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REVIEW ARTICLE

Innovative Biosensor Technologies in the Diagnosis of Urinary Tract Infections: A Comprehensive Literature Review

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Abstract Urinary tract infections (UTIs) are prevalent bacterial infections globally, posing significant challenges due to their frequency, recurrence, and antibiotic resistance. This review delves into the advancements in UTI diagnostics over the past decade, particularly focusing on the development of biosensor technologies. The emergence of biosensors, including microfluidic, optical, electrochemical, immunosensors, and nanotechnology-based sensors, offers enhanced diagnostic accuracy, reduced healthcare costs. Despite these advancements, challenges such as technical limitations, the need for cross-population validation, and economic barriers for widespread implementation persist. The integration of artificial intelligence and smart devices in UTI diagnostics, highlighting the innovative approaches and their implications for patient care. The article envisions a future where multidisciplinary research and innovation overcome current obstacles, fully leveraging the potential of biosensor technologies to transform biosensor-based UTIs diagnosis. The ultimate goal is to achieve rapid, accurate, and non-invasive diagnostics, making healthcare more accessible and effective.

Keywords Urinary tract infection · Biosensors · Point of care · Uropathogens · Leukocyte esterase · Nitrite

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Introduction

Urinary tract infections (UTIs) are among the most common bacterial infections which affect millions of people globally. The most common disease is community-acquired UTIs (CAUTIs), which affects more than 150 million people every single year. They usually result in hospitalization and have a major impact on the healthcare systems. Healthcare-associated UTIs (HAUTIs), which are primarily catheter-related, range in incidence from 1.4 to 5.1%, with the community-onset HAUTIs growing in importance [25, 68]. They are more prevalent in females, and also a large proportion of them have repeated episodes. Also, UTIs are the most common infections in people of any age, especially in the elderly [88]. UTIs can be cystitis, which is a simple bladder infection, or pyelonephritis, which is a more serious kidney infection [20, 55]. The impact of UTIs on the health care systems is very significant due to both the direct costs of treatment and also indirect costs such as absenteeism and the lost quality of life. Early diagnosis of UTIs is very important because of the possibility of septicemia and also long-term consequences [5, 18].

UTIs primarily affect women, with nearly half experiencing at least one episode in their lifetime [29]. Also, at-risk populations include infants, pregnant womens, elderly people, and those with certain medical conditions [29, 34]. The global burden of UTIs has been on the rise, with the highest incidence rates [96]. Recurrent UTIs are a significant and main concern [87]. The increasing antibiotic resistance in UTIs further complicates their treatment [87]. Data on UTI burden in 6 countries from 2011 to 2021 were obtained from the Institute for Health Metrics and Evaluation (IHME) (https://vizhub.healthdata.org/gbd-results/) (date of data extraction, 25 June 2024) (Table 1).

UTIs are traditionally diagnosed on the clinical symptoms and are confirmed with the laboratory testing. To diagnose UTIs, it is first necessary to gather a thorough history of the illness and any medications taken [6, 32]. This is followed by a physical examination of the pelvic area and the evaluation of urine samples for uropathogens using different diagnostic methods [39]. The conventional diagnostic procedure is the urine culture wherein the presence of pathogenic bacteria is identified. UTI could be diagnosed by a urine culture, a urine reagent strip, or both. The gold standard diagnostic procedure is the urine culture wherein the presence of pathogenic bacteria is identified. However, this approach is very time-consuming [17, 43]. Currently, there are many fast tests for UTIs diagnosis. Such rapid tests as the dipstick tests provide more rapid results by detecting markers such as leukocyte esterase (LE) and nitrites (NITs). Their sensitivity and selectivity is also very variable according to the used biosensor, environment, and specimen [22, 94]. There are many analytes in urine which are used in UTI biosensors to diagnose UTIs. These biosensors can target different analytes and use a recognition element which is specific to analyte. An interaction between analyze and recognition element produces signals which can be interpreted quantitative or semi-quantitative (Fig. 1).

The management of UTIs is largely based on an early and correct identification and the determination of the antimicrobial susceptibility of uropathogens. Urine dipsticks are very convenient and appropriate for the UTIs testing [25]. In a study, LE test had 82.8% sensitivity and 68.1% specificity, with 52.1% positive predictive value and negative predictive value 90.5% [37]. Urine culture combined with antimicrobial susceptibility testing requires a clinical laboratory and it takes 2 to 3 days [93]. The overuse of empirical antibiotics has resulted in the development of many multidrug-resistant organisms, driving up the treatment costs and also limiting treatment options. This can be

Table 1 Average UTI incidence on the last decades and associated problems in some countries

Country	UTI incidence (per 100,000)	Associated problems
United States	7.902,804	Antibiotic Resistance, Healthcare Costs, Recurrent UTIs [52, 81]
United Kingdom	5.257.18	Antibiotic Resistance, Primary Care Burden [59, 82, 91]
Germany	9.241.569	Recurrent UTI (Bleidom et al., 2016)
India	8.667.779	Antibiotic Misuse, Healthcare Access [14, 54, 69]
China	1.475.149	Antibiotic Resistance [46, 97]
Japan	6.189.688	High economic burden and hospitalization [2, 76]

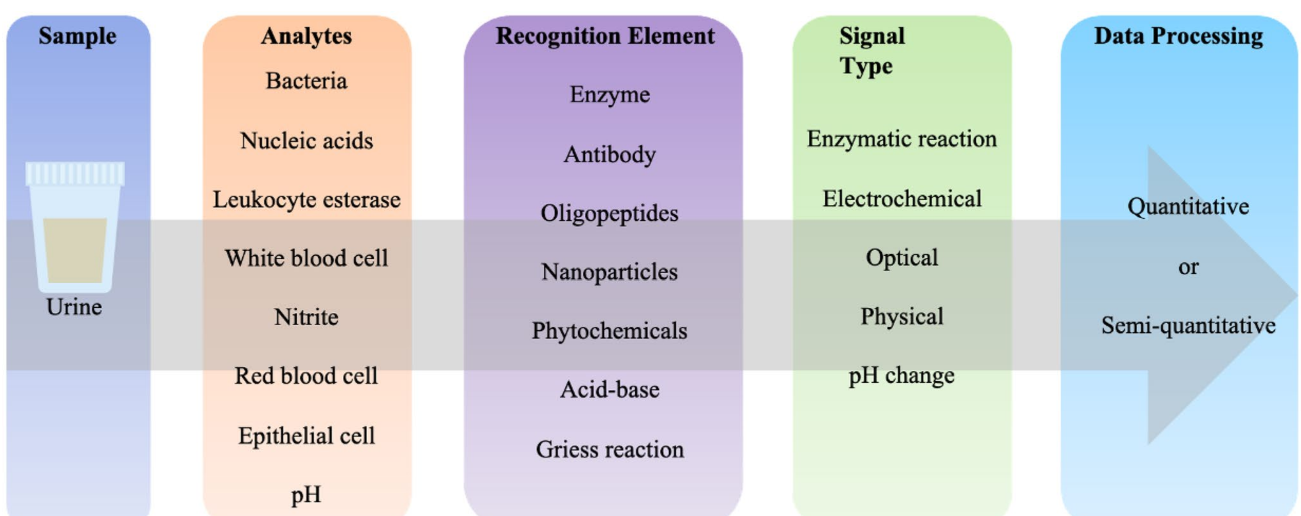

Fig. 1 A workflow and elements of UTI biosensors for diagnosis from urine

addressed by the improved antimicrobial control, the novel antimicrobial development, and the innovative diagnostics for the timely microbial identification and determination of antimicrobial susceptibilities [8, 25]. Despite the fact that the new technologies for diagnosis of UTI might potentially reduce the time to diagnosis if perfected for direct urine testing. New technologies including AI integrated biosensors platforms also point to the future of UTI diagnosis, promising direct detection of pathogens from the urine samples and also point-of-care (POC) testing. The development and implementation of these technologies would usher in a new age in precision medicine and would revolutionize patient care and also public health.

UTIs detection by biosensors has significant advancement. Their main advantages include speed, sensitivity and specificity, ease of use, and real-time on-site monitoring. Biosensors can provide results much more rapidly than traditional culture methods, facilitating quicker diagnosis and treatment. Main properties of biosensors include stability, cost-friendly, user-friendly, portability, sensitivity and selectivity [77]. Advanced biosensors offer high accuracy, potentially surpassing conventional dipstick tests [42]. Many biosensor designs are user-friendly, allowing for potential at-home testing scenarios [35]. Certain biosensor technologies enable continuous and on-site monitoring, which is beneficial for patients with recurrent UTIs [40].

This review focuses on the developments in UTI biosensors over the last decade. The biosensor types are varied such as microfluidic, optical biosensors, electrochemical biosensors, immunosensors and nanotechnology-based biosensors. Also, this review makes a glace to their integration with digital health technologies such as AI and mobile applications. The purpose of this review is to provide a comprehensive overview of current and emerging biosensor technologies for UTI detection, assessing their potential to improve diagnostic accuracy, reduce healthcare costs, and enhance patient outcomes. The review aims to collect recent studies, challenges, and future directions in the field of UTI biosensor development.

Methods and Materials

A comprehensive literature search was conducted to identify relevant studies on the topic of UTIs and biosensors that are used to diagnose. The databases Scopus, PubMed, and Web of Science Core Collection were utilized to ensure a wide and inclusive range of sources. Studies were included to literature review based on several criterias such as published in peer-reviewed journals, focused on UTIs and related biosensors studies, data or analysis related to the incidence, treatment, and biosensor-based diagnosis of UTIs. We excluded studies which are not peer-reviewed, articles not related to UTIs or UTIs biosensor, and non-English publications. The literature search was conducted using a combination of keywords related to UTIs and biosensors. The search terms included urinary tract infection, UTI, epidemiology, treatment, and UTI biosensor. In this review, we analyzed a total of 98 articles.

Current Approaches for UTIs Diagnosis

The increasing frequency and reoccurrence of UTIs, coupled with the global escalation of antibiotic-resistant bacteria, are complicating the diagnosis and management of both lower and upper UTIs in medical practice [3, 45].

