ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 13, Issue 9, 2020

Online - 2455-3891
Print - 0974-2441

Research Article

PRESCRIBING PATTERNS OF CEPHALOSPORIN IN CHILDREN FOLLOWING IMPLEMENTATION OF ANTIBIOTIC STEWARDSHIP PROGRAM IN A TERTIARY CARE HOSPITAL AT WESTERN INDIA

ANURADHA JOSHI[1], URVI KHUMBANI[2], JAISHREE GANJIWALE[3], BARNA GANGULY[1]

[1]Department of Pharmacology, Pramukhswami Medical College, Karamsad, Gujarat, India. [2]Department of Pharmacovigilance, APCER Life Sciences, Ahmedabad, Gujarat, India. [3]Central Research Services, Charutar Arogya Mandal, Pramukhswami Medical College, Karamsad, Gujarat, India. Email: annuradhaj7@gmail.com

Received: 21 May 2020, Revised and Accepted: 26 June 2020

ABSTRACT

Objective: The objective of the study was to study the prescribing patterns of cephalosporins in children following the implementation of Antibiotic Stewardship Program (ASP) in a tertiary care hospital at western India.

Methods: This was an observational study of records using data of pre- and post-implementation of ASP. Data were collected from case files of children admitted to pediatric wards in the years 2012 and 2014, respectively. Data were analyzed to find the prescribing pattern of cephalosporin and its appropriateness in relation to ASP program guidelines.

Results: Three hundred case files were collected and analyzed (n=150 each from the year 2012 and 2014). The mean age of patients in both years was 6.21 years±5.63 (the year 2012) and 5.88 years±5.88 in (the year 2014). Majority of children, that is, 47.3% were suffering from infectious diseases in the year 2012 while in the year 2014, 38.7% suffered from infectious diseases. Post-implementation of ASP, there was an improvement in the appropriateness of cephalosporin prescribing in terms of prophylactic and empirical treatments. Switch over of parenteral cephalosporins to oral was observed in 54.0% patients in 2012, while in 2014, it was seen in 51.3% of patients. There was a 4.6% rise in prescriptions containing 1st generation cephalosporins. Overall there was a significant impact of ASP in terms of appropriate cephalosporin prescribing (p=0.039).

Conclusion: Implementation of ASP and its adherence by pediatricians can improve antibiotic prescribing in children.

Keywords: Antimicrobial stewardship program, Cephalosporins, Pediatrics.

 DOI: http://dx.doi.org/10.22159/ajpcr.2020.v13i9.38403

INTRODUCTION

Children constitute approximately 40% of India's net population, they are highly vulnerable to contact illnesses and, at the same time, highly sensitive to the harmful effects of drugs, especially antimicrobials [1,2]. Various interventions like Antibiotic Stewardship Program (ASP) are aimed at improving and monitoring appropriate antimicrobial use by selecting the most optimal drug regimen, including the type of drug used, the dose, the duration of therapy, and the route of administration.

Literature reports that inappropriate use of antimicrobials in children is associated with an increased rate of adverse events and antimicrobial resistance [3,4]. Successful stewardship programs in hospitals promote improved patient care, decreased antimicrobial use and resistance, and reduced unnecessary hospital and pharmacy expenditures [5-7]. ASP was first implemented at our hospital in year 2013, consisting of updated antibiotic policy guidelines meticulously prepared by health-care professionals such as microbiologists, physicians, pediatricians, pharmacist, and pharmacologists. Cardinal features of ASP include a list of "Restricted antibiotics" with their indications, details of categorization of patient risk stratification, guidelines for antibiotic prophylaxis in surgical departments, guidelines for rational antibiotic use in medical, surgical, and pediatric units; the latter has been provided to every consultant and resident at the hospital for adherence to prevent injudicious use of antimicrobials and thereby control its resistance. In addition, antibiotic policy audit forms and checklist are also provided in the policy document.

