

Investigation of Asymptomatic Microscopic Haematuria in Adults

**A National Clinical Guideline
recommended for use**

in

Scotland

by the

**Scottish Intercollegiate
Guidelines Network**

Pilot Edition

August 1997



S I G N

Getting validated guidelines into local practice

This guideline was issued in August 1997 and will be reviewed in 1999. Comments are invited to assist the review process. All correspondence and requests for further background information regarding the guideline should be sent to:

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The definitions of the types of evidence and the grading of recommendations used in this guideline originate from the US Agency for Health Care Policy and Research⁽¹⁾ and are set out in the following tables.

Level	Type of Evidence
Ia	Evidence obtained from meta-analysis of randomised controlled trials.
Ib	Evidence obtained from at least one randomised controlled trial.
IIa	Evidence obtained from at least one well-designed controlled study without randomisation.
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study.
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
IV	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.

Grade	Recommendation
A (Evidence Levels Ia, Ib)	Required - at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing specific recommendation.
B (Evidence Levels IIa, IIb, III)	Required - availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation.
C (Evidence level IV)	Required - evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates absence of directly applicable clinical studies of good quality.

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Summary of Recommendations

Grade

All patients over 13 years with *substantiated* microscopic haematuria on dipstix testing (≥ 5 RBCs/hpf on urine microscopy) should be investigated. B

Assessment in primary care should include history-taking and examination, the measurement of renal function, e.g. by estimation of serum creatinine, urea, electrolytes, and urine microscopy and culture. The results of culture may obviate the need for referral. B

Referral for further investigation should first be directed to a urological service *unless* any of the following are present: B

- Proteinuria > trace on stix testing
- Red cell casts on microscopy
- Renal impairment on biochemical testing

in which case referral should be directed to a nephrological service C

Urological investigation should include renal tract imaging including: B

- Intravenous urography
or ultrasound scan plus plain abdominal *x*-ray
 - Flexible cystoscopy
-

Follow up of patients in whom no surgical cause for haematuria is found should be undertaken by general practitioners. It is suggested that they monitor urinalysis and blood pressure at biennial intervals, and refer patients back to the appropriate specialist when indicated. B

Note: These recommendations are based on the finding of microscopic haematuria when urinalysis has been undertaken as part of a general medical examination. They are not designed for nor intended to advocate population screening.

1 Introduction

1.1 Definitions

Development of this guideline has been hampered by the arbitrary and variable definitions of haematuria used in the published research.

Microscopic haematuria is defined in this guideline as a positive result on dipstix testing and/or greater than five red blood cells per high power field (RBCs/hpf) on urinary microscopy of unspun urine, or around 12500 RBC/ml.

Asymptomatic microscopic haematuria in this guideline refers to all cases of occult haematuria, regardless of the means of its detection. This term excludes haematuria visible to the naked eye, the coexistence of urinary tract pain, infection or other symptoms, and the presence of proteinuria >trace.*

1.2 The purpose of this guideline

Isolated microscopic haematuria may be an innocuous finding or may herald a number of serious medical and surgical conditions. Since the majority of patients with asymptomatic haematuria will have an entirely benign prognosis, the correct course of investigation after its detection is the subject of debate.

This clinical guideline suggests an approach to the investigation of this problem based on a systematic review of the current scientific evidence. The purpose of the guideline is to ensure the detection of clinical disease while avoiding needless investigation and follow up at hospital clinics.

1.3 This guideline is designed for the investigation of patients found to have microscopic haematuria in the following situations:

- Medical examinations for insurance purposes
- Well-man and well-woman clinics
- General Practitioner urinalysis
- Routine urinalysis at hospital outpatient departments.

Further cases of microscopic haematuria may be detected as a consequence of testing urine for protein, where either dipstix detecting a range of urinary components are used to screen for proteinuria, or microscopy of urine is performed and erythrocytes are seen directly.

* See SIGN Guideline on Investigation of Asymptomatic Proteinuria in Adults (SIGN guideline no. 18)

There is no evidence that screening for microscopic haematuria is useful in any age group and no evidence that detection of disease at an earlier stage improves outcome.

1.4 **Target patient group**

The guideline should be applied to patients over the age of 13 years with a positive dipstix test for haematuria or with 5 or more RBCs/hpf on urine microscopy.

2 Detection of Haematuria

*Note: These recommendations are based on the finding of microscopic haematuria when urinalysis has been undertaken as part of a medical examination. They are **not** designed for population screening.*

2.1 Normal range

The presence of erythrocytes in normal urine has been recognised since Addis reported his findings in normal medical students in 1926.⁽²⁾ The frequency of their detection depends on the sensitivity of the means of analysis.^(3, 4) It is impossible to recognise a normal range: if lower numbers of red cells are considered abnormal then more patients are needlessly investigated; as higher numbers of red cells are considered normal more pathology is missed.

2.2 Microscopy

Microscopy is now rarely carried out by the general practitioner or as a hospital side-room test. In the vast majority of patients 'microscopic' haematuria is detected by the use of urine dipstix.

2.3 Dipstix

Dipstix detect the peroxidase activity of haem as a constituent of red blood cells, free haemoglobin or myoglobin, by means of peroxidase and orthotolidine.

False positive reactions may be caused by:

- Oxidising contaminants such as bacterial peroxidases
- Iodine and hypochlorite ions present in antiseptic solutions.

