Treatment of Membranous Nephropathy in the Elderly

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MN is relatively common in the elderly and can lead to significant morbidity and mortality as a result of complications of the nephrotic syndrome and end-stage renal disease. Some cases of MN may be missed as asymptomatic urinary abnormalities and progressive renal disease may be attributed incorrectly to vascular disease or normal aging. Urinary abnormalities and changes in renal function should be evaluated in the elderly using the same criteria as applied in younger individuals. When MN is diagnosed in an elderly individual, it has the same risks for progression as in younger individuals; thus, therapy for hypertension, hyperlipidemia, edema, and proteinuria should be instituted. When appropriate, elderly individuals should receive immunosuppressive therapy to induce a remission of the nephrotic syndrome and reduce the risk for progressive loss of renal function using criteria similar to younger patients. Most studies show response rates to be comparable in all age groups examined. The only consistent recommendation is to avoid high-dose corticosteroids when possible. Recognize that drug dosages need to be modified and carefully monitored and that the elderly may be particularly prone to side effects and infectious complications of immunosuppressive therapy. Although treatment of MN in the elderly has unique challenges, reducing the need for renal replacement therapy in this population merits special attention.

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AS IN OTHER ADULTS, membranous nephropathy (MN) is the most common cause of idiopathic nephrotic syndrome in the elderly, accounting for 35% to 75% of glomerular disease.[1,2] Of patients with MN, the elderly account for 23% of cases.[2] Although immune function is altered in normal aging, it does not appear to contribute to increased risk for development of MN. Yet, the underlying alterations in immune function render the elderly more prone to complications of nephrotic syndrome and immunosuppressive treatment.[3,4] Alterations in hepatic function, decrements in glomerular filtration rate (GFR), changes in pharmacokinetics, and increased risk for hypertension and vascular disease justify special attention to treatment decisions in elderly individuals with MN.

CLINICAL CHARACTERISTICS OF MN IN THE ELDERLY

In studies of glomerular disease in the elderly (usually defined as $>$ age 60), MN is the most common cause of nephrotic syndrome. The proportion of nephrotic patients with MN varies from 35% to 75%, depending on the degree of proteinuria and whether or not systemic diseases such as diabetes had been excluded from the study population.[1,2,5] When compared with younger subjects, a smaller proportion of the elderly present with asymptomatic urinary abnormalities as compared with nephrotic syndrome.[5] This apparent difference in presentation may be misleading because minor urinary abnormalities that are incorrectly attributed to normal aging less often prompt referral of an elderly individual for renal biopsy examination. As in younger patients, men outnumber women with MN from 2:1 to 3:1.[6] The reason for the increased incidence in men is unknown. Postmenopausal women lose their sex-based advantage for slower rates of decline of renal function and lower rates of end-stage renal disease; yet, sex differences in MN in the elderly have not been reported.

Severe, unremitting nephrotic syndrome, hypertension, and an elevated creatinine level at the time of diagnosis are indicators of a worse prognosis for all patients with renal disease and this includes elderly individuals with MN.[2] Elevated serum creatinine levels may be the consequence of progressive MN or underlying aging-related glomerulosclerosis.[7] In either case, individuals with glomerulosclerosis progress to end-stage disease over a shorter period of time. Thrombotic complications of MN are more frequent in the elderly,[8] and are more common than in younger cohorts.[8] As the number of elderly patients who require renal replacement therapy has reached 50% of the dialysis population in the United States, attention to treatment of renal disease in the elderly is particularly important.[9]

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CHANGES THAT OCCUR WITH AGING THAT IMPACT DIAGNOSIS AND MANAGEMENT OF MN

Although there is some debate regarding the cause and degree of changes that occur with normal aging, changes in renal function are common in individuals over the age of 60.[10] Glomerular basement membrane thickens and in some cases there is progressive glomerulosclerosis.[7,11] Clearly in individuals with vascular disease, these changes are more pronounced, but it is unclear whether or not all sclerotic changes associated with aging are a direct consequence of vascular disease.[12] Small decrements in GFR and minimal proteinuria accompany these changes,[13] which may make it difficult to identify the presence of additional renal disease, including MN, in elderly individuals.[14] In addition to the glomerular changes, changes in the interstitium are common in the elderly.[15] These may be secondary to glomerular loss, vascular disease, or obstructive uropathy. Interstitial changes are associated with abnormalities in urinary concentrating ability, drug metabolism, and acid excretion.[10,15] Abnormal tubular function influences the risk for side effects from medications used to treat MN. The presence of changes in renal function in the elderly, which may incorrectly be attributed to aging per se, may lead to a delay in diagnosis and underdiagnosis of MN in the elderly. Inappropriate diagnosis and treatment of MN may be a contributor to the growing rates of end-stage renal disease in our aging population. Because most studies report that the elderly respond to therapy with rates comparable with younger individuals,[2,9,16] appropriate diagnosis and treatment should be pursued in all individuals with renal disease irrespective of age.