The current study mainly emphasizes on the use of cephalosporins in children, as latter is one of the most commonly prescribed antibiotics in the pediatric department and intensive care unit settings. Reports regarding the prescribing of cephalosporins in children, especially in context to ASP are lacking; therefore, this study is an attempt to find the prescribing patterns of cephalosporins in children (pediatric in-patients), following the implementation of ASP and see the impact of the same.

METHODS

Study design and setting

This study was conducted in pediatric wards at a tertiary care, academic medical center situated in western India. This was an observational study. The study protocol was approved by Institutional Ethics Committee (Reference no. HMPCMCE: HREC/UGPG/23/Session 1/9) before conducting the study and written, informed consent was obtained from patients as well as parents/guardians of children in vernacular language. They were also explained the purpose and nature of the research study.

Inclusion criteria

The following criteria were included in the study:

- Only those case files were studied wherein patients were mainly prescribed cephalosporins during their hospitalization
- Children who were suffering from bacterial infections during their hospitalization.

Exclusion criteria

The following criteria were excluded from the study:

- Patients not willing to give written informed consent
- Patients suffering from viral infections
- All O.P.D. (outpatient department) and immunocompromised pediatric patients were excluded from the study.

Data collection

Prospective and retrospective data were collected from patients files admitted in pediatrics wards as follows: A total of 300 case files of patients admitted to pediatrics wards were included in the study. Out of these, 150 case files were from the years 2012 and 2014 each, that is, pre- and post-implementation of ASP. Data from inpatients aged 0–18 years, diagnosed with acute gastroenteritis, lower respiratory tract infection, upper respiratory tract infection, enteric fever, and other bacterial infections were focused for analysis. As discussed earlier ASP was developed as a part of the hospital infection control policy and implemented at our hospital in the year 2013. Hospital numbers and records of pediatric patients who were admitted and on "Cephalosporins" during the years 2012 and 2014 were retrieved from electronically generated medical record systems for data collection.

Data on demographic details, disease conditions, details of cephalosporin prescribing and its generations, choice of individual drug, dose, frequency and duration, type/s of treatment advocated (prophylactic, empirical, and definitive), switch over from parenteral to oral cephalosporins with their regimen, number of culture sensitivity tests done, and total duration of hospitalization were recorded. All the data from the year 2012 were analyzed and compared to that of the year 2014 with reference to ASP for prescribing pattern of cephalosporins and any change in prescribing pattern following ASP.

Outcome measures

For each condition that resulted in cephalosporin prescription, the appropriateness of therapy was assessed by consulting the ASP. Accordingly, conditions were grouped into three categories:

Conditions where cephalosporin treatment was (1) appropriate (always justified, i.e., in terms of indication, patient risk stratification in terms of community-acquired infection or hospital-acquired infection, prescribing cephalosporin according to ASP, whether antibiotic was changed or not changed as per culture report); (2) sometimes appropriate (conditionally justified, e.g., depending on symptoms); or (3) inappropriate (never justified). In any conditions where guidelines were missing or ambiguous, antibiotic appropriateness was determined through a consultant senior pediatrician. If a single prescription was linked to multiple conditions, the condition giving the highest chance of appropriate prescribing was assumed to underlie the prescription.

Statistical analysis

Data were entered in Microsoft Excel 2007, and analysis was done. Descriptive statistics in terms of frequency and percentages were used for variables like demographic profile, disease conditions, and cephalosporins prescribing patterns. Chi-square test was applied to find out the prescribing pattern of cephalosporins and appropriateness of treatment, pre- and post-implementation of ASP in terms of choice of individual drug, dose, frequency, and duration, type/s of treatment (prophylactic, empirical, and definitive), switch over from parenteral to oral cephalosporins with their regimen. Results were considered significant if $p<0.05$.