False negative reactions are caused by:

- Acidic urine
- Excess ascorbic acid⁽⁵⁾
- Rifampicin and phenolphthalein.

The limit of detection of urinalysis dipstix has improved since their introduction. Most types will detect 15-20,000 RBC/ml (that is, around 8 RBC/hpf).⁽⁶⁾ Hence, they are rather less sensitive than the upper limit of normal as defined in section 1.1 above.

The result of dipstix testing should be confirmed by undertaking the test at least twice. Manufacturers' instructions for their use must be carefully followed.

3 Significance of Microscopic Haematuria

With the widespread use of urinary dipstix, the number of patients who are shown to have microscopic haematuria is likely to rise.⁽⁷⁾ Does asymptomatic microscopic haematuria herald significant pathology in sufficient cases to justify its investigation?

3.1 Hospital clinic studies

In studies of patients who have been referred to hospital urology and nephrology services, the yield of investigation of microscopic haematuria is relatively high, with 14–20% of patients referred with asymptomatic microscopic haematuria having significant pathology.^(8–11) The authors of these studies concluded that all cases of asymptomatic microscopic haematuria should be investigated.

3.2 Population-based studies

The findings of studies based on healthy populations of subjects have not been so consistent. Of two studies reported in 1986, one retrospective study in over 10,000 men tested for dipstix haematuria on a routine health check found a prevalence for occult haematuria of 2.5%.⁽¹²⁾ Amongst those 30% of patients investigated, 28% had ‘significant abnormalities’. These authors concluded that all patients should be investigated with cystoscopy and intravenous urography. The second study⁽⁴⁾ in residents of Minnesota found a greater prevalence of asymptomatic microscopic haematuria—defined as greater than 1 erythrocyte/hpf—at 13%. Only 2.3% of these patients had ‘serious’ pathology—tumours, ureteric calculi and hydronephrosis. Another 14% of patients had glomerulonephritis or renal failure which were classified as ‘moderately serious’ diseases.

3.3 The effect of age

The likely yield of the investigation of patients with occult haematuria has also been examined with respect to patient age. A study of 1000 men aged 18–33 years^(13,14) found a point prevalence of haematuria of 1.2%, taking 5 RBC/hpf as the upper limit of normal. The cumulative incidence, with an average of 12 annual examinations per individual, was 14.8%. These patients were not all investigated but the follow up period of eight years allowed any pathology present to declare itself. The diagnoses made were urolithiasis: 7 subjects; urethritis: 1; glomerulonephritis: 1; transitional cell carcinoma of the bladder: 1. In this age group haematuria was relatively uncommon and investigation demonstrated pathology only in a small proportion of cases.

A recent study of male patients in the context of screening for bladder cancer found that 20% (474 of 2356) of men over 60 years of age had dipstix haematuria.⁽¹⁵⁾ 319 of these were investigated by intravenous urogram and cystoscopy and 17 were shown to have asymptomatic transitional cell tumours. The incidence of other pathologies was not reported. A similar study reported that 21.1% of 1,340 men over 50 years of age had occult haematuria on dipstix testing over a two-week period.⁽¹⁶⁾ Of the 192 men who were fully investigated, 16 had transitional cell tumours while a further 47 had other urological pathology requiring management: stones, outflow tract obstruction, infections and nephropathies. In both of these series repetitive urine testing was performed and bladder tumours were found in patients in whom only *one* of a number of urinalyses was positive.

3.4 The influence of gender

There are no large population surveys of haematuria in women. However, three studies which commented specifically on incidence and diagnosis according to sex reported that pathological causes of microscopic haematuria were identified more frequently in males than females.⁽¹⁷⁻¹⁹⁾ One study reported specifically on females: a prospective evaluation of asymptomatic haematuria in women with a follow up of up to 11 years, which found no tumours. Six ‘significant’ lesions were discovered, all of which were diagnosed on intravenous urography.⁽¹⁸⁾

3.5 Conclusions

These population studies vary in their definitions of haematuria and in the pathologies which they report—whether specifically transitional cell tumours or all pathologies. Notwithstanding, a number of conclusions can be drawn:

- Microscopic haematuria can herald serious pathology at any age but is very rare under the age of 40 years.
- A single positive urinalysis may be significant.
- The incidence of microscopic haematuria rises with patient age.
- The incidence of serious pathology in patients with microscopic haematuria increases with age in men.
- The incidence of significant pathology is lower in women, with tumours rarely described in women under 40 years of age.

Published prospective population-based studies are not adequate to allow the guideline development group to make an unequivocal statement of the risk of underlying pathology in patients with microscopic haematuria according to their age and sex. No data are available that describe whether early detection of ‘significant pathology’ improves the outcome.

It is recommended that all cases of asymptomatic microscopic haematuria (as defined in section 1.1) should be investigated, on the basis that this is the only way in which significant pathology will be detected

Grade B, level II & III

Implementation of such a recommendation would result in large numbers of normal investigations in men and women under the age of 40 years. The resource implications and economic value of this approach require to be established in different age groups (*see recommendations for further research, section 9.2*).

4 Investigation at Presentation

The guideline development group suggests the following investigation at presentation. Both positive and negative responses and results may provide indications of the cause of asymptomatic microscopic haematuria.

4.1 History

In taking the history and, indeed, throughout the investigation of asymptomatic haematuria, it is useful to consider the causes of haematuria topographically: renal glomerular and non-glomerular; post-renal; haematological and factitious.

