Paraproteins and Renal Disease
CASE 1

Mrs RF

- Phone referral from Wagga Wagga
  - Recent onset nephrotic syndrome
    - sAlb 18 g/l, 8 g/day proteinuria, no haematuria
    - No other symptoms

- Type II DM – 4 yrs
  - No known retinopathy
  - No macrovascular disease

- What would you do?
Renal Biopsy - H&E
Renal Biopsy – Congo Red
Renal Biopsy - EM
Renal Biopsy - EM
Case 1

- What further investigations do you want?
- What would you tell her about her prognosis?
- What would you do next?
Case 1

- IgG $\lambda$ BJP 0.31 g/day
  - Normal serum
  - Normal bone marrow

- Echo normal

- Referred haematology
  - GSF stimulated stem cell mobilisation
  - High dose mephalan
  - Autologous stem cell transplant
CASE 2

- Mrs WH 62 yo
  - Known myeloma – 12 months
    - IgG \( \lambda \), 40 % plasma cells. Rx prednisone / pamidronate
  - Referred with rising creatinine – 100 – 160 umol/l
    - Proteinuria – 1.2 g/day
    - Paraprotein – 0.4 g/day

- What is your differential diagnosis?

- What would you do next?
Biopsy – Case 2
Case 2

- Diagnosis
  - Pamidronate induced FSGS

- Medication ceased
  - Resolution albuminuria over 4 months
  - Creatinine stable at 140-150 umol/l
CASE 3

- Mrs RB 66 yo
  - IgA myeloma diagnosed 04/2002
    - 80% plasma cells, IgA 40-60 g/l
    - \( \lambda \) light chain BJP, 1 g/day
  - PCAB and plasmapheresis
    - SCT 11/2002
      - 8% plasma cells, IgA 20 g/l
  - R/o retroperitoneal Leiomyoma – 05/2003
Case 3

- Commenced Thalidomide / Prednisone 09/03

- Presented with R LL Pneumonia and ARF in Melbourne 07/2005
  - Prior to this IgA levels and BJP excretion were stable

- Transferred
  - Paraprotein levels unchanged
  - Dialysed
  - ?? Obstruction → stented → no change

- What would you do next?
Case 3 renal Biopsy
Case 3 Renal Biopsy
Case 3

- Commenced haemodialysis
- Subsequent change to PD

- Worsening myeloma / infections
  - Deceased 2 years later
Monoclonal Plasma Cell Diseases and Renal Disease

What are the diseases involved?

Why the different phenotypes?

Why can Cast Nephropathy develop with stable paraprotein level?

What to do?
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Disease Definition</th>
<th>Clinical Manifestations and course</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGUS</td>
<td>Serum monoclonal protein &lt;30g/l</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td></td>
<td>Bone marrow plasma cells &lt;10%</td>
<td>1% per year progress to myeloma or related malignancy</td>
</tr>
<tr>
<td></td>
<td>Absence of end-organ damage</td>
<td></td>
</tr>
<tr>
<td></td>
<td>anaemia, hypercalcaemia, bone, renal</td>
<td></td>
</tr>
<tr>
<td>Smoldering multiple myeloma</td>
<td>Serum monoclonal protein (IgG or IgA) ≥3g/dL and/or bone marrow plasma cells ≥10%</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td></td>
<td>Absence of end organ damage</td>
<td>10% per year progress to myeloma</td>
</tr>
<tr>
<td>Multiple Myeloma</td>
<td>Bone marrow plasma cells ≥10%</td>
<td>Presence of end-organ damage is needed for diagnosis</td>
</tr>
<tr>
<td></td>
<td>Presence of serum and/or urinary monoclonal protein (except in patients with true non-secretory multiple myeloma)</td>
<td>Median survival is approximately 4 years</td>
</tr>
<tr>
<td></td>
<td>• Evidence of end organ damage</td>
<td></td>
</tr>
<tr>
<td>Waldenström macroglobulinemia</td>
<td>IgM monoclonal gammopathy ≥10% bone marrow lymphoplasmacytic infiltration (usually intertrabecular) by small lymphocytes that exhibit plasmacytoid or plasma cell differentiation and a typical immunophenotype</td>
<td>Clinical features include hyperviscosity, anemia, lymphadenopathy, and hepatosplenomegaly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median survival is approximately 5-6 years</td>
</tr>
<tr>
<td>(AL) Amyloidosis</td>
<td>Amyloid-related systemic syndrome (such as renal, liver, heart, gastrointestinal tract, or peripheral nerve involvement)</td>
<td>Any organ can be involved. Most common are heart, kidney, peripheral nerves, gastrointestinal tract, and liver</td>
</tr>
<tr>
<td></td>
<td>Positive amyloid staining by Congo red in any tissue</td>
<td>Median survival is approximately 2 years</td>
</tr>
<tr>
<td></td>
<td>Evidence that amyloid is light-chain related established by direct examination of the amyloid tissue</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Evidence of a monoclonal plasma cell proliferative disorder</td>
<td></td>
</tr>
</tbody>
</table>
## Paraproteinaemic Renal Disease

