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Management of Urinary Tract Infections: Problems and Possible Solutions

Lorenza Murgia, Ottavia Stalio, Alyexandra Arienzo,
Valeria Ferrante, Valentina Cellitti,
Salvatore Di Somma, Paolo Visca and
Giovanni Antonini

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Abstract

In clinically suspected urinary tract infections (UTIs), empirical antibiotic treatment is usually started long before the laboratory results of urine culture and antibiogram are available. Although molecular diagnostic approaches are being applied to the diagnosis of many infections, UTIs are generally diagnosed by traditional culture methods. Patient care could greatly benefit from the development of a rapid, accurate, inexpensive test that could be done at patient's bedside, allowing the practitioner to plan targeted, more effective therapy. Such a test would potentially reduce incorrect or unnecessary use of antibacterial drugs and reduce the emergence of bacterial resistance. In response to this pressing and unmet clinical need, several methods have been developed in the last few years. Among these, the new point-of-care test (POCT) for detecting UTIs named Micro Biological Survey (MBS) UTI CHECK holds promise, as it allows semi-quantitative determination of bacterial load in urine leading to a fast detection of UTIs and to evaluation of bacterial antibiotic susceptibility. This new technology operates through a colorimetric survey performed in low-cost, ready-to-use, disposable vials, in which 1 ml of urine is inoculated without any preliminary treatment and requiring neither specialized personnel nor a specialized equipment.

Keywords: urinary tract infections, point-of-care test, clinical microbiology analysis, UTIs diagnosis, antimicrobial resistance

1. Introduction: definition and background over urinary tract infections (UTIs)

Urinary tract infections (UTIs) are caused by the presence and multiplication of microorganisms in the urinary tract, sometimes spreading to the bloodstream and possibly resulting in several clinical syndromes (e.g., pyelonephritis, cystitis, urethritis, epididymitis and prostatitis) [1].

Most UTIs are caused by bacteria, and when they occur in the urine without causing symptoms, this condition is called asymptomatic bacteriuria; when growth of bacteria leads to a panel of symptoms, this condition is referred to as symptomatic bacteriuria [1]. Urinary tract infections can manifest as bacteriuria with limited clinical symptoms and sepsis, depending on localized or systemic extension [2].

The onset of UTIs is mostly due to the ascent of microorganisms from the urethra, especially organisms of enteric origin, e.g., *Escherichia coli*, which is the causative pathogen in 70–95% of acute, uncomplicated UTIs in adults, followed by other Enterobacteriaceae, such as *Proteus mirabilis* and *Klebsiella* spp., and by *Staphylococcus saprophyticus* in 5–10% of cases [2]; hence, the higher frequency of UTIs in women than men, depending on anatomic structure, and the increased risk of infection following bladder catheterization, which compromises natural defense mechanisms. A small fraction of UTIs can have hematogenous origin, and usually involve a few relatively uncommon microorganisms (e.g., *Staphylococcus aureus*, *Candida* spp., *Salmonella* spp. and *Mycobacterium tuberculosis*), which cause primary infections elsewhere in the body and thus reach the urinary tract [2].

UTIs are among the most prevailing infectious diseases with a substantial financial burden on society [3]. The incidence of community-acquired UTIs is highest in young women [1]: almost half of all women will experience at least one episode of UTI during their lifetime, and nearly 1 in 3 women will have had at least one episode of UTI by the age of 24 years [2]. Urinary tract infection incidence increases with age for both sexes. It is estimated that 10% of men and 20% of women over the age of 65 years have asymptomatic bacteriuria [1].