Presently, UTIs relies on identifying clinical symptoms and corroborating them with results from the NIT strip test, which detects urinary bacteria, and assessments of white blood cell counts in urine [26, 57]. This approach is preferred because urine culture, another method for diagnosing UTIs, is both time-consuming and expensive [36]. Recent efforts have been focused on discovering new biomarkers for UTI diagnosis. A range of promising biomarkers in serum and urine, such as LE, NIT, procalcitonin (PCT), elastase alpha (1)-proteinase inhibitör, lactoferrin (LF), secretory immınoglobulin A (SIgA), heparin-binding protein (HBP), xanthine oxidase (XO), myeloperoxidase (MPO), Soluble triggering receptor expressed on myeloid cells-1 (TREM1), α-1 microglobulin (α1Mg) and α1Mg/creatinine ratio and tetrazolium nitroblue test (TNB) have gained significant attention lately [53, 86].

However, accurately measuring these biomarkers, especially when they are present in low concentrations, remains a challenge. Accurately identifying infectious pathogens is crucial in healthcare for improving patient care, selecting appropriate treatments, and preventing the spread of infections [10]. Consequently, a variety of diagnostic methods for UTIs have been proposed such as μPAD, microfluidic, electrochemical immunosensor and polymer-based biosensors [16, 30, 41, 89]. Some of these methods may be slow, less precise, too costly, or have a prolonged response time.

Biosensor Types and Their Biomarkers For UTIs Diagnosis

Over the last decade, the field of biosensor technology for the detection of UTIs has undergone significant advancements. This review article discusses the development of UTI biosensors from different sub-fields including microfluidic, colorimetric, optical biosensors, electrochemical biosensors, immunosensors and nanotechnology-based biosensors. Urine test strips or dipsticks are easy to perform, rapid, inexpensive and are suitable for POC testing. Only LE and NIT are direct markers for UTI, but can be complemented by other markers such as pH (Fig. 2). False negative NIT results are known to occur for abnormal urobilinogen levels and pH < 6, while proteins may interfere with LE results [43, 60].

UTIs can be detected using other biomarkers, and recent advances in technology have led to the development of more sensitive and specific methods for their detection. Common UTI biomarkers are bacterial DNA, RNA, proteins and enzymes [39, 49]. Different types of biosensors, including microfluidic, optical, electrochemical, immunosensors, and nanotechnology-based biosensors, are employed for this purpose. Microfluidic biosensors detect bacterial cells or DNA specific to UTI-causing pathogens such as *Escherichia coli* and *Klebsiella pneumoniae* [56]. *K. pneumoniae* causes a variety of human infections, including urinary tract infections [58].

Optical biosensors rely on light-based detection techniques for the detection of the pathogens or specific molecules [23, 84]. May identify changes in the urine color, turbidity, or fluorescence, which are the signs of bacterial proliferation. It can be engineered to target certain bacterial antigens or nucleic acids. Optical biosensors function by detecting physical parameters (such as light absorption and reflection intensity, and the luminescence of the object) to generate analytical signals, instead of relying on chemical interactions between the target component and the sensitive element. These optical characteristics encompass various aspects like turbidity (turbidimetric biosensors), color change (colorimetric biosensors), absorbance (densitometric biosensors), refractive indices (refractometric biosensors) [21, 33, 62].

Electrochemical biosensors detect the electrical changes in a sample resulting from the introduction of the UTI-causing bacteria. It can identify certain ions or molecules produced by the bacteria or in response to the infection, such as NITs [28, 83]. Some electrochemical sensors are made to sense the enzyme activity connected to the UTI pathogens [89].

Immunosensors are antibody-based and they detect the UTI-causing bacteria-specific antigens. It can detect bacterial proteins or any other pathogen-associated molecules in the urine. Very specific and can distinguish between the different bacterial types [13, 80].

Use of the nanoparticles or nanocomposites in the nanotechnology-based biosensor increases the detection sensitivity [51]. Can detect DNA, RNA, or any specific proteins associated with the UTI pathogens [98]. Nanoparticles such as gold nanoparticles can amplify the signal detection, allowing the detection of very low levels of biomarkers [11].

Different types of biosensors have their own benefits in terms of sensitivity, specificity, and also ease of use, and the selection of the biosensor is based on the needed application, available resources, and also the desired sample throughput. The past decade has brought about revolutionary changes in the biosensor technology for the UTI detection. Each advancement has contributed significantly to the field of diagnostics, improving the accuracy, speed, and convenience of UTIs detection.

Recent Developments in UTI Biosensors

Colorimetric Biosensors

The diagnosis of UTIs is a critical aspect of clinical treatment and disease monitoring [4]. Currently, culture-based methods are the gold standard for diagnosing UTIs. However, these methods have limitations, such as a long assay time and the need for skilled professionals to perform the tests [78, 94]. A major part of colorimetric detection popularity is attributed to its ease of application and easy visual detection of the end point. On the other hand, it can even

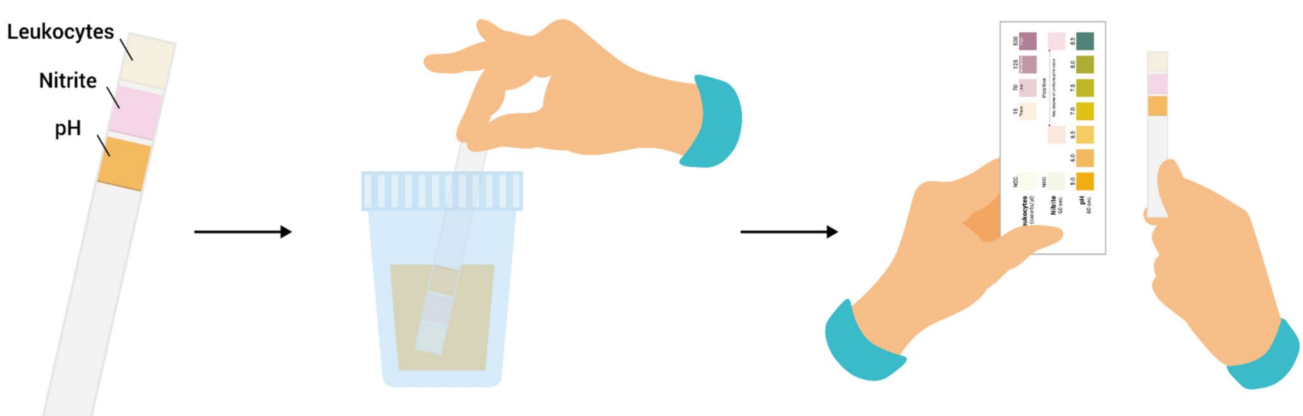

Fig. 2 A basic testing protocol for UTI through urine strip test based on leukocyte esterase, nitrite, and pH levels

be beset with disadvantages like poor detection limits and minimal linear ranges together with low sensitivity [65].

Colorimetric biosensors, in particular, have shown great potential for rapid and accurate detection of UTIs [12]. These biosensors work by detecting specific biomarkers in urine samples, indicating the presence of an infection. Using colorimetric methods, the biosensors can produce a visual color change or signal that is proportional to the concentration of biomarkers in the urine sample. This allows for easy interpretation and analysis of the results, even by untrained users and personnel [21].

The study conducted by Razack and colleagues introduces a rapid colorimetric sensing methodology using natural anthocyanin (AC) loaded nanosilver particles, specifically targeting urinary tract bacterial pathogens (Fig. 3). The novel approach utilizes anthocyanin from eggplant (*Solanum melongena)* peels, acting as a pH-responsive sensor when loaded onto silver nanoparticles (AgNP) to stabilize the pigment. The study showcases a unique capability of this compound to differentiate multiple uropathogens, both as monocultures and consortia, by exhibiting discrete colors based on the pH of the urine sample. The detection mechanism revolves around the deprotonation and protonation of anthocyanin due to the metabolic by-products of the microbes, resulting in a visible color change. This method not only offers rapid and precise detection but also holds the promise of being a specific, sensitive, and affordable POC diagnostic tool for UTIs, overcoming the limitations of conventional diagnostic methods [75].

Couto and colleagues delves into the development of a high-sensitivity colorimetric assay for the detection of multiple UTI biomarkers. This novel approach utilizes a paper-based microfluidic device, designed to be attached to a diaper, enabling the collection and quantitative analysis of specific urine components indicative of UTIs. The device, made from inexpensive materials, addresses the unmet limitations of existing technologies by incorporating a swelling-based "self-locking" mechanism and hydrophobic channels to prevent interference between reagent pads. This innovative design promises to enhance patient comfort by providing a portable, easy-to-operate, and rapid diagnostic solution, thereby making early detection and diagnosis of UTIs more accessible and efficient [19].

The study by Gebrentensaie and colleagues aimed at determining the diagnostic accuracy of LINEAR Cromatest and Laboquick URS 10-T dipsticks to traditional urine culture for detection of UTIs. The research was conducted by using a cohort of patients that had already been identified as having possible UTIs cases. The study of 446 urine samples was made, with bacterial growth detected in 141 (31.6%) of them, mainly women. The research reported that the LINEAR Cromatest dipstick had a sensitivity of 83.7% and specificity of 67.9%, whereas the Laboquick URS 10-T dipstick showed slightly higher sensitivity (87.9%) and specificity (68.5%), both of which were significant (P-value < 0.001) and with AUC > This proves that both dipsticks can be used for UTI diagnosis in those settings where the standard culture of urine is not available but the healthcare outcome can