RESULTS

As depicted in the demographic profile in Table 1: According to age, children were divided into 0-1 year, 1–5 years, 5–12 years, and 12–18 years age groups, respectively. The mean age of patients (in years) was 6.21±5.63 in 2012, while in the year 2014, it was 5.88±5.88. 61.3% of males and 38.7% of females pediatric patients were admitted in the year 2012, while in the year 2014, distribution was as follows 62.7% males and 37.3% female pediatric patients. In the year 2012, the mean weight of patients (in kg) was reported to be 18.12±12.61 while it was 17.90±14.56 in the year 2014. This is depicted below in Tables 1 and 2.

In the current study, the majority of the children, that is, 71 (47.3%) were suffering from infectious diseases, lower respiratory tract diseases 33 (22%) children, and gastrointestinal (GI) conditions 21 (14%) children in the year 2012 while in the year 2014, the indices showed

Table 1: Distribution of mean age of children according to various age groups across 2 years

Age groups	Number of patients (mean age±SD)			
	Year 2012		Year 2014	
	Male	Female	Male	Female
0–1 years	34	20	28	17
1–5 years	14	10	29	15
5–12 years	29	18	18	10
12–18 years	15	10	19	14

Table 2: Distribution of mean weight of children according to age groups across 2 years

Age groups	Mean weight±SD			
	Year 2012		Year 2014	
	Male (mean±SD)	Female (mean±SD)	Male (mean±SD)	Female (mean±SD)
0–1 year	7.78±2.178	6.14±2.221	6.03±2.045	6.46±1.945
1–5 years	11.88±2.260	11.66±2.722	10.48±2.090	10.47±2.422
5–12 years	24.43±9.474	20.54±5.317	22.03±8.284	20.55±10.726
12–18 years	38.40±5.906	38.22±5.797	43.26±9.938	37.23±8.042

that 58 (38.7%) of the children suffered from general infections such as viral fever, abscess, and sepsis, 30 (20%) children were suffering from lower respiratory tract infections and 26 (17.3%) from GI conditions, respectively (Fig. 1).

The most commonly prescribed cephalosporin was ceftriaxone prescribed in 125 (83.3%) cases in the year 2012, while in the year 2014, it was prescribed in 131 (87.3%) cases. Other drugs prescribed were cefazolin 5.30% in the year 2012 and 0.70% in the year 2014, cefotaxime 1.30% in year 2012 and 0.70% in the year 2014, cefixime 6.00% in the year 2012 and 14.70% in the year 2014, and cefepime 0.70% in year 2012 and 0.00% in year 2014 (Fig. 2).

In both years, all drugs were prescribed by generic names.

Overall treatment was categorized into three main groups, namely, prophylactic, empirical, and definitive, respectively. On the comparison between the two years, the data revealed that in the year 2012, 22 (14.7%) patients were advocated prophylactic treatment, 115 (76.7%) patients were managed with empirical treatment, and 13 (8.6%) patients were on definitive treatment while in the year 2014, 26 (17.3%) patients were on prophylactic treatment, 117 (78%) patients were managed by empirical therapy whereas 7 (4.7%) patients were managed by definitive therapy.

In regards to the appropriateness of prophylactic and empirical treatment in terms of choice, dose, frequency, duration, and overall use, the data highlight that there were significant changes in the appropriateness of prophylactic and empirical treatments as shown in (Tables 3 and 4). While 130 (86.7%) patients were prescribed intravenous cephalosporins in the year 2012 verses, 141 (94%) patients in the year 2014. Out of this switch, over to oral cephalosporins was initiated in 77 (51.3%) cases in the year 2012 while in the same was done in 81 (54%) cases in the year 2014, as shown in (Table 5).

