# Paraprotein-related renal disease

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## Abstract

Paraprotein-related renal disease represents a diverse group of rare diseases characterized by distinct renal injury caused by the direct or indirect effects of a nephrotoxic paraprotein secreted by a clone of B cells. Early diagnosis and use of rapidly effective chemotherapy agents have improved patient and renal outcomes for these disorders. Patients can present with proteinuric renal impairment or tubular dysfunction. Diagnosis is often challenging because of the wide range of disease manifestations, difficulties with detection of the pathogenic clone and the common finding of an incidental paraprotein in elderly individuals. A renal biopsy along with haematological work-up is required to link a paraprotein with kidney disease. Chemotherapy directed at the plasma cell clone can halt the production of the paraprotein, which can in turn benefit renal function.

**Keywords** Amyloid; cast; glomerulonephritis; monoclonal gammopathy of renal significance; MRCP; myeloma; paraprotein; plasma cell; serum free light chain

## Key points

- Patients with unexplained proteinuria or renal dysfunction should be screened for monoclonal protein, including with serum protein electrophoresis and serum and urinary free light chain assays
- A monoclonal gammopathy can produce renal disease even with a very low paraprotein concentration
- Paraprotein-related renal diseases can present as acute kidney injury (AKI), progressive proteinuric renal disease and/or Fanconi syndrome
- Most elderly patients with renal impairment and monoclonal gammopathy of undetermined significance have unrelated kidney disease
- Prompt commencement of chemotherapy is crucial in multiple myeloma and AKI, and patients with monoclonal gammopathy of renal significance usually require chemotherapy

## Introduction

A paraprotein is a monoclonal immunoglobulin (MIg) or its components (light or heavy chain) produced by the clonal proliferation of plasma cells or other cells of B cell lineage. The spectrum of disease associated with a monoclonal gammopathy is wide, from overt malignancy such as multiple myeloma (MM) to the premalignant condition monoclonal gammopathy of undetermined significance (MGUS). This latter term is used when a circulating MIg causes no detectable tissue damage. MGUS is a relatively common finding in elderly individuals, with an estimated prevalence of 3% in those >50 years old, and carries a 1% per year risk of progression.

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In most patients with kidney disease and a monoclonal gammopathy, the paraprotein is incidental to the renal pathology. Monoclonal gammopathy of renal significance (MGRS) is rare and refers to kidney diseases caused by a nephrotoxic paraprotein. The underlying clonal disorder is usually low grade; this may previously have been wrongly labelled as MGUS. Although the underlying clone does not cause tumour complications or meet current haematological criteria for treatment, specific therapy aimed at the clone can be required to prevent further renal damage or slow progression to end-stage renal failure (ESRF).[1]

The range of haematological conditions that can produce a nephrotoxic MIg and result in MGRS includes smouldering MM, smouldering Waldenström's macroglobulinaemia (WM), monoclonal B cell lymphocytosis, low-grade chronic lymphocytic lymphoma and other low-grade lymphomas. Once the haematological condition progresses to requiring treatment in its own right, i.e. to overt MM, WM, advanced chronic lymphocytic lymphoma or malignant lymphoma, it is no longer considered an MGRS and is instead managed according to disease-specific protocols.[1]

MGRS-associated kidney diseases encompass a wide spectrum of renal pathology and can be categorized according to the ultrastructural characteristics of the kidney deposits (Figure 1). The innate structural and physiochemical properties of the individual light or heavy chain in combination with the renal environment determines the type of renal lesion. In most cases of immunoglobulin light chain (AL) amyloidosis λ light chains are found, whereas monoclonal κ light chains are found in three-quarters of light chain deposition disease (LCDD). The MIg can cause renal injury by intratubular cast formation as in cast nephropathy, direct tubular toxicity or deposition in various compartments, as in amyloid.

