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A systematic review of recent advances in urinary tract infection interventions and treatment technology

M.S. ALAM[1], M.J. ANWAR[2], M.S. AKHTAR[3], P. ALAM[4], A.A.S. MOHAMMAD[3], A.F. ALMUTAIRY[2], A.S. NAZMI[1], T.K. MUKHERJEE[5]

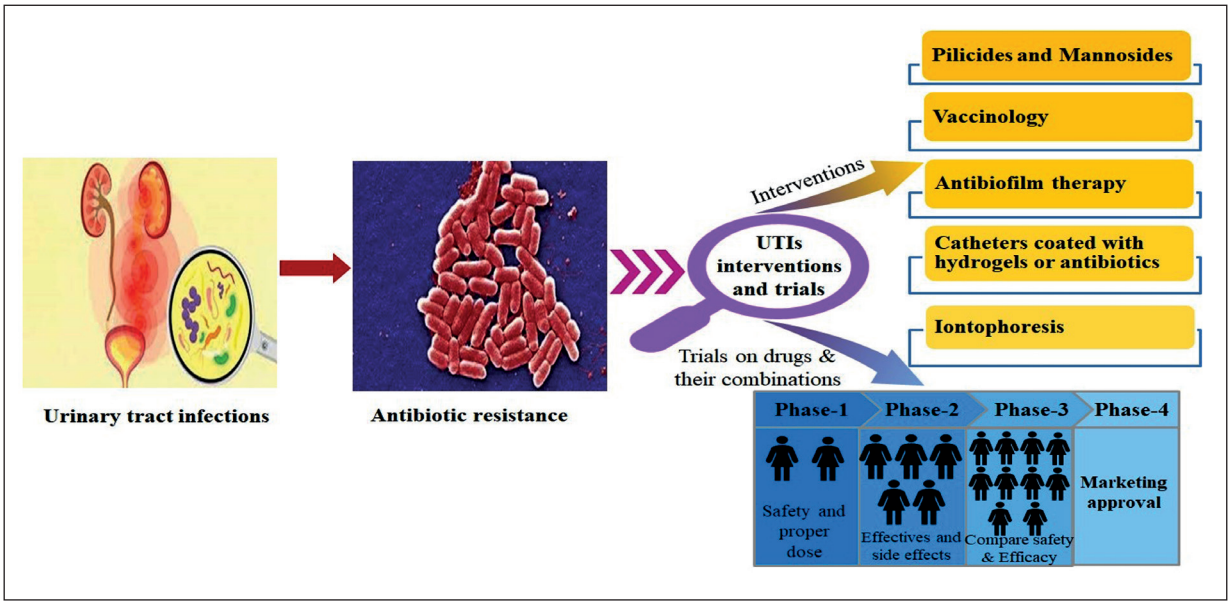
[1]Department of Pharmacy Practice, College of Pharmacy, National University of Science and Technology, Bosher-Muscat, Oman
[2]Department of Pharmacology and Toxicology, College of Pharmacy, Qassim University, Buraydah, Saudi Arabia
[3]Department of Clinical Pharmacy, College of Pharmacy, King Khalid University, Asir-Abha, Kingdom of Saudi Arabia
[4]Department of Pharmacognosy, College of Pharmacy, Prince Sattam Bin Abdulaziz University, P.O. Box 173, Al-Kharj 11942, Saudi Arabia
[5]Amity Institute of Biotechnology, Amity University, Action Area II-36, 37, 38, Rajarhat, New Town, Kolkata, West Bengal, India

ABSTRACT. – OBJECTIVE: Urinary tract infection is one of the most common extraintestinal infectious diseases encountered in clinics. It affects both genders and all age groups and constitutes a major health issue in clinical practice worldwide. Uropathogens often develop resistance to therapeutic agents, creating a formidable challenge for physicians to treat these infections.

The goal of the current review is to provide current information on therapeutic advancements and interventions in the treatment of urinary tract infections.

MATERIALS AND METHODS: Databases like MEDLINE, PubMed, and ClinicalTrials.gov were used as search engines to collect the relevant articles, and the required information was extracted.

RESULTS: Research data suggest an increasing prevalence of pathogenic strains that are resistant to standard antimicrobial regimens recommended for the treatment of urinary tract



Graphical Abstract. UTIs and microbial resistance, and recent advances in treatment and technology.

Corresponding Authors: Jamir Anwar, MD; e-mail: m.anwar@qu.edu.sa
Shamshir Alam, MD; e-mail: shamshir_pharma@yahoo.com; mdshamshir@nu.edu.om

infections. Targeted therapies for urinary tract infections, such as mannosides and pilicides, as well as vaccinations against uropathogenic Escherichia coli, have been developed recently. The efficacy of other strategies like iontophoresis, hydrogel-coated catheters, and antibiofilm therapy is also investigated. Clinical trials conducted between 2014 and 2019 show a rise in interest in a variety of therapies, highlighting the need for a thorough strategy to treat urinary tract infections, particularly in populations of women.

CONCLUSIONS: Antimicrobial-resistant strains of Escherichia coli are becoming more common in urinary tract infections, which have led to the development of targeted medicines such as mannosides and pilicides, as well as immunizations against the pathogenic *Escherichia coli* strains. There is continuing research into alternate approaches, such as hydrogel-coated catheters, antibiofilm therapy, and iontophoresis. Clinical trials conducted between 2014 and 2019 showed a rise in interest in these different treatment approaches.

Key Words:

Urinary tract infection, Urinary tract infection therapy, Antibacterial resistance, Hydrogel antibiotic, Antibiofilm, Enzyme inhibitor, Pilicide.

Introduction

A urinary tract infection (UTI) encompasses a wide range of infectious illnesses impacting different parts of the urinary system, from the urethra to the kidneys[1], typically accompanied by bacteriuria and pyuria. UTI is one of the most common problems and is a considerable challenge to physicians in clinical practice. UTI ranks second on the list of prevalent infectious infections[2], following respiratory tract infection. The incidence of recurrent UTIs contributes to a substantial increase in healthcare costs and hurts the quality of life[3,4]. It constitutes a remarkable cause of hospitalization in infants, elderly males, and females of all age groups[5]. Uncomplicated UTIs are more common in sexually active women, while only a few cases have been reported in elderly women or pregnant women.

