

## ORIGINAL ARTICLE

## Antibiotic selection patterns in acutely febrile new outpatients with or without immediate testing for C reactive protein and leucocyte count

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**Background:** Excessive use of broad spectrum antibiotics is related to the spread of drug resistant bacterial strains in the community.

**Aim/methods:** The effects of immediate testing for C reactive protein (CRP) and white blood cell count (WBC) on physicians' choices of antibiotic was investigated in patients with acute infection. Acutely febrile new outpatients were randomised into two groups: group 1 (147 patients) underwent CRP and WBC testing before initial consultation (advance testing). Prescriptions were compared with those in group 2 (no advance testing; 154 patients).

**Results:** In non-pneumonic acute respiratory tract infections, 61 (58%) and 122 (91%) of group 1 and 2 patients were prescribed antibiotics, respectively. Cefcapene pivoxil (third generation cephalosporin) and amoxicillin were the most frequently chosen drugs for group 1 and 2, respectively. Total prescriptions of newer, extended spectrum antibiotics (cefcapene pivoxil and clarithromycin (advanced macrolide)) were reduced by 25% in group 1, although they increased in rate (41 (67%) v 55 (45%) prescriptions) because of the decreased prescription of amoxicillin. In group 1, cefcapene pivoxil was preferentially selected when WBC values were greater than  $9 \times 10^2$ /litre. Prescription shifted to macrolides (mainly clarithromycin) in patients without leucocytosis. Patient treatment outcome did not significantly differ between the two groups.

**Conclusions:** The availability of CRP and WBC data during initial consultation greatly reduced prescription of amoxicillin, but had a lesser effect on newer, potent, broad spectrum antibiotics.

Although recent progress in developing newer classes of antimicrobial drugs has contributed to the control of infectious disease, the increasing use of newer, broad spectrum antibiotics has led not only to rising drug costs but also to the emergence and spread in the community of antibiotic resistant bacterial strains, which in turn has resulted in increased morbidity and mortality and higher healthcare costs.<sup>1,2</sup> Indeed, too often physicians prescribe antibiotics to patients with common infections such as uncomplicated acute respiratory tract illness.<sup>3–6</sup> Furthermore, recent studies demonstrated that in acute respiratory tract infections, non-recommended, broad spectrum antibiotics were chosen in more than 50% of ambulatory patients prescribed an antibiotic.<sup>7–9</sup> Although the mechanisms of resistance to the various antimicrobial drugs are complex, the major risk factor for carriage and spread of resistant bacteria clones is clear—previous and current antibiotic use.<sup>10,11</sup> Therefore, the successful reduction of antibiotic prescription for common infectious conditions would probably provide enormous public benefit through decreased resistance in bacteria and prolonged antibiotic efficacy.

“Too often physicians prescribe antibiotics to patients with common infections such as uncomplicated acute respiratory tract illness”

Various reasons have been given for why many physicians prescribe unnecessary antibiotics to patients with common infections, including patient expectations, purulent secretions, physician workload, and financial incentives, in addition to diagnostic uncertainty.<sup>12–16</sup> Reports show that a

large proportion of uncomplicated acute respiratory tract infections, even with purulent clinical manifestations, are caused by viruses.<sup>17</sup> However, at the individual patient level, physicians may not be able to satisfy themselves of the viral nature of the infection from symptoms and physical findings alone, leaving the possibility of bacterial origin. Standard microbiological procedures take too long and are not available during consultation. Therefore, diagnostic uncertainty will probably tempt physicians to prescribe antibiotics and to choose ones that can cover all possible causative bacteria. We hypothesised that if physicians were provided with test results suggestive of non-bacterial infection while the patient is in the surgery, unnecessary antibiotic prescription might decrease.