## Diagnosis

Patients with unexplained urinary abnormalities (proteinuria and/or haematuria) or renal impairment should have a paraprotein screen. This includes serum protein electrophoresis with immunofixation, urine protein electrophoresis with immunofixation and serum free light chain (sFLC) analysis.

A renal biopsy is integral to diagnosing the underlying renal lesion, which can help to guide treatment and is prognostically important. A kidney biopsy should include immunofluorescence and electron microscopy to establish monoclonality and characterize the immunoglobulin deposit ultrastructurally.

A detailed haematological work-up (bone marrow aspirate and biopsy, flow cytometry, immunohistochemistry, fluorescence *in situ* hybridization and possibly lymph node biopsy) is required to correlate the specific immunoglobulin found on renal biopsy with that found on haematological work-up, to establish a link between the paraprotein and the kidney disease.

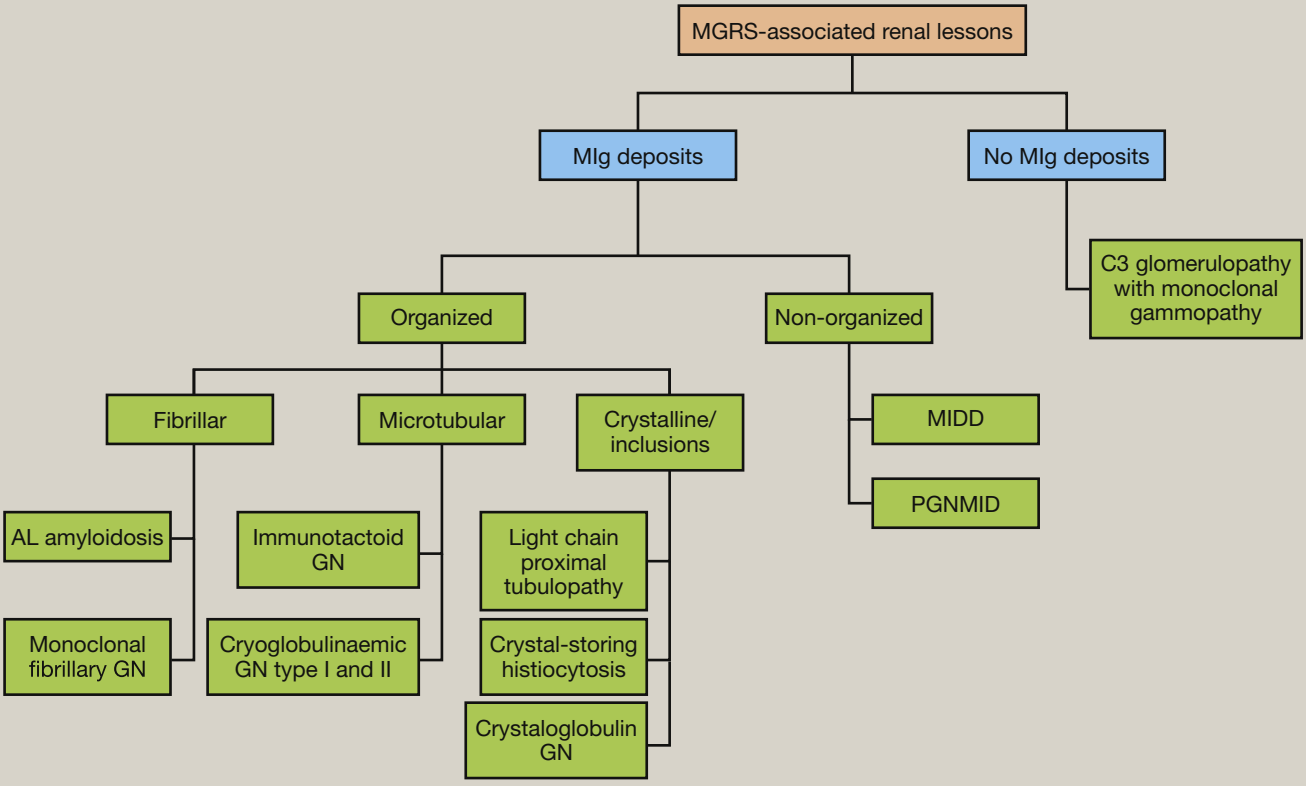
## Myeloma

MM is a cancer of plasma cells and accounts for almost 10% of all haematological malignancies. The worldwide incidence varies from 4 to 50 cases per million population per year. In the UK, 5500 new cases of MM are diagnosed each year. The median age at onset is 70 years, and the condition is more common in men and African-American individuals.

Renal impairment is a common complication of MM: up to 50% of patients present with some degree of dysfunction. Approximately 20% of patients have severe renal disease classifying the disease as a myeloma-defining event, and up to 5% have severe acute kidney injury (AKI) requiring dialysis[2]; 90% of severe AKI in myeloma is the result of myeloma cast nephropathy.

The revised International Myeloma Working Group diagnostic criteria for MM comprise the presence of clonal plasma cells and a myeloma-defining event of one or more of the classic 'CRAB' features — hyper**c**alcaemia, **r**enal failure, **a**naemia and/or destructive **b**one lesions — or evidence of a heavy tumour burden

**Classification of MGRS-associated renal lesions based on the ultrastructural appearance of deposits**




AL, immunoglobulin light chain amyloidosis; GN, glomerulonephritis; MGRS, monoclonal gammopathy of renal significance; MIg, monoclonal immunoglobulin; MIDD, monoclonal immunoglobulin deposition disease; PGNMID, proliferative glomerulonephritis with monoclonal immunoglobulin deposits.

Source: Adapted from Leung et al. (2019).[1]

