



Title	A challenge to appropriate antibiotic use in children with respiratory infections: a 5-year single-institution experience
Author(s)	Matsumoto, Ayumi; Hashimoto, Koichi; Kawasaki, Yukihiko; Hosoya, Mitsuaki
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[Review]

A CHALLENGE TO APPROPRIATE ANTIBIOTIC USE IN CHILDREN WITH RESPIRATORY INFECTIONS : A 5-YEAR SINGLE-INSTITUTION EXPERIENCE

AYUMI MATSUMOTO, KOICHI HASHIMOTO, YUKIHIKO KAWASAKI
and MITSUAKI HOSOYA

Department of Pediatrics, Fukushima Medical University, Fukushima, Japan

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Abstract :

Background

We have studied the rate of emergence of antibiotic-resistant *Streptococcus pneumoniae* (*S. pneumoniae*) and *Haemophilus influenzae* (*H. influenzae*) and the subsequent antibiotic use in host patients of those isolates at the Department of Pediatrics, Soma General Hospital, Fukushima. Moreover, we carried out several studies investigating the risks and benefits of antibiotic-free treatment for children with respiratory infections. In this report, we summarize our research and suggest better treatment options for pediatric patients with respiratory infections.

Methods

We investigated the necessity of antibiotic use in the treatment of pediatric inpatients with respiratory syncytial virus (RSV) infection, and tested our hypothesis that antibiotic-free treatment for common cold will reduce the number of resistant *S. pneumoniae* strains in the pediatric nasopharynx. Therefore, we restricted prescribing antibiotics for pediatric patients with respiratory infections. The rates of resistant *S. pneumoniae* and *H. influenzae* and the medication history of the host patients before and after the intervention were compared.

Results

We found that most of the RSV-infected patients recovered without antibiotic treatment, and that the antibiotic-free treatment inhibited the emergence of antibiotic-resistant strains. The rate of penicillin-resistant *S. pneumoniae* decreased but the rate of ampicillin-resistant *H. influenzae* did not change significantly during the study.

Conclusion

We concluded that patients with respiratory infections can be treated without antibiotics, under careful examination and observation. Continued monitoring of such new interventions as well as recommending their use to other caregivers and physicians will help inhibit the spread of resistant strains.

Key words : *Streptococcus pneumoniae*, antibiotics, common cold, children

INTRODUCTION

Emergence of antibiotic-resistant microbes is a global concern. In pediatrics, the increase in the rate of development of antibiotic resistance in

Streptococcus pneumoniae (*S. pneumoniae*) and *Haemophilus influenzae* (*H. influenzae*) is of great concern, because these bacteria are the major etiologic agents causing serious invasive pediatric infections such as meningitis and septicemia. They are

松本歩美, 橋本浩一, 川崎幸彦, 細矢光亮

Corresponding author : Ayumi Matsumoto, MD E-mail address : b-walk@fmu.ac.jp
<http://www.jstage.jst.go.jp/browse/fms> <http://fmu.ac.jp/home/lib/F-igaku/>

also responsible for sinusitis, middle ear infections, and pneumonia.

Penicillin-resistant *S. pneumoniae* was first isolated in the 1980s, and has spread rapidly in Japan¹⁻³. It is well known that penicillin resistance in *S. pneumoniae* is caused by alteration in the genes encoding penicillin-binding proteins (PBPs), chiefly, *pbp1a*, *pbp2b*, and *pbp2x*. The Japanese pneumococcal isolates often have an altered *pbp2x* gene; this is considered as the reason for decreasing cephalosporin susceptibility. In other countries, isolates with altered *pbp1a* or *pbp2b* that induce penicillin resistance predominate the clinical scenario^{2,4-6}. The number of ampicillin-resistant *H. influenzae* strains has also increased in our country. This resistance to ampicillin and other beta-lactam antibiotics in *H. influenzae* has been attributed to the production of beta-lactamase and/or the presence of an alteration in the *ftsI* gene encoding PBP3. Generally, an ampicillin-resistant *H. influenzae* strain producing beta-lactamase is termed "beta-lactamase-producing ampicillin-resistant" (BLPAR), and the strain that does not produce beta-lactamase is termed "beta-lactamase-non-producing ampicillin-resistant" (BLNAR). Compared to the other countries with common occurrence of BLPAR isolates, BLNAR isolates predominate in Japan^{7,8-12}.