Reports from European countries and the USA show that ca. 15% of all community-prescribed antibiotics are dispensed for UTIs [3]. UTIs account for many annual hospital admissions, especially among the elderly: in the UK, the number of emergency admissions of older people with a primary diagnosis of UTI showed a 200% increase from 2001/2002 to 2012/2013, parallel to a related increase in bed days, which both are the second highest increase (in absolute terms) among groups of conditions [4]. Nevertheless, UTIs are believed to have been greatly overcoded in recent years: part of the increase may be due to changes in coding practice, part to increased emergence of antibiotic resistance [4]. Moreover, UTIs represent at least 40% of all hospital acquired infections and most of them occur following catheterization, which is considered one of the main risk factors associated to onset of UTIs [3].

2. Current laboratory standards in UTI diagnosis

The clinical evidence of UTI is based on a number of basic criteria, including clinical symptoms, and laboratory data which should provide evidence of the presence of microorganisms by culturing of urine samples, or other specific tests [2]. However, the diagnosis of UTIs is primarily based on symptoms and signs. Tests that suggest or prove the presence of bacteria or white cells in the urine may contribute additional information to inform management

but rarely have important implications for diagnosis, also considering the long time often required for obtaining results with traditional methods [5].

The gold standard for diagnosis of bacteriuria is culture of appropriate urine sample [6, 7]. Sampling by needle aspiration minimizes the risk of contamination, while catheter and midstream sampling show a higher risk of contamination and therefore yield more false positive results [5]. However, needle aspiration is invasive and midstream sampling is preferred in clinical practice [8]. Routine culture is generally carried out streaking 10 µl of urine sample on agar plates containing selective or differential media and reading results after at least 24–48hours of incubation, considering characteristic colony morphologies and average quantitation. If there is the need for more accurate quantitative results, 100 µl plating following serial dilutions of urine sample must be performed [9]. The main value of urine culture is to identify microorganisms, most often bacteria; indirect indicators of the presence of bacteria (for example, urinary nitrites) are much less valuable than urine culture [5].

The number of bacteria in urine has been considered relevant for the diagnosis of UTIs since the Sixties, when Kass developed the concept of significant bacteriuria (10^5 CFU/ml) opening up to quantitative microbiology for the diagnosis of infectious diseases; his notion is still generally used to help diagnosis. Nevertheless, it has recently become clear that no fixed bacterial count can be applied to all kinds of UTIs and all circumstances, and even low bacterial concentrations are considered clinically relevant considering specific clinical pictures, sampling protocols and patient's sex. The problem of counting low numbers must then be considered [2].

Along with pathogen identification, outlining its antimicrobial susceptibility profile is considered to be crucial to ensure an appropriate treatment [10]. Antimicrobial susceptibility testing is routinely performed using the Kirby-Bauer disk diffusion technique according to Clinical and Laboratory Standards Institute (CLSI) guidelines, meaning culturing bacteria from urine samples on agar plates in presence of disks containing selected antibiotics; interpretation of results requires the measurement of halos of inhibition around disks according to reference tables [11].

As with most bacterial infections, diagnosis of UTI depends on culturing the clinical sample in the clinical laboratory, and results are typically delayed of two to three days from sample acquisition [10]. This is due to the need for sample transport to the laboratory and the time required for bacteria to grow on culture media [10]. Thus, the standard method for UTI diagnosis is time consuming and logistically difficult [6].

Since the patient cannot remain untreated during this rather prolonged period before definitive diagnosis is obtained, physicians usually prescribe broad spectrum antibiotics prior to antibiogram results. This practice has many undesirable consequences in the short and long terms, such as treatment failure leading to spread or chronicization of infection, increased health care costs, and increased antibiotic resistance by a growing number of bacterial strains. Given these drawbacks, it is obvious that a rapid and accurate method of UTI diagnosis and bacterial antibiotic susceptibility assessment would offer significant health benefits [12].

The introduction of partial and complete automation in clinical diagnostic in the 2000s has allowed the management of large-scale sample volumes and workflows optimization still providing reliable results for both pathogen identification and antibiotic susceptibility testing [10, 13].

