinical recognition of oliguria in adults requires the detection of urine flow of less than 0.5 ml/kg/h for six consecutive hours. The objective is to detect oliguria as soon as possible to identify pre-renal failure that can progress to ATN if not treated promptly. Anuria is defined as a passage of less than 50 mL of urine per day and represents a late stage of the pre-renal failure – presuming urinary obstruction has been ruled out. The recent RIFLE and AKIN classifications specify the duration of oliguria as >6h, >12h or >24h, recognising that the greater the duration of oliguria (increasing RIFLE class) the greater the severity of injury and hospital mortality. Studies applying the urinary output, in addition to the serum creatinine criteria, showed an increased ability of the AKIN classification to predict mortality.

If oliguria or anuria is suspected, urinary output should be monitored hourly. In patients with urinary catheters in situ, an initial assessment of the urinary catheter's position and patency should be performed. This can be achieved if indicated by 'flushing' the urinary catheter and examining the abdomen for a palpable bladder. Once the clinician has established there is no mechanical reason for the oliguria/anuria, further evaluation and diagnosis should proceed. A full clinical history and physical examination can frequently identify events and/or disease processes that underlie AKI and suggest an underlying diagnosis. Although the diagnosis of AKI currently relies on increased serum creatinine or a reduction in urine volume, the recent emergence of novel AKI biomarkers is anticipated to aid the early diagnosis of AKI.

The diagnosis of AKI into three distinct pathophysiological categories (pre-renal, intrinsic renal and post-renal) is of real clinical utility. The clinical circumstance usually suggests the category of renal impairment.

Pre-renal failure (azotaemia) is most common among hospitalised patients. Pre-renal indicates that the cause lies outside the kidney, specifically ‘before’ the kidney. A history of high output gastrointestinal losses, haemorrhage, sepsis, congestive heart failure (CHF) and/or decreased oral intake resulting in hypovolaemia or a combination of these factors associated with hypotension and decreased urine output suggests AKI due to pre-renal disease (or ATN if persistent). When more than 10–15% of the circulating volume is lost, findings on physical examination may include: tachycardia, dry mucous membranes, hypotension, low central venous pressure, oliguria, peripheral hypoperfusion with altered mentation and cold clammy skin with delayed capillary return.

Causes of ‘intrinsic’ renal failure depend on the clinical setting. In the ICU, pre-renal failure is the most common diagnosis, usually from hypovolaemia or sepsis. A failure of haemodynamic restoration with a trial of fluid replacement to restore urine output and the exclusion of post-renal pathologies supports the diagnosis. Allergic interstitial nephritis, usually due to antibiotics may also be responsible.

Post-renal failure is due to urinary tract obstruction and accounts for <5% of cases of AKI. Patients with complete bilateral urinary tract obstruction may present with anuria. Obstruction of the bladder neck is the most common cause of post-renal AKI and may complicate prostatic disease (e.g. hypertrophy, neoplasia, or infection), neurogenic bladder, or therapy with anticholinergic drugs. Less common causes of acute lower urinary tract obstruction include blood clots, calculi, and urethritis with spasm.

Persistent severe oliguria or anuria (lasting several weeks) should prompt suspicion of severe ATN (5% of survivors do not recover renal function) or cortical necrosis. Classically severe, prolonged renal hypoperfusion results in patchy focal tubular damage including necrosis and apoptosis of tubular cells.

Diagnosis

According to the AKIN/RIFLE criteria, the diagnosis of AKI is based on either elevation of serum creatinine or the presence of oliguria. Measurements of blood urea nitrogen and serum creatinine to assess glomerular filtration rate (GFR) are done daily in the ICU but can be monitored more frequently e.g. 12 hourly. A rise in serum creatinine is associated with a parallel decrease in GFR and generally implies a reduction in kidney function, and vice versa. The rate of change of urea and creatinine blood levels may differ in different pathologic situations and this change (of one relative to the other) can be used diagnostically.

In 'pre-renal' disease, the urinary macroscopic appearance is concentrated, the dipstick specific gravity (SG) is high (>1.018), as is the osmolality (>350 mosm/l); the spot urine Na is low (<10 mmol/l) and the fractional excretion of sodium (FeNa) is reduced ($<1\%$). These indices become unreliable once the patient has received diuretic therapy and may also be confounded by endogenous osmolar substances such as glucose or urea. FeUrea may be at least as reliable, if not more so, than FeNa. The FeUrea appears more accurate in detecting pre-renal azotaemia, in particular in patients taking diuretics. Typical biochemical values associated with 'intrinsic' renal oliguria are: high urinary sodium concentration (>20 mmol/l), FeNa is $>1\%$), and urinary osmolality <350 mosm/l.

Some authorities advocate examining the urinary sediment; others do not. Hyaline and fine granular casts are common in pre-renal disease, ATN usually is associated with coarse granular casts, muddy brown casts and tubular epithelial cell casts. The presence of red blood cell casts indicates glomerular disease. The urinary sediment in post-renal failure is often very bland in appearance, without casts. The discriminating ability of these findings is of limited practical value, particularly in the ICU setting. A systematic review of studies describing urinary biochemistry indices, and microscopy in AKI demonstrated significant variability and inconsistency in these measures. In fact, no single measure of urinary biochemistry, derived index, or pattern on microscopy can be used reliably to diagnose AKI or classify or predict the clinical course of AKI in septic patients.

Biomarkers of AKI

Serum creatinine is widely used in the diagnosis of AKI and is considered to be specific but generally an insensitive biomarker of renal dysfunction. With the recognition of the importance of small changes in serum creatinine of >0.3 mg/dL (26.4 μ mol/L), the sensitivity of serum creatinine to detect early renal injury has improved. However, significant renal tubular injury can occur before such creatinine increments have had time to develop. Serum creatinine concentration is greatly influenced by changes in muscle mass and tubular secretion, body weight, race, age, sex, total body volume, drugs, muscle metabolism and protein intake. For these reasons it is generally considered a poor marker of early AKI and an even poorer reflection of kidney function because patients with AKI are not in steady state and serum creatinine therefore lags far behind renal injury. The recent development of novel biomarkers for the early detection of AKI promises to be a real advance in critical care and acute nephrology. The most promising of these include: NGAL (neutrophil gelatinase-associated lipocalin), IL-18, KIM-1, Cystatin C, and L-FABP.

Urinary NGAL distinguished AKI from other forms of kidney dysfunction and predicted excess morbidity after hospital admission. Logistic regression analysis demonstrated that NGAL was a better predictor of nephrology consultation, dialysis, ICU admission and death than other conventional or novel biomarkers of acute kidney injury. The AUROC (area under the receiver-operating characteristic) curves was 0.95, sensitivity was 0.900 (95% CI 0.730 to 0.980) and specificity was 0.995 (95% CI 0.990 to 1.000) for prediction of AKI using a cutoff value of 130 μ g/g.

With the inevitable introduction of the urinary and serum AKI biomarkers into clinical practice, the specific use of individual and combination biomarkers across patient cohorts e.g. septic patients, patients with pre-existing renal disease and other high-risk AKI clinical settings needs further investigation. On the basis of existing literature, serum but not urinary NGAL has limited capacity to detect early AKI in septic patients.

The performance of biomarkers of AKI in patients with pre-existing renal disease with tubular damage has recently been studied. Many biomarkers, such as urinary NGAL and glutathione S-transferases, perform better in those with no history

of chronic kidney disease. Continued comparison among the different AKI biomarkers across the different patient cohorts is essential for the ongoing development of the biomarkers in the evolving field of AKI and it is possible that ultimately an AKI biomarker package will emerge.

Ultrasonography

Ultrasonography is a bedside, non-invasive investigation, which avoids the need for administration of potentially nephrotoxic contrast media. The main purpose of the investigation is to diagnose or rule out an obstructive cause of oliguria/anuria. It also provides information on kidney size, enlarged kidneys being typical for AKI but small kidney(s) for chronic kidney disease. Papillary necrosis can be detected and might be useful in the diagnosis of analgesic nephropathy. Duplex sonography may distinguish between intrinsic and pre-renal disease. Small kidneys are suggestive of long-standing (rather than acute) renal disease. Congenital abnormalities e.g. polycystic kidney disease and kidney agenesis may be diagnosed. Assessment of renal parenchymal appearance can provide information on renal cortex pathologies such as glomerulonephritis or cortical infarction. Duplex Doppler images of renal artery can provide further information on renal artery occlusion by embolus.

Radiology

Plain films are useful for detecting kidney stones and calcification and for determining renal size. Hydroureter in ureterovesical junction obstruction and/or hydronephrosis due to obstruction at the pelviureteric junction may be seen. In bladder outlet obstruction, bilateral ureteric dilatation is seen.

Intravenous urogram

This carries a risk of nephropathy caused by the intravenous contrast agent, particularly in diabetic patients. In severe obstruction, the nephrogram may be delayed

CT scanning

A CT renal study is not commonly done in the critically ill but is a useful non-contrast study to diagnose nephrolithiasis or pyelonephritis as a cause of AKI.

Retrograde and antegrade contrast studies

Where the risk of contrast-induced nephropathy is great and when considering surgical intervention, retrograde or antegrade (urological/percutaneous) contrast studies, may be employed.

Haemodynamic assessment

Assessment of circulatory status may require CVP monitoring, pulmonary artery catheterisation or other techniques for assessing cardiac output and filling pressures e.g. non-invasive measurement of cardiac output. Mixed venous oxygen saturation is used as an indirect indication of oxygen balance which can be affected by cardiac output, haemoglobin, arterial saturation and tissue oxygen consumption. Central venous oxygen saturation has been shown to be a useful early guide to targeted resuscitation in septic patients. Transthoracic or transoesophageal echocardiography (TOE) should be considered where greater knowledge of cardiac function is required for complete assessment. Targeted therapy entails frequent serial measurement and therapeutic adjustment.

Bladder pressure measurement

Often an overlooked reason for acute oliguria is abdominal compartment syndrome defined as intra-abdominal pressure greater than 20 mmHg and abdominal perfusion pressure less than 60 mmHg occurring in association with a new and attributable organ dysfunction e.g. in a bleeding postoperative abdominal surgical patient or in those with severe ascites or other cause of acute abdominal distension. Abdominal compartment syndrome causes oliguria and AKI mainly by directly increasing renal outflow pressure and reducing renal perfusion. Using the in-dwelling urinary catheter, no more than 25ml of sterile saline is infused into the bladder, following which intravesical pressure is measured using a water manometer or a pressure transducer connected to a side-port needle or three-way tap in the catheter system. Appropriately modified catheter systems are available. Sugrue has advocated a more standardised diagnostic approach to intra-abdominal pressure measurement and the international conference of experts has brought this forward.

1.3.3 Hyperaminoaciduria

Hyperaminoaciduria is significant as a manifestation of aberrant cellular function in the kidney and in other organs (bone, liver, and brain in particular). The various patterns of hyperaminoaciduria may be described in terms of the endogenous renal clearances of the individual amino acids.

Physiology

Normally, those amino acids with the higher plasma concentrations or with the higher endogenous renal clearances or with both appear in the urine in the greater concentrations. The pattern of generalized renal aminoaciduria results when mechanisms common to the reabsorption of all amino acids are impaired. This pattern is nonspecific and may be seen in a variety of syndromes, the most common of which are the Fanconi syndrome and vitamin D deficiency states. Generalized renal hyperaminoaciduria may be distinguished from the generalized “overflow” aminoaciduria of severe hepatic cell damage and from the specific patterns of renal and systemic origin.

Causes

The finding of generalized renal hyperaminoaciduria in diseases of varied etiology suggests that this type of aminoaciduria is a very sensitive manifestation of impaired renal tubular function. Although the aminoaciduria results from renal injury, defects involving many organs may be present in these diseases. Indeed, cerebral and hepatic features may predominate the clinical picture in some of these diseases (e.g., galactosemia, lead encephalopathy, and Wilson's disease).

The occurrence of the triad of renal aminoaciduria, glycosuria, and hypophosphatemia provides further evidence of an interrelationship between the renal tubular mechanisms for the reabsorption of these substances. Still other derangements of renal tubular function may be present when this triad is found. This emphasizes the need for complete studies of renal function in clinical problems in which any one discrete tubular function is obviously deranged.

Distinctive “patterns of aminoaciduria” are found in various forms of rickets and osteomalacia. As the therapy differs in each, urinary amino acid studies may be helpful in therapeutic management. Likewise, specific patterns of aminoaciduria

facilitate the accurate diagnosis of some forms of cerebral defect which have similar clinical features (e.g., phenylketonuria and “maple syrup urine disease”).

Testing

The study of patterns of aminoaciduria has proved to be a valuable technique in genetic surveys and in the unraveling of obscure metabolic disorders in which the metabolism of individual amino acids and closely related intermediates is involved.

Cystinuria

Cystinuria is characterized by the excessive urinary excretion of cystine and the dibasic amino acids ornithine, lysine, and arginine.

Etiology and Pathogenesis

These four amino acids share a transport system on the brush border membrane of the proximal tubule. Because of the relative insolubility of cystine when its urine concentration exceeds 250 mg/l (1 mmol/l), patients with cystinuria have recurrent renal calculi.

Cystinuria is an autosomal recessive trait with a disease incidence of 1 in 15,000. Initially, there appeared to be three genetic types on the basis of in vitro studies of intestinal transport and amino acid excretion in heterozygotes. More recently, two genes (SLC3A1 and SLC7A9) have been identified that are defective in cystinuria. SLC3A1 heterozygotes have normal excretion rates for cystine. SLC7A9 heterozygotes have cystine excretion rates that range from normal to nearly that of homozygous patients. On the basis of these data, a new classification has been proposed. Type A involves mutations in both SLC3A1 genes, and type B mutations in SLC7A9. Type AB is compound heterozygote. Type A accounts for 38% of cystinuria patients, type B for 47%, and type AB for 14%.

Clinical Manifestations

Cystine stones are typically yellow-brown and are radiopaque. Cystine crystals appear as microscopic, flat hexagons in the urine, and this is a clue to the diagnosis.

Diagnosis

Patients can be screened for cystinuria with the cyanide-nitroprusside test, but type B heterozygotes may also give a positive result. The definitive test is to quantify

cystine and dibasic amino acid excretion in a 24-hour urine specimen. Homozygotes excrete more than 118 mmol cystine/mmol creatinine (250 mg/g).

Treatment

The aim of therapy in cystinuria is to lower the urine cystine concentration to below 300 mg/l (1.25 mmol/l). The first step is to increase fluid intake. However, because most patients with cystinuria excrete 0.5 to 1 g/day of cystine, a urine output of 2 to 4 l/day is needed to achieve this goal. Cystine solubility increases in alkaline urine, but the urine pH must be above 7.5 to be effective. In patients with recurrent stone disease, thiols, such as penicillamine, are extremely useful through the formation of a more soluble mixed disulfide of the thiol and cysteine from cystine. The thiols also reduce the overall excretion of cystine through an unknown mechanism. Penicillamine should be started at 250 mg/day and gradually increased (maximum, 2 g/day) during 3 months to achieve a urine cystine concentration below 300 mg/l in conjunction with a high fluid intake. Tiopronin is equally effective and is better tolerated than penicillamine. It should also be started at a low dose and slowly increased (maximum, 2 g/day). Captopril can be useful (an effect resulting from its thiol structure, not its angiotensin-converting enzyme inhibitor effect), but the dose range (75 to 150 mg/day) may be limited by its hypotensive effects.

Hartnup Disease

Hartnup disease is an autosomal recessive trait characterized by a neutral aminoaciduria that arises from a defect in a specific carrier for neutral amino acid transport present in both the intestine and the proximal renal tubule. The gene responsible for Hartnup disease is SLC6A19. It codes for the neutral amino acid transporter B0AT1. From newborn screening programs, the genetic defect is more common than originally thought because most individuals with the aminoaciduria never manifest any symptoms. Individuals who become symptomatic with Hartnup disease have pellagra-like clinical features, including a photosensitive dermatitis, ataxia, and psychotic behavior. These symptoms appear to be secondary to niacin deficiency that is in part due to inadequate intestinal absorption of tryptophan, the precursor for niacin synthesis. However, most individuals who inherit the Hartnup

transport defect do not have symptoms, so there must be other environmental or genetic factors that contribute to disease. Nicotinamide supplementation leads to clearing of the skin disease and, on occasion, some of the neurologic problems. The renal loss of neutral amino acids appears to have little clinical importance.

Iminoglycinuria

Iminoglycinuria is a benign heritable defect in the proximal tubule transporter PAT1, leading to incomplete reabsorption of proline, hydroxyproline, and glycine.

Lysinuric Protein Intolerance

Lysinuric protein intolerance is associated with recurrent bouts of hyperammonemia after a protein load, resulting from the decreased renal and intestinal dibasic amino acid transport.

Other Aminoacidurias

Rare individuals have been described with abnormalities in the excretion of other amino acids. These usually occur in association with mental retardation.

1.3.4 Oxaluria

Oxaluria also known as hyperoxaluria, is a disorder where the body is unable to properly metabolize oxalate. It is defined as excretion of an excess of oxalic acid or oxalates, especially calcium oxalate, in the urine. Oxalate is an organic salt that is able to dissolve with potassium and sodium. Oxalate is not needed for any processes in the human body, so a normal healthy liver excretes the majority of it.

Cause

Hyperoxaluria is usually a genetic or hereditary disorder and it could start from a very early age without much notice, until one goes for diagnosis. It starts to occur when there is a deficiency of an enzyme that inhibits the formation of oxalates. The compound that could form kidney stones in any individual. Although hyperoxaluria is usually classified into primary, enteric or mild hyperoxaluria among others, the disease is nonetheless bad to have and it could lead to renal or kidney failure and death.

Primary hyperoxaluria an autosomal recessive disorder characterized by urinary excretion of oxalate, with nephrolithiasis, nephrocalcinosis, early onset of

renal failure, and often a generalized deposit of calcium oxalate. High levels of oxalate in the urine lead to Hyperoxaluria, divided into two different types, Type 1 and Type 2.

Primary hyperoxaluria Type 1 is more common than Type 2. It is a genetically inherited disease caused by the absence of an enzyme. The enzyme that is absent is alanine-glyoxalate aminotransferase, an enzyme necessary to detoxify the enzyme glyoxalate. The liver then produces too little of the enzyme glyoxalate. The deficiency of this enzyme results in higher amounts oxalate in the body. Oxalate cannot be metabolized, so it must be eliminated by means of the kidney and the urine. This results in high amounts of oxalate in the urine, thus causing hyperoxaluria type 1.

Primary hyperoxaluria Type 2 is a very rare disease, and is much less common than Type 1. The occurrence of Type 2 is estimated to be 1 in 100,000 to 1,000,000. Type 2 is also a genetically inherited disease. In people with Type 2 Oxaluria, the enzyme glyoxalate reeducates is missing in the liver. This enzyme is found in cells of the liver. When there is too little of this enzyme in the liver, high levels of oxalate are produced. This in turn causes high levels of oxalate in the urine, from which kidney stones are produced.

Oxalate is usually absorbed through the colon, but it can be absorbed elsewhere in the urinary tract. Enteric hyperoxaluria formation of calcium oxalate calculi in the urinary tract, occurring after extensive resection or disease of the ileum, due to excessive absorption of oxalate from the colon. Hyperoxaluria is a urinary infection disease, which occurs when there is too much oxalate present and escaping in the urine. This disease infection could easily lead to kidney stones forming in the kidneys and this could easily cause kidney damage and breakdown in any one individual if care is not taken to quickly treat the condition.

Clinical

The conditions of hyperoxaluria can worsen with damage to the kidneys which only increases the amount of oxalate in the system, building up more damage over time. In the most severe cases, hematological problems can occur such as anemia and

thrombocytopenia which can have very serious consequences. Other Oxaluria symptoms include lack of urine production, nausea, vomiting, abdominal pain, dry or burning mouth and the presence of oxalate crystals in various organs of the body including the heart and eyes.

Some Oxaluria symptoms can be misdiagnosed as other illnesses and in such cases getting a second opinion can be important in catching this disease early enough to avoid more serious treatments. Be sure to consult with your doctor when receiving your diagnosis.

But the important side effect of Oxaluria Symptoms include renal failure which can lead to other complications including dialysis, which can control some of the effects of renal failure but cannot remove the excess oxalate from the blood. A renal transplant can be more effective and is a primary treatment for severe Hyperoxaluria. Also, a liver transplant may be required as well to help control the Oxaluria symptoms by correcting the metabolic effect of the disease.

Recognizing Oxaluria symptoms is the first step towards getting proper treatment of this painful and debilitating disease. Understanding Oxaluria causes early on for those who may be susceptible can result in a change to the diet or addition of Vitamin B6 which may reduce if not prevent the more serious Oxaluria symptoms which can grow more painful and reduce the quality of life day by day.

Treatment

There are many options available for oxaluria treatment, including taking oxaluria medication and switching to an oxaluria diet. Patients have responded favorably to an oxaluria medication such as pyridoxine, or vitamin B6, which helps to reduce the production of oxalate. Pyridoxine is sometimes combined with orthophosphate which can provide long-term benefits in patients suffering from hyperoxaluria. Orthophosphate helps to lower the calcium level in the urine. Pyridoxine can also be combined with magnesium supplements which also helps to decrease excess calcium oxalate.

In addition to taking oxaluria medication, oxaluria treatment also involves making some changes to your diet. It is important to maintain an oxaluria diet by

avoiding foods which contain high amounts of oxalate. Such foods include things like spinach, parsley, nuts, rhubarb and berries. Studies have shown that vegetables high in oxalate can be boiled in order to reduce the oxalate level and then consumed, however, boiling also removed the valuable nutrients. Without the nutrients, the vegetables have little benefit so it is more preferable to avoid these high-oxalate foods altogether.

Vitamin C may also contribute to the development of oxaluria by converting to oxalate in the body. Individuals with oxaluria should avoid taking vitamin C supplements and foods high in vitamin C such as cranberry juice and cranberry products. Limiting your fat intake has also been suggested as part of an oxaluria diet.

Another vital addition to the oxaluria diet is to drink plenty of water. Drinking at least two liters per day will assist in the success of the oxaluria treatment and urinary tract treatment. The water helps to keep the calcium oxalate from building up by flushing out the kidneys and urinary tract. This can work towards preventing the formation of kidney stones. If large kidney stones have formed and are obstructing the flow of urine, further urinary tract treatment may be required, such as having the stones removed or broken up so they may pass through the urine. If you suffer from hyperoxaluria, you should see your health care provider to discuss oxaluria treatment options. Your doctor can work with you to decide on the most beneficial oxaluria medication and discuss maintaining an appropriate diet. If your symptoms are more serious and you require urinary tract treatment, your health care provider can make sure you receive the proper care that you need.

1.3.5 Uricosuria

Uric acid is the final product of purine metabolism in human beings. Despite the fact that uric acid was first identified approximately 2 centuries ago, certain pathophysiologic aspects of hyperuricemia are still not clearly understood. For years, hyperuricemia has been identified with or thought to be the same as gout, but uric acid has now been identified as a marker for a number of metabolic and hemodynamic abnormalities.

Uric acid excretion depends on dietary, genetic reason and breakdown of purines. However, Urate secretion does appear to correlate with the serum urate concentration because a small increase in the serum concentration results in a marked increase in urate excretion. Urate handling by the kidneys involves filtration at the glomerulus, reabsorption, secretion, and, finally, postsecretory reabsorption. Consequently, altered uric acid excretion can result from decreased glomerular filtration, decreased tubular secretion, or enhanced tubular reabsorption. While decreased urate filtration may not cause primary hyperuricemia, it can contribute to the hyperuricemia of renal insufficiency. Decreased tubular secretion of urate occurs in patients with acidosis (eg, diabetic ketoacidosis, ethanol or salicylate intoxication, starvation ketosis). The organic acids that accumulate in these conditions compete with urate for tubular secretion. Finally, enhanced reabsorption of uric acid distal to the site of secretion is the mechanism thought to be responsible for the hyperuricemia observed with diuretic therapy and diabetes insipidus.

Underexcretion of urate can be identified in follow:

- Idiopathic
- Familial juvenile gouty nephropathy: This is a rare autosomal dominant condition characterized by progressive renal insufficiency. These patients have a low fractional excretion of urate (typically 4%). Kidney biopsy findings indicate glomerulosclerosis and tubulointerstitial disease but no uric acid deposition.
- Renal insufficiency: Renal failure is one of the more common causes of hyperuricemia. In chronic renal failure, the uric acid level does not generally become elevated until the creatinine clearance falls below 20 mL/min, unless other contributing factors exist. This is due to a decrease in urate clearance as retained organic acids compete for secretion in the proximal tubule. In certain renal disorders, such as medullary cystic disease and chronic lead nephropathy, hyperuricemia is commonly observed even with minimal renal insufficiency.
- Syndrome X: This metabolic syndrome is characterized by hypertension, obesity, insulin resistance, dyslipidemia, and hyperuricemia. This is associated with a decreased fractional excretion of urate by the kidneys.

- **Drugs:** Causative drugs include diuretics, low-dose salicylate, cyclosporine, pyrazinamide, ethambutol, levodopa, nicotinic acid, and methoxyflurane.

- Hypertension

- **Acidosis:** Types that cause hyperuricemia include lactic acidosis, diabetic ketoacidosis, alcoholic ketoacidosis, and starvation ketoacidosis.

- **Preeclampsia and eclampsia:** The elevated uric acid associated with these conditions is a key clue to the diagnosis because uric acid levels are lower than normal in healthy pregnancies.

- Hypothyroidism

- Hyperparathyroidism

- Sarcoidosis

- **Lead intoxication (chronic):** History may reveal occupational exposure (eg, lead smelting, battery and paint manufacture) or consumption of moonshine (ie, illegally distilled corn whiskey) because some, but not all, moonshine was produced in lead-containing stills).

- Trisomy 21

Oversecretion is due to purine-rich diet: A diet rich in meats, organ foods, alcohol, and legumes can result in an overproduction of uric acid. Ethanol increases the production of uric acid by causing increased turnover of adenine nucleotides. It also decreases uric acid excretion by the kidneys, which is partially due to the production of lactic acid. Exercise may result in enhanced tissue breakdown and decreased renal excretion due to mild volume depletion.

Testing

Urinary uric acid excretion

If uric acid levels are found to be persistently elevated, an estimation of total uric acid excretion may be needed. The estimation of uric acid excretion is recommended in young males who are hyperuricemic, females who are premenopausal, people with a serum uric acid value greater than 11 mg/dL, and patients with gout.

One protocol recommends obtaining two 24-hour urine collections for creatinine clearance and uric acid excretion. The first collection is performed while patients are on their usual diet and alcohol intake. At the end of the first 24-hour collection, serum creatinine and urate levels are checked for an estimation of the creatinine clearance. The patient then goes on a low-purine, alcohol-free diet for 6 days, with a repeat 24-hour urine collection performed on the last day, followed by a serum creatinine and uric acid evaluation.

Depending on the 24-hour urine uric acid levels before the purine-restricted diet and after the purine-restricted diet, patients who are hyperuricemic can be categorized into 3 groups.

- High-purine intake - Prediet value greater than 6 mmol/d, postdiet value less than 4 mmol/d
- Overproducers - Prediet value greater than 6 mmol/d, postdiet value greater than 4.5 mmol/d
- Underexcretors - Prediet value less than 6 mmol/d, postdiet value less than 2 mmol/d

Fractional excretion of urate on a low-purine diet

This test should be used to investigate the degree of underexcretion in patients with hyperuricemia or gout in patients for whom the cause cannot be determined. The fractional excretion of urate is calculated by the following formula:

$$\text{Fractional excretion of urate} = \frac{[(\text{urine uric acid}) * (\text{serum creatinine}) * (100\%)]}{[(\text{serum uric acid}) * (\text{urine creatinine})]}$$

The reference intervals for patients on a low-purine diet and normal renal function are as follows:

- Males - 7-9.5%
- Females - 10-14%
- Children - 15-22%

Spot urine ratio of uric acid to creatinine

If a 24-hour urine collection is not possible, measure the ratio of uric acid to creatinine from a spot urine collection. A ratio greater than 0.8 indicates overproduction. The ratio also helps differentiate acute uric acid nephropathy from the hyperuricemia that occurs secondary to renal failure. The ratio is greater than 0.9 in acute uric acid nephropathy and usually less than 0.7 in hyperuricemia secondary to renal insufficiency.

Treatment

Treatment is directed at the cause.

Uric acid nephrolithiasis

Allopurinol is the mainstay of drug therapy in patients with hyperuricemia who develop uric acid stones. Patients with calcium stones who are hyperuricosuric may also benefit from allopurinol because urate crystals in the urine may act as a nidus for other stones to form. Potassium citrate and occasionally sodium bicarbonate or acetazolamide may be required to alkalinize the urine and to decrease the solubility of uric acid. Adequate hydration is recommended to maintain a high urine output of at least 2 L unless otherwise contraindicated for other medical conditions where volume overload may be a concern.

Uric acid nephropathy

Over the years, efforts to prevent uric acid nephropathy, especially in the oncological setting, have resulted in a decrease in mortality from uric acid nephropathy. Intravenous hydration with saline and the administration of furosemide or mannitol (to dilute the urine) are necessary to prevent further precipitation of uric acid. Alkalinizing the urine with sodium bicarbonate or acetazolamide may be necessary to further enhance uric acid elimination. Rasburicase, a recombinant urate oxidase, is now approved for use in preventing complications of hyperuricemia during the tumor lysis syndrome. It facilitates the conversion of urate to a more soluble product, allantoin.

Higher doses than usual (600-900 mg/d) are administered to decrease uric acid production prior to chemotherapy in patients with leukemias and lymphomas; allopurinol and hydration are continued for several days. If acute renal failure

develops despite these measures, then early hemodialysis is indicated to reduce the total body burden of uric acid, thereby facilitating recovery of renal function.

1.3.6 Glucosuria

Renal glycosuria refers to the appearance of readily detectable glucose in the urine when the plasma glucose concentration is in a normal range. When the plasma glucose concentration is in a physiologic range, virtually all the filtered glucose is reabsorbed in the proximal tubule. Filtered glucose enters the proximal tubule through two specific carriers (SGLT1 and SGLT2) coupled to sodium and exits the cell through the sugar transporters GLUT1 and GLUT2. However, when the plasma level exceeds the physiologic range, the filtered load exceeds the capacity of these carriers, and glucose begins to appear in the urine; this is termed the renal threshold.

Causes

The inherited form usually involves a reduction in the glucose transport maximum (the maximum rate at which glucose can be resorbed) and subsequent escape of glucose in the urine. The acquired form of renal glucosuria occurs primarily in advanced chronic kidney disease.

The inherited disorder is usually transmitted as an autosomal dominant trait but is occasionally recessive. Renal glucosuria may occur without any other abnormalities of renal function or as part of a generalized defect in proximal tubule function (see Renal Transport Abnormalities: Type 2 (proximal) RTA). It also may occur with various systemic disorders, including Fanconi syndrome, cystinosis, Wilson's disease, hereditary tyrosinemia, and oculocerebrorenal syndrome (Lowe syndrome).

Clinical

Renal glucosuria is asymptomatic and without serious sequelae. However, if there is an associated generalized defect in proximal tubular function, symptoms and signs may include hypophosphatemic rickets, volume depletion, short stature, muscle hypotonia, and ocular changes of cataracts or glaucoma (oculocerebrorenal

syndrome) or Kayser-Fleischer rings (Wilson's disease). With such findings, transport defects other than glucosuria should be sought.

Diagnosis

The disorder is typically initially noted on routine urinalysis. Diagnosis is based on finding glucose in a 24-h urine collection (when the diet contains 50% carbohydrate) in the absence of hyperglycemia (serum glucose < 140 mg/dL). To confirm that the excreted sugar is glucose and to exclude pentosuria, fructosuria, sucrosuria, maltosuria, galactosuria, and lactosuria, the glucose oxidase method should be used for all laboratory measurements. A normal result on an oral glucose tolerance test is also required for the diagnosis according to some experts.

Treatment

Isolated renal glucosuria is benign; no treatment is necessary.

1.3.7 Calceuria

Approximately 90% of cases of calceuria are caused by malignancy or hypoparathyroidism. About 20-30% of patients with cancer have hypercalcemia during the course of the disease, and its detection may signify an unfavorable prognosis. Of the cases due to malignancy, approximately 80% are due to bony metastases, while the other 20% are due to PTHrP effects. The remaining 10% of cases of calceuria are caused by many different conditions, including vitamin D-related problems, disorders associated with rapid bone turnover, thiazides, tubulal dysfunction or renal failure, and, in rare cases, familial causes. Those related to malignancy (lung, breast, and myeloma are the most common tumors) include the following:

- Solid tumor metastases
- Solid tumors with humoral effects
- Hematologic malignancies

Those related to the parathyroid include the following:

- Primary hypoparathyroidism
- Multiple endocrine neoplasia type 1 or type 2A
- Lithium-related release of PTH

- Familial cases of high PTH

Those related to vitamin D include the following:

- Vitamin D toxicity
- Granulomatous disease (especially sarcoidosis)

Those related to high bone turnover include the following:

- Hyperthyroidism
- Immobilization (especially in Paget disease)
- Thiazides
- Vitamin A intoxication

Renal failure (milk-alkali syndrome)

Other causes related to particular mechanisms are as follows:

- Increased intestinal calcium absorption
- Idiopathic infantile hypercalcemia (Williams syndrome)
- Vitamin D intoxication
- Vitamin A intoxication
- Granulomatous disorders, eg, sarcoidosis

Increased renal calcium excretion

- Hypoparathyroidism

Increased bone resorption

- Immobilization
- Malignancy

Uncertain mechanism

- Hypophosphatasia
- Dietary phosphate deficiency

Treatment

- Treatment is directed at the cause

1.3.8 Phosphateuria

Increased excretion of phosphate in urine is a more common mechanism for the development of hypophosphatemia. The most common cause of increased renal

phosphate excretion is hyperparathyroidism due to the ability of PTH to inhibit proximal renal tubule phosphate transport. However, frank hypophosphatemia is not universal and is most often mild. Increased excretion of phosphate can also be induced by forced saline diuresis due to the inhibitory effect of saline diuresis on all proximal renal tubule transport processes. Again, the degree of hypophosphatemia is generally minimal. Vitamin D deficiency not only impairs intestinal absorption, but also decreases renal absorption of phosphate. Several genetic and acquired syndromes of phosphate wasting and associated skeletal abnormalities have been described.

Clinic

Most patients with phosphaturia are asymptomatic. History alone rarely alerts the physician to the possibility of phosphaturia. In cases of oncogenic osteomalacia or in some of the genetic causes of phosphate wasting, patients complain of bone pain and fractures. Otherwise, physicians must have a high index of suspicion and must be aware of the clinical conditions that might be complicated by hypophosphatemia.

Patients with chronic phosphate-wasting syndromes frequently present with bone pain, muscle weakness, and skeletal disorders. In the genetic syndromes of renal phosphate wasting or acquired oncogenic osteomalacia, the serum phosphate level is generally moderately depressed. Symptoms are predominantly muscle weakness and bone pain or fractures.

Lab Studies

Serum calcium, magnesium, and potassium

In addition to serum phosphate studies, calcium and magnesium studies can be helpful. High calcium levels coupled with low phosphate levels suggest primary hyperparathyroidism, while low calcium levels suggest vitamin D deficiency or malabsorption. Because of the many factors that regulate calcium independently of phosphate, serum calcium concentrations may be within reference ranges in either of these circumstances and thus cannot be used for a definitive diagnosis. Low magnesium levels are also suggestive of poor nutrition.

Serum potassium derangements, especially hypokalemia, may occur with certain hypophosphatemic conditions, such as DKA and alcoholism.

Serum albumin

Because almost half of serum albumin is bound to serum calcium, changes in serum albumin levels affect the total calcium concentration. Thus, in hypoalbuminemia, a decrease in albumin of 1 g/dL causes a fall in total calcium of approximately 0.8 mg/dL.

Intact PTH and vitamin D levels

Primary hyperparathyroidism is very common, especially in elderly persons. Vitamin D deficiency is also very common, especially in geriatric or chronically ill persons. The excellent assays available for evaluation of PTH and vitamin D levels have simplified confirmation of the diagnosis of PTH and vitamin D disorders. A high PTH level in the presence of high calcium and low phosphate levels is very suggestive of primary hyperparathyroidism. If the PTH level is high and the calcium and phosphate levels are low, secondary hyperparathyroidism is probable, perhaps due to intestinal malabsorption. The intestinal malabsorption could be due to isolated vitamin D deficiency or to a primary gastrointestinal disorder.

Arterial blood gas: An arterial blood gas study should be ordered if respiratory alkalosis is under consideration as a cause of hypophosphatemia. Serum lactate, CBC with differential, and serum ammonia level, may be useful in selected patients to investigate some of the common causes of hypophosphatemia, such as sepsis and hepatic encephalopathy, which can cause respiratory alkalosis with subsequent hypophosphatemia.

Urinary phosphorus determination

A 24-hour urine collection for phosphate can be performed if the question of phosphate wasting is unresolved. A fractional excretion of phosphate of greater than 15% in the presence of hypophosphatemia confirms the presence of renal phosphate wasting.

Urinalysis

Phosphate wasting and subsequent hypophosphatemia can be due to proximal tubule disorders such as Fanconi syndrome. To determine if the patient has a generalized proximal renal tubule disorder, urinalysis should be performed and serum

bicarbonate, serum glucose, and serum uric acid levels should be measured. Full-blown Fanconi syndrome consists of renal glycosuria, aminoaciduria, type II renal tubular acidosis, hypouricemia due to hyperuricosuria, and hypophosphatemia due to phosphate wasting.

Urinalysis demonstrates the presence of amino acids (proteinuria) and glucose. If the urine dipstick is positive for glucose at a time when the serum glucose concentration is less than 180 mg/dL, then renal glycosuria or renal glucose wasting is also present. Uric acid levels are also low, often less than 2 mg/dL. Evidence of mild nonanion gap metabolic acidosis is observed on the renal profile.

Medical Care

Medical care is highly dependent on 3 factors: cause, severity, and duration. Phosphate distribution varies among patients, so no formulas reliably determine the magnitude of the phosphate deficit. The average patient requires 1000-2000 mg (32-64 mmol) of phosphate per day for 7-10 days to replenish the body stores.

Prognosis

Prognosis depends on underlying disease.

1.3.9 Leukocyturia

Leukocyturia (LEU) is more than 15 leukocytes per high power field. Differential diagnoses include urinary tract infections, urogenital tuberculosis (sterile leucocyturia), nephrolithiasis and foreign bodies. Isolated pyuria is unusual since inflammatory reactions in the kidney or collecting system are also associated with hematuria. The presence of bacteria suggests infection, and white blood cell casts with bacteria are indicative of pyelonephritis. White blood cells and/or white blood cell casts may also be seen in tubulointerstitial processes such as interstitial nephritis, systemic lupus erythematosus, and transplant rejection.

Interpretation.

The presence of LEU could be interpreted as a marker of interstitial nephritis. The association between a history of tuberculosis and LEU possibly reflects sequelae of the urological extension of tuberculosis which is common but underdiagnose. The proportion of patients with a history of tuberculosis was very high. Those patients

may have had urological extension of tuberculosis and may have had secondarily developed leukocyturia. The availability of tuberculosis diagnosis tools such as mycobacterial culture is limited. The association of LEU and NSAID is not surprising. Interstitial nephritis has been reported after exposure to NSAID with leukocyturia tending to last from a month to a year. The mechanism and risk factors of NSAID toxicity have not yet been clearly identified]. NSAID may also aggravate previously damaged kidneys. In South Africa using a once-off dipstick and reported leukocyturia in 30.3% of the patients, 70.9% of whom were sterile. Many authors hypothesized that this could be caused by interstitial nephritis, either due to HIV-infection or to drug toxicity.

1.3.10 Isolated Hematuria

Hematuria is RBCs in urine, specifically > 3 RBCs per high-power field on urine sediment examination. Urine may be red or bloody (gross hematuria) or not visibly discolored (microscopic hematuria). Isolated hematuria is urinary RBCs without other urine abnormalities (eg, proteinuria, casts).

Red urine is not always due to RBCs. Red or reddish brown discoloration may result from the following:

- Hb or myoglobin in urine
- Porphyria (most types)
- Foods (eg, beets, rhubarb, sometimes food coloring)
- Drugs (most commonly phenazopyridine, but sometimes cascara, diphenylhydantoin, methyldopa, phenacetin, phenindione, phenolphthalein, phenothiazine, and senna)

Pathophysiology

RBCs may enter urine from anywhere along the urinary tract - from the kidneys, collecting system and ureters, prostate, bladder, and urethra.

Etiology

Most cases involve transient microscopic hematuria that is self-limited and idiopathic. Transient microscopic hematuria is particularly common in children,

present in up to 5% of their urine samples. There are numerous specific causes (Table 1.3.10.1).

The most common specific causes differ somewhat by age, but overall the most common are

- UTI
- Prostatitis
- Urinary calculi (in adults)
- Cancer and prostate disease are a concern mainly in patients > 50,

although younger patients with risk factors may develop cancer. Glomerular disorders can be a cause at all ages. Glomerular disorders may represent a primary renal disorder (acquired or hereditary) or be secondary to many causes, including infections (eg, group A β -hemolytic streptococcal infection), connective tissue disorders (eg, SLE at all ages, Henoch-Schönlein purpura [HSP] in children), and blood disorders (eg, mixed cryoglobulinemia, serum sickness). Worldwide, IgA nephropathy is the most common form of glomerulonephritis. *Schistosoma haematobium*, a parasitic fluke that causes significant disease in Africa (and, to a lesser extent, in India and parts of the Middle East), can invade the urinary tract, causing hematuria. Schistosomiasis is considered only if people have spent time in endemic areas.

- ***Evaluation***

- ***History***

- History of present illness includes duration of hematuria and any previous episodes. Urinary obstructive symptoms (eg, incomplete emptying, nocturia, difficulty starting or stopping) and irritative symptoms (eg, irritation, urgency, frequency, dysuria) should be noted. Patients should be asked about the presence of pain and its location and severity.

Table 1.3.10.1

Some Common Specific Causes of Hematuria

Cause	Suggestive Findings	Diagnostic Approach
Infection	Urinary irritative symptoms, with or without fever	Urinalysis and culture
Calculi	Sudden-onset, usually colicky, severe flank or abdominal pain, sometimes with vomiting	Abdominal CT without contrast or ultrasonography of the abdomen
Glomerular disease (numerous forms)	In many patients, hypertension, edema, or both Possibly red or dark (cola-colored) urine Sometimes preceding infection, family history of renal disorders, or connective tissue disorder	Urinalysis Urine sediment examination for RBC cast and dysmorphic RBCs Serologic tests Renal biopsy
Cancer (bladder, kidney, prostate, ureter)	Mainly in patients > 50 or with risk factors (smoking, family history, chemical exposures) Sometimes voiding symptoms with bladder cancer Often systemic symptoms with renal cell carcinoma	In men, PSA, pelvic and prostate ultrasonography, biopsy In all patients, cystoscopy
Prostatic hyperplasia	Mainly in patients > 50 Often, urinary obstructive symptoms Palpably enlarged prostate	PSA Measurement of postvoid residual urine volume Ultrasonography of pelvis

Prostatitis	Mainly in patients > 50 Often, urinary irritative and obstructive symptoms Painful, tender prostate	Clinical evaluation Sometimes transrectal ultrasonography or cystoscopy
Polycystic kidney disease	Chronic flank or abdominal pain Hypertension Large kidneys	Ultrasonography or noncontrast CT of the abdomen
Sickle cell disease or trait	In blacks, mainly children and young adults, often with known disease	Sickle cell preparation Hb electrophoresis
Endometriosis	Hematuria coinciding with menses	Clinical evaluation
Trauma (blunt or penetrating)	Usually, presentation as injury rather than as hematuria	CT of the abdomen and pelvis
Loin pain-hematuria syndrome	Flank pain Hematuria	CT
Nutcracker syndrome	Hematuria Left testicular pain Varicocele	CT angiography

Note: CT – computer tomography, PSA - prostate-specific antigen

Review of systems should seek symptoms of possible causes, including joint pain and rashes (connective tissue disorder). Past medical history should include questions about any recent infections, particularly a sore throat that may indicate a group A β -hemolytic streptococcal infection. Conditions known to cause urinary tract bleeding (particularly kidney calculi, sickle cell disease or trait, and glomerular disorders) should be sought. Also, conditions that predispose to a glomerular

disorder, such as a connective tissue disorder (particularly SLE and RA), endocarditis, shunt infections, and abdominal abscesses, should be identified. Risk factors for GU cancer should be identified, including smoking (the most significant), drugs (eg, cyclophosphamide, phenacetin), and exposure to industrial chemicals (eg, nitrates, nitrotriacetate, nitrites, trichloroethylene).

Family history should identify relatives with known polycystic kidney disease, a glomerular disorder, or GU cancer. Patients should be asked about travel to areas where schistosomiasis is endemic. Drug history should note use of anticoagulants or antiplatelet drugs (although anticoagulation itself does not cause hematuria).

Physical examination:

Vital signs should be reviewed for fever and hypertension. The heart should be auscultated for murmurs (suggesting endocarditis). The abdomen should be palpated for masses; flanks should be percussed for tenderness over the kidneys. In men, a digital rectal examination should be done to check for prostate enlargement, nodules, and tenderness. The face and extremities should be inspected for edema (suggesting a glomerular disorder), and the skin should be inspected for rashes (suggesting vasculitis, SLE, or HSP).

Red flags: The following findings are of particular concern:

- Gross hematuria
- Persistent microscopic hematuria, especially in older patients
- Age > 50
- Hypertension and edema

Interpretation of findings

Clinical manifestations of the various causes overlap significantly, so urine and often blood tests are required. Depending on results, imaging tests may then be needed. However, some clinical findings provide helpful clues.

- Blood clots in urine essentially rule out a glomerular disorder. Glomerular disorders are often accompanied by edema, hypertension, or both; symptoms may be preceded by an infection (particularly a group A β -hemolytic streptococcal infection in children).

- Calculi usually manifest with excruciating, colicky pain. Less severe, more continuous pain is more likely to result from infection, cancer, polycystic kidney disease, glomerulonephritis, and loin pain–hematuria syndrome.
- Urinary irritative symptoms suggest bladder or prostate infection but may accompany certain cancers (mainly bladder and prostate).
- Urinary obstructive symptoms usually suggest prostate disease.
- An abdominal mass suggests polycystic kidney disease or renal cell carcinoma.
- A family history of nephritis, sickle cell disease or trait, or polycystic kidney disease suggests that as a cause.
- Travel to Africa, the Middle East, or India suggests the possibility of schistosomiasis.

On the other hand, some common findings (eg, prostate enlargement, anticoagulant use), although potential causes of hematuria, should not be assumed to be the cause without further evaluation.

Testing

Before testing proceeds, true hematuria should be distinguished from red urine by urinalysis. In women with vaginal bleeding, the specimen should be obtained by straight catheterization to avoid contamination by a nonurinary source of blood. Red urine without RBCs suggests myoglobinuria or hemoglobinuria, porphyria, or ingestion of certain drugs or foods.

Presence of casts, protein, or dysmorphic RBCs (unusually shaped, with spicules, folding, and blebs) indicates a glomerular disorder. WBCs or bacteria suggest an infectious etiology. However, because urinalysis shows predominantly RBCs in some patients with cystitis, urine culture is usually done. A positive culture result warrants treatment with antibiotics. If hematuria resolves after treatment and no other symptoms are present, no further evaluation is required for patients < 50, especially women.

If patients < 50 (including children) have only microscopic hematuria and no urine findings suggesting a glomerular disorder, no clinical manifestations suggesting

a cause, and no risk factors for cancer, they can be observed, with urinalysis repeated every 6 to 12 mo. If hematuria is persistent, ultrasonography or CT with contrast is suggested. Patients < 50 with gross hematuria require ultrasonography or CT of the abdomen and pelvis. If urine or clinical findings suggest a glomerular disorder, renal function is evaluated by measuring BUN, serum creatinine, and electrolytes; doing a urinalysis; and periodically determining the urine protein/creatinine ratio. Further evaluation of a glomerular disorder may require serologic tests, kidney biopsy, or both. All patients ≥ 50 yr require cystoscopy, as do patients who are < 50 but have risk factors, such as a family history of cancer. Men ≥ 50 require testing for prostate-specific antigen; those with elevated levels require further evaluation for prostate cancer.

Treatment

Treatment is directed at the cause.

In conclusion, red urine should be differentiated from hematuria (RBCs in urine). Urinalysis and urine sediment examination help differentiate glomerular from nonglomerular causes. Risk of serious disease increases with aging and with duration and degree of hematuria. Cystoscopy and imaging tests are usually needed only for patients > 50 or for younger patients with risk factors for cancer.

1.4 Nephrotic syndrome

Nephrotic syndrome is characterized by heavy proteinuria (> 3 g per day), hypoalbuminemia, edema, hypercholesterolemia, and normal renal function.

Classification

Nephrotic syndrome can be primary, occurring as part of a recognized systemic disease, or secondary, resulting from some evident cause.

Primary causes include the following:

- Postinfectious etiologies
- Collagen vascular disease (eg, systemic lupus erythematosus [SLE], rheumatoid arthritis, polyarteritis nodosa)
- Henoch-Schonlein purpura
- Hereditary nephritis (Alport' disease)

- Sickle cell disease
- Diabetes mellitus
- Amyloidosis
- Malignancy (eg, leukemia, lymphoma, Wilms tumor, pheochromocytoma)
- Toxins (eg, bee sting, poison ivy and oak, snake venom)
- Medications (eg, probenecid, fenoprofen, captopril, lithium, warfarin, penicillamine, mercury, gold, trimethadione, paramethadione)
- Heroin use

Secondary causes are related to postinfectious causes and include the following:

- Group A beta-hemolytic streptococci
- Syphilis
- Malaria
- Tuberculosis
- Viral infections (eg, varicella, hepatitis B, HIV type 1, infectious mononucleosis)

Nephrotic syndrome can be classified further according to histological findings. According to the International Study of Kidney Diseases in Childhood (ISKDC), 84.5% of all children have minimal-change nephrotic syndrome (MCNS), 9.5% have focal segmental glomerulosclerosis (FSGS), 2.5% have mesangial proliferation, and 3.5% have membranous nephropathy or other etiologies. Increasing trends of FSGS incidence in children with idiopathic nephrotic syndrome are being reported, but MCNS remains the most important cause of chronic renal disease in children. MCNS is a disorder of primary T lymphocyte dysfunction, where the lymphocytes are altered with IL2 expression during a relapse, resulting in increased vascular and glomerular basement membrane (GBM) permeability, leading to the typical clinical features seen in nephrotic syndrome.

The histological classifications of glomerular lesions associated with primary and secondary nephrotic syndrome are minimal-lesion nephrotic syndrome, diffuse

mesangial hypercellularity, focal glomerulosclerosis, membranous glomerulonephritis, fibrillary glomerulosclerosis, and membranoproliferative glomerulonephritis. The classifications of primary congenital nephrotic syndrome include infantile microcystic disease (Finnish type), infantile microcystic disease (non-Finnish type), diffuse mesangial sclerosis, minimal-lesion nephrotic syndrome, and FSGS. The classifications of secondary congenital nephrotic syndrome include intrauterine infections (eg, toxoplasmosis, cytomegalovirus, rubella, syphilis), gonadal dysgenesis, nail-patella syndrome, and Lowe syndrome. From a therapeutic perspective, nephrotic syndrome may be classified as steroid sensitive, steroid resistant, steroid dependent, or frequently relapsing.

Pathophysiology

Filtration of low molecular weight anionic plasma proteins across the glomerular basement membrane is normally prevented by a negatively charged filtration barrier, which consists of proteoglycan molecules of heparan sulfate. In persons with nephrotic syndrome, the concentration of heparan sulfate mucopolysaccharide in the basement membrane is lower, and large amounts of protein cross the barrier and are excreted. High glomerular permeability leads to hyperalbuminuria and, eventually, to hypoalbuminemia. In turn, hypoalbuminemia lowers the plasma colloid osmotic pressure, causing greater transcapillary filtration of water and the development of edema. Capillary hydrostatic pressure and the gradient of plasma to interstitial fluid oncotic pressure determine the movement of fluid from the vascular compartment to the interstitium. The oncotic pressure is mainly determined by the protein content, and the interstitial fluid has a protein concentration of 25-50% that of plasma. Fluid that is not absorbed back into the vascular system until it has reached the venous end of the capillary bed is usually absorbed by the lymphatics and returned back to the vascular space. In a steady state, the flux of water across the capillary wall can be expressed by the following formula:

$$Q_w = K ([P_c - P_i] - [p_p - p_i])$$

In this formula, Q_w is net flux of water, K is the capillary filtration coefficient, P_c is plasma fluid hydrostatic pressure, and P_i is the interstitial fluid hydrostatic pressure. Also, p_p is the plasma oncotic pressure, and p_i is the interstitial fluid oncotic pressure. When the fall of D_p is wide, the amount of fluid filtered exceeds the maximal lymphatic flow, and edema occurs. In most patients with nephrotic syndrome, this causes a reduction in plasma volume. A hyperreninemic state ensues, resulting in increased sodium and water retention by the kidney.

An alternate hypothesis is that a condition of renal sodium retention occurs because of the proteinuria, but this is not related to intravascular volume or serum protein concentration. The evidence supporting this hypothesis is sodium retention is observed even before the serum albumin level starts falling; intravascular volume is normal or even increased in most patients with nephrotic syndrome; Starling forces are unchanged in nephrotic syndrome until late in the disease course because p_i remains equivalent to p_p ; and the sites of renal sodium retention are predominantly in the distal nephron, not in the proximal nephron, as is expected by changes in Starling forces.