Over the last 2 decades, worldwide studies have been carried out on the risk factors associated with carriage of resistant strains; the most important factor was found to be previous antibiotic use¹³⁻²⁷. Moreover, studies since the late 1990s have reported about campaigns to promote appropriate antibiotic use²⁸⁻³⁴. Contrary to the international scenario, oral cephalosporin has been commonly used for treating children with respiratory infections without signs of bacterial infection in Japan. It is suggested that cephalosporin overuse has caused the alteration of *pbp* genes in both *S. pneumoniae* and *H. influenzae*¹⁻³.

We investigated the rate of resistant *S. pneumoniae* and *H. influenzae* and the medication history of the host patients of those isolates at the pediatric department of Soma General Hospital, Fukushima. We discovered that, throughout our investigation, the prevalence of resistant isolates was extremely high. We started to reduce antibiotic use in patients with respiratory infections, and have used amoxicillin rather than cephalosporin antibiotics as a first choice for empirical therapy of respiratory infections since 2004. We chose amoxicillin because it has some positive pharmacokinetic properties³⁵⁻³⁸. We also performed the studies to investigate

questions like "Will patients recover without problems even if they do not receive antibiotics?" and "Will the resistant strain truly vanish from host children after an antibiotic-free term?" The clinical trial was designed to answer these questions.

Conjugate vaccines of *S. pneumoniae* and *H. influenzae* type b have now been introduced; it is time to reconsider the use of antibiotics. The purpose of this report is to review 5 years of promoting appropriate antibiotic use, and to consider how to treat pediatric patients with respiratory infections in this new era of preventive medicine.

STUDIES

1) The prevalence of resistant *S. pneumoniae* and *H. influenzae* strains in the initial 2 years, and the associated host risk factors

This first study was performed from September 2001 to June 2003. We had prescribed cephalosporin antibiotics for pediatric outpatients with respiratory infections. The aims of the study were to investigate the rate of antibiotic prescription, the antimicrobial susceptibility of *S. pneumoniae* and *H. influenzae* isolates, and the risk factors associated with the carriage of resistant strains. During the study period, the annual pediatric patient number was about 20,000, and we collected nasopharyngeal swabs from patients with respiratory tract infections.

Of all cases, previous oral antibiotic use was reported in 54.4%, and oral administration of cephalosporin was reported in 20.8%. Of the 949 *S. pneumoniae* isolates, 443 isolates (46.7%) were intermediate-resistant (0.12-1.0 mg/L), and 321 isolates (33.8%) were resistant (≥ 2.0 mg/L), according to the previous susceptibility breakpoints set by the National Committee for Clinical Laboratory Standards (NCCLS). Gene detection was performed in 226 randomly chosen isolates. Of the 226 isolates, 200 isolates (88.5%) had 1 or more altered *pbp* gene(s)^{39,40}. Moreover, of the 791 *H. influenzae* isolates detected, 81 isolates (10.2%) were BLNAR, and 61 isolates (7.7%) were BLPAR; thus, 142 (17.9%) isolates were ampicillin-resistant^{39,41}.

Data of the background of the host patients, including previous use of antibiotics, age, daycare attendance, and siblings, were taken into consideration using a questionnaire and/or referring to medical records. The relation between carriage of *S. pneumoniae* isolates with 1 or more *pbp* genes and each risk factor was analyzed. Antibiotic use in the

last 3 months in children (2 years of age and younger) was substantially related with the carriage of resistant isolates ($p < 0.01$). Children with day-care exposure tended to carry resistant strains ($p = 0.06$) (Table 1). Fig. 1 shows that previous antibiotic use was significantly correlated with the alteration of *pbp* genes. Orally administered cephalosporin and macrolide antibiotics were significantly related to isolates with 1-point *pbp* alteration ($p < 0.01$). Other antibiotics, including fosfomycin and minocyclin, were also significantly related to isolates with more than 2-point *pbp* alteration ($p < 0.01$)⁴⁰⁾.

