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Rational Use of Oral Antibiotics for Pediatric Infections

Summary: We carried out a survey in Japan to investigate compliance among children given oral antibiotics in an outpatient setting. The results of our survey revealed that, in Japan, approximately one-quarter of patients did not take their full course of antibiotics. Reasons for unsupervised self-discontinuation included: (1) the parent or guardian judged the infection to be cured; (2) the child refused to take the drug; and (3) the appearance of side effects. Causative organisms often involved in respiratory infections experienced in outpatient medicine include pneumococci, streptococci, staphylococci, *Haemophilus influenzae, Moraxella (Branhamella) catarrhalis* and *Mycoplasma pneumoniae.* The β-lactams are effective against all of these bacterial species, with the exception of *M. pneumoniae.* We conducted a survey of β-lactam antibiotics currently on the Japanese market and compared them to other oral antibiotics used to treat respiratory infections. Ease of administration, based on the incidence of adverse effects, particularly diarrhea, the dosage form, taste, dosage per administration and the number of doses required per day, are reported.

Introduction

Antibiotics are an effective and important means of curing patients with microbial infections. However, the physician must consider a number of important factors in order to select the best antibiotic for each individual case. To ensure optimum effectiveness of oral antibiotics in the pediatric setting, consideration needs to be given to the following points. In addition to being safe, the oral antibiotics must be easily administered and have good gastrointestinal absorption, as well as an appropriate antibacterial spectrum against the likely causative bacteria. Attention must also be paid to the existence of any possible side-effects that may be peculiar to children.

This paper reports on a survey carried out to investigate compliance in children prescribed oral antibiotics, and to find out, in those with poor compliance, the reasons why medications were discontinued. By learning why parents stop giving oral antibiotics to their children, it becomes possible for the physician to overcome these difficulties, thus ensuring optimum compliance and patient care.

Patients and Methods

We carried out a survey utilizing a questionnaire that was given to 192 parents with children who were treated as outpatients. Parents were asked to complete and return the questionnaire by mail. To be eligible, children had to take antibiotics for 4 days or more.

The questionnaire investigated the following points: 1) the actual versus prescribed administration of the medication; 2) in cases where the parents stopped giving antibiotics to their children, their reasons for stopping; and 3) the parents' "wish list" regarding possible improvements they would like to see made in the antibiotic treatment schedules.

This survey was a multicenter study, involving six institutions.

Results

Although 72% of patients completed the full course of medication, in the remaining 28% of cases the antibiotics that had been prescribed by the physician were not completely given. The majority of incomplete treatments were due to parents stopping before the required number of days. In 3% of cases, parents did not always give the correct amount of each individual dose.

An important reason given by parents for non-completion of treatment was lack of knowledge. They felt that the importance of taking the full course of medication was not explained sufficiently or emphasised to them. In approximately a third (36%) of cases parents stopped because they believed that their children had been cured and no longer required treatment. In another 23% medication was stopped solely because parents forgot to administer it to their children. Children were also often noted to be reluctant to take any medication and this contributed to incomplete treatment in 19% of cases. Other reasons cited for stopping treatment prematurely included the development of side-effects such as diarrhea (8%), or difficulties in the size of the dose, which was seen as too large in 6% of cases.

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Ways to Improve Antibiotics

Parents wanted to see improvements to a variety of different factors regarding oral antibiotics (Figure 1). The majority of parents when questioned first wanted a safe medication (26.8%). Many wanted a change in dosage schedules, with a reduction in the number of doses required each day (22.4%) as well as fewer days of administration (8.7%). In addition they wanted improvements in taste and smell (22.4%), and a better dosage form that children would take more easily (9.4%). A small number of parents also wanted improvements in drug efficacy.

