Problems of basing patient recruitment for primary care studies on routine laboratory submissions

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J Clin Pathol 2007;60:1290–1293. doi: 10.1136/jcp.2007.046854

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Accepted 18 February 2007
Published Online First
2 March 2007

Background: Use of routine urine submission rates for estimation of patient enrolment in primary care studies of acute urinary symptoms may overestimate patient recruitment rate.

Aims: To compare the rates of submission of urines and significant bacteriuria from patients presenting with acute urinary symptoms in study general practices to routine microbiology laboratory urines.

Methods: Routine laboratory urine submissions were determined by counting all mid-stream urine specimens submitted to the laboratory from 12 large general practitioner (GP) practices served by Gloucester and Southmead microbiology departments over two years (2000–02). Urine specimens were requested from all patients with acute urinary symptoms referred at research nurse practice visits over the same time period. The annual study urine submission was calculated using the ratio of the number of nurse practice visits to the annual number of possible consulting sessions. Significant bacteriuria was defined as a urine growing a single organism reported as $>10^5$ colony forming units/ml. Rates per 1000 patients were calculated using practice population data.

Results: The urine submission rate from study patients with acute urinary symptoms was one-third the routine urine submission rate from the same practices. The significant bacteriuria rate attained from the study was less than half the routine significant bacteriuria rate.

Conclusion: Two-thirds of routine urine samples submitted by GPs are probably not for the investigation of acute urinary symptoms. Basing consultation sample size power calculations for primary care studies or sentinel practice-based surveillance in urinary tract infection on routine laboratory submissions is unreliable and will lead to significant overestimation of recruitment rate.

The use of microbiology laboratories by general practitioners (GPs) in England for the investigation of urinary symptoms and renal disease varies greatly.¹ Patients with more severe symptoms, recurrence and the elderly are more likely to have specimens submitted.² For the past five years the South West Antimicrobial Resistance Surveillance Group has been investigating sampling strategies in primary care. Patient enrolment from sentinel practices was slower in this study and others^{3–5} than expected from the sample size calculation based on routine laboratory data.

Antimicrobial resistance is a major public health concern, with a relentless rise in the hospital and community settings.^{6–10} Antimicrobial resistance surveillance systems are designed to inform disease management and guide empirical use of antimicrobials in patients presenting with suspected infections. Selection bias in antibiotic resistance surveillance causes distortion of the resistance rates detected due to the manner in which the patients (and thence isolates) are selected.^{11–13} In the primary care setting the distortion of resistance rates due to patient selection bias may be greater than in the hospital setting, as patients are often given empirical treatment and microbiology specimens are not routinely advised in uncomplicated infections.¹⁴

We wished to test the hypothesis that urine samples submitted to the routine diagnostic laboratory are not representative of urine samples that would be obtained if cultures had been provided from all patients presenting with acute urinary symptoms in general practice, and therefore, basing consultation sample size power calculations for primary care studies or surveillance on laboratory submissions is flawed.

METHODS

Ethics

This study was part of an ongoing investigation of antibiotic resistance surveillance in primary care and was approved by the Southmead and Gloucester Local Research Ethics Committees (062/99 and 99/51G respectively). Patients gave informed consent to be enrolled into the study.

Selection of the study practices

The study was undertaken in the general practices served by Gloucester and Southmead microbiology departments. We randomly selected practices with a patient population of over 7000. Practices were invited by telephone and then letter to participate. Twelve of the 18 general practices in Avon and Gloucestershire approached agreed to participate in the South West primary care antibiotic resistance surveillance study.³ Lack of time or space for the research nurse was the reason given for non-participation by practices.

We compared rates of urine specimen submissions and significant bacteriuria, from patients with acute dysuria syndrome presenting to the research nurse in the selected general practices in the South West surveillance study,³ to submission of all mid-stream urine (MSU) specimens to the two laboratories from the same practices over the same time period (26 months, 1 April 2000–31 July 2002).