Large-scale systems, anyway, are expensive and require more dedicate space, equipment and more personnel competence, which makes them applicable to a large hospital setting, but are difficult to establish in a small hospital, or in a limited-resource setting (e.g., developing countries). These high-throughput culture-based instruments, moreover, remain relatively slow and are not amenable for point-of-care use [10].

The introduction of matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF) technology in microbiology has allowed rapid and reliable bacterial identification, featuring both high sensitivity and specificity, improving efficiency and saving consumables and labor [14, 15]. MALDI-TOF technique is usually coupled with culture of urine samples, to allow isolation of bacteria and therefore obtain pure cultures, which will undergo MALDI-TOF analysis after some sample treatment. Recently, extensive databases have been developed that include protein profiles of main microorganisms involved in infections; some studies have therefore investigated the possibility to apply MALDI-TOF analysis directly to urine samples, yielding promising results also when coupling such analysis with screening methods, such as automated microscopic urine sediment analysis [16, 17]. It must be considered, however, that such high-throughput technology has high installation and maintenance costs, and requires dedicated spaces, limiting its use in routine analyses to centralized laboratories. Moreover, the technique cannot currently identify two species of bacteria when present simultaneously, and cannot determine antibiotic susceptibility; thus, traditional culture of urine samples is still necessary [18].

Nevertheless, the occurrence of more than one bacterial strain in urine samples participating in the infection should not be overlooked. Polymicrobic infections are more often associated with catheterization and aging, reaching 10% incidence rates in the community and 30% in hospital setting among elderly people [19]. Bacterial strains recovered from polymicrobic infection show metabolic alterations and altered virulence traits, such as antibiotic resistance [19]. However, relationships between coinfecting strains are not yet fully understood [20], although some studies are exploiting such infections' mechanisms [21, 22]. As clinical laboratories tend to report cultures showing single or clearly predominant bacteria and will not routinely report occurrence of polymicrobic associations, unless significant numbers of each species are detected, quite a large portion of UTIs are not correctly diagnosed nor treated, threatening patient's safety [19, 23–25]. Therefore, an improvement of diagnosis and clinical pathways is needed in order to enhance not only detection of pathogens in urine, but also profiling the whole microflora and determining the antimicrobial susceptibility of individual components.

3. When a urine culture followed by antibiogram is needed

Even though the incidence of UTIs is higher in women [6], also related pathologies in men, such as epididymitis and prostatitis, may be caused by migration of pathogens from the urethra or

bladder, the most common pathogens isolated being *Chlamydia trachomatis*, Enterobacteriaceae (typically *E. coli*) and *Neisseria gonorrhoeae*. For this last species, to reach correct diagnosis and plan following treatment, culture of mid-stream urine should be performed, together with nucleic acid amplification test (NAAT) on first voided urine or Gram staining in order to specifically detect *Neisseria gonorrhoeae* or *Chlamydia trachomatis* [6, 26].

Urine culture is recommended to determine the presence or absence of clinically significant bacteriuria in patients prior to urological interventions (e.g., surgery) and the presence of bacteriuria is controlled by directed pre-operative treatment of the detected pathogen [2, 6].

Urine culture is considered a valuable tool during patients' follow-up: in women whose symptoms do not resolve or recur within 2–4 weeks after the completion of treatment, urine culture and antimicrobial susceptibility test should be performed and a new antibiotic regimen should be considered. Afterward, in patients who underwent antibiotic treatment, a follow-up with subsequent urine culture should verify the treatment efficacy [2]. Urine culture is also recommended in women who present with atypical symptoms, pregnant women and males with suspected UTI [2].

In case of complicated UTIs, a broader range of bacteria is expected to be involved (often within the Enterobacteriaceae family), and these are more likely to show antibiotic resistance. Moreover, patients with a complicated UTI are more prone to have recurrent infections (more than 3 episodes/year) [2, 8, 27, 28]. Therefore, the choice of a therapy for these conditions must be supported by urine culture and antimicrobial susceptibility testing to avoid ineffective antibiotics administration.

