Review

Patient compliance with antibiotic treatment for respiratory tract infections

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Despite doctors’ expectations, non-compliance is common in short-term antibiotic therapy of respiratory tract infections (RTIs). This phenomenon has profound practical implications. It leads to ineffective management, the deterioration of patients’ health, hospital admissions, additional costs and the emergence of antibiotic-resistant microorganisms. This article reviews methods of measuring compliance with antibiotics in the outpatient-based management of RTIs and research results. Causes of non-compliance are also discussed. Factors influencing compliance are analysed, as well as practical strategies for addressing non-compliance with antibiotic therapies for RTIs. The influence of the frequency of doses on compliance is particularly stressed, as it has been observed that once daily dosing has almost a 100% compliance rate. As a number of once-daily antibiotic preparations are available now, the possibility of using once-daily schedules for improving compliance in RTI cases is stressed.

Introduction

Non-compliance is defined as any deviation by a patient from a doctor’s instructions. Non-compliance with medications is particularly important in clinical practice. This form of non-compliance has been found to be associated with treatment failure and all its consequences, namely: deterioration of patients’ health, the need for additional consultations, the use of extra drugs, additional hospital admissions and increases in direct and indirect costs of management.1–3

Treatment failure can certainly be a result of other factors; non-compliance is an important but not an exclusive cause. In the case of antibiotic therapy, the right choice of medication, taking into account the pathogen’s susceptibilities, and appropriate dosage are especially important. There is, however, a strong causal relationship between compliance with doctors’ instructions and the results of the treatment. For instance, it was noted that, among children with recurrent urinary tract infections (UTIs), compliance had a significant influence on the frequency of recurrence. In compliant children there were on average 3.0 episodes per year, in partially compliant children there were 4.8 episodes per year and in the completely non-compliant group 7.2 episodes of UTIs per year.4

Non-compliance with medication is frequently perceived as occurring exclusively in chronic conditions. Although doctors dealing with chronic conditions were not always aware of the frequency of this problem,5 they were likely to suspect some patients treated for asymptomatic chronic conditions, such as hypertension or hyperlipidaemia, of partial non-compliance. In cases of acute respiratory tract infections (RTIs) with troublesome symptoms, such as cough, fever, aches and malaise, this issue seems to be less obvious. Such patients are certainly motivated and should be compliant. Doctors unexpectedly found non-compliance in these cases, and were unable to predict accurately which patients were likely to be compliant or not.6,7 Even in cases of acute infection, a significant percentage of patients are not fully compliant with such basic medications, including antibiotics.

In this article, methods of measuring compliance and the results obtained for antibiotic treatment of RTIs are reviewed. Causes of non-compliance with antibiotic therapy are also discussed. Contributing factors to this phenomenon are analysed. The influence of the frequency of doses is particularly stressed, as this is an easily modifiable factor that greatly affects patient compliance. Lastly, the methods of improving compliance in cases of RTIs in outpatients are discussed.

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Methods of measuring patient compliance

Different methods of measuring compliance have been developed and used in numerous studies. In early studies of compliance, direct interviews, telephone interviews and surveys were used. Later, it was found that these forms of research reveal only a proportion of cases of non-compliance. For example, among patients treated for Chlamydia trachomatis, 90% said that they were taking doxycycline according to the instructions. Objective electronic testing indicated that in fact only 16% were fully compliant.8

One of the most common mistakes made by patients is the unintentional omission of single doses. It is a particularly frequent mistake during a short treatment period, such as occurs in antibiotic therapy for RTIs. As patients are unaware of the mistake, they cannot notify the researcher about them. Moreover, patients eager to fulfill their doctors’ expectations consciously overestimate their degree of compliance in their reports. These factors cause falsely high compliance results when they are measured by interviews or surveys.

An important development in the research methods for compliance was the introduction of objective measuring methods. The simplest and most widely available method is to count the remaining tablets. This method has been used commonly in clinical studies. However, it has not escaped criticism. Patients aware of the purpose of tablet counting either ‘forget’ to bring them along for consultations or remove unused tablets before the visit. This may lead to false results. In a study investigating compliance in children with antibiotic therapy, Rodewald & Pichichero,9 found that, compared with the test. Since the test is qualitative it will not detect missedcompliance. Nevertheless, tablet counting is the simplest of objective methods of compliance assessment and, as such, is still used in clinical research. Its reliability can be enhanced by counting tablets during an unannounced visit at the patient’s home, rather than in the doctor’s surgery.