Gram-positive and Gram-negative bacteria, as well as fungi, are the causative agents of UTIs. Bacterial virulence plays an initial role in the pathogenesis of disease. However, the presence of anatomic and/or functional anomalies in the kidneys, bladder, or collecting systems, obstruction to normal urine flow, cystic renal disease, metabolic diseases like diabetes mellitus, abnormalities in host defense mechanisms, and infections following urinary tract surgery or procedures are the most favorable conditions for UTIs[1]. Further, it is hypothesized that the replacement of the natural flora of periurethral regions by pathogenic microbes might result in bacterial cystitis. These infections may ascend to the kidneys and cause bacterial pyelonephritis. Ascending infection occurs due to bacterial virulence characteristics, which allow better adhesion, infection, and colonization by uropathogens[6,7]. Contrary to this, there are some reports of uncomplicated UTIs in healthy hosts without any structural or functional anomalies of the urinary tract[7]. UTIs have various pathologic repercussions, including frequent recurrences, pyelonephritis with sepsis, kidney injury in young infants, premature birth, and antimicrobial use-related problems such as substantial antimicrobial resistance and *Clostridium difficile*-induced colitis. Secondary bloodstream infections are frequently caused by catheter-associated UTIs, which substantially raise the rates of morbidity and mortality[8].

Since the discovery of penicillin, humans have achieved significant advancement in the fight against bacterial illnesses, particularly after the discovery and synthesis of various novel antibiotics, including new-generation beta-lactam antibiotics. Despite these achievements, the emergence of resistant bacterial strains in UTI infection appears to be a significant impediment to therapeutic progress. In the recent past, a multitude of studies[9,10] have documented a concerning surge in microbial resistance, which has extended to nearly all frequently employed antimicrobial agents. In addition, there is a significant increase in the prevalence of antibiotic-resistant pathogens, and a growing number of these pathogens are acquiring multidrug resistance (MDR), which raises the likelihood that they will not respond to conventional treatment[11]. Moreover, the primary contributors to antibiotic resistance in the contemporary era are the inadequate development of novel medicines by the pharmaceutical industry and the overuse and misuse of antibiotics (including failure to adhere to prescribed dosage and duration of treatment)[12]. In light of this, this review provides an update on the epidemiology of UTIs, their risk factors, pathology, current therapeutic management options, new breakthroughs in antimicrobials, and intervention technologies for better care of UTI patients.

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Materials and Methods

Search Strategy, Study Selection, and Eligibility

We searched for relevant articles using various search engines, including MEDLINE/PubMed, Google Scholar, and ClinicalTrials.gov. A literature search was conducted to retrieve all aspects of the studies that examined the prevalence, etiological agents, pathogenesis, new treatment options for UTI, current developments in the field of medications, and techniques in different clinical trial phases aimed at treating UTI.

The articles included in the current review are limited to clinical studies, and contain information about prevalence, causative agents, pathogenesis, antimicrobial treatment, and newer therapeutic options. The clinical studies that were published on these search engines between 2014-2019 were included in this systematic review. The present systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Figure 1 describes a flow chart for the evaluation of UTI clinical trials. Only those clinical studies that were related to drugs, devices, procedures, and others, were included in this review. Further, any registered clinical trials with missing or unavailable information on clinical phases, delayed, terminated, or unknown status were excluded from this review.

Study Selection

The selection process involved screening titles, abstracts, and full texts of retrieved articles. Two independent reviewers assessed the eligibility of studies based on predefined inclusion and exclusion criteria. Discrepancies were resolved through discussion or by consulting a third reviewer.

Data Synthesis and Analysis

Data extracted from selected studies were synthesized to provide a comprehensive overview of UTI interventions and treatment technologies.

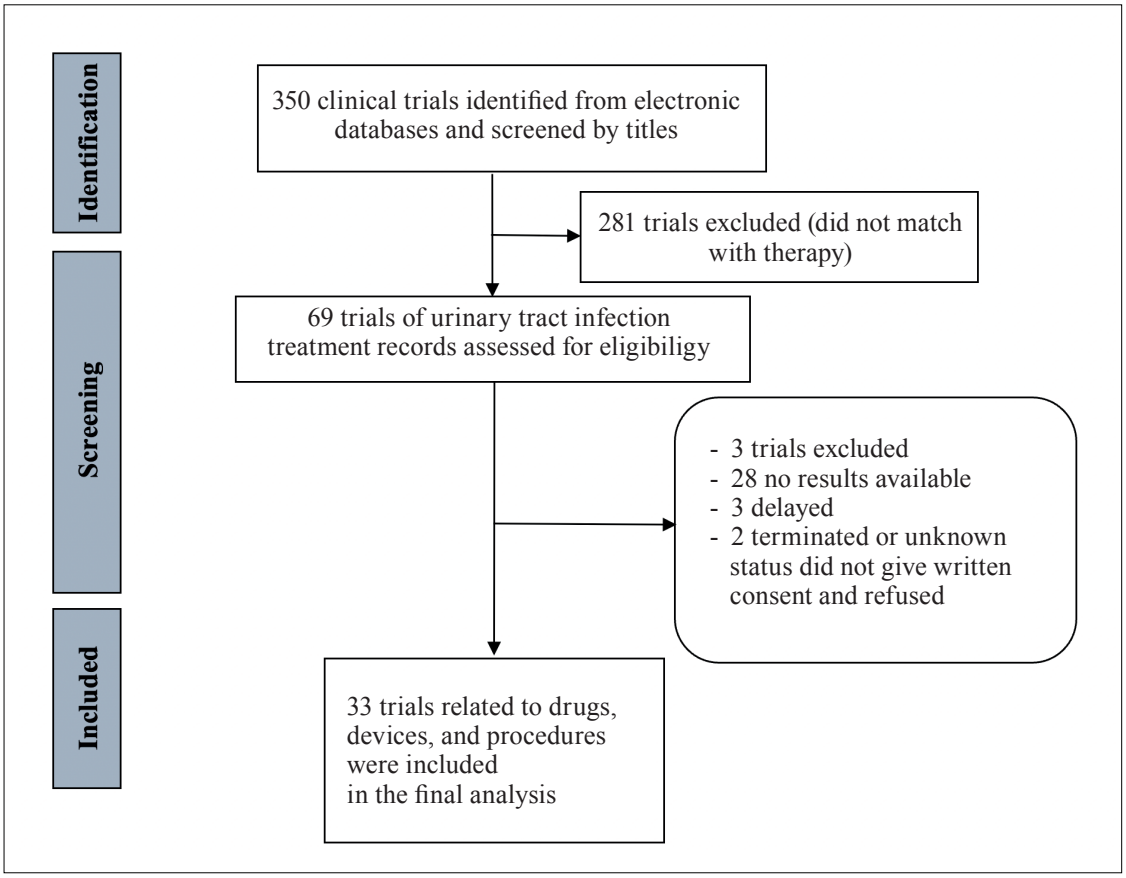

Figure 1. Flow chart for literature search and evaluation of clinical trials (2014-2019) following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines indicators.

