Identification, management and referral of adults with chronic kidney disease: concise guidelines*

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ABSTRACT – Chronic kidney disease (CKD) is often thought to be a relatively rare condition requiring specialist care. However, early CKD is common and referral of all patients would completely overwhelm existing specialist services. The purpose of this concise guidance is to inform general physicians and general practitioners about the identification and management of CKD, and who to refer for specialist care.

KEY WORDS: chronic kidney disease, diabetes, guidelines, hypertension

Introduction

Established renal failure (ERF) is uncommon but its treatment with dialysis or transplantation is very expensive. The number of patients receiving renal replacement therapy (RRT) in the UK is rising and is unlikely to reach steady state for another 25 years,[1] costing over 2% of the total NHS budget. These figures make any improvement in the cost-effective treatment of early kidney disease highly desirable.

It is therefore important to note that:

- Chronic kidney disease (CKD) increases in prevalence exponentially with age; the most common identifiable causes are diabetes and vascular disease. ERF is more common in ethnic minority populations.
- Late referral of patients with established renal failure requiring renal replacement therapy to specialist renal services is associated with significant extra cost and poor clinical outcomes.
- The great majority of patients starting RRT have progressed from earlier stages of CKD and many could have been identified and referred earlier.
- The great majority of patients with early CKD do not progress to ERF but do have increased risks of cardiovascular disease; the risk of death outweighs the risk of progression.
- Progression is associated with proteinuria and uncontrolled hypertension.
- Optimal management of the risk factors for cardiovascular disease also reduces the risk of progression from early CKD to ERF.

Guideline development

This concise guidance is extracted from *Chronic kidney disease in adults: UK guidelines for identification, management and referral*.[2] Details of the development process are given in the full guidelines and summarised in Table 1 (overleaf).

Recommendations were graded using the same system as for the National Service Framework (NSF) for Renal Services (see Table 2 overleaf).

- Many of the questions posed by this guidance are about surveillance for, or referral of, kidney disease which have not been addressed by randomised controlled trials, and we have had to rely mostly on expert opinion/consensus.
- Recommendations about the diagnosis of kidney disease are based largely on observational diagnostic accuracy (DA) studies in which the test under consideration is compared with a reference standard; for simplification we have put diagnostic studies as level 3 DA to distinguish them from non-analytic intervention studies, and without subdivision by quality.
- As recommendations on organisation of care, rather than therapy, present problems with grading evidence, many of our recommendations are level 4.
- **All recommendations are graded as level 4 evidence unless otherwise stated.**

Implementation and cost implications

Disease-specific guidelines pose particular difficulties for implementation when applied to patients with multiple conditions.[3] Many patients with kidney disease have diabetes, hypertension, or cardiovascular disease. For this reason, these guidelines

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*The guidelines were developed by: the Joint Specialty Committee on Renal Disease of the Royal College of Physicians of London and the Renal Association with representatives from the Royal College of General Practitioners, the Association for Clinical Biochemistry, the Society for District General Hospital Nephrologists, the British Geriatric Society, the Professional Advisory Council of Diabetes UK and the National Kidney Federation. For membership of the Guideline Development Committee, see end of paper.

Table 1. Guideline development process. The guidelines have been developed in accordance with the principles laid down by the AGREE collaboration (Appraisal of Guidelines for Research and Evaluation).[12,13]