In the year 2012, culture sensitivity tests were performed in 71 (47.3%) pediatric cases, whereas, in the year 2014, it was performed in 32 (21.3%) cases. Out of this, it was observed that 12 (8%) patients were treated in accordance with the culture sensitivity reports in the

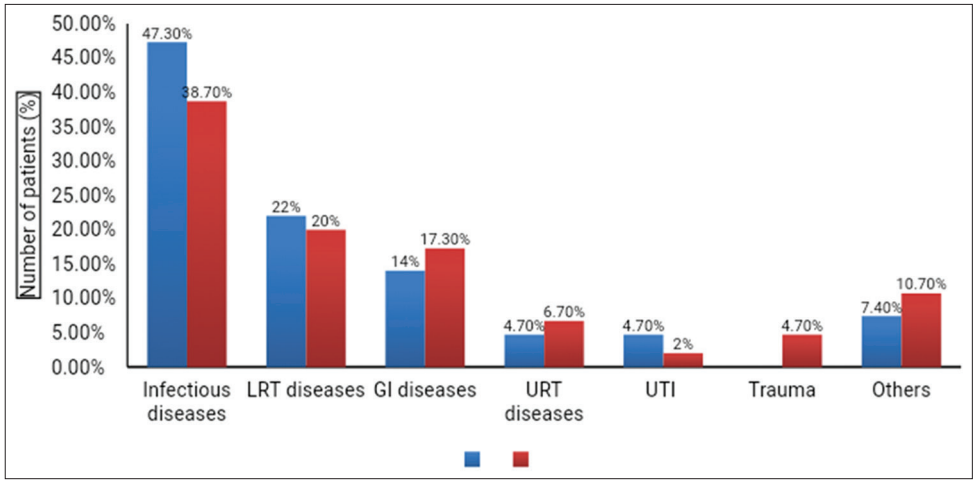

Fig. 1: Distribution of disease conditions for which patients were admitted in pediatrics departments in 2012 and 2014. (*Red: 2012 and Blue: 2014)

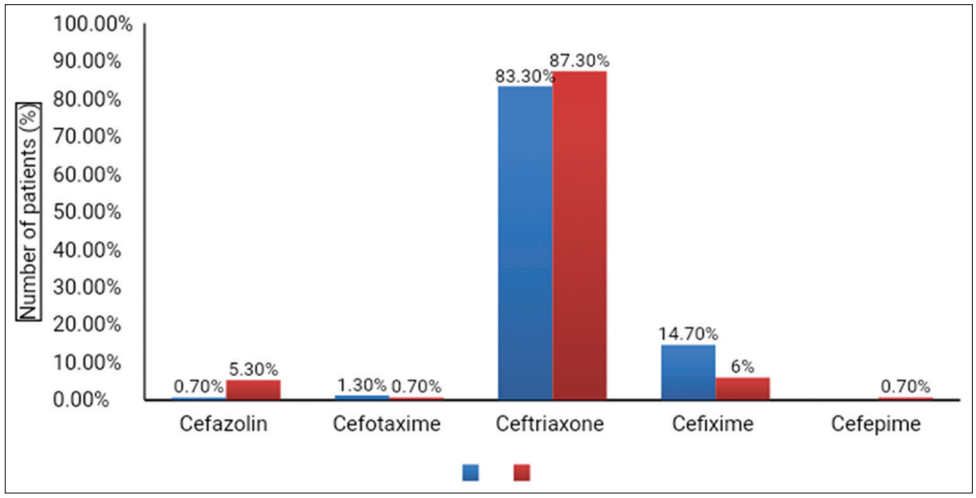

Fig. 2: Distribution of individual cephalosporin prescribed in the year 2012 and 2014. (*Red: 2012 and Blue: 2014)

Table 3: Prophylactic treatment and their appropriateness following ASP

Parameters	Number of patients (%)		
	Year 2012 (n=22 [14.7%])	Year 2014 (n=26 [17.3%])	p-value
	Appropriate	Appropriate	
Choice	3 (13.6)	23 (88.5)	<0.0001*
Dose	18 (81.8)	21 (80.8)	0.926
Frequency	20 (90.9)	23 (88.5)	0.782
Duration	9 (40.9)	7 (26.9)	0.306
Overall	1 (4.5)	4 (15.4)	0.221

*p-value statistically significant. ASP: Antibiotic Stewardship Program

Table 4: Empirical treatment and their appropriateness following ASP

Parameters	Number of patients (%)		
	Year 2012 (n=115 [76.7%])	Year 2014 (n=117 [78%])	p-value
	Appropriate	Appropriate	
Choice	103 (89.6)	103 (88)	0.712
Dose	93 (80.9)	82 (70.1)	0.056
Frequency	108 (93.9)	103 (88)	0.119
Duration	51 (44.3)	40 (34.2)	0.306
Overall	32 (27.8)	21 (17.9)	0.073

ASP: Antibiotic Stewardship Program

year 2012, while in the year 2014, 24 (16%) patients were treated in accordance with sensitivity reports (p=0.039). Mean hospitalization stay of patients was 4.98 days in the year 2012 and 2014.