2) *The risks and benefits of appropriate antibiotic use : The experience of the antibiotic-free treatment for inpatients with a lower respiratory infection caused by respiratory syncytial virus*

Our first study revealed a high rate of resistant isolates in our department. We considered that overuse of cephalosporin antibiotics exacerbated this problem. Although we tried to restrict antibiotic use in pediatric patients with respiratory infections, we were concerned about the risks of antibiotic-free treatment. In order to evaluate antibiotic-free treatment, we investigated the necessity of antibiotic use in the treatment of pediatric inpatients

Table 1. Risk factors for carriage of *Streptococcus pneumoniae* with altered *pbp* genes

Risk factor	N[%] [*]	P value
2 years of age and younger	146[64]	<0.01
Sibling	99[44]	0.11
Day care center exposure	61[27]	0.06
Use of antibiotics within the last 3 month	125[55]	<0.01

* indicates Numbers of patients having *Streptococcus pneumoniae* with altered *pbp* genes. The χ^2 test was performed for comparing the backgrounds of the children with the resistant strain and those children with a susceptible strain. The result was considered statistically significant if the value of *P* was less than 0.05.

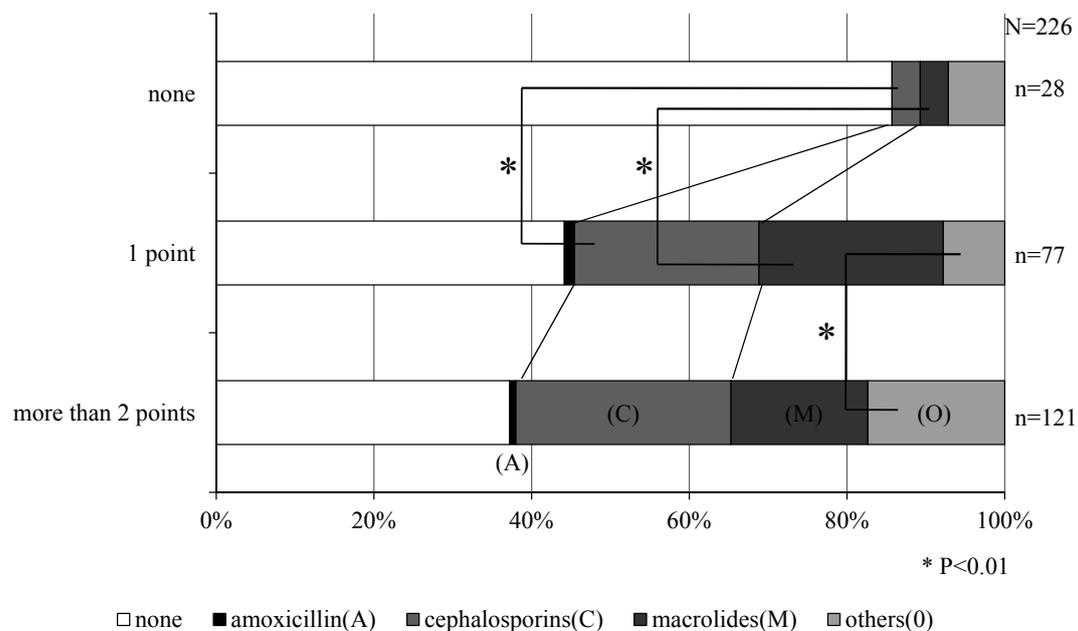


Fig. 1. The relation between antibiotic history and carriage of *Streptococcus pneumoniae* with altered *pbp* gene(s) in a study performed from 2001 to 2003.

“Others” includes fosfomycin and minocyclin. The virtual line indicates the number of *pbp* gene alterations. The χ^2 test was performed for comparing the antibiotic history of patients with resistant isolates with that of patients with susceptible isolates. * indicates a *p* value less than 0.01.

with respiratory syncytial virus (RSV) infection, from 2003 to 2004. Sixty cases diagnosed as RSV infection by the rapid antigen test were involved in this study. We compared the duration of fever and hospitalization and the cost of hospitalization between patients treated with and without antibiotics. The duration of fever and the cost of hospitalization were similar in the group treated with antibiotics (antibiotic treatment group) and the group treated without antibiotics (antibiotic-free treatment group). However, the duration of hospitalization was longer in the antibiotic-free treatment group. Furthermore, in case of nasopharyngeal *S. pneumoniae* and/or *H. influenzae* isolates, the duration of hospitalization was significantly longer in the antibiotic-free treatment group (Table 2). Two patients in the antibiotic-free treatment group failed to recover without antibiotics. They showed no improvements in the symptoms and laboratory findings 5 days after admission; therefore, we administered antibiotics.

Our study showed that it was possible to treat most cases without antibiotics. However, it also suggests that antibiotics can decrease the duration of hospitalization in cases involving bacterial isolates, and that some patients fail to recover without antibiotics. We concluded that we could, in principle, treat patients with viral respiratory infections without antibiotics, but that these patients should be observed very closely for complications of bacterial infection⁴²⁾.

