ABSTRACT

Compliance, or adherence, is the extent to which the time history of drug administration corresponds to the prescribed regimen. Patients in hospital are generally compliant with treatment because they are provided with each dose at the relevant time. However, noncompliance is a frequent problem in the outpatient setting and can result in patients receiving inappropriate doses of medication. Patient noncompliance with acute antibiotic therapy develops consciously and subconsciously: the longer and more complex the regimen, the poorer the compliance. Noncompliance can affect clinical outcomes and increase treatment costs. Thus, comprehensive methods to improve compliance need to be introduced and widely used. The links between poor compliance and resistance have been clearly demonstrated in chronic infections, such as tuberculosis. There is less evidence from respiratory tract infections (RTIs), but there is evidence that inappropriate dosing can lead to resistance development. In children with RTIs, there is convincing evidence that high-dose, short-course amoxicillin is effective, tolerable, offers improved compliance, and is associated with less short-term resistant carriage rates in the individual than standard therapy. High-dose, short-course macrolide therapy has not been studied as extensively, but in the appropriate setting it reduces noncompliance and has comparable effectiveness to long-course β-lactam therapy. (Adv Stud Med. 2006;6(7C):S652-S658)
Testing for the presence of the drug in body fluids, such as urine, is also used to measure compliance, but the results only give a snapshot of the time immediately before the test. Both of these methods are still used in clinical research, but the gold standard in compliance research is now microelectronic devices, such as the Medication Event Monitoring System (MEMS; Aprex, Union City, Calif). These consist of a standard container with a screw top that contains a microcircuit that records when the container is opened. If medication is taken each time the container is opened, this provides the most accurate measurement of compliance.

**Prevalence of Noncompliance**

Kardas et al used meta-analysis to assess noncompliance with antibiotics in the outpatient setting in 46 papers identified from 2848 articles. The 51 estimates from nearly 30,000 subjects gave an overall noncompliance rate of 37.8% (range 0%–90.5%); 18 estimates from nearly 17,000 patients in 9 studies gave an overall rate of keeping leftover antibiotics for a later episode of 28.6%. The lowest rate of noncompliance was found among patients prescribed antibiotics for a respiratory tract infection (RTI; 27.4%), whereas the highest rates were for acute diarrhea (59.7%) and genitourinary tract infections (58.9%). Children had a better noncompliance rate than adults (33.6% vs 42.1%). Noncompliance rates assessed by assay and telephone interview were consistently lower than those assessed using objective methods, especially MEMS.

**Reasons for Noncompliance**

Several factors contribute to patient noncompliance with antibiotic therapy: cost of drugs, formulation, rapid improvement of symptoms, forgetfulness, frequent dosing, side effects, and patient beliefs. For example, patients may not believe that the antibiotic is necessary, or they may worry that it will interact with other drugs or alcohol, or that they may harm the immune system. Chen et al found that 40% of Taiwanese patients believe that it is harmful to follow physicians’ directions when taking antibiotics and that almost all Taiwanese (93%) believe that taking less antibiotic than prescribed is more healthy. In a study in 5 European countries and Turkey, patients who stopped taking their medication early gave 3 main reasons for not completing the treatment course: feeling better (87%), forgetting (5%), and disliking the taste of the medication (2%). Almost 50% of patients (47%) will discontinue therapy once their symptoms subside.

Because of this wide variety of reasons for noncompliance, it is not possible to predict which patient will comply with treatment and which will not. This may go some way to explain why physicians seldom use techniques that effectively improve patient compliance.

**Patterns of Noncompliance**

The most common form of noncompliance is the unintentional omission of a single dose, but noncompliance ranges from failure to fill the prescription or to start therapy, through conscious omission of doses and changes in dose frequency and dose interval, to periodic dose increase, premature cessation of therapy, and use of leftover antibiotics. In a study of doxycycline use in *Chlamydia trachomatis*, 90% of patients reported that they had taken all doses, but electronic measurement showed that only...
16% of patients actually took their medication as directed. A study in 9 countries found that 69% of patients reported finishing their entire course of antibiotics, ranging from 90% in the United Kingdom to 53% in Thailand.

