"Fallacies and misconceptions in diagnosing urinary tract infection"

Abstract:

Urinary tract infections (UTIs) are amongst the most prevalent infectious diseases, associated with significant morbidity and mortality. They place a substantial financial burden on healthcare systems worldwide [1]. The diagnosis of UTI is important in clinical medicine

Background:

"Lower urinary tract symptoms" (LUTS) is a collective term that includes storage symptoms, such as frequency, urgency, urge incontinence; symptoms of stress urinary incontinence; voiding symptoms such as hesitancy, reduced stream and intermittency; and finally sensory symptoms that include various degrees and expressions of pain. The prevalence of LUTS increases with age and is reported in up to 40% of men and 28% of women aged 70-79 years [2, 3]. Nowadays UTI is increasingly implicated in the aetiology of LUTS, most notably in patients presenting with voiding and overactive bladder symptoms. Whilst LUTS have been very much in the mind of clinicians since the dawn of medicine the importance of infection to these symptoms has become evident only recently with the recognition of the serious shortcomings of the tests used routinely to exclude UTI from the differential [4,5]. Regrettably, there is a widespread confusion over appropriate diagnostic criteria and the application of quantitative microbiology [6, 7]

Problems with Diagnostic Tests

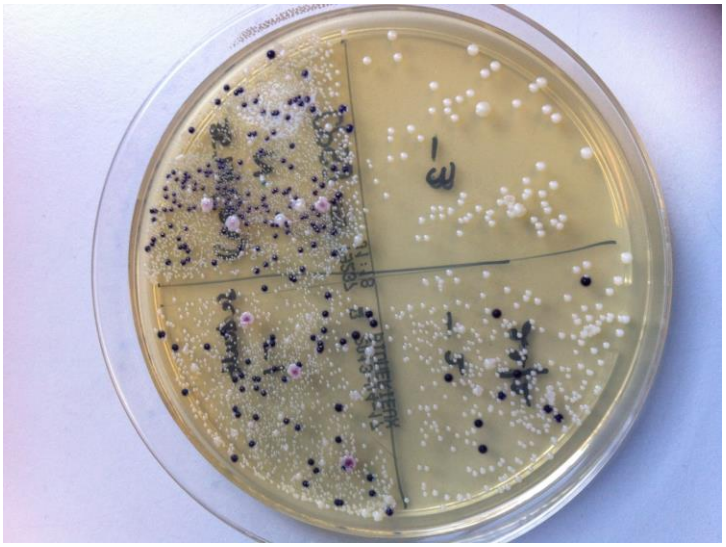
MSU Culture:

Throughout the world UTI diagnosis is subordinate to quantitative microbial culture applied to a clean catch midstream urine sample (MSU). The diagnostic threshold adopted varies, unaccountably, between 10^2 and 10^6 colony forming units (cfu) ml^{-1}, of a single species of a known urinary pathogen. These criteria are derived from the publication by Kass of 1957. This reported a study of 74 women, with acute pyelonephritis, and 335 asymptomatic controls [8]. Subsequently Kass used a sample of pregnant women with pyelonephritis to represent severe infection in a further analysis during his quest for a diagnostic threshold which he set at 10^5 cfu ml^{-1} [9]. Why such a diagnostic threshold should have come to be used ubiquitously across the spectrum of human

disease is a mystery. It was criticised by some authors in the 70's but their warnings have gone unheeded [10, 11].

Kass made the assumption that the normal urinary tract was sterile and so any microbe isolated from an uncontaminated specimen must be considered pathological. The idea that normal urine must be sterile flies in the face of what we now understand from Darwinian evolution and it has now been refuted Khasriya 2010 [12]. Another problem was the acceptance of Koch's postulates which stipulate a single organism. There never was evidence to endorse this and nowadays it is clear that polymicrobial infection is the norm (Figure 1). Kass used quantitative threshold to distinguish between pathogens and contaminants but he made assumptions about the nature of contaminants that were not justified. We now know that a properly collected clean catch MSU is remarkably free of contamination with its contents coming from the bladder [13]. There is nothing to justify the belief that the number of microbes that are cultured bears any relationship to pathogenicity. Thus there are very serious concerns about the validity of routine quantitative microbiological urinalysis. The situation is made worse by the fact that the entire surrogate methods of testing for urinary infection are calibrated to the error wrought MSU culture.