Will an antibiotic-free term reduce the rate of resistant pneumococci ?

The benefits of restricting antibiotic use are unclear. From 2003 to 2004, we tried to demonstrate that antibiotic-free treatment for the common cold will reduce the rate of antibiotic-resistant *S. pneumoniae* in the pediatric nasopharynx. Forty-five children diagnosed with common cold were randomly selected from pediatric patients who had consumed antibiotics in the past 3 months. We collected nasopharyngeal swabs from all the participants before and after an antibiotic-free period of 2-3 months. *S. pneumoniae* strains were isolated from 24 of these patients. Susceptibility tests and detection assays for drug-resistant genes were performed on these strains. All the patients recovered without complications. The susceptibility test revealed that patients with penicillin-resistant isolates decreased in number from 17 to 7 ($p < 0.01$). The test also revealed that these patients had cefditoren-resistant isolates. Figure 2 shows the dynamics of *pbp* gene alteration in *S. pneumoniae* in these 24 patients. The graph clearly shows that no patients had the isolate-acquired altered *pbp* gene(s). We found that the number of altered *pbp* genes had decreased in 11 patients, and that the remaining isolates had the same gene(s) as the rest of the patients did. Our study suggests that antibiotic-free treatment inhibits the emergence of penicillin-resistant *S. pneumoniae*⁴³⁾.

Table 2. Comparison between the antibiotic-use group and the non-antibiotic group

	the non-antibiotic group N[%], the mean	the antibiotic-use group N[%], the mean	P value
total	30	30	
the duration of fever (days)	3.1	3	0.94
the duration of hospitalization (days)	6.1	5.4	0.028
the cost for hospitalization (yen)	167,000	163,000	0.561
The cases with isolates*	13 [43.3]	18 [60.0]	
the duration of fever (days)	4.3	3.3	0.074
the duration of hospitalization (days)	6.3	5.2	0.024
the cost for hospitalization (yen)	173,000	156,000	0.165
The cases without isolates**	17 [56.7]	12 [40.0]	
the duration of fever (days)	1.9	2.5	0.44
the duration of hospitalization (days)	5.9	5.6	0.546
the cost for hospitalization (yen)	162,000	171,000	0.543

*indicates the cases with *S. pneumoniae* and/or *H. influenzae* isolates from their nasopharynx

**indicates the cases without isolates of *S. pneumoniae* and/or *H. influenzae*

The χ^2 test was performed for comparing the results of the non-antibiotic group and the antibiotic-use group. The result was considered statistically significant if the value of *P* was less than 0.05.

3) *Studies during the intervention involving a reduction in antibiotic use :*

The prevalence of resistant S. pneumoniae and H. influenzae

On the basis of our previous studies, in 2004, we decided to promote appropriate antibiotic use. Physicians working at Soma General Hospital

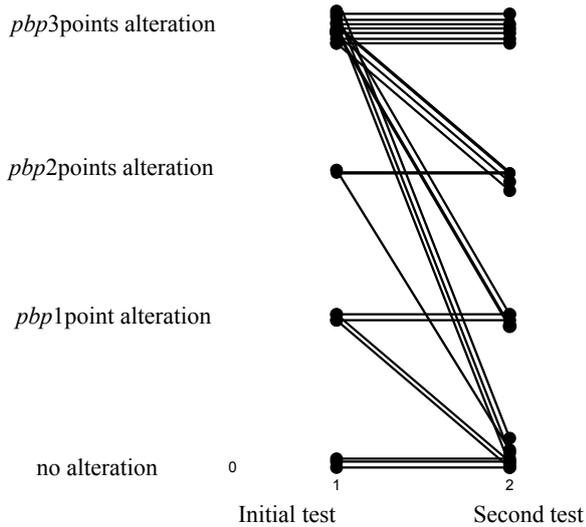


Fig. 2. Changes in the *pbp* gene alteration pattern of *Streptococcus pneumoniae* between the first and second tests in individuals.