Compliance decreases with time, and the decrease is greater with more frequent dosing (Figure 1). Claxton et al found that 79% of patients prescribed once-daily therapy followed the correct schedule, whereas only 51% of those required to take their medication 4 times daily managed to take the drugs as directed. In patients with acute exacerbations of chronic bronchitis, overall compliance (finishing the course of antibiotics) and compliance with the correct number of doses and correct interdose interval was significantly better with once-daily than twice-daily dosing. In a study in patients prescribed twice-daily antibiotics for 5 to 14 days for an RTI, urinary tract infection (UTI), or skin infection, 97% of patients took all the necessary medication, but only 33% managed to take all their doses within 1 hour of the 12-hour interval.

CONSEQUENCES OF NONCOMPLIANCE

CLINICAL OUTCOME

Noncompliance with antibiotic therapy can lead to treatment failure, complications, and recurrent disease. Antibiotic regimens are designed for maximum benefit, according to the drug's pharmacokinetics. For some antibiotics, such as penicillin, cephalosporins, erythromycin, and clarithromycin, the time above the minimum inhibitory concentration (MIC) is vital, whereas for others, such as the quinolones, aminoglycosides, and azithromycin, the ratio of the exposure over 24 hours (area under the concentration-time curve) to the MIC provides the best measure of appropriate dosing.

Noncompliance leads to treatment failure, as demonstrated by the Multicentre Amoxicillin Short Course Therapy (MASCOT) pneumonia study and the IndiaClen Short Course Amoxicillin Pneumonia (ISCAP) study. In the MASCOT study, 2000 children with nonsevere pneumonia were treated with amoxicillin, 1000 for 3 days and 1000 for 5 days. Noncompliance, defined as taking less than 80% of the prescribed doses, was more common in those patients with treatment failure (2% in the 3-day group and 6% in the 5-day group) than in those with treatment success (1% and 2%, respectively). Noncompliance was the most important risk factor for treatment failure (odds ratio [OR] 4.5). The ISCAP study also used amoxicillin to treat children with nonsevere pneumonia: 1095 received a 3-day regimen and 1093 received a 5-day regimen. The investigators defined noncompliance as taking less than 66% of the prescribed doses. Only 7.4% of patients with treatment success were noncompliant, compared to 79.1% of those with treatment failure. Again, noncompliance was the most important risk factor for treatment failure (OR 11.6).

Noncompliance can also increase the risk of recurrent infections. In a study of UTIs in children, patients who were fully compliant had fewer UTIs (3.0 episodes/year) than those who were partially compliant (4.8 episodes/year) or noncompliant (7.2 episodes/year).

COSTS

The clinical consequences of noncompliance with antibiotic therapy have cost implications. For example, the complications and recurrent disease may require additional consultations, tests and treatment, and may necessitate hospital admissions. The cost of noncompliance includes increased out-of-pocket expenses, increased healthcare costs (for office visits, tests, and hospitalizations), additional treatment costs, and lost productivity.

In a primary-care study in 2328 children with 3677 episodes of respiratory or ear infections, treatment failure was defined as the need for a second antibiotic within 4 weeks of receiving the first. Follow-up costs for visits were significantly greater in patients with treatment failure ($216) than in those with treatment success ($53; P <.01); drug costs, including those of the second antibiotic, were also higher in patients with treatment failure ($75 vs $23; P <.01).