We previously demonstrated the usefulness of C reactive protein (CRP) and leucocyte count (white blood cell count; WBC) in differentiating between infections of bacterial and non-bacterial origin.<sup>18–20</sup> Furthermore, immediate availability of CRP and WBC data during initial consultation has certainly decreased antibiotic prescriptions.<sup>21</sup> Therefore, immediate test result notification might be an effective means of altering physicians' prescribing decisions. In addition, it is of interest to analyse the influence of immediate testing on physician's antibiotic choices, in connection with the appropriate usage of antibiotics. In our present study, we analysed physicians' antibiotic selection patterns in the presence or absence of CRP and WBC test results, with particular attention to newer, broad spectrum antibiotic prescribing.

**Abbreviations:** CRP, C reactive protein; WBC, white blood cell count

## PATIENTS AND METHODS

### Patients and study design

Among the new outpatients who visited the general/internal medicine clinic of Nishi-Ohmiya Hospital (a regional/community hospital), Japan, 305 patients presenting with an acutely febrile condition and suspected of having infection were entered into our study. A total of 11 physicians participated in patient clinical examination during the study period from December 2000 to January 2003. These physicians were heterogeneous in age (29–53 years old), clinical experience (5–29 years of experience in clinical practice), educational background, and work style (three full time and eight part time physicians). Patients who had clinically relevant fever ( $\geq 37.5^{\circ}\text{C}$ ) and symptom(s) suspected of infection at the time of (or during the week before) the initial consultation were randomised by a study controller into two groups. One patient group universally underwent CRP and WBC testing before the initial consultation (advance testing group; 147 patients). In this group, the patient consultation was concurrent with the testing process, so that the initial clinical diagnosis and prescribing decisions were made after the test results were reported. The other patient group did not receive tests before the initial consultation, and the diagnosis and decision making for patient treatment and management were essentially based on history taking and physical examination (non-advance testing group; 154 patients). Each physician, except for a small number who saw few patients, examined almost equal numbers of patients with and without advance testing. In both the patient groups, our study design did not restrict urgent testing thought to be necessary by the physician, such as chest x ray and chemistry tests or CRP and WBC subsequent to history taking and physical examination. Thus, the patients who did not receive universal advance testing suffered no clinical or ethical disadvantage. The results of non-urgent tests ordered at the initial consultation (additional or subsequent tests) were evaluated on the patient's next visit. All patients were informed of the study design and registered only after providing written informed consent to the study. The research protocol was approved by the hospital's clinical study committee.

### Measurement of CRP and complete blood count

CRP was measured with an automated multichannel analyser (model TBA-30FR; Toshiba, Saitama City, Japan). Complete blood count was analysed with an automated blood cell counter (model KX-21; Sysmex, Kobe, Japan). Approximately 40–50 minutes was required to obtain a CRP result and 10 minutes for a WBC measurement, provided that the analysers were ready to use. Between run imprecision (coefficient of variation) ranged from 3.3% to 6.3% at 5–22 mg/litre for CRP and from 5.3% to 5.9% at  $2.5\text{--}6.8 \times 10^9/$

litre for WBC.<sup>21</sup> The reference intervals used by physicians were  $\leq 5$  mg/litre for CRP and  $3.5\text{--}9.0 \times 10^9/\text{litre}$  for WBC.

### Clinical data assembly

In addition to the patient's essential clinical characteristics, we collected data on test results (advance test items and other urgent or non-urgent tests), clinical diagnosis, physician's differentiation of infection (bacterial or non-bacterial), prescription menu (antimicrobials and other drugs), and physician's decision for patient management. The medical records of all patients were reviewed thoroughly to identify the physician's diagnosis and decisions and clinical action that followed.

The clinical course of individual patients was pursued on the medical record and on our follow up questionnaire. Among the indicators used to assess treatment outcome at the individual patient level were patient reconsultation rate, number of febrile days after starting treatment, number of patients prescribed oral and/or intravenous antibiotics during reconsultation (initial treatment failure), number of patients receiving treatment modification during the disease course, and requirement of further testing at the follow up consultation.

### Statistical analysis

Data were analysed by statistical comparison using the  $\chi^2$  test or the Fisher exact test for categorical and binary variables. The distribution of continuous data was analysed using the Mann-Whitney U test or the Student's *t* test (StatFlex 5.0; Artec Inc, Tokyo, Japan). All statistical tests were two tailed.