4.1.1 Note particularly:

<i>Urinary symptoms</i>	<ul style="list-style-type: none"> • Renal and ureteric pain or previous macroscopic haematuria • Frequency, nocturia, dysuria or strangury • Poor stream, dribbling
<i>Medical history</i>	<ul style="list-style-type: none"> • Renal trauma • Urinary tract infection and pyelonephritis • Radiotherapy to the pelvis • Sexually transmitted disease predisposing to urethral stricture • Tuberculosis
<i>Drug history</i>	<ul style="list-style-type: none"> • Non-steroidal anti-inflammatory drugs and second-line anti-rheumatic drugs • APC-type mixed analgesics • Previous cytotoxic or immunosuppressive drug therapy • Warfarin and other anticoagulants (including aspirin)* • Some dietary agents (e.g. Worcestershire sauce) which, if taken in grossly inflated amounts, may cause amino-aciduria and haematuria⁽²¹⁾ • Drugs causing false-positive dipstix reactions (see above) • Exposure to industrial carcinogens • Tobacco smoking
<i>Family history</i>	<ul style="list-style-type: none"> • Renal disease or hypertension, e.g. Alport's syndrome or adult (autosomal dominant) polycystic kidney disease • Microscopic haematuria • Sickle-cell trait • Urolithiasis

* One study of subjects taking warfarin who had haematuria found urological pathology in 80% of them and it is unsafe to accept anticoagulants alone as the cause of haematuria ⁽²⁰⁾

4.1.2 A number of points in the history may suggest glomerular disease:

- Recent sore throat or tonsillitis suggesting post-streptococcal glomerulo-nephritis
- Current upper respiratory tract infection or gastro-enteritis suggesting IgA nephropathy
- Constitutional symptoms of rash, arthralgia or myalgia suggesting vasculitis, e.g. Henoch Schonlein purpura or crescentic glomerulo-nephritis
- Diabetes mellitus
- Deafness or positive family history of renal disease or hypertension suggesting hereditary nephritis or polycystic kidney disease
- Evidence of a bleeding diathesis.

4.2 Examination

Examination may not always be revealing but should include:

- Inspection of tonsils and skin
- Measurement of blood pressure
- Search for the signs of fluid overload
- Auscultation of the heart for a murmur
- Kidneys and bladder palpation for enlargement or tenderness
- Digital rectal examination in males.

4.3 Investigation

Preliminary investigations undertaken by the general practitioner or other primary care professional should help to identify which patients should be referred for further investigation, and to whom.

4.3.1 Blood

Venous blood should be taken for measurement of:

- full blood count
- urea
- electrolytes
- creatinine

4.3.2 Urine

- dipstix tests for protein and glucose (if not done already)
- send for culture and microscopy to identify both cells and casts.

The results of culture may obviate the need for referral (*see section 5*).

Routine microscopy may show bacteriuria suggesting urinary tract infection, or pyuria without bacteriuria suggesting glomerulonephritis, stones or tuberculosis. The presence of protein with red cell casts is pathognomonic of a glomerular source of haematuria, but white cell casts are non-specific.⁽²²⁾ Urine microscopy can also reveal sickled erythrocytes in patients who have haematuria caused by sickle cell trait or sickle cell disease.⁽²³⁾

Good practice point: *The freshness of the urine sample when it reaches the laboratory is crucial to the success of both investigations. Samples should, ideally, reach the laboratory within two hours or be refrigerated*

Glomerular bleeding without proteinuria may be recognised by two other means (available only in some centres):

- Urinary erythrocyte morphology⁽²⁴⁻²⁷⁾
- Immunocytochemical staining of urine red cells.⁽²⁸⁾

4.4 **Minimum Data Set**

A minimum data set for collection in all patients with asymptomatic microscopic haematuria is presented at Annex 3.

5 Urological or Nephrological Referral

- 5.1 The general practitioner or hospital doctor discovering microscopic haematuria will have to decide which patients should be referred, and to whom, on the basis of the investigations outlined.

Patients should *not* be referred immediately in the following circumstances:

- ***Menstruating women*** should have urinalysis repeated between menses. They should be referred for assessment only if haematuria persists.
- ***Women with urinary tract infection.*** Infection proven on urine culture may be accepted as the cause of microscopic haematuria. An appropriate course of antibiotics should be prescribed and a one week post-antibiotic urine sample collected for culture and analysis. Three episodes of infection in twelve months are generally accepted as the threshold at which such patients should be investigated.⁽²⁹⁾
- ***Where false positive results are suspected.*** Withdrawal of the suspected agent(s) and repeat urinalysis is appropriate before referral.
- ***Exercise-induced haematuria*** is commonly regarded as glomerular although, in its milder forms, it truly represents myoglobinuria,⁽¹⁹⁾ and may factitiously indicate haematuria on dipstix testing. Repeat urinalysis more than 48 hours after the last episode of strenuous exercise should be undertaken.

Grade B, level II & III

5.2 Urological referral

The initial referral of most patients should be to a urologist

In male patients, a single episode of proven urinary tract infection should lead to urological referral

Grade B, level IIa & level IIb

The effect of rapidity of investigation and management on the outcome of urogenital cancers is discussed in section 6.4.

