New Approaches to the Treatment of Dense Deposit Disease


Dense Deposit Disease Focus Group

Affiliations are listed after Acknowledgments.

In the past two decades, the development of new clinical treatment protocols has revolved around evidence-based guidelines that focus on randomized, controlled trials. For rare renal diseases, such stringent requirements can represent a significant challenge. Dense deposit disease (DDD; also known as membranoproliferative glomerulonephritis type II) is a prototypical rare disease. It affects only two to three people per million and leads to renal failure within 10 yr in 50% of affected children. On the basis of pathophysiology, this article presents a diagnostic and treatment algorithm for patients with DDD. Diagnostic tests should assess the alternative pathway of complement for abnormalities. Treatment options include aggressive BP control and reduction of proteinuria, and on the basis of pathophysiology, animal data, and human studies, plasma infusion or exchange, rituximab, sulodexide, and eculizumab are additional options. Criteria for treatment success should be prevention of progression as determined by maintenance or improvement in renal function. A secondary criterion should be normalization of activity levels of the alternative complement pathway as measured by C3/C3d ratios and C3NeF levels. Outcomes should be reported to a central repository that is now accessible to all clinicians. As the understanding of DDD increases, novel therapies should be integrated into existing protocols for DDD and evaluated using an open-label Bayesian study design.


In the past two decades, the development of new clinical treatment protocols has revolved around evidence-based guidelines. Randomized, controlled trials have become the favored metric for assessing the effectiveness of novel interventions, with anything falling below this level of certainty running the danger of being discounted.1 For rare diseases, this requirement represents a significant challenge.

A rare disease makes the randomized, controlled study design impractical for numerous reasons: Sample size is small and geographically dispersed; the use of historical controls is often impossible; and randomization can be seen as unethical, especially in the face of significant disease morbidity.2 Because rarity, by definition, suggests an insubstantial public health care concern, one approach to this conundrum is to avoid rare diseases in favor of more common and substantial problems. However, this option is impractical because rare diseases, in aggregate, still represent a substantial health care problem in the developed world.

There are 5000 to 6000 rare diseases, most of which are genetic in origin, and with the continued separation of broad disease categories into smaller, well-defined entities, approximately 250 new rare diseases are described each year.3 For a disease to be considered rare in the United States, it must affect fewer than 200,000 citizens, reflecting a prevalence of approximately six per 10,000, whereas in Europe, the definition is slightly stricter: Up to five per 10,000.4 Thus, an estimated 25 million North Americans and 30 million Europeans are afflicted with rare diseases. How, then, are therapeutic advances to be developed for these populations? This article focuses on dense deposit disease (DDD; also known as membranoproliferative glomerulonephritis type II), which is rare even among...
rare diseases, and uses DDD as a model for how new treatment guidelines can be proposed on the basis of evidence derived from animal studies and genetic and molecular data and how outcomes can be followed using Bayesian analysis.

**DDD: CLINICAL PHENOTYPE**

DDD affects an estimated two to three people per million. It accounts for <20% of all cases of membranoproliferative glomerulonephritis in children and only a fractional percentage of cases in adults. The name itself is descriptive of a fractional percentage of cases in all cases of membranoproliferative factor (C3NeF). This is an though most patients are positive for C3 logic markers of disease activity, al-

**Figure 1.** Histopathology of dense deposit disease (DDD). (A) The classic light microscopic appearance showing a membrano-proliferative pattern (seen in approximately 25% of patients; periodic acid Schiff stain). (B) C3 in loops and mesangial areas. The prominent granular deposits in the mesangium result in rings of immunofluorescence that are characteristic of DDD (fluorescein-conjugated anti-C3 antibody stain). (C) Electron photomicrograph showing highly electron-dense transformation of the glomerular basement membranes diagnostic of DDD (unstained). Magnifications: ×400 in A and B; ×5000 in C.