TREATMENT OF MN IN THE ELDERLY

Seventy-five percent of elderly patients with MN present with nephrotic syndrome, which directly causes significant morbidity and mortality.[5] The natural history of untreated MN is unclear because the rate of progression varies in different studies,[17] this makes it difficult to evaluate the impact of treatment in studies with relatively small numbers of patients. One quarter to one half of patients with MN progress to end-stage renal disease, but they do so over a variable period of time. In elderly patients with mild nephrotic syndrome and preserved renal function, conservative therapy is appropriate. Because the majority of elderly patients with MN present with nephrotic syndrome, the first goal is to manage the nephrotic syndrome and reduce the risk for complications associated with it. The second goal is to reduce the risk for progression to end-stage renal disease. In some cases both can be approached with the same treatment because remission of the nephrotic syndrome is also associated with an improved prognosis for long-term preservation of renal function. When renal function is adequate, and life expectancy or other factors preclude treatment with immunosuppressive agents, treatment specifically directed at minimizing the nephrotic syndrome and risk for complications is appropriate. When these measures fail, immunosuppressive therapy may be used to control severe nephrotic syndrome and to protect GFR.

NEPHROTIC SYNDROME

Nephrotic syndrome per se is associated with edema, hypertension, hypercoagulopathy, increased risk for infection, and hypercholesterolemia.[18] Also, proteinuria may directly injure tubules thereby contributing to progressive loss of renal function. The hyperlipidemia associated with nephrotic syndrome accelerates progression of vascular disease, and the hypercoagulable state increases the risk for thrombotic events, particularly in sites of underlying vascular disease. Elderly individuals with underlying atherosclerotic disease are at increased risk for stroke and myocardial infarction in the face of nephrotic syndrome.[8] Recent studies in the Heymann rat model of MN have shown that proteinuria is a consequence of intracellular lipid peroxidation, which prompted a small study of probucol in humans.[19] In that study, probucol, but not lovostatin, was associated with a significant reduction in proteinuria. Although these observations require confirmation in more subjects, efforts to reduce lipid-mediated injury to vascular tissues and the kidney are important considerations in the management of elderly individuals with MN. Should individuals with known vascular disease not respond to therapy designed to reduce proteinuria, anticoagulation or other measures to treat vascular disease should be considered.

Management of the Nephrotic Syndrome

Nephrotic syndrome accounts for significant morbidity and mortality in elderly patients with

MN. The severity of the nephrotic syndrome determines its management.[18] In milder forms, with serum albumin concentrations greater than 2.5 mg/dL, significant sodium retention, volume expansion, and hypertension treatment may be directed at those manifestations. Only patients with milder forms of nephrotic syndrome should be treated with diuretics and antihypertensive agents alone. Those with severe nephrotic syndrome will likely require immunosuppressive agents to significantly reduce heavy proteinuria. In the face of severe nephrotic syndrome, albumin may be less than 2.5 mg/dL, and intravascular volume depletion may accompany the marked reduction in plasma oncotic pressure. These individuals tend to have a low blood pressure, and diuretic use in them may precipitate acute renal failure. Patients with profound nephrotic syndrome also may have serum immunoglobulin G levels below 600 mg/dL, which renders them particularly susceptible to sepsis. When accompanied by intravascular volume depletion, serum viscosity is elevated and in the face of hypercoagulability, these individuals are particularly prone to venous and arterial thrombosis. Management of nephrotic syndrome can be particularly difficult in the elderly who are prone to congestive heart failure and who develop more edema because of venous insufficiency. In fact, many elderly individuals with nephrotic syndrome are diagnosed incorrectly as having congestive heart failure. Additional details of the management of nephrotic syndrome have been reviewed elsewhere,[18] and generally these recommendations apply to the elderly. Because of pre-existing malnutrition and frailty, hepatic disease with inadequate synthetic response to albumin losses, underlying osteoporosis, atherosclerotic disease, and increased risk for infection, management decisions can be particularly challenging in the elderly.