<table>
<thead>
<tr>
<th>Light Chain</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>more common</td>
<td>rare</td>
</tr>
<tr>
<td>AL Amyloid</td>
<td>AH Amyloid</td>
</tr>
<tr>
<td>ML(H) CDD</td>
<td>MH CDD</td>
</tr>
<tr>
<td>Cast Nephropathy</td>
<td>Immunotactoid GN*</td>
</tr>
<tr>
<td>Proximal Tubulopathy</td>
<td>Type 1 Cryoglobulinaemic GN</td>
</tr>
<tr>
<td></td>
<td>GN with monoclonal deposits</td>
</tr>
<tr>
<td></td>
<td>Waldenstroms</td>
</tr>
</tbody>
</table>

* Fibrillary GN
Incidence of Monoclonal Gammopathy Related Renal Disease

- Varies depending on definitions
  - In myeloma patients, renal insufficiency is noted in 18% to 56%
  - At autopsy, renal involvement is seen in approximately 50% of patients with multiple myeloma
    - Light chain cast nephropathy (29%-32%)
    - AL amyloidosis (5%-11%)
    - LCDD (3%-5%)
  - Acute tubular necrosis
    - Common finding
    - Can occur alone or in conjunction with other pathologies
Incidence of Monoclonal Gammopathy Related Renal Disease

- Less is known about the incidence of monoclonal gammopathy related kidney disease in patients without myeloma

- In patients who have significant proteinuria or renal insufficiency warranting a renal biopsy, more than half have a monoclonal gammopathy-related kidney disease
  - Cryoglobulinemic glomerulonephritis – 16.5%
  - LCDD – 11.6%
  - Light chain cast nephropathy – 10.7%
  - AL amyloidosis – 10.7%
  - Light heavy chain deposition disease – 4.1%
The Immunoglobulin Light Chain Molecule - (one light chain disease per patient)

FR  Framework region, little variability,
CDR  Complementarity determining regions, hypervariable,
      synthesised by V and J gene segments (V_κ/λ 30-50 / 20-30, J_κ/λ 5, 20-30)
      CDR3 most variable – V-J recombination, insertion non-germline nucleotides
No two light chains identical, each light chain has unique toxicity
κ_IV  usually associated with MC(H) CDD
λ_VI  usually associated with AL Amyloid
CDR3 responsible for binding to Uromodulin binding site (TH protein) and initiating cast nephropathy
Renal Handling of Immunoglobulin Light Chains

- Potential interaction every segment of nephron
  - Freely filtered at glomerulus
  - Presented to proximal tubule
    - Endocytosed after binding to megalin-cubulin complex
    - Degraded in lysosomes and aa returned to circulation
  - If endocytic uptake saturated then light chains appear in tubular fluid of distal nephron segments
    - Present in urine = BJP
Pathogenesis of Cast formation

Proximal tubule overwhelmed by rising light chain load

Light chain concentration in filtrate rises with plasma concentration as a result of fall in GFR, increased production and reduced clearance/catabolism

Light chain binds to THP and aggregates to form casts in the distal tubule
Mechanisms of renal Injury