## RESULTS

### Antibiotics prescribed to study patients

Nine oral antibiotics and five antibiotics for intravenous infusion were administered to patients enrolled in our study. The oral antibiotics prescribed were grouped into: broad spectrum penicillin (amoxicillin); first generation (cefaclor) and third generation (cefcape pivoxil) cephalosporins; older generation (erythromycin), 16 membered ring (rokitamycin), and advanced (clarithromycin) macrolides; and fluoroquinolones (norfloxacin, levofloxacin, and ofloxacin). The five parenteral antibiotics used were: cephalosporins (cefazolin, cefotiam); fosfomycin; oxacephem antibiotic (flomoxef); and carbapenem antibiotic (panipenem/betamipron).

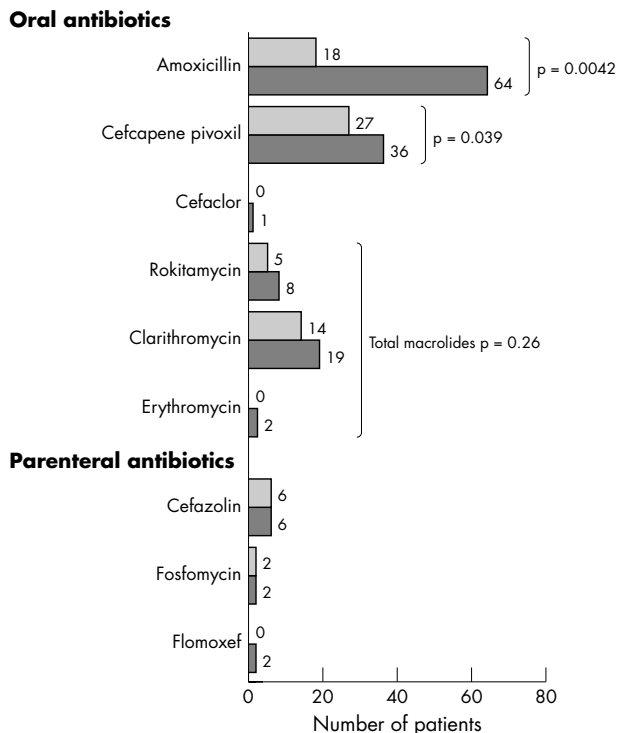
### Clinical diagnosis and antibiotic use

The patients' clinical characteristics were almost identical between the two groups.<sup>21</sup> Three patients in the advance testing group required hospitalisation at the initial visit (two patients) or at reconsultation (one patient), and two patients in the other group were admitted at the initial visit. Table 1

**Table 1** Clinical diagnosis of study patients and number of patients receiving antibiotic(s)

| Diagnosis   | With advance testing (n = 147) |  | Without advance testing (n = 154) |  |
|---|--------------------------------|--|-----------------------------------|--|
|   | No. of patients diagnosed      | No. of patients prescribed antibiotic(s) | No. of patients diagnosed         | No. of patients prescribed antibiotic(s) |
| Acute upper or lower respiratory tract infections       | 106                            | 61*                                      | 134                               | 122*                                     |
| Pneumonia/pleuritis                                     | 6                              |  | 1                                 | 1  |
| Influenza   | 27                             | 5  | 11                                | 4  |
| Systemic viral infection†                               | 5                              | 1  | 1                                 | 1  |
| Acute gastroenteritis                                   | 15                             | 3  | 17                                | 3  |
| Urinary tract infection                                 | 0                              | 0  | 2                                 | 2  |
| Others  | 4                              | 0  | 6                                 | 2  |
| Total no. of diagnoses and patients given antibiotic(s) | 163                            | 76*                                      | 172                               | 135*                                     |

\* $p < 0.001$  for difference in prescription between the two patient groups; †diagnosed as Epstein-Barr virus infection (3 patients), chicken pox (2 patients), and causative virus unknown (1 patient).



