AIN and protect renal function. When indicated, the usual approach includes high-dose intravenous methylprednisolone (250 mg consecutively for 3 days), followed by oral prednisone (1 mg/kg) and tapering over 4 to 6 weeks. Patients who are intolerant or resistant to steroids may benefit from mycophenolate mofetil (500 to 1000 mg twice daily).

Most cases of drug-related AIN resolve after removal of the offending drug. The overall prognosis depends on the duration of the AIN; a longer interval between onset of AIN and drug withdrawal can lead to irreversible kidney damage. Because of the rapid transformation of interstitial cellular infiltrates into fibrosis, up to 40% of patients may not fully recover baseline renal function, and about 10% of the patients may become dialysis dependent.

CHRONIC INTERSTITIAL NEPHRITIS

Chronic interstitial nephritis (CIN) is a clinicopathologic diagnosis. Prolonged exposure to a causative agent initiates an indolent inflammatory process, and chronic interstitial nephritis can lead to permanent renal damage over months to years before it manifests clinically. Patients usually have a gradual decline in renal function. CIN is common and accounts for 15% to 30% of all cases of end-stage renal disease (ESRD).

Histologically, CIN shows tubular atrophy, flattened epithelial cells, tubule dilation, interstitial fibrosis, and areas of mononuclear cell infiltration within the interstitial compartment (E-Fig 29-3). The infiltrates are typically less conspicuous compared with AIN, and there is more interstitial fibrosis. In earlier stages of CIN, glomeruli are usually spared, but with progression, glomerular abnormalities such as segmental and global sclerosis can develop.

Patients with CIN usually have no renal symptoms until they develop overt chronic kidney disease. The features are nonspecific and include fatigue, lack of appetite, nausea, vomiting, hypertension, and sleep disturbances, and other laboratory and clinical findings may develop as listed in Table 29-2. CIN also can cause proximal or distal tubular dysfunction, which can lead to defects in acidification of the urine, partial or complete Fanconi's syndrome, and decreased concentrating ability. Laboratory data for these patients may show elevated levels of creatinine, proteinuria, hematuria, glycosuria, and pyuria. Due to the destruction of erythropoietin-producing interstitial cells, anemia, associated fatigue, and decreased exercise tolerance are common as CIN progresses.

The histologic findings of CIN are nonspecific, and the differential diagnosis can be extensive, as shown in Table 29-3. Repeated injuries from drugs, toxins, radiation nephritis, and reflux nephropathy can result in a similar histologic picture. The most common cause of CIN is chronic NSAID use. Other causes of include infections, immune-mediated disorders, drug reactions, hematologic disorders, chronic urinary tract obstruction, and urinary reflux. Some metabolic disorders and exposure to heavy metals can also lead to CIN. The clinical importance, distinguishing features, causes, and management of several forms of CIN are discussed in the following sections.

TABLE 29-2 CLINICAL FINDINGS THAT SUGGEST CHRONIC INTERSTITIAL NEPHRITIS

Hyperchloremic metabolic acidosis (out of proportion to the degree of renal insufficiency)
Hyperkalemia (out of proportion to the degree of renal insufficiency)
Reduced maximal urinary concentrating ability (e.g., polyuria, nocturia)
Partial or complete Fanconi's syndrome (e.g., phosphaturia, bicarbonaturia, aminoaciduria, uricosuria, glycosuria)
Modest proteinuria (<2 g/day)
Anemia
Hypertension

Analgesic Nephropathy

Analgesic nephropathy is the prototype CIN, and it occurs commonly worldwide. This disorder is caused by long-term ingestion of aspirin in various combinations with phenacetin, caffeine, or acetaminophen. In its most severe form, analgesic nephropathy is associated with papillary necrosis.

The cumulative amount of phenacetin-acetaminophen combination required to cause chronic interstitial nephritis is estimated to be at least 2 to 3 kg. Although initially thought to be exclusively associated with phenacetin-containing combinations, all analgesics, including acetaminophen, aspirin, and NSAIDs, are capable of inducing CIN.

Analgesic nephropathy is most commonly detected in women in the sixth and seventh decades of life. Patients with analgesic nephropathy have renal insufficiency, modest proteinuria, sterile pyuria, and anemia. Occasionally, patients may have flank pain

TABLE 29-3 CONDITIONS ASSOCIATED WITH CHRONIC INTERSTITIAL NEPHRITIS

ASSOCIATED CONDITIONS	EXAMPLES
Hereditary diseases	Autosomal dominant polycystic kidney disease
Metabolic disturbances	Hypercalcemia, nephrocalcinosis Hyperuricemia Hyperoxaluria Hypokalemia Cystinosis
Drugs and toxins	Analgesics, nonsteroidal anti-inflammatory drugs Lead Nitrosoureas Cisplatin Cyclosporine Tacrolimus Lithium Chinese herbs Olanzapine
Immune-mediated diseases	Granulomatosis with polyangiitis (Wegener's granulomatosis) Sjögren syndrome Systemic lupus erythematosus Vasculitis Sarcoidosis Crohn's disease
Hematologic disease or malignancy	Multiple myeloma Sickle cell disease Lymphoma
Infection	Chronic pyelonephritis Xanthogranulomatous pyelonephritis
Obstruction	Tumors Stones Bladder outlet obstruction Vesicoureteral reflux
Miscellaneous disorders	Radiation nephritis Hypertensive arterionephrosclerosis Renal ischemic disease