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Research Article

Mitigation and Management of Urinary Tract Infection in a Urodynamics Clinic

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ABSTRACT

The prevalence of Urinary Tract Infection (UTI) varies by age, sex, race, pregnancy status, and pathology, with an increasing burden among older adults and those in regions with low socio-demo- graphic indices. UTIs are predominantly caused by bacteria and fungi; e.g. Candida spp.. They can cause and compound Lower Urinary Tract Symptoms (LUTS), and make invasive diagnostic tests like Urodynamics risky in terms of exacerbation. Infection control combines horizontal measures— hand hygiene, aseptic techniques, cleaning protocols—and vertical strategies focusing on specific pathogens. The latter being costlier.

Screening mid-stream urine (MSU) with dipstick tests prior to invasive testing minimises the risks associated with infection. Where pathology or communication limitations make sample collection difficult, alternative methods can be attempted, including: Quick-Wee for infants; supra-pubic tapping for spinal cord injury patients; and intermittent catheterization. Traditional MSU culture re- mains the gold standard technique for diagnosing UTI with a cut-off ≥10^5 CFU/ml, reduced to ≥10^4 CFU/ml for paediatric samples obtained by intermittent cathterisation and ≥10^3 CFU/ml for those with indwelling catheters. Advanced technologies like MALDI-TOF-MS and POC lateral flow assays can minimise the delay in obtaining test results and give accurate results including in- formation on any microbes susceptibility to treatment. Urine biomarkers can also aid in diagnosing bladder dysfunctions, highlighting the potential of POC urine testing in the urodynamics clinic.

Treatment guidelines from NICE recommend age and sex-specific antibiotic regimens for sympto- matic bacterial UTIs, with asymptomatic bacteriuria treated only in pregnancy. Fungal UTIs are typically managed with fluconazole, often in hospital settings, but drug resistance is increasing in both kingdoms. Alternative treatment approaches target intracellular bacterial communities or em- ploy innovative therapies such as antimicrobial peptides and photodynamic therapy.

Keywords

Urinary Tract Infection, Biomarker, Diagnostic Test, Urodynamics, Point-of-Care Testing, Patient care directions.

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Acronyms and Abbreviations

AMP: Antimicrobial Peptides, ASB: Asymptomatic Bacteriuria, ATP: Adenosine Tri-Phosphate, BJU: British Journal of Urology, CFU: Colony Forming Units, CIC: Clean Intermittent Catheterisation, CMOS: Complementary Metal Oxide Semiconductor, CVA: Cerebrovascular Accident, DALYs: Disability-Adjusted Life Years, DO: Detrusor Overactivity, ELISA: Enzyme Linked Immunosorbant Assays, LUTS: Lower Urinary Tract Symptoms, MUI: Mixed Urinary Incontinence, MALDI-TOF-MS: Matrix-associated Laser Desorption Ionization Time of Flight Mass Spectroscopy, MSU: Mid-Stream Urine, NGAL: Neutrophil Gelatinase-Associated Lipocalin, NICE: National Institute for Health and Care Excellence, POC.auris: Point-of-Care testing for Candida auris, PDT: Photodynamic Therapy, PGD: Patient Group

Directive, SCI: Spinal Cord Injury, TESSLA: Trans-cutaneous Electrical Spinal Stimulation for LUT Functional Augmentation, uNGF: Urinary Nerve Growth Factor, USI: Urodynamic Stress Incontinence.

Background

The prevalence of Urinary Tract Infection (UTI) varies with age, race and sex [1], pregnancy, parity, and pathology [2]. Lower Urinary Tract Symptoms (LUTS) can be bothersome and embarassing, and UTI can be causative, secondary, or acquired nosocomially during diagnosis and treatment. Urodynamics is a key part of the diagnosis of LUTS [3] and often repeated following subsequent surgery or medical treatment.

Infection Control is paramount in the management of any clinical service. Horizontal strategies are the uni- versal and broad ranging measures like hand washing during any patient contact, aseptic technique for invas- ive procedures, and cleaning schedules for specific clinical areas [4]. Vertical strategies focus on a specific pathogen and are relatively expensive [5]. This article aims to summarise current and aspirational methods of detection and management of UTI in a Urodynamics service.

Global Burden of UTI

A systematic review and meta-analysis of a million individuals worldwide found that the incidence of UTI varied from 1.1% to 3.7% depending on region [6]. A focused study of older women revealed an increase of 132% in incidence, presumably reflecting the ageing population [7], however, the number of deaths and total disability-adjusted life years (DALYs) have also increased independently of age [idem] suggestive of an in- crease in intractable infections. Prevalence has increased by 4% since 1990 especially in women, older men and regions with low socio-demographic indices [8].

Nature of Urinary Tract Infection

Urinary Tract Infections are a type of microbial infection that can take place in any portion of the urinary system [9]. They can be caused by a range of microbes, though bacteria and fungi are the main culprits [10,11]. Cystitis is an infection of the lower urinary tract [12] and encompasses fungi- the most common nosocomial UTI; more specifically Candida *spp*. [13].