Abbreviations: CFU, colony forming unit; GP, general practitioner; MSU, mid-stream urine; UTI, urinary tract infection

Table 1 Comparison of routine mid-stream urines submitted to the two laboratories, and urines submitted from patients with acute urinary symptoms from the same 11 practices over 26 months

Practice	*2004 index of multiple deprivation score (for LSOA)	Practice patient numbers			Number of specimens submitted		Number of specimens submitted/1000 pts/y		Significant bacteriuria/1000 pts/y		
		All	Patients >65 years	%	Routine laboratory urines	Study with acute urinary symptoms	Routine urines	Study with acute urinary symptoms	Routine urines	Study with acute urinary symptoms	Ratio routine/study rate
1B	8.80	8000	1851	23	2673	10	155	28	36	14.9	2.4
2B	37.47	13400	1544	12	2365	10	82	11	18	3	6.0
3G	16.09	10084	1527	15	1283	8	59	13	17	6.6	2.6
4G	15.36	12376	2150	17	1235	12	46	12	10	5.5	1.8
5G	65.18	7800	1338	17	1009	19	60	37	13	12.5	1.0
6B	18.17	10700	1177	11	2023	10	88	15	21	2.1	10.0
7G	5.01	7016	1619	23	1289	16	85	38	22	12.7	1.7
8B	21.10	10800	1092	10	1924	16	82	25	19	13.5	1.4
9G	12.43	8930	1833	21	649	9	34	16	7	8	0.9
10G	24.86	10121	1816	18	1461	13	67	10	18	5.2	3.5
11B	15.13	9000	1938	22	2230	10	115	19	34	10.2	3.3
Total		108227	17885	17.2	18141	133	79	20.4	19.5	8.6	2.3

*Deprivation score of lower super output area (LSOA). The lower the score the greater the deprivation. Minimum/maximum of all general practices in LSOAs sampled = 1.52/79.98.

Routine laboratory submission rate of urine specimens from general practices

This was determined by counting all urine specimens submitted to the two laboratories over the study period from patients ≥ 17 years of age, registered with the same 12 practices. Clinical details were not used to exclude any urine specimens. The submission rate (number of urines submitted per practice/1000 population served/year) was calculated using 2001 population data for each practice obtained from the primary care trusts. Urines were referred to the local microbiology laboratory (Southmead or Gloucester) on the routine transport system which visits practices each weekday. Specimens were cultured every day in the laboratory.

Rate of acute episodes of suspected urinary tract infection seen in study practices

On the days the research nurse visited, clinicians were asked to refer to her all patients aged ≥ 17 years with any signs and symptoms of a urinary infection of less than 10 days duration. Referral slips, which were readily accessible on each clinician's desk, were used to refer patients to the nurse immediately after their consultation with a clinician, during which normal care occurred. The nurse reminded the clinicians about the study at the beginning of each surgery. Patients gave oral consent, were asked to provide an MSU and were asked to complete a short questionnaire. The questionnaire confirmed that their urinary symptoms were indicative of urinary tract infection (UTI), and asked about urine infections in the past 12 months, current and past antibiotic usage and other significant health problems. The research urines were cultured at Southmead microbiology laboratory on the day of collection.

As there was only one research nurse, practices were only visited on a limited number of days (range 26–33 days per practice). Where possible, visits were systematically organised by the statistician so that the nurse visited each practice a similar number of times on each weekday. The number of patient episodes of acute urinary symptoms per year was calculated from the ratio of visits to possible days of practice consulting per year (247).

Significant bacteriuria

Urines were cultured according to national standard operating procedures.¹⁵ Significant bacteriuria was defined as a urine growing a single organism reported as $>10^5$ colony forming

units (CFU)/ml. The number of specimens with significant bacteriuria was obtained from the surveillance study database and the two routine laboratory databases for the 12 practices over the same study period.

Data analysis

Urine specimen submission rates and significant bacteriuria rates per thousand population were determined using the general practice primary care trust 2001 population data. We then calculated the ratio of significant bacteriuria in routine urine specimens to study practice urine specimens.

We used linear correlation to determine if there was any association between the number of patients over 65 years of age in the practice and specimen submission or bacteriuria rate for routine and study specimens.

