NEW
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URINARY TRACT INFECTION

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SERIES EDITOR'S FOREWORD

Urinary tract infection remains one of the most common reasons for an individual seeking medical advice. Although the associated morbidity varies widely in adults, such infections are less common but may constitute severe, life-threatening illness in children and in the elderly. Diagnostic tests and treatment have been rationalized in recent years but many practising doctors still have difficulty in appreciating the patho-physiological principles involved.

Particular difficulty is often experienced when treating patients with recurrent urinary tract infections, covert bacteriuria, vesico-ureteric reflux, elderly patients and those with indwelling catheters. These topics are fully discussed in this volume. Each chapter has been written by a recognized expert and practical aspects of patient management have been emphasized. The information presented in this volume should prove of interest not only to nephrologists but to all practising clinicians.

ABOUT THE EDITOR

Professor Graeme R. D. Catto is Professor in Medicine and Therapeutics at the University of Aberdeen and Honorary Consultant Physician/Nephrologist to the Grampian Health Board. His current interest in transplant immunology was stimulated as a Harkness Fellow at Harvard Medical School and the Peter Bent Brighton Hospital, Boston, USA. He is a member of many medical societies including the Association of Physicians of Great Britain and Ireland, the Renal Association and the Transplantation Society. He has published widely on transplant and reproductive immunology, calcium metabolism and general nephrology.

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RECURRENT URINARY TRACT INFECTIONS INCLUDING COVERT BACTERIURIA

R. MASKELL

INTRODUCTION

During the past thirty years there have been many important changes in the diagnosis and management of urinary tract infection (UTI), and research undertaken during this period has led to a better understanding of the significance of bacteriuria. The great upsurge of interest in the subject in the sixties and seventies, in response to the work of Kass, has been followed by the workload and financial pressures of the eighties. Decisions must constantly be made, by clinicians and by laboratories, about the appropriate use of resources in the diagnosis and management of UTI. It is useful, therefore, to survey the current state of knowledge in the field and to endeavour to lay down some guidelines for laboratory and clinical work. Aspects which will be considered in this review will include a concept of UTI which takes account of infection anywhere in the urinary tract or its adjacent structures rather than, as has been customary, confining attention to the kidneys and bladder only; the changes in laboratory methods and diagnosis which have resulted from this concept; the clinical significance of UTI, the management of symptoms, and ways in which the small minority of bacteriuric patients who are at risk from serious consequences may be identified; antibacterial agents and management protocols and, finally, the problem of covert bacteriuria.

INFECTIONS OF THE URINARY TRACT AND ADJACENT STRUCTURES

Significant bacteriuria

The concept of 'significant bacteriuria' originated from the work of Kass[1,2] who validated the midstream specimen (MSU) as a means of diagnosing bladder bacteriuria. This was soon acccepted as synonymous with urinary tract infection – a proposition which, almost from the outset, was shown to be unsatisfactory but which, largely for simplicity of clinical and laboratory diagnosis, has persisted. The definition of 'significant bacteriuria', as enunciated by Kass from culture of first early morning MSU specimens from symptom-free women, has been generally accepted as the presence of at least 100 000 organisms of a recognized aerobic urinary pathogen, usually in pure culture, per ml of a fresh carefully-collected MSU – the finding preferably confirmed in a repeat specimen. The limitations of this definition in the clinical context are obvious, but it is only in very recent years that attention has been paid to these limitations and efforts have been made to provide more accurate diagnosis.

The most obvious fallacies in the concept of 'significant bacteriuria' relate to bacterial count and bacterial species. A high count is dependent upon incubation of organisms in the bladder urine for a sufficient length of time; the possibility of lower counts, either due to the presence of bacteria in tissues such as the kidney or prostate, whence they may be shed into the urine in small numbers, or to the constant dilution of the bacterial count in the bladder that occurs in patients with severe frequency and thirst, is ignored. Secondly, it has been accepted too readily that only the aerobic organisms, which can survive in the relatively high oxygen tension of bladder urine and are easily detected by overnight aerobic culture, cause urinary tract infection.

