Antibody-coated bacteria in urine: when, where and why?

Prognosis and proper management of urinary tract infection (UTI), depends on the site of infection. Clinical symptoms and signs are often unreliable and misleading (Brumfitt, 1972). Several direct and indirect methods have therefore been developed to determine whether the upper or the lower tract is involved. Direct tests, which are the most reliable include ureteral catheterization (Stamey, Govan & Palmer 1965) and the bladder washout technique (Fairley et al., 1967), both of which, however, are uncomfortable, time consuming and even hazardous for the patient. Papanayiotou & Dontas (1972) described another direct technique, the water loading test, which is based on the forced diuresis effected either by administration of a large water intake or by co-administering frusemide (Dontas et al., 1974), to provoke diuresis-induced bacteriuria. However, good cooperation of the patient is a prerequisite. Indirect methods include urine enzyme assays such as catalase, β-glucuronidase, lactic dehydrogenase isoenzymes IV and V, assessment of maximal urine concentrating ability, urinary leucocyte excretion rate and leucocyte casts, as well as determination of specific serum antibody against the infecting organism. These tests present no risk to the patient and are easily performed but they have been considered as less specific. Thomas, Shelokov & Forland (1974) were the first to describe a non-invasive, safe, simple and inexpensive direct immunofluorescence technique, for the detection of 'antibody-coated bacteria' (ACB) in the urinary sediments of bacteriuric patients. This test was based on the assumption that the kidney itself produces specific antibodies against the infecting bacteria, unrelated to the specific serum antibodies, which are subsequently produced when the source of bacteriuria is the upper tract.

Since the first publications, related to the correlation of the presence of ACB with evidence of upper UTI with the established direct methods, several similar papers have appeared (Jones, Smith & Sanford, 1974; Harding et al., 1978; Hellerstein et al., 1978; Riedasch et al., 1978b) providing the possibility of evaluating the new test in terms of sensitivity and specificity. Sensitivity, defined as the association of renal bacteriuria with positive ACB, ranged in various studies between 72–100% and specificity, defined as the proportion of patients with bladder bacteriuria and negative ACB, from 50 to 100%. What are the reasons for obtaining either false positive or false negative results with a method that in the original studies had an almost 100% correlation with the underlying urinary-tract pathology?

Interpretation and definition of a 'positive test' differs significantly among the various investigators. In the original description of the method, the test was considered as positive when ≥20% of the bacteria in each hpf were brilliantly fluorescing, while other investigators used ratios of 1% to 25% (Hellerstein et al., 1978; Hawthorne et al., 1978; Riedasch et al., 1978b; Rumans & Vosti 1978). Jones & Johnson (1977) used the presence of ≥2 fluorescing organisms in a total of 200 hpf fields and Harding et al. (1978) used ≥5 bacteria after a 5 min screening. Therefore, since the cut off point varies, false-positive or false-negative results will vary according to the strictness of criteria. Schaberg et al. (1977) after three independent observers disagreed in 12% out of 253 specimens, reported on interobserver variabilities. Finally variability between laboratories can also be based on the applied methodology since instead of using all three immunoglobulins, only anti-human IgG has been tested in some laboratories.

Upper UTI can certainly be associated with false-negative results in the following instances: (a) In acute pyelonephritis, when the duration of the renal parenchymal exposure to bacterial antigens may be too brief to elicit a detectable immune response (Rumans & Vosti, 1977). Thomas et al. (1975) have reported that 20% of acute pyelonephritis
complicating obstetric procedures was followed by negative tests, while studies in rabbit pyelonephritis have shown that it takes from 8 to 21 days before ACB appear in urine (Smith, Jones & Kajiser, 1977). (b) In upper UTI with superimposed cystitis (Jones & Johnson, 1977) and in neurogenic bladder dysfunction with coexisting kidney infection (Merritt & Keys, 1982). (c) In mucoid P. aeruginosa infections where the extracellular polysaccharide blocks antibody adherence onto the bacterial surface (Marrie et al., 1979). (d) In the presence of an insufficient quantity of antibodies. In such cases antibodies are detected by the more sensitive radioimmunoassay technique (Ratner, Thomas & Sanford, 1981). (e) When long courses of β-lactam antibiotics were given in the recent past (Giamarellou et al., 1983), an observation in favour of prolonged treatment schedules in cases of chronic pyelonephritis. (f) In the extremes of age (Giamarellou et al., 1978b; Hellerstein et al., 1978). However in immunocompromised patients with UTI in whom false negative tests might be expected the kidney does not lose its ability to produce antibodies (Keren et al., 1977; Riedasch et al., 1978a).

False-positive ACB have been described: (a) After urine contamination with immunoglobulins derived from the urogenital tract, as in patients with lower UTI and concomitant urethritis or vaginitis (Montplaisir, Courteau & Roche, 1977). Since the presence of yeast also causes non specific immunoglobulin attachment, the possibility of coexisting candidal vaginitis, should also be considered. Gurtler (1977) has speculated that with the use of indwelling catheters false positive results could be obtained by introducing immunoglobulins into the tract. However, other investigators accept that the presence of ACB in catheterized patients present evidence of upper UTI directly correlated with the duration of catheterization (Goniee et al., 1975; Giamarellou et al., 1982). (b) In chronic prostatitis (Jones, 1974; Riedasch et al., 1977). (c) In cases with ileal conduits (Woodside et al., 1978). (d) When coating antibodies persist as free molecules after an upper UTI has subsided. Cross reactivity with a new bladder pathogen sharing common antigens with the original pathogen could result in false ACB (Thomas et al., 1978). (e) In patients with deep bladder wall tissue lesions that elicit a local immune response i.e. haemorrhagic and chronic cystitis, bladder tumours and bladder stones (Forsum et al., 1978; Riedasch et al., 1978b). However, with the exception of the first category, only small numbers of bacteria with weak fluorescence will be coated and therefore false positive results appear as directly correlated with the definition of a positive test.

