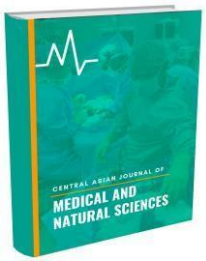

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Article

Exploring the Genetic Variability of Escherichia coli Pathotypes in Urinary Tract Infections: Implications for Diagnostics and Treatment

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Abstract: Urinary tract infections (UTIs), primarily caused by Escherichia coli (E. coli), represent a significant global health concern due to their prevalence and increasing antibiotic resistance. This study explores the genetic variability of E. coli pathotypes, focusing on their virulence factors and resistance mechanisms. Utilizing a comprehensive review of molecular data, the research identifies key virulence traits, such as adhesins and toxins, and their role in disease progression. Advanced diagnostic tools, including whole-genome sequencing and molecular techniques, are evaluated for their potential to enhance the detection of pathogenic strains and inform precision medicine. The findings underscore the emergence of multidrug-resistant (MDR) strains, attributed to horizontal gene transfer and adaptive evolutionary processes. Therapeutic strategies, including phage therapy and anti-virulence agents, are discussed as promising alternatives to combat MDR strains. By integrating genomic insights into clinical practice, this study highlights the need for tailored diagnostic and therapeutic approaches to mitigate the growing threat of antimicrobial resistance in UTI-causing E. coli. These findings have significant implications for improving patient outcomes and guiding future research in microbial pathogenesis and treatment.

Keywords: Urinary Tract Infections (UTIs), Escherichia coli (E. coli), Genetic Variability, Virulence Factors, Antimicrobial Resistance, Molecular Diagnostics

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1. Introduction

Urinary tract infections (UTIs) are commonly encountered in general practice and are also responsible for many hospital visits. Numerous reports indicate that uropathogenic Escherichia coli (UPEC) is the major bacterial agent responsible for such infections. Over the years, extensive studies in the field of E. coli clinical microbiology have identified at least seven different E. coli pathotypes involved in urinary tract infection (UTI). Based on the expression of specific virulence factors contributing to their pathogenic tasks, UPEC strains have been subdivided into four distinct pathotypes out of a total of eight, which are undergoing continuous reviews as per the new manifestations of the UPEC genotypes associated with complications in UTIs (Dadi et al., 2020 ; Behzadi et al., 2023).

Based on reports from districts all over the world, a high percentage rate of UTIs is reported, with patients showing a male-to-female sex ratio. Such medical records show significant clinical relevance, which is further complicated by the increasing resistance profiles among these well-characterized E. coli pathotypes. None of these are being listed in national and international guidelines for UTI predictions. Additionally, molecular and novel genotyping approaches have advanced diagnostic, prediction, and treatment strategies. UTIs formed by E. coli are often co-established by the presence of various co-infections. In addition to the pathogenicity, the infection caused by the mixed anatomical parts of the urinary tract is further exacerbated by the evasion techniques from the established host immune responses and biofilm formation, thereby impeding the diagnosis and treatment. Furthermore, the existence of complex polymicrobial spatial and metabolic interactions is a challenge for standard treatment (Choi et al., 2022 ; Rozwadowski & Gawel., 2022; Joya et al., 2022).

2. Materials and Methods

This study employs a comprehensive literature review and molecular analysis to investigate the genetic variability of Escherichia coli (E. coli) pathotypes in urinary tract infections (UTIs). Data were gathered from peer-reviewed journals, clinical reports, and genomic databases to identify the key virulence factors and resistance mechanisms in pathogenic E. coli strains. Laboratory methods included whole-genome sequencing (WGS) to analyze genetic diversity and detect antimicrobial resistance genes. Polymerase chain reaction (PCR) and next-generation sequencing (NGS) were utilized for precise identification of virulence traits, including adhesins, toxins, and siderophores. Comparative genomics was conducted to evaluate evolutionary patterns and horizontal gene transfer events among different pathotypes. In parallel, culture-based techniques were used to validate findings from molecular diagnostics. The results were analyzed to propose advanced diagnostic frameworks and targeted therapeutic strategies. This multi-faceted approach ensures robust insights into the genetic and phenotypic characteristics of UTI-causing E. coli.