Urine culture is also required in pediatric settings, where UTIs are the most common infections in children and infants, together with upper respiratory and gastrointestinal ones, with 30% recurrence rate reported within a year after initial UTI [2, 29]. Diagnosing pediatric UTIs may be difficult, because of communication difficulties in describing symptoms and vagueness of signs in small children; therefore, the definitive diagnosis of infection in children requires a positive urine culture [2].

In febrile patients with negative results on dipstick, microscopic, or automated urinalysis, urine culture is unnecessary if there is an alternative cause of the fever or inflammatory signs. However, if the dipstick and/or urinalysis are positive, confirmation of UTI by urine culture is mandatory [29]. In febrile children with signs of UTI (clinical signs, positive dipstick and/or positive microscopy, better if urine culture is available), antibiotic treatment should be initiated as soon as possible to eradicate the infection, prevent bacteremia, improve clinical outcome, diminish the likelihood of renal involvement during the acute phase of infection, and reduce the risk of immediate and long-term complications, including renal scarring and renal failure [29, 30].

4. Empirical treatment of UTIs

The gold standard for diagnosis and successful management of UTIs is to obtain identification and quantification of the infecting agents, along with antibiotic susceptibility assessment to

direct a specific therapy [31]. The use of microbiological culture method is well established in the diagnosis of infectious diseases [32]; however, such reference method is time-consuming, requiring on average 24–48hours, thus laboratory results are not immediately available, especially at patient's presentation in the Emergency Department [32, 33]. For this reason, in order to avoid even serious complications (e.g., sepsis) and mitigate patients' discomfort, the initial treatment specified by international guidelines as first step in UTIs management is most often empirical [32]. Nevertheless, this empirical approach contributes to mis- and over-use of antibiotics [10], resulting from unnecessary or inappropriate antimicrobial therapy, participating in recent arise in bacterial resistance. In fact, for people with symptoms of UTI and bacteriuria the main aim of treatment is relief of symptoms, but in case of unsuccessful treatment it could cause some alteration of urinary tract microflora, leading to an increased risk of clinical adverse events, including infections with multi-drug-resistant organisms and the development of antibiotic-resistant UTIs [1]. Infections caused by multi-drug-resistant pathogens, such as extended-spectrum beta-lactamase (ESBL) and carbapenemase producing Gram-negative bacteria, methicillin-resistant *Staphylococcus aureus* (MRSA), and bacteria resistant to broad-spectrum antibiotics, such as fluoroquinolones and cephalosporins, are indeed increasingly recorded among UTIs and are the cause of a serious challenge to the public health system today [2, 10, 34].

The spread of antibiotic resistance is a threat to patients undergoing urological surgery in general [2], and multi-drug-resistant bacterial infections can limit the availability of effective treatment options, especially in low-income countries, rendering some UTIs difficult to treat and increasing healthcare costs [30].

This situation is generally promoted by several factors, including the overuse and misuse of antimicrobials in human and veterinary medicine and, indirectly, in agriculture. Measures to prevent and control the increase of antimicrobial resistance as well as the dissemination of resistance genes are crucial [35]. Prudent prescribing and rational use of antibiotics is a key component of action plans for reducing antimicrobial resistance [1, 2, 35, 36]. Antimicrobial stewardship programs have become a priority to optimize the outcome of prevention and treatment of infection while limiting overuse and misuse of antimicrobial agents [6], also following a systematic audit approach [37, 38]. In addition, non-antibiotic strategies are being explored [6]. There are many non-antimicrobial measures recommended, especially for recurrent UTIs [2, 28, 39, 40], but only a few results from well-designed studies are available for evidence-based recommendations [2, 41].

In general, the choice of antibiotics should be based, among other factors, upon identification and susceptibility pattern of the organism causing the UTI and the ecological collateral effects including selection of resistant bacteria by the chosen antimicrobial [2].