The presence of drug in body fluids can also be tested to determine medication intake. The presence of antibiotics, in particular, can be detected in urine through a simple and inexpensive biological test. A positive result does not, however, give information on compliance within the whole of the treatment time, but only for a relatively short period of time before the test. Since the test is qualitative it will not detect missed doses in a regimen that has multiple doses per day. It is well known from many studies that the degree of compliance increases shortly before the planned visit to the doctor’s office.10 Therefore, this method provides little information about genuine compliance, but in the case of antibiotic therapy is a proof of its continuation. Because of its simplicity it is still used in clinical trials.

Since their introduction in 1986, microelectronic devices have become the ‘gold standard’ in compliance research.11–13 The most commonly used system is MEMS (Medication Event Monitoring System; Aprex, Union City, CA, USA) and its newer version eDEM (Electronic Drug Exposure Monitor; AARDEX, Switzerland and Union City, CA, USA). It consists of a standard container for tablets with a ‘screw on’ top, inside which the electronic microcircuit is placed. This device records when the container with medication is opened. Assuming that medication is taken on these occasions, compliance can be measured accurately. Comparison studies indicate that this electronic measurement gives the most accurate insight into patient compliance. For example, in the case of patients taking isoniazid for tuberculosis prophylaxis, tablet counting and urine testing overestimated compliance compared with results obtained with MEMS.14

The introduction of electronic devices has enabled the precise quantitative estimation of compliance. For the first time, it has also provided detailed insight into the times that doses were taken, which can then be compared with the prescribed regimen. In the majority of clinical situations, particularly in the case of antibiotic therapy, the time interval between doses is extremely important. In most cases, because of the pharmacokinetics of the drugs, doses should not be taken later than indicated to ensure maximum therapeutic action. A prolonged time interval between doses has been found to lead not only to reduced effectiveness, but also to the emergence of antibiotic-resistant pathogens.15,16

Causes of non-compliance during antibiotic treatment

Antibiotic treatment on an outpatient basis is usually as short-term therapy. During its course, patients tend to make different mistakes than during treatment of chronic conditions (Table 1). The most common mistake is the omission of single doses of antibiotics. With the use of electronic devices for compliance assessment, Favre et al.17 documented other characteristic types of behaviour among patients. For example, some patients take additional doses of antibiotics, especially at the beginning of the treatment. This may be associated with severity of the symptoms and the patients’ desire to get better promptly. A premature halt in taking medication is also characteristic in antibiotic treatment. One reason behind it could be symptomatic relief occurring before the recommended treatment time elapsed, especially in cases of milder infections.18–20 Another reason could be the occurrence of adverse effects, which force patients to stop therapy. A pan-European survey showed that patients expect clinical improvement after 3 days of antibiotic treatment. This belief may cause non-compliance with therapy.21 Large and difficult-to-swallow pills or the unpleasant flavour of a suspension may also lead to non-compliance.1

Another type of mistake is caused by changes to the dosing regimen. Some patients decrease the frequency of their doses,
for example twice a day instead of three times a day. It may be related to the fact that patients still working, while unwell, may have difficulties with taking medication during work hours. Difficulties in adjusting the dosing regimen to a patient’s lifestyle may also influence changing the time intervals between doses from every 8 or 12 hours to an asymmetrical regimen with a prolonged interval in the daytime (for example up to 16 hours) and shortened at night, or the reverse.17

Some patients who are prescribed antibiotics do not file the prescription with a pharmacist. If the patient has to pay for the medicine partially or completely out of their own pocket, economic issues should be taken into account. This is medicine partially or completely out of their own pocket, prescription with a pharmacist. If the patient has to pay for the prescription, or many patients do not buy or use medicines. Some people believe that antibiotics may be harmful to the gastrointestinal tract or the immune system. Some patients want to see whether the infection resolves without treatment, and so delay the start of the therapy. In the case of antibiotic treatment, as with other therapies, conscious omission of single doses of the medication takes place. The reasons frequently given by patients include fear of interactions with alcohol or other medications.

