

Editorial Review

Does urinary tract infection cause proteinuria or microalbuminuria? A systematic review

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Introduction

Proteinuria, the presence of increased quantities of protein in the urine [1,2] can be detected by a variety of methods [3] including reagent-strip tests (e.g. AlbustixTM), which can be used in a point-of-care testing environment, and chemical tests available in the laboratory. Highly specific immunoassays for specific proteins including albumin are also used. Screening for proteinuria has diagnostic value in the initial detection and confirmation of proteinuric renal disease. Proteinuria is also an important predictor of progressive kidney damage [4] and a potent independent cardiovascular risk marker and predictor [5]. Among patients with suspected or proven chronic kidney disease (CKD), including diabetic nephropathy, reflux nephropathy and early glomerulonephritis, urinalysis for proteinuria is accepted as a useful way of identifying patients at risk of progressive kidney disease. Urinalysis for proteinuria is recommended as part of the initial assessment of patients with hypertension [6–8]. In people with diabetes mellitus the identification of increased urinary albumin excretion allows the diagnosis of diabetic nephropathy. Microalbuminuria also serves as a risk marker for progressive kidney disease and increased cardiovascular risk [9], even among non-diabetic individuals [10–13]. Urinary tract infections (UTIs) are commonly said to be associated with positive results in reagent-strip urinalysis for proteinuria, with some reviews suggesting between 63 and 83% of cases of culture-confirmed UTI having reagent-strip positive tests for

protein [14]. Symptomatic UTIs account for 2–3% of all consultations in general practice and around 6% in the case of women. Asymptomatic UTI is found in approximately 4–7% of pregnant women, 10% of elderly men and 20% of elderly women. Uropathogenic strains of *Escherichia coli* account for the majority of UTIs that occur in the community [15,16].

Because of the reported association between UTI and proteinuria and the high prevalence of asymptomatic UTI, many published guidelines and expert consensus opinions recommend the exclusion of a UTI if a test result for urinary total protein is positive [1,17–19] or, prior to the diagnosis of microalbuminuria, in patients with diabetes [20,21]. Thus, common current clinical practice requires physicians to submit a second mid-stream urine sample to the microbiology department for a urine culture to either exclude UTI as a potential cause of proteinuria or consider it as a confounding factor. If there is a UTI, the patient is treated, and ~2 weeks post-treatment a further biochemical investigation is required to confirm whether proteinuria/albuminuria is present. Further tests are also necessary when a UTI has been excluded. Our experience is that the yield of positive culture and sensitivity in this situation is very low.

We have attempted to identify the origins of these recommendations for proteinuria screening with respect to UTI by conducting a systematic review to determine if there is quality evidence underpinning the common clinical practice of excluding UTI in patients with positive tests for protein. We researched the literature to answer the series of questions detailed in the following text:

- (i) Does asymptomatic UTI cause proteinuria/albuminuria?
- (ii) Does symptomatic UTI cause proteinuria/albuminuria?
- (iii) What is the nature of proteinuria in patients with UTI?

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Table 1. Literature search criteria

	Search Criteria	Database	Results
1	proteinuria and urinary tract infection (unlimited)	PubMed	536
2	Proteinuria	PubMed	19642
3	Urinary tract infection	PubMed	28660
4	2 and 3 (proteinuria and urinary tract infection)	PubMed	383
5	Albuminuria and urinary tract infection (unlimited)	PubMed	90
6	Albuminuria	PubMed	6653
7	6 and 3 (albuminuria and urinary tract infection)	PubMed	62
8	Pyuria and proteinuria (unlimited)	PubMed	153
9	Pyuria	PubMed	735
10	9 and 2 (pyuria and proteinuria)	PubMed	62
11	pyuria and albuminuria (unlimited)	PubMed	26
12	9 and 6 (pyuria and albuminuria)	PubMed	14
13	Proteinuria	Embase	8402
14	Urinary tract infection	Embase	19895
15	13 and 14 (proteinuria and urinary tract infection)	Embase	78
16	Albuminuria	Embase	2501
17	16 and 14 (albuminuria and urinary tract infection)	Embase	11
18	Pyuria	Embase	1127
19	18 and 13 (pyuria and proteinuria)	Embase	37
20	18 and 16 (pyuria and albuminuria)	Embase	7

Highlighted results represent the number of abstracts that were selected initially for consideration.