Lipid-Lowering Agents

Hypercholesterolemia needs to be treated in patients with nephrotic syndrome because this is an important contributor to progressive loss of renal function and increased morbidity and mortality from cardiovascular disease in patients with renal insufficiency. The best treatment is to reverse the abnormal physiology associated with nephrotic syndrome by inducing a remission. When patients fail to respond to specific therapy for MN or when immunosuppressive therapy is contraindicated, specific treatment of hyperlipidemia should be considered. Statins appear to be the safest and most effective agents at lowering lipids in patients with nephrotic syndrome.[18] Based on recent concepts of risks associated with hypertriglyceridemia and the role of lipid peroxidation, more specific agents such as probucol and peroxisome proliferator-activated receptor (PPAR) receptor agonists may prove to be therapeutic choices in the future.

Antihypertensive Therapy

Angiotensin-converting enzyme (ACE) inhibitors have beneficial effects on blood pressure, reduce renal scarring through their effects on transforming growth factor β and other cytokines, and reduce proteinuria through modulation of intraglomerular hemodynamics. Patients with modest degrees of proteinuria and hypertension should be treated with ACE inhibitors or angiotensin receptor blockers. In patients with severe nephrotic syndrome, ACE inhibitors may have only a modest effect on the amount of proteinuria, unless doses are pushed to the degree that they induce a significant reduction in GFR. This approach to reduce heavy proteinuria should be reserved for those patients who fail to respond to immunosuppressive therapy.

PRESERVATION OF RENAL FUNCTION

Other sections of this issue have focused on the controversies and approaches to the treatment of MN. Because these have been covered in detail, only comments relevant to unique features in the elderly will be discussed herein. Although elderly patients have been included in most studies of the response to various immunosuppressive regimens, they are few in number and there have been no specific studies of treatment of MN in the elderly. In the absence of specific data inferences must be drawn, and logical recommendations must be based on what is known about underlying immune system abnormalities and alterations in pharmacokinetics in the elderly. There is general consensus that immunosuppressive therapy is associated with higher complication rates in the elderly, however, specific data are lacking.[2,4]

IMMUNE SYSTEM FUNCTION IN THE ELDERLY

Abnormalities in both the cellular and humoral arms of the immune system occur in normal aging.

These abnormalities increase the rates of autoimmunity, change tumor surveillance, and render the elderly more susceptible to infection, which is the leading direct cause of death in individuals over the age of 65.[20] Abnormalities in humoral immunity can be detected by impaired antibody response to immunization.[21] Intrinsic B-cell function appears normal because B cells respond appropriately to T-dependent antigens and differentiate into high-affinity antibody-secreting cells. Yet, specific studies in mice[22] show that an abnormal microenvironment and impaired costimulatory functions provided by T cells limit the capacity of B cells to respond appropriately to antigens during new infections. Toll-like receptors, which recognize conserved molecular patterns on microbes, link innate and adaptive parts of the immune system.[23] Decreased expression in aging mice is associated with reduced stimulation of interleukin 6 and tumor necrosis factor α, which creates poor adaptive immune responses.[23] During the early stages of T-cell receptor interaction with antigen-presenting cells, the cytoskeleton must reorganize to bring signal transduction molecules into proper subcellular compartments. Because early cytoskeletal reorganization is abnormal in aging, subsequent steps in antigen processing are impaired.[24] Abnormal antigen processing by dendritic cells renders elderly patients particularly susceptible to skin infections.[25]

Abnormal T-cell function also influences the high levels of autoreactive antibodies that result from dysregulation of expressed memory B cells later in life.[26] Memory functions of the immune system are relatively well preserved, as are most effector functions. Age-related accumulation of oligoclonal, memory T cells, and a reduction in the naive T-cell pool lead to a reduction in the CD8 T-cell repertoire. In one study, up to a quarter of the total CD8 T-cell population was cytomegalovirus specific.[27] Such a dramatic accumulation of virus-specific effector T cells might impair the host's ability to respond to other infections and may underlie the negative influence of cytomegalovirus seropositivity on survival in the elderly. Thus, altered T-cell function represents the most consistent change, thereby affecting both humoral and cellular arms of the immune system.[26] Because the peak incidence of MN occurs at ages 40 and 60, without a significant increase after age 60, it seems unlikely that increased autoantibodies or immune system dysfunction of aging influence the development of MN. Rather, the abnormal function of the immune system may increase the risk for infections that are common in patients with severe nephrotic syndrome and in elderly patients treated with immunosuppressive drugs.[3,4]