Each black dot represents 1 patient.

minimized the prescription of antibiotics to pediatric outpatients with respiratory infections. When the cases necessitated antibiotic use, we administered amoxicillin as a first choice for empirical therapy. We again investigated the rate of penicillin-resistant *S. pneumoniae* from 2004 to 2006. There were 1190 isolates of *S. pneumoniae*. Of the 1190 isolates, 525 (44.2%) isolates were intermediate-resistant, and 332 (27.9%) isolates were resistant, according to previous susceptibility breakpoints. Compared to the previous study (2001-2003), the rate of resistant isolates showed a decrease of 5.9% ($p < 0.01$), whereas the rate of susceptible isolates showed an increase of 8.5% ($p < 0.01$) (Fig. 3). Gene detection was performed for 202 randomly chosen isolates. Table 3 shows the results of gene detection; gene alteration was observed in 15.5% isolates in the 2001-2003 study and in 21.8% isolates in the latter study ($p = 0.09$). The percentage of isolates with more than 2 altered *pbp* genes did not change significantly during the studies⁴⁴.

We also investigated 1137 isolates of *H. influenzae* from 2004 to 2006. Of the 1137 isolates, 119 (10.5%) isolates were BLNAR, and 63 (5.5%) isolates were BLPAR. Thus, the total percentage of ampicillin-resistant isolates was 18%, and did not statistically differ from the results of a previous study⁴⁵.

These studies showed some improvements in

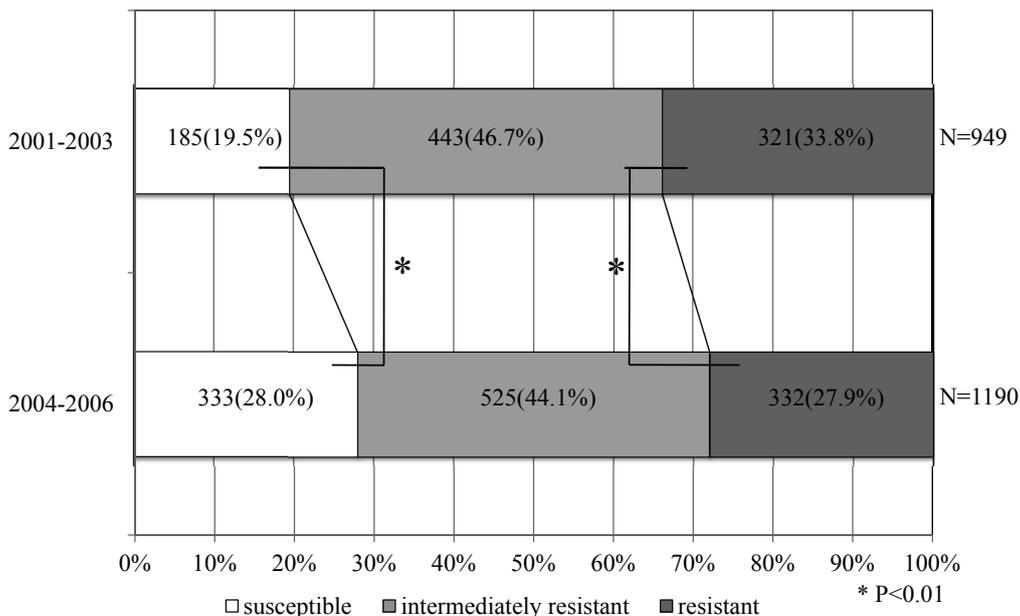


Fig. 3. The rates of penicillin-resistant *Streptococcus pneumoniae* in the former study performed from 2001 to 2003 and in the latter study performed from 2004 to 2006 “Susceptible” indicates penicillin-susceptible isolates (MIC < 0.12 mg/L), “intermediate-resistant” indicates isolates with intermediate resistance to penicillin (MIC = 0.12-0.10 mg/L), and “resistant” indicates penicillin-resistant isolates (MIC ≥ 2.0 mg/L).

the carriage of resistant strains in children. However, changes were not as obvious as predicted. Findings might show only a small incidence of *S. pneumoniae* resistance, even though we tried to reduce antibiotic use. Moreover, the carriage of resistant strains is expected to be influenced by the prescribing habits of the physicians in the surrounding areas. This research should be continued to monitor the trends in development of resistance.

Is amoxicillin a safe alternative ?

We have investigated the antibiotic history of host patients of *S. pneumoniae* and *H. influenzae*. Fig. 4 shows the rate of antibiotic use in the 2001-2003 and 2004-2006 studies. The total rate

of antibiotic use did not decrease significantly during the 2 tests. As we have used amoxicillin as a first choice for empirical therapy of respiratory infection, the frequency of amoxicillin use was much higher than that of cephalosporin antibiotics. Fig. 5 exhibits the obvious correlation between amoxicillin use and the accretion of *pbp* genes in *S. pneumoniae*. It suggests that development of resistance in these isolates might have been influenced by amoxicillin, which was used more frequently than cephalosporin antibiotics.

