

Guidelines for Identification, Management and Referral of Adults with Chronic Kidney Disease

Summary of recommendations

This document summarises the recommendations made in the full guidelines, which are issued separately. A “desktop guide” is also available.

Classification of chronic kidney disease

Recommendation:

We recommend adoption of the classification of chronic kidney disease (CKD) proposed by the US K-DOQI group [1].

This classification is based on estimated glomerular filtration rate (GFR), and recognises five stages of kidney disease, as follows:

- Stage 1: Normal GFR; GFR >90 ml/min with other evidence of chronic kidney damage*
- Stage 2: Mild impairment; GFR 60-89 ml/min with other evidence of chronic kidney damage*
- Stage 3: Moderate impairment; GFR 30-59 ml/min
- Stage 4: Severe impairment: GFR 15-29 ml/min
- Stage 5: Established renal failure (ERF): GFR < 15 ml/min or on dialysis (For CKD Stage 5 we have adopted the term established renal failure instead of end-stage renal disease or end-stage renal failure, as this is the term used in the National Service Framework for Renal Services.

* The “other evidence of chronic kidney damage” may be one of the following:

- Persistent microalbuminuria
- Persistent proteinuria
- Persistent haematuria (after exclusion of other causes, e.g. urological disease)
- Structural abnormalities of the kidneys demonstrated on ultrasound scanning or other radiological tests, e.g. polycystic kidney disease, reflux nephropathy
- Biopsy-proven chronic glomerulonephritis (most of these patients will have microalbuminuria or proteinuria, and/or haematuria)

Patients found to have a GFR of 60-89 ml/min without one of these markers should **not** be considered to have CKD

Measurement of excretory kidney function

Methods

Recommendation

Kidney function in patients with CKD should be assessed by formula-based estimation of GFR using either the 4-variable Modification of Diet in Renal Disease (MDRD) [2] or Cockcroft and Gault [3] equations (BOX 1).

All clinical biochemistry laboratories should report estimates of GFR alongside measurements of serum creatinine. Laboratories should communicate to their users (possibly using the laboratory report) the following information:

- a) which formula has been used in the estimation
- b) that GFR estimates between 60 and 89 mL/min/1.73 m² do not indicate chronic kidney disease unless there is other laboratory/clinical evidence of disease
- c) that, where information on ethnic origin is unavailable, GFR estimates may be approximately 20% higher in African-Caribbeans

There is **no** need to collect 24 h urine samples to measure creatinine clearance in primary care.

Within a renal network, which may or may not be co-terminous with a pathology network, laboratories should provide comparable creatinine results, ideally by the use of identical methodology. This should be audited by internal quality control procedures across the network and satisfactory performance in a national quality assessment scheme. Renal/pathology networks should agree a common approach to the estimation of GFR.

Indications for measurement of serum creatinine concentration

Recommendation:

Serum creatinine concentration should be measured, allowing calculation of estimated GFR, at initial assessment and then **at least annually** in all adult patients with :

- Polycystic kidney disease
- Reflux nephropathy
- Chronic glomerulonephritis (proven by biopsy or suspected) including persistent proteinuria or urologically unexplained haematuria
- Any other documented CKD

- Known or suspected bladder outflow obstruction

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Neurogenic bladder caused by spina bifida or spinal cord injury (N.B. calculated GFR may overestimate true GFR in these patients because of decreased muscle mass)

Urinary diversion surgery

Urinary stone disease due to primary hyperoxaluria, cystinuria, Dent's disease, infections (with struvite stones), anatomical abnormalities or a stone episode rate of > 1/y

Hypertension

Diabetes mellitus

Heart failure

Coronary, cerebral or peripheral vascular disease

Any condition requiring treatment with angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) or diuretics

Multisystem disease e.g. systemic lupus erythematosus (SLE), vasculitis, myeloma, rheumatoid arthritis

Population screening for CKD by GFR estimation

Recommendation

We not advocate screening for CKD in any other groups.

Frequency of measurement of serum creatinine concentration

Recommendation

Kidney function should be measured at least annually in the risk groups outlined above. (Acute renal failure must be excluded in all patients with newly detected abnormal kidney function – see page **XX**.)

