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ANTIMICROBIAL RESISTANCE AND GENETIC DIVERSITY THROUGH PROTEIN PROFILING OF UROPATHOGENIC *ESCHERICHIA COLI*: A REVIEW

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Abstract
Urinary tract infections (UTIs) are the most prevalent nosocomial and community-acquired illnesses. Uropathogenic Escherichia coli (UPEC) is a significant cause of UTIs. E. coli strains to the genetic investigation of antibiotic resistance are discussed in this article. Nitrofurantoin and fosfomycin are indicated for managing uncomplicated cystitis, and UPEC resistance to these antimicrobials remained limited. Specific drug-resistance genes were very rare or nonexistent. In recent years, resistance to trimethoprim-sulfamethoxazole, routinely used as the first antibiotic therapy for uncomplicated UTIs, has grown in several nations. In European countries, UPEC resistance to this antibiotic medication ranges from 14.6% to 60%. Frequent outpatient use of fluoroquinolones (FQs), notably ciprofloxacin, is the cause of an ongoing increase in resistance to these drugs. In impoverished nations, UPEC's resistance to FQs is much higher (55.5–85.5%) than in prosperous ones (5.1–32.5%). It is generally accepted that mobile genetic elements (MGEs) are the critical propagators of antibiotic resistance in many bacterial species, including UPEC E. coli strains to study antimicrobial resistance and genetic diversity. Researchers can identify critical drug resistance changes by comparing the whole-cell protein profiles of MDR, XDR, and sensitive strains. Moreover, SDS-PAGE can also be used to assess genotyping, providing a comprehensive understanding of the genetic diversity of these bacteria. The presence of specific genes and mutations indicates a significant potential for multidrug resistance in bacteria.
Keywords: *Antimicrobial resistance, Genetic diversity, Protein profiling, SDS-PAGE, Urinary tract infections*

INTRODUCTION

Molecular analyses are becoming increasingly prevalent in routine diagnostics. Understanding the genetic causes of pathogenesis and antibiotic resistance is vital for limiting the spread of hazardous bacteria, especially Multiple Drug Resistant (MDR) strains (1). Uropathogenic *Escherichia coli* strains (UPEC) are the most common cause of urinary tract infections (2). Hence beta-lactam antibiotics get the most consideration (3, 4). Many types of -lactamase-encoding genes (*bla* genes) are often seen on plasmids. ESBLs commonly transfer resistance to all penicillins, cephalosporins (except cephamycins), and monobactams since they are inhibited by -lactam inhibitors (5), and they are the leading source of enterobacterial resistance to third- and fourth-generation cephalosporins (6, 7). CTX-M enzymes (mostly CTX-M-1 lineage) are the most prevalent ESBLs in *E. coli*, followed by SUVs and, more recently, the less prevalent TEMs (8). Cephalosporinases of the *AmpC* type are a further subclass of acquired -lactamases responsible for resistance to -lactams of the newer generation (9). These are derivatives of Enterobacter cloacae, Citrobacter freundii, and Morganella morganii-specific enzymes (10). Their resistance profile is generally comparable to ESBLs, except for resistance to cephamycins, but not fourth-generation cephalosporins and -lactam-inhibitor combinations containing clavulanic acid (11). The group derived from C. Freundii is the most prominent identified family of acquired *AmpC*-type enzymes, including CMY-2, the most abundant enzyme (12).