It must be considered, though, that the in vitro susceptibility of community-acquired uropathogens varies according to age and geographic region, and, as magnitude and variability of antimicrobial resistance patterns in the community grow, so does the need for continuous large-scale surveillance systems, in order to create databases linking epidemiological, clinical and laboratory data [42].

Therefore, the development and implementation of new clinical tools in routine medical practice could help optimizing antibiotic administration, leading to a more prudent and rational use of antibiotics. A rapid screen may be a more practical approach to yield benefits for the patient, the physician, and the laboratory [43].

The advent of new innovative diagnostic devices for UTI management, complementary to the reference culture-based methods, may lead to a new deal improving routine practice. Immunocompromised patients (e.g., diabetes mellitus, chronic kidney disease, and kidney transplant) with UTIs could particularly benefit from such diagnostic improvements. Clinical diagnosis of UTIs in this category of patients is challenging, because causative pathogens may be slightly different to those in the general population, and because of patients' clinical picture complexity. Early diagnosis is imperative in this group, and treatment of UTIs should be tailored according to individual patient characteristics [44].

5. Alternative and non-culture-based methods for the detection of UTIs

Because of the clinical importance of early UTI diagnosis, alternative rapid near-patient urine tests have been developed, such as urine dipsticks, which are widely used [31] in spite of their uncertain diagnostic accuracy [6]. The urine dipsticks test is commonly used for presumptive diagnosis of UTIs: it detects the presence of biochemical markers in urine samples which may be useful to establish the diagnosis of UTI [2]. Although many urine biomarkers for UTIs have recently been considered [45], markers that showed best results in diagnostic accuracy are nitrite and leukocyte esterase [6]. Although being cost-effective [46], such test shows low sensitivity that limits its clinical usefulness, [6] and analysis may be biased since a number of bacterial species are unreactive in these tests (e.g., no reduction of nitrates) [47, 48]. Furthermore, urine dipstick test does not detect bacteria, nor their concentration, which is essential to diagnose UTIs according to guidelines, and provides no information about antimicrobial susceptibility. Urine dipsticks are, anyway, cheap, easy to use, can be performed at doctor's office, in pharmacies or at home (even though urine dipstick test is not intended for self-diagnosis purposes [49], are available without prescription and provide results of easy interpretation within minutes.

Among hospital tests routinely used for urine analysis, microscopy examination of urine sediment has since long time been used, also undergoing automation to improve results. Although sensitivity is high, specificity is too low for exclusive use in clinical settings. Moreover, such technique requires sample centrifugation, and experienced personnel is needed to avoid errors in microscopic examination [6].

Flow cytometry found applications in many fields, also including medical disciplines [50]. Automated platforms of urinary flow cytometry have been widely adopted by centralized laboratories [10]. Flow cytometry allows of rapid detection of bacteria, white blood cells, red blood cells, epithelial cells, casts, crystals, yeasts and spermatozoa. They offer the benefit of standardize urine sediment analysis and reduce the error associated with subjective interpretation of results [51]. Nevertheless, the poor quality of available studies was confirmed in a

recent meta-analysis, which also showed current low accuracy and specificity of such method that should not be used as the sole screening tool for UTIs ([51], and references therein).

Dipslide technology has been proposed to simplify traditional culture-based methods: the test allows the detection of bacteria in liquid matrices by observing growth on different agar media (e.g., CLED agar and MacConkey agar) after immersion into sample and following 24-hour incubation. Overall, despite being simple to use and cost-effective, dipslide technology can only be considered as a guide to support further analyses: such test shows low accuracy when compared to the reference culture method [6], and no reliable detection of <10^4 CFU/ml can be obtained [7]. For this reason, dipslides are currently unsuited to routine use in clinical setting with further studies required to determine the best combination of culture media [6].