Hypoalbuminemia results mainly from increased catabolism and is not caused only by urinary loss of albumin; however, no evidence of decreased albumin synthesis exists in patients with nephrotic syndrome.

The structural changes believed to be responsible for causing proteinuria are:

- damage to the endothelial surface, causing loss of the negative charge;
- damage to the glomerular basement membrane;
- effacement of the foot processes

The foot processes are firmly attached to the visceral surface of the glomerular basement membrane. The space between the bases of the foot processes form the filtration slits, and this space constitutes the site for the convective forces that govern the filtration through the visceral epithelium. The podocyte forms a cover to the filtration slits. To date, they seem to have receptors for vasoactive agents such as endothelin, atrial natriuretic peptide, nitrous oxide, and, possibly, angiotensin II. Recently, congenital nephrotic syndrome of the Finnish type has been determined to

be caused by mutations in the gene known as NPHS1. This gene codes for a cell adhesion protein called nephrin, which is synthesized by podocytes. The role of nephrins in acquired kidney diseases is not known; however, nephrin and another podocyte protein called podocin are associated with the development of proteinuria, at least in the congenital type of nephrotic syndrome and in experimental models of glomerular disease. Recently, the tandem endocytic receptors megalin and cubilin in the luminal membrane of proximal tubule cells have been shown to play an important role in endocytosis of albumin and low molecular weight proteins that may be filtered in the glomerulus. The presence of these receptors likely serves to protect the tubules from the toxic effects of undegraded albumin. These receptors are not specific for albumin. Therefore, proteinuria is now believed to be at least partly due to inhibition of albumin retrieval and degradation pathways.

Urinary immunoglobulin losses lower the patient's resistance to infections and increase the risk of serious sepsis and peritonitis. The loss of antithrombin III and plasminogen via urine and the simultaneous increase in clotting factors, especially factors I, VII, VIII, and X, increases the risk for arterial thrombosis, venous thrombosis, and pulmonary embolism, which occurs in 5% of children with nephrotic syndrome. High glomerular permeability causes the excretion of vitamin D-binding protein and complexes in the urine, leading to malabsorption of calcium and development of bone disease (eg, osteitis fibrosa cystica) because of enhanced parathyroid hormone production and osteomalacia because of impairment in mineralization. In the nephrotic state, levels of almost all serum lipids are elevated. Two pathogenic processes are operative, including hypoproteinemia stimulating generalized protein synthesis in the liver, including the lipoproteins, and diminution of lipid catabolism caused by reduced plasma levels of lipoprotein lipase.

Frequency

The incidence of nephrotic syndrome is reportedly 2-7 cases in children per 100,000 children per year. However, in adults, the frequency varies significantly in different regions. Because of a much higher prevalence of diabetic nephropathy, which varies significantly from region to region, the incidence of nephrotic syndrome

tends to be higher in the southern region compared to the northern region. Because diabetes is now emerging as a major cause of nephrotic syndrome, American Indians, Hispanic persons, and African Americans have a clearly higher incidence of nephrotic syndrome compared to white persons. Incidence varies according to the type of glomerular disease. Nephrotic syndrome is 15 times more common in children than in adults. Most cases of primary nephrotic syndrome are in children and are due to minimal-change disease. The age at onset varies with the type of nephrotic syndrome. In adults, the most common form of glomerulopathy causing nephrotic syndrome is membranous glomerulonephritis, followed by FSGS. In certain countries and in certain regions of the same country, diabetic nephropathy is emerging as a major cause of nephrotic syndrome.

Mortality/Morbidity

Although most adult patients have a glomerulopathy that is secondary to a systemic disease process (eg, diabetes mellitus, hypertension, SLE), primary or idiopathic glomerulonephritis is not uncommon. In most patients, the mortality rate is directly related to the primary disease process; however, once nephrotic syndrome manifests, the prognosis worsens because of the increased incidence of renal failure and the complications secondary to nephrotic syndrome (eg, thrombotic episodes, hypoalbuminemia, hyperlipidemia) or the treatment-related conditions (eg, increased incidence of infection from steroid therapy and blood dyscrasia from other immunosuppressive medications).

History

The first sign in children is usually swelling of the face; periorbital edema is a common presentation. This is followed by swelling of the entire body. Adults can present with edema of dependent parts. In most cases, this includes the ankles or legs. Facial swelling or anasarca can be the presenting symptom. In certain instances, patients notice frothy urine, which leads to investigations that reveal evidence of nephrotic syndrome. A hypercoagulable state leading to thrombotic complications, such as deep vein thrombosis of the calf veins or the renal vein, may be the first clue indicating nephrotic syndrome.

Physical

Patients present with increasing edema over a few days or weeks, lethargy, poor appetite, weakness, and occasional abdominal pain. The initial episode and the subsequent relapses may follow an apparent viral upper respiratory tract infection. Edema is the predominant feature and initially develops around the eyes and lower extremities. With time, the edema becomes generalized and may be associated with an increase in weight, the development of an ascitic or pleural effusion, and a decline in urine output. Hematuria and hypertension are unusual but manifest in a minority of patients.

Causes

Nephrotic syndrome reportedly has a familial cause in 2-8% of patients, and most familial cases involve siblings. Congenital nephrotic syndrome of the Finnish type is inherited in an autosomal recessive fashion. Recently, the gene responsible for this disease entity has been identified (ie, NPHS1).

Lab Studies

Although the diagnosis is made based on clinical findings, results from the following investigations aid in determining the etiology and in planning and monitoring treatment.

Urine

In adults, perform a urinalysis, urine microscopy, testing for the ratio of urinary protein to urinary creatinine, and a determination of light-chain protein excretion. The normal amount of protein in the urine varies with age, but children excrete up to 4 mg/m²/h or 166 mg/1.73 m²/d. Adults excrete up to 150 mg/d. Proteinuria may be measured by performing the urine dipstick test, an early morning urine (EMU) collection and determining the ratio of urinary protein to urinary creatinine, or a 24-hour quantitative urine protein excretion test. A quantitative estimation of 24-hour urine protein excretion is the standard method, but EMU testing and determining the ratio of urinary protein to urinary creatinine is the method of choice for proteinuria quantification. Because this method is convenient for children who are incontinent, errors and difficulties associated with timed urine collection are avoided. This

method also simplifies sample handling by the laboratory and is inexpensive. Nephrotic levels of proteinuria are associated with a ratio of urinary protein to urinary creatinine of greater than 2.

Blood

Perform a serum chemistry profile, including values for serum creatinine, urea nitrogen, serum albumin, and serum lipids. Also, perform a complete blood cell count, hepatitis B and hepatitis C testing, HIV screening, serum complement values, and varicella serology.

Other tests

In adult's, testing cryoglobulins and performing serum protein electrophoresis or urine protein electrophoresis can be useful for detecting the etiology of nephrotic syndrome.

Imaging Studies

Renal ultrasonography is an essential tool to help establish the presence of 2 kidneys that are of normal size and architecture. The presence of hydronephrosis or cysts in the kidney that will undergo biopsy mandates caution. Similarly, small kidneys may not yield enough information and may be associated with an increased incidence of complications.

Other Tests

If the clinical features are atypical, further tests, such as the following, may be useful:

- Antistreptolysin O titers
- Serum protein electrophoresis or immunofixation for light-chain proteins
- Antinuclear antibodies

Procedures

Renal biopsy

Before attempting a renal biopsy, ensure that a renal ultrasound scan is ordered to confirm that the patient has 2 functioning kidneys, that the kidneys are of normal size, and that the kidney architecture is normal (ie, devoid of cysts and vascular malformations). A renal biopsy is indicated in the following circumstances:

- Congenital nephrotic syndrome
- Children older than 8 years at onset
- Steroid resistance
- Frequent relapses or steroid dependency
- Significant chronic nephritic manifestations
- Adult nephrotic syndrome

Note that a renal biopsy is not indicated in adults when the nephrotic syndrome is due to an obvious cause such as diabetes mellitus, ie, when the patient has other diabetes-related overt complications.

Abdominal fat pad biopsy or gingival biopsy

- May be useful in adult patients to help diagnose either primary or secondary amyloidosis
- Rarely performed in pediatric patients

Histologic Findings

The histologic findings are determined by the cause of the nephrotic syndrome. The details of the histologic findings are discussed in the appropriate articles

Medical Care

Acute management

With good parental and patient education and close outpatient follow-up care, hospitalization is not usually necessary. Hospitalization should be considered if a patient has generalized edema severe enough to cause respiratory distress, if a patient has tense scrotal or labial edema, if a patient is experiencing complications (eg, bacterial sepsis, peritonitis, pneumonia, thromboembolic phenomenon, failure to thrive), and if patient or family compliance with treatment is in doubt. Diuretics and intravenous albumin may be needed. Furosemide (1 mg/kg/d) and spironolactone (2 mg/kg/d) are not always indicated but may help when fluid retention is severe, provided no signs of renal failure or volume contraction are evident. Achieving a satisfactory diuresis is difficult when the patient's serum albumin level is less than 1.5 g/dL. An effective regimen is to give salt-poor albumin at 1 g/kg, followed by intravenous furosemide. Close monitoring is obligatory to prevent pulmonary edema.

Some evidence suggests that albumin may delay the response to steroids and may even induce more frequent relapses, probably by causing severe glomerular epithelial damage. The time required for remission is prolonged with a longer duration of administration and larger volumes of infused albumin. Fluid removal and weight loss remain transient unless proteinuria remits. With regard to infection, oral penicillin can be prescribed as prophylaxis for children with gross edema. Abdominal paracentesis should be performed if the patient develops signs of peritonitis, and any bacterial infection should be treated promptly. A nonimmune patient with varicella should receive zoster immunoglobulin therapy if exposed to chickenpox, and acyclovir therapy should be administered if the patient develops chickenpox.

Routine immunizations should be delayed until the patient is free of relapses and is off immunosuppression for 3 months. Pneumococcal and influenza vaccines are recommended but are not routinely used because their efficacy is not established. Children who have received immunosuppressive therapy in the preceding 3 months and are not immune to varicella should receive zoster immunoglobulin if they are exposed to chickenpox or shingles. These patients should also receive acyclovir if they develop chickenpox.

Among the nephropathies causing nephrotic syndrome, only minimal-change disease is treatable. Most patients with minimal-change disease are steroid-sensitive, especially children.

Drugs used in the treatment of nephrotic syndrome include corticosteroids (eg, prednisone), levamisole, cyclophosphamide, and cyclosporine. The response to corticosteroids correlates with the histologic type of nephrotic syndrome. The ISKDC reports that 91.8% of patients who responded had minimal-change glomerulonephritis, compared with only 25% of patients who did not respond. In patients who do not respond to corticosteroid treatment and are younger than 6 years, approximately 50% had minimal-change glomerulonephritis; in those older than 6 years, only 3.6% had minimal-change glomerulonephritis.

The Southwest Pediatric Nephrology Study Group reports that 63% of patients with diffuse membranous hypercellularity and approximately 30% of patients with

focal glomerular sclerosis responded to corticosteroid therapy. Congenital nephrotic syndrome is usually resistant to corticosteroid treatment. Most patients experience relapses; recent data suggest rates of 76-97%, with frequently relapsing rates up to 50%. The first 2 relapses are treated in the same manner as the initial presentation; frequent relapses are treated with a maintenance dose of prednisone at 0.1-0.5 mg/kg on alternate days for 3-6 months and then tapered. Monitoring steroid toxicity: Monitoring every 3 months in the outpatient clinic is necessary to help detect adverse effects and to record growth. A yearly checkup is necessary to help detect cataracts.

Complications of corticosteroid treatment include obesity; cushingoid features; striae; retarded growth; and increased susceptibility to infections, hypertension, osteoporosis, cataracts, peptic ulcer disease, and diabetes mellitus.

Other immunosuppressive medications

These medications are usually reserved for steroid-resistant cases in patients who are persistently edematous or steroid dependent with significant steroid-related adverse effects.

Levamisole is an immunostimulant with weak steroid-sparing effects and may permit the reduction, or even cessation, of prednisone therapy. The recommended dose is 2.5 mg/kg on alternating days for 4-12 months. Adverse effects are rare, but neutropenia and encephalopathy have been reported. This drug is not commonly used.

Cyclophosphamide at 3 mg/kg/d for 8 weeks is highly effective for patients who have frequently relapsing steroid-sensitive nephrotic syndrome, and half the children enter a prolonged remission. Associated complications include bone marrow suppression, hair loss, azoospermia, hemorrhagic cystitis, malignancy, mutations, and infertility.

Cyclosporin is an inhibitor of T-lymphocyte function and is indicated when relapses occur after cyclophosphamide treatment. Cyclosporin may be preferable in a pubertal male who is at risk of developing cyclophosphamide-induced azoospermia. Cyclosporin is highly effective maintenance therapy for patients with steroid-sensitive nephrotic syndrome who are able to stop steroids or take lower doses;

however, some evidence suggests that remission is maintained as long as cyclosporin is administered but relapses are frequent when treatment is discontinued. Cyclosporin can be nephrotoxic and can cause hirsutism, hypertension, and gingival hypertrophy.

A cornerstone of treatment of nephrotic syndrome in adults is ACE inhibitors and/or adrenergic receptor binders. The mechanism by which improvement is achieved is not clearly known. However, the reduction in proteinuria is not solely related to the decrement of intraglomerular pressure.

Previously, the traditional therapy for a decrement of proteinuria was the administration of nonsteroidal anti-inflammatory drugs (NSAIDs), which caused a significant decrease in glomerular filtration and thus reduced the proteinuria. However, this therapy is seldom used in current practice because the nephrotoxic effects of NSAIDs are enhanced in patients with nephrotic syndrome.

Diet

The diet should provide adequate energy (caloric) intake and adequate protein (1-2 g/kg/d). A diet with no added salt is advised if the patient is edematous. Management of hyperlipidemia is controversial and could be of some importance if the nephrotic state is prolonged. Fluid restriction is not usually required unless the edema is severe.

Complications

Infection is the major complication; patients have an increased susceptibility to infection with *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Escherichia coli*, and other gram-negative organisms. Varicella infection is also common. The most common infectious complications are bacterial sepsis, cellulitis, pneumonia, and peritonitis. Proposed explanations for these complications include decreased immunoglobulin levels, edema fluid acting as a culture medium, protein deficiency, decreased bactericidal activity of the leukocytes, immunosuppressive therapy, decreased perfusion of the spleen caused by hypovolemia, and urinary loss of a complement factor (properdin factor B) that opsonizes certain bacteria.

Thromboembolism is dependent on the etiology of the nephrotic syndrome. It is encountered most frequently in patients with membranous glomerulonephritis, less

frequently in patients with FSGS, and least frequently in patients with diabetic glomerulopathy. The factors involved in the development of venous and arterial thromboembolism include thrombocytosis, enhanced platelet and red blood cell aggregation, and increased coagulability. Venous and arterial thrombus in a variety of sites has been described in the literature. Not uncommonly, patients with nephrotic syndrome present with life-threatening thrombotic episodes such as pulmonary embolism, especially when the underlying glomerular lesion is membranous glomerulonephritis. Renal vein thrombosis in children with childhood nephrotic syndrome is uncommon except in association with congenital nephrotic syndrome. Hoyer et al found pulmonary embolism in 28% of children with nephrotic syndrome. Subclinical episodes of thromboembolism may be more common in children with nephrotic syndrome than is presently appreciated.

Hypovolemia occurs when hypoalbuminemia decreases the plasma oncotic pressure, resulting in a loss of plasma water into the interstitium and causing a decrease in circulating blood volume. Hypovolemia is generally observed only when the patient's serum albumin level is less than 1.5 g/dL. Symptoms include vomiting, abdominal pain, and diarrhea. The signs include cold hands and feet, delayed capillary filling, oliguria, and tachycardia. Hypotension is a late feature.

Acute renal failure may indicate an underlying glomerulonephritis but is more often precipitated by hypovolemia or sepsis. Edema of the kidneys that causes a pressure-mediated reduction in the glomerular filtration rate has also been hypothesized.

Arterial hypertension may signify an acute nephritis or may be part of the hyperreninemic state of nephrotic syndrome induced by hypovolemia and reduced perfusion of the kidneys.

Failure to thrive may develop in patients with chronic edema, including ascites and pleural effusion. Failure to thrive may be caused by anorexia, hypoproteinemia, increased protein catabolism, or frequent infectious complications. Edema of the gut may cause defective absorption, leading to chronic malnutrition.

Tetany is a reported complication. The hypocalcemia may be significant enough to cause tetany. A positive Chvostek or Trousseau sign may be present.

Adverse effects of treatment may occur. Corticosteroids and other immunosuppressive drugs (eg, cyclophosphamide, levamisole, cyclosporin) all have significant adverse effects (see above).

Prognosis

The prognosis for patients with primary nephrotic syndrome varies depending on the histological type. The prognosis is worse with congenital nephrotic syndrome, resulting in death from renal failure in 3-18 months in most cases. The prognosis for children with minimal-change glomerulonephritis is excellent. Most children respond to steroid therapy; nevertheless, approximately 50% have 1-2 relapses within 5 years and approximately 20% continue to relapse 10 years after diagnosis. Only 30% of children never have a relapse after the initial episode. Approximately 3% of patients who initially responded to steroids become steroid resistant. Progressive renal insufficiency occurs in fewer than 1% of patients, and most deaths among patients with minimal-change glomerulonephritis are from infections and nonrenal complications. Frequent relapses are more common with young age of onset and in boys. A linear relationship exists between the length of remission and risk of subsequent relapse. Poor patient response to steroid therapy seems to be the finding most predictive of a poor outcome, but children who present with hematuria and hypertension are more likely to be steroid resistant and have a poorer prognosis than those who do not present with hematuria and hypertension. Only approximately 20% of patients with FSGS undergo remission of proteinuria; an additional 10% improve but remain proteinuric. Many patients experience frequent relapses, become steroid dependent, or become steroid resistant. End-stage renal disease develops in 25-30% of patients with FSGS by 5 years and in 30-40% by 10 years. Approximately 50% of patients with diffuse mesangial proliferation undergo complete remission of proteinuria during steroid therapy, an additional 20% have delayed remission, approximately 20% have continued proteinuria, and 6% progress to renal insufficiency. The outlook for patients with membranoproliferative

glomerulonephropathy is commonly regarded as poor, and the benefits of treatment are not clear. In some comparative studies, no difference was evident in the outcome between treated and untreated patients; 30% of patients developed end-stage renal disease within 5 years of diagnosis.

Pitfalls

Recurrence risk in transplanted kidneys: The types of nephrotic syndrome that may recur in a transplanted kidney include primary nephrotic syndrome with FSGS, immunoglobulin-A nephropathy, membranoproliferative glomerulonephritis, rarely membranous glomerulonephritis, and secondary nephrotic syndrome caused by SLE.

1.5 Nephritic syndrome

In nephrotic syndrome, the glomerular injury is manifested primarily as an increase in permeability of the capillary wall to protein. By contrast, in the nephritic syndrome, there is evidence of glomerular inflammation resulting in a reduction in GFR, non-nephrotic proteinuria, edema and hypertension (secondary to sodium retention), and hematuria with red cell casts.

Etiology

The classification is even more challenging than for nephrotic syndrome as some diseases are identified by histology (IgA nephropathy), others by serology and histology (ANCA-associated vasculitis and lupus nephritis), and others by etiology (postinfectious GN).

Diagnosis.

The classic nephritic syndrome presentation is that seen with acute poststreptococcal GN in children. These children usually present with rapid onset of oliguria, weight gain, and generalized edema during a few days. The hematuria results in brown rather than red urine, and clots are not seen. The urine contains protein, red cells, and red cell casts. Because proteinuria is rarely in the nephrotic range, serum albumin concentration is usually normal.

Circulating volume increases with hypertension, and pulmonary edema follows without evidence of primary cardiac disease. The distinction between typical nephrotic syndrome and nephritic syndrome is usually straightforward on clinical and

laboratory grounds, and the use of these clinical descriptions is particularly helpful in the approach to patients with suspected GN at first presentation, helping to narrow the differential diagnosis. However, the classification systems are imperfect, and patients with certain glomerular disease patterns, for example, MPGN, may present with either a nephrotic or a nephritic picture.

Clinical

Nephritic syndrome is characterized by:

- hematuria (blood in the urine), with red blood cell (RBC) casts present in the urine
- proteinuria (protein in the urine) - small amounts of protein are lost in the urine, but this is usually trivial (<3.5 g/day)
- hypertension[4] (high blood pressure)- mild
- uremia - due to retention of waste products
- variable renal insufficiency, with azotemia or oliguria (low urine output <400 mL/day)

The main features are arterial hypertension and RBC casts. The proteinuria in nephritic syndrome is not usually severe, but may occasionally be heavy enough to be in the range usually found in nephrotic syndrome.

Treatment

Treatment is dependent on the underlying etiology (cause) and the degree of kidney dysfunction and ESRD.

Prognosis.

Because nephritic syndrome is not a disease, just a collection of symptoms, the prognosis depends on the underlying etiology.

1.6 Arterial hypertension

Arterial hypertension is very common in GN; it is virtually universal as chronic GN progresses toward end-stage renal disease and is the key modifiable factor in preserving renal function. Sodium and water overload is an important part of the pathogenetic process, and high-dose diuretics with moderate dietary sodium restriction are usually an essential part of the treatment.

As in other chronic renal diseases, the aim of blood pressure control is not only to protect against the cardiovascular risks of hypertension but also to delay progression of the renal disease.

Normal Blood Pressure Control

Systemic arterial blood pressure (BP) is produced by the contraction of the left ventricle (producing blood flow) and the resistance of the arteries and arterioles. Systolic blood pressure (SBP), or maximum BP, occurs during left ventricular systole. Diastolic blood pressure (DBP), or minimum BP, occurs during ventricular diastole. The difference between SBP and DBP is the pulse pressure. The mean arterial pressure (MAP) is clinically defined as the DBP plus one third of the pulse pressure.

Blood flow (Q) is defined by Ohm's law and varies directly with the change in pressure (P) across a blood vessel and inversely with the resistance R (defined as $Q = P/R$). Rearrangement shows that pressure varies directly with blood flow and resistance ($P = QR$). Ohm's law suffices for an overall view of the circulation. However, for a more detailed picture of the resistance to flow in any given vessel, the relationship of Hagen-Poiseuille should be applied:

Here, r is the radius of the pipe, L is its length, and η is the coefficient of viscosity. Thus, as the lumen of a vessel decreases, the pressure will increase to the fourth power of the radius for the same blood flow. In other words, a 50% reduction in radius will require a 16-fold increase in pressure to maintain equivalent flow.

Normal BP is controlled by cardiac output and the total peripheral resistance and is dependent on the heart, the blood vessels, the extracellular volume, the kidneys, the nervous system, humoral factors, and cellular events at the membrane and within the cell. Cardiac output is determined by the stroke volume (liters/minute) and the heart rate. In turn, stroke volume is dependent on intravascular volume regulated by the kidneys as well as on myocardial contractility. Myocardial contractility is a complex function involving sympathetic and parasympathetic control of heart rate, intrinsic activity of the cardiac conduction system, complex membrane transport and cellular events requiring influx of calcium that lead to

myocardial fiber shortening and relaxation, and effects of humoral substances (e.g., catecholamines) on stimulating heart rate and myocardial fiber tension.

Total peripheral resistance is regulated by complex interactive mechanisms, including baroreflexes and sympathetic nervous system activity, response to neurohumoral substances and endothelial factors, myogenic responses, and intercellular events mediated by receptors and mechanisms for signal transduction. For example, there are two major neural reflex arcs. Baroreflexes are derived from high-pressure baroreceptors in the aortic arch and carotid sinus and low-pressure cardiopulmonary baroreceptors in ventricles and atria. These receptors respond to stretch (high pressure) or filling pressures (low pressure) and send tonic inhibitory signals to the brainstem (nucleus tractus solitarius). If BP increases and tonic inhibition increases, inhibition of sympathetic efferent outflow occurs and decreases vascular resistance and heart rate. However, if BP decreases, less tonic inhibition ensues from the baroreflexes and both heart rate and peripheral vascular resistance increase, thereby increasing BP.

The brainstem cardiovascular centers are localized in the dorsomedial medulla. Neural afferents from cranial nerves IX and X are integrated in the nucleus tractus solitarius (NTS). From here, vasoconstriction and increased heart rate are mediated through the caudal and rostral ventrolateral medulla by the sympathetic nervous system. Also, NTS efferents communicate with the nucleus ambiguus (vagal nucleus) to decrease heart rate through the vagus nerve. In addition, the neural control of renal function produces alterations in renal blood flow, glomerular filtration rate (GFR), excretion of sodium and water, and release of renin and other vasoactive substances. These factors, in turn, have effects on the regulation of intravascular volume, vascular resistance, and BP.

Numerous vasoactive substances have effects on blood vessels, the heart, the kidneys, and the central nervous system and often counterbalance one another. The renin-angiotensin system (RAS) and aldosterone are extremely important effector systems that regulate both volume and peripheral vascular resistance. Angiotensin II (Ang II) constricts vascular smooth muscle; stimulates aldosterone secretion;

potentiates sympathetic nervous system activity; stimulates salt and water reabsorption in the proximal tubule; stimulates prostaglandin, nitric oxide, and endothelin release; increases thirst; and is a growth factor. When it is present in excess, Ang II can induce remodeling, inflammation, and vasculopathy. The kallikrein-kinin system produces vasodilator kinins that in turn may stimulate prostaglandins and nitric oxide and counterbalance the RAS. Aldosterone mediates changes in sodium channels in distal renal tubular epithelium, leading to sodium retention and potassium excretion. The hormone also functions as a growth factor and exerts complex nongenomic and genomic events through the mineralocorticoid receptor in vascular cells and in the heart.

Plasma concentrations of renin and aldosterone are both inversely related to salt intake and are influenced by various medications. Aldosterone is measured by radioimmunoassay. Plasma renin is measured as plasma renin activity based on the generation of angiotensin in the presence of angiotensin-degrading enzyme inhibitors or as plasma renin concentration by immunoassay.

A second major effector system is the sympathetic nervous system. Nerve endings release norepinephrine. This potent neurotransmitter is a vasoconstrictor through α -adrenergic receptor-mediated mechanisms. Vascular cells, renal cells, and many other cells (e.g., adipocytes) are innervated. Epinephrine increases heart rate, stroke volume, and SBP through α - and β -adrenoceptors. The hormone is released from the adrenal medulla. There is compelling evidence that increased sympathetic tone has long-term influences on cardiovascular regulation and that disturbed sympathetic tone may cause hypertension. In the kidneys, sympathetic nerves are important mediators of renin release. Furthermore, innervation of each individual nephron has an important bearing on sodium reabsorption. Thus, the sympathetic nervous system regulates both effective circulating fluid volume and peripheral vascular resistance.

Prostaglandin E and prostacyclin act to counterbalance vasoconstriction by Ang II and norepinephrine. Two endothelium-derived factors have opposite effects on the blood vessels: nitric oxide is a vasodilator, whereas the endothelins are

vasoconstrictors. Natriuretic peptides induce vasodilation, and natriuresis and inhibit other vasoconstrictors (RAS, sympathetic nervous system, and endothelin). Renalase is a recently discovered flavin adenine dinucleotide–dependent amine oxidase that is secreted by the kidney, circulates in the blood, and modulates cardiac function and systemic BP. It acts by metabolizing catecholamines, and its discovery should further our understanding of sympathetic regulation. Urotensin II is a cyclic vasoactive peptide expressed in many organ systems and is inversely related to norepinephrine and brain natriuretic peptide. High plasma levels of urotensin II, a cyclic vasoactive peptide predict reduced cardiovascular complications in patients with chronic kidney disease (stages 2 to 5). Heme oxygenase (HO) has recently been found to suppress arachidonic acid metabolism and to decrease BP in several models of hypertension. The HO system may have an important role in regulating BP and kidney function.

Postreceptor intracellular signaling events also regulate peripheral vascular resistance. For instance, the small guanosine triphosphatase Rho and its effector, Rho-associated kinase (Rho-kinase) are important in Ca^{2+} -independent regulation of smooth muscle contraction. The Rho,Rho-kinase pathway modulates the level of phosphorylation of the myosin light chain of myosin II, mainly through inhibition of myosin phosphatase, and contributes to agonist-induced Ca^{2+} sensitization in smooth muscle contraction. Rho,Rho-kinase mechanisms also participate in a variety of the cellular functions of nonmuscle cells, such as stress fiber formation, cytokinesis, and cell migration. A specific pharmacologic Rho-kinase inhibitor (fasudil) has been developed that may have utility in treating cerebral artery spasm and other forms of severe vascular constriction.

Guyton and Hall have analyzed the temporal sequence for adjustment of BP. In their analysis, central nervous system mechanisms (e.g., baroreflexes) provide regulation of the circulation within seconds to minutes. Other mechanisms, such as the renin-angiotensin-aldosterone system and fluid shifts, occur during minutes to hours. It was once considered that only the kidneys have the ability for long-term adjustments in BP, predominantly through regulation of extracellular volume; but recent evidence indicates that long-term afferent baroreflex stimulation by an

electrical device can lower BP chronically in several different animal models. The critical role for the kidney in the long-term control of BP received strong support from kidney cross-transplantation experiments.

Definition of Hypertension

BP is normally distributed in the general population. Thus, any definition of hypertension is arbitrary. Hypertension is usually asymptomatic; patients are more typically symptomatic from the sequelae of hypertension or its treatment. Hypertension may be defined by its associated morbidity and mortality, as increases over arbitrary cutoff points, or by thresholds defining therapeutic benefit.

Blood Pressure in Relation to Morbidity and Mortality

The first approach defines hypertension by relating BP levels to the risk of morbidity and mortality. The association of SBP and DBP with cardiovascular and renal complications is continuous over the entire BP range. Observational studies involving more than 1 million individuals have found that death from both ischemic heart disease and stroke increases progressively and linearly from BP as low as 115 mm Hg SBP and 75 mm Hg DBP upward. The increased risks are present in all age groups ranging from 40 to 89 years. For every increase of 20 mm Hg SBP or 10 mm Hg DBP, the mortality from both ischemic heart disease and stroke doubles. On the basis of these data, the Joint National Committee (JNC) 7 report introduced a new classification that includes the term prehypertension for those with BP ranging from 120 to 139 mm Hg SBP or 80 to 89 mm Hg DBP. The designation prehypertensive identifies persons in whom early intervention (lifestyle) could reduce BP or avoid further increases. Since JNC 7, the Writing Group of the American Society of Hypertension (WG-ASH) has proposed a new definition of hypertension not based on BP values alone but considering hypertension as a complex cardiovascular disorder. The new definition includes target organ damage, early disease markers, and cardiovascular risk factors. Although it is not uniformly agreed on, the risk-based approach seeks to identify individuals with an increased likelihood of future cardiovascular events at any BP level.

Elevation of Blood Pressure by Arbitrary Cut Points

A second approach defines hypertension by the frequency distribution within a population. This statistical approach will arbitrarily designate values above a certain percentile as hypertensive. This method is used in defining hypertension in children. The values defining hypertension will vary according to age, gender, body size, and race. This frequency distribution method is not helpful for determining a value for initiation of antihypertensive treatment but is useful in epidemiologic studies, for example, defining the prevalence of hypertension in various age groups or the changing prevalence of hypertension in a given population over time. The prevalence of hypertension in adults in the United States, defined as BP of 140/90 mm Hg or higher, has increased progressively from 11% of the population in 1939 to 29.3% in 2004. The prevalence of hypertension in six European countries has been reported at 44%, and it is 66.3% in those older than 60 years.

Threshold of Therapeutic Benefit

The third concept for defining hypertension is derived from randomized trials that have demonstrated reductions in mortality and morbidity. As a result of these clinical trials, consensus has been reached on intervention levels for moderate and severe hypertension but not for lower levels of hypertension. The Hypertension Optimal Treatment (HOT) study showed benefits of lowering BP to 138/83 mm Hg in hypertensive subjects in the absence of diabetes mellitus, chronic kidney disease, coronary artery disease risk, or target organ damage. For subjects with these complications, a treatment goal below 130/80 mm Hg is recommended (JNC 7).

Operational Definitions

The European Society of Hypertension (ESH) divides normotension into three categories (optimum, normal, and high-normal) and describes hypertension as mild, moderate, or severe. The ESH also gave values for automated 24-hour BP measurements, divided into daytime and nighttime.

In the United States, the JNC 7 defined hypertension for individuals 18 years of age and older. The Committee settled on normal, prehypertension, and stage 1 and stage 2 hypertension. For children, the JNC considers that BP at the 95th percentile or higher at each age is elevated.

Clinicians evaluate hypertensive patients and treatment goals on the basis of overall cardiovascular risk factors, not by BP alone. Age, gender, and ethnicity cannot be altered and are important risk factors. However, cholesterol, high-density lipoprotein (HDL) cholesterol, smoking, control of diabetes, obesity, and left ventricular hypertrophy are potentially modifiable. The cluster of risk factors that increase cardiovascular risk and are often associated with hypertension is termed the metabolic syndrome. Decreased renal function is also recognized as an independent cardiovascular risk factor. The same is true for proteinuria, starting with the barely detectable amount of more than 6 mg/day albumin.

Special Definitions

Prehypertension (High-Normal or Borderline Hypertension)

Despite lack of uniform agreement, prehypertension is most usefully defined as BP of 130 to 139/85 to 89 mm Hg (also called stage 2 prehypertension; stage 1 prehypertension, 120 to 129/80 to 84 mm Hg). An older definition of “borderline hypertension” defined individuals whose BP was sometimes above 140/90 mm Hg but would decrease to levels below this with rest. Estimates of prehypertension or borderline hypertension have ranged between 12% and 30% of the adult population. Individuals with prehypertension (stage 2) have a threefold greater likelihood for development of sustained hypertension. During a 20-year follow-up, weight gains of 15 to 20 pounds (6.8 to 9.1 kg) in this group may be associated with a higher risk for development of sustained hypertension. Some of these individuals have a high cardiac output and increased catecholamine turnover. Borderline hypertension may represent an exaggeration of normal physiologic responses to stress. Individuals with prehypertension may have a greater frequency of obesity, abnormal lipids, and other cardiovascular risk factors, with twice the cardiovascular events compared with those with BP below 120/80 mm Hg. Because all BP is “labile” (variable) and generally varies on a diurnal cycle, the term labile hypertension is not helpful and should not be used.

White Coat Hypertension

White coat hypertension is defined as BP that is normal during usual daily activities but is hypertensive in a clinical setting. Normal pressures outside the physician's office are determined by measurement with standard techniques or by ambulatory BP recordings. White coat hypertension can be seen at all ages, including the elderly. The white coat phenomenon is seen less frequently when a nurse or technician takes the BP rather than a physician. White coat hypertension is present in approximately 20% of hypertensive persons. Guidelines are available to assist in assessing patients with isolated clinic hypertension or isolated ambulatory hypertension.

The significance and prognosis of white coat hypertension are unclear. Some studies show that the office- or clinic-induced increase in BP is benign. Other studies report that white coat hypertension is characterized by increases in left ventricular mass index at levels intermediate between normotensive and persistently hypertensive persons. White coat hypertensive patients have impaired diastolic function and higher levels of catecholamines, plasma renin activity, aldosterone, and low-density lipoprotein (LDL) cholesterol. There is also some evidence that subjects with white coat hypertension may be at increased risk for development of persistent hypertension. Thus, each patient with white coat hypertension needs evaluation for cardiovascular risk factors and correction of these, if present, as well as continued follow-up.

Masked Hypertension

Masked hypertension is defined as BP that is lower in the office or clinic compared with ambulatory BP. In one study, the 10-year risk of stroke and cardiovascular mortality in subjects with masked hypertension was similar to that of patients with sustained hypertension.

Sustained Hypertension

Sustained hypertension, also called persistent hypertension, defines individuals whose BP levels are elevated both inside and outside the clinic setting, including at home and during usual daily activities. Office BP readings are frequently higher in sustained hypertensives compared with their ambulatory BP.

Pseudohypertension

Pseudohypertension is defined as “a condition in which the cuff pressure is inappropriately higher when compared to the intra-arterial pressure because of excessive atheromatosis and/or medial hypertrophy in the arterial tree.” Pseudohypertension can be suspected by the “Osler maneuver,” in which the BP cuff is inflated above the SBP (detected by auscultation). If either the brachial or radial artery remains palpable, when pulseless, the patient is considered to be Osler maneuver positive. In general, patients with pseudohypertension have intra-arterial DBP measurements 10 to 15 mm Hg below indirect BP cuff diastolic measurements. None of the definitions specifically addresses the SBP. If a patient is suspected of having pseudohypertension, confirmation by intra-arterial pressure measurement may be considered, with decision for treatment goals based on the intra-arterial findings.

Isolated Systolic Hypertension

Arteriosclerosis, characterized by remodeling and stiffening of large elastic arteries, is the most significant manifestation of vascular aging. The increased stiffening is believed to originate from a gradual mechanical senescence of the elastic network, alterations in cross-linking of extracellular matrix components, fibrosis, and calcification of elastic fibers. Stiffening of large arteries reduces their capacitance and accelerates pulse wave velocity, thus contributing to a widening of pulse pressure and to the increased prevalence of isolated systolic hypertension (ISH) with age. Perhaps as a consequence, the increase in SBP continues throughout life, in contrast to DBP, which increases until the age of 50 years and decreases later in life. Diastolic hypertension is more common before the age of 50 years, either alone or in combination with elevated SBP. After the age of 50 years, SBP is more important than DBP.

ISH is defined as SBP of 140 mm Hg or higher and DBP of 90 mm Hg or lower. The prevalence of ISH increases with age and affects most individuals older than 60 years. In the Framingham study, elevations in SBP determined a greater risk of both heart attacks and strokes compared with elevations of DBP. Indeed, JNC 7 assigned SBP a higher level of importance than DBP. Several clinical trials have

clearly demonstrated that treatment of ISH reduces the cardiovascular event rate. Nevertheless, controversy exists as to the choice of antihypertensive agents. Elderly hypertensive patients should be treated aggressively to the same target BPs identified for younger patients. However, it is appropriate to initiate treatment with lower doses of antihypertensive agents and to bring the pressure down more slowly, monitoring for orthostatic hypotension, impaired cognition, and electrolyte abnormalities.

Resistant Hypertension

Resistant hypertension is defined as BP that is not at treatment goal despite optimal doses of three antihypertensive drugs, including a diuretic. Although it is not well quantified, some clinical trials suggest that resistant hypertension may occur in 30% of hypertensive subjects. Older age and obesity are strong risk factors. Secondary hypertension is more common in resistant hypertension, with primary aldosteronism reported in 18% to 23% of patients.

Accelerated Hypertension/Hypertensive Urgencies and Emergencies

Accelerated hypertension is severe diastolic hypertension (usually >120 mm Hg) in the presence of grade III retinopathy (arteriolosclerotic changes of arteriolar narrowing and nicking plus hypertensive changes of flame-shaped hemorrhages and soft exudates). In the past, “malignant” hypertension referred to severe diastolic hypertension and grade IV retinopathy (grade III plus papilledema). Because the prognosis for untreated severe hypertension with grade III or IV retinopathy is so poor, there is little clinical rationale for using the two terms separately. More recently, accelerated hypertension with hypertensive retinopathy is defined as a hypertensive urgency if treatment is required to decrease BP within hours, whereas hypertensive emergencies are clinical conditions in which severe hypertension must be lowered within minutes. Emergencies include acute dissection of the aorta, acute left ventricular failure, intracerebral hemorrhage, and crises caused by pheochromocytoma, drug abuse, and eclampsia.

Hypertension in Children and in Pregnancy

Hypertension in children is defined by average SBP or DBP at or above the 95th percentile for gender and age, measured on at least three occasions. The reported

causes of hypertension in children vary. Most prepubertal hypertension is thought to have renal causes, although some children may have BP levels above the 95th percentile because of an earlier growth spurt and large size. In postpubertal children, mild hypertension is likely to be primary hypertension, whereas more severe hypertension is usually of renal cause. Primary aldosteronism and thyroid disease seem rare.

Hypertension may occur in more than 5% of all pregnancies and in approximately 5% of women taking oral contraceptives.

Classification by Cause of Hypertension

Although a large number of causes are recognized for hypertension, the etiology in 90% to 95% of patients with hypertension is unknown. These patients are considered to have primary (or essential) hypertension. The more common causes of secondary hypertension include renal parenchymal disease (2% to 6% of all hypertensives), renovascular hypertension (1% to 4%), and all endocrine hypertension (traditionally thought to be 1%, including primary aldosteronism, pheochromocytoma, Cushing's syndrome, and others). More recent studies have shown an increasing prevalence of primary aldosteronism, ranging from 2% to 13% in stage 1 to stage 3 hypertension. Other causes include coarctation of the aorta (0.1% to 1.0%) and obstructive sleep apnea and obesity. An often overlooked cause of hypertension is drug induced (1%), including oral contraceptives, decongestants or sympathomimetic agents, and nonsteroidal anti-inflammatory drugs (NSAIDs).

Proper Measurement of Blood Pressure

Arterial BP is usually measured in the brachial artery by use of the cuff-based sphygmomanometer, in which the arterial pressure is recorded by detecting sounds that are generated (auscultatory method) or by recording vascular pulsations (oscillometric method) after decompression of a compressed artery. Unfortunately, if it is not properly used, the method can be unreliable and inaccurate. The most common reason for inaccuracy is an inappropriate cuff size as the accuracy of these measurements is influenced by the size of the inflatable bladder relative to the girth of the compressed limb. To provide uniform compression of the underlying artery,

the length of the bladder should be at least 80% of the upper arm circumference, and the width of the bladder should be at least 40% of the upper arm circumference. A simple bedside maneuver to check the appropriateness of the cuff size consists of aligning the cuff so that its long axis is parallel to the long axis of the arm. The bladder width should then be sufficient to encircle half of the upper arm circumference. If the bladder width encompasses less than half of the upper arm, a larger cuff must be selected. No change in cuff size is necessary if the cuff width encircles more than half the upper arm because large cuffs on thin limbs do not produce considerable errors in the BP measurement. Another potential error relates to the auscultatory method, which relies on the ability to hear the Korotkoff sounds. The human ear has a sound threshold of about 16 Hz. The Korotkoff sounds occur at slightly above this level (25 to 50 Hz). Thus, the human ear is almost deaf to the sounds it must hear to measure BP. The bell-shaped stethoscope head should be used to measure BP. Interestingly, many physicians and most nurses are not equipped with a bell-shaped stethoscope head.

The oscillometric method is based on the principle of plethysmography to detect pulsatile pressure changes in a nearby artery. When an arm cuff is inflated, pulsatile pressure changes in an underlying artery produce periodic pressure changes in the inflated cuff. The oscillometric method thus measures periodic pressure changes, oscillations, in an inflated cuff as an indirect measure of pulsatile pressure in an underlying artery.

There are three types of sphygmomanometer in use worldwide. Because of environmental concerns, the standard mercury manometer has been abandoned in some areas. The second type in wide use is the aneroid manometer. There are also numerous semiautomatic oscillometric electronic recording manometers. The manufacturers must ensure accuracy, and in many countries, the local hypertension societies have arranged for certification of these devices. The technical capabilities of the devices have increased greatly. Physicians must be aware that many patients purchase devices and measure their own BP. These devices should be inspected and checked by the physician.

Variability of Blood Pressure

Wake-Sleep Cycle and Office Versus Home Blood Pressure

BP varies considerably in individual subjects and may vary significantly throughout the day. This variation causes considerable difficulties in identifying individuals who are hypertensive, especially in terms of the preceding classification schemes. The differing BP values are due to both biologic variation (variations of pressures within a given individual) and variation in the measurement itself. Errors in measurement can be minimized by attention to the proper technique for recording BP, as noted previously. Biologic variation is addressed by repeated BP measurement at a given visit (at least two pressures taken at least 30 seconds apart or additional BP measurements if there is a difference of 5 mm Hg between repeated measures). In addition, in most patients with milder forms of hypertension, repeated measurements during different clinic visits over time are recommended to approach the true BP.

Readings of BP at home, and outside the clinic or office setting, are recommended to assess the severity and frequency of hypertension and BP control during treatment. The instruments used at home must be checked against a standard on a regular basis, and the techniques for correct BP measurement must be taught to the patient. This includes having the brachial artery at the level of the heart when BP is measured. Levels measured at home are generally lower than those measured in the clinic or office. Patients should be discouraged from very frequent home BP measurement and from frequent adjustment of medications, which may result in unnecessary emergency department visits and hospital admissions for symptomatic hypotension or uncontrolled hypertension. It is worthwhile to ask the patient to keep a daily calendar and to measure BP under controlled conditions two or three times daily, for instance, while sitting quietly in the mornings, afternoons, and evenings. If three fourths of the measurements achieve goal or better, office control is generally also achieved.

Biologic variation during the day is related to physical and mental activity and emotional factors. There is also diurnal variation, with a decrease in BP during sleep (averaging 20%) secondary to a decrease in sympathetic activity; similar reductions

in BP occur after hospital admission and bed rest. The normal diurnal pattern includes an increase in BP before awakening that has been associated with increased incidence of myocardial infarction, stroke, and sudden death in the first few hours after awakening. Those with the usual pattern of BP decrease during sleep are known as nocturnal “dippers.” Those whose BP does not fall during sleep are called “nondippers.” The failure to decrease BP during sleep has been associated with increased incidence of left ventricular hypertrophy and raises the possibility of secondary hypertension.

Ambulatory Blood Pressure

Because of the variability in BP that occurs throughout the day, home BP and ambulatory BP monitoring are used to define BP more clearly. Home BP monitoring is advised for all patients and may help identify white coat hypertension and borderline hypertension and may also help monitor response to therapy, including identification of hypotension as well as hypertension. The instructions to each patient must be individualized, but home BP monitoring may be advised two or three times per day while the patient is awake. These BP values must be self-recorded and reviewed. The prognostic value of ambulatory and home BP compared with office BP in the general population was recently reported from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. A total of 2051 persons were observed for 10 years; risk of death increased more with a given increase in home or ambulatory BP than in office BP. The overall ability to predict death, however, was not greater for home and ambulatory than for office BP, although it was somewhat increased by the combination of office and outside-of-office values. SBP was almost invariably superior to DBP, and night BP was superior to day BP.

Ambulatory BP monitoring is recommended for certain indications beyond the information available from home BP recording. Ambulatory BP monitoring uses a noninvasive system. The BP is determined by auscultation with use of either oscillometry, which measures variations in pressure within the cuff, or a microphone placed under the cuff and over the brachial artery. The ambulatory BP device can be programmed to record at frequent intervals during the daytime (e.g., every 10

minutes) and less frequently at night during sleep (e.g., every 30 minutes). The ambulatory BP equipment might not provide accurate readings in patients with large upper arms due to obesity or increased musculature, and the equipment may be inaccurate during vigorous activity. The equipment generally records BP during a 24-hour period. Although most patients adjust to the repetitive measurements throughout the day, some patients may have a startle response with each BP recording. Most patients are able to sleep, although some have their sleep disturbed by the BP recording, and therefore determination of nocturnal fall in BP is inaccurate.

There are disadvantages to use of the ambulatory BP equipment. Trained personnel must place the monitoring equipment. Calibration of ambulatory BP equipment with a mercury manometer must be recorded at the beginning and end of the ambulatory BP session. Three to six readings must be taken at each time, and the SBP and DBP measurements must both agree within 5 mm Hg. The end calibration is critical to ensure proper functioning of the ambulatory BP monitor throughout the 24-hour period. The cuff inflation may interfere with activities, work, or sleep. The cuff may cause discomfort or skin irritation, or it may malfunction and fail to deflate, causing pain and interruption of recording. The data correlating ambulatory BP with target organ disease are limited. Standards for assessment of data and their use in decisions for therapy are limited. In addition, equipment is expensive and its use is limited by lack of reimbursement by health insurance systems in a number of countries, including the United States and some European countries.

Evaluation for Primary Versus Secondary Hypertension

The medical history, the physical examination, and a limited number of laboratory tests provide critical information in deciding which individuals require further evaluation for secondary hypertension and target organ disease. All hypertensive persons should be assessed for cardiovascular risk factors, including total cholesterol, HDL and LDL cholesterol, fasting triglycerides, renal function, and proteinuria (according to the Kidney Disease Outcomes Quality Initiative classification), and for the presence of diabetes mellitus or the metabolic syndrome.

Some authorities advocate assessment of patients with primary hypertension in terms of their plasma renin activity (renin profiling). The notion is to treat patients with low plasma renin activity with drugs aimed at volume reduction and those with higher values with drugs aimed at peripheral vascular resistance. Although a 24-hour urine collection for sodium excretion is helpful information, the collection is not mandatory, nor must all medication be discontinued before a renin measurement. According to renin profiling, patients with plasma renin activity below 0.65 ng/ml/h are more likely to have volume-related hypertension, whereas those with values above 0.65 ng/ml/h have more predominant vasoconstriction. Systematic drug rotation studies have shown that the rank order of response to different drugs indeed varies substantially among patients. In support of renin profiling, two broad patterns of response emerged. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and β -blockers were useful primarily in hypertensive patients with higher renin values. These patients are generally younger Caucasians. Calcium channel blockers and diuretics were more useful in low-renin hypertension, which is commonly observed in Afro-Caribbeans, African Americans, and older Caucasians.

If the history, physical examination, or screening laboratory studies suggest secondary hypertension, additional studies are warranted. If renal parenchymal disease is suspected, quantitative studies to assess GFR and urinary protein excretion should be performed. Renal ultrasound is useful to evaluate renal size and echogenicity (to help assess chronicity) and to evaluate for obstructive uropathy. Renal artery stenosis should be suspected by the presence of severe hypertension with abnormal renal function or with asymmetric renal size. If primary aldosteronism is suspected because of hypokalemia, the ratio of plasma aldosterone to plasma renin activity may be useful. If the ratio is above 25 to 30 and plasma aldosterone concentration is more than 20 ng/dl, the diagnosis should be pursued further. The extended results of patients undergoing operation have been published. Resolution of hypertension after adrenalectomy for primary aldosteronism was independently

associated with a lack of family history of hypertension and preoperative use of two or fewer antihypertensive agents.

In finally, the ideal target blood pressure is not finally established, but in the Modification of Diet in Renal Disease (MDRD) study, patients with proteinuria (>1 g/day) had a better outcome if their blood pressure was reduced to 125/75 mm Hg rather than to the previous standard of 140/90 mm Hg. There are strong theoretical and experimental reasons for ACE inhibitors and ARBs to be first-choice therapy, and this is now well documented in clinical studies. Nondihydropyridine calcium channel blockers may also have a beneficial effect on proteinuria as well as on blood pressure. As in primary hypertension, lifestyle modification (salt restriction, weight normalization, regular exercise, and smoking cessation) should be an integral part of the therapy. If target blood pressure cannot be achieved with these measures, antihypertensive therapy should be stepped up according to current guidelines

1.7 Anemia

By definition, anemia refers to an absolute reduction of the total number of circulating red blood cells (RBCs). For practical purposes, anemia is considered when one or more of the following are decreased: hemoglobin, hematocrit, or red blood cell (RBC) count. The European Best Practice Guidelines for the management of anemia in patients with chronic kidney disease propose that the lower limit of normal for hemoglobin be 11.5 g/dL in women, 13.5 g/dL in men age 70 and under, and 12.0 g/dL in men older than age 70. In the United States, the working definition of anemia in chronic kidney disease has been influenced by government policy, as the Medicare program is the primary payer for its therapy. The National Kidney Foundation's Kidney Dialysis Outcomes Quality Initiative (K/DOQI) recommends a workup for anemia in patients with chronic kidney disease if the hemoglobin level is less than 11.0 g/dL (hematocrit < 33%) in premenopausal women and prepubertal patients, and when the hemoglobin is less than 12.0 g/dL (hematocrit < 37%) in adult men and postmenopausal women. These levels correspond to a decline to approximately 80% of the mean level for defined healthy subgroups.

Frequency

Anemia is very common in patients with chronic kidney disease and probably causes many of its symptoms. Physicians should start thinking about anemia when their patient's glomerular filtration rate (GFR) declines to 60 mL/minute/1.73 m² or less. In the third National Health and Nutrition Examination Survey (NHANES), the prevalence of anemia in stage 3 chronic kidney disease (ie, a GFR of 30 to 59 mL/minute/1.73 m²) was 5.2%, rising to 44.1% in stage 4, and becoming almost universal in stage 5. (NHANES defined anemia as hemoglobin < 12.0 g/dL in men and < 11.0 g/dL in women.) African Americans and patients with diabetes⁵ have even higher rates of anemia at each stage of kidney disease. Moreover, chronic kidney disease itself is very common: nearly 6 million Americans are estimated to have stage 3 chronic kidney disease. The chance of developing anemia increases as kidney disease gets worse. A study has shown anemia affected 28% of people with mild kidney disease and 87% of people with severe kidney disease.

Etiology

Factors likely contributing to anemia in chronic kidney disease include blood loss, shortened red cell life span, vitamin deficiencies, the "uremic milieu," erythropoietin (EPO) deficiency, iron deficiency, and inflammation. Unfortunately, we know little about the relative contributions of the different factors and conditions in the early stages of chronic kidney disease.

