Dense deposit disease (DDD) is a glomerular disease defined at the electron microscopic level by a transformation of the lamina densa of the glomerular basement membrane by ribbon-like, highly electron-dense material, which by immunofluorescence stains predominantly for C3. The disease was first recognized in France in 1963 by Galle (1). For many years, DDD was also called membranoproliferative GN (MPGN) type II. Because recent studies have indicated that the light microscopic pattern in most patients is not membranoproliferative, the modern trend is to consider DDD a distinct entity, rather than a variant of MPGN (2,3). The rarity of DDD, which afflicts only two to three individuals per million population (4), has impeded studies into its clinical course and outcome differences between these age groups. Herein, we report the largest North American series addressing the clinicopathologic characteristics and outcome in patients with DDD. Thirty-two patients, including 14 children and 18 adults, were studied with particular emphasis on identifying clinical, pathologic, and outcome differences between these age groups.

Materials and Methods

Thirty-two patients with DDD were identified in a retrospective review of all native renal biopsies received at Columbia University Medical Center from 1977 to 2007. The diagnosis of DDD was based on the ultrastructural finding of a transformation of glomerular basement membranes by ribbon-like, highly electron-dense material and predominant immunofluorescence staining for C3. The Renal Pathology Labo-
ratory of Columbia University processed 15 of the 32 initial renal biopsies. The remaining seventeen were processed at local hospitals and sent to Columbia University for a second opinion at the request of the treating nephrologist. Renal biopsy samples were processed by standard techniques for light microscopy (LM), immunofluorescence (IF), and electron microscopy (EM). For each sample, multiple glass slides were stained with hematoxylin and eosin, periodic acid–Schiff, Masson trichrome, and Jones methenamine silver. Ultrastructural evaluation was performed using a transmission electron microscope. IF was performed on 3-μm cryostat sections using polyclonal FITC-conjugated antibodies to IgG, IgM, IgA, C3, C1q, and kappa and lambda light chains. IF staining intensity was graded 0 to 3+ on a semiquantitative scale.

Patients’ medical records were reviewed for demographic information, presenting clinical and laboratory findings, treatment, and outcome. For purposes of age stratification, patients <16 yr of age were considered as children and those ≥16 yr of age as adults. The following definitions were applied: nephrotic range proteinuria, 24 h urine protein ≥3 g/d or spot urine protein/creatinine ratio ≥3; hypoaalbuminemia, serum albumin ≤3.5 g/dl in adults and ≤2.5 g/dl in children; renal insufficiency, serum creatinine >1.2 mg/dl in adults and more than the age-related normal values in children; and hematuria, >5 red blood cells per high power field on microscopic examination of the urinary sediment or positive blood by dipstick. Nephrotic syndrome was defined as nephrotic range proteinuria, hypoaalbuminemia, and peripheral edema.

Statistical analyses were performed using SPSS for Windows, version 15.0 (SPSS, Chicago, Illinois, USA) and StatXact for Windows, version 6.0 (Cytel Software Corporation, Cambridge, Massachusetts, USA). Continuous variables are reported as the mean ± SEM. Analyses were performed by nonparametric exact statistical methods using the Wilcoxon rank-sum test, the Kruskal–Wallis test, and the Fisher exact test, as appropriate for variable type. Response was defined as follows: (1) complete response (CR), remission of proteinuria to <500 mg/d with normal renal function; (2) partial response (PR), reduction in proteinuria by at least 50% and to <2 g/d with stable renal function (no more than a 20% increase in serum creatinine); and (3) no response (NR), failure to meet criteria for either CR or PR, including patients with unremitting proteinuria, progressive chronic kidney disease, or progression to ESRD. Survival estimates (endpoint = ESRD) were computed by the method of Kaplan and Meier. Multivariate survival analyses were performed using the Cox proportional hazards model (Cox regression). Statistical significance was assumed at P < 0.05.

The study was approved by the Institutional Review Board of Columbia University Medical Center.