Descriptive analyses were utilized to summarize key findings, including prevalence rates, identified risk factors, pathogenic mechanisms, and efficacy of novel therapeutic approaches.

Studies' Characteristics

Following a comprehensive search of an electronic database, we assessed the inclusion eligibility of 350 publications. Out of these, 281 studies were excluded on the grounds of mismatched therapy. We assessed the incorporation of the remaining 69 studies pertaining to treatments for UTIs. Out of 69 articles, 36 were disqualified for various reasons, including failure to meet inclusion criteria (N=3), absence of available results (N=28), delayed (N=3), either terminated or unknown outcomes (N=2).

After the deletion of unqualified studies, 33 trials[13-45] were screened by evaluating the title, abstract, and outcomes for descriptive analysis. The summary of selected trials and the selection procedure are illustrated in Figure 1 and Table I, respectively.

Ethical Consideration

In the present systematic review of UTI therapies, ethics approval and informed consent are not applicable because the analysis is based on existing research rather than direct human involvement. However, ethical considerations related to transparent and unbiased synthesis of evidence were followed to maintain the integrity of the review process.

Results

A Systemic Representation of the Diagnosis of UTI and the Type of Microbial Infection

A schematic diagrammatic representation (Figure 2) illustrates the various steps and methods involved in diagnosing various microbes involved in the UTI[46]. The diagnosis is based on patient history, physical examination, and laboratory tests.

Microbes

UTIs can be caused by a diverse array of microorganisms, such as specifically selected fungi and Gram-negative and Gram-positive bacteria. Despite this, bacterial infection, encompassing both Gram-positive and Gram-negative bacteria, is the most prevalent etiology of UTIs. *Escherichia coli* (*E. coli*) is the most common bacteria in UTIs, followed by *Staphylococcus saprophyticus*[47]. Other uropathogens include *Enterococcus*, *Pseudomonas aeruginosa*, *Candida species*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Enterobacter* Group B *Streptococci* (Figure 3)[48,49]. In general, *E coli* is the most abundantly available microorgan-

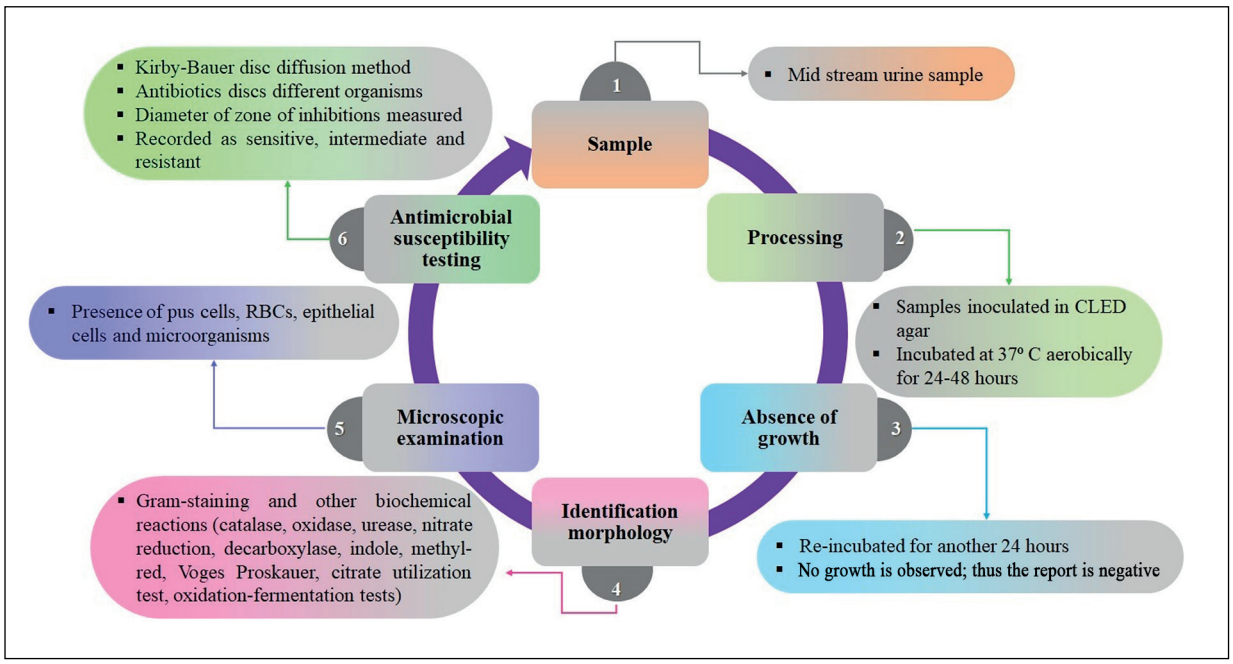

Figure 2. Systematic representation of the diagnostic process of UTI. CLED: cysteine lactose electrolyte deficient.

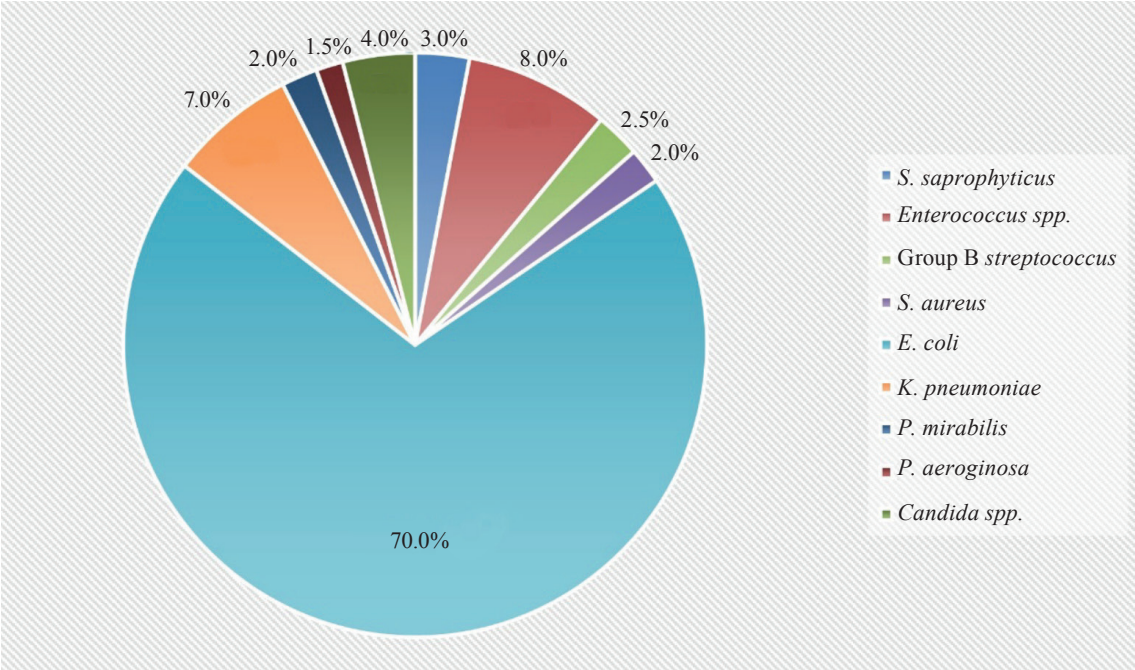

Figure 3. Common uropathogens causing UTIs (complicated and uncomplicated).

ism in the environment. While most of the strains of *E. coli* are nonpathogenic, a few of them cause pathogenicity. *E. coli* is also a prevalent contributor to uncomplicated UTIs, accounting for between 75 and 95 percent of all infections[47].