Similarly, specific plasmids are often associated with *E. coli* resistance to other antibiotics, such as sulfonamides and aminoglycosides used to treat UTIs. Three genes (sul1, *sul2*, and *sul3*) determine the sulfonamide resistance of a cell (13). Gene sul1 is often found on giant conjugative plasmids, while gene *sul2* is typically found on tiny non-conjugative plasmids. Subsequently, *sul2* was discovered on large conjugative plasmids associated with streptomycin resistance (14). *Sul3* is the least-studied and rarest plasmid gene in *E. coli* (15) and is the least commonly discovered. Our understanding of sul genes and the individuals that have them varies widely between reservoirs (including human and animal populations) (13). Similarly, plasmid-borne genes are linked to aminoglycoside resistance. The gentamycin, tobramycin, neomycin, and other aminoglycosides are linked to the *aadB*, *aac(3)-II*, and *aac(3)-IV* genes. They are the most common genes found in different strains of *Escherichia coli* and other Gram-negative bacteria (16). It was found that bacterial resistance to antimicrobials and other forms of resistance grew in tandem with the use of broad-spectrum antibiotics. In Asia, Africa, and Latin America, preventive antibiotic therapy of urological patients occurred most often (86%, 85%, and 84%, respectively), followed by Europe (66%). Fluoroquinolones are linked to the widespread antibiotic resistance of UPEC strains (41).

DNA gyrase (*gyrA*) and topoisomerase IV (*parC*) genes are the primary targets of their mutation induction. The alterations of genes responsible for fluoroquinolone accumulation are also described (17) in the scientific literature. The *Qnr* protein (*QnrA*, *QnrB*, *QnrS*) prevents the antibiotic targets from being affected by quinolone therapy, and hence plasmids that produce this protein may enable resistance to fluoroquinolones. Although it has been established that the presence of *Qnr* plasmids induces low-level resistance, it also greatly enhances the quinolone resistance determined by other mechanisms (16).

However, UPEC is being watched for the establishment of MDR strains and the unceasing spread of resistance (17). Hence, frequent testing of widespread bacterial illnesses, such as UPEC, is necessary to manage drug sensitivity profiles in different populations (10). Antibiotic resistance genes should also be monitored as they propagate across a population. If we have this knowledge, we may take steps to prevent the spread of strains that are likely to exhibit MDR. High rates of inadequate antibiotic evidence-based therapies prescribed without antibiotic susceptibility testing are associated with the rise of antibiotic-resistant bacteria and the emergence of multidrug-resistant (MDR) pathogens during UTI, both of which contribute to the ineffectiveness of UTI treatment (18).

THE BACTERIUM *ESCHERICHIA COLI* IS A LEADING CAUSE OF UTIS

UTIs may be caused by a wide variety of bacteria and fungi, including Enterobacteriaceae members Klebsiella pneumoniae (about 7%) and Proteus mirabilis (around 5%), as well as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Staphylococcus aureus*, *Staphylococcus saprophiticus*, *Enterococcus faecalis* and Uropathogenic *Escherichia coli* strains (UPEC) are the most prevalent bacterial species linked to UTIs. Many studies suggest that *E. coli* strains harboring the virulence genes that cause UTIs in people are present in livestock. High similarity was found between *E. coli* strains obtained from UTI patients, farm animals, or meat (especially chicken) when tested for antibiotic resistance and genetic virulence factors (20). Strains belonging to the UPEC phylogroups B2 and D are often recovered from UTI, and these four primary UPEC phylogroups were identified based on the genomic Pathogenicity Islands (PAI) occurrence (21).

UROPATHOGENIC *ESCHERICHIA COLI* AND ANTIBIOTIC RESISTANCE

The widespread use of antibiotics to treat UTIs has consequences for bacterial ecology and the propagation of antibiotic resistance. In recent decades, UPEC antimicrobial resistance and the emergence of MDR UPEC have become clinical issues, especially for women who suffer from recurrent UTIs (22).

PFGE ANALYSIS IN MDR- AND XDR-UPEC

Proteins of different molecular weights may be separated and analyzed using Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis (SDS-PAGE). It may be used to evaluate variations in the whole-cell protein profile across strains of uropathogenic *E. coli* in the context of antibiotic resistance and genetic diversity in these bacteria. Multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains of

uropathogenic *E. coli* are of particular concern because they may cause difficult-to-treat urinary tract infections. Antimicrobial resistance is an increasing public health problem (23). Scientists may determine whether or not a protein's expression pattern is linked to antimicrobial resistance by employing SDS-PAGE to compare the whole-cell protein profiles of MDR and XDR *E. coli* strains. Research has shown that multidrug-resistant (MDR) *E. coli* strains and susceptible bacteria have distinct protein expression patterns, suggesting that specific proteins may play a role in resistance (24).