5.3 Nephrological referral

Patients with any one of the following findings in addition to haematuria should initially be referred for nephrological investigation:

- *Proteinuria > trace*
- *Other clinical evidence of parenchymal renal disease*
- *Elevated blood urea or creatinine*

Grade C, level III & IV

See SIGN guideline on Investigation of Proteinuria in Adults.⁽³⁰⁾

6 Urological Investigation

The urologist may wish to repeat elements of history taking, examination, urine culture and analysis, and blood testing. The cornerstones of urological investigation, however, are imaging of the urinary tract and cystourethroscopy. The place of urine cytology in the initial investigation of occult haematuria is also discussed here.

6.1 Radiological imaging

6.1.1 Intravenous urography and ultrasonography

In the past, intravenous urography (IVU) was the imaging investigation of choice and, until recently, was the only imaging investigation available. The advent of widely available ultrasonography has challenged this position. Intravenous urography has been criticised on the basis of the patient-radiation dose involved—around 4.36mSv, equivalent to 80 chest *x*-rays⁽³¹⁾—and identified as an area where population-radiation dose restriction should be possible.⁽³²⁾

A number of authors have suggested that ultrasonography should replace intravenous urography as the primary imaging technique in the investigation of haematuria.⁽³³⁻³⁴⁾ The guideline development group does not believe this argument has been resolved. The arguments in favour of ultrasound are based on the fact that ultrasonography detects a higher proportion of transitional cell carcinomas (TCC) than does intravenous urography,⁽³³⁾ but this is only true when bladder tumours are included. Ultrasonography detects only around 25% of bladder transitional cell carcinomas⁽³⁶⁾ and cannot supplant cystoscopy. It may be argued that the low incidence of transitional cell carcinoma of the upper tract makes intravenous urography unjustified,⁽¹³⁾ but transitional tumour is not the only pathology which is sought. There is no doubt that in the diagnosis of urolithiasis, intravenous urography is superior to ultrasonography.⁽³⁷⁾ On the other hand, renal parenchymal tumours are more common than upper tract TCC.

6.1.2 CT scanning

Computed tomography has no place in the initial investigation of haematuria but is certainly more sensitive than intravenous urography or ultrasonography in identifying small intra-renal lesions.⁽³⁸⁾ If these are suspected in spite of normal intravenous urography and ultrasonography, CT scanning should be used.

Two alternative imaging strategies should be considered:

- ***Intravenous urography (IVU)*** *The IVU may miss some small renal cell tumours and cysts but will detect most other significant pathology except nephritis. The majority of pelvic and ureteric lesions will be picked up, so some patients with diagnosed (not TCC) upper tract pathology may not require cystoscopy.*
 - ***Ultrasound scan and plain film of renal tract*** *Ultrasound and a plain film will miss many small TCC in the bladder or upper tracts so most of these patients with a negative or equivocal examination will require cystoscopy.*
- Grade B, level IIa & IIb*

6.2 Cystourethroscopy

Although radiological imaging investigations are not sensitive enough to make cystoscopy unnecessary, their results may modify that procedure: for example, pathology identified by imaging may indicate the need for rigid endoscopy for ureteric cannulation or resection.

The results of radiological imaging should always be to hand before cystoscopy is performed

Grade B, level IIa & IIb

Results of flexible cystoscopy show high concordance with those of rigid cystoscopy⁽³⁹⁾ and the procedure is preferred by most patients.⁽⁴⁰⁾ Unlike rigid cystoscopy, flexible cystoscopy does not require general anaesthesia and it has recently been demonstrated that even local anaesthesia is unnecessary.⁽⁴¹⁾ The use of the flexible cystoscopy allows the urological investigation of haematuria to be completed in a single patient visit, which is both efficient of medical time and causes a minimum of disturbance for patients.⁽⁴³⁻⁴⁵⁾

For the vast majority of patients flexible cystoscopy should be the preferred investigation

Grade B, level IIa & IIb

6.3 Urine cytology

Urine cytology identifies malignant transitional cells in voided urine.⁽⁴⁵⁾ It may offer a means whereby patients with an established diagnosis of transitional cell carcinoma can be followed up without the expense of regular cystoscopy.⁽⁴⁶⁾

However, it is a highly operator-dependent investigation and may have a sensitivity as low as 55%.⁽⁴⁷⁾ This is not sufficiently high for a diagnostic procedure. In patients investigated by flexible cystoscopy, there is little to gain by the addition of urine cytology.

Urine cytology should be used only if there is a suspicion of carcinoma-in-situ or if part of the urothelium cannot be visualised (e.g. in a bladder diverticulum)

Grade C, level IV

6.4 Speed of investigation – haematuria clinics

The primary role of haematuria clinics is in the investigation of frank haematuria but, if sufficient appointments are available, they should be used for the investigation of asymptomatic patients.

