RCC occurs in up to 70% of patients with VHLD. It is usually bilateral and the clear cell type. RCC affects younger patients with a mean age at presentation of 26 years. For a high-risk patient, the diagnosis of VHLD is suggested by central nervous system or retinal hemangioblastoma, RCC, or pheochromocytoma. These patients should be referred for detailed assessment. When indicated, genetic testing can be performed to assess possible mutations of the *VHL* gene.

NEPHROLITHIASIS

Epidemiology and Pathogenesis

Nephrolithiasis is a common clinical disorder that imposes a substantial burden on human health and resource use. Calcium-containing stones are the most common types, and stones composed of cystine, struvite, and pure uric acid are less common but have high recurrence rates. Based on National Health and Nutrition Examination Survey, the prevalence of kidney stones has increased from 3.2% in the 1976-1980 period to 8.8% in the 2007-2010 period. Diet and lifestyle factors likely play significant roles in the changing epidemiology.

Nephrolithiasis increases with age and is more common in men than in women, except after menopause, when the incidence tends to equalize. The prevalence is higher among white males, intermediate among Hispanics and Asians, and rare among blacks. After the first manifestation, there is a high rate of stone recurrence, approaching about 50% in 5 to 10 years. The risk factors for recurrence include a younger age at initial presentation, a family history of urolithiasis, underlying medical conditions, and recurrent urinary infections.

Stone formation occurs as a result of supersaturation of urinary solutes, expressed as the ratio of solute concentration in urine to its known solubility. A ratio greater than 1 indicates that urine is supersaturated, promoting crystallization. In all cases, low urine volumes increase the probability of urine solute supersaturation and promote stone formation.

Additional factors are involved. Higher urinary calcium and oxalate concentrations promote calcium oxalate stones, whereas alkaline urine and high urinary calcium concentrations promote calcium phosphate crystal formation. Acidic urine is a major determinant of uric acid crystal formation. Normal urine contains substances such as citrate, pyrophosphate, magnesium, Tamm-Horsfall glycoprotein, glycosaminoglycan, osteopontin, and calgranulin that can inhibit aggregation of crystals in urine. Citrate is the only inhibitor that can be modified in clinical settings.

Clinical Presentation and Diagnosis

Patients with nephrolithiasis are often asymptomatic, and calculi are detected as incidental findings on imaging studies. When symptoms occur, flank pain with or without gross hematuria is characteristic. The pain can vary in intensity from mild to severe and is classically abrupt in onset, paroxysmal, and follows a waxing and waning course over hours. Other associated symptoms include dysuria, urgency, nausea, and vomiting. Some patients may pass "gravel" in their urine, a finding more characteristic of uric acid stones. Complications associated with nephrolithiasis include urinary tract obstruction, hydronephrosis, infection, and acute kidney injury from obstructive uropathy in the setting of bilateral obstruction or unilateral obstruction in the setting of solitary kidney.

A detailed history is crucial for patients with kidney stones and should include age at the first episode, number of stones, bilateral or unilateral occurrence, frequency of stone formation, type of stone if known, type and number of surgical interventions, family history of stone disease, and associated infections. Certain clues elucidated by the history may point toward a systemic cause of nephrolithiasis; for example, patients with malabsorptive states may be predisposed to calcium oxalate stones. The history should include detailed dietary habits, including the amount of fluid intake and dietary levels of sodium, protein, oxalate, and calcium, to determine the potential cause of or contributors to stone formation. Medications that can potentiate stone formation are shown in Table 29-7.

Except during an acute episode of stone passing, most patients have normal physical examination. However, physical examination may sometimes reveal findings suggesting systemic condition such as tophi in patients with hyperuricosuria and uric acid stones.

Laboratory testing includes a complete metabolic profile with attention to calcium, phosphate, and uric acid levels. Hypokalemia and metabolic acidosis suggest renal tubular acidosis, which is associated with a higher incidence of stone formation. A careful urinalysis may identify crystals, and other findings may indicate a specific cause (Table 29-8). When possible, it is important to retrieve stones for chemical analysis. Identification of stone type can guide therapy.

A 24-hour urine collection is the cornerstone of evaluation of most patients with nephrolithiasis and includes quantitation of

TABLE 29-7 MEDICATIONS ASSOCIATED WITH STONE FORMATION

MEDICATION	MECHANISM
Acetazolamide	Hypocitraturia
Vitamin C	Hypocitraturia
Vitamin D	Hypercalciuria
Antacids	Hypercalciuria
Theophylline	Hypercalciuria
Nifedipine	Hypercalciuria
Probenecid, aspirin	Hyperuricosuria
Topamax	Hypocitraturia
Indinavir	Precipitation within the tubule
Acyclovir	Precipitation within the tubule

TABLE 29-8 URINALYSIS AND RADIOGRAPHIC FINDINGS OF RENAL CALCULI

STONE TYPE	URINE MICROSCOPIC FINDINGS	RADIOLOGIC FINDINGS
Calcium oxalate monohydrate	Dumbbell shaped; under polarized light, appear coarse and needle shaped	Opaque, round, multiple calculi
Calcium oxalate dihydrate	Envelope shaped	Opaque
Struvite, magnesium ammonium phosphate	Coffin lid	Opaque, may be staghorn
Uric acid	Pleomorphic, often rhombic plates or rosettes	Radiolucent
Cystine	Hexagonal	Opaque