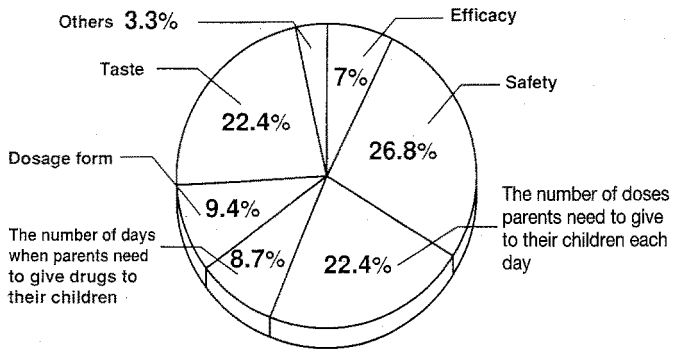

Figure 1: Improvements requested by parents related to antibiotics. Questionnaires from six facilities (n=299).

Changes in Administration Schedules

The most requested administration schedule was twice daily (61.7%) (data not shown). This was followed by 22.3% who preferred a three times daily schedule, 14.9% wanted once daily, and 1.1% requested four times a day. Reasons why parents preferred to give the antibiotics to their children twice a day included the following: they were tired of giving drugs to their children several times a day; multiple daily doses created difficulties with child care, as many preschools do not care for children requiring antibiotics during the day; and they had reservations about the efficacy of a once daily dosage.

Common Pediatric Respiratory Pathogens Requiring Treatment

In general *Streptococcus pneumoniae*, group A *Streptococcus*, *Staphylococcus aureus*, *Haemophilus influenzae*, *Moraxella (Branhamella) catarrhalis* and *Mycoplasma pneumoniae* are the most common pathogens causing respiratory infections in children in the outpatient setting.
These results were confirmed by a recent study carried out over a 1-year period, which was undertaken to investigate a new oral antibiotic in the pediatric setting. In this study we found that the most common bacterium causing pediatric community-acquired pneumonia was *H. influenzae* (74.5%), followed by *S. pneumoniae* (12.8%), *M. catarrhalis* (10.6%) and *S. aureus* in 2.1 % [1].

Review of Available Oral Antibiotics for Pediatric Pneumonia

We reviewed the typical oral antibiotics available for treating pediatric respiratory infections, including a large number of β-lactam oral antibiotics, looking at them from the perspective of what features they had that would ensure maximum compliance among the pediatric population. In this regard we investigated them for ease of administration, including dosage form and number of administrations a day, side effect profile, safety, taste and smell. All of these factors had been cited by parents as areas they would like to see improved.
β-Lactam antibiotics are effective against all of the most common pathogens causing pediatric pneumonia except for *M. pneumoniae.*

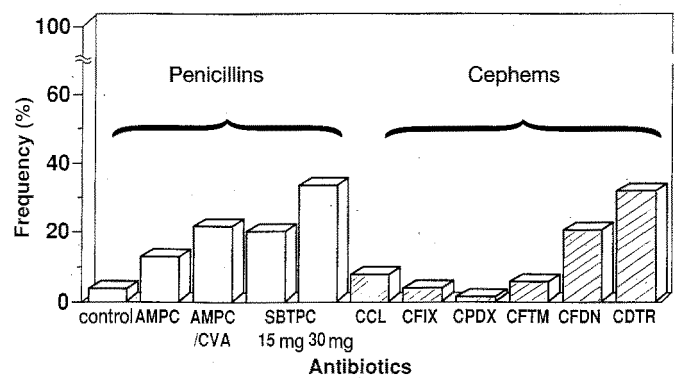

Figure 2: Frequency of development of diarrhea and loose bowel movements according to individual oral antibiotics given to children. AMPC: amoxicillin, CVA: clavulanic acid, SBTPC: sultamicillin, CCL: cefaclor, CFIX: cefixime, CPDX: cefpodoxime proxetil, CFTM: cefteram, CFDN: cefdinir, CDTR: cefditoren-pivoxil.

