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Factors responsible for developing common oral antibiotic resistant to urinary tract infection (UTI) among the children

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ABSTRACT: The present study is designed to access the factors responsible for developing recurring infection and antibiotic resistance among children with urinary tract infection (UTI). The socio-demographic characteristics of the respondents are important to determine the level of awareness regarding antibiotic resistance; 16.1% children were between 1 to 5 years of age, 21.9% between 5.1 to 9 years, 29.9% between 9.1 to 12 years and 32.1% between 12.1 to 15 years of age who were suffering from UTI. Out of 137 children, 17.5% males were suffering from UTI and the rest 82.5% were females; it reveals that 34.3% children intakes less than 500 ml of water every day while 40.1% intakes 500 to 1000 ml of water, 21.1% children take about 1000 to 1500 ml of water and only 4.4% intakes more than 1500 ml of water every day. The present investigation showed that 50.4% of the children had a history of taking antibiotics while 29.9% did not know whether the child had a history of taking antibiotics and 5.8% has no history of taking antibiotic. Out of the 81 children who received treatment for UTI, 76.5% were fully cured after receiving antibiotic while 19.8% were not cured after taking antibiotic. Out of the 43 children who took the antibiotic on time, 79% took it for 1 to 3 days, 16.3% took it for 3 to 5 days and 4.7% took it for 5 to 7 days. Positive correlation found with male children, maintaining toilet hygiene and recurrent UTI.54.4% respondent used water to maintain the child's toilet hygiene suffered from recurrent UTI and 92.8% respondent used other means excluding water to maintain the child's toilet hygiene suffered from recurrent UTI ($p<0.05$). The major factors for developing recurrent UTI and resistance to certain antibiotics are taking medicine from pharmacy, doing self-prescription, incomplete medication courses along with lack of hygiene and insufficient water intake. There should be rational use of antibiotic and culture sensitivity for urine should be a mandatory test before administering antibiotics for UTI. There is need to build awareness about antibiotic resistance through health campaigns.

Keywords: Antibiotic, resistance, children, toilet hygiene, UTI, water intake.

INTRODUCTION

Bacterial infections resistant to antibiotics can limit the availability of effective treatment options, rendering some commonly encountered bacterial infections difficult to treat, including those of the urinary tract (Kahlmeter, 2000). The changing pattern of antibiotic resistance in the causative microorganism of urinary tract infection (UTI) in children is a growing problem, as it is an important cause of morbidity in childhood (Talan et al., 2000). UTI is caused as an inflammatory response of urothelium to the invading pathogenic organisms (Gupta et al., 1999; Nazme, et al., 2017). Worldwide, about 150 million people are being diagnosed with UTI every year (Phillips et al., 2000). UTIs are associated with increased morbidity and mortality and it is one of the commonest nosocomial infections (Prats et al., 2000). The symptoms of UTI include fever, dysuria, urinary urgency and cloudy urine (Foxman et al., 2000b). It is estimated that 3% of girl's and 1% of the boy's experience at least one episode of UTI before 11 years of age (Phillips et al., 2000).

Escherichia coli (*E. coli)* is the commonest organism causing UTI. *E. coli* belongs to the family *Enterobactericeae* and accounts for 75 to 90% of all UTI in

inpatients and outpatients (Hooton and Stamm, 1997; Rustom et al., 2020). Reports reveal that *E. coli* is the most common cause of UTI and antibiotic resistance is reported to be high among the strains (Gupta et al., 1999; Foxman, 2002). UTI is initiated by *E. coli*, which is a commensal in the gastrointestinal tract (Foxman et al., 2000a; Hooton and Stamm, 1997). Antimicrobial resistance (AMR) is an internationally recognized threat to health and antibiotic resistance is one of the important issues to think about. The contribution of primary healthcare to induce antibiotic resistance is particularly important as this is where almost 80% of all antibiotics used within the health service are prescribed (Foxman et al., 2000b). According to the guidelines of Infectious Diseases Society of America (IDSA) the recommended drug for treatment of UTI is Trimethoprim/ Sulphamethoxazole where the resistance prevalence is <10 to 20%. Ciprofloxacin is recommended where the resistance is >20% (Foxman et al., 2000b). Early treatment with an appropriate and effective antibiotic is essential for prevention of long-term complications (Supplemental Tables, 2000).