Results

Clinical Features

The cohort consisted of 14 children, all ≥5 yr of age, including nine (64.3%) who were <10 yr, and 18 adults including seven (39%) who were >60 yr of age (Table 1). The female/male ratio was 1.9 and most patients were Caucasian (84.4%). There was no difference between children and adults with respect to gender or race/ethnicity. Only one child developed partial lipodystrophy and one child was known to have retinal involvement (drusen). Comorbid conditions were present in 11 adults: chronic hypertension in five, plasma cell dyscrasia in four (monoclonal gammopathy in three and multiple myeloma in one), ulcerative colitis in one, rheumatoid arthritis in one, and coronary artery disease in one. A single child had a history of type 1 diabetes without evidence of diabetic nephropathy.

Pathologic Features

The most distinctive feature in LM was thickening of the glomerular basement membranes (GBM) by ribbon-like glassy intramembranous deposits. The deposits stained highly eosinophilic with hematoxylin and eosin, periodic acid–Schiff-positive, trichrome-gray or -red, and nonarroyphophilic (Figure 1A). Similar intramembranous ribbon-like deposits were also seen involving Bowman’s capsule and tubular basement membranes in some patients. The most frequent histologic pattern of glomerular injury with LM was MPGN, found in 43.8% of patients,
Table 2. Clinical characteristics at presentation

| Characteristic                                      | All  
|----------------------------------------------------|-----------------------------------------------|
|                                                     | All  
|                                                     | Children  
|                                                     | Adults  
|                                                     | (n = 32 (%)) | (n = 14 (%)) | (n = 18) | P  
| Peripheral edema                                   | 12 (37.5) | 6 (42.8) | 6 (33.3) | NS  
| Mean 24-h urine protein                            | 4.6 g     | 4.0 g     | 5.1 g     |  
| Proteinuria <1 g/24 h                              | 5/30 (16.7) | 2/13 (15.4) | 3/17 (17.6) | NS  
| Proteinuria 1 to 3 g/24 h                          | 8/30 (26.7) | 4/13 (30.8) | 4/17 (23.5) | NS  
| Proteinuria >3 g/24 h                              | 17/30 (56.7) | 7/13 (53.8) | 10/17 (58.8) | NS  
| Full nephrotic syndrome                            | 10/30 (33.3) | 4/13 (30.7) | 6/17 (35.3) | NS  
| Mean serum albumin                                 | 2.8 g/dl  | 2.9 g/dl  | 2.7 g/dl  |  
| Hematuria (microscopic or macroscopic)             | 27/31 (87.1) | 13/13 (100) | 14 (77.8) | NS  
| Macrscopic hematuria                               | 5/31 (16.1) | 3/13 (23.1) | 2 (11.1) | NS  
| Red blood cell casts                               | 8/30 (26.7) | 6/13 (46.2) | 2/17 (11.8) | 0.049  
| Mean serum creatinine at biopsy                    | 2.2 mg/dl  | 0.8 mg/dl  | 3.2 mg/dl  | <0.001  
| Renal insufficiency at presentation                | 19 (59.4)  | 5 (35.7)  | 14 (77.8) | 0.029  
| Low C3                                             | 20/30 (66.7) | 13/13 (100) | 7/17 (41.2) | 0.001  
| Low C4                                             | 1/30 (3.3)  | 0 (0)     | 1/17 (5.9) | NS  
| Positive C3 nephritic factor                       | 7/9 (77.8)  | 6/6 (100)  | 1/3 (33.3) | 0.027  
| Preceding infection                                | 9 (28.1)   | 8 (57.1)b | 1 (5.6)c  | 0.004  