Blood loss

Patients with chronic kidney disease are at risk of blood loss due to platelet dysfunction. The main cause of blood loss is dialysis, especially hemodialysis, and the loss results in absolute iron deficiency. Hemodialysis patients may lose 3 to 5 g of iron per year. Normally, we lose 1 to 2 mg per day (Fig. 1.7.1), so the iron loss in dialysis patients is 10 to 20 times higher. Therefore, iron supplementation is a mainstay of anemia management.

Shortened red blood cell life span.

The life span of red cells is reduced by approximately one third in hemodialysis patients.

Vitamin deficiencies

It is difficult to determine whether vitamin deficiencies play a significant role in causing anemia in chronic kidney disease. Most patients with chronic kidney disease take a multivitamin daily, although there is no strong evidence that this is beneficial. Therefore, even the prevalence of vitamin deficiencies in chronic kidney disease has been hard to establish.

'Uremic milieu'

The "uremic milieu" is a term that is overused in attempts to explain the multiple organ dysfunction of chronic kidney disease. In studies in vitro, the term has been invoked when cultured cells were exposed to serum from patients with chronic kidney disease, with results that mimicked some of the clinical observations. For example, "uremic" serum has been shown to inhibit primary bone marrow cultures of early erythroid cell lines. However, the lack of specificity in these studies has been criticized because this serum also affects other cell lines. In studies in vivo, the concept of a uremic milieu may explain why the level and prevalence of anemia correlate with the severity of the kidney disease. A GFR lower than 60 mL/minute/1.73 m² has been associated with a higher prevalence of anemia, which reached 75% in some studies. In addition, in a study in patients who had been receiving hemodialysis, the hematocrit rose when the intensity of dialysis was increased, implying that reducing uremia restores or improves bone marrow function. However, this study could not distinguish the independent effects of the increased dialysis dose and the effect of changing to a more permeable dialysis membrane during the study.

EPO deficiency

EPO deficiency is considered the most important cause of anemia in chronic kidney disease. Researchers postulate that the specialized peritubular cells that produce EPO are partially or completely depleted or injured as renal disease progresses, so that EPO production is inappropriately low relative to the degree of anemia. Thus, measuring EPO levels in this population is of no use and should not be ordered: in fact, it can even be misleading if the value is normal when it ought to be high. However, the reason for this inappropriately low EPO production is not well

understood. EPO is produced when its gene is transcribed, in a process that depends on the binding of a molecule called hypoxia-inducible factor 1 alpha to the hypoxia-responsive element on the erythropoietin gene. Production of this factor increases in states of relative oxygen deficiency. Therefore, the balance between oxygen supply and consumption determines the production of hypoxia-inducible factor 1 alpha and, in turn, production of EPO. It is proposed that the relative EPO deficiency in chronic kidney disease could be a functional response to a decreased glomerular filtration rate. The theory is that the EPO-producing kidney cells themselves may not be hypoxic: if the glomerular filtration rate is low, there is less sodium reabsorption - and sodium reabsorption is the main determinant of oxygen consumption in the kidney. In this situation there may be a local relative excess of oxygen that could down-regulate EPO production. Moreover, dialysis patients in one study maintained the ability to increase EPO production when exposed to high altitude. However, the best example that native kidneys have the potential for restoring EPO production is seen in some patients who developed erythrocytosis after receiving kidney transplants, a situation in which the uremic milieu is eliminated.

Iron deficiency

Human iron metabolism is unique because no excretory route exists: it is mostly regulated via uptake. Iron homeostasis depends on iron being absorbed in the duodenum and also recycled from senescent red blood cells. Most of the iron is bound to hemoglobin and is stored in hepatocytes and macrophages of the reticuloendothelial system. Iron is delivered to the maturing erythrocytes by a protein called transferrin, which transports both the iron absorbed and the iron released from macrophages (mainly from recycled senescent red blood cells). Iron homeostasis appears to be altered in chronic kidney disease. For reasons not yet known (perhaps malnutrition), transferrin levels in chronic kidney disease are one half to one third of normal levels, diminishing the capacity of the iron-transporting system. This situation is then aggravated by the well-known inability to release stored iron from macrophages and hepatocytes in chronic kidney disease. Clinically, diminished iron transport and accumulated iron stores are manifested as low transferrin saturation and

elevated serum ferritin levels. These characteristics suggest that the interorgan iron transport pathways may be rate-limiting factors in erythropoiesis in these patients. Interplay between increased iron losses (as discussed previously) and abnormal interorgan iron transport results in an absolute or functional iron deficiency that can be corrected only by aggressive iron replacement therapy.

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Chapter 2

Contemporary diagnostic methods and Interventional procedures in nephrology

A variety of procedures are essential to the care of nephrology patients and include assessment of renal function, ultrasound, renal biopsy, insertion of hemodialysis and peritoneal dialysis (PD) catheters, creation of arteriovenous (AV) fistulas, and diagnostic and interventional procedures on hemodialysis accesses. These procedures have traditionally been performed by other specialists, and this may lead to fragmented care. The desire to provide more continuity of care has led an increasing number of nephrologists to perform these procedures, the field of diagnostic and interventional nephrology.

2.1 Assessment of Renal Function

2.1.1 Measurement of the Glomerular Filtration Rate

Glomerular filtration rate (GFR) is a product of the average filtration rate of each single nephron, the filtering unit of the kidneys, multiplied by the number of nephrons in both kidneys. The normal level for GFR is approximately 130 ml/min per 1.73 m² for men and 120 ml/min per 1.73 m² for women, with considerable variation among individuals according to age, sex, body size, physical activity, diet, pharmacologic therapy, and physiologic states such as pregnancy. To standardize the function of the kidney for differences in kidney size, which is proportional to body size, GFR is adjusted for body surface area, computed from height and weight, and is expressed per 1.73 m² surface area, the mean surface area of young men and women. Even after adjustment for body surface area, GFR is approximately 8% higher in young men than in women and declines with age; the mean rate of decline is approximately 0.75 ml/min per year after the age of 40 years, but the variation is wide and the sources of variation are poorly understood. During pregnancy, GFR increases by about 50% in the first trimester and returns to normal immediately after delivery. GFR has a diurnal variation and is 10% lower at midnight compared with

the afternoon. Within an individual, GFR is relatively constant over time but varies considerably among people, even after adjustment for the known variables.

Reductions in GFR can be due to either a decline in the nephron number or a decline in the single-nephron GFR (SNGFR) from physiologic or hemodynamic alterations. An increase in SNGFR due to increased glomerular capillary pressure or glomerular hypertrophy can compensate for a decrease in nephron number, and, therefore, the level of GFR may not reflect the loss of nephrons. As a result, there may be substantial kidney damage before GFR decreases.

GFR cannot be measured directly. Instead, it is measured as the urinary clearance of an ideal filtration marker.

Concept of Clearance

Clearance of a substance is defined as the volume of plasma cleared of a marker by excretion per unit of time. The clearance of substance x (C_x) can be calculated as $C_x = A_x / P_x$, where A_x is the amount of x eliminated from the plasma, P_x is the average plasma concentration, and C_x is expressed in units of volume per time. Clearance does not represent an actual volume; rather, it is a virtual volume of plasma that is completely cleared of the substance per unit of time. The value for clearance is related to the efficiency of elimination: the greater the rate of elimination, the higher the clearance. Clearance of substance x is the sum of the urinary and extrarenal clearance; for substances that are eliminated by renal and extrarenal routes, plasma clearance exceeds urinary clearance.

Urinary Clearance

The amount of substance x excreted in the urine can be calculated as the product of the urinary flow rate (V) and the urinary concentration (U_x). Therefore, urinary clearance is defined as follows:

- Urinary excretion of a substance depends on filtration, tubular secretion, and tubular reabsorption. Substances that are filtered but not secreted or reabsorbed by the tubules are ideal filtration markers because their urinary clearance can be used as a measure of GFR. For substances that are filtered and secreted, urinary clearance

exceeds GFR; and for substances that are filtered and reabsorbed, urinary clearance is less than GFR.

- Measurement of urinary clearance requires a timed urine collection for measurement of urine volume as well as urine and plasma concentrations of the filtration marker. Special care must be taken to avoid incomplete urine collections, which will limit the accuracy of the clearance calculation.

Plasma Clearance

There is an increasing interest in measurement of plasma clearance because it avoids the need for a timed urine collection. GFR is calculated from plasma clearance (Cx) after a bolus intravenous injection of an exogenous filtration marker, with the clearance (Cx) computed from the amount of the marker administered (Ax) divided by the plasma concentration (Px), which is equivalent to the area under the curve of plasma concentration versus time.

The decline in plasma levels is secondary to the immediate disappearance of the marker from the plasma into its volume of distribution (fast component) and to renal excretion (slow component). Plasma clearance is best estimated by use of a two-compartment model that requires blood sampling early (usually two or three time points until 60 minutes) and late (one to three time points from 120 minutes onward). Like urinary clearance, plasma clearance of a substance depends on filtration, tubular secretion, and tubular reabsorption and, in addition, extrarenal elimination.

Exogenous Filtration Markers

Inulin, a 5200-d uncharged polymer of fructose, was the first substance described as an ideal filtration marker and remains the gold standard against which other markers are evaluated. The classic protocol for inulin clearance requires a continuous intravenous infusion to achieve a steady state and bladder catheterization with multiple timed urine collections. Because this technique is cumbersome, and inulin measurement requires a difficult chemical assay, this method has not been used widely in clinical practice and remains a research tool. Alternative exogenous substances include iothalamate, iohexol, ethylenediaminetetraacetic acid, and diethylenetriaminepentaacetic acid, often chelated to radioisotopes for ease of

detection. Alternative protocols to assess clearance have also been validated, including subcutaneous injection and spontaneous bladder emptying. There are advantages to alternative exogenous filtration markers and methods, but also limitations. Understanding of the strengths and limitations of each alternative marker and each clearance method will facilitate interpretation of measured GFR

Endogenous Filtration Markers

Creatinine is the most commonly used endogenous filtration marker in clinical practice. Urea was widely used in the past, and cystatin C presently shows great promise. For filtration markers that are excreted in the urine, urinary clearance can be computed from a timed urine collection and a single measurement of serum concentration. If the serum level is not constant during the urine collection, as in acute kidney disease or when residual kidney function is assessed in dialysis patients, it is also necessary to obtain additional blood samples during the urine collection to estimate the average serum concentration.

Estimation of GFR from Plasma Levels of Endogenous Filtration Markers

There is relationship of plasma concentration of substance x to its generation (G_x) by cells and dietary intake, urinary excretion ($U_x \times V$), and extrarenal elimination (E_x) by gut and liver. The plasma level is related to the reciprocal of the level of GFR, but it is also influenced by generation, tubular secretion and reabsorption, and extrarenal elimination, collectively termed non-GFR determinants of the plasma level. In the steady state, a constant plasma level of substance x is maintained because generation is equal to urinary excretion and extrarenal elimination. Estimating equations incorporate demographic and clinical variables as surrogates for the non-GFR determinants and provide a more accurate estimate of GFR than the reciprocal of the plasma level alone. Estimating equations are derived from regression of measured GFR on measured values of the filtration marker and observed values of the demographic and clinical variables. Estimated GFR may differ from measured GFR in a patient if there is a discrepancy between the true and average values for the relationship of the surrogate to the non-GFR determinants of the filtration marker. Other sources of errors include measurement error in the

filtration marker (including failure to calibrate the assay for the filtration marker to the assay used in the development of the equation), measurement error in GFR in development of the equation, and regression to the mean. In principle, all these errors are likely to be greater at higher values for GFR.

Creatinine Metabolism and Excretion

Creatinine is a 113-d end product of muscle catabolism. Advantages of creatinine include its ease of measurement and the low cost and widespread availability of assays. Disadvantages include the large number of non-GFR determinants, leading to a wide range of GFR for a given plasma creatinine level. Creatinine is derived by the metabolism of phosphocreatine in muscle as well as from dietary meat intake or creatine supplements. Creatinine generation is proportional to muscle mass, which can be estimated from age, gender, race, and body size. Figure 3.4 lists factors that can affect creatinine generation.

Creatinine is released into the circulation at a constant rate. It is not protein bound and is freely filtered across the glomerulus and secreted by the tubules. Several medications, such as cimetidine and trimethoprim, competitively inhibit creatinine secretion and reduce creatinine clearance. These medications thus lead to a rise in the serum creatinine concentration without an effect on GFR.

In addition, creatinine is contained in intestinal secretions and can be degraded by bacteria. If GFR is reduced, the amount of creatinine eliminated through this extrarenal route is increased. Antibiotics can raise serum creatinine concentration by destroying intestinal flora, thereby interfering with extrarenal elimination, as well as by reduction of the GFR. The rise in serum creatinine concentration after inhibition of tubular secretion and extrarenal elimination is greater in patients with a reduced GFR. Clinically, it can be difficult to distinguish a rise in serum creatinine concentration due to inhibition of creatinine secretion or extrarenal elimination from a decline in GFR, but processes other than a decline in GFR should be suspected if serum urea concentration remains unchanged despite a significant change in serum creatinine concentration in a patient with an initially reduced GFR.

Creatinine clearance is usually computed from the creatinine excretion in a 24-hour urine collection and single measurement of serum creatinine in the steady state. In a complete collection, creatinine excretion should be approximately 20 to 25 mg/kg per day and 15 to 20 mg/kg per day in healthy young men and women, respectively, and deviations from these expected values can give some indication of errors in timing or completeness of urine collection. Creatinine clearance systematically overestimates GFR because of tubular creatinine secretion. In the past, the amount of creatinine excreted by tubular secretion at normal levels of GFR was thought to be relatively small (10% to 15%), but with newer, more accurate assays for low values of serum creatinine, it appears that this difference may be substantially greater. At low values of GFR, the amount of creatinine excreted by tubular secretion may exceed the amount filtered.

Creatinine Assay

Historically, the most commonly used assay for measurement of serum creatinine was the alkaline picrate (Jaffe) assay that generates a color reaction. Chromogens other than creatinine are known to interfere with the assay, giving rise to errors of up to approximately 20% in normal subjects. Modern enzymatic assays do not detect non-creatinine chromogens and yield lower serum levels than with the alkaline picrate assays. Until recently, calibration of assays to adjust for this interference was not standardized across laboratories.

To address the heterogeneity in creatinine assays, the College of American Pathologists has prepared fresh-frozen serum pools with known creatinine levels that enable standardization of creatinine measurements and calibration of equipment. Until standardization is complete globally, the variability in the calibration of creatinine assays will remain an important limitation of the use of GFR estimating equations, especially at higher levels of estimated GFR. This will affect the ability to compare the level of kidney function based on serum creatinine concentration reported by different laboratories, especially when the estimated GFR is more than 60 ml/min per 1.73 m². Standardization will reduce, but not completely eliminate, the error at higher levels of GFR.

Formulae for Estimating the Glomerular Filtration Rate from Serum Creatinine

GFR can be estimated from serum creatinine by equations that use age, sex, race, and body size as surrogates for creatinine generation. Despite substantial advances in the accuracy of estimating equations based on creatinine during the past several years, no equation can overcome the limitations of creatinine as a filtration marker. None of these equations is expected to work as well in patients with extreme levels for creatinine generation, such as amputees, large or small individuals, patients with muscle-wasting conditions, or people with high or low levels of dietary meat intake. Because of differences among racial and ethnic groups according to muscle mass and diet, it is unlikely that equations developed in one racial or ethnic group will be accurate in multiethnic populations.

Cockcroft-Gault Formula

The Cockcroft-Gault formula estimates creatinine clearance from age, sex, and body weight in addition to serum creatinine. There is an adjustment factor for women that is based on a theoretical assumption of 15% lower creatinine generation due to lower muscle mass. Comparison to normal values for creatinine clearance requires computation of body surface area and adjustment to 1.73 m². Because of the inclusion of a term for weight in the numerator, this formula systematically overestimates creatinine clearance in patients who are edematous or obese.

Urea

The serum urea level has limited value as an index of GFR, in view of widely variable non-GFR determinants, primarily urea generation and tubular reabsorption. Urea is a 60-d end product of protein catabolism by the liver. Factors associated with the increased generation of urea include protein loading from hyperalimentation and absorption of blood after a gastrointestinal hemorrhage. Catabolic states due to infection, corticosteroid administration, or chemotherapy also increase urea generation. Decreased urea generation is seen in severe malnutrition and liver disease.

Urea is freely filtered by the glomerulus and then passively reabsorbed in both the proximal and distal nephrons. Owing to tubular reabsorption, urinary clearance of urea underestimates GFR. Reduced kidney perfusion in the setting of volume depletion and states of antidiuresis are associated with increased urea reabsorption. This leads to a greater decrease in urea clearance than the concomitant decrease in GFR. At GFR of less than approximately 20 ml/min per 1.73 m², the overestimation of GFR by creatinine clearance due to creatinine secretion is approximately equal to the underestimation of GFR by urea clearance due to urea reabsorption.

Cystatin C

Cystatin C is a 122-amino acid protein with a molecular mass of 13 kd. It has multiple biologic functions including extracellular inhibition of cysteine proteases, modulation of the immune system, exertion of antibacterial and antiviral activities, and modification of the body's response to brain injury. The serum concentration of cystatin C remains constant from approximately 1 to 50 years of age. In analyses of the National Health and Nutrition Examination Survey (NHANES) III, the median and upper 99th percentile levels of serum cystatin C for people 20 to 39 years of age without history of hypertension and diabetes were 0.85 mg/l and 1.12 mg/l, respectively, with levels lower in women, higher in non-Hispanic whites, and increasing steeply with age.

Cystatin C has been thought to be produced at a constant rate by a “housekeeping” gene expressed in all nucleated cells. Cystatin C is freely filtered at the glomerulus because of its small size and basic pH. After filtration, approximately 99% of the filtered cystatin C is reabsorbed by the proximal tubular cells, where it is almost completely catabolized, with the remaining uncatabolized form eliminated in the urine. There is some evidence for the existence of tubular secretion as well as extrarenal elimination, which has been estimated to be between 15% and 21% of renal clearance. Because cystatin C is not excreted in the urine, it is difficult to study its generation and renal handling. Thus, understanding of determinants of cystatin C other than GFR relies on epidemiologic associations. There are suggestions that inflammation, adiposity, thyroid diseases, certain malignant neoplasms, and use of

glucocorticoids may increase cystatin C levels. In two studies, key factors that led to higher levels of cystatin C after adjustment for creatinine clearance or measured GFR were older age, male gender, fat mass, white race, diabetes, higher C-reactive protein level and white blood cell count, and lower serum albumin level. Altogether, these studies suggest that factors other than GFR must be considered in interpreting cystatin C levels.

Assay

There are currently two main automated methods for assay of cystatin C: immunoassays based on turbidimetry (particle-enhanced turbidimetric immunoassay, PETIA) and nephelometry (particle-enhanced nephelometric immunoassay, PENIA). The two methods result in different results. International standardization of the assay is in process. The assays are considerably more expensive than those for creatinine determination.

Use as a Filtration Marker

Some studies show that elevations in cystatin C level are a better predictor of the risk of cardiovascular disease and total mortality than is an estimated GFR based on serum creatinine concentration. Whether this is due to its superiority as a filtration marker or to confounding by non-GFR determinants of cystatin C and creatinine remains to be determined. Several studies have compared accuracy of serum cystatin C and creatinine in relation to measured GFR. The majority of studies have found serum cystatin C levels to be a better estimate of GFR than serum creatinine concentration is. However, cystatin C or equations based on cystatin C are not more accurate than creatinine-based estimating equations. In studies of patients with chronic kidney disease, the combination of the two markers resulted in the most accurate estimate. In certain populations, such as in children, elderly, transplant recipients, patients with neuromuscular diseases or liver disease, or those with higher levels of GFR, in whom serum creatinine-based equations are less accurate, cystatin C may result in a more accurate estimate, but this has not been rigorously evaluated. In patients with acute kidney injury, serum cystatin C increases more rapidly than serum creatinine. More data are required to establish whether it is a more sensitive

indicator of rapidly changing kidney function than creatinine is. In the future, GFR estimating equations using the combination of serum cystatin C and creatinine may have potential to provide more accurate estimates of GFR than do equations using serum creatinine. However, this is feasible only after standardization, widespread availability, and cost reductions of cystatin C assays as well as further investigation of non-GFR determinants of serum cystatin C.

2.1.2 Clinical Application of Estimated Glomerular Filtration Rate

Chronic Kidney Disease

Estimation of GFR is necessary for the detection, evaluation, and management of chronic kidney disease (CKD). Current guidelines recommend testing of patients at increased risk of CKD for albuminuria as a marker of kidney damage or a reduced estimated GFR to assess kidney function and staging of the severity of CKD by the level of the estimated GFR. Use of serum creatinine alone as an index of GFR is unsatisfactory and can lead to delays in detection of CKD and misclassification of the severity of CKD. Use of estimating equations allows direct reporting of GFR estimates by clinical laboratories whenever serum creatinine is measured. Current estimating equations will be less accurate in people with factors affecting serum creatinine concentration other than GFR. In these situations, more accurate GFR estimates require a clearance measurement, by use of either an exogenous filtration marker or a timed urine collection for creatinine clearance. In the future, improved estimating equations using creatinine and possibly cystatin C will allow more accurate GFR estimates.

Acute Kidney Injury

In the non-steady state, there is a lag before the rise in serum level due to the time required for retention of an endogenous filtration marker. Conversely, after recovery of GFR, there is a lag before the excretion of the retained marker. During this time, neither the serum level nor the GFR estimated from the serum level accurately reflects the measured GFR. Nonetheless, a change in the estimated GFR in the non-steady state can be a useful indication of the magnitude and direction of the change in measured GFR. If the estimated GFR is falling, the decline in estimated

GFR is less than the decline in measured GFR. Conversely, if the estimated GFR is rising, the rise in estimated GFR is greater than the rise in measured GFR. The more rapid the change in estimated GFR, the larger the change in measured GFR. When the estimated GFR reaches a new steady state, it more accurately reflects measured GFR.

2.1.3 Markers of Tubular Damage

Low-molecular-weight plasma proteins are readily filtered by the glomerulus and subsequently reabsorbed by the proximal tubule in normal subjects, with the result that only small amounts of the filtered proteins appear in the urine. The urinary excretion of these proteins rises when proximal tubular reabsorption is impaired. Because there is no distal tubular reabsorption, measurement of urinary low-molecular-weight proteins has been widely accepted as a marker of proximal tubular damage. Examples of low-molecular-weight proteins that could be measured in clinical practice are β 2-microglobulin (11,800 d), the light chain of the class I major histocompatibility antigens; α 1-macroglobulin (33,000 d), a glycosylated protein synthesized in the liver; and retinol-binding protein. β 2-Microglobulin is unstable in acidic urine (pH <6), leading to underestimation, whereas α 1-macroglobulin is stable and not readily affected by urine pH. Urine cystatin C and N-acetyl- β -glucosaminidase (NAG) have also been proposed as markers of tubular damage. Two more recently described markers of tubular damage are urinary kidney injury molecule 1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL).

The 24-Hour Protein Excretion

This remains the reference (gold standard) method. It averages the variation of proteinuria due to the circadian rhythm and is the most accurate for monitoring of proteinuria during treatment, but it can be impractical in some settings (e.g., outpatients, elderly patients). Moreover, this method is subject to error due to overcollection or undercollection. One advantage is that 24-hour urine protein is usually measured by methods that quantify total protein rather than simply albumin, and hence this can result in detection of light chains in subjects with myeloma.

Protein-Creatinine Ratio on a Random Urine Sample

This is a practical alternative to the 24-hour urine collection. It is easy to obtain, it is not influenced by variation in water intake and rate of diuresis, and the same sample can also be used for microscopic investigation. There is a strong correlation between the protein-creatinine ratio in a random urine sample and the 24-hour protein excretion. However, although a normal protein-creatinine ratio is sufficient to rule out pathologic proteinuria, an elevated protein-creatinine ratio should be confirmed and quantified with a 24-hour collection. Moreover, the reliability of the protein-creatinine ratio for monitoring of proteinuria during treatment is still not proven.

2.3 Imaging

In recent years, there has been a significant change in imaging evaluation of patients with renal disease. Intravenous urography (IVU) is infrequently used and has mostly been replaced by ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and nuclear medicine scanning. There are major technologic advances in each of these modalities with the rapid changes in computer-based data manipulation. Three-dimensional and even four-dimensional (time-sensitive) image analysis is now available. “Molecular” imaging, in which biomarkers are used to visualize cellular function, is beginning to provide functional as well as anatomic information. The American College of Radiology has published Appropriateness Criteria, guidelines that suggest the choice of imaging to provide a rapid answer to the clinical question while minimizing cost and potential adverse effects to the patient, such as contrast-induced nephrotoxicity and radiation exposure. Risks of imaging and cost need to be balanced against benefits.

2.3.1 Ultrasound examination

An important reason for nephrologists to be involved in this procedure is that many of the findings on ultrasound are not specific and require clinical correlation. Detailed anatomic depiction of the renal parenchyma (cortex and pyramids) requires dedication to a meticulous sonographic technique in an attempt to define the normal anatomic appearances and pathologic processes to best advantage. A routine set of images showing only the whole kidney in each image constitutes an inadequate

examination. Although these images may be useful to define the geography of the kidney as a whole and its relationship to adjacent structures, these images will not necessarily provide the detailed imaging required to evaluate the parenchyma adequately. Therefore, magnification of selected parts of each kidney is essential to depict smaller structures in the parenchyma to best advantage.

Applications and Limitations of Ultrasound

Ultrasound is an excellent tool for examination of the kidneys and urinary tract. Under optimal conditions, kidneys, the renal artery and vein, the proximal and distal ureter (when enlarged), and the bladder can be visualized. The ureter is usually apparent only when it is dilated. The middle portion of the ureter is usually obscured by overlying bowel but still may be visible when it is much dilated. In transplants, the entire ureter can be visualized, even when it is not markedly dilated, because of the proximity to the probe and the lack of overlying bowel. In very ill patients who cannot be optimally positioned or cannot control their breathing or have abdominal wounds or distention, views of the kidneys may be limited, but it is still possible in most of these patients to determine whether hydronephrosis is present.

Kidney Size

The kidney is imaged in transverse and sagittal planes and is normally 9 to 12 cm in length in adults. Differences in renal size can be detected with all imaging modalities.

Renal Echo Pattern

The normal cortex is hypoechoic compared with the fat-containing echogenic renal sinus. The cortical echotexture is defined as isoechoic or hypoechoic compared with the liver or spleen. In children, the renal pyramids are hypoechoic, and the cortex is characteristically hyperechoic compared with the liver and the spleen. In adults, an increase in cortical echogenicity is a sensitive marker for parenchymal renal disease but is nonspecific. Decreased cortical echogenicity can be found in acute pyelonephritis and acute renal vein thrombosis. The normal renal contour is smooth, and the cortical mantle should be uniform and slightly thicker toward the poles. Two common benign pseudomasses that can be seen with ultrasound are the

dromedary hump and the column of Bertin. The column of Bertin results from bulging of cortical tissue into the medulla; it is seen as a mass with an echotexture similar to that of the cortex, but it is found within the central renal sinus. The renal pelvis and proximal ureter are anechoic. An extrarenal pelvis refers to the renal pelvis location outside the renal hilum. The ureter is not identified beyond the pelvis in nonobstructed patients. Obstruction can be identified by the presence of hydronephrosis. Parenchymal and pelvicalyceal nonobstructing renal calculi as well as ureteral obstructing calculi can be readily detected. The upper ureter will also be dilated if obstruction is distal to the pelviureteral junction. False-negative ultrasound examination findings with no hydronephrosis occasionally occur in early obstruction. Obstruction without ureteral dilation may also occur in retroperitoneal fibrosis and in transplanted kidneys as a result of periureteral fibrosis.

Renal Cysts

Cysts can be identified as anechoic lesions and are a frequent coincidental finding during renal imaging. Ultrasound usually readily identifies renal masses as cystic or solid. However, hemorrhagic cysts can sometimes be mistakenly called solid because of increased echogenicity. Differentiation of cysts as simple or complex is required to plan intervention.

Simple Cysts

A simple cyst on ultrasound is anechoic, has a thin or imperceptible wall, and demonstrates through-transmission because of the relatively rapid progression of the sound wave through fluid compared with adjacent soft tissue.

Complex Cysts

Complex cysts contain calcifications, septations, and mural nodules. Instead of being anechoic, they may contain internal echoes representing hemorrhage, pus, or protein. Complex cysts may be benign or malignant; malignancy is strongly suggested by cyst wall nodularity, septations, and vascularity. Complex cysts identified by ultrasound require further evaluation by contrast-enhanced CT (or MRI) to identify abnormal contrast enhancement of the cyst wall, mural nodule, or septum.

Chronic Kidney Disease

Ultrasound is indicated in any patient presenting with chronic kidney disease (CKD) to establish renal size and to rule out polycystic kidney disease or urinary tract obstruction. Small, echogenic kidneys indicate severe irreversible disease, eliminating the need for a biopsy.

Acute Kidney Injury

Although the diagnostic yield is very low in patients in whom the basis for renal failure is likely to be acute tubular necrosis or prerenal causes, ultrasound is still indicated in certain patients to rule out obstruction and to identify preexisting CKD.

Renal Transplant

Ultrasound is indicated when there is an acute decline in renal transplant function because urinary obstruction is common in this setting. In the immediate post-transplantation period, Doppler evaluation of renal blood flow should also be performed to rule out thrombosis. Additional indications in transplant patients are pain, swelling, ipsilateral leg edema, and infection. Another important indication in both native and transplanted kidneys is guidance for percutaneous biopsy, nephrostomy, or drainage of fluid collections.

Renal Biopsy

Ultrasound is the method of choice to guide percutaneous renal biopsy. Except in rare cases, computed tomography offers no advantages over ultrasound and results in unnecessary irradiation.

Urinary Bladder

Ultrasound is the procedure of choice for measurement of postvoid residual volume because it is painless and sufficiently accurate and, when a scanner is readily available, a simple task. Additional indications include checking the location and patency of Foley catheters and examination of the distal ureters. Placement of the catheter in the proximal urethra is uncommon but not rare, and obstruction of catheters is frequent, so examination of the bladder should always be considered when urine output decreases. Prostatic hypertrophy, prostatitis, bladder carcinoma, mucosal edema, blood clots, stones, stents, and other foreign bodies can be recognized by ultrasound, but transabdominal ultrasound is not the appropriate test to

rule out bladder cancer (which requires cystoscopy) or prostatic cancer (which requires transrectal ultrasound and biopsy).

Hemodialysis Access

Ultrasound is essential in the management of vascular access, including guidance of catheter insertion, evaluation of fistula dysfunction, preoperative vein mapping, and monitoring of access flow. Of these, the first two can be readily performed by nephrologists. Guidance of catheterization is best performed with a dedicated scanner but can be done with any scanner that has a vascular probe and does not require Doppler imaging. Examination of dysfunctional fistulas is also straightforward and does not necessarily require Doppler analysis. Vein mapping and monitoring of access flow are both best performed by an experienced vascular technician.

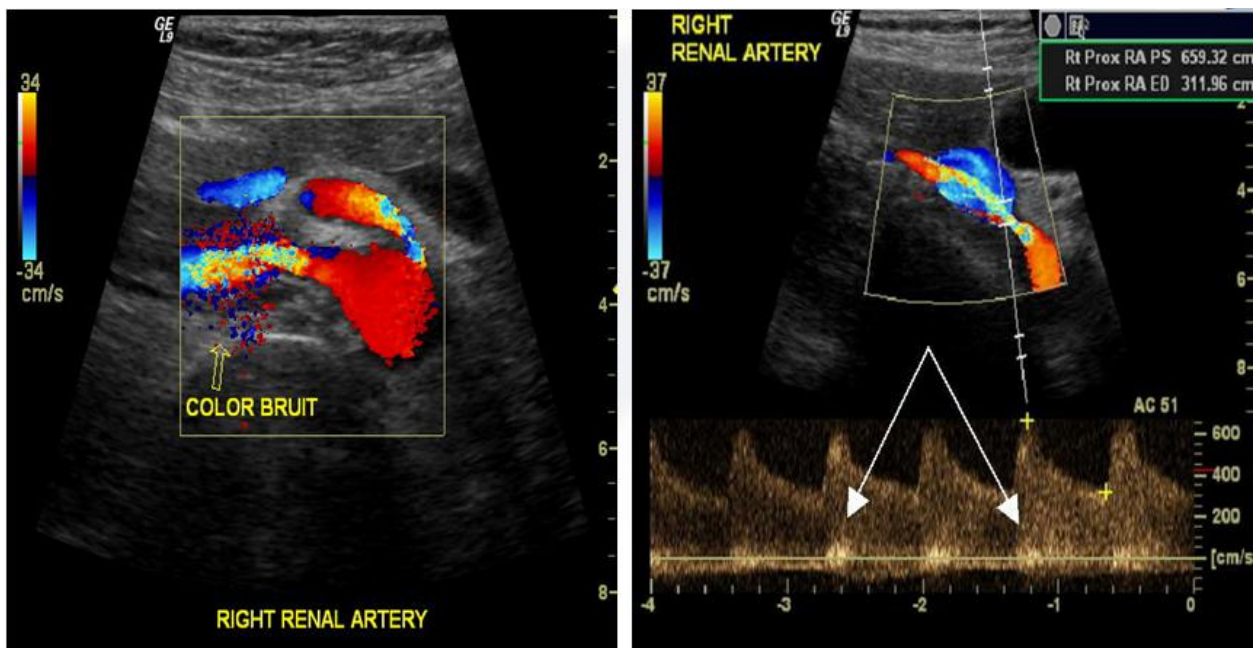
Contrast-Enhanced and Three-Dimensional Ultrasound

Ultrasound contrast agents, initially introduced to assess cardiac perfusion, are now being used to evaluate perfusion to other organs, such as the kidney. These intravenous agents are microbubbles that consist of a shell surrounding the echo-producing gas core; they are 1 to 4 μm in diameter, smaller than erythrocytes. The microbubbles oscillate in response to the ultrasound beam frequency and give a characteristic increased echo signal on the image. Preliminary studies evaluating renal perfusion in dysfunctional kidneys show reduced flow compared with normal kidneys and improved lesion detection. However the clinical utility of microbubble imaging in the kidney remains uncertain, particularly given the general availability and robustness of CT and MRI. Two-dimensional ultrasound images can be reconstructed into three-dimensional volume images by a process similar to three-dimensional reconstructions for MRI and CT. Although the current techniques are time-consuming, technical improvements should decrease reconstruction time. Potential applications include vascular imaging and fusion with MRI or positron emission tomography (PET).

Renovascular Ultrasound

Doppler ultrasound of renal arteries and veins is a difficult study requiring an experienced operator and is not usually practical for nephrologists. Tracings from segmental arteries are more easily obtained and can be useful in diagnosis of renal vein thrombosis. However, measurement of resistive index can be unreliable (it can be influenced by external factors such as systemic blood pressure and heart rate) and is of questionable clinical utility. Doppler ultrasound is also useful in distinguishing between cystic and vascular lesions and between renal vein and ureter.

The direct method involves Doppler interrogation of the entire length of the main renal artery, including any accessory renal arteries is presented Fig. 2.3.1.1. Although stenosis is usually located near the renal artery origin, fibromuscular dysplasia is more often located in the mid to distal segment, thus requiring a look at the entire length of each artery. Since a stenosis in an accessory renal artery can cause renovascular hypertension, it is important to search for and interrogate these vessels.



A

B

Fig. 2.3.1.1 Color Doppler image of a stenotic right renal artery origin.

2.3.2 Plain Radiography and Intravenous Urography

The use of Intravenous Urography (IVU) has receded as cross-sectional imaging by CT or MRI has become more widely applied to the urinary tract. Contrast

medium is injected into a vein in the person's arm, travels through the body to the kidneys, and makes urine visible on the X ray. The contrast medium also shows any blockage in the urinary tract. The procedure is performed in a health care provider's office, outpatient center, or hospital by an x-ray technician, and the images are interpreted by a radiologist - a doctor who specializes in medical imaging; anesthesia is not needed. An IVU can help locate problems in the kidneys, ureters, or bladder that may be caused by urinary retention or reflux (Fig. 2.3.2.1)

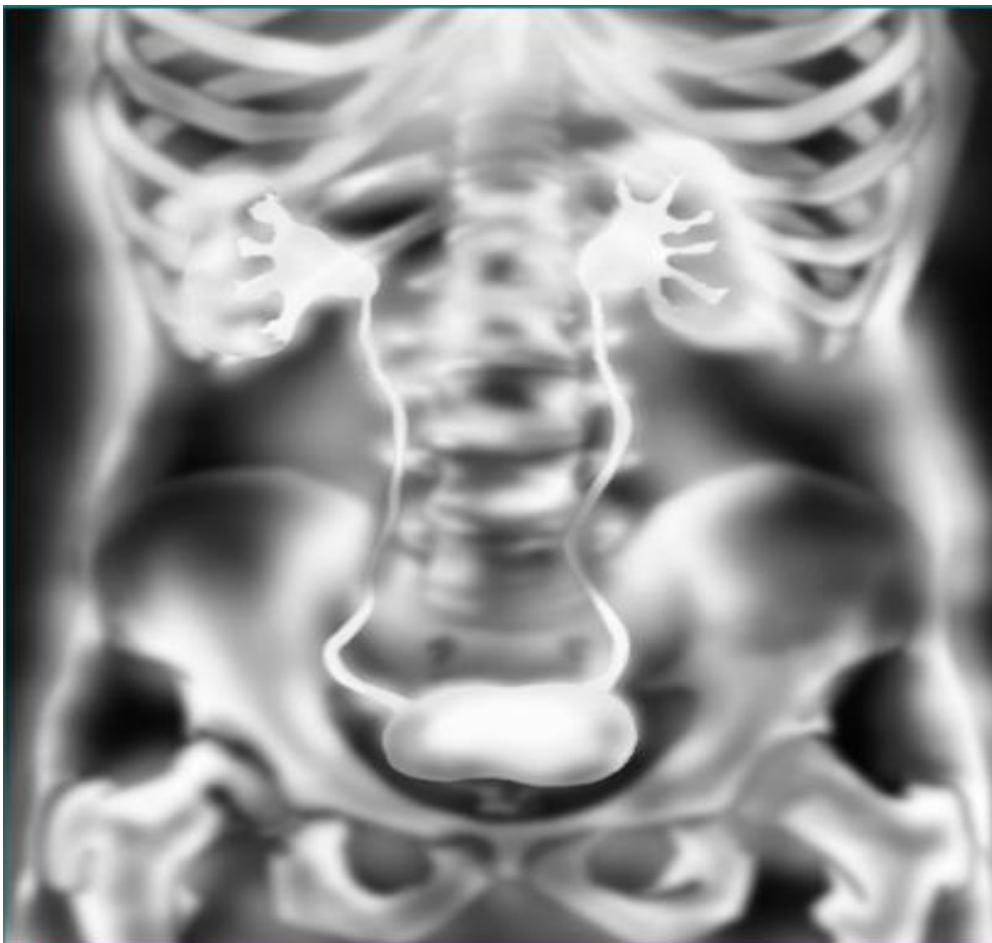


Fig. 2.3.2.1 Contrast Intravenous urography

Contrast urography now has few primary indications in many centers, but it may still be a key investigation in parts of the world where economic limitations mean that cross-sectional imaging is not available. However, plain radiography (often

called a KUB-kidneys, ureter, bladder), still has an important role in the identification of soft tissue masses, bowel gas pattern, calcifications, and renal location.

Renal Calcification

Most renal calculi are radiodense, although only ~60% of urinary stones detected on CT are visible on plain films. CT demonstrates nonopaque stones, which include uric acid, xanthine, and struvite stones. However, neither CT nor plain films may detect calculi associated with protease inhibitor therapy. Oblique films are sometimes obtained to confirm whether a suspicious upper quadrant calcification is renal in origin. Calculi that are radiolucent on plain films are usually detected as filling defects on IVU. Although IVU has a higher sensitivity compared with plain films, the sensitivity is lower compared with CT, which, if it is available, is the imaging modality of choice for detection of urinary calculi. Nephrocalcinosis may be medullary or cortical and is localized or diffuse.

Retrograde Pyelography

Retrograde pyelography is performed when the ureters are poorly visualized on other imaging studies or when samples of urine need to be obtained from the kidney for cytology or culture. Patients who have severe allergies to contrast agents or impaired renal function can be evaluated with retrograde pyelography. The examination is performed by placing a catheter through the ureteral orifice under cystoscopic guidance and advancing it into the renal pelvis. With use of fluoroscopy, the catheter is slowly withdrawn while radiographic contrast material is injected. This technique provides excellent visualization of the renal pelvis and ureter and can be used for cytologic sampling from suspect areas.

Antegrade Pyelography

Antegrade pyelography is performed through a percutaneous renal puncture and is resorted to when retrograde pyelography is not possible. Ureteral pressures can be measured, hydronephrosis evaluated, and ureteral lesions identified. The examination is often performed as a prelude to nephrostomy placement. Both antegrade and retrograde pyelography are invasive and should be performed only when other studies are inadequate

Ileal Conduits

After cystectomy, or bladder failure, there are numerous types of continent or incontinent urinary diversions that can be surgically created. One of the most common diversions is the ileal conduit: an ileal loop is isolated from the small bowel, and the ureters are implanted into the loop. This end of the loop is closed, and the other end exits through the anterior abdominal wall. This type of conduit can be evaluated by an excretory study or a retrograde study. The excretory or antegrade study is performed and monitored in the same way as an IVU. A retrograde examination, also referred to as a loop-o-gram, is obtained when the ureters and conduit are suboptimally evaluated on the excretory study. A Foley catheter is placed into the stoma, and contrast material is then slowly instilled. The ureters should fill by reflux because the ureteral anastomoses are not of the antireflux variety

Cystography

A cystogram is obtained when more detailed radiographic evaluation of the bladder is required. Voiding cystography is performed to identify ureteral reflux and to assess bladder function and urethral anatomy. A urethral catheter is placed into the bladder, and the urine is drained; contrast material is infused, and the bladder is filled under fluoroscopic guidance. Early supine frontal and oblique films are obtained while the bladder is filling. Ureterocele are best identified on early films. When the bladder is full, multiple films are obtained with varying degrees of obliquity. Reflux may be seen on these films. To obtain a voiding cystogram, the catheter is removed, and the patient voids. The contrast material is followed into the urethra. On occasion, bladder diverticula are seen only on the voiding films. When the patient has completely voided, a final film is used to assess the amount of residual urine as well as the mucosal pattern. Radionuclide cystography is an alternative often used in children. It is useful in the diagnosis of reflux, but it does not provide the detailed anatomy that is seen with contrast cystography.

2.3.3 Computed Tomography

CT examination of the kidneys is performed to evaluate suspect renal masses, to locate ectopic kidneys, to investigate calculi, to assess retroperitoneal masses, and

to evaluate the extent of parenchymal involvement in patients with acute pyelonephritis. Helical CT scanners allow the abdomen and pelvis to be scanned at 3- to 5-mm intervals with one or two breath-held acquisitions, which eliminates motion artifact. Newer multidetector row CT results in multiple slices of information (currently 64-slice and now even 320-slice machines are becoming commonplace) being acquired simultaneously, allowing the entire abdomen and pelvis to be covered in one breath-hold, using even submillimeter intervals. However, the improved CT imaging comes at a price of significant radiation exposure to the patient. The CT data can be reconstructed in multiple planes and even in three dimensions for improved anatomic visualization and localization.

Tissue Density

The Hounsfield unit (HU) scale is a measurement of relative densities determined by CT. Distilled water at standard pressure and temperature is defined as 0 HU; the radiodensity of air is defined as -1000 HU. All other tissue densities are derived from this. Tissues can vary in their exact HU measurements and will also change with contrast enhancement. Water, fat, and soft tissue can often look identical on the scan, depending on the window and level settings of the image, so actual HU measurement is essential to correctly characterize the tissues.

Contrast-Enhanced and Noncontrast Computed Tomography

CT examination of the kidneys can be performed with or without intravenous administration of contrast material. Noncontrast imaging allows the kidneys to be evaluated for the presence of calcium deposition and hemorrhage, which are obscured after the administration of contrast material (Fig. 2.3.3.1).



Fig. 2.3.3.1 Noncontrast CT of abdomen: presence of calcium deposition in right kidney (arrow)

Noncontrast CT (CT urography, CTU) is the examination of choice in patients with suspected nephrolithiasis and has replaced the KUB and intravenous urography in most situations. The study consists of unenhanced images from the kidneys through the bladder for detection of calculi. CTU has the advantage of being both highly sensitive (97% to 100%) and specific (94% to 96%) for diagnosis of urinary calculi. It can identify a possible obstructing calculus as well as the extent of parenchymal and perinephric involvement.

In cases other than stone evaluation, the kidneys are imaged after the administration of contrast material. The kidneys are imaged in the corticomedullary phase for evaluation of the renal vasculature as well as in the nephrographic phase for evaluation of the renal parenchyma. The degree of enhancement can be assessed in

both solid masses and complex cysts (Fig. 2.3.3.2). Also hydrocolicosis can be identified (Fig. 2.3.3.3).

A compression device can be used as in IVU. Delayed images through the kidneys and bladder are performed for evaluation of the opacified and distended collecting system, ureters, and bladder. Once the axial images have been obtained, they can be reformatted into coronal or sagittal planes to optimize visualization of the entire collecting system. The study can be tailored to the individual clinical scenario. For example, the corticomedullary phase can be eliminated to decrease the radiation dose if there is no concern about a vascular abnormality or no need for presurgical planning. A diuretic or saline bolus can be administered after the contrast agent to better distend the collecting system and ureters during the excretory phase.

The kidneys should be similar in size and show equivalent enhancement and excretion. During the cortical medullary phase, there is brisk enhancement of the cortex. The cortical mantle should be intact. Any disruption of the cortical enhancement requires further evaluation; it may be caused by acute pyelonephritis, scarring, mass lesions, or infarction. During the excretory phase, the entire kidney and renal pelvis enhance. Delayed excretion and delay in pelvicalyceal appearance of contrast material can be findings in obstruction but also in renal parenchymal disease such as acute tubular necrosis.



Fig. 2.3.3.3 Noncontrast CT: hydrocolicosis of left kidney (arrow)

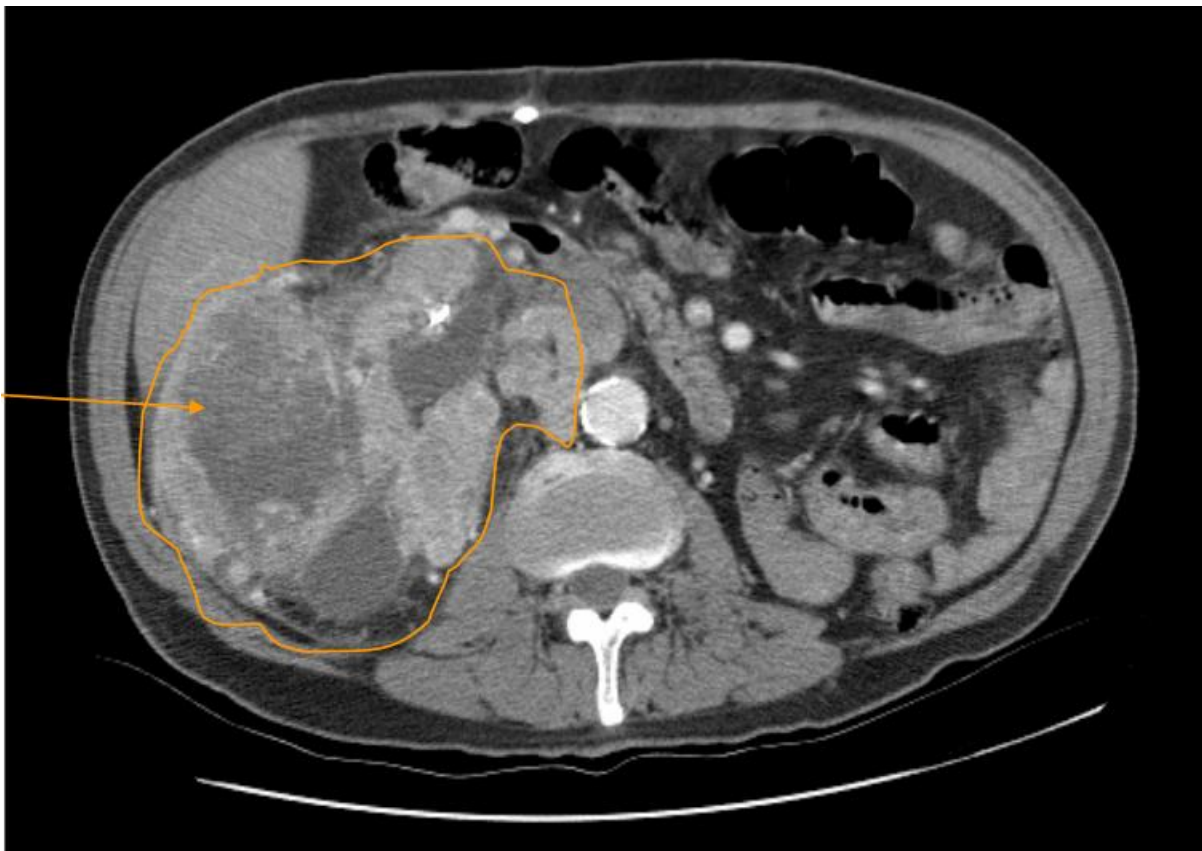


Fig. 2.3.3.3 Noncontrast CT: mass infiltrating in right kidney (arrow)

Computed Tomographic Angiography

Helical scanning facilitates CTA, which can produce images that are similar to those of conventional angiography, but it is less invasive. A bolus of contrast material is administered, and the images are obtained at 0.5- to 3-mm consecutive intervals. The contrast bolus is timed for optimal enhancement of the aorta. Thinner collimation of the CT beam allows higher resolution and better subsequent multiplanar reconstructions. The aorta and branch vessels are well demonstrated. This technique is now widely used in living transplant donor evaluation, providing information not only on arterial and venous anatomy but also on size, number, and location of the kidneys as well as any ureteral anomalies of number or position.

CT is very sensitive to metal artifact and motion of the patient. Retroperitoneal clips and intramedullary rods will cause extensive streak artifact, which severely degrades the images. Patients who are unable to remain motionless will also have suboptimal or even nondiagnostic studies, and sometimes sedation or general anesthesia may be needed to obtain diagnostic scans, particularly in children. Intensive care unit and critically ill patients can be scanned by CT as long as they are stable enough to be transported to the CT suite.

2.3.4 Magnetic Resonance Imaging

MRI should only rarely be the first examination used to evaluate the kidneys, but it is typically an adjunct to another imaging technique. The major advantage of MRI over the other imaging modalities is direct multiplanar imaging, whereas CT is limited to slice acquisition in the axial plane of the abdomen, and coronal and sagittal planes are acquired only by reconstruction, which can lead to loss of information.

Tissues contain an abundance of hydrogen, the nuclei of which are positively charged protons. These protons spin on their axis, producing a magnetic field (magnetic moment). When a patient is placed in a strong magnetic field in an MRI scanner, some of the protons align themselves with the field. When a radiofrequency pulse is applied, some of the protons aligned with the field will absorb energy and reverse their direction. This absorbed energy is given off as a radiofrequency pulse as the protons relax (return to their original alignment), producing a voltage in the receiver coil. The coil is the hardware that covers the region of interest. For renal

imaging, a body coil or torso coil is used. Relaxation is a three-dimensional event giving rise to two parameters: T1 relaxation results in the recovery of magnetization in the longitudinal (spin-lattice) plane, whereas T2 results from the loss of transverse (spin-spin) magnetization. A rapid-sequence variant of T2 in common use is fast spin echo (FSE). Hydrogen ions move at slightly different rates in the different tissues. This difference is used to select imaging parameters that can suppress or aid in the detection of fat and water. Fluid, such as urine, is dark or low in signal on T1-weighted sequences and bright or high in signal on FSE sequences. Fat is bright on T1 and not as bright on FSE sequences. The sequences and imaging planes selected must be tailored to the individual case. Diffusion-weighted imaging is a newer technique that evaluates the freedom of water molecules to diffuse in tissues; restriction of diffusion is imaged as bright areas on the scan and is seen in infection, neoplasia, inflammation, and ischemia. Standard imaging usually includes T1, T2, or FSE sequences and often additional contrast-enhanced T1 images.