Asymptomatic bacteriuria (ASB) describes significant bacteria in clean-catch urine from an asymptomatic patient [14]. It's incidence increases with age, and if left untreated in pregnancy, the rate of subsequent UTI has been demonstrated to be 25% [15]. Pyelonephritis (upper tract UTI) is often secondary to cystitis, and in pregnant women it carries a risk of miscarriage and premature delivery [2], explaining treatment in this cohort.

Methods of Urine Collection

To perform any analysis of urine it is necessary to obtain a sample, and a voluntary mid-stream sample (MSU) on arrival at the clinic is ideal. However, pathology or limitations in communication can make this difficult and there is little guidance on how to obtain the urine sample and if it can ever be omitted. The 'Quick-Wee' method was first described in 2016 and encapsulates the use of a gauze soaked in cold water and rubbed on the stomach of an infant to stimulate the cutaneous voiding reflex [16]. It increased the success rate in clean-catch urine collection in two different cohorts [17,18]. Patients with upper motor neuron Spinal Cord Injury (SCI) use supra-pubic tapping to elicit (reflex) detrusor contraction which can be supplemented by clean intermittent catheterisation (CIC) [19]. Trans-cutaneous electrical spinal stimulation for LUT functional augmentation (TESSLA) can re-engage the spinal circuits of the Lower urinary tract and facilitate normal bladder and urethral function after SCI [20].

The Crede manouvre is the simple method of pushing on the lower abdomen to increase pressure and stimulate voiding and has been successful in obtaining a urine sample in those with underactive bladders [21]. The Valsalva manouvre involves holding the nose and blowing out through the ears [22], or blowing into a syringe case with the plunger removed. It increases abdominal pressure and facilitates urine leakage. However, neither Credè or Valsalva manoeuvres are recommended in those with Detrusor overactivity (DO) [23], and it is important to consider the patients dignity when deliberately causing incontinence.

Intermittent catheters can be used by the patient or clinician, however, they do carry a risk of introducing UTI, strictures and false passageways with repeated use [24].

Biomarkers for UTI

Dipsticks identify the presence of blood, nitrites and leucocyte esterase in the urine which are all indirect indicators of the presence of microbes in the urinary tract. According to local procedure, the MSU will occasionally be sent for culture. The gold standard measure of UTI is finding $\geq 10^5$ colony forming units (CFU) per ml of any microbe in this culture after a few days [25]. In samples obtained from children using intermit- tent catheters, this threshold is reduced to $\geq 10^4$ CFU [26] and further reduced to $\geq 10^3$ in patients with in- dwelling catheters [27].

In patients with residual urine secondary to neurogenic bladders, and an elderly cohort, the cytokine interleukin 6 (IL-6) was able to differentiate UTI from asymptomatic bacteriuria and quantify symptom severity [28,29]. Chemokines CXL1 and CXC8 were also diagnostic in the elderly group and testing procedures for all signalling proteins can take less than 24 hours. IL-6 and IL-10 have also been measured from sweat patches worn by older adults for 72 hours [30] which could avoid a visit to hospital for urine sample collection.

Technology to Measure Biomarkers Urine

Cultures are counted by a microbiologist looking into a microscope. Urine dipsticks are judged manually by a trained healthcare professional, or can be read by a reflectance spectrophotometer, which can measure down to 25 leucocytes per µl and correct for dehydration and other sample attributes in a few seconds. Other

optical methods include Phase-contrast microscopy, Automated Flow Cytometry and Matrix-associated laser desorption ionization time of flight mass spectroscopy (MALDI-TOF-MS) [31]. During Flow Cytometry, markers are labelled with fluorophores then the sample is passed through an argon laser beam for counting [32]. It can identify different leucocyte subsets and cytokines [33] but the process can take up to a week.

MALDI-TOF-MS reduces this to a few hours.
Enzyme linked immunosorbent assays (ELISA) use antibodies to to quantify a target cytokine in a liquid sample, and Multiplex versions now exist to look at a range of biomarkers simultaneously [29]. A Raspberry Pi with a camera was programmed to collect strip images and identify blood and leucocytes with good accuracy [34].

Point-of-Care testing for Candida auris (POC.auris) is a type of lateral flow assay that uses droplet magneto- fluidics to identify the nucleic acid of Candida auris, a fungus that is becoming resistant to treatment [35].

While Fungal UTIs do produce white blood cells, the count is lower than for bacterial infection [36] and would be less likely to show on dipstick screening. Rapid and sensitive indicators are therefore highly desirable.

Complementary Metal Oxide Semiconductors (CMOS) can be used to scan urine dipsticks for very sensitive, and immediate, readings of leucocyte esterase [37]. Low cost, portable aptasensors use DNA to bind to s.aureas then trigger signal transduction and will soon be available at the point of care [38]. A personal glucose meter and silver nanoparticle-invertase complexes can identify E.coli and S. aureus and assess their anti- microbial susceptibility within 4 hours [39] which could be very useful in providing treatment and prophylaxis in the Urodynamics clinic. And finally, a non-faradic electrochemical impedence spectroscope can detect IL-6 from human urine at the POC [40].