**Figure 1**

defined by one or more of >60% plasma cells on bone marrow biopsy, an sFLC ratio >100, or >1 focal bone lesion on magnetic resonance imaging. Patients can present with systemic clinical features such as weight loss, anaemia, recurrent infections, hypercalcaemia and bone pain. Some patients present with AKI, low-grade proteinuria and a bland urinary sediment.

The current overall survival from first diagnosis is 4 years, and disease-free survival (from first remission to relapse) is around 18 months. With the introduction of new therapies, there has been an improvement in the past decade in overall survival for patients with MM.

## Myeloma cast nephropathy

Monoclonal FLCs aggregate with Tamm–Horsfall protein to produce casts (Figure 2). Histologically, they are often seen as large, fractured or laminated casts within the distal tubule or collecting ducts. They are often surrounded by multinucleated giant cells, and there is evidence of chronic interstitial damage. Myeloma casts cause tubular obstruction that in turn leads to AKI.

Certain conditions, such as dehydration, hypercalcaemia, sepsis or insults from radiological contrast media or non-steroidal anti-inflammatory drugs, give FLCs a higher propensity to precipitate as casts and can worsen the renal insult.

Cast nephropathy is more common when the sFLC concentration exceeds 500 mg/litre. In patients presenting with severe AKI and evidence of a high concentration of light chains, the haematological work-up should take priority to enable treatment to begin quickly; a renal biopsy is not usually indicated as it will not alter management.

Severe renal impairment is an adverse determinant of outcome, and survival improves if there is early recovery of kidney function. Since the introduction of bortezomib-based chemotherapy and better supportive care, around 50% of patients with MM who require dialysis at presentation recover independent kidney function.

Studies have shown no benefit of plasma exchange in myeloma cast nephropathy. Two randomized controlled trials have recently been completed: Multiple Myeloma and Renal Failure due to Myeloma Cast Nephropathy (MYRE) and European Trial of Free Light Chain Removal by Extended Haemodialysis in Cast Nephropathy (EuLITE). Both have reported no difference in renal recovery at 3 months in patients treated with dialysis using high cut-off membranes compared with standard high-flux haemodialysis. There was an increase in overall renal recovery in the MYRE study, but not in the EuLITE study, where an increased mortality was reported at 2 years in patients who were given treated with high cut-off membranes.