Figure 1: Clean catch specimen showing a mixed growth culture in a symptomatic patient with Chronic UTI using the spun sediment culture technique. Routine MSU culture was reported as no growth. The picture shows 5 different organisms: wet, white, small and medium colonies – 2 different types of Staphylococcus; Purple colonies - Enterococcus Feacalis; Pin point white colonies –Streptococcus; white with mauve centre - Ecoli.



Urine Microscopy:

The measurement of pyuria has replaced bacterial culture in many clinical services. Evaluated by microscopy or urinary dipstick, or automated methods, it is often used as a stand-alone surrogate, to triage samples submitted for bacteriological culture. The absence of 'significant' pyuria is frequently considered definitive evidence of the absence of UTI. The validity of this assumption has been refuted comprehensively [14]. None of the tests for pyuria have the sensitivity to claim such power over the diagnostic process. "No evidence of disease" should never be confused with "Evidence of no disease" (NED ≠ END).

The identification of urinary leucocytes using light microscopy was first described in 1893. Early pioneers studied the centrifuged deposits of large volumes of collected urine [15], although doubts about the veracity of this approach were expressed by some [16, 17]. Dukes (1928) came to dominate the debate [18] by using methods a cell counting chamber and fresh, uncentrifuged urine. His study of 300 midstream urine (MSU) samples from asymptomatic controls produced estimates for normal mean leucocyte counts of 1.6 wbc μl^{-1} and 5.4 wbc μl^{-1} for males and females respectively. These data showed wide dispersion and positive skew in the range 0-50 wbc μl^{-1}. His use of the mean to summarise his data was wrong. Had he correctly used the median he would have considered the proposition that any pyuria was potentially pathological. Regrettably he arbitrarily set a threshold between normal and abnormal of ≥10 wbc μl^{-1}.

His experiments were not replicated until the 1950's, when several groups, making the same statistical errors and adopting similar assumptions, reported results), that ultimately bound us to the ≤10 wbc μl^{-1} threshold in clinical practice. The veracity of this has now been comprehensively refuted [14].

From recent studies it is clear that urine needs to be evaluated for pyuria immediately after collection, as rapid leucocyte lysis occurs in the hours following sampling. This cell destruction appears to be retarded by boric acid, although significant cell loss appears inevitable. Urinary centrifugation affects cell salvage so variably that it is inappropriate for use in clinical practice. Vital staining appears to confer no significant influence on leucocyte detection [14].

Urinary Dipstick

Meta-analyses of the use of urinary dipsticks in adults [19, 20] and in children [19] have been reported. Hurlbut and Littenberg [1991] concluded that dipsticks do not exclude infection reliably in most clinical settings. Deville et al [2004] referencing the MSU Kass criterion of 10^5cfu/ml, reported a leukocyte esterase sensitivity of 0.76 [95% CI 0.6–0.98] and a specificity of 0.46 [95% CI 0.32–0.68], and a nitrite sensitivity of 0.49 [95% CI 0.38–0.62] and specificity of 0.85 [95% CI 0.73–1.0] in the primary care setting [21]. The considerable variance in these measures is not reassuring.

A recent study by Khasriya et al [12] examined the performance of dipsticks in patients with chronic lower urinary tract symptoms without dysuria. A total of 508 midstream urine samples were used to compare leukocyte esterase, nitrite dipstick and urine microscopy with cultures seeking 10^5 cfu/ml. Similarly 470 catheter urine samples were used to compare the same surrogates with 10^5 cfu/ml and with an enhanced culture method seeking 10^2 cfu/ml. A comparison of leukocyte esterase against microscopic pyuria was made using the 508 midstream and 470 catheter specimens of urine (CSU). Midstream urine specimens were provided by 42 normal volunteers for comparison.

For a midstream urine culture at 10^5 cfu/ml was 56% for leukocyte esterase [95%CI 46–66], 10% for nitrite [95% CI 6–18] and 56% for microscopic pyuria [95% CI 46–66] with specificities of 66% [95% CI 61–70], 99% [95% CI 98–100] and 72% [95% CI 67–76], respectively (table 1]. In CSU samples the sensitivity for the gold standard was 59% for leukocyte esterase [95% CI 47–70], 20% for nitrite [95% CI 12–31] and 66% for microscopic pyuria [95% CI 54–77] with specificities of 84% [95% CI 80–87], 97% [95% CI 95–99] and 73% [95% CI 69–78), respectively. The enhanced method of CSU culture [102 cfu/ml] proved positive in 137 subjects [29%], inevitably more than the gold standard did in 71 [15%]. The surrogate markers were less sensitive for 10^2 cfu/ml [table 1]. In CSU samples the sensitivity for the enhanced standard was 45% for leukocyte esterase [95% CI 36–53], 13% for nitrite [95% CI 8–20] and 53% for microscopic pyuria [95% CI 45–62] with specificities of 86% [95% CI 82–90], 98% [95% CI 96–99] and 76% [95% CI 71–80], respectively. Table 2 contains the data comparing the leukocyte esterase test results with the microscopic pyuria data. The sensitivity of leukocyte esterase for microscopic pyuria was 81% [95% CI 75–87] and specificity was 83% [95% CI 78–87].