The criterion of 'significant bacteriuria' with an aerobic pathogen provides no explanation for the symptoms of about one-half of the women and two-thirds of the men who present with urinary symptoms – the symptoms in these patients usually being clinically indistinguishable from those with 'significant bacteriuria'. It also leaves much pyuria unexplained. The validity of low counts of aerobic organisms was addressed many years ago, and there was evidence, both from suprapubic aspiration (SPA)[3] and catheterization[4], that

organisms were often present in the bladder urine in counts of fewer than 10^5/ml. The recent work of Stamm and his colleagues[5] has again drawn attention to this fact. However, even when low counts have been accepted as significant[6] and more attention paid to purity than to count (it is impossible for a urine specimen to be contaminated with a single bacterial species, the sites from which contamination may occur all having a mixed commensal flora), the symptoms of many patients and much pyuria have remained unexplained.

In recent years, progress has been made towards a better understanding of urinary symptoms by enlarging the concept of UTI to include the whole urinary tract, above and below the bladder, and its adjacent structures, and by considering the possibility that, in some sites and under some particular circumstances, organisms other than the recognized aerobic pathogens may be responsible for infection. It seems reasonable to suppose that microaerophilic organisms which cannot survive in the oxygen tension of bladder urine could multiply and cause infection in the prostate or paraurethral tissues of women, or in scarred bladder or kidney tissue. There is now a large body of evidence that such organisms can be isolated from the urine of patients with prostatitis, urethral syndrome, chronic pyelonephritic scarring, and chronic or 'interstitial' cystitis. This evidence was reviewed[7] in 1986 and more recent studies have confirmed the findings[8,9]. The changes in laboratory diagnostic methods necessitated by these new considerations of bacterial counts and urinary pathogens are discussed below.

Localization of infection within the urinary tract

One of the major clinical problems in the diagnosis and management of UTI is the difficulty of determining the site of infection within the urinary tract. With the exception of the classical symptoms and signs of acute pyelonephritis it is not possible to determine the site of infection by clinical means, and there has been disappointingly little progress in the development of laboratory tests for this purpose. Clinical diagnosis is bedevilled by the problem of referred pain – for example from the bladder or urethra to the loin – and by the important phenomenon of apparently asymptomatic infection. Culture of urine specimens

obtained by ureteric catheterization under general anaesthesia remains the only definitive way of proving kidney infection; for obvious reasons, this is not a procedure which is often undertaken. Laboratory tests, such as the detection of antibody-coated bacteria or P-fimbriated bacteria in the urine, have not proved definitive and are not in general use. Bladder infection can be confirmed by SPA, which is now often undertaken in babies but seldom in adults, and prostatic infection may be detected by collection of urine after prostatic massage. However, in general clinical practice, the diagnosis of UTI depends upon microscopy and culture of an MSU, and it is on the interpretation of the findings of this investigation that the majority of clinicians rely.

CHANGES IN LABORATORY DIAGNOSTIC METHODS

It is regrettable that the widespread acceptance of Kass' numerical criteria of significance led rapidly to a more rigid unthinking approach to urine microbiology than had been practised previously. In many laboratories the interpretation of urine cultures was delegated to laboratory scientific workers, often quite junior and usually without the clinical insight required for such interpretation. Few had actually read Kass' papers or were aware of the limitations of the numerical criterion which Kass himself acknowledged. The possibility of infection of tissues below the bladder, and the likelihood of lower bacterial counts from infections in that situation, were ignored. The fact that bacteriuria can be significant in the absence of pyuria was used, in some laboratories, as a reason for dispensing with urine microscopy as a routine procedure; the obvious fact that pyuria may be very important in the apparent absence of bacteriuria was forgotten. During the years that these new practices were developing – years of the great increase in laboratory workload and the consequent financial pressures – evidence of the significance of low bacterial counts, of apparently 'sterile' pyuria, and of the pathogenicity of organisms other than aerobes in parts of the urinary tract and its adjacent structures was accumulating. As clinicians begin to accept this new evidence and to require more extensive and accurate work from laboratories, the latter are faced with the difficulty of reversing the trend away from interpretation by rules of thumb and moving towards protocols which require greater

medical input and consideration of the findings in each urine specimen on its merits. Factors which must now be taken into account include the age and sex of the patient, the type of specimen (for example MSU or indwelling catheter specimen), pyuria, bacterial count and purity of growth, and relevant clinical factors including antibacterial treatment. This approach has two major advantages – it is more likely to provide the correct result for each individual patient and thus to prompt appropriate clinical management, and it results in wiser use of antibacterial agents, with all the advantages to individual patients and the community in general which are consequent on this. Both these considerations will be discussed later.