Retrospective research carried out in the 1960s demonstrated an improvement in the 3-year crude survival rate of transitional cell bladder tumours if they were managed within one month of the onset of frank haematuria.⁽⁴⁸⁾ However, a more recent and well-conducted study⁽⁴⁹⁾ did not demonstrate any useful improvement in survival when treatment delay in bladder cancer was low. It has also been demonstrated that the early investigation of frank haematuria does not reduce the stage at presentation of bladder tumours,⁽⁵⁰⁾ although the situation where bladder cancer is diagnosed in asymptomatic patients may be different.⁽⁵¹⁾

Haematuria clinics using the flexible cystoscope, whereby intravenous urography and cystoscopy can be carried out in one day, seem to reduce the delay before management of bladder cancer.⁽⁴²⁻⁴⁴⁾ However, the investigation of asymptomatic microscopic haematuria in this setting may swamp such services.⁽⁷⁾

Clearly the results of management of any condition will be poor if treatment is unduly delayed. However, the accelerated investigation of haematuria, at least on the data presently available, should be justified by its capacity to relieve patients' anxieties, rather than the possibility that it improves outcome.⁽⁵²⁾

7 Nephrological Investigation

- 7.1 The extent of investigation undertaken by the nephrologist will reflect local practice. Most nephrologists would agree on a certain minimum of routine laboratory investigation but different practices emerge in the decision to perform a renal biopsy.
- 7.2 There are no population studies of renal biopsy in patients with asymptomatic haematuria. Most series of patients biopsied for haematuria alone yield a large proportion of diagnoses of IgA nephropathy, particularly where the source of patients is armed forces screening,^(53, 54) although this is not a universal experience.⁽⁵⁵⁾

8 Follow up

8.1 After urological investigation

Having completed their course of urological investigations, should patients be seen further in urology clinics if no abnormality has been demonstrated?

A study involving a very intensive follow up regime for such patients in 1980⁽⁹⁾ was reported in 1991.⁽⁵⁶⁾ Six monthly urinalysis and cytology and biennial cystoscopy and intravenous urography for 20 years found only 4 cases of benign prostate hyperplasia and 2 cases of urolithiasis in a group of 128 patients. Not surprisingly, further follow up has been abandoned except when symptoms develop. Another study⁽⁵⁷⁾ followed up 104 patients for an average of 36 months and found no pathology whatever.

While the clinician's suspicions may be raised by individual patients, and he or she may wish to follow them up in spite of normal investigations, most patients with negative investigations can be discharged to the care of the general practitioner. Patients seen initially by a urological surgeon should be referred for a nephrological opinion only if urological investigation reveals evidence of parenchymal renal disease and with the agreement of the general practitioner.

8.2 After nephrological investigation

Patients seen initially by a renal physician should be referred to a urologist for imaging and cystoscopy if they fulfil the referral criteria outlined in section 5.

If renal biopsy was performed and was normal, patients should be followed up at routine triennial general practitioner review. Patients with abnormal biopsies will be followed-up according to local nephrological practice.

Where biopsy has not been performed, renal physicians may wish to observe patients for a period of time to exclude the development of hypertension or proteinuria,⁽⁵⁸⁾ but these patients should be referred back for biennial general practitioner review.

Most patients with asymptomatic microscopic haematuria should be followed up by their general practitioner depending on local circumstances and the following should be monitored on a biennial basis:

- *Blood pressure*
- *Urinalysis for blood and protein*

Grade B, level II & III

9 Review and Further Research

9.1 Review

The Scottish Intercollegiate Guidelines Network will have continuing responsibility for the review and updating of the guideline. The guideline will be formally reviewed in 1999; amendments will be disseminated as required at that time or, exceptionally, at any other time when significant amendment becomes necessary.

9.2 Recommendations for further research

During the preparation of this guideline, it became apparent that the current state of knowledge of this common medical problem is unsatisfactory.

It is timely and urgent to consider further research because significant resources are being used now, and will be in the future, in the investigation and management of these patients.

The guideline group were unable to identify any large randomised studies that addressed the problems of who to investigate, when and by which methods. A number of open community studies suggest that isolated or asymptomatic microscopic haematuria is common but that few of these patients have serious pathology requiring early intervention. It is not known whether identification of transitional cell carcinoma at this stage or later makes any difference to the outcome(s).

The guideline development group recommends that research be undertaken in the following three main areas of deficiency:

- population-based studies to establish the prevalence and significance of microscopic haematuria in different demographic groups
- comparative, blinded studies of intravenous urography and ultrasound scanning as investigation of the upper urinary tract in microscopic haematuria
- studies to assess any benefit in identifying and treating pathology when declared only by microscopic haematuria.

10 Implementation of the Guideline

10.1 Development of local protocols

It is expected that the guideline will be adopted after local discussion involving clinical staff and provider and purchaser management. The Area Clinical Audit Committee should be fully involved. Local arrangements will then be made for the derivation of specific local protocols to implement the national guideline in individual hospitals, units and practices and for securing compliance with them.

This will be done by a variety of means including patient-specific reminders, continuing education and training, and clinical audit. Service contracts should reflect the arrangements fully along with their related costs.

Staff groups who require to be involved in development and implementation of local protocols derived from this national guideline are set out in Annex 2.

10.2 Audit

Criteria for local audit are likely to include the proportion of patients found on initial investigation to have significant urinary pathology. However, the expected proportion of patients with significant pathology is extremely low and prolonged follow up data may be required to indicate the usefulness of early intervention to treat such pathology.

It is unlikely that a single centre would provide a sufficiently large number of patients to obtain a clinically useful result. Ideally, local protocols should therefore be developed and audited by several centres working in co-operation.

A suggested minimum data set for investigation of asymptomatic microscopic haematuria is presented at Annex 3.

10.3 Statement of intent

This report is not intended to be construed or to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns evolve.

- These parameters of practice should be considered guidelines only. Adherence to them will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results.