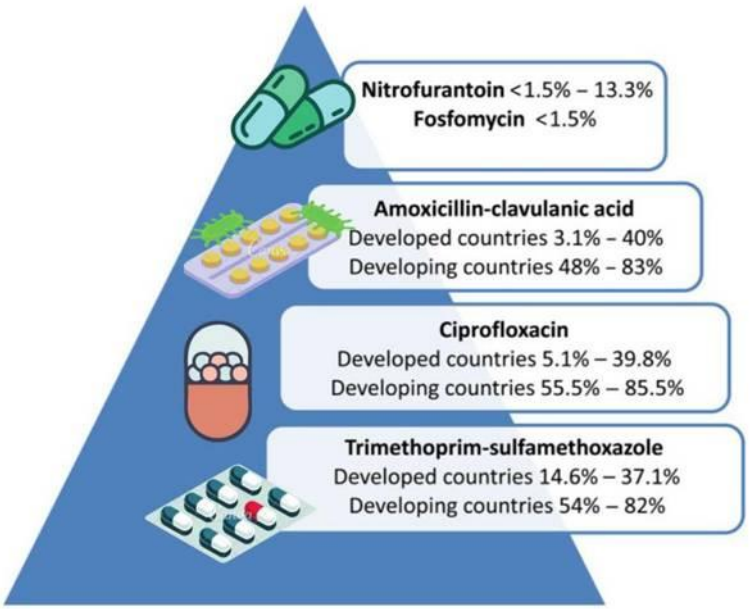

Fig. 1. Resistance of UPEC to antimicrobials used to treat urinary tract infections and designed using Canvas.com

SDS-PAGE may evaluate genetic diversity in uropathogenic *E. coli* strains in addition to antibiotic resistance. Researchers may determine whether or not variations across strains are due to genetic diversity by analyzing the protein profiles of each strain. In one investigation, researchers used SDS-PAGE to compare the protein profiles of uropathogenic *E. coli* strains recovered from patients with varying clinical outcomes. Many proteins were expressed differently amongst the groups, and the researchers hypothesized that these discrepancies could be related to variations in virulence or pathogenicity (25). In research, protein fingerprinting by SDS-PAGE was employed to categorize uropathogenic *E. coli* strains into distinct genotypes based on their unique protein profiles (26).

Protein fingerprinting is a method used in SDS-PAGE analyses to evaluate genotyping. Protein fingerprinting compares the whole protein profiles of several strains to detect distinguishing protein patterns. Scientists can tell the genetic changes across strains by analyzing their protein signatures. For instance, one research employed SDS-PAGE protein fingerprinting to determine the genotypes of methicillin-resistant Staphylococcus aureus (MRSA) strains.

Overall, SDS-PAGE is an effective method for studying the genetic diversity and antibiotic resistance of uropathogenic *E. coli* strains. Researchers may utilize protein fingerprinting to evaluate genotyping and analyze changes in protein expression patterns related to these features by assessing the whole-cell protein profile. The limitations of SDS-PAGE in detecting low-abundance proteins and post-translational changes suggest that other methods, like mass spectrometry, may be required to complement these investigations.

ANTIBIOTIC RESISTANCE AND MOBILE GENETIC ELEMENTS (MGES)

The emergence of new MDR strains that threaten world health may be attributed to the transfer and acquisition of previously established ARGs across varied bacterial populations, as opposed to the production of novel resistance genes. It is generally accepted that mobile genetic elements (MGEs) are the critical propagators of antibiotic resistance in many bacterial species, including UPEC. MGEs, consisting of integrons, transposons, and plasmids, are genetic materials that may travel within a genome or be passed from one strain or replicon (28).