Some researchers previously reported the relation between alteration of *pbp* genes and the development of amoxicillin resistance in the clinical isolates of *S. pneumoniae*⁴⁶⁻⁴⁸. We are concerned that

Table 3. The results of *pbp* gene detection

	2001-2003 <i>N</i> =226 <i>n</i> [%]*	2004-2006 <i>N</i> =202 <i>n</i> [%]*
none	26[11.5]	20[9.9]
an altered <i>pbp</i> gene	35[15.5]	44[21.8]
<i>pbp1a</i>	0	1[0.5]
<i>pbp2b</i>	0	2[1.0]
<i>pbp2x</i>	35[15.5]	41[20.3]
more than two altered <i>pbp</i> gene	165[73.0]	138[68.3]
<i>pbp1a</i> +2 <i>x</i>	20[8.8]	16[7.9]
<i>pbp2x</i> +2 <i>b</i>	24[10.6]	14[6.9]
<i>pbp1a</i> +2 <i>x</i> +2 <i>b</i>	121[53.5]	108[53.5]

*Numbers of *Streptococcus pneumoniae* isolates.

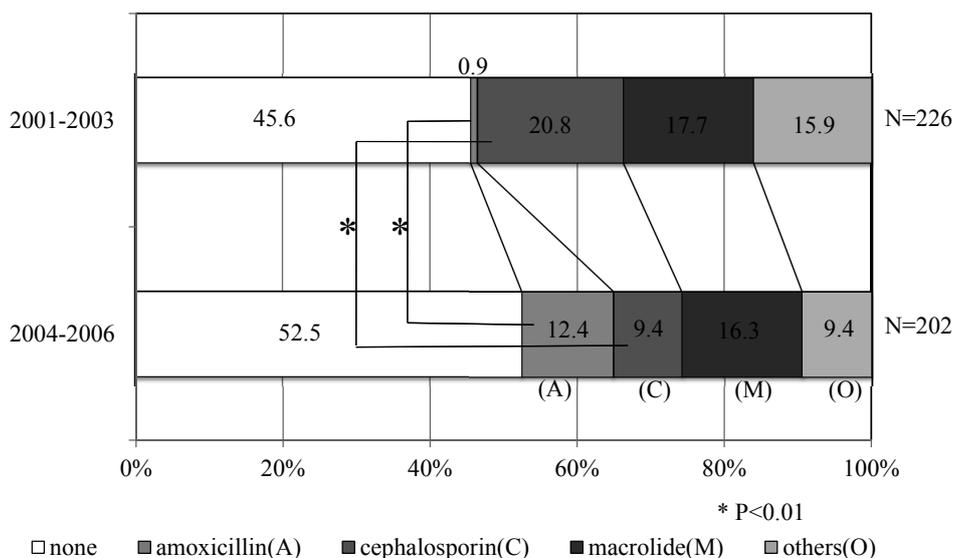


Fig. 4. The classification of antibiotics administered to the host patients of *Streptococcus pneumoniae* in the past 3 months.

"Others" includes fosfomycin and minocyclin. The numbers indicate the percentage of number of patients in each category. The χ^2 test was performed for comparing the results of the former and latter studies. * indicates a *p* value less than 0.01.