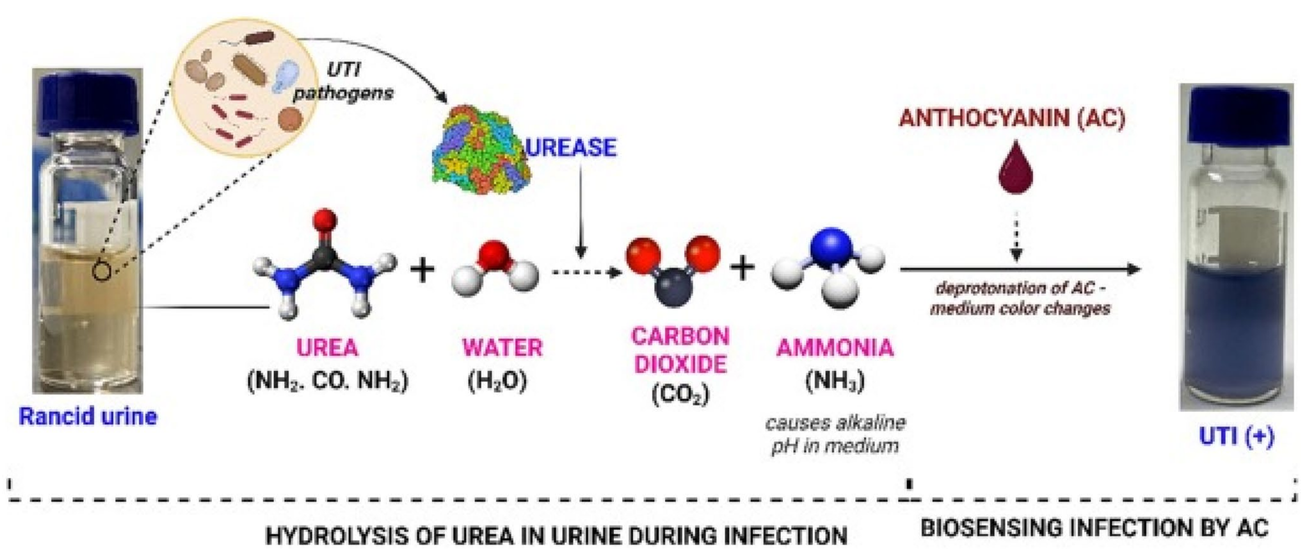

Fig. 3 Mechanism of colorimetric pathogen detection using anthocyanin. The enzyme urease, found in urease-positive bacterial cells, reacts with urea present in infected urine. This reaction hydrolyzes urea, producing carbon dioxide and ammonia. The resulting ammonia makes the medium alkaline. When the sensor AC is added, the increased alkalinity converts AC into its quinoidal form, changing the medium's color from yellow to blue, thus detecting the infection. Reused from [75]. Copyright from 2024, Elsevier

be improved by reducing the number of misdiagnosis and inappropriate treatments [31]..

The study conducted by Chernaya and her colleagues was aimed at assessing the efficiency of urine dipstick analysis in identifying cases of significant bacteriuria among patients who had been admitted to the emergency department. The cross-sectional study included 500 adult patients, comparing the results of dipstick analysis to urinary cultures. The results showed that LE had a sensitivity of 80.9% and a specificity of 58%, while NIT had a sensitivity of 46.5% and a specificity of 90%. Gender played a role in the predictive values, as LE and NIT showed different levels of accuracy for negative and positive urine cultures. The study found that no single dipstick parameter or their combinations could have a reliable prediction of a positive urine culture in women, whereas negative NITs and LE were the most accurate predictors of a negative urine culture in men. The data imply that the antibiotic therapy in female patients with positive dipstick results should be delayed until culture results are available to reduce antibiotic use [15].

The findings of the study have profound implications for the management of UTIs in clinical settings. The field of UTIs diagnosis has come a long way from the traditional culture-based assays to the latest innovations in colorimetric biosensors such as dipstick tests. These developments provide faster, more convenient, and cheaper techniques for determining urinary tract infections. Researchers demonstrate the power of using colorimetric sensing and dipstick methods to overcome the limitations of the conventional diagnostic approach. Such advantages include quick and particular identification of UTIs markers, patient comfort through non-invasive testing techniques, and the ability to perform diagnostics in low-resource settings without the presence of specialized professionals. The impressive findings from these studies lead to the broad utilization of UTIs strips and colorimetric biosensors in clinical practice. The main goal of the transition from traditional UTIs diagnostics to the new approach is not only to improve the diagnostic efficiency but also to guarantee timely and accurate treatment for patients, thus improving the overall health outcomes and reducing healthcare costs. Hence, we profoundly recommend the use of UTIs strips as a key instrument in the early diagnosis and treatment of urinary tract infections. The studies collectively represent the forefront of innovation in colorimetric biosensors for UTIs diagnosis, each contributing a unique approach to address the challenges of rapid, accurate, and user-friendly detection of urinary pathogens.

Microfluidic-Based Biosensors

In the field of biosensor technology, the use of microfluidic platforms has heralded a new era in the diagnosis of UTIs. The advent of these sophisticated devices has revolutionized the approach to rapid, sensitive, and user-friendly detection of pathogens, leveraging the convenience of smartphones and the precision of nano-scale engineering.

The study by Cho and colleagues introduces a pioneering approach to the detection of UTI-causing *E. coli* and the STD pathogen *Neisseria gonorrhoeae*. The research harnesses the capabilities of a microfluidic paper analytical device (μPAD), ingeniously integrating it with smartphone technology for expedited analysis. Unlike traditional methods reliant on culturing and microscopic examination, this device utilizes antibody-conjugated particles for specific bacterial detection, offering a swift assay time of under 30 s and a remarkably low detection limit of 10 CFU/mL for both pathogens. This method not only eclipses the performance of existing commercial kits in terms of sensitivity but also circumvents the need for sample pretreatment, marking a significant leap in POC diagnostics, especially for UTIs [16].

Elevating the utility of smartphone integration in microfluidic devices, Jalal and colleagues devised a hybrid lab-on-a-chip (LOC) for the colorimetric analysis of urine. This innovative device, a fusion of paper and plastic microfluidics, capitalizes on a smartphone-based optical platform and a dedicated app for precise measurement of urine analytes. The incorporation of a conventional reagent test strip within the device's microchannel, coupled with a finger-actuating micropump, ensures controlled reaction volumes and mitigates the time-dependent variability inherent in traditional dipstick methods. This approach not only enhances the accuracy of urinalysis but also promotes user-friendly, cost-effective, and disposable solutions for POC applications [41].

Noiphung and Laiwattanapaisal paved the way for in situ cultivation with their multifunctional paper-based analytical device (PAD). Tailored for the detection of *E. coli* infections, this device couples bacterial cultivation with the rapid testing of NIT levels, employing the Griess reaction for NIT detection and β-glucuronidase activity for specific *E. coli* identification (Fig. 4). The device's ability to support bacterial growth and provide results within a mere 6 h, even in real urine samples, positions it as a formidable tool for UTI screening, particularly in resource-limited settings [64].

These studies collectively underscore the transformative potential of microfluidic-based biosensors in medical diagnostics. By converging the realms of microfluidics, smartphone technology, and nanomaterials, these devices pave the way for rapid, accurate, and accessible health monitoring, promising a new horizon in the management and diagnosis of UTIs and related infections.

Optical-Based Biosensors

Recent developments in the optical-based biosensors have provided encouraging results for the diagnosis of UTIs, which affects over 150 million people worldwide.

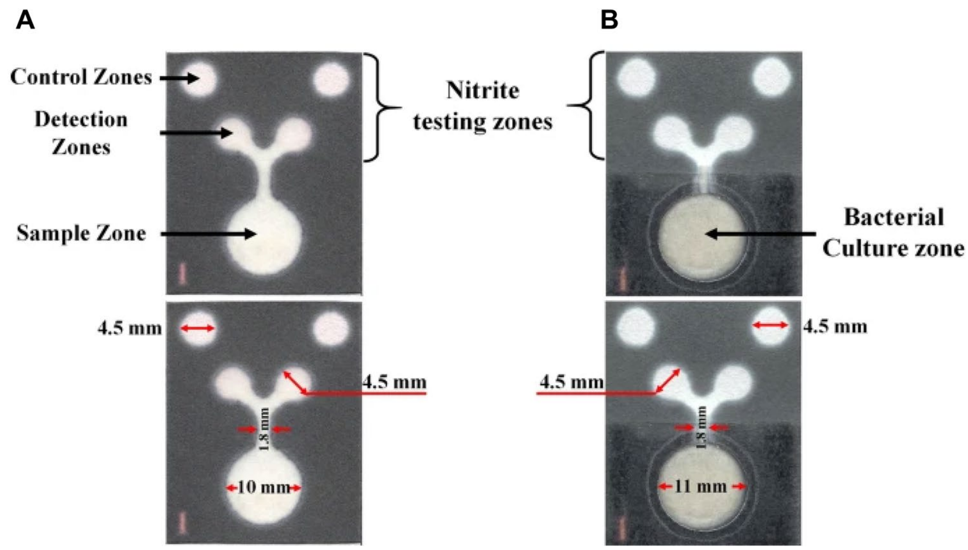

Fig. 4 **a** Design of a paper-based analytical device (PAD) for nitrite quantification (Top). Dimensions of the testing area in the PAD after heating and sterilization (Bottom). **b** Design of the multifunctional PAD for nitrite determination and bacterial cultivation and identification (Top). Dimensions of the PAD testing area after heating and sterilization (Bottom). Reused from [64]. Copyright from 2019, Springer Nature

Recently, two pioneering studies in 2021 have shown remarkable progress in this field, utilizing unique methods to address the issue of early and rapid pathogen detection.

Liu and colleagues introduce an intelligent diagnostic system that utilizes an immuno biosensor, a signal-amplification biochip, and an image processing algorithm based on machine vision. This system is designed to quickly detect bacteria by collecting enhanced luminescence signals enabled by photonic crystals integrated into the biochip. The machine vision algorithm plays a crucial role in analyzing these minute luminescence signals, ensuring a low detection limit and a wide dynamic range. This breakthrough offers a digital diagnostic solution that is not only affordable and accessible but also user-friendly. It holds the potential to be integrated into wearable technology, offering a promising avenue for improving the treatment of UTIs by facilitating rapid and accurate diagnosis [48].

Petrovszki and colleagues have made a significant contribution with the development of an integrated electro-optical biosensor system. This system is designed for rapid and low-cost detection of bacteria, addressing the crucial need for early-stage pathogen detection in medical treatment. The researchers have achieved this by constructing a novel microsystem that combines dielectrophoretic surface-electrodes, a rib waveguide, and a microfluidic channel for label-free optical detection of bacteria from fluid samples (Fig. 5). A key feature of this system is its ability to observe significant changes in the light scattered by living Escherichia coli cells, even when using objectives of moderate magnification. This implies that the detection of cells can be accomplished using low-cost cameras. Furthermore, the system has established an optimal frequency for the dielectrophoretic cell-collecting process, achieving a detection limit of approximately 10^2 CFU × mL^{-1}, which is highly relevant for the concentrations of pathogens typically found in body fluids like urine [70].

Both studies represent significant advancements in the field of optical-based biosensors for UTI diagnosis. Liu and colleagues' approach leverages photonic crystals and machine vision to enhance the sensitivity and range of bacterial detection, potentially paving the way for integration with wearable technology. Meanwhile, the work of Petrovszki and colleagues focuses on creating a cost-effective and rapid detection system utilizing dielectrophoresis and optical sensing techniques. These innovative approaches not only promise to improve the diagnostic process for UTIs but also reflect the broader potential of optical-based biosensors in medical diagnostics.

