Original Article

Ciprofloxacin Use in Hospitalized Children: Approved or Off-label?

Toktam Faghihi[1,2], Leila Yavari Tekmehdash[1], Mania Radfar[1], Kheirollah Gholami[1]

[1]Department of Clinical Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

[2]Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran

Abstract

Objective: Fluoroquinolones are not routinely used as the first-line antimicrobial therapy in pediatrics. The American Academy of Pediatrics (AAP) and the United States Food and Drug Administration (FDA) approved fluoroquinolones on certain indications in children. The aim of this study was to evaluate to what extent and how ciprofloxacin is used on approved indication or as off-label. Besides, dose adequacy and treatment duration were assessed. **Methods:** In a 10-month observational study, all children receiving systemic ciprofloxacin were assessed. We classified ciprofloxacin prescription to an AAP/FDA or off-label indication. The off-label prescriptions were further categorized to justified and unjustified therapy subgroups. The AAP/FDA category and the justified subgroup constituted the appropriate prescriptions. **Findings:** During the study period, 32 patients were prescribed ciprofloxacin. In general, 37% (12) of prescriptions determined to be appropriate. Of the appropriate prescriptions, 7 were AAP/FDA-approved indications. Children with Crohn's disease with abdominal abscess and children with infectious bloody diarrhea constituted the off-label; justified therapy subgroup. Unjustified prescriptions mainly occurred in the presence of a suitable alternative antibiotic for ciprofloxacin. Mean ± SD of ciprofloxacin dose (mg/kg/day) and duration (days) were 21.25 ± 6.35 and 13.56 ± 8.48, respectively. Of the appropriate prescriptions, 41% were underdosed. Underdosing was more encountered in patients with cystic fibrosis. Duration of treatment of the appropriate prescriptions was determined to be appropriate. **Conclusion:** The majority of children were receiving ciprofloxacin off-label and in an inappropriate manner. This issue emphasizes that antimicrobial stewardship program on ciprofloxacin use in pediatric hospitals should be implemented. Further studies evaluating clinical and microbiological outcomes of these programs in children are needed.

Keywords: *Ciprofloxacin, pediatric, prescription*

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Introduction

Fluoroquinolones, the antibiotic class with optimal pharmacokinetic and pharmacodynamic properties, have been associated with cartilage toxicity in animals.[1] Trials in children have not reported arthropathy as illustrated in juvenile animals.[2-6] However, despite emerging data on their reasonable safety,[1] the first-line therapy of fluoroquinolones in children is not recommended.[1,7] Concerns over antimicrobial resistance as well as the cartilage side effect profile lead to restricted use of this class of antibiotics in children.[7,8]

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The US Food and Drug Administration (FDA) approves ciprofloxacin for certain indications in children. Besides, the American Academy of Pediatrics (AAP) has provided a list of possible appropriate uses of systemic fluoroquinolones in children after risk/benefit assessment[1,7] [Table 1]. Meanwhile, off-label use of systemic fluoroquinolones has expanded in children.[6,8-11]

In the present study, we evaluated the use of systemic ciprofloxacin in children. The primary end point was to

Address for correspondence:
Dr. Toktam Faghihi, E-mail: tfaghihi@razi.tums.ac.ir

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Table 1: AAP list of possible uses* and the FDA-approved indications for fluoroquinolones in children

Serial number	AAP
1	UTIs caused by *P. aeruginosa*
2	UTIs caused by other MDR Gram-negative bacteria
3	Chronic suppurative otitis media by *P. aeruginosa*
4	Malignant otitis externa by *P. aeruginosa*
5	Acute osteomyelitis or osteochondritis associated with *P. aeruginosa*
6	Chronic osteomyelitis or osteochondritis associated with *P. aeruginosa*
7	Exacerbation of pulmonary disease in CF children colonized with *P. aeruginosa* who can be treated in an ambulatory setting
8	Gram-negative infections in immunocompromised children in which oral therapy is indicated and resistance to alternative antibiotics exists
9	Mycobacterial infections caused by isolates susceptible to fluoroquinolones
10	Gastrointestinal infections caused by MDR *Shigella*, *Salmonella* species, *V. cholerae*, *or C. jejuni*
11	Serious infections susceptible to fluoroquinolones in children with life-threatening allergy to other antimicrobials
12	Documented bacterial septicemia or meningitis caused by organisms with *in vitro* resistance to approved antibiotics
13	Documented bacterial septicemia or meningitis, in immunocompromised host, after parenteral therapy with appropriate antibiotics has failed
Serial number	**FDA (for ciprofloxacin)**
14	Treatment and prophylaxis of plague and postexposure prophylaxis of inhalation anthrax in all ages
15	Pyelonephritis caused by *E. coli* in children aged 1-17 years
16	Complicated UTIs caused by *E. coli* in children aged 1-17 years