- Tubular precipitation
  - Light chain cast nephropathy
- Deposition
  - Amyloid
  - Monoclonal immunoglobulin deposition disease
  - Fanconi
- Hyperviscosity
  - Waldenstroms
  - Elevated serum Ig
    - IgM > 30 g/l
    - IgA > 60 g/l
    - IgG > 40g/l
- Glomerular
  - Amyloid, MIDD, MPGN, immune complex
  - Pamidronate MCN, FSGS
- Tubular
  - ATN and ATIN
### Use of Specific tests in Diagnosis of Paraproteinaemic Renal Disease

<table>
<thead>
<tr>
<th>Test</th>
<th>AL-amyloid</th>
<th>MLH(CD)</th>
<th>Cast nephropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum and urine protein</td>
<td>Not recommended as a screening test</td>
<td>Not recommended as a screening test</td>
<td>Not recommended as a screening test</td>
</tr>
<tr>
<td>electrophoresis</td>
<td>Combined sensitivity of 80–90%; not diagnostic</td>
<td>Combined sensitivity of 75–85%; not diagnostic</td>
<td>Combined sensitivity approaches 100%; not diagnostic</td>
</tr>
<tr>
<td>Serum and urine immunofixation</td>
<td>Sensitivity about 90%; not diagnostic</td>
<td>Sensitivity about 90%; not diagnostic</td>
<td>Sensitivity approaches 100%; not diagnostic</td>
</tr>
<tr>
<td>electrophoresis</td>
<td>Diagnostic*</td>
<td>Diagnostic*</td>
<td>Diagnostic*</td>
</tr>
<tr>
<td>Quantitative serum light</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>chains</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal biopsy with light</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>immunofluorescence, and electron microscopy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow aspiration with flow cytometry</td>
<td>Ancillary tests; characterizes and quantifies the underlying plasma cell dyscrasia</td>
<td>Ancillary tests; characterizes and quantifies the underlying plasma cell dyscrasia</td>
<td>Ancillary tests; characterizes and quantifies the underlying plasma cell dyscrasia</td>
</tr>
<tr>
<td>Radiographic and/or MRI</td>
<td>Ancillary tests; helpful in determining plasma cell burden</td>
<td>Ancillary tests; helpful in determining plasma cell burden</td>
<td>Ancillary tests; helpful in determining plasma cell burden</td>
</tr>
<tr>
<td>imaging of skeleton</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 37% patients with monoclonal gammopathy on SEP UPEP had renal disease related to paraprotein 
  AJKD 2003:42;87-95

↓10% patients with presumed AL amyloid may have hereditary amyloid (transthyretin, apo A-I, etc)
24% hereditary amyloid have serum monoclonal light chains (nil in urine)
IF on biopsy may not show light or heavy chain
Case 1 – Al Amyloid - clinical

- 75% nephrotic proteinuria
  - >20 g/d in ~ 30%
  - Albumin (dipstix) +ve
- 50% CKD
- Hypotension
  - Often ACEi intolerant
  - Orthostatic
    - Volume and neuropathy
- Light chain
  - Lambda > kappa (3:1)
  - $V_{\lambda}/V_{1}$

- Extrarenal
  - Cardiac
    - CCF and conduction defects
- Neurological
  - Peripheral and autonomic
- Liver
  - Hepatomegaly
- Soft tissue
  - Carpal tunnell
  - Tongue enlargement
Case 1 – Al Amyloid - prognosis

- 18% progress to ESRD
  - Median time from diagnosis to ESRD 14 months
  - Median dialysis survival 8 months

- Median survival overall
  - 18-24 months
Case 1 – Al Amyloid - therapy

- **Conventional - Melphalan plus high dose steroid**
  - 33% haematologic response
  - Low treatment related mortality
  - Option for non-transplant patients

- **HDCT with Autologous Stem Cell Tx**
  - 8 prospective, selected trials. 1 retrospective case control
  - 40% complete response
  - Organ response follows hematologic response
  - Long-term survival in organ responders

- **In ESRD**
  - Stem cell can be performed
  - Response similar to non-ESRD
  - Higher morbidity
  - Responders have undergone renal Tx