- (iv) Have studies linking UTI and proteinuria/albuminuria taken technical interferences including urinary pH into consideration?

Methods and results

We performed an electronic search of the PubMed (1951 to 31st March 2006) and Embase (1974 to 31st March 2006) databases using the search terms listed in Table 1. Unless otherwise stated, all searches were limited to medical sub heading (MeSH) terms. Full text articles were selected, on the basis of the title and abstract, following examination by two researchers (J.L.C. and E.J.L.) who also independently read all the selected articles. We aimed to include articles that provided relevant information to answer the questions detailed here.

The highlighted results (Table 1) represent the number of abstracts that were selected initially for consideration. Duplicates were removed and only the remaining abstracts in English were read to identify relevant articles. We selected 80 articles for full text scrutiny. The search was expanded further by the inclusion of relevant articles that were either known to us or had been referenced in the original articles or retrieved from the related articles' links on the PubMed database searches listed in Table 1. Only full articles and letters were included in the search. Unless indicated otherwise, UTI was considered present according to the commonly used definition of a pure growth of $\geq 10^5$ colony-forming units (CFU)/ml and asymptomatic bacteriuria was defined as the incidental finding of $\geq 10^5$ CFU/ml in patients whose urine was cultured despite the absence of urinary tract symptoms. In this review, the term 'proteinuria' refers to abnormal protein excretion detected using non-specific chemical methods, including reagent-strip devices, and the term 'albuminuria' refers to increased albumin excretion measured using a specific immunoassay method.

i. Does asymptomatic UTI cause proteinuria/albuminuria?

Several authors have reported associations between proteinuria and asymptomatic UTI [22–31]. In a Swedish study of bacteriuria amongst 514 asymptomatic diabetic patients, Brauner *et al.* [26] observed 29 positive urine cultures over a 1-year period. Those patients with UTI were more likely ($P=0.09$) to have diabetic nephropathy (known proteinuria defined as total protein concentration >200 mg/l on more than one occasion) prior to UTI, but the relationship between current UTI and the presence of proteinuria was not examined. Among Dutch women with type 1 diabetes, Geerlings *et al.* [23] demonstrated a high prevalence of asymptomatic bacteriuria. Pre-existing proteinuria, but not microalbuminuria, was a risk factor for asymptomatic UTI. The authors postulate that asymptomatic bacteriuria and other diabetic complications including nephropathy may have their origins in common pathophysiological processes (e.g. endothelial dysfunction and oxidative stress). Phanichphant and Boonpucknavig [25] provide further evidence that female glomerulopathic patients with proteinuria exceeding 1 g/day are more likely to harbour asymptomatic UTI than equivalent patients with lower levels of protein excretion. Similarly, Rai *et al.* [22] have demonstrated that among patients with nephrotic syndrome the concomitant presence of asymptomatic bacteriuria was associated with higher urinary protein excretion ($P<0.05$). These studies provide some evidence that patients with more advanced nephropathy, defined in terms of urinary protein excretion, may be more susceptible to UTI, but they neither refute nor support the existence of a causative relationship between UTI and proteinuria.

