Original Article

Compliance to antibiotic therapy at paediatric out-patient clinic

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Abstract

Background: Poor compliance to antibiotic therapy leads to ineffective treatment. **Objective:** The objective of this study is to assess compliance to oral antibiotic therapy in paediatric patients and factors affecting it. **Methods:** Patients aged less than 18 years, coming to outpatient department, who were prescribed oral antibiotics in last 1 week, were eligible for participation in the study. Compliance to oral antibiotic therapy and factors affecting it were evaluated through verbal interview of their caretakers. **Results:** Out of total of 815 participants in the study, 241 (29.6%) were non-compliant either due to not completing the course [142 (17.4%)] or due to not complying with the frequency [99 (12.2%)]. Causes of incomplete course were adverse effects [28 (19.7%)], poor palatability [30 (21.1%)] and no improvement [84 (59.2%)]. Gender, religion, age, development of child and education or occupational status of caregiver did not affect the compliance. Multivariable logistic regression showed two or more drugs in addition to antibiotic therapy (odds ratio [OR] 1.73; 95% confidence interval [CI] 1.03–2.92); more frequency intake of antibiotic in a day, that is, either twice a day (OR 2.13; 95% CI 1.24–3.66) or thrice a day (OR 3.7; 95% CI 2.18–6.48), was significantly associated with non-compliance. Though syrup formulation and low cost of prescription were associated with better compliance on univariate analysis, they did not have any impact in multivariable logistic regression. **Conclusions:** Restricting use of unnecessary drugs with antibiotic therapy, preferring once-a-day frequency and carefully selecting antibiotic with minimal adverse effects and better palatability improve the compliance to oral antibiotic therapy in paediatric patients.

Keywords: Adherence, caregiver, children, medication

Introduction

Appropriate antibiotic therapy is one of the essential components of treating bacterial infections and reducing mortality. As per the World Health Organization's (WHO) report on world health statistics, in India, approximately 67% of the children under age of 5 years with symptoms of acute respiratory infections (ARIs) were taken to healthcare facility, and of these, 13% received antibiotic therapy.[1] Poor compliance to appropriate antibiotic therapy may lead to delay in recovery or deterioration of patients' health. It may also lead to increased hospital admissions and costs as well as emergence of antibiotic-resistant microorganisms.[2]

Approximately one-third of patients do not complete relatively short-term treatment regimens. Duration, schedule, formulation, palatability, cost and adverse effects of medication may contribute to compliance. Compliance to medications in children varies widely, that is, from 11% to 93%.[3,4]

Understanding on the part of patient and caregiver of the need and importance of following prescribed treatment has

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been identified as an important element in compliance. This takes on a special meaning in the paediatric context, given the unique communication triad (e.g. provider–caregiver–patient).[5] Environmental factors also affect this understanding, including health literacy, education, culture and socioeconomic factors.[3]

Use of antibiotic is rampant as about 52% patients are prescribed antibiotics during the visit to healthcare providers in low-to-middle income countries and it is even more worrisome at public sector where bulk of antibiotics are prescribed. There is paucity of information about antibiotic use in outpatient facilities.[6] In addition to rational antibiotic use, better compliance is also important to improve the outcome. We found various studies on antibiotic prescribing in India, but none of them focused on understanding the compliance toward oral antibiotics therapy.[7-9] This study presents this issue in context of incidence, promoting and hindering factors for compliance to oral antibiotics, and provides general principles to improve compliance in paediatric population.

Methods

Study site: This study was carried out at the paediatrics outpatient department (OPD) of a tertiary care teaching hospital. Paediatric OPD (now referred to as OPD) caters to patients below 18 years of age. Physicians enter the patients' details and prescribe the medications in the online records system. Patients get printed copies of the prescription mentioning the dose, frequency and duration of the medication. In addition to this, pharmacists label the drugs with frequency and dosage manually in local language and explain the prescription to the caregivers. Caregivers are also advised to come back to OPD with medicines which are again cross-checked and caregivers are re-counselled by the prescribing physician. Patients who receive antibiotics are advised for follow-up within 1 week of prescription.

Inclusion criteria: Paediatric patients (<18 years of age) revisiting OPD who had received oral antibiotics within last 1 week were included in the study.

Exclusion criteria: Non-availability of the primary caregiver (i.e. adult person who had looked after and had given medicines to the child at home during the sickness).