DISCUSSION

Bacterial infections continue to be a major contributing factor to mortality in the world, and at the same time, antimicrobial resistance has become a ubiquitous problem throughout the world, especially in India [8-10]. Antibiotic use has been seen to be high in India with one recent surveillance study indicating 40% of patients in the community who were on antibiotics had a higher rate of inappropriate use of antibiotics [8]. Besides, drug administration, its response in pediatric patients is affected by a number of factors such as age, weight, rapidly changing physiological variables, altered pharmacokinetic profile, dose, formulation, route of drug administration, and duration of therapy. One of the strategies to counter such problems in antibiotic prescribing is the implementation of ASPs in hospital settings [11,12]. The current study reports the prescribing pattern of one of the commonly used antibiotics in the pediatric age group, that is, cephalosporins especially

Table 5: Distribution of oral cephalosporins after switch over from parenteral cephalosporins

Oral cephalosporins	No. of patients (%)	
	Year 2012	Year 2014
Cefixime	70 (90.9)	75 (92.6)
Cefpodoxime	4 (5.2)	6 (7.4)
Cefpodoxime-Clavulanic Acid	3 (3.9)	0 (0)
Total (%)	77 (100)	81 (100)

in relation to ASP which was first implemented in our hospital in the year 2013.

In our study, the mean age of pediatric participants was 6.21 years in 2012, while in the year 2014, it was 5.88 years, which is comparable with the study conducted by Kanish *et al*. wherein mean age was 4.6 years [13]. Since the majority of patients were suffering from infections, so cephalosporins have been favored over other antibiotics and because the latter are relatively safer to prescribe in pediatric patients. In the given study, the majority of the children who were prescribed cephalosporins, that is, 71 (47.3%) in the year 2012 versus 58 (38.7%) in the year 2014, were suffering from bacterial infections. Those suffering from lower respiratory tract diseases were 33 (22%) in the year 2012 versus 30 (20%) in the year 2014 and those suffering from GI infections were 21 (14%) in the year 2012 versus 26 (17.3%) in the year 2014. Frequent use of cephalosporins could be mainly attributed to the broad-spectrum antimicrobial activity of these drugs along with good efficacy and safety profile in the pediatric population [3].

Generation wise prescribing pattern of cephalosporins in the year 2012 was as follows: 1st generation in 1 (0.7%) and 3rd generation in 149 (99.3%) patients, while the distribution of cephalosporin according to its generation, in the year 2014 was as follows: 8 (5.3%) patients were prescribed 1st generation while 141 (94%) were prescribed 3rd generation and only 1 (0.7%) patient was on 4th generation respectively. Hence, it is clear that in both years, there was a preference for prescribing 3rd generation cephalosporins (Table 3). This is in similar lines to a study conducted by Satravanan and Muthukumar which also shows a higher prescribing of third-generation cephalosporins (81.56%) in the urban population [14]. Thus, the findings of the current study revealed that following the implementation of ASP, the use of 3rd generation cephalosporins declined in the year 2014. This finding is supported by a study conducted by Cairns *et al*., who found a 10.9% decline in the use of 3rd and 4th generation cephalosporins after implementation of ASP [12].

In this context, in the present study, it is evident that individually, the most common drug prescribed among cephalosporins was ceftriaxone in 125(83.3%) cases in the year 2012 while in the year 2014, 131 (87.3%) patients were prescribed ceftriaxone. This is similar to a study conducted by Kanish *et al*., wherein 51.8% ceftriaxone was prescribed [13]. Again, frequent use of ceftriaxone by pediatricians could be due to its better penetration, longer half-life, and elimination primarily through bile rather than renal or hepatic [14,15].