Electrochemical-Based Biosensors

In recent years, the field of electrochemical biosensors has seen significant advancements, particularly in the diagnosis of UTIs, a prevalent condition that requires timely and accurate detection. Three pioneering studies exemplify this progress, each introducing innovative biosensor technologies aimed at improving the specificity, sensitivity, and convenience of UTI detection.

The study conducted by Ganguly and colleagues, introduced a Label-Free, Lateral Flow Prostaglandin E2 Electrochemical Immunosensor. This sensor stands out due to its non-faradaic operation mode and the use of Electrochemical Impedance Spectroscopy for the quantification of Prostaglandin E2, a key biomarker for for recurrent UTIs in postmenopausal women [27]. The innovation lies in the nanoconfinement of assay biomolecules within a three-electrode planar gold microelectrode system, which is situated atop a lateral flow nanoporous membrane. The sensor's

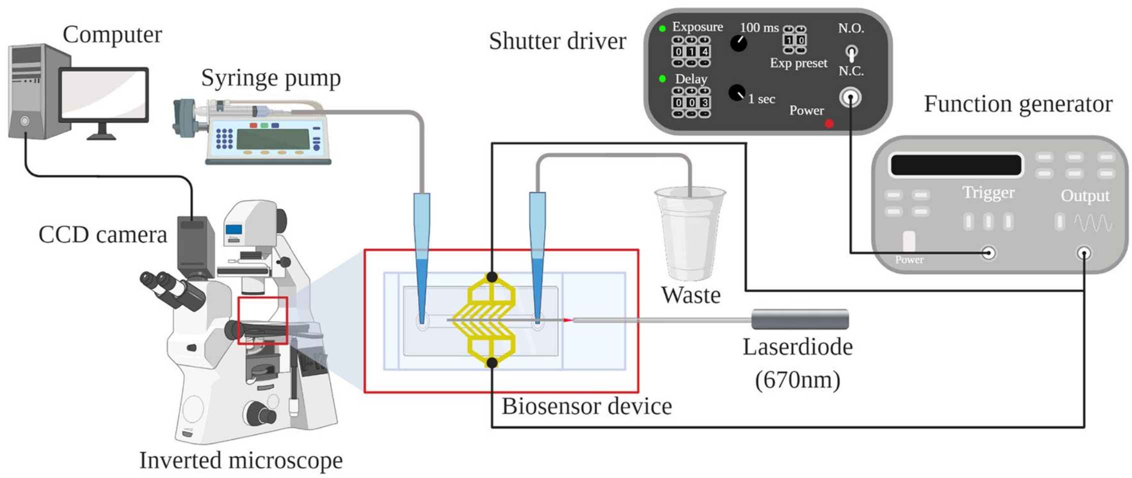

Fig. 5 An illustration of the experimental setup of an optical-based biosensor to detect pathogenic bacteria. The sample was pumped through the microfluidic channel using a syringe pump. A red light from a laser diode was coupled to the waveguide via a single-mode optic fiber. The electrodes were connected to a signal generator controlled by a shutter-driver timer. Image capturing was done using a CCD camera attached to an inverted microscope, with image processing performed on a connected computer (The figure was created with BioRender.com). Reused from [70]. Copyright from 2021, Elsevier

ability to process low microliter volumes of unprocessed urine and provide results within five minutes marks a significant leap in POC diagnostic tools. Its broad dynamic range (100–4000 pg/mL) for urinary PGE2 and the ability to differentiate between varying levels of PGE2 empowers it to effectively categorize urine samples as UTI positive or negative. The sensor's superior specificity and reduced false-positive rates, as compared to existing commercial UTI dipsticks, highlight its potential for widespread use in both clinical and home settings, promising more accurate UTI diagnosis, better patient outcomes, and cost-effective treatment [30].

Naseri and colleagues developed a multivalent aptamer-based electrochemical biosensor for the detection of lactoferrin, another crucial biomarker for UTIs. Recognizing the need for a more versatile biosensor due to the wide concentration range of lactoferrin in urine samples, this study innovated by immobilizing a novel multivalent aptamer on the surface of a screen-printed gold electrode. This aptasensor's label-free detection system exhibits a wide linear detection range (10–1300 ng/mL) and an impressively low limit of detection (0.9 ng/mL). The multivalent aptamer's high affinity and specificity towards human lactoferrin not only enhance the electrochemical signals but also broaden the working window of the biosensor. Its outstanding performance in buffer solutions and spiked urine solutions, coupled with advantages like ease of miniaturization, simplicity, low-cost, and fast response, underline the aptasensor's substantial potential in early UTI detection [61].

A pilot study by Tseng and colleagues, ventured into multi-analyte detection by developing an electrochemical conducting polymer-based biosensor for the simultaneous detection of LE and NIT, both markers for UTIs. This sensor utilized a novel approach by conjugating an LE antibody to a carboxylic acid-functionalized poly(3,4-ethylenedioxythiophene) modified glassy carbon electrode. The use of PEDOT-COOH as the substrate not only facilitated the integration with biomolecules for selective recognition of LE and NIT but also expanded the sensing range due to its excellent electroactivity. The electrode's characterization through various spectroscopic and electrochemical techniques established its credibility, exhibiting a wide linear range and low limits of detection for both NIT and LE (Fig. 6). The sensor's performance was further validated with urine samples from patients, showing high diagnostic sensitivity and specificity. The sensor's ease of use, rapid response, and ability to detect multiple analytes simultaneously suggest that it could be a formidable alternative to traditional urine strip tests [89].

In conclusion, these studies collectively mark a paradigm shift in the field of electrochemical biosensors for UTI diagnosis. The innovative approaches, from nanoconfinement in immunosensors to multivalent aptamers and conducting polymers in aptasensors, not only enhance the detection capabilities but also offer practical benefits such as rapid analysis, high sensitivity, and specificity, paving the way for advanced POC diagnostic tools for UTIs. As these technologies continue to evolve, they hold the promise of revolutionizing UTI diagnosis, ensuring prompt and accurate treatment, and significantly improving patient care.

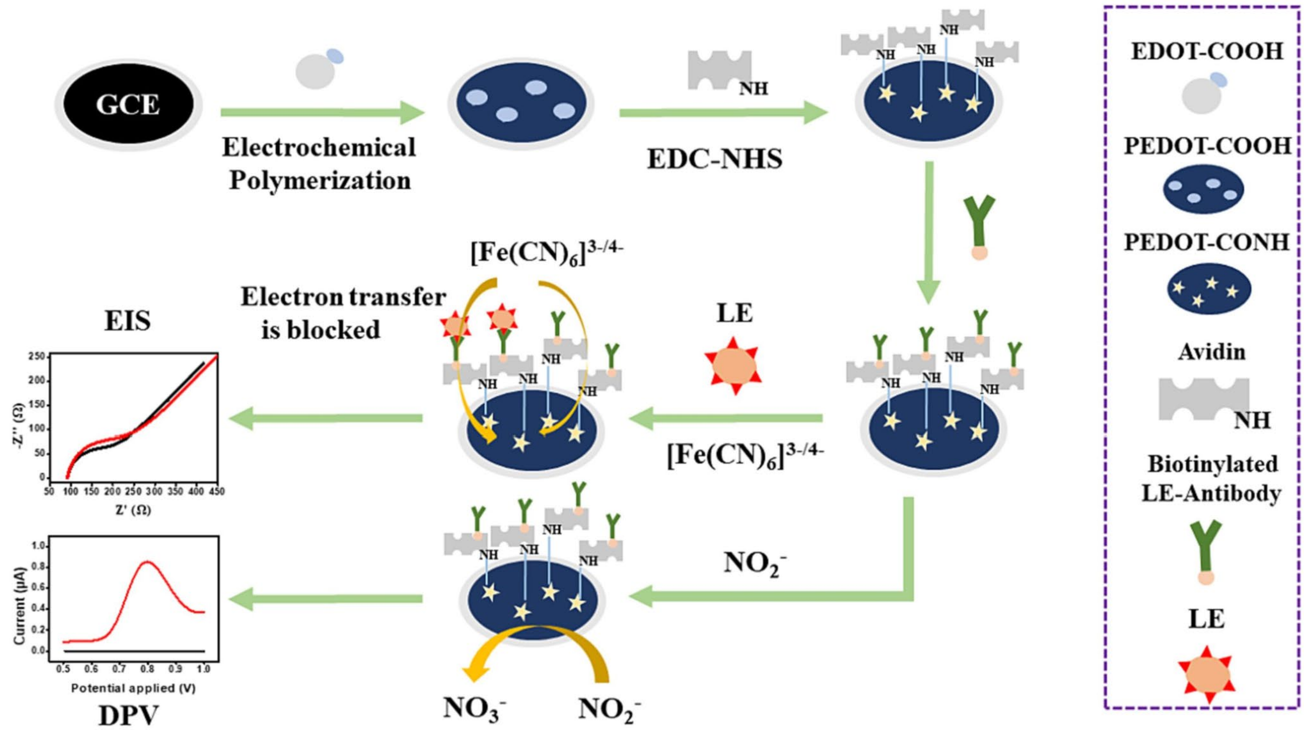

Fig. 6 An illustration of the fabrication process of the leukocyte esterase Antibody/Avidin/EDC-NHS/PEDOT-COOH/GCE electrode and the electrochemical Method for detecting nitrite and leukocyte esterase. Reused from [89]. Copyright from 2023, Elsevier

Immunosensors-Based Biosensors

In the realm of medical diagnostics, especially for UTIs, recent advancements have showcased innovative approaches that promise rapid, accurate, and on-the-spot results. Two notable studies in this field have introduced groundbreaking biosensors, each with unique methodologies and applications.

The study conducted by Adrover-Jaume and colleagues, introduces mobile origami colorimetric immunosensors as a swift and reliable diagnostic tool for UTIs, specifically targeting infections caused by *E. coli*. The ingenuity of these biosensors lies in their design—a single piece of paper ingeniously folded, embedded with antibody-decorated nanoparticles. The presence of *E. coli* in a urine sample triggers a visual reaction, forming colored spots on the paper strip. These spots are then quantitatively analyzed through a mobile app, which assesses the pixel intensity in real-time (Fig. 7). The precision of these biosensors is noteworthy; they are highly specific, showing no cross-reactivity with other common uropathogens. Their reliability is further underscored by an impressive record in tests, yielding only one false negative in a panel of 57 patient urine samples. The combination of rapid assay time (under 7 min), smartphone-based detection, and high sensitivity and specificity positions these mobile origami immunosensors as a transformative solution for bedside diagnosis of UTIs [1].