Factors influencing compliance

A large, country-wide German study recently assessed compliance rates among children treated with antibiotics for various infections.22 A urine test confirmed the presence of antibiotic in 69.5% patients. Although the study involved 584 patients, its results should not be treated as universally applicable to antibiotic treatment for RTIs. Compliance depends on many factors, and in different studies different values of compliance are obtained.

A major factor influencing compliance is the frequency of doses. Numerous studies show that the less frequent the doses, the higher the compliance. A review of over 100 studies by Greenberg5 published in 1984, i.e. before the era of electronic measurement, confirmed this tendency. The average compliance was 73% for once daily (od) regimens, 70% for twice daily (bd), 52% for thrice daily (tds) and 42% for four times a day regimens (qds). The difference between compliance with od and bd regimens was not significant, but more frequent dosing was associated with significantly worse compliance rates.

A literature review performed recently by Claxton et al.13 took into account only the studies that used electronic devices for compliance measurement. The 76 publications available to date were analysed. Compliance decreased with increased complexity of regimen and was 79% ± 14% for od dosing, 69% ± 15% for bd dosing, 65% ± 16% for tds dosing and 51% ± 20% for qds dosing. The difference in compliance between od and bd dosing was not statistically significant.

The highest compliance during antibiotic therapy is also associated with od dosing; with more frequent dosing compliance decreases.23 However, compliance rates observed in antibiotic treatment of RTIs tends to be much better than those observed with other medications. In the case of an od antibiotic regimen, compliance reaches values approaching 100%. For example, compliance was 97% with an od regimen of azithromycin24 and 98% with od cefitbuten.25

More frequent dosing is generally associated with worse compliance in antibiotic therapy. In a study conducted by Cockburn et al.,7 where patients were randomly prescribed antibiotics with the dosage in the range 1–3 doses per day, increasing complexity of the regimen significantly decreased the probability that the patient would not miss any doses of the course. Cook et al.26 showed that, for bd and tds co-amoxiclav, the compliance rate was 90% and 87%, respectively. During a 5 day treatment for RTIs, at least one dose was missed by 34% of patients in a bd regimen, and by 76.5% of patients taking the medication three times a day.25 Electronic measurement revealed that 70% of patients taking trimethoprim twice daily for RTI therapy were fully compliant, compared with only 39% of patients taking cefalexin four times a day.27 When antibiotic suspensions for children were given twice daily, compliance was higher than with thrice daily regimens.28,29 Of the patients taking antibiotics four times a day for a 5 day therapy, none took all of the recommended doses.30 Based on the data collected for short-term antibiotic therapy, Cockburn et al.31 found that increasing the number of doses to be taken daily by one increased the probability of a patient being non-compliant by 72%. These results are in agreement with patients’ beliefs; patients expressed interest in once-daily antibiotic dosing in a large pan-European survey.21

Compliance depends also on the length of treatment. This general rule is confirmed in antibiotic therapy for RTIs. Better compliance was observed for regimens shorter than 7 days duration compared with longer ones.20,22 In a study assessing compliance during treatment with penicillin for streptococcal infections, for example, compliance was 95% for 5 days, but only 70% for 14 days.23
infections by tablet count, on the third day of treatment 44% of children were fully compliant, on the sixth day 29% and on the ninth day only 18%. In another study of children taking oral penicillin for β-haemolytic streptococcal infection, 81% of patients were taking the antibiotic on the fifth day, but only 56% on the ninth day.6 Similar results were achieved by Schrag et al.,31 who studied children aged 6–59 months treated for pneumococcal infection with amoxicillin 90 mg/kg/day for 5 days or with 40 mg/kg/day for 10 days. Compliance was measured by the amount of remaining antibiotic suspension. Compliance in this study was significantly better for the shorter therapy (82%) compared with the longer one (74%). Among children receiving antibiotic for the longer period, compliance was significantly higher (79%) for days 0–5 compared with days 6–10 (57%).