**a**NS, not significant (P > 0.05).

**b**Pneumonia in four, upper respiratory tract infection in three, and bronchitis in one.

**c**Urinary tract infection.

Figure 1. Light microscopic patterns of dense deposit disease (DDD). (A) In this patient with membranoproliferative pattern, there are large nonargyrophilic deposits expanding the mesangium and thickening the glomerular capillary walls, with segmental duplications. (Jones methenamine silver, ×400). (B) An example of mesangial pattern illustrates the mild increase in mesangial cell number and matrix, with preservation of luminal patency. (periodic acid–Schiff, ×600). (C) The endocapillary proliferative and exudative pattern features global occlusion of glomerular capillaries by endocapillary cells, including infiltrating neutrophils and monocytes, with lobular accentuation. Many of the glomerular basement membranes display ribbon-like thickening. (hematoxylin and eosin, ×400). (D) An example of crescentic proliferation with membranoproliferative features in the underlying tuft. There is prominent ribbon-like thickening of the glomerular basement membranes and nodular mesangial expansion. (periodic acid–Schiff, ×400).
followed by mesangial proliferative GN (28.1%), endocapillary proliferative GN (18.8%) with (12.5%) or without (6.3%) exudative features (defined as neutrophil infiltration), and crescentic GN (defined by the presence of crescents in 50% of glomeruli) (9.4%) (Table 3) (Figures 1A-1D). Compared with other patterns, the MPGN pattern was associated with more segmental sclerosis (P < 0.003), interstitial inflammation (P = 0.026), and foot process effacement (P = 0.005). Crescentic GN was seen only in three children. Focal crescents, however, were common and present in over half of patients, whereas necrosis was rare (15.6%). Glomerular pattern of injury by LM did not correlate with age, gender, race/ethnicity, depression of C3, serum creatinine at biopsy, degree of proteinuria, serum albumin, the percentage of global or segmental glomerulosclerosis, or the degree of tubular atrophy/interstitial fibrosis, interstitial inflammation, or arteriosclerosis. Adult patients had a significantly higher percentage of global glomerulosclerosis (P < 0.001) and a greater degree of tubular atrophy/interstitial fibrosis (P < 0.0001) and arteriosclerosis (P < 0.0001) than children. The proportion of glomeruli with segmental sclerosis, endocapillary hypercellularity, exudative features, crescents, and necrosis was not statistically different between children and adults (Table 4).

Table 3. Histological pattern by light microscopy

<table>
<thead>
<tr>
<th>Pattern</th>
<th>All n = 32 (%)</th>
<th>Children n = 14 (%)</th>
<th>Adults n = 18 (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesangial proliferative GN</td>
<td>9 (28.1)</td>
<td>4 (28.6)</td>
<td>5 (27.8)</td>
<td>NS^a</td>
</tr>
<tr>
<td>Endocapillary proliferative GN with or without exudative features</td>
<td>6 (18.8)</td>
<td>3 (21.4)</td>
<td>3 (16.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Membranoproliferative GN</td>
<td>14 (43.8)</td>
<td>4 (28.6)</td>
<td>10 (55.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Crescentic GN^b</td>
<td>3 (9.4)</td>
<td>3 (21.4)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
</tbody>
</table>

^aNS, not significant (P > 0.05).
^bDefined by the presence of crescents affecting ≥50% of glomeruli.