Nikopensius and colleagues delves into another innovative approach for the rapid detection of UTIs, predominantly those instigated by uropathogenic *E. coli* (UPEC). The conventional methods for identifying uroinfection-causing pathogens, like microbiological cultivation, qPCR, and MALDI-TOF mass spectrometry, are time-consuming. Addressing the urgent need for speed in diagnostics, this study presents a biosensor that significantly cuts down the detection time. The biosensor operates on the principle of antigen–antibody biorecognition, with a focus on achieving a detection limit below 10^3 CFU/mL, crucial for diagnosing recurrent uroinfections and related conditions. The process involves attaching the pathogens onto a single-use column, followed by specific detection using *E. coli* antibodies conjugated with a fluorescence marker. The integration of a bead-injection analysis platform for fluidics further refines the process, enabling the detection and quantification of *E. coli* in urine samples with remarkable sensitivity (<3 and <5 cells/mL, respectively). The entire analysis is completed within 17 min, and the results show a good correlation with those obtained from conventional methods, proving that the biosensor's performance is not hindered by the complex urine matrix of UPEC patients [63].

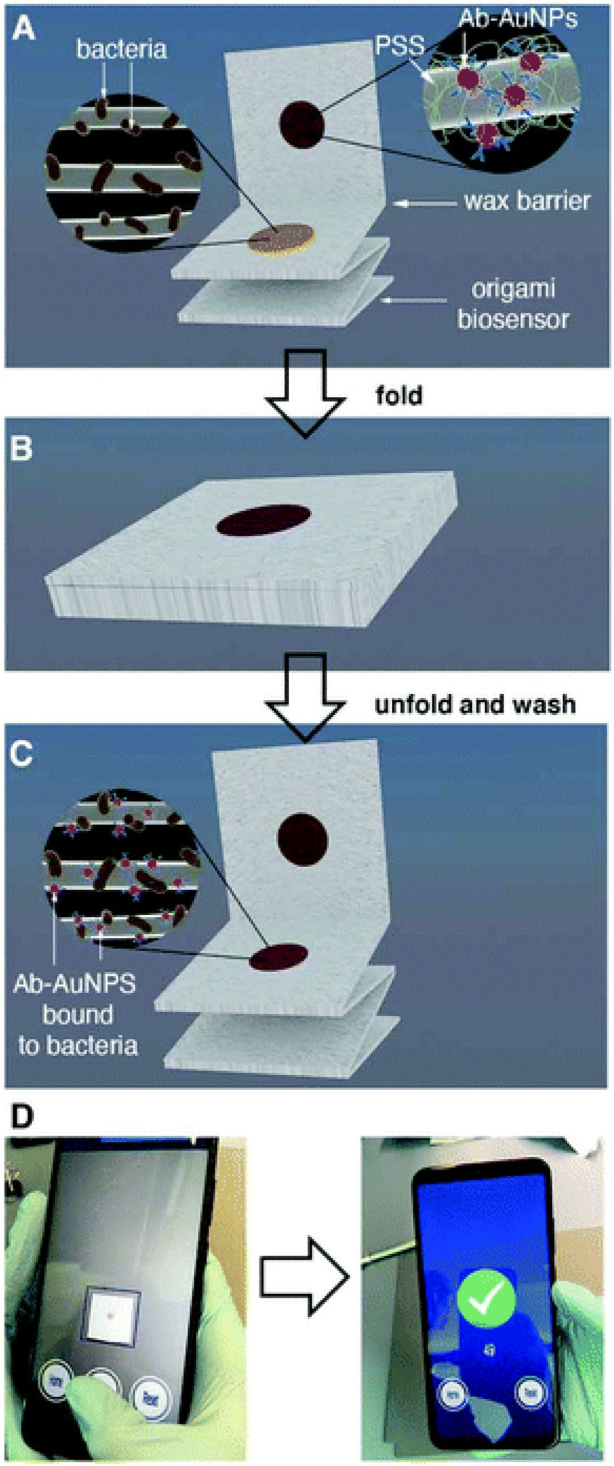

Fig. 7 A schematic representation of the mobile origami biosensors based on immunosensor. **A** Urine samples are dried on a paper strip, which contains a reservoir of antibody-decorated gold nanoparticles (Ab-AuNPs) and polystyrene sulfonate (PSS) to prevent irreversible interactions with the paper; **B** upon folding the paper, the nanoparticles move to the detection area, where they specifically recognize E. coli; **C** after washing, a colored spot remains on the paper, with the pixel intensity corresponding to the concentration of E. coli in the sample; **D** the pixel intensity is calculated within seconds using a smartphone app. Reused from [1]. Copyright from 2020, Royal Society of Chemistry

Together, these studies not only underscore the rapid advancements in the field of biosensors for UTI diagnostics but also highlight the shift towards more patient-friendly, rapid, and accurate diagnostic methodologies. The mobile origami immunosensors and the fluorescence detection-based immunosensor each open new pathways for on-site, quick, and reliable UTI diagnostics, marking significant strides in the management and treatment of this prevalent condition.

Nanotechnology-Based Biosensors

Nanotechnology-based biosensors for UTIs diagnosis represent a cutting-edge approach in medical diagnostics. In biosensors, nanomaterials can enhance sensitivity and specificity [50]. They can be designed to detect biological markers associated with diseases at very low concentrations, which is crucial for early detection. UTI-based bionanosensors, which leverage nanomaterials, excel in diagnosing UTIs with remarkable sensitivity and precise detection limits, distinguishing various types of infections effectively (Table 2).

The study conducted by Özgür and colleagues, they developed a biomimetic sensor using surface plasmon resonance to detect UTIs, specifically *E. coli*, with a detection limit of 0.57 CFU/ml. This sensor's sensitivity is enhanced by the entrapment of silver nanoparticles in a polymeric film [67].

Urena-Saborio and colleagues study delves into the unique properties of cranberry proanthocyanidins (PAC) and their application in UTI detection. Their study explores the potential of cranberry PAC in agglutinating extraintestinal pathogenic *E. coli*, a common UTI-causing bacterium (Fig. 8). The research demonstrates the efficacy of cranberry PAC in vitro and further innovates by fabricating functionalized screen-printed electrodes (SPEs) modified with PAC-polyaniline (PANI) nanocomposites. The resulting PAC-PANI/SPE biosensor exhibits high sensitivity and a linear response over a wide concentration range, presenting a promising and innovative alternative for the detection and diagnosis of ExPEC-associated UTIs. This approach not only leverages the natural properties of cranberry PAC but also showcases the integration of nanotechnology in developing functionalized biosensors, marking a significant leap in UTI diagnostic methods [90].

Zagorovsky and colleagues introduce an innovative approach to the diagnosis of UTIs, addressing the critical limitations of current diagnostic methods. UTI diagnosis has traditionally been hindered by slow processing times and a lack of comprehensive information, often leading to the premature prescription of antibiotics before the accurate identification of bacterial pathogens. This not only exacerbates the issue of antibiotic resistance but also complicates patient management. Their research marks

Table 2 Nanomaterials used UTI-based bionanosensors for the diagnosis of UTIs and their type of sensing, sensitivity, and limit of detection

Nanomaterials	Target	Type of sensing	Sensitivity	Limit of detection	Reference
Cysteamine-attached ZnO NP	N-acyl homoserine lactone	Photoluminescence (PL)-based	97%	10–120 nM	Vasudevan et al. [92]
Silver NP	Leukocyte esterase	Paper-based analytical device (LE-PAD)	87.5%	1.92 (×5.1 U mg − 1 mL − 1; 20 WBC per μL	Ho et al. [38]
Cysteine gold nanoparticles	*E. coli*	Colorimetric sensing	1×10^3–4×10^3 cells/mL	100 cells/mL	Raj et al. [73]
Antibody-decorated gold nanoparticles (Ab-AuNPs)	*E. coli*	Colorimetric sensing	10^4 and 10^7 cells per mL	10^5 cells per mL	Adrover-Jaume et al. [1]
Gold nanoparticle	*E. coli, K. pneumoniae, Staphylococcus saprophyticus, Enterococcus faecalis, and Proteus mirabilis*	Colorimetric sensing	51–73%	10^5 bacteria/mL	Zagorovsky et al. [95]

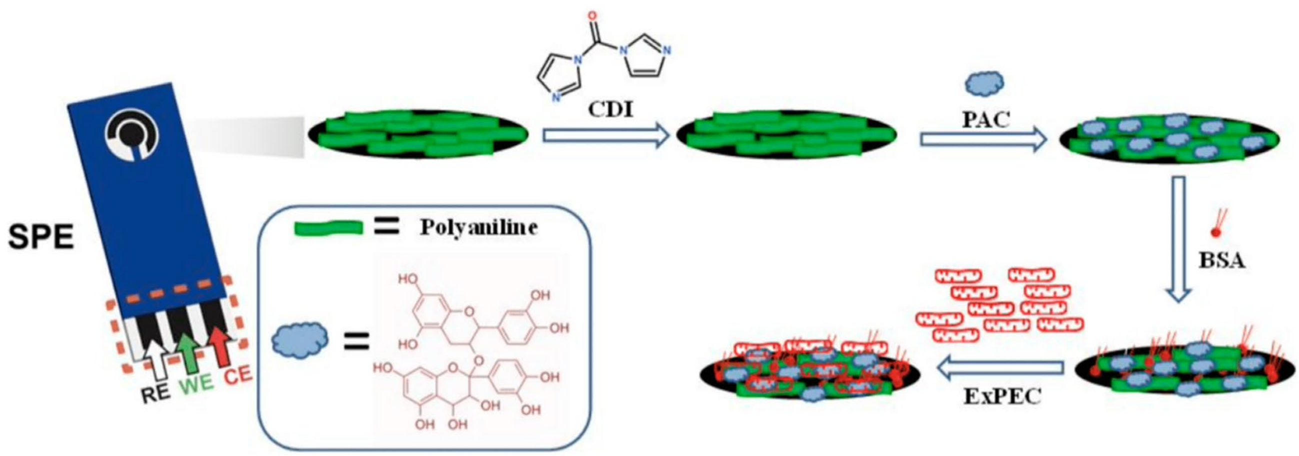

Fig. 8 Scheme for the electrochemical detection of UTI-causing extra-intestinal pathogenic E. coli utilizing a screen-printed electrode functionalized with a cranberry proanthocyanidins-polyaniline nanocomposite. Reused from [90] Copyright from 2021, MDPI

a significant advancement in this field by leveraging the unique properties of gold nanoparticles in a colorimetric approach, integrated with the ubiquity and technological capabilities of smartphones. The study demonstrates the development of a smartphone platform capable of the parallel identification of five major UTI pathogens including *E. coli*, *Proteus mirabilis*, and *K. pneumoniae* at clinically relevant concentrations. This high degree of specificity and sensitivity is achieved through the use of bacteria-specific and universal probes, ensuring accurate pathogen detection. One of the standout features of this diagnostic technology is its speed and efficiency. The assay can successfully identify the infecting pathogen with a specificity of over 98% and a sensitivity ranging from 51 to 73% within just 3 h. This rapid processing time significantly surpasses traditional culturing methods, making it a highly desirable option for healthcare settings where time is of the essence. Moreover, the study underlines the practicality and cost-effectiveness of the platform. At a cost of only $0.38 per assay, the technology offers an affordable solution for UTI diagnosis. Additionally, the ability to wirelessly store and transmit results enhances the platform's utility, facilitating seamless communication within healthcare networks and ensuring timely and informed decision-making in patient care [95].