A major disadvantage of the ACB test is in infancy, where the results of several investigators have shown poor correlation between the presence of ACB and underlying upper UTI (Forsum, Hjelm & Jonsell, 1976; Silverberg, Jackson & Bryan, 1976; Barnett & Abbott, 1978; Hellerstein et al., 1978). In the young, specimen collection problems could well result in false positive ACB because of contamination with small numbers of ACB derived from the perineal area, while, particularly in cases with asymptomatic bacteriuria, an impaired immunologic response related to immaturity has been considered and could explain the false-negative tests.

There is no doubt that despite their disadvantages the bladder washout test and urethral catheterization still remain as the most reliable tests to localize the exact site of UTI. Reconsidering the ACB test, which up to date is the better studied and the easiest-to-perform indirect test, after excluding the paediatric age group, it is clear that less false-negative and more false-positive tests can be obtained. Since the first is related mainly to patients with acute pyelonephritis or mucoid Pseudomonas infections, such discrepancies can be expected and correctly interpreted. Even when a test is considered as false negative, the feasibility of reproducing and repeating it so easily and at any time during the course of the disease can help to clarify a disputed result.

On the other hand false positives (with the exception of underlying bladder wall invasive lesions) are related to low numbers of weakly fluorescing bacteria. A strongly positive test should therefore be interpreted as indicating the existence of underlying upper UTI or bacterial invasion of the bladder uroepithelium.

What is the importance of localization tests and more specifically, the ACB test? There is no doubt that strongly positive ACB are closely correlated with underlying genitourinary anatomical abnormalities (Thomas et al., 1974; Pujol et al., 1976; Giamarellou et al., 1978a, b). In clinical practice their presence should point out the patients in whom careful investigation of the genitourinary tract, including pyelograms, have to be performed. ACB
should also have an important role in the prognosis and management of UTI. It is widely accepted that the dose and duration of antibiotic therapy in UTI should be related to the site of the underlying disease. After conventional treatment schedules the great majority of therapeutic failures (and those characterized bacteriologically as relapses), occur in patients with renal parenchymal involvement or whenever lower tract infections are associated with bladder wall invasion. In contrast uncomplicated infections, when restricted to the bladder mucosa, are associated with reinfections. Recently the use of short courses or even of single dose therapy in lower UTI has been shown to be very successful by several investigators. This is to be expected as cystitis is a superficial infection, and extremely high concentrations of drug are obtained in urine, even after a single dose of any antimicrobial. One im dose of kanamycin has been found effective in curing 92% of uncomplicated lower UTI by Ronald, Boutros & Mourtada (1976). The advantages of short therapy, i.e. convenience of administration, less cost and minimized side effects, as well as the increased patient cooperation are self-evident. Therefore the possibility to differentiate easily renal from uncomplicated bladder infections, which before required invasive techniques, can be simplified on the basis of results of the ACB test. Fang, Tolkoff-Rubin & Rubin (1978) were the first to use a positive test as a criterion in deciding the duration of treatment in women presenting with symptoms of cystitis. The results of the ACB assay predicted therapeutic response in their patients. Both single-dose and the conventional ten-days therapy with amoxycillin were completely successful in patients with negative ACB tests. On the other hand conventional treatment failed in 50% of those who presented with positive assays. Similar results in the treatment of ACB-negative UTI have also been reported by the same group of investigators, when a single 3 g dose of amoxycillin was compared to 10 day courses of co-trimoxazole or ampicillin (Rubin et al., 1980). However, recurrent UTI in male patients with positive ACB assays, have been associated with fewer relapses whenever therapy was extended for 6 weeks (Gleckman, Crowley & Natsios, 1979; Smith et al., 1979).

Harris, Thomas & Shelokov (1976), trying to evaluate asymptomatic bacteriuria of pregnancy, have reported that in a high percentage of patients ACB-associated infections were correlated with elevation of the serum creatinine and subsequent decreases of creatinine clearance, while intrauterine growth retardation was more frequently observed in infants born to mothers with positive ACB tests. It seems therefore that positive assays in pregnancy not only predict the patients who require very careful therapy and prolonged follow-ups, but also indicate those in whom frequent renal function evaluation should be performed.

Therefore it is suggested that in UTI with negative ACB in both sexes, short term courses of therapy are now indicated, while a positive assay in the male patient strongly indicates a prolonged treatment course. However in female patients with positive assays, it has not yet been clear whether the recurrence rate after prolonged courses of antimicrobials will be decreased. A possible exception could be the pregnant woman with positive tests who should probably not be given short-term therapy. Despite the progress in the field of diagnosis and management of UTI there are still challenges for the investigator.

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References
Leading article


bacteriuria. *Archives of Internal Medicine* 138, 1077-81.