Minimum frequency of measurement of kidney function according to estimated GFR:

Normal	(stage 1)	GFR >90	annual
Mildly impaired kidney function	(stage 2)	GFR 60-89	annual
Moderately impaired kidney function	(stage 3)	GFR 30-59	6 monthly
Severely impaired kidney function	(stage 4)	GFR 15-29	3 monthly
Established renal failure	(stage 5)	GFR < 15	3-monthly

Kidney function should also be checked during intercurrent illness in all patients with stage 2-5 CKD.

Interpretation of kidney function measurements in older people

Recommendation

The same criteria should be used for assessment of kidney function in older people as in younger people. “Age-adjusted” reference ranges for GFR are **not** recommended.

Recognition of Acute Renal Failure (ARF)

Recommendation

Formula-based estimated GFR **should be interpreted with caution** in ARF, because the formulae rely on a stable serum creatinine concentration.

Because ARF requires emergency treatment, **all patients with newly detected abnormal kidney function should be assumed to have ARF until proven otherwise**, although the majority will turn out to have CKD.

ARF is a clinical syndrome characterised by a rapid decline in excretory function occurring over a period of hours or days. ARF should be suspected if there is a >1.5-fold rise in serum creatinine concentration, or a fall in estimated GFR of >25%, or oliguria (defined as urine output <0.5 ml/kg/h), in the context of an acute illness. If baseline serum creatinine concentration or GFR is not known, it should be assumed that baseline GFR was 75 ml/min/1.73 m².

A blood test showing abnormal GFR in a patient who is not **known** to have established CKD with abnormal GFR should prompt:

- Review of medication, particularly recent additions (e.g. diuretics, non-steroidal anti-inflammatory drugs (NSAIDs), any drug capable of causing interstitial nephritis)
- Urinalysis: haematuria and proteinuria suggest the possibility of glomerulonephritis, which may be rapidly progressive
- Clinical assessment, looking for underlying conditions such as sepsis, heart failure, hypovolaemia
- Repeat measurement of serum creatinine concentration within a maximum of 5 days.

All patients with suspected ARF should be referred to a nephrologist

Recognition of acute on chronic kidney disease

Recommendation

A fall in estimated GFR of >25% since the last measurement of kidney function in a patient with CKD should prompt a repeat measurement of kidney function and referral if the deterioration is confirmed.

Detection of proteinuria

Methods

Recommendation

There is no need to perform 24 h urine collections for the quantitation of proteinuria

A positive dipstick test (1+ or greater) should result in a urine sample (preferably early morning) being sent to the laboratory for confirmation by measurement of the total protein:creatinine ratio or albumin:creatinine ratio (depending on local practice) after exclusion of urinary tract infection (see appendix 2&3).

Urine protein:creatinine or albumin:creatinine ratios of ≥ 30 mg/mmol should be considered as positive tests for proteinuria

Positive tests for proteinuria should be followed by tests to exclude urinary tract infection and then to exclude postural proteinuria, by analysis of an early morning urine sample, unless this has already been done

Patients with two or more positive tests for proteinuria, preferably spaced by 1 to 2 weeks, should be diagnosed as having persistent proteinuria

Indications for testing for proteinuria

Recommendation

Dipstick urinalysis for protein is indicated –

As part of the initial assessment of patients with

- Newly discovered reduced GFR
- Newly discovered haematuria
- Newly diagnosed hypertension
- Unexplained oedema
- Suspected heart failure
- Suspected multisystem disease, e.g. SLE, vasculitis, myeloma

As part of the annual monitoring of patients with

- Hypertension

- Glomerulonephritis
- Reflux nephropathy
- Asymptomatic microscopic haematuria
- Asymptomatic proteinuria
- Diabetes mellitus (patients with diabetes mellitus should also have annual testing for albumin:creatinine ratio if the dipstick urinalysis for protein is negative)

We do not recommend screening of any other groups using dipstick urinalysis

Detection of “microalbuminuria”

Methods

Recommendation

Detection of “microalbuminuria”

Methods

Recommendation

Urine albumin should be measured using a laboratory method in an early morning (preferred) or random mid-stream urine sample and expressed as an albumin:creatinine ratio. If dipsticks designed to detect urinary albumin are used, positive tests should be followed by laboratory confirmation.