Table 4. Light microscopic findings

<table>
<thead>
<tr>
<th>Pathologic Findings</th>
<th>All n = 32 (%)</th>
<th>Children n = 14 (%)</th>
<th>Adults n = 18 (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean number of glomeruli</td>
<td>20.6</td>
<td>24.4</td>
<td>17.6</td>
<td>NS^d</td>
</tr>
<tr>
<td>Percent of globally sclerotic glomeruli</td>
<td>18.5</td>
<td>2.9</td>
<td>30.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Percent of segmentally sclerotic glomeruli</td>
<td>4.8</td>
<td>0</td>
<td>8.6</td>
<td>NS</td>
</tr>
<tr>
<td>Percent of cases with crescents^a</td>
<td>19 (59.4)</td>
<td>11 (78.6)</td>
<td>8 (44.4)</td>
<td>NS</td>
</tr>
<tr>
<td>focal</td>
<td>16</td>
<td>8</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>diffuse</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Number of cases with necrosis</td>
<td>5 (15.6)</td>
<td>1 (7.1)</td>
<td>4 (22.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Number of cases with endocapillary hypercellularity^a</td>
<td>20 (62.5)</td>
<td>10 (71.4)</td>
<td>10 (55.6)</td>
<td>NS</td>
</tr>
<tr>
<td>focal</td>
<td>15</td>
<td>6</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>diffuse</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Number of cases with intracapillary neutrophil infiltration^a</td>
<td>14 (43.8)</td>
<td>8 (57.1)</td>
<td>6 (33.3)</td>
<td>NS</td>
</tr>
<tr>
<td>focal</td>
<td>11</td>
<td>6</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>diffuse</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Interstitial inflammation: none/focal/diffuse^b</td>
<td>5/21/6</td>
<td>5/7/2</td>
<td>0/14/4</td>
<td>NS</td>
</tr>
<tr>
<td>Tubular atrophy and interstitial fibrosis: none/mild/moderate/severe^c</td>
<td>8/13/7/4</td>
<td>8/5/1/0</td>
<td>0/8/6/4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Arteriosclerosis and arteriolar hyalinosis: none/mild/moderate/severe</td>
<td>15/7/8/2</td>
<td>13/1/0/0</td>
<td>2/6/8/2</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

^aFocal, <50% of glomeruli; diffuse, ≥50% of glomeruli.
^bFocal, ≥50% of cortical surface area; diffuse >50%.
^cMild, (0 to 25% of cortical surface area); moderate (26 to 50%); severe (>50%).
^dNS, not significant (P > 0.05).
Intense C3 staining was detected in all patients (mean intensity 2.5/H11001) in the mesangium as granular or ring-like deposits and along glomerular capillary walls (GCW) in a linear to semilinear pattern (Figures 2A, 2B). In some patients the linear staining appeared as narrow tram tracks outlining the inner and outer aspects of the thickened GCW (Figure 2A). Focal linear or semilinear C3 staining was also seen along tubular basement membranes in 60% of patients and along Bowman’s capsule in 30% of patients. In 47% of patients, the glomerular deposits weakly stained for one or more additional immune reactants, including IgM (36.7% of patients), IgG (26.7%), IgA (13.3%), and C1q (10%) (Table 5). IgM positivity was more frequent in children than adults (57.1% versus 18.8%, $P/1.10220.019$).

Ultrastructural evaluation, performed on all 32 patients, exhibited large highly electron-dense intramembranous deposits that irregularly thickened and transformed the lamina densa (Table 6) (Figure 3A). In most glomerular loops, the intramembranous deposits were interrupted, producing a “sausage string” appearance to the GBM. In some patients, they were particularly prominent involving the GBM reflection over the mesangium, with less involvement of the peripheral GCW. Similar intramembranous electron-dense deposits were identified focally in Bowman’s capsule and tubular basement membranes in 44 and 50% of patients, respectively (Figure 3B). Segmental or global electron-dense deposits were also seen embedded in the expanded mesangium in all patients. In 56% of patients, the mesangial deposits formed large, rounded nodules (“ring forms”), whereas in the remaining 44% of patients they appeared small and granular (Figure 3C). Large hump-shaped, subepithelial electron-dense deposits were identified in ten patients (31%), including eight adults and two children ($P/1.068$). The subepithelial humps were rare ($2$) in six patients and multiple in the remaining four patients. Half of the patients had few small subendothelial deposits, which in most instances appeared to represent extensions of intramembranous deposits into the subendothelial space. In a few patients, large, highly electron-dense deposits pooled in the subendothelial region with sparing of the lamina densa, a finding described by McEn-