Adopting this new approach, however, is not easy at a time when financial and workload pressures are increasing and the advent of serious new infections threatens to take up an ever greater proportion of laboratory resources. To those who question the justification for giving the time, thought and some additional resources to undertaking accurate and useful laboratory work in the field of UTI, it is salutary to pose two other questions. Is the money spent on examining large numbers of urine specimens using rules of thumb for interpretation, and providing results which may be inaccurate, unhelpful, often irrelevant and sometimes harmful, wasted? In view of the very large number of patients who suffer from urinary symptoms, is it not wiser to spend a little extra on accurate laboratory diagnosis than to incur the considerable expense of repeated antibacterial treatment and investigations which are often unnecessary and sometimes harmful?

Laboratory procedures

Without entering into too many technicalities, the major changes in laboratory procedures which enlarge the diagnostic potential of urine microscopy and culture are:

1. Incubation of cultures in an atmosphere containing 7–10% CO_2. This technique is now widely used for incubation of cultures from other diagnostic specimens, such as swabs and blood cultures; it is equally necessary for urine cultures.
2. Incubation for 48 h of cultures from patients with symptoms,

pyuria, or organisms seen on microscopy which are unexplained by overnight culture. 48 h incubation will reveal the presence of the majority of fastidious organisms which are present in the urine.

3. Use of culture media additional to the primary isolation medium for examination of specimens from patients with symptoms or pyuria in whom the above procedures have yielded negative results. This will only be required for a small minority of specimens. It can also usefully be employed in the first instance for specimens from patients with particular clinical syndromes in which fastidious organisms requiring these additional media have been shown to be important, e.g. 'interstitial cystitis', prostatitis, post-prostatectomy infection, epididymo-orchitis, and infection in patients undergoing pelvic radiotherapy.

Interpretation and reporting of urine cultures

If the correct interpretation of urine microscopy and culture is to be made, every specimen must be considered 'on its merits'. The factors which must be taken into account have already been listed; if the report is to be intelligible and helpful to the requesting clinician, it must be factual and carry an interpretation comment if necessary. Terms such as 'no significant growth', which are often applied at the bench by non-medical laboratory staff, should not be used. They usually indicate a mechanical approach to interpretation and ignore the clinical context. For example, a low count of a Gram-negative organism may be of considerable significance in an adult male with prostatitis and certainly requires sensitivity tests, whereas a high count of such an organism in an elderly woman with an indwelling catheter when she is well and symptom free is not significant; sensitivity testing of the isolate will almost certainly prompt ill-advised antibacterial treatment and is contraindicated. The former, however, will often be reported as 'no significant growth' whereas the latter is likely to be reported as significant. There are many other such examples.

Therefore, in reporting urine cultures, the identity and count of the isolates should be stated (obvious contaminants, such as a mixed growth of urethral commensals may be recorded as 'mixed Gram-

positive organisms') and a decision as to the significance of the isolates should be made by medical staff or by experienced scientific staff who have been trained appropriately. In the latter case, it should always remain open to medical staff to reconsider the interpretation put on the findings if necessary. It follows, of course, that this approach to correct diagnosis depends upon the accuracy and completeness of the request form that accompanies the specimen. In my experience, the relevant information required on such forms is only obtained if they are written by the doctor who makes the decision to request the investigation. I do not share the increasingly prevalent view that such forms may appropriately be written by nurses – still less by clerical staff. Restriction of laboratory requests for urine culture to those accompanied by a form actually written by a doctor will do more to save unnecessary, and often harmful, work than any other single effort in this direction.

Automated and screening procedures

In an attempt to solve the problem of increasing laboratory workloads in this field, many such procedures have been developed. The use of such techniques approaches the problem from the opposite direction from the one outlined above – instead of attempting to restrict the requests to appropriate and well-documented specimens, it presupposes that the number of specimens will continue to rise unchecked, and that ways must be found in the laboratory either to examine them rapidly using minimum labour or, by screening techniques, to select those which merit microscopy and culture and to discard the rest.

At the time of writing, there are many reasons why this approach should be rejected:

1. The published data show that the automated procedures at present available are insufficiently sensitive and specific to detect all significant infections (which, of course, include significant low bacterial counts)[10].
2. There are no published data on the detection of fastidious urinary pathogens by such methods.

3. Screening devices for selection of specimens for microscopy and culture, such as the various chemical dip sticks which are available, are insufficiently sensitive and specific[11], and their use does not result in an appreciable saving in time or money.