Staphylococcus saprophyticus, which causes lower urinary tract infections, has been identified in 3.0% of reproductive-aged, non-pregnant women who engage in sexual activity and experience pyelonephritis[50]. In addition, species of *Proteus, Pseudomonas, Klebsiella,* and *Enterobacter* have been identified in females diagnosed with cystitis or pyelonephritis, and these organisms have been linked to structural irregularities in the urinary tract, renal calculi, and indwelling catheters[51]. Furthermore, *Enterococcus* species have been identified in females who present with anatomical anomalies of the urogenital tract. Gram-positive microorganisms, specifically *Streptococci*, were found in females with catheters implanted together with fungal infections[51]. Anaerobic microorganisms and mycoplasmas are seldom identified from infections such as the genitourinary tract and play a minimal impact in urinary tract pathology[50].

The Pathogenesis of UTI and the Epidemiological Representation of the Population Affected by UTI Epidemic

Pathogenesis

The occurrence of numerous urinary infections can be attributed to either repeated microbial infections or persistent bacterial presence, with the former being more common[7]. The biological and behavioral features of the hosts, in addition to the attributes of the infecting uropathogens, exert an influence on the intricate pathogenesis of an uncomplicated UTI. Overwhelmingly determined by the anatomical or functional characteristics of the genitourinary tract, postmenopausal women are at a greater risk for UTIs than younger women. The current progress in comprehending uropathogenesis indicates that the dysregulation of specific genes in people increases the likelihood of recurring UTIs[52]. Recurring UTIs have also been associated with a genetic factor, as demonstrated by the correlation between recurrent UTIs in specific age groups and the non-secretion of ABO blood antigen phenotype, a history of UTIs in the mother, and early age onset UTIs. Further, infections

Table I. Clinical trials details for the management of UTIs during six years.

Title	Interventions	Sex	Phases of trial	Star year	Author/References
A randomized, double-blind, placebo-controlled pilot study to assess bacterial anti-adhesive activity in human urine following consumption of a cranberry supplement	Cranberry chews *vs*. placebo	Female	Phase 1	2014	Liu et al[13]
Safety, immunogenicity, and preliminary clinical efficacy of a vaccine against extraintestinal pathogenic Escherichia coli in women with a history of recurrent urinary tract infection: a randomised, single-blind, placebo-controlled phase 1b trial	*E. coli* serotypes (ExPEC4V) intramuscular *vs.* placebo	Female	Phase 1	2014	Huttner et al[14]
A Multicenter, Randomized, Double-Blind, Phase 2 Study of the Efficacy and Safety of Plazomicin Compared with Levofloxacin in the Treatment of Complicated Urinary Tract Infection and Acute Pyelonephritis.	Plazomicin *vs.* Levofloxacin	Female	Phase 3	2018	Connolly et al[15]
A Trial Comparing Antibiotics Versus no Treatment in the Prevention of Symptomatic Urinary Tract Infection in Kidney Transplant Recipients with Asymptomatic Bacteriuria	Antibiotics (Fluoroquinolone, amoxicillin, amoxicillin-clavulanic acid, nitrofurantoin, cotrimoxazole, and fosfomycin-trometamol) *vs.* no therapy	Both	Phase 4	2014	Coussement et al[16]
Fosfomycin Versus Meropenem or Ceftriaxone in Bacteriemic Infections Caused by Multidrug Resistance in *E.Coli*	Fosfomycin disodium (4 g/6 hours) or a comparator (ceftriaxone or meropenem)	Both	Phase 3	2014	Sojo-Dorado et al[17]
Effect and Safety of Meropenem–Vaborbactam versus Best-Available Therapy in Patients with Carbapenem-Resistant Enterobacteriaceae Infections: The TANGO II Randomized Clinical Trial	Meropenem-vaborbactam *via* IV infusion *vs.* polymyxins, carbapenems, aminoglycosides, or tigecycline monotherapy or in combination	Both	Phase 3	2014	Wunderink et al[18]
Genetic engineering of probiotic *Escherichia coli* Nissle 1917 for clinical application.	*E. coli* Nissle 1917	Both	Phase 1	2014	Ou et al[19]
Nitric oxide charged catheters as a potential strategy for prevention of hospital acquired infections	Nitric oxide impregnated catheter	Both	Phase 1	2014	Margel et al[20]
Antibiotic Treatment for 7 Days Versus 14 Days in Patients with Acute Male Urinary Tract Infection	Ceftriaxone and ofloxacin *vs. p*lacebo of ofloxacin	Male	Phase 3	2015	Lafaurie et al[21]
Should Asymptomatic Bacteriuria Be Systematically Treated in Kidney Transplant Recipients? Results From a Randomized Controlled Trial	7 days course of antibiotic treatment *vs.* 14 days course of antibiotic treatment	Both	Phase 2	2015	Origüen et al[22]
A Randomized Controlled Trial of Preoperative Prophylactic Antibiotics Prior to Percutaneous Nephrolithotomy in a Low Infectious Risk Population: A Report from the EDGE Consortium	7 days of antibiotic treatment (Nitrofurantoin monohydrate macrocrystalline capsules, ampicillin, gentamicin, vancomycin, ceftriaxone) *vs.* reduced risk of sepsis in moderate to high-risk patients	Both	Phase 4	2015	Chew et al[23]
Pharmacokinetics of Ciprofloxacin in Pediatric Patients	Ciprofloxacin in pediatric patients with complicated UTIs	Both	Phase 4	2015	Meesters et al[24]
Prevention of Post-operative Urinary Retention	Tamsulosin *vs.* placebo	Both	Phase 3	2015	Madani et al[25]
Lactobacillus Probiotic for Prevention of UTI	*Lactobacillus crispatus* probiotic *vs.* placebo	Female	Phase 2/Phase 3	2015	Forster et al[26]
Effect of Active vs. Passive Voiding Trials on Time to Discharge, Urinary Tract Infection, and Urinary Retention	Active voiding trial *vs.* passive voiding trial	Both	Phase 3	2015	Mills et al[27]
Evaluation of the Efficacy and Safety of MV140	MV140 *vs.* placebo	Female	Phase 3	2015	Benito-Villalvilla et al[28]

Table continued

Table I. ***(Table continued).*** Clinical trials details for the management of UTIs during six years.