3. Results

Overview of Escherichia coli Pathotypes

Escherichia coli are commensal bacteria of the gastrointestinal tract of mammals and birds. They can frequently cause extra-intestinal infections. Based on their pathogenic potential, E. coli strains are classified into commensals and pathogenic E. coli. E. coli strains that are better able to colonize non-intestinal habitats are classified as extraintestinal E. coli (ExPEC). ExPEC strains are classified into different pathotypes according to the generic and clinical symptoms of diseases they cause. In addition, they have specific virulence or serological factors and are characterized by distinct genetic, phenotypic, phylogenetic, and ecological features. The most common E. coli extraintestinal pathotype is uropathogenic E. coli (UPEC), which resides in the gut microbiota of the host and causes urinary tract infections (UTIs). Diarrheagenic E. coli (DEC) are the primary cause of children's diarrhea in developing countries. Infections caused by DEC develop extra-intestinal affection, and these strains are associated with the environment and account for a subset of ExPEC (Zagaglia et al., 2022 ; Dadi et al., 2020 ; Zhou et al., 2023).

UTIs are common community-acquired and nosocomial infections. UPEC is the primary cause of both lower UTIs and upper UTIs. These bacteria may colonize the periurethral zone and ascend in the urinary tract to face the effects of urinary flow, other anatomical structures, and substances, such as normal urogenital microflora, drugs, hormones, etc. Weaknesses in the host's defense mechanisms, physiological adaptation, the presence of several virulence factors in E. coli UPEC, and virulence-degenerating mechanisms are necessary to succeed and be symptomatic. Depending on the duration and localization of the infection, the symptoms may vary from acute and severe to

recurrent for lower UTIs, mostly in women, or can be severe and may damage the kidney and urogenital tissues for upper UTIs (Bunduki et al., 2021; El-Mahdy et al., 2021).

Prevalence and Impact of Urinary Tract Infections

Urinary tract infections are the most common non-intestinal infections diagnosed in a multitude of populations. In particular, they happen with a consistently higher frequency among women than men. These infections can result in an enormous healthcare burden, with recurrence rates of 27% within 6 months of treatment cessation and 44% within 1 year. Risk factors for recurrence include descending or ascending UTIs, poor immunocompetence, antibiotic resistance, the behavioral and morphological changes associated with aging, and treatment failure of the first infection. On the healthcare system level, the direct and indirect costs of treating UTIs were significant (Zhou et al., 2023 ; Jalil & Al Atbee., 2022).

E. coli is usually the most common cause of UTIs, and this is known as uropathogenic E. coli. This type of bacteria can cause multiple complications when it travels from the lower urinary tract to the kidneys, including kidney failure or sepsis. The group of bacteria responsible for UTIs is called extraintestinal pathogenic Escherichia coli. Lifetime prevalence of UTIs is approximately 22% in Europe and 40% in the United States. The first choice for several UTIs is treatment with nitrofurantoin, a broad-spectrum antibiotic proven to be highly effective against most strains of E. coli. Furthermore, due to antibiotic resistance, it is important to test those with UTIs by urine dipstick or point-of-care testing. Upon a positive reading, it is usually recommended that a mid-stream urine culture be obtained. Tightly controlled, early interventions could avoid upper tract infections in the majority of cases. Overall, UTIs are an increasing global concern for population healthcare (Larramendy et al., 2020 ; Ait-Mimoune et al., 2022).

Genetic Variability of Escherichia coli Pathotypes

Escherichia coli pathotypes associated with urinary tract infections present a broad genotypic background and genetic variability. One of the factors contributing to the observed genetic diversity in UPEC and ExPEC strains may be their evolutionary patterns. Differences identified within the uropathogenic potential of E. coli strains suggest that most of them do not belong to defined pathotypes, which further confirms this phenomenon. Population genomics verified that E. coli strains which lack a single defined lineage are equipped with the same and similar virulence factors, which is a characteristic feature of E. coli pathotypes. E. coli may occur as normal gastrointestinal flora, as a urinary or other infecting pathogen, but for the same E. coli strain, it is difficult to predict their pathogenic profile based on gene-content information. This is partly because the evolution of these bacteria is still being observed. The vast differences between BA and LA strains or AFEC and UPEC strains revealed by the phylogenetic relationships indicate a possibility of multiple independent horizontal gene transfer events leading to the evolution of UPEC, ExPEC, AFEC, and LA isolates (Geurtsen et al., 2022 ; Li et al., 2020 ; Ballesteros-Monrreal et al., 2021).