Scope and purpose	
Overall objective of the guidelines	To promote optimal management of patients with chronic kidney disease (CKD) within the NHS.
The patient group covered:	Adults with (or at risk of) CKD.
Target audience	All clinicians, including general physicians, GPs and other health professionals who are involved in the management of patients with CKD – in particular those working in diabetes, geriatrics or cardiovascular subspecialties.
Clinical questions covered	Identification of patients, reduction of risks associated with CKD, and who to refer to specialist services.
Stakeholder involvement	
The Guideline Development Group (GDG)	The Guidelines were instigated by the Joint Specialty Committee on Renal Disease of the Royal College of Physicians of London and the Renal Association, in association with: • Royal College of General Practitioners • Association for Clinical Biochemistry • Society for District General Hospital Nephrologists • British Geriatrics Society • Professional Advisory Council of Diabetes UK • National Kidney Federation.
Funding	Cost of travel and accommodation for attending meetings were met by the Department of Health for England.
Conflicts of interest	No external funding has been sought or obtained. All authors and group members have declared, and provided details of, any actual or potential conflicts of interest.
Rigour of development	
Evidence gathering	Evidence for these guidelines was provided by review of Cochrane Library, and Medline searches by individual members of the group according to their area of expertise. They draw on existing guidance including the relevant NSFs, NICE guidelines, and similar guidelines from other countries.
Review process	Drafts were circulated regularly and the group met on 10 occasions.
Links between evidence and recommendations	The system used to grade the evidence and guidance recommendations is that used by the NSF for Renal Services (see Table 2).
Piloting and peer review	The final draft was widely circulated to all relevant parties and their comments incorporated together with the results of pilot exercises on patient referral.
Implementation	
Tools for application	Brief summaries are being prepared for use in clinics and surgeries together with versions suitable for electronic booking. Decision support software is being developed.
Plans for review	Review is planned in 4 years.

NICE = National Institute for Health and Clinical Excellence; NSF = National Service Framework.

Table 2. Levels of evidence used in the guidelines and in the National Service Framework for Renal Services.

Level 1	Meta-analyses, systematic reviews of randomised controlled trials, or randomised controlled trials.
Level 2	Systematic reviews of case-control or cohort studies, or case-control or cohort studies
Level 3	Non-analytic studies, eg case reports, case series
Level 3 DA	Diagnostic accuracy studies in which a test is compared with a reference standard
Level 4	Expert opinion (in the absence of any of the above). This includes the views and experiences of people with CKD and their carers.

Many of the questions posed by this guidance have not been tested by randomised controlled trials and rely on expert evidence. All recommendations are graded level 4 unless stated otherwise.

Table 3. Classification of chronic kidney disease (CKD).

Stage	Description	Minimum test frequency
1	Normal GFR GFR >90 mL/min/1.73 m^2 *with other evidence of chronic kidney damage**	12 monthly
2	Mild impairment GFR 60–89 mL/min/1.73 m^2 *with other evidence of chronic kidney damage**	12 monthly
3	Moderate impairment GFR 30–59 mL/min/1.73 m^2	6 monthly (12 if stable)**
4	Severe impairment GFR 15–29 mL/min/1.73 m^2	3 monthly (6 if stable)**
5	Established renal failure (ERF) GFR <15 mL/min/1.73 m^2 or on dialysis	3 monthly

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

- persistent microalbuminuria
- persistent proteinuria
- persistent haematuria (after exclusion of other causes, eg urological disease)
- structural abnormalities of the kidneys demonstrated on ultrasound scanning or other radiological tests, eg polycystic kidney disease, reflux nephropathy
- biopsy-proven chronic glomerulonephritis.

Patients found to have a GFR of 60–89 mL/min/1.73 m^2 *without* one of these markers

- should not be considered to have CKD and
- should not be subjected to further investigation (unless there are additional reasons to do so).

** stable = <2 mL/min/1.73 m^2 change over 6 months or more

GFR = glomerular filtration rate.

Table 4. Estimation of the glomerular filtration rate.

The GFR may be estimated using the 4-variable Modification of Diet in Renal Disease (MDRD) equation:

GFR (mL/min/1.73 m^2) = 186 ×
{[Serum Creatinine (μmol/L)/88.4] $^{-1.154}$}
× age (years)$^{-0.203}$
× 0.742 if female, and
× 1.21 if African American.

Until laboratories are able to report results in this way, prediction tables can be used to estimate GFR from serum creatinine, age, gender and ethnicity (see Appendix in full version, booklet version and on the web page[2a,b]). These tables are in the full document which is also available on the Renal Association website.[2c] Alternatively, an online GFR calculator based on this equation is available at:
<http://cgi.www.renal.org/cgi-bin/www.renal.org/eGFR/GFR.pl

Table 5. Criteria for referral to specialist services.