Title	Interventions	Sex	Phases of trial	Star year	Author/References
Efficacy of CLR Compared to Fosfomycin Trometamol in Acute Lower UTIs	Fosfomycin trometamol *vs.* fosfomycin trometamol-placebo	Female	Phase 3	2015	Wagenlehner et al[29]
Contrast-Enhanced Ultrasound for Evaluation of Reflux Nephropathy	Sulfur hexafluoride type-a lipid microspheres in vesicoureteral reflux	Both	Phase 2	2016	Zhang et al[30]
Efficacy of Temocillin in Urinary Tract Infection Due to ESBL Producing and AmpC Hyperproducing Enterobacteriaceae	Temocillin in UTIs	Both	Phase 4	2016	Laterre et al[31]
Cytoscopic Antibiotic Irrigant to Reduce Postoperative Urinary Tract Infection	Cystoscopic fluid containing Neosporin *vs.* cystoscopic fluid with placebo	Female	Phase 4	2016	Slopnick et al[32]
Safety and Efficacy of ZTI-01 (IV Fosfomycin) *vs.* Piperacillin/Tazobactam for Treatment cUTI/AP Infections	ZTI-01 (fosfomycin) *vs.* piperacillin-tazobactam	Both	Phase 2 Phase 3	2016	Kaye et al[33]
The clinical and microbiological efficacy of temocillin versus cefotaxime in adults with febrile urinary tract infection, and its effects on the intestinal microbiota: a randomised multicentre clinical trial in Sweden	Temocillin *vs.* cefotaxime	Both	Phase 4	2016	Edlund et al[34]
Methenamine hippurate compared with trimethoprim for the prevention of recurrent urinary tract infections: a randomized clinical trial	Methenamine hippurate *vs.* trimethoprim	Female	Phase 4	2016	Botros et al[35]
Comparison of single-dose fosfomycin tromethamine and other antibiotics for lower uncomplicated urinary tract infection in women and asymptomatic bacteriuria in pregnant women: A systematic review and meta-analysis	Phosphomycin *vs.* other antibiotics for lower uncomplicated UTIs	Female	Phase 2	2016	Wang et al[36]
A randomized controlled trial of sitafloxacin *vs*. ertapenem as a switch therapy after treatment for acute pyelonephritis caused by extended-spectrum β-lactamase-producing *Escherichia coli*: A pilot study	Sitafloxacin *vs.* ertapenem in acute pyelonephritis	Both	Phase 2 Phase 3	2016	Malaisri et al[37]
Emerging evidence-based innovative approaches to control catheter-associated urinary tract infection: a review	Sharklet catheter insertion *vs.* silicone foley catheter insertion	Both	Phase 1	2016	Rajaramon et al[38]
Antibiotic prophylaxis in the prevention of urinary tract infection in patients with sterile urine before extracorporeal shock wave lithotripsy	Ofloxacin *vs.* placebo prophylaxis in prevention of UTI following lithotripsy	Both	Early Phase 1	2016	Shafi et al[39]
The efficacy and safety of eravacycline compared with current clinically common antibiotics in the treatment of adults with complicated intra-abdominal infections: A Bayesian network meta-analysis	Eravacycline *vs.* antibiotics (tigecycline, meropenem, ertapenem, ceftazidime/avibactam + metronidazole, piperacillin/tazobactam, imipenem/cilastatin, and ceftriaxone + metronidazole)	Both	Phase 3	2017	Meng et al[40]
Study to assess the efficacy, safety, and pharmacokinetics of orally administered Tebipenem Pivoxil Hydrobromide (SPR994) compared to intravenous ertapenem in patients with complicated urinary tract infection (cUTI) or Acute Pyelonephritis (AP)	Tebipenem pivoxil hydrobromide (TBPM-PI-HBr) *vs.* ertapenem	Both	Phase 3	2019	Eckburg et al[41]
Efficacy and Safety of Oral Fosfomycin-Trometamol in Male Urinary Tract Infections with Multidrug-Resistant Enterobacterales	Fosfomycin-trometamol oral suspension in UTIs of multidrug resistant *Enterobacterale*s	Male	Phase 2	2019	Bouiller et al[42]
CERTAIN-1: A Phase 3 Study of Cefepime-Taniborbactam Efficacy and Safety in the Treatment of Complicated Urinary Tract Infections (cUTI), including Acute Pyelonephritis (AP)	Cefepime/taniborbactam in UTIs	Both	Phase 3	2019	McGovern et al[43]
Urinary tract infection prevention after urogynecological surgery	Methenamine hippurate *vs.* placebo in UTIs	Female	Phase 2	2019	Tam et al[44]
Clinical trial on the preventive effect of Intravaginal prasterone on recurrent urinary tract infections in postmenopausal women	Prasterone *vs.* placebo in recurrent UTIs	Female	Phase 3	2019	Labrie et al[45]

UTI: urinary tract infection.

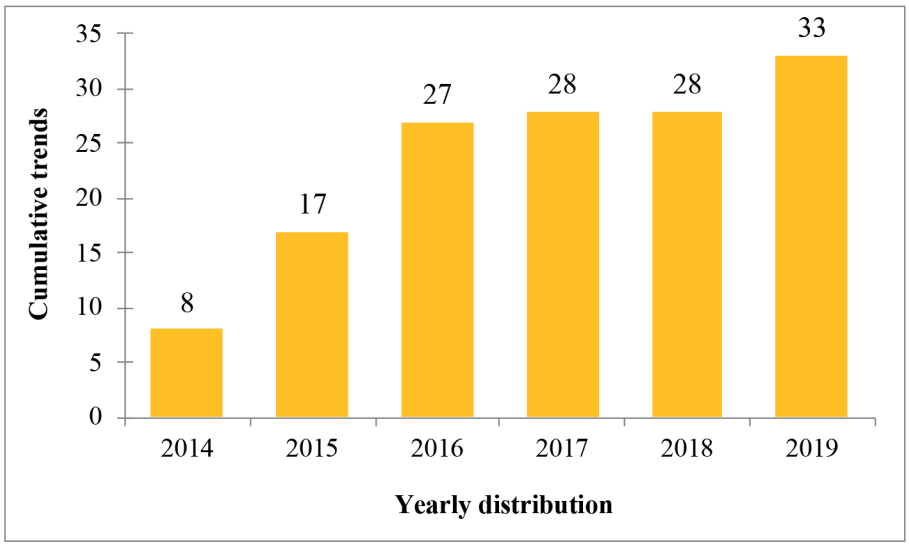

Figure 4. Six years cumulative trend in UTI clinical trials.