*After risk/benefit assessment. AAP=American Academy of Pediatrics, FDA=US Food and Drug Administration, *P. aeruginosa=Pseudomonas aeruginosa*, *V. cholera=Vibrio cholera*, *C. jejuni=Campylobacter jejuni*, *E. coli=Escherichia coli*, MDR=Multidrug-resistant, UTIs=Urinary tract infections, CF=Cystic fibrosis

evaluate to what extent and how ciprofloxacin is administered based on the AAP policy statements or FDA-approved indications. In addition, off-label prescriptions were also determined and were classified to justified and unjustified therapy subgroups. The secondary outcomes were to evaluate dose adequacy and treatment duration.

Methods

The present work was conducted prospectively in general wards and Intensive Care Units of a referral tertiary-level hospital; the Children's Medical Center. This study was approved by Tehran University of Medical Sciences' Ethics Committee. The study was done only on inpatients. Outpatient populations were not included in this study.

Medical records of all children who received oral or intravenous ciprofloxacin for at least 48 h were evaluated. Demographic and clinical data including age, gender, weight, underlying medical conditions on admission, and baseline serum creatinine were recorded for all patients. Age groups were categorized according to the European Medicines Evaluation Agency (age category).[12] Ciprofloxacin administration data including dosage form, dose, indication, concomitant antibiotics, and duration of therapy were also recorded. There was no predefined written protocol for ciprofloxacin administration in our center.

Concomitant antibiotics were defined as any other antibiotics prescribed for 48 h simultaneously to ciprofloxacin. In case of culture proven infections, pathogen susceptibility data were recorded as multidrug resistant (MDR), extensively drug resistant (XDR), pandrug resistant (PDR), and, MDR; possible XDR, based on a standard definition.[13]

Indication for ciprofloxacin prescription was categorized to "AAP/FDA" or "off-label." Ciprofloxacin prescription was considered "off-label" if it was used in clinical situations other than stated by the AAP and FDA. We further classified off-label prescriptions to "justified" and "unjustified" therapy subgroups. Definitions of ciprofloxacin prescriptions are presented in Table 2. The "AAP/FDA" and the "justified" groups constituted the "appropriate" prescriptions.

Of note, there was no overlap between the "AAP/FDA" category and the "justified" therapy subgroup. Indeed, the "AAP/FDA" indications encompassed only culture-positive infections, while "justified" therapy subgroup included two settings; first, positive cultures other than those stated in the AAP/FDA category, second, culture-negative infections (empiric therapies) prescribed based on clinical judgment and both in the settings of an absent appropriate alternative antibiotic. Based on the authors' definition, an appropriate alternative antibiotic was defined as any other nonfluoroquinolone antibiotic that could be prescribed instead of ciprofloxacin based on the clinical indication, spectrum of activity, or susceptibility testing; except colistin, chloramphenicol, tigecycline, and tetracyclines. Tigecycline use in children should be reserved when no alternative antibiotics are available, because of effects on bone and tooth development and no available safety and efficacy data in children. Besides, there are concerns on increased mortality with tigecycline in adult

patients. Chloramphenicol use in children should be reserved when less potentially toxic antibiotics will be effective, because of fatal blood dyscrasias and the need to monitor serum levels in children. Colistin is reserved for pan-resistant nosocomial infections.[14-18] Thus, based on the above evidence, we did not consider colistin, chloramphenicol, tigecycline, and tetracyclines as the appropriate alternative antibiotics for ciprofloxacin, when ciprofloxacin is used on an FDA/AAP indication.