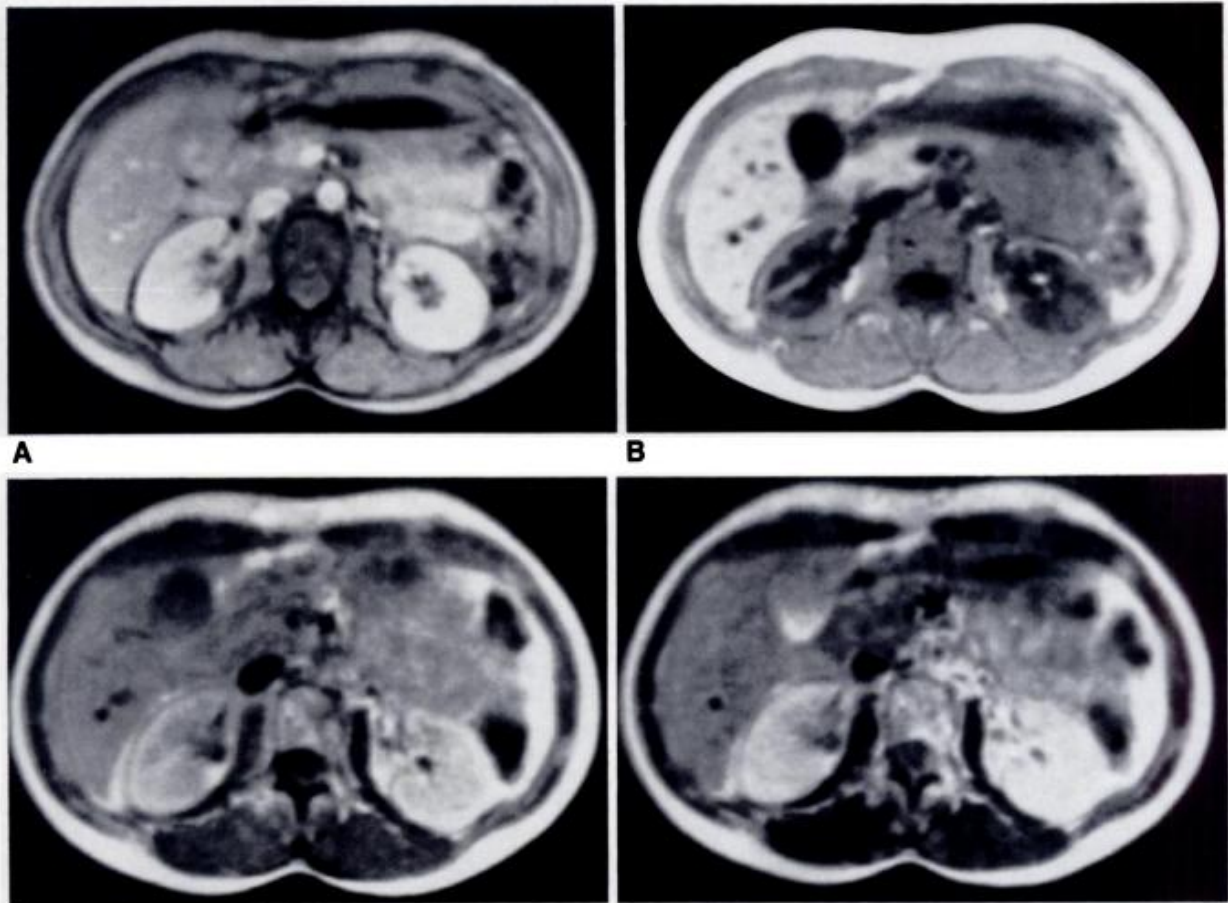


Fig. 2.3.4.1 MRI: normal kidneys.

The imaging plane varies according to the clinical concerns. Usually, at least one sequence is performed in the axial plane. Sagittal and coronal images cover the entire length of the kidney and can make some subtle renal parenchymal abnormalities more conspicuous (Fig. 2.3.4.2).

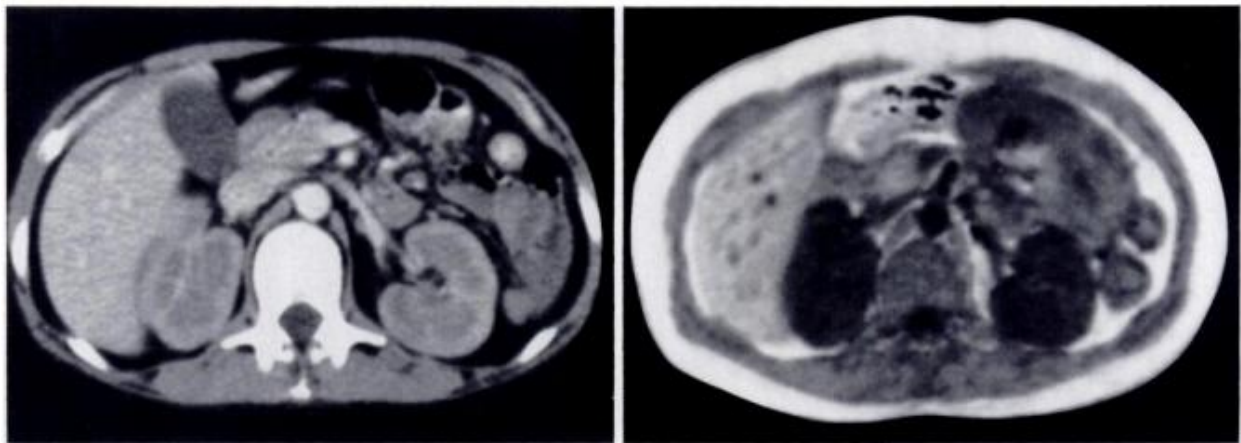


Fig. 2.3.4.2 MRI: focal segmental glomerulosclerosis. Corticomedullary differentiation is apparent on CT (left figure) but is lost on MRI (right figure).

Renal cyst can be verified also very well and usually has low signal intensity due to the long T1 (Fig. 2.3.4.3).

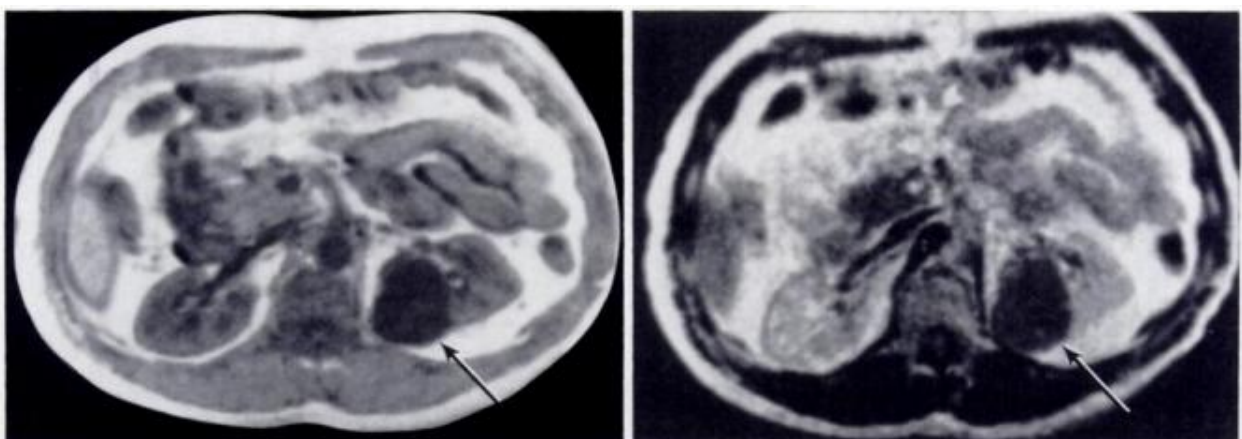


Fig. 2.3.4.3 MRI: Renal cyst (arrow)

2.3.5 Angiography

Angiography is now most often performed for therapeutic intervention, such as embolotherapy or angioplasty and stenting, preceded by diagnostic angiography to evaluate the renal arteries for possible stenosis. With improved resolution and scanning techniques, CTA and MRA have replaced conventional angiography, even for detection of accessory renal arteries, which are often small and bilateral but not infrequently a cause of hypertension (Fig. 2.3.5.1, Fig.2.3.5.2). However, angiography remains the gold standard test for the diagnosis of renal artery stenosis and fibromuscular dysplasia. There also remains a role for diagnostic angiography in the evaluation of medium- and large-vessel vasculitis and detection of renal infarction.

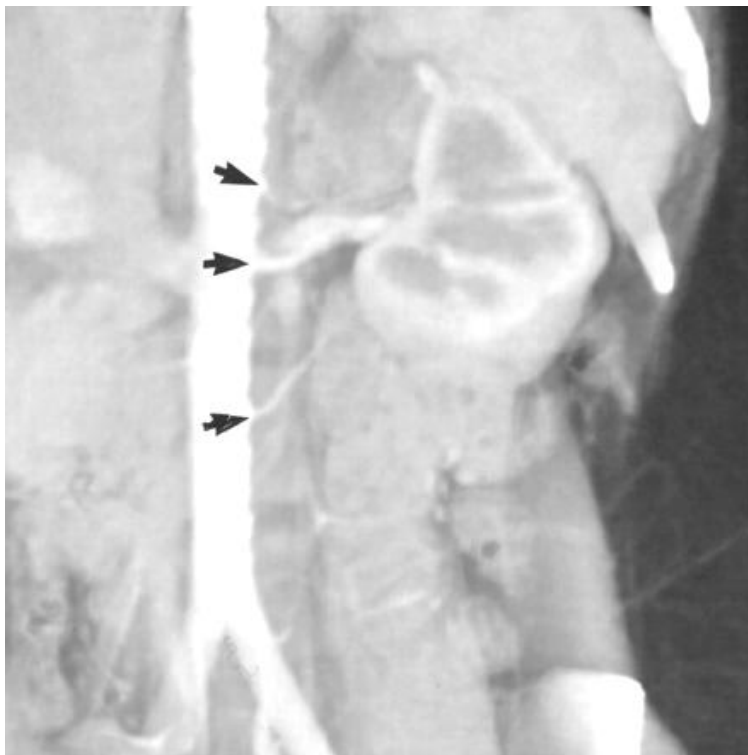


Fig. 2.3.5.1 Multidetector CT angiograms: additionally two small arteries of less than 2 mm in diameter upper and under normal kidney artery (allow arrows).

The conventional angiogram is performed through arterial puncture followed by catheter placement in the aorta. An abdominal aortogram is obtained to identify the renal arteries.



Fig. 2.3.5.2 Coronal maximum-intensity-projection image of gadopentetate dimeglumine-enhanced MR angiogram: accessory renal artery (arrow)

Selective renal artery catheterization can be performed as necessary. Contrast material is administered intra-arterially, and the images are obtained with conventional film or more commonly with digital subtraction angiography. Conventional angiography images are superior but require higher doses of contrast material and more radiation exposure. Digital subtraction angiography uses computer reconstruction and manipulation to generate the images, with the advantage that previously administered and excreted contrast material and bones can be digitally removed to better visualize the renal vasculature (Fig. 2.3.5.3).

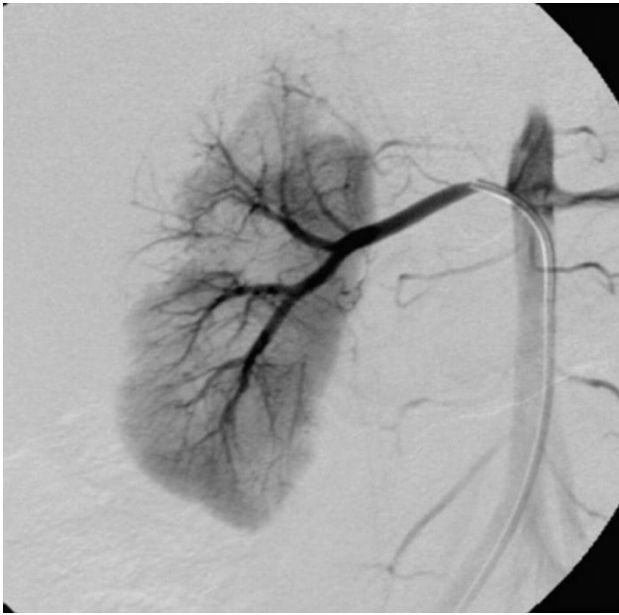


Fig. 2.3.5.3 Angiography of arterial vascularisation of the right kidney showing diffuse narrowing of the small arteries and loss of cortical visualization mainly in the upper pole, consistent with renal segmental hypoplasia

As well as with the risk of contrast-induced nephropathy, angiography is associated with a risk of cholesterol embolization. Whereas pathology evidence of cholesterol embolization is frequent, clinically significant symptoms are very uncommon (1% to 2%).

2.3.6 Positron Emission Tomography

PET scanning uses radioactive positron emitters (most commonly ^{18}F -labeled fluorodeoxyglucose [FDG]). The FDG is intravenously injected and distributes in the body according to metabolic activity. Any process, such as tumor or infection, that causes increased metabolic activity will result in an area of increased uptake on the scan. These areas of abnormality need to be differentiated from normally hypermetabolic tissues, such as brain, liver, bone marrow, and to some extent heart and bowel. Because FDG is cleared through the kidneys and excreted in the urine, PET scanning has a limited role in renal imaging, but it is useful in the staging and follow-up of metastatic renal cancer.

2.3.7 Molecular Imaging

With molecular imaging, radiology is moving from the identification of generic anatomy and nonspecific enhancement patterns to assessment of specific molecular

differences in tissues and disease processes. Nuclear imaging presently is molecular based but still nonspecific (e.g., FDG-PET, renal DTPA). The newer focus of molecular imaging studies dynamic processes like metabolic activity, cell proliferation, apoptosis, receptor status, and antigen modulation. Typically, this involves imaging of biochemical and physiologic processes. Techniques are being developed with use of optical scanning, MRI, and ultrasound as well as with radionuclides. Applications are established in clinical practice, particularly in oncology (e.g., CD20 imaging in lymphoma), and work is under way for renal-specific molecular imaging. For example, MR renal cell imaging may soon be available to help differentiate acute tubular necrosis from renal rejection and renal cell cancer from benign tumors.

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Chapter 3

Glomerulonephrities

Many diseases affect kidney function by attacking the glomeruli, the tiny units within the kidney where blood is cleaned. Glomerular diseases include many conditions with a variety of genetic and environmental causes, but they fall into two major categories:

- Glomerulonephritis describes the inflammation of the membrane tissue in the kidney that serves as a filter, separating wastes and extra fluid from the blood.
- Glomerulosclerosis describes the scarring or hardening of the tiny blood vessels within the kidney.

Although glomerulonephritis and glomerulosclerosis have different causes, they can both lead to kidney failure. A variety of histologic patterns can produce diverse clinical syndromes; thus, for example, nephritic syndrome and hematuria can be produced by membranoproliferative glomerulonephritis (GN), diffuse endocapillary proliferative GN (acute), IgA nephropathy, and so on. A nephrotic syndrome (NS) can be produced by several diseases: membranous GN, focal and segmental glomerulosclerosis, minimal change disease, amyloidosis, diabetic nephropathy, and others. In a disease different patterns of pathologic changes can be seen; for example, in lupus may appear only mesangial changes, diffuse endocapillary proliferation, membranoproliferative-like lesions, membranous pattern, or focal segmental (chronic) lesions. This variability in the morphologic expression has given origin to the classification of lupus nephritis. A type of pathologic change can be caused by several diseases: for example, a membranoproliferative pattern can be seen in lupus, infections, hepatitis and cryoglobulinemia. The changes found in a renal biopsy rarely are specific of a disease; for example, in some hereditary diseases like Alport syndrome and Anderson-Fabry disease. Therefore the renal diagnosis is a process that integrates the clinical information, laboratory data, morphology and immunopathology to reach the “better diagnosis”.

Different diseases can have a same pathogenic mechanism; for example, crescentic GN can be seen in lupus, acute GN, anaphylactoid purpura, IgA

nephropathy, and in all these conditions the formation mechanism of crescents is related to rupture of glomerular capillary walls with protein passage to the Bowman's space.

The leading clinical presentations around primary glomerular diseases are nephrotic and nephritic syndromes with or without hematuria. The spectrum of primary nephrotic syndrome includes a variety of causes, presentations, histopathologic findings, and outcomes. These disorders may appear at any age, may be exquisitely sensitive or highly resistant to therapy, and have varied implications for long-term renal function. Past efforts to develop an organized approach to these diseases have largely centered on histopathology. Although these approaches were helpful in defining lesions, for each morphologic entity there is a wide range in response to treatment and outcome. This observation suggests that traditional pathologic description alone is insufficient to classify these disorders.

The diseases that cause nephrotic syndrome can be divided into three categories: Diseases with antibody-mediated mechanisms (e.g., lupus, membranoproliferative glomerulonephritis, and membranous nephropathy), diseases that are associated with metabolic disorders (e.g., diabetes, amyloid, and Fabry disease), and diseases that are caused by abnormal glomerular cell function. Current thinking suggests that virtually all cases in this last category begin with podocyte damage or dysfunction. For this reason, these diseases have been termed podocytopathies. Efforts to characterize the relationship among the podocytopathies have evolved in the past three decades. Initially, studies that focused on pathologic presentation suggested that minimal-change nephrotic syndrome; focal segmental glomerulosclerosis (FSGS), and mesangioproliferative glomerulonephritis had a common cause and could transition among these different pathologic findings. Subsequent iterations recognized that, among the various forms of primary glomerular disease, response to glucocorticoid treatment is the critical determinant of outcome. Thus, different etiologies might cause the same histologic picture, accounting for heterogeneity of clinical course when predicted solely on the basis of histopathology. However, the nature of the underlying disorders remained unclear.

3.1 Primary Glomerular Diseases

Glomerular disease may have a wide variety of causes and clinical presentations. Some glomerular diseases are given the generic title of glomerulonephritis (GN), which implies an immune or inflammatory pathogenesis. Although there are some situations in which specific diagnosis can be made on the basis of clinical presentation and laboratory tests, a renal biopsy is useful for both classification and prognosis in most cases. Ideally, the renal biopsy specimen should be examined by light microscopy, immunofluorescence, and electron microscopy. By use of this approach, a histologic pattern can be diagnosed. Some histologic patterns can be coupled with other laboratory test results to identify a specific etiology, but the condition is idiopathic in many cases. These diseases are indicated as primary. However, because treatments are often developed for specific histologic patterns, this approach is currently favored in the management of these disorders.

3.1.1 Glomerular Diseases That Cause Nephrotic Syndrome

Primary Glomerular Diseases That Cause Nephrotic Syndrome are divided into three main axes:

- Non-Immune Complex Glomerular Diseases
- Immune Complex Glomerular Diseases
- Immunotactoid Glomerulopathy

3.1.1.1 Podocytopathies (Non-Immune Complex Glomerular Diseases)

On the basis of our current knowledge, the taxonomy of the podocytopathies is organized along two axes:

- Histopathology, defined by podocyte number and the four patterns of glomerular morphology: Minimal Change Disease (MCN), Focal Segmental Glomerulosclerosis (FSGS), Diffuse mesangial sclerosis (DMS), and Collapsing Glomerulopathy (CG).
- Etiology, including idiopathic, genetic, and reactive forms It is expected that, in the future, additional variables (proteomics, transcriptomics, and others) will be added to define better each category and subclass and provide a more reliable basis for selecting therapy and determining prognosis.

Taxonomy of the podocytopathies and three distinct pathways of injury and repair characterize the podocytopathies are presented on Figure 3.1.1.1.1.

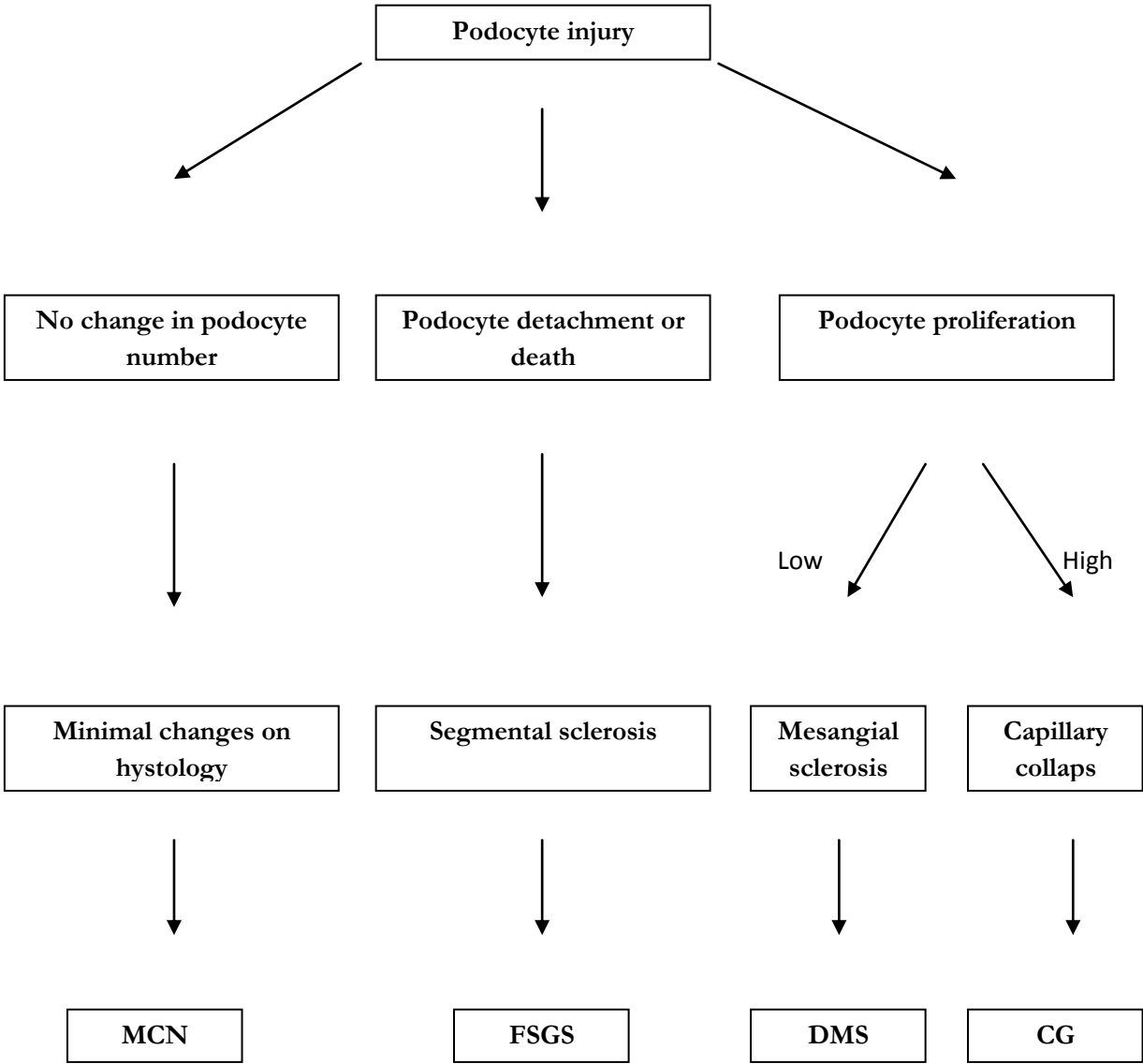


Figure 3.1.1.1.1 Taxonomy of the podocytopathies

First, in minimal-change nephropathy (MCN), podocyte injury is limited to foot process effacement, and podocyte number remains normal. Second, a more severe form of podocyte injury may occur, leading to podocyte detachment and death. This event initiates an injury cascade that results in the segmental scar characteristic of FSGS. Third, podocyte injury may lead to delayed cellular maturation (DMS), dedifferentiation (CG), and proliferation, with either low rates of

podocyte proliferation (manifesting as diffuse mesangial sclerosis [DMS]) or high rates of proliferation (manifesting as collapsing glomerulopathy [CG]). Causes of podocyte injury resulting in foot process effacement are provided in Table 3.1.1.1.1.

Table 3.1.1.1.1

Causes of podocyte injury

Intrinsic Podocyte Stress: Genetic Mutations		Extrinsic Podocyte Stress	
Nucleus	WT1, PAX2, and LMX1B mutations	Viral	infection or circulating viral protein
Cytoskeleton	ACTN4 mutations	Toxic	medication (pamidronate, interferon), toxin (puromycin aminonucleoside, Adriamycin)
Slit diaphragm complex	NPHS1, NPHS2, and CD2AP mutations	Lymphokine or other host protein	IFN- α , IFN- β , FSGS permeability factor
Plasma membrane	ITGB4 and TRPC6 mutations	Mechanical	Podocyte stretch (glomerulomegaly)
Mitochondria	tRNA mutations, COQ2 mutations	Acute	ischemia associated with thrombotic microangiopathy
Metabolic	Fabry disease Extracellular matrix: LAMB2	Immunologic	Immune complex deposition or in situ formation (lupus, IgA nephropathy, membranous nephropathy)
		Metabolic	Diabetes mellitus

3.1.1.1.1.Minimal Change Disease

Minimal Change Disease (MCN) is usually characterized by normal histology and extensive podocyte foot process effacement on ultrastructural analysis, accompanied by condensation of the actin-based cytoskeleton against the “sole” of the podocyte and by microvillous transformation. It has been used the term “minimal-change nephropathy” for several reasons. First, it includes what is often called minimal-change nephrotic syndrome or minimal-change disease. Second, the term presents a more parallel construction with the other diagnostic terms, avoiding a clinical descriptor (nephrosis) that may not be uniformly applicable.

Pathophysiology

It is postulated that MCD is a disorder of T cells, which release a cytokine that injures the glomerular epithelial foot processes. This, in turn, leads to a decreased synthesis of polyanions. The polyanions constitute the normal charge barrier to the filtration of macromolecules, such as albumin. When the polyanions are damaged, leakage of albumin follows. The identity of this circulating permeability factor is uncertain, although it is postulated that it may be hemopexin. Some of the cytokines that have been studied in MCD are interleukin-12 (IL-12) and interleukin-4 (IL-4). IL-12 levels have been found to be elevated in peripheral blood monocytes during the active phase and normalized during remission. Interleukin-18 (IL-18) can synergize with IL-12 to selectively increase the production of vascular permeability factor from T cells. In addition, levels of IL-4 and CD23 (a receptor for immunoglobulin E) have been found to be elevated in peripheral blood lymphocytes.

Synaptopodin is a proline-rich protein intimately associated with actin microfilaments present in the foot processes of podocytes. Greater synaptopodin expression in podocytes is associated with a significantly better response to steroid therapy. On the other hand, the expression of synaptopodin does not predict progression of MCD or diffuse mesangial hypercellularity to focal segmental glomerulosclerosis (FSGS). Thus, this marker could be used in the future to help determine appropriate therapy. Interleukin-13 (IL-13) has been implicated in the pathogenesis of MCD. In a study on Singapore Chinese children, it was shown that

IL-13 genetic polymorphisms correlate with the long-term outcome of MCD. In patients who develop acute renal failure, endothelin 1 expression is greater in the glomeruli, vessels, and tubules than in the nonacute renal failure group. The glomerular epithelial cells (podocytes) and the slit diaphragm connecting the podocyte foot processes play a primary role in the development of proteinuria. Nephrin is a major component of the slit diaphragm. The slit diaphragm is often missing in MC nephrotic syndrome (MCD) kidneys. The role of nephrin and the slit diaphragm in MCD is not known. However, genetic variants of a glomerular filter protein may play a role in some patients with MCD. Lack of glomerular dysferlin expression has been recently associated with minimal change nephropathy in a patient with limb-girdle muscular dystrophy type 2B. Two of the three patients with this disease had increased microalbuminuria. Although there have been a multitude of studies recently published, the mechanism by which T cells increase glomerular permeability has remained unproven. Podocyte injury in MCN may be idiopathic, genetic, or reactive. The major clinical distinction among subgroups of this category is response to glucocorticoid therapy. Idiopathic and reactive forms of MCN seem to be generally steroid sensitive. Steroid-resistant forms have a similar morphology but worse outcome and likely have distinct etiologies.

Causes

Almost all cases are idiopathic, but a small percentage of cases (approximately 10-20%) may have an identifiable cause. Causes may include the following:

- Idiopathic MCN
- Reactive or Secondary MCN

Idiopathic MCN.

Idiopathic MCN usually presents with florid nephrotic syndrome, although it may not always do so, and is typically steroid sensitive, particularly in children. Several variants are described. IgM nephropathy seems to have a clinical outcome similar to typical MCN, whereas diffuse mesangial hypercellularity has a worse prognosis. Glomerular tip lesion is discussed later as a transcategorical entity. Genetic MCN. Three genetic forms have been identified. Steroid-resistant MCN that

presents in infancy or childhood with autosomal recessive inheritance may be caused by mutations in NPHS2, encoding podocin. Autosomal dominant nephrotic syndrome, presenting as FSGS or less commonly as MCN, has been linked to a nearby locus on chromosome 19q, for which the gene remains unidentified. Recently, MCN was reported in a patient with limb girdle muscular dystrophy type 2B, which is caused by mutations in dysferlin (DYSF).

Reactive MCN.

Most cases of MCN may be reactive in nature, in view of their association with immunogenic stimuli or malignancy. Medications that are effective in treating MCN may affect the cellular immune system. A variety of extended MHC haplotypes have been associated with recurrent MCN. For these and other reasons, cell-mediated immunity has been invoked as an etiologic factor in the development of MCN. The molecular pathways that link immune dysregulation to podocyte injury remain to be defined.

It has lacked reliable tools to discriminate among the various forms of MCN, especially to predict those with good response to steroid therapy versus those that are steroid resistant. Some patients with steroid-sensitive, nephritic MCN manifest decreased podocyte expression of dystroglycan (an adhesion molecule that is expressed on the abluminal surface of the podocyte). Its expression is preserved in other podocyte cytopathies such as FSGS. In these patients, downregulation of dystroglycan is reversed once foot processes are reconstituted. This phenomenon does not necessarily reflect a general effect of the reorganization of the foot processes. Preliminary data indicate that the use of staining for dystroglycan may segregate patients with a diagnosis of MCN at renal biopsy into two groups: Those with a high likelihood of favorable response to corticosteroid therapy, when dystroglycan expression is reduced, and those with a likely poor response, when dystroglycan expression is comparable to normal. In contrast to steroid-sensitive MCN, glomeruli of patients with genetically determined, steroid-resistant MCN may have decreased detection of podocyte-specific proteins by immunostaining.

Mortality/Morbidity

Very few patients progress to end-stage renal disease. These patients are those who have FSGS that has been misdiagnosed as MCD. Hypovolemic shock is perhaps the most serious complication of MCD. Hypovolemic shock typically occurs during the edema-forming phase of relapse and may be precipitated by diarrhea, sepsis, drainage of ascitic fluid, or the use of diuretics. Hypertension, somewhat paradoxically, also may occur in approximately 9-14% of children. Hypertension occurs in approximately 30% of adults, with a greater incidence in older patients (>60 y). Thromboembolic events are serious complications of nephrotic syndrome. Peripheral thrombosis may result in gangrene, and deep venous thrombosis in the legs or pelvic veins may be a source of pulmonary emboli. Bacterial infections, especially peritonitis, occur with greater frequency, partly because of the loss of immunoglobulin G (IgG) and complement factors B and D in the urine. In fact, the largest reduction in mortality in these patients follows the introduction of antibiotics rather than any specific therapy. The incidence peaks in children aged 2 years, with approximately 80% being younger than 6 years at the time of diagnosis. In adults, the mean age of onset is 40 years.

History

Edema may be preceded by an upper respiratory tract infection, an allergic reaction to a bee sting, or the use of certain drugs or malignancies.

- Facial edema is noted first.
- Malaise and easy fatigability can occur.
- Weight gain often is an additional feature.
- The patient also may present with the following:
 - Hypovolemia
 - Hypertension
 - Thromboembolism
 - Infection

Physical

The blood pressure usually is normal in children but may be elevated in adults. Dependent edema is the most prominent sign. The retina has a wet appearance.

Subungual edema with horizontal lines (called Muehrcke lines) also may occur. Hernias may be found, and the elasticity of the ears may be decreased. Heavy proteinuria over an extended period of time leads to a state of protein depletion with muscle wasting, thinning of the skin, and growth failure. Pleural and ascitic fluid can accumulate. Rarely, cellulitis, peritonitis, or pneumonia may be the first indication of an underlying nephrotic syndrome. Children may have growth failure.

Lab Studies

Urine analysis is benign, but profound proteinuria and oval fat bodies may be observed. In children, the critical level for diagnosis is more than 40 mg/h/m². In adults, the threshold is more than 3.5 g/d/1.73 m². A random albumin-to-creatinine concentration ratio is in excess of 5. Urine specific gravity is high because of proteinuria. A 24-hour urine measurement is obtained for protein and creatinine clearance. Hypoalbuminemia is an important marker of nephrotic syndrome. The level at which edema occurs varies, but it tends to be lower in children than in adults. Nephrotic syndrome in children is defined by a serum albumin of less than 2.5 g/dL. Hyperlipidemia also is a feature of a nephrotic state.

Renal function usually is normal except in cases of undiagnosed FSGS or in those cases that progress to acute renal failure. Serologic workup (including antinuclear antibodies, complements, and cryoglobulins) is normal. Hyponatremia often is observed, which is, in part, a spurious finding secondary to the hyperlipidemic state. This condition also occurs from water retention caused by hypovolemia and antidiuretic hormone release. Elevated hemoglobin and hematocrit are consequences of plasma volume contraction.

Histologic Findings

Light microscopy: In patients with MCD, the glomerulus is, by definition, normal or nearly so when examined with the light microscope; however, the precise limits of normal are not clearly defined. This creates difficulty in differentiating the appearance of minimal change with mild mesangial proliferation from a mesangial proliferative glomerulonephritis. Diagnosis can be even more difficult because, at the peak age of onset (approximately 3 y), the mesangial and epithelial cells are more

prominent. In adult patients, diagnosis is made more challenging by superimposed arterionephrosclerosis secondary to hypertension. In children with frequently relapsing MCD, some involuted glomeruli may be present. These lesions are small and sclerotic but retain their podocyte and parietal epithelial cell constituents. The presence of these glomeruli is related to the duration of the disease. The most common tubular lesion is protein and lipid droplets in epithelial cells due to increased reabsorption. The presence of areas of tubular atrophy and interstitial fibrosis should raise the suspicion of FSGS.

Immunohistology

These studies usually do not demonstrate significant glomerular deposition of immunoglobulins or complement components in patients with MCD. Some biopsy specimens may be positive for low-level IgM deposits not accompanied by mesangial dense deposits.

Electron microscopy

Retraction of the epithelial foot processes is observed consistently in patients with MCD. This is, at times, erroneously described as foot-process fusion and results from disordered epithelial cell structure with withdrawal of the dendritic process. This finding is not unique to MCD, and the diagnosis is one of exclusion of other diseases based on lack of other processes on light microscopy, immunohistology, or electron microscopy.

Medical Care

Corticosteroids are the treatment of choice, leading to complete remission of proteinuria in most cases. Approximately 90% of children respond within 2 weeks to prednisone at a dose of 60 mg/msq/d. The treatment is continued for another 6 weeks, at lower doses of prednisone, after the remission of proteinuria. In some children, proteinuria fails to clear by 6-8 weeks, and performing a renal biopsy may be useful to determine if another process may be present.

Adults respond more slowly than children. A response in up to 80-90% has been recorded in adolescents and adults. However, the time to remission is up to 16

weeks. If patients are steroid-resistant or they relapse frequently, a trial of immunosuppressants is given.

The choice of immunosuppressants includes cyclophosphamide and chlorambucil. These drugs expose the patient to a wide range of serious adverse effects that include life-threatening infections, gonadal dysfunction, bone marrow dysfunction, and, in the case of chlorambucil, increased risk of leukemia. Pulse cyclophosphamide failed to adequately suppress recurrence of minimal change nephrotic syndrome in a small group of children who were steroid-dependent. Cyclosporine is considered to be an acceptable drug for maintenance therapy in patients with frequent relapses and steroid dependency. However, it is less efficacious than cyclophosphamide at maintaining sustained remission.

Mycophenolate mofetil (MMF) has been shown in limited studies to be beneficial to patients who are steroid-dependent or with frequent remissions. Unfortunately, the evidence for the benefit of this drug is scant at this time, and it should be considered only when patients develop serious adverse effects to steroid treatment and refuse treatment with cyclophosphamide. One case report describes long-term remission with rituximab (an anti-CD20 antibody) in a patient who had failed conventional immunosuppressive therapy. MCD secondary to Hodgkin lymphoma is frequently resistant to steroids and will remit with cure of the primary disease.

Angiotensin converting enzyme inhibitors and angiotensin II receptor blockers, alone or in combination should be used with a goal of reducing the proteinuria. Blood pressure and renal function should be monitored closely in patients on angiotensin converting enzyme inhibitors and angiotensin II receptor blockers.

Hypovolemia

This necessitates immediate volume expansion with purified plasma protein fraction and isotonic sodium chloride solution. The administration of parenteral albumin infusion is not appropriate long-term management for patients with hypoalbuminemia because it has only a transient effect. Such crises should be avoided with recognition of the earlier signs of hypovolemia, including abdominal

pain, increase in hematocrit, and response to contributing factors (eg, diarrhea, septicemia, diuretic therapy).

Edema

This condition should be controlled by dietary sodium restriction. Small amounts of edema are not of much clinical significance. The use of diuretics should be reserved for patients with severe cases of edema, particularly in the presence of respiratory or gastrointestinal symptoms, and when the condition restricts activity.

Thrombotic episodes should be prevented by mobilization and meticulous attention to venipuncture and intravenous infusion sites. Established episodes should be managed with heparinization.

Infections

These must be treated aggressively. Cellulitis, peritonitis, otitis, and pneumonia are common infections. Susceptibility to pneumococcal infections warrants the administration of penicillin prophylaxis to patients in relapse; corticosteroids increase the problem of infection.

Diet

An adequate dietary protein intake, in accordance with the recommended daily allowance (RDA) is necessary. No evidence suggests that hepatic albumin synthesis is elevated with protein intake that is higher than the RDA. Dietary sodium restriction helps forestall the progression of edema and also is prudent in the management of hypertension.

Activity

Mobilization, rather than bed rest, is indicated to avoid thromboembolic complications.

Complications

The most common complications are from the adverse effects of medications. Additional complications may include peritonitis, infections, and acute renal failure. Acute renal failure occurs because of either acute tubular necrosis or acute tubulointerstitial nephritis. Patients with nephrotic syndrome have an increased incidence of arterial and venous thromboemboli, particularly deep vein and renal vein

thrombosis. Renal vein thrombosis is known to occur in patients with MCD, although the incidence is lower than in patients with membranous nephropathy. Hypercholesterolemia and hypertriglyceridemia can lead to accelerated atherosclerosis and perhaps cause progressive glomerular injury.

Prognosis

Use of antibiotics and glucocorticoids and better-organized schedules of management have substantially reduced the mortality rates associated with MCD. Deaths still occur from disease complications. Relapses eventually cease. Only approximately 5% of children continue to have steroid-responsive relapses when older than 18 years. Adults have a similarly good prognosis. Survival rates of 85-90% are observed 10 years or more after disease onset. Chronic renal failure is extremely rare in patients who are steroid-responsive. If chronic renal failure occurs, the possibility that the pathologic lesion is different or has evolved must be considered.

3.1.1.1.2 Focal Segmental Glomerulosclerosis

Focal Segmental Glomerulosclerosis (FSGS) is defined as segmental solidification of the glomerular capillary tuft with accumulation of extracellular matrix, often with an adhesion (synechia) between the capillary tuft and Bowman's capsule. Hyalinosis and foam cells also can be present. The common pathophysiologic principle is absolute or relative podocyte depletion; podocyturia also may occur. Positive staining for IgM and C3 may be present by immunofluorescence and is believed to represent macromolecular trapping rather than specific deposition. On ultrastructural analysis, electron-dense material may be found in the mesangium and in the subendothelial compartment, consistent with hyalinosis. Podocyte injury in FSGS can be idiopathic, genetic, or reactive (postadaptive FSGS or medication-associated FSGS).

FSGS can be classified as follows.

1. Primary (idiopathic) FSGS
 - FSGS with hyalinosis
 - Progression from minimal-change disease

- Progression from immunoglobulin M (IgM) nephropathy
- Progression from mesangial proliferative glomerulonephritis
- Superimposed on other primary glomerulonephritis conditions (eg, membranous glomerulonephritis, immunoglobulin A [IgA] nephropathy)

Variants of primary FSGS

- Cellular variant (endocapillary and extracapillary hypercellularity)
- FSGS with mesangial hypercellularity
- FSGS with glomerular tip lesions

2. Secondary FSGS

Drugs

- Intravenous heroin
- Analgesics

Viruses

- Hepatitis B
- HIV
- Parvovirus

Hemodynamic factors - With reduced renal mass

- Solitary kidney
- Renal allograft
- Renal dysplasia
- Renal agenesis
- Oligomeganephronia
- Segmental hypoplasia
- Vesicoureteric reflux

Hemodynamic causes - Without reduced renal mass

- Massive obesity
- Sickle cell nephropathy
- Congenital cyanotic heart disease
- Malignancies
- Lymphomas

- Other malignancies

Scarring - Postinflammatory in postinfectious glomerulonephritis

Miscellaneous

- Hypertensive nephrosclerosis
- Alport syndrome
- Sarcoidosis
- Radiation nephritis

In other words, factors as diverse as infections, inflammations, toxins, and intrarenal hemodynamic alterations can initiate injury and lead to glomerulosclerosis.

Idiopathic FSGS.

Idiopathic FSGS is the most common variant of FSGS and likely includes various etiologic forms that will ultimately be recognized as distinct entities, including new genetic forms and recurrent FSGS associated with a circulating permeability factor.

The Columbia classification defines morphologic criteria for idiopathic FSGS, using five categories: Collapsing variant, tip lesion, perihilar variant, cellular variant, and not otherwise specified (NOS). Tip lesion is discussed further as a transcategorical entity. In our taxonomy, collapsing FSGS is believed to have a different pathogenetic mechanism. It is included as CG and is discussed further. The cellular FSGS variant in the Columbia classification includes cases with endocapillary proliferation and/or podocyte proliferation but without glomerular collapse. A recent study indicated that, whereas some cases of the cellular lesion progress extremely rapidly, behaving clinically like more aggressive forms of podocytopathies such as CG, the overall percentage of patients who progress to renal failure is similar for the cellular and NOS categories of the Columbia criteria. This observation raises the possibility that there may be heterogeneity among patients with the cellular lesion.

Genetic FSGS.

Patients may manifest genetic FSGS as part of a syndrome or in renal-limited (nonsyndromic) disease. Genetic mutations that are responsible for syndromic FSGS include mutations in GBM proteins such as the mutated COL4 genes, encoding collagen IV chains, in Alport syndrome; transcription factors that are critical for podocyte differentiation, such as WT1, encoding the Wilms' tumor 1 protein, and LMX1B, encoding a homeobox protein, in nail-patella syndrome; metabolic disorders (GLA, encoding α -galactosidase-A in Fabry disease) and mitochondriopathies (mitochondrial tRNA mutations that causing MELAS [mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes] syndrome or isolated FSGS, and COQ2 mutation). Genetic mutations that are responsible for renal-limited FSGS include those that encode proteins in the actinbased cytoskeleton complex or the slit diaphragm complex and adhesive proteins.

Most of the genetic forms of FSGS have Mendelian inheritance, including autosomal recessive, autosomal dominant, and sex-linked patterns. Exceptions include WT1 and mitochondrial gene mutations. To date, each of the mutations that are associated with FSGS has involved genes that are expressed in podocytes. This finding underscores the centrality of podocyte injury in the etiology of FSGS. The distinction between genetic FSGS and idiopathic FSGS will continue to shift as new Mendelian forms are discovered. Recently, association studies showed that certain single-nucleotide polymorphisms or haplotypes are associated with increased risk for sporadic FSGS; it is likely that many such variants will be found. These findings need extensive replication in diverse populations before they have clinical utility. Genomic profiling is likely to enter medical practice in the next decade, in support of personalized medicine. This profiling will likely include many of the Mendelian genetic FSGS variants and may include genetic mutations that increase FSGS risk

The mutations that most commonly are associated with podocytopathies are in NPHS2, encoding podocin. NPHS2-associated renal disease follows autosomal recessive inheritance, with homozygous or compound heterozygous mutations, and accounts for approximately 20% of pediatric FSGS or steroid-resistant nephrotic syndrome. Most of the affected patients develop the disease during childhood, but

onset occurs up to the fourth decade. These patients present with a range of morphologic patterns of glomerular injury, including MCN, diffuse mesangial hypercellularity, and FSGS. Genetic testing is important, because these patients are consistently resistant to glucocorticoid therapy and show limited response to other immunosuppressive therapy. Antibodies against podocin are available, and their use should be included in the evaluation of renal biopsies in patients with suspected genetic podocytopathy. Patients with NPHS2 mutations show heterogeneity in podocin expression, including either absence or abnormal cytoplasmic staining. Two different available antibodies recognize the N-terminal and C-terminal domains, respectively, of podocin. Because mutations may occur in any portion of the gene, the pattern of staining may vary between the two antibodies when both are used in the same biopsy. Autosomal dominant, familial FSGS typically presents in adulthood, although earlier onset has been described. Three genetic loci have been identified: ACTN4 encoding α -actinin-4 on chromosome 19q13, an unidentified gene near the same location, and TRPC6, encoding transient receptor potential cation channel 6.

Patients with ACTN4 mutations, reported in five families, tend to present late in life and to progress to ESRD slowly. In biopsies that are taken from patients with these mutations, foot process effacement is patchy, which challenges the belief that the extent of foot process effacement is a reliable indicator of genetic or idiopathic FSGS compared with “secondary” forms of FSGS. Patients with TRPC6 mutations, reported in six families, present at ages 20 to 50 yr and progress more rapidly to ESRD. Patients with mutations mapped to chromosome 19q13 present with morphologic heterogeneity that is similar to that seen with NPHS2 mutations, ranging from steroid-resistant, apparent MCN through mesangial hypercellularity and FSGS). These data underscore that morphologic criteria are not sufficient to characterize a disease fully.

WT1 mutations of have been described in patients with Frasier syndrome but also in genetically female patients with isolated FSGS. Most WT1 mutations are felt to be new mutations rather than inherited mutations. It is generally believed that genetic forms of FSGS do not respond to steroid therapy. Recently, however,

nontruncating mutations of PLCE1, encoding phospholipase C ϵ 1, were found in patients with steroid-sensitive FSGS and also in patients with intermittent proteinuria that resolves spontaneously.

Reactive FSGS.

Reactive FSGS may develop through postadaptive mechanisms or may be associated with certain medications. Postadaptive FSGS, which may also include hyalinosis, begins when the glomerulus undergoes an adaptive response that is characterized by glomerular hyperperfusion and hyperfiltration, leading to glomerulomegaly. These events occur in the presence of either reduced renal mass (e.g., renal dysplasia, surgical renal mass reduction, reflux nephropathy, chronic interstitial nephritis) or initially normal renal mass (obesity, sickle cell anemia, or cyanotic congenital heart disease). In the former setting, glomerular hyperperfusion is compensatory; in the latter setting, the mechanisms that are responsible for hyperperfusion are unknown. After a period of months (rats) to years (humans), postadaptive FSGS emerges. It is believed that, in response to glomerular capillary hypertension and glomerulomegaly, podocytes undergo hypertrophy and, as noted, continue to provide structural support to the capillary loop at the expense of hydraulic conductivity. Alternative but less accurate terms for postadaptive FSGS include secondary FSGS, which has been extended beyond the podocytopathies to other conditions, including scarring as a result of glomerulonephritis, and hyperfiltration FSGS, which may mislead by implying that hyperfiltration has been established as the central pathogenic process, rather than glomerulomegaly (Figure 3.1.1.1.2).

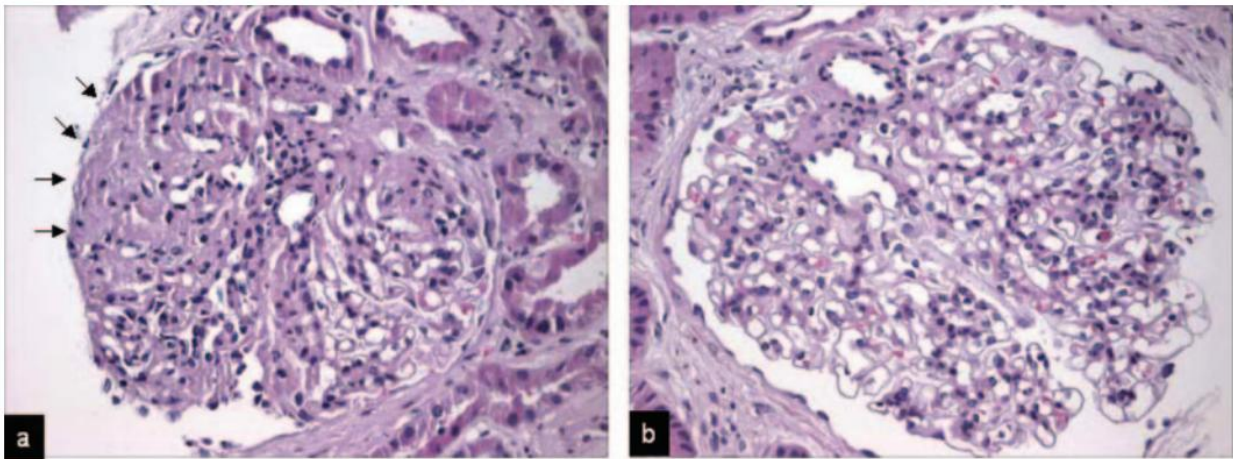


Figure 3.1.1.1.2 Postadaptive FSGS. (A) Large glomerulus with segmental solidification of the tuft and hyalinosis (arrows). (B) Very large glomerulus without sclerosis within the same biopsy (glomerulomegaly). Magnification, $\times 20$ (hematoxylin and eosin).

The distinction between idiopathic FSGS and postadaptive FSGS seems to have clinical relevance, because patients with postadaptive FSGS may have sizable reductions in proteinuria with conservative therapy and the role of immunosuppressive therapy is unproved.

Clinically, the diagnosis of postadaptive FSGS is influenced by the presence of appropriate history. This approach is understandable, but it risks errors such as classifying a case of idiopathic FSGS in a morbidly obese individual as being postadaptive. In general, patients with postadaptive FSGS have higher serum albumin concentrations (despite significant proteinuria) and lesser degrees of foot process effacement. Perhaps related to these findings, they also are less likely to manifest florid nephrotic syndrome.

However, these markers may not be reliable in individual cases. Arguably the most reliable criterion is the presence of glomerulomegaly, although this determination requires direct measurement of the maximal glomerular diameter observed on multiple sections. As an approximation, the glomerulus is considered to be enlarged when the diameter exceeds 50% of the field of view using a $\times 40$

objective. Problems with both approaches are the small number of glomeruli available on clinical renal biopsies (approximately 50 glomeruli are required for reliable determination of diameter) and the need for a sample that includes both superficial and juxtamedullary nephrons.

Thus, specific molecular markers to distinguish postadaptive FSGS are needed. Although hypertension is commonly cited as cause of postadaptive FSGS, this association was challenged recently.

Frequency

Typically, idiopathic FSGS is observed in persons aged 18-45 years, although no age group is exempt from the disease. In children with NS, FSGS is found in 7-10% of renal biopsies; incidence is much greater in those who are resistant to steroid and cyclophosphamide therapy. In adults, the lesion is more common in men and is observed in 20-30% of patients with NS. Incidence of FSGS is 3-7 times higher in young black men as compared to whites.

The annual incidence of secondary FSGS in patients who are addicted to intravenous heroin is 30 times higher (611 cases per million population). Heroin-associated FSGS accounted for 11.4% of end-stage renal disease (ESRD) patients in the 1970s and 1980s, although the disease has gradually disappeared in the 1990s. Most patients with HIV-associated FSGS are young black men (mean age, 33 y; male-to-female ratio, 10:1); 50% are intravenous drug abusers; and the remaining are either gay or bisexual men, heterosexual contacts of infected persons, or children with HIV infection. HIV-associated FSGS is distinctly rare in whites. In the United States and elsewhere, more than 95% of patients are black. Typically, idiopathic FSGS is observed in persons aged 18-45 years, although no age group is exempt from the disease. In children with NS, FSGS is found in 7-10% of renal biopsy specimens; incidence is much greater in those who are resistant to steroid and cyclophosphamide therapy.

Mortality/Morbidity

The natural history of FSGS varies a great deal. A typical course runs from edema that is difficult to manage to proteinuria refractory to corticosteroids and other

immunosuppressive agents to worsening hypertension and progressive loss of renal function. In patients who do not respond to therapy, the average time from the onset of gross proteinuria to ESRD is 6-8 years, although wide variations in the time course occur. One of the key factors that determines renal survival is the persistence and degree of proteinuria. In patients with unresponsive massive proteinuria of greater than 10 g/d, most will develop ESRD within 5 years. The prognosis is much worse in blacks compared to whites. In the collapsing form of FSGS, the disease is marked by severe hypertension, more massive proteinuria, a very poor response to corticosteroids, and a much faster rate of progression to ESRD.

History

The natural history of FSGS varies a great deal. A typical course runs from edema that is difficult to manage to proteinuria refractory to corticosteroids and other immunosuppressive agents to worsening hypertension and progressive loss of renal function. In nonresponders, the average time from the onset of proteinuria to ESRD is 6-8 years, although wide variations in the time course occur. The prognosis is much worse in blacks compared with whites. In the collapsing form of FSGS, the disease is marked by severe hypertension, more massive proteinuria, a very poor response to corticosteroids, and a much faster rate of progression to ESRD. In HIV-associated FSGS, the renal functional deterioration is rapid, leading to ESRD within a few weeks to 1 year. In recent times, with the introduction of highly active antiretroviral therapy (HAART), renal function is well preserved when the viral load decreases.

Physical

The most common clinical presenting feature is NS characterized by generalized edema, massive proteinuria, hypoalbuminemia, and hyperlipidemia. Common causes of nephrotic syndrome in adults include minimal change disease, membranous glomerulonephritis, systemic lupus erythematosus, focal sclerosis, HIV infection, IgA nephropathy, diabetes mellitus, and amyloidosis. In patients with primary (essential) hypertension and analgesic abuse, NS is not a common manifestation (although hypertension may be observed in patients with NS from all causes). Occasionally, routine urinalysis may reveal proteinuria, prompting referral to

a nephrologist. Less than a third of patients with FSGS present with nonnephrotic proteinuria along with microscopic hematuria and hypertension. Typically, edema develops over a few weeks, but the onset may be abrupt, with weight gain of 15-20 lb or more. Frequently, the onset of edema follows a recent upper respiratory tract infection. Pleural effusion and ascites may be present; pericardial effusions are rare. Gross edema may predispose patients to ulcerations and infections in dependent areas (eg, lower extremities). Abdominal pain, a common finding in children, may be a sign of peritonitis. Rarely, xanthomas may be evident in association with severe hyperlipidemia. In many patients, physical examination findings are normal except for generalized or dependent edema. Severe hypertension (ie, diastolic BP of 120 mm Hg or more) is not uncommon, especially in black patients with renal insufficiency. Rarely, patients experience severe renal failure with signs and symptoms of advanced uremia (eg, nausea, vomiting, bleeding, seizures) or altered mental status.