In this study, the majority of children were treated with empirical treatment in both the years, that is, 115 (76.7%) cases in 2012 while in the year 2014, 117 (78%) cases. This could be mainly to prevent treatment failure, the transmission of secondary infections, and longer hospital stay. In-depth analysis of data reports that post-implementation of ASP, there was an improvement mainly in the empirical treatment in 2014, especially in terms of choices, which is an important confounder to the judicious use and prevention of resistance due to antimicrobials. On the other hand, there was not much improvement in dose, frequency, and duration of empirical treatment in the year 2014 since optimization of empirical treatment requires certain important information such as patient's age, weight, compliance, and information regarding patient's immune status, comorbid conditions, pharmacokinetic mechanisms, vulnerability to infections, and the infecting agent [16].

Incomplete information could be the reason for inappropriateness in terms of dose, frequency, and duration of empirical treatment. Although we encountered less data for definitive treatment in the year 2012 and 2014, the findings conclude that there was a gradual improvement in the use of definitive treatment post-implementation of ASP.

According to the current study, more parenteral cephalosporins were used in the year 2014 as compared to 2012. This might be due to the advantages of parenteral cephalosporins which are faster acting, can be administered in neonates, unconscious patients, and/or dysphagic patients. Although parenteral ceftriaxone has many advantages over other parenteral antimicrobials, it is one of the restricted and a reserve antibiotic, the overuse of parenteral preparations should be discouraged because the latter could be one of the reasons for the emergence of multi-drug resistant Gram-positive and Gram-negative microorganisms [17].

The switch over from parenteral to oral cephalosporins was initiated in 77 (51.3%) cases in the year 2012, while in the year 2014, switch over was done in 81 (54%) cases which is an indicator of good clinical practice. Since early switchover from parenteral to oral route in case of antibiotics is one of the key recommendations in ASP and a major determinant in safe antimicrobial prescribing, the findings of our study reveal awareness on the part of clinicians regarding early switchover of antimicrobials like cephalosporins [6].

The current study revealed that there was an increase in the appropriateness of overall cephalosporin prescribing and treatment in pediatric patients from 8% to 16% in the year 2014 post-ASP implementation and the change was statistically significant (p=0.039). This is in line with a meta-analysis conducted by Davey *et al*., who found that the impact of ASP ranged from 3% to 42% after 1 year of implementation [18]. Furthermore, these findings are similar to the study conducted by Borde *et al*. which concluded that an intensified ASP targeting cephalosporin use in the setting of a large academic hospital is an effective intervention [15] and a systemic review conducted by Kaki *et al*. which highlighted that ASP is associated with improved antimicrobial utilization without compromising the short-term clinical outcomes [19].

CONCLUSION

It is imperative for clinicians to be judicious in prescribing cephalosporins in children. Successful implementation of ASP and its adherence can improve antibiotic prescribing patterns in clinical practice. The current study has provided baseline information regarding the appropriateness of the prescribing pattern of cephalosporins in pediatric patients pre- and post-implementation of ASP. These data will be useful in ensuring successful adherence to ASP by clinicians in the future. Long term and more extensive studies of this type will be helpful in identifying the impact of ASP on antimicrobial prescribing, especially in terms of cephalosporins.

AUTHORS' CONTRIBUTIONS

All the authors have contributed in conduct of the study and preparation of manuscript.

CONFLICTS OF INTEREST

The authors declared no conflicts of interest regarding the research, authorship, and publication of the article.

AUTHORS' FUNDING

Self-funding.

REFERENCES

1. Chavda D, Mistry R, Solanki K, Suthar SD, Desai BL, Mistry SD. Drug utilization study in the inpatients of pediatric department of a tertiary care hospital. Int J Basic Clin Pharmacol 2015;4:729-33.