DDD affects female individuals slightly more frequently than male individuals. The DDD Database, a patient-parent-driven epidemiologic study, reports a 3:2 female:males ratio among the 56 patients with DDD that it has accrued. This database also reports that progression to ESRD occurs in approximately half of patients who have carried the diagnosis for at least 10 yr, in agreement with data reported by other investigators. The North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) database outcomes are similar. Of the 119 registered children with DDD, 81 have progressed to ESRD (personal communication, William Harmon, MD, Children’s Hospital, Boston, MA; March 2, 2007). From the DDD Database, it seems that progression to ESRD develops rapidly, usually within 4 yr of diagnosis, and is the more likely outcome in younger (≤10 yr) than older patients (P = 0.006; Figure 2). Girls may have a more aggressive disease course than boys (P = 0.16).

There have been fewer than 200 transplants in patients with DDD. Five-year allograft survival approximates 50%, which is significantly worse than the NAPRTCS database as a whole (P = 0.001). Living-related donor grafts fair better than deceased-donor grafts (P < 0.005). Histologic evidence of recurrent DDD develops in nearly all grafts and is the predominant cause of graft failure in 15 to 50% of transplant recipients. (Graft loss typically occurs within 2.5 years of transplantation. There are few data to sug-

**ANIMAL STUDIES AND DDD**

The first animal model in which DDD was described was the Norwegian York-
shire breed of piglets. Affected piglets seemed healthy at birth but after a few weeks failed to thrive as a result of a rapidly progressive glomerulonephritis that inevitably led to death (median 37 d; n = 25). Hegasy et al. showed that the molecular basis for kidney failure was a point mutation leading to an isoleucine-to-arginine change at amino acid position 1166 (I1166R), which resulted in a nonfunctional factor H gene product. The factor H gene, \( CFH \), encodes a soluble member of the regulators-of-complement-activation family that acts at the level of the C3 and C5 convertases. The I1166R mutation effectively impedes extracellular release of factor H, resulting in a decrease in serum factor H levels and unchecked and deregulated activation of the alternative pathway of complement.

Although the DDD Norwegian Yorkshire pigs are no longer available (sperm has been stored), a mouse with a targeted deletion of Factor H (\( Cfh^{-/-} \)) has been made. Deletion of factor H, like its intracellular retention, results in uncontrolled activation of the alternative pathway of complement, evidenced in these mice by significantly reduced concentrations of C3 and the presence of C3 breakdown products in the homozygous mutants. \( Cfh^{-/-} \) mice also develop renal disease characterized by the deposition of C3 on glomerular capillary walls, mesangial hypercellularity with marked matrix expansion, peripheral capillary loop thickening with the deposition of periodic acid-Schiff–positive material, and double-contouring of the GBM, entirely consistent with the diagnosis of DDD and in concordance with the histology that develops in the porcine kidney. However, unlike the Norwegian Yorkshire pig, the factor H–deficient mouse has only 25% 8-mo mortality.

Mouse mutants that are null for both factors H and B (\( Cfh^{-/-}.Cfb^{-/-} \)) have a normal renal phenotype, as would be predicted from the alternative pathway complement cascade, because factor B is necessary for the formation of C3bBb, the alternative pathway convertase (Figure 3). The absence of factor B in the \( Cfh^{-/-}.Cfb^{-/-} \) mutant precludes formation of this convertase, making the absence of factor H inconsequential. This finding also suggests that uncontrolled activation of C3 is an absolute requirement for the development of DDD and is consistent with the observation that C3 deposition in the GBM is evident before the appearance of the dense deposits.

Cleavage of C5 by C5 convertase is the

Figure 2. Age at diagnosis versus outcome (stable or ESRD). Patients who are ≤10 yr of age are more likely to progress to ESRD than are older patients (\( P = 0.006 \)). Progression to ESRD typically occurs within 4 yr of diagnosis.