Estimated GFR	Referrral
<15 mL/min/1.73 m^2	*Immediate referral* but see section C3
15–29 mL/min/1.73 m^2	*Urgent referral* (routine referral if known to be stable) See section C3
30–59 mL/min/1.73 m^2	*Routine referral* if: • Progressive fall in GFR/increase in serum creatinine • Microscopic haematuria present • Urinary P/CR >45 mg/mmol • Unexplained anaemia (Hb <11 g%), abnormal potassium, calcium or phosphate • Suspected systemic illness, eg SLE • Uncontrolled BP (>150/90 on 3 agents)
60–89 mL/min/1.73 m^2	**Referral not required** unless other problems present (see below and Table 3)
Renal problems irrespective of GFR	*Immediate referral* for: • Malignant hypertension • Hyperkalaemia (potassium >7.0 mmol/l) *Urgent referral* for • Proteinuria with oedema and low serum albumin (nephrotic syndrome) *Routine referral* for: • Dipstick proteinuria present and urine P/CR >100 mg/mmol • Dipstick proteinuria and microscopic haematuria present • Macroscopic haematuria but urological tests negative

When making referral, quote all information listed in Table 6.

BP = blood pressure; P/CR = protein/creatinine ratio; SLE = systemic lupus erythematosus.

Table 6. Information needed for referral.

1. General medical history
2. Urinary symptoms
3. Medication
4. Examination, eg BP, oedema, palpable bladder or other positive findings
5. Urine dipstick for blood and protein
6. Urine protein/creatinine ratio, if proteinuria present – early morning urine (EMU) preferable (in diabetes, result of urine albumin/creatinine ratio if dipstick proteinuria negative)
7. Blood count
8. Serum creatinine, sodium, potassium, albumin, calcium, phosphate, cholesterol,
9. HbA1c (in diabetes)
10. All previous serum creatinine results with dates
11. Result of renal ultrasound scan if available (see Guidelines, section C2)

BP = blood pressure.

The guidelines

A. Identification and classification of chronic kidney disease (CKD)

Level of evidence

1 Glomerular fitration rate (GFR)

- **Kidney function should be assessed by estimated GFR,** and CKD is to be classified on this basis (see Table 3)
- **The GFR should be estimated from serum creatinine** using the 4-variable MDRD equation (see Table 4 for calculation if not provided by local laboratories). **3 DA**

2 Serum creatinine measurement to allow estimation of the GFR:

Serum creatinine concentration should be measured at initial assessment and then at least annually in all adult patients with:

- *Previously diagnosed* CKD including:
  - Identified renal pathology (eg polycystic kidney, biopsy proven glomerulonephritis, reflux nephropathy)
  - Persistent proteinuria
  - Urologically unexplained haematuria
- *Conditions associated with a high risk of silent development of obstructive kidney disease*:
  - Bladder voiding dysfunction (outflow obstruction, neurogenic bladder)
  - Urinary diversion surgery
  - Urinary stone disease (>one episode/year)
- *Conditions associated with a high risk of silent development of parenchymal kidney disease*:
  - Hypertension, diabetes mellitus, heart failure,
  - Atherosclerotic coronary, cerebral, or peripheral vascular disease
- *Conditions requiring long-term treatment with potentially nephrotoxic drugs:*
  - eg ACEIs, ARBs, NSAIDs, lithium, mesalazine, cyclosporin, tacrolimus
- *Multi-system diseases that may involve the kidney:*
  - eg systemic lupus erythematosus (SLE), vasculitis, myeloma, rheumatoid arthritis.

3 Testing for urinary protein

Dipstick urinalysis for protein should be undertaken:

- *As part of the initial assessment of patients with*
  - Newly discovered hypertension, haematuria or reduced GFR
  - Unexplained oedema or suspected heart failure
  - Suspected multi-system disease, eg SLE, vasculitis, myeloma
  - Diabetes mellitus
- *As part of the annual monitoring of patients with*
  - Biopsy-proven glomerulonephritis
  - Reflux nephropathy
  - Urologically unexplained haematuria or persistent proteinuria
  - Diabetes mellitus
  - (patients with diabetes mellitus should also have annual testing for albumin:creatinine ratio to exclude 'microalbuminuria' if the dipstick urinalysis for protein is negative)
- *As part of routine monitoring for patients receiving nephrotoxic agents* eg gold, penicillamine, according to the recommendations in the British National Formulary.