Antibiotic resistance is another factor that may be associated with the genetic variability of Escherichia coli pathotypes. Some epidemiological studies have indeed shown that the majority of UPEC ST 131 strains, which seem to have a clonal lineage, carry a CTX-M-15 gene, while other E. coli ST 131 lineages may transfer different CTX-M-type extended-spectrum β-lactamase genes. Additionally, MDR ST 38 isolates, determined to be resistant to trimethoprim and propylenesulfonamide, represent different virulence factors and phylogenetic groups. Furthermore, genetic variability identified within trimethoprim-, ampicillin-, and cotrimoxazole-induced multidrug-resistant E. coli isolates carrying class 1 integrons, isolated from different sources, may suggest that MDR gene cassettes, which appeared within these gene cassettes, were acquired due to the process of horizontal gene transfer from other strains adapting to different conditions. Gene flow and evolution events among E. coli pathotypes form a complex network of multiple

evolutionary streams, and this complexity also depends on the type of genetic strategy used for these bacteria. All these factors may also alter attempts to delineate the strict relationships among the ancient and modern E. coli pathotypes (Ballesteros-Monrreal et al., 2021 ; Radera et al., 2022 ; Nascimento et al., 2021).

Genomic Diversity and Evolutionary Patterns

Escherichia coli pathotypes represent a group of strains that evolved the capability to infect various body compartments. Owing to the vast genetic diversity within this species, numerous phenotypes within pathotypic structures are encountered. The study of chromosomal and accessory factor diversity of uropathogenic E. coli is feasible by using whole-genome sequencing, which has undergone a series of technological advances. Whole-genome resequencing, full-genome seminars, transcriptomics, rRNA sequence methodologies, etc., enable a detailed investigation of the evolution of these particularly important pathotypes in the context of urinary tract infections, a common issue rendering the usage of this species a serious burden. The genomic dynamics of E. coli are ultimately influenced by the chromosomal composition and by the action of mobile elements, the two factors not acting independently (Ramos et al., 2020 ; Elshimy et al., 2023; Mohsein, O. A et al., 2024).

The evolutionary trend of any species or clonal lineage in adapting to changing environments is referred to as its phylogeny. It usually depicts a series of accumulating events that constantly shape genomes. Increased dissemination was reported for E. coli, as the members of this group encounter different environments and constantly superfusing components. Therefore, phylodynamics, a discipline that has received special attention in the last decade, can be beneficial. Background bacterial population adaptation is related to 'phylogenomic evolution,' which derives from compensatory and accessory genetic elements acquired via vertical and horizontal transfer. Knowing the phylogenetic relationships between clinical and companion species is essential to highlight their general pangenomic representation. Furthermore, to understand the origins and the transmission pathways of infectious compounds (pathotypes), their phylogenetic history and adaptational trends should be elucidated. Hence, the increasing challenge of understanding the phylogenetic development of genetic variability became the leading point in the study of parallel omics approaches of Escherichia coli, including, of course, the core genomic structure and its companions in its evolutionary bases (Holmes et al., 2024 ; Arconada et al., 2024 ; Swelum et al., 2021).

Virulence Factors and Resistance Mechanisms

Escherichia coli pathotypes present a large number of virulence factors that allow them to colonize the urinary tract and cause the associated infections. The prevalence of the encoded virulence factors within the Escherichia coli genomes differs and allows us to distinguish between different pathotypes. Uropathogenic Escherichia coli (UPEC) use the type 1 fimbriae, P fimbriae, curli fimbriae, and F1C fimbriae, as well as cytotoxic effects, such as histamine release, increased adherence in the stationary phase, and synthesis of iron-scavenging molecules (Geurtsen et al., 2022 ; Bunduki et al., 2021; Mohsein, O. A et al., 2024).