Figure 3. The alternative pathway is constitutively active at low levels through the hydrolysis of the thioester in C3 to C3(H2O). Hydrolyzed C3 combines with factor B, and in the presence of factor D, C3(H2O)Bb is formed. This intermediate convertase leads to the production of C3a and C3b from C3, and C3b enters the C3bBb amplification loop. Amplification on soluble C3bBb occurs with low efficiency because free C3b is rapidly inactivated by factors H and I. However, if C3b binds covalently to surfaces or as a covalent dimer to fluid-phase IgG, then it is partially protected from inactivation. In its dimeric form (C3bC3bIgG), it is seven to 10 times more efficient in generating a C3 convertase than surface-bound monomeric C3b.

The very same enzyme on surfaces or on IgG in the fluid phase becomes a C5 convertase by acquiring an additional C3b in its vicinity, which increases the affinity of the enzyme for C5. Here we show in red just one of the possible amplification routes, which seems to be the most relevant in DDD (see text). In the absence of factor H to control levels of C3b in the fluid phase, the \( Cfh^{-/-} \) mouse mutant develops DDD. Because factor B is critical to the formation of C3bBb, its absence in the \( Cfh^{-/-}.Cfb^{-/-} \) mutant rescues the disease phenotype and DDD does not develop. In the \( Cfh^{-/-}.C5^{-/-} \) mutant and the \( Cfh^{-/-} \) mutant treated with anti-C5 antibodies, the degree of kidney disease is decreased compared with the degree of kidney disease seen in the \( Cfh^{-/-} \) mutant.
C3b to the C3 convertase, C3bBb. This trimolecular C5 convertase (i.e., C3bBbC3b) converts C5 into C5a and C5b. C5b, in turn, complexes with C6 and C7, which recruit C8 and trigger binding and polymerization of C9 to form C5b-9, the membrane attack complex (MAC). MAC creates pores in membranes that are not protected by complement regulators and promote destruction of pathogenic organisms or immune complex–coated cells.

Although serum convertases that are formed with monomeric C3b are inefficient in converting C5 into C5a and C5b, in DDD, the continued cleavage of C3 and the formation of C3b-C3b dimers on the GBM is a particularly effective mechanism for promoting the formation of C5 convertase at this site. To determine the effect of C5 and downstream proteins of the complement cascade in DDD, Pickering et al. studied the renal phenotype in Cfh−/−·C5−/− mice and in 12-mo-old animals observed less severe renal disease with reduced mortality and reduced glomerular cellularity as compared with age-matched Cfh−/− mice. However, the proteinuria at 12 mo did not differ between the Cfh−/− and Cfh−/−·C5−/− mice, suggesting that chronic deposition of C3 along the GBM alone is sufficient to disrupt the glomerular permeability barrier.

Suspecting that renal inflammation during DDD flare-ups may critically depend on C5 activation, they next explored the effect of C5 inhibition using a monoclonal anti-C5 antibody and found that it protected Cfh−/− mice that were exposed to a nephrotoxic insult triggered by nephrotoxic serum.  

The GENETICS OF DDD

DDD is a complex genetic disease. Only a few families in which more than one member has DDD have been identified, although there are several families in which multiple members have a variety of other autoimmune diseases such as Celiac disease, thyroiditis, and type 1 diabetes. Included in the latter group of families is one in which there are identical twins, one with DDD and the other with type 1 diabetes, suggesting that in the presence of a permissive genotype, environmental factors may be important determinants of disease phenotype.

Of the genes associated with DDD, the most robust data are available for factor H. Consistent with animal data implicating deletion of this gene in dysregulation of the alternative pathway and the development of a DDD renal phenotype, one family of consanguineous parentage has been reported in which two siblings’ DDD was diagnosed by renal biopsy. Both children were positive for C3NeF and had low C3 and alternative pathway–mediated hemolysis (APH) 50 levels with increased levels of the C3 degradation product C3d. (APH 50 measures total hemolytic activity of the alternative pathway.) Mutation screening of the factor H gene, CFH, showed that the affected children were homozygous for the deletion of a lysine residue at position 224 (ΔK224).