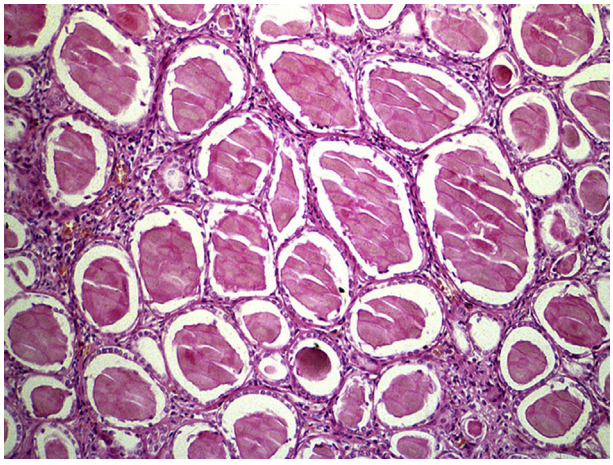


**Figure 2** Myeloma kidney: multiple casts within distal tubules exhibiting fractured planes on H&E staining.

## Waldenström's macroglobulinaemia

WM is caused by clonal proliferation of lymphoplasmacytic cells. Renal complications are less common than in patients with MM. The renal lesion is typically caused by intracapillary thrombi, secondary to IgM deposition, and can be associated with cryoglobulinaemia. WM can also cause light chain cast nephropathy, nephrotic syndrome (caused by amyloid deposition) and non-amyloid nephrotic syndrome (with a minimal change-like picture). Treatment is generally rituximab-based.

## AL amyloidosis

Amyloidosis is a disorder of protein misfolding and refers to the extracellular deposition of low-molecular-weight proteins as

### Clinical manifestations of AL amyloidosis

| | |
|---|---|
| **Visible tissue infiltration (10% of cases)** | **Autonomic neuropathy (15% of cases)** |
| Easy bruising (often periorbital) | Orthostatic hypotension |
| Macroglossia with altered taste and dry mouth | Cardiac arrhythmias |
| Thyroid and salivary gland enlargement | Diarrhoea |
| Muscle and joint pseudohypertrophy | Erectile dysfunction and impaired bladder emptying |
| **Renal (70% of cases)** | **Peripheral neuropathy (20% of cases)** |
| Progressive chronic kidney disease | Carpal tunnel syndrome |
| Proteinuria | Symmetrical distal axonal sensorimotor neuropathy |
| **Cardiac (60% of cases)** | **Gastrointestinal** |
| Restrictive cardiomyopathy with congestive cardiac failure | Weight loss, anorexia, bloating |
| Low limb voltages and pseudo-infarct pattern on ECG | Blood loss |
| | Constipation |
| **Hepatic** | **Adrenal axis** |
| Hepatomegaly | Biochemical hypoadrenalism (rare) |
| Increased ALP and GGT | |
| Hepatic failure (rare) | |
| **Pulmonary** | **Lymphoreticular system** |
| Recurrent pleural effusions | Splenomegaly, features of hyposplenism |
| Interstitial lung involvement — usually asymptomatic | Lymphadenopathy |

AL, amyloid light chain; ALP, alkaline phosphatase; GGT, γ-glutamyl transferase.

**Table 1**

fibrils. AL amyloidosis results from the deposition of light chains, which undergo a conformational change and are deposited in the extracellular space as amyloid fibrils. Accumulation of these fibrils causes progressive disruption of organ structure and function.

An estimated 500–600 people are diagnosed with AL amyloidosis every year in the UK. The median age at diagnosis is 64 years, and it is more common in male patients. The clinical presentation in AL amyloidosis depends on the number and nature of the organs affected (Table 1). Many patients present with non-specific symptoms such as malaise and weight loss.

