Diagnostic Evidence Co-operative Oxford

NHS National Institute for Health Research

Point-of-care testing for urinary tract infections

Horizon Scan Report 0045

June 2016

Clinical Question:

In diagnosing patients with suspected urinary tract infections, what is the accuracy and utility of point-of-care tests compared to the current standard of urine microscopy, culture and antibiotic sensitivity analysis?

Background, Current Practice and Advantages over Existing Technology:

Background

Urinary tract infections (UTIs) are among the most common types of infections, with an estimated 92 million people affected worldwide in 2013.[1] The global burden of this disease is rising, with 16.1% increase in age-standardised incidence between 1990 and 2013 and 58,000 years lost to disability (YLD) in 2003 alone.[1] UTIs are also a significant cause of mortality especially among the elderly population with 4835 deaths in England and Wales reported in 2012.[2] UTI symptoms accounted for 1-3% of all primary care consultations[3] and it was the main indication for 13.7% of community antibiotic prescriptions.[4] The 1994/5 cost estimates of treating UTIs in the National Health Service were £124 million.[5] Two decades on, it can only be assumed that with the rising prevalence of UTIs combined with the emergence of antibiotic-resistant organisms, the health and economic burden of the disease is likely to have increased.

UTIs are broadly defined as infection of the urethra, bladder, ureters or kidneys by non-commensal micro-organisms, most commonly *Escherichia coli, Staphylococcus saprophyticus* and *Enterococcus faecalis*.[6] Other causative uropathogens include *Enterobacteriaceae sp.* (*Proteus mirabilis* and *Klebsiella sp.*), group *B streptococci, Pseudomonas aeruginosa,* and *Citrobacter sp.* They frequently arise from peri-urethral contamination by uropathogens found in faecal flora which then ascend into the bladder via the urethra.[7] Further migration of uropathogens from the bladder via the ureters into the kidneys results in pyelonephritis.

UTIs are categorised as either uncomplicated or complicated. Uncomplicated UTIs can be further sub-classified into cystitis (lower urinary tract) and pyelonephritis (upper urinary tract). Patients with cystitis typically present with dysuria, frequency, urgency, haematuria and/or suprapubic pain; pyelonephritis classically manifests with flank pain, costovertebral angle tenderness, fever, nausea and vomiting in addition

to urinary symptoms.[7,8] Children present with atypical symptoms such as abdominal pain, vomiting, fever and irritability, and often without urinary tract symptoms.[9] UTIs in children could have serious sequelae of renal scarring and end-stage renal failure.[8,9] Uncomplicated UTIs occur in otherwise healthy individuals with no underlying structural or neurological urinary tract abnormalities. Risk factors include female gender, prior UTI, sexual activity, vaginal infection, diabetes, obesity and genetic susceptibility.[10]

Complicated UTIs occur when the urinary tract or host defense is compromised, e.g., secondary to urinary obstruction, urinary retention caused by neurological disease, immunosuppression (including diabetes), renal failure, renal transplantation, pregnancy and the presence of foreign bodies such as calculi, indwelling catheters or other drainage devices.[8] These patients are particularly susceptible to recurrent UTIs, perinephric abscesses, renal failure, urosepsis and death.[11]

Current practice

The current standard for diagnosing patients with suspected UTI is microscopy, culture and antibiotic sensitivity analysis of a midstream, clean-catch urine specimen, although this is not recommended for first-time uncomplicated UTI. The results of these tests are typically available within 24-72 hours after the microbiology laboratory receives the specimen.[12] In routine practice, clinicians can perform a urine dipstick test which confirms the presence of a urinary tract infection with 45% sensitivity and 99% specificity based on positive urine leucocyte esterase and nitrites.[13] However, the test cannot specify the causative uropathogen(s) involved and antibiotic sensitivities. Under usual circumstances when patients present with UTI symptoms, clinicians prescribe antibiotics empirically (for broad-spectrum coverage of the most common uropathogens) or based on a positive urine dipstick test.[14] The corollary of empirical treatment is the emergence of multi-drug-resistant uropathogenic organisms especially among *Enterobacteriaceae* family members, which are increasingly acquiring extended-spectrum β-lactamases (ESBLs), such as cefotaximases (CTX-Ms), oxacillinases (OXAs), AmpC-type β-lactamases and carbapenemases.[8] Empirical therapy without evidence of infection can also needlessly put patients at risk of serious super-infections i.e. *Clostridium difficile* colitis and MRSA sepsis.[8,15] The prevalence of these multi-drug resistant infections is on the rise, which will evidently augment the health and economic burden of this disease.[4]

Asymptomatic bacteriuria in women is defined as isolation of the same bacterial strain in quantitative counts $\geq 10^5$ CFU/mL in two consecutive, voided, clean-catch urine specimens from an individual without clinical signs and symptoms of UTI.[11,16] For pregnant women, if two urine culture results are positive for significant bacteriuria, a course of antibiotics is indicated.[17] A Cochrane review found that screening of pregnant women for asymptomatic bacteriuria with urine cultures reduces the incidence of pyelonephritis, low fetal birthweight, and preterm delivery, and that it is also cost-effective.[18]

Management of UTIs in patients with indwelling urethral catheters has its own challenges. It is well established that patients with indwelling catheters are at increased risk of UTIs, along with pyelonephritis, urosepsis, renal stones and renal failure.[19] Counterintuitively, the evidence states that screening for asymptomatic bacteriuria and antibiotic prophylaxis in this population, is ineffective in preventing sepsis.[11,20,21] Instead, indwelling catheters should only be inserted when indicated, discontinued when it is no longer necessary and antibiotics should only be prescribed on sound clinical grounds (i.e. signs of sepsis) rather than urine culture results alone.[17]

Advantages over existing technology

Point-of-care (POC) testing for UTIs can potentially:

- decrease the time involved in getting an accurate diagnosis.
- provide doctors with specific guidance on which antibiotics to prescribe for maximum therapeutic benefit.
- reduce laboratory load of urine specimens and associated costs.
- mitigate the increasing prevalence of antibiotic resistance with inappropriate broad-spectrum antibiotic prescribing.
- minimise the number of GP visits and hospital admissions associated with mismanaged urinary tract infections and adverse effects of inappropriately prescribed antibiotics.