Procedure: Physicians seeing patients in OPD were trained to collect the detailed information using structured case record form. Demographic details, diagnosis and detailed prescription of the patient were entered in the form. It included standard set of close, semi-closed and open-ended questionnaire for interaction with primary caretaker to get details about the adherence to oral antibiotic therapy at home and its related factors. Information on dosage, duration and frequency of oral antibiotics received was recorded through subjective measurements obtained by interacting with primary caregivers as well as through objective measurements obtained by counting left-over pills. Non-adherence was considered present when patient did not comply with dose, duration and frequency of the prescribed antibiotic medication. Counselling aspects with regard to prescription were also checked. Details regarding other medicines and adverse effects were recorded.

Statistical analysis: Descriptive analysis was done to depict categorical variables. Logistic regression and Chi-square test were used to assess the association between compliance and various factors. To get the unconfounded effects of various factors on compliance, multivariable logistic regression was performed. *P* value less than 0.05 was deemed as statistically significant. Statistical analysis was performed using Stata 14.2 (StataCorp, College Station, TX, USA).

Ethical considerations: The institutional ethics committee approved the study. Primary caretakers were informed in detail about the study procedure and written informed consent/assent was procured.

Results

A total of 38,039 patients visited paediatric OPD during the study period from December 2016 to September 2018. Of these, 5364 (14.1%) patients were prescribed oral antibiotics. This is almost equivalent to 139 oral antibiotic prescriptions per 1000 OPD visits per year. Out of these 5364 patients, 1064 (19.8%) revisited the paediatric OPD within 1 week of antibiotic prescription and of which 815 participants were included in the study (38 denied for consent, primary caretaker was not available in 85 cases and physicians were not able to evaluate 126 cases due to time constraints). Most common indication for starting antibiotic therapy was ARIs [Table 1]. Most commonly prescribed antibiotics were amoxicillin, amoxicillin-clavulanic acid and azithromycin [Table 2].

From 815 participants, a total of 241 (29.6%) were non-compliant, and from these non-compliant participants, 142 (17.4%) did not complete the course of antibiotics due to various reasons and remaining 99 (12.2%) participants did not comply with the frequency of medication but took the medications for the duration as advised. Out of those 142 participants, 28 (19.7%) participants stopped the antibiotic due to adverse effects, 30 (21.1%) participants discontinued the course of antibiotic

Table 1: Indications of antibiotic therapy

Diagnosis	No. of participants (%)
Acute respiratory infection	554 (67.9)
Fever without focus	118 (14.5)
Abdominal pain	38 (4.7)
Pyoderma	16 (1.9)
Acute otitis media	14 (1.7)
Urinary tract infection	14 (1.7)
Diarrhoea	9 (1.1)
Enteric fever	8 (1)
Other	34 (4.2)

Table 2: List of antibiotics prescribed and their formulations

Name of antibiotic	Syrup [*n* (%)]	Tablet [*n* (%)]
Amoxicillin	60 (17.9)	276 (82.1)
Amoxicillin-clavulanic acid	73 (66.4)	37 (33.6)
Azithromycin	155 (83.3)	31 (16.7)
Cefixime	78 (51.3)	74 (48.7)
Cefpodoxime	11 (61.1)	7 (38.9)
Cefadroxyl	4 (36.4)	7 (63.6)
Erythromycin	0	1 (100)
Metronidazole	1 (100)	0

due to poor palatability and the rest 84 (59.2%) participants stopped the drug prematurely because of no improvement. Out of 28 participants who had adverse effect, 27 (96.4%) participants were prescribed amoxicillin/clavulanic acid and only one was prescribed azithromycin ($P = 0.01$ by Fisher's exact test). Of 30 participants who stopped because of poor palatability, 23 (76.7%) were prescribed tablets and 7 (23.3%) were prescribed syrup. Out of 433 participants who received tablet form, 23 (5.3%) stopped due to poor palatability, and out of 382 participants who received syrup formulation, 7 (1.8%) stopped due to poor palatability ($P = 0.009$ by Fisher's exact test).