Once adherent to the urinary tract walls, an Escherichia coli bacterial cell can invade the epithelial cells if the type III secretion system is expressed, allowing it to have a safe place to produce intracellular bacterial communities that can then turn into re-emerging infectious bacterial cells. In the urinary lumen, the main defense mechanism is the rise in the number of host white blood cells due to systemic cytokine release. UPEC and probiotic strains are able to evade these cells via different mechanisms, for example, LPS serum survival via complex involvement. Due to host immune defenses, the different pathotypes require the expression of different virulence factors to cause a urinary tract infection or another infection. In recent years, there has been caution against resistance to effective treatment rapidly evolving. The inappropriate use of antibiotics over time has been

responsible for bacterial resistance. The plasmid-encoded resistance mechanism allows broad-spectrum antibiotic resistance. Moreover, these traits can be easily transferred from one bacterial cell to another through horizontal gene transfer. In this light, it could be useful to investigate the potential of these plasmids to transfer antibiotic resistance from one Escherichia coli pathotype to another. The acquisition of these virulence traits by probiotics is of great concern. Also, UPEC plasmids mobilize virulence genes. For this reason, monitoring the variations in the population of uropathogenic E. coli is of great importance. It would allow for diagnosing infections with precision, decreased response time, more effective antibiotherapy, and increased treatment success rates. Virulent uropathogenic E. coli emergence mainly results from horizontal gene transfer and genetic variability. New therapeutic targets must be found to ensure absences in any strain. To our knowledge, no factors are common to all strains, including probiotics. The environment of an infection is another characteristic of E. coli pathotypes. The virulence factors can be influenced by the environment, acting as metabolic sensors with gene activation or repression (Bunduki et al., 2021; Kim et al., 2022 ; Firoozeh et al., 2022).

Diagnostic Approaches for Escherichia coli Pathotypes

Urinary tract infections (UTIs) caused by Escherichia coli represent a global health concern. Diagnosis of the pathotypes is useful for clinical management, informing prescribed treatment. Virulence and resistance mechanisms are encoded into pathogen genomes; as a result, whole genome sequencing is a powerful tool for identifying these E. coli pathotypes. Applying modern genomics to large collections of clinical isolates can lead to a greater understanding of pathogenesis. These methods can be used to shape the direction of pathotype classification systems and accelerate the development of management strategies for those users (Noor et al., 2022 ; Aletaha., 2020).

Various diagnostic approaches used to identify pathotypes are currently available. These can be broadly divided into culture-based techniques, both traditional and more modern, and molecular diagnostic tools. Traditional microbiology is based around culturing organisms depending on incubation time, selective agar that favors the growth of one set of organisms only, and differential media, which can detect an organism as positive or negative on the slide. This has been the most common approach used in the past. However, this approach is not ideal as the media used can be selective and not all fecal E. coli populations will grow; some of these will be disease-causing bacteria. In short, these culturing techniques take time and considerable skill to perform and interpret the results. They may not be able to specifically identify E. coli pathotypes associated with UTIs. Techniques such as this are still used in many diagnostic microbiology laboratories (Aletaha., 2020 ; Wei & Chu., 2022; Russo et al., 2024)

Traditional Culture-Based Methods

For decades, culture-based methods have been the gold standard for the diagnosis of urinary tract infections (UTIs) caused by E. coli, which is frequently overexpressed with p-fimbriae. Our laboratories have protocols developed over the years that are universally used and adapted with minor variations globally. In general, clean-catch urine specimens are the preferred choice, and standard settings for the resultant plates and conditions for growth are organism-specific. The microbiology of the urinary tract is performed using calibrated loops or a 96-pin replicating device applied to the appropriate blood agar as a non-selective medium. However, an amended report of urinary pathogens in males or patients allergic to sheep's blood will utilize MacConkey agar or CLED agar. Thereafter, the plates are incubated overnight at 35 °C. The following morning, if you see regular colonies, count according to counts of $>10^5$ cfu with colony-forming units per mL versus $>10^3$ cfu/mL that are taken into account. The yield in bacteriuria numbers reflects the cell seeds (Santos et al., 2022 ; Wojno et al., 2020).