There are other factors influencing compliance associated with the convenience of therapy. Ellerbeck et al.34 investigated the relationship between compliance and the form of medication in children (aged between 2 months and 5 years) given for pneumonia. By the fourth day, 82% of patients taking a syrup continued to take their antibiotics, compared with 71% and 55% of patients who took their medication in the form of sachets and tablets, respectively. Compliance was significantly associated with the parents’ impression of the ease or difficulty of administering the drug.

In some studies the influence of other factors on compliance has been noticed. Compliance was higher if the infection was localized to the lower respiratory tract25,30 or the patients thought that they had a severe disease.6,30,31 It has also been observed that compliance depended on the length of time for which the general practitioner (GP) had been practising; patients treated by younger doctors being significantly more compliant.31 In another study, it was found that compliance in the case of children taking penicillin was higher if the GP had been looking after that family for no more than 4 years.6 On the other hand, non-compliance is associated with poor communication between doctor and patient. It was shown that compliance with antibiotic therapy improved if the patient thought that he knew the prescribing doctor well.35 In a study performed in Mexico, Reyes et al.20 showed that patients were more likely to be non-compliant if they did not know the name of the prescriber.

Despite doctors’ expectations, numerous studies have shown that compliance did not depend on patients’ age, gender, marital status, education, income or social class.5,13 Similar findings were discovered in the case of antibiotic therapy, where again compliance did not depend on patients’ gender, marital status or education.5,25,27,30,36 Likewise, the degree of non-compliance during antibiotic therapy was not related to the cost of the medication to the patient or to whether or not the medication was free of charge.20

Mistakes involving the administration of antibiotics at times other than those recommended are common. In a survey conducted by Dawson & Newell,37 only seven of 75 parents giving antibiotics to their children reported that they were fully compliant with the recommended administration times. The introduction of electronic devices has enabled the precise estimation of administration times. Favre et al.17 studied compliance of 68 patients taking antibiotics twice a day for acute infections. The number of times when the MEMS container was opened (‘taking compliance’) was nearly perfect (99.6%). On the other hand, compliance with administration times (‘timing compliance’) was much poorer. Only 32.6% doses were taken within 12 ± 1 h of the previous dose. A review of the studies using the electronic compliance measurement showed that the frequency of doses significantly affects compliance with the correct intervals between doses: the more frequent the doses, the less precise the compliance. The mean dose-timing compliance was 74% for an od regimen, 58% for bd, 46% for tds and 40% for qds regimens, respectively.13

**Methods of improving compliance**

One conclusion from the above is that compliance depends on many different factors, and doctors may influence some of them. As compliance is far from perfect in real-life conditions, doctors should take an opportunity to improve compliance among patients treated with antibiotics for RTIs (Table 2).

In the case of antibiotic treatment for RTIs, the patient is not expected to have detailed knowledge about the disease process and management. For cure, simple measures such as taking medication according to instructions, decreased physical activity and/or bed rest are enough. That is why the patient’s education does not seem to have primary importance in such conditions. Nevertheless, to ensure maximum compliance, the patient should receive information from the doctor about possible adverse effects and their influence on continuing the treatment. In order to enhance the patient’s understanding, directions should be simple, given in straightforward language and always accompanied by a written version.

| Table 2. Factors influencing compliance among patients treated with antibiotics for RTIs |
|-------------------------------------|-------------------------------------|
| Patient’s education                | Appropriate form and content of doctor’s instructions |
| Low price of antibiotics           | Short-term therapy                  |
| Infrequent doses                   | Convenient and acceptable form of the antibiotic for the patient |
| Easy-to-use packaging              | Lack of adverse effects             |
| Reminders                          | Commitments                        |

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While the low price of a medication does not guarantee that the patient is going to buy it, it does remove a possible obstacle for compliance. There are, however, situations when it is worthwhile to encourage the patient to purchase a more expensive medicine. The cost of an antibiotic is only a small part of the general costs associated with antibiotic treatment. The choice of an antibiotic that ensures good compliance may reduce the direct and indirect costs of the therapy.38 For the patient, the benefits can be an earlier return to full health and work. In the case of prescribing expensive antibiotics, the doctor should ask the patient as to affordability; even the best antibiotic will not work if it is not purchased. The influence of the length of therapy on compliance has been mentioned earlier: the shorter the treatment, the higher the compliance. Newer antibiotics and revised treatment regimens increase the chance for a shorter therapy and consequently for better compliance and better treatment results.33

