

**Rationalising the use of investigation for urinary tract infections: Analysis of 700 patients and proposal for a diagnostic algorithm.**

Ibifuro I Dokubo<sup>1</sup>, Felicity Reeves<sup>1</sup>, Sophia Cashman<sup>1</sup> & Vincent J Gnanapragasam<sup>1,2,3</sup>

**Keywords:** Cystoscopy, recurrent urinary tract infection, cytology, imaging, males, females

<sup>1</sup> Department of Urology, Cambridge University Hospitals Trust, UK

<sup>2</sup> Division of Urology, Department of Surgery, University of Cambridge, UK

<sup>3</sup> Cambridge Urology Translational Research and Clinical Trials Office, Cambridge Biomedical Campus, Cambridge, UK

**Abbreviations:** rUTI- recurrent urinary tract infection, UTI – urinary tract infection, RCC – renal cell carcinoma AML – angiomyolipoma. EAU – European Association of Urology, NICE – National Institute for Health and Care Excellence. PUJ – pelviureteric junction.

**Corresponding author:** Vincent J Gnanapragasam, [vjg29@cam.ac.uk](mailto:vjg29@cam.ac.uk), Cambridge Urology Translational Research and Clinical Trials Office, Cambridge Biomedical Campus, CB2 0QQ, Cambridge, UK.

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## **Abstract**

**Aims:** To evaluate the diagnostic yield of investigations performed on patients with a history of urinary tract infections (UTI).

**Methods:** A retrospective review was conducted on patients who underwent cystoscopy and imaging for a history of UTI between 2014-2019 in a single UK teaching hospital. Data was collected on demographics, cystoscopy and radiological findings requiring further management. The cohort was stratified by age, gender, and a confirmed history of recurrent UTI (rUTI). The subsequent algorithm was re-tested in a second cohort to validate its use.

### **Results:**

700 patients were included in the primary analysis, 427 female and 273 males. 331 meet the criteria of rUTI. The median age was 64y(18-97). Imaging abnormalities were equally frequent in males 6.3%(15/241) and females 8%(30/380) and the majority noted in patients aged  $\geq 55$ y, 30/45(66.7%). Amongst those who did not meet the definition of rUTI, abnormal imaging was identified in 5-7% regardless of age group and gender. Cystoscopy abnormalities (n=24) were twice more likely in males, 5.5%(15/273) than females, 2%(9/427). 88%(21/24) were identified in patients  $\geq 55$ y. There were no positive findings in women  $< 55$ y. Applying baseline imaging but confining cystoscopy to those aged  $\geq 55$ y and men with a confirmed history of rUTI would have saved 44% of procedures, missed no abnormalities with an overall diagnosis detection rate of 9.8%(69/700). This algorithm was validated in a separate cohort of 63 patients; applying it would have saved 46%(29/63) of cystoscopies with a positive diagnostic rate of 9.5% and no missed findings.

**Conclusion:** To our knowledge this is one of the largest studies reporting the outcomes of investigations for UTI and rUTI. Our result suggests that imaging is a useful baseline assessment, but cystoscopy should be limited to specific subgroups. We propose and validate a simple decision algorithm to manage investigations for referrals for UTI in secondary care.

**What is known?**

A review of guidelines on urinary tract infections reveals no clear consensus on stratification and investigation of patients referred to secondary care. The few studies out there were carried out on women referred on account of recurrent urinary tract infections and none on men.

**What is new?**

This is the largest studies reporting the outcome of investigations for UTI and rUTI in both males and females. We have formulated and validated an simple algorithm to help stratify patients who should have investigations for UTI.

## Introduction

Urinary tract infections are one of the most frequent reasons for referral to urological clinics. Around 10-20% of women will experience a symptomatic UTI during their lifetime [1]. Consultations for UTIs represent between 1% and 6% of all medical visits (~7 million visits and ~US\$1.6 billion annually) and are associated with a significant burden of morbidity and mortality in the elderly, among whom UTIs are most prevalent [2][3]. Men too are often referred with UK data suggesting an incidence of 2.81–3.04 per 1000 life years in those aged 65–74 years [4].

A review of guidelines on UTI reveals no clear consensus on stratification and investigation of patients referred to secondary care. What data there is often confined to those who are classed having recurrent urinary tract infection (rUTI) and for women. rUTI in adults is defined as two or more urinary tract infection (UTIs) in the last 6 months or three or more UTIs within a 12-month period [5],[2]. According to the European Association of Urology (EAU) guidelines, extensive routine workup including cystoscopy and imaging is not routinely recommended because the diagnostic yield is low [2]. The American Urological Association states that only women with complicating factors, like multidrug resistant bacteria need further investigation with both flexible cystoscopy and imaging [6]. In the United Kingdom however neither the National Institute for Health and Care Excellence (NICE) nor Scottish Intercollegiate Guidelines Network (SIGN) have guidelines on investigations to be carried out in women for men who present with UTI [1] [7].