2. Walson PD. Pediatric clinical pharmacology and therapeutics. In: Speight TM, Holford NH, editors. Avery's Drug Treatment. Auckland, New Zealand: Adis International; 1997. p. 127-223.
3. Reddy NS, Kejiya G, Lakshmi P, Manohar B, Ranganayakulu D. Evaluation of cephalosporins use among pediatric in-patients at Tertiary care teaching hospital. Int J Inst Pharm Life Sci 2015;5:85-94.
4. Remesh A, Retnavally K, Salim S, Gayathri AM. Antibiotics prescribing pattern in the in-patie t departments of a tertiary care hospital. Arch Pharm Pract 2013;4:71.
5. Cosgrove SE, Kaye KS, Eliopoulous GM, Carmeli Y. Health and economic outcomes of the emergence of third-generation cephalosporin resistance in *Enterobacter* species. Arch Intern Med 2002;162:185.
6. Macdougall C, Polk RE. Antimicrobial stewardship programs in health care systems. Clin Microbiol Rev 2005;18:638-56.
7. Chandy SJ, Michael JS, Veeraraghavan B, Abraham OC, Bachhav SS, Kshirsagar NA. ICMR program on antibiotic stewardship, prevention of infection and control (ASPIC). Indian J Med Res 2014;139:226-30.
8. Khan A. Patterns of prescription of antimicrobial agents in the department of otorhinolaryngology in a tertiary care teaching hospital. Afr J Pharm Pharmacol 2011;5:1732-8.
9. Mathai E, Chandy S, Thomas K, Antoniswamy B, Joseph I, Mathai M, *et al*. Antimicrobial resistance surveillance among commensal *Escherichia coli* in rural and urban areas in Southern India. Trop Med Int Health 2008;13:41-5.
10. Jain D, Sinha S, Prasad KN, Pandey CM. *Campylobacter* species and drug resistance in a north Indian rural community. Trans R Soc Trop Med Hyg 2005;99:207-14.
11. Dellit TH, Owens RC, McGowan JE Jr., Gerding DN, Weinstein RA, Burke JP, *et al*. Infectious diseases society of America and the society for healthcare epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis 2007;44:159-77.
12. Cairns KA, Jenney AW, Abbott IJ, Skinner MJ, Doyle JS, Dooley M, *et al*. Prescribing trends before and after implementation of an antimicrobial stewardship program. Med J Aust 2013;198:262-6.
13. Kanish R, Gupta K, Juneja S, Bains HS, Kaushal S. Prescribing pattern of antibiotics in the department of pediatrics in a tertiary care medical college hospital in Northern India. Asian J Med Sci 2014;5:69-72.
14. Satravanan R, Muthukumar A. A surveillance study of antibiotic use in Pondicherry. Int J Basic Clin Pharmacol 2012;1:202-10.
15. Borde JP, Kaier K, Steib-Bauert M, Vach W, Geibel-Zehender A, Busch H, *et al*. Feasibility and impact of an intensified antibiotic stewardship programme targeting cephalosporin and fluoroquinolone use in a tertiary care university medical center. BMC Infect Dis 2014;14:201.
16. Petri WA. Penicillins, cephalosporins and other β lactam antibiotics. In: Brunton LL, Hilal-Dandan R, Knollmann BC, editors. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 12th ed. United States: McGraw Hill; 2011. p. 1477-504.
17. List of Recommended Antimicrobial Restrictions. QUAH Antimicrobial Stewardship Toolkit. Clinical Excellence Commission; 2013. http://www.cec.health.nsw.gov.au/programs/quah. [Last accessed on 2019 Oct 04].
18. Davey P, Brown E, Charani E, Fenelon L, Gould IM, Holmes A, *et al*. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev 2013;4:CD003543.
19. Kaki R, Elligsen M, Walker S, Simor A, Palmay L, Daneman N. Impact of antimicrobial stewardship in critical care: A systematic review. J Antimicrob Chemother 2011;66:1223-30.