in decreased tubular calcium reabsorption and depletion of urinary citrate.

Thiazide diuretics are commonly used to decrease urine calcium excretion in recurrent calcium stone formers. They reduce hypercalciuria and stone recurrence regardless of the underlying pathophysiologic mechanism because they promote increased proximal tubule calcium absorption. Thiazides can cause hypokalemia-induced hypocitraturia, and thiazide use should be supplemented with potassium. Potassium citrate has an advantage over other agents because it provides both potassium and citrate.

Hyperoxaluria

Hyperoxaluria (>45 mg/day in women and 55 mg/day in men) is detected in 10% to 50% of calcium stone formers. Hyperoxaluria increases calcium oxalate supersaturation and promotes calcium oxalate stone formation. Hyperoxaluria can result from increased dietary intake, increased gastrointestinal absorption of oxalate, or overproduction of oxalate caused by an inborn error in metabolism.

Dietary issues can be important. Foods known to increase urinary oxalate excretion include rhubarb, spinach, beets, most nuts, chocolate, tea, raspberries, figs, and plums. Enteric hyperoxaluria occurs in patients with malabsorption of fat. Dietary calcium binds to fatty acids in the enteric lumen. The released free oxalate is then available for augmented absorption. Enteric hyperoxaluria is commonly seen in patients with chronic diarrhea, inflammatory bowel diseases, celiac disease, and intestinal resection or after bariatric surgery.

Concomitant risk factors for stone formation include low urine volume, acidic urine, and hypocitraturia. Rarely, hyperoxaluria is caused by inborn errors in metabolism such as primary hyperoxaluria, a rare autosomal recessive genetic disorder of oxalate synthesis. Patients should be advised to avoid excessive vitamin C (>500 mg/day). For patients with enteric hyperoxaluria, measures should be instituted to reduce steatorrhea, such as a low-fat diet, cholestyramine, and administration of medium-chain triglycerides.

Hypocitraturia

Citrate, an endogenous inhibitor of calcium stone formation, is the only inhibitor that is measured and can be modified in clinical settings. Citrate binds to urinary calcium to form a soluble complex and prevent precipitation of calcium with oxalates or phosphates. Citrate also directly inhibits crystal agglomeration. Hypocitraturia can be a consequence of metabolic acidosis, high-protein intake, carbonic anhydrase inhibitors, or hypokalemia, or it may be an idiopathic disorder. Decreases in tubular fluid pH result in conversion of the trivalent citrate anion into the divalent anion, which is more easily reabsorbed by the sodium citrate cotransporter in the luminal membrane. Acidosis results in increased cell citrate use and upregulation of proximal renal tubular reabsorption of citrate, leading to hypocitraturia.

Potassium citrate is more effective in preventing calcium stone formation compared with sodium citrate because the sodium load can worsen hypercalciuria. The usual dose for potassium citrate is 15 to 25 mmol two or three times per day. A potential concern with alkali therapy is the risk of calcium phosphate stone formation. Among patients with reduced kidney function, serum potassium needs to be monitored closely because of the risk of hyperkalemia.

Calcium Phosphate Stones

Calcium phosphate stone formation is a result of hypercalciuria, hypocitraturia, and persistently alkaline urine. Calcium phosphate stones can be seen in patients with distal renal tubular acidosis, with use of carbonic anhydrase inhibitors such as acetazolamide (which inhibit bicarbonate reabsorption in the proximal tubule), and with use of antiepileptic drugs such topiramate that can inhibit carbonic anhydrase.

Uric Acid Stones

Three major urinary abnormalities causing uric acid precipitation are low urinary pH (urine pH <5.5), low urine volume, and hyperuricosuria. When urinary pH is acidic, changes in physical chemistry result in conversion of more soluble urate into less soluble uric acid, thereby facilitating lithogenesis. Excessive acid loads (e.g., diet high in animal protein) or chronic bicarbonate loss in patients with chronic diarrhea can result in low urinary pH, increasing the propensity for uric acid stone formation. The increased incidence of uric acid stones among patients with insulin resistance and type 2 diabetes mellitus has been linked to impaired ammonia synthesis resulting in reduced urinary pH. Hyperuricosuria also may be seen in certain clinical conditions such as myeloproliferative disorders, tumor lysis syndrome, rare genetic disorders linked to the uric acid synthetic pathway, and mutations in renal uric acid transporters.

Alkaline therapy along with increasing urine volume is the most effective treatment of uric acid stones. Potassium citrate, given as 30 to 80 mmol in divided doses, is prescribed to maintain a urine pH of 6.5 to 7. Further increases in urinary pH to above 7 may result in calcium phosphate precipitation and should be avoided. When marked hyperuricosuria persists (urinary uric acid excretion >600 mg/day in women and 700 mg/day in men) despite dietary animal protein limitation and other measures, xanthine oxidase inhibitors such as allopurinol can be used at doses of 100 to 300 mg/day.

Struvite Stones

Struvite or triple phosphate stones are composed of magnesium ammonium phosphate and calcium carbonate apatite. They can grow rapidly and, if untreated, can fill the entire pelvis, resulting in staghorn calculi. They also can cause chronic kidney disease, including ESRD. Struvite stones result from chronic urinary tract infections with urea-splitting organisms (Table 29-11), which increase urine pH by generating ammonium to produce stones composed of ammonium-magnesium-phosphate.

The mainstay of treatment for struvite stones includes early surgical removal of bacteria-laden stones and eradication of

TABLE 29-11 UREASE-PRODUCING BACTERIA

Corynebacterium	*Providencia* (most species)
Haemophilus	*Pseudomonas*
Klebsiella	*Serratia*
Proteus (most species)	*Staphylococcus*