### Table 5. Immunofluorescence findings

<table>
<thead>
<tr>
<th></th>
<th>All $n = 30$</th>
<th>Children $n = 14$</th>
<th>Adults $n = 16$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>C3</td>
<td>30 (100)</td>
<td>14 (100)</td>
<td>16 (100)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>(2.5+)</td>
<td>(2.6+)</td>
<td>(2.3+)</td>
<td></td>
</tr>
<tr>
<td>C1q</td>
<td>3 (10)</td>
<td>3 (21.4)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>(1.8+)</td>
<td>(1.8+)</td>
<td>(1.2+)</td>
<td></td>
</tr>
<tr>
<td>IgG</td>
<td>8 (26.7)</td>
<td>5 (35.7)</td>
<td>3 (18.8)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>(1.1+)</td>
<td>(1.3+)</td>
<td>(0.5+)</td>
<td></td>
</tr>
<tr>
<td>IgM</td>
<td>11 (36.7)</td>
<td>8 (57.1)</td>
<td>3 (18.8)</td>
<td>0.019</td>
</tr>
<tr>
<td></td>
<td>(0.7+)</td>
<td>(0.9+)</td>
<td>(0.5+)</td>
<td></td>
</tr>
<tr>
<td>IgA</td>
<td>4 (13.3)</td>
<td>1 (7.1)</td>
<td>3 (18.8)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>(0.6+)</td>
<td>(1+)</td>
<td>(0.5+)</td>
<td></td>
</tr>
</tbody>
</table>

Data indicate the number (percentage) of positive patients and the mean intensity of staining when positive (scale, 0.5, 1 to 3+). NS, not significant ($P > 0.05$).

*Figure 2. Immunofluorescence features of DDD. (A) Staining for C3 highlights the glomerular capillary walls globally in a semilinear pattern. In some capillaries, there appears to be a double layer of linear staining (arrows). A few ring forms are seen in the mesangium. Semilinear deposits are also present in Bowman’s capsule and adjacent tubular basement membranes. ($\times400$). (B) In this example, the mesangium contains numerous characteristic ring forms staining for C3, with weaker linear staining of the glomerular capillary walls ($\times400$).*
ery and McAdams as the “dropping off” phenomenon (17) (Figure 3D). In two patients (6%), a few electron-dense deposits were identified in arteriolar walls.

Repeat biopsies were performed in five children and one adult (three repeat biopsies in three patients and two in three patients) at 34 mo to 22 yr after the initial biopsy. All six patients undergoing repeat biopsies were treated with steroids [in addition to renin angiotensin system (RAS) blockade in three, cyclosporine in one, and tacrolimus in one]. All six patients were NR, including five with persistent renal dysfunction and one who progressed to ESRD. Repeat biopsies showed similar degrees of mesangial sclerosis but greater global glomerulosclerosis (five patients), tubular atrophy, and interstitial fibrosis (four patients), consistent with disease progression. Endocapillary hypercellularity including intracapillary neutrophils, present in three of these six patients on the initial biopsy, resolved in two patients and persisted in one patient on subsequent biopsies. The histologic pattern with LM changed in four patients (mesangial proliferative GN to MPGN in three and crescentic GN to mesangial proliferative GN in one). The IF and EM findings on repeat biopsies were not significantly different from those seen on the initial biopsy.

**Outcome**

Clinical follow-up was available in 27 patients (84.4%) including 13 children and 14 adults (Table 7). The mean duration of follow-up for the entire cohort was 63.4 mo (range 2 mo to 24 yr). Treatment included immunosuppression (IS) alone in seven patients, RAS blockade (angiotensin-converting enzyme inhibitor and/or angiotensin II receptor blocker) alone in six patients, and combined IS/RAS blockade in eleven patients. IS consisted of steroids in all 18 patients: five received a second agent including mycophenolate mofetil in two, cyclosporine in two, and tacrolimus in one. Two patients were not treated with RAS blockade or IS. No information about treatment was available in the remaining patient. Patients who received IS therapy (with or without RAS blockade) had a significantly lower serum albumin (\( P = 0.015 \)), a higher percent of crescents (\( P = 0.008 \)), and less arteriosclerosis (\( P = 0.037 \)) than the patients who did not receive IS. IS-treated and untreated patients were not different with respect to 24-h urine protein, serum creatinine at biopsy, percent global or segmental sclerosis, tubular atrophy/interstitial fibrosis, or interstitial inflammation.