Diagnosis.

Distinguishing FSGS from minimal-change disease, mesangial proliferative glomerulonephritis, membranoproliferative glomerulonephritis, or membranous glomerulonephritis is clinically difficult. Rarely, NS may be the initial manifestation in patients with SLE. Young patients presenting with NS due to amyloidosis of the kidneys (except in rare familial forms) is very uncommon. Although hematuria is the most common presentation in whites with IgA nephropathy, NS and renal insufficiency may also be present.

Lab Studies

Urinalysis reveals large amounts of protein, along with hyaline and broad waxy casts, whereas RBC casts are generally absent. Broad casts may be observed in persons with advanced cases.

Serum creatinine (SCr) concentration or creatinine clearance (CrCl) is usually within reference ranges in early stages. In patients with idiopathic FSGS, investigational findings for an underlying etiology, such as systemic lupus erythematosus (serum complement C4/C3 levels, antinuclear antibody/anti-DNA titers), hepatitis B or C infection, or vasculitis (antineutrophil cytoplasmic antibody

titers, serum protein electrophoresis), are generally negative. In patients thought to have secondary FSGS, obtain HIV antibody, CD4, and viral load studies. FSGS can be considered in patients with proteinuria on the basis of NS; however, in young patients with an absence of RBC casts and negative serologic study findings, definitive diagnosis rests on a kidney biopsy.

Imaging Studies

In the early stages, ultrasound examination reveals normal or large kidneys with increased echogenicity, suggesting diffuse intrinsic medical renal disease. In patients with advanced renal failure, kidneys are small and shrunken, indicating severe glomerular scarring and interstitial fibrosis. In HIV-associated FSGS, ultrasound generally reveals large echogenic kidneys.

Procedures

Kidney biopsy is the most definitive way to establish the diagnosis.

Medical Care

Treatment of FSGS can be divided into the following:

Nonspecific; nutritional management

Nonimmunosuppressive therapy - Diuretics for edema, angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) for reduction of proteinuria, other antihypertensive agents for hypertension, and lipid-lowering drugs for hyperlipidemia

Nonspecific treatment goals in NS include maintenance of adequate nutrition, minimization or elimination of proteinuria, and prevention of complications resulting from edema. Control of hypertension is one of the most important aspects of overall management. Lowering of lipid levels is necessary to reduce cardiovascular risk and to possibly delay the progression of renal disease.

The mainstay of treatment is reduction in daily salt intake to 2 g of sodium (6 g of salt) and the use of diuretics in varying doses and combinations. A high level of protein intake may further aggravate proteinuria, adversely affecting renal function. Current recommendations call for an intake of 1-1.3 g of high biologic value protein per kilogram of body weight and a reduction of fat intake.

In most patients, loop diuretics (eg, furosemide) are needed to promote diuresis. Patients with massive edema with impaired oral absorption may require intravenous administration. In patients with refractory conditions, addition of other diuretics (eg, metolazone) and potassium-sparing agents (eg, spironolactone, triamterene) facilitates diuresis and prevents hypokalemia. Rarely, some patients (especially children) with intractable edema may need intravenous albumin and mannitol in a hospital setting to initiate diuresis. Protracted use of intravenous albumin should be discouraged because the regimen is both expensive and ineffective, as most of the infused albumin is lost in the urine.

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are nonspecific agents that reduce proteinuria because of their antihypertensive and intrarenal hemodynamic effects of reducing glomerular capillary pressure and resistance. ACEIs and ARBs are effective in reducing protein loss even in normotensive patients. These agents do not eliminate proteinuria completely or reverse the primary glomerular disease process.

Since most patients with idiopathic FSGS develop hypertension, which further contributes to renal functional deterioration, meticulous attention must be paid to maintain BP in the reference range. All classes of antihypertensive agents, which effectively lower BP, have a beneficial effect in reducing proteinuria. In many patients, combination antihypertensive therapy may be needed to maintain normal blood pressure. Another nonspecific therapy uses lipid-lowering agents to control hyperlipidemia. The statin class of drugs is better tolerated than some of the older agents.

Specific treatment

Idiopathic FSGS is a difficult disease to treat because of its highly variable clinical course. The specific treatment approach is still empirical, and no consensus has evolved because of a lack of prospective controlled trials. Current evidence, mostly derived from retrospective analyses, favors prolonged corticosteroid therapy (6 mo or longer) to induce remission in patients with idiopathic FSGS. Since long-term steroid therapy may lead to serious toxicity, patient counseling and close

monitoring for adverse effects are essential before embarking on such a protracted regimen. The current approach calls for initiating therapy with prednisone in a dose of 1 mg/kg (60-80 mg/d) for 2-6 months or longer, depending on patient response as assessed by presence or absence of edema, 24-hour urine protein excretions, CrCl, SCr, serum albumin, and lipid levels.

Studies indicate that 30-60% of patients may undergo complete or partial remission to such a regimen, and relapses are frequent when steroids are discontinued. Complete remission is protein excretion of less than 200-300 mg/d, and partial response is excretion of 200-3500 mg/d, or a greater than 50% reduction in baseline proteinuria. In children, results from several studies show a remission of proteinuria in 11% of patients, persistence of NS with preservation of renal function in 31%, decline in the glomerular filtration rate in 23%, and development of ESRD in 21%. In adults, 10-year renal survival in nephrotic patients ranges from 25-55%, compared with 85-90% in patients with mild proteinuria.

Blacks and patients with collapsing FSGS are generally refractory to treatment and progress to renal failure. In responding patients, the goal is to titrate prednisone to the lowest dose needed to stop proteinuria and to prevent relapses. Use of steroids on alternate days can also reduce toxicity. The optimal treatment duration is uncertain; some authorities recommend the use of steroids indefinitely. In patients refractory to 2-3 months of prednisone therapy, the recommendation is to reduce the steroid dose and to add cyclophosphamide (2.5 mg/kg [150-200 mg/d]). Monitor patients for bone marrow suppression, and encourage them to drink adequate fluids to prevent hemorrhagic cystitis. Prolonged use of cyclophosphamide may lead to gonadal toxicity; therefore, persisting with cyclophosphamide beyond 3 months in patients who do not respond is unwise.

Because of favorable results in other glomerular diseases, mycophenolate mofetil has also been evaluated in FSGS. Although the experience is limited, the suggested dose is 750-1000 mg twice daily in patients refractory to corticosteroids and in whom calcineurin inhibitors may not be appropriate. Despite all attempts, some patients continue to deteriorate and progress to ESRD. A well-informed patient

can choose among maintenance hemodialysis, continuous ambulatory peritoneal dialysis, or cadaver or living donor transplantation. FSGS may recur in the transplanted kidney, but most renal physicians do not consider this a contraindication for renal transplantation. Management of secondary FSGS is directed toward the etiology or associated disorder. In selected patients with HIV and FSGS, corticosteroid therapy is associated with a significant improvement and, in some patients, discontinuation of dialysis therapy. In heroin-associated FSGS, discontinuation of the drug may result in remission of proteinuria and improvement in renal function.

Diet

The mainstay of treatment is reduction in daily salt intake to 2 g of sodium (6 g of salt) and the use of diuretics in varying doses and combinations. Potassium supplementation may be needed in patients treated with diuretics who develop hypokalemia. High protein intake may further aggravate proteinuria, adversely affecting renal function. Current recommendations call for an intake of 1-1.3 g of high biologic value protein per kilogram of body weight and a reduction of fat intake.

Transplantation of kidney

Idiopathic FSGS may recur in the transplanted kidney, in which it presents with severe proteinuria and nephrotic syndrome. Children with FSGS and patients who manifest with more severe proteinuria and a more rapid course to renal failure in their native kidneys are at greater risk of recurrence in the allograft. Those who have lost a prior allograft because of recurrent FSGS are at highest risk of recurrence. Recurrence in the allograft may be seen immediately after transplantation, supporting the existence of a circulating factor, or years later. Interestingly, the histologic variant of recurrent FSGS was the same as that documented in the native kidney in 81% of cases, validating the fidelity of the histologic subclassification. Plasma exchange has been used successfully to induce remissions of the proteinuria associated with recurrence, but the results are more favorable in children than in adults. Rituximab has been used in some patients for recurrent FSGS with varied outcomes.

Analysis of the outcomes of renal transplantation in children with FSGS shows a profound effect of race. Among African American children with FSGS, allograft survival was not different from that of non-FSGS patients. Among non-African American children with FSGS, the risk of allograft failure was 1.3 times higher than for other causes of ESRD. Nevertheless, for non-African American children, a transplant from a living related donor gave a better allograft survival than that from a cadaveric donor. An analysis of all FSGS transplants in the United States Renal Data System (USRDS) database showed no risk of graft loss for zero-mismatched transplants in FSGS patients. However, this analysis may have included patients with secondary forms of FSGS that would be unlikely to recur, thereby underestimating the overall risk of recurrence. Whereas most patients with genetic forms of FSGS have not experienced a recurrence in the allograft, this is not universally true, especially in those with compound heterozygous mutations.

Further Outpatient Care

Patients must be monitored for prednisone toxicity (eg, infections, hypertension, hyperglycemia). If cyclophosphamide is used, watch for leukopenia and hemorrhagic cystitis. During cyclosporine therapy, monitor BUN and SCr. Adjust diuretic doses according to fluid retention. Monitor WBC count and liver function during mycophenolate mofetil therapy. Patients receiving HAART will need periodic determination of viral load to assess the effectiveness of drugs used.

Prognosis

The natural history of FSGS varies a great deal. A typical course runs from edema that is difficult to manage to proteinuria refractory to corticosteroids and other immunosuppressive agents to worsening hypertension and progressive loss of renal function. Average time from the onset of proteinuria to ESRD is 6-8 years, although wide variations in the time course occur. Prognosis is much worse in blacks compared with whites. In the collapsing form of FSGS, the disease is marked by severe hypertension, more massive proteinuria, poorer response to corticosteroids, and a much faster rate of progression to ESRD.

3.1.1.1.3 Collapsing Glomerulopathy

The Columbia classification defines collapsing FSGS as the presence of segmental capillary tuft collapse (wrinkling and folding) in at least one glomerulus (3.1.1.1.3), in association with podocyte hypertrophy and/or hyperplasia. The term “collapsing glomerulopathy” (CG) seems more appropriate than FSGS, because the lesion is defined by pseudocrescent formation and by collapse of the capillary loops rather than accumulation of extracellular matrix; glomerulosclerosis is a later manifestation. Importantly, CG differs from FSGS in exhibiting podocyte proliferation rather than podocyte depletion, and the actin cytoskeleton may not appear condensed but rather absent. On ultrastructural analysis, podocytes resemble immature precursor cells, with a cuboidal shape and loss of primary processes and foot processes. Exuberant podocyte hyperplasia seems to generate the apparent pseudocrescents within Bowman’s space. Recently, this theory was challenged, and it has been suggested that cells that migrate from Bowman’s capsule participate in pseudocrescent formation. This difference of opinion derives from the anatomic observation that visceral and parietal cells represent distinct populations that meet only at the point of reflection of the glomerular tuft into the Bowman’s capsule. However, bridging of epithelial cells from Bowman’s capsule to the glomerular tuft now seems to be a common event even under nonpathologic circumstances. That why at the moment CG describes a pattern of glomerular injury, the main feature of which is severe injury to podocytes with loss of markers of differentiation, proliferation of podocytes and/or parietal epithelial cells filling Bowman’s space, and global or segmental collapse of the capillary tuft.

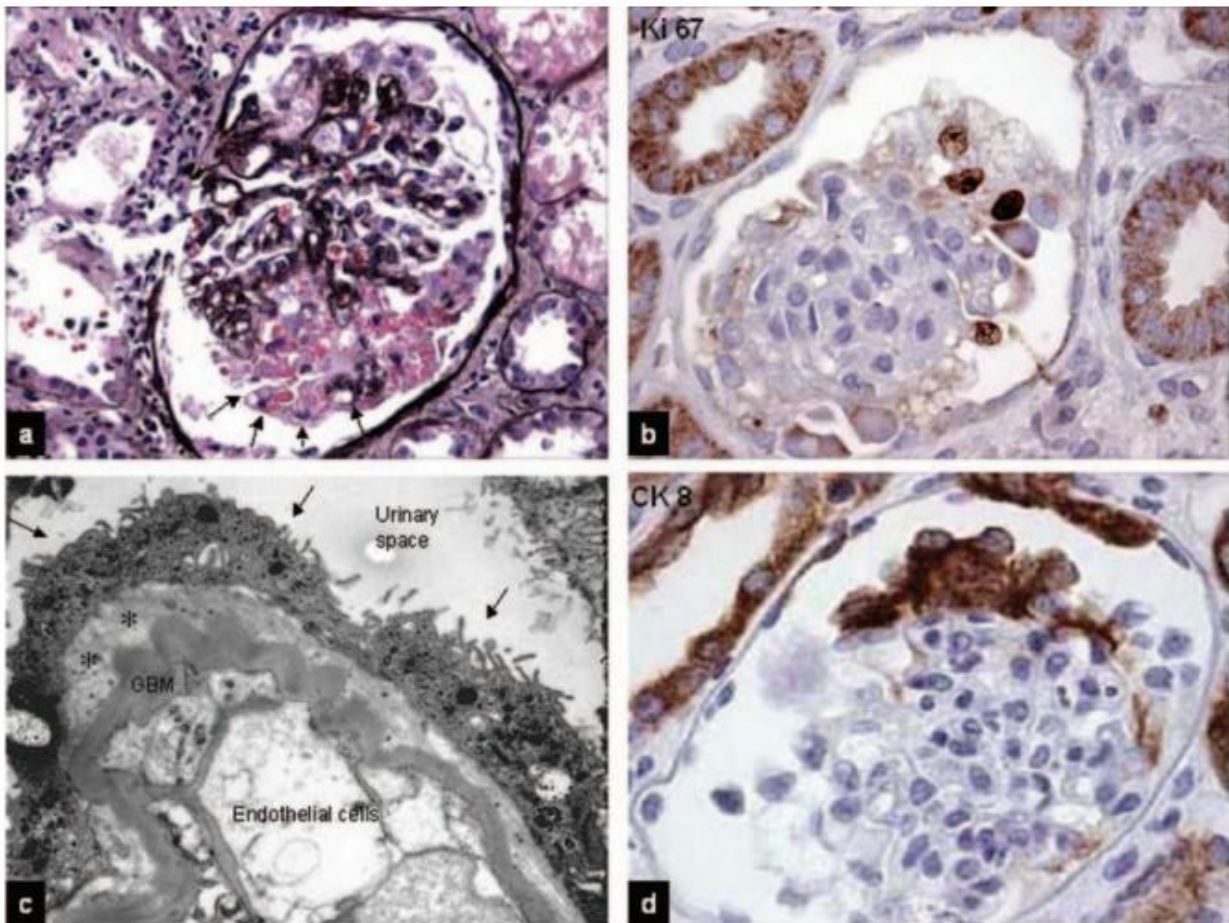


Figure 3.1.1.1.3 Collapsing glomerulopathy.

(A) Transplant biopsy in a patient with CG secondary to thrombotic microangiopathy. Segmental collapse and pseudocrescent formation are present (arrows) (Silver stain). (B) The proliferative marker Ki67 is detected in podocyte nuclei in this 2-yr-old patient with CG associated with COQ_2 mutation (immunoperoxidase). (C) Electron microscopy shows podocytes overlying mildly wrinkled glomerular basement membrane (GBM). The podocytes have lost both primary processes and foot processes (arrows). Podocytes are separated from the original GBM by newly formed extracellular matrix (*). (D) Dedifferentiated podocytes re-express other proteins that are normally expressed only during development, such as cytokeratin (immunoperoxidase). Magnifications: $\times 40$ in A; $\times 60$ in B and D; $\times 5000$ in C.

The difficulty in proving that one cell rather than the other is the central participant in the disease comes from the fact that these cells change their phenotype during disease states. Furthermore, a new subset of cells has been identified along the

inner surface of the Bowman's capsule. Some of these cells express podocyte markers, and others express adult stem cell markers. These findings suggest not only that bridging of cells that migrate from the inner side of the Bowman's capsule is not a pathologic event but also that cells other than parietal epithelial cells, such as migrated podocytes or stem cells, could participate in pseudocrescent formation. Ongoing studies will clarify the exact nature of bridging cells in pathologic states.

Etiology

Multiple etiologies of CG have been described, including certain viral infections (most notably HIV but also parvovirus B19 and hepatitis C), drugs, gene mutations, and vascular occlusion, in addition to idiopathic forms. CG occurring in the setting of Systemic Lupus Erythematosus (SLE) shares certain demographic, clinical, morphologic, and immunohistologic features with idiopathic and HIV-associated CG (HIVAN): a strong association with persons of African descent; a typical clinical presentation with heavy proteinuria and often renal insufficiency; frequent progression to ESRD, especially in the absence of a therapy-induced remission of proteinuria; frequent tubular injury and tubulointerstitial scarring in addition to the characteristic glomerular lesions of CG; loss of certain podocyte differentiation markers, especially in glomeruli with CG lesions; and proliferation of glomerular epithelial cells as indicated by Ki67 staining. However, there are also differences, especially at a molecular level, that suggest unique pathogenic aspects of CG in SLE. In the majority of cases of the latter, glomerular staining for WT-1 was preserved, and loss of synaptopodin was not global as is typical in idiopathic CG and HIVAN, but rather limited to collapsed segments. This more limited loss of podocyte differentiation markers is seen in "reactive" lesions of CG. However, CG may be idiopathic, genetic, or reactive in etiology.

Idiopathic CG.

Idiopathic CG is characterized by a dysregulated phenotype, manifested by loss of maturity markers in areas of collapse (synaptopodin, podocalyxin, GLEPP1, and CALLA) and re-expression of immaturity markers (PAX2 and cytokeratin). Immature podocytes re-enter the cell cycle and proliferate, expressing Ki67.

Moreover, podocytes lose the expression of WT-1, a transcription factor that is normally expressed by podocytes beginning in fetal development and continuing through adulthood. Loss of its expression indicates that the dedifferentiated podocyte manifests functional phenotypic changes. Significantly, podocytes in seemingly normal glomeruli demonstrate loss of synaptopodin and WT-1 expression, suggesting that dedifferentiation and dysregulation precede capillary collapse.

Genetic CG.

Families with arthritis or neurologic disease and CG have been reported, although the responsible genes have not been identified. Recently, mutations in COQ2, encoding a gene that is involved in ubiquinone synthesis, have been associated with CG as well as FSGS. These findings suggest that mitochondrial dysfunction may result in podocyte loss (FSGS) or podocyte proliferation (CG); the responsible pathways are not known.

Reactive CG

The morphologic features of podocyte hypertrophy were initially described in association with HIV infection (HIV-associated nephropathy), and later an idiopathic form of CG was recognized. Both forms share a similar altered podocyte phenotype. More etiologic factors have been added to the list of possible causes of CG, including infections, medications, and acute ischemia associated with thrombotic microangiopathy. The biologic mechanisms for these associations remain to be determined. Several mechanisms have been suggested to be involved, including intrinsic injury of podocytes (e.g., intracellular expression of a viral genome, dysregulation of vascular endothelial growth factor expression) or extrinsic injury (dysregulation of the immune system, release of cytokines from infected cells in the circulation or renal parenchyma, ischemia, and toxic damage).

Pathogenesis

The pathogenesis of the remaining cases of CG in patients with SLE presented by Salvatore et al., as well as in prior reports, remains unclear, although it should be noted that the great majority of these patients had active systemic disease (often a lupus flare) and a significant number had concurrent lupus nephritis, albeit

usually mild (most often International Society of Nephrology/Renal Pathology Society class II). This certainly suggests involvement of humoral and/or cell-mediated immunity, both of which have been implicated in the pathogenesis of podocytopathies and of SLE. The relative contributions of various immune pathways may play a key role in determining the responsiveness of these lesions of CG to therapy. Deciphering the involved pathways of cell-mediated and humoral immunity, as well as cytokines and other mediators involved, may thus offer clinicians insight as to which therapeutic approaches might be most effective in treating patients with SLE and CG, with or without concurrent lupus nephritis. The treatments given the patients of Salvatore et al., with the exception of one patient given IVIG, appear directed more at T cell-mediated than antibody-mediated processes, and the one patient treated with IVIG did show a substantial reduction in proteinuria and stable, although reduced, renal function 2 years after biopsy. However, this patient, like the majority of those who did not develop ESRD, had reasonably preserved renal function (serum creatinine, 2 mg/dl) at the time of biopsy.

3.1.1.1.4 Diffuse mesangial sclerosis

Diffuse mesangial sclerosis (DMS) is defined by mesangial expansion as a result of accumulated extracellular matrix protein, together with podocyte hypertrophy and mild hyperplasia. In contrast to the FSGS category, lesions that are assigned to DMS show relatively dedifferentiated or less-differentiated podocyte phenotype. In contrast to the CG category, although the podocytes show increased expression of proliferation markers (e.g., Ki67), rates of proliferation are low.

DMS Variants

DMS occurs in a syndromic form and a sporadic form, both of which tend to be refractory to therapy. Many DMS cases have a genetic basis. Congenital DMS is associated with WT1 mutations (Denys-Drash syndrome) and mutations of LAMB2, encoding laminin β_2 chain (Pierson syndrome). In the former case, immunostaining reveals markedly reduced expression of WT-1 in podocyte nuclei with simultaneous increased expression of PAX2, a WT-1 target gene. In both forms, there is increased expression of proliferative markers, such as Ki67, and increased podocyte expression

of cytokeratin, reflecting a dedifferentiated phenotype. The expression of other podocyte maturity markers such as synaptopodin, nephrin, and α -actinin-4 is preserved, and negative staining for these markers is observed only when glomerulosclerosis develops, as a result of podocyte loss. These forms, as well as the recently described familial form of DMS that is caused by truncated mutation of PLCE1, are associated with podocyte developmental arrest. Rarely, patients with NPHS2 mutations may also present at the renal biopsy with a morphologic picture that resembles mesangial sclerosis.

Another form of congenital renal disease that falls into this category is congenital nephrotic syndrome of Finnish type (CNF). CNF is caused by homozygous or compound heterozygous mutations in NPHS1, encoding nephrin. In contrast to other DMS variants, in CNF, the earliest histologic finding is not only mesangial expansion but also mesangial cell hypercellularity. Podocyte phenotype is altered and nephrin is not expressed, but the expression of other podocyte proteins such as zona occludens 1 (ZO-1) seems to be maintained. In the early phases of the disease, podocyte proliferative rate is low. Podocyte detachment and podocyturia also are detected, and it is intriguing to speculate that this may represent the mechanism of progression toward sclerosis. In fact, the disease rapidly progresses, and subsequent changes include glomerulosclerosis, Bowman's space dilation, and tubulointerstitial abnormalities, including tubular microcysts.

3.1.1.1.5 Transcategorical Entities

There are at least three axes defined as transcategorical entities for primary non-immune glomerulopathies:

- Glomerular Tip Lesion
- Diffuse Mesangial Hypercellularity
- C1q Nephropathy

Glomerular Tip Lesion

Glomerular tip lesion has been a controversial subject since its description by Howie in 1984. It is situated at the portion of the glomerular tuft located adjacent to the origin of the proximal convoluted tubule and consists of a collection of

intracapillary foam cells or accumulation of the extracellular matrix, overlaid by hypertrophic podocytes bridging toward the Bowman's capsule or the most proximal portion of the tubule. Some cases are associated with FSGS, whereas in other instances, tip lesions are the only morphologic abnormalities in glomeruli that otherwise appear normal on light microscopy. It has been suggested that the latter cases may be part of the MCN spectrum of diseases. Against this proposal is the definition of MCN itself, if we accept that for a diagnosis of MCN all glomeruli should appear normal on light microscopy. However, such cases very often behave clinically like MCN. Tip lesion has been included in the Columbia classification as a variant of FSGS, regardless of the presence of segmental sclerosis in the biopsy. It also has been described in other proteinuric conditions, including membranous nephropathy (where it is present in 64% of cases), postinfectious glomerulonephritis, and diabetic nephropathy. On the basis of these observations, it has been argued that the tip lesion is a response to prolonged heavy proteinuria and does not represent a specific disease entity. The prognosis in FSGS tip lesion may be more benign than in other morphologic forms of FSGS, leading some authorities to postulate that it is an intermediate form between MCN and FSGS. However, given these data, it would seem at least as likely that it is a distinct process that is overlaid onto the various podocytopathy categories and other proteinuric states.

Diffuse Mesangial Hypercellularity

Diffuse mesangial hypercellularity is an uncommon form of relatively steroid-resistant nephrotic syndrome. The glomerular morphology resembles MCN or FSGS, with superimposed mesangial hypercellularity. Genetic forms have been associated with NPHS2 mutations and the locus on chromosome 19q13. Patients with idiopathic forms of diffuse mesangial hypercellularity are at increased risk for recurrent nephrotic syndrome after renal transplantation, which makes the clinical recognition of the disorder important.

C1q Nephropathy

C1q nephropathy was first described as the presence of mesangial C1q staining, either dominant or co-dominant with IgG, IgM, and/or C3, and the lack of

serologic or clinical findings of lupus. The immune deposits are predominantly mesangial, although occasionally the deposits extend into glomerular capillary loops. C1q and other members of the newly recognized C1q/TNF superfamily share a structurally similar globular domain. C1q functions as a major link between innate and acquired immunity. Human genetic C1q deficiency is associated with lupus, presumably by impairing apoptotic cell clearance and thereby exposing the immune system to nuclear and cytoplasmic antigens. The pathogenesis of C1q nephropathy, particularly in relation to podocyte injury, remains uncertain. Some authors have suggested that the disease fits best among the podocytopathies. Because C1q deposits are found in nonpodocytopathic glomerular disease, however, it is not clear whether this entity should belong to the podocytopathies or be considered as part of the complement-mediated glomerulopathies.

3.1.1.2 Immune Complex

Immune Complex Glomerular Diseases includes membranous nephropathy (MN), Membranoproliferative Glomerulonephritis (MG), Dense Deposit Disease (DDD) and Fibrillary Glomerulonephritis (FG).

3.1.1.2.1 Membranous Glomerulonephritis

Membranous nephropathy (MN) is a glomerular disease in which immune deposits of IgG and complement components develop predominantly or exclusively beneath podocytes on the subepithelial surface of the glomerular capillary wall. Deposit formation is associated with a marked increase in glomerular permeability to protein, which is manifested clinically as nephrotic syndrome. The disease occurs in association with a variety of conditions, some of which are likely to be causal and some of which probably represent only associations. However, most occurrences (two thirds) are without obvious initiating events. Idiopathic MN is the most common cause of primary nephrotic syndrome in older (>60 years) Caucasian adults and is rare in children. The term membranous refers to thickening of the glomerular capillary wall by light microscopy, but the entity now referred to as MN was defined when immunofluorescence and electron microscopy became routine tools in the study of renal biopsy specimens in the 1960s. These techniques demonstrated diffuse,

finely granular immune deposits in the subepithelial space that are now regarded as pathognomonic of MN. Consequently, MN is a pathologic diagnosis made when glomeruli exhibit these deposits without associated hypercellularity or inflammatory changes

Etiology

The frequent occurrence of MN in autoimmune disorders (such as lupus and type 1 diabetes) and its remarkable similarity to a lesion induced in rats with antibody to antigens expressed on the foot processes of glomerular podocytes have fueled speculation that the disease is caused by deposits of autoantibody to fixed components of the podocyte membrane. A large number of agents appear to be capable of initiating MN in genetically susceptible individuals. These include viruses such as hepatitis B (HBV) and hepatitis C (HCV); drugs, including gold, penicillamine, and nonsteroidal anti-inflammatory drugs (NSAIDs); environmental toxins, such as hydrocarbons and formaldehyde; and a variety of chronic immune disorders, such as lupus, thyroiditis, graft-versus-host disease, anti-glomerular basement membrane (anti-GBM) and antineutrophil cytoplasmic antibody (ANCA)-positive crescentic glomerulonephritis (GN), and the chronic immune response to renal allografts. In about two thirds of patients, however, no obvious etiologic agent or condition can be identified.

Mechanisms of Immune Deposit Formation

Regardless of the initiating events, MN appears to be mediated primarily by the Th2 humoral immune response, which leads to formation of deposits of IgG and complement on the outer surface of the glomerular capillary wall. Experimental evidence suggests that such deposits are produced by local or in situ immune complex formation involving antigens that could be exogenous or endogenous. Subepithelial immune complex deposits can form in three ways. Antibodies can bind to exogenous antigens that localize on the subepithelial surface because of their cationic charge and small size; second, antigens and antibodies can be trapped as immune complexes on the inner surface of the capillary wall, dissociate, traverse the glomerular basement membrane (GBM), and reform in the subepithelial space; and

finally, the antigens could be endogenous constituents of a fixed subepithelial structure, such as a podocyte membrane protein. The absence of deposits at subendothelial (and mesangial) sites in idiopathic MN as well as the ability to exactly replicate the clinical and pathologic features of MN in rats with anti-podocyte antibodies (Heymann nephritis) strongly favors the third, or autoimmune, mechanism. In the Heymann nephritis models, the antigens responsible are components of the Heymann nephritis antigenic complex: a large (516-kd) glycoprotein, called megalin, bound to a smaller receptor-associated protein expressed in the clathrin-coated pits of the podocyte foot processes. Whereas antibodies to small antigenic determinants on both molecules can form subepithelial immune complex deposits, additional antigen-antibody systems involving an unidentified glycolipid antigen that activates complement as well as antibodies that neutralize complement regulatory proteins are required to induce proteinuria in animals. Once formed, these complexes of antigen and antibody are capped and shed from the cell surface, where they bind to underlying GBM, resist degradation, and persist for weeks or months as immune deposits detectable by immunofluorescence and electron microscopy.

Confirmation that a similar mechanism may be operative in idiopathic MN in humans has come from two sources. Several cases of congenital MN have been shown to be mediated by an antibody to neutral endopeptidase (NEP), an antigen expressed on the podocyte membrane. In these cases, mothers with a hereditary absence of NEP become sensitized during pregnancy and passively transfer anti-NEP IgG to the infant, who is born with congenital nephrotic syndrome caused by MN through an alloimmune mechanism. NEP has also been documented in glomerular deposits in some patients with de novo MN after renal transplantation but not in adult patients with idiopathic MN. A particularly promising study in adults has identified antibody to phospholipase A2 receptor (PLAR), another antigen expressed on podocyte foot processes, in a majority of patients with active idiopathic MN and correlated antibody levels with disease activity and response to therapy. This antibody has also been eluted from glomeruli of patients with MN. Anti-PLAR

antibody has been identified only in primary idiopathic MN and not in MN secondary to other causes.

Mechanism of Glomerular Injury

Based entirely on studies in animal models, the mechanism of glomerular damage sufficient to cause proteinuria appears to involve sublytic effects of complement C5b-9 (a multimer comprising several complement components and also known as the membrane attack complex) on the podocyte, although complement-independent mechanisms of proteinuria have also been described in some studies. When complement activation occurs at the site of deposit formation, it leads to cleavage of C5, which generates C5a and C5b. C5b combines with C6 to form a lipophilic complex that inserts into the lipid bilayer of the podocyte, where C7, C8, and multiple C9 molecules are added to create a pore-forming complex, C5b-9. The podocyte is resistant to lysis and endocytoses the C5b-9, transporting the complex intracellularly in multivesicular bodies and extruding it into the urinary space. However, the membrane insertion of C5b-9, although insufficient to cause apoptosis or cell lysis, does induce cell activation and signal transduction. This results in increased production of multiple potentially nephritogenic molecules, including oxidants, proteases, cytokines, growth factors, vasoactive molecules, and extracellular matrix. Current evidence is strongest for the role of podocyte-derived oxidants in producing the GBM damage that leads to increased protein filtration in MN. When antibody deposition, deposit formation, and complement activation are occurring, increased urinary excretion of C5b-9 and viable podocytes occurs.

Consequences of Injury Induced by C5b-9

The glomerular injury mediated by C5b-9 induces a nonselective proteinuria through loss of both the size- and the charge-selective properties of the glomerular capillary wall. The subsequent reduction in glomerular filtration rate (GFR) that occurs in progressive MN has both glomerular and interstitial components. In the glomerulus, there is thickening of the GBM resulting from overproduction of several different extracellular matrix molecules that accumulate between and around the immune deposits to form the subepithelial “spikes” characteristic of this disease when

a biopsy specimen is studied with silver methenamine staining. This appears to occur in part through upregulation of podocyte production of transforming growth factor (TGF) β 2 and β 3 as well as increased expression of TGF- β receptors in response to C5b-9. Podocyte cell number decreases because of apoptosis and cell detachment as the glomerulus expands secondary to increased pressures and flows. The podocyte itself has limited ability to proliferate and to cover denuded areas of GBM because of C5b-9-induced overexpression of cyclin kinase inhibitors and cell cycle arrest, and the consequent podocytopenia leads to progressive glomerulosclerosis. In the interstitium, there is an increased macrophage infiltrate and overproduction of matrix by interstitial myofibroblasts, leading to interstitial fibrosis a response common to all nonselective proteinuric disorders. When nephrotic-range proteinuria persists, the consequence is glomerular sclerosis as well as interstitial fibrosis and progression to renal failure at a rate that is usually directly related to both the magnitude and the duration of increased protein filtration.

Epidemiology

MN is uncommon in children; it usually accounts for less than 5% of pediatric patients undergoing biopsy for nephrotic syndrome. About 30% of all biopsy specimens for primary nephrotic syndrome reveal MN in adults and about 50% in older Caucasian adults. There is some variation in these figures among different countries, with slightly lower numbers in the United Kingdom and higher numbers in Greece and Macedonia. The United States Renal Data System in 2008 reported the incidence of end-stage renal disease (ESRD) due to MN from 2002 to 2006 at about 460 patients per year, which represents 0.4% of the total ESRD population. Because only 20% of all patients with MN progress to ESRD, the real incidence of MN is approximately 2300 patients per year in the United States or about 8 patients per million population per year. There is a threefold increased risk for MN in Caucasian patients with HLA-DR3, and associations with HLA-B8 and HLA-B18 have also been reported. HLA-DR5, in addition to HLA-DR3, increases the risk of progression in Caucasians. In Japan, MN is associated with HLA-DR2. Some Caucasian patients

have a deletion of C4 with the HLA-B8-DR3 haplotype. Rare examples of familial MN have also been reported, usually presenting in siblings

Clinical Manifestations

MN affects patients of all ages and races but is more common in men than in women by 2:1. Idiopathic MN is most often diagnosed in middle age, with the peak incidence during the fourth and fifth decades of life. MN in childhood is more often secondary (such as due to hepatitis B virus). Seventy percent to 80% present with the nephrotic syndrome. The remaining 20% to 30% present with subnephrotic asymptomatic proteinuria (<3.5 g/24 h). Proteinuria is nonselective. Microscopic hematuria is common (30% to 40%), but macroscopic hematuria and red cell casts are rare and suggest a different glomerular pathologic process. In idiopathic MN, serum complement levels are normal despite evidence of intraglomerular complement activation, and serologic markers such as antinuclear antibodies, ANCA, and rheumatoid factor are normal or absent. At the time of diagnosis, only 10% to 20% have hypertension. Renal function is usually normal at presentation, with only a small fraction (<10%) presenting with renal impairment. These presenting features can be modulated by age or preexisting hypertension; tubulointerstitial and vascular changes on biopsy may be related to these factors rather than to the severity of the MN. This is supported by recent evidence that age per se does not influence the rate of progression in MN but does influence the GFR at presentation. Other complications related to the nephritic syndrome include dyslipidemia, which probably contributes to the increased cardiovascular risk, and a high prevalence (10% to 40%) of thromboembolic events including renal vein thrombosis.

Pathology

The earliest pathologic feature of MN relates to the initial formation of subepithelial immune complexes of IgG and complement along the outer surface of the capillary wall in which glomeruli appear histologically normal and therefore may be mistaken for minimal change nephrotic syndrome if only light microscopy is performed. After immune complex formation, changes occur first in the podocyte, then in glomerular barrier function leading to proteinuria, then in the renal

interstitium (probably as a consequence of the proteinuria), and finally in the GBM itself, which becomes thickened (membranous) through the accumulation of additional matrix material along the outer surface, often in an irregular or spike-like pattern.

Light Microscopy

In the earliest stages of the disease, the glomeruli and interstitium appear normal by light microscopy, and the diagnosis is made by immunohistology and electron microscopy. The next stage of MN involves a homogeneous thickening of the capillary wall, seen with light microscopy in sections stained with hematoxylin and eosin or with periodic acid–Schiff reagent. By silver methenamine staining, early projections of the GBM between deposits may be detected in a characteristic spike-like configuration. Later lucencies may develop in the GBM as immune deposits are resorbed, resulting in some areas of the GBM appearing as double contours by silver methenamine staining.

Leukocyte infiltration is absent in glomeruli in MN, probably because chemotactic products of complement activation follow filtration forces into the urinary space rather than diffusing backward into the capillary lumen, and the intervening GBM prevents immune adherence mechanisms from being operative. Although similar deposits at other sites may induce proliferation of glomerular endothelial and, particularly, mesangial cells, podocytes in vivo seem terminally differentiated and rarely proliferate. As a result, the pathologic lesion of MN is characterized only by changes in podocytes and basement membrane without any associated glomerular hypercellularity.

The podocyte response to this form of injury includes effacement of foot processes visible only by electron microscopy. In general, there are no visible mesangial or endothelial cell abnormalities. The presence of significant mesangial hypercellularity suggests immune deposit formation in the mesangium and is more consistent with a secondary MN, such as class V lupus nephritis. In some patients with heavy proteinuria and progressive disease, glomeruli exhibit reduced podocyte numbers and areas of focal sclerosis that are similar to the appearance of idiopathic

focal segmental glomerulosclerosis (FSGS). These patients often have a more rapidly progressive course and a poor response to therapy. These sclerotic lesions may be a consequence of glomerular hypertrophy accompanied by an inability of the terminally differentiated podocytes to proliferate, leading to areas of denuded GBM, attachment to Bowman's capsule, and subsequent capillary collapse. As in all glomerular diseases, tubulointerstitial injury is common and correlates with both the renal function and the level of proteinuria. Some studies suggest that the long-term outcome correlates in general with the severity of the tubulointerstitial damage.

Immunohistology

The pattern of IgG staining in MN is characteristic and easily recognizable by immunohistology. Positive staining for IgG marks the finely granular subepithelial deposits, which are present on the outer surface of all capillary walls. The predominant IgG subclass in idiopathic MN is IgG4. Positive staining for IgG1 or IgG3, IgA, or IgM or significant staining in the glomerular mesangium suggests lupus as an underlying mechanism. Complement C3 is also present in about 50% of patients and usually reflects staining for C3c, a breakdown product of C3b that is rapidly cleared. Consequently, positive C3 staining probably reflects active, ongoing immune deposit formation and complement activation at the time of the biopsy, whereas the absence of C3 suggests that the process of forming deposits has ceased. When it is looked for, staining for C5b-9 is generally present as well, consistent with the proposed pathogenetic role of C5b-9 in this disease. C1 and C4 are often absent, indicating activation of complement primarily through the alternative pathway as a consequence of podocyte damage or downregulation of complement regulatory proteins expressed on the podocyte membrane.

Electron Microscopy

The presence of subepithelial electron-dense deposits by electron microscopy parallels IgG staining. In idiopathic MN, immune deposit formation occurs in a subepithelial distribution, and deposits are not seen in mesangial or subendothelial sites. These deposits in early stages of the disease process are homogeneous and may even be confluent in some areas with overlying podocyte foot process effacement and

little change in the underlying GBM (stage I). As the disease persists, there is projection of basement membrane material up between the deposits to form subepithelial spikes that can be detected by light microscopy with use of a silver methenamine stain and are easily visible by electron microscopy (stage II). Later, the spikes extend and the deposits may become surrounded by new basement membrane–like material (stage III). In stage IV disease, the basement membrane is overtly thickened, the deposits incorporated in it become more lucent, and the spikes are less apparent. The extent to which individual patients will exhibit these stages as sequential changes depends on the duration of the underlying immunopathologic process and its severity. Although these changes clearly reflect the severity and duration of disease, they do not correlate well with clinical manifestations or outcome.

Diagnosis and Differential Diagnosis

When the initial presentation includes the nephrotic syndrome, the differential diagnosis includes minimal change disease (MCD), FSGS, membranoproliferative glomerulonephritis (MPGN) type I and dense deposit disease (DDD), amyloidosis, light-chain deposition disease, lupus nephritis, and diabetic nephropathy. In the 20% to 25% whose initial presentation is asymptomatic proteinuria, the differential is even more extensive. Whereas clinical clues may increase the likelihood for one etiology over another, the etiology of the nephrotic syndrome is best determined by renal biopsy.

Patients presenting with clinical features including less than 3.5 g/day of proteinuria, no red cell casts, no hypertension, normal renal function, and no systemic features suggestive of a secondary cause have a relatively benign prognosis. If no renal biopsy is performed, these patients must be monitored because up to 50% may later develop nephrotic-range proteinuria, the majority within the first 2 years of presentation.

Secondary MN represents 20% to 30% of all cases; the most common causes are systemic lupus, hepatitis B, malignant neoplasms, and drugs. In addition to a careful history and physical examination, appropriate laboratory evaluation for

potential secondary causes should include a complement profile, antinuclear antibodies, hepatitis serology, chest radiography, stool testing for occult blood, mammography in women, and prostate-specific antigen testing with or without digital rectal examination in men. In women between the ages of 20 and 50 years, a high index of suspicion is warranted for underlying lupus. This diagnosis can be particularly difficult to make because the majority of these patients have no systemic symptoms and serologic markers of systemic lupus erythematosus are often absent. Membranous lupus accounts for 8% to 27% of cases of lupus nephritis.

In adults, regardless of age, malignant neoplasia is the most common secondary cause of MN. The colon, kidney, and lung are the most common primary sites, and in some patients, the tumor may not have been discovered at the time the patient presents with renal disease. Although it is hypothesized that antigens derived from the tumor account for deposit formation and injury in glomeruli, very few tumor-related antigens have actually been demonstrated.

Hepatitis B (HBV)-associated MN is also a very common secondary cause in countries where HBV is endemic. It can affect both adults and children who are chronic carriers of HBV (positive HBsAg, HBcAg, and usually HBeAg). This can occur with or without a history of overt liver disease. In children, HBV-associated MN most commonly presents as the nephrotic syndrome and usually follows a benign course. In adults, progressive renal impairment is a more common outcome. Hypocomplementemia is present in approximately 50% of cases of MN with HBV.

MN secondary to drugs usually resolves after discontinuation of the offending agent. The time to resolution, however, varies significantly from as early as 1 week (e.g., for NSAIDs) to several years for gold or d-penicillamine. Many other renal disorders have been seen in association with or superimposed on MN, including IgA nephropathy, FSGS, crescentic GN (anti-GBM disease, ANCA vasculitis), acute interstitial nephritis, and diabetic nephropathy.

Clinical Course, Outcomes, and Complications

The clinical course of MN varies widely. Spontaneous remissions in proteinuria have been reported in up to 30% of cases. As the severity of proteinuria at

presentation increases, the frequency of spontaneous remission appears to decrease. Female sex and lower grade (non-nephrotic) proteinuria at presentation are the only two features associated with a higher likelihood of spontaneous remission. This is likely to produce a bias in renal survival because the majority of studies reporting 10-year outcomes in untreated patients have included those with subnephrotic proteinuria (<3.5 g/24 h). For example, one study reported a 72% renal survival at 8 years for 100 untreated patients, but 37% of the patients were non-nephrotic at presentation and more than 50% had less than 5 g/day. In addition, deaths were excluded from the kidney survival analysis. Even so, there was a 25% ESRD rate by 8 years and almost 50% by 15 years. In summary, although the majority of MN patients do reasonably well long term, MN is still the second or third leading cause of ESRD among subjects with primary GN. What is still missing from most MN survival data is the much higher than expected (standard incidence ratio) death rate due to cardiovascular disease or thromboembolic events seen in patients who remain nephrotic. When another renal condition is superimposed on MN, there is often an associated acceleration in the rate of deterioration in renal function. The most common conditions to consider in this setting are drug-induced interstitial nephritis, superimposed anti-GBM disease, and renal vein thrombosis.

Predictors of Poor Outcome

Given the wide variation in the natural history of MN and the current lack of a serologic marker of disease activity, other clinical markers that predict individual outcome would be valuable. Both age and sex influence outcome, with male sex and increasing age associated with a higher risk for renal failure. However, both have limitations. Age seems to be related to the underlying pathologic process at the time of presentation rather than to the severity of disease because it does not influence rate of deterioration in function, and the sex of the patient seems more closely related to the severity of proteinuria at presentation rather than representing an independent risk factor for progression.

The severity of chronic changes seen on the biopsy specimen (i.e., degree of glomerulosclerosis, tubulointerstitial fibrosis, and vascular disease) has been

associated with a poor prognosis but more closely reflects initial GFR than the subsequent rate of renal functional deterioration. Other pathologic features, including the percentage of glomeruli with glomerulosclerosis and the configuration of the immune deposits (synchronic/single stage or heterogeneous/multistage) on electron microscopy, have also been suggested as predictors of both outcome and response to treatment but have not been validated in prospective studies. The degree of renal impairment at presentation has also been found to correlate with long-term renal survival, but a better and more sensitive predictor of long-term prognosis is the ongoing rate of renal function loss as measured by the decline of creatinine clearance over time. One of the best models to calculate risk takes into consideration the initial creatinine clearance, the slope of the creatinine clearance during a fixed period, and the lowest level of proteinuria during that observation period. This risk score assessment has a reported sensitivity of 60% to 89%, specificity of 86% to 92%, and overall accuracy from 79% to 87%.

The model predicts that patients with a normal creatinine clearance at presentation that remains stable during 6 months and with persistent proteinuria of less than 4 g/24 h have less than a 5% chance of progression, and only conservative treatment is recommended. In contrast, those patients with proteinuria that remains above 4 g but less than 8 g/24 h during the same time frame have a 55% probability for development of chronic renal impairment; and those with persistent proteinuria above 8 g/24 h have a 66% to 80% probability of progression to chronic kidney disease within 10 years.

Recently, other biomarkers including urinary α 1-microglobulin, β 2-microglobulin, IgM, and IgG have also been strongly associated with progression. These markers measured together at a single time point have a higher positive predictive value than proteinuria alone, but none has yet been validated in an independent data set.

Relapse from a complete remission occurs in approximately 25% to 40% of MN cases with an unpredictable time line. Relapses have been reported up to 20 years after the primary remission. However, the great majority of patients will relapse

only with subnephrotic-range proteinuria and will maintain stable long-term kidney function with conservative management alone. In contrast, the relapse rate is as high as 50% in those achieving only a partial remission. Achievement of either a complete or partial remission, however, significantly slows progression and increases renal survival. A recent review of 348 nephrotic MN patients documented a 10-year renal survival in patients with a complete remission of 100%; with partial remission, 90%; and with no remission, only 45%

Treatment

Nonimmunosuppressive Therapy

Conservative management is directed at control of edema, hypertension, hyperlipidemia, and proteinuria and is similar to that used for nephrotic syndrome of any etiology. Blood pressure control is important for both renal and cardiovascular protection. For patients with proteinuria of more than 1 g/day, the target for blood pressure is 125/75 mm Hg. Numerous studies have shown that angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are cardioprotective and can reduce proteinuria and slow progression of renal disease in both diabetic and nondiabetic chronic nephropathy patients. A recent meta-analysis of the largest renal protection trials using ACE inhibitors showed that the degree of protection is closely correlated to the degree of proteinuria reduction. None of these studies has focused on the specific effect of renin-angiotensin system (RAS) blockade in MN. In secondary analyses, the number with MN has been small, and although the use of ACE inhibitors has been associated with significant improvement in some series, their antiproteinuric effect was modest (<30% reduction in proteinuria) in others. When effective, the benefit of RAS blockade occurs early, usually within the first 3 months of initiation of treatment. Even patients at low risk for progression (proteinuria <4 g/24 h) should be treated with ACE inhibitors or ARBs because this may reduce proteinuria and offer additional renal protection with little chance of significant adverse effect. Patients must also follow a low-salt diet to achieve the maximum benefit from RAS blockade.

Proteinuria is also an independent risk factor for cardiovascular morbidity and mortality. When the proteinuria is in the nephrotic range, there is a clear increase in cardiovascular risk, with a threefold to fivefold increase in both coronary events and death rates in this population. Patients with significant proteinuria almost always have elevated serum cholesterol and triglyceride levels. Although it is not proven, we recommend the use of statins to reduce low-density lipoprotein cholesterol to 100 mg/dl (2 mmol/l) or lower. It is recommended that both RAS blockade and lipid control be initiated early in the MN patients, although reaching a goal of complete remission or even partial remission in patients at higher risk of progression (with persistent proteinuria >5 g/24 h) with conservative treatment alone is unlikely. Dietary protein intake may be restricted to 0.8 g/kg body weight per day of high-quality protein with additional dietary protein (gram per gram) to correct for urinary losses. Dietary protein restriction has been associated with reduced proteinuria (15% to 25%) and a slowing in renal disease progression but has never been shown to induce a complete remission or to add to effects obtained with RAS blockade. Protein restriction must be carefully monitored in nephrotic patients to avoid malnutrition. Patients with severe nephrotic syndrome are at increased risk for thromboembolic complications, and prophylactic anticoagulation has been shown in retrospective reviews to be beneficial in reducing fatal thromboembolic episodes in nephrotic patients with MN without a concomitant increase in the risk of bleeding. However, no randomized controlled trial has ever been done. Hence, there is no current consensus about prophylactic anticoagulation and no laboratory test that can predict with any accuracy such an event in any one patient. Certain clinical scenarios do have a higher likelihood of such an event and thus deserve more careful physician monitoring. These include patients with severe and persistent nephrotic syndrome (proteinuria >10 g/day and serum albumin <2.5 g/day). The majority of practicing nephrologists, however, will still wait until a primary thromboembolic event has occurred before using anticoagulants. Other agents that have been tried with modest effects in small numbers of patients include probucol, a lipid peroxidation scavenger, and high-dose

intravenous immune globulin, an agent with multiple effects on antibody-mediated tissue injury.

Immunosuppressive Therapy

Several regimens using a variety of immunosuppressive agents have been shown to be successful in reducing proteinuria in MN, but many questions remain unresolved: What should be the duration of conservative therapy while awaiting a spontaneous remission? How is it determined when to initiate immunosuppressive therapy? What is the most effective and safest of the available agents? How long should treatment be given before futility is assessed?

Corticosteroids

There have been three randomized controlled trials (RCTs) of corticosteroids in the treatment of idiopathic MN. The overall consensus has been no significant long-term beneficial effect on proteinuria, rate of disease progression, or renal survival. The use of oral corticosteroids as a single agent for the treatment of MN is therefore not recommended. The one exception may be the Asian population, in which long-term observational studies have indicated improvement in both proteinuria and renal function preservation with use of corticosteroids as monotherapy.

Cytotoxic Agents Combined with Corticosteroids

In patients at moderate risk of progression, a significant benefit has been described with the combination of a daily oral dose of a cytotoxic agent (either cyclophosphamide or chlorambucil) alternating monthly with corticosteroids (methylprednisolone pulses 3×1 g, intravenously, at months 1, 3, and 5; and oral prednisone, 0.5 mg/kg on alternate days for 6 months); complete or partial remission of the nephrotic syndrome was seen in close to 80% of treated patients, a threefold to fourfold increase compared with the control group. Both progression rate and renal survival were significantly improved. Both treatment regimens were remarkably safe, although relapses were seen within 2 years in 30% of the treatment group. Very similar results were obtained in an RCT using this same regimen to treat MN patients of Asian ethnicity. Because the results of a cyclophosphamide-based regimen were similar to one based on chlorambucil, cyclophosphamide is most commonly used

because of a better safety profile. The only RCT using cytotoxic agents in patients at high risk of progression (mean creatinine, 2.3 to 2.7 mg/day; proteinuria, 11 g/day) noted no statistical differences in proteinuria, remission rate, or rate of decline of renal function between the corticosteroid-alone and the combined treatment group. In older, smaller studies, these cytotoxic agents, even with appropriate adjustments in dose, have produced variable effects on outcome and significant adverse events in a high percentage of patients. The most recent longer term studies in high-risk patients prospectively studied 65 patients with MN and serum creatinine concentration above 1.5 mg/dl treated with oral cyclophosphamide for 12 months and corticosteroids (same scheme as before). Renal survival was 86% after 5 years and 74% after 7 years. Partial remission occurred in 56 patients. The relapse rate was similar to earlier cytotoxic-corticosteroid regimens, 30% at 5 years. Treatment-related complications were significant and occurred in two thirds of patients, mainly bone marrow suppression and infections. The majority of adverse events could be handled by dose reduction, although some required permanent discontinuation of treatment. A recent meta-analysis showed that the use of alkylating agents was associated with higher remission rates (partial or complete remission), but no statistical benefit of cytotoxic drug therapy was demonstrated compared with placebo in rates of ESRD or death. The difficulty with this type of analysis is that the endpoint of renal survival is far beyond the termination point of most clinical trials.