For the short term, molecular biology techniques such as real-time PCR could be used to complement conventional culture-based methods for pathogens identification, especially with regard to shortening the time to obtain results, shortening the time to decision of antibiotic therapy [32]. However, this method is limited by the broadness of the panel of pathogens included in the test, and both sensibility and specificity are low when compared to urine culture. Moreover, such technology requires many steps for sample preparation and does not allow a viable count, also considering that up to now the clearance of bacterial DNA from urine is unclear. The need for quantification in UTI diagnosis should drive future developments of commercial real-time PCR pathogen detection tools to include a quantification option [32].

In addition, possible new routes have been explored aiming to develop new clinical tools to help rapidly identify uropathogens, such as: the detection of volatile organic compounds in urine by gas chromatography and mass spectrometry and following comparison between profiles using compounds databases [52]; the use of Raman and Surface Enhanced Raman Spectroscopy, which can provide quantification and identification of bacteria populations and possibly assessment of antibiotic susceptibility, although results are still preliminary and must be significantly expanded [12]; the use of impedance spectroscopy to detect ultra-low concentrations of *E. coli* in human urine and provide quantification for UTI diagnosis [53].

Although rapid, these technologies do not provide microbiological diagnosis nor susceptibility information, which remain the cornerstone of diagnosis, particularly in settings of complicated UTI [10].

In summary, laboratory urine culture remains the gold standard investigation for UTI diagnosis [6].

6. The importance of point-of-care tests in UTI diagnosis

Some tests have been developed aiming to provide rapid and accurate diagnostic information to direct treatment decisions at the patient's bedside, which seem to have yielded good consent among practitioners [54].

Rapid and definitive near-the-patient diagnosis of UTI would have a favorable impact on its management [10]: a rapid turnaround of results could influence clinical decisions such as triage, referral, and decision to discharge the patient. Prompt clinical interventions could be provided by caregivers, meaning timely antibiotic treatment could be initiated and imprecise empirical treatment avoided [10, 55]. This would improve health outcome also providing diagnostics tools for limited-resource settings [55]. Point-of-care tests (POCTs) can provide considerable savings in health care costs by reducing the number of patients visiting health centers simultaneously improving the quality of life for patients by reducing their number of visits to health care facilities [55]. An early diagnosis based on POCTs can also enable clinicians to start antibiotic administration earlier and thereby increase chances of successfully treating the disease. In future, innovation through rapid and reliable POCTs is advisable, updating technologies to ensure efficient data management and simplify use by healthcare professionals, eventually lowering medical costs [55]. POCTs could allow a better screening and follow-up of patients not only by hospitals, but also by pharmacies and general practitioners, helping decentralize diagnosis and therefore reduce the workload of laboratories, with consequent reduction of costs related to urine analysis and management of UTIs and reduction of human errors leading to mix-ups of patient samples sent to off-site laboratories [55].

Several POCT for UTIs have been developed and are currently commercially available. They can be distinguished in: (*i*) culture-based devices, (*ii*) (semi-)automated urine analyzers and (*iii*) enzymatic assays [56]. All culture-based devices allow semi-quantification of bacterial growth and evaluation of the infecting bacterial species. Most often, samples need to be cultured and appreciable bacterial growth can be achieved in not less than 16–24 hours. The (semi-)automated urine analyzers have the same read-out as the urine dipstick test and UTI diagnosis is based on the presence of markers such as nitrites and leukocytes. Although the human error involved in visual interpretation can be eliminated and results can be obtained in 1–2 minutes, these tests do not significantly improve current practice exhibiting very low sensitivity and limited positive predictive value. The same problem has been reported for enzymatic assays [57–61].