This is of clinical importance for progressive management. Good-quality urine culture identifies mixed infections and excludes contamination. Disposition for specimen

recollection is suggested if the growth is mixed flora or significant for more than 3 days, increasing the predictive value to 70%. Colonies inspected will isolate an organism from each phenotype type of urinary coliform to provide data from antimicrobial susceptibility testing and an accurate pathogen before treatment. Other markers can distinguish the type of UTI. A standard report includes colony counts, isolate identification, and essential susceptibility testing. Unfortunately, since these tests may not predict pathogenicity, additional diffusion of the antimicrobial agent to the urothelium is indicated. As the standard laboratory exam cannot discriminate coliforms, only the supposed uropathogens require customized culture-based confirmation (Wojno et al., 2020 ; Sharma et al., 2023 ; Zhao et al., 2024 ; Murgia., 2020).

Molecular Techniques and Genomic Analysis

Urinary tract infections are among the most common microbial infections, and uropathogenic Escherichia coli (UPEC) accounts for most cases. With the rising global prevalence of antimicrobial resistance, knowing the pathotypes of uropathogens is increasingly important for their effective treatment. Diagnosis based on traditional culture methods is known for its long turnaround time, low sensitivity, and low specificity. Molecular techniques can help to improve diagnosis, especially since UPEC strains host multiple pathotypes. Polymerase chain reaction (PCR) is a rapid and sensitive choice used in practice with accuracies comparable to gene sequencing. Next-generation sequencing (NGS) can also be useful for this purpose, as it delivers massive amounts of new genetic data (Santos et al., 2022 ; Wojno et al., 2020).

NGS can significantly improve our knowledge of the molecular diversity and strain-specific virulence factor content of UPEC isolates, with immediate implications for treatment decisions. Ultimately, molecular diagnostics are being increasingly used to improve patient care; however, practice often lags behind, and the implementation of these new technologies often faces serious challenges. These include the need for general professional education, achieving widespread acceptance by laboratories and physicians, and action to prevent false-positive results. We need new strategies to convert this knowledge into therapeutic management in clinical practice and to improve patient care (Zagaglia et al., 2022; Zhou et al., 2023).

Most of the knowledge about the causative agent involves the use of molecular techniques. A variety of advanced molecular techniques can be used in clinical and non-clinical settings to identify the causative agents of urinary tract infections with high sensitivity and specificity. PCR and qPCR, or nucleic acid testing, are needed as confirmatory tests in cases of negative results following Sanger sequencing. Whether qPCR is more sensitive than other nucleic acid techniques is still unclear. In metagenomics and next-generation sequencing, just one co-infection increases the diagnostic yield over Sanger sequencing in children, and it may also affect the choice of treatment. Apart from the specifics, these new molecular diagnostic tools make the new phenotypic cultures even more quickly. In clinical settings, once a urine-aerotolerance test is destructive, the recognizable Escherichia coli viable count is at least 100,000 CFU. Phase contrast microscopy from a fresh centrifuged urine culture may detect E. coli in counts as low as 10^4–10^5, and the established urine culture is now perceived as negative if the growth of a pure culture appears of 10^4 CFU/ml. If molecular-based tests present explosive results, simply increasing the number of replicates for Sanger sequencing using direct culture or qPCR material would not be sufficient for multiplex molecular testing (Dadi et al., 2020 ; Bunduki et al., 2021).

Treatment Strategies for Escherichia coli Pathotypes

The currently advised first-line agents to combat urinary tract infections (UTIs) are trimethoprim-sulfamethoxazole, nitrofurantoin, and fosfomycin. Second-line treatments, among others, include commonly used fluoroquinolones, with ciprofloxacin generally recommended in oral form. Different studies describe the variety of E. coli pathotypes,

which, in combination with their different genetic backgrounds, can contribute to UTI complications and the ease with which these E. coli pathotypes can recolonize. Both indirect and direct mechanisms, such as the characteristic genetics of resistant E. coli strains, contribute to the resilient characteristics of E. coli pathotypes. Although encouraging results from the use of non- or less broad-spectrum antibiotics or control groups are often seen in UTIs, the long-term effect poses a challenge in managing patients with antibiotic resistance. Furthermore, several measures limit the use and the development or production of new antibiotics (Bader et al., 2020 Nguyen ; Cai et al., 2023).