An albumin: creatinine ratio ≥ 2.5 mg/mmol in a male or ≥ 3.5 mg/mmol in a female is consistent with microalbuminuria. Patients demonstrating albumin:creatinine ratios above, or equal to, this cut-off should have urine samples sent to the laboratory on two further occasions (ideally within one month) for albumin estimation. Patients demonstrating increased albumin: creatinine ratios in one or both of these further samples have microalbuminuria.

The diagnosis of microalbuminuria cannot be made in the presence of infection or an acute metabolic crisis. Urinary tract infection should be excluded in patients demonstrating increased urinary albumin:creatinine ratio on initial testing. The best possible metabolic control of diabetes should be achieved before investigating patients for microalbuminuria. Patients should not be screened during intercurrent illness.

It is important to consider other causes of increased albumin excretion, especially in the case of type 1 diabetes present for <5 years. In addition to the above caveats, these can include non-diabetic renal disease, menstrual contamination, vaginal discharge, uncontrolled hypertension, heart failure, intercurrent illness and strenuous exercise.

Indications for testing for microalbuminuria

Recommendation

Patients with diabetes mellitus who have persistent proteinuria (as defined above) do not require testing for microalbuminuria.

All other patients with diabetes mellitus should undergo, as a minimum, annual testing for microalbuminuria.

There is currently no proven role for screening for microalbuminuria in patients who do not have diabetes.

Detection of haematuria

Method

Recommendation

Dipstick urinalysis is the test of choice for confirmation of macroscopic haematuria and for detection of microscopic haematuria. Infection, trauma, and menstruation should be excluded before confirmation of haematuria. There is no need in routine clinical practice for confirmation of haematuria by microscopy of a midstream urine sample.

Indications for testing for haematuria

Recommendation

Dipstick urinalysis for blood is indicated as part of the initial assessment of patients with

- Newly found increased serum creatinine concentration/ reduced GFR
- Newly discovered proteinuria
- Suspected multisystem disease with possible renal involvement

“Screening” of unselected populations for haematuria is not recommended.

MANAGEMENT AND REFERRAL OF CKD

Definition of CKD

Recommendation

The K-DOQI classification (p XX) should be used for the definition and stratification of CKD. This definition of CKD includes

- diabetic patients with microalbuminuria
- non-diabetic patients with persistent proteinuria
- patients with urologically unexplained haematuria
- patients with known structural abnormalities of the kidneys
- patients with GFR < 60 ml/min, irrespective of the presence of other markers of kidney disease

Recommendations

Methods should be developed that enable the recall, audit and implementation of a care plan for all adult patients with CKD, irrespective of age, that includes:

- Regular measurements of kidney function using serum creatinine concentration, depending on the severity of kidney impairment (annual in stage 1 and 2, 6-monthly in stage 3)
- Advice on smoking cessation.
- Advice on weight loss if obese.
- Individualised consideration of lipid-lowering drug therapy, depending on the presence or absence of macrovascular disease and diabetes (see section below)
- Aspirin for all patients with vascular disease and if patient is aged ≥ 50 years with BP controlled to less than 150/90 and target organ damage, diabetes mellitus or 10 year risk of cardiovascular disease of $\geq 20\%$.
- Meticulous control of hypertension if present (see section below)

Antihypertensive therapy in patients with kidney disease

Blood pressure should be measured at least annually in all patients with CKD.

Blood pressure measurement should conform to British Hypertension Society standards (see below)

The threshold for initiation of antihypertensive therapy should be 140/90 mm Hg for patients without proteinuria, and 130/80 for those with urine protein:creatinine ratio > 100 mg/mmol or for diabetic patients with microalbuminuria

Antihypertensive therapy should be adjusted to achieve blood pressure < 130/80, or < 120/75 mm Hg for those with urine protein:creatinine ratio > 100 mg/mmol or for diabetic patients with microalbuminuria

ACEIs should be used as first line therapy for patients with proteinuria (urine protein:creatinine ratio > 100 mg/mmol), diabetic patients with microalbuminuria, and for those with a history of vascular disease; ARBs may be used as alternatives to ACEIs.

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Patients with refractory hypertension, defined as sustained BP > 150/90 despite combination therapy with drugs from 4 complementary classes should be referred for specialist evaluation.