Diarrhea Associated with Oral β-Lactams

One common problem encountered by children taking oral antibiotics is the development of diarrhea or loose bowel movements. Therefore we compared the commonly used oral antibiotics looking at the rate with which they produced diarrhea in children. The results of this are shown in Figure 2. This illustrates that amoxicillin/clavulanate produced diarrhea in approximately a quarter of children, while an even greater percentage was found for sultamicillin at a 30 mg dosage. In comparison, many of the most commonly used cephem antibiotics had much lower rates of diarrhea associated with their use, with cefixime and cefpodoxime only causing a very low rate similar to the control population. However there were differences among the cephem class of compounds, with cefdinir or cefditoren-pivoxil causing a much greater incidence of diparrhea comparable to the penicillins [2].
The incidence of diarrhea caused by antibiotics tends to be higher in the relatively younger age group due to younger children and infants having intestinal bacterial flora that are more likely to be compromised. When the frequency of development of diarrhea was investigated according to age in children given cefdinir it was found that the inci-

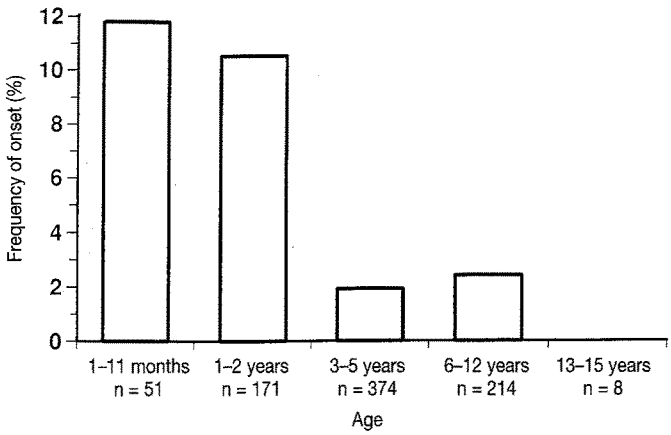

Figure 3: Frequency in onset of side effects by age in 818 cases given cefdinir.

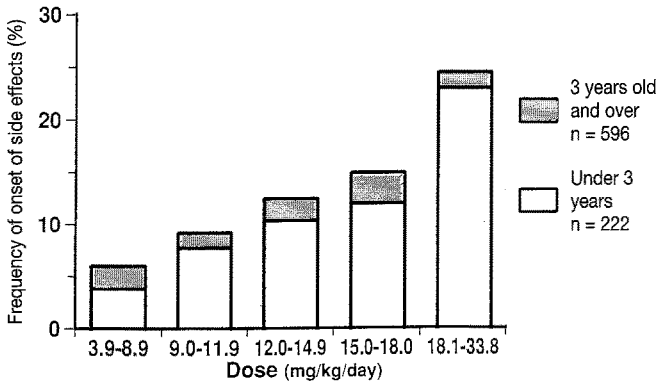

Figure 4: Frequency in onset of side effects according to dose administered each day (mg/kg/day) in 818 cases given cefdinir.

dence of diarrhea was greatest in infants under 3 years of age (Figure 3) [3].

This was further investigated with children divided into two different age groups (Group 1: 3 years and over, Group 2: under 3 years of age). The frequency of side effects was then analyzed in these children according to the amount of their daily drug dosage in mg/kg. In infants under 3 years of age, the greater the daily dose, the higher the incidence of development of diarrhea. However, this tendency was not seen in children aged 3 years or over (Figure 4). A similar result was obtained for other cephalosporins [4].

Importance of Taste in Achieving Optimum Compliance

Oral antibiotics currently on the market in Japan were analyzed from the standpoint of taste. The usual flavors that are used include orange, cola, mixed fruits, strawberry, and banana. Drugs were classed according to palatability as being easy to take, slightly difficult, or difficult. More than half of the children in each age group were reluctant to take the oral antibiotics because of their unpleasant taste and smell. This is a particular problem for the penicillin compounds, as they all have a distinctive and unpleasant smell. In addition, the macrolide clarithromycin was not easily administered to children, with many complaining of its bitter taste. In comparison, the majority of the cephem antibiotics were reported as easy to take with very few children reluctant to take these compounds (Table 1). This is an important advantage offered by cephalosporins to help ensure maximum compliance in the pediatric setting [5].

