Solutions to eAJKD’s Test Your Knowledge: Anti-GBM Disease

1B. NC1 domain of the alpha-3 chain of type IV collagen
Type IV collagen in the glomerular basement membrane is made up of 6 genetically distinct polypeptides called alpha chains 1-6. Each alpha chain has three domains: the amino terminal 7s domain help form the tetramers of the collagen superstructure, the middle triple helical domain that is the longest (around 1400 amino acids in length), and the NC1 domain at the carboxy terminal which measures 220 amino acids in length. Auto-antibodies against the NC1 domain of the alpha-3 chain of type IV collagen are the most commonly detected antibodies in patients with anti-GBM disease, although antibodies against the alpha-4 and alpha-5 chains have also been detected in some patients. The alpha-3 chain of type IV collagen is expressed primarily in the basement membranes of the alveolus and glomerulus, which explains the occurrence of pulmonary hemorrhage and glomerular damage in patients with anti-GBM antibodies. In contrast, most other tissues with type IV collagen express alpha-1 and alpha-2 chains.

2B. HLA-DR15
Genetic factors, along with pulmonary infections, have been associated with the development of anti-GBM disease. There is evidence of increased susceptibility of developing anti-GBM disease in patients with HLA-DR15 (HLA-DRB1*1501 allele), which is especially true in the white, Chinese, and Japanese populations. Similarly, studies have shown a reduced risk of anti-GBM disease in patients with HLA-DR1 and DR7. There is no proven association between HLA-DP1 and anti-GBM disease.

3B. Double positive patients more often present with c-ANCA than p-ANCA.
Presence of ANCA (anti-neutrophil cytoplasmic antibodies) in patients with anti-GBM disease has been shown to alter outcomes after treatment. Patients who are double positive for ANCA and anti-GBM have a better overall survival. These double positive patients also have more systemic manifestations of vasculitis on presentation, and are more often p-ANCA or anti-MPO positive. Prognosis for kidney recovery in patients presenting with anti-GBM glomerulonephritis and 100% crescents on kidney biopsy when requiring dialysis is very poor.

4C. Alport syndrome
Hereditary nephritis is a genetic condition where an altered alpha chain of type IV collagen leads to a defective GBM. When these patients receive a kidney transplant for kidney failure, the donor kidney may stimulate an immune response in the recipient to this previously unseen antigen in the donor kidney GBM. This causes a de novo anti-GBM glomerulonephritis in the transplanted kidney.