Table 1. *Sensitivities and specificities of surrogate markers against gold standard and enhanced standard*

	Leukocyte Esterase		Nitrite		Microscopic Pyuria	
	No. Culture Pos (%)	No. Culture Neg (%)	No. Culture Pos (%)	No. Culture Neg (%)	No. Culture Pos (%)	No. Culture Neg (%)
			MSU samples: comparison of surrogate markers to gold standard 10^5 cfu/ml			
Pos	59 (12)	138 (27)	11 (2)	2 (0.4)	59 (125)	113 (22)
Neg	47 (9)	264 (52)	95 (19)	400 (79)	49 (9)	290 (57)
Chi-square	17		40		30	
			CSU samples: comparison of surrogate markers to gold standard 10^5 cfu/ml			
Pos	42 (9)	64 (14)	14 (3)	10 (2)	47 (10)	106 (23)
Neg	29 (6)	335 (71)	57 (12)	389 (83)	24 (5)	293 (62)
Chi-square	17		40		42	
			CSU samples: comparison of surrogate markers to enhanced standard 10^2 cfu/ml			
Pos	61 (13)	45 (10)	18 (4)	6 (1)	73 (16)	80 (17)
Neg	76 (16)	288 (61)	119 (25)	327 (70)	64 (14)	253 (54)
Chi-square	53		30		41	

Sensitivity is the proportion of patients with the disease correctly identified by the test. Specificity is the proportion of patients who are disease-free correctly identified by the test.
All values p <0.001, df = 1.

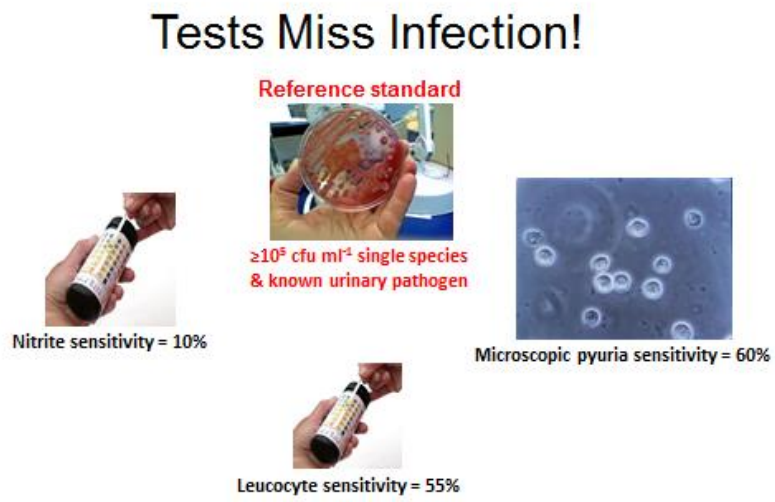
Table 2. *Sensitivities and specificities of leukocyte esterase for detecting pyuria*

	MSU Samples		CSU Samples	
	No. Pyuria Pos (%)	No. Pyuria Neg (%)	No. Pyuria Pos (%)	No. Pyuria Neg (%)
Leukocyte esterase pos	140 (28)	57 (11)	98 (21)	8 (2)
Leukocyte esterase pos	32 (6)	279 (55)	55 (12)	309 (66)
Chi-square	198		167	

All values p <0.001, df = 1.

[12; Khasriya et al 2010]

Figure 2: Illustrates the performance of available tests.



Given these exhaustive data, and despite many official guidelines and widespread use, these tests are not up to the task of excluding significant UTI and they should not be used for this purpose. It is reasonable to conclude that if any are at all positive then the probability of UTI is very high. All negative results offer no useful information (Figure 2).

Systemic markers of infection

There is an ill-found expectation that systemic inflammatory markers should be elevated particularly in more serious urinary tract infection. Unfortunately, this is not the case and negative data has no power to reassure [22].

