



Are antibiotics beneficial to children suffering from enterovirus infection complicated with a high C-reactive protein level?



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ARTICLE INFO

Article history:

Received 14 February 2014

Received in revised form 9 April 2014

Accepted 11 April 2014

Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:

Enterovirus

Herpangina

Hand

foot and mouth disease

High C-reactive protein

Antibiotics

SUMMARY

Background: Enteroviruses are seasonally prevalent each year in Southeast Asia. Elevated C-reactive protein (CRP) levels have been noted in minor populations of patients, and antibiotics may be prescribed under the impression of a suspected bacterial infection. This prescription might be inappropriate, resulting in further bacterial resistance and medical expense. The aim of this study was to delineate how effective antibiotics are for children suffering from enterovirus infection complicated with a high CRP level.

Methods: The medical records of children hospitalized between January 2008 and December 2012 with herpangina or hand, foot and mouth disease were reviewed retrospectively. The children enrolled were divided into three groups, A, B, and C, by CRP level, which were <40, 40–80, and ≥80 mg/l, respectively. A case–control study of group C divided into subgroups according to the prescription of antibiotics for at least 24 h during the admission was conducted for further analysis.

Results: A total 3566 cases were identified; 214 were in group C and 71.0% of them received a prescription for antibiotics. There was a linear trend between a relatively higher CRP level and a higher proportion of antibiotics prescribed in the three groups ($p = 0.001$). In the case–control study, there were no significant differences in age, sex, mean CRP, or febrile days. However, a relatively longer stay of hospitalization was recorded in the subgroup with an antibiotic prescription ($p = 0.020$).

Conclusions: The present study indicated that antibiotics might