Compliance was assessed in relation to gender, religion, age, development of a child, primary caretaker, education of caretaker, experience of taking oral medications in past, difficulty in giving medications, total drugs to be given in 1 day, type of formulation, frequency in a day, cost of medication and counselling by the pharmacist or physician [Table 3]. To get the unconfounded effects of various factors in compliance, multivariable logistic regression was done as shown in Table 4. As there were only 10 participants in the cost group of more than 300 Indian rupees (INR), it was merged with the group of cost >200 INR. We analysed number of drugs, frequency of antibiotic in a day, cost and type of formulation in a multivariable analysis as they were found to be associated with compliance in univariate analysis. The coefficient of determination (R^2) was 0.0587. We did not include past history of consumption of medication in the multivariable analysis as we considered it as clinically not important. Value 1 was given for noncompliance during the analysis. We found twice a day or thrice a day frequency of the antibiotic and two or more drugs prescribed in addition to antibiotic decreased compliance to a significant level.

Discussion

Poor compliance to appropriate antibiotic therapy leads to ineffective management.[2] Evidence of compliance to oral antibiotic therapy in children of Indian population is evolving. This study presents the issue in context of incidence, promoting and hindering factors for compliance to oral antibiotics and provides general principles to improve compliance in paediatric population.

Number of antibiotic prescription varies in OPD at different places.[10] During the year 2014, the OPD prescriptions of antibiotic for the US population less than 20 years of age as reported by CDC were 778 per 1000 persons per year, and for the year 2016, it was 790.[11,12] This represents that the overall use of antibiotics at our set-up is quiet low as compared to the US figures.

Usage of antibiotic is highly prevalent in all sectors. In a study from Delhi, 39% of the patients attending private retail pharmacies and public facilities and 43% of patients of all age groups visiting private clinics were prescribed at least one antibiotic, which is very high as compared to 14.1% at our set-up for paediatric patients, while in a study from Vellore from health facilities such as private hospitals, private general practitioner clinics and pharmacy shops found 40.9% antibiotic encounters from 52,788 patients observed.[7,8] In a study conducted at a non-governmental organization from Bathalapalli, a rural area from Andhra Pradesh, India, overall, 12.5% of outpatients received antibiotics. But if we assess based on causes, nearly 83% of diarrhoea and 52% of the upper respiratory tract infection patients received antibiotics.[9]

In the current study, there was no impact of gender or religion on compliance to oral antibiotic therapy. The relationship of sex and religion with adherence is inconsistent in the literature, with many studies showing no association.[13-17]

It was observed in the current study that compliance was not affected by the age of the participant. McQuaid *et al*.[18] studied the correlation between adolescent age and its impact on medication adherence in asthmatic patients aged 8–16 years and found that age was associated with increased knowledge of the disease but not with improved adherence. No association was found between adherence and knowledge, reasoning or responsibility for asthma management. Llor *et al*.[19] conducted a prospective observational study in 5 general medicine outpatient clinics in Catalonia, Spain, in 481 patients aged 18 years or older, presenting to the primary care practice with uncomplicated, acute (<7 days), suspected bacterial pharyngitis and lower respiratory tract infections and found no correlation of age with adherence to antibiotic therapy and adherence was better with once daily (OD) and short course regimen.

The current study shows that the level of education of caregiver did not have any impact on the compliance to antibiotic therapy. Jimmy *et al*.[20] found that none of the common demographic factors such as age, marital status, living alone, sex, race, income, occupation, number of dependents, intelligence, level of education or type of personality were related to non-compliance. As most of the participants were literate, we were not able to study the impact of illiteracy on compliance.

As most of the participants were counselled by either pharmacist or doctor, we were not able to study the impact of no counselling with regard to dose, frequency and duration of the medication.