Generally, up to 95% of the cases with severe symptoms are treated without bacteriological investigations (Wayne, 2000). Infectious diseases are major health problems in Bangladesh requiring frequent use of antimicrobials. Infection with resistant bacteria was first reported over more than 60 years ago (Sharples and Lloyd, 1990). Antibiotic resistant infections are also twice as likely to be associated with greater morbidity and mortality and are associated with increased healthcare costs (Hulton et al., 1991). Children receive a disproportionately high number of antibiotics compared with middle aged populations (Hulton et al., 1991). Young children are more vulnerable to immediate and long-term complications, including renal scarring and renal failure (Versalovic et al., 1991; Ahmed and Swedlund 1998; Foxman et al., 2000b; Bakker et al. 2004).

The emergence of antibiotic resistance in the management of UTIs is a serious public health issue, particularly in the developing countries, including Bangladesh. Bacterial resistance to antibiotics complicates the treatment of UTI and the antibiotic sensitivity pattern shows geographical variations (Supplemental Tables, 2000).

The microbial etiology of urinary infections has been regarded as well-established and reasonably consistent. *Escherichia coli* remains the predominant uropathogen (80%) isolated in acute community-acquired uncomplicated infections, followed by *Staphylococcus saprophyticus* (10 to 15%). *Klebsiella*, *Enterobacter*, and *Proteus* species and *Enterococci* infrequently cause uncomplicated cystitis. The etiology of UTI is also affected by underlying host factors such as age, diabetes, spinal cord injury, or catheterization that complicate UTI. Etiologic pathogens associated with UTI among patients with diabetes include *Klebsiella* spp., Group B *streptococci*, and *Enterococcus* spp., as well as *E. coli*. Other common uropathogen include *Pseudomonas* and *Proteus mirabilis* (Daschner and Marget, 1975; Ronald, 2002; Yüksel et al., 2006).

The extensive use of antibiotics in the community and hospitals has fueled this crisis. Mechanisms such as antibiotic control programs, better hygiene, and synthesis of agents with improved antimicrobial activity need to be adopted in order to limit bacterial resistance (Neu, 1992; Ladhani and Gransden, 2003; Lutter et al., 2005; Sood and Gupta, 2012).

According to OECD (Organization for Economic Co-operation and Development) in the more developed countries antibiotics are obtained mostly only by prescription, whereas in “developing” non-OECD countries like Bangladesh many antibiotics (Nahar et al., 2006; Khanum et al., 2012) including those commonly used to treat urinary tract infection, can be obtained over the counter, without the need for a prescription (Wayne, 2000; Sharples and Lloyd, 1990; Hulton et al., 1991; Versalovic et al., 1991; Versalovic et al., 1994).The study is designed to assess the risk factors for developing antibiotic resistant UTI among children and this may help to prevent the irrational use of antibiotics in children (Simmering et al., 2017).

MATERIALSAND METHODS

A cross sectional study was carried out in Dhaka Shishu Hospital, Sher-E-Bangla Nagor, Dhaka. The study was conducted during January 2018 to June 2018. Attendants of child patient (137) aged 1 to 15 years with UTI who came for treatment in Dhaka Shishu Hospital, Agarga, Dhaka. For sample collection, clean catch, midstream urine samples (MSU) were collected in sterile, wide mouthed, universal containers from the patients clinically suspected to have UTI.

After collection, the specimens were immediately transported to the laboratory and processed within two hours of the collection. Quantitative un-spun wet mount microscopic examination was done for the well mixed un-centrifuged urine sample. 50 µl of urine sample was placed on clean grease free glass slide and covered with 20 mm×20 mm coverslip and was examined under high power field of microscope for the presence of pus cells. The cut off for the significant finding was 1 pus cell / 7 high power fields (hpfs) (Colleen et al., 2003). Data was checked for the completeness and consistency on daily basis after data collection and entered in SPSS, MS-Excel, Epi-info was used. Data was analyzed in order to measure/assess the specific objective(s). The percentage, frequency, mean, median S.D was measured and for association, chi-Square was used.

RESULTS

In the present study, out of 137 children, 16.1% children were between 1 to 5 years of age, 21.9% between 5.1 to 9 years, 29.9% between 9.1 to 12 years and 32.1% between 12.1 to 15 years of age who were suffering from UTI. Here,

17.5% children suffering from UTI were males and the rest 82.5% were females. Study shows that 40.1% of the child's mother completed primary level education, 20.4% completed secondary level education, 5.8% completed graduation, 1.5% completed post-graduation and 32.1% had no formal education.