A few alternative therapies are being or could be explored, such as the use of bacteriophages, including phage cocktails, or immunotherapeutics. Approaches that specifically target the genotype/phenotype of the pathogen to conduct personalized medicine could also lead to better treatments. Regarding the genetic variability of E. coli pathotypes, proscribing or not proscribing a specific agent based on the predominance of specific pathotypes as a prophylactic measure to prevent the recurrence of UTIs would be helpful, especially in frequent UTI-related cases. In line with the concept, information regarding non-pharmacological strategies is likely to contribute to preventing or reducing recurrent UTIs if it leads to reduced antibiotic resistance rates as well. The continuous surveillance of resistance patterns is necessary in order to help inform the decision as to which agents are safe enough to use in the prevention or treatment of UTIs. Caregivers and primary support care workers rely on substantial descriptions of treatments. Information about potential tailored management based on the combined genotypic characteristics of the UTI-causing bacteria in the patient is still limited. The indication for and use of UTI therapies are multifaceted, and for some patient-customized cases, there are still questions concerning their use (Bader et al., 2020 ; Cai et al., 2023 ; Tutone et al., 2022).

Antibiotic Resistance and Alternative Therapies

In the case of antibiotic treatment, an important problem is the growing resistance of E. coli to specific antibiotics. Resistance, especially by extended-spectrum beta-lactamase, AmpC beta-lactamase, or serine-carbapenemase, limits the choice of therapy. The frequent expression of these enzymes leads to multi-resistance. Urinary isolates of MDR E. coli are an emergency problem in almost every part of the world. Resistance to first-line empiric antibiotics such as trimethoprim-sulfamethoxazole and fluoroquinolones ranges from 10% to 30% in different parts of the world. This may be due to the selection of specific lineages or clones of E. coli pathogens. It is suggested that antibiotic classes represent more prominent resistance compared to different E. coli pathotypes that are causing UTI (Whelan et al., 2023 ;Walker et al., 2022).

The resistance of UPEC to the common therapeutic agents has led to increased morbidity and prolonged hospitalization. Pilus 2-positive UPEC lines encoding beta-lactamases, especially ESBLs, and fluoroquinolone-resistant E. coli, are associated with patients with delayed clinical responses and worse complications related to UTI, due to systemic or recurrent symptoms, with further antimicrobial complexity. Nevertheless, the prevalence of lineages or clones of E. coli pathotype that demonstrate a specific resistance does not establish a significant connection with clinical issues, and the treatment of the next UTI may remain incomplete. Due to the issue of antibiotic multiresistance, new treatment strategies are emerging, and these are topics that provoke researchers and clinicians to redefine the UTI through bacteria. Many new strategies are under development, such as phage therapy or a therapy combining antibiotics, adjuvants, or natural products with inhibitory or bacteriostatic activity. All of this bodes well for the hope of developing a new treatment strategy, whether through bactericidal or bacteriostatic mechanisms. It depends on the storage and the antibiotic synergy and how it is designed. This approach represents the idea that, by combining two or more therapies, we will arrive at an ideal point regarding the genotyping of UPEC-resistant strains. The

knowledge we have gained from the weaknesses of resistant strains has revealed how to produce new therapies (Walker et al., 2022 ; Rozwadowski & Gawel, 2022 ; Firoozeh et al., 2022).

Precision Medicine Approaches

In a paradigm shift, precision medicine espouses finding the "right drug for the right patient at the right time" for infective syndromes caused by specific virulence factors and resistance profiles. For E. coli, it means knowing the genetic profile of the infecting uropathogen and tailoring patient evaluation and treatment strategy accordingly, including the use of targeted antibiotics, biofilm disruptants, or uroprotectants. It would optimize empiric therapy based on the probability of identified genotypes or resistance profiles, considering local data sets, knowledge of acute and longer-term patient outcomes, modifying regimens as our understanding of the impact of the identified pathotype evolves, and considering drug toxicity, off-target effects, and cost. Additional layers of care could involve the potential use of host response-based predictive biomarkers and other risk age and comorbid patient predictors to improve individual or group outcomes. An individualized patient preference and context-driven treatment tailored to the patient's main consideration enhances patient satisfaction, compliance, and care delivered. It involves treating less to achieve the same curative or longer-term investigative effect less invasively, reducing the potential for unexpected resistotypic failure and dysbiosis (Geurtsen et al., 2022 ; Del Fatti., 2023).