- **Newer drugs**
  - Thalidomide and dexamethasone
    - 19% haematologic response, 26% organ response
    - 65% treatment toxicity
  - Lenalidomide and dexamethasone
Case 3: Cast Nephropathy - clinical

- More likely with higher tumour burden
- ARF, 10-15 with ESKD
- > 75% sub-nephrotic proteinuria
- Precipitating
  - Dehydration
  - Hypercalcaemia
  - NSAIDs
  - IV contrast
  - Infection

- Prognosis
  - Recovery 26-58%
    - Hypercalcaemia
    - Lower creatinine
  - Recovery affects survival
    Response to chemotherapy also affects survival
Case 3: Cast Nephropathy - Rx

- Restore volume / perfusion
- Remove toxins
- Reduce light chain levels
  - Chemotherapy
    - Thalidomide plus dexamethasone
    - Bortezomib plus dexamethasone
  - Plasma exchange (controversial)
    - Efficacy in 2 older studies
    - More recent study no benefit on overall survival
    - Standard treatment in hyperviscosity (Waldenstroms)
Management of ESKD

- Survival significant diminished in patients with dysproteinaemia and ESKD
  - Median survival
    - 4 years LCDD
    - 2 years AL amyloid
    - 1 year MM
1/3 have myeloma, rest plasma cell dyscrasia

Similar trials / consideration to AL amyloid

Recurrence in transplants (AJKD 2004:43;147-153)
- Median graft survival 37.4 months
- Median patient survival 6.1 years
Fibrillary / Immunotactoid GN

- Fibrillary
  - Haematuria/proteinuria and CKD
  - Extra-renal reported
  - LM
    - MPGN, crescentic
  - IF
    - IgG1 and 4, not IgG2, 3
  - Random congo –ve fibrils
    - Diameter 13-29 mm

- Immunotactoid GN
  - ? Subgroup of fibrillary
  - Fibrils typically
    - Larger
    - Hollow centre
    - Organised pattern resembling microtubules
  - Of stains positive for monoclonal immunoglobulins
LM Immunotactoid GN
EM – Fibrillary and Immunotactoid GN

Fibrillary GN

Immunotactoid GN
AA Amyloid
# Underlying Disorders and Treatment in 374 Patients with AA Amyloidosis

**Table 1. Underlying Disorders and Treatment in 374 Patients with AA Amyloidosis.**

<table>
<thead>
<tr>
<th>Underlying Disorder</th>
<th>No. of Patients (%)</th>
<th>Examples of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic inflammatory arthritis</td>
<td>224 (60)</td>
<td>Immunosuppressive agents: chlorambucil (Leukeran, GlaxoSmithKline) or cyclophosphamide (Cytoxan, Bristol-Myers Squibb); methotrexate (Rheumatrex, Wyeth-AYERST). Biologic agents: anti-IL17 therapies and interleukin-1–receptor antagonists</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>123 (33)</td>
<td></td>
</tr>
<tr>
<td>Juvenile idiopathic arthritis</td>
<td>64 (17)</td>
<td></td>
</tr>
<tr>
<td>Other chronic inflammatory arthritides</td>
<td>37 (10)</td>
<td></td>
</tr>
<tr>
<td>Chronic sepsis</td>
<td>56 (15)</td>
<td></td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>20 (5)</td>
<td>Surgery, physiotherapy, and antibiotics</td>
</tr>
<tr>
<td>Injection-drug abuse</td>
<td>13 (4)</td>
<td>Drug rehabilitation programs and antibiotics</td>
</tr>
<tr>
<td>Complications of paraplegia (infected pressure sores, urinary infection)</td>
<td>8 (2)</td>
<td>Physiotherapy, treatment of pressure ulcers, procedures for urinary drainage, and antibiotics</td>
</tr>
<tr>
<td>Other</td>
<td>7 (2)</td>
<td>Surgery and antibiotics</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>5 (1)</td>
<td>Surgery and antibiotics</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>3 (1)</td>
<td>Antituberculous therapy</td>
</tr>
<tr>
<td>Periodic fever syndromes</td>
<td>32 (9)</td>
<td></td>
</tr>
<tr>
<td>Familial Mediterranean fever</td>
<td>20 (5)</td>
<td>Colchicine</td>
</tr>
<tr>
<td>TNF-receptor–associated periodic fever syndrome</td>
<td>6 (2)</td>
<td>Anti-TNF therapy</td>
</tr>
<tr>
<td>Muckle-Wells syndrome</td>
<td>4 (1)</td>
<td>Interleukin-1–receptor antagonist</td>
</tr>
<tr>
<td>Hyper-IgD and periodic fever syndrome</td>
<td>2 (&lt;1)</td>
<td>Anti-TNF therapies and interleukin-1–receptor antagonist</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>17 (5)</td>
<td>Anti-TNF therapies, surgical resection, immunosuppressive agents</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>22 (6)</td>
<td></td>
</tr>
<tr>
<td>Castleman’s disease</td>
<td>7 (2)</td>
<td>Surgical excision</td>
</tr>
<tr>
<td>Neoplasia (lymphoma, mesothelioma)</td>
<td>4 (1)</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>4 (1)</td>
<td>Immunosuppressive agents</td>
</tr>
<tr>
<td>Other</td>
<td>7 (&lt;2)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>23 (6)</td>
<td></td>
</tr>
</tbody>
</table>