Adequacy of prescribed dose was assessed in three clinical subgroups; adequate, under, and over dose. Adequate dose was defined as oral dose of 40 mg/kg/day in cystic fibrosis (CF) patients[19,20] and 20–30 mg/kg/day oral or intravenously in other clinical situations.[21]

Statistical software SPSS version 11.5 (IBM company, Chicago, IL, USA) was applied for analysis. We have reported continuous variables as mean ± standard deviation (SD) for age, treatment duration, and dose.

Results

During a 10-month period, there were a total of 14,511 hospital admissions. During this period, 32 patients were prescribed ciprofloxacin. There were 14 boys. Mean age of the participants was 8.85 ± 3.87 years. Ciprofloxacin administration mostly occurred in children aged 2–11 years (n = 25) and adolescents aged 12–18 years (n = 5).

Among the participants, 9% (n = 3/32) had CF and received ciprofloxacin for community-acquired infection, while 91% (n = 29/32) had received ciprofloxacin for hospital-acquired infection.

Of the total 32 children who received ciprofloxacin, 7 (22%) were prescribed in accordance to the AAP/FDA criteria. Twenty-five (78%) children had received ciprofloxacin as off-label. Among the 25 off-label prescriptions, 5 (15%) were categorized as justified therapy and 20 (63%) were noted as unjustified. Thus, the appropriate indication for ciprofloxacin therapy occurred in 12 (37%) participants. A detailed description of appropriate ciprofloxacin prescriptions is outlined in Table 3. Regarding unjustified therapies (20 patients); in 7 children, it was not administered based on clinical judgment or pathogen susceptibility data; in 6 children, it was prescribed based on clinical judgment but in the presence of an appropriate alternative antibiotic; and in 7 children, it was prescribed based on culture data but in the presence of an appropriate alternative antibiotic.

Among the study participants, four children received ciprofloxacin for Crohn's disease with abdominal abscess. Among these, three children received ciprofloxacin as off-label, justified [Table 3].

Among the study participants, two children received ciprofloxacin for *Acinetobacter baumannii* infection.

Table 2: Descriptions of ciprofloxacin prescriptions

Category	Description
AAP/FDA	Administered according to the AAP policy statements or the FDA regulations
Off-label	
Justified	Administered based on pathogen susceptibility data in the absence of an appropriate alternative antibiotic Or Administered based on clinical judgment in the absence of an appropriate alternative antibiotic
Unjustified	Not administered according to clinical judgment or pathogen susceptibility data Or Administered based on clinical judgment but in the presence of an appropriate alternative antibiotic Or Administered based on pathogen susceptibility data but in the presence of an appropriate alternative antibiotic

AAP=American Academy of Pediatrics, FDA=US Food and Drug Administration

Table 3: Description of appropriate ciprofloxacin prescriptions

Description	Number
AAP/FDA	
Documented bacterial meningitis, pathogens with in vitro resistance to approved agents	1
Exacerbation of pulmonary disease in a child with CF, with Pseudomonas aeruginosa colonization who can be treated in an outpatient setting	2
MDR Salmonella species	2
Mycobacterium avium complex pulmonary infection	1
Complicated E coli UTI	1
Off-label; Justified[a]	5
Crohn disease with abdominal abscess	3
Bloody diarrhea	2
Underlying disease	
With CF	2
Without CF	10
Organism	
Pseudomonas aeruginosa	2
Acinetobacter baumannii	2
Salmonella Serogroup C	1
Mycobacterium avium complex	1
E coli	1
Empiric Therapy	5
Route of administration	
Parenteral	7
Oral	5

CF=Cystic fibrosis, MDR=Multidrug-resistant, UTI=Urinary tract infection, [a]Administered based on clinical judgment (empirically) in the absence of an appropriate alternative antibiotic

One child had meningitis by MDR, possible XDR *A. baumannii*. Antibiotic regimen consisted of colistin plus amikacin and ciprofloxacin. Ciprofloxacin was added to colistin due to repeated positive cultures, despite antibiogram showing resistance to ciprofloxacin. Ciprofloxacin use was considered to be in line with the AAP guideline in this case being defined as documented bacterial meningitis, pathogens with *in vitro* resistance to approved agents [Table 3]. No increase in seizure frequency was observed in this patient. The other patient had ventilator-associated pneumonia due to MDR, possible XDR *A. baumannii*. A combination of colistin, amikacin, and ciprofloxacin was used. Ciprofloxacin administration was considered off-label; unjustified. Bacteriological clearance occurred in both patients.