Details of Technology:

We identified 20 commercially available point-of-care UTI tests. Five of these point-of-care UTI tests are culture-based devices, which all require mid-stream samples of urine. In all five tests, one can compare bacterial colony densities against the reference chart to semi-quantify bacterial load. It is also possible to evaluate the species present on the culture medium by colour-matching the chromogenic media with a reference chart in four of these tests. One culture-based test, namely FLEXICULT™, additionally provides basic antibiotic sensitivity analysis. All of the samples need to be cultured in an incubator at a temperature of 35-37°C. A result for the culture-based devices can be expected within 16-24 hours.

The (semi)automated urine analysers have the same read-out as the urine dipstick test, (i.e. specific gravity, pH, leukocytes, nitrite, protein, glucose, ketone, urobilinogen, bilirubin, erythrocytes) although the human error involved in visual interpretation can be eliminated. The parameters of interest for detecting UTI are positive nitrites and leukocytes. The enzymatic assay, Uriscreen®, looks at catalase activity in the urine sample to detect bacteriuria. Urine analysers and enzymatic assays principally aim to detect the presence of bacteriuria but provide limited information on the causative pathogen and antibiotic sensitivities.

Overall, their relative rapidity, simplicity and user-friendliness appear to be their key advantages over the current standard of laboratory based urine culture, microscopy and sensitivity analysis. A summary of the commercial POC UTI tests available can be found in Table 1.

TABLE 1: SUMMARY TABLE OF POINT-OF-CARE UTI DEVICES

Product	Manufacturer / Location	Description of device	Type of sample analysed (Volume of sample)	Analysis Time	Portable	Additional equipment required	Positive result outcomes	Storage Temp. (Degrees Celsius)	Method Principle	CE Mark	FDA approved
CULTURE BASED DEVICES											
FLEXICULT ™	Statens Serum Institut Diagnostica / Denmark	Chromogenic agar plate with 6 segments - 5 evaluating antibiotic sensitivities and 1 control segment	Midstream urine sample ; (NS)[1]	24 hours	✓	Incubator	Semi-quantification of bacterial growth, evaluation of the species present, and assessment of sensitivity to the antibiotics in each of the plate segments	Store at 2-8 °C.	Culture and susceptibility testing	✓	✗
Uricult Trio	Orion Diagnostics / Finland	Plastic slide with CLED/MacConkey + E.coli agar medium	Randomly voided, midstream, clean-catch and catheterized samples ; (NS)[1]	16-24 hours when incubated at 36.8°C or 1-3 days at room temperature	✓	Incubator	Semi-quantification of bacterial growth, evaluation of the species present	Room temp (15-25°C)	Culture	✓	✓
DipStreak (Chromostreak)	Novamed / Israel	Plastic paddle with two opposing agar media (UriSelect3 chromogenic agar and MacConkey), housed in a closed transparent plastic tube	Midstream urine sample ; (NS)[1]	18-24 hours	✓	Incubator	Semi-quantification of bacterial growth, evaluation of the species present	Store at 2-8 °C.	Culture	✓	✓
DiaSlide	Novamed / Israel	Hinged plastic case containing two opposing agar media (CLED/MacConkey or UriSelect3 chromogenic agar and MacConkey)	Midstream urine sample ; (NS)[1]	24 hours	✓	Incubator	Semi-quantification of bacterial growth	Room temp (15-25°C)	Culture	?	✓
onSite	Trek Diagnostics System / USA	Hinged plastic case containing two opposing agar media (MacConkey agar + one of TSA/Columbia CNA/CLED agar	Midstream urine sample ; (NS)[1]	Not specified	✓	Incubator	Semi-quantification of bacterial growth, evaluation of the species present	2-25°C	Culture	?	✗
ENZYMATIC ASSAY											
UriScreen	Savyon Diagnostics Ltd / Israel	Enzymatic (catalase) test	Midstream urine sample ; (1.5-2mL)	2 minutes	✓	No	Detects bacteriuria / pyuria	Room temp (10-28°C)	Assay	✓	✓

All of the used tests should be disposed in an infectious laboratory bin.
(NS)[1] = volume not specified

TABLE 1: SUMMARY TABLE OF POINT-OF-CARE UTI DEVICES (CONTINUED)