*Percentages may not sum to 100 because of rounding. A patient may have had more than one underlying disease. TNF denotes tumor necrosis factor.*

Changes in Amyloid Burden from Baseline to Most Recent Follow-up in 221 Patients and Changes in Amyloid Burden and Renal Function during Follow-up in 178 Patients with a Baseline Creatinine Clearance of More Than 20 ml per Minute
Regression of AA Amyloid Deposits in a Patient with Familial Mediterranean Fever

### Table 3. Unadjusted Relative Risk of Death Associated with the Most Recent Median Annual SAA Concentration during Follow-up.*

<table>
<thead>
<tr>
<th>SAA Octile (mg/liter)</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>≥4 to &lt;9</td>
<td>3.9 (1.5–10.4)</td>
<td>0.007</td>
</tr>
<tr>
<td>≥9 to &lt;16.7</td>
<td>5.1 (2.7–9.4)</td>
<td>0.003</td>
</tr>
<tr>
<td>≥16.7 to &lt;28</td>
<td>7.0 (3.7–13.4)</td>
<td>0.07</td>
</tr>
<tr>
<td>≥28 to &lt;45.6</td>
<td>9.1 (4.8–17.2)</td>
<td>0.008</td>
</tr>
<tr>
<td>≥45.6 to &lt;87</td>
<td>12.1 (6.9–21.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥87 to &lt;155</td>
<td>17.0 (8.6–33.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥155</td>
<td>17.7 (8.7–36.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* The SAA value is the median concentration within each 12-month period and was incorporated into the Cox regression model as a time-dependent covariate.
Factors Significantly Associated with the Risk of Death or Progression to End-Stage Renal Failure (Cox Regression Models)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Unadjusted Relative Risk (95% CI)</th>
<th>P Value</th>
<th>Adjusted Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per additional decade of age)</td>
<td>1.02 (1.01–1.03)</td>
<td>&lt;0.001</td>
<td>1.03 (1.02–1.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White race</td>
<td>2.03 (2.02–3.32)</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underlying disease</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>0.23 (0.14–0.36)</td>
<td>&lt;0.001</td>
<td>0.23 (0.14–0.36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Periodic fever syndromes</td>
<td>0.21 (0.09–0.49)</td>
<td>&lt;0.001</td>
<td>0.16 (0.06–0.46)</td>
<td>0.03</td>
</tr>
<tr>
<td>C-Reactive protein</td>
<td>0.11 (0.01–0.90)</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undetermined disease</td>
<td>0.27 (0.10–0.73)</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein burden on SAP imaging scans</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>1.19 (1.19–3.30)</td>
<td>0.000</td>
<td>1.19 (1.19–3.30)</td>
<td>0.000</td>
</tr>
<tr>
<td>Moderate</td>
<td>1.52 (1.04–2.23)</td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Light</td>
<td>0.69 (0.45–1.09)</td>
<td>0.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of inflammatory disease (per 5 yr interval)</td>
<td>0.09 (0.06–0.13)</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factors that could change during follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum albumin (mg/dL)</td>
<td>0.78 (0.72–0.85)</td>
<td>&lt;0.001</td>
<td>0.78 (0.72–0.85)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.20 (1.18–1.23)</td>
<td>&lt;0.001</td>
<td>1.20 (1.18–1.23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serine proteases (by a factor 2)</td>
<td>0.46 (0.27–0.79)</td>
<td>&lt;0.001</td>
<td>0.46 (0.27–0.79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min/1.73 m2)</td>
<td>0.05 (0.03–0.07)</td>
<td>&lt;0.001</td>
<td>0.05 (0.03–0.07)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>End-stage renal failure</td>
<td>2.83 (2.02–3.93)</td>
<td>&lt;0.001</td>
<td>2.83 (2.02–3.93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in amyloid deposits</td>
<td>2.97 (2.15–3.41)</td>
<td>&lt;0.001</td>
<td>2.97 (2.15–3.41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Progressed</td>
<td>1.41 (1.01–1.98)</td>
<td>0.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Regressed</td>
<td>0.01 (0.00–0.32)</td>
<td>&lt;0.001</td>
<td>0.01 (0.00–0.32)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Factors Associated with Progression to End-stage Renal Failure