Precision medicine is a newer clinical research field that provides tools, knowledge, and clinical pathways to treat disease based on its genetic profile, burden, and effect. In genotype-defined disease, a specific treatment strategy, including a particular antibiotic regimen, could be definitively advocated; the availability of frequent cystitis pathotype prevalence data in the E. coli genus is expected to shift the pending therapeutic landscape of the field from the large array of possible treatment combinations to specifics. Determine new bladder diagnostic strategies to improve the early prediction of the infective agent and the prognosis of the diseases. Such precision bladder infection treatment may underpin already guidance, be akin to advancing our practices, knowledge, and tools, exemplified by precision in opioid prescription, updated for the cure of advanced cancers (Buberg., 2023; Morales et al., 2023; Barua., 2023).

Implications for Clinical Practice

Urinary tract infection (UTI) is one of the most common infections and the main reason for antibiotic treatment in ambulatory and hospital care worldwide. Clinicians are accustomed to diagnosing UTI and treating the most common pathogen, uropathogenic Escherichia coli (UPEC). However, it is currently known that UPEC is a mixture of a multitude of different pathotypes of E. coli with potential differences in severity, treatment, and acquisition mode, although this is not yet incorporated in clinical guidelines. The challenge for clinicians lies in different diagnoses, potential different treatment strategies, and different predictive tools. Educating clinicians and other healthcare professionals must be an ongoing concern, and tools should match each other and not be antagonistic for clinical guidance (Ballesteros-Monrreal et al., 2021; Zagaglia et al., 2022).

Translational research is essential in pushing forward healthcare. Not only should new diagnostics be developed based on research, but also understanding this research and its future implications adjusts the clinical guidelines of today. Technical implementation of research diagnostics into healthcare must always be accompanied by education and training, ideally in multiple languages, and be user-friendly. Algorithms should be integrated and not contradict each other nor burden healthcare. Interoperability is necessary. Furthermore, clinical research may benefit from exploring possible differences in pathobiology between these strains. Properly quantifying the number of resistances present in different E. coli pathotypes would also be of interest. Associations between the

different E. coli pathotypes and detailed patient characteristics, presentation, complications, and patient outcomes are in high clinical demand as well. Pharmacodynamics, pharmacokinetics, and antibiotic resistance can also impact these pathotypes differently. Clinical research involving host factors influencing the evolution of different UTI severities could lead to further insights (Ballesteros-Monrreal etal., 2021; Zagaglia et al., 2022 ; Geurtsen et al., 2022).

Translational Research and Implementation Challenges

Although research is required to generate the knowledge necessary to translate that knowledge into beneficial diagnostic tools or other applications, research for its own sake does not directly bring new technologies into the setting of clinical care. The effort of translating research into practical tools for disease control is called translational research. Translational research often involves identifying and validating new biomarkers or predictors of disease and is particularly useful in infectious disease outbreaks, especially in the implementation of rapid diagnostic tests for point-of-care testing. A diagnostic test is a rapid genetic or other type of test that can indicate the presence of a disease so that clinical care can be adjusted to better manage that disease (Williams et al., 2020 ; Becerril-Montekio et al., 2022).

Several challenges must be overcome to bring advances in genomics and microbiological research into the clinic. Challenges include diversity of healthcare delivery systems and clinical care needs, regulatory, logistical, cost, and expertise barriers to implementing new laboratory techniques, as well as patient, clinician, policy-maker, and community-level barriers to using information provided by new laboratory tests or novel treatments. Research will only go to practice if researchers, clinicians, and policy-makers respect the expertise and perspectives of the other groups and work together. In practice, what is still lacking are resources to guide practitioners in the use of next-generation RDTs for the management of urinary tract infections. Many research teams are organizing prospective studies to validate new tests and are also liaising with regulatory bodies to ensure that new drugs and treatments are well studied in clinical practice before they are introduced in the event of a pandemic (Becerril-Montekio et al., 2022; Françoise et al., 2022).