Table 3: Compliance in relation with various factors

Factors	Compliant (%)	Non-compliant (%)	*P*
Gender			
Male	366 (71.3)	147 (28.7)	0.455
Female	208 (68.8)	94 (31.2)	
Religion			
Hindu	511 (69.8)	221 (30.2)	0.415
Muslim	42 (73.7)	15 (26.3)	
Other (Christian, Sikh)	21 (80.8)	5 (19.2)	
Age (*n*=652)			
<2 months	5 (55.6)	4 (44.4)	0.804
2-12 months	117 (71.3)	47 (28.7)	
1-5 years	235 (69.9)	101 (30.1)	
5-10 years	61 (69.3)	27 (30.7)	
>10 years	41 (74.5)	14 (24.5)	
Development			
Normal	555 (70.8)	229 (29.2)	0.548
Delayed	19 (61.3)	12 (38.7)	
Caregiver stayed with the child whole day			
Yes	552 (70.6)	230 (29.4)	0.628
No	22 (66.7)	11 (33.3)	
Education of caregiver (*n*=801)			
Primary	39 (73.6)	14 (26.4)	0.533
Secondary	205 (70.5)	86 (29.5)	
Higher secondary	174 (68.2)	81 (31.8)	
Graduate	150 (74.3)	52 (25.7)	
Consumed medicines in past			
Yes	195 (75.3)	64 (24.7)	0.038
No	379 (68.2)	177 (31.8)	
Difficulty in giving medicine to child			
Yes	380 (69.2)	169 (30.8)	0.276
No	194 (72.9)	72 (27.1)	
Total drugs prescribed			
1	183 (77.2)	54 (22.8)	0.019
2	321 (68.3)	149 (31.7)	
≥3	70 (64.8)	38 (35.2)	
Formulation of drug			
Syrup	300 (78.5)	82 (21.5)	< 0.001
Tablet	274 (63.3)	159 (36.7)	
Frequency of drug in a day			
Once a day	166 (86.5)	26 (13.5)	<0.001
Twice a day	221 (73.4)	80 (26.6)	
Thrice a day	187 (58.1)	135 (41.9)	
Cost of therapy (Indian rupees)			
≤100	425 (71.1)	173 (28.9)	0.002
101-200	104 (68)	49 (32)	
201-300	43 (79.6)	11 (20.4)	
>300	2 (20)	8 (80)	
Counselling about the prescription			
By both pharmacist and physician	364 (69.6)	159 (30.4)	NA
By either pharmacist or physician	208 (72)	81 (28)	
None	2 (66.7)	1 (33.3)	

Sanii *et al*.[21] did a randomized study in 154 patients between the age 18 and 65 years and divided them in the intervention group who received pharmacist counselling and necessary education about their prescribed medications at discharge and control group who did not receive such counselling. It showed that medication adherence was significantly high (93.2%) in intervention group as compared to control group (50.3%). This shows that pharmacists may play an influential role in patient adherence.

In the current study, it was observed that when two or more drugs were prescribed with antibiotic, the compliance reduced, while Munoz *et al*.[22] from Spain studied the effect of an educational intervention to improve patient antibiotic adherence during dispensing in a community pharmacy which showed that there was no association between the number of drugs prescribed and the compliance.

There was no difference in compliance with syrup as compared to tablet form in the logistic regression. However, we noticed that

Table 4: Multivariable logistic regression for non-compliance

	OR	CI (95%)		*P*
		Lower	Upper	
Number of different drugs in a day				
1 (Only antibiotic)	1			
2 (One more drug in addition to antibiotic)	1.35	0.93	1.96	0.11
≥3 (Two or more drugs in addition to antibiotic)	1.73	1.03	2.92	0.03
Frequency of antibiotic in a day				
Once a day	1			
Twice a day	2.13	1.24	3.66	0.006
Thrice a day	3.7	2.18	6.48	<0.001
Cost of antibiotic				
INR 1-100	1			
INR 101-200	0.89	0.59	1.34	0.57
>INR 200	1.27	0.66	2.43	0.46
Tablet versus syrup				
Syrup	1			
Tablet	1.34	0.89	2.01	0.15

OR=odds ratio; CI=confidence interval

more patients stopped the antibiotic prematurely because of poor palatability with tablet form as compared to syrup formulation. Ellerbeck *et al*.[23] studied the effect of antibiotic formulations on compliance in 400 children, aged 2 months to 5 years. All of the caregivers adhered to the prescription on the first day of therapy, but by the fourth day, 82% of those who received syrup were still taking their medication compared to 71% and 55% of those receiving sachets and tablets, respectively ($P < 0.01$). Thus, the use of simplified regimens of age-appropriate delivery mechanisms and better taste may enhance the ability of paediatric patients to adhere to their drug therapy.[24]