The diagnosis of AL amyloidosis requires evidence of a monoclonal plasma cell disorder and direct demonstration of amyloid fibrils on biopsy. The presence of amyloid fibrils can be confirmed by their characteristic appearance on electron microscopy and by their ability to bind Congo red with green birefringence under polarized light. The type of protein within the amyloid fibrils can be determined by immunohistochemical staining, immunofluorescence or laser microdissection with mass spectrometry. Whole body $^{123}$I-labelled serum amyloid P scintigraphy can identify amyloid in solid organs and can be used in serial follow-up assessments to track the total body amyloid load (Figure 3).

**Figure 3** Anterior whole-body scintigraphic image after injection of $^{123}$I-human serum amyloid P in a patient with AL amyloidosis. Uptake is seen in the bones, liver and spleen.

Median survival in untreated patients is only 12–15 months depending on the organs involved. Poor prognostic factors in patients with renal amyloid include high NT-pro B-type natriuretic peptide, older age, higher total sFLC concentration, lower serum albumin, hypotension and hyperbilirubinaemia. The degree of renal impairment, serum albumin concentration and amount of proteinuria are all associated with progression to dialysis. Outcome on dialysis is only slightly better than in patients with myeloma but is improving with time, and patients with isolated renal involvement can do well. Renal transplantation in selected patients with sustained clonal remissions can achieve an excellent outcome, and recurrence in the graft is not commonly found.[3]

## Monoclonal immunoglobulin deposition disease (MIDD)

MIDD is characterized by deposition of MIg or its components in various organs; the kidney is most commonly affected. The diagnosis differs from amyloidosis as here the light (or heavy) chain fragments do not form fibrils and deposits are Congo-red-negative. Three subtypes are LCDD, heavy chain deposition disease, and light and heavy chain deposition disease. Of these, LCDD is the most common, accounting for 80% of cases.

LCDD is characterized by the deposition of non-organized granular deposits composed of MIg light chains along the glomerular and tubular basement membranes. The diagnosis is usually made on electron microscopy. The kidney is the principal target organ as light chains are filtered by the glomeruli, reabsorbed in the proximal tubules and degraded in tubular cells by lysosomal enzymes.

LCDD usually presents in the sixth decade and is more common in men. Presentation is usually with hypertension and microscopic haematuria, and 50% of cases have associated nephrotic syndrome. Most cases have advanced chronic kidney disease, and ESRF occurs in up to 30%. LCDD is associated with κ light chains in 80% of patients, and >60% have underlying myeloma. Extra-renal manifestations of LCDD are seen in approximately 30% of patients, with cardiac infiltration occurring in 20% and clinically overt liver involvement in 10–20%. There have also been reports of LCDD in gastrointestinal tract and skin biopsies, but this is extremely rare.

LCDD has a better outcome than other paraprotein-related renal diseases, with a median patient survival of 7 years. LCDD should be aggressively treated with chemotherapy as achieving a deep clonal response prolongs renal survival, and prevents allograft failure from recurrent LCDD in those who given renal transplants.[4] Extra-renal involvement and lack of clonal response to chemotherapy are both features of a poor prognosis.

## Other paraprotein-related renal diseases

**Fibrillary glomerulonephritis** is a glomerular disease characterized by Congo-red-negative fibrils that are randomly arranged and larger than amyloid fibrils. Presentation is similar to LCDD, with 50% of patients presenting with nephrotic-range proteinuria. Haematuria and hypertension are also common features. There is some evidence that it is more common in the context of malignancy, dysproteinaemias and autoimmune disease. There are very limited data regarding the response to treatment, and the optimal management of this condition has yet to be established.

**Immunotactoid glomerulonephritis** is rare; fibrils are larger, usually >30 nm in diameter and arranged in parallel microtubules. There can be an underlying lymphoplasmacytic disorder.