TRANSPOSONS

Transmission elements (TEs) contribute to the development of antibiotic resistance because they may give resistance to many different kinds of antimicrobial medicines, including both first-line -lactams and last-resort antibiotics like colistin. Carvalho *et al*. have characterized a multidrug-resistant UPEC BH100 strain. In 1974, this strain was collected from the urinary tract of a Brazilian lady. The genome of the strain was analyzed using the Next Generation Sequencing (NGS) method, and it was discovered that the bacteria has two MDR cassette-carrying plasmids, pBH100 and pAp, with conjugative and mobilization characteristics, respectively (20). According to the scientists, Tn21 is a member of the Tn21 family of transposons, which also includes many other closely related transposons that play a significant role in the global dissemination of antibiotic resistance factors in gram-negative bacteria (21).

The *blaTEM* gene, which encodes the ß-lactamase TEM-1 type enzyme, is located on the Tn3 transposon, which was reported by Carvalho *et al*. (22). The Tn3 transposon family is a large, consistent set of bacterial TES pivotal in spreading antibiotic resistance. TES also contributes to the dispersal of tetracycline resistance. A developing, highly resistant UPEC ST38 01:H15 strain has been described by Rafaque *et al*. (29). This strain has many antibiotic resistance genes (ARGs) and multidrug efflux pumps (MGES), including the *tetA* gene carried by two transposons, Tn2 and Tn3.

INTEGRONS

Three main parts make up an integron, which classifies it as a member of the multiple gene expression system (MGES): I a gene encoding for a site-specific recombinase-integrase (*intI*); (ii) a recombination site (*att*!), which is associated with different gene cassettes and is recognized by the integrase; and (iii) a promoter (P Integrase was shown to change already-inserted gene cassettes inside integrons and to have a role in recruiting new gene cassettes. This process is responsible for the evolution of bacteria and the development and spread of antibiotic resistance (30). Three broad categories of integrons have been identified, each defined by the *intI* gene. Antimicrobial resistance genes tend to propagate with the help of class-1 integrons. Poey and Lavina (31) claim that sul1 integrates the Intl-conserved platform, making class-1 integrons the most common cause of sulfonamide resistance. In addition, streptomycin (*aadA* gene) and trimethoprim (*dfrA* gene) resistance cassettes are often found with members of this integron family (32). Classes 1 and 3 integrons were linked to resistance to ceftriaxone, ceftazidime, gentamicin, and nalidixic acid; classes 2 and 4 integrons were linked to resistance to imipenem, nalidixic acid, and co-trimoxazole.

PLASMIDS

Specific plasmids have antimicrobial resistance genes that may be transmitted across bacteria. Hence they contribute significantly to the global spread of antibiotic resistance. So far, 28 antibiotic-resistant plasmid types have been identified based on the Inc plasmid typing method. Plasmids of the IncF type are ubiquitous in *E. coli*, including UPEC, and have been detected in human and animal sources. In particular, IncFs are linked to ESBL resistance due to the dissemination of *blaCTX-M*, *blaTEM-1*, and *blaNDM* genes. According to a recent study by Kenyan researchers Muriuki *et al*., ESBL and plasmid-mediated -lactamase synthesis is the primary resistance mechanism to -lactam drugs in UPEC (p*AmpC*s). Bacteria-producing *AmpC* -lactamases resist penicillins, cephalosporins, and monobactams but are still killed by carbapenems. Although PMQR only induces little resistance to quinolones, it can potentially transfer to other bacteria and cause the selection of resistant strains.

RESISTANCE TO ANTIBIOTICS IN THE NATURAL AND AGRICULTURAL ENVIRONMENTS

Potentially significant contributors to the emergence of resistance include using antimicrobials in livestock production and dumping medical and industrial waste (33). The contamination of the environment by humans and animals means that the water supply in any country may have *E. coli* with a high resistance (30). Antibiotic-resistant pathogens found in human and animal populations are identical in the food and food web (28); multi-resistant isolates can be transmitted from pets to humans, and domesticated animals

and wild animals are susceptible to infection (29). Furthermore, seagulls play a crucial role in disseminating resistance linked to previously identify human pathogens (34).