In summary, cyclophosphamide used in combination with corticosteroids appears to be effective in the treatment of patients with nephrotic-range proteinuria due to idiopathic MN, especially if renal function is well preserved at the time of initiation of therapy. This combination may work even in those with impaired renal function, but the supporting data are much less compelling, adverse effects are higher, and the likelihood of benefit is reduced, especially in patients with advanced renal failure (GFR <30 ml/min). The favorable effects are maintained beyond the 1-year treatment period, but relapse rates approach 35% by 2 years. The adverse effects of cyclophosphamide when it is used long term are the major drawbacks to the universal application of this form of therapy. These include increased susceptibility to

infections, anemia, thrombocytopenia, nausea, vomiting, sterility, and, in the long-term, malignant disease. Recent evidence suggests that the risk of cancer is accelerated at a much lower level of exposure than previously considered; the standardized incidence ratio was increased in a number of malignant neoplasms with total cyclophosphamide exposure as low as 36 g (approximately equivalent to 100 mg/day for 1 year).

Calcineurin Inhibitors

Early uncontrolled studies using cyclosporine suggested an initial benefit but a high relapse rate. Cyclosporine may reduce proteinuria not only through its immunosuppressive effects but also by direct effects on the podocyte. In a single blind RCT, 51 patients with corticosteroid-resistant MN were treated for 6 months with cyclosporine (2 to 5 mg/kg) plus low-dose prednisone and compared with placebo plus prednisone.[49] Complete remission and partial remission were seen in 75% of cyclosporine-treated patients versus 22% of the placebo controls. Cyclosporine was well tolerated, and no adverse events requiring discontinuation of treatment were seen. However, relapses were common at 45% within 1 year after discontinuation of treatment. There has been only one RCT using cyclosporine in patients with high-grade proteinuria and progressive renal failure. A reduction in both proteinuria and rate of loss of renal function was seen with cyclosporine compared with placebo that was sustained for up to 2 years after the drug was discontinued. Treatment with longer term cyclosporine (i.e., 12 months) has resulted in a higher rate of complete remission and partial remission (84%). In addition, persistence of remission was maintained with doses of cyclosporine as low as 1 to 2 mg/kg, although relapses were still common if the cyclosporine level fell below 100 ng/ml. Time to remission with use of cyclosporine varies from a few weeks to several months. This suggests that if no significant reduction in proteinuria (<40%) is noted within 3 to 4 months, a change in therapy may be warranted.

Significant adverse effects seen with this agent include hypertension, gingival hyperplasia, gastrointestinal complaints, muscle cramps, and, most important, nephrotoxicity, which is dose and duration of treatment dependent. Patients at

particular risk are those with initial impaired renal function, especially if it is accompanied by extensive intrarenal vascular disease or chronic tubulointerstitial damage on biopsy. The relapse rate after stopping of the drug, however, approached 50% by the end of 2 years of follow-up.

Mycophenolate Mofetil

Studies using mycophenolate mofetil (MMF) in MN have produced conflicting results. However, even in the most optimistic study, although initial response was high (used in combination with prednisone), the relapse rate within months approached 50%. The most pessimistic study (the only RCT), in comparison to conservative management only, showed no difference in remission rates. Follow-up time was limited and the numbers in the latter study were small, but the reason behind the marked differences between these two trials is not obvious. In a small retrospective study in corticosteroid-resistant Asian MN patients, a higher response with MMF was observed, partial remission rate approaching 50%, possibly related to the ethnic characteristics of the population studied. The role of MMF in the treatment of MN is currently uncertain.

Rituximab

In several pilot studies, rituximab, despite substantial variations in the dose and timing of the drug, consistently reduced proteinuria by 60% to 70%. The relapse rate, however, may be significantly less than with calcineurin inhibitor or cytotoxic-based regimens. The best predictor of which patients will respond to rituximab is unknown, although the absence of interstitial disease on the biopsy specimen may improve response rate. An RCT needs to be done before widespread use of this agent is advocated, given its very high cost and unknown long-term toxicity in this disease.

Eculizumab

Eculizumab is a humanized anti-C5 monoclonal antibody designed to prevent the cleavage of C5 into its proinflammatory byproducts. An RCT in 200 patients with MN that compared this agent with placebo during a total of 16 weeks showed no significant effect on proteinuria or renal function, but effective complement inhibition was not achieved.

Adrenocorticotrophic Hormone

Two small studies have reported the use of an intramuscular long-acting synthetic form of adrenocorticotrophic hormone (ACTH) in MN. The exact mechanism of action of this agent in MN is unknown but likely unrelated to corticosteroid effects because corticosteroids alone are not beneficial in MN. A dose escalation study showed prolonged remission in the majority of MN patients when they were treated with ACTH 1 to 2 mg weekly intramuscularly for a year. In a small RCT, ACTH, with use of a similar dose regimen, was compared with a standard cytotoxic plus corticosteroids regimen. The remission rate was equal in the two groups, between 80% and 90%, but the relapse rate in the ACTH group was lower (14% versus 30%) after a follow-up of 1 year. Side effects of ACTH were few and included fluid retention, sleep disturbances, and bronze discoloration of the skin. Potassium supplementation was required in the majority of patients in one trial.

Treatment Summary

Control of proteinuria, specifically achieving either a complete or partial remission of the nephrotic syndrome, is associated with prolonged renal survival and a slower rate of renal disease progression in MN. Supportive or conservative care should be given in all cases first and should include the use of diuretics, antihypertensive agents such as ACE inhibitors and ARBs (potentially renal protective), and lipid-lowering agents. In patients who require disease-specific therapy, the choice of agents remains controversial.

Both cytotoxic-corticosteroid combinations and calcineurin inhibitors have proved effective in reducing proteinuria in moderate or high-risk MN patients. The physician, in concert with the patient, must take into account all factors related to risk-benefit to arrive at the best decision about which of these therapies should be used first. These approaches are not mutually exclusive and can be used in sequence if the first one chosen does not succeed in inducing a remission or adverse effects are untenable. Ideally, one should leave 2 to 3 months between treatment regimens to help immune system recovery. Alternatively, a second course of the same immunosuppressive regimen could be used, but at the potential cost of cumulative

toxicity, or a switch to another treatment regimen may be indicated if the patient's risk profile has changed. Preliminary evidence on the use of rituximab or long-acting ACTH suggests that both may be effective, and safer, than our current regimens, but both need to be assessed further before being widely recommended. Patients with severe renal impairment (GFR <30 ml/min) are less likely to benefit from immunosuppressive therapy, and the risks of treatment may favor conservative therapy as the best option for these patients

3.1.1.2.2 Membranoproliferative Glomerulonephritis

Membranoproliferative glomerulonephritis (MPGN), or mesangiocapillary glomerulonephritis (GN), is characterized by diffuse proliferative lesions and widening of the capillary loops, often with a double-contoured appearance. MPGN may be idiopathic or secondary to chronic infections, cryoglobulinemia, or systemic autoimmune disorders that result in aberrant immune complex formation.

Three types of MPGN have been described. Type I is characterized by immune deposits in the subendothelial space (capillary wall thickening) and in the mesangium. Type II, also known as dense deposit disease (DDD), is defined by dense deposits within the mesangium and in the basement membranes of the glomeruli, tubules, and Bowman's capsules. On the basis of its unique ultrastructural appearance and the varied morphologic patterns of injury, DDD is best considered a disease entity separate from MPGN. We include DDD in this chapter because of the extensive literature that identifies it as MPGN type II. Type III is a variant of type I, characterized by extensive subendothelial and subepithelial electron-dense deposits. This process is accompanied by alterations and remodeling of the lamina densa of the glomerular basement membrane (GBM) and newly elaborated lamina densa-like material.

Etiology and Pathogenesis

Although it is frequently idiopathic, the histologic diagnosis of MPGN should provoke a search for secondary causes. In children and young adults (<30 years) with DDD (MPGN type II), the disease is often associated with the presence of nephritic factors, which are IgG or IgM autoantibodies that bind to and stabilize the C3

convertase of the alternative (C3bBb) or classical (C4b2b) pathway, thus resulting in continued complement activation with a depletion of various complement components. In older adults (>30 years), MPGN type I is frequently associated with cryoglobulinemia and hepatitis C virus (HCV) infection.

MPGN type I is most likely to occur in the setting of chronic immune complex diseases, for example, when the host cannot eliminate a foreign antigen effectively despite a humoral response. This may account for the MPGN observed with chronic blood-borne viral (hepatitis C and hepatitis B), bacterial (endocarditis, infected ventriculoatrial shunt), and malarial infections. A histologic pattern resembling MPGN can also be observed in chronic immune complex diseases associated with autoimmune diseases such as lupus. Chronic immune complex disease and MPGN may also occur if the host has a defect in clearing immune complexes, as in complement deficiency, or when the reticuloendothelial system is impaired, as occurs with liver or splenic disease. Hereditary deficiencies of the classical pathway of complement (C1q, C2, C4) and of C3 are associated with the development of MPGN in addition to predisposing to lupus and bacterial infections. MPGN type I also is associated with some malignant neoplasms (especially chronic lymphocytic leukemia and lymphoma).

MPGN type I results from the glomerular deposition of immune complexes from the circulation or from circulating antigens and immunoglobulins that deposit in the glomerulus to form immune complexes in situ. These complexes preferentially localize in the mesangium and subendothelial space of the capillary walls. Once localized, the immune complexes typically activate complement through the classical pathway, leading to the generation of chemotactic factors (C5a), opsonins (C3b), and the membrane attack complex (C5b-9) as well as low C3 and C4 serum levels. In some patients, complement is activated by the C4 nephritic factor; in other cases, activation of complement may occur by the mannose-binding lectin pathway. Mannose-binding lectin, a lectin that binds IgG and activates complement, has been localized to the immune deposits of some patients with MPGN type I. Complement activation results in the release of chemotactic factors that promote platelet and

leukocyte accumulation. Leukocytes release oxidants and proteases, mediating capillary wall damage and proteinuria and a fall in the glomerular filtration rate. Cytokines and growth factors released by both exogenous and endogenous glomerular cells lead to mesangial proliferation and matrix expansion.

The pathogenesis of DDD is intricately linked to continual overactivation of the alternative pathway of complement. This can occur in humans through a dysfunctional constitutive inhibitor of alternative pathway activation (e.g., of factor H, see later discussion), such that there is unregulated and sustained activity of C3, or through the presence of an IgG or IgM autoantibody (C3 nephritic factor [C3Nef]) that binds the alternative pathway C3 convertase (C3bBb) and prevents its inactivation by factor H. The consequence is a low C3 level but normal circulating levels of C2 and C4 and terminal (C5 through C9) complement pathway components. The most commonly encountered defect in DDD is the C3Nef interaction with C3 convertase. C3Nef, although it is highly associated with DDD, is not specific for DDD and may also be encountered in some patients with MPGN type I and even in some healthy individuals. The presence or absence of C3Nef therefore does not have clinical prognostic significance and does not independently predict recurrence of disease in allograft kidneys. Likewise, C3 levels in serum also have no significant prognostic importance. Most patients with acquired partial lipodystrophy, an abnormality associated with DDD, also have circulating C3Nef and low serum C3 levels. The lipodystrophy results from complement-dependent loss of the adipocyte, mediated by activation of complement on the adipocyte surface due to both the presence of C3Nef and the overproduction by the adipocyte of adipisin, a protein that is identical to factor D of the alternative pathway.

Mutations in regulatory proteins of the alternative pathway also can lead to overactivity of C3 and DDD. Genetic mutations in factor H, a cofactor that normally inhibits continued activation of C3 convertase, have been found in patients with DDD and in a spontaneous porcine model of this disease. Factor H-deficient mice also develop GN with some features of DDD, which can be blocked by creation of additional mutations in components of the alternative pathway (e.g., factor B) that

prevent further downstream activation of this pathway. Although most patients with DDD do not have factor H gene mutations, genetic population studies show an association of DDD with individuals having several alleles of both complement factor H gene and the complement factor H-related 5 gene. One of these is the tyrosine-402-histidine (Y402H) polymorphism, which is present in both DDD and age-related macular degeneration, a condition characterized in part by ocular drusen bodies, which are also found in many patients with DDD.

The pathogenesis of MPGN type III is similar to that of MPGN type I, except that certain characteristics of the immune complexes may favor localization in the subepithelial space. MPGN type III patients exhibit depressed levels of properdin, C3, C5, and one or more of the other four terminal components and elevated levels of C5b-9. This rare disease was mapped to chromosome 1q31-32 in an Irish family.

Cryoglobulins are immunoglobulins that precipitate in the cold. They are categorized as types I through III. The mixed cryoglobulinemias (types II and III) are most commonly associated with MPGN; these have been strongly associated with chronic HCV infection in up to 80% to 90% of the patients with cryoglobulinemic vasculitis. The non-HCV cases have been associated with other infections (chronic hepatitis B, bacterial endocarditis), collagen-vascular diseases (systemic lupus), and other immunologic disorders (notably poststreptococcal GN). Chronic lymphocytic leukemia may also be associated with cryoglobulinemia and MPGN; interestingly, some of these patients are also infected with HCV and have a circulating monoclonal IgM- κ . Chronic lymphocytic leukemia and lymphoma also have been associated with MPGN in the absence of cryoglobulinemia.

How chronic HCV infection causes cryoglobulinemia is not entirely known. Most patients with HCV infection and cryoglobulinemia have an IgM- κ monoclonal antibody with rheumatoid factor activity. This rheumatoid factor can be found with anti-HCV IgG and HCV RNA in the cryoprecipitates. It has been postulated that the IgM is produced by dysregulated B cells infected with HCV. Cryoglobulinemia does not develop until many years (often >10 years) after HCV infection; but by the time chronic active hepatitis or cirrhosis develops, as many as 30% to 40% of patients will

have circulating cryoglobulins or other evidence of cryoglobulinemia if it is searched for. Most of these patients will not develop renal disease, but in some patients, possibly those in whom the cryoglobulins have an affinity for fibronectin, the cryoglobulins containing HCV antigens will deposit in glomeruli.

Specific HCV-related proteins have been detected in glomeruli, tubulointerstitium, and vessels in patients with cryoglobulinemic HCV-positive MPGN, although difficulties with the antisera available to detect HCV render such findings controversial. In these studies, glomerular HCV deposits have displayed two different patterns:

- a linear homogeneous deposition along glomerular capillary walls, including endothelial and subendothelial spaces;
- a granular appearance with distinct deposits in mesangial and paramesangial areas. IgG, IgM, and C3 deposits display features comparable to those of HCV RNA and core protein deposits, suggesting that in cryoglobulinemic HCV-positive MPGN, deposits consist of HCV containing immune complexes that may directly contribute to renal damage.

Further pathogenetic insight will likely be provided by new mouse models, including the transgenic thymic stromal lymphopoietin (TSLP) mouse, which develops mixed cryoglobulinemia and MPGN type I, and a DDD model, the factor H-deficient mouse

Epidemiology

In North America and Europe, MPGN (types I and III) and DDD constitute less than 5% of all primary glomerulonephritides. MPGN accounts for 5% to 10% of primary renal causes of nephrotic syndrome in children and adults. It occurs equally in males and females and in the United States is relatively more common in Caucasians than in African Americans. MPGN presenting in childhood (primarily between the ages of 8 and 14 years) includes types I and III MPGN and DDD and is frequently idiopathic or associated with nephritic factors. By contrast, MPGN presenting in adults (typically older than 18 years) is usually type I or type III and is commonly associated with cryoglobulinemia and HCV infection. The prevalence of

MPGN type I is decreasing in Europe, presumably because some chronic infections are becoming less common. On the contrary, in the Middle East (Saudi Arabia), South America (Peru), and Africa (Nigeria), MPGN type I is still quite common because of its association with chronic bacterial, viral, and parasitic infections. The disease may be familial in rare cases, and different histologic lesions may occur in family members (i.e., type I in one member and type III in another).

Clinical Manifestations

MPGN and DDD may present as microscopic hematuria and non-nephrotic proteinuria (35%), as nephrotic syndrome with minimally depressed renal function (35%), as a chronically progressive GN (20%), or with rapidly deteriorating renal function with proteinuria and red cell casts (10%). Systemic hypertension is present in 50% to 80% of patients, and it may occasionally be so severe that the presentation may be confused with that of malignant hypertension.

Pediatric Population

MPGN type I in children and young adults is usually idiopathic and presents as a primary kidney disease without systemic manifestations. Asymptomatic Japanese children diagnosed as a consequence of a urinalysis screening program at school had lower blood pressure, proteinuria, and serum creatinine concentration compared with subjects who were diagnosed after presenting with symptoms. Thus, early identification of the disease by urinary screening may allow early treatment.

DDD affects females slightly more frequently than males (3:2). It is usually diagnosed in children who are between 5 and 15 years old. Patients present with hematuria, proteinuria, hematuria plus proteinuria, acute nephritic syndrome, or nephrotic syndrome.

Adult Population

MPGN in adults is also often limited to the kidney; but in patients with DDD, partial lipodystrophy that preferentially involves the face and upper body may be present. It may precede the renal disease by many years. Some patients with DDD will also have mild visual field and color defects and prolonged dark adaptation with mottled retinal pigmentation (drusen bodies) and sometimes deterioration of vision.

Eye examinations, including dark adaptation, electroretinography, and electro-oculography, should be performed on first presentation and annually thereafter. Indocyanine green angiography of the retina may reveal dense deposits in the ciliary epithelial basement membrane (abnormal fluorescent dots) and choroidal neovascularization. When MPGN is associated with systemic cryoglobulinemia, patients usually have chronic HCV infection and present with the triad of weakness, arthralgias, and purpura. The arthralgias are only rarely accompanied by arthritis, are usually symmetric, and classically involve the knees, hips, and shoulders. The purpura is usually painless, palpable, and nonpruritic; it occurs in “crops” that last 4 to 10 days and preferentially localizes to the extremities. Other manifestations may include ulcerative, vasculitic lesions that classically involve the lower extremities and buttocks, Raynaud's phenomenon, digital necrosis, peripheral neuropathy, hepatomegaly, and, rarely, signs of cirrhosis (clubbing, spider angiomas, ascites). Although most patients with cryoglobulinemia have a chronic waxing and waning course, occasional patients may have a more fulminant presentation, with congestive heart failure (from an HCV-induced cardiomyopathy), infiltrates in the lung from deposition of cryoglobulins, pulmonary hypertension, severe systemic hypertension, or mesenteric ischemia. In view of the conditions associated with MPGN, signs of bacterial infection, viral infection, systemic lupus, malignant disease, and chronic liver disease should be sought.

Laboratory Findings

MPGN is often associated with depressed complement levels (C3 and total hemolytic complement [CH50]). In MPGN type I and in cryoglobulinemic MPGN, the classical pathway is often activated (low C3, low C4, and low CH50); in DDD, the alternative pathway is activated (low C3, normal C4, and low CH50); and in type III, C3 is generally low in association with a depression of terminal complement components (C5 through C9). C3Nef activity, strongly but not exclusively associated with DDD, is usually detected in plasma by the hemolytic test or the C3NeF IgG solid-phase assay. The presence of rheumatoid factors or cryoglobulins should prompt testing for anti-HCV antibody and HCV RNA. However, MPGN can be

associated with HCV infection in the absence of cryoglobulinemia or rheumatoid factors. Failure to detect the cryoglobulins may result from improper handling of specimens or may occur because the cryoglobulinemia was transient; however, in some patients (especially in renal transplant recipients), test results for cryoglobulinemia may be persistently negative. Clinical or laboratory evidence of liver disease should prompt a search for causes of chronic liver disease, including hepatitis C, hepatitis B, and, if appropriate, rare entities such as schistosomiasis and α 1-antitrypsin deficiency.

DDD accounts for less than 20% of cases of MPGN in children and a very low percentage of cases in adults. It is estimated to affect two to three people per million.

Pathology

By light microscopy, MPGN type I is classically described as hypercellular because of both the influx of circulating leukocytes and intrinsic glomerular cell proliferation (typically mesangial cells), leading to a lobular appearance in some cases. Accumulation of extracellular material, predominantly matrix, contributes to the frequent mesangial expansion. The glomerular appearance can range from markedly hypercellular to predominantly sclerotic. In its most advanced form, sclerosis can be manifested as nodules indistinguishable from diabetic nodular mesangial sclerosis. Silver stain often shows a double contouring of the GBM (“tram tracks”) as a result of the interposition of mesangial cells, leukocytes, or endothelial cells in the capillary wall with the synthesis of new basement membrane material. Monocytes and macrophages are commonly present in the glomerulus and the periglomerular areas.

DDD is characterized by dense deposits within the mesangium and the basement membranes of the glomeruli, tubules, and Bowman's capsules, often visible with eosin and periodic acid–Schiff stains but characteristically identified by electron microscopy. Whereas glomerular changes similar to those of MPGN type I were the most common histopathologic findings in a study in DDD, another study identified a mesangial proliferative pattern of injury as most common (45% of patients). Other histopathologic patterns identified in this latter series included MPGN (25%), acute

proliferative and exudative GN (12%), and crescentic GN (18%); a few could not be readily classified (3%). This histologic heterogeneity of DDD, frequently manifested with a histopathologic pattern other than that of MPGN, and its unique ultrastructural appearance (described later) and unique pathogenesis provide the basis for separation of this entity from its historic classification as a type of MPGN. As in most glomerular diseases, the presence of a significant number of crescents portends a poor prognosis; the prognostic significance of the other glomerular injury patterns is unclear. The hallmark of MPGN type III is the interruption of lamina densa associated with subendothelial and subepithelial deposits, often confluent, and interspersed with multilayers of new lamina densa. Type I and type III MPGN form a morphologic continuum and thus are not always separable by light microscopy.

Immunofluorescence in MPGN type I and type III frequently shows the deposition of IgM, IgG, and C3 in a granular capillary wall distribution, although the immunoglobulin deposits may be scant. Staining for C3 in a peripheral (lobular) pattern involving capillary walls and mesangial areas is the most constant and strongest pattern; staining for classical pathway complement components (C1q, C4) may also be seen in MPGN type I. In DDD, C3 but neither classical complement pathway components nor immunoglobulins are detected; this helps distinguish it from other types of injury with an MPGN pattern. The C3 stain is thought to bind to an unidentified substrate at the surface of the dense deposits, which occasionally gives an appearance of tram tracks or mesangial rings.

By electron microscopy, discrete immune deposits can be observed in the subendothelial portions of the capillary walls and mesangial regions in MPGN type I, often in association with platelet and leukocyte infiltration. The deposits are often discrete but may be confluent in their involvement of the capillary wall. They can be small and sparse or large and numerous such that they are visible by light microscopy. A separation of the endothelium from the GBM can occasionally be observed, usually with some synthesis of new basement membrane material under endothelial cells that have detached from the original basement membrane. Between

these layers (old and new) of basement membranes, interposed cells of mesangial, endothelial, or leukocyte origin as well as immune deposits and matrix may be found.

In DDD, electron microscopy shows replacement of large sections of the GBM with an extremely electron-dense band of homogeneous material, the identity of which remains unknown. Involvement of mesangial regions, Bowman's capsules, and tubular basement membranes by the deposits is common.

Perhaps 15% of MPGN cases demonstrate both subendothelial and subepithelial deposits associated with minute disruptions of the lamina densa and newly elaborated lamina densa-like material (MPGN type III). There can be a continuum of subepithelial deposits in MPGN type I and type III from none or scanty to numerous, making it difficult to separate all cases into type I (scanty or no subepithelial deposits) or type III (numerous deposits) categories. After a number of years of normocomplementemia, the type III lesions can disappear, but this not inevitable.

Cryoglobulinemic MPGN may appear histologically identical to MPGN type I. However, the cryoprecipitates can occasionally be observed by light microscopy as intracapillary hyaline-like deposits, and there is often a more pronounced infiltration of macrophages within capillary lumina. Electron microscopy may also show highly organized microtubular or finely fibrillar structures consisting of the precipitated cryoglobulins.

Diagnosis and Differential Diagnosis

MPGN is diagnosed by renal biopsy in patients presenting with nephrotic or non-nephrotic proteinuria, especially when it is accompanied by microhematuria. By light microscopy, other entities may appear histologically similar, including poststreptococcal GN, the thrombotic microangiopathies, paraproteinemias, and fibrillary GN. Immunofluorescence and electron microscopy are critical for separating these diseases. Systemic lupus usually can be eliminated by serologic testing. Other useful tests are serum C3, C4, CH50, total hemolytic activity of the alternative complement pathway (APH50), and factor H levels. Low complement levels can also be observed in atheroembolic renal disease (low C3 with

eosinophilia), in thrombotic microangiopathy, in chronic liver disease (because of decreased synthesis), and in several glomerular diseases including systemic lupus (low C3 and C4) and poststreptococcal GN (low C3). The detection of C3NeF activity in plasma suggests DDD, but C3NeF can also be identified in a significant proportion of patients with MPGN type I and even in healthy individuals. In cases of otherwise idiopathic DDD, screening for mutations of factor H gene is recommended.

Natural History

Idiopathic MPGN in childhood has a relatively poor prognosis, with 40% to 50% of untreated patients progressing to renal failure during 10 years. Idiopathic MPGN in adults also carries an unfavorable prognosis. Five years after biopsy, 50% of patients either die or need renal replacement therapy (dialysis or transplantation). This proportion increases to 64% after 10 years. Risk of progression increases with elevated creatinine, nephrotic proteinuria, and severe hypertension or if a biopsy specimen shows more than 50% crescents or marked interstitial fibrosis.

Transplantation

The severity of crescent formation in native kidney biopsy specimens has predictive value for recurrence of disease in subsequent renal allografts. For further discussion of recurrent MPGN and DDD, refer to Chapter 104. Systemic activation of the complement system makes recurrence more likely. HCV-associated MPGN can also occur de novo or recur in renal transplant recipients and after liver transplantation.

Treatment

The initial approach to MPGN aims at identification of the etiology, if possible, and initiation of supportive antiproteinuric and antihypertensive measures.

Idiopathic Membranoproliferative Glomerulonephritis in Childhood

Some studies that primarily used historical or nonrandomized controls demonstrated a benefit of alternate-day corticosteroids in childhood MPGN, particularly with administration in the first year of presentation. Although these data are not definitive, we recommend an initial corticosteroid treatment in this population. For children with MPGN with moderate proteinuria (<3 g/day) and

normal renal function, we administer prednisone (40 mg/m²) on alternate days for 3 months. In patients with nephrotic syndrome or impaired renal function, this dose of corticosteroids is administered for 2 years. In case of reduction of proteinuria or improvement of renal function, prednisone is tapered to a maintenance dose of 20 mg on alternate days for 3 to 10 years. Treatment may be associated with a reduction in hematuria (80%), partial or complete reduction of proteinuria (25% to 40%), and better preservation of renal function (80% at 10 years versus 50% in historical controls). The most important side effects are exacerbation of hypertension, growth retardation, weight gain, and obesity. If no benefit is seen after 1 year of treatment, corticosteroids should be withdrawn and supportive therapy only continued. Responses to alternate-day corticosteroids are superior in children with type I MPGN, whereas children with type III MPGN are more likely to have a progressive reduction in renal function, slower reduction of serum C3, more persistent urinary abnormalities, and more frequent relapses.

In children with DDD, corticosteroids and calcineurin inhibitors lack efficacy. Removal of C3NeF from the serum through plasma exchange improved serum creatinine in only a few cases. The utility of immunosuppressive agents such as mycophenolate mofetil (MMF) has not been established. Plasma infusion with the use of fresh frozen plasma or recombinant factor H can be an effective therapy in patients with DDD secondary to pathologic mutations of factor H gene (CFH). This therapy replaces deficient factor H with normal factor H, correcting the complement defect.

Idiopathic Membranoproliferative Glomerulonephritis in Adults

For patients with normal renal function and asymptomatic non-nephrotic-range proteinuria, no specific therapy is necessary. Close follow-up every 3 to 4 months is recommended. In patients with nephrotic syndrome and normal or impaired renal function, a 3- to 6-month course of corticosteroids (prednisone 1 mg/kg body weight per day) may be prescribed. If there is considerable reduction of proteinuria, corticosteroids may be continued at the minimal effective dose. If no response is

observed within 3 months, corticosteroids should be stopped; treatment with cyclosporine, tacrolimus, or MMF has been recommended.

Hepatitis B Virus–Associated Membranoproliferative Glomerulonephritis

In hepatitis B virus (HBV)–associated MPGN, treatment with antivirals aimed at eradication of HBV (interferon, lamivudine) is the recommended initial treatment. Immunosuppressive agents are discouraged because they promote further HBV replication and occasional deterioration of hepatic function.

Hepatitis C Virus–Associated Membranoproliferative Glomerulonephritis and Cryoglobulinemia

Treatment options in mixed cryoglobulinemia with renal involvement include corticosteroids, cytotoxic drugs such as cyclophosphamide, and parenteral administration of interferon alfa alone or in association with ribavirin. Parenteral interferon alfa often improves extrarenal manifestations in close association with reduced levels of viremia, but relapse is common after cessation of therapy. The current treatment of choice in patients with HCV-associated MPGN or cryoglobulinemic MPGN with moderate proteinuria and nonrapid but progressive renal failure is standard interferon alfa (3 MU three times per week) or pegylated interferon alfa (1.5 µg/kg per week) and ribavirin, adapting the dose to the creatinine clearance or to a trough plasma concentration of 10 to 15 mmol/l. The anti-HCV therapy should be prolonged for 12 months.

High-dose interferon alfa may cause severe influenza-like symptoms, depression or psychosis, the development of hypothyroidism, and, rarely, the development of proteinuria (with a minimal change type of lesion). The most frequent serious adverse side effect of ribavirin is hematopoietic toxicity as well as hemolytic anemia and teratogenic effect. Rituximab is a human-mouse chimeric monoclonal antibody that reacts with the CD20 antigen (thereby selectively targeting B cells). It seems to be as efficient as cyclophosphamide in blocking cryoglobulin production, is better tolerated, and does not enhance HCV replication. It should be administered at a dose of 375 mg/m² per week for 4 weeks. Alternatively, oral cyclophosphamide may be used (2 mg/kg per day for 2 to 4 months). In patients with

nephrotic-range proteinuria or progressive renal failure, the anti-HCV therapy is the same. Moreover, treatment may include plasma exchange (3 liters of plasma three times per week for 2 or 3 weeks) and methylprednisolone pulses (0.5 to 1 g/day for 3 consecutive days) followed by oral prednisone 60 mg/day with slow tapering during 2 to 3 months. Cryofiltration, that is, double-filtration plasmapheresis with a cooling unit, has been introduced as a means to remove cryoglobulins.

Other Types of Membranoproliferative Glomerulonephritis

MPGN associated with other infections may respond to effective treatment of the underlying pathogenic agent. MPGN associated with α 1-antitrypsin deficiency has been reported to be cured by liver transplantation, which cures the genetic defect. MPGN associated with malignant disease, such as B-cell lymphoma, may respond to effective treatment of the underlying cancer.

3.1.1.2.3 Mesangial Proliferative Glomerulonephritis without IgA Deposits

Mesangial proliferative glomerulonephritis (MesPGN) encompasses a heterogeneous collection of disorders of diverse and largely unknown etiology and pathogenesis that have in common a histologic pattern by light microscopy of glomerular injury characterized by mesangial proliferation. MesPGN is noted for a diffuse and global increase in mesangial cells, often accompanied by an increase in mesangial matrix. Other cells (e.g., monocytes) may also contribute to the hypercellularity.

Other forms of cellular proliferation that occur within the mesangial zones but are more focally and segmentally distributed are not included. These focal and segmental forms of proliferative glomerulonephritis (GN) (often accompanied by areas of segmental necrosis of the glomerular tufts and very localized crescents) may be a part of the evolutionary stages of an initially pure MesPGN, but they very often signify the presence of systemic disease processes, including systemic lupus erythematosus (SLE), Henoch-Schönlein purpura and IgA nephropathy, infective endocarditis, microscopic polyangiitis, Wegener's granulomatosis, Goodpasture's disease, rheumatoid vasculitis, and mixed connective tissue disease. On occasion, a lesion of focal and segmental proliferative GN is discovered in the absence of any

recognizable multisystem disease process and in the absence of IgA deposits (i.e., idiopathic focal and segmental proliferative GN). Such patients have a clinical presentation, course, and response to treatment that are similar to those described for pure MesPGN, but they are not discussed further in this section.

In “pure” MesPGN, the peripheral capillary walls are thin and delicate without obvious deposits, reduplication, focal disruptions, or cellular necrosis. The visceral and parietal epithelial cells, although occasionally enlarged, have not undergone proliferation. Crescents and segmental sclerosis should be absent in the pure disease. In addition, large deposits staining with periodic acid–Schiff or fuchsin in the mesangium should be absent, as they suggest IgA nephropathy or lupus nephritis. The tubulointerstitium and vasculature are usually normal, unless reduced renal function or hypertension is present or the patient is of advanced age.

On immunofluorescence microscopy, a wide variety of patterns are observed. Most commonly, diffuse and global IgM and C3 deposits are found scattered diffusely throughout the mesangium in a granular pattern (so-called IgM nephropathy), but isolated C3, C1q, or even IgG deposits may also be seen. If IgA is the predominant immunoglobulin deposited, the diagnosis is IgA nephropathy. Not uncommonly, no immunoglobulin deposits are found at all. On electron microscopy, the number of mesangial cells is increased, with an occasional infiltrating monocyte or polymorphonuclear leukocyte. The amount of mesangial matrix is commonly diffusely increased. Electron-dense deposits within the mesangium can be seen in many cases, particularly those with immunoglobulin (IgG, IgM, or IgA) deposits on immunofluorescence microscopy.

Very large mesangial or paramesangial electron-dense deposits suggest IgA nephropathy even if immunofluorescence microscopy is not available. Subendothelial and subepithelial deposits are not seen. If present, they suggest a postinfectious etiology or underlying lupus nephritis. Deposits of multiple immunoglobulin classes identified by immunohistology and large numbers of tubuloreticular inclusions on electron microscopy suggest underlying lupus nephritis. The clinical presentation of MesPGN is varied, although persistent or recurring microscopic or macroscopic

hematuria with mild proteinuria is most common. Nephrotic syndrome with heavy proteinuria is a less frequent initial presentation but is seen more frequently in association with diffuse mesangial IgM deposits (IgM nephropathy) or C1q deposits (C1q nephropathy). Pure MesPGN is a rather uncommon lesion (<5%) in patients diagnosed with idiopathic nephrotic syndrome. Renal function and blood pressure are usually normal, at least initially. Serologic studies are generally unrewarding. Serum C3 and C4 complement components and hemolytic complement activity (CH50) are normal. Assay results for antinuclear antibody (ANA), antineutrophil cytoplasmic autoantibody (ANCA), anti-glomerular basement membrane (anti-GBM) autoantibody, and cryoimmunoglobulins are negative. Nevertheless, these studies should be performed in most patients to exclude known causes. MesPGN can also be a finding in resolving postinfectious (poststreptococcal) GN. Isolated C3 deposits with scanty subendothelial or subepithelial (hump-like) deposits on electron microscopy may be seen in this situation.

Mesangial Proliferative IgM Nephropathy

IgM nephropathy is characterized by diffuse and generalized glomerular deposits of IgM often accompanied by C3. Mesangial electron-dense deposits are also observed. On light microscopy, a picture of pure MesPGN is observed. Patients may present with recurring macroscopic hematuria and proteinuria, the latter in the nephrotic range in as many as 50% of patients. Persisting abnormalities and a poor response to corticosteroids or immunosuppressive therapy are often seen. As many as 50% of patients will eventually progress to typical focal and segmental glomerulosclerosis and, if unresponsive to corticosteroids, will slowly develop chronic kidney disease (CKD) and end-stage renal disease (ESRD). The etiology and pathogenesis are unknown.

Mesangial Proliferative Glomerulonephritis Associated with Minimal Change Disease

MesPGN may also be a part of the spectrum of minimal change disease (MCD)–focal segmental glomerulosclerosis (FSGS) lesions. Distinct mesangial hypercellularity superimposed on a lesion of MCD (diffuse foot process effacement

seen on electron microscopy) may point to a greater likelihood for corticosteroid unresponsiveness and an eventual evolution to the FSGS lesion.

Natural History of Mesangial Proliferative Glomerulonephritis

The natural history of MesPGN is quite varied, undoubtedly the result of etiologic heterogeneity. In many patients, a benign course ensues, especially if hematuria and scant proteinuria (<1 g/day) are the principal features. Persisting nephrotic syndrome has a less favorable prognosis, and such patients may evolve into FSGS and accompanying progressive CKD.

Treatment of Mesangial Proliferative Glomerulonephritis

The treatment of pure MesPGN, unaccompanied by other underlying diseases or lesions such as SLE, C1q nephropathy, IgM nephropathy, minimal change lesion, or IgA nephropathy, has not been well defined. No prospective, randomized, controlled trials have been performed because of the uncommon nature of the disorder. As the prognosis for patients with isolated hematuria or hematuria combined with mild proteinuria (<500 mg/day) is generally benign, no treatment other than management of hypertension is needed. For those patients with nephrotic syndrome, with or without impaired renal function, a more aggressive approach is often recommended, especially in the presence of diffuse IgM deposits, because many such patients will eventually progress to FSGS. Even in the absence of controlled trials, an initial course of corticosteroid therapy may be justified in most patients with nephrotic-range proteinuria (e.g., prednisone 60 mg/day or 120 mg every other day for 2 to 3 months followed by lowered doses, on an alternate-day regimen, for 2 to 3 additional months). About 50% of patients so treated will experience a decrease in proteinuria to subnephrotic levels. Complete remissions occasionally occur. However, relapses of proteinuria are common when corticosteroids are tapered or discontinued. Such relapsing, partially corticosteroid responsive patients might benefit from the addition of cyclophosphamide, chlorambucil, or even cyclosporine or mycophenolate mofetil (MMF) to the regimen, although information on the therapeutic efficacy and safety of these agents in pure MesPGN is limited. Patients with persistent treatment-unresponsive nephrotic

syndrome will almost invariably progress to ESRD during a period of several years. Whereas transplantation is not contraindicated, those patients who do progress to ESRD rapidly and who develop superimposed FSGS may have a high risk of recurrence of proteinuria and FSGS in the transplanted kidney.

3.1.1.3 Immunotactoid Glomerulopathy

Immunotactoid glomerulopathy is a distinct clinico-pathological entity which has recently been defined. The term immunotactoid refers to highly organized immune depositions appearing as rod-like microtubular structures in ultrastructural examination.

Cause.

It has been postulated that there is a relationship between the syndrome of immunotactoid glomerulopathy and systemic lupus erythematosus.

Clinical

It has been describe a patients with mixed connective tissue disease who demonstrates characteristic features of immunotactoid glomerulopathy. The diagnosis was usually made after excluding amyloidosis, cryoglobulinaemia and lupus nephritis. In addition to immunotactoid microtubules, ultrastructural examination also demonstrated presence of fingerprint depositions which were intimately mixed with immunotactoid structures. Fingerprint deposits have been described in lupus nephritis and cryoglobulin-related nephropathy, but rarely in other glomerulonephritis.

Treatment

Treatment depends on underlying diseases. Aggressive immunosuppressive therapy is recommended optionally.

Prognosis

Prognosis of immunotactoid glomerulopathy depends on a leading cause and underlying comorbide disorders that can contribute onset of this disease.

3.1.2 Glomerular Diseases That Cause Hematuria Or Nephritic Syndrome

3.1.2.1 Postinfectious Glomerulonephritis

Poststreptococcal Glomerulonephritis

Poststreptococcal glomerulonephritis (PSGN) is more common in males (2:1) and usually affects children 2 to 14 years old. Traditionally, only certain nephritogenic strains of group A *Streptococcus pyogenes* result in GN.

Epidemiology

In the tropics PSGN usually follows streptococcal impetigo of M types 47, 49, 55, and 57. Throat infections with streptococcus types 1, 2, 4, and 12 are also nephritogenic. More recently, ingestion of unpasteurized milk contaminated with group C streptococcus (*Streptococcus zooepidemicus*) has caused clusters of cases and at least one large epidemic. The risk of nephritis in epidemics may range from 5% in throat infections to as high as 25% in M type 49 pyoderma. A genetic predisposition is suggested as there is an association of PSGN with HLA-DR4 and DR1 and higher attack rates in siblings than expected for the general population. The risk of PSGN is reduced by early antibiotic treatment.

PSGN is becoming less common in industrialized countries and is changing its epidemiologic pattern from one that primarily affects children to one that now occurs more commonly in debilitated elderly individuals, particularly alcoholics, diabetics, and intravenous drug users. Nevertheless, PSGN remains common in developing countries, where it may affect 9.3 to 9.8 cases per 100,000 population, especially in communities with poor socioeconomic conditions. The reduction in incidence of PSGN likely relates to more rapid and frequent use of antibiotics. The common practice of fluorination of water may also be protective as fluoride reduces the expression of virulence factors in cultures of *S. pyogenes*.

Pathogenesis

Two nephritogenic streptococcal antigens have been identified: nephritis-associated plasmin receptor (NAPLr), which was identified as glyceraldehyde-3-phosphate dehydrogenase (GAPDH); and streptococcal proteinase exotoxin B (SPEB) and its more immunogenic precursor, zymogen. GAPDH and SPEB have been identified in renal biopsy specimens of acute PSGN, and antibody titers to both these antigens are elevated in most convalescent sera. GAPDH has been localized in areas of the glomeruli with plasmin-like activity, suggesting a local direct mechanism

of glomerular inflammatory damage, but it is not co-localized with complement or immunoglobulin. In contrast, SPEB is co-localized with both complement and IgG, suggesting a participation in the immune-mediated glomerular damage. Furthermore, SPEB is the only putative streptococcal nephritogenic antigen that so far has been demonstrated in the subepithelial electron-dense deposits known as humps, the most typical histologic lesion of acute PSGN. In studies from Latin America and central Europe, SPEB but not GAPDH is usually detectable in renal biopsy specimens of PSGN patients. In contrast, GAPDH was present in PSGN in a study of Japanese patients. These contrasting results raise the interesting possibility that different streptococcal antigens are capable of inducing acute nephritis in different ethnic groups. Indeed, a study of the group C *S. zooepidemicus* strain that caused the epidemic outbreak in Brazil revealed an absence of the gene related to SPEB, which documents that this antigen was not involved in that epidemic

Viral Infections

Viral infections may cause acute GN (hepatitis A virus, parvovirus B19, measles, Epstein-Barr virus), chronic GN (hepatitis B virus [HBV], hepatitis C virus [HCV], human immunodeficiency virus [HIV], parvovirus B19), and interstitial nephritis (Hantavirus, influenza virus, dengue, BK virus, coronavirus, cytomegalovirus, hepatitis A virus). The most common infections are those associated with HBV, HCV, and HIV. Pathogenetic mechanisms include deposition or in situ formation of exogenous (viral) immune complexes; autoantibody formation directed to endogenous antigen modified by viral injury; virus-induced release of proinflammatory cytokines, chemokines, adhesion molecules, and growth factors; and direct cytopathic effects of viral proteins.

Treatment of HBV-Associated Glomerulonephritis

Treatment is aimed at eradication of HBV virus. Interferon alfa (5 million units daily for 6 months) or pegylated interferon alfa may result in remission, especially in HBV-associated MN. Lamivudine (100 mg orally once daily for 52 weeks) has also been reported to clear HBV virus and to induce remission in HBV-associated MN. A reduction of the dose is necessary when the glomerular filtration rate (GFR) is

reduced below 50 ml/min per 1.73 m². If the GFR is 30 to 49 ml/min per 1.73 m², the initial dose is 100 mg, and this is followed by 50 mg orally daily; if the GFR is 15 to 29 ml/min per 1.73 m², the initial dose is the same and subsequent doses are reduced to 25 mg daily. In patients with ESRD, the initial dose is 35 mg followed by 10 mg daily. Lamivudine-resistant strains may arise with prolonged use. Entecavir and adefovir dipivoxil may provide an alternative, but the nephrotoxicity of adefovir is a deterrent, although the risk is low at standard dosing if renal function is normal. Corticosteroid treatment is contraindicated because it is ineffective and may delay or prevent seroconversion and accelerate the progression of liver disease.

The prevailing view has been that treatment is not required for children with HBV-associated MN because the majority of children undergo spontaneous remission. However, clearance of HBV DNA and HBeAg has been achieved in about half of the children in controlled studies, with a higher incidence of resolution of the proteinuria in the treated group. Because HBV-associated MN may rarely progress to ESRD in children, it is reasonable to treat when proteinuria is severe or there is progression of renal disease. Active immunization is the most effective prevention measure as shown by the 10-fold decline in the incidence in Taiwan and 67% reduction in the United States 10 years after universal vaccination was implemented in 1991.

3.1.2.2 IgA Nephropathy

Immunoglobulin A (IgA) nephropathy (also known as Berger disease) was first described by Berger and Hinglais in 1968. IgA nephropathy is characterized by predominant IgA deposition in the glomerular mesangium. Long-term follow-up data illustrated that some patients with IgA nephropathy progress to end-stage renal disease (ESRD). IgA nephropathy is now the most common cause of glomerulonephritis in the world.

IgA nephropathy is highly variable, both clinically and pathologically. Clinical features range from asymptomatic hematuria to rapidly progressive glomerulonephritis (RPGN). IgA nephropathy is most often associated with microscopic hematuria or recurrent macroscopic hematuria, and spontaneously

resolving acute renal failure can occur. The condition can sometimes lead to chronic kidney disease as well. Pathologically, a spectrum of glomerular lesions can be seen, but mesangial proliferation with prominent IgA deposition is observed in almost all biopsies. Although IgA nephropathy is a limited nonsystemic renal disease, many systemic diseases are sporadically associated with mesangial IgA deposition. Henoch-Schonlein purpura (HSP), a systemic illness, has been closely linked to IgA nephropathy. Other systemic diseases in which mesangial deposits of IgA are regularly observed include systemic lupus erythematosus, hepatitis, dermatitis herpetiformis, and ankylosing spondylitis.

Epidemiology

IgAN is the most prevalent pattern of glomerular disease in most countries where renal biopsy is widely used as an investigative tool. However, there is striking geographic variation. Genetic variations may be important. For example, in North America, IgAN is less common in African Americans than in Caucasians of European origin. It is also very uncommon among black South Africans. In New Zealand, IgAN is much less common among Polynesians than among Caucasians of European origin, even though Polynesians have an increased prevalence of ESRD due to other renal diseases. Perceived prevalence of IgAN may also be influenced by attitudes to the investigation of microscopic hematuria. A country with an active program of routine urine testing will inevitably identify more individuals with urine abnormalities, but IgAN will be identified only if renal biopsy is performed. Even then, the prevalence of IgAN will be underestimated; a study of kidney donors suggests that the prevalence of IgAN with mesangial proliferative changes and glomerular C3 deposits in the general population in Japan may be 1.6%. The condition accounts for about 10% of biopsies performed for glomerular disease. IgA nephropathy is observed in up to 40% of all biopsies performed for glomerular disease in Asia, compared to 20% in Europe and 10% in North America. High prevalence rates are observed in Singapore, Japan, Australia, Hong Kong, Finland, and southern Europe, whereas low prevalence rates are the rule in the United Kingdom, Canada, and the United States. In Asia, routine urinalyses are performed

for schoolchildren, and renal biopsies are performed for patients with asymptomatic hematuria, thus raising the reported prevalence of the disease. IgA nephropathy is more common in males than in females. Virtually all studies show a male predominance of at least 2:1, with reported ratios of up to 6:1.

In children, HSP is usually diagnosed on clinical grounds without biopsy confirmation of tissue IgA deposition. Transient urine abnormalities are very common in the acute phase. However, only those with persistent urine abnormalities or with more overt renal disease will come to renal biopsy. Therefore, the incidence of HS nephritis is almost certainly underestimated, with many unidentified mild and transient cases. There is no information on geographic variations in HSP.

Pathophysiology

Almost 40 years after IgA nephropathy was first described the pathogenesis of this disease remains incompletely understood. The characteristic pathologic findings by immunofluorescence microscopy of granular deposits of IgA and complement 3 (C3) in the glomerular mesangium suggest that this disease is the result of the deposition of circulating immune complexes leading to the activation of the complement cascade. Deposited IgA is predominantly polymeric IgA1, which is mainly derived from the mucosal immune system. The association of some cases of IgA nephropathy with syndromes that affect the respiratory tract or gastrointestinal tract, such as celiac disease, led to the suggestion that IgA nephropathy is a disease of the mucosal immune system. This concept is also supported by the clinical observation that hematuria worsens during or after upper respiratory tract or gastrointestinal tract infections. The role of the complement system in the pathogenesis of IgA nephropathy is controversial. While IgA antibodies cannot activate complement through the classic pathway, studies have shown that complement can be activated by the alternate pathway.

IgA in the mesangium is likely to be deposited from the circulation as IgA-containing immune complexes. This hypothesis is supported by the high recurrence rate of IgA nephropathy in renal transplant recipients who have IgA nephropathy and, conversely, by the disappearance of the deposits from donor kidneys with IgA

nephropathy when transplanted into donors without the disease. Furthermore, the mesangial pattern of IgA deposits suggests that circulating IgA complexes are responsible for the disease. Serum IgA levels are elevated in approximately half of patients with IgA nephropathy, but that increase is unlikely to play a role in the pathogenesis of the disease, as markedly elevated IgA levels are observed in patients with AIDS who do not have IgA nephropathy. However, IgA is probably accumulated and deposited because of a systemic abnormality rather than a defect intrinsic to the kidney.

Mortality/Morbidity

This disorder is thought to follow a benign course in most cases. However, many patients are at risk for slow progression to ESRD, which develops in approximately 15% of patients by 10 years and 20% by 20 years, though these percentages depend on how the disease is defined.

History

Two common presentations of patients with IgA nephropathy are episodic gross hematuria and persistent microscopic hematuria. Recurrent macroscopic hematuria, usually associated with an upper respiratory tract infection, or, less often, gastroenteritis is the most frequent clinical presentation and is observed in 40-50% of presenting patients. In 30-40% of patients, the disease is asymptomatic, with erythrocytes (RBCs), RBC casts, and proteinuria discovered on urinalysis. Patients with IgA nephropathy can also present with acute or chronic renal failure.

Hematuria

Many patients present with episodes of recurrent macroscopic hematuria. Eighty percent of these episodes are associated with upper respiratory tract infections, mainly acute pharyngotonsillitis. This synchronous association of pharyngitis and macroscopic hematuria has been dubbed synpharyngitic nephritis. Gross hematuria usually appears simultaneously or within the first 48-72 hours after the infection begins; persists less than 3 days; and, in about a third of patients, is accompanied by loin pain, presumably due to renal capsular swelling. Urine is usually brown rather than red, and clots are unusual. The presenting illness of episodic, grossly visible

hematuria is more common in younger people, whereas that of abnormal urine sediment is more frequent in older individuals.

Episodes of gross hematuria in IgA nephropathy have been associated with a variety of other infections.

- Urinary tract infections
- Pneumonia
- Staphylococcal sepsis
- Staphylococcal osteomyelitis
- Acute gastroenteritis
- Influenza
- Infectious mononucleosis

Gross hematuria has also followed tonsillectomy, vaccinations, strenuous physical exercise, and trauma. Between episodes of gross hematuria, many patients have persistent microhematuria, proteinuria, or both. It is rare for proteinuria to occur without microscopic hematuria in IgA nephropathy. Mild proteinuria is common. Nephrotic range proteinuria is uncommon, occurring in only 5% of patients with IgA nephropathy, and is more commonly seen in children and adolescents. Nephrotic range proteinuria can be seen at different stages of the disease, both in patients early in the disease course and in patients with advanced disease. Patients with heavy proteinuria and nephrotic syndrome are likely to have IgA deposition with diffuse proliferative glomerular lesions or minimal-change light microscopic findings.

Acute renal failure

Acute renal failure, with edema, hypertension, and oliguria, occurs in fewer than 5% of patients. It can develop from either of 2 distinct mechanisms. Acute severe immune injury can manifest as necrotizing glomerulonephritis and crescent formation. Alternatively, only mild glomerular injury is observed with gross hematuria, and renal failure is presumably due to tubular occlusion by RBCs. This is reversible, and renal function recovers with supportive measures.

Hypertension

Hypertension seldom occurs at the time of initial presentation but more commonly manifests as the course of the disease lengthens or when patients develop chronic renal insufficiency and ESRD.

Chronic renal failure

Chronic renal insufficiency seldom develops but is usually slowly progressive. Approximately 1-2% of all patients with IgA nephropathy develop ESRD each year.

Physical

A minority of patients have hypertension; otherwise, physical examination findings in patients with IgA nephropathy are usually unremarkable.

Causes

Most cases of IgA nephropathy are idiopathic, but the onset or exacerbation of the disease is often preceded by a respiratory tract infection. Association with some bacteria, such as *Haemophilus parainfluenzae*, has been reported. A variety of other disorders have also been linked with IgA nephropathy, as discussed below.

Cirrhosis and other liver diseases

Glomerular IgA deposition is a common finding in cirrhosis, occurring in up to a third of patients. Liver disease is accompanied by impaired removal of IgA-containing complexes by the Kupffer cells, predisposing patients to IgA deposition in the kidney. Glomerular IgA deposits are common in advanced liver disease, but most adults have no clinical signs of glomerular disease, whereas up to 30% of children may have asymptomatic hematuria or proteinuria. Those abnormalities usually resolve after successful liver transplantation.