Product	Manufacturer / Location	Description of device	Analysis Time	Portable	Read-out printed	Additional equipment required	Positive result outcomes*	Method Principle	CE Mark	FDA approved
(SEMI)AUTOMATED URINE ANALYSERS										
URI TEX	Cormay / Poland	Semi-automated portable analyser	60 seconds	✓	Optional software	Urine dipstick strips	*1	Reflectance photometer	?	✗
Uro-Dipcheck ® 240e	Erba Diagnostics Mannheim / Germany	Automated portable analyser	55 seconds	✓	✓	Urodip 10 e, Dekaphan test strips	*1	Reflectance photometer	?	✗
Convergys® Urostar 100	Invergent Technologies / UK	Automated portable analyser	1-2 minutes	✓	✓	Convergys® Urostar Strips or CM	*1 + Creatinine & Albumin and Microalbumin to Creatinine ratio	Semi-quantitative reflex photometer with 3 x LED + color detector	✓	✗
AUTION ELEVEN™ AE-4020	Arkray / Japan	Semi-automated portable analyser	7 seconds	✓	✓	AUTION test strips	*1 + automatic protein/creatinine and albumin/creatinine calculation	Reflectance photometer	✓	✗
Aution Micro	A. Menarini Diagnostics / Italy	Automated portable analyser	45 seconds	✓	✓	AUTION Sticks 10EA, Uriflet 9UB	*1	Dual or Single (BLD only) Wavelength Reflectance Method	✓	✗
URIT-30	URIT / China	Automated portable analyser	60 seconds	✓	✓	URIT 11G/10G urine reagent strips	*1	Dual Wavelength Reflectance Method	✓	✗
BioDoctor BS-502	Bionics Co. Ltd / Korea	Semi-automated portable analyser	5 seconds	✓	✗	Urine dipstick strips (unspecified brand) + iOS device - Results sent to smart phone device	*1 + free radicals	Details not specified	✓	✗
AS120	ChungDo Pharm. Co., Ltd / China	Automated portable analyser	Details not specified	✓	Unspecified	Self-Stick + test strips	*1 + ascorbic acid	Details not specified	?	✗
E-Reader 120	AccuBioTech. Co., Ltd / China	Semi-automated portable analyser	Details not specified	✗	Unspecified	ABT-UM-A33/34 test strips	*1 + ascorbic acid	Reflectance photometer	?	✗
BC401	Contec Medical Sysems™	Automated portable analyser	Details not specified	✓	✗	Details not specified	*1 + ascorbic acid	Details not specified	?	✗
Uryxxon Relax	Macherey Nagel / Germany	Automated analyser	30 - 60 seconds	✗	✗	Medi-Test Uryxxon Stick 10	*1	Reflectance photometer	?	✓
Urisys 1100	Roche Diagnostics Ltd / Switzerland	Semi-quantitative analyzer	70 seconds	✓	✓	CHEMSTRIP test strips	*1	Reflectance photometer	✓	✓
Clinitek Status+	Siemens Healthcare /Germany	Automated portable analyser	60 seconds	✓	✓	CLINITEK Multistix® urine test	*1 + protein/creatinine and albumin/creatinine calculation	Reflectance photometer	?	✓
Urilyzer ® 100 Pro	Analyticon Biotechnologies AG / Germany	Automated portable analyser	60 seconds	✓	✓	CombiScreen® 5/7/11SYS PLUS	*1	Reflectance photometer	?	✗

*1 : includes 10 parameters - *Specific Gravity, pH, Leukocytes, Nitrite, Protein, Glucose, Ketone, Urobilinogen, Bilirubin, Erythrocytes*

Patient Group and Use:

- To diagnose adults with symptomatic bacteriuria
- To diagnose children with suspected urinary tract infections
- To diagnose patients with indwelling urinary catheters with symptomatic bacteriuria
- To screen pregnant women for asymptomatic bacteriuria

Importance:

Urine microscopy, culture and sensitivity analysis in a microbiology laboratory is considered the reference standard for UTI diagnosis. However, this requires adequate laboratory facilities, it is expensive and labour-intensive (needing trained technicians and microbiologists to interpret the results), culminating in a 24-72 hour delay in diagnosis. Antibiotic prescribing following urine dipstick screening has been a widely adopted management approach for UTIs with one study showing this to be cost-effective if the value of saving a day of moderately bad symptoms is valued at ≥ £10.[22] However, this practice is also known to be a major contributor to the emergence of multi-drug resistant bacterial strains (e.g., *Enterobactericeae* with extended-spectrum beta-lactamases and Methicillin-resistant *Staphylococcus aureus* (MRSA)).[8,15]

For this reason, there has been growing interest in developing new and efficient technology, which can (1) rapidly and accurately diagnose UTIs and (2) inform the clinician on which antibiotic to prescribe for maximum therapeutic benefit. Prompt diagnosis and treatment of UTI is necessary in reducing the morbidity and mortality associated with urosepsis, especially in the paediatric and geriatric population. However, in a primary care setting, full culture-based assay with microscopy and sensitivity analysis are not feasible. Implementation of an accurate, user-friendly UTI POC device which performs pathogen identification and sensitivity assays, promises to have far-reaching impact on clinical practice, patient outcomes and the demand on health-care resources.

Previous Research:

We retrieved twelve studies which assessed the diagnostic accuracy of eleven POC UTI devices. We could not obtain accuracy data for the nine remaining devices. Five of these studies evaluated the accuracy of culture-based devices (FLEXICULT™, Uricult Trio (2), Dipstreak, Diaslide); six examined the enzymatic assay (1Uriscreen) and one study evaluated the diagnostic accuracy and considered the clinical impact of six POC urine analysers (Aution Eleven™, Aution Micro, Uryxxon Relax, Unisys 1100, Clinitek Status +, Urilyzer ® 100 Pro).

These devices were tested in different sub-populations (children, pregnant women, patients with indwelling catheters, general population etc.) and most of the samples were taken in a primary care setting. The following tables present the diagnostic accuracies for each of these devices based on existing research, and if data was not available, this is also indicated. The accuracies of the culture-based devices and catalase enzymatic assay were compared to the urine microscopy and culture reference standard (Table 2). The urine analysers were compared to the laboratory urinalysis reference test, Urisys 2400 (Table 3).

Accuracy compared to existing technology

FLEXICULT™

Bongard et al.[23] evaluated the analytical laboratory performance of the FLEXICULT™ device in 200 urine samples compared to urine microscopy and culture. These samples were submitted in the course of routine patient care and selected for analysis by Public Health Wales laboratory staff. 124 samples were submitted from outpatients (primary care, outpatient clinics and emergency department), and 76 from hospital inpatients. Specific information on the demographics of their patient population was not reported. According to this study, this test has a sensitivity of 87.0% (95%CI: 67.9-95.5%), specificity of 83.2% (95%CI: 74.7-89.2), positive predictive value (PPV) of 54.1% (95%CI: 38.4-69.0) and negative predictive value (NPV) of 96.6% (95%CI: 90.4-98.8%), for semi-quantification of bacterial load. Further studies are currently under way to assess the diagnostic accuracy and utility.[24,25]

Uricult Trio

Two studies assessed the diagnostic accuracy of the Uricult Trio dip-slide test. However, with no confidence intervals provided, the data from both studies must be interpreted with caution.