K244 is located within the complement regulatory region in the fourth of the 20 short consensus repeats (SCR) of factor H. Functional studies of factor H ΔK224 have shown that binding to heparin, C3d, and human umbilical vein endothelial cells is not altered, consistent with its intact C-terminal recognition and cell-binding properties. However, binding to C3b is weak; consequently, both co-factor activity of factor H ΔK224 in the presence of factor I and decay-accelerating activity are markedly reduced.

Most patients with DDD do not have disease-causing mutations in CFH; however, several alleles of both CFH and the complement factor H–related 5 gene (CFHR5) are preferentially associated with DDD. Of these associations, one of the potentially most interesting is the tyrosine-402-histidine (Y402H) polymorphism. The frequency of the factor H H402 variant is increased in both DDD and age-related macular degeneration, which may be germane because patients with DDD develop early-onset macular drusen.

The Y402H polymorphism lies in SCR7. This SCR contributes to one of at least three glycosaminoglycan (GAG)-recognition sites in factor H and participates in binding to C-reactive protein and a number of pathogens that seques-ter factor H for protection against complement. Structural studies have shown that the substitution occurs toward the center of SCR7, well away from boundaries with SCR8 and 9, and that the three-dimensional structures of both allotypic variants are otherwise identical. Nevertheless, binding studies indicate that the Y402H change alters the specific types of GAG that are recognized by this particular site, which is interesting in view of the fact that mutations disrupting SCR20 affect binding to C3d/C3b and are linked to another rare kidney disorder, atypical hemolytic uremic syndrome.

In vitro functional studies have shown that binding to both human umbilical vein endothelial cells and C-reactive protein is reduced for the H402 variant of factor H as compared with the Y402 variant. Heparin-binding assays of the H402 and Y402 variants produce equivocal results. Significant associations with DDD have also been found with the two common allotypes of C3, glycine 102 (G102) and arginine 102 (R102), designated C3F (fast, G102) and C3S (slow, R102) on the basis of differences in electrophoretic mobility. C3F is the less common variant and is found in only 20% of
white, 5% of black, and 1% of Asian indi-

cividuals.37–39 It is in linkage disequilib-

rium with a second polymorphism of C3, 

leucine314proline (L314P): R102 prefer-

tentially segregates with P314 and G102 

preferentially segregates with L314.40 An 

increased prevalence of C3F has been 

linked to a number of immune-mediated 

diseases, including IgA nephropathy,41 

systemic vasculitis,42 and unspecified 

glomerulonephritis.43 We have found that 

the uncommon C3 haplotype—C3 

G102/P314—is associated with DDD, 

consistent with other reports.39,40 

To identify additional associations 

between DDD and other complement-

related genes, we completed a single-nu-

cleotide polymorphism—based first-pass 

analysis of approximately 80 genes in 20 

patients with DDD and more than 100 

control subjects. For 17 genes, one or 

more exonic and/or intronic SNP gener-

ated P < 0.05 with >10% association. 

In aggregate, these data suggest that 

most patients with DDD segregate par-

ticular variants of several complement or 

related genes. The functional impact of 

these variants may be to alter the kinetics 

of complement regulation or to expose 

novel amino acid epitopes that facilitate 

formation of autoantibodies such as 

C3NeF, with the common outcome be-

ing dysregulation of the alternative path-

way of complement. The consequence is 

unchecked damage to unprotected ex-

tracellular matrices such as the GBM and 

Bruch’s membrane.

**DIAGNOSIS OF DDD**

A renal biopsy is essential to diagnose 

DDD, with the pathognomonic feature 

being electron-dense deposits along the 

GBM that are resolved by electron mi-

eroscopy.6 Immunofluorescence stain-

ing for C3 is almost always positive in 
capillary loops and in mesangial areas; 

staining for Ig is usually negative. 