Given the lack of guideline consensus, we tested the diagnostic yield of investigations carried out in patients referred to our centre with a history of UTI. Our goal was to assess the diagnostic utility of tertiary investigations, particularly imaging and cystoscopy in these patients to help rationalise and target investigations. We were also interested in the value of investigations in those referred but who did not meet the strictly defined criteria for rUTI and also the outcome in men referred.

## Methods

A retrospective digital case notes review of the hospital's (EPIC®) system was conducted of all patients who underwent invasive investigations for a primary care referral of UTI between 2014-2019 in a single UK hospital. This represents the practice of 16 different consultants all of whom see generic patients.

The hospital's coding list was interrogated to acquire the list of patients who meet the inclusion criteria. A database was created to include the following parameters: demographics, referral history, urine culture, radiological imaging, cytology results and outcomes of flexible cystoscopy. Patients who had visible haematuria or indwelling catheter or another competing indication for cystoscopy were excluded. Those who also had only imaging and/or cytology were not included. Only objective cystoscopy findings that were considered to require further intervention (e.g. stone, fistula, foreign body in bladder, tumour) were recorded in this study. The cohort was also further stratified by age and gender and those who did and did not meet the definition of rUTI using the 2017 EAU guidelines for Urological Infections and NICE guidelines [NG112] i.e. defined as 2 or more documented UTIs in 6 months or 3 or more UTI in 12 months.

A second cohort was assembled and digital case notes reviewed following the first cohort analysis (2019-2020). The study was registered and approved by the hospital audit department (ID2242 PRN-8242 & ID3328).

## Results

### Patient demographics

A total of 700 patients were included in the primary analysis, 427 females and 273 males. Of these about half the cohort (331/700) meet the criteria of rUTI. The median age of patients in this study was 64 yrs (range 18-97). 621/700 cases had at least one form of imaging carried out and 521/700 had a urine cytology sent. Patient characteristics are summarized in Table 1.

### Outcome of investigations

In the 621 cases with imaging. 45/621 patients (7.2%) had anatomical abnormalities identified including 28 renal calculi, 1 bladder calculi, 2 ureterocoele, 1 PUJ obstruction, 3 Colo-vesical fistula, 9 renal masses and 1 Colo-vaginal fistula (Table 2). Of the renal masses identified on imaging, 2 were renal cell carcinoma (RCC) and 7 angiomyolipoma (AML). At cystoscopy 13/700 (1.8%) procedures identified benign abnormalities including 2 bladder stones, 1 foreign body and 10 urethral strictures (Table 2). A further 11/700 (1.6%) patients had bladder lesions with subsequent rigid cystoscopy and biopsy identifying 3 cancers (0.43% = 3/700). 521 patients (74.4%) also had urine cytology sent with malignant cells identified in only 3 cases (0.6%) (Table 2). All 3 were identified to have bladder tumours from cystoscopy and biopsy.

### Subgroup analysis by gender, age and referral criteria

*Imaging:* Overall, imaging abnormalities were equally frequent in males 6.3% (15/241) and females 8% (30/380) (Table 3 and Supplementary Figure S1). The majority were noted in patients aged  $\geq 55$  years with 30/45 (66.7%) imaging abnormalities found including 8/9 renal masses and both diagnosed renal cell carcinomas (Table 3). If imaging had been confined to only those who met the guideline criteria for rUTI, 20 findings would have been missed including 16 kidney stones, 2 renal masses (AML) and 2 ureterocoeles. In the rUTI subgroup, imaging abnormalities were also equally frequent in men (11.8%) and women (10.9%) (Table 4 and Supplementary Figure S1). Overall, amongst those who did not meet the guideline definition of rUTI, abnormal findings were identified in between 5-7% regardless of age group and gender (Table 5 and Supplementary Figure S1). These data suggest that if a minimum diagnostic yield of 5% was used as a threshold then imaging is a useful baseline test regardless of UTI definition, age or gender.

*Cystoscopy:* Overall, abnormalities were twice more likely in males compared to females 5.5% (15/273) vs 2% (9/427) respectively (Table 3 and Supplementary Figure S1). Of the 24 findings noted on cystoscopy, 21/24 (88%) were identified in patients  $\geq 55$  years while the remaining 3 abnormalities were urethral strictures in men  $< 55$ y. If cystoscopy had been confined to only those who met the guideline criteria for rUTI (n=331), 9 findings would have been missed including 6 urethral strictures, 1 bladder stone (not identified on imaging) and 2 bladder lesions (benign on biopsy). 8/9 of these were found in men (Table 4&5 and Supplementary Figure S1). There were no positive findings in women  $< 55$ y. These results suggest that cystoscopy may have a reasonable yield if confined to specific subgroups of patients.