On follow-up, 25.9% of patients (7.1% of adults and 46.1% of children, \( P = 0.033 \)) had a CR and the remaining 74.1% had NR including 48.1% who had persistent renal dysfunction and 25.9% (7.7% of children and 42.9% of adults, \( P = 0.033 \)) who progressed to ESRD. No patient met criteria for PR. Two patients underwent renal transplantation, one of whom developed recurrent DDD on a background of chronic rejection diagnosed in two successive allograft biopsies performed for graft dysfunction at 4 and 8 yr posttransplant. The recurrent DDD exhibited mild mesangial proliferative GN by LM (different from the MPGN pattern seen in the native kidney), but characteristic features by IF and EM. The mild severity of the recurrence suggested that it was not contributing significantly to the allograft dysfunction. Three adults who were on permanent hemodialysis died, one because of congestive heart failure, one because of myocardial infarction, and one of undetermined cause.

On univariate analysis, the correlates of reaching ESRD were: older age (\( P = 0.005 \)), higher creatinine at biopsy (\( P = 0.003 \)), the degree of arteriosclerosis on biopsy (\( P = 0.041 \)), and the presence of subepithelial humps by EM (\( P = 0.023 \)). IS (with or without RAS blockade therapy) was protective but did not quite reach statistical significance (\( P = 0.051 \)). Combined therapy (IS with RAS blockade) was more efficacious than IS or RAS blockade therapy alone (\( P = 0.031 \)). Gender, race/ethnicity, depression of C3, the degree of proteinuria, serum albumin, the glomerular pattern by LM, the percentage of global or segmental sclerosis, the presence of crescents, and the degree of tubular atrophy/interstitial fibrosis and interstitial inflammation did not correlate significantly with ESRD outcome.

**Table 6.** Electron microscopic findings

<table>
<thead>
<tr>
<th>Location of Highly Electron-Dense Deposits</th>
<th>All ( n = 32 ) (%)</th>
<th>Children ( n = 14 ) (%)</th>
<th>Adults ( n = 18 ) (%)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamina densa of GBM(^a)</td>
<td>32 (100)</td>
<td>14 (100)</td>
<td>18 (100)</td>
<td>NS(^c)</td>
</tr>
<tr>
<td>segmental(^b)</td>
<td>10 (4)</td>
<td>4</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>global(^b)</td>
<td>22 (10)</td>
<td>10</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Mesangial</td>
<td>32 (100)</td>
<td>14 (100)</td>
<td>18 (100)</td>
<td>NS</td>
</tr>
<tr>
<td>segmental</td>
<td>18 (7)</td>
<td>7</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>global</td>
<td>14 (7)</td>
<td>7</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Subepithelial hump-shaped deposits</td>
<td>10 (31.3)</td>
<td>2 (14.3)</td>
<td>8 (44.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Subendothelial</td>
<td>16 (50)</td>
<td>5 (35.7)</td>
<td>11 (61.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Bowman’s capsule</td>
<td>14 (43.8)</td>
<td>6 (42.9)</td>
<td>8 (44.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Tubular basement membranes</td>
<td>16 (50)</td>
<td>6 (42.9)</td>
<td>10 (55.6)</td>
<td>NS</td>
</tr>
</tbody>
</table>

\(^a\)GBM, glomerular basement membranes.
\(^b\)Segmental, involving <50% of the total glomerular loops; global, involving ≥50% of the total glomerular loops.
\(^c\)NS, not significant (\( P > 0.05 \)).
Figure 3. Electron microscopic features of DDD. (A) Highly electron-dense intramembranous deposits thicken the glomerular basement membranes. In areas, the deposits are interrupted, producing sausage shapes. There is circumferential mesangial interposition ($\times 4000$). (B) Intramembranous interrupted electron-dense deposits are present within a tubular basement membrane ($\times 3000$). (C) The ring forms seen by immunofluorescence correspond to rounded electron densities within the mesangium, shown here. A few small intramembranous deposits are also present in the glomerular basement membranes ($\times 2000$). (D) Some of the glomerular capillary wall deposits “drop off” the lamina densa, forming inframembranous densities ($\times 4000$).
By Kaplan–Meier survival estimates (endpoint = progression to ESRD), predictors of ESRD were adult age (using age 16 yr as the cutoff) at biopsy, absence of combined IS/RAS blockade, the presence of subepithelial humps, and the presence of arteriosclerosis (any degree) (Table 8) (Figure 4). Gender, race/ethnicity, nephrotic range proteinuria, and the degree of tubular atrophy/interstitial fibrosis or interstitial inflammation did not predict renal survival.