In summary, nanotechnology-based biosensors for UTI diagnosis are an innovation in the field of medical technology, providing the possibility of much faster, more reliable, and also more accessible diagnostics. The technology is a major component of the broader movement towards personalized and precision medicine that provides diagnostics and treatments based on the patient's needs.

Integration of UTI Diagnosis to Digital Health Technologies

In the realm of digital health technology, significant strides have been made in enhancing the diagnosis and management of UTIs, a prevalent condition that affects a vast population globally. The integration of artificial intelligence (AI) and smart devices into this field is not only revolutionizing diagnosis but also improving patient care, especially in populations with specific needs such as the elderly. The following paragraphs delve into the recent advancements in this domain, highlighting the innovative approaches and their implications for healthcare.

Ozkan and colleagues made a significant contribution with their research. Their study underscores the complexity of diagnosing UTIs due to the similarity of symptoms across different infections within the urinary tract. To address this challenge, the researchers developed an AI model designed to aid in the diagnosis of UTIs with complex symptoms. They employed various AI models including Decision Tree (DT), Support Vector Machine (SVM), Random Forest (RF), and Artificial Neural Network (ANN), with ANN exhibiting the highest accuracy of 98.3%. Remarkably, this model simplifies the diagnosis process by requiring only a few key indicators such as pollacuria, suprapubic pain, and erythrocyte levels, mitigating the need for invasive procedures. This study presents a promising medical decision support system, offering advantages in terms of reduced diagnosis cost and time, and eliminating the need for invasive diagnostic methods [66].

Sung and Cheng introduced an innovative approach tailored for the elderly population, particularly those who wear diapers. Recognizing the challenges in urine sampling for this demographic, they developed a cotton-based in-vitro diagnostic device that detects NIT concentrations in urine, a biomarker for UTI. The device's integration with a smartphone-based application for image analysis enhances its practicality and accessibility. The device's ability to change color correlating with NIT concentration and its structural integration with diapers makes it a viable, cost-effective, and simple solution for early UTI diagnosis, potentially elevating the quality of life for the elderly population worldwide [85].

Karlsen and Dong presented a pioneering solution with their study. They explored the potential of smartphones as practical POC devices for the colorimetric detection of UTIs, aiming to empower nurses and medical personnel with a tool that circumvents the need for additional equipment. The challenge of maintaining consistent camera color perception across different illuminations and devices was addressed through black and white reference correction and comprehensive color image normalization. This work laid the groundwork for a smartphone-based application capable of effectively normalizing color differences due to varying illumination, marking a crucial step towards a practical and portable diagnostic solution [43].

The study conducted by Burton and colleagues introduced a method for optimizing the efficiency of microbiological screenings. Their study addresses the inefficiency in urine sample screenings, where a significant portion typically yields negative results. By applying machine learning (ML) algorithms such as Random Forest, Neural Network, and Extreme Gradient Boosting, and comparing these with a heuristic model, they demonstrated the potential of AI in reducing the workload of diagnostic laboratories significantly. Their tailored approach, which involves separate algorithm training for different patient groups (pregnant patients, children, and others), achieved a notable workload reduction of 41% and a classification sensitivity of 95% for each group. This model's successful implementation in routine clinical practice exemplifies the practical application of AI in enhancing service efficiency, particularly in resource-constrained public healthcare settings [9].

The convergence of AI, smart device technology, and healthcare expertise in these studies represents a transformative evolution in the diagnosis and management of UTIs. These advancements not only promise more accurate and timely diagnoses but also herald a new era of personalized, cost-effective, and patient-friendly healthcare solutions. As these technologies continue to evolve and integrate into healthcare systems, they hold the potential to significantly improve the quality of life for patients and streamline the workload of healthcare providers.

Challenges and Limitations

UTIs are among the most common bacterial infections, posing significant healthcare challenges globally. The development of UTI biosensors marks a significant stride in diagnostics, offering the potential for rapid, accurate detection of infections. However, the deployment of these biosensors come with challenges such as technical, clinical, and economic domains.

The technical challenges in the development and implementation of UTIs biosensors are multifaceted, involving material stability, sensor lifespan, and miniaturization [7]. The materials used in biosensor construction must maintain their functional integrity under various conditions. For UTIs biosensors, this means they must resist degradation by urine components, temperature fluctuations, and pH variations. Material instability can lead to decreased sensor sensitivity and specificity, rendering the biosensor unreliable [51]. Advances in nanomaterials and bio-compatible materials offer promising pathways.

The operational lifespan of a biosensor is crucial, particularly for continuous or long-term monitoring applications

[79]. The challenge is to ensure that the biosensor maintains its functional characteristics over its intended usage period without the need for frequent recalibration or replacement. This is particularly challenging in the urinary environment, where factors such as flow dynamics, presence of various metabolites, and microbial activity can affect sensor performance [71]. The trend in biosensor development is towards miniaturization, offering convenience and patient comfort [21, 47]. However, miniaturizing UTIs biosensors as POC devices without compromising their sensitivity and specificity is a complex task.

For UTIs biosensors to be widely adopted, they must be cost-effective, not only in terms of the initial investment for the device but also regarding the cost per test, maintenance, and potential savings in preventing complications from untreated UTIs. Balancing advanced technology with affordability is a formidable challenge, requiring innovative manufacturing techniques.

Future Perspectives

The landscape of UTI diagnostics is on the brink of a significant transformation, propelled by the emergence of innovative biosensor technologies. These advancements promise to revolutionize UTI detection and management by offering rapid, accurate, and non-invasive testing methods. Nanotechnology, for instance, is at the forefront of this revolution, enabling the development of biosensors with enhanced sensitivity and specificity. These nanoscale biosensors can detect UTI-causing pathogens at incredibly low concentrations, facilitating early diagnosis and treatment [72].

Furthermore, the integration of AI and ML algorithms with biosensor technology is set to redefine UTI diagnostics. These intelligent systems can analyze complex datasets, learning from patterns to improve diagnostic accuracy over time. The fusion of AI with biosensors, through the integration of ML algorithms, not only speeds up the diagnostic process but also reduces human error, ensuring more dependable outcomes while transforming disease screening and monitoring by analyzing complex data patterns [7, 44].

The advent of advanced biosensors holds immense promise for POC diagnostics, a paradigm shift that could fundamentally alter the management of UTIs. POC biosensors enable on-the-spot or at-home diagnosis, eliminating the need for complex laboratory equipment and specialized personnel [21, 47]. This immediacy not only accelerates the treatment process but also significantly reduces the risk of complications associated with delayed treatment.

Moreover, POC biosensors have the potential to democratize healthcare by making UTI diagnostics accessible to underserved populations. Their ease of use, coupled with the ability to deliver rapid results, can empower individuals to take proactive measures in their health management. This is particularly beneficial for recurrent UTIs sufferers who require frequent monitoring [24, 49, 74].

In conclusion, the future perfective of UTI biosensors is marked by a convergence of emerging technologies, targeted research endeavors, and the potential reshaping of POC diagnostics. While challenges remain, the relentless pace of innovation suggests a not-so-distant future where UTI management is more proactive, patient-centered, and efficient.

Conclusion

This is a critical review of UTI biosensor technology that provides a wide range of breakthroughs and contributions to the management and diagnosis of UTIs, a common disease affecting millions of people worldwide. The review summarizes the drawbacks of the common diagnostic methods, such as urine culture and dipstick tests. Biosensor-based technologies are the novel approaches for real time, accurate, and non-invasive detection of UTIs, the exigent need for efficient diagnostic tools.

The different types of biosensors that were reviewed include microfluidic, optical, electrochemical, immunosensors, as well as nanotechnology-based biosensors. These biosensors have their own advantage either in terms of sensitivity, specificity or ease of use. These technologies permit the direct pathogen detection from urine samples, which will aid POC testing and real-time monitoring for patients with recurrent UTIs. Moreover, the combination of biosensors with digital health technologies like AI and mobile apps shows the importance of a great leap towards precision medicine which improves the accuracy of diagnosis while cutting healthcare costs and improving patient outcomes.

Looking forward, our review posits an optimistic future for UTI diagnostics, driven by continuous innovation in biosensor technology and its integration with digital health. The prospect of nanotechnology to increase biosensor sensitivity and specificity, when combined with AI and ML techniques, is likely to transform UTI diagnostics. These breakthroughs may pave the way for mass production of POC biosensors which will provide quick, dependable and easily accessible diagnostics, especially important for the populations that are the most vulnerable, such as the elderly or those in resource-poor settings.

In summary, while significant progress has been made in the development of UTI biosensors, realizing their full potential will necessitate overcoming existing technical, clinical, and economic challenges. Continued research and collaboration across disciplines are essential to ensuring these innovative diagnostic tools can be effectively integrated into clinical practice, ultimately transforming UTI management and improving global health outcomes.

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Declarations

Conflict of interest The authors declare no competing interests.