- The ultimate judgement regarding a particular clinical procedure or treatment plan must be made by the doctor in light of the clinical data presented by the patient and the diagnostic and treatment options available.
- A background paper on the legal implications of guidelines, prepared by Dr Pamela Abernethy of Simpson & Marwick W.S., is available from the SIGN secretariat.

11 Development of the Guideline

11.1 Responsible Bodies

This pilot guideline was developed by the Haematuria Guideline Development Group acting on behalf of the Scottish Intercollegiate Guidelines Network (SIGN) and using the methodology adopted by SIGN. This guideline has been accepted by SIGN as the Scottish national guideline from which local protocols should be derived.

11.2 Guideline Development Group

Name	Discipline	Location
Dr Margaret McMillan (Chair)	Nephrologist	Glasgow
Dr John Anderton	Nephrologist	Lothian
Dr John Burton	Nephrologist	Highland
Dr Janette Clinkenbeard	General Practitioner	Lothian
Mr R Fletcher Deane	Urologist	Glasgow
Dr Keith Donaldson	General Practitioner	Lothian
Dr David Jenkins	Nephrologist	Fife
Mr Alan Paul	Urologist	Grampian
Dr Charles Swainson	Nephrologist	Lothian
Dr S Roger Wild	Radiologist	Lothian

Declarations of interests are held by the SIGN Secretariat.

11.3 Development Process

The Guideline Development Group met on eight occasions between November 1993 and July 1995. Successive drafts were developed by synthesis of the literature, correspondence and full discussion. Details of the literature search undertaken are given at Annex 1.

An open meeting (sponsored by Bayer) to which all urologists, nephrologists and Lothian general practitioners were invited to attend, was held in November 1994 to discuss the recommendations. This led to some modification although the core recommendations, based on the published scientific literature, were not challenged or altered. **Clear evidence of a professional split was evident between those who recognised that no investigation other than cystoscopy could diagnose all cases of transitional cell carcinoma and others who believed that resources were not used wisely if all patients with all grades of microscopic haematuria were to be subjected to cystoscopy.**

The guideline was submitted, in draft, to the following external referees:

Dr Anthony Breslin	Public Health, Grampian Health Board
Professor J Stewart Cameron	Nephrologist, Guy's Hospital, London
Professor Alex Davison	Nephrologist, St James's Hospital, Leeds
Dr Kenneth Harden	General Practitioner, Glasgow
Dr Giovanni Fogazzi	Nephrologist, Ospedale Maggiore, Milan
Dr Allan Merry	General Practitioner, Ardrossan
Dr Dorothy Moir	Public Health, Lanarkshire Health Board
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Professor Andrew Rees	Nephrologist, Aberdeen Royal Infirmary
Dr John Reid	General Practitioner, Alford
Dr Anthony Rogers	Urologist, Stirling Royal Infirmary

11.4 **SIGN Editorial Board**

The guideline was reviewed before publication by the SIGN Editorial Board:

Professor James Petrie	Royal College of Physicians of Edinburgh Chairman of SIGN
Dr Doreen Campbell	CRAG secretariat, Scottish Office
Dr Patricia Donald	Royal College of General Practitioners
Dr Jeremy Grimshaw	Health Services Research Unit, University of Aberdeen
Mr Douglas Harper	Royal College of Surgeons of Edinburgh
Dr Grahame Howard	Royal College of Radiologists Vice Chairman of SIGN

11.5 **Dissemination**

The guideline will be sent to:

- named practitioners in each of the relevant staff groups (*see Annex 2*) throughout Scotland
- Chief Executives and Clinical Directors in Trusts and hospitals in Scotland
- Board General Managers and Directors of Public Health and other chief professional officers in each Health Board
- Chairmen of Area Clinical Audit Committees and of Area Medical and other professional Advisory Committees
- Local Medical Committees
- Relevant education and training bodies
- Selected others.

References

- 1 US Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research (1992). Acute Pain Management: Operative or Medical Procedures and Trauma. Agency for Health Care Policy and Research Publications, Rockville, MD. (AHCPR Pub 92-0038).
- 2 Addis T. The number of formed elements in the urinary sediment of normal individuals. *J Clin Invest* 1926; 2: 409-413.
- 3 Freni SC, Heederik GJ, Hol C. Centrifugation techniques and reagent strips in the assessment of microhaematuria. *J Clin Pathol* 1977; 30: 336-340.
- 4 Mohr DN, Offord KP, Owen RA, Melton LJ, III. Asymptomatic microhaematuria and urologic disease: a population based study. *JAMA* 1986; 256: 224-229.
- 5 Ames [product literature], "Multistix" technical information bulletin, Stoke Poges: Miles Laboratories Inc., 1987; pp. 1-4.
- 6 Asberg A, Lehmann EH, Pettersen JE. Evaluation of dipstix for the assessment of microhaematuria. *Scand J Clin Lab Invest* 1984; 44: 377-380.
- 7 Marazzi P, Gabriel R. The haematuria clinic: faster diagnosis but no evidence yet of improved prognosis. *BMJ* 1994; 308:356.
- 8 Carson CC, III, Segura JW, Greene LF. Clinical importance of microhaematuria. *JAMA* 1979; 241: 149-150.
- 9 Golin AL, Howard RS. Asymptomatic microscopic haematuria. *J Urol* 1980; 124: 389-391.
- 10 Murakami S, Igarashi T, Hara S, Shimazaki J. Strategies for asymptomatic microscopic haematuria: A prospective study of 1034 patients. *J Urol* 1990; 144: 99-101.
- 11 Mariani AJ, Mariani MC, Macchioni C, Stams UK, Hariharan A, Moriera A. The significance of adult haematuria: 1000 haematuria evaluations including a risk-benefit and cost-effectiveness analysis. *J Urol* 1989; 141: 350-355.
- 12 Ritchie CD, Bevan EA, Collier StJ. Importance of occult haematuria found at screening. *BMJ* 1986; 292: 681-683.
- 13 Fromm B, Ribak J, Benbassat J. The significance of haematuria in young adults. *BMJ* 1984; 288: 20-22.
- 14 Fromm B, Gross M, Ribak J, Barzilay J, Benbassat J. The effect of age on the prevalence of asymptomatic microscopic haematuria. *Am J Clin Pathol* 1986; 86: 656-657.
- 15 Britton JP, Dowell AC, Whelan P, Harris CM. A community study of bladder cancer screening by the detection of occult urinary bleeding. *J Urol* 1992; 148: 788-790.
- 16 Messing EM, Young TB, Hunt VB, Roecker EB, Vaillancourt AM, Hisgen WJ, et al. Home screening for haematuria: results of a multi-clinic study. *J Urol* 1992; 148: 289-292.
- 17 Greene LF, O'Saughnessy EJ Jr., Hendricks ED. Study of five hundred patients with asymptomatic haematuria. *JAMA* 1956; 161: 610-613.
- 18 Bard RH. The significance of asymptomatic haematuria in women and its economic implications. *Arch Intern Med* 1988; 148: 2629-2632.