Level of evidence

4 Confirmation of proteinuria

There is no need to perform 24 hr urine collections for quantification of proteinuria in primary care. **3 DA**

If protein dipstick test is positive (≥1+) the following should be undertaken:

- *MSU* for culture to exclude urinary tract infection (UTI).
- *Laboratory confirmation of proteinuria* preferably on early morning urine (EMU) sample, to exclude postural proteinuria **3 DA**
- *Positive tests for proteinuria are* **3 DA**
  - Urine protein:creatinine ratio ≥45 mg/mmol or
  - Albumin:creatinine ratio of ≥30 mg/mmol
- *Persistent proteinuria* should be defined as
  - two or more positive tests for proteinuria, preferably spaced by 1 to 2 weeks.

In annual diabetes monitoring, if dipstick test negative request albumin/creatinine ratio (ACR). Microalbuminuria is defined as ACR >2.5 mg/mmol (men) or >3.5 mg/mmol (women) on 2 or 3 occasions (see section B5). **3 DA**

5 Haematuria

Routine screening for haematuria is not recommended.

- *Dipstick urinalysis for blood is the test of choice for* **3 DA**
  - confirmation of macroscopic haematuria
  - detection of microscopic haematuria

  Infection, trauma, and menstruation should be excluded first. There is no need for microscopy of an MSU sample to detect or confirm haematuria.
- *Dipstick urinalysis for blood is indicated as part of initial assessment* of patients with
  - Newly found increased serum creatinine concentration/reduced GFR
  - Newly discovered proteinuria
  - Suspected multi-system disease with possible renal involvement.

The guidelines

B. Interpretation of tests/Initial management

Level of evidence

1 Recognition of acute renal failure (ARF)

ARF is characterised by rapid deterioration of renal function over a period of hours or days.
ARF should be suspected in the context of an acute illness in the presence of:

- A 50% rise in serum creatinine concentration
- A fall in estimated GFR of >25% (if baseline unknown assume 75 mL/min/1.73m^2) but GFR must be interpreted with caution as formulae rely on a stable creatinine concentration **3 DA**
- Oliguria (urinary output <0.5 mL/kg/hr)

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

2 In newly diagnosed GFR <60 mL/min/1.73 m^2

Management should include:

- *Review of all previous measurements of serum creatinine*
  - to estimate GFR and assess rate of deterioration
- *Review of medication,* particularly
  - recent additions (eg diuretics, non-steroidal anti-inflammatory drugs (NSAIDs), or any drug capable of causing interstitial nephritis, eg penicillins, cephalosporins, mesalazine, diuretics)
- *Urinalysis* (see section A):
  - haematuria and proteinuria suggest glomerulonephritis, which may progress rapidly
- *Clinical assessment,*
  - eg looking for sepsis, heart failure, hypovolaemia, palpable bladder
- *Repeat serum creatinine measurement within 5 days*
  - to exclude rapid progression
- *Check criteria for referral (see Tables 5 and 6)*
  - ***if not indicated, ensure entry into a chronic disease management programme.***

3 Haematuria

Management should include:

- *Checking of serum creatinine concentration* in all patients
  - refer to nephrologist if GFR < 60 mL/min/1.73 m^2.
- *Checking for proteinuria* in all patients.

If GFR normal:

- *Macroscopic haematuria*, with or without proteinuria:
  - ***fast track urology referral; refer to nephrology if initial investigations negative.***
- *Microscopic haematuria (dipstick* ***or*** *laboratory microscopy) without dipstick proteinuria:*
  - Age >50 years: refer to urology
  - Age <50 years, or >50 years after exclusion of urological cancer: treat as CKD

  (includes measurement of serum creatinine concentration, annual repeat if initially normal).
- *Microscopic haematuria with urine protein:creatinine ratio >45 mg/mmol*
  - refer to nephrology.

