to be adjusted compared to their usage for myeloma. The proteasome inhibitor bortezomib has also been found to be effective in single-center and multicenter trials. Anti-fibril small molecules and humanized monoclonal antibodies are also being tested. Clinical trials are essential in improving therapy for this rare disease.

Supportive care is important for patients with any type of amyloidosis. For nephrotic syndrome, diuretics and supportive stockings can ameliorate edema; angiotensin-converting enzyme inhibitors should be used with caution and have not been shown to slow renal disease progression. Effective diuresis can be facilitated with albumin infusions to raise intravascular oncotic pressure. Congestive heart failure due to amyloid cardiomyopathy is best treated with diuretics; it is important to note that digitalis, calcium channel blockers, and beta blockers are relatively contraindicated as they can interact with amyloid fibrils and produce heart block and worsening heart failure. Amiodarone has been used for atrial and ventricular arrhythmias. Automatic implantable defibrillators have reduced effectiveness due to the thickened myocardium, but they may benefit some patients. Atrial ablation is an effective approach for atrial fibrillation. For conduction abnormalities, ventricular pacing may be indicated. Atrial contractile dysfunction is common in amyloid cardiomyopathy and is an indication for anticoagulation even in the absence of atrial fibrillation. Autonomic neuropathy can be treated with α agonists such as midodrine to support the blood pressure; gastrointestinal dysfunction may respond to motility or bulk agents. Nutritional supplementation, either oral or parenteral, is also important.

In localized AL disease, amyloid deposits can be produced by clonal plasma cells infiltrating local sites in the airways, bladder, skin, or lymph nodes (Table 137-1). These deposits may respond to surgical intervention or low-dose radiation therapy (typically only 20 Gy); systemic treatment generally is not appropriate. Patients should be referred to a center familiar with management of these rare manifestations of amyloidosis.

AA AMYLOIDOSIS

Etiology and Incidence AA amyloidosis can occur in association with almost any chronic inflammatory state (e.g., rheumatoid arthritis, inflammatory bowel disease, familial Mediterranean fever [Chap. 392], or other periodic fever syndromes) or chronic infections such as tuberculosis or subacute bacterial endocarditis. In the United States and Europe, AA amyloidosis has become less common, occurring in fewer than 2% of patients with these diseases, presumably because of advances in anti-inflammatory and antimicrobial therapies. It has also been described in association with Castleman's disease, and patients with AA amyloidosis should undergo CT scanning to look for such tumors as well as serologic and microbiologic studies. AA amyloidosis can also be seen without any identifiable underlying disease. AA is the only type of systemic amyloidosis that occurs in children.

Pathology and Clinical Features Organ involvement in AA amyloidosis usually begins in the kidneys. Hepatomegaly, splenomegaly, and autonomic neuropathy can also occur as the disease progresses; cardiomyopathy occurs, albeit rarely. The symptoms and signs of AA disease cannot be reliably distinguished from those of AL amyloidosis. AA amyloid fibrils are usually composed of an 8-kDa, 76-amino-acid *N*-terminal portion of the 12-kDa precursor protein SAA. This acute-phase apoprotein is synthesized in the liver and transported by high-density lipoprotein (HDL3) in the plasma. Several years of an underlying inflammatory disease causing chronic elevation of SAA levels usually precede fibril formation, although infections can lead to AA deposition more rapidly.

TREATMENT AA AMYLOIDOSIS

Primary therapy for AA amyloidosis consists of treatment of the underlying inflammatory or infectious disease. Treatment that suppresses or eliminates the inflammation or infection also decreases the SAA concentration. For familial Mediterranean fever, colchicine at a dose of 1.2–1.8 mg/d is the standard treatment. However, colchicine has not been helpful for AA amyloidosis of other causes or for other amyloidoses. Tumor necrosis factor and interleukin 1 antagonists can be effective in syndromes related to cytokine elevation. For this disease, there is also a fibril-specific agent: eprodisate was designed to interfere with the interaction of AA amyloid protein with glycosaminoglycans and to prevent or disrupt fibril formation. The drug is well tolerated and delays progression of AA renal disease. Randomized phase III clinical trials with eprodisate are ongoing; the drug is not otherwise available.

ATTR AND AF AMYLOIDOSIS

The familial amyloidoses are autosomal dominant diseases in which, beginning in midlife, a variant (FINE) plasma protein forms amyloid deposits. These diseases are rare, with an estimated incidence of <1 case/100,000 population in the United States, although founder effects in isolated areas of Portugal, Sweden, and Japan have led to a much higher incidence. The most common form of AF amyloidosis is ATTRm in the updated nomenclature, caused by mutation of the abundant plasma protein transthyretin (TTR, also known as *prealbumin*). More than 100 TTR mutations are known, and most are associated with ATTR amyloidosis. One variant, V122I, has a carrier frequency that may be as high as 4% in the African-American population and is associated with late-onset cardiac amyloidosis. The actual incidence and penetrance of disease in the African-American population is the subject of ongoing research, but ATTR amyloidosis warrants consideration in the differential diagnosis of African-American patients who present with concentric cardiac hypertrophy and evidence of diastolic dysfunction, particularly in the absence of a history of hypertension. Other familial amyloidoses, caused by variant apolipoproteins AI or AII, gelsolin, fibrinogen Aα, or lysozyme, are reported in only a few families worldwide. New amyloidogenic serum proteins continue to be identified periodically, including recently the leukocyte chemotactic factor LECT2, a cause of renal amyloidosis in Hispanic and Pakistani populations. To date, no mutation in the coding sequence for the LECT2 gene has been identified, so the heritability of ALECT2 is uncertain.

TTR deposits composed of unmutated fibrils occur with aging, and ATTRwt is being diagnosed with increasing frequency in Caucasian men >65 years of age with amyloid cardiomyopathy. Formerly termed senile systemic amyloidosis, ATTRwt has been found at autopsy in 25% of hearts from patients older than age 80 years. Why a wild type protein becomes amyloidogenic, and why patients bearing mutant TTR genes do not express disease until adulthood, remains a mystery.

Clinical Features and Diagnosis AF amyloidosis has a presentation that is variable but is usually consistent within kindreds affected by the same mutant protein. A family history makes AF disease more likely, but many patients present sporadically with new mutations. ATTR amyloidosis typically presents as a syndrome of familial amyloidotic polyneuropathy or familial amyloidotic cardiomyopathy. Peripheral neuropathy begins as a small-fiber lower-extremity sensory and motor neuropathy and progresses to the upper extremities. Autonomic neuropathy manifests as diarrhea with weight loss and orthostatic hypotension. Patients with TTR V30M, the most common mutation, have normal electrocardiograms but may develop conduction defects late in the disease. Patients with TTR T60A and several other mutations have myocardial thickening similar to that caused by AL amyloidosis, although heart failure is less common and long-term survival rates are usually better. Vitreous opacities caused by amyloid deposits are pathognomonic for ATTR amyloidosis.

Typical syndromes associated with other forms of AF disease include renal amyloidosis with mutant fibrinogen, lysozyme, or apolipoproteins; hepatic amyloidosis with apolipoprotein AI; and amyloidosis of cranial nerves and cornea with gelsolin. Patients with AF amyloidosis can present with clinical syndromes that mimic those of patients with AL disease. Rarely, AF carriers can develop AL disease or AF patients may have monoclonal gammopathy without AL.