- 19 Hamilton RW, Gardner LB, Penn AS. Acute tubular necrosis caused by exercise-induced myoglobinuria. *Ann Intern Med* 1972; 77: 77-82.
- 20 Antolak SJ Jr., Mellinger GT. Urologic evaluation of haematuria occurring during anti-coagulant therapy. *J Urol* 1969; 101: 111-113.
- 21 Rivera M, Salcedo JR. Worcestershire sauce-induced haematuria. *J Urol* 1982; 127: 554.
- 22 Shenoy UA. Current assessment of microhaematuria and leukocyturia. *Clin Lab Med* 1985; 5: 317-329.
- 23 Fogazzi GB, Leong S-O, Cameron JS. Don't forget sickled cells in the urine when investigating a patient for haematuria. *Nephrology Dialysis Transplantation* 1996; 11: 723-725.
- 24 Fairley KF, Birch DF. Haematuria: A simple method for identifying glomerular bleeding. *Kidney Int* 1982; 21: 105-108.
- 25 Fassett RG, Horgan BA, Matthew TH. Detection of glomerular bleeding by phase-contrast microscopy. *Lancet* 1982; i: 1432-1434.
- 26 Banks RA, Reynolds S, Hanbury D. Identification of the source of haematuria by automated measurement of red cell volume. *Br J Urol* 1989; 64: 45-48.
- 27 De Caestecker MP, Hall CL, Basterfield PT, Smith JG. Localisation of haematuria by red cell analysers and phase-contrast microscopy. *Nephron*. 1989 52:170-173.
- 28 Janssens PMW, Kornaat N, Tieleman R, Monnens LAH, Willems JL. Localizing the site of haematuria by immunocytochemical staining of erythrocytes in urine. *Clin Chem* 1992; 38: 216-222.
- 29 Shanson DC. Infections of the urinary tract. In: Shanson DC, editor. *Microbiology in Clinical Practice*. 2nd ed. London: Wright, 1989: 430-451.
- 30 Scottish Intercollegiate Guidelines Network (SIGN). Investigation of Proteinuria in Adults. Edinburgh: SIGN, 1997. (SIGN publication no. 18).
- 31 Faulkner K, Waul B. Patient doses and risks in diagnostic radiology: are x-rays safe enough? York: Institute of Physical Sciences in Medicine; 1988. Report No: 55.
- 32 National radiological protection board. Patient dose reduction in diagnostic radiology. Oxford: National radiological protection board, 1990.
- 33 Spencer JS, Lindsell D, Mastorakou I. Ultrasonography compared with intravenous urography in the diagnosis of adults with haematuria. *BMJ* 1990; 301: 1074-1076.
- 34 Aslaksen A, Gadeholt G, Gothlin JH. Ultrasonography versus intravenous urography in the evaluation of patients with microscopic haematuria. *Br J Urol* 1990; 66: 144-147.
- 35 Corwin HL, Silverstein MD. The diagnosis of neoplasia in patients with asymptomatic microscopic haematuria: a decision analysis. *J Urol* 1988; 139: 1002-1006.
- 36 Itzchak Y, Singer D, Fischelovitch Y. Ultrasonographic assessment of bladder tumors. I. tumor detection. *J Urol* 1981; 126: 31-33.
- 37 Cattell WR, Webb JAW, Whitfield HN. Investigation of adults with haematuria. *BMJ* 1990; 301: 1396-1397.
- 38 Warshauer DM, McCarthy SM, Street L, Bookbinder MJ, Glickman MG, Richter J, et al. Detection of renal masses: Sensitivities and specificities of excretory urography/linear tomography, US and CT. *Radiology* 1988; 169: 363-365.