References

1. Adrover-Jaume C, Rojo-Molinero E, Clemente A, Russell SM, Arranz J, Oliver A, de la Rica R (2020) Mobile origami immunosensors for the rapid detection of urinary tract infections. Analyst 145:7916–7921
2. Akiyama Y, Saito S, Tsuzuki S, Mezaki K, Ohmagari N (2022) 2245. Urinary tract infections in the elderly population in Japan; long hospital stay, high medical costs, and decline in the activities of daily living scores. In: Open forum ınfectious diseases, vol 9, No Supplement_2, pp. ofac492–1863. US: Oxford University Press
3. Bader MS, Loeb M, Brooks AA (2017) An update on the management of urinary tract infections in the era of antimicrobial resistance. Postgrad Med 129:242–258
4. Beahm NP, Nicolle LE, Bursey A, Smyth DJ, Tsuyuki RT (2017) The assessment and management of urinary tract infections in adults: guidelines for pharmacists. Can Pharm Journal/Revue des Pharmaciens du Canada 150:298–305
5. Behzadi P, Behzadi E, Pawlak-Adamska EA (2019) Urinary tract infections (UTIs) or genital tract infections (GTIs)? It's the diagnostics that count. GMS hygiene and infection control, 14
6. Bent S, Nallamothu BK, Simel DL, Fihn SD, Saint S (2002) Does this woman have an acute uncomplicated urinary tract infection? JAMA 287:2701–2710
7. Bhatia D, Paul S, Acharjee T, Ramachairy SS (2024) Biosensors and their widespread impact on human health. Sens Int 5:100257
8. Bleidorn J, Hummers-Pradier E, Schmiemann G, Wiese B, Gágyor I (2016) Recurrent urinary tract infections and complications after symptomatic versus antibiotic treatment: follow-up of a randomised controlled trial. GMS German Med Sci 14
9. Burton RJ, Albur M, Eberl M, Cuff SM (2019) Using artificial intelligence to reduce diagnostic workload without compromising detection of urinary tract infections. BMC Med Inform Decis Mak 19:1–11
10. Caliendo AM, Gilbert DN, Ginocchio CC, Hanson KE, May L, Quinn TC, Infectious Diseases Society of America (IDSA) (2013) Better tests, better care: improved diagnostics for infectious diseases. Clin Infect Dis 57:S139–S170
11. Cao X, Ye Y, Liu S (2011) Gold nanoparticle-based signal amplification for biosensing. Anal Biochem 417:1–16
12. Celik C, Kalin G, Cetinkaya Z, Ildiz N, Ocsoy I (2023) Recent advances in colorimetric tests for the detection of infectious diseases and antimicrobial resistance. Diagnostics 13:2427
13. Cesewski E, Johnson BN (2020) Electrochemical biosensors for pathogen detection. Biosens Bioelectron 159:112214
14. Chakraborty D, Debnath F, Majumdar A, Chakrabarti A, Sharma M, Walia K, Dutta S (2024) Diagnostic validation study of rapid urinary tract infection diagnosis kit at peripheral health facilities of West Bengal, India. Sci Rep 14:297
15. Chernaya A, Søborg C, Midttun M (2021) Validity of the urinary dipstick test in the diagnosis of urinary tract infections in adults. Dan Med J 69:A07210607
16. Cho S, San Park T, Nahapetian TG, Yoon JY (2015) Smartphone-based, sensitive µPAD detection of urinary tract infection and gonorrhea. Biosens Bioelectron 74:601–611
17. Choi K, Chang I, Lee JC, Kim DK, Noh S, Ahn H, Kim HC (2016) Smartphone-based urine reagent strip test in the emergency department. Telemed e-Health 22:534–540
18. Claeys KC, Blanco N, Morgan DJ, Leekha S, Sullivan KV (2019) Advances and challenges in the diagnosis and treatment of urinary tract infections: the need for diagnostic stewardship. Curr Infect Dis Rep 21:1–9
19. Couto AMSS (2017) Development of high-sensitivity colorimetric assay for detection of multiple urinary tract infection biomarkers on diaper (Doctoral dissertation)
20. Czajkowski K, Broś-Konopielko M, Teliga-Czajkowska J (2021) Urinary tract infection in women. Menopause Review/Przegląd Menopauzalny 20:40–47
21. Çelik H, Caf BB, Geyik C, Çebi G, Tayfun M (2023) Enhancing urinalysis with smartphone and AI: a comprehensive review of point-of-care urinalysis and nutritional advice. Chem Pap:1–14
22. Dadzie I, Quansah E, Puopelle Dakorah M, Abiade V, Takyi-Amuah E, Adusei R (2019) The effectiveness of dipstick for the detection of urinary tract infection. Can J Infect Dis Med Microbiol:2019
23. Damborský P, Švitel J, Katrlík J (2016) Optical biosensors. Essays Biochem 60:91–100
24. Daurai B, Gogoi M (2023) Point-of-care biosensors for healthcare applications. In: Nanobiosensors for point-of-care medical diagnostics, Springer, Singapore, pp 1–23
25. Davenport M, Mach KE, Shortliffe LMD, Banaei N, Wang TH, Liao JC (2017) New and developing diagnostic technologies for urinary tract infections. Nat Rev Urol 14:296–310
26. Dilbaz K, Özen EEÖ, Karadeniz S (2023) Reliability of the urine spot test in predicting urinary tract infections during pregnancy: a cross-sectional study. Türk Kadın Sağlığı ve Neonatoloji Dergisi 5:85–91
27. Ebrahimzadeh T, Kuprasertkul A, Neugent ML, Lutz KC, Fuentes JL, Gadhvi J, De Nisco NJ (2021) Urinary prostaglandin E2 as a biomarker for recurrent UTI in postmenopausal women. Life Sci Alliance 4
28. Feng Y, Zhou D, Gao L, He F (2020) Electrochemical biosensor for rapid detection of bacteria based on facile synthesis of silver wire across electrodes. Biosens Bioelectron 168:112527
29. Foxman B (2002) Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. Am J Med 113:5–13
30. Ganguly A, Ebrahimzadeh T, Zimmern PE, De Nisco NJ, Prasad S (2021) Label free, lateral flow prostaglandin E2 electrochemical immunosensor for urinary tract infection diagnosis. Chemosensors 9:271
31. Gebretensaie Y, Atnafu A, Alemu Y, Girma S, Desta K (2023) Evaluation of the diagnostic performance of the LINEAR cromatest and laboquick URS 10-T dipsticks among urinary tract ınfection suspects in Addis Ababa, Ethiopia: a cross-sectional study. Res Rep Urol:437–445
32. Grigoryan L, Trautner BW, Gupta K (2014) Diagnosis and management of urinary tract infections in the outpatient setting: a review. JAMA 312:1677–1684