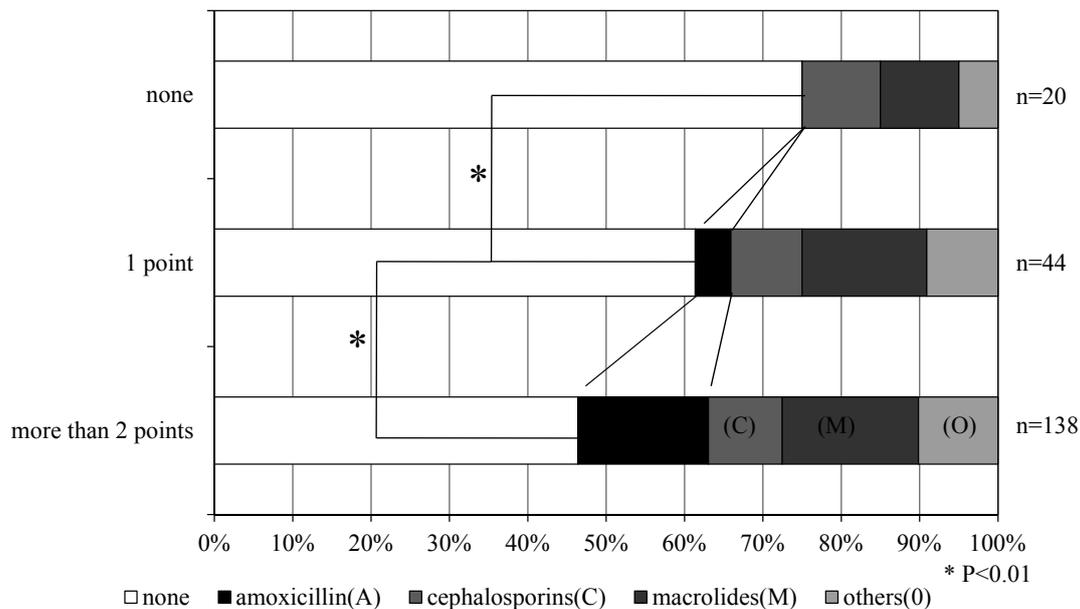


Fig. 5. The relation between antibiotic history and carriage of *Streptococcus pneumoniae* with altered *pbp* gene(s) in the study performed from 2004 to 2006.

“Others” includes fosfomycin and minocyclin. The virtual line indicates the number of *pbp* gene alterations. The χ^2 test was performed for comparing the antibiotic history of patients with resistant isolates with that of patients with susceptible isolates. * indicates a *p* value less than 0.01.

amoxicillin is not a safe alternative to prevent the emergence of resistant strains. The research should proceed to clarify the relation between amoxicillin use and resistance development in *S. pneumoniae*, which is essential for the reassessment of a beneficial approach for the treatment of pediatric respiratory infections^{44,45}.

The problem with the indication for macrolide antibiotics

Figure 4 shows the rate of use of macrolide antibiotics in both studies. The rate was 16.3% in the latter study, and it did not significantly differ from that observed in the initial study (2001–2003). We considered that one of the reasons that physicians frequently decide to prescribe macrolide antibiotics is concern over possible *Mycoplasma pneumoniae* or *Bordetella pertussis* infections. These respiratory infections are important examples of indication for macrolide antibiotics, and it is difficult for physicians to diagnose these infections only on the basis of physical findings. A previous study explained that macrolide antibiotics have an intense effect on *S. pneumoniae* resistance against both beta-lactam and macrolide antibiotics⁴⁹. In our former study, macrolide antibiotic use was obviously related to the alteration of *pbp* genes (Fig. 1, Fig. 5), unlike in the latter study. Further investigation is

required to clarify how macrolide antibiotics affect resistance not only to macrolide antibiotics but also to beta-lactam antibiotics. The method used to rule out the indication for macrolide antibiotics when we treat patients with respiratory infections also needs to be reconsidered.

CONSIDERATIONS

Can we prescribe fewer antibiotics ?

Despite intervention for restrictive antibiotic use, 47.5% of patients with respiratory infection were still administered antibiotics. It is necessary to reconsider the techniques used to promote appropriate use of antibiotics. Previous studies reported that the leading cause of physicians prescribing antibiotics was parents' request^{31,50–56}. The parents' lack of knowledge about proper antibiotic use can, therefore, be expected to cause inappropriate antibiotic prescription. However, even when parents have a good understanding of the issue, physicians tend to prescribe antibiotics, because they perceive parents' queries about the treatment plan as an expectation for antibiotic use^{50,53,54}. A previous study reported that parents were satisfied when the physicians took what they perceived as an adequate amount of time to examine their child, regardless of

whether an antibiotic was subsequently prescribed⁵⁷). It is necessary for physicians to be aware of the parents' beliefs and to improve their communication skills.

Diagnostic uncertainty also results in inappropriate antibiotic use⁵⁴). Currently, quick and easy devices for detecting antigens of etiological agents such as *Mycoplasma*, influenza virus, RSV, and adenovirus, are being developed. This should allow physicians to rule out the need for antibiotic use. Some studies reported a "wait-and-see" strategy for middle ear infections⁵⁸⁻⁶³). They concluded that most patients with non-severe middle ear infections recover without antibiotics. However, antibiotic-free treatment is not risk free. Another study proposing the "wait-and-see" strategy for middle ear infection mentioned that children who failed to improve without antibiotics were younger than those who improved, and were colonized with pathogens⁶³). In our study of antibiotic-free therapy for inpatients with RSV infection, we found that isolation of nasopharyngeal strains of *S. pneumoniae* and/or *H. influenzae* was a risk factor for the failure of antibiotic-free treatment⁴²). We considered that a "wait-and-see" strategy would work for pediatric patients with non-severe viral respiratory infections. The chief point is to carefully monitor the patients while waiting for treatment response. Further studies need to be performed to develop a tool to predict the patients who will recover without antibiotic use.