Key Points

- Current gold standard references used to diagnose UTI in chronic and acute disease states appear to have serious shortcomings.
- Surrogate tests like urine dipsticks and urine microscopy are much less reliable than the discredited MSU culture

Discussion

The data described in this chapter provide compelling evidence of major deficiencies in the clinical tests currently used to exclude urinary tract infection. Replacement tests are certainly needed but the history narrated here cautions us to invest in careful validation, which will take time. In the meantime we should face the facts. We have some tests that will confirm a suspected infection but provide no other guidance. This means that we must use the patients' symptoms to plan treatment and tailor that treatment in reaction to the symptom response.

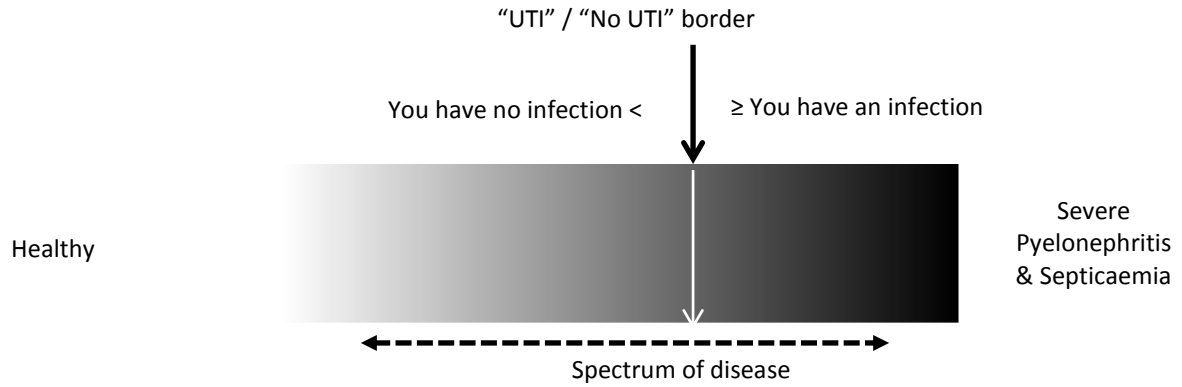
One of the explanations for the muddle that we have got ourselves into may lie with the liberal use of categories.

The use of a universal diagnostic threshold of $\geq 10^5$ cfu ml^{-1} of a single species of a known urinary pathogen imposes a dichotomy: "Urinary tract infection" or "No urinary tract infection" but this makes no sense when applied to biological systems. Medicine has always used categories to help understand the complexity of the data we attempt to assimilate. Unfortunately we rarely question their true validity. Immanuel Kant warned that categories are inventions of the mind that should not be confused with reality [23]. More recently, Karl Popper encouraged us to abandon the absolutism of

categorisation on the grounds that they generate ill-advised certitude. So instead of informing a patient that “you do not have an infection” we should instead be using statements of probability, drawing on the whole clinical picture and which take full account of our uncertainty [24]

Figure 3 illustrates the problem that we must confront. A spectrum is drawn between two extremes of no urinary tract infection and infection sufficient to threaten life. A single diagnostic threshold places an arbitrary boundary on the continuum and declares all below as “No UTI” and all above as “UTI”. On reflection this seems crass.

Figure 3 – Categorisation imposed on the disease spectrum



It is simply wrong to impose categories, least of all dichotomies, on natural spectra. Nature is inimical to categories. Biological phenomena are dispersed across continua. Charles Darwin never tired of emphasising the gradualism in nature [25] and Dawkins wrote a devastating criticism of “The tyranny of the discontinuous mind” [26]. Slavish adherence to such arbitrariness is bound to generate error.

Somehow we have to cure ourselves of this cognitive aberration because by persisting in the delusion we ill-serve our patients.

Conclusion:

The accepted tests for excluding urinary tract infection from the differential diagnosis suffer from numerous shortcomings. There is a pressing need to find alternatives. A novel diagnostic marker, validated accurately across the entire spectrum of LUTS, will take time to achieve [27].