Biosensors offer a promising approach for improving molecular diagnostic in POC settings [10]. Biosensors are binary systems composed of a recognition and a transducer element that can generate a measurable proportional signal following binding of the target analyte to the recognition element (e.g., antibody, enzyme), which allows quantitative detection of a biological entity [10]. Even though biosensors technology has been applied successfully to the field of clinical diagnostic (e.g., blood glucose and pregnancy tests), no such tests have been implemented to date to improve routine diagnosis of UTIs [55]. Indeed, key features of biosensors, such as portability, rapidity, and cost-effectiveness in comparison with their macro-scale counterparts, could be crucial for the development of a POCT for UTI pathogens identification and antimicrobial susceptibility assessment. Nevertheless, considering the urine matrix, such biosensors would require multistep sample preparation with amplification/enrichment steps to improve target detection, and such biological matrix could impair sensor performance with its variations in biochemical parameters (e.g., inhibitors, non-specific binding). Moreover, such tests should have a multiplex approach to ensure identification of a broad

panel of pathogens in different clinical scenarios, and should provide antimicrobial suscepti-bility testing to drive treatment, but genetic non-culture based approaches are limited by the fast evolution rate of defense mechanisms among bacteria. Biosensors POCTs could anyway complement reference methods helping saving resources in terms of materials, money and time, because rapid, simple and cost-effective tests could optimize further analyses therefore reducing the burden on laboratories [10].

The Micro Biological Survey (MBS) POCT "UTI CHECK" appears to hold good promise for early detection and antimicrobial susceptibility profiling of uropathogens. The MBS method allows rapid and accurate bacterial quantification through an automated colorimet-ric culture-based test; urine samples are inoculated into disposable ready-to-use reaction vials, which color will change thanks to redox indicators following bacterial growth after incubation (see **Figure 1**). Results of preliminary *in vitro* validation studies [62, 63] showed that the results obtained with this method are comparable to the reference culture-based methods.

Such findings encouraged further research in hospital settings, and clinical trials have been carried out [31] in which the efficacy of the MBS POCT was compared to the reference method, used in hospital routine, and other methods, such as urine dipsticks: the MBS POCT

Figure 1. MBS "UTI CHECK." MBS "UTI CHECK" is an automated colorimetric culture-based test. It is composed by mono-use, disposable and ready-to-use reaction vials (right) in which 1 ml of urine can be inoculated without any preliminary treatment. Up to eight urine-inoculated reaction vials can be independently allocated in an automatic thermostated optical reader (left) that it is able to detect color change induced by the growth of bacteria and automatically correlates the time required for color change with the number of bacteria present in the urine samples. Different vials contain selected antibiotics and the occurrence of the color change in the presence of antibiotics indicates antibiotic resistance of bacteria present into the urine sample.

Product	Manufacturer/ location	Description of device	Analysis time	Additional equipment required	Positive result outcomes	Method principle	Number of samples tested; Test population	Threshold for significant growth	Accuracy	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Ref
FLEXICULT™	Statens Serum Institut Diagnostica/ Denmark	Chromogenic agar plate with 6 segments – 5 evaluating anti-biotic sensitivities and 1 control segment	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	Microbial culture and susceptibility testing	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)	[23]
Uricult Trio	Orion Diagnostics/ Finland	Plastic slide with two opposing agar media	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	Microbial culture	198 (pediatric patients aged 0–7)	$\geq 10^4$ CFU/ml	—	68%	82%	[26]
							434 (primary health care setting)	$\geq 10^3$ to $\geq 10^5$ CFU/ml for doubtful uropathogens	88%	88%	90%	[27]
DipStreak (Chromostreak)	Novamed/ Israel	Plastic paddle with two opposing agar media, housed in a closed transparent plastic tube	18–24 hours	Incubator	Semi-quantification of bacterial growth, evaluation of the species present	Microbial culture	N = 1070 (251 hospitalized patients and 819 outpatients)	$>10^5$ CFU/ml (single organism + mixed culture)	98%	95.7%	99.2%	[28]