Regarding the profession of the fathers, 48.9% of the child's father does not have any formal education, 21.9% completed higher secondary level, 16.8% completed their graduation, 5.1% completed post graduate and 7.3% completed primary level of education. Whereas, it was found that 40.1% of the child's mother completed primary level education, 20.4% secondary, 5.8% were graduate, 1.5% post-graduate and 32.1% had no formal education. Among all the respondents, 33.6% belonged to lower class, 37.2% lower middle class, 23.4% middle class and 5.8% upper class. In this study, 40.9% of the child's mother was housewives, 19.0 % were service holders and 40.1% belonged to other professions.

Present study reveals that 34.3% children intakes less than 500 ml of water every day while 40.1% intakes 500 to 1000 ml of water. 21.1% children take about 1000 to 1500 ml of water and only 4.4% intakes more than 1500 ml of water every day (Table 1). Study shows that 52,6% children voids 5 to 6 times a day and 29.9% voids 4 to 5 times a day. 13.1% voids 3 to 4 times a day while 4.4% voids 2 to 3 times a day. 49.6% children maintain toilet hygiene by using water, 9.5% tissue paper, 24.8% diaper and 16.1% uses other forms to maintain toilet hygiene (Table 2).

The present investigation study found that 78.1% of the children had history of hospital admission while, 5.1% did not have any history of hospital admission; 20.4% of the respondents did not know if the child had any history of hospital admission (Table 3). Out of the 102 children who had a history of hospital stay, 64% stayed in hospital as they were ordered by the doctor, 17% stayed in hospital as the health condition of the child worsened while 19 % stayed in hospital as there was no positive change with previous medication (Figure 1).

The present study shows that 50.4% of the children had a history of taking antibiotics while 29.9% did not know whether the child had a history of taking antibiotics and 5.8% has no history of taking antibiotic. This study shows that, out of the 69 children who received antibiotics (Table 4); 72.5% got the medication from pharmacy while 24.6% got it from free samples. About 58% of the children took the antibiotics on time and 37.7% did not take the antibiotic on time. Out of the 43 children who took the antibiotic on time, 79% took it for 1 to 3 days, 16.3% took it for 3 to 5 days and 4.7% took it for 5 to 7 days (Table 5).

Out of the 69 children who had a history of antibiotic intake, 11.6% could name Ciprofloxacin as the antibiotic they gave the child to take and 10.1% could name Azithromycin. A majority of 78.3% could not state the name of the antibiotic they gave their child to take (Table 6). Also, 12% were suggested by family to take antibiotic, 10% were suggested by doctor, 62% were suggested by pharmacy and 16% followed previous prescription (Figure 2).

Table 1. Distribution of respondents according to the amount of water intake by the child.

Amount of water intake by the child	Frequency	Percentage
< 500ml	47	34.3
500- 1000ml	55	40.1
1000-1500ml	29	21.1
> 1500ml	6	4.4
Total	137	100

Table 2. Distribution of respondents according to how the child maintains toilet hygiene.

How the child maintains toilet hygiene?	Frequency	Percentage
Using water	68	49.6
Using Tissue	13	9.5
Diaper	34	24.8
Others	22	16.1
Total	137	100

Table 3. Distribution of respondents according to any history of hospital admission.

History of hospital admission	Frequency	Percentage
Yes	102	78.1
No	7	5.1
Do not know	28	20.4
Total	137	100

Table 4. Distribution of respondents according to history of taking antibiotic.

Any history of taking antibiotic	Frequency	Percentage
Yes	69	50.4
No	8	5.8
Do not know	41	29.9
Total	137	100

The present investigation reveals that 73.7% of the children were previously diagnosed with UTI while, 16.8% were not diagnosed with UTI previously. Table 7 shows that out of the 101 children who previously got diagnosed with UTI, 80.2% got treatment while 10.9% did not receive any treatment. Study shows that 50.6% of the respondents have a tendency to start the previous antibiotic without further advice while 49.4% do not have the tendency.