There is no need for laboratory confirmation of dipstick positive haematuria. **3 DA**

Level of evidence

4 Proteinuria

Management should include:

- *Quantification of proteinuria, test for haematuria, estimate GFR* (see section A)
  - Urine protein/creatinine ration (P/CR) >100 mg/mmol – refer to nephrologist irrespective of GFR
  - Urine P/CR >45 mg/mmol with microscopic haematuria – refer irrespective of GFR.
- *Check criteria for referral (see Tables 5 and 6)*
  - ***if not indicated ensure entry into chronic disease management programme.***

5 Diabetes mellitus (DM) and 'microalbuminuria' or proteinuria

Recommended tests:

- Urinary albumin/creatinine ratio should be measured using a laboratory method if dipstick protein negative (see section A4) preferably on an EMU, and not during acute illness, intercurrent infection or menstruation **3 DA**
- Persistent urinary albumin/creatinine ratios of ≥2.5 mg/mmol (male) or ≥3.5 mg/mmol (female) on 2–3 occasions are consistent with microalbuminuria.

Manage patients with DM (Type I or II) and microalbuminuria or proteinuria as follows:

- *Achieve good glycaemic control* (HbA1c 6.5–7.5%) **1**
- *Prescription of an ACEI* (or ARB in the presence of a firm contraindication to ACEI), titrated to full dose, irrespective of initial blood pressure **1**
- *Control of hypertension* if necessary: Addition of other antihypertensive drugs in combination to reach the blood pressure goal (see section C1) **1**
- *Measurement at least once a year* of
  - urine albumin:creatinine ratio (or P/CR)
  - serum creatinine concentration (for estimated GFR).
- ***Referral to diabetes team – a local protocol should be agreed***
- ***Referral to a nephrologist – as for patients without diabetes***
- *Co-ordination of care* is needed between the primary care team and specialist teams (including nephrology, ophthalmology, cardiology, and vascular surgery) at all stages of CKD including stage 5.

6 Investigation for atherosclerotic renal artery stenosis

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

- *Refractory hypertension* (ie BP >150/90 mmHg despite 3 anti-hypertensive agents). **3 DA**
- *Recurrent episodes of pulmonary oedema despite normal left ventricular function* on echocardiography (so-called 'flash pulmonary oedema', usually associated with hypertension). **3 DA**
- *Rising serum creatinine concentration* (rise of >=20% or fall of GFR of >15%)
  - over 12 months with a high clinical suspicion of widespread atherosclerosis. **3 DA**
  - during the first 2 months after initiation of ACEI or ARB treatment. **3 DA**
- *Unexplained hypokalaemia with hypertension.*

(continued)

The guidelines – *continued*

C. Management of CKD

Level of evidence

1 All stages

Local arrangements should be made for the implementation of care plans for all adult patients with CKD irrespective of age, shared between primary, secondary and tertiary care as appropriate and to include:

- *Regular measurements of kidney function* and other laboratory tests depending on the severity of kidney impairment (see Table 3).
- *General health advice* as appropriate on:
  - smoking cessation — 2
  - weight loss — 1
  - aerobic exercise
  - limiting alcohol intake
  - limiting sodium intake
- *Cardiovascular prophylaxis*
  For patients with 10-year risk of cardiovascular disease of >20%[14] consider:
  - Aspirin treatment if BP <150/90 mmHg — 2
  - Lipid-lowering drug therapy (or entry into a trial) — 2
- *Blood pressure monitoring*
  - Blood pressure should be measured according to British Hypertension Society standards at least annually
- *Control of hypertension*
  - Hypertension should be meticulously controlled
  - Threshold for initiation of anti-hypertensive medication: — 2
    - if urine protein/creatinine ratio (P/CR) <100 mg/mmol
      - threshold 140/90 mmHg – Target 130/80
    - if urine P/CR >100 mg/mmol
      - threshold 130/80 mmHg – Target 125/75
  - ACEIs or ARBs to be included: — 1
    - if urine P/CR >100 mg/mmol
    - in diabetic patients with microalbuminuria (see sections A4 and B5)

    Serum creatinine and potassium should be checked
    - before starting medication
    - two weeks after starting, and after subsequent increases in dose

    If creatinine increase of >20% or fall in GFR of >15%
    - Repeat creatinine, check potassium, and refer for specialist opinion on whether to stop treatment or to investigate for renal artery stenosis
- *If hyperkalaemia present (serum K >6 mmol/l):*
  – stop relevant drugs, eg NSAIDs and potassium-retaining diuretics
  – check diet and proprietary treatments, eg LoSalt.
  If hyperkalaemia persists the ACE or ARB should be stopped.