**Figure 1** Antibiotics prescribed to patients with acute infections of the upper (pharyngitis, tonsillitis, laryngitis, and common cold) and lower (acute bronchitis) respiratory tract. Lightly shaded columns indicate patients in the advance testing group and the darker columns those in the non-advance testing group. In total, 61 of 106 advance testing patients and 122 of 134 non-advance testing patients were prescribed antibiotic(s) for non-pneumonic acute respiratory tract infections.

lists the clinical diagnoses obtained from history taking and physical examination with or without CRP and WBC test results (and/or other urgent tests when deemed necessary). Acute infection of the upper (pharyngitis, tonsillitis, laryngitis, and common cold) or lower (acute bronchitis) respiratory tract was the most frequent diagnosis in both patient groups, being diagnosed in 72% and 87% of advance testing and non-advance testing patients, respectively. Sixty one (58%) of the 106 advance testing patients diagnosed with non-pneumonic acute upper or lower respiratory tract infection received antibiotic(s). In contrast, in the non-advance testing group, 122 (91%) of the 134 patients with non-pneumonic respiratory tract infections received antibiotic(s).

Figure 1 compares the oral and parenteral antibiotics administered to patients with non-pneumonic acute respiratory tract infections in the two patient groups. In both patient

groups, most of the antibiotics given were broad spectrum agents. Cefcapene pivoxil was the most frequently prescribed in advance testing patients, whereas amoxicillin was given to more than half of the non-advance testing patients. Significant differences were seen between the two groups in the prescribing of these antibiotics (fig 1), particularly in amoxicillin prescription. The absolute number of patients receiving newer, extended spectrum antibiotics (cefcapene pivoxil (third generation cephalosporin) and clarithromycin (advanced macrolide)) was reduced by 25% in the advance testing group, although the rate was increased (41 of 61 (67%) v 55 of 122 (45%); p = 0.0031).

**Antibiotic selection based on CRP and WBC values**

In advance testing patients, we analysed the relation between the physician’s choice of antibiotics and the results of the CRP and WBC tests (table 2). The physicians prescribed amoxicillin or cefcapene pivoxil to 29 of the 47 patients with CRP values  $\geq 40$  mg/litre and to 34 of the 43 patients with WBC values  $\geq 9 \times 10^9$ /litre, whereas only seven of the 81 patients who had CRP values  $< 40$  mg/litre and WBC values  $< 9 \times 10^9$ /litre received these bactericidal antibiotics. Cefcapene pivoxil was selected in a significantly higher proportion of patients with WBC values of  $\geq 9 \times 10^9$ /litre (51% of patients prescribed any antibiotic) than those without leucocytosis (26%; p = 0.025). More than 60% of patients with CRP and WBC values lower than 40 mg/litre and  $9 \times 10^9$ /litre, respectively, received no antibiotics. A macrolide antibiotic (mainly clarithromycin) was selected preferentially when patients had a WBC value of  $< 9 \times 10^9$ /litre compared to one of  $\geq 9 \times 10^9$ /litre (19 (50%) of 38 versus 3 (7.7%) of 39 patients receiving antibiotics; p < 0.001); however, the shift to macrolides was less obviously related to CRP values (p = 0.051).

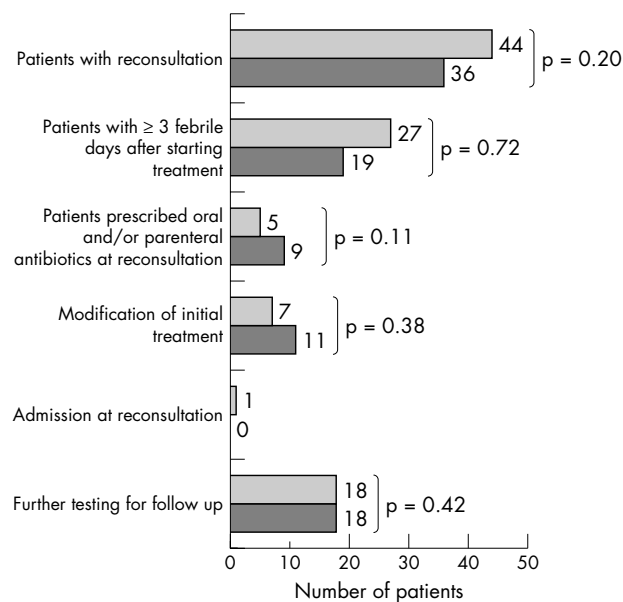
**Treatment outcome at the individual patient level**