1. In one study by Anacleto et al.,[26] the authors compared the accuracy of the Uricult Trio device against conventional urine microscopy and culture. They tested 198 mid-stream clean-catch, randomly voided (i.e. urine collected at any point in the stream) or catheterized urine samples from children aged 0-7 if the sample had been screened positive for nitrites or leukocyte esterase with a urine dipstick test. A urine sample was obtained from children <2 years of age if they presented with crying on urination, frequency, haematuria, gastrointestinal symptoms or fever without a focus. Samples were taken from children >2 years of age if they presented with dysuria, urgency, flank pain, new onset enuresis or chills. The overall sensitivity of the test was 68%; specificity, 82%; PPV, 81%; and NPV, 71%. 98/198 (49%) participants had significant bacteriuria according to conventional urine culture results.

2. Ferry et al.[27] compared the accuracy of the Uricult Trio device with the results of conventional urine microscopy and culture. 434 consecutive urine samples were taken from a total of 183 patients who either had a suspected UTI or had already received antibiotic therapy after confirmed UTI diagnosis (multiple episodes per patient). The study was conducted in one primary health care centre in Sweden over a period of 12 months. Further details were not provided on how the patients presented or the demographics of the study's patient population. The study reported that the test had 88% sensitivity, 90% specificity, PPV of 92% and NPV of 85%. 254/434 (59%) samples from 165/183 patients were positive for bacteriuria according to laboratory urine culture (when the threshold for significant bacteriuria was $\geq 10^4$ CFU/ml).

Of note in these studies is the rather high prevalence rate.

DipStreak (Chromostreak)

Yagupsky et al.[28] examined the accuracy of the DipStreak culture-based device compared to conventional urine microscopy and culture using 1070 clean-catch urine samples (251 from hospitalized patients and 819 from outpatients). No details were provided on how the patients in the study presented, how they selected the samples or the patient demographic. They reported that the DipStreak test had a sensitivity of 95.7%, specificity of 99.2%, PPV of 98.5% and NPV of 97.7%. 270/1070 (25%) samples were positive for significant bacteriuria on urine culture. No confidence intervals were reported.

Diaslide

Rosenberg et al.[29] evaluated the accuracy of the DiaSlide culture-based device. Samples were initially obtained from 700 patients— 30% of the samples from geriatric and chronically ill hospitalised patients and 70% of the samples from the hospital wards and outpatient clinics. 700 samples were pre-screened for catalase enzyme activity using the Uriscreen® test (refer below), of which 473 samples had positive catalase activity and 227 samples had negative catalase activity. The 473 samples with positive catalase activity were then tested with the DiaSlide culture test and its accuracy was compared against conventional urine microscopy and culture. Overall, the test had 98.3% sensitivity, 97.5% specificity, PPV of 98.3% and NPV of 97.5% when compared to the laboratory culture results and when the samples were prescreened with Uriscreen®. 243/473 (51.3%) were positive for significant bacteriuria on urine culture when the threshold was 10^4CFU/ml. Confidence intervals were not reported.

Uriscreen ®

Six studies evaluated the accuracy of the Uriscreen catalase enzymatic assay in diagnosing UTIs.[30-35] Confidence intervals were not provided in three studies.

Pregnant women

1. Millar et al.[30] obtained urine samples from 383 women for prenatal screening of asymptomatic bacteriuria. Five of these samples were contaminated; so the accuracy of Uriscreen® was compared to conventional urine microscopy and culture in the remaining 378 samples. Overall, the study reported that Uriscreen® had a sensitivity of 70(±13.5)%, specificity of 45(±5.5)%, PPV of 14(±5)% and NPV of 92(±4)% in diagnosing UTIs. 43/378 (11%) specimens had significant bacteriuria according to laboratory urine culture results.
2. Hagay et al.[31] analysed randomly voided and mid-stream urine samples from 313 consecutive pregnant women who presented to a Maternal-Fetal Medicine Unit in a hospital in Israel over a period of 6 months. The study wanted to evaluate the accuracy of the Uriscreen® test to screen for asymptomatic bacteriuria compared to urine culture and microscopy. The study reported that the test had 100% sensitivity, 81% specificity, 30% PPV and NPV of 100% compared to conventional culture. 24/313 (7.6%) specimens had laboratory urine culture results indicating significant bacteriuria.

Catheterised patients

3. Teppa et al.[32] study assessed the accuracy of Uriscreen® compared to urine microscopy and culture in detecting asymptomatic bacteriuria in a sample of 150 catheterised urine specimens from pregnant women. The study reports that the test had a sensitivity of 60.7(±18.1)%, specificity of

89.3(±5.6)%, PPV of 56.6% and NPV of 90.8% in this test population when the threshold for significant bacteriuria was >10^5 CFU/ml. The prevalence was reported to be 18.7%.

4. Macías et al.[33] tested the accuracy of Uriscreen® compared to urine microscopy and culture in detecting bacteriuria-candiduria in 57 hospitalised patients with indwelling catheters. This study reported that Uriscreen® had a sensitivity of 88.5%, specificity 42.6%, PPV of 66.7% and NPV of 74.1%. 57/108 (57.4%) cultures were positive for significant bacteriuria when the threshold for significant bacteriuria was >10^3 CFU/ml.
5. Palmer et al.[34] tested the diagnostic accuracy of Uriscreen® compared to urine microscopy and culture in detecting significant bacteriuria in catheterised urine specimens from 200 consecutive children scheduled to undergo urodynamic evaluation who were asymptomatic for UTI. The study reported that test had sensitivity of 65.2%, specificity of 85.7%, PPV of 57.7% and NPV of 89.2%. 46/200 (23%) cultures were positive for significant bacteriuria when using the cut-off value of >5×10^4 CFU/ml. The lower accuracy of the study can be explained to a degree by the higher cut-off value for significant bacteriuria.

Paediatric patients

6. Waisman et al.[35] tested the diagnostic accuracy of Uriscreen® compared to urine culture in early detection of UTIs in urine specimens obtained through midstream void technique, bladder catheterization, or suprapubic aspiration from children aged 1 month to 17 years of age. The study was conducted over a period of 6 months on a random sample of 121 children who presented to the emergency department of a pediatric tertiary care centre (Israel) with symptoms suggestive of UTI. The sensitivity was reported to be 100%; specificity, 68.6%; PPV, 56.4%; and NPV, 100%. 35/121 (29%) cultures were positive for significant bacteriuria. The study used varying cut-off values for significant bacteriuria depending on how the samples were retrieved (i.e. >10^5 CFU/mL for clean catch or urine bag specimens; >10^3 CFU/mL for bladder catheterization specimens; >10^2 CFU/mL for urine collected by suprapubic aspiration). Interestingly, 30/35 positive cultures were from female patients (85.7%), and the most commonly affected age group was 3-7 years (40.0%), followed by 8-17 years (31.4%), 3 months-2 years (22.9%), and 0-2 months (5.7%).