Use of ACEIs and/or ARBs in patients with kidney disease and/or heart failure

“Dual blockade” with combinations of ACEIs and ARBs should only be initiated under nephrological supervision.

Serum creatinine concentration and potassium should be checked prior to starting ACEI and/or ARBs, within 2 weeks of starting, and within 2 weeks after subsequent increases in dose; and at annual intervals thereafter, or more frequently if indicated, according to kidney function.

A rise of serum creatinine concentration of > 20 % or fall in estimated GFR of > 15% after initiation or dose increase should prompt referral to a nephrologist

Hyperkalaemia (serum potassium > 6.0 mmol/L) should result in stopping of concomitant nephrotoxic drugs (e.g. NSAIDs), reduction or cessation of potassium-retaining diuretics (amiloride, triamterene, spironolactone), and reduction of loop diuretic dosage if there is no sign of congestion.

Management of electrolyte abnormalities in patients with kidney disease

Patients with unexplained hyponatraemia (serum sodium < 130 mmol/L) should be referred to an endocrinologist or nephrologist.

Patients with hypernatraemia (serum sodium > 145 mmol/L) should be referred to an endocrinologist.

Hypokalaemia (serum potassium < 3.0 mmol/L) and hyperkalaemia (serum potassium > 6.0 mmol/L) should be confirmed by analysis of a freshly drawn blood sample, avoiding delays between phlebotomy and analysis.

Patients with unexplained hypokalaemia should be referred to an endocrinologist or nephrologist.

Patients with hyperkalaemia that persists after revision of possibly causative medications and that is confirmed on repeat testing should be referred to a nephrologist.

Lipid-lowering drug therapy in patients with kidney disease

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All patients with CKD who are offered lipid-lowering drug treatment should be informed of the lack of certainty about the risks and benefits of such treatment in the presence of CKD.

Patients with established macrovascular disease should receive treatment for hyperlipidaemia according to the current Joint British Societies Guidelines [4]

Patients with diabetes and CKD but no established macrovascular disease should be offered lipid-lowering drug treatment or entry into a trial of such treatment [5].

Patients with CKD who do not have diabetes and who do not have established macrovascular disease should be offered lipid-lowering treatment if they are thought to be at particularly high risk due to the presence of additional risk factors; otherwise they should be offered entry into a trial of such treatment [5].

Management and referral of non-diabetic patients with proteinuria

Proteinuria should be quantified, urine tested for haematuria and GFR estimated.

Non-diabetic patients with early morning urine protein:creatinine ratio >100 mg/mmol (approximately 1 g/24 h or 2+) should be referred to a nephrology service for consideration of kidney biopsy

Non-diabetic patients with early morning protein:creatinine ratio 30-100 mg/mmol *without haematuria* should be considered to have CKD and entered into a CKD disease management programme, with referral only if other criteria for referral are met

Patients with both haematuria and proteinuria (PCR >30 mg/mmol) should be referred to a nephrology service for investigation irrespective of GFR.

Management of patients with diabetes mellitus and microalbuminuria or proteinuria

Patients with type 1 or 2 diabetes mellitus and microalbuminuria or proteinuria should be managed as follows:

- Continued efforts to achieve good glycaemic control (HbA1c 6.5-7.5%)
- Prescription of an ACEI (or ARB in the presence of a firm contraindication to ACEI), titrated to full dose, **irrespective of initial blood pressure**, followed by addition of other antihypertensive drugs in combination to reach the blood pressure goal if necessary
- Measurement of urine albumin:creatinine ratio and serum creatinine concentration at least once a year
- Referral to a nephrologist as for patients without diabetes
- Referral to a nephrologist if there is increasing proteinuria without diabetic retinopathy

Management of haematuria

Check serum creatinine concentration in all patients and refer to nephrologist if GFR < 60 ml/min (see page **XX**)

Check for proteinuria in all patients

If GFR normal:

- Macroscopic haematuria: fast track urology referral
- Macroscopic haematuria with proteinuria; fast track urology referral; **refer to nephrology if initial investigations negative.**
- Microscopic haematuria (dipstick **or** laboratory microscopy) without dipstick proteinuria:
 - Age >50: refer to urology
 - Age <50, or >50 after exclusion of urological cancer: treat as CKD (includes measurement of serum creatinine concentration, annual repeat if initially normal)
- Microscopic haematuria (dipstick **or** laboratory microscopy) with urine protein:creatinine ratio > 30 mg/mmol: refer to nephrology

There is no need for laboratory confirmation of dipstick positive haematuria.