Screening studies of children conducted during the 1960s and 1970s have shown either no [32–35] or weak [28–31] evidence of an association between asymptomatic bacteriuria and proteinuria. El-Garhy and Richardson [31] noted two out of 541 schoolchildren to have proteinuria and pyuria: conversely, six had asymptomatic bacteriuria and no

proteinuria. Johnson *et al.* [28] reported that of the 1684 girls screened, 10 had proteinuria (≥ 0.3 g/l) of whom three had coexistent bacteriuria. Conversely, 42 girls had asymptomatic bacteriuria and no proteinuria. In 1973, Silverberg *et al.* [29] examined urine abnormalities in a large cohort ($n=23\,427$) of otherwise healthy schoolgirls. The overall incidence of UTI and proteinuria was 1.9 and 0.5%, respectively. Of the girls with bacteriuria, only 5% had proteinuria (>0.3 g/l). Conversely, of the girls with proteinuria, only 2.3% had bacteriuria. A relatively small Nigerian study of urine abnormalities in apparently healthy children reported an association of proteinuria with asymptomatic UTI in children under the age of 18 months [30]. In an urban group nine out of 100 children were found to have proteinuria, of whom one had bacteriuria and pyuria. Of the 50 children in a rural group, nine had albuminuria, of whom eight had bacteriuria. The apparently high prevalence of proteinuria in these children was not discussed. None of these studies established whether a causal link existed between UTI and proteinuria. Further, four large-scale screening studies of school children have found no evidence of an association between asymptomatic UTI and proteinuria, generally reporting an absence of proteinuria in the vast majority of children found to be harbouring a UTI [32–35].

Overall, these screening studies do not support the existence of a causal relationship between asymptomatic UTI and proteinuria in children. Asymptomatic bacteriuria in children is sometimes associated with proteinuria, but more commonly is not: in most cases asymptomatic UTI exists in the absence of proteinuria and *vice versa*. Proteinuria does not appear to be a useful screening test for identifying asymptomatic bacteriuria. However, none of these studies set out to formally test whether a causal relationship exists, and none provided evidence on the effect of antibiotic treatment in bacteriuric individuals on proteinuria. In a small study of eight children with relapsed nephrotic syndrome and coexistent bacteriuria (mostly asymptomatic), treatment of the infection with antibiotics was found to have an additional effect on reducing proteinuria (estimated 'semi-quantitatively') in addition to the treatment with steroids alone [27]. This could be interpreted as evidence that UTI contributed to proteinuria although it is difficult to establish whether the UTI was the cause of the relapse or the result of it.

Asymptomatic bacteriuria, predominantly due to *E. Coli*, is relatively common among female patients with diabetes. Further, the presence or absence of microalbuminuria may influence treatment decisions in these patients. The question of whether or not asymptomatic bacteriuria causes microalbuminuria is therefore important. Parving *et al.* [36] noted higher levels of urinary albumin excretion in females with type 1 diabetes and asymptomatic bacteriuria but causality was not established. Baskar *et al.* [37] screened >1800 patients with diabetes for the presence of microalbuminuria. Amongst the 248 patients identified as being microalbuminuric, asymptomatic bacteriuria was present in 31 (12.5%). They concluded that routine screening for asymptomatic bacteriuria in the setting of microalbuminuria testing should be abandoned. Useful observational and prospective data in this situation are provided by two studies [38,39]. Hernandez *et al.* [38] observed similar albumin excretion rates (AERs) among 59 patients with type 2 diabetes and asymptomatic UTI compared with a control group of 56 patients with type

2 diabetes and no UTI. Further, they also reported that AER did not change after antimicrobial treatment either in the whole group ($n=59$, 13.8 vs 8.5 $\mu\text{g}/\text{min}$, $P=0.14$) or in the 46 patients in whom infection was eradicated (11.7 $\mu\text{g}/\text{min}$ vs 7.1 $\mu\text{g}/\text{min}$, $P=0.14$). The apparent decrease in AER after anti-microbial therapy did not exceed the biological variation of AER and whether patients were classified as normo- or microalbuminuric was unaffected. They concluded that UTI does not increase AER and that excluding UTI is unnecessary when AER is measured in patients with diabetes. Watts *et al.* [39] investigated the influence of urinary infection on albumin excretion in 172 patients with type 1 diabetes who were being screened for microalbuminuria, 20 of whom developed UTI during the study. AER did not differ significantly between patients with and without bacteriuria (10.4 vs 9.4 $\mu\text{g}/\text{min}$, $P>0.05$). Further, successful eradication of the infection did not alter AER ($P=0.463$). Only one patient, with a symptomatic, pyuric UTI, had an elevated AER (43 $\mu\text{g}/\text{min}$), which normalized following antimicrobial therapy. The authors conclude that, unless patients are symptomatic, examination of the urine for infection is probably unwarranted when testing for microalbuminuria.