#### Proposal and testing of a diagnostic algorithm

Based on the above we propose a simple diagnostic algorithm to help decide on investigations for women and men seen in urology clinics with a history of UTI (Figure 1). This mandates imaging for all patients with a history of UTI and cystoscopy would be confined to those with a history of rUTI and  $\geq 55$  years. Men with rUTI and  $< 55$ y also may benefit from cystoscopy especially if a urethral stricture is suspected. This pathway would eliminate cystoscopy need in 44% (311/700) of patients in our cohort without missing any significant abnormalities and giving an overall diagnostic detection rate of 9.8% (69/700) from imaging and cystoscopy. To test the utility of this algorithm we applied this to a new cohort of 63 patients (38 female and 25 males, mean age 67 years, range 23-90). Investigational findings are summarized in Supplementary Table T1. In this cohort 1 renal stone and 1 AML were detected by imaging and 3 cystoscopy abnormalities found (2 strictures and 1 bladder tumour). Applying the algorithm would have detected all these and saved 46% (29/63) of cystoscopies with an overall positive diagnostic rate of 6/63 (9.5%) from imaging and cystoscopy.

## Discussion

Referral from primary care for investigation of urinary tract infections (UTI) is an extremely common presentation to urology departments. There have been a number of publications on the value of investigations but primarily focused on recurrent urinary tract infections in women (rUTI) [8-15]. There is, however, little evidence for the management of patients who do not meet the criteria for rUTI or indeed in males. Although infrequent, abnormal findings on imaging and/or cystoscopy can have important bearings on how to tailor the next step in management for these referrals [16].

In this study we were interested to identify if invasive investigations could be completely eliminated from patients with UTI and whether diagnostic yields were clearly lower compared to strict rUTI presentation criteria. Our key findings are that imaging may be a useful baseline test for any patient referred with a history of UTI, but cystoscopy should be limited to specific subgroups. Namely patients aged  $\geq 55$ y and men who meet the criteria for rUTI regardless of age. These findings are based on an accepted positive yield of at least 5% from these investigations. We note that this threshold is similar from the reported investigation yields for non-visible haematuria [17][18]. Cytology should not be used in this population for assessment.

The rate of positive findings amongst women varies greatly from study to study [8-11], [13-15]. Imaging carried out in women with rUTI in 2 different studies showed a high detection rate of 13.5% in a study by Pagano *et al* but only 5.5% in a study by vanHaarst *et al* [9][14]. Santoni *et al* in a review found an overall diagnostic rate from cystoscopy of 2.8% in a review of 7 reported studies (compared to 2% in our series). However, findings by age group were not reported [12]. Certainly women  $<55$ y and without a clear rUTI history do not need investigation (with detection rates of 0-1% in our study). The rates of pick up from diagnostic investigations in men with urinary tract infections, to our knowledge, has rarely been reported. A prospective cohort study done nearly 20 years ago to review investigations carried out in men who presented with UTI revealed imaging abnormalities of 53% though

several men had more than one diagnosis [19]. The UK NICE guideline only refers to men who have had a UTI concurrent with lower urinary tract symptoms [20]. In these cases, cystoscopy is recommended though the yield from this guidance is unknown. In our study cystoscopy had a reasonable rate of identifying abnormalities (6.5-9.5%) in all men except those <55y who did not meet the guideline criteria for rUTI. Amongst younger men who did have rUTI the predominant abnormality was a urethral stricture. While this could arguably have been suspected at a clinic flow rate, it is reasonable to confirm this by flexible cystoscopy and hence a justified use of this investigation.

Our study represents one of the large cohorts in the literature for evaluation of UTI diagnostic yield and is unique in exploring this in both sexes, by age as well as by UTI type. It does however have the expected limitations of a retrospective single centre study. The cohort represents patients managed by several different consultants and there was no centralised proforma for investigations. Indeed, this was one of the reasons for the study and production of the diagnostic algorithm. 79 cases (11.3%) of the primary analysis group had no form of imaging performed. We did not have data on flow rate and post void results and cannot say if these may have detected the strictures found on cystoscopy or perhaps were triggers for cystoscopy themselves. We also cannot comment on patients seen in outpatients and discharged without any further investigations. Hence our cohort is biased towards the patients who did receive investigations. Despite these shortcomings, our data does suggest a pragmatic approach to investigations for UTI and rUTI which will reduce unneeded investigations while not missing pathology that can be corrected. We intend to further retest our model in a large prospective cohort to determine its veracity and applicability.

In conclusion, we present here a rational evidence-based approach to investigations of UTI and rUTI in the urology clinic. Our findings have been summarised in a simple diagnostic algorithm to rationalise the use of investigations but does need further validation in other cohorts. In the absence of clear national and international guidelines for UTI investigations we hope that this will help clinicians have a rational way to manage the patients and the potential for imaging to be used by GPs before referral to screen out those who do and do not have abnormalities.

## **DECLARATIONS**

### *Conflicting interests*

None declared.

### *Funding*

None declared.

### *Ethical approval*

Not applicable. We had the permission of the Audit department of Addenbrookes Hospital to carry out the research with registration number (ID2242 PRN-8242 & ID3328)

### *Guarantor*

Ibifuro I Dokubo

### *Contributorship*

IID was involved in data collection and analysis and drafted the manuscript. FR and SC reviewed and edited the manuscript. VJG conceived the study and edited the manuscript. All authors reviewed and approved the final version of the manuscript.

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None

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