ALTERED PHARMACOKINETICS IN THE ELDERLY

As individuals age, there are alterations in drug absorption, distribution, metabolism, and elimination. As the proportion of fat to total body weight increases (which alters the volume of distribution of drugs), dosing based only on body weight may lead to toxicity. Drugs that are stored in fat may accumulate and clear slowly. Significant reductions in serum albumin that accompany the nephrotic syndrome also may alter the volume of distribution and influence clearance rates. In general, drug dosages for both renally and hepatically cleared medications should be reduced in the elderly. Estimates of GFR are important in calculating appropriate reductions in drug dosages because renal function often is reduced in the elderly and serum creatinine concentrations in the normal range may not adequately reflect reductions in GFR. The aging liver has reduced sinusoidal fenestrations and increased subendothelial collagen deposition, which because of reduced oxygen delivery causes a reduction in oxidative drug metabolism. Microsomal enzyme function per se is preserved with aging. These hepatic abnormalities primarily influence metabolism of rapidly cleared drugs with less affect on slowly cleared drugs.[28] It generally is recommended that substances that are metabolized and excreted by the liver be reduced by 30% to 40% in the elderly.[29]

Glucocorticoids

There is general agreement that the elderly are more susceptible to side effects of glucocorticoids. These include sodium retention with edema and hypertension. There is significant risk for new-onset glucose intolerance and glucocorticoids will aggravate the management of pre-existing diabetes. Elderly with vascular disease and mild cognitive impairment may do poorly with the mood changes associated with high-dose glucocorticoids. Older individuals have elevated basal cortisol levels and reduced response to adrenocorticotropic hormone, leading to abnormal stress responses dur-

ing illness or withdrawal from treatment with glucocorticoids.[30] No studies have examined the change in pharmacokinetics of administered glucocorticoids in the elderly. In the field of transplantation, there is growing experience with the use of low-dose steroids and steroid-free protocols. Gradually, this approach is being tried in other clinical settings, which may be particularly applicable in the elderly. For these reasons, most investigators suggest the use of steroid-sparing regimens or reduced dosages of steroids in older individuals.

Cyclophosphamide and Chlorambucil

Cyclophosphamide and chlorambucil are the most common agents added to glucocorticoids in the treatment of MN. Both are potent immunosuppressive agents with an accompanying risk for infectious complications. Most studies show comparable response rates in the elderly, as well as younger individuals; however, the elderly have higher rates of infectious complications.[3]

Cyclosporine and Tacrolimus

Both of these calcineurin inhibitors are excreted renally, so careful monitoring of drug levels is important in elderly individuals with reduced GFR. Both drugs can reduce glomerular perfusion leading to acute decrements in GFR and they have been associated with interstitial fibrosis. These risks are increased in the face of underlying renal and vascular disease. Cyclosporine and tacrolimus have many drug-drug interactions that affect both the efficacy and toxicity of themselves and other drugs. Given the large number of other medications that are prescribed frequently in the elderly, special attention to these interactions is required. Both agents are associated with lymphomas and skin cancers with long-term use. These agents may also aggravate underlying hypertension, which will require frequent monitoring and adjustment of antihypertensive agents. There are no specific data available regarding the response rates or use of calcineurin inhibitors in elderly patients with MN; however, the relapse rate may be as high as 50% after cyclosporine has been discontinued.[31]

Sirolimus

Similar to calcineurin inhibitors, sirolimus binds to FKBP12, but it has no effect on calcineurin activity. It inhibits mTOR, which by inhibiting cytokine-driven T-cell proliferation has a broader role in both cellular and humoral immunity. Sirolimus is metabolized in the liver, but its clearance is unaffected in the elderly. The major complications of the use of sirolimus are viral infections, including acute reactivation of cytomegalovirus, herpes simplex virus esophagitis, and colitis. These are more common when sirolimus is combined with other potent immunosuppressive agents as is common in transplantation. There is less experience with sirolimus alone. Generally, treatment of MN with sirolimus is reserved for patients who have failed to respond to more conventional treatments. No specific studies have been performed in the elderly.

Mycophenolate Mofetil

There is growing use of mycophenolate mofetil in the treatment of a variety of immunologically mediated diseases including renal disease. Although most studies report its use in individuals who have failed more conventional treatment,[32] the low rate of side effects and complications have lead to a growing number of practitioners using it as a first-line choice, including in minimal change disease, focal and segmental glomerulosclerosis, and lupus nephritis.[33] Pharmacokinetics of mycophenolate mofetil have not been studied in the elderly. Experience in MN is limited[32] and there are no data that specially address its use in the elderly.

Pneumocystis carinii Prophylaxis

The rate of this complication in elderly individuals treated with immunosuppressive agents is unknown; however, prophylaxis is given routinely to transplant recipients including those over the age of 60. Reports of cases of pneumocystis pneumonia in the elderly justify this approach.[1,17] No data are available regarding the duration of treatment, but generally prophylaxis is given during the first 3 months after initiating immunosuppressive treatment and in some cases it is continued throughout treatment.

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