Using the Cox proportional hazards model, the only independent predictors of progression to ESRD on multivariate analyses were older age [hazard ratio (HR) 1.081, 95% confidence interval (CI) 0.994 to 1.176, \( P = 0.07 \)] and serum creatinine at biopsy (HR 2.885, 95% CI 1.202 to 6.924, \( P = 0.018 \)). When serum creatinine at biopsy was not included in the model, the only independent predictor of progression to ESRD was age (HR 1.052, 95% CI 1.013 to 1.091, \( P = 0.008 \)).

**Discussion**

This study reports our experience with a series of 32 patients with DDD. To our knowledge, this is the largest North American series dealing with the clinicopathologic characteristics and outcome of DDD. We particularly focused on the clinical and outcome differences between children and adults and sought to identify the features associated with poor renal outcome, aspects of the disease that are not adequately addressed in the literature.

The percentage of adult patients older than 60 yr in our study was 39%, compared with 0% in the 1975 French study by Habib et al., the 1975 French-Belgian study by Galle and Mahieu, the 1983 U.K. study by Cameron et al., and several other smaller studies (5,6,8,10,13,14). The reason for the larger representation of elderly patients in our study is unclear. Because all but one of the patients >60 yr of age in our cohort were diagnosed within the current decade, contributing factors may be our center’s increasingly large referral base for adult nephrology, the aging population trends in the United States, and the aggressive modern use of renal biopsy in the elderly. In our patient population there was a female predominance (1.9:1), similar to the reports by Cameron et al., Bennett et al., and Little et al. (6,13,15). In other studies, the female/male ratio ap-

**Table 7. Clinical follow-up**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>All n = 27 (%) Duration of follow-up: mean (range) in months</th>
<th>Children n = 13 (%)</th>
<th>Adults n = 14 (%)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>2 (7.4) 0 (0)</td>
<td>63.4 (2 to 288)</td>
<td>79.4 (2 to 288)</td>
<td>48.5 (4 to 156)</td>
</tr>
<tr>
<td>RAS(^a) blockade alone</td>
<td>6 (22.2) 2 (15.4)</td>
<td>6 (22.2) 2 (15.4)</td>
<td>4 (28.6)</td>
<td>NS</td>
</tr>
<tr>
<td>IS(^a) alone</td>
<td>7 (25.9) 3 (23.1)</td>
<td>11 (40.7) 8 (61.5)</td>
<td>1 (3.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Combined IS/RAS blockade</td>
<td>11 (40.7) 8 (61.5)</td>
<td>11 (40.7) 8 (61.5)</td>
<td>1 (3.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Not available</td>
<td>1 (3.7) 0 (0)</td>
<td>1 (3.7) 0 (0)</td>
<td>1 (7.1)</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Outcome\(^b\)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All n = 27 (%)</th>
<th>Children n = 13 (%)</th>
<th>Adults n = 14 (%)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>complete response</td>
<td>7 (25.9) 6 (46.1)</td>
<td>7 (25.9) 6 (46.1)</td>
<td>1 (7.1)</td>
<td>0.033</td>
</tr>
<tr>
<td>persistent renal dysfunction</td>
<td>13 (48.1) 6 (46.1)</td>
<td>13 (48.1) 6 (46.1)</td>
<td>7 (50)</td>
<td>NS</td>
</tr>
<tr>
<td>ESRD</td>
<td>7 (25.9) 1 (7.7)</td>
<td>7 (25.9) 1 (7.7)</td>
<td>6 (42.9)</td>
<td>0.033</td>
</tr>
<tr>
<td>death</td>
<td>3 (11.1) 0 (0)</td>
<td>3 (11.1) 0 (0)</td>
<td>3 (21.4)</td>
<td>NS</td>
</tr>
</tbody>
</table>

\(^a\)RAS, renin angiotensin system; IS, immunosuppressive agents (steroids with or without a second agent).