Once a diagnosis of DDD is made, the 

status of the complement system should 

be documented by ordering CH50, APH 

50, C3, C3d, C4, and FH; C3NeF should 

be measured; and CFH should be 

screened for mutations using bidirec-
tional sequencing (Figure 4). Compli-

cement protein measures in DDD are dis-


tinctive, with most patients having only 

low C3 levels, whereas properdin, C5, 

and other terminal proteins are within 

the normal range. Factor H levels can be 

low, as has been reported with missense 
mutations in the coding sequence that 

block protein secretion from the endo-

plasmic reticulum.25 (For a list of labora-
tories providing these tests, please con-
tact the correspondence author.)

**TREATMENT GUIDELINES FOR DDD**

Most treatment guidelines for DDD are 

primarily based on case series before 

1995,44–48 Recent animal and genetic 

data, however, suggest that novel inter-

ventions should be coupled with nonspe-
cific treatments to retard progression of 
glomerular disease. Treatment options 

should reflect and be driven by diagnos-
tic test results.

**Nonspecific Treatments**

Nonspecific measures that are effective 

in slowing progression of numerous 

chronic glomerular diseases include ag-

gressive BP control and reduction of pro-

teinuria.6 Angiotensin-converting en-

zyme (ACE) inhibitors and angiotensin 

II type 1 receptor blockers are first-line 

agents to decrease proteinuria, improve 

renal hemodynamics, and possibly limit 

leukocyte infiltration in the kidney.49,50 

Although not widely used in children, in 

the presence of hyperlipidemia, lipid-

lowering agents such as hydroxymethyl-

glutaryl CoA reductase inhibitors may 

also delay progression of renal disease, 
correct endothelial cell dysfunction, and 
alter long-term atherosclerotic risks.51,52 

The use of steroid therapy is probably 

not effective in DDD,6 although it is ex-
	remely effective in a form of glomerulo-

nephritis called juvenile acute nonpro-

liferative glomerulonephritis, which can be 

confused with DDD.53 The two diseases 
can be distinguished clinically, because 

DDD is typically associated with C3NeF-

induced hypocomplementemia, often 

with nephrotic syndrome and hyperten-

sion, whereas in juvenile acute nonpro-
liferative glomerulonephritis, C3 levels 

remain at the lower limit of normal.

Strategies to reduce C3NeF in DDD 

using mycophenolate mofetil to inhibit 

differentiation, maturation, and allo-

stimulatory function of B and T lympho-

cytes or rituximab, a chimeric IgG1 mAb 

that specifically targets the CD20 surface 

antigen expressed on B lymphocytes, 

have not been studied.6 The use of ritux-

imab may be justified in patients who are 

positive for C3NeF, do not have a mutation 

in CFH, and show evidence of C3 

consumption (Figure 4). Standard ritux-
imab protocols for the treatment of renal 
disease should be used, following C3NeF 

levels and complement assays to docu-

ment any response.54

**Disease-Specific Treatments**

In patients with defined pathologic mu-
tations of CFH (and perhaps those carry-
ing CFH risk alleles), specific treatment 
guidelines should include infusion of 

fresh frozen plasma or plasmapheresis 

and exchange with plasma, rather than 

albumin, to provide functionally intact 

factor H (recombinant factor H is not 
currently available). The siblings re-

ported by Licht et al.24 were treated with 

infusions of 10 to 15 ml of fresh frozen 

plasma per kg body weight at 14-d inter-

vals, a dosing schedule based on the mea-
sured half-life of factor H of 6 d.55 Except 

for one episode of mild hypotension and 
a few episodes of nonspecific abdominal 
pain that was responsive to antihi-

stamines, the treatment has been well toler-

ated and kidney function has been shown 
to be preserved. Of historical note, trans-

fusion of normal porcine plasma to af-
fected Norwegian Yorkshire piglets also 
ihibited complement activation and in-

creased survival.56

An additional DDD-specific treat-

ment that is supported by animal data is 
the use of an anti-C5 antibody such as 
eculizumab (Soliris; Alexion Pharma-

