Notes on Chronic Recalcitrant Cystitis

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A summary of the facts

The gold standard test for diagnosing urinary tract infection during the last sixty years has been to culture a midstream urine specimen and identify a pure growth of a known urinary pathogen [1].

The threshold counts may be adopted, ranging from 10^2 to 10^6 but these do not escape the facts. The quantitative urinary culture thresholds rest on assumptions that were not properly checked:

(1) *The normal bladder is sterile* – It is not sterile - several groups have refuted this [2-9].

(2) *There is a quantitative relationship between the culture results and the probability of infection* - Culture numbers are more likely to depend on the ease of growth [2, 3, 4 , 8-17].

(3) *The infection should be caused by a single species* – Modern published data imply that with mixed organisms is more likely [2, 3, 6, 8, 9, 18]

(4) *Cultures of mixed organisms imply contamination* - Modern data refute the notion of mixed growth of doubtful significance – they are significant [2, 3, 6 , 8, 9, 18]

(5) *If epithelial cells are seen in the midstream urine specimen then it indicates contamination [19]* – This is not true, most of these cells come form the bladder and reflect bacterial cystitis [8, 20-26].

(6) *If the culture is negative then there is no infection* – This is not true, the cultures are incapable of this property [1, 2, 8-10, 18, 27-32]

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(8) *Systemic markers of inflammation such as the ESR and C-reactive protein can exclude a significant infection if negative*: This is not true as numerous researchers have found [33-39, 40]

The wrong gold standard

It is common for a patient with appropriate symptoms to be undiagnosed on negative culture. That confuses absence of evidence of disease with evidence of absence of disease –. Recently Heytens et al (2017) have claimed that ““The woman that is visiting you with typical urinary complaints has an infection. There is nothing more to explore.” The culture misleads [41]. The influence of guidelines and the imposition of three-day UTI treatment regimens followed by culture-based treatment seems to be generating a surge in patients with chronic recalcitrant bladder pain and recurrent cystitis who get diagnosed with IC/BPS/PBS.

Screening tests

The popular screening test for UTI, used throughout the health services, involving dipstick analysis of the urine has been calibrated to quantitative urine culture assuming it to be an

accurate gold standard. By doing this the errors of the culture method are added to the errors of the dipstick making matters worse [8, 15, 17]. It should be no surprise therefore that there is a substantial literature that criticises the sensitivity and performance of this test. Nevertheless numerous symptomatic people are dismissed as normal on the grounds of a negative dipstick test. There is no scientific justification for this [9].

These tests cannot exclude acute or chronic UTI and do not take into account differences in bacterial strain virulence, host genetic variability, intracellular bacterial reservoirs, or even the dilution of the urine specimen due to high liquid intake before the test. Therefore, it is conceivable that legitimate infections will be missed when relying on a rigid numerical threshold to distinguish between 'infected' and 'not infected' [7].

The frequentist Yes/No categorisations are a hallmark of diagnostic test interpretation. Richard Dawkins' essay "The tyranny of the discontinuous mind" (2004) [42], discusses this problem well (https://richarddawkins.net/2013/01/the-tyranny-of-the-discontinuous-mind christmas-2011/). It is Procrustean to force patients into arbitrary categories that take no account of their specific circumstances. Bayesian methods are much better suited to diagnosis and clinical data assimilation.

Treatment failure

Uncertain diagnosis is not the only area that complicates UTI management. The treatment of acute cystitis also has its limitations. Whilst success rates of 84% to 100% have been claimed for 3 and 14 day treatments [31], others have reported microbiological and symptomatic failure in up to 28% and 37% of patients within 4 to 14 weeks of treatment [43]. Among healthy young women who suffer from their first UTI, the risk of recurrence within 6 months is 24%. If they have a history of one or more UTIs, the risk of recurrence rises to 70% in that same year [44]. In a Canadian surveillance study, 14% of the 30,851 residents with UTI suffered more than one episode during the two-year study period, and 2% had six or more episodes [45].

How does all this effect people with cystitis?

A young girl of 23 years has sex. The following day she develops urinary frequency and notices that when she passes urine it is slow to start, the stream is reduced, stops, starts and dribbles at the end. She does not describe pain. You might think "no pain therefore no infection" and you would be wrong. She is experiencing the typical early symptoms of a urine infection. She decides to drink plenty to get things going. She would be wrong because increased fluid intake dilutes the urine of the natural antibodies and immune chemicals. A day later she has pain when she passes urine and is distressed. The pain symptoms arrive when the infection has increased. She goes to her primary care centre and a nurse tests her urine with a dipstick. The test is negative, an infection is excluded; increased fluids and cranberry juices are advised. Wrong again; the dipstick test will miss at least 50% of infections. The nurse confuses absence of evidence of disease with evidence of absence of disease; a howling error of logic. Cranberry juice is without evidence. One day later the girl is much worse and returns to see a doctor. Another dipstick test reveals there is a "trace positive result" so the urine is sent for culture. Had the doctor examined the girl, tenderness on bladder compression may have been evident. She is treated with three days of an antibiotic and advised to drink plenty, thereby diluting the antibiotic in the urine. Three days later she feels partially better but not cured. The urine culture is reported as negative and free of infection: Wrong again; a standard

laboratory culture will miss well over 50% of infections: Absence of evidence is not evidence of absence. A response failure to the guideline treatment of three days of antibiotic is no surprise; 20% to 30% of patients will fail recommended treatment whether prescribed for three days or 14 days [43].

It is equally plausible that similarly affected women are experiencing untreated chronic urinary infection, over years, because the tests and guidelines directing treatment are erroneous.
isolates.

The ethical and clinical governance dilemma

Many of the problems that we have had to address are well reviewed by Greenhalgh *et al* (2014) in "Evidence based medicine: a movement in crisis?"[46].

Is it ethical to treat these people with antibiotics because your diagnosis of urinary infection, relies heavily on data from basic science studies? Is it ethical to treat on your clinical judgement and best available evidence drawing on "Practical wisdom" [47, 48]. See
https://www.ted.com/talks/barry_schwartz_on_our_loss_of_wisdom.

Some argue that the patients should not be treated because there are no clinical trial data available to justify this: Guyatt *et al* (1992) of the Evidence Based Medicine working Group stated "*Evidence-based medicine de-emphasizes intuition, unsystematic clinical experience, and pathophysiologic rationale as sufficient grounds for clinical decision making and stresses the examination of evidence from clinical research*" [49].

Others argue that there is no disease, because these women have tested negative on all common tests, including tests for systemic inflammation. Some go as far as to suggest that the symptoms have a psychological origin.
If after ceasing treatment the symptoms, signs and pathological signals return is it ethical to reinstate an antibiotic prescription? Some would argue that this involves risk and point to safety concerns, others fear antibiotic resistance; these being used to advocate no treatment. However, if the patient is suffering and was not suffering when on treatment what is the ethical thing to do?

There are no treatment guidelines for this patient group. NICE admits this by recording a "Placeholder statement" for chronic recurrent urinary infection. Should you not treat because there are no guidelines? Some believe that you should not.

What is the ethical approach to patients who suffer from conditions that have yet to be explored in clinical trials and for whom there are no guidelines? Is it ethical to base treatment decisions on the evidence that is available upstream of clinical trials?

Some believe, strongly, that these patients should not be treated and so they are not.

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