Mean ± SD of treatment duration was 13.56 ± 8.48 days. Duration of treatment of the appropriate prescriptions was determined to be appropriate.

Four children received prolonged ciprofloxacin duration. One patient had chronic mucocutaneous candidiasis. The child had chronic diarrhea and received ciprofloxacin for 81 days. One patient had chronic granulomatous disease and received 98 days of therapy with ciprofloxacin for sensitive Salmonella typhi urinary tract infection and as antibacterial prophylaxis thereafter. One patient had common variable immunodeficiency and received ciprofloxacin for diarrhea for 35 days. Finally, one patient received ciprofloxacin for ventilator-associated pneumonia due to *A. baumannii*. The child received 32 days of treatment guided by clinical course. Regarding treatment indication, all the above cases were considered as off-label; unjustified. That is ciprofloxacin initiation was prescribed based on clinical situation but in the presence of an alternative antibiotic.

Mean ± SD ciprofloxacin dose (mg/kg/day) was 21.25 ± 6.35. Adequacy of dose prescribed was evaluated only in participants in the appropriate indication group. Among 12 children with "appropriate" ciprofloxacin prescriptions, 58% (n = 7) received adequate dose and 41% (n = 5) were underdose, including two children with CF in the latter group.

Among the 12 appropriate prescriptions, ciprofloxacin was prescribed as a part of combination regimen in two children which occurred in documented bacterial meningitis and *Mycobacterium avium* complex pulmonary infection.

Among the "appropriate" prescriptions, ciprofloxacin was administered empirically in five and microbiologically documented in seven patients, in which, *Pseudomonas aeruginosa* was the most common pathogen for which ciprofloxacin had been prescribed. Susceptibility of pathogens for which ciprofloxacin was prescribed appropriately comprised five MDR, possible XDR organisms. Susceptibility pattern could not be determined for two of the pathogens.

Two patients developed generalized erythematous rash on days 4 and 8 of therapy, which resolved after cessation of ciprofloxacin. The drug was not re-challenged. No case of arthropathy was observed during hospitalization, based on patients' or their caregivers' reports or in some patients by physical examination performed by physician. It should be noted that the short-term monitoring of patients (only during the course of hospitalization) hampered any assessment of musculoskeletal adverse events.

Discussion

In the present study, we assessed ciprofloxacin use mainly in non-CF children with hospital-acquired infections. Results of this study showed that only 37% of children received ciprofloxacin appropriately. Most of the appropriate prescriptions were AAP/FDA-approved indications. Children with Crohn's disease with abdominal abscess and children with infectious bloody diarrhea constituted the off-label; justified therapy subgroup. On the other hand, the unjustified prescriptions mainly occurred in the setting of the presence of a suitable alternative antibiotic for ciprofloxacin.

Yang *et al*. evaluated indication for ciprofloxacin usage in hospitalized children.[10] In corroboration with our results, the study demonstrated that the majority of children were receiving ciprofloxacin in an inappropriate manner. While Yang *et al*'s. definition of inappropriate therapy was the same as our study; definition of appropriate therapy differed with our study. Yang *et al*. considered appropriate therapies as (i) prescriptions that were based on susceptibility testing, in the absence of an appropriate alternative antibiotic; defined as aminoglycoside or colistin or (ii) prescriptions when ciprofloxacin was the only oral therapy available. In addition, the AAP/FDA indications were not addressed in their study.

In contrast to Yang *et al*'s. study, we defined a broader range of appropriate therapies including the AAP/FDA guidelines as well as empiric prescriptions (based on clinical judgment) in the absence of an appropriate alternative antibiotic. We also did not include aminoglycosides as an appropriate alternative antibiotic, which is considering ciprofloxacin use after an aminoglycoside.

