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Original Research Article

A Prospective Study to Investigate the Virulence Factors and Antibiotic Resistance Profile of Escherichia Coli, the Pathogen Responsible for Urinary Tract Infections in Pregnant Women

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Conflict of interest: Nil

Abstract

Aim: To investigate the virulence factors and antibiotic resistance profile of Escherichia coli, the pathogen responsible for urinary tract infections in pregnant women.

Materials and Methods: This prospective study was conducted Department of Microbiology, Jawaharlal Nehru medical college and Hospital, Bhagalpur, Bihar, India for one year. A total of 150 samples were collected. The following data was also gathered from the participants: maternal age, gravidity and residence. The collected samples were directly transported the laboratory. The samples were processed for culture and antimicrobial drug susceptibility tests following routine microbiological techniques. Semi quantitative urine culture using a calibrated loop was performed to isolate bacterial pathogens on Blood and MacConkey's agar as per the recommendations of Kass. The culture plates were incubated at 37°C for 24 hours. The negative (growth) culture plates were incubated for an additional 48 hrs. Bacterial strains were isolated from the cultures and identified using standard biochemical tests. UTI was diagnosed on the basis of pathogens being present at least 10 colony forming unit (CFU)/ml of urine. However, the study dealt with only the *E. coli* isolates present.

Results: The incidence of in vitro biofilm formation by *E. coli* was 63.93%. Of the 61 isolates, biofilm formation was detected in 39 isolates by all the three methods for biofilm detection. 32.30% isolates showed biofilm formation by Tube method, 53.84% by CRA method and 27.69% by TCP method. Haemolysin production was seen in 25 isolates (40.98%) and 49.18% of the isolates were positive for ESBL detection. All isolates showed the highest resistance to the antibiotic Ampicillin (96.72%), followed by Amoxicillin- clavulanic acid (62.29%), Cefuroxime (55.73%) and Ceftriaxone (54.09%). *E. coli* isolates which formed biofilm displayed a significant increase in the resistance pattern to all the antibiotics and proved to be statistically significant. The data clearly shows similarity in the sensitivity pattern of all the *E. coli* isolates. The isolates were sensitive to broad spectrum antibiotics like Imipenem (100%), Piperacillin-tazobactam (93.44%), Nitrofurantoin (90.16%), and to the drugs Chloramphenicol and Gentamicin (83.60%). Further, unpaired t test analysis indicated that the difference in the resistance pattern of biofilm and non-biofilm forming isolates against the 11 different antibiotics which were tested was statistically significant ($p < 0.031$).

Conclusion: The association between virulence factors and antibiogram was perceived in our study. Hence, screening for virulence factors and antimicrobial sensitivity must be scheduled along with the other standard tests for pregnant women.

Key Words: Antibiotic resistance, ANC, Biofilm, UTI, Uropathogenic *E. coli*, Virulence factors

Introduction

Urinary tract infections (UTIs) are a common health concern, particularly among pregnant women, where they pose significant risks to both maternal and fetal health. Escherichia coli (E. coli), a gram-negative bacterium, is the leading causative agent of UTIs, responsible for up to 90% of cases. The pathogenicity of E. coli in the urinary tract is largely attributed to its arsenal of virulence factors and its ability to form biofilms, which enhance its survival and persistence in the urinary tract environment. [1-6] E. coli employs various virulence factors that contribute to its pathogenicity. Adhesins, such as

type 1 fimbriae and P fimbriae, allow the bacteria to adhere to the epithelial cells of the urinary tract, facilitating colonization and infection. These adhesins bind specifically to receptors on the host cells, enabling the bacteria to resist flushing by urine flow. The production of toxins, such as hemolysins, further damages host tissues and promotes bacterial invasion. Hemolysins can lyse red blood cells and other cell types, releasing nutrients that support bacterial growth. [7-12] Biofilm formation is another crucial virulence factor of E. coli. Biofilms are structured communities of bacteria encased in a self-produced extracellular matrix, which provides protection against the host immune response and antibiotic treatment. Within a biofilm, E. coli can persist in a dormant state, making it difficult to eradicate the infection completely. The presence of biofilms is associated with chronic and recurrent UTIs, complicating treatment and increasing the risk of complications. [13-16] The ability of E. coli to produce extended-spectrum beta-lactamases (ESBLs) is a significant concern in the treatment of UTIs. ESBLs are enzymes that confer resistance to a wide range of beta-lactam antibiotics, including penicillins and cephalosporins. The emergence of ESBL-producing E. coli strains has limited the effectiveness of these commonly used antibiotics, necessitating the use of more potent and often more toxic alternatives. This resistance mechanism is often plasmid-mediated, allowing for horizontal gene transfer between bacteria and the rapid spread of resistance. [17-21] Pregnant women are particularly susceptible to UTIs due to physiological changes during pregnancy that affect the urinary tract. Hormonal changes and the growing uterus can cause urinary stasis and ureteral dilation, creating an environment conducive to bacterial growth. Additionally, the immune response is modulated during pregnancy to protect the fetus, which may reduce the body's ability to fight infections. Untreated or inadequately treated UTIs in pregnant women can lead to serious complications, including pyelonephritis, preterm labor, and low birth weight. The antibiogram of E. coli isolates from pregnant women with UTIs is essential for guiding effective treatment. Antibiograms provide a profile of the antibiotic susceptibility of bacterial isolates, helping clinicians choose the most appropriate antibiotics for treatment. Commonly tested antibiotics include ampicillin, ciprofloxacin, gentamicin, and nitrofurantoin. However, the increasing prevalence of antibiotic-resistant E. coli strains complicates treatment strategies. Resistance to ampicillin is particularly high, often exceeding 70-80% in many regions, limiting its use as a first-line treatment. Nitrofurantoin remains a preferred choice for treating uncomplicated UTIs due to its low resistance rates and efficacy in targeting urinary pathogens. [22-25] The treatment of UTIs in pregnant women requires careful consideration to avoid adverse effects on the fetus. Antibiotics such as trimethoprim-sulfamethoxazole are generally avoided in the first trimester due to the risk of congenital malformations, and fluoroquinolones are avoided due to potential teratogenic effects. Safe and effective alternatives, such as beta-lactams and fosfomycin, are preferred, but their use is often limited by the susceptibility profile of the infecting E. coli strains. Preventive measures are also crucial in managing UTIs among pregnant women. These include promoting good hygiene practices, adequate hydration, and regular prenatal check-ups to monitor and address urinary symptoms promptly. Educating pregnant women about the importance of completing antibiotic courses and recognizing the early signs of UTIs can help reduce the incidence and recurrence of infections.

Materials and Methods

Study Population and Sample Collection:

This prospective study was conducted at the Department of Microbiology, Jawaharlal Nehru medical college and Hospital, Bhagalpur, Bihar, India for one year. Mid-stream urine samples were obtained in a sterile wide-mouth container. A total of 150 samples were collected. The following data was also gathered from the participants: maternal age, gravidity and residence. The collected samples were directly transported the laboratory.

Bacteriological Analysis of the Urine Samples:

The samples were processed for culture and antimicrobial drug susceptibility tests following routine microbiological techniques. Semi quantitative urine culture using a calibrated loop was performed to isolate bacterial pathogens on Blood and MacConkey's agar as per the recommendations of Kass. [18] The culture plates were incubated at 37°C for 24 hours. The negative (growth) culture plates were incubated for an additional 48 hrs. Bacterial strains were isolated from the cultures and identified using standard biochemical tests. UTI was diagnosed on the basis of pathogens being present at least 10^5 colony forming unit (CFU)/ml of urine. However, the study dealt with only the *E. coli* isolates present.

Antibiotic Sensitivity Testing:

Antibiotic sensitivity testing was performed according to Kirby Bauer's disc diffusion method on Mueller Hinton agar. CLSI guidelines were followed during the experimentation. [19],[20] Sensitivity was tested against the following antibiotics: Ampicillin (AMP 10mcg), Amikacin (AK 30 mcg), Amoxicillin-clavulanic acid (AMC 30 mcg), Cefriaxone (CTR 30 mcg), Cefuroxime (CXM 30mcg), Ciprofloxacin (CIP 5mcg), Gentamicin (GEN 10mcg), Imipenem (IPM 10mcg), Nitrofurantoin (NIT 300mcg), Norfloxacin (NX

10mcg), and Piperacillin- tazobactam (PIT 100/10 mcg) (HiMedia Laboratories, Mumbai, India).

Statistical Analysis

Statistical software package SPSS version 22 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) was used to analyse the data. Unpaired t test was applied to calculate significance differences of resistance among biofilm producing and non-biofilm producing isolates. *P*-value <0.05 was considered statistically significant.

Results

Prevalence of UTI and Patients Profile:

Among 150 samples tested, *E. coli* could be isolated from 61 samples with colony count of 10^5 CFU/ml of urine and a prevalence rate of 40.66% (Table 1). The majority of pregnant women were in their 2nd and 3rd trimester (1st trimester- 6.2%, 2nd -14.53%, 3rd - 22.6%). The mean age of the participants was 24 years. Most of the urine samples were obtained from pregnant women in the age range of 18 to 23 years (55.73%; 43 in number). Pregnant women in the age range of 27 to 29 years contributed to the least number of samples (3.27%; 26 in number) (Table 2). The rate of infection was high among the participants in the age group of 18-23 years. Among those infected, 69.2% were from the urban locality and 30.76% from rural areas. Most of them attended ANC unit on need basis and not regularly.

Table 1: Prevalence of E. coli

Bacteria	Source	N=150 (%)
Escherichia coli	Mid-stream urine samples	61 (40.66)

Among the 150 samples tested, E. coli was isolated from 61 samples, showing a prevalence rate of 40.66%.

Table 2: Percentage Distribution of E. coli Isolated from Pregnant Women According to Age

Age	Number of Samples	Frequency (n=61)	%
≤18-23	72	34	55.73
24-26	43	14	22.95
27-29	09	02	3.27
≥30	26	11	18.03
Total	**150**	**61**	**100**

The highest rate of infection was among participants aged 18-23 years (55.73%), followed by ages 24-26 years (22.95%), ≥30 years (18.03%), and 27-29 years (3.27%).

Virulence characters of UPEC Isolates:

The incidence of in vitro biofilm formation by *E. coli* was 63.93%. Of the 61 isolates, biofilm formation was detected in 39 isolates by all the three methods for biofilm detection. 32.30% isolates showed biofilm formation by Tube method, 53.84% by CRA method and 27.69% by TCP method. Haemolysin production was seen in 25 isolates (40.98%) and 49.18% of the isolates were positive for ESBL detection.

Antimicrobial profile of the isolates:

All isolates showed the highest resistance to the antibiotic Ampicillin (96.72%), followed by Amoxicillin- clavulanic acid (62.29%), Cefuroxime (55.73%) and Ceftriaxone (54.09%). *E. coli* isolates which formed biofilm displayed a significant increase in the resistance pattern to all the antibiotics and proved to be statistically significant. Table 3 displays the multi- drug resistant pattern of the UPEC *E. coli.* Details included are for both the biofilm producing and non-producing bacteria. The data clearly shows similarity in the sensitivity pattern of all the *E. coli* isolates. The isolates were sensitive to broad spectrum antibiotics like Imipenem (100%), Piperacillin-tazobactam (93.44%), Nitrofurantoin (90.16%), and to the drugs Chloramphenicol and Gentamicin (83.60%). Further, unpaired t test analysis indicated that the difference in the resistance pattern of biofilm and non-biofilm forming isolates against the 11 different antibiotics which were tested was statistically significant (p <0.031).

Table 3: Antibiotic susceptibility pattern of the biofilm producing and non-producing Uropathogenic *E. coli*

	Non-Biofilm producer (n=22)		Biofilm producer(n=39)		p value
	R %	S %	R %	S %	
Antibiotics					
Ampicillin	21 (95.45%)	01 (4.54%)	38 (97.43%)	01 (2.56%)	p <0.031*
Amikacin	05 (22.72%)	17 (77.27%)	05 (12.83%)	34 (87.17%)	
Amoxicillin-clavulanic	12 (54.54%)	10 (45.45%)	34 (87.19%)	05 (12.82%)	
Ceftriaxone	07 (31.81%)	15 (68.18%)	24 (61.53%)	15 (38.46%)	
Cefuroxime	07 (31.81%)	15 (68.18%)	28 (71.79%)	11 (28.20%)	
Ciprofloxacin	04 (18.18%)	18 (81.81%)	24 (61.53%)	15 (38.46%)	
Gentamicin	0 (0%)	22 (100%)	06 (15.38%)	33 (84.61%)	
Imipenem	0 (0%)	22 (100%)	0 (0.00%)	39 (100%)	
Nitrofurantoin	0 (0.00%)	22(100%)	01(2.56%)	38 (97.43%)	
Norfloxacin	04 (18.18%)	18 (81.81%)	18 (46.15%)	21 (53.84%)	
Piperacillin-tazobactam	01 (4.54%)	21(95.45%)	02 (5.12%)	37 (94.87%)	

* Significant at $p< 0.05$. R= Resistant S= Sensitive.

Discussion

Urinary tract infection (UTI) is the foremost bacterial infections among pregnant women. [25] During pregnancy, women tend to have shorter urethra. This results in colonization of the peri-urethral area by pathogens that ascend from the gastro-intestinal tract and colonize the urinary bladder or kidneys. [26] Pregnant women are more prone to UTI than non-pregnant women. The fundamental differences in the prevalence of UTI among the pregnant population is based on the following factors: age, parity, gestation age and level of education. [27] The primary causative organisms for UTI in pregnant women are gram-positive and gram-negative bacteria, as well as yeast. Our study was designed to understand the prevalence rate of UTI due to E. coli among pregnant women of Bhagalpur district. In addition, the virulence characteristics and antibiotic profile were investigated. Our study revealed a higher incidence rate (43.33%) of UTI among females in the second and third trimester of pregnancy. According to our results, the prevalence of UTI is high in north Karnataka region as compared to other parts of Karnataka with commonest isolated pathogen as E. coli. [28] Annie Rajaratnam et al... conducted a similar study in coastal Karnataka and recorded an overall low prevalence of 13.2%. [29] Our study revealed the highest infection rate of UTI in pregnant women and among the age group of 20-25 years, in agreement with the findings documented by Kasinathan A, Thirumal and Chandel, Lata R., *et al*. [30,31] In this region, phenotypic traits of UPEC isolates are not well known. In addition, the association of these traits with antibiotic resistance patterns needs to be determined among the pregnant women with UTI Furthermore, no documented studies are available. The effectiveness of antibiotic treatment depends on the analysis of virulence factors and antimicrobial resistance pattern of uropathogens responsible for UTI. Antimicrobial prophylaxis for women with recurrent UTI includes β- lactam drugs and Cephalosporins. Since there is emergence of drug resistance in UTI, we aimed to study the sensitivity pattern of *E. coli,* which is the predominant pathogen causing UTI. When the microbes were tested against various antimicrobials to determine their susceptibility, isolates showed high resistance to the β- lactam group of antimicrobials. This fact is a matter of concern because this group of drugs is traditionally used in UTI therapy. Similar accounts of resistance to the extended spectrum of β-lactamases among the general population infected with urinary pathogens have been reported. [32,33] In our study, we found significant correlation between the virulence factor biofilm and antibiotic resistance. Biofilm forming UPEC isolates showed maximum resistance to the antibiotics than non-biofilm producers. Isolates showed increased resistance to the drugs Ampicillin, Cefuroxime, Ceftriaxone, Ciprofloxacin and Aminopenicillins, which are considered to be safe in pregnancy and are the commonly used antibiotics to treat UTI. Similar findings were reported in a study performed by Tajbakhsh, Elahe, *et al.* in Iran. [34] Among other antibiotics, carbapenems such as Imipenem is the most competent against all UPEC strains (100%), especially for the extended-spectrum beta lactamase (ESBL) strains. [35] The other proven proficient antibiotics include Nitrofurantoin (97.43%), Piperacillin– tazobactem (94.87%), Amikacin (87.17%) and Gentamicin (84.61%). UPEC strains were moderately susceptible to Norfloxacin. Studies by ME Terlizzi et al. and Chakraborty et at. Concur to these finding. Their work consented to a significant correlation between virulence factors and antimicrobial resistance. In addition, they showed a high resistance of the isolates to the antibiotics generally used in UTI therapy. [36,37] Screening for antimicrobial sensitivity must be scheduled along with the other standard tests and scans for pregnant women. Such

measures could help prescribe safe and effective drugs so that appropriate therapy may be initiated. These measures help in controlling the associated complications. Prescribing antibiotics for UTI treatment without bacterial characterization could trigger enhanced resistance among uropathogens. In addition, it restricts the choice of drugs available for the treatment of UTI. Hence, our study showed that the drugs Imipenem, Nitrofurantoin, and PIT are recommended for the treatment of suspected UTI among pregnant women. In our study's setting, these drugs would help avoid further complications.

Conclusion

The association between virulence factors and antibiogram was perceived in our study. Hence, screening for virulence factors and antimicrobial sensitivity must be scheduled along with the other standard tests for pregnant women. In addition, routine urine cultures would help in timely detection of UTI. Such measures could help prescribe safe and effective drugs so that appropriate therapy may be initiated. Further, periodic studies are recommended, especially among the pregnant population, to screen changes in the susceptibility pattern of UPEC. Our study assists in understanding the local antibiotic resistance rate and virulence pattern of *E. coli,* which a clinician needs take into consideration when deciding on therapy.

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