cueticals, Cheshire, CT) to decrease C5a-

mediated glomerular damage. Its de-

velopment was based on a murine 

prototype (N19-8), which almost com-

pletely inhibits terminal complement 

complex formation and C5a release in 
vitro.57 Safety and efficacy of eculizumab
Figure 4. Flow diagram illustrating the diagnostic evaluation and treatment of a patient with DDD. The diagnosis is made by renal biopsy. Serologic tests of complement should be obtained, C3NeF should be assayed, and CFH should be screened for mutations. In the presence of C3NeF, removal or dilution of the autoantibody should be considered via plasma exchange or infusion, and anti-B cell agents such as rituximab might be valuable. In the presence of pathologic mutations in CFH that lead to absent or dysfunctional factor H protein, plasma infusion should be considered (with the use of recombinant factor H in the future). In addition, nonspecific treatment should be aimed at controlling BP and proteinuria. Other treatments that should be considered include eculizumab (an anti-C5 antibody [see Figure 3]) and sulodexide (a heparanase inhibitor [see Figure 5]). The criterion for treatment success should be prevention of disease progression as determined by maintenance of or prevention of decrease in renal function. The secondary criterion should be normalization of activity levels of the alternative complement pathway as measured by C3/C3d ratios and C3NeF levels. After having reached a clinical steady state, reasonable follow-up steps could be monthly for the first 3 to 6 mo, every 2 mo for the rest of the first year, and subsequently every 6 mo, adjusting clinical monitoring if a flare in disease activity occurs.

have been tested by Hillmen et al., in patients with paroxysmal nocturnal hemoglobinuria (PNH). In a double-blind, randomized, placebo-controlled, multicenter phase III trial involving 87 patients, these investigators observed stabilization of hemoglobin levels in nearly 50% of patients who were on eculizumab (21 of 43) versus none in the placebo group (0 of 44). Patients in the treatment group received infusions of 600 mg of eculizumab every week for 4 wk, followed thereafter by a maintenance dose of 900 mg of eculizumab every 2 wk for the duration of the study. Serious adverse events were reported in four patients in the eculizumab group and nine patients in the placebo group (0 of 44). Patients in the treatment group more frequently in the eculizumab group than in the placebo group (Figure 5). (Note: Eculizumab has now been approved by the Food and Drug Administration for PNH.)

The use of sulodexide is another treatment that may slow disease progression in DDD. Sulodexide is a combination of two GAGs—an electrophoretically fast-moving low molecular weight heparin (80% by weight) and dermatan sulfate (20%)—and can be given orally, subcutaneously, or by intravenous injection. It has profibrinolytic and antithrombotic properties and has an effective inhibitor of heparanase, a β-D-endoglycosidase. Glomerular heparanase expression is increased in DDD and contributes to disease pathogenesis by selectively degrading the negatively charged GAG side chains of heparan sulfate proteoglycans within the GBM or at the surface of podocytes and the glomerular endothelium (Figure 5). This leads to altered permselective properties, loss of glomerular epithelial and endothelial cell anchor points, or liberation of heparan sulfate–bound factors, such as growth factors, chemokines, and cytokines. Desulfation of critical GAG also weakens interactions with factor H, which may prove pathogenic in individuals with factor H mutations that attenuate GAG binding.

Upregulation of glomerular heparanase expression has been observed in several other experimental and human glomerular diseases, and its inhibition seems to be beneficial at least in animal models. Glomerular heparanase expression is augmented by reactive oxygen species, angiotensin II, and proinflammatory cytokines. In in vitro models of activated glomerular endothelial cells, heparanase expression not only is increased but also is associated with structural changes to cell surface heparan sulfates. Heparan sulfates on glomerular endothelium also play a prominent role during inflammation and in local complement activation and regulation.