A factor particularly influencing compliance for drugs in general is the frequency of doses. This relationship is also confirmed in the case of antibiotic treatment. Optimum compliance can be achieved by using once daily antibiotic dosage. It has been suggested that, because of patients’ natural tendency to skip single doses of medications, twice daily dosing may be more beneficial in maintaining continuity of antibiotic action.18 However, these observations were based on studies of chronic conditions such as hypertension, when even with a once daily dosage, a significant number of patients were not compliant. The recent introduction of once daily antibiotic formulations has enabled assessment of the influence of this type of regimen on compliance during short-term antibiotic therapy. Results indicate that almost 100% of patients are fully compliant with once daily antibiotic regimens.24,25 Therefore, wherever possible, the use of a once daily regimen seems fully justified. An additional argument for using antibiotics once daily is that some newer antibiotics, for example azithromycin, are active for much longer than 24 h after a single dose.39 They are called ‘forgiving’ drugs, because they continue to be effective, despite delay in taking a dose or even missing single doses.40,41

Pharmaceutical companies are well aware of the importance of dosage frequency and have, in recent years, introduced a number of oral antibiotics that can be taken no more than twice a day. In the case of older antibiotics, for example cefaclor, which because of its pharmacokinetics should be taken three times a day, slow release preparations have been introduced with the advantage of bd dosing. To maximize compliance, even antibiotics that can be taken twice a day are being changed to once daily forms. An example is clarithromycin.42 Nowadays, doctors can choose from a variety of once a day forms of antibiotics from different therapeutic groups.

A convenient and acceptable form of medicine for the patient is a factor that positively affects compliance in any situation. It should be remembered that, in the case of oral antibiotic therapy, large and difficult-to-swallow tablets could be a genuine obstacle and discourage patients from taking their medications. For children, the taste of antibiotic syrup is an important factor.1 Therefore, if doctors have the opportunity to choose the most acceptable form of a medication for their patients, they should take it.

The form of packaging of the medication is a rarely mentioned factor influencing compliance. However, if one takes into account the fact that 10% of patients admitted to geriatric wards experienced difficulties with opening at least one of the types of widely available drug packaging, this issue is quite important. The commonly used type of blister packaging should not cause patients serious difficulties. However, antibiotics in child-safe containers can trouble the elderly and people with poor dexterity. In these cases, replacement packaging should be advised.

The choice of antibiotics with a good safety profile, free of frequent or serious side effects, is another step that can be taken to make the therapy more ‘user friendly’, and so lead to better compliance.

One of the most common forms of non-compliance during the antibiotic treatment of respiratory infections is the unintentional omission of single doses. There are some actions that can be taken to prevent this happening. One recommended method is to combine taking the medication with one of the patient’s usual daily activities. In particular, antibiotics can be taken with meals or with morning and evening toothbrushing. Even simple reminders such as a clock printed on the prescription label with appropriate medication times, or bright stickers to be posted at home, increase compliance.44

Putnam et al.45 have presented interesting results regarding the influence of psychological mechanisms on compliance. The study involved 60 patients taking antibiotics for 10 days for various infections. The control group participated in activities of the same length and structure as the experimental group, but not in relation to the issue of compliance. The experimental group participated in classes related to compliance, reinforcing the ineffectiveness of other treatment methods and the value of antibiotic treatment. Next, they prepared a plan aimed at helping them to remember to take their medication. They also made verbal and written commitment to adhere to the antibiotic regimen. The adherence, measured by unannounced pill counts, was significantly higher for the experimental group. This suggests the possibility of using a formal patient–doctor contract to improve compliance during antibiotic treatment.

It was shown that doctors rarely use techniques that effectively improve compliance during antibiotic therapy.46 As this review indicates, there are multiple simple interventions available for doctors that do not require additional time or work. Considering the high cost of non-compliance, and also
the obvious benefits of patients’ compliance on management, it is worth using such interventions.

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References