We compared treatment outcome between the two groups (fig 2). The reconsultation rate was slightly higher in patients subjected to advance testing, but was not significantly different between the two groups (fig 2). Among patients who filled out and returned our follow up questionnaire (59 and 45 patients with and without advance testing, respectively), the incidence of prolonged fever ( $\geq 3$  febrile days) after starting treatment was similar between the two groups (27 (45%) and 19 patients (42%), respectively). In the advance testing group, oral and/or intravenous antibiotic administration was begun in five patients at the follow up consultation because of unimproved physical condition, whereas seven received some modification to the initial treatment (such as change of antibiotic or addition of intravenous fluid supplement). The rate of initial treatment failure—indicated by start of antibiotic treatment on reconsultation—was higher in patients without advance testing

**Table 2** Influence of CRP and WBC count data on physicians’ choices of antibiotics in patients with acute infection

|                              | CRP $\geq 40$ mg/l<br>(n=47) | CRP $< 40$ mg/l<br>(n=100) | WBC $\geq 9 \times 10^9$ /l<br>(n=43) | WBC $< 9 \times 10^9$ /l<br>(n=104) | CRP $\geq 40$ mg/l and<br>WBC $\geq 9 \times 10^9$ /l<br>(n=24) | CRP $< 40$ mg/l and<br>WBC $< 9 \times 10^9$ /l<br>(n=81) |
|------------------------------|------------------------------|----------------------------|---------------------------------------|-------------------------------------|---|---|
| Amoxicillin                  | 13                           | 9                          | 14                                    | 8                                   | 6   | 1   |
| Cefcapene pivoxil            | 16                           | 14                         | 20*                                   | 10*                                 | 12  | 6   |
| Rokitamycin                  | 2                            | 5                          | 1                                     | 6                                   | 1   | 5   |
| Clarithromycin               | 5                            | 10                         | 2]**                                  | 13]**                               | 1   | 9]***   |
| Fluoroquinolones             | 2                            | 1                          | 2                                     | 1                                   | 1   | 0   |
| No antibiotic administration | 8                            | 63                         | 3                                     | 68                                  | 1   | 61  |
| Antibiotic infusion          | 6                            | 5                          | 9                                     | 2                                   | 5   | 1   |
| Admission                    | 3                            | 0                          | 3                                     | 0                                   | 3   | 0   |

Number of patients receiving an antibiotic prescription.  
\*p=0.025 for difference in prescription between two categories. \*\*p<0.001; \*\*\*p<0.001 for differences in prescription of total macrolides.



**Figure 2** Treatment outcome in study patients. Outcome was assessed by the reconsultation rate, number of febrile days after starting treatment, changes to initial treatment at follow up consultation, decision to admit patient to hospital on reconsultation, and ordering of further laboratory tests to follow up patient condition. Lightly shaded columns indicate the number of patients in the advance testing group and darker columns the number in the group without advance testing. Duration of febrile days was evaluated in patients who filled in and returned our follow up questionnaire (59 and 45 patients with and without advance testing, respectively). The incidence of prolonged fever ( $\geq 3$  febrile days) was thus 45% and 42% in the respective patient groups.

(nine v six patients, with the latter including one admitted to hospital for intensive antibiotic treatment), although the difference was not significant ( $p = 0.20$ ).