Sulodexide may therefore have multiple effects that could make it effective in DDD, including inhibition of glomerular heparanase activity and interference with binding of leukocytes and/or activated complement components to glomerular endothelium. It is approved in Europe to treat vascular thrombotic conditions, and there are recent data to support its use in diabetes. It has been used in several small phase II studies to treat early diabetic nephropathy and can induce an additional 40 to 70% reduction in albuminuria in individuals with tight glycemic and BP control. There are two ongoing clinical trials to evaluate its effect in diabetes (Phase III: http://www.clinicaltrials.gov/ct/show/NCT00130208; Phase IV: http://www.clinicaltrials.gov/ct/show/NCT00130312). At dosages of 200 mg/d, sulodexide has no anticoagulant properties and has an excellent safety profile. An international study to test its efficacy in DDD is planned, and as newer structurally well-defined GAGs...
There are two essential differences between the Bayesian and the double-blinded approach. The first difference is that a Bayesian study design allows the investigator to have some opinion about the probable outcome of the trial. This preconception is expressed in terms of a prior probability of a successful outcome (something greater than 0.5). The traditional clinical trial, in contrast, assumes the likelihood of a successful or an unsuccessful outcome to be equal (i.e., 50:50).

If one assumes, for example, that eculizumab has a measurable beneficial effect on patients with PNH 75% of the time, then one might expect the effect of eculizumab in DDD to be similar, making the prior probability of success 0.75. This assumption moves the expected distribution of outcomes to the positive side and allows the investigator to make decisions with fewer observations when comparing eculizumab-treated with non-eculizumab-treated patients with DDD. Thus, the investigator, being limited in available patients, takes advantage of the fact that treatments are offered with a reasonable expectation of a positive outcome.

Because the estimation of prior probability is subjective and can be affected by animal data and results of trials for related disorders, different investigators will assume different prior probabilities. Some investigators may assume that the effect of eculizumab on DDD is 0.80, whereas others might assume it to be 0.50 (no effect). One approach to addressing variability in prior probability is to take the average suggested from a group of investigators who are familiar with DDD or in dealing with the drug being tested.

The second difference between the Bayesian and traditional double-blinded clinical trial is that the Bayesian trial is open-ended. Decisions about continuance and efficacy are made as every data point is collected. This concept is a natural outgrowth of Wald’s method of sequential analysis, which minimizes the sample size required for decision making.89,90 The Bayesian approach codifies the intuitive decision making of an investigator when treating a rare disease. If, for example, the first three treatments are a success, then one would be inclined to continue; if they fail, then one would be inclined to stop treatment.

Because DDD is very rare, treatments and outcomes should be reported on all patients on the DDD Outcome Database (http://genome.uiowa.edu/ddd). This resource, which is available to all health care personnel, is intended to provide an up-to-date assessment of outcomes as related to treatment protocols. Ultimately, by registering patients on the DDD Outcome Database, physicians will be able to offer care on the basis of a collective experience with a large number of cases.

CONCLUSION

DDD is the prototypical rare disease, affecting only two to three people per million. It causes significant morbidity, leading to ESRD within 10 yr in 50% of people who are younger than 10 yr at diagnosis. Renal transplantation is not a reliable treatment option, because up to 50% of recipients eventually lose their graft as a result of disease recurrence.

All patients who receive a diagnosis of DDD should undergo a standard battery of tests, including review of renal biopsies, serum markers of complement activity, screening for C3NeF, and genetic testing of CFH. These tests focus on assessing the alternative pathway of complement for abnormalities. Treatments and outcomes should be followed by
monitoring indices of renal function and serum levels of complement activity.

Data should be reported to a central repository that is accessible in real time to all clinicians. This reporting system will allow “best available” therapies to be used in patient treatment. As our understanding of DDD increases and novel treatments develop (e.g., recombinant factor H), the use of these treatments should be integrated into DDD protocols that are continually analyzed and evaluated in an open-label Bayesian study design.

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This article is dedicated to patients with DDD with the hope and expectation that the ideas contained herein will lead to the eventual development of therapies to treat this disease. We hope that this model for studying DDD can be applied to other rare diseases as well.

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