4. Any laboratory protocol which results in the acceptance of unlimited numbers of specimens, and the discarding of some of them unexamined, inevitably leads to poor liaison between clinician and laboratory in the diagnosis of UTI. It leads to increased use of antibacterial agents for treatment of symptoms without any attempt at laboratory diagnosis, with all the consequent disadvantages to patient and community in terms of side effects and resistant organisms, and loses the opportunity to educate clinicians in the appropriate use of the laboratory.

Restriction of laboratory workload by elimination of unnecessary specimens and laboratory procedures

This can be achieved in the following ways:

1. Insistence that, with a few agreed and necessary exceptions, all specimens should be accompanied by a request form written by a doctor.

2. Bacteriuria screening programmes, for example of pregnant women, should be discontinued if audit shows that communications are poor and the results are not acted on effectively.

3. Submission of specimens from patients with indwelling catheters at times when they are well should be discouraged. Sensitivity testing of isolates from such specimens should only be undertaken if the request form states specifically that the patient is unwell, feverish or confused.

4. Submission of 'routine' specimens from departments where specimen collection techniques are poor (e.g. bag specimens from babies) should be discouraged. Good specimens can be obtained from babies if the requesting doctor takes an interest in the method of specimen collection and transport.

5. 'Stix' testing of all urine specimens in the laboratory is unnecessary, wasteful and often inaccurate. If proteinuria testing is either requested or considered appropriate in the laboratory, an accurate test, such as the sulphosalicylic acid test, should be employed. Screening 'stix' tests are easily undertaken in clinical areas, and laboratory confirmation of positive tests may be requested.

6. Centrifugation of urine for microscopy is unnecessary, inaccurate and more time consuming than inverted microscopy of uncentrifuged urine.

7. A single primary isolation medium is sufficient for the great majority of urine specimens. The use of two or more media can be helpful if a multipoint inoculation technique is used, but the time and expertise required to interpret the findings of such techniques correctly is not always available. Direct plating methods need only one effective primary medium, for example CLED agar; the use of additional media is time consuming and expensive.

8. Full biochemical identification of all Gram-negative isolates is expensive and unnecessary except in the rare clinical circumstances of outbreaks of cross-infection, associated septicaemia, or isolation of very resistant (e.g. gentamicin-resistant) organisms. After brief screening tests to identify *Pseudomonas* spp, *Proteus* spp. and *Salmonella* spp., the remainder may be reported as 'coliform'. Any laboratory which finds it necessary to fully identify many Gram-negative urinary isolates for any of the reasons given above should suspect that there is something seriously wrong, either with instrumentation procedures or the use of broad-spectrum antibacterials, in its area. In our laboratory, we have occasion to identify only about 20 Gram-negative urinary isolates for all the above reasons each year.

9. Abbreviated methods for identification and reporting of Gram-positive urinary isolates, for example the use of novobiocin resistance for identification of *Staphylococcus saprophyticus*, have been validated and may be used in routine laboratory practice.

10. The culture of urine specimens for *Mycobacterium* spp. is rarely indicated. The presence of fastidious organisms as an explanation

for pyuria should first be sought by culture on appropriate media and prolonged incubation in 7–10% CO_2.

CLINICAL SIGNIFICANCE OF BACTERIURIA

There are three principal considerations in determining the significance of bacteriuria:

1. Is it giving rise to urinary symptoms with/without systemic upset?
2. Is it associated with, or the cause of, inflammatory changes in the kidneys, bladder, prostate or paraurethral tissues of women?
3. Is it associated with, or the cause of, calculi in the kidneys, bladder or prostate?

Urinary symptoms with/without systemic upset

Symptoms related to micturition – frequency, dysuria, nocturia, haematuria, pain, perineal discomfort, dyspareunia, urge incontinence or post-micturition dribble – may result from infection anywhere in the urinary tract and its adjacent structures. In addition, pain may be referred from the site of infection to other parts of the urinary tract. It is difficult to be dogmatic about the frequency with which systemic upset of any kind accompanies bacterial infection of the urinary tract – for example, the body temperature of women with cystitis is seldom recorded – but certain clinical syndromes in which systemic upset occurs are well recognized. The loin pain, fever, and rigors of acute pyelonephritis are characteristic, and many men with prostatitis are feverish and have evidence, such as rigors, of bacteraemia. Elderly patients often become acutely confused as a result of bacteriuria and babies may be non-specifically unwell.

Until recently, as already mentioned, no infective cause was found for the urinary symptoms of one-half of the women and two-thirds of the men who present to their doctors, and many non-infective causes have been proposed. Failure to prove a definitive cause has often resulted, and regrettably still often results, in a variety of psychological