Level of evidence

2 CKD stage 3

Additional management should include:

- *Annual measurement of Hb, potassium, calcium and phosphate*
- *If Hb <11 and other causes excluded:*
  – treat with intravenous iron ± erythropoiesis stimulating agents to maintain Hb 11–12 g/dl depending on the patient's functional needs. — 1
- *Request renal ultrasonography* in
  – patients with lower urinary tract symptoms
  – refractory hypertension
  – unexpected progressive fall in GFR
- *Immunise* against influenza and pneumococcus
- *Review all prescribed medication regularly* to ensure appropriate doses
  – avoid nephrotoxic drugs including NSAIDs wherever possible
- *Check parathyroid hormone (PTH)* concentration when Stage 3 first diagnosed
  – If raised check serum 25-hydroxyvitamin D
  – if this is low treat with ergocalciferol or cholecalciferol with calcium supplement (not calcium phosphate)
  – Repeat PTH after 3 months and refer if still raised.

3 CKD Stages 4–5

Additional management:
Care of all patients with stage 4 or 5 CKD should be discussed formally with a nephrologist once the appropriate investigations obtained, *even if* it is not anticipated that renal replacement therapy will be appropriate.
Exceptions may include:

- patients in whom stage 4 or 5 CKD supervenes as part of another terminal illness
- patients with stable function in whom all the appropriate investigations and management interventions have been performed and who have an agreed and understood care pathway
- patients in whom further investigation and management is clearly inappropriate.

Management should be shared with GP and/or other healthcare professionals and should include:

- *3-monthly tests: serum creatinine (for GFR), Hb, calcium, phosphate, bicarbonate, PTH*
- *dietary assessment*
- *immunisation against hepatitis B*
- *investigation and treatment of phosphate retention and hyper-parathyroidism*
- *correction of acidosis* — 2
- *information about options for treatment*
- *timely provision of dialysis access depending on treatment choice.* — 2

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BP = blood pressure; GFR = glomerular filtration rate; MDRD = Modification of Diet in Renal Disease; MSU = midstream urine; NSAID = non-steroidal anti-inflammatory drug;

have been developed to be consistent, wherever possible, with existing UK guidelines and are designed to be integrated into the management of cardiovascular risk and diabetes in the NHS.

Full implementation will require:

- revision of the electronic coding of CKD in the NHS, both in hospital episode statistics and in primary care computer systems
- standardisation and simplification of management of CKD
- incorporation of markers of quality care of CKD into the Quality and Outcomes Framework and other NHS quality and safety standards
- measurement of outcomes such as late referral for dialysis and disparities in access to care
- use of the chronic care model,[4] with particular emphasis on decision support systems
- educational packages for GPs, hospital physicians and surgeons, and community-based nurses, on the recognition and management of CKD, including the booklet version of these guidelines
- standardisation of creatinine assay methods
- full funding of extra laboratory costs.

We have deliberately not addressed the question of which individuals should be responsible for the care plan for CKD outlined here.

- We anticipate that a variety of models will emerge, including conventional shared care between GPs and hospital-based nephrologists, geriatricians, diabetologists, and other secondary care physicians; specialist GPs;[5,6] specialist nurses working at general practice or primary care trust (PCT) level; and computer-based shared care, including systems to prompt clinical actions.[7]
- Disease registers based on primary care IT systems and an adequate IT infrastructure will be an essential prerequisite for delivery of the care plan for CKD.
- The development of community nephrologists[8] may help to break down unnecessary barriers to the delivery of comprehensive chronic disease management.

Implementation of these guidelines will carry cost implications, particularly for the treatment of patients with anaemia, which is not covered by existing funding. It is important that the NHS develops a clear strategy for equitable funding of the management of CKD. Any system for implementation should be designed to reduce existing ethnic and socioeconomic differences in the consequences of CKD.[9–11]

Acknowledgement

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Dr David Newman died in March 2003. He had contributed enormously to British nephrology, with many original research contributions as well as active input into the UK Renal Registry and to this Committee.