advancing from the lower part of the urinary tract into the bladder account for a large proportion of UTIs. The female urethra is shorter in length, and the external one-third part is often inhabited by microorganisms from normal vaginal and enteric flora. Furthermore, mechanical devices, urethral massage therapy, or sexual activity can also transfer pathogenic microorganisms from the urethra to the urinary bladder. Upon entering the bladder, bacterial factors significantly contribute to the processes of colonization and infection. A different hypothesis suggests that UTIs may be brought about by the intermittent colonization of the vaginal and periurethral region by other microorganisms[51,53]. While ascending bacterial infection is perhaps the most prevalent mode of transmission of infections in the urinary tract, hematogenous and lymphatic dissemination are also viable routes of infection. In addition, blood-borne infections have the potential to enter and establish themselves in the renal parenchyma during bouts of bacteremia. Furthermore, *Staphylococcus aureus*-associated bacteremia and endocarditis are the etiologies of renal abscesses. Pyelonephritis in hospitalized patients is infrequently observed and is predominantly caused by *Candida* species.

Epidemiology

UTIs are bacterial infections that impose a significant financial burden on healthcare systems worldwide, with an estimated annual incidence of 150 million cases[5,54]. UTI-related ambulatory visits amounted to approximately 10.5 million in 2007, while emergency room visits accounted for 2 to 3 million, resulting in a combined expenditure of $3.5 billion[5]. In Indian hospitals, UTIs are frequently encountered bacterial infections. A recent study[55] in Northern India documented a 17% positivity rate in urine samples. In young, sexually active, non-pregnant women, the occurrence of asymptomatic bacteriuria is 5-6%, higher as compared to young men (less than 0.1%). The incidence rate can reach up to 20% in elderly women who are over 65 years old[56]. Approximately 40% of females and 12% of males get at least one symptomatic UTI in their lifetime, and up to 40% of affected females have recurring UTIs[57]. The occurrence of UTIs (both silent bacteriuria and symptomatic illness) in pregnant women in India varies from 3% to 24%[58].

The Preventive and Therapeutic Strategies for UTIs

The primary objective of recently developed treatments is to prevent bacteria from adhering to the urothelium and forming bothersome reservoirs of infection. This section examines the effectiveness of various clinical trials, different treatment options for patients with UTIs, and the potential of different vaccines to prevent various types of UTIs.

Pilicides and mannosides

Both mannosides and pilicides show intriguing potential for future therapy for uncomplicated cystitis and recurrent UTIs and may assist in circum-

venting the rising tendency of antibiotic-resistant microorganisms. Pilicides, derivatives of ring-fused-2-pyridone, are tiny compounds that disrupt the assembly of mono- and poly-sticky structures in the chaperone-usher pathway (CUP). Pilicides have a wide range of activities and are assembled through CUP[59]. They work by targeting CUP periplasmic chaperones, causing type 1 pilus adhesin on the surface of bacterial cells to be inhibited, lowering bacterial adhesion qualities. As a result, during urination, free bacteria are effectively flushed out of the urinary system by urine flow[60].

Mannosides are the tip subunit of type 1 pili of *E. coli* fimH, and they can prevent bacterial attachment to epithelial cells mediated by fimH adhesin[61,62]. A randomized, open-label, placebo-controlled trial[63] demonstrated a remarkable effect of D-mannose after 6 months of treatment at a daily dose of 2 g for the prevention of recurrent UTIs. Both patients with and without neurological disorders reported that an initial combination of D-mannose and salicin therapy, as well as maintenance and/or prophylactic combinations of D-mannose and probiotics (especially *Lactobacillus acidophilus*), were effective in the treatment and prevention of recurrent cystitis caused by *E. coli*[64]. The potential issue is the adverse effects documented with systemic dosing of either mannosides or pilicides[65]. However, in the present scenario, pilicides and mannosides are probably less problematic than current antibiotic therapy protocols, though this hypothesis needs to be confirmed[66].

Vaccinology

Although there is currently no effective vaccine available for UTI infection, it has been proposed that a vaccine could serve as a candidate for the eradication of residual bladder bacteria. The development of anti-uropathogenic *E. coli* (anti-UPEC) vaccines has impelled researchers to look for vaccine antigens that are exceptionally efficacious against uropathogens that are accountable for recurrent urinary tract infections. Advances in vaccination antigen should improve antibody response efficacy while decreasing cross-reactivity with nonpathogenic microorganisms[66]. A waxing-based technique led to the finding of 22 potential UPEC-specified vaccination targets while distinguishing outer membrane proteins with homologous amino acid motifs among UPEC strains[67]. While the functions of several remain unknown, only a few have been identified as being present in UPEC during UTI, but not many have been demonstrated to provide protection against cystitis[68]. Further, advancements are being achieved in the field of reverse vaccinology, the collection of *in silico* techniques that permit the examination of an expanding number of ordered genomes of microbes in search of surface-localized antigens specific to pathogens[69]. Furthermore, when combined with gene expression characterization, proteomic analysis, and upcoming high throughput genomic screens, reverse vaccinology has the potential to dramatically improve the ability to identify viable vaccine targets[66]. Proteases and toxins, which play a crucial role in the pathogenic process of UTIs, are another prospective target for rational vaccine design and development. The conventional vaccine approach, which primarily targets virulence factors such as fimH of type 1 fimbriae, has yielded promising results in animal models[70].

Antibiofilm therapy

The bacterium that attaches to the epithelial tissues of the urinary system creates biofilms that can infiltrate other tissues, leading to the emergence of pyelonephritis or chronic prostatitis. Macrolides, including erythromycin, clarithromycin, and azithromycin, are the preferred drugs for their significant antibiofilm activity in both *in vitro* and *in vivo* settings[71]. The biofilm-forming bacteria are difficult to eradicate as a result of their antibiotic-resistant phenotype, hence, combination therapy has been recommended for such infections. It is believed that biofilm-forming bacteria exhibit a variable degree of antibiotic resistance, mainly due to reduced penetration of drugs deeper inside the biofilm and restricted entry of oxygen, glucose, and other nutrients. Notwithstanding the aforementioned strategies, ongoing research investigates novel therapeutic alternatives in lieu of conventional antibiotic treatments in order to prevent the development of resistant bacteria in underlying tissues and biofilm formation[72]. Several strategies, such as weak acids, bacteriophages, and photo inactivation, have been proposed for the eradication of bacterial infections forming biofilm[73]. Recently, a study[74] has advocated the use of ceragenins for the eradication of biofilm-forming infections of the urinary tract that may act by reinforcing the production of the antimicrobial LL-37 peptide from the epithelium of the urinary tract.