Clausen *et al.* [40] screened 3645 asymptomatic adults for urinary abnormalities (leucocyte esterase, nitrite, haemoglobin and glucose) using Nephur-Test+Leuco Urinalysis Strip (Boehringer-Mannheim, Germany). Positive dipstick analysis for one of these four parameters was observed in 19% of subjects, predominantly due to a positive test for leucocyte esterase. These subjects had a significantly ($P<0.001$) increased urinary AER (4.9 mg/24 h) compared with subjects who tested negative (3.0 mg/24 h). However, excretion rates were still markedly lower than levels considered to be consistent with microalbuminuria (20 – 200 mg/24 h). No sub-analysis was provided limiting this analysis only to those subjects with positive leucocyte esterase or nitrite tests. Further, positive tests were associated with, among other characteristics, a history of diabetes, renal or urological disease, raising the possibility that the association may reflect confounding. A further study of asymptomatic bacteriuria in 15 non-diabetic pregnant women failed to observe any cases of significant albuminuria using a sensitive immunoassay [41]. Only one study provides evidence to support a relationship between asymptomatic UTI and albuminuria and even here causality was not demonstrated. Pedersen and Milman [24] studied 524 overnight urine samples from 389 out-patients without diabetes, hypertension or known renal disease. Bacteriuric samples ($n=36$) had a significantly higher urinary AER than sterile urines (12.1 vs 8.7 $\mu\text{g}/\text{min}$, $P<0.01$).

There is no evidence to confirm that asymptomatic UTI causes proteinuria or microalbuminuria. Although some studies reported an association between asymptomatic UTI and proteinuria, there was no evidence to suggest a causal link. It is possible that individuals with asymptomatic UTI and proteinuria may have pre-existing complications such as diabetes or nephropathy that are independently associated with an increased risk for these common clinical events.

ii. Does symptomatic UTI cause proteinuria/albuminuria?

Proteinuria is a common finding amongst patients with symptomatic UTI, although it has poor specificity for UTI.

Sultana *et al.* [42] subjected urine from 400 consecutive patients presenting with typical features of UTI to protein-reagent-strip testing (Ames Multiple Reagent Strip, Bayer Diagnostics); 87 of these patients subsequently had culture-confirmed ($\geq 10^4$ CFU/ml), predominantly *E.Coli* UTI. The sensitivity and specificity of protein reagent strip testing (>0.15 g/l) for detecting UTI were 71 and 53%, respectively. Another study examined 60 female patients in the emergency department with a triage diagnosis of UTI, 24 of whom subsequently had culture-proven, predominantly *E.Coli* UTI. A positive (≥ 0.3 g/l) urinalysis test (Nepheur-Test+Leuco Urinalysis Strip) had sensitivity and specificity for UTI of 83 and 50%, respectively (positive predictive value 53%, negative predictive value 82%) [43]. Sandberg *et al.* [41] reported significant albuminuria (measured by immunoassay) in 8 of 15 non-pregnant women with cystitis. Amongst 100 consecutive hospitalized patients with culture-confirmed UTI, a reagent-strip (Multistix 10SG, Bayer Diagnostics) result \geq trace for protein showed a sensitivity for UTI of 63% [44]. In contrast, Van Nostrand *et al.* [45] used a stepwise binary logistic regression analysis to test the ability of various urinalyses (Chemstrip, Boehringer Mannheim) to predict infection amongst 225 urine samples, 33 of which were culture positive. Proteinuria did not have a statistically significant independent relationship with presence of UTI (odds ratio 1.29, $P = 0.504$).