Urine analysers

One study by Schot et al.[36] evaluated the diagnostic accuracies of six POC urine analysers compared to the laboratory-based urine analyser, Urisys 2400, using 77 urine samples submitted for routine investigation at one of the four participating general practices. All devices had 100% sensitivity (67-100%), specificities ranging from 94-100%, PPV ranging from 73-100% and NPV of 100% (93-100%) for nitrite detection, which is considered the main marker for UTIs. However, the study would have had greater external validity if these devices were compared with conventional culture, because in reality, urine microscopy and culture is used clinically to diagnose UTIs, not urinalysis.

We did not identify any published research studies for the following devices: onSite, URI TEX, Uro-Dipcheck ® 240e, Convergys ® UroStar 100, URIT-30, BioDoctor BS-502, AS120, E-Reader 120 and BC401.

TABLE 2. ACCURACY OF POINT-OF-CARE UTI CULTURE-BASED DEVICES AND ENZYMATIC ASSAYS

Product	Manufacturer / Location	Number of samples tested ; Test population	Threshold for significant growth	Accuracy	Sensitivity (%)(95% CI)	Specificity (%)(95% CI)	PPV (%)(95 % CI)	NPV (%)(95% CI)	Ref
CULTURE-BASED DEVICES									
FLEXICULT ™	Statens Serum Institut Diagnostica / Denmark	N=200 124 (outpatient setting) 76 (secondary care setting)	$\geq 10^5$ CFU/ml	—	87.0% (67.9-95.5)	83.2% (74.7-89.2)	54.1% (38.4-69.0)	96.6% (90.4-98.8)	23
Uricult Trio	Orion Diagnostics / Finland	198 (paediatric patients aged 0-7)	$\geq 10^4$ CFU/ml	—	68%	82%	81%	71%	26
		434 (primary health care setting)	$\geq 10^3$ CFU/ml for primary uropathogens (E.coli, S. saprophyticus) ; $\geq 10^4$ CFU/ml for secondary uropathogens ; $\geq 10^5$ CFU/ml for doubtful uropathogens	88%	88%	90%	92%	85%	27
DipStreak (Chromostreak)	Novamed / Israel	N=1070 (251 hospitalized patients and 819 outpatients)	$>10^5$ CFU/ml (single organism + mixed culture)	98%	95.7%	99.2%	98.5%	97.7%	28
DiaSlide	Novamed / Israel	473 (prescreened hospital urine specimens using UriScreen)	$\geq 10^4$ CFU/ml	—	98.3%	97.5%	98.3%	97.5%	29
ENZYMATIC ASSAY									
UriScreen ®	Savyon Diagnostics Ltd / Israel	378 women (prenatal screening for bacteriuria)	$\geq 10^4$ CFU/ml	—	70% (±13.5%)	45% (±5.5%)	14% (±5%)	92% (±4%)	30
		313 (pregnant women)	$>10^5$ CFU/ml	—	100%	81% (±4.5%)	30% (±10%)	100%	31
		150 (catheterised urine samples from pregnant women)	$>10^5$ CFU/ml (single organism culture)	—	60.7% (± 18.1%)*	89.3% (±5.6%)*	56.6%	90.8%	32
		108 cultures from 57 patients with indwelling catheter	$\geq 10^3$ CFU/ml	—	88.5%	42.6%	66.7%	74.1%	33
		200 catheterised urine specimens from children	$\geq 5 \times 10^4$ CFU/ml	81%	65.2%	85.7%	57.7%	89.2%	34
		121 paediatric patients in emergency department)	10^5 CFU/mL for clean catch or urine bag specimens; 10^3 CFU/mL for bladder catheterization specimens; 10^2 CFU/mL for urine collected by suprapubic aspiration.		100%	68.6%	56.4%	100%	35

* Unclear measure of error.

TABLE 3. ACCURACY OF POC URINE ANALYSERS COMPARED TO THE PRIMARY LABORATORY REFERENCE TEST (URISYS 2400).[36]