In the present study, off-label, justified therapy subgroup, encompassed children with Crohn's disease with abdominal abscess and children with infectious bloody diarrhea. The North American Society for Pediatric

Gastroenterology Hepatology and Nutrition clinical report illustrates fluoroquinolones as an oral treatment option in Crohn's disease.[22] However, it should be emphasized that this report is in agreement with the general principle of ciprofloxacin administration in pediatrics; using this drug when no safe and effective alternative exists.[1,7] Based on this, one patient with Crohn's disease and intra-abdominal abscess taking oral ciprofloxacin was determined to have received it as "unjustified," since there was an alternative.

In the present work, empiric therapy of a bloody infectious diarrhea, when no pathogens were isolated, was considered an off-label; justified use. Justification was based on the WHO recommendation: ciprofloxacin being the drug of choice for all patients with bloody diarrhea, irrespective of age.[21]

Regarding *A. baumannii* infection, the choice of combination antibiotic therapy in children for this MDR organism and outcome using ciprofloxacin remains to be elucidated in further studies.

Unfortunately, only 41% of appropriate prescriptions were in adequate dose. Similarly, Yang *et al*'s. study showed that 39.1% of children in whom ciprofloxacin was prescribed appropriately received incorrect dose.[10] Our results showed that children with CF are vulnerable groups to receive insufficient dose. This might be due to unawareness of health-care professionals regarding recommended higher doses of ciprofloxacin in these patients.[19,20] It has been illustrated that suboptimal dosing of ciprofloxacin may be associated with decreased susceptibility of *P. aeruginosa* in CF patients.[19,20]

In this study, we rated the appropriate use of ciprofloxacin as either monotherapy or combination therapy. It should be noted that appropriate use of ciprofloxacin could occur in both settings.

In the present study, arthropathy was not seen. Although it has been illustrated that arthropathy is not dose or duration dependent,[23] mostly a longer follow-up is required to detect this side effect.[2]

Results of the present study underscore the need for antimicrobial stewardship program (ASP) on ciprofloxacin use in pediatric hospitals. Advantage of ASP in the adult setting includes reducing errors in antibiotic selection, dosing, and enhancing adherence to guidelines.[24,25] In particular, pediatric ASP has demonstrated decreased antibiotic utilization, cost, and prescription errors.[24,26] However, decreased development of bacterial resistance has not been elucidated.[26] Regarding pediatric ASPs evaluating antibiotic utilization, days of therapy/1000 patients was the main metrics assessed, while antibiotic selection patterns, de-escalation, and adherence to guidelines are also important aspects that should be evaluated.[26]

The limitations of the current work include the short duration of observation for detecting musculoskeletal adverse events, reliance on patients' or caregivers' self-reports and in some children, reliance on physical examination performed by the treating physician to detect this side effect, which was not applicable in all patients. Besides, there was no predefined checklist for evaluation of potential short-term adverse effects associated with ciprofloxacin including peripheral neuropathy, drug–drug interactions, and QT prolongation.

The majority of children were receiving ciprofloxacin off-label and inappropriately. This issue emphasizes that ASP on ciprofloxacin use in pediatric hospitals should be implemented. Further studies evaluating clinical and microbiological outcomes including antibiotic selection patterns, adherence to evidence-based guidelines, and antibiotic resistance with such ciprofloxacin ASPs in children are needed.

Authors' Contribution

Toktam Faghihi contributed in concept, designed the study, interpreted the data, carried out statistical analysis, drafted and revised the manuscript. Leila Yavari Tekmehdash selected patients, obtained and interpreted data. Mania Radfar contributed in concept and revised the manuscript. Kheirollah Gholami contributed in concept and supervised the study.

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Conflicts of interest

There are no conflicts of interest.