Factors at baseline

<table>
<thead>
<tr>
<th>Factor</th>
<th>Unadjusted Relative Risk (95% CI)</th>
<th>P Value</th>
<th>Adjusted Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Juvenile idiopathic arthritis</td>
<td>0.41 (0.24–0.72)</td>
<td>0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic capillary</td>
<td>2.16 (1.94–2.40)</td>
<td>0.000</td>
<td>4.19 (1.95–8.98)</td>
<td>0.000</td>
</tr>
<tr>
<td>C-Reactive protein</td>
<td>5.48 (1.94–16.88)</td>
<td>0.000</td>
<td>4.19 (1.95–8.98)</td>
<td>0.000</td>
</tr>
<tr>
<td>Protein burden</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>0.36 (0.24–0.54)</td>
<td>0.000</td>
<td>0.24 (0.17–0.31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Moderate</td>
<td>2.08 (1.86–4.15)</td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Light</td>
<td>2.17 (1.13–4.19)</td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic amyloid deposits</td>
<td>1.73 (0.97–3.1)</td>
<td>0.06</td>
<td>1.98 (1.00–3.92)</td>
<td>0.04</td>
</tr>
<tr>
<td>Duration of inflammatory disease (per 5 yr interval)</td>
<td>1.31 (1.20–1.40)</td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine (by a factor 2)</td>
<td>2.31 (1.67–3.19)</td>
<td>&lt;0.001</td>
<td>2.31 (1.67–3.19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Factors that could change during follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum albumin (mg/dL)</td>
<td>0.74 (0.64–0.86)</td>
<td>&lt;0.001</td>
<td>0.74 (0.64–0.86)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.33 (0.14–1.00)</td>
<td>0.02</td>
<td>0.24 (0.06–0.96)</td>
<td>0.06</td>
</tr>
<tr>
<td>Change in amyloid deposits</td>
<td>0.14 (1.04–0.99)</td>
<td>&lt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progressed</td>
<td>1.09</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable</td>
<td>0.46 (0.21–0.99)</td>
<td>0.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regressed</td>
<td>0.14 (0.04–0.50)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*These are other groups were self-reported.

*The variable [variable name] of patients with a history of disease of AA amyloidosis, evidence of hypertensive nephropathy, or other non-rheumatic disease, or patients in whom amyloidosis was present were compared with those who had any of the other underlying diseases, and in whom amyloidosis was not present or not yet diagnosed.
Eprosidate in treatment of AA Amyloid