Product	Manufacturer / Location	Number of samples tested ; Test population	Leukocytes (%)(95% CI)				Erythrocytes (%)(95% CI)				Nitrites (%)(95% CI)				Ref
			Sensitivity	Specificity	PPV	NPV	Sensitivity	Specificity	PPV	NPV	Sensitivity	Specificity	PPV	NPV	
(SEMI)AUTOMATED URINE ANALYSERS															
AUTION ELEVEN™ AE-4020	Arkray / Japan	77 (primary care)	0.93 (0.78-0.99)	0.96 (0.84 - 0.99)	0.94 (0.78-0.99)	0.96 (0.84 - 0.94)	0.36 (0.23 - 0.52)	1 (0.87 - 1)	1 (0.76 - 1)	0.54 (0.41 - 0.67)	1 (0.67-1)	1 (0.93-1)	1 (0.68-1)	1 (0.93-1)	36
Aution Micro	A. Menarini Diagnostics / Italy	77 (primary care)	0.94 (0.78 - 0.99)	0.98 (0.87 - 1)	0.97 (0.81 - 1)	0.96 (0.84 - 0.94)	0.55 (0.39 - 0.69)	1 (0.87 - 1)	1 (0.83 - 1)	0.62 (0.48 - 0.75)	1 (0.67-1)	1 (0.93-1)	1 (0.68-1)	1 (0.93-1)	36
Uryxxon Relax	Macherey Nagel / Germany	77 (primary care)	0.94 (0.78 - 0.99)	0.98 (0.87 - 1)	0.97 (0.81 - 1)	0.96 (0.84 - 0.99)	0.75 (0.59 - 0.86)	0.94 (0.78 - 0.99)	0.94 (0.79 - 0.99)	0.74 (0.58 - 0.86)	1 (0.67-1)	1 (0.93-1)	1 (0.68-1)	1 (0.93-1)	36
Urisys 1100	Roche Diagnostics Ltd / Switzerland	77 (primary care)	0.78 (0.60 - 0.90)	1 (0.90 - 1)	1 (0.83 - 1)	0.87 (0.74 - 0.94)	0.64 (0.48 - 0.77)	1 (0.97 - 1)	1 (0.85 - 1)	0.67 (0.52 - 0.80)	1 (0.67-1)	1 (0.93-1)	1 (0.68-1)	1 (0.93-1)	36
Clinitek Status+	Siemens Healthcare /Germany	77 (primary care)	0.56 (0.38 - 0.73)	1 (0.90 -1)	1 (0.78-1)	0.76 (0.63-0.86)	0.55 (0.39 - 0.69)	1 (0.87 - 1)	1 (0.83 - 1)	0.62 (0.48 - 0.75)	1 (0.67-1)	1 (0.93-1)	1 (0.68-1)	1 (0.93-1)	36
Urilyzer ® 100 Pro	Analyticon Biotechnologies AG / Germany	77 (primary care)	0.66 (0.47-0.81)	1 (0.90-1)	1 (0.81-1)	0.80 (0.67 - 0.89)	0.73 (0.57 - 0.85)	0.97 (0.82 - 1)	0.97 (0.82 - 1)	0.73 (0.57 - 0.85)	1 (0.67-1)	0.94 (0.84-0.98)	0.73 (0.45-0.91)	1 (0.93-1)	36

Impact compared to existing technology

There are currently no studies evaluating the clinical impact or utility of culture-based POC UTI devices in a primary care setting, but two study protocols for evaluating the FLEXICULT device have been published: Bates et al. aim to evaluate the clinical and cost-effectiveness of FLEXICULT compared to the usual care arm with the study outcomes being appropriate antibiotic prescribing at day 3 in both arms, and incidence of treatment failures, recurrence, complications, hospital admissions and health care costs at 3 months follow up.[24] The study by Holm et al. primarily aims to compare the rates of appropriate antibiotic prescribing in the FLEXICULT and usual care arm.[25]

Schot et al.'s study[36] assessed the user-friendliness of six commercially available point-of-care urine analysers as the secondary outcome measure. A sample of seven GP assistants and two midwives who were unfamiliar with these devices were asked to perform tests on all six POC urinalysers in random order. After each test, they were asked to complete a standardised questionnaire, which contained five questions concerning user-friendliness of the analyser, test procedure and susceptibility to flaws (in preparation of the analyser, performing the analysis and reading the test results). First-time users were then asked if they deemed the device useful in their daily practice, if it would improve their productivity and efficiency and if it would lead to more accurate evaluation of the urine test strip. The authors also collated data from manufacturers' information sheets to evaluate user-friendliness.

The results of the questionnaire were that all first-time users found the POC urine analysers easy to use, and most frequently did not have problems getting a read-out. The potential for error in the process of manual handling and result interpretation was considered lowest in Uryxxon Relax (Macherey Nagel) and Urisys 1100 (Roche). Overall, the Uryxxon Relax was found to be the most user-friendly by six of the nine first-time users. The majority felt that these devices would be useful in daily practice (6/9), improve efficiency and productivity, and lead to more accurate evaluation of the urine test strip (7/9).[36]

Guidelines and Recommendations

The Health Protection Agency recommends that urine culture should not be routinely performed in adult, non-pregnant women aged 65 years and under with urinary symptoms unless they have severe or ≥3 urinary symptoms (dysuria, frequency, urgency, haematuria and/or suprapubic pain) with the absence of vaginal discharge or irritation. In women with mild symptoms, a urine dipstick test is recommended before the sample is sent for culture. Urine should be sent for culture in symptomatic men and pregnant women, patients with suspected pyelonephritis, or previously failed antibiotic treatment or persistent symptoms, as well as those with recurrent UTI, abnormalities of the genitourinary tract and renal impairment. Urine should not be sent for culture in the asymptomatic elderly or those with indwelling catheters based on positive dipstick tests, as bacteriuria is common and treatment would be unnecessary. UTIs should be considered in any sick child and every young child with unexplained fever > 38^{o}C.[17]

NICE has not published any guidelines for treatment of UTIs in the adult, pregnant or catheterised patient population, rather 6 'quality standards' which provide guidance on how to diagnose or manage a UTI under limited circumstances.[37] They have published a clinical guideline on diagnosis and management of UTIs in the paediatric population.[38] In short, this guideline includes information on the various clinical manifestations of

UTI as well as information on recommended urine-testing strategies according to age group. Urgent urine microscopy and culture, empirical antibiotic therapy, and referral to specialist paediatric care should be arranged for children < 3 years old with suspected UTI or at intermediate/high risk of serious illness. For children > 3 years of age, the guideline states that dipstick testing for leukocyte esterase and nitrite is a safe and adequate alternative to microscopy and culture for diagnosing UTIs; if the results return positive, the sample can then be sent for microscopy and culture. Antibiotic treatment can be commenced if nitrites were positive on the urine dipstick test. The guideline also lists the indications for urine culture and further investigation (i.e. imaging, urodynamic studies).