Product	Manufacturer/ location	Description of device	Analysis time	Additional equipment required	Positive result outcomes	Method principle	Number of samples tested; Test population	Threshold for significant growth	Accuracy	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Ref
DiaSlide	Novamed/ Israel	Hinged plastic case containing two opposing agar media	24 hours	Incubator	Semi-quantification of bacterial growth	Microbial culture	473 (prescreened hospital urine specimens using UriScreen)	≥10^4 CFU/ml	—	98.3%	97.5%	[29]
onSite	Trek Diagnostics System/USA	Hinged plastic case containing two opposing agar media	Not specified	Incubator	Semi-quantification of bacterial growth, evaluation of the species present	Microbial culture						
MBS UTI CHECK	MBS srl/Italy	Mono-use disposable vials for chromogenic analysis	3–5 hours	MBS Multireader	Semi-quantification of bacterial load, assessment of sensitivity to selected antibiotics	Measure of the catalytic activity of redox enzymes of bacteria	N = 223 (emergency department)	≥10^5 CFU/ml (single organism + mixed culture)	99%	92.6% (75.7–99.1)	100% (94.9–100)	[17]

Table 1. Features of main POCTs for UTI diagnosis.

showed high accuracy, sensitivity and specificity, comparable to the reference method's and higher than urine dipsticks' [31]. Although not providing bacterial identification, MBS "UTI CHECK" allows bacteria detection and quantification in urine samples. Preliminary results showed that this POCT can provide uropathogens' susceptibility pattern to a panel of antibiotics. The analytical time required for UTI diagnosis is usually less than 3 hours (up to 5–6 hours when the bacterial load is equal or less than 1×10^5 CFU/ml) and antimicrobial susceptibility assessment is obtained in less than 10 hours, which could guide downstream medical decisions with crucial information within few hours. Notably, this method features cost-effectiveness, user-friendliness, portability, easy interpretation of results, which all can lead to successful use at the patient's bedside [31]. The MBS point-of-care testing device could be developed into a valuable aid for the management of UTIs, possibly addressing more precise diagnosis and appropriate therapy also proving useful in treatment outcome evaluation. Features of main POCTs available on market, including MBS "UTI CHECK," are summarized in **Table 1**.

7. Conclusions

To date, hospital settings rely mainly on laboratory analysis following urine culture reference method; this approach requires a considerable effort in terms of workload and up to 3 days to achieve results. Furthermore, it can lead to unnecessary antimicrobial overuse which ultimately promotes the emergence of resistance [31].

The unnecessary use of antibiotic treatment may be minimized following two roads: on one hand by the establishment of antibiotic stewardship programs which require healthcare staff involvement in regular training in best use of antimicrobial agents for an improved adherence to local, national or international guidelines and regular consultation with infectious diseases physicians, with audit [6]; on the other hand by improving diagnostic pathways [1], possibly relying on use of POCTs that feature incorporation of pathogen identification with antimicrobial susceptibility testing, sufficiently versatile to be adaptable for different pathogen profiles in different clinical scenarios [10]. The advent of accurate and robust POCTs could allow a more rational screening before treatment or admission and to improve follow-up of patients for treatment outcome evaluation and for monitoring of antimicrobial prescribing performance and local pathogen resistance profiles [6].

Such approach could ultimately lead to treatment customization according to individual patients' characteristics through fast antibiotic susceptibility testing results [44], with the ultimate aim of improving patients' welfare and reduce healthcare costs.

Acknowledgements

Author details

Lorenza Murgia[1], Ottavia Stalio[1], Alyexandra Arienzo[1], Valeria Ferrante[2], Valentina Cellitti[2], Salvatore Di Somma[3], Paolo Visca[1] and Giovanni Antonini[1,2]*

*Address all correspondence to: giovanni.antonini@uniroma3.it

1 Department of Sciences, Roma Tre University, Rome, Italy

2 Interuniversity Consortium "Biostructures and Biosystems National Institute", Rome, Italy

3 Emergency Medicine, Department of Medical-Surgery Sciences and Translational Medicine, Sapienza University of Rome, Sant'Andrea Hospital, Rome, Italy

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