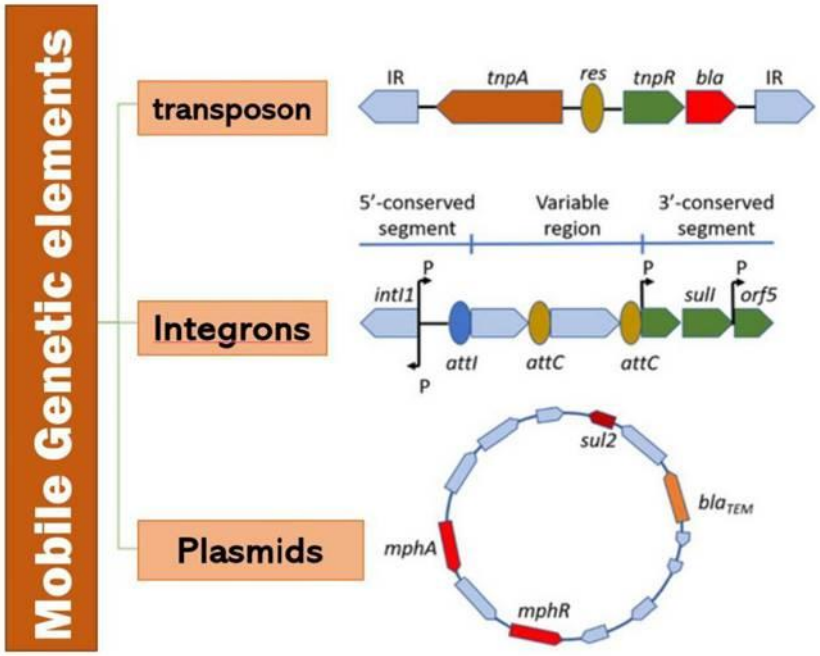

Fig. 2. Mobile Genetic Elements (MGEs) such as transposons, integrons and plasmids are the primary agents responsible for the spread of antibiotic resistance in UPEC. Designed by using Canvas.com

ANTIBIOTIC RESISTANCE GENES

The table provides a concise overview of the UPEC ARGs, the antimicrobials they are resistant to, and the method by which they exert their resistance.

Bacterial antibiotic resistance may arise from various pathways beyond those listed above. Random point mutations or alterations in the permeability of the cell membrane are other possible causes of antibiotic resistance (37). Horizontal gene transfer (HGT) and mobile genetic elements are two ways that bacteria might gain resistance to several antimicrobials.

ANTIBIOTIC-RESISTANT UPEC AND ITS UNDERLYING MECHANISMS

Often causing UTIs, uropathogenic *Escherichia coli* (UPEC) has recently become a serious public health problem due to the advent of antibiotic-resistant strains. Biofilm generation, efflux pumps, decreased permeability, and enzymatic inactivation is ways that UPEC might acquire antibiotic resistance.

I. One prevalent form of resistance in UPEC is the production of enzymes that make antibiotics ineffective, such as beta-lactamases and aminoglycoside-modifying enzymes. Another form of resistance involves UPEC modifying or mutating the target areas of antibiotics, such as the bacterial ribosome or DNA gyrase, rendering them resistant to the medicines.

II. A frequent resistance method in Gram-negative bacteria, including UPEC, is reduced permeability, in which the bacteria alter their outer membrane so that fewer drugs may penetrate the cell. To counteract the effects of antibiotics, bacteria have evolved efflux pumps, which remove the medication from the cell. Bacteria may avoid being killed by drugs and the immune system by forming a protective habitat called a biofilm.

III. Efflux pumps: UPEC may generate efflux pumps, transport proteins that expel antibiotics from the bacterial cell, lowering the drug concentration and making it ineffective.