Catheters coated with hydrogels or antibiotics

UTIs due to catheterization constitute a major global health issue, accounting for about 40% of

hospital-acquired infections, which in turn leads to septicemia with a 30% mortality rate[75]. Consequently, catheters that have been coated with hydrogels or antibiotics are made of cross-linked, insoluble, hydrophilic polymers that capture water. Catheter encrustation can be mitigated in part by water entrapment, which provides support for the catheter through enhanced surface lubrication, thereby preventing bacterial adhesion to the surface[76]. Hydrogels, which are a class of hydrophilic, swellable, and insoluble polymers, induce a greater propensity for planktonic cells to aggregate, leading to an accumulation of nucleated crystals. This phenomenon accelerates the obstruction of catheters when compared to uncoated silicone[72]. Through this process of progress, a multitude of antibacterial agents and other compounds have been employed to apply an outer coating on catheters[77,78]. However, contrary to this, a study[79] on 226 catheterized patients compared the prevalence of catheter-associated nosocomial illnesses of the urinary tract (CAUTI) between hydrogel-coated and silicone-coated catheters, wherein there was no significant difference in CAUTIs reported among those groups. In contrast, minocycline-rifampicin-coated catheters inhibited the formation of biofilm by all Gram-positive and Gram-negative bacteria with the exception of *P. aeruginosa* and *Candida* species[72,80]. Nanoparticles have the ability to adhere to and infiltrate cell membranes of bacteria, causing disruption to the bacterial membrane and damaging chromosomal DNA[81]. It is noteworthy that the application of MgF nanoparticle coating on glass surfaces led to a diminution in the growth of biofilms caused by both *E. coli* and *S. aureus*[81]. Furthermore, nanoparticles of yttrium fluoride (YF_3) are advantageous with their low solubility, extended protection, and reduced risk of cytotoxicity. The use of microwave-irradiated CaO nanoparticles (CaO-NPs) has a suppressive impact on the formation of biofilms caused by both Gram-negative and Gram-positive bacteria[82].

Iontophoresis

Iontophoresis is a technique by which ions traverse a barrier induced by the application of an electric field in order to increase the efficacy of antibiofilm medications in experimental settings[72]. Evidence suggests that the efficacy of biocides and tobramycin against *P. aeruginosa* biofilm is augmented by low electrical currents. Nevertheless, this enhancement is predominantly limited to antibiotics that exhibit efficacy against planktonic cells. It has been demonstrated that the application of electric current to silver electrode-fitted catheters produced a significant reduction in *P. mirabilis* encrustation[83]. In addition, enzyme inhibitors have demonstrated encouraging outcomes in combating biofilm, including urease, which catalyzes the conversion of urea to ammonium ions in *P. mirabilis* and is vital to the development of novel antibiofilm compounds. Furthermore, fluorofamide (a urease inhibitor) prevented the increase in pH by *P. mirabilis in vitro*, thereby inhibiting the formation of urea crystals and, subsequently, encrustation and catheter obstruction[72]. Additionally, urease inhibitory activity was observed in herbal compounds, including vanillic acid[84], plum juice[85], and germa-γ-lactones[86], which consequently reduced microbial proliferation and crystallization in catheters[72].

A new drug, zerbaxa, which is a beta-lactamase inhibitor and a combination of ceftolozane and tazobactam, was approved by the FDA in 2014. Its intended use is the treatment of catheter-related urinary tract infections (CAUTIs), the eradication of bacteria, and the inhibition of bacterial enzyme production, which is the primary cause of antibiotic therapy. In a recent study[87] (ASPECT-cUTI phase III trial), it was found that zerbaxa (ceftolozane/tazobactam) exhibits greater effectiveness against levofloxacin-resistant and multidrug-resistant pathogens, as well as microbiologic eradication, and clinical cure. A fixed-dose combination of ceftazidime and avibactam has been approved by the FDA under the Generating Antibiotic Incentives Now (GAIN) title of the FDA Safety and Innovation Act[88]. It reinstates the efficacy of ceftazidime, a third-generation cephalosporin, against a wide variety of Gram-positive bacteria that produce beta-lactamases[89]. The combination has been shown to address complex UTIs caused by Gram-negative bacteria, such as *E. coli*, *Klebsiella* species, and *P. aeruginosa*[87,88].

Clinical Trial Evaluation

Any newly discovered molecule is not immediately available to the general public. It must first go through a series of clinical tests. This testing of a new drug molecule on selected healthy volunteers and patients is called a clinical trial. There are four phases of clinical trials[90]. Data derived from clinical trials pertaining to urinary tract infections (UTIs) were gathered between the years 2014 and April 2019 with the purpose of conducting a clinical trial evaluation (Table I). Year-by-year trends in clinical trials, gender distribution,

kinds of therapies, and stages of development are among the analyses performed.

Trends and Technological Advancement in Clinical Trials

The cumulative trend was analyzed for the last six years. Figure 4 depicts the trends in clinical trials on urinary tract infections. Table I and Figure 4 show that the number of cumulative clinical trials on UTIs has been steadily increasing over the last six years. However, more trials were carried out in 2014, 2015, and 2016 than in any of the previous three years. The number of trials that were conducted annually has reduced in successive years. It is important to note that, with the advancement of medical science, researchers are no longer only focused on developing and testing new synthetic derivatives. A plethora of research has been undertaken on novel devices, natural extracts, and other non-pharmacological interventions for the treatment of UTIs.

As shown in Table I, several interventions for UTIs have been studied, accounting for approximately 27 (81.8%), 3 (9.1%), 2 (6.1%), and 1 (3%) of research based on drugs, others, and observational, devices, and procedures, respectively. Sharklet catheter insertion, Silicone Foley catheter insertion, ID Flexicult™, and Nitric Oxide (SSI Diagnostica, Hillerød, Denmark**)** impregnated catheter are some of these devices. These interventions are in phase 1 (6, 18.2%), phase 2 (5, 15.1%), phase 2/3 (3, 9.1%), phase 3 (12, 36.4%) and phase 4 (7, 21.2%) of development (Table I). Out of 33 interventions, most of them (36.4%) are in phase 3 of the development. This implies that they are potential candidates to get marketing approval within the next few years. The fact is that the number of interventions in each phase is very closely distributed, implying that it is a very mature field of research. Further, analysis was done based on gender (Table I). It is a fact that UTIs are more common in females than in males. This can be observed in the gender distribution wherein 11 (33.3%) of the trials have enrolled female candidates in comparison to only 2 (6.1%) males.