**Light chain proximal tubulopathy** shows the formation of localized crystals or inclusions of light chains within the proximal tubules. Patients present with Fanconi syndrome (e.g. aminoaciduria, normoglycaemic glycosuria, hypophosphataemia, hypouricamia, subnephrotic-range proteinuria). In patients who have significant renal impairment and/or proteinuria, treatment with clone-directed chemotherapy seems a reasonable approach.

**Proliferative glomerulonephritis with monoclonal immunoglobulin deposits** mimics an immune complex glomerulonephritis. The most common pattern is a membranoproliferative glomerulonephritis (MPGN). Immunofluorescence reveals monotypic deposits, and 20% of patients have a detectable paraprotein. Patients with MPGN on light microscopy should be evaluated for an underlying clone.

**C3 glomerulopathy with monoclonal gammopathy** is characterized by lack of renal MIg deposits, although 60–80% patients aged >50 years have a clone at the time of diagnosis. Here the MIg acts as a C3 nephritic factor or anti-factor H antibody and results in uncontrolled activation of the alternative complement pathway. Observational studies support targeted chemotherapy if a clone is detected, or based upon the isotype of the circulating monoclonal protein detected in the serum or urine.

### General treatment principles

Treatment of paraprotein-related kidney disease is indicated to preserve or restore kidney function and prevent recurrence after kidney transplantation. The choice of chemotherapy regimen depends on the nature of the underlying clone, i.e. whether it is lymphocytic or plasmacytic in origin. The renal response correlates strongly with the nature of the haematological response, and rapid suppression of MIg secretion with chemotherapy is required to improve outcomes. Effective treatment involves disease-specific management and supportive care.

### Chemotherapy

The aim of treatment is to rapidly suppress paraprotein production, producing a deep and sustained clonal response while minimizing treatment-related mortality and morbidity. Response to treatment is assessed by measuring the change in the sFLC and paraprotein concentrations.

The choice of chemotherapy depends on the underlying haematological diagnosis, the degree of renal failure and/or other organ involvement and the local availability of therapeutic agents. In patients with MM who are unsuitable for a stem cell transplant, first-line treatment is usually a combination of either thalidomide or bortezomib with an alkylating agent and corticosteroids.

### General management

The most common cause of death is sepsis, so patients on chemotherapy require prophylaxis to reduce the risk of bacterial and viral infections. Prompt treatment of suspected infection is vital. In patients with proteinuria, scrupulous attention must be paid to salt and water balance, and maintenance of circulating volume. Hypercalcaemia is a common cause of renal impairment in patients with MM and should be treated promptly with hydration and bisphosphonates. Elective surgery and general anaesthesia are best avoided, and care must be taken to avoid exposure to potentially nephrotoxic drugs, particularly analgesics, contrast media and antimicrobials.

### Preservation and replacement of organ function

The requirement for dialysis has a major impact on both survival and quality of life, but patient outcomes are improving. The responses to chemotherapy in dialysis patients are equivalent to those in dialysis-independent individuals, but chemotherapy can be difficult in ESRF, with a higher incidence of adverse effects, even with novel agents.

MGRS can recur frequently and sometimes rapidly after kidney transplantation, so it is recommended that complete haematological remission is achieved before transplantation. ◆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## TEST YOURSELF

To test your knowledge based on the article you have just read, please complete self-assessment questions.

**Question 1**

A 62-year-old woman presented to secondary care with nephrotic range proteinuria. She reported increasing leg swelling over the last 3 months but she had no other relevant medical history. Clinical examination revealed peripheral and sacral pitting oedema. The rest of the examination was unremarkable. Blood pressure 101/50 mmHg.