RESULTS

One study practice in Avon failed to recruit any patients with acute urinary symptoms, and was therefore removed from the analysis. The total patient population was 108 227.

The list size of the 11 practices ranged from 7016 to 13 400. Age/sex make-up of the 11 practices was similar to the whole population served by the two laboratories and was a mixture of urban and rural practices and range of deprivation (table 1).

Routine urine submissions

Over the 26 month period, the 11 practices submitted 117 649 urine specimens to the two laboratories, of which 85.5% were MSUs (table 1). Significant bacteriuria ($\geq 10^5$ CFU/ml) was present in 24.2% of MSUs. The rate of routine MSU submissions from the 11 practices to the two laboratories varied fivefold from 34 to 155/1000 patients per year (table 1). The submission rate for the Gloucester practices (mean 52.2, SD 13.1, median 59.0) was lower than that of the Bristol practices (mean 104.4, SD 31.4, median 88.0; $p = 0.013$). Cases of significant bacteriuria in these routine MSUs varied fivefold from 7 to 36 cases/1000 patients per year (table 1).

Urine specimens from patients with acute urinary symptoms

Over the 26 month study period, 133 patients with acute urinary symptoms were referred to the research nurse. All patients consented to provide a urine sample and each study

practice referred between 8 and 19 patients. This equated to an annual submission rate of urine specimens from patients with acute urinary symptoms of between 10 and 38 specimens/1000 patient population (table 1). Significant bacteriuria was found in 43% (57/133) of the patients with acute urinary symptoms. This equated to a significant bacteriuria rate of between 2.1 and 14.9/1000 patients per year.

Comparison of study practice and routine urine submission and bacteriuria rates

Urine submission rate from the study practices was approximately one-third of the routine laboratory urine submission rates (table 1). The significant bacteriuria rate from the study practices was less than half the significant bacteriuria found in routine laboratory urine submissions. It ranged from tenfold lower in practice 6B to equivalent in practice 9G compared to significant bacteriuria rate from the routine laboratory (table 1).

There was no association between the proportion of patients over 65 years in a practice, and practice routine urine submission and bacteriuria rates or study urine submission and bacteriuria rates (r^2 values for the proportion of elderly to routine urine submissions 0.072 ($p = 0.54$); routine urine bacteriuria 0.112 ($p = 0.45$); study urine submission 0.135 ($p = 0.42$); study urine bacteriuria 0.229 ($p = 0.33$)).

DISCUSSION

Summary of main results

We found that the overall study urine submission rate from patients with acute urinary symptoms presenting to a research nurse in the 11 general practices was one-third the routine urine submission rate from the same practices. The significant bacteriuria rate attained from the study was less than half the routine urine rate. The difference varied by practice and the study rate in one practice was ten times less than the routine rate. Increased submission was not necessarily related to a larger elderly patient population.

Interpretation of results

The rate of urine specimen submission to the routine diagnostic laboratory is not representative of study urine specimen submission rates from patients with acute urinary symptoms in general practice. This may be due to under-referral of patients to the research nurse or, alternatively, many of the urine specimens sent routinely to the laboratory are not for the investigation of acute urinary symptoms. Although most urine specimen request forms state "query UTI" in the clinical details, it seems possible that they are submitted to exclude UTI rather than to confirm it. Doctors may send in urine specimens for reasons other than suspected infection (eg, suspected haematuria, investigation of incontinence or other urinary symptoms) or to rule out infection in patients with diagnostic difficulties (eg, non-specific abdominal pain, or confusion in the elderly). Alternatively, some routine urines may be submitted without a surgery-based consultation, directly from nursing homes, following a telephone consultation or following a home visit or out-of-hours consultation.