## Cox Proportional-Hazards Models for the Primary End Point

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Covariates of adjusted models</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0.58 (0.37–0.93)</td>
<td>0.02</td>
</tr>
<tr>
<td>Underlying disease†</td>
<td>0.56 (0.35–0.90)</td>
<td>0.02</td>
</tr>
<tr>
<td>Baseline serum creatinine concentration</td>
<td>0.61 (0.38–0.98)</td>
<td>0.04</td>
</tr>
<tr>
<td>Baseline creatinine clearance</td>
<td>0.57 (0.37–0.94)</td>
<td>0.03</td>
</tr>
<tr>
<td>Baseline urinary protein excretion</td>
<td>0.56 (0.35–0.90)</td>
<td>0.02</td>
</tr>
<tr>
<td>Baseline use of ACE inhibitor or ARB</td>
<td>0.60 (0.37–0.95)</td>
<td>0.03</td>
</tr>
<tr>
<td>Baseline blood pressure‡</td>
<td>0.57 (0.36–0.92)</td>
<td>0.02</td>
</tr>
<tr>
<td>Baseline SAA concentration</td>
<td>0.61 (0.38–0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>SAA concentration throughout study</td>
<td>0.59 (0.37–0.95)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Components of primary composite outcome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doubling of serum creatinine concentration</td>
<td>0.41 (0.19–0.86)</td>
<td>0.02</td>
</tr>
<tr>
<td>≥50% Reduction in creatinine clearance</td>
<td>0.48 (0.28–0.82)</td>
<td>0.01</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>0.54 (0.22–1.37)</td>
<td>0.20</td>
</tr>
<tr>
<td>Death</td>
<td>0.95 (0.27–3.29)</td>
<td>0.94</td>
</tr>
</tbody>
</table>

* All models were adjusted for the stratification variable of nephrotic status. ACE denotes angiotensin-converting enzyme, ARB angiotensin II-receptor blocker, and SAA serum amyloid A protein.
† Underlying disease was categorized as rheumatoid arthritis, familial Mediterranean fever, or other.
‡ Mean arterial blood pressure values were calculated from systolic and diastolic blood pressure measurements.

Kaplan-Meier Estimates of Event-free Survival

Table 3: Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Epidemiene (N=81)</th>
<th>Placebo (N=94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with at least one adverse event</td>
<td>87 (98)</td>
<td>87 (93)</td>
</tr>
<tr>
<td>Most common non-serious adverse events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthmatic bronchospasm</td>
<td>11 (13)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>24 (28)</td>
<td>23 (24)</td>
</tr>
<tr>
<td>Upper respiratory symptoms</td>
<td>20 (25)</td>
<td>28 (29)</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>24 (27)</td>
<td>21 (23)</td>
</tr>
<tr>
<td>Abdominal pain or dyspepsia</td>
<td>22 (27)</td>
<td>30 (32)</td>
</tr>
<tr>
<td>Cough or bronchitis</td>
<td>21 (25)</td>
<td>20 (21)</td>
</tr>
<tr>
<td>Edema</td>
<td>16 (19)</td>
<td>17 (18)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13 (16)</td>
<td>9 (10)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9 (11)</td>
<td>10 (11)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>6 (7)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Tachycardia, palpitations, or atrial fibrillation</td>
<td>8 (10)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Tachypnea</td>
<td>6 (8)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Anemia</td>
<td>7 (8)</td>
<td>10 (11)</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>4 (5)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (5)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2 (3)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>3 (4)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>5 (6)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Anemia</td>
<td>5 (6)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Patients with at least one serious adverse event</td>
<td>32 (38)</td>
<td>39 (42)</td>
</tr>
<tr>
<td>Most common serious adverse events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>7 (9)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (6)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (3)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Pancytopenia</td>
<td>1 (1)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>5 (6)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>8 (10)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Infarction</td>
<td>9 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Hyperalgesia</td>
<td>2 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>7 (8)</td>
<td>11 (12)</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>3 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>5 (6)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Death</td>
<td>5 (6)</td>
<td>5 (5)</td>
</tr>
</tbody>
</table>

* P<0.05 for all comparisons between treatment groups.
† The most common non-serious adverse events are defined as those experienced by at least 5% of the patients in the epidural group.
‡ A serious adverse event is defined as one event that was fatal; life-threatening; or resulted in hospitalisation or prolongation of a hospitalisation; or was associated with a congenital abnormality or birth; or was regarded by the investigator as serious.
§ The most common serious adverse events are defined as those experienced by at least 2% of all patients or by at least two patients in either group.