Kidney biopsy in CKD

Recommendation

Patients with significant proteinuria (urine protein:creatinine > 100 mg/mmol) should be referred for consideration of kidney biopsy. Patients with lower levels of proteinuria (urine protein:creatinine ratio 30-100 mg/mmol) who also have haematuria should also be referred for kidney biopsy. Patients with isolated microscopic haematuria and no or minimal proteinuria do not require kidney biopsy but should be assumed to have CKD.

Investigation for atherosclerotic renal artery stenosis

Recommendation

Patients should be referred for further investigation for atherosclerotic renal artery stenosis (ARAS), with a view to intervention, in the following situations:

- refractory hypertension (inadequate control, defined as BP > 150/90 mm Hg despite 4 antihypertensive agents)
- recurrent episodes of pulmonary oedema despite normal left ventricular function on echocardiography (so-called “flash pulmonary oedema”, usually associated with hypertension)
- rising serum creatinine concentration (rise of $\geq 20\%$ or fall of GFR of $>15\%$ over 12 months) with a high clinical suspicion of widespread atherosclerosis
- a rise in serum creatinine concentration of $\geq 20\%$ or fall of GFR of $>15\%$ during the first 2 months after initiation of ACEI or ARB treatment

- unexplained hypokalaemia with hypertension

Investigation for multiple myeloma

Recommendation

Patients with CKD should not be subjected to routine “myeloma screening” prior to referral.

Management and referral of stage 3 CKD

Recommendations (in addition to those for stage 1 and 2)

All patients with stage 3 CKD should undergo

- 6-monthly measurement of haemoglobin, potassium, calcium and phosphate in stage 3
- Treatment of anaemia with intravenous iron \pm epoietins, after exclusion of other causes of anaemia. The threshold Hb concentration for initiation of epoietin should be 10 g/dL, and treatment adjusted to maintain Hb between 10 and 12 g/dL.
- Measurement of parathyroid hormone (PTH) concentration when stage 3 CKD is first diagnosed.
- Treatment of disorders of calcium, phosphate, or PTH concentrations according to the algorithm set out below.
- Renal ultrasonography in patients with lower urinary tract symptoms or refractory hypertension.
- Immunisation against influenza, pneumococcus, and hepatitis B.
- Regular review of all prescribed medication, to ensure appropriate dose adjustments and the avoidance, wherever possible, of nephrotoxic drugs, including NSAIDs.

Renal osteodystrophy: assessment/management in CKD

Recommendations

Antiresorptive treatment for suspected or proven reduced bone mineral density should not be commenced in patients with CKD until treatable disorders of calcium, phosphate, PTH and serum 25-hydroxyvitamin D metabolism have been sought and treated.

No measurements of calcium, phosphate, or PTH are required in stage 1 or 2 CKD unless the patient has suspected or proven reduced bone mineral density.

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In stage 3 CKD, serum corrected calcium and phosphate should be measured every 12 months. Abnormal values should be confirmed on a repeat sample. Patients with confirmed abnormalities of serum corrected calcium or phosphate should be referred to a nephrologist.

In stage 3 CKD, plasma PTH should be checked when the diagnosis of CKD stage 3 is first made. If the PTH is < 70 ng/L, no further checking is required unless the patient progresses to stage 4 CKD (which should prompt referral to a nephrologist)

If the PTH is > 70 ng/L, serum 25-hydroxyvitamin D should be checked. If the serum 25-hydroxyvitamin D is low, therapy should be commenced with ergocalciferol or colecalciferol 800 units/day in a preparation that contains calcium carbonate or calcium lactate but not calcium phosphate; or colecalciferol 10,000 units monthly by intramuscular injection. PTH should then be rechecked after 3 months of replacement therapy. There is no need to repeat the measurement of serum 25-hydroxyvitamin D unless non-adherence or malabsorption is suspected. Vitamin D therapy should be continued long-term unless the clinical situation changes.