Strengths

The strength of this study is that it was carried out as part of a well-funded antibiotic surveillance study in a range of urban and rural practices in two geographical areas. Therefore, the results are likely to be generalisable to other UK primary care studies and sentinel general practice surveillance systems. Our routine laboratory submission and bacteriuria rate/1000 was similar to that found in a South West England study.¹

Weaknesses

We cannot rule out under-referral of patients to the research nurse, although an audit of medical records of consultations on days on which the research nurse was in attendance in one practice (7G) did not reveal a high level of under-referral. We consider that any under-referral to the research nurse would be similar in other general practices involved in studies or sentinel surveillance. If we had more practice visits we may have been able to increase patient recruitment to the study; however, we had expected patient referral to be much greater, and therefore we only had one research nurse visiting the practices. Staffing will be a barrier to recruitment in any study or sentinel surveillance system run by visiting clinicians. As the number of patients recruited in the study practices was so low we were unable to compare antibiotic resistance rates in the two groups. As the specimen pots did not contain any borate, some overgrowth of bacteria may have occurred during transport of the routine urines. However we do not think this would have influenced our results, as there was daily specimen transport to the laboratory during surgery opening hours, and therefore there would have been minimal delays.

Other work in this area

In a spotter practice model, Richards asked clinicians from three general practices to submit MSUs from all patients presenting with symptoms suggestive of UTI.¹⁶ This spotter practice system did not involve research nurses and collected over 2000 urine specimens in a year, which is ten times the number in our study. The percentage of patients with significant bacteriuria rate was low (26%), suggesting that many of their patients did not have acute dysuria syndrome.^{5 14} In contrast, 1991 General Practice Morbidity Statistics found that the consultation rate with a doctor for cystitis was 147/10,000,¹⁷ which is lower than our mean urine study submission rate.

A laboratory survey of bacterial susceptibility in urinary tract pathogens showed that the prevalence of trimethoprim resistance in urinary pathogens isolated from primary care specimens doubled when general practices were asked to use urine dipsticks to guide management and to culture urines only in complicated UTI.¹⁸ A study investigating clinical outcomes in acute uncomplicated UTI in primary care found that the trimethoprim resistance rate was half that found in routine laboratory data collected over the same time period.⁵ These studies support the hypothesis that routine laboratory urine samples are not representative of urines from primary care patients with uncomplicated UTI.

Implications

Further research is needed to understand the reasons why GPs submit urinary samples to microbiology laboratories. Basing consultation sample size power calculations for primary care based studies in UTI or surveillance on routine laboratory submissions is unreliable and will lead to great overestimation of recruitment rate. It may be more accurate to base recruitment on general practice morbidity statistics,¹⁷ or searches based on Reid codes within the local general practices involved.

An alternative approach in antibiotic resistance surveillance is the development of programmes based on the potential pathogens carried within a population, similar to those used successfully for zoonotic organisms in farmed animals and patients in secondary care facilities.¹⁹ Most community-acquired UTIs arise from the perineal flora; antibiotic resistance surveillance of perineal carriage in a representative asymptomatic community population may therefore be more feasible. Bruinsma *et al* attained a 25% response rate to a postal request

Take-home messages

- Urine submission rate from patients with acute urinary symptoms presenting to a research nurse in study general practices was one-third the routine urine submission rate from the same practices.
- Urine specimens submitted to the routine diagnostic laboratory are not representative of urine specimens that would be obtained if cultures had been provided from patients presenting with acute urinary symptoms in general practice.
- Basing consultation sample size power calculations for primary care based studies or surveillance in urinary tract infections on routine laboratory submissions is unreliable and will lead to great overestimation of recruitment rate.
- To obtain a sufficient sample size, an alternative recruitment approach may be needed in surveillance systems in primary care.

for a stool specimen from a randomly selected Dutch population.²⁰ The South West Antibiotic Surveillance Group is now exploring the feasibility and validity of postal surveillance methods, using first pass urine specimens.³

ACKNOWLEDGEMENTS

We would like to thank all the general practices that took part in this study; the laboratory staff, and Walter Palmer in microbiology at Gloucestershire Royal Hospital; Rosy Reynolds for statistical support for the paper; and Becky Carron and Emma Henderson for enrolling patients.

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Funding: This study was funded by the NHS South and West Research and Development Directorate.

Competing interests: None. (All authors work in the field of antibiotic resistance and could be considered to have vested interests in investment in this area, whether by governments, charities or industry.)

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