- 39 Meyhoff HH, Andersen JT, Klarskov P, Steven K. Flexible fiberoptic versus conventional cystourethroscopy in bladder tumour patients: a prospective study. *Scand J Urol Nephrol* 1988; 2 suppl 100: 237-240.
- 40 Flannigan GM, Gelister JSK, Noble JG, Milroy EJG. Rigid versus flexible cystoscopy: a controlled trial of patient tolerance. *Br J Urol* 1988; 62: 537-540.
- 41 Birch BRP, Ratan P, Morley R, Cumming J, Smart CJ, Jenkins JD. Flexible cystoscopy in men: is topical anaesthesia with lignocaine gel worthwhile? *Br J Urol* 1994; 73: 155-159.
- 42 Paul AB, Collie DA, Wild SR, Chisholm GD. An integrated haematuria clinic. *Brit J Clin Pract* 1993; 47: 128-130.
- 43 Hasan ST, German K, Derry CD. Same day diagnostic service for new cases of haematuria - a district general hospital experience. *Br J Urol* 1994; 73: 152-154.
- 44 Lynch TH, Waymont B, Dunn JA, Hughes MA, Wallace DMA. Rapid diagnostic service for patients with haematuria. *Br J Urol* 1994; 73: 147-151.
- 45 Esposti PL, Moberger G, Zajicek J. The cytological diagnosis of transitional cell tumours of the urinary bladder and its histological basis. A study of 567 cases of urinary-tract disorder including 170 untreated and 182 irradiated bladder tumours. *Acta Cytol* 1970; 14: 145-155.
- 46 Juul N, Torp-Pedersen S, Larsen S, Rasmussen F, Holm HH. Bladder tumour control by abdominal ultrasound and cytology. *Scand J Urol Nephrol* 1986; 20: 275-278.
- 47 Bishop MC. Diagnostic procedures. In: Zingg EJ, Wallace DMA editors. *Bladder cancer*. Berlin, Springer-Verlag, 1985: 87-115.
- 48 Wallace DM, Harris DL. Delay in treating bladder tumours. *Lancet* 1965; ii: 332-334.
- 49 Gulliford MC, Petruckevitch A, Burney PGJ. Survival with bladder cancer, evaluation of delay in treatment, type of surgeon, and modality of treatment. *BMJ* 1991; 303: 437-440.
- 50 Bishop MC. The dangers of a long urological waiting list. *Br J Urol* 1990; 65: 433-440.
- 51 Whelan P, Britton JP, Dowell AC. Three-year follow-up of bladder tumours found on screening. *Br J Urol* 1993; 72: 893-896.
- 52 Britton JP. Effectiveness of haematuria clinics. *Br J Urol* 1993; 71:247-252.
- 53 Sinniah R, Pwee HS, Lim CH. Glomerular lesions in asymptomatic microscopic haematuria discovered on routine medical examination. *Clin Nephrol* 1976; 5: 216-228.
- 54 Copley JB, Hasbargen JA. 'Idiopathic' haematuria: a prospective evaluation. *Arch Intern Med* 1987; 147: 434-437.
- 55 Kupor LR, Mullins JD, McPhaul JJ Jr. Immunopathologic findings in idiopathic renal haematuria. *Arch Intern Med* 1975; 135: 1204-1211.
- 56 Howard RS, Golin AL. Long-term follow up of asymptomatic microhaematuria. *J Urol* 1991; 145: 335-336.
- 57 Yazaki T, Nemoto S, Ishikawa H, Kanoh S, Koiso K, Terasaki T, et al. Long-term follow-up of patients with asymptomatic haematuria. *Jap J Nephrol* 1985; 27: 1247-51.
- 58 Nieuwhof C, Doorenbos C, Grave W, De Heer F, De Leeuw P, Zeppenfelt E, et al. A prospective study of the natural history of idiopathic non-proteinuric haematuria. *Kidney Int* 1966; 49: 222-225.

Annex 1

Literature search strategy

The National Library of Medicine and Excerpta Medica databases were searched for all relevant papers (not review articles), using the key term ‘asymptomatic microscopic haematuria’. Only papers relating to adults and in English were considered which fulfilled the following criteria:

- (i) randomised, controlled trials of investigation or treatment of microscopic haematuria (papers identified: 2)
- (ii) controlled, non randomised studies (6)
- (iii) open, uncontrolled non-randomised comparative studies in hospital populations (11)
- (iv) open, uncontrolled, non-randomised, descriptive studies in communities (15)
- (v) uncontrolled studies in clinic populations (18)
- (vi) expert committee reports (4)

No meta-analyses were identified.

Annex 2

Staff groups who require to be involved in development and implementation of local protocols derived from this national guideline

Hospital and primary care medical staff

Public Health specialists

Management

Area Audit Committees

Deans and Postgraduate Deans of University Faculties of Medicine in Scotland and other relevant professional educational bodies.

Annex 3

Minimum Data Set

Demographic data
Results of dipstix tests, including proteinuria
Result of MSU
Recording of <ul style="list-style-type: none">• blood pressure• serum creatinine
Positive history of familial kidney disease
Past history of kidney disease or hypertension
Current drug treatment
Results of ultrasound <i>or</i> IVU and plain film
Referral to urologist/nephrologist
Specialist diagnosis
Follow-up arrangements: <ul style="list-style-type: none">• biennial result of dipstix, blood pressure and plasma creatinine for the period of follow-up• final outcome at end of period of follow-up

Quick Reference Guide

A B C refers to **grade of recommendation**