Pharmacokinetics and pharmacodynamics of medications should be evaluated in paediatrics population as they direct the frequency and dosing. The current study shows that compliance is best with once-a-day dosing. Kardas *et al*.[25] in Poland concluded that once-daily dosage provides significantly better compliance with antibiotic therapy of respiratory tract infection than twice-daily dosage. Of 501 patients studied, 81.2% showed full compliance. Frequency of antibiotic dosage was the only factor affecting antibiotic compliance on logistic regression (odds ratio = 21.4; 95% confidence interval 8.2–55.7). With OD dosage, 97.6% of patients complied, whereas with twice-daily (BID) dosage, only 64.9% complied ($P < 0.001$). Llor *et al*.[26] assessed the drug compliance among patients with lower respiratory tract infection treated with OD, BID and thrice-daily (TID) antibiotic regimens. A total of 251 patients were enrolled (136 in the TID group, 70 in the BID group and 45 in the OD group). It was observed that the rate of compliance was very low, mainly when antibiotics were administered TID in regimens of 7 days or more. A similar study was done to investigate patient compliance with two different dosage regimens. The results showed that the mean compliance with the four times daily (QID) regimen was 67% compared to 85% with the BID regimen. Drug-intake behaviour was more erratic with the QID than the BID regimen.[27] A meta-analysis studied adherence with different schedules and costs with optimal/suboptimal adherence among patients with acute and chronic diseases. It showed that OD schedules were associated with higher adherence and compliance rates. This meta-analysis suggested that reducing dosage frequency from multiple dosing to OD dosing might improve adherence to therapies amongst patients with acute or chronic illnesses.[28]

The overall non-compliance at our paediatric OPD was 29.6% while 17.4% did not finish full course. In a study from rural Malawi, on adherence to oral antibiotics in children diagnosed with pneumonia, it was found high level of non-adherence to oral antibiotics, with 20% of children not finishing full course of antibiotics.[29] Reyes *et al*.[30] analysed factors associated with antibiotic noncompliance among patients suffering ARI and acute diarrhoea (AD) in four primary healthcare clinics in Mexico City through patient interviews and direct observations. Total 222 patients with ARI and 155 with AD were included, which showed 60% and 55.5% non-compliance, respectively. Factors responsible for poor compliance were prolonged illness, complex treatment, three or more doses per day, treatment for more than 7 days, younger age and an inadequate physician–patient relationship.

In the current study, majority of the participants, who stopped the drug early because of adverse effects, were prescribed amoxicillin containing preparation. As majority of the prescriptions were for respiratory tract infections, azithromycin may be considered to be an alternative antibiotic. In a systematic review on azithromycin for acute lower respiratory tract infections, there was unclear evidence that azithromycin was superior to amoxicillin but adverse events were lesser in azithromycin group.[31] Another factor that may help is OD frequency of azithromycin as compared to BID/TID for amoxicillin and this may further augment the adherence which needs to be studied further. Usually, azithromycin is also prescribed for a shorter duration, that is, 3 or 5 days. Shorter

courses of antibiotics in children for community-acquired pneumonia have been found to provide comparable results with lesser side effects.[32,33] In a study from Zambia, trained community health workers prescribed oral amoxicillin for pneumonia in children, Graham *et al*.[34] found that 46% were fully adherent to the antibiotic therapy and reasons of non-adherent were forgetfulness and cure.

This topic is of interest not only for paediatricians but also for primary care physicians, as they are the first level of contact for the community and antibiotics are one of the commonest drugs prescribed. Its use is alarmingly high in primary care settings in India.[35] In addition to rational use of antibiotics, appropriate understanding of factors which improve compliance would change the pattern of antibiotic prescribing.

To summarize, for improving compliance, healthcare providers should restrict the use of supportive medications to barely minimal essential ones with antibiotics. Appropriately selected antibiotics which can be given in lesser frequencies also improve the compliance.

This study adds to the existing knowledge that lesser number of supportive medications and antibiotics with once-a-day frequency improves compliance, while type of formulation, age, gender, level of education of caregiver, difficulty in giving medicine and stay of caregiver with the child at home had no impact on compliance to antibiotics; however, using syrup formulation may reduce incomplete course.

Conclusions

To highlight, minimal use of supportive medications with oral antibiotic therapy and keeping the frequency intake of oral antibiotic therapy to once or to a maximum twice a day improve the compliance to antibiotic therapy in paediatric population. The evidence needs to be strengthened further by controlled trials to study compliance with different formulations and duration of antibiotic therapy.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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