## DISCUSSION

In our present study, we analysed the effects of CRP and WBC data provided to a physician at initial consultation on antibiotic selection. The main effect of the CRP and WBC intervention was a drastic reduction in the amount of amoxicillin used, resulting in a rise in the proportion of extended spectrum antibiotics prescribed. Because our results indicate that the decision to prescribe newer, more potent, extended spectrum antibiotics was less affected by CRP and WBC advance testing than amoxicillin prescription, there may be influences driving the use of these antibiotics. Physicians probably selected amoxicillin in the non-advance testing patients because, although common acute respiratory tract infections are mainly caused by viruses and are self limiting, the occasional bacterial infection can occur. In other words, lack of diagnostic certainty at initial consultation may have induced physicians to prescribe an antibiotic such as amoxicillin to cover such occasional cases, and it is not surprising that test results confirming non-bacterial infection reduced this unnecessary prescription of amoxicillin. Indeed, more than 60% of advance testing patients with CRP values  $< 40$  mg/litre and WBC values  $< 9 \times 10^9$ /litre received no antibiotics (table 2). In contrast, when there was evidence of probable bacterial infection, physicians chose more powerful antibiotics, such as cefcapene pivoxil, rather than amoxicillin (table 2). A large decrease in amoxicillin use in patients with advance testing would be justified, because patient treatment outcome did not differ between the two groups (fig 2). However, our results also indicate that test result based, selective chemotherapy using newer, more potent antibiotics

## Take home messages

- The availability of C reactive protein concentrations and white blood cell counts during initial consultation greatly reduced the prescription of amoxicillin, but had less of an effect on newer, potent, broad spectrum antibiotics
- This reduction had no effect on patient outcome
- A physician education programme should be introduced to encourage the judicious use and appropriate selection of antimicrobial drugs

did not significantly improve treatment efficacy compared with amoxicillin predominant treatment in the non-advance testing group.

A wide variety of antibiotics is used in primary care, but there is little information to help physicians determine the best initial choice of antibiotic for common infectious conditions. Other investigators also reported a trend to prescribe newer, non-recommended, broad spectrum antibiotics even for common acute respiratory tract infections.<sup>7-9</sup> However, there has been controversy as to whether any of the newer, more potent antibiotics are significantly more effective than older, less expensive drugs such as amoxicillin. Recent meta-analyses showed that amoxicillin is essentially as effective as newer, more potent, extended spectrum drugs for the initial treatment of some common infections, such as uncomplicated acute sinusitis.<sup>22 23</sup>

In the advance testing group, we subsequently analysed the influence of CRP and WBC values on the physician's choice of antibiotic. High WBC values ( $\geq 9 \times 10^9$ /litre) were more strongly correlated with choice of amoxicillin or cefcapene pivoxil than were raised CRP values ( $\geq 40$  mg/litre) (table 2). Prescription shifted to macrolides when patients had a WBC value of  $< 9 \times 10^9$ /litre, but this shift was less prominently related to CRP values. These results indicate a stronger reliance on WBC values than CRP values when differentiating infection and selecting a particular antibiotic. The shift to macrolide selection in patients without leucocytosis is possibly attributable, at least in part, to physicians' attention to atypical pathogens such as *Mycoplasma pneumoniae* and chlamydia species, against which macrolides are effective. Again, physicians preferentially chose a more potent one (clarithromycin).

*"Our results indicate a stronger reliance on white blood cell counts than C reactive protein values when differentiating infection and selecting a particular antibiotic"*

There are limitations to our present study. We analysed physicians' antibiotic selection patterns mainly in patients with non-pneumonic acute respiratory tract infections. Thus, our data may not apply to infections at other sites, such as urinary tract infection and pneumonia, to which antibiotic treatment should be directed in most patients. In addition, our study was carried out in a single hospital with a small number of patients and a limited number of physicians. Heterogeneity in physicians' age, educational background, and clinical experience may have influenced our results. Therefore, this pilot clinical study should be extended to involve large numbers of patients and physicians in multiple institutes to enable further analyses for confounding variables.

In conclusion, immediate testing for CRP and WBC could provide information on the origin of infection, reduce

uncertainty about infection origins, and thereby decrease overall unnecessary antibiotic use. Although advance testing resulted in a large reduction in amoxicillin prescription without deterioration of patient treatment outcome, this approach had a smaller effect on newer, more potent, broad spectrum antibiotics. Our results suggest that a physician education programme should be introduced to encourage the judicious use and appropriate selection of antimicrobial drugs.

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