**Investigations**

- Haemoglobin 148 g/litre (115–165)
- Platelet 300 × $10^9$/litre (150–450)
- $HbA_{1c}$ 31 mmol/mol (20–42); 5% (4.0–6.0)
- Serum corrected calcium 2.45 mmol/litre (2.20–2.60)
- Estimated glomerular filtration rate 59 ml/minute/1.73 $m^2$ (70–140)
- Albumin:creatinine ratio 487 mg/mmol (<2.5)
- Antinuclear antibody-negative
- Antineutrophil cytoplasmic antibody (ANCA)-negative
- Serum complement levels were normal
- Serum immunoglobulins normal
- Immunofixation immunoglobulin (Ig)G λ paraprotein, clonal Ig quantitation 16.17 g/litre
- Serum free light chains showed evidence of FLC clonality:
  - κ light chain 20.6 mg/litre (3.3–19.4)
  - λ light chain 290 mg/litre (5.7–26.3)
  - κ:λ ratio 0.071 (0.26–1.65)
- Ultrasonography of the kidneys was normal
- Skeletal survey was normal

**What is the most likely diagnosis?**

A. Monoclonal gammopathy-related renal disease
B. Hypertensive renal disease
C. Diabetic nephropathy
D. ANCA-associated vasculitis
E. Haemolytic–uraemic syndrome/thrombotic thrombocytopenic purpura

## Question 2

A 67-year-old man presented with tiredness and weakness. He had no significant past history.
On clinical examination, he looked anaemic but there were no other abnormalities. Urinalysis showed 2+ protein and 3+ blood.

**Investigations**

- Haemoglobin 81 g/litre (130–180)
- Mean cell volume 84 fl (80–96)
- Serum corrected calcium 2.45 mmol/litre (2.20–2.60)
- Creatine 1500 micromol/litre (60–110)
- Estimated glomerular filtration rate 3 ml/minute/1.73 $m^2$ (70–140)
- Albumin:creatinine ratio 11.3 mg/mmol (<2.5)
- Serum immunoglobulins showed immunoparesis
- Immunofixation showed IgA λ paraprotein, clonal Ig quantitation 26.0 g/litre
- Serum free light chains showed evidence of clonal excess:
  - κ light chain 15.0 mg/litre (3.3–19.4)
  - λ light chain 5835 mg/litre (5.7–26.3)
  - κ:λ ratio 0.003 (0.26–1.65)
- Ultrasonography of the kidneys was normal
- Skeletal survey was normal
- Bone marrow trephine biopsy showed neoplastic plasma cells accounting for 60–70% of the cellularity

The patient required emergency dialysis.

**What is the single most important determinant of renal recovery in this patient?**

A. Prompt start of chemotherapy
B. Extracorporeal removal of serum free light chains
C. Prompt renal replacement therapy
D. Intravenous fluids
E Prophylactic antibiotics.

## Question 3

A 70-year-old man presented for review of a low-grade clonal gammopathy. He had no symptoms. He was taking candesartan 4 mg daily for hypertension. Clinical examination was normal, Blood pressure 133/87 mmHg.

**Investigations**

- Haemoglobin 124 g/litre (130–180)
- Serum corrected calcium 2.34 mmol/litre (2.20–2.60)
- Creatine 231 micromol/litre (60–110) (180, 3 months previously)
- Estimated glomerular filtration rate 25 ml/minute/1.73 $m^2$ (70–140) (32, 3 months previously)
- Albumin:creatinine ratio 148 mg/mmol (<2.5)
- Antinuclear antibody-negative
- Antineutrophil cytoplasmic antibody negative
- Serum complement normal
- Serum immunoglobulins normal
- Immunofixation IgG κ paraprotein, clonal Ig quantitation 2.6 g/litre
- Serum free light chains showed:
  - κ light chain 91.4 mg/litre (3.3–19.4)
  - λ light chain 42.1 mg/litre (5.7–26.3)
  - κ:λ ratio 2.17 (0.26–1.65)
- Ultrasonography of the kidneys, normal

**What is the next most appropriate step in the management of this patient?**

A. Perform a kidney biopsy
B. Perform a bone marrow trephine biopsy
C. Titration of candesartan
D. Request a skeletal survey
E. Wait and watch approach