Discussion

UTIs continue to be a major global health concern, requiring ongoing research into innovative interventions and therapeutic approaches. This review was conducted to evaluate the current developments in the treatment of UTIs, including vaccination, the use of mannosides and pilicides, antibiofilm therapy, hydrogel or antibiotic-coated catheters, iontophoresis, and novel pharmacotherapies. A number of experiments have been carried out to develop a vaccination that is effective against different *E. coli* phenotypes. Vaccines against extraintestinal *E. coli* were created using the capsular[14] and iron scavenger receptors[91] as models. Developments in reverse vaccinology provide new paths for the identification of surface antigens unique to UTI pathogens by fusing *in silico* methods with gene expression and proteomic investigations[92]. Although no vaccine against uropathogenic *E. coli* (UPEC)-induced UTIs has received broad clinical approval to date, research on vaccines against UPEC-induced UTIs appears promising. Furthermore, focusing on the proteases and toxins implicated in the pathogenesis of UTIs is a sensible strategy for developing vaccines, as preliminary research in animal models[93] indicates encouraging outcomes.

Emerging treatments for simple cystitis and recurrent UTIs include mannosides and pilicides, which provide alternatives to traditional antibiotic therapy. They work by targeting the chaperone-usher pathway, which disrupts bacterial adherence. Small molecule compounds, including curlicides and pilicides, have the ability to interfere with the formation of sticky fimbriae and curli, which could result in reduced virulence and a shortage of biofilm in UPEC[94]. Furthermore, there is hope for reducing bacterial motility and biofilm formation by blocking quorum-sensing pathways with substances such as plant extracts. However, more research and scientific innovations are needed before these strategies may be used in clinical settings[95]. Similarly, mannosides in clinical studies have been found to be effective in preventing recurrent UTIs by blocking bacterial attachment to epithelial cells, which is mediated by fimH adhesin. While a high-affinity polyvalent α-d-mannopyranoside-based inhibitor has many potential uses, its high molecular weight and hydrophilic nature may affect its oral bioavailability and hinder its ability to treat UPEC-induced UTIs[96]. Although there are worries about side effects from systemic dosage, mannosides and pilicide may be safer options for treating UTIs than antibiotics.

One major problem in treating UTIs is the production of biofilms by uropathogens, which can lead to antibiotic resistance and treatment failure. By enhancing antibiotic susceptibility and upsetting the structure of biofilms, antibiofilm treatment offers new ways to treat UTIs[97]. Macrolides, includ-

ing azithromycin and erythromycin, have strong antibiofilm properties, and combination treatment approaches target bacteria that build biofilms resistant to antibiotics[98]. New treatments that show promise in stopping the production of biofilms and eliminating those that have already formed include photoinactivation[99] and bacteriophages[100].

In order to stop bacterial colonization and biofilm formation, catheters coated with hydrogels or antibiotics have been developed. Catheter-associated urinary tract infections (CAUTIs) represent a significant healthcare concern due to their high prevalence and associated complications. Hydrogel coatings prevent catheter encrustation and bacterial adherence by providing improved surface lubrication. It has been demonstrated that natural medicines like ajoene and emodin can control the biofilms produced by a variety of bacteria, including *S. aureus*, *P. aeruginosa*, and *E. coli*[101,102]. Antibiotic-coated catheters release antimicrobial compounds to stop the growth of biofilms, yet there have been conflicting results in clinical trials about how effective they are in preventing the growth of bacterial biofilm[102]. Catheter coating technologies could go in new directions as nanoparticles like yttrium fluoride and magnesium fluoride demonstrate promise in preventing biofilm formation on catheter surfaces.

Iontophoresis is a non-invasive technique for treating UTIs that uses low electrical currents. Research[103] reveals that iontophoresis improves the way antibiofilm medications work against uropathogens, especially *P. aeruginosa*. Furthermore, there is encouraging evidence that enzyme inhibitors, including urease inhibitors, can prevent catheter encrustation and biofilm growth[104,105]. Innovative pharmacotherapies that fill significant gaps in the available treatment choices, such as ceftazidime-avibactam and zerbaxa, have demonstrated great success against complex UTIs and microorganisms resistant to several drugs[106].

Conclusions

Recent developments in UTI interventions are described in this systematic review, with an emphasis on preventive and treatment measures. The burden from UTIs on both clinical and financial aspects of health care is immense and on the rise. Promising treatments include vaccinations against uropathogenic *E. coli* and pilicides and mannosides, which target bacterial adherence. Other strategies being investigated include antibiofilm therapy, iontophoresis, hydrogel or antibiotic-coated catheters, iontophoresis, and enzyme inhibitors.

Upon reviewing clinical trial data from 2014 to 2019, it is evident that the number of clinical trials has been steadily increasing each year. A relatively large number of trials have investigated the impact of drug-based interventions than device-based interventions in UTIs. In the developmental stages of newer options, most of the trials are running in phase 3 stages. Hopefully, in near future, a combination of drug-based and device-based interventions may be effectively able to cure UTIs in a small duration treatment regime.

In summary, new developments in UTI treatments and treatment technologies have the potential to enhance patient outcomes and lessen the prevalence of UTIs worldwide. Ongoing research projects aim to solve important issues in UTI management, ranging from novel vaccine candidates and antibiofilm agents to sophisticated catheter coatings and iontophoresis technology. To improve UTI treatment outcomes and incorporate these developments into clinical practice, cooperation between researchers, physicians, and industry stakeholders is crucial.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Authors' Contributions

Conceptualization, M.S.A., M.J.A., and T.K.M.; methodology, M.S.A., M.J.A., T.K.M., and A.S.N.; validation, M.S.A., M.J.A., T.K.M., and P.A.; data curation, M.S.A., M.S.A., T.K.M., and P.A.; writing original draft, M.S.A., M.J.A., T.K.M., A.A.S.M., and A.F.A.; writing review and editing, M.S.A., M.J.A., and T.K.M. All authors have reviewed and consented to the final published version of the work.

Ethics Approval and Informed Consent

Not applicable due to the design of the study.

Availability of Data and Materials

This article incorporates all of the data that was collected for the current review.

ORCID ID
M.S. Alam: 0000-0001-6959-2137
M.J. Anwar: 0000-0002-9895-8166
M.S. Akhtar: 0000-0002-1064-0365
P. Alam: 0000-0002-7632-3426
A.A.S. Mohammad: 0000-0002-7990-5536
A.F. Almutairy: 0009-0007-7954-4893
A.S. Nazmi: 0000-0001-5626-3799
T.K. Mukherjee: 0000-0001-6737-8321

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We hereby declare that this paper was not produced using any artificial intelligence or assisted technologies, including the preparation of any figures or illustrations.

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