A review of 22 pharmacoeconomic evaluations that used sensitivity analysis to assess the impact of noncompliance on the cost effectiveness of pharmaceuticals showed that as the rate of compliance decreased, the benefits of treatment also decreased (Figure 2). The effect on cost varied widely. In one study, when compliance with treatment for Chlamydia decreased from 100% to 60%, cure rates...
fell from 98% to 90%, and costs increased from $29 to $115.16

**Antibiotic Compliance and Antibiotic Resistance**

**The Tuberculosis Story**

Tuberculosis (TB) treatment provides the best evidence for the relationship between resistance and compliance with antibiotic therapy, based on directly observed therapy (DOT) data. DOT ensures close to 100% compliance because a healthcare worker watches a patient take each dose of medication.17

Between 1969 and 1976, Baltimore had one of the highest incidence rates of TB among major cities in the United States. In 1978, when clinic-based DOT was introduced, the annual incidence was 50/100 000, but by 1981, when community-based DOT was initiated, this had fallen to 36/100 000. In 1985, the incidence of TB across the United States began to increase, rising by 20% between 1985 and 1992.18,19 In addition, in 1991, 33% of all TB cases in New York City were caused by drug-resistant strains.20 However, the incidence in Baltimore continued to fall during this period: it was 24/100 000 in 1985, 17/100 000 in 1992, and 3.7/100 000 in 2003, when Baltimore was ranked 64th in TB incidence among US cities with populations larger than 100 000.21 Across the United States, there was a massive increase in the use of DOT from 1992, leading to a sharp reduction in the number of new cases (Figure 3). This DOT evidence shows that compliance is essential for decreasing the incidence of TB and the prevalence of resistance.

Prolonged use of DOT in Baltimore has resulted in a lower incidence of TB and has significantly decreased the rate of drug-resistant TB. However, the proportion of cases due to recent transmission remains high, similar to the level seen in cities with poorer TB control programs, showing that compliance has no effect on the fundamental dynamics of disease transmission.22 HIV and TB research show that it is impossible to generalize the effects of non-compliance across antimicrobial classes, as different classes show different degrees of tolerance to non-compliance. For example, isoniazid is intolerant to noncompliance, as shown by the fact that 4.4% of new TB cases in the United States are caused by a strain resistant to only isoniazid, whereas rifampicin
is more tolerant (only 0.4% of new cases are caused by a strain monoresistant to rifampicin).21

**Pediatric Respiratory Tract Infections**

It is impossible to extrapolate TB findings to RTIs, as the epidemiology and drug regimens are very different. For example, there is no infectious carrier state for TB, as there is for many organisms that cause RTIs. RTIs are treated for a much shorter time than TB, often using single-drug rather than multidrug therapy. In addition, the drugs used to treat RTIs are not associated with significant adverse-event profiles and are generally overused in the United States, unlike anti-TB therapy.

There is a dearth of published information on the link between noncompliance with antibiotic therapy for RTIs and the prevalence of resistance. For TB, which has an annual US incidence of 14 511, there are 276 citations in the literature covering compliance and resistance, whereas for *Streptococcus pneumoniae* pneumonia, otitis, and meningitis, with a combined annual incidence in the United States of more than 6 million, there are only 41 similar citations.

Three important studies have assessed the impact of compliance with short-course therapy in RTIs on resistance: an observational study of the risk factors for penicillin-resistant *S pneumoniae* (PRSP); a randomized controlled trial of short-course, high-dose macrolide therapy for group A β-hemolytic streptococcus (GABHS) pharyngitis; and a randomized controlled trial of short-course, high-dose amoxicillin compared to 10-day standard treatment for childhood RTIs.23–25

Guillemot et al assessed PRSP carriage in French children according to parental reporting of antibiotic use in the 30 days prior to screening.23 Oropharyngeal swabs were taken from 941 children aged 3 to 6 years at 20 schools in a 5-week period in early summer 1995 and the MIC was determined for each isolate of *S pneumoniae*. Fifty-five children (5.7%) carried *S pneumoniae*, and 16 (29%) of these had PRSP. A total of 203 children had used antibiotics in the 30 days prior to screening. There was no significant difference in demographic or clinical characteristics between children carrying penicillin-sensitive or -resistant *S pneumoniae*. However, PRSP carriers were significantly more likely to have received amoxicillin (OR 3.0; *P* = .03) or a cephalosporin (OR 3.7; *P* = .01) in the last 30 days. Children who had received a low oral dose (lower than the clinically recommended dose; OR 5.9; *P* = .002) or a long duration of β-lactam therapy (OR 3.5; *P* = .02) had an increased risk of PRSP carriage. This relationship was stronger for amoxicillin than for cephalosporins. These results show that low daily doses and long antibiotic regimens (>5 days) are associated with PRSP carriage, which supports the link between inappropriate dosing and resistance.