If the PTH is > 70 ng/L despite a normal serum 25-hydroxyvitamin D or treatment with ergocalciferol or colecalciferol, the patient should be referred to a nephrologist

To convert PTH (ng/L) to SI units (pmol/L) multiply by 0.11

Management of stage 4-5 CKD

Recommendations

All patients with stage 4 or 5 CKD should be referred to a nephrologist for consultation and follow-up once this degree of CKD is identified and the appropriate investigations obtained, **even if** it is not anticipated that renal replacement therapy will be appropriate.

Management should continue to be shared with the GP and/or with other healthcare professionals, agreed on a case-by-case basis, and a care plan developed.

Management should include, in **addition to all interventions listed for stage 3 CKD**:

- 3-monthly measurements of serum creatinine concentration, haemoglobin, calcium, phosphate, bicarbonate, and PTH concentrations
- Dietary assessment
- Treatment of hyperparathyroidism and phosphate retention
- Correction of acidosis
- Counselling and education about the options for treatment, including (when appropriate) home or hospital haemodialysis, peritoneal dialysis, kidney transplantation, and conservative (non-dialytic) management.
- Pre-emptive kidney transplantation wherever possible
- Timely provision of vascular access in all patients for whom haemodialysis is planned
- Timely placement of a peritoneal dialysis catheter in patients for whom peritoneal dialysis is planned
- Agreement in advance for an active conservative/palliative care treatment plan if the patient chooses not to undergo renal replacement therapy; conservative treatment may still include drug treatment of hypertension, anaemia, phosphate retention, hyperparathyroidism and acidosis; palliative care teams may also be involved.

Urgency of referral to a nephrology service

All nephrology services should offer 24 hour telephone access to qualified advice.

Referrals should be made as follows:

Immediate

- Suspected ARF

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- ARF superimposed on CKD
- Newly detected ERF (GFR < 15 ml/min)
- Accelerated or malignant phase hypertension
- Hyperkalaemia, serum potassium > 7 mmol/L

Urgent outpatient

- Nephrotic syndrome
- Newly detected stage 4 or stable stage 5 CKD
- Multisystem disease (e.g. SLE) with any evidence of kidney disease
- Hyperkalaemia, serum potassium 6-7 mmol/L (after exclusion of artefactual and treatable causes)

Routine outpatient

- Refractory hypertension (defined as sustained BP >150/90 mm Hg despite combination therapy with 4 drugs from complementary classes)
- Acute deterioration in kidney function (defined as a fall of GFR of > 15% or rise of SCr of >20% from baseline) associated with use of ACEIs or ARBs
- Hypokalaemia (serum potassium < 3.0 mmol/L), unexplained hyponatraemia (serum sodium < 130 mmol/L), hypercalcaemia (serum corrected calcium > 2.7 mmol/L), hypocalcaemia (serum corrected calcium < 2.1 mmol/L), hyperphosphataemia (serum phosphate > 1.2 mmol/L)
- Proteinuria (urine protein > 100 mg/mmol) without nephrotic syndrome
- Proteinuria with haematuria
- Diabetes with increasing proteinuria but without diabetic retinopathy
- Stage 3 CKD with haematuria
- Urologically unexplained macroscopic haematuria (with or without proteinuria)
- Recurrent unexplained pulmonary oedema with clinical suspicion of ARAS
- Falling GFR (>15% fall over 12 months) with clinical suspicion of ARAS
- PTH > 70 ng/L (7.7 pmol/l) after exclusion or treatment of vitamin D deficiency
- Stable stage 4 CKD

GP care +/- “virtual” nephrology support/advice

- Isolated microscopic haematuria (after negative urological evaluation where appropriate)
- Isolated proteinuria with urine protein:creatinine ratio < 100 mg/mmol
- Known or suspected polycystic kidney disease with normal GFR
- Known reflux nephropathy in stage 1-3 without the above
- All other stage 1-2 CKD

Information required for referral or letter of advice

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The minimum data set for referral of a patient with CKD to a nephrologist should include:

- A tabular list of the dates and results of all previous measurements of serum creatinine concentration (unless or until this can be downloaded automatically to the nephrology service database)
- A full medical history including current drug treatment (and previous drug treatment, if any possibility of drug-associated kidney disease/dysfunction)
- Blood pressure
- The results of dipstick urinalysis plus urine protein:creatinine ratio if there is more than trace proteinuria on dipstick

References

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