Current Treatment of UTI

Any individual with a symptomatic LUTI who doesn't use a catheter in the UK is subject to NG109 [12]. It advocates waiting for culture and susceptibility results and prescribing a narrow spectrum antibiotic, with specific drugs recommended for children up to the age of 16, pregnant girls and women, and men and women over 16 years. The dose and treatment regimen also varies with age. Asymptomatic bacteriuria is only treated in pregnant women, in keeping with other countries, and for those presenting with symptoms of Acute Pyelonephritis (UUTI) a broad spectrum antibiotic and consideration of hospitalisation is appropriate.

Once the culture results are available, then a narrow spectrum antibiotic to which the microbe is susceptible can be substituted.
Symptomatic UTI is always treated with antibiotics in those using catheters, and referral to hospital is necessary in: pregnancy; immunosuppression; high risk of complications; resistance to oral antibiotics; predisposition to recurrent UTI; the very dehydrated; and those unable to take oral medicines. There is a small overlap between the drugs recommended for cathterised and uncatheterised patients. [idem]

Whilst we know fungal infections of the urinary tract are common, they are not detailed by the NICE treatment guidelines, perhaps because they are treated in hospital more often than primary care. However, the literature describes the use of fluconazole for all fungal infections of the urinary tract [41,42] including pyelonephritis in a kidney transplant patient [43]. It is important to consider the source of the fungus in a urine sample. For example, dysuria in women can often be caused by urine coming into contact with peri-urethral tissue that is inflamed due to candidal vaginitis.

A current perspective article suggests future management of recurrent UTI's should consider intracellular bacterial communities (IBCs) and bacterial persistence [44]. The former respond well to the macrolide, fluoroquinolone, tetracycline and rifampicin classes of antibiotics,[idem] and techniques involving Antimicrobial Peptides (AMPs), Photodynamic Therapy (PDT) and Electroporation have been proposed for resistant microbes [45].

When to test for UTI

NICE Clinical Summaries advocate urine dipstick testing in patients under 65 years, but not older given a reduction in reliability [46,47]. So different methods may be required for screening in future Urodynamics clinics. Thankfully, the flourish of research and innovation in this area means POC technology is becoming available, and can multitask diagnostically.

Diagnostic and Monitoring potential of Urine

The concept of POC testing urine can work for diagnosis or exclusion of other bladder symptoms. While the presenting symptoms are similar, elevation of CXCL-1, CXCL-8 and CXC-10 were seen in UTI but not OAB, and very responsive to antibiotics in a general adult cohort [48]. In females with Mixed Urinary Incontinence (MUI) and those with pure Detrusor Overactivity (DO), the urinary nerve growth factor (uNGF): creatinine ratio was larger than in a control group and those with pure Urodynamic stress incontinence (USI), and even higher in those with de-novo DO following incontinence surgery [49]. In a different cohort, the uNGF level is correlated with the severity of neurological impairment following Cerebrovascular Accident (CVA), but not the symptoms of urgency or the urodynamic diagnoses [50]. In the majority of patients with overactive bladder symptoms, 4mg of tolterodine daily halved the ratio of uNGF/creatinine and was associated with a similar reduction in symptom score [51]. In paediatric patients with Vesico-ureteral reflux (VUR) Neutrophil gelatinase-associated lipocalin (NGAL) was significantly increased compared to control subjects, and the ratio of NGAL:creatinine and cathelicidin (LL7):creatinine were correlated with the severity of this reflux [52]. However, the latter metric was significantly lower in those with renal scarring (RS). [idem].

Conclusions

This review has considered when and how to test urine for microbial infection, and highlighted the diagnostic potential of biomarkers in urine. POC testing could extend the range of diagnoses to which a urodynamic service could contribute. Additionally, patient-group directives [53] would allow healthcare professionals to provide antimicrobial treatment and prophylaxis for some patients in the UK. The concept of sending a sample to microbiology could be extended to assessing the cleanliness of a clinical area, and bioluminescence meters are now available to rapidly measure Adenosine Tri-Phosphate (ATP) in clinical areas for day-to-day quality assurance of a service [54].

Given that fungal infections give rise to less leucocytes for detection by urine dipsticks, and are increasingly reistant to treatment, the need for sensitive POC testing is urgent. At the moment, any sample testing positive for leucocytes on a screening dipstick needs to be sent for microbial culture in case of *c.auris*. The risks during pregnanacy should be placed in context; by the final few weeks of pregnancy, no mother with ASB developed pyelonephritis [55], but the risks are larger in earlier trimesters. Finally, it is worth considering that gram negative bacteria can kill some fungi (i.e. c. *albicans*) and conversely, fungi can modulate bacteria's virulence, viability and susceptibility to antibiotics [56].

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