There is also reported evidence that treatment of symptomatic UTI reduces protein excretion [46,47]. A double-blind placebo-controlled multi-centre study examining the effects of prophylactic oral immunotherapy amongst 166 patients with recurrent UTIs examined proteinuria (albuminuria measured by a reagent strip and recorded as negative, trace or positive) alongside several other clinical outcome measures. Treatment with the immunotherapeutic extract reduced recurrence rate and also significantly reduced the prevalence of proteinuria [46]. Pedersen and Milman [24] followed 48 patients with UTI but with no other significant disease after antibiotic treatment. In the patients in whom treatment successfully eradicated infection ($n = 44$), AER fell from 11.5 to 5.9 $\mu\text{g}/\text{min}$ ($P < 0.00001$).

Two canine studies are informative. Bagley *et al.* [48] experimentally induced *E.Coli* cystitis in five dogs and noted a significant ($P < 0.05$) increase in the urinary protein/creatinine ratio at 72 and 96 h post-inoculation. Normal renal histopathology was confirmed in all dogs at the end of the study. The authors concluded that inflammatory disorders, including infection, of the lower urogenital system may significantly alter the protein/creatinine ratio due to post-renal, and not renal, proteinuria. A recent study [49] observed that animals with pyuria and bacteriuria were more likely ($P < 0.05$) to have increased urinary albumin (measured by immunoassay), but not total protein (measured using benzethonium chloride), concentrations. However, the majority of pyuric samples were not albuminuric or proteinuric and there was no correlation between the degree of pyuria and magnitude of increase in urinary albumin concentration or urinary protein/creatinine ratio. The authors warn against attributing the presence of albuminuria/proteinuria to pyuria as opposed to significant glomerular disease.

Many studies have assessed the impact of upper UTI (pyelonephritis) on proteinuria/albuminuria and the excretion of other specific proteins. A study of

predominantly Caucasian female adults with reflux nephropathy ($n = 294$) observed proteinuria, detected by reagent strip, at presentation in only 4.8%: most (80.3%) patients had presented with a complicating UTI. After 17 years of follow-up, proteinuria was found present in 31% of the cohort, being more frequent in those with severe bilateral reflux nephropathy [47]. Therefore, proteinuria was not commonly induced by the initial precipitating UTI, but developed over time presumably as a result of renal pathology including focal and segmental glomerulosclerosis with hyalinosis [50].

Linne *et al.* [51] measured urinary albumin (by immunoassay) and the tubular-derived enzyme *N*-acetyl- β -D-glucosaminidase (NAG) in 39 children (aged from 2 weeks to 9.4 years) with acute pyelonephritis presenting for the first time with UTI. Excretion of both albumin and NAG was increased by pyelonephritis and was also higher than that observed in control patients with non-renal fever. Treatment with antibiotics rapidly normalized protein excretion. Chiou *et al.* [52] measured urinary albumin and β 2-microglobulin (B2M) by immunoassay in 61 paediatric patients with febrile UTI and noted increased urinary albumin, but not B2M, excretion compared with a control group with febrile illness of non-renal origin.