Other Factors Affecting Compliance

The particle size of drugs was also found to be important in deciding whether younger children would easily take oral compounds [6]. Larger particle size was particularly a problem for babies under one year of age and caused them to reject certain drugs. Augmentin was noted to have a problem in respect to its particle size.

The amount required for each individual dose of drug also affected its ease of administration. There was a large difference between drugs in this regard, with amoxicillin/clavulanate and ampicillin requiring the largest amount in g per dose. Cephalosporin compounds, cefdinir and the new cefditoren-pivoxil needed a much lower dose with a three-fold difference between them and amoxicillin clavulanate (Figure 5) [4]. An excessive amount for each individual dose was cited as one of the reasons why children aged 1 year and over were reluctant to take certain oral medications.

Table 1: Ease of administration of oral antibiotics to children.

Antibiotic group	Easy	Slightly difficult	Difficult
Penicillin		AMPC SBTPC	BAPC
		AMPC/CVA	
Cephalosporin	CEX CXD CCL	CFTM-PI CPDX PR	
	CFIX CFDN	CDTR-PI	
Macrolide	MOM	EM JM RKM	CAM

Abbreviations: CEX: cefalexin, CXD: cefroxadine, CCL: cefaclor, CFIX: cefixime, CFDN: cefdinir, MOM: miocamycin, AMPC: amoxicillin, SBTPC: sultamicillin, CVA: clavulanic acid, CFTM-PI: cefteram pivoxil, CPDX PR: cefpodoxime proxetil, CDTR-PI: cefditoren-pivoxil, EM: erythromycin, JM: josamycin, RKM: rokitamycin, BAPC: bacampicillin, CAM: clarithromycin.
Flavors: CEX: orange, CXD: fruits, CFDN: strawberry, MOM: banana, EM: odorless, SBTPC: cola.

Conclusions

Patient compliance is always an extremely important aspect of therapy and needs to be kept as high as possible to ensure not only optimum treatment, but also to help stop the development of resistant organisms.

In this study it was found that over a quarter of pediatric cases were not completing their full course of antibiotics. The first reason identified by parents for incompletion of treatment included lack of knowledge. They felt that the importance of taking the full course of medication was not explained sufficiently or emphasized to them. This is a single problem to overcome, and the importance of telling parents to use up all medications should be emphasized by the practitioners.

The need for ease of administration to ensure good compliance is even more important in the pediatric population where oral medications are often required. We investigated how compliance of oral antibiotics can be improved in the pediatric setting and found that among all the commonly used drugs, the cephem antibiotics were the best in this regard.

Cefixime fulfils many of the requirements needed for a good oral pediatric antibiotic (Table 2). It also has other important advantages in that it has a very low frequency of causing diarrhea [7], has a pleasant taste and smell that

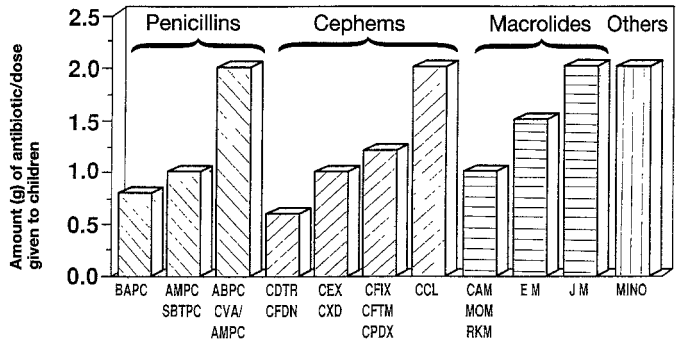

Figure 5: Amount (g) of antibiotics given once to children. (Weight is assumed to be 20 kg). BAPC: bacampicillin, AMPC: amoxicillin, SBTPC: sultamicillin, ABPC: ampicillin, CVA: clavulanic acid, CDTR: cefditoren-pivoxil, CFDN: cefdinir, CEX: cefalexin, CXD: cefroxadine, CFIX: cefixime, CFTM: cefteram, CPDX: cefpodoxime proxetil, CCL: cefaclor, CAM: clarithromycin, MOM: miocamycin, RKM: rokitamycin, EM: erythromycin, JM: josamycin, MINO: minocycline.