\(^b\)Overall comparison, complete response/persistent renal dysfunction/ESRD in children versus adults, \( P = 0.015 \).

**Table 8. Predictors of ESRD by Kaplan and Meier survival estimates**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Mean Time from Biopsy to ESRD in Months ± SEM</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Pediatric 244.8 ± 38.6</td>
<td>0.033</td>
</tr>
<tr>
<td></td>
<td>Adult 62.0 ± 17.7</td>
<td></td>
</tr>
<tr>
<td>IS therapy (with or without RAS blockade)</td>
<td>Yes 239.6 ± 31.4</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>No 27.9 ± 8.1</td>
<td></td>
</tr>
<tr>
<td>Any therapy</td>
<td>RAS blockade 29.5 ± 9.7</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>IS 90.6 ± 19.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Combined No endpoints</td>
<td></td>
</tr>
<tr>
<td>Subepithelial humps</td>
<td>Yes 109.1 ± 48.6</td>
<td>0.017</td>
</tr>
<tr>
<td></td>
<td>No 124.5 ± 16.4</td>
<td></td>
</tr>
<tr>
<td>Presence of arteriosclerosis (any degree)</td>
<td>Yes 49.9 ± 18.8</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>No 252.0 ± 32.9</td>
<td></td>
</tr>
</tbody>
</table>
The optimal treatment of DDD remains undefined because of the disease’s rarity and the lack of large, prospective, randomized clinical trials. Several therapeutic regimens have been used, including RAS blockade, anticoagulants, steroids and other immunosuppressive agents, and plasmapheresis/plasma exchange, singly or in combination (22). Proposed new treatments include etulizumab (an anti-C5 antibody) and sulodexide (a mixture of low-molecular-weight heparin and dermatan sulfate that inhibits heparanase) (4). The effectiveness of steroids is controversial. A randomized placebo-controlled study by the International Study of Kidney Disease in Children of 80 children with MPGN (including 14 with DDD) demonstrated that a regimen of long-term alternate-day prednisone improved
outcome in a heterogeneous group of patients with MPGN I, II, and III, collectively, but not in those with DDD specifically (23). Conversely, McEnery and McAdams reported improvement in glomerular morphology and good clinical outcomes in six patients who were treated with long-term alternate-day prednisone (17). No studies have compared the efficacy of steroids alone versus steroids/RAS blockade in patients with DDD. Most patients in our cohort were treated (by nephrologists from 11 different states representing a broad geographic region) with RAS blockade, IS (steroids alone or with a second agent), or both, for variable periods of time. In this large retrospective study we found that combined IS/RAS blockade was superior to either agent alone. A prospective, controlled study is needed to confirm these findings. None of our patients received disease specific treatments, except for one child who was on RAS blockade and was just started on sulodexide at the time of last follow-up.

In summary, our study indicates that DDD is clinically and pathologically heterogeneous. Contrary to its stereotypic characterization as a childhood disease, DDD can present over a broad age range. Because adults are less likely than children to exhibit the usual heralds of a preceding infection and low serum complement, the renal pathologist must be particularly careful not to overlook the possibility of DDD in the older patient with atypical presentation. Predictors of poor prognosis in DDD are older age and higher serum creatinine at biopsy. Combined IS and RAS blockade appears superior to either agent alone, but requires validation in prospective controlled studies. In the future, routine testing for etiologic factors, such as the presence of a disease-causing autoantibody versus genetic deficiency, should allow the design of more rational, individualized therapies.

Disclosures
None.

References


Access to UpToDate on-line is available for additional clinical information at http://www.cjasn.org/