Future Directions in Diagnostics and Treatment

Emerging Technologies:

In a world of rapidly advancing diagnostics and treatment options for infectious diseases, the last few years have seen several possible future directions for urinary tract infections (UTIs) caused by Escherichia coli. The utilization of rapid molecular diagnostics using adjusted antimicrobial breakpoints may help in determining the usefulness of a specific therapeutic option for a bacterial pathogen. For UTIs, rapid molecular diagnostics exist, relying on municipalities to increase this service for sample testing. Molecular diagnostics offer rapid testing and could increase their treatment options as panels will detect virulent genes and antimicrobial resistance sequences, as well as pathogens in blood culture, compared to the standard of care. In addition, although hindered by scientific advancements and biosafety, some treatments are currently in the pipeline of pharmaceutical companies to try to increase their ability to penetrate the blood-brain barrier without having negative central nervous system effects. This molecule would be best used either intramuscularly or orally (Szlachta-McGinn et al., 2022; Harris & Fasolino., 2022).

Additionally, artificial intelligence and machine learning have offered a transformative approach, including the functional prediction of yet uncharacterized proteins through machine learning in a more top-down manner. Trends toward personalized medicine in identifying a patient's infectious profile will be a major help in identifying native pathways that can cause severe sequelae with spinal cord injury in addition to common scientific insights. More personalized medicine treatment trends to address bacteria's ability to "outsmart" antimicrobials include identifying the increased

expression of regulatory molecules, such as long noncoding RNA, which has been reported to increase the invasiveness and pathogenesis of the UPEC strain. Finally, as new therapeutic treatments in additional host regulatory molecules are researched, it can help to identify newer therapeutics approaching clinical trials targeting resistance mechanisms to current antibiotics in Escherichia coli and urinary tract infections, particularly as they relate to virulence factors (Szlachta-McGinn et al., 2022 ; Harris & Fasolino., 2022; mohsein, O. A et al., 2023).

New information on alterations of virulence gene expression levels in UPEC and mutagenesis. Recent findings on the E. coli UPEC dataset indicate alternative strategies of adhesion to anticipate if an E. coli UPEC has an intracellular bacterial community or other attachment capacity, as well as resistance to the bladder in urine as an indication for admitting patients. However, despite the many promising new ideas in UTI infection personalized medicine treatments, robust studies and the development of academic practice guidelines will need to be assessed. They effectively and safely address massive proteinuria treatment options currently available. Ongoing clinical trials with live biotherapeutics can be seen. For phage therapy, because studies report that the success of phage cocktails depends on the base composition, studies are still underway to correctly assess the specific components. With ongoing research, both novel therapeutics can be used with and without an already proposed antibiotic to E. coli UTI anti-infective options, and the field should take possible directions into consideration when addressing UTI anti-infective diagnosis and treatment for urinary tract infections in the upcoming years (Harris & Fasolino., 2022 ; Carpenter., 2024 ; Grey et al., 2023).

4. Conclusion

Staphylococcus aureus remains a critical public health challenge due to its capacity to develop antibiotic resistance and produce diverse virulence factors. The genomic adaptability of this pathogen, driven by horizontal gene transfer, mutations, and regulatory networks, has enabled it to persist in various environments and evade therapeutic interventions. Understanding the genetic mechanisms behind resistance and virulence, particularly in strains like MRSA, is crucial for developing targeted treatments and effective infection control strategies. Advances in genomic technologies, such as whole-genome sequencing, have provided valuable insights into the evolution and adaptability of S. aureus, paving the way for precision medicine approaches. However, combating this pathogen requires a multifaceted effort, including enhanced surveillance, innovative therapeutic development, and better stewardship of existing antibiotics. By integrating genomic insights with clinical practices, the global healthcare community can work toward reducing the burden of S. aureus infections and improving patient outcomes.

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