In another study in France, Cohen et al compared treatment outcome to penicillin V (10 days of 45 mg/kg/day in 3 divided doses; *n* = 167), low-dose azithromycin (10 mg/kg once daily for 3 days; *n* = 169), and high-dose azithromycin (20 mg/kg once daily for 3 days; *n* = 165) in 501 children aged 2 to 12 years with GABHS pharyngitis.24 Pharyngeal swabs were taken before treatment and at 14 and 30 days. After 14 days, the eradication rate was greatest with high-dose azithromycin (94.2%), followed by penicillin V (84.2%), and low-dose azithromycin (57.8%). This trend continued for microbiologic success at 30 days (82.8%, 81.6%, and 56.8%, respectively). After treatment with low-dose azithromycin, 8 of the bacterial strains that were not eradicated showed increased azithromycin MICs. In contrast, in the group treated with high-dose azithromycin, no strains recovered after treatment had increased azithromycin MICs. Compliance was significantly lower with the 30-dose penicillin V regimen (62%) than with either 3-dose azithromycin regimen (94%–95%; *P* < .0001). These study results demonstrate that 3 days of high-dose azithromycin was statistically more effective for GABHS than 3 days of standard-dose azithromycin and comparable to 10 days of penicillin V. The 3-dose regimen was associated with significantly improved adherence.

A randomized controlled trial conducted in the Dominican Republic by the Centers for Disease Control and Prevention assessed PRSP carriage in children aged 6 months to 5 years with RTIs treated with low-dose amoxicillin (40 mg/kg/day for 10 days; *n* = 397) or high-dose, short-course amoxicillin (90 mg/kg/day for 5 days; *n* = 398).25 Of the 795 children, 58% had acute RTIs, 29% had acute otitis media, 10% had pneumonia, and 3% had sinusitis. Nasopharyngeal swabs were taken before treatment and at 5, 10, and 28 days. The 2 treatment groups
were similar for baseline PRSP carriage and *S. pneumoniae* infection. Significant risk factors for baseline carriage of PRSP were antibiotic use in the previous 2 months and at least 3 children in the home. A significantly higher proportion of children who received low-dose amoxicillin had PRSP carriage at 28 days (32% vs 24%; *P* = .03; relative risk 0.77), and compliance was greater in the high-dose, short-course group (82% vs 74%; *P* = .02). Thus, high-dose, short-course amoxicillin therapy was associated with lower PRSP carriage rates at 28 days and higher compliance rates.

**CONCLUSIONS**

Poor patient compliance with antibiotic therapy is a widespread problem and can result in patients receiving inappropriate doses of medication. Patient non-compliance with acute antibiotic therapy develops consciously and subconsciously—the longer and more complex the regimen, the poorer the compliance. There is evidence that noncompliance can affect clinical outcomes and increase treatment costs, thus comprehensive methods to improve compliance need to be introduced and widely used.

The links between poor compliance and resistance have been clearly demonstrated in chronic infections, such as TB. In RTIs, there is less evidence, but links between appropriate dosing and good resistance outcomes can be made. In children, there is convincing evidence that high-dose, short-course amoxicillin is effective, tolerable, offers improved compliance, and is associated with less short-term resistance carriage rates in the individual than standard therapy. High-dose, short-course macrolide therapy has not been studied as extensively, but in the appropriate setting it reduces noncompliance and has comparable effectiveness to long-course β-lactam therapy.

**REFERENCES**

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