SIGN appears to have a more comprehensive summary of recommendations for diagnosing and managing suspected UTIs in adults, pregnant women and patients with indwelling catheters, with the level of evidence indicated with each recommendation.[15] The guidelines also discuss the role of 'near-patient' testing (urine microscopy and dipstick testing) for diagnosing UTIs in each of these sub-populations. For example, the guideline stipulates that dipstick testing should not be used to diagnose UTI in patients with catheters (Recommendation 6.2.2, Grade B evidence) or screen for bacterial UTI in pregnant women at the first or subsequent antenatal visits (Recommendation 4.2, Grade A evidence).[15] It also states that dipstick testing can be used to guide management in otherwise healthy women under 65 years of age presenting with mild or ≤2 symptoms of UTI (Recommendation 3.2.3, Grade B evidence).[15]

Briefly, the Infectious Diseases Society of America (IDSA) and the European Society for Microbiology and Infectious Diseases have jointly published "International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women,"[39] however this document makes recommendations on treatment rather than diagnosis of UTIs. In addition, IDSA have published "International Clinical Practice Guidelines on the Diagnosis, Prevention, and Treatment of Catheter-Associated Urinary Tract Infection in Adults".[19]

Future directions:

Researchers are developing new POC UTI tests such as microfluidics,[40] biosensor technologies,[41] real-time optical screening systems[42] and mobile phone-based micro-photometric systems[43] for rapid pathogen identification and susceptibility testing. There is also work in progress in finding new molecular markers e.g. heparin-binding protein that can diagnose UTIs with higher sensitivity and specificity as opposed to leucocyte esterase and nitrites alone.[44]

Research Questions:

1. What is the clinical impact of implementing point-of-care UTI devices in a primary health care setting compared to current practice on rates of:
    1. antibiotic prescribing,
    2. adverse effects of antibiotics,
    3. hospital admissions related to complications,
    4. UTI-related mortality/morbidity?

2. What is the cost-effectiveness of utilising point-of-care UTI devices versus using a urine dipstick test or urine microscopy, culture and sensitivity analysis?

Suggested next steps:

1. Study evaluating accuracy of commercially available UTI diagnostics in a primary care setting and in different sub-populations (pregnant women, children, elderly patients, patients with indwelling catheters, non-pregnant women <65 years of age etc.).
2. Studies evaluating the utility of implementing these point-of-care UTI devices in a primary health care setting.

Acknowledgements:

The authors would like to thank Nia Roberts for helpful discussions. This work is supported by the National Institute for Health Research (NIHR) Diagnostic Evidence Co-operative Oxford at Oxford Health NHS Foundation Trust. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

This report was prepared by the Primary Care Diagnostic Horizon Scanning Centre Oxford.

Authors: Sarah T. Thomas, Carl Heneghan, Christopher P. Price, Ann Van den Bruel, Annette Plüddemann

Contact details: Dr. Annette Plüddemann; Email: dec@phc.ox.ac.uk

References:

1. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet.* 2015 Aug 22;386(9995):743-800. doi: 10.1016/S0140-6736(15)60692-4.
2. Office for National Statistics. Deaths Registered in England and Wales, 2014. http://www.ons.gov.uk/ons/rel/vsob1/mortality-statistics--deaths-registered-in-england-and-wales--series-dr-/2014/rft-table-1-4-6-14.xls. Published 2015. Accessed Jan 20, 2016.
3. National Institute for Health and Clinical Excellence . Common infections: urinary tract infection Data focused commentary: management of acute uncomplicated urinary tract infection. http://www.npc.nhs.uk/therapeutics/common_infections/uti/resources/dfc_common_infect_uti.pdf. Published 2009. Accessed Jan 20, 2016.
4. Health Protection Agency. English National Point Prevalence Survey on Healthcare-associated Infections and Antimicrobial Use, 2011: Preliminary data. Published 2012. Accessed Jan 20, 2016.
5. Plowman R et al. An economic model to assess the cost and benefits of the routine use of silver alloy coated urinary catheters to reduce the risk of urinary tract infections in catheterized patients. *Journal of Hosp Infection.* 2001;48: 33-42.
6. Stamm WE, Hooton TM. Management of urinary tract infections in adults. *N Engl J Med.* 1993;329(18):1328-34.
7. Lee UJ. Urinary tract infection in women [Internet]. London: BMJ Publishing Group Ltd. 2015 [cited 2016 Jan 20]. Available from: Best Practice.
8. Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections: Epidemiology, mechanisms of infection and treatment options. *Nat Rev Microbiol*. 2015;13(5):269-84. doi: 10.1038/nrmicro3432.
9. Goilav B, Kaskel F. Urinary tract infection in children [Internet]. London: BMJ Publishing Group Ltd. 2015 [cited 2016 Jan 20]. Available from: Best Practice.
10. Foxman, B. Urinary tract infection syndromes: occurrence, recurrence, bacteriology, risk factors, and disease burden. *Infect. Dis. Clin. North Am.* 2014;28: 1–13.
11. Nicolle LE et al. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. *Clin Infect Dis.* 2005;40(5):643-54.
12. Pagana K, Pagana T, Pagana T. *Mosby's Diagnostic and Laboratory Test Reference.*12th ed. St Louis, United States: Mosby; 2013:968.
13. St John A, Boyd JC, Lowes AJ, Price CP. The use of urinary dipstick tests to exclude urinary tract infection: a systematic review of the literature. *Am J Clin Pathol.* 2006;126(3):428-36.
14. Morgan MG, McKenzie H. Controversies in the laboratory diagnosis of community-acquired urinary tract infection. *Eur J Clin Microbiol Infect Dis.* 1993;12(7):491-504.
15. Scottish Intercollegiate Guidelines Network. Management of suspected bacterial urinary tract infection in adults. Scottish Intercollegiate Guidelines Network site. Published 2012. Available at: http://www.sign.ac.uk/guidelines/fulltext/88/. Accessed Jan 20, 2016.
16. Fekete T, Hooter TM. Approach to the adult with asymptomatic bacteriuria. In: UpToDate, Bloom, A (Ed), UpToDate, Waltham, Massachusetts, 2015. Available from: http://www.uptodate.com/contents/approach-to-the-adult-with-asymptomatic-bacteriuria?source=search_result&search=asymptomatic+bacteriuria&selectedTitle=1~45#H1. Accessed Jan 31, 2016.
17. Health Protection Agency. Diagnosis of UTI Quick Reference Guide for Primary Care. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/323398/UTI_guidelines_with_RCGP_logo.pdf. Published 2011. Accessed Jan 20, 2016.
18. Widmer M, Lopez I, Gülmezoglu AM, Mignini L, Roganti A. Duration of treatment for asymptomatic bacteriuria during pregnancy. *Cochrane Database Syst Rev.* 2015;11;11:CD000491. doi: 10.1002/14651858.CD000491.pub3.