33. Guliy OI, Karavaeva OA, Smirnov AV, Eremin SA, Bunin VD (2023) Optical sensors for bacterial detection. Sensors 23:9391
34. Gupta K, Trautner B (2012) Urinary tract infection. Ann İnternal Med 156:ITC3-1
35. Haleem A, Javaid M, Singh RP, Suman R, Rab S (2021) Biosensors applications in medical field: a brief review. Sens Int 2:100100
36. Hajar F, Taleb M, Aoun B, Shatila A (2011) Dipstick urine analysis screening among asymptomatic school children. N Am J Med Sci 3:179
37. Hataysal EP, Saraçlıgil B, Hatice TÜRK, Vatansev H (2019) How accurate is the urine dipstick test for diagnosing urinary tract infection?. Eur Res J 5:613–617
38. Ho ML, Liu WF, Tseng HY, Yeh YT, Tseng WT, Chou YY, Pan SW (2020) Quantitative determination of leukocyte esterase with a paper-based device. RSC Adv 10:27042–27049
39. Horváth J, Wullt B, Naber KG, Köves B (2020) Biomarkers in urinary tract infections–which ones are suitable for diagnostics and follow-up?. GMS İnfect Dis :8
40. Hwang C, Lee WJ, Kim SD, Park S, Kim JH (2022) Recent advances in biosensor technologies for point-of-care urinalysis. Biosensors 12:1020
41. Jalal UM, Jin GJ, Shim JS (2017) Paper–plastic hybrid microfluidic device for smartphone-based colorimetric analysis of urine. Anal Chem 89:13160–13166
42. Kadadou D, Tizani L, Wadi VS, Banat F, Alsafar H, Yousef AF, Hasan SW (2022) Recent advances in the biosensors application for the detection of bacteria and viruses in wastewater. Journal of environmental chemical engineering, 10(1), 107070.ary tract infection?. Eur Res J 5:613–617
43. Karlsen H, Dong T (2015) A smart phone-based robust correction algorithm for the colorimetric detection of Urinary Tract Infection. In: 2015 37th annual ınternational conference of the IEEE engineering in medicine and biology society (EMBC). IEEE, pp 1251–1254
44. Krishnan G, Singh S, Pathania M, Gosavi S, Abhishek S, Parchani A, Dhar M (2023) Artificial intelligence in clinical medicine: catalyzing a sustainable global healthcare paradigm. Front Artif Intell 6
45. Lee DS, Lee SJ, Choe HS (2018) Community-acquired urinary tract infection by Escherichia coli in the era of antibiotic resistance. BioMed Res İnt 2018
46. Li X, Chen Y, Gao W, Ye H, Shen Z, Wen Z, Wei J (2017) A 6-year study of complicated urinary tract infections in southern China: prevalence, antibiotic resistance, clinical and economic outcomes. Ther Clin Risk Manag:1479–1487
47. Liu D, Wang J, Wu L, Huang Y, Zhang Y, Zhu M, Yang C (2020) Trends in miniaturized biosensors for point-of-care testing. TrAC, Trends Anal Chem 122:115701
48. Liu H, Li Z, Shen R, Li Z, Yang Y, Yuan Q (2021) Point-of-care pathogen testing using photonic crystals and machine vision for diagnosis of urinary tract infections. Nano Lett 21:2854–2860
49. Mach KE, Wong PK, Liao JC (2011) Biosensor diagnosis of urinary tract infections: a path to better treatment? Trends Pharmacol Sci 32:330–336
50. Malhotra BD, Ali MA (2018) Nanomaterials in biosensors: fundamentals and applications. Nanomater Biosens 1–74. https://doi.org/10.1016/B978-0-323-44923-6.00001-7
51. Malik S, Singh J, Goyat R, Saharan Y, Chaudhry V, Umar A, Baskoutas S (2023) Nanomaterials-based biosensor and their applications: a review. Heliyon
52. Mancuso G, Midiri A, Gerace E, Marra M, Zummo S, Biondo C (2023) Urinary tract infections: the current scenario and future prospects. Pathogens 12:623
53. Masajtis-Zagajewska A, Nowicki M (2017) New markers of urinary tract infection. Clin Chim Acta 471:286–291
54. Mathur P, Malpiedi P, Walia K, Srikantiah P, Gupta S, Lohiya A, Velayudhan A (2022) Health-care-associated bloodstream and urinary tract infections in a network of hospitals in India: a multicentre, hospital-based, prospective surveillance study. Lancet Glob Health 10:e1317–e1325
55. McKertich K, Hanegbi U (2021) Recurrent UTIs and cystitis symptoms in women. Aust J Gen Pract 50:199–205
56. Meile S, Du J, Staubli S, Grossmann S, Koliwer-Brandl H, Piffaretti P, Kilcher S (2023) Engineered reporter phages for detection of Escherichia coli, Enterococcus, and Klebsiella in urine. Nat Commun 14:4336
57. Mohanna AT, Alshamrani KM, SaemAldahar MA, Kidwai AO, Kaneetah AH, Khan MA, Khan MA (2021) The sensitivity and specificity of white blood cells and nitrite in dipstick urinalysis in association with urine culture in detecting infection in adults From October 2016 to October 2019 at King Abdulaziz Medical City. Cureus 13
58. Monteiro ADSS, Cordeiro SM, Reis JN (2024) Virulence factors in klebsiella pneumoniae: a literature review. Indian J Microbiol:1–13
59. Moon A, Veeratterapillay R, Garthwaite M, Harding C (2018) Urinary tract infection management–do the guidelines agree? J Clin Urol 11:81–87
60. Najeeb S, Munir T, Rehman S, Hafiz A, Gilani M, Latif M (2015) Comparison of urine dipstick test with conventional urine culture in diagnosis of urinary tract infection. J Coll Physicians Surg Pak 25:108–110
61. Naseri M, Halder A, Mohammadniaei M, Prado M, Ashley J, Sun Y (2021) A multivalent aptamer-based electrochemical biosensor for biomarker detection in urinary tract infection. Electrochim Acta 389:138644
62. Nejadmansouri M, Majdinasab M, Nunes GS, Marty JL (2021) An overview of optical and electrochemical sensors and biosensors for analysis of antioxidants in food during the last 5 years. Sensors 21:1176
63. Nikopensius M, Jõgi E, Rinken T (2021) Determination of uropathogenic escherichia coli in urine by an immunobiosensor based upon antigen-antibody biorecognition with fluorescence detection and bead-injection analysis. Anal Lett 55:1040–1051
64. Noiphung J, Laiwattanapaisal W (2019) Multifunctional paper-based analytical device for in situ cultivation and screening of Escherichia coli infections. Sci Rep 9:1555
65. Noviana E, McCord CP, Clark KM, Jang I, Henry CS (2020) Electrochemical paper-based devices: Sensing approaches and progress toward practical applications. Lab Chip 20:9–34
66. Ozkan IA, Koklu M, Sert IU (2018) Diagnosis of urinary tract infection based on artificial intelligence methods. Comput Methods Programs Biomed 166:51–59
67. Özgür E, Topçu AA, Yılmaz E, Denizli A (2020) Surface plasmon resonance based biomimetic sensor for urinary tract infections. Talanta 212:120778
68. Öztürk R, Murt A (2020) Epidemiology of urological infections: a global burden. World J Urol 38:2669–2679
69. Patel HB, Soni ST, Bhagyalaxmi A, Patel NM (2019) Causative agents of urinary tract infections and their antimicrobial susceptibility patterns at a referral center in Western India: an audit to help clinicians prevent antibiotic misuse. J Fam Med Prim Care 8:154–159
70. Petrovszki D, Valkai S, Gora E, Tanner M, Bányai A, Fürjes P, Dér A (2021) An integrated electro-optical biosensor system for rapid, low-cost detection of bacteria. Microelectron Eng 239:111523
71. Psotta C, Nilsson EJ, Sjöberg T, Falk M (2023) Bacteria-infected artificial urine characterization based on a combined approach using an electronic tongue complemented with 1H-NMR and flow cytometry. Biosensors 13:916

72. Qindeel M, Barani M, Rahdar A, Arshad R, Cucchiarini M (2021) Nanomaterials for the diagnosis and treatment of urinary tract infections. Nanomaterials 11:546
73. Raj V, Vijayan AN, Joseph K (2015) Cysteine capped gold nanoparticles for naked eye detection of E. coli bacteria in UTI patients. Sens Bio-Sens Res 5:33–36
74. Rasmi Y, Li X, Khan J, Ozer T, Choi JR (2021) Emerging point-of-care biosensors for rapid diagnosis of COVID-19: current progress, challenges, and future prospects. Anal Bioanal Chem 413:4137–4159
75. Razack SA, Maknuna L, Kang HW (2024) A rapid colorimetric sensing methodology for urinary tract bacterial pathogens as a point-of-care approach using natural anthocyanin loaded nanosilver. Microchem J 199:109943
76. Sako A, Yasunaga H, Matsui H, Fushimi K, Yanai H, Gu Y, Ohmagari N (2021) Hospitalization for urinary tract infections in Japan, 2010–2015: a retrospective study using a national inpatient database. BMC Infect Dis 21:1–10
77. Saylan Y, Kiliç S, Denizli A (2024) Printed electronics-based biosensors. Hacettepe J Biol Chem 52:31–39
78. Schmiemann G, Kniehl E, Gebhardt K, Matejczyk MM, Hummers-Pradier E (2010) The diagnosis of urinary tract infection: a systematic review. Dtsch Arztebl Int 107:361
79. Shanbhag MM, Manasa G, Mascarenhas RJ, Mondal K, Shetti NP (2023) Fundamentals of bio-electrochemical sensing. Chem Eng J Adv:100516
80. Sharma S, Byrne H, O'Kennedy RJ (2016) Antibodies and antibody-derived analytical biosensors. Essays Biochem 60:9–18
81. Simmering JE, Tang F, Cavanaugh JE, Polgreen LA, Polgreen PM (2017) The increase in hospitalizations for urinary tract infections and the associated costs in the United States, 1998–2011. In: Open forum infectious diseases (Vol. 4, No. 1, p. ofw281). US: Oxford University Press
82. Smith CM, Shallcross LJ, Dutey-Magni P, Conolly A, Fuller C, Hill S, Fragaszy EB (2021) Incidence, healthcare-seeking behaviours, antibiotic use and natural history of common infection syndromes in England: results from the Bug Watch community cohort study. BMC Infect Dis 21:1–11
83. Simoska O, Stevenson KJ (2019) Electrochemical sensors for rapid diagnosis of pathogens in real time. Analyst 144:6461–6478
84. Singh AK, Mittal S, Das M, Saharia A, Tiwari M (2023) Optical biosensors: a decade in review. Alex Eng J 67:673–691
85. Sung WH, Cheng CM (2019) Urinalysis for diaper-wearing elderly people using a combination of cotton-based diagnostic devices and smartphone-based image analysis. Health Technol 3:1–5
86. Swamy SNN, Jakanur RK, Sangeetha SR, Narayanaswamy S, Sangeetha SR (2022) Significance of C-reactive protein levels in categorizing upper and lower urinary tract infection in adult patients. Cureus 14(6)
87. Tamadonfar KO, Omattage NS, Spaulding CN, Hultgren SJ (2019) Reaching the end of the line: urinary tract infections. Microbiol Spect 7:10–1128
88. Thomas-White KJ, Gao X, Lin H, Fok CS, Ghanayem K, Mueller ER, Wolfe AJ (2018) Urinary microbes and postoperative urinary tract infection risk in urogynecologic surgical patients. Int Urogynecol J 29:1797–1805
89. Tseng WT, Chou YY, Wu JG, Wang YC, Tseng TN, Pan SW, Ho ML (2023) An electrochemical conducting polymer-based biosensor for Leukocyte esterase and nitrite detection for diagnosing urinary tract infections: a pilot study. Microchem J 188:108493
90. Urena-Saborio H, Udayan APM, Alfaro-Viquez E, Madrigal-Carballo S, Reed JD, Gunasekaran S (2021) Cranberry proanthocyanidins-pani nanocomposite for the detection of bacteria associated with urinary tract infections. Biosensors 11:199
91. Van Hecke O, Wang K, Lee JJ, Roberts NW, Butler CC (2017) Implications of antibiotic resistance for patients' recovery from common infections in the community: a systematic review and meta-analysis. Clin Infect Dis 65:371–382
92. Vasudevan S, Srinivasan P, Rayappan JBB, Solomon AP (2020) A photoluminescence biosensor for the detection of N-acyl homoserine lactone using cysteamine functionalized ZnO nanoparticles for the early diagnosis of urinary tract infections. J Mater Chem B 8:4228–4236
93. Werneburg GT, Rhoads DD (2022) Diagnostic stewardship for urinary tract infection: a snapshot of the expert guidance. Clevel Clin J Med 89:581–587
94. Xu R, Deebel N, Casals R, Dutta R, Mirzazadeh M (2021) A new gold rush: a review of current and developing diagnostic tools for urinary tract infections. Diagnostics 11:479
95. Zagorovsky K, Fernández-Argüelles MT, Bona D, Elshawadfy AM, Syed AM, Kadhiresan P, Chan WC (2022) Gold nanoparticle smartphone platform for diagnosing urinary tract infections. ACS Nanosci Au 2:324–332
96. Zeng Z, Zhan J, Zhang K, Chen H, Cheng S (2022) Global, regional, and national burden of urinary tract infections from 1990 to 2019: an analysis of the global burden of disease study 2019. World J Urol 40:755–763
97. Zhang K, Fang X, Zhang Y, Chao M (2024) A retrospective study of uropathogen and its antibiotic resistance among children with urinary tract infection from a single center in China. Heliyon
98. Zhang L, Huang W, Zhang S, Li Q, Wang Y, Chen T, Chen Y (2022) Rapid detection of bacterial pathogens and antimicrobial resistance genes in clinical urine samples with urinary tract infection by metagenomic nanopore sequencing. Front Microbiol 13:858777