Table 2: Comparison among oral antibiotics for children relating to ease of administration.

Palatability	No problem in taste: CEX CCL CXD CFIX CFDN	Drugs have unpleasant taste and smell, but children may take them: AMPC SBTPC CVA/AMPC CFTM CPDX CDTR EM RKM	Unpalatable and children were reluctant to take drugs: BAPC CAM
Particle size	Particles are minute: SBTPC CPDX CCL CEX EM RKM	Particles are intermediate: AMPC CFIX CFDN CAM	Particles are coarse: CVA/AMPC
The number of administrations a day	Once or twice: CFIX CPDX CAM	Three times: SBTPC AMPC CVA/AMPC CCL CXD CFTM CFDN CDTR RKM MOM	Four times: EM
Amount of antibiotic/dose given to children	1g or less: BAPC CDTR CFDN	1–1.5 g: AMPC SBTPC CEX CXD CFIX CFTM CPDX CAM MOM RKM	1.5 g or more: ABPC CVA/AMPC CCL JM EM
Side-effect (diarrhea) incidence	5% or less: BAPC CPDX CFIX EM	5–15%: AMPC ABPC CCL CFTM CAM RKM	15% or more: SBTPC CVA/AMPC CFDN CDTR

CEX: cefalexin, CCL: cefaclor, CDX: cefroxadine, CFIX: cefixime, CFDN: cefdinir, SBTPC: sultamicillin, CPDX: cefpodoxime proxetil, EM: erythromycin, RKM: rokitamycin, CAM: clarithromycin, BAPC: bacampicillin, CDTR: cefditoren-pivoxil, AMPC: amoxicillin, CVA: clavulanic acid, CFTM: cefteram, MPC: mecillinam, MOM: miocamycin, ABPC: ampicillin, JM: josamycin.

children like, has a small particle size making it easily swallowed by infants, and is also very effective in a twice-daily schedule, the preferred administration schedule cited by parents.

Zusammenfassung: Rationale Antibiotikatherapie bei pädiatrischen Infektionen. Die Compliance bei ambulanter Antibiotikatherapie im Kindesalter wurde überprüft. Dabei stellte sich heraus, daß in Japan etwa ein Viertel der Patienten nicht die volle Antibiotikadosis einnahmen. Gründe für ein eigenmächtiges Absetzen waren 1). die Eltern oder Betreuer sahen die Infektion als geheilt an. 2.) Das Kind verweigerte die Einnahme. 3.) Nebenwirkungen. Zu den häufigen Erregern von Atemwegsinfektionen im ambulanten Bereich gehören Pneumokokken, Streptokokken, Staphylokokken, *Haemophilus influenzae*, *Moraxella (Branhamella) catarrhalis* und *Mycoplasma pneumoniae*. Die β-Laktamantibiotika sind gegen alle diese Bakterienspezies mit Ausnahme von *M. pneumoniae* wirksam. Wir überprüften die derzeit auf dem japanischen Markt verfügbaren β-Laktamantibiotika und verglichen sie mit anderen oralen Antibiotika, die zur Behandlung von Atemwegsinfektionen eingesetzt werden. Berichtet wird über die Inzidenz von Nebenwirkungen, vor allem Durchfall, Zubereitungsart, Geschmack, Einzeldosis und erforderliche Anzahl von Tagesdosen.

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Q&A

Q. Why did parents say they would prefer to have a drug that they can give twice a day, rather than once a day? You would think that once-a-day dosing would be very attractive.

A. Yes. But many parents want something that makes them feel that they are doing something for their child that is sick.

Q. They feel they are doing more for their sick child if they give it twice a day?

A. Yes.

Q. How is the taste of clarithromycin in Japan?

A. Many children say it is bitter, so it is difficult to administer. In Japan, the company is going to change the taste. Maybe next year, it will be more acceptable.