The introduction of vaccines against S. pneumoniae and H. influenzae

An *H. influenzae* type b (Hib) conjugate vaccine, first developed in the late 1980s, has been in worldwide use. The World Health Organization (WHO) has recommended a national routine immunization schedule including the Hib vaccine since 1998^{64,65}). Previous studies reported that the incidence of Hib disease had decreased after the introduction of routine immunization⁶⁶⁻⁷²). A pneumococcal conjugate vaccine including 7 serotypes has been available since 2000. The WHO has also recognized the safety and effectiveness of the pneumococcal vaccine, and has recommended the vaccine to be included in national immunization programs⁷³). Routine immunization with pneumococcal vaccine has showed a decreased incidence of vaccine-type pneumococcal invasive diseases and nasopharyngeal colonization in vaccinated individuals⁷³⁻⁸³). The costs and benefits of these vaccines have been well investigated in previous studies; most studies showed

that routine immunization with these vaccines is cost effective⁸⁴⁻⁸⁷). The previous report also proved the cost-effectiveness of using Hib vaccine in our country⁸⁸).

The arrival of Hib and pneumococcal conjugate vaccines in Japan will influence the methods used for ruling out the indication for antibiotics. A previous study showed that physicians prescribe antibiotics less frequently in vaccinated patients than in patients who have not been vaccinated⁸⁹). The vaccines may contribute not only to decrease the incidence of invasive diseases caused by *S. pneumoniae* and *H. influenzae* but also to decrease antibiotic prescription for pediatric patients.

LIMITATIONS

Our studies had several limitations. First, the method used to isolate *S. pneumoniae* strains could cause a possible bias, because only a single colony of *S. pneumoniae* was examined from each patient. Since the nasopharyngeal strains are considered to have varied susceptibilities to antibiotics, a single colony might not provide a representative resistance rate. It would be logical to assume that we investigated only the predominant strains. Second, the term of patient's symptoms might be biased. For example, during antibiotic-free treatment for inpatients with RSV infection, we had administered antibiotics on day 5 of fever, and the duration of fever was possibly limited because of antibiotic use. Since the studies were performed clinically, priority must be given to patient recovery. It is, therefore, difficult to present a definitive outcome of antibiotic-free treatment. When planning the next study, we need to consider the design of the study from different angles. Third, it is not appropriate to generalize from our results because the studies were performed at a single institution. Reports about promoting proper antibiotic use need to be generated from different areas, and the facts and findings from these reports should be considered when we apply our particular experience to actual medical examinations.

CONCLUSION

We reviewed a 5-year period of intervention for appropriate antibiotic use at a single institution. During this period, we found that an antibiotic-free term inhibited the emergence of antibiotic-resistant strains. We also found that although most pediatric patients with respiratory infections recovered with-

out antibiotic treatment, few patients did not. We concluded that a “wait-and-see” strategy would work for patients with respiratory infections under conditions of careful examination and observation. Despite the intervention, we could not reduce the rate of antibiotic prescription as expected. We should recommend such interventions to colleagues as well as to caregivers and physicians in the surrounding areas. It is highly necessary to educate the parents so that they understand appropriate use of antibiotics, and to improve the physicians’ communication skills. It is also important to inform the physicians about the rate of resistance to maintain awareness about appropriate use of antibiotics^{90–96}. The methods used for ruling out the indication for antibiotics are bound to change in this new era. Using rapid antigen tests, physicians can easily exclude patients testing positive for a viral infection. They also need to consider whether patients have been vaccinated for *S. pneumoniae* and *H. influenzae*.

Medicine has long benefitted from the use of antibiotics. However, we are now faced with the victims of resistant microbes that have been generated by the overuse of antibiotics. Reducing inappropriate antibiotic use is a very difficult task for physicians. However, there are suggestions on the possible methods to achieve this in pediatric patients. A previous report concluded that treatment plans should focus on making a child feel better, rather than on antibiotic use⁵². We believe that the problems of inappropriate use of antibiotics and emergence of resistant strains will be improved by this fundamental step in the pediatric treatment.

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