19. Hooton TM, Bradley SF, Cardenas DD et al. Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. *Clin Infect Dis.* 2010. 50(5):625-63.
20. Leone M, Perrin AS, Granier I et al. A randomized trial of catheter change and short course of antibiotics for asymptomatic bacteriuria in catheterized ICU patients. *Intensive Care Med.* 2007;33:726-79.
21. Lin K, Fajardo K. Screening for asymptomatic bacteriuria in adults: evidence for the U.S. Preventive Services Task Force reaffirmation recommendation statement. *Ann Intern Med.* 2008;149:20-4.
22. Turner D et al., Cost effectiveness of management strategies for urinary tract infections: results from randomised controlled trial. *BMJ.* 2010;340: c346. doi: 10.1136/bmj.c346.
23. Bongard E et al. Analytic laboratory performance of a point of care urine culture kit for diagnosis and antibiotic susceptibility testing. *Eur J Clin Microbiol Infect Dis.* 2015;34(10): 2111-2119. doi: 10.1007/s10096-015-2460-4.
24. Bates J et al. Point of care testing for urinary tract infection in primary care (POETIC): protocol for a randomised controlled trial of the clinical and cost effectiveness of FLEXICULT™ informed management of uncomplicated UTI in primary care. *BMC Fam Pract.* 2014;15:187. doi: 10.1186/s12875-014-0187-4.
25. Holm A et al. Point of care susceptibility testing in primary care - does it lead to a more appropriate prescription of antibiotics in patients with uncomplicated urinary tract infections? Protocol for a randomized controlled trial. *BMC Fam Pract.* 2015;16:106. doi: 10.1186/s12875-015-0322-x.
26. Anacleto FE et al. Bedside diagnosis of outpatient childhood urinary tract infection using three-media dipslide culture test. *Pediatr Nephrol.* 2009;24(8):1539-1543.
27. Ferry S et al. Uricult and Sensicult dipslides for diagnosis of bacteriuria and prediction of drug resistance in primary health care. *Scand J Prim Health Care*. 1989;7:123-8.
28. Yagupsky P, Rider M, Peled N. Clinical evaluation of a novel chromogenic agar dipslide for diagnosis of urinary tract infections. *Eur J Clin Microbiol Infect Dis.* 2000;19(9):694-8.
29. Rosenberg M et al. Initial testing of a novel urine culture device. *J Clin Microbiol.* 1992;30(10):2686-91.
30. Millar L et al. Rapid enzymatic urine screening test to detect bacteriuria in pregnancy. *Obstet Gynecol.* 2000 Apr;95(4):601-4.
31. Hagay Z et al. Uriscreen, a rapid enzymatic urine screening test: useful predictor of significant bacteriuria in pregnancy. *Obstet Gynecol.* 1996;87(3):410-3.
32. Teppa RJ, Roberts JM. The uriscreen test to detect significant asymptomatic bacteriuria during pregnancy. *J Soc Gynecol Investig.* 2005;12(1):50-3.
33. Macías AE et al. Catalase test (Uriscreen) in the detection of bacteriuria-candiduria in hospitalized adults with Foley catheter. *Rev Invest Clin.* 2002;54(6):521-6.
34. Palmer LS, Richards I, Kaplan WE. Clinical evaluation of a rapid diagnostic screen (URISCREEN) for bacteriuria in children. *J Urol.* 1997;157(2):654-7.
35. Waisman Y, Zerem E, Amir L, Mimouni M. The validity of the uriscreen test for early detection of urinary tract infection in children. *Pediatrics.* 1999 Oct;104(4):e41.
36. Schot MJ et al. Analytical performance, agreement and user-friendliness of six point-of-care testing urine analysers for urinary tract infection in general practice. *BMJ Open.* 2015;5(5):e006857. doi: 10.1136/bmjopen-2014-006857.
37. National Institute for Health and Clinical Excellence. Urinary tract infections in adults (NICE quality standard [QS90]). National Institute for Health and Clinical Excellence site. Published 2015. Available at: https://www.nice.org.uk/guidance/QS90/chapter/List-of-quality-statements. Accessed Jan 20, 2016.
38. National Institute for Health and Clinical Excellence. Urinary tract infection in under 16s: diagnosis and management (NICE clinical guideline [CG54]). National Institute for Health and Clinical Excellence site. Published 2013. Available at: http://www.nice.org.uk/guidance/cg54. Accessed Jan 20, 2016.
39. Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clinical Infect Dis.* 2011;52:e103–20.

40. Cho S et al. Smartphone-based, sensitive micro PAD detection of urinary tract infection and gonorrhea. *Biosens Bioelectron.* 2015;74:601-611.
41. Mach KE et al. Biosensor diagnosis of urinary tract infections: a path to better treatment?. *Trends Pharmacol Sci.* 2011;32(6):330-336.
42. Fredborg M. et al. Real-time optical antimicrobial susceptibility testing. *J Clin Microbiol.* 2013;51(7):2047-53. doi: 10.1128/JCM.00440-13.
43. Kadlec MW et al. A Cell Phone-Based Microphotometric System for Rapid Antimicrobial Susceptibility Testing. *J Lab Autom.* 2013;19(3):258-266.
44. Kjölvmark C, Påhlman LI, Åkesson P, Linder A. Heparin-binding protein: a diagnostic biomarker of urinary tract infection in adults. *Open Forum Infect Dis.* 2014;1(1):ofu004. doi: 10.1093/ofid/ofu004.

Abbreviations:

CFU/ml:	Colony-Forming Units per millilitre
IDSA:	Infectious Diseases Society of America
MRSA:	Methicillin-resistant *Staphylococcus aureus*
NHS:	The National Health Service
NICE:	The National Institute for Health and Care Excellence
NPV:	Negative Predictive Value
POC:	Point-of-care
PPV:	Positive Predictive Value
SIGN:	Scottish Intercollegiate Guidelines Network
UTI:	Urinary tract infection