Several studies have attempted to distinguish between upper and lower UTIs in children and younger adults on the basis of tubular proteinuria; in particular urinary B2M excretion. Schardijn *et al.* [53] and Mengoli *et al.* [54] reported elevated concentrations of urinary B2M in patients with pyelonephritis, but reported normal B2M excretion in patients with cystitis or control patients [53] or in patients with asymptomatic bacteriuria [54]. Mengoli *et al.* [54] report similar patterns for the tubular markers NAG, lysozyme and lactate dehydrogenase isoenzyme V and Everaert *et al.* [55] found α 1-microglobulin (A1M) useful in distinguishing between pyelonephritis and cystitis in children. Sandberg *et al.* [41] further report the presence of increased excretion of albumin, A1M and retinol-binding protein, in addition to B2M and NAG, in patients with acute pyelonephritis, but found normal concentrations in patients with acute cystitis or asymptomatic bacteriuria. In this study, low-molecular-weight proteinuria was similarly a feature of fever of non-renal origin demonstrating that tubular proteinuria may also occur as part of the systemic response to fever, a point reinforced by Jantusch *et al.* [56]. It should be noted that the clinical distinction between 'upper' UTI ('acute pyelonephritis') and 'lower' UTI ('cystitis') is inherently unreliable when compared with the results of localization studies with ureteric catheterization; the systemic symptoms (fever, loin pain) and the associated tubular proteinuria associated with 'upper' UTI can occur when infection is confined to the bladder with sterile ureteric urine [57].

These observations are in broad agreement with studies which have used a sodium dodecyl sulphate gradient polyacrylamide gel electrophoresis (SDS-PAGE) analysis approach to distinguish the patterns of proteinuria in different renal diseases [58,59]. Generally, upper UTI has been associated with the presence of a tubular protein pattern, sometimes also including albumin, whereas this pattern is not seen in cystitis. These studies are described in further detail in the following text.

There is evidence that symptomatic UTI is commonly associated with proteinuria and albuminuria and that

proteinuria can be ameliorated following anti-bacterial treatment. A tubular pattern of proteinuria can discriminate between upper (pyelonephritis) and lower (cystitis) UTI, although increased excretion of tubular proteins may also be observed in non-renal febrile disease.

iii. What is the nature of proteinuria in patients with UTI?

Most studies addressing the issue of proteinuria and UTI have used non-specific reagent-strip testing methods or measured urinary albumin by immunoassay. However, a few studies have addressed the nature of proteinuria using either SDS-PAGE approaches or a range of specific immunoassays.

Brocklebank *et al.* [59] studied 32 children with recurrent UTI. Those with uncomplicated infections with normal urinary tracts demonstrated albumin (i.e. physiological proteinuria) only on SDS-PAGE. Conversely, patients with ureteric reflux, with or without renal scarring, demonstrated a mixed tubular/glomerular pattern of proteinuria. SDS-PAGE of urine from 50 patients with cystitis also demonstrated the presence of physiological traces of albumin only in the majority of cases. In six cases, other higher-molecular-weight proteins were also present, generally in association with haematuria suggesting a plasma origin [58]. In contrast, patients with acute pyelonephritis demonstrated tubular proteinuria and, particularly in cases of vesicoureteric reflux, albuminuria [58].

A series of studies using specific quantitative immunoassays have demonstrated tubular proteinuria patterns in patients with pyelonephritis [41,53–55]; these have been described in earlier passages in the article.

*There is relatively little research examining the nature of proteinuria in patients with cystitis, although the data of Pedersen and Milman [24] and Sandberg *et al.* [41] suggest that albuminuria may be present, but is not a consistent feature. Upper UTI is characterized by a tubular proteinuria pattern with albumin occasionally being seen.*

iv. Have studies linking UTI and proteinuria taken technical interference including urinary pH into consideration?

In addition to true positive tests, positive results for proteinuria as detected by reagent-strip urinalysis in individuals with symptomatic and asymptomatic UTI may be caused by urinary alkalization (pH>8.0) due to the breakdown of urea by bacteria [60] and possibly by the reaction of the protein test pad with leucocytes, bacterial proteins and sloughed cells from the lower urinary tract. Urinary alkalization is a commonly described cause of false-positive results for urine total protein using reagent-strip technology, although it should be noted that a Medical Devices Agency evaluation found many manufacturer's protein test pads to be relatively robust in the face of pH-adjusted urine [61]. Of the studies reviewed here, only that of Durakovic and Mimica [62] systematically excluded this as a cause of false-positive data. However, the studies of Pedersen and Milman [24] and Sandberg *et al.* [41], both of which report albuminuria in patients with lower UTI, used immunoassay technology unlikely to be influenced by urinary pH.