IV. UPEC may create a biofilm on surfaces like urinary catheters and the bladder's lining to avoid being killed by antibiotics and the immune system.

V. Horizontal gene transfer contributes to the spread of antibiotic resistance when UPEC acquires resistance genes from other bacteria in the environment. New tactics to tackle these infections and decrease the formation of antibiotic-resistant strains need an understanding of the processes of UPEC resistance to antibiotics.

Table I. List of UPEC Antibiotic resistance genes

Antibiotic agent/class	ARGs	Mechanism of resistance
β-lactam	*blaTEM* *blaOXA* *blaCTX-M* *blaSHV* *blaVEB* *blaPER* *blaKPC* *blaVIM* *ampC*	• Hydrolysis of the antibiotic molecule (29).
Aminoglycosides	*aadA* *armA* *rmtB* *aaC(3)—IIa* *aacA2* *aacA4*	• Antibiotic molecule modification. • Drug target modification (methylase) (25, 26, 30). • Antibiotic molecule modification (acetyltransferase)
Quinolones	*qnrA* *qnrB* *qnrC* *qnrD* *qnrS* *mfpA* *qepA* *oqxAB*	• Drug Target Modification • Efflux pump (35)
Tetracyclines	*tet(a)(b)*	• Efflux pump • Drug target modification (36).
Sulfonamides	*dfrA1* *sul1* *sul2*	
Macrolides	*ere(2)* *acrB* *acrA* *macB* *mph(A)*	• Hydrolysis of the antibiotic molecule • Efflux pump
Vancomycin	*VanA*	• Drug target modification • Drug target modification (29).
Cloistin	*mcR-1*	*(Phosphatidylethanolamine transferase)*

QUINOLONE-RESISTANT BACTERIA

Resistant strains of bacteria develop when their targets undergo mutations in certain amino acids. When mutations happen in the genes that code for the target antibiotics, the type II topoisomerases, the result

is resistance to fluoroquinolones. In Gram-negative bacteria, the serine 83 *gyrA* mutation is the most frequent. The target genes *gyrA* and *gyrB* encode subunits of DNA gyrase, whereas the target genes *parC* and *parE* encode subunits of DNA topoisomerase IV. The small DNA sequence in which mutations occur is the crucial quinolone resistance-determining region (QRDR) (28). Mutations here cause amino acid substitutions, altering the protein's structure. This causes a change in the enzyme's binding to fluoroquinolones, leading to resistance (38).

NITROFURANTOIN RESISTANCE

UPEC resistance to nitrofurantoin is currently relatively low, encouraging its usage as a first-line antibacterial treatment. According to a retrospective study by Sanchez *et al*. (2016), nitrofurantoin continues to exhibit significant antibiotic efficacy against urinary *E. coli* (39). Although there was a slight uptick in reports of nitrofurantoin-resistant *E. coli* isolates from adults between 2003 and 2012, the rate remained barely 0.7%. The investigation on the prevalence of antibiotic-resistant *E. coli* in Dutch urology clinics found that 95% of the strains tested were susceptible to nitrofurantoin (35). The same percentage of UPEC in Mexico showing resistance to nitrofurantoin (12.7%) was reported (in Mexico that is) (40). According to these findings, nitrofurantoin is still the best medication for treating uncomplicated cases of cystitis. Nitrofurantoin is the therapy of choice for an uncomplicated UTI in women, and for a good reason. It is very effective, low cost, and has a less harmful environmental impact.

FOSFOMYCIN RESISTANCE

Fosfomycin is effective against many different types of Enterobacteriaceae, including those that generate metallo-lactamases or ESBLs (MBL). A single dose of fosfomycin in the amount of 3 grams is allowed for use in the treatment of women who have simple UTIs caused by *E. coli* in several European countries (41). In a study that compared the sensitivity of UPEC in Germany, Belgium, and Spain to fosfomycin, only around 1.5% of the isolates tested positive for resistance to this antibiotic (42). After treatment with fosfomycin for uropathogenic-resistant urinary tract infections, an overall microbiological cure rate of 59% was observed (36). The antibacterial efficacy of fosfomycin is inferior to that of other therapies used in the first line of defense.

TRIMETHOPRIM-SULFAMETHOXAZOLE-RESISTANT BACTERIA

Profound TMP-SMZ resistance in *E. coli* (24.5%). Urinary *E. coli* was recorded in Switzerland between 2012 and 2015 (43). Resistance to UPEC to TMP-SMZ varied greatly by location and age group, with the most vigorous resistance being seen in some European locations and among young women. India's TMP-SXT resistance rate rose from 52 percent in 2013 to 59.6 percent in 2017 (44). As shown by these findings, the significant prevalence of UPEC resistance to this antibiotic suggests that TMP-SMZ should not be utilized in empiric UTI treatment in many countries.

AMOXICILLIN-CLAVULANIC ACID-RESISTANT BACTERIA

Amoxicillin-clavulanic acid resistance rates are not uniform throughout the country. Researchers Morrill *et al*. (2017) looked at E. Analysis of *E. coli* urine isolates from inpatients and outpatients in the United States Veterans Affairs Medical System from 2009 to 2013 revealed an incidence of resistance to amoxicillin or ampicillin/beta-lactamase inhibitors of about 40%. Rates of amoxicillin-clavulanic acid resistance among *E. coli* have increased. Urine samples from patients at a German tertiary care hospital showed a 5.3% prevalence of *E. coli* isolation from 2015-2017 (42). In contrast, 83% of UPEC isolates from Jordanian hospital patients demonstrated resistance to amoxicillin-clavulanic acid (45). These findings reveal that UPEC resistance to amoxicillin-clavulanic acid differed significantly across study locations and patient demographics. That's why it's essential to consider the local susceptibility of *E. coli* when developing empiric regimens for both simple and complex UTs. *E. coli*. Nevertheless, when the findings of UPEC susceptibility testing become available, they should be used to inform the development of standard regimens.

CONCLUSION

E. coli is consistently present in the environment, and owing to its persistence and poor bioavailability, it contributes to the global issue. It is possible to increase the effectiveness of a natural substance by including nanoparticles or coating on a particular surface. Silver nanoparticle-coated medical instruments and wound dressings effectively eradicated *E. coli* biofilm. The development of biofilms by *E. coli* was significantly impeded after being sprayed with the antimicrobial nanospray JUC. Most UTIs may be traced back to Gram-negative bacilli (Enterobacteriaceae), and most of these strains are multidrug-resistant. Tobramycin, ciprofloxacin, and amikacin were the most effective antimicrobial medicines against Gram-negative bacilli, while *E. coli* was the most often identified bacterium from UTIs. Drug resistance and food component contamination may be mitigated using new, better food safety treatment procedures. For these MDR bacteria to be treatable, a new, natural antibiotic with a wide range of potential action mechanisms must emerge. Mobile genetic components mostly facilitate the spread of genes for antimicrobial resistance among bacteria. SDS-PAGE is a valuable technique for analyzing protein profiles of uropathogenic *E. coli* strains to study antimicrobial resistance and genetic diversity. Researchers can identify critical drug resistance changes by comparing the whole-cell protein profiles of MDR, XDR, and sensitive strains. Moreover, SDS-PAGE can also be used to assess genotyping, providing a comprehensive understanding of the genetic diversity of these bacteria. Overusing medicines has led to a worrying rise in antibiotic resistance among dangerous bacteria. We need to find new ways to treat bacterial infections since there are no new classes of antimicrobial medications. Bacteria may quickly adapt to different stress circumstances by using the SOS pathway. It seems that SOS inhibitors are a viable option since they have been shown to be effective, and the mechanism they stop is conserved across many different bacterial species. Nonetheless, further research is needed into SOS modulators, and now, efforts should be directed toward enacting reasonable antibiotic policy.

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