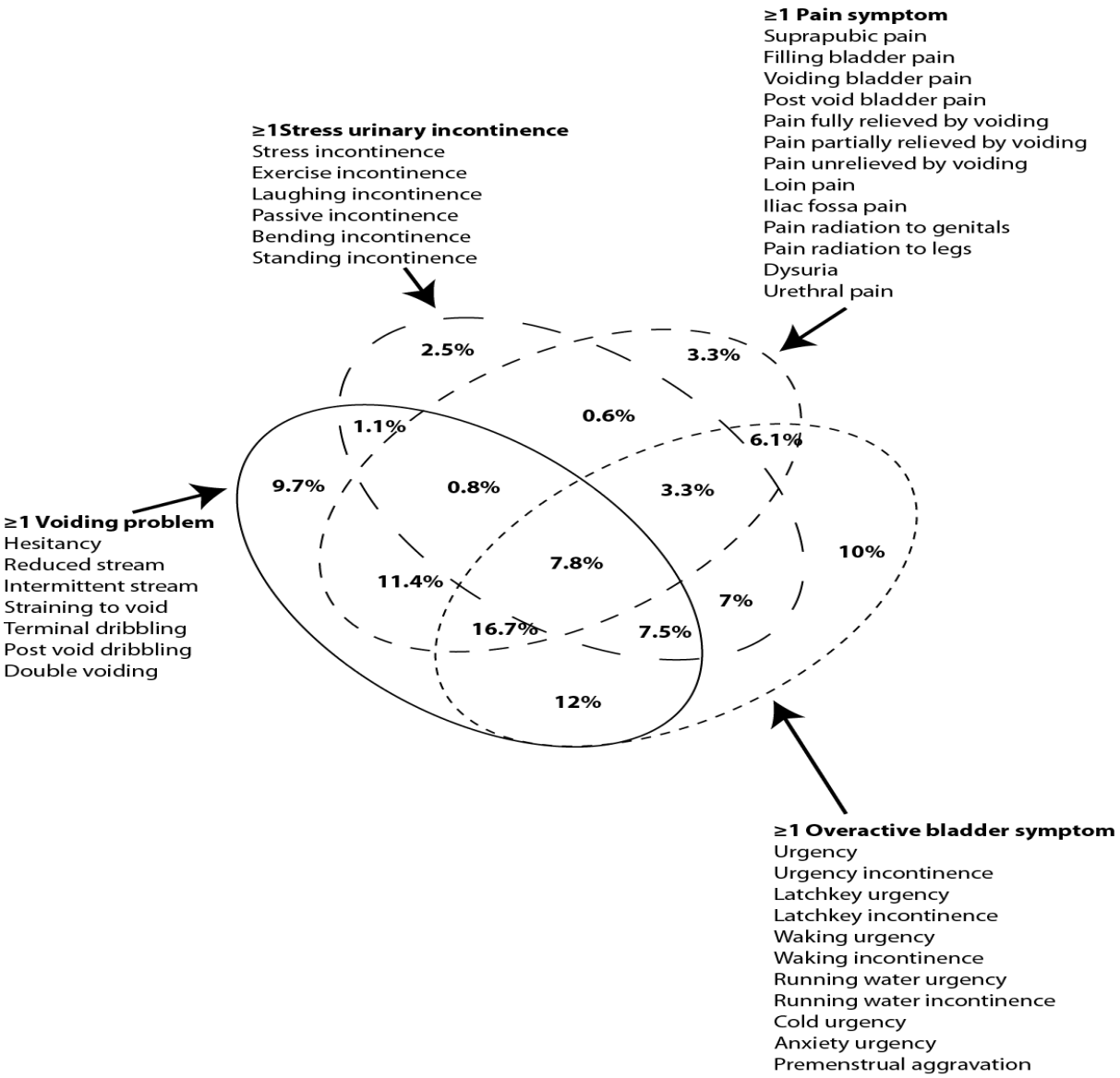
While we await these developments, what should we do about the current patients? Symptoms appear to be the key to the diagnosis [28, 29, 30]. The most sensitive marker for UTI in both male and female patients without acute disease are not pain but voiding symptoms namely, hesitancy, reduced stream, intermittency and terminal dribble. Dysaesthesia is more common than acute dysuria. Uriniferous odour is also associated with UTI. Suprapubic tenderness and loin tenderness do appear to be important markers of disease activity in patients with chronic infections. A great deal of emphasis focusses on a good history to clinch the clinical diagnosis.

Patients with recalcitrant overactive bladder symptoms, who exhibit microscopic pyuria, but negative MSU culture, have responded to treatment with lengthy courses of oral antibiotics (Figure 4). These data coming from prospective observational studies and encourage us to consider infection where previously it was denied [29, 30].

Key Point:

- If the patient has symptoms then the probability that they have an infection is high, irrespective of whether they have a positive test.
- A test should be interpreted given specific consideration to the clinical presentation.

Figure 4: Venn diagram showing symptom distribution in patients with LUTS who exhibit pyuria >10cfu/ml and negative routine MSU culture. Only a small minority present with acute dysuria [30].



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