It is also possible that urinary infection could negatively influence urinary albumin concentration through *in vitro* effects, e.g. hydrolysis of albumin by bacterial proteases causing a false-negative test. An extensive study of this possibility found no effect of infection on measured urine albumin concentration [63].

UTI is often accompanied by haematuria. It is therefore possible that the presence of blood in urine could determine the association between UTI and proteinuria. This is unlikely to be an issue with studies that have relied on reagent-strip devices. The protein reagent pads themselves are relatively unreactive towards haemoglobin and even urines demonstrating '3+' haematuria will contain negligible amounts of plasma protein compared with the amount in normal urine [64]. However, the addition of haemolysate to urines at concentrations which cannot be detected visually has been shown to cause significant positive bias in some laboratory methods for total protein measurement, in particular pyrogallol red and benzethonium chloride, but not benzalkonium chloride, assays [65]. Gross haematuria could also conceivably contribute sufficient plasma albumin to increase measured urinary albumin concentration, and menstrual contamination in particular is cited as a potential confounder [21], although we have been unable to source basic laboratory research defining this effect.

The evidence supporting an association between symptomatic UTI and proteinuria is unlikely to be artefactual.

Conclusions

With the rapid increase in incidence and awareness of renal disease, accurate screening for proteinuria in high-risk groups is now considered a valuable diagnostic and prognostic tool [19,66,67]. Although UTI is often associated with proteinuria, the relationship between proteinuria and UTI remains incompletely defined.

Despite the practice of excluding UTI in patients found to have proteinuria being universally recommended in management guidelines, we have found no evidence of an association between asymptomatic UTI and proteinuria. Further, among patients with diabetes there is evidence, based on sensitive and specific immunoassay technology, that asymptomatic bacteriuria does not cause albuminuria. Over-emphasis of the importance of exclusion of UTI in this situation may reduce the reliability of establishing the diagnosis of proteinuria by introducing several additional steps in the diagnostic pathway: obtaining a fresh sample, submitting a request to the laboratory, laboratory analysis, receiving and acting on the laboratory report (remembering that in this instance both positive and negative reports should prompt action — which is rarely the default action with other laboratory tests), treating and confirming eradication of the infection when indicated, obtaining a further sample from the patient and re-analysing for protein content. Thus, delays in such investigations may have a negative effect on the early detection of proteinuria in non-diabetic patients as well as in the higher-risk group of diabetic patients with possible deleterious consequences.

We conclude that it is unnecessary to screen asymptomatic patients with demonstrable proteinuria or albuminuria for UTI.

Proteinuria is a common observation in symptomatic UTI, although the nature of the proteinuria is poorly defined. Further, we were unable to find evidence of a threshold beyond which proteinuria could be definitively attributed to intrinsic renal disease as distinct from a superimposed UTI. It is a widely held view that positive reagent-strip tests may occur as a consequence of the reaction of the protein test pad with leucocytes and bacterial proteins present in the bladder of individuals harbouring infections, with sloughed bladder cells or as a result of pH changes (alkalinization) in the urine, rather than due to intrinsic renal leakage (glomerular or tubular) of proteins. We were unable to find reports confirming the non-renal nature of the proteins reacting with the test pads. This area warrants further research, in particular using specific immunoassay methods which are not susceptible to the problems of reagent-strip tests. In the interim, it is prudent to treat and eradicate symptomatic UTI prior to investigating protein excretion. Tubular proteinuria is a well-characterized feature of febrile UTI.

In conclusion, there is no indication that asymptomatic UTI causes proteinuria or microalbuminuria and guidelines should reflect this until data convincingly prove otherwise.

Conflict of interest statement. None declared.

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