References

1. Bradley JS, Jackson MA, Committee on Infectious Diseases. American Academy of Pediatrics. The use of systemic and topical fluoroquinolones. Pediatrics 2011;128:e1034-45.
2. Bradley JS, Kauffman RE, Balis DA, Duffy CM, Gerbino PG, Maldonado SD, *et al*. Assessment of musculoskeletal toxicity 5 years after therapy with levofloxacin. Pediatrics 2014;134:e146-53.
3. Schaad UB. Will fluoroquinolones ever be recommended for common infections in children? Pediatr Infect Dis J 2007;26:865-7.
4. Forsythe CT, Ernst ME. Do fluoroquinolones commonly cause arthropathy in children? Can J Emerg Med 2007;9:459-62.
5. Grady R. Safety profile of quinolone antibiotics in the pediatric population. Pediatr Infect Dis J 2003;22:1128-32.
6. Nydert P, Lindemalm S, Nemeth A. Off-label drug use evaluation in paediatrics – Applied to ciprofloxacin when used as treatment of cholangitis. Pharmacoepidemiol Drug Saf 2011;20:393-8.

7. Committee on Infectious Diseases. The use of systemic fluoroquinolones. Pediatrics 2006;118:1287-92.
8. Kaguelidou F, Turner MA, Choonara I, Jacqz-Aigrain E. Ciprofloxacin use in neonates: A systematic review of the literature. Pediatr Infect Dis J 2011;30:e29-37.
9. Sung L, Manji A, Beyene J, Dupuis LL, Alexander S, Phillips R, *et al.* Fluoroquinolones in children with fever and neutropenia: A systematic review of prospective trials. Pediatr Infect Dis J 2012;31:431-5.
10. Yang ZT, Zahar JR, Méchaï F, Postaire M, Blanot S, Balfagon-Viel S, *et al.* Current ciprofloxacin usage in children hospitalized in a referral hospital in Paris. BMC Infect Dis 2013;13:245.
11. Sideri G, Kafetzis DA, Vouloumanou EK, Papadatos JH, Papadimitriou M, Falagas ME, *et al.* Ciprofloxacin in critically ill children. Anaesth Intensive Care 2011;39:635-9.
12. EMEA. Guideline on Conduct of Pharmacovigilance for Medicines used by Paediatric Population. EMEA/CHMP/PhVWP/235910/2005-rev. 1. London; 25 January. Available from: http://www.ema.europa.eu/pdfs/human/phvwp/23591005en.pdf. [Last accessed on 2007 Jan 25].
13. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, *et al.* Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: An international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 2012;18:268-81.
14. Up to date, Topic of: Tigecycline: Pediatric drug information.
15. Up to date, Topic of: Antibiotic studies for the treatment of community-acquired pneumonia in adults.
16. Up to date, Topic of: Tetracyclines.
17. Up to date, Topic of: Chloramphenicol: Pediatric drug information.
18. Up to date, Topic of: Colistin an overview.
19. Stockmann C, Sherwin CM, Zobell JT, Young DC, Waters CD, Spigarelli MG, *et al*. Optimization of anti-pseudomonal antibiotics for cyctic fibrosis pulmonary exacerbations: III. fluoroquinolones. Pediatr Pulmonol 2013;48:211-20.
20. Guillot E, Sermet I, Ferroni A, Chhun S, Pons G, Zahar JR, *et al*. Suboptimal ciprofloxacin dosing as a potential cause of decreased pseudomonas aeruginosa susceptibility in children with cystic fibrosis. Pharmacotherapy 2010;30:1252-58.
21. Kliegman RM, Stanton BF, Geme JW, Schor NF, Behrman RE. Nelson textbook of pediatrics. 19th ed. Philadelphia: Elsevier; 2011. p. 961.
22. Pfefferkorn MD, Marshalleck FE, Saeed SA, Splawski JB, Linden BC, Weston BF. NASPGHAN clinical report on the evaluation and treatment of pediatric patients with internal penetrating crohn disease: Intraabdominal abscess with and without fistula. JPGN 2013;57:394-400.
23. Adefurin A, Sammons H, Jacqz-Aigrain E, Choonara I. Ciprofloxacin safety in pediatrics: A systematic review. Arch Dis Child 2011;96:874-80.
24. Magsarili HK, Girotto JE, Bennett NJ, Nicolau DP. Making a case for pediatric antimicrobial stewardship programs. Pharmacotherapy 2015;35:1026-36.
25. Dellit TH, Owens RC, McGowan JE, 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.
26. Smith MJ, Gerber JS, Hersh A. Inpatient antimicrobial stewardship in pediatrics: A systematic review. J Pediatric Infect Dis Soc 2015;4;e125-e35.