Gluten enteropathy

Glomerular IgA deposition occurs in up to a third of patients with gluten enteropathy. Most of these patients have no clinical manifestations of the disease. However, IgA nephropathy and gluten hypersensitivity are associated, and withdrawal of gluten from the diet of these patients has resulted in clinical and immunological improvement of the renal disease.

HIV disease

IgA nephropathy has been reported in patients with HIV infection, both whites and blacks, despite the rarity of typical IgA nephropathy in the black population. Clinically, patients have hematuria, proteinuria, and, possibly, renal insufficiency. Histologically, findings range from mesangial proliferative glomerulonephritis to collapsing glomerulosclerosis with mesangial IgA deposits. Several patients have circulating immune complexes containing IgA antibodies against viral proteins.

Familial IgA nephropathy

While IgA nephropathy is usually a sporadic disease, data suggest that genetic factors are important in susceptibility to development of mesangial glomerulonephritis. Several cases of familial disease have been reported in Italy and the United States, and an autosomal dominant form has been linked to band 6q22-23.

Lab Studies

The first step in confirming the diagnosis is a careful urinalysis of a first-void urine sample performed by an experienced urine analyst. Direct examination of the urine sediment is required to identify RBCs, leukocytes, and RBC casts, all of which indicate glomerular injury. Quantitating proteinuria testing can be accomplished by a 24-hour measurement of urinary protein or semiquantitatively by measuring a urine protein/creatinine ratio. A normal ratio should be less than approximately 0.1. Also, adults older than 50 years with proteinuria should have a urine protein electrophoresis performed to exclude monoclonal light chains as a cause of proteinuria. Assess renal function in patients with proteinuria or hematuria by a 24-hour creatinine clearance test, or the glomerular filtration rate (GFR) can be estimated using the Modification of Diet in Renal Disease (MDRD) formula. Although the serum IgA level is elevated in up to half of patients, this finding is insensitive, nonspecific, and of no clinical utility.

Procedures and Histologic Findings

Diagnosis of IgA nephropathy is confirmed by renal biopsy

Light microscopy

The most common light microscopy findings are focal or, more often, diffuse mesangial proliferation and extracellular matrix expansion. Morphology can range

from normal to moderate or severe intracapillary or extracapillary proliferative lesions. While some patients have IgA deposits on immunofluorescence and little or no change by light microscopy, a few patients have segmental necrotizing lesions with crescent formation due to extensive disruption of the capillaries. Occasionally, patients have focal glomerular sclerosis indistinguishable from focal segmental glomerulosclerosis on light microscopy. A number of other findings can be observed in advanced disease, including interstitial fibrosis, tubular atrophy, and vascular sclerosis. These findings can be helpful prognostic tools in patients with IgA nephropathy.

Electron microscopy

Electron microscopy shows mesangial hypercellularity and increased mesangial matrix. The important finding is electron-dense deposits in the mesangium, but deposits in the subendothelial and subepithelial region of the glomerular capillary wall are found in a minority of patients, especially those with more severe disease.

Immunofluorescence

Immunofluorescence findings are the pathologic hallmark of this disease. IgA is deposited in a diffuse granular pattern in the mesangium and occasionally in the capillary wall. Immunoglobulin G (IgG) may accompany IgA, and C3 is often present.

Medical Care

IgA nephropathy is a common cause of glomerulonephritis. Although it is a benign disease in most patients, chronic renal failure and ESRD occur in about 20-40% of patients within 20 years of presentation. Currently, no cure exists for IgA nephropathy, but therapies that can delay the onset of need for dialysis and transplantation are available. Current recommendations include the following: Monitor patients with isolated hematuria without proteinuria or hypertension with urinalysis, renal function testing, and blood pressure measurement.

Treat hypertension early and aggressively.

ACE inhibitors are the preferred agents for lowering blood pressure. They are beneficial in decreasing proteinuria and should be strongly considered even in

normotensive patients with proteinuria. The decrease in proteinuria with ACE inhibitors may be an effect of decreasing the intraglomerular pressure and of changing the glomerular size selectivity. Recent reports have demonstrated that ACE inhibitors are more effective than other antihypertensive drugs in slowing the progression of proteinuric renal disease. A recent randomized controlled trial followed patients for a mean of approximately 6 years. The group that received ACE-I had an improved renal survival rate compared to the group receiving other antihypertensive agents.

Angiotensin II receptor blockers should be used for patients who cannot tolerate ACE inhibitors. ACE inhibitors and angiotensin II receptor blockers may have an additive effect in decreasing proteinuria. Whether high doses of ACE inhibitors better preserve renal function than combined therapy with ACE inhibitors and angiotensin II receptor blockers is unknown.

The combination of an ACE-I and the angiotensin receptor blocker losartan has shown an additive urinary protein-lowering effect compared to doubling the dose of monotherapy. However, patients on combination therapy should be monitored closely for the development of hyperkalemia, and combination therapy should be avoided in patients with advanced kidney failure.

Administer prednisone for 4-6 months to patients who have IgA nephropathy with preserved renal function, nephrotic syndrome, and minimal-change findings on light microscopy. Early treatment with prednisone in patients with proliferative IgA nephropathy has been shown to be effective in reducing proteinuria and improving histologic findings, such as proliferation and cellular crescents. Additionally, corticosteroids given for 6 months (1-3.5 g/d) were beneficial against deterioration in renal function in patients with moderate proteinuria. A randomized, controlled, long-term study on the effectiveness of steroids in IgA nephropathy showed improved 10-year renal survival in the steroid treated group compared to the control group. Patients had a proteinuria of 1.9 g/d on average in the treatment group and 1.7 g/d in the control group. Steroids were given for 6 months.

Mycophenolate mofetil has been used in patients with IgA nephropathy associated with proteinuria, even though some reports have shown some benefit and others have not. The studies are of small size, and longer term studies are required for more information. Patients with crescentic RPGN can be treated similarly to patients with idiopathic RPGN by using intravenous pulse prednisone followed by oral prednisone and cyclophosphamide.

Fish oil (omega-3 fatty acids) at a dose of 12 g/d has been used with controversial and conflicting results, but it is frequently used in patients with declining renal function. Deficiencies of essential fatty acids have been detected in IgA nephropathy, and fish oil is rich in long-chain omega-3-polyunsaturated fatty acids. These produce altered and less biologically effective prostaglandins and leukotrienes, as well as reduced platelet aggregation.

Surgical Care

Renal transplantation

Renal transplantation is effective in patients with IgA nephropathy. Survival of cadaveric kidney transplants in patients with IgA nephropathy is among the highest observed among common causes of ESRD. IgA nephropathy frequently recurs after transplantation (20-60%). The higher recurrence rates in transplantation from living related donors suggest genetic susceptibility to the disease. Some patients present with microscopic hematuria and proteinuria; others have only positive histologic findings. The disease usually progresses slowly, similarly to the disease in the native kidneys, and graft loss due to recurrent disease occurs in fewer than 10% of patients.

Diet

A low-antigen diet, which consists of restricting dietary gluten and avoiding meats and dairy products, has been recommended to decrease mucosal antigen exposure but has not been shown to preserve renal function. Low-protein diets have been recommended to slow the rate of progression of many nephropathies. No large trial explicitly addresses the role of low-protein diets in slowing the decline in renal function in IgA nephropathy. The MDRD Study Group trial is the largest trial of low-protein diets to date, but it included patients with a variety of renal diseases. This trial

was unable to determine whether a low-protein diet was beneficial. Although the meta-analysis of studies of low-protein diets suggests some benefits, the effects are subtle and difficult to apply to a given patient

Prognosis

Natural history of IgA nephropathy: Although this disease usually follows a benign course, ESRD occurs in 15-20% of patients within 10 years of onset and in about 25-30% of patients by 20 years. However, these observations are obtained from biopsy-proven disease and do not include patients with isolated hematuria, who typically do not have a biopsy performed and have a good prognosis. Predictors of disease progression: IgA nephropathy is characterized by a highly variable clinical course. Many efforts have been made to determine clinical and histological features associated with progression to ESRD. Clinically, patients with microscopic hematuria tend to have a higher risk than those with macroscopic hematuria. This phenomenon could be due to the ability to identify patients with gross hematuria at an earlier stage of disease. Sustained hypertension, impaired renal function, persistent hematuria, and proteinuria above 1 g/d are also poor prognostic markers. Histologically, interstitial fibrosis, tubular atrophy, and glomerular scarring predict a worse outcome. As with other glomerular diseases, the risk of progression is more closely correlated with tubulointerstitial findings than with glomerular changes. However, worse prognosis for patients with familial IgA nephropathy, as compared to sporadic IgA nephropathy is showed.

3.2 Secondary Glomerular Diseases

Secondary glomerular diseases are defined after getting evidence of induced factors that contribute clinical manifestation around these diseases.

3.2.1 Diseases Associated With Nephrotic Syndrome

Glomerular diseases associated with nephrotic syndrome are usually include monoclonal immunoglobulin deposition disease (MIDD), renal amyloidosis, light chain deposition disease and myeloma disease, and also other nephropaties due to infective and inherited reasons.

3.2.1.1 Monoclonal Immunoglobulin Deposition Disease

It was known from the late 1950s that nonamyloidotic forms of glomerular disease “resembling the lesion of diabetic glomerulosclerosis” could occur in multiple myeloma. Subsequently, monoclonal light chains were detected in these lesions. In clinical and pathologic terms, light-chain, light- and heavy-chain, and heavy-chain deposition disease (LCDD, LHCDD, and HCDD, respectively) are similar and may therefore be referred to as MIDD. They differ from amyloidosis in that the deposits lack affinity for Congo red and do not have a fibrillar organization. The distinction also relates to different pathophysiology of amyloid, which implicates one-dimensional elongation of a pseudocrystalline structure, and MIDD, which rather involves a one-step precipitation of immunoglobulin chains.

Epidemiology

LCDD is found in 5% of myeloma patients at autopsy, whereas the prevalence of AL amyloidosis is about 11%. LCDD and HCDD may occur in a wide range of ages (28 to 94 years) with a male preponderance. More than 20 patients with HCDD have been described so far, but the disease is most likely underdiagnosed.

Pathogenesis

Light-chain deposition may require light chains with distinct properties that favor deposition in tissues. Various properties of light-chain variable domains may contribute to MIDD pathogenesis:

- Restricted usage of three κ germline genes, with an apparent overrepresentation of the rare V κ IV variability subgroup.
- Size abnormalities of light chains, present in one third of patients.
- Unusual amino acid substitutions in LCDD light chains may modify the light-chain conformation or be responsible for hydrophobic interactions between V domains or between V domains and extracellular matrix proteins.
- When pathogenic light chains were absent in serum and urine, they seemed to be N-glycosylated, suggesting that glycosylation increases their propensity to precipitate in tissues. However, as in AL amyloidosis, extrinsic conditions may also contribute to aggregation of the light chain. The same light chain can form

granular aggregates or amyloid fibrils, depending on the environment, and different partially folded intermediates of the light chain may be responsible for amorphous or fibrillar aggregation pathways.

HCDD may also be associated with unique heavy chains. A deletion of the first constant domain CH1 was found in deposited or circulating heavy chains in patients with γ -HCDD. In the blood, the deleted heavy chain either was associated with light chains or circulated in small amounts as a free unassembled subunit. It is likely that the CH1 deletion facilitates the secretion of free heavy chains that are rapidly cleared from the circulation by organ deposition. The variable VH domain also is likely to be required for tissue precipitation. A striking feature of LCDD and HCDD is extracellular matrix accumulation. Nodules are made of normal matrix constituents. In cultured mesangial cells, LCDD light chains enhance the production of tenascin-C and of profibrotic cytokines, such as transforming growth factor β and platelet-derived growth factor.

Clinical Manifestations

MIDD is a systemic disease with immunoglobulin chain deposition in a variety of organs leading to various clinical manifestations, but visceral immunoglobulin chain deposits may be totally asymptomatic and found only at autopsy.

Renal Manifestations

Renal involvement is a constant feature of MIDD, and renal symptoms, mostly proteinuria and CKD, often dominate the clinical presentation. In 18% to 53% of LCDD patients, albuminuria is associated with the nephrotic syndrome. However, in about one fourth, it is less than 1 g/day, and these patients exhibit mainly a tubulointerstitial syndrome. Albuminuria is not correlated with the presence of nodular glomerulosclerosis, at least initially, and may occur in the absence of significant light microscopic glomerular lesions. Hematuria is more frequent than one would expect for a nephropathy in which cell proliferation is usually modest. The high prevalence, early appearance, and severity of CKD are other salient features of LCDD. In most cases, GFR declines rapidly, which is a main reason for referral.

CKD occurs with comparable frequency in patients with either low or heavy protein excretion and may present in the form of a subacute tubulointerstitial nephritis or a rapidly progressive glomerulonephritis (RPGN), respectively. The prevalence of hypertension is variable, but it must be interpreted according to associated medical history. Renal features of patients with HCDD are basically similar to those seen in LCDD and LHCDD, with a higher prevalence of hypertension and hematuria; extrarenal manifestations are less frequent.

Extrarenal Manifestations

Liver and cardiac involvement occurs in about 25% of patients with LCDD and LHCDD. Liver deposits are constant. They are either discrete and confined to the sinusoids and basement membranes of biliary ductules without associated parenchymal lesions or massive with marked dilation and multiple ruptures of sinusoids, resembling peliosis. Hepatomegaly with mild alterations of liver function test results is the most common symptom, but patients may also develop life-threatening hepatic insufficiency and portal hypertension. Cardiac involvement is also frequent and may be responsible for cardiomegaly and severe heart failure. Arrhythmias, conduction disturbances, and congestive heart failure are seen. Echocardiography and catheterization may reveal diastolic dysfunction and reduction in myocardial compliance similar to that found in cardiac amyloid. Deposits may also occur along the nerve fibers and in the choroid plexus as well as in the lymph nodes, bone marrow, spleen, pancreas, thyroid gland, submandibular glands, adrenal glands, gastrointestinal tract, abdominal vessels, lungs, and skin. They may be responsible for peripheral neuropathy (20% of the reported cases), gastrointestinal disturbances, pulmonary nodules, amyloid-like arthropathy, and sicca syndrome. Extrarenal deposits are less common in patients with HCDD.

Hematologic Findings

Myeloma is diagnosed in about 50% of the patients with LCDD or LHCDD and in about 25% of those with HCDD. MIDD, like AL amyloidosis, is often the presenting disease that leads to the discovery of myeloma at an early stage. MIDD may occasionally complicate Waldenström's macroglobulinemia, chronic

lymphocytic leukemia, and nodal marginal zone lymphoma. It often occurs in the absence of a detectable malignant process, even after prolonged (>10 years) follow-up. A monoclonal bone marrow plasma cell population is then easily detectable by immunohistologic examination.

Pathology

Light Microscopy

MIDD is not only a glomerular disease, and tubular lesions may be more conspicuous than the glomerular damage. Tubular lesions are characterized by the deposition of a refractile, eosinophilic, periodic acid–Schiff (PAS)–positive, ribbon-like material along the outer part of the tubular basement membrane. The deposits predominate around the distal tubules, the loops of Henle, and, in some instances, the collecting ducts, whose epithelium is flattened and atrophied. Typical myeloma casts are only occasionally seen in pure forms of MIDD. In advanced stages, a marked interstitial fibrosis including refractile deposits is frequently associated with tubular lesions.

Glomerular lesions are heterogeneous. Nodular glomerulosclerosis is the most characteristic; it is found in 30% to 100% of patients with LCDD. Expansion of the mesangial matrix with nodular glomerulosclerosis characterizes HCDD. Mesangial nodules are composed of PAS-positive, membrane-like material and are often accompanied by mild mesangial hypercellularity. Lesions resemble diabetic nodular glomerulosclerosis. Distinctive characteristics include the following: the distribution of the nodules is fairly regular in a given glomerulus; the nodules are often poorly argyrophilic; and exudative lesions such as fibrin caps and extensive hyalinosis of the efferent arterioles are not observed. In occasional cases with prominent endocapillary cellularity and mesangial interposition, the glomerular features mimic membranoproliferative glomerulonephritis (MPGN). Milder forms of LCDD show increased mesangial matrix or cells and a modest basement membrane thickening, with abnormal brightness and rigidity. Glomerular lesions may be detectable only by immunostaining or ultrastructural examination in early stages or if they are induced by light chains with a weak pathogenic potential.

Arteries, arterioles, and peritubular capillaries all may contain PAS-positive deposits in close contact with their basement membranes. Deposits do not show the staining characteristics of amyloid, but Congo red-positive amyloid deposits co-occur in approximately 10% of patients.

Immunohistology

Immunohistology is central in the diagnosis of the various forms of MIDD. A criterion required for the diagnosis of MIDD is monotypic light-chain (mostly κ) or heavy-chain fixation along tubular basement membranes. The tubular deposits stain strongly and predominate along the loops of Henle and the distal tubules, but they also often are detected along the proximal tubules. In contrast, glomerular immunohistology patterns display marked heterogeneity. In patients with nodular glomerulosclerosis, deposits of monotypic immunoglobulin chains are usually found along the peripheral GBM and, to a lesser extent, in the nodules themselves. Glomerular staining is typically weaker than that observed along the tubular basement membranes. This may not relate to the actual amount of deposited material because glomerular immunohistology may be negative despite prominent granular glomerular deposits observed by electron microscopy. Local modifications of deposited light chains thus might change their antigenicity. In patients without nodular lesions, glomerular staining occurs along the basement membrane and less frequently in the mesangium. A linear staining usually decorates Bowman's capsule. Deposits are frequent in vascular walls and interstitium.

In patients with HCDD, immunohistology with anti-light-chain antibodies is negative despite typical nodular glomerulosclerosis. Monotypic deposits of γ , α , or μ heavy chains may be identified. Any γ subclass may be observed. Analysis of the kidney biopsy specimen with monoclonal antibodies specific for the constant domains of the γ heavy chain allowed identification of a deletion of the CH1 domain in all tested cases. In most cases of HCDD, especially when a γ 1 or γ 3 chain is involved, complement components including C1 could be demonstrated in a granular or pseudolinear pattern. Complement deposits were often associated with signs of complement activation in serum.

Electron Microscopy

The most characteristic ultrastructural features are finely to coarsely granular electron-dense deposits along the outer (interstitial) aspect of the tubular basement membranes. In the glomerulus, they predominate in a subendothelial position along the GBM and are located mainly along and in the lamina rara interna. They can also be found in mesangial nodules, Bowman's capsule, and the wall of small arteries between the myocytes. Nonamyloid fibrils have been reported in a few patients with LCDD or HCDD.

Diagnosis

The diagnosis of MIDD must be suspected in any patient with the nephrotic syndrome or rapidly progressive tubulointerstitial nephritis or with echocardiographic findings indicating diastolic dysfunction and the presence of a monoclonal immunoglobulin component in the serum or the urine. The same combination is also seen in AL amyloidosis, but AL amyloidosis is more often associated with the λ light-chain isotype. Because sensitive techniques including immunofixation fail to identify a monoclonal immunoglobulin component in 10% to 20% of patients with LCDD or LHCDD and about 40% of patients with HCDD, renal biopsy plays an essential role in the diagnosis of MIDD and the associated dysproteinemia. The definitive diagnosis is made by the immunohistologic analysis of tissue from an affected organ, in most cases the kidney, with use of a panel of immunoglobulin chain-specific antibodies, including anti- κ and anti- λ light-chain antibodies to stain the non-congophilic deposits. When the biopsy specimen stains for a single heavy-chain isotype and does not stain for light-chain isotypes, the diagnosis of HCDD should be suspected. The diagnosis of the plasma cell dyscrasia relies on bone marrow aspiration and bone marrow biopsy with cell morphologic evaluation and, if necessary, immunophenotyping with anti- κ and anti- λ antisera to demonstrate monoclonality.

Outcome

The outcome of MIDD remains uncertain, mainly because extrarenal deposits of light chains can be totally asymptomatic or cause severe organ damage leading to

death. Survival from onset of symptoms varies from 1 month to 10 years. In the largest series of LCDD patients, 36 of the 63 patients reached uremia, 37 of those patients died during follow-up, and patient survival was 66% at 1 year and 31% at 8 years, although most were treated by chemotherapy. By multivariate analysis, the only variables independently associated with renal survival were age and degree of chronic kidney disease (CKD) at presentation or the time of renal biopsy. Those variables independently associated with a worse patient survival were age, initial creatinine level, associated multiple myeloma, and extrarenal light-chain deposition. Survival of the patients treated with dialysis was not different from that of the patients not reaching ESRD. Renal and patient survivals were significantly better in patients with pure MIDD (mean, 22 and 54 months, respectively) compared with those who presented with cast nephropathy (mean, 4 and 22 months, respectively).

Treatment

As in AL amyloidosis, treatment should be aimed at reducing immunoglobulin production. Clearance of the light-chain deposits has been demonstrated in a few patients after intensive chemotherapy with syngeneic bone marrow transplantation or blood stem cell autografting. Nodular mesangial lesions and light-chain deposits are reversible, also disappearing after long-term chemotherapy. In a retrospective study of 11 LHCDD patients (younger than 65 years) treated by high-dose therapy with the support of autologous blood stem cell transplantation, no treatment-related death occurred. A decrease in the monoclonal immunoglobulin level was observed in eight patients, with complete disappearance from serum and urine in six cases. Clinical improvement was observed in six patients, and histologic regression was documented in cardiac, hepatic, and skin biopsy specimens. These results were confirmed in two small North American series. Reversal of dialysis dependency and sustained improvement in renal function were also occasionally noted. Whether high-dose chemotherapy with blood stem cell transplantation provides benefits compared with conventional chemotherapy including high-dose dexamethasone, with or without bortezomib, remains to be established. As with AL amyloidosis, monitoring of light-chain production should rely on serum free light-chain assay, particularly when a

blood or urine monoclonal component cannot be detected by conventional methods. Kidney transplantation in a few patients with MIDD usually led to recurrence of the disease and should therefore not be performed in LCDD patients unless measures have been taken to reduce light-chain production.

Renal Diseases Associated with Monoclonal Immunoglobulin Deposition Disease

Myeloma Cast Nephropathy

The association of monoclonal light chain deposits, mostly along renal tubular basement membranes, with typical myeloma cast nephropathy is more frequent than reported initially. It was found in 11 of 34 patients with MIDD. Nodular glomerulosclerosis is, however, infrequent (<10%), and some ribbon-like tubular basement membranes are seen in less than half of the patients. In addition, one third of the patients do not have granular dense deposits on electron microscopy.

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Chapter 4

Kidney Amyloidosis

Amyloid deposits are found in one or more organs in about 7% of LCDD patients. Because amyloid deposits are focal, their true incidence may be markedly underestimated. Although this association may result from peculiar light chains endowed with intrinsic properties that make them prone to form both fibrillar and nonfibrillar deposits, depending on the environment, one cannot exclude the possibility that the coexisting diseases are induced by different variant clones.

The glomerular capillaries are a favorite site for the deposition of abnormal proteins. In most cases, the resulting diseases are caused by a monoclonal immunoglobulin subunit, and those can be classified into two categories by electron microscopy. The first category includes diseases with fibril formation, mainly amyloidosis, and diseases with microtubule formation, including cryoglobulinemic and immunotactoid glomerulonephritis (GN). The second category is characterized by nonorganized electron-dense granular deposits. They are localized along basement membranes in most tissues, especially in the kidney, and define a disease now termed monoclonal immunoglobulin deposition disease (MIDD). In some cases, monotypic immune complex–like deposits are observed in the setting of proliferative GN.

General Characteristics of Amyloidosis

Amyloidosis is a generic term for a family of diseases defined by morphologic criteria. The diseases are characterized by the deposition in extracellular spaces of a proteinaceous material. Amyloid deposits are composed of a felt-like array of 7.5- to 10-nm-wide rigid, linear, nonbranching, aggregated fibrils of indefinite length. One amyloid fibril is made of two twisted 3-nm-wide filaments, each displaying the typical “cross- β ” structure, where antiparallel β -sheets are perpendicular to the filament axis.

Amyloid Precursor–Based Classification

Amyloidoses are classified by the type of precursor protein that composes the main component of fibrils. The amyloidogenic propensity is related to the ability of

this precursor to form intermolecular β -sheets. Besides these structural properties, which may relate to genetically transmitted mutations, the amyloidogenic potential is enhanced by overproduction or impaired clearance of the precursor. Renal amyloidoses mostly include immunoglobulin light chain (AL) and systemic secondary (AA) amyloidoses. Other precursors, such as transthyretin, fibrinogen, apolipoprotein A-I, and lysozyme, are responsible for rare familial cases.

Other Components of All Amyloid Fibrils

Glycosaminoglycans (GAGs) are tightly associated with amyloid fibrils. GAGs are polysaccharide chains made of repeating hyaluronic acid–hexosamine units normally linked to a protein core, thus forming proteoglycans. Proteoglycans, mostly of the heparan sulfate type, appear to induce and to stabilize the β -pleated amyloid structure. Another constituent of all amyloid deposits is serum amyloid P component (SAP). SAP is resistant to proteolytic digestion, and coating of amyloid fibrils with SAP could result in their protection from catabolism. The high affinity of SAP toward amyloid was exploited for diagnosis, location, and monitoring of the extent of systemic amyloidosis by scintigraphy with [123I]-SAP.

General Mechanisms of Fibrillogenesis

Amyloidogenesis involves a nucleation-dependent polymerization process. Formation of an ordered nucleus is the initial and thermodynamically limiting step, followed by addition of monomers and elongation of the fibrils. Fibrillogenesis may involve several mechanisms of processing of the amyloid precursor, including partial proteolysis and conformational modifications. Conformational changes lead to a soluble, partially folded intermediate, whose subsequent ordered self-assembly results in fibril formation. Macrophages have a central role in AA amyloidosis by providing the intralysosomal processing of the precursor. In AL amyloidosis, the variable domain of the light chain VL is the main component, which suggests a role of partial proteolysis of the light-chain precursor.

Pathology

On light microscopy, the deposits are extracellular, eosinophilic, and metachromatic. After Congo red staining, they appear faintly red and show

characteristic apple-green birefringence under polarized light. Metachromasia is also observed with crystal violet, which stains the deposits red. The earliest lesions are located in the mesangium, along the glomerular basement membrane (GBM), and in the blood vessels. Mesangial deposits are primarily in the mesangial matrix and spread from lobule to lobule until eventually the whole mesangial area is replaced. Amyloid deposits may also infiltrate the GBM or be localized on both sides of it. When subepithelial deposits predominate, spikes similar to those seen in membranous nephropathy (MN) may be observed. Advanced amyloid typically produces a nonproliferative, noninflammatory glomerulopathy and marked enlargement of the kidney. The amyloid deposits replace the normal glomerular architecture, with a consequent loss of cellularity. When glomeruli become massively sclerotic, the deposits may be difficult to demonstrate by Congo red staining. Electron microscopy may be helpful then and also in the very early stages, which may not be detected by light microscopy examination in patients presenting with the nephrotic syndrome. Amyloid deposits are characterized by randomly oriented, nonbranching fibrils with an 8- to 15-nm diameter.

Except for fibrinogen amyloidosis, which characteristically does not affect renal vessels, the media of the blood vessels is prominently involved at early stages. Vascular involvement may predominate and occasionally occurs alone, particularly in AL amyloidosis. Deposits may also affect the tubules and the interstitium, leading to atrophy and disappearance of the tubular structures and to interstitial fibrosis. Given the heterogeneity of amyloidoses, immunohistology should be routinely performed. Immunohistochemical classification of amyloid type is possible in most cases. Immunohistology with antibodies specific for immunoglobulin chains may be more difficult to interpret than that with anti-AA antiserum, perhaps because of the absence or inaccessibility of light-chain epitopes. A genetic cause should be sought in all patients with amyloidosis in whom confirmation of the amyloid precursor cannot be obtained by immunohistochemistry.

Immunoglobulin-Associated Amyloidosis (AL and AA)

Free immunoglobulin subunits, mostly light chains, secreted by a single clone of B cells, are the cause of the most frequent and severe amyloidosis affecting the kidney. Studies on the mechanisms of AL amyloidogenesis are made particularly difficult by the unique structural heterogeneity of the precursor: each monoclonal light chain is different from all others, so each patient is unique. The involvement of an immunoglobulin heavy chain in amyloidosis remains exceptional.

Pathogenesis

Determinant factors are borne by the precursor light chain. In AL amyloidosis, there is a striking overrepresentation of the λ isotype, which is twofold to fourfold more frequent than the κ isotype. A rarely expressed homology family of light-chain variable regions, the V λ VI variability subgroup, is found only in amyloid-associated monoclonal immunoglobulins.

Amyloidogenicity is associated with physicochemical features including low-molecular-mass light-chain fragments in the urine, abnormal disulfide bonding of light chains, and low isoelectric point (pI). An analysis of nearly 200 light-chain sequences identified 12 positions in κ chains and 12 in λ chains where certain residues were associated with amyloidosis. Four structural risk factors were shown to define most fibril-forming κ light chains. Because of their high dimerization constants, light chains from patients with AL amyloidosis may behave like antibodies with affinity for extracellular structures. The tropism of organ involvement may be influenced both by the germline gene used for the light-chain variable region (VL) and by somatic mutations occurring in the secreting clone. Patients expressing a monoclonal light chain of the V λ VI subgroup are more likely to present with dominant renal involvement and less frequent cardiac and multisystem disease. Patients with κ light chains are more likely to have dominant hepatic involvement. In addition, organ-specific environmental factors are also involved. For example, high intrarenal concentrations of urea enhance fibril formation by reducing the nucleation lag time.

Amyloid light chains may contribute directly to the pathogenesis, independent of extracellular fibril deposition. In the heart and the kidney at least, the infiltration

alone does not correlate well with clinical manifestations. Light chains from amyloid patients incubated with mesangial cells induce a macrophage-like phenotype, whereas those from light-chain deposition disease patients induce a myofibroblast-like phenotype.

Epidemiology

The incidence of AL amyloidosis is nine per million per year. Fewer than one of four patients with AL amyloidosis is considered to have an overt immunoproliferative disease, which usually is multiple myeloma, although other forms are seen, such as Waldenström's macroglobulinemia. Amyloid deposits are found in approximately 10% of all patients with myeloma and in 20% of those with pure light-chain myeloma. The apparent prevalence of myeloma depends on the diagnostic criteria used. Epidemiologic characteristics of primary amyloidosis, that is, amyloidosis without overt immunoproliferative disease, and myeloma are not significantly different. The median age at diagnosis is 64 years in patients with primary amyloidosis, with a slight predominance of male patients.

Clinical Manifestations

The main clinical symptoms at presentation are weakness and weight loss. Except for bone pain, the initial symptoms in patients with and without myeloma are similar. However, nephrotic syndrome, orthostatic hypotension, and peripheral neuropathy are more frequent in patients with AL amyloidosis without myeloma. Amyloidosis is also different from many types of kidney disease in that the kidney is often enlarged and hypertension is absent even when renal function is impaired. Proteinuria, mainly albuminuria, occurs in the absence of microscopic hematuria. Indeed, the presence of hematuria should prompt examination for a bleeding lesion in the urinary tract. Renal manifestations may also include renal tubular acidosis (mostly as a part of Fanconi syndrome) and polyuria-polydipsia (resulting from urinary concentration defect), when amyloid deposits occur around proximal tubules and Henle's loops (or collecting ducts), respectively.

AL amyloidosis may infiltrate almost any organ other than the brain and therefore can be responsible for a wide variety of clinical manifestations. Restrictive

cardiomyopathy is found at presentation in up to one third of patients and causes death in about one half. Infiltration of the ventricular walls and the septum may be recognized by echocardiography. Amyloid may also induce arrhythmias and the sick sinus syndrome. Amyloid deposits in the coronary arteries may result in angina and myocardial infarction. Cardiac troponins and N-terminal pro-brain natriuretic peptide are sensitive markers of myocardial dysfunction and powerful predictors of overall survival in patients with AL amyloidosis.

Involvement of the gastrointestinal tract is common and can cause motility disturbances, malabsorption, hemorrhage, or obstruction. Macroglossia may interfere with eating and obstruct airways. Abnormalities of hepatic function are usually mild. Hyposplenism diagnosed by abnormal peripheral smear and liver spleen scan, commonly associated with splenomegaly, predisposes to fatal bacterial infections. Peripheral nerve involvement may result in a painful sensory polyneuropathy followed later by motor deficits. Autonomic neuropathy causing orthostatic hypotension, lack of sweating, gastrointestinal disturbances, bladder dysfunction, and impotence may occur alone or together with peripheral neuropathy. Orthostatic hypotension is one of the major hampering complications of AL amyloidosis, with some patients being bedridden. Skin involvement may take the form of purpura, characteristically around the eyes, and ecchymoses, papules, nodules, and plaques, occurring usually on the face and upper trunk. AL amyloidosis may also infiltrate articular structures and mimic rheumatoid or an asymmetric seronegative synovitis. Infiltration of the shoulders may produce severe pain and swelling (shoulder pad sign). A rare but potentially serious manifestation of AL amyloidosis is an acquired bleeding diathesis that may be associated with deficiency of factor X or factor IX or with increased fibrinolysis. It should be systematically sought before any biopsy of a deep organ. Widespread vascular deposits may also be responsible for bleeding. Prothrombin time and activated partial thromboplastin time measurements as well as determination of bleeding times are required to assess bleeding diathesis.

Monoclonal light chains can be detected by immunoelectrophoresis in 73% of the urine samples of patients with AL amyloidosis. The λ isotype is twice as frequent

as the κ , contrasting with the 1:2 ratio of λ to κ observed in myeloma alone. With the use of more sensitive immunochemical techniques, a monoclonal immunoglobulin is found in the serum or the urine in nearly 90% of patients. The combination of immunochemical techniques and serum-free light-chain assay detects an abnormal result in 99% of patients.

AL amyloidosis associated with IgM paraproteinemia characterizes a distinctive subset of patients who have a wider variety of underlying, often lymphoid clonal disorders (including 75% Waldenström's macroglobulinemia), usually low-level free light chains with a predominance of κ isotype, and higher prevalence of lymph node (31% versus 3%) and lung (17% versus 2%) involvement compared with patients with non-IgM monoclonal component.

Diagnosis

AL amyloidosis should be considered in any patient who presents with nephrotic-range proteinuria with or without renal impairment, nondilated cardiomyopathy, peripheral neuropathy, hepatomegaly, or autonomic neuropathy, whether or not a paraprotein can be detected in the serum or urine. Particular vigilance should be maintained in patients with multiple myeloma or monoclonal gammopathy of undetermined significance (MGUS), especially of the λ isotype. Initial investigation should confirm the diagnosis of amyloidosis on tissue biopsy, and this should be followed by investigations to establish the type of amyloid present and the extent of organ involvement.

All patients require immunofixation of serum and urine in an attempt to demonstrate the presence of a monoclonal light chain. A bone marrow specimen is necessary because 10% of patients will not have a demonstrable monoclonal light chain by immunofixation, and a clone of plasma cells detected in the bone marrow by immunohistochemistry is strong evidence of AL amyloidosis. Immunonephelometric quantitation of serum free light chains complements immunofixation because it shows remarkable specificity and sensitivity.

Biopsy of an affected organ is usually diagnostic, but less invasive alternatives should be preferred first. Biopsies of salivary glands or subcutaneous abdominal fat

yield positive results in 80% to 90% of cases. Rectal biopsy is diagnostic in more than 80% of cases, provided the biopsy specimen contains submucosal vessels in which early deposits are located. Bone marrow biopsy specimens should be stained with Congo red for the presence of amyloid, and involvement of the bone marrow (observed in about 50% of patients) is strongly suggestive of the AL type. Evaluation of adequate specimens in experienced laboratories is necessary to maintain high diagnostic sensitivity and specificity. It is not always easy to be certain that amyloidosis is of the AL type because immunohistochemical staining for immunoglobulin light chains may not be diagnostic (because of loss of epitopes), and the presence of a monoclonal component is strong but not conclusive evidence of the AL type. Caution is required when patients have an intact monoclonal immunoglobulin in the serum without evidence of circulating free light chains in the serum or urine. In those cases, hereditary forms of amyloidosis should be considered because they may produce clinical syndromes indistinguishable from AL and coexist with MGUS. In cases of doubt, DNA analysis or amyloid fibril sequencing by mass spectrometry may be necessary.

Natural History and Treatment

AL amyloidosis is among the most severe complications of plasma cell proliferative disorders. Median survival is about 10 months. Cardiac involvement responsible for congestive heart failure and arrhythmias account for at least 40% of deaths. Therapy is aimed at annihilation of the plasma cell clone. All patients with AL amyloidosis deserve a trial of chemotherapy because of the improved survival of responders. In the responders, gradual regression of AL amyloid deposits is possible. However, the results of chemotherapy in AL amyloidosis are difficult to document because there is no easy way to measure amyloid load. Resolution of the nephrotic syndrome does not necessarily reflect loss of amyloid deposits, which can progress even with improved clinical and laboratory findings. Scintigraphy after the injection of [123I]-SAP component may be helpful for monitoring the extent of systemic amyloidosis, but this technique is available in a few centers only. The definition of a response in amyloidosis should be hematologic and organ based. A complete

hematologic response is defined by negativity of serum and urine for a monoclonal protein by immunofixation, normal free light-chain ratio by the serum free light-chain assay, and less than 5% plasma cells in the bone marrow. There are consensus criteria for organ response and organ disease progression. Until 15 years ago, the only treatment of AL amyloidosis was melphalan with prednisone administered orally in repeated cycles during many months. This treatment had a modest impact on survival because of its delayed action and low rate of hematologic remission. A more aggressive approach consisting of high-dose melphalan (HDM) administered in myeloablative doses (140 to 200 mg/m²) followed by autologous stem cell transplantation (ASCT) started in the mid-1990s, with complete hematologic response and significant functional improvement in a substantial proportion of highly selected patients. However, treatment-related mortality was consistently higher than in patients treated with ASCT for multiple myeloma or other malignant neoplasms. An alternative to HDM/ASCT consists of treatment with oral melphalan (10 mg/m²/day) together with dexamethasone administered at a high dosage (40 mg/day) in 4-day cycles each month (M/Dex). Early reports of M/Dex treatment described rapid eradication of light-chain production and rapid reduction in N-terminal brain natriuretic peptide. A recent trial randomly assigned 100 AL amyloidosis patients to HDM/ASCT or M/Dex. Among the 65 patients for whom hematologic response could be evaluated, there was no significant difference in complete response, with 32% of those treated with M/Dex and 41% with HDM/ASCT responding. In an intention-to-treat analysis, median survival was 56.9 months in the M/Dex group compared with 22.2 months in the HDM/ASCT group (P = 0.04). The study investigators concluded that HDM/ASCT is not superior to M/Dex.

Problems of the trial included that

- only 37 of the patients who were randomly assigned to HDM/ASCT actually underwent the treatment
- treatment-related mortality in the HDM group (24%) was higher than that reported in single-center studies from amyloidosis referral centers (4% to 14%).

The high mortality was likely due to enrollment of patients who had severe organ dysfunction and would not be eligible for HDM/ASCT at many referral centers. However, a subset analysis of patients with low risk for an adverse outcome of intensive treatment also showed similar survival at 3 years of 80% in the M/Dex group and 58% in the HDM/ASCT group ($P = 0.13$). Furthermore, patients who survived for at least 6 months after randomization and who received their assigned treatment exhibited similar (20% to 30%) mortality rates.

On the basis of these findings, the following recommendations are proposed:

- patients with severe organ dysfunction should receive M/Dex as first-line treatment;
- patients with less severe disease are eligible for M/Dex or HDM/ASCT, still considered the reference treatment in experienced centers in the United States.

Patients should be carefully monitored by assessment of free light chains. In those who do not show hematologic responses after 3 to 6 months (>50% decrease of free monoclonal light chain), treatment should be changed to alternatives such as lenalidomide- (or thalidomide-) or bortezomib-based regimens.

Dialysis and Transplantation

Most studies of the clinical course and outcome of dialysis patients include both AL and AA amyloidosis. The patient's survival rate is about 70% at 1 year and decreases to 30% to 44% at 5 to 6 years. Median survival is shorter in patients with AL amyloidosis (26 months) than with AA amyloidosis; sepsis and cardiac deaths are the main causes of mortality. Cardiac amyloid is the most important predictor of mortality in dialysis patients with AL amyloidosis. The management of patients with AL amyloid on hemodialysis (HD) is often complicated by persistent hypotension, gastrointestinal hemorrhage, chronic diarrhea, and difficulties in the creation and maintenance of vascular access. It has therefore been suggested that peritoneal dialysis (PD) could have several advantages over HD in the management of end-stage renal amyloidosis, including avoidance of vascular access and deleterious effects on blood pressure; but PD may induce protein loss in the dialysate and thus enhance malnutrition. However, the survival rate of AL and AA amyloidosis patients treated

with PD is similar to that of patients on HD. Renal transplantation is limited by the severity of heart involvement and the recurrence of deposits in the transplanted kidney. There are a few cases and small series reported in the literature of renal transplantation in AL amyloidosis. Renal transplantation may be considered in patients whose underlying clonal plasma cell disease has remitted after chemotherapy. Heart transplantation can also be envisaged in specific cases as a tandem with HDM/ASCT or after remission.

AA Amyloidosis

Epidemiology

AA amyloidosis develops in 5% of patients with sustained elevation of serum amyloid A protein (SAA). Patients at risk are those with a long duration of chronic inflammatory disease (median, 17 years), high magnitude of acute-phase SAA response, homozygosity for SAA1 isotype, familial Mediterranean fever (FMF) trait (heterozygosity for variant pyrin), and family history of AA amyloidosis. An important epidemiologic aspect of AA amyloidosis is the changing spectrum of underlying diseases. Pyogenic and granulomatous infections, especially tuberculosis, account for far fewer cases today (15%) than previously. Thus, antibiotic treatment efficiently prevents AA amyloidosis by suppressing its cause. In contrast, the prevalence of chronic inflammatory arthritis has increased dramatically (60%). AA amyloidosis in patients with Hodgkin's disease has virtually disappeared with more efficient treatment of the hematologic disease. Hereditary AA amyloidoses associated with familial recurrent fever syndromes account for an increasing proportion of cases, about 10% in recent series.

Clinical Manifestations

The main target organ is the kidney, which is affected in almost all patients with AA amyloidosis. Presentation may be acute with nephrotic syndrome or very insidious. Proteinuria is absent in about 5% of cases. Gastrointestinal disturbances (including diarrhea, constipation, and malabsorption) and hepatosplenomegaly are the next most common manifestations. In contrast with AL amyloidosis, congestive heart

failure, peripheral neuropathy, macroglossia, and carpal tunnel syndrome occur infrequently.

Diagnosis

A systematic search for amyloidosis is recommended in patients with active, long-lasting inflammatory arthritis, even in the absence of proteinuria and chronic kidney disease (CKD). Although findings on kidney biopsy are positive in almost 100% of symptomatic patients, less invasive biopsy procedures should be attempted first. Biopsies of accessory salivary glands, abdominal fat, and rectal mucosa yield positive results in 50% to 80% of patients. Immunohistochemical staining using antibodies to SAA is required to confirm that Congo red–positive amyloid deposits are of the AA type. SAP scintigraphy shows that bones are not affected (contrary to AL amyloidosis).

Natural History and Treatment

Survival time of patients with AA amyloidosis is 133 months, much longer than with AL amyloidosis. Main causes of death are infections and dialysis-related complications but not cardiac complications. Amyloid load and clinical outcome relate to circulating concentrations of SAA. The relative risk of death among patients with an SAA concentration below 4 mg/l is almost 18 times lower than among patients with an SAA concentration of 155 mg/l or greater. Even a very modest elevation in the SAA concentration of 4 to 9 mg/l is associated with a risk of death increased by a factor of 4. These data emphasize the importance of vigorous treatment of the underlying inflammatory disease. SAA (preferable to C-reactive protein) levels should be monitored monthly and maintained at a target value of less than 4 mg/l.

Amyloid deposits regress in 60% of patients who have a median SAA concentration below 10 mg/l, and survival among these patients is superior to survival when amyloid deposits do not regress. Other factors associated with increased mortality are older age and end-stage renal disease (ESRD). Eprodisate, a member of a new class of compounds interfering with interactions between amyloidogenic proteins and GAGs and thereby inhibiting polymerization of amyloid

fibrils, slowed the decline of renal function in patients with AA amyloidosis. However, eprodisate had no beneficial effect on proteinuria, ESRD, amyloid content of abdominal fat, or risk of death. Although eprodisate may be a promising treatment option for AA amyloidosis, emphasis should remain on treatment of the underlying inflammatory disorder. Most described patients receiving renal transplantation in AA amyloidosis are those with rheumatic diseases. Amyloid deposits recur in about 10% of the grafts. Infection is the main cause of early death.

Familial Mediterranean Fever and Other Hereditary Recurrent Fever Syndromes

FMF represents a particular type of AA amyloidosis and the most frequent cause of familial amyloidosis. Colchicine has proved to be efficient in its prevention and treatment. FMF is usually transmitted as an autosomal recessive disorder and occurs most commonly in Sephardic Jews and Armenians. It is caused by mutations of the gene (MEFV) encoding a protein called pyrin or marenostrin. Clinically, there are two independent phenotypes. In the first, brief, episodic, febrile attacks of peritonitis, pleuritis, or synovitis occur in childhood or adolescence and precede the renal manifestations. In the second, renal symptoms precede and may be the only manifestation of the disease for a long time. The attacks are accompanied by dramatic elevations of acute-phase reactants, including SAA. Amyloid deposits are responsible for severe renal lesions with prominent glomerular involvement, leading to ESRD at a young age, and for early deaths. Colchicine can prevent the development of proteinuria, may occasionally reverse the nephrotic syndrome, and may prevent the glomerular filtration rate (GFR) decline in patients with non-nephrotic proteinuria. It is less effective in preventing progression in patients with nephrotic syndrome or renal impairment. The minimal daily dose of colchicine for prevention of amyloidosis is 1 mg, and patients with clinical evidence of amyloidotic kidney disease should receive daily doses of 1.5 to 2 mg. However, about 10% of patients are unresponsive to colchicine. Interleukin-1 receptor antagonists are second-line agents. In patients with intolerance of colchicine, the drug should be stopped, then reintroduced at lower doses. The recent identification of genes responsible for syndromes of periodic fever

with amyloidosis has opened the way to a molecular diagnosis of hereditary AA amyloidosis. These syndromes include the tumor necrosis factor receptor–associated periodic syndrome, the Muckle-Wells syndrome, and the familial cold autoinflammatory syndrome. Only a few cases of systemic AA amyloidosis have been reported in the hyperimmunoglobulinemia D with periodic fever syndrome.

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Chapter 5

Urinary Tract Infection. Pyelonephrities

Urinary tract infection (UTI) in adults can be categorized into six groups: young women with acute uncomplicated cystitis, young women with recurrent cystitis, young women with acute uncomplicated pyelonephritis, adults with acute cystitis and conditions that suggest occult renal or prostatic involvement, complicated UTI, and asymptomatic bacteriuria.

Complicated UTI is defined as UTI that increases the risk for serious complications or treatment failure. Patients with various conditions are at increased risk for complicated UTI. Complicated UTIs may require different pretreatment and post-treatment evaluation and type and duration of antimicrobial treatment than for uncomplicated UTI. On occasion, complicated UTIs are diagnosed only after a patient has a poor response to treatment. The physician often must decide, on the basis of limited clinical information, whether to embark on a more extensive evaluation and treatment course when confronted with a patient with UTI.

Epidemiology

Acute uncomplicated UTIs are extremely common, with several million episodes of acute cystitis and at least 250,000 episodes of acute pyelonephritis occurring annually in the United States. The incidence of cystitis in young sexually active women is about 0.5 per 1 person-year. Acute uncomplicated cystitis may recur in 27% to 44% of healthy women, even though they have normal urinary tracts. The incidence of pyelonephritis in young women is about 3 per 1000 person-years.

Complicated UTIs encompass an extraordinarily broad range of infectious entities. Nosocomial UTIs are a common type of complicated UTI and occur in 5% of admissions in the university tertiary care hospital setting; catheter-associated infections account for most of the infections. Catheter-associated bacteriuria is the most common source of gram-negative bacteremia in hospitalized patients.

Asymptomatic bacteriuria is defined as two separate consecutive clean-voided urine specimens both with 10⁵ or more colony-forming units (cfu)/ml of the same uropathogen in the absence of symptoms referable to the urinary tract. Asymptomatic

bacteriuria is found in about 5% of young adult women but rarely in men younger than 50 years. The prevalence increases up to 16% of ambulatory women and 19% of ambulatory men older than 70 years and up to 50% of elderly women and 40% of elderly men who are institutionalized. Asymptomatic bacteriuria may be persistent or transient and recurrent, and many patients have had previous symptomatic infection or develop symptomatic UTI soon after having asymptomatic bacteriuria. Asymptomatic bacteriuria is generally benign, although as discussed later, it may lead to serious complications in some clinical settings.

Uncomplicated Infection

Most uncomplicated UTIs in healthy women result when uropathogens (typically *Escherichia coli*) present in the rectal flora enter the bladder through the urethra after an interim phase of periurethral and distal urethral colonization. In the male, colonizing uropathogens may also come from a sex partner's vagina or rectum. Hematogenous seeding of the urinary tract by potential uropathogens such as *Staphylococcus aureus* is the source of some UTIs, but this is more likely to occur in the setting of persistent blood stream infection or urinary tract obstruction.

Many host behavioral, genetic, and biologic factors predispose young healthy women to uncomplicated UTI. Risk factors include sexual intercourse, use of spermicide products, and a history of previous recurrent UTI. Nonsecretors of ABO blood group antigens have an increased risk for recurrent cystitis, the P1 blood group phenotype is a risk factor for recurrent pyelonephritis in women, and mutations in the gene for CXCR1, the interleukin-8 receptor, are more frequent and expression of CXCR1 is lower in children prone to pyelonephritis compared with controls. Factors protecting individuals from UTI include the host's immune response; maintenance of normal vaginal flora, which protects against colonization with uropathogens; and removal of bladder bacteriuria by micturition.

Certain strains of *E. coli* have a selective advantage for colonization and infection. P-fimbriated strains of *E. coli* are associated with acute uncomplicated pyelonephritis, and their adherence properties may stimulate epithelial and other cells to produce proinflammatory factors that stimulate the inflammatory response. Other

virulence determinants include adherence factors (types 1, S, and Dr fimbriae), toxins (hemolysin), aerobactin, and serum resistance. Bacterial virulence determinants associated with cystitis and asymptomatic bacteriuria have been less well characterized.

Factors affecting the large difference in UTI prevalence between men and women include the greater distance between the usual source of uropathogens (the anus and the urethral meatus), the drier environment surrounding the male urethra, and the greater length of the male urethra. Risk factors associated with UTIs in healthy men include intercourse with an infected female partner, anal intercourse, and lack of circumcision, although these factors are often not present in men with UTI. Most uropathogenic strains infecting young men are highly virulent, suggesting that the urinary tract in healthy men is relatively resistant to infection.

Complicated Infection

The initial steps leading to uncomplicated UTI discussed earlier probably also occur in most individuals who develop a complicated UTI. Factors that predispose individuals to complicated UTI generally do so by causing obstruction or stasis of urine flow, facilitating entry of uropathogens into the urinary tract by bypassing normal host defense mechanisms, providing a nidus for infection that is not readily treatable with antimicrobials, or compromising the host immune system. UTIs are more likely to become complicated in the setting of impaired host defense, as occurs with indwelling catheter use, vesicoureteral reflux, obstruction, neutropenia, and immune deficiencies.

Etiologic Agents

Uncomplicated upper and lower UTI is most commonly due to *E. coli* (present in 70% to 95%) and *Staphylococcus saprophyticus* (present in 5% to more than 20%). *S. saprophyticus* only rarely causes acute pyelonephritis. Less common causes of uncomplicated UTI include other Enterobacteriaceae, such as *Proteus mirabilis* or *Klebsiella* species; enterococci; group B streptococci; and rarely *Pseudomonas aeruginosa*, *Citrobacter* species, or other uropathogens.

A broader range of bacteria can cause complicated UTI, and many are resistant to broad-spectrum antimicrobial agents. Although *E. coli* is the most common, *Citrobacter* species, *Enterobacter* species, *P. aeruginosa*, enterococci, and *S. aureus* account for a relatively higher proportion of cases compared with uncomplicated UTIs. The proportion of infections caused by fungi, especially *Candida* species, is increasing. Patients with chronic conditions, such as spinal cord injury and neurogenic bladder, are more likely to have polymicrobial (multiorganism) and multidrug-resistant infections.

Acute Uncomplicated Pyelonephritis in Women

Acute pyelonephritis is suggested by fever (temperature $\geq 38.5^{\circ}\text{C}$), chills, flank pain, nausea and vomiting, and costovertebral angle tenderness. Cystitis symptoms are variably present. Symptoms may vary from a mild illness to a sepsis syndrome with or without shock and renal failure. Pyuria is almost always present, but leukocyte casts, specific for UTI, are infrequently seen. Gram stain of the urine sediment may aid in differentiating gram-positive and gram-negative infections, which can influence empiric therapy. A urine culture, which should be performed in all women with acute pyelonephritis, will have 10^4 cfu/ml or more uropathogens in up to 95% of patients. On pathologic examination, the kidney shows a focal inflammatory reaction with neutrophil and monocyte infiltrates, tubular damage, and interstitial edema. Although imaging studies are generally not performed, the infected kidney is often enlarged, and contrast-enhanced computed tomography (CT) shows decreased opacification of the affected parenchyma, typically in patchy, wedge-shaped, or linear patterns.

The availability of effective oral antimicrobials, especially the fluoroquinolones, allows initial oral therapy in appropriate patients or, in those requiring parenteral therapy, the timely conversion from intravenous to oral therapy and reduced need for hospitalization. Indications for admission to the hospital include inability to maintain oral hydration or to take medications; uncertain social situation or concern about compliance; uncertainty about the diagnosis; and severe illness with high fevers, severe pain, and marked debility. Outpatient therapy is safe and effective

for selected patients who can be stabilized with parenteral fluids and antibiotics in an urgent care facility and sent home with oral antibiotics under close supervision. In one population-based study of acute pyelonephritis in adult women, only 7% were hospitalized.

The management strategy for acute uncomplicated pyelonephritis

There are many effective parenteral and oral regimens for acute uncomplicated pyelonephritis. In the outpatient setting, an oral fluoroquinolone should be used for initial empiric treatment of infection caused by gram-negative bacilli. Trimethoprim-sulfamethoxazole or other agents can be used if the infecting strain is known to be susceptible. If enterococci are suspected from the Gram stain, amoxicillin should be added to the treatment regimen until the causative organism is identified. Second- and third-generation cephalosporins also appear effective, although published data are sparse. Neither nitrofurantoin nor fosfomycin is approved or recommended for the treatment of pyelonephritis.

For hospitalized patients, ceftriaxone is an effective and inexpensive agent if the Gram stain is not suggestive of gram-positive bacterial infection. If enterococci are suspected on the basis of a stain showing gram-positive bacteria, ampicillin plus gentamicin, ampicillin-sulbactam, and piperacillin-tazobactam are reasonable broad-spectrum empiric choices. Trimethoprim-sulfamethoxazole should not be used alone for empiric therapy for pyelonephritis in areas with a high prevalence of resistance to this combination. Patients with acute uncomplicated pyelonephritis can often be switched to oral therapy after 24 to 48 hours, although longer intervals of parenteral therapy are occasionally indicated in patients whose symptoms and signs do not improve rapidly (such as those with continued high fever, severe flank pain, or persistent nausea and vomiting). Treatment of acute uncomplicated pyelonephritis can be limited to 7 days for mildly to moderately ill patients who have a rapid response with resolution of fever and symptoms soon after initiation of treatment. However, β -lactam regimens shorter than 14 days have been associated with unacceptably high failure rates in some studies. One study demonstrated superiority of a 7-day ciprofloxacin regimen over a 14-day trimethoprim-sulfamethoxazole

regimen, with the difference accounted for entirely by the higher rate of resistance of the uropathogens to trimethoprim-sulfamethoxazole.

Complicated Infections

Complicated UTI may present with classic signs of cystitis and pyelonephritis but may also be associated with vague or nonspecific symptoms, such as fatigue, irritability, nausea, headache, and abdominal or back pain. Signs and symptoms may exist for weeks to months before diagnosis. Complicated UTI, like uncomplicated UTI, is generally associated with pyuria and bacteriuria, although these may be absent if the infection does not communicate with the collecting system.

For initial treatment in more seriously ill, hospitalized patients, several parenteral antimicrobial agents are available. In contrast to uncomplicated UTI, *S. aureus* is more common in complicated UTIs, and if it is suspected, the therapeutic regimen should have activity against this pathogen. Studies show that a high proportion of *S. aureus* isolates, even in the community are methicillin-resistant (MRSA), so vancomycin should be included in the empiric treatment regimen if *S. aureus* is suspected. Potential concerns that must be considered in the management of complicated UTI include the increasing prevalence of resistance to fluoroquinolones in institutional settings and the frequency of enterococcal infections.

The antimicrobial regimen can be modified when the infecting strain has been identified and antimicrobial susceptibilities are known. Patients who are given parenteral therapy can be switched to oral treatment after clinical improvement. Few studies have been performed that evaluate duration of treatment in populations with complicated UTIs. However, it is desirable to limit the duration of treatment, especially for milder infections, to reduce the selection pressure for drug-resistant flora. In one study, clinical and microbiologic success rates after treatment were almost identical in patients with acute pyelonephritis or complicated UTI treated with a 5-day course of levofloxacin or a 10-day course of ciprofloxacin. These data suggest that a 7- to 10-day regimen is reasonable for most patients with complicated UTI, depending on their clinical response; shorter regimens, such as a 5-day regimen of a urinary fluoroquinolone, are likely to be sufficient in those patients who are less

severely ill, are infected with uropathogens susceptible to the antibiotic used, and have a rapid response to treatment. At least 10 to 14 days of therapy is recommended in those patients who have a delayed response.

Renal Abscess

Renal cortical and corticomedullary abscesses and perirenal abscesses occur in 1 to 10 per 10,000 hospital admissions. Patients usually present with fever, chills, back or abdominal pain, and costovertebral angle tenderness but may have no urinary symptoms or findings if the abscess does not communicate with the collecting system, as is often the case with a cortical abscess. Bacteremia may be primary (cortical abscess) or secondary (corticomedullary or perirenal). The clinical presentation may be insidious and nonspecific, especially with perirenal abscess, and the diagnosis may not be made until admission to a hospital or at autopsy. CT is recommended to establish the diagnosis and location of a renal or perirenal abscess. Empiric antibiotic therapy should be broad and cover *S. aureus* and other uropathogens causing complicated UTI and modified once urine culture results are known.

A renal cortical abscess (renal carbuncle) is usually caused by *S. aureus*, which reaches the kidney by hematogenous spread. Treatment with antibiotics is usually effective, and drainage is not required unless the patient is slow to respond. A renal corticomedullary abscess, in contrast, usually results from ascending UTI in association with an underlying urinary tract abnormality, such as obstructive uropathy or vesicoureteral reflux, and is usually caused by common uropathogenic species such as *E. coli* and other coliforms. Such abscesses may extend deep into the renal parenchyma, perforate the renal capsule, and form a perirenal abscess. Treatment with antimicrobial agents without drainage may be effective if the abscess is small and if the underlying urinary tract abnormality can be corrected. Aspiration of the abscess may be necessary in some patients, and nephrectomy may occasionally be required in patients with diffuse renal involvement or with severe sepsis. Perirenal abscesses usually occur in the setting of obstruction or other complicating factors and result from ruptured intrarenal abscesses, hematogenous spread, or spread from a

contiguous infection. Causative uropathogens are those commonly found in complicated UTIs, including *S. aureus* and enterococci; polymicrobial infections are common. Anaerobes or *Mycobacterium tuberculosis* may be causative. A previously high mortality rate has been lowered with earlier diagnosis and therapy. In contrast to the other types of abscess, drainage of pus is the cornerstone of therapy, and nephrectomy is sometimes indicated.

Papillary Necrosis

More than half of those who develop papillary necrosis have diabetes, almost always in conjunction with a UTI, but the condition also complicates sickle cell disease, analgesic abuse, and obstruction. Renal papillae are vulnerable to ischemia because of the sluggish blood flow in the vasa recta, and relatively modest ischemic insults may cause papillary necrosis. The clinical features are those typical of pyelonephritis. In addition, passage of sloughed papillae into the ureter may cause renal colic, renal insufficiency or failure, or obstruction with severe urosepsis. Papillary necrosis in the setting of pyelonephritis is associated with pyuria and a positive urine culture. Causative uropathogens are those typical of complicated UTI. Spiral CT is the preferred diagnostic procedure. Radiologic findings include an irregular papillary tip; dilated calyceal fornix; extension of contrast material into the parenchyma; and a separated crescent-shaped papilla surrounded by contrast material, called the ring sign. Broad-spectrum antibiotics are indicated. Papillae obstructing the ureter may require removal with a cystoscopic ureteral basket or relief of obstruction by insertion of a ureteral stent.

Emphysematous Pyelonephritis

Emphysematous pyelonephritis is a fulminant, necrotizing, life-threatening variant of acute pyelonephritis caused by gas-forming organisms, including *E. coli*, *K. pneumoniae*, *P. aeruginosa*, and *Proteus mirabilis*. Up to 90% of cases occur in diabetic patients, and obstruction may be present. Symptoms are suggestive of pyelonephritis, and there may be a flank mass. Dehydration and ketoacidosis are common. Pyuria and a positive urine culture are usually present. Gas is usually detected by a plain abdominal radiograph or ultrasound. CT is the diagnostic

modality of choice, however, because it can better localize the gas than ultrasound can. Accurate localization of gas is important because gas may also form in an infected obstructed collecting system or renal abscess; although serious, these conditions do not carry the same grave prognosis and are managed differently. Parenteral broad-spectrum antibiotics and percutaneous catheter drainage with relief of obstruction may be adequate for those less severely ill, but nephrectomy is warranted for those who are more severely ill and those less severely ill who do not respond to the preceding steps. Medical treatment is associated with a mortality rate of 60% to 80%, which is lowered to 20% or less with surgical intervention.

Renal Malacoplakia

Malacoplakia is a chronic granulomatous disorder of unknown etiology involving the genitourinary, gastrointestinal, skin, and pulmonary systems. It is characterized by an unusual inflammatory reaction to a variety of infections and is manifested by the accumulation of macrophages containing calcified bacterial debris called Michaelis-Gutmann bodies. The underlying disorder appears to be a monocyte-macrophage bactericidal defect. The diagnosis is made by histologic examination of involved tissue. Genitourinary malacoplakia, most commonly involving the bladder, is usually associated with gram-negative UTI. Patients with renal malacoplakia generally have fever, flank pain, pyuria and hematuria, bacteriuria, and, if both kidneys are involved, impaired renal function. CT scanning usually shows enlarged kidneys with areas of poor enhancement, and the condition may be indistinguishable from other infectious or neoplastic lesions. On occasion, the malacoplakia may extend through the renal capsule into the perinephric space, simulating a renal carcinoma. Treatment consists of therapy with a broad spectrum antimicrobial; correction of any underlying complicating conditions if possible, and improvement of renal function. Nephrectomy is recommended for advanced unilateral disease. When the disease is bilateral or occurs in a transplanted kidney, the prognosis is very poor.

Xanthogranulomatous Pyelonephritis

Xanthogranulomatous pyelonephritis is a poorly understood, uncommon, but severe chronic renal infection associated with obstruction of the urinary tract.[34]

The renal parenchyma is replaced with a diffuse or segmental cellular infiltrate of foam cells, which are lipid-laden macrophages. The process may also extend beyond the renal capsule to the retroperitoneum. Its pathogenesis appears to be multifactorial, with infection complicating obstruction and leading to ischemia, tissue destruction, and accumulation of lipid deposits. Patients with xanthogranulomatous pyelonephritis are characteristically middle-aged women and have chronic symptoms such as flank pain, fever, chills, and malaise. Flank tenderness, a palpable mass, and irritative voiding symptoms are common. The urine culture is usually positive with *E. coli*, other gram-negative bacilli, or *S. aureus*. CT generally shows an enlarged nonfunctioning kidney, often the presence of calculi and low-density masses (xanthomatous tissue), and, in some cases, involvement of adjacent structures. It may be difficult to distinguish from neoplastic disease. Broad-spectrum antimicrobials are indicated, but total or partial nephrectomy is usually necessary for cure.

Asymptomatic Bacteriuria

Asymptomatic bacteriuria, as noted previously, is a common and generally benign infection. Pyuria is often present, especially in elderly people, and is a predictor for subsequent symptomatic UTI in some groups. Causative uropathogens are the same as those causing UTIs in the same population. Screening for and treatment of asymptomatic bacteriuria is generally not warranted. However, patients at high risk for serious complications warrant a more aggressive approach to diagnosis and treatment, including pregnant women and patients undergoing urologic surgery. Current management strategies in patients with a renal transplant, including long-term antimicrobial prophylaxis, help prevent both asymptomatic bacteriuria and symptomatic urinary infection. It is not clear, however, whether screening for or treatment of asymptomatic bacteriuria in such patients is worthwhile. Some authorities advise treatment of asymptomatic bacteriuria found in patients with anatomic or functional abnormalities of the urinary tract, diabetic patients, and patients with urea-splitting bacteria, such as *P. mirabilis*, *Klebsiella* species, and others. Evidence-based guidelines for screening and treatment of asymptomatic bacteriuria in these populations are needed. Asymptomatic bacteriuria in catheterized

patients in hospitals and long-term care facilities, although thought to be generally benign, represents a large reservoir of antimicrobial-resistant urinary pathogens that increases the risk of cross-infection among catheterized patients and results in frequent inappropriate antimicrobial use.

Lab Studies

In the outpatient setting, pyelonephritis is usually suggested based on the history and physical examination and is supported by urinalysis results, which should include microscopic analysis. Other lab studies are used to evaluate for complicating conditions and to assist in determining if the patient should be admitted. Most easily diagnosed cases occur in women, both pregnant and nonpregnant. Men, patients at the extremes of age, patients harboring subclinical pyelonephritis, and patients who are hospitalized may present with an insidious onset. This section presents information relative to the perspective of pyelonephritis versus UTIs, in general.

Urinalysis

Gross hematuria occurs infrequently with pyelonephritis and is more common with lower UTI (hemorrhagic cystitis). When present, the differential should include calculi, cancer, glomerulonephritis, tuberculosis, trauma, and vasculitis. Pyuria is defined as more than 5-10 WBCs per high-power field (hpf) on a specimen spun at 2000 rpm for 5 minutes. Almost all patients with pyelonephritis have significant pyuria (>20 WBCs/hpf), although the numbers may be smaller, particularly in those with subacute pyelonephritis. The dipstick leukocyte esterase test (LET) helps screen for pyuria. LET results have a sensitivity of 75-96% and a specificity of 94-98% for detecting more than 10 WBC/hpf. The nitrite production test (NPT) for bacteriuria has 92-100% sensitivity and 35-85% specificity and may be falsely negative in the presence of diuretic use, low dietary nitrate, or organisms that do not produce nitrate reductase (eg, Enterococcus, Pseudomonas, Staphylococcus). Combined, the LET-NPT has a sensitivity of 79.2% and a specificity of 81%, which is too low for it to be used as the only screening study for bacteriuria. Microscopic examination may reveal hematuria, but other causes should be considered, particularly calculi. This is especially true if the patient does not respond to therapy. White cell casts are

suggestive of pyelonephritis; however, centrifuge speeds (>2000 rpm) used for urinalysis sediment preparation often fracture them and lead to their absence in the sediment. Proteinuria is expected (up to 2 g/d). When it exceeds 3 g/d, glomerulonephritis should be considered. The presence of a single bacterium in an unspun urine specimen by oil-immersion microscopic examination is equivalent to at least 10⁵ organisms. Bacteria are identified much more easily on a stained versus an unstained specimen.

Urine culture

Urine culture is indicated in any patient with pyelonephritis, whether treated in an inpatient or an outpatient setting, because of the possibility of antibiotic resistance. Specimens can be collected by clean catch, catheter, or suprapubic puncture (rarely performed or indicated).

Blood cultures

Blood cultures are indicated in any patient who is being admitted or who has already been admitted. Approximately 12-20% are positive for infection. Bacteremia has not been associated with a poor outcome unless sepsis or another significant comorbidity is present.

Imaging Studies

Imaging studies are rarely indicated for the diagnosis of acute pyelonephritis in the adult who presents with typical signs and symptoms. Imaging may be warranted if the presentation is atypical or confusing. It is also warranted if the patient deteriorates or does not respond to therapy, as illustrated by the following scenarios, in which the important considerations are nephrolithiasis, obstructive uropathy, and perinephric abscess:

- The patient has a fever or positive blood culture results that persist for longer than 48 hours.
- The patient's condition suddenly worsens.
- Toxicity persists for longer than 72 hours.
- The patient has a complicated UTI.

Medical Care

Supportive care

- Rest
- Antipyretics as needed
- Oral or parenteral pain medications as needed
- Oral or parenteral antiemetics as needed
- Urinary tract analgesics to relieve dysuria (up to 3 d)
- Intravenous or oral fluids to maintain hydration status

Reasons for hospital admission

- Cannot tolerate oral intake
- Unstable social situation (eg, possibility of poor compliance or poor follow-up)
- Unstable vital signs
- Severe signs and symptoms
- Pregnancy
- Comorbid disorders that increase the complexity of management or the complication rate (eg, diabetes mellitus, chronic lung disease, congenital or acquired immunodeficiency syndrome)

Antibiotic selection

- Antibiotic selection is typically empirical, because the results of blood or urine cultures are rarely available by the time a decision must be made.
- Initial selection should be guided by local antibiotic resistance patterns. Urine cultures should be checked in 48 hours to determine antibiotic efficacy.
- When using an oral-only regimen, the initial dose should be administered at the time of the evaluation.

Chapter 6

Tubulointerstitial nephritis

Chronic tubulointerstitial nephritis is a histologic entity characterized by progressive scarring of the tubulointerstitium, with tubular atrophy, macrophage and

lymphocytic infiltration, and interstitial fibrosis. Because the degree of tubular damage accompanying interstitial nephritis is variable, the term tubulointerstitial nephritis is used interchangeably with interstitial nephritis. Tubulitis refers to infiltration of the tubular epithelium by leukocytes, usually lymphocytes.

There are many primary as well as secondary causes of chronic interstitial nephritis. Tubulointerstitial injury is clinically important because it is a better predictor than the degree of glomerular injury of present and future renal function. Although any glomerular disease can injure the tubulointerstitium secondarily through mechanisms involving the direct effects of proteinuria and ischemia, we restrict our discussion to primary chronic interstitial nephritis.

Pathogenesis

The tubulointerstitium can be injured by toxins (e.g., heavy metals), drugs (e.g., analgesics), crystals (e.g., calcium phosphate, uric acid), infections, obstruction, immunologic mechanisms, and ischemia. Regardless of the initiating mechanism, however, the tubulointerstitial response shows little variation. Tubular injury results in the release of chemotactic substances and the expression of leukocyte adhesion molecules that attract inflammatory cells into the interstitium. Tubular cells express human leukocyte antigens, serve as antigen-presenting cells, and secrete complement components and vasoactive mediators, all of which may further stimulate or attract macrophages and T cells. Growth factors released by tubular cells and macrophages, such as platelet-derived growth factor and transforming growth factor β , may stimulate fibroblast proliferation and activation, leading to matrix accumulation. The source of fibroblasts in renal interstitial fibrosis remains controversial but may include an intrinsic fibroblast population, migration of circulating fibrocytes from perivascular areas, and transdifferentiation of tubular cells, pericytes, and endothelial cells into fibroblasts. Over time, a loss of peritubular capillaries and decreased oxygen diffusion due to expansion of the interstitium render the kidney hypoxic, and progressive apoptosis leads to local hypocellularity and fibrosis. Renal function becomes severely decreased, and renal replacement therapies are required.

Epidemiology

Whereas chronic interstitial nephritis occurs with progressive renal disease of all etiologies, primary chronic interstitial nephritis is not a common cause of end-stage renal disease (ESRD); reports range from 42% in Scotland to 3% to 4% in China and the United States. This variability in incidence may relate to differences in how diagnoses are made, etiologies and toxin or drug exposure, and treatment modalities.

Pathology

The pathologic features of chronic interstitial nephritis are nonspecific. They include tubular cell atrophy or dilation; interstitial fibrosis that is composed of interstitial (types I and II) collagens; and mononuclear cell infiltration with macrophages, T cells, and occasionally other cell types (neutrophils, eosinophils, and plasma cells). Tubular lumina vary in diameter but may show marked dilation, with homogeneous casts producing a thyroid-like appearance, hence the term thyroidization. Whereas a noncaseating granulomatous pattern is observed in sarcoidosis, interstitial granulomatous reactions also occur in response to infection of the kidney by mycobacteria, fungi, or bacteria; drugs (rifampin, sulfonamides, and narcotics); and oxalate or urate crystal deposition. Interstitial granulomatous reactions also have been noted in renal malacoplakia, Wegener's granulomatosis, and heroin abuse and after jejunioileal bypass surgery.

Clinical Manifestations

The impaired renal function is often insidious, and the early manifestations of the disease are those of tubular dysfunction, which may go undetected. Diagnosis is often made incidentally on routine laboratory screening or during evaluation of hypertension, in association with reduced glomerular filtration rate (GFR). Proteinuria is commonly less than 1 g/day. The urinalysis may show only occasional white blood cells and, rarely, white blood cell casts. Hematuria is uncommon. Anemia may occur relatively early because of loss of erythropoietin-producing interstitial cells. The tubular dysfunction is often generalized, but some conditions may present with proximal tubular defects including aminoaciduria, phosphaturia, proximal renal tubular acidosis (RTA), or, rarely, a complete Fanconi syndrome.

Distal tubular defects can be associated with type 4 RTA. Concentrating defects (increased urinary frequency and nocturia) can be a sign of medullary dysfunction and may be severe enough to result in nephrogenic diabetes insipidus. Some subjects will also have an inability to conserve salt on a low-salt diet with subsequent salt-wasting syndrome. Others, particularly with microvascular disease, may have a relative inability to excrete salt with resultant salt-sensitive hypertension.

Treatment

Treatment includes identification and elimination of any exogenous agents (drugs, heavy metals), metabolic causes (hypercalcemia), or conditions (obstruction, infection) potentially causing the chronic interstitial lesion. Specific treatments may be required for a condition, such as corticosteroids for sarcoidosis. General measures include control of blood pressure. Most clinicians favor the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), which reduce glomerular and systemic pressures, decrease proteinuria, and increase renal blood flow.

Drug-Induced Chronic Interstitial Nephritis

Several drugs and herbs can cause chronic interstitial nephritis.

Lithium Nephropathy

Definition and Epidemiology

Lithium is commonly used in the treatment of bipolar disorder. Complications of lithium treatment include nephrogenic diabetes insipidus, acute lithium intoxication, and chronic lithium nephrotoxicity. A meta-analysis of the data of 14 studies involving 1172 patients receiving chronic lithium therapy showed that the prevalence of reduced GFR was 15%.

Pathogenesis

Diabetes insipidus results from accumulation of lithium in the collecting tubular cells after entry into these cells through sodium channels in the luminal membrane. Lithium blocks vasopressin-induced reabsorption by inhibiting adenylate cyclase activity, and hence cyclic adenosine monophosphate production, and also by decreasing the apical membrane expression of aquaporin 2, the collecting tubule

water channel. Chronic lithium-induced interstitial nephritis may also occur, possibly due to inositol depletion and inhibition of cell proliferation.

Pathology

Biopsies show focal chronic interstitial nephritis with interstitial fibrosis, tubular atrophy, and glomerular sclerosis. Whereas similar histologic changes have been reported in psychiatric subjects without a history of lithium therapy, subjects with lithium exposure often show microcystic changes in the distal tubule; interstitial inflammation and vascular changes are relatively minimal. The degree of interstitial fibrosis is related to the duration of administration and cumulative dose.

Clinical Manifestations

Lithium-Associated Diabetes Insipidus

The most common presentation of lithium-induced nephrotoxicity is nephrogenic diabetes insipidus, characterized by resistance to vasopressin, polyuria, and polydipsia. Impaired renal concentrating ability is found in about 50% of patients, and polyuria due to nephrogenic diabetes insipidus occurs in about 20% of patients chronically treated with lithium. Lithium is also rarely a cause of hypercalcemia, which could potentially exaggerate the tubular concentrating defect and contribute to the development of chronic interstitial nephritis in lithium-treated patients. Nephrogenic diabetes insipidus in lithium treatment may be associated with distal RTA, although this partial functional defect is virtually never of clinical importance.

Chronic Lithium Nephropathy

Nephrogenic diabetes insipidus induced by lithium may persist despite the cessation of treatment, indicating irreversible renal damage. In one study, the mean serum creatinine concentration of patients with biopsy-proven chronic lithium nephrotoxicity was 2.8 mg/dl (247 μ mol/l) at the time of biopsy, and 42% of patients had proteinuria greater than 1 g/day. After renal biopsy, all but one patient discontinued treatment with lithium, but seven patients nevertheless progressed to ESRD. Magnetic resonance imaging or ultrasound may help in the detection of the microcysts in the kidney.

Treatment

After other potential causes of polyuria and polydipsia have been excluded, particularly psychogenic polydipsia, the first step to consider is a reduction in lithium dosage. The potassium-sparing diuretic amiloride improves the polyuria and also blocks lithium uptake through sodium channels in the collecting duct. Thiazide diuretics should be avoided as they increase the risk for acute lithium intoxication because of the resultant volume contraction and an increase in sodium and lithium reabsorption in the proximal tubule. Patients receiving long-term lithium treatment should have renal function (serum creatinine and estimated GFR) and 24-hour urine volume measured yearly. Lithium has a narrow therapeutic index, so levels should be monitored and maintained between 0.6 and 1.25 mmol/l. The severity of chronic lithium intoxication correlates directly with the serum lithium concentration and may be categorized as mild (1.5 to 2.0 mmol/l), moderate (2.0 to 2.5 mmol/l), or severe (>2.5 mmol/l). Once-daily regimens are less toxic than multiple daily dose schedules, perhaps because of the possibility of renal tubular regeneration with a once-daily dosing schedule. Prevention of volume depletion is also important.

Because progressive renal injury with reduced GFR in patients without prior acute lithium intoxication is relatively unusual, raised serum creatinine concentration should initially be treated by a dose reduction. If there is persistently elevated serum creatinine, a renal biopsy should be considered, although the findings rarely mandate the complete cessation of lithium treatment. At all times, the risk for discontinuation in a patient with a severe unipolar or bipolar affective disorder needs to be balanced with the relatively low risk for progressive renal injury.

Analgesic Nephropathy

Definition and Epidemiology

Analgesic nephropathy resulted from the abuse of analgesics, commonly mixtures containing phenacetin, aspirin, and caffeine that were available as over-the-counter preparations in Europe and Australia. It is now rare; indeed, some doubt that new cases are still presenting, following restrictions in compound analgesic sales. Long-term use of aspirin alone is not associated with analgesic nephropathy, and

although long-term nonsteroidal anti-inflammatory drug use has been associated with chronic interstitial nephritis in a small number of patients, a large-scale case-control study found no increased risk of ESRD in users of combined or single formulations of phenacetin-free analgesics. A large study in the United States also showed no association between use of current analgesic preparations and increased risk of renal dysfunction.

Pathogenesis and Pathology

The primary injury in analgesic nephropathy is medullary ischemia due to toxic concentrations of phenacetin metabolites combined with relative medullary hypoxia, aggravated by inhibition of vasodilatory prostaglandin synthesis. The main pathologic consequence is papillary necrosis, with secondary tubular atrophy, interstitial fibrosis, and a mononuclear cellular infiltrate.

Clinical Manifestations

Analgesic nephropathy was five to seven times more common in women than in men. Renal manifestations are nonspecific and consist of slowly progressive chronic renal failure with impaired urine concentrating ability, urinary acidification defects, and impaired sodium conservation. Urinalysis showed sterile pyuria and mild proteinuria. Patients with analgesic nephropathy are at increased risk for transitional cell carcinoma of the uroepithelium.

Diagnosis

Papillary necrosis is present histologically in almost all patients, but it can be detected radiologically only if part or all of the papilla has sloughed. Papillary necrosis is not pathognomonic of analgesic nephropathy; it is also seen in diabetic nephropathy (particularly during an episode of acute pyelonephritis), sickle cell nephropathy, urinary tract obstruction, and renal tuberculosis. Non-contrast-enhanced computed tomography (CT) demonstrates a decrease in renal mass with either bumpy contours or papillary calcifications.

Treatment

Management consists of stopping or at least reducing the intake of analgesic medications. Because of the increased incidence of uroepithelial tumors, close follow-up is necessary. New hematuria requires early referral for urologic evaluation.

Chronic Interstitial Nephritis Due to Metabolic Disorders

Chronic Urate Nephropathy

Historically, chronic interstitial nephritis associated with chronic hyperuricemia was called gouty nephropathy. Before drugs that lower uric acid levels became available, more than 50% of patients with gout had impaired renal function and nearly 100% had renal disease at autopsy. In the early 1980s, the concept of gouty nephropathy as a disease was challenged because the renal injury observed in subjects with gout was ascribed to coexistent hypertension, vascular disease, or aging-associated renal injury. However, epidemiologic studies suggest that an elevated serum uric acid level may carry an independent and dose-dependent risk for kidney disease. These increases in risk remained significant even after adjustment for estimated GFR, proteinuria, age, and components of the metabolic syndrome. These studies raise the interesting possibility that chronic hyperuricemia may be both a true risk factor for the development of chronic kidney disease (CKD) and a risk factor for progression of established CKD.

Pathogenesis

It has been suggested that chronic hyperuricemia and uricosuria result in intratubular sodium urate crystal deposition, with local obstruction, rupture into the interstitium, and subsequent granulomatous response and interstitial fibrosis. The determinants of uric acid solubility are its concentration and the pH of the tubular fluid, and the major sites of urate deposition are the renal medullae. If deposition occurs in an acid medium, as in the tubular fluid, birefringent uric acid crystals are formed; whereas in an alkaline medium, as in the interstitium, amorphous urate salts are deposited. Crystalline deposits of urate may account for some degree of renal injury, but subjects with gouty nephropathy often have diffuse renal disease with arteriolosclerosis, focal and global glomerulosclerosis, and interstitial fibrosis. Although it is difficult to ascribe diffuse renal disease to the presence of focal

crystalline deposits, experimental studies have suggested that hyperuricemia may induce chronic renal injury independent of crystal formation. The mechanism appears to be the development of preglomerular arteriolar disease that impairs the renal autoregulatory response and thereby causes glomerular hypertension.

Pathology

Renal functional abnormalities are observed in 30% to 50% of patients who have had gout for many years, and histologic changes are observed in more than 90%. On histologic examination, the lesion is characterized by tubulointerstitial fibrosis, often with arteriolosclerosis and glomerulosclerosis. Within the kidney, there are often precipitated uric acid crystals in the tubules and in the interstitium, particularly in the medulla. On occasion, medullary renal tophi are found on gross anatomic dissection.

Clinical Manifestations

Patients present with hypertension with mildly impaired renal function, mild proteinuria, unremarkable urinary sediment, and minor tubular dysfunction (usually impairment of urine concentrating ability manifested as isosthenuria). Uric acid nephropathy should be particularly considered if there is a disproportionate elevation in serum uric acid in relation to the degree of renal impairment.

Diagnosis

The most important differential diagnosis for gouty nephropathy is chronic lead nephropathy. Familial juvenile hyperuricemic nephropathy is a rare autosomal dominant disease that mimics chronic gouty nephropathy but that presents in adolescence or during early childhood.

Treatment

Whether lowering of uric acid is renoprotective remains controversial. One prospective, randomized, controlled trial demonstrated that allopurinol therapy is associated with preservation of renal function in mild to moderate CKD. Withdrawal of allopurinol from patients with stable CKD resulted in worsening of hypertension and acceleration of kidney dysfunction. One reason for caution is the accumulation of the xanthine oxidase inhibitor allopurinol in renal failure. It is prudent to initiate

allopurinol at a dose of 50 to 100 mg/day, increasing to 200 or 300 mg/day if it is tolerated. A small minority of patients (0.1%) develop a hypersensitivity syndrome that can be fatal, and this risk is increased with renal dysfunction. Experimentally, allopurinol can also be associated with nephrotoxicity in the setting of significant renal dysfunction by formation of allopurinol microcrystals. The newer xanthine oxidase inhibitor febuxostat does not require modification of dose in renal failure, nor is it associated with hypersensitivity or nephrotoxicity, but more studies are required before its use can be recommended.

Hypokalemic Nephropathy

Hypokalemia, if persistent for prolonged periods, can induce renal cysts, chronic interstitial nephritis, and progressive loss of renal function, so-called hypokalemic nephropathy, which can be inherited or acquired.

Pathology

The characteristic finding is vacuolation of the renal tubules due to dilation of cisternae of the endoplasmic reticulum and basal folding, which is generally limited to the proximal tubule segments. This abnormality generally requires at least one month to develop and is reversible with potassium supplementation. More prolonged hypokalemia can lead to more severe changes, predominantly in the renal medulla, including interstitial fibrosis, tubular atrophy, and cyst formation. There is experimental evidence that hypokalemic injury may be due to hypokalemia-induced renal vasoconstriction with ischemia. Local ammonia production stimulated by hypokalemia may also lead to intrarenal complement activation that may contribute to the renal injury. Furthermore, the associated intracellular acidosis can stimulate cell proliferation, which may account for the occasional development of cysts in hypokalemic subjects.

Clinical Manifestations

Impaired urine concentration, presenting with nocturia, polyuria, and polydipsia, may occur, particularly when plasma potassium concentration is consistently below 3.0 mmol/l for months or years. The average duration of hypokalemia reported in patients with chronic hypokalemic nephropathy is between

3.5 and 9 years. The renal defect is associated with decreased collecting tubule responsiveness to vasopressin, possibly due to decreased expression of aquaporin 2.

Diagnosis

Although degenerative changes in proximal tubular cells are a consistent but nonspecific finding in hypokalemic nephropathy, a particularly characteristic finding is vacuolar changes in the proximal tubules. Similar vacuolization of the convoluted tubules is observed in ethylene glycol poisoning.

Treatment

Hypokalemia can usually be treated with oral potassium supplements.. Coarse cytoplasmic vacuoles may persist for some time after normalization of serum potassium values.

Hypercalcemic Nephropathy

Hypercalcemia can cause both a transient and reversible renal vasoconstriction with a decrement in renal function and a chronic interstitial nephritis secondary to tubular cell necrosis and intratubular obstruction. In addition, hypoparathyroidism (especially surgically induced after treatment of hyperparathyroidism) can also result in marked hypercalciuria and a similar syndrome in the absence of hypercalcemia.

Pathology

Focal degeneration and necrosis of the tubular epithelium, primarily in the medulla where calcium is concentrated, develop soon with persistent hypercalcemia. Although focal degenerative and necrotic lesions of the tubular epithelium can be observed in acute hypercalcemic patients, the most distinctive histologic feature of long-standing hypercalcemia is calcific deposits in the interstitium (nephrocalcinosis). Deposition begins in the medullary tubules, followed by deposition in the cortical proximal and distal tubules and within the interstitial space, and secondarily leads to mononuclear cell infiltration and tubular necrosis.

Clinical Manifestations

Macroscopic nephrocalcinosis is often detected on radiography or ultrasound. A defect in urinary concentration is the most notable tubular dysfunction and is manifested as polyuria and polydipsia. The mechanism is incompletely understood,

but the impairment relates both to a reduction in medullary solute content and to interference with the cellular response to vasopressin. Reversible impairment of renal function can result from either acute or chronic hypercalcemia by decreased renal blood flow and GFR. Irreversible renal failure is a rare consequence of long-standing hypercalcemia and is almost invariably associated with calcium crystal deposition in the interstitium of the kidney.

Treatment

Treatment of chronic tubulointerstitial nephritis is depended on ethiology. Chapter 7 is reported the basic principles of renoprotective therapy that could suitable for patients with known chronic tubuloiterstitial nephritis.

Chapter 7

Chronic kidney disease

Chronic kidney disease is a worldwide public health problem. There is a rising incidence and prevalence of kidney failure, with poor outcomes and high cost. There is an even higher prevalence of earlier stages of chronic kidney disease. Increasing evidence, accrued in the past decades, indicates that the adverse outcomes of chronic kidney disease, such as kidney failure, cardiovascular disease, and premature death, can be prevented or delayed. Earlier stages of chronic kidney disease can be detected through laboratory testing. Treatment of earlier stages of chronic kidney disease is effective in slowing the progression toward kidney failure. Initiation of treatment for cardiovascular risk factors at earlier stages of chronic kidney disease should be effective in reducing cardiovascular disease events both before and after the onset of kidney failure. Unfortunately, chronic kidney disease is “under-diagnosed” and “under-treated”, resulting in lost opportunities for prevention. One reason is the lack of agreement on a definition and classification of stages in the progression of chronic kidney disease. A clinically applicable classification would be based on laboratory evaluation of the severity of kidney disease, association of level of kidney function with complications, and stratification of risk for loss of kidney function and development of cardiovascular disease (Fig.7.1)

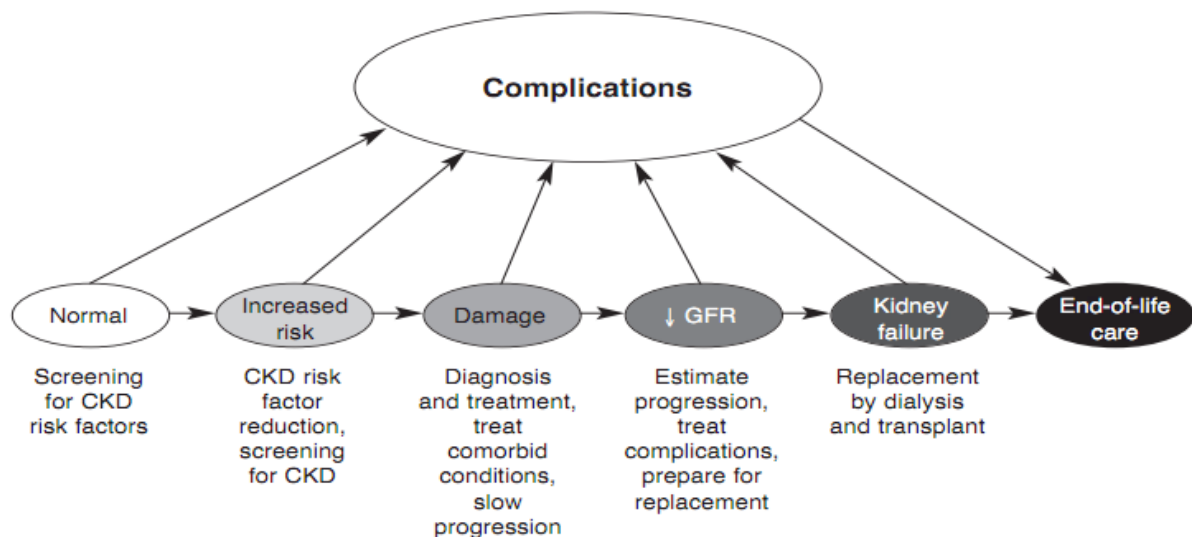


Fig. 7.1 Chronic kidney disease: an overall health approach.

Note: GFR – glomerular filtration rate, CKD – chronic kidney disease

Chronic kidney disease (CKD) includes conditions that affect the kidney, with the potential to cause either progressive loss of kidney function or complications resulting from decreased kidney function. Chronic kidney disease was thus defined as the presence of kidney damage or glomerular filtration rate (GFR) below 60 ml/min per 1.73 m² for 3 months or more, irrespective of diagnosis.

The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines have classified CKD into five stages. This classification, although useful in simplifying the categorization of CKD, has its limitations, which include classifying people with isolated microalbuminuria as suffering from CKD, labeling mild and stable kidney damage as CKD, and not differentiating between age-related impaired kidney function and progressive disease-induced CKD. In 2005, the Kidney Disease: Improving Global Outcomes (KDIGO) group suggested clarifications including the addition of the suffix T for patients with renal allografts and D to identify CKD stage 5 patients on dialysis. The U.K. National Institute of Health and Clinical Excellence (NICE) has modified, in 2008, the KDOQI CKD classification by subdividing CKD stage 3 into 3A and 3B, estimated GFR of 45 to 59 ml/min per 1.73 m² and 30 to 44 ml/min per 1.73 m², respectively (Table 7.1.1). The NICE CKD guidelines also stipulated that the suffix (p) be added to the stages in proteinuric patients. This

refinement of the initial CKD classification by NICE assumes that there is a distinction between patients with GFR below 60 ml/min per 1.73 m² and those with GFR below 45 ml/min per 1.73 m² in terms of prognosis and that the presence of significant proteinuria has to be acknowledged in the classification.

Table 7.1.1

Chronic kidney disease classification accordingly Kidney Disease Outcomes Quality Initiative with modification U.K. National Institute of Health and Clinical Excellence (2008)

Stage	Description	GFR, ml/min per 1.73 m ²
1	Kidney damage and normal in GFR (protein in the urine)	>90
2	Kidney damage or mild decrease in GFR	60-89
3A	Moderate decrease in GFR	30-44
3B		45-59
4	Severe reduction in GFR	15-29
5	Kidney failure (dialysis or kidney transplant needed)	<15

7.2 Epidemiology of Chronic Kidney Disease

The true incidence and prevalence of CKD within a community are difficult to ascertain as early to moderate CKD is usually asymptomatic. However, various epidemiologic studies attempted to clarify that issue and have made relatively similar observations suggesting a prevalence of CKD of around 10%, albuminuria (mostly microalbuminuria) of around 7%, and GFR below 60 ml/min per 1.73 m² of around 3%.

Of note, most of these studies are limited by the fact that individuals were tested only once, thus precluding a clear assumption of chronicity. Incidence of end-stage renal disease (ESRD) refers to the number of patients with ESRD beginning renal replacement therapy (RRT) during a given time (usually a year) in relation to the general population; it is usually expressed as number of patients per million population per year. Of note, the incidence of ESRD according to most national registries does not take into account patients not treated by RRT; therefore, it underestimates the overall true incidence of ESRD (CKD stage 5).

The prevalence of ESRD is the proportion in a specific population who have ESRD at a given time; it encompasses both new and continuing patients on RRT; it is expressed as patients per million population. Prevalence is a function of the incidence (new cases) and outcomes (transplantation or death) rates of ESRD in a given population. The global epidemiology of ESRD is heterogeneous and influenced by several factors. Consequently, the incidence and prevalence of ESRD vary widely from country to country. Disparities in the incidence and prevalence of ESRD within and between developed countries reflect racial and ethnic diversities as well as their impact on the prevalence of diabetes and hypertension in respective countries and communities. Recently, different progression rates of CKD in the population, referral patterns, and quality of pre-ESRD care have been linked to the heterogeneity of ESRD rates in different parts of the world. Disparities with developing countries are likely to reflect availability of and access to RRT in low and middle economies.

7.3 Screening for Chronic Kidney Disease

Current Screening Guidelines

In view of the rising number of those suffering from ESRD and the perceived high prevalence of CKD in communities, interest has focused on the early detection of CKD and those at risk. Several guidelines for screening, mostly targeted to high-risk individuals, have been issued and implemented worldwide. Those include the U.S. KDOQI, the U.K. CKD NICE, and the Australian Caring for Australasians with Renal Impairment (CARI) guidelines, to name a few. There are few differences as to the recommended targeted populations, but they invariably include individuals with

hypertension and diabetes mellitus. Other groups include those with a family history of CKD; obese individuals; those with cardiovascular diseases, especially congestive heart failure; people with multisystem diseases; ethnic groups with high prevalence of CKD; and those with urologic conditions, such as nephrolithiasis. The KDOQI guidelines additionally recommend screening those older than 65 years. Screening should consist of a urine albumin/protein estimation as well as measurement of serum creatinine and estimation of GFR. General population CKD screening is unlikely to be realistic or cost-effective. Targeted screening is the most cost-effective approach. Overall, CKD screening would best be associated with broader national strategies and programs to minimize cardiovascular disease (CVD).

7.4 Natural History of Chronic Kidney Disease

The natural history of CKD stages 1 and 2 remains to be fully defined. It has generally been assumed that the majority of patients with CKD stages 3B to 5 progress relentlessly to ESRD. This has recently been challenged as progression is variable, and a sizable percentage of these patients have stable kidney function or die prematurely of CVD. A Canadian study showed the natural history of CKD stages 3 and 4 to be variable and reflecting the patient's risk factor profile. Many CKD patients with GFR below 60 ml/min per 1.73 m² die from cardiovascular or other causes before reaching ESRD.

A straight-line relationship is often found between the reciprocal of serum creatinine (1/SCr) values or the estimated GFR and time. However, a significant percentage of patients do not progress in a predictable linear fashion and have breakpoints in their progression slopes, suggesting acceleration or slowing down of the rate of progression of CKD. These breakpoints could be either spontaneous or secondary to events such as infections, dehydration, changes in the adequacy of systemic blood pressure control, and exposure to nephrotoxins, in particular nonsteroidal anti-inflammatory drugs (NSAIDs) or radiocontrast agents. Attention has also been drawn recently to the impact of intercurrent acute kidney injury (AKI) events on the rate of progression of CKD. It is also important to appreciate that some patients with mild to moderate CKD have stable renal function for sustained periods.

7.5 Factors of CKD progression

Renin-Angiotensin System

The links between systemic hypertension, proteinuria/albuminuria, and CVD may be mediated by changes in the RAS in CKD. A number of experimental and clinical data have implicated the RAS in the pathogenesis of hypertension, proteinuria, and renal fibrosis throughout the course of CKD. Consequently, interventions aimed at inhibition of the RAS have proved extremely effective in slowing the progression of CKD.

Glycemia

A number of observations as well as randomized clinical trials have demonstrated during the last 25 years that tight diabetes control can potentially slow the rate of progression of diabetic microvascular complications, including diabetic nephropathy in both type 1 and type 2 diabetes mellitus.

Obesity

Several studies have linked obesity, and the associated metabolic syndrome, with increased risk of CKD. Excessive body weight and a raised body mass index have also been linked to a faster rate of progression of CKD. Anecdotal reports suggest that weight reduction reduces obesity-related renal hemodynamic changes as well as CKD-associated proteinuria. Recent data derived from general population studies suggest that body weight reduction reduces albuminuria, and increased weight gain is associated with its progression.

Lipids

Dyslipidemia may contribute to glomerulosclerosis and tubulointerstitial fibrosis. A number of studies of diabetic and nondiabetic nephropathies have confirmed by multivariate analysis that dyslipidemia is a risk factor for a faster rate of CKD progression.

Smoking

Smoking has been shown to increase the risk of albuminuria as well as that of progression of CKD. Possible mechanisms whereby cigarette smoking may

contribute to kidney damage include sympathetic nervous system activation, hypertension, endothelial injury, and potential direct tubulotoxicity.

Uric Acid

Hyperuricemia has been associated with systemic hypertension, CVD, and CKD. Hyperuricemia may cause hypertension and renal injury through crystal-independent pathways, notably a stimulation of the RAAS. In a small Japanese study, hyperuricemic patients with IgA nephropathy had a worse prognosis compared with those with normal serum uric acid levels, and a serum uric acid of 6.0 mg/dl or higher was an independent predictor of ESRD in women. However, a more recent observation from the United States suggested that in patients with CKD, hyperuricemia appears to be an independent risk factor for all-cause and CVD mortality but not for kidney failure.

Additional Factors Implicated in Progression of Chronic Kidney Disease

- Alcohol and recreational drugs
- Analgesics and NSAIDs
- Lead and heavy metals exposure

7.6 Therapy for Natural Progression

Because of the gravity of ESRD and the benefit of even small decreases in CKD progression rate, a strong argument can be made for an aggressive, multiple risk factor intervention to slow GFR decline. This, however, does not apply for patients with low ESRD risk. This includes corticosteroid-responsive minimal change disease (MCD), a solitary kidney that is normal and acquired in adulthood and not accompanied by other CKD risk factors, hereditary nephritis or thin glomerular basement membrane disease in a normotensive adult whose only renal manifestation is microscopic hematuria, and the elderly with idiopathic and moderately elevated serum creatinine (1.30 to 2.00 mg/dl) and minor proteinuria (24-hour urine PC ratio <1.0) and whose renal parameters have been stable for at least 1 year. The last group is much more likely to die of cardiovascular disease (CVD) than to progress to ESRD.

The recommendations categorized as level 1 (highest) are based on one or more large randomized clinical trials (RCTs) that have documented effects on GFR decline.

Level 2 recommendations are based on secondary analysis of the level 1 RCTs, or RCTs that have documented effects on proteinuria but not GFR decline, or RCTs that appear to be of high quality but may not be definitive because of study size. The goals of progression therapy are (1) to reduce proteinuria as much as possible, ideally to less than 500 mg/day, and (2) to slow GFR decline as much as possible, ideally to about 1 ml/min per year, which is the rate of GFR decline attributable to aging.

Control Blood Pressure

The low blood pressure goal is recommended for all CKD patients. On the basis of the relevant RCTs, we suggest a sitting systolic blood pressure in the 120s or lower, if it is tolerated. “Optimal” blood pressure (systolic blood pressure <120 mm Hg) is associated with significantly lower CVD risk than “normal” blood pressure (systolic blood pressure of 120 to 129 mm Hg), and there is no convincing evidence that systolic blood pressure below 120 mm Hg is harmful if it is well tolerated (not associated with fatigue, lightheadedness, tachycardia, or decline in kidney function). Sitting blood pressure is recommended because it is the position used in the relevant RCTs. Systolic blood pressure is the recommended goal because in the relevant RCTs, achieved systolic blood pressure strongly correlated with GFR decline, but achieved diastolic blood pressure did not. Specifying a goal with both a systolic and diastolic blood pressure component is not recommended. ACE Inhibitor therapy is recommended as first-line therapy in mild-to-moderate CKD patients. ARBs are protective in the nephropathy of type 2 diabetes and probably in other nephropathies. ARBs are recommended as first-line therapy in those who are ACE inhibitor intolerant (cough, angioedema, or allergy). In CKD, ARBs may raise serum potassium less than ACE inhibitors.

Control of Protein Intake

Reducing dietary protein intake from the usual level (about 1 to 1.5 g/kg ideal body weight per day) to about 0.7 g/kg ideal body weight per day (low-protein diet) slows GFR decline in those with proteinuria of more than 1 g/day. Another benefit of the

lower protein intake is that it slows proteinuria progression in CKD, even in those who at baseline have low-level proteinuria (e.g., <250 mg/day).

Restrict NaCl Intake and Diuretic Therapy

A high salt intake (e.g., 200 mmol NaCl/day, 4.6 g sodium, 11.6 g NaCl) can completely override the antiproteinuric effects of ACE inhibitor, ARB, or NDHP-CCB therapy. The recommended NaCl intake in CKD (assuming that renal salt wasting is not present) is about 80 to 120 mmol/day (2 to 3 g Na). The NaCl intake in the average North American adult is about 170 mmol/day (3.9 g Na, 9.9 g NaCl).

Control of Fluid Intake

The patients with the higher urine volumes showed higher blood pressure, lower serum sodium, and frankly hypotonic urine, suggesting that they were intentionally taking in excess fluid (“pushing fluids”). Excessive fluid intake in a CKD subject may be difficult to excrete and can lead to volume overload. CKD is associated with both impaired concentration and dilution. Thus, one should neither restrict nor push fluids in CKD.

Nondihydropyridine Calcium Channel Blocker Therapy

This class of agents, which includes diltiazem and verapamil, is antiproteinuric and may be renoprotective. NDHP-CCB together with a DHP-CCB is a potent antihypertensive combination when it is used along with other antihypertensive therapies.

β-Blocker Therapy

The AASK study showed that β-blocker therapy is more antiproteinuric and slows GFR decline more than DHP-CCB. However, β-blockers increase the likelihood of diabetes and, as monotherapy or combined with diuretic, increase the mortality rate of hypertension management compared with ACE inhibitors plus diuretic. β-Blockers should be used in CKD to manage heart disease but should not be first-line therapy for blood pressure and proteinuria. Carvedilol, which possesses both β-blocker and α1-blocker effects, may be better tolerated than metoprolol when it is used in combination with an ACE inhibitor.

Smoking Cessation

There is strong epidemiologic evidence that cigarette smoking promotes progression of all forms of kidney disease and that this effect may be of greater magnitude in African Americans.

Allopurinol Therapy

Allopurinol therapy mitigates these risk factors, perhaps by mechanisms beyond lowering of serum uric acid. However, allopurinol can be associated with a severe allergic reaction (Stevens-Johnson–like syndrome). If allopurinol is administered to CKD subjects, the dose needs to be reduced. Although there is substantial evidence supporting the use of allopurinol in hyperuricemic CKD patients, some experts recommend that allopurinol not be used for asymptomatic hyperuricemia in CKD until better information becomes available because of the risk of severe toxicity. A new xanthine oxidase inhibitor, febuxostat, is now available. It is safe in patients allergic to allopurinol and does not need dose adjustment in CKD.

Other Measures to Retard Progression of Chronic Kidney Disease

- Avoid multiple daily doses of acetaminophen, particularly in women, because of the evidence that it is significantly associated with rising serum creatinine during prolonged follow-up.
- Avoid nonsteroidal anti-inflammatory drugs (NSAIDs) altogether (or, at most, take no more than once or twice weekly) because of their known nephrotoxicity. Daily low-dose aspirin, however, appears to provide net benefit in CKD.
- Avoid herbal therapy unless the safety of the herb has been proved. Many herbals appear to be nephrotoxic
- Avoid prolonged severe hypokalemia because it can cause progressive renal interstitial fibrosis.
- Avoid phosphate cathartics. These can cause acute kidney injury (AKI) and CKD by causing intratubular calcium phosphate deposits.
- Avoid intravenous bisphosphonates in CKD. Some may exacerbate renal failure.
- Avoid oral estrogen in elderly women with CKD. It may promote progression.

- NaHCO_3 to correct metabolic acidosis should be considered because of its anticatabolic effects. Also, the nephrotoxicity of nonselective proteinuria appears to be strongly related to activation of the alternative complement pathway in the renal tubular compartment. NaHCO_3 inhibits this process by raising tubular fluid pH.
- Control hyperphosphatemia and hyperparathyroidism.
- Control anemia
- Control vitamin D3 deficiency
- Kidney replacement therapy is required to be performed as life-safety care

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