The study reveals that 86.4% respondent who were

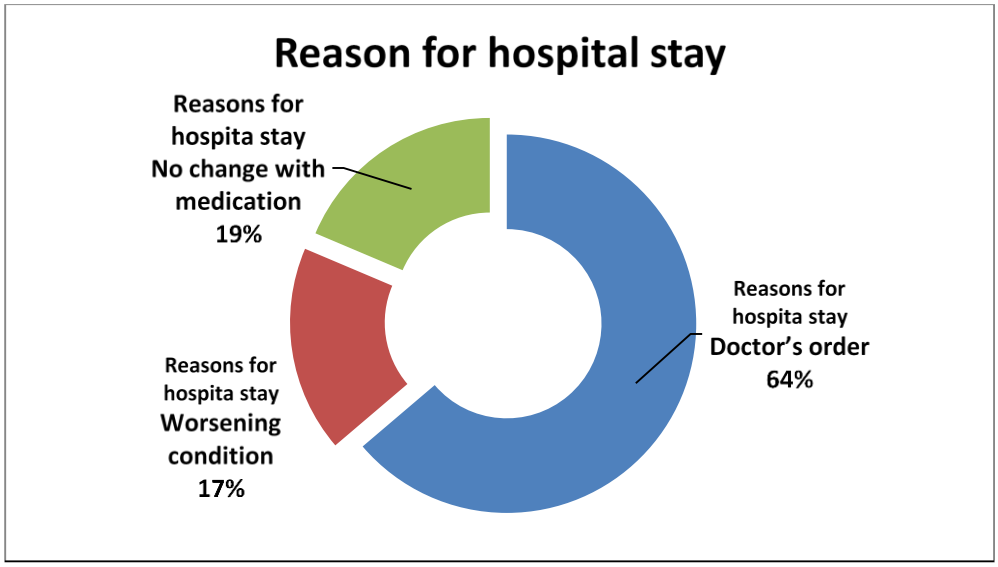

Figure. 1. Distribution of history of hospital stay of the children affected by UTI.

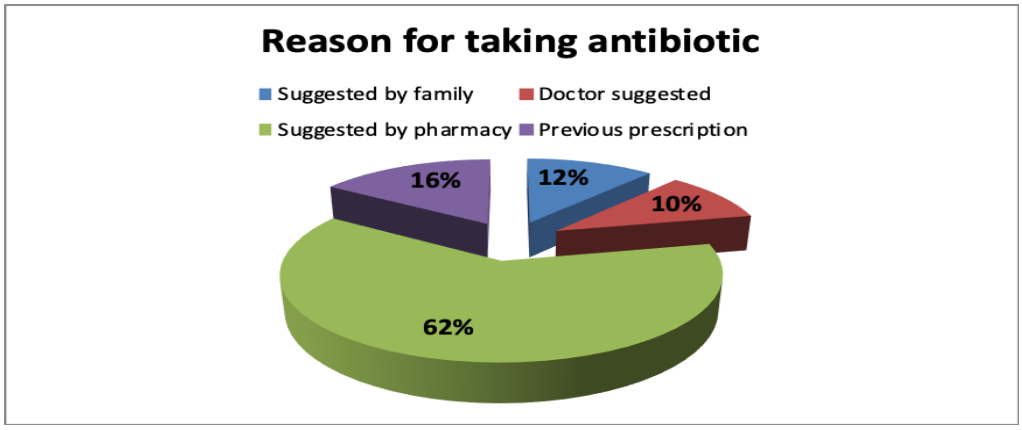

Figure 2. Distribution of respondents according to urine culture sensitivity.

Table 5. Distribution of respondents according to the length the respondent continued the treatment.

How long the respondent continues the antibiotic	Frequency	Percentage
1-3 days	35	79.0
3-5 days	6	16.3
5-7 days	2	4.7
Total	43	100

Table. 6. Distribution of respondents according to the name of the antibiotic used.

Name of the antibiotic	Frequency	Percentage
Ciprofloxacin	8	11.6
Azithromycin	7	10.1
Do not know the name	54	78.3
Total	69	100

females suffered from recurrent UTI and 22.2% respondent who were male had recurrent UTI ($p<0.05$). Therefore, there was statistical significant relationship between gender and recurrent UTI. The relative risk was 3.886 and attributable risk was 0.641 (Table 8).

The present observation reveals that 88.6% respondents who were illiterate had their child suffering from recurrent UTI and 66.7% respondents who were literate had their child suffering from recurrent UTI ($p<0.05$). Therefore, there was statistically significant relationship between educational status of the mother and recurrent UTI. The relative risk was 1.330 and attributable risk was 0.220 (Table 9).

Table 7. Distribution of respondents according to past history of UTI.

respondent was diagnosed with UTI previously	Frequency	Percentage
Yes	101	73.7
No	23	16.8
Do not know	13	9.5
Total	137	100

Table 8. Relationship between gender of child and the recurrent UTI.

Gender		Recurrent UTI		Total	Chi square	P Value	Relative risk	Attributable risk
		Present	Absent					
Female	N	95	15	110	46.039	0.0010	3.886	0.641
	%	86.4	13.6	100%				
Male	N	6	21	27				
	%	22.2	77.8	100%				
Total	N	101	36	137				
	%	73.7	26.3	100%				

Table 9. Relationship between educational status of the mother and recurrent UTI.

Educational status of mother		Recurrent UTI			Chi square	P-value	Relative risk	Attributable Risk
		Present	Absent	Total				
Illiterate	N	39	5	44				
	%	88.6	11.4	100%				
Literate	N	62	31	93	7.442	0.0010	1.330	0.220
	%	66.7	33.3	100%				
Total	N	101	36	137				
	%	73.7	26.3	100%				

The present investigation reveals that 54.4% respondent used water to maintain the child's toilet hygiene suffered from recurrent UTI and 92.8% respondent used other means excluding water to maintain the child's toilet hygiene suffered from recurrent UTI ($p<0.05$). Therefore, there was statistically significant relationship between gender and recurrent UTI. The relative risk was 0.587 and attributable risk was -0.383 (Table 12).

DISCUSSION

Factors for recurrent UTI

In the study, 34.3% children intakes less than 500 ml of water every day while 40.1% intakes 500 to 1000 ml of water. 21.1% children take about 1000 to 1500 ml of water and only 4.4% intakes more than 1500 ml of water every day (Table 1). About 49.6% children maintain toilet hygiene by using water, 9.5% uses tissue paper, 24.8% uses diaper and 16.1% uses other forms to maintain toilet hygiene (Table 2). And it is evident in many studies that these are causes or risk factors of recurrent UTI (Prakash and Saxena, 2013; Shaikh et al., 2008).

Antibiotic

In the present investigation, 50.4% of the children had a history of taking antibiotics while 29.9% did not know whether the child had a history of taking antibiotics. Out of 69 children who had a history of antibiotic intake, 11.6% could name ciprofloxacin as the antibiotic they gave the child to take and 10.1% could name Azithromycin. A majority of 78.3% could not state the name of the antibiotic they gave their child to take. Out of the 43 children who took the antibiotic on time, 79% took it for 1 to 3 days, 16.3% took it for 3 to 5 days and 4.7% took it for 5 to 7 days. The children (73.7%) were previously diagnosed with UTI and 16.8% were not diagnosed with UTI previously (Table 8). Table 10 suggests that out of the 81 children who received treatment for UTI, 76.5% were fully

Table 10. Distribution of respondents according to whether the patient fully cured after receiving the antibiotic.

Was the patient fully cured after receiving the antibiotic	Frequency	Percentage
Yes	62	76.5
No	16	19.8
Do not know	3	3.7
Total	81	100

Table 11. Distribution of respondents according to urine culture antibiotics sensitivity.

Urine culture	Sensitive		Resistant	
	Frequency	Percentage	Frequency	Percentage
Ampicillin	45	63.3	23	32.4
Cephalexin	34	47.9	12	16.9
Ceftazidime	56	78.9	4	5.6
Cefixime	61	85.9	10	14.1
Amikacin	66	93.0	5	7.0
Ciprofloxacin	50	70.4	12	16.9
Cotrimoxazole	54	76.1	8	11.2
Piperacillin	67	94.4	2	2.8
Cefepime	70	98.6	2	2.8
Gentamicin	44	62.0	7	9.9
Netilmicin	65	91.5	6	8.5
Nalidixic acid	62	87.3	4	5.6
Nitrofurantoin	50	70.4	13	18.3
Total	71	100	71	100

cured after receiving antibiotic while 19.8% were not cured after taking antibiotic (Table 10).

Study showed that out of 71 children who had urine culture sensitivity test, 32.4% are resistant to ampicillin, 16.9% to cephalexin, 5.6% to ceftazidime, 14.1% to cefixime, 7% to amikacin, 16.9% to ciprofloxacin, 11.2% to cotrimoxazole, 2.8% to piperacillin, 2.8% to cefepime, 9.9% to gentamicin, 8.5% to netilmidin, 5.6% to nalidixic acid and 18.3% to nitrofurantoin (Table 11).

Table 12 reveals that 54.4% respondent used water to maintain the child's toilet hygiene suffered from recurrent UTI and 92.8% respondent used other means excluding water to maintain the child's toilet hygiene suffered from recurrent UTI($p<0.05$). Therefore, there was statistical significant relationship between gender and recurrent UTI. The relative risk was 0.587 and attributable risk was -0.383.

The present observation explains that the correlation between gender and mode of toilet hygiene with recurrent UTI is strong. Whereas the strength of the correlation is moderate between recurrent UTI with educational status of mother and amount of water intake (Table 13).

A previous study in a mixed population of children with UTIs demonstrated that history of UTI as a risk factor for increased antibiotic resistance. Other studies have shown that urinary malformations, history of urinary catheter, hospitalization within the last year, and recent treatment with antibiotics are additional risk factors for resistant organisms (Colleen et al., 2003) which are similar as the present study. Previous pediatric studies found higher sensitivity to Ceftazidime (Colleen et al., 2003) but present study found highest Amikacin 93% sensitive.

Out of the 101 children who previously got diagnosed with UTI, 80.2% got treatment while 10.9% did not receive any treatment. It was observed that there is a wide array of resistance to antibiotics. This might be accountable to the irrational use of such medicines and self-medications (Geerlings, 2016; Foxman, 2010).

Association, relative risk and attributable risk

About 86.4% respondent who were females suffered from recurrent UTI and 22.2% (Table 8). Respondent who were male had recurrent UTI ($p<0.05$). Therefore, the relationship between gender and recurrent UTI was statistically significant. The relative risk was 3.886 and attributable risk was 0.641. The present result correlates with the study by Johnson and O'Bryan (2000) on improved repetitive-element PCR fingerprinting for

Table 12. Relationship between mode of water use for toilet hygiene and the recurrent UTI.

Mode of toilet hygiene		Recurrent UTI		Total	Chi square	P Value	Relative risk	Attributable risk
		Present	Absent					
Water	N	37	31	68	25.990	0.0010	0.587	-0.383
	%	54.4	45.6	100%				
Non water	N	64	5	69				
	%	92.8	7.2	100%				
Total	N	101	36	137				
	%	73.7	26.3	100%				

Table 13. Correlation coefficient with recurrent UTI and the strength of the relationship.

Parameters	Correlation co-efficient with recurrent UTI (r Value)	Strength of relationship
Gender	0.7	Strong
Educational status of mother	-0.3	Moderate
Amount of daily water intake	-0.5	Moderate
Mode of toilet hygiene	0.6	Strong

resolving pathogenic and nonpathogenic phylogenetic groups within *Escherichia coli*, where it states that short urethra, close proximity of female urethral meatus to anus influence higher prevalence of UTI in women. Among males, UTI caused by *E. coli* was high in younger age group of 0 to 9 years, as uncircumcised boys have higher risk (Nahar et al., 2006; Islam et al., 2010).

From the study, 54.4% respondent used water to maintain the child's toilet hygiene suffered recurrent and 92.8% respondent used other means excluding water to maintain the child's toilet hygiene suffered from recurrent UTI ($p<0.05$) (Table 12). Therefore, the relationship between mode of toilet hygiene and recurrent UTI was statistically significant. The relative risk was 0.587 and attributable risk was -0.383.

Therefore, there were statistically significant relationship between gender, mode of toilet hygiene, amount of daily intake of water, educational status of the mother and recurrent UTI. About 50.6% of the respondents have a tendency to start the previous antibiotic without further advice while 49.4% do not have the tendency. All these are factors for developing recurrent UTI and resistance to certain antibiotics (Prakash and Saxena, 2013; Singh and Bijoylakshmi, 2016).

The source for the drugs such as antibiotic is questionable as the patients or their attendants seem to get it mostly from pharmacies without any prescription or doctors order which is evident from this study. Even when people are taking these antibiotics, they are not using it for the appropriate time duration as well (Nahar et al., 2006; Islam et al., 2010). There is need to build awareness about antibiotic resistance through health campaigns and there should be rational use of antibiotic in all sectors of healthcare (Pardeshi, 2018; Flores-Mireles et al., 2015).

Conclusion and recommendation

It can conclude that, lack of awareness about going to specialist doctors for UTI treatment and taking medicine from pharmacy and doing self-prescription and medication along with lack of hygiene and water intake remains the major factors for recurrent UTI among children. All these are factors for developing recurrent UTI and resistance to certain antibiotics. There is need to build awareness about antibiotic resistance through health campaigns and there should be rational use of antibiotic in all sectors of healthcare. Culture sensitivity for urine should be a mandatory test before administering antibiotics for UTI. Proper counseling should be done to patients about the use of antibiotics. Shopkeepers and pharmacies should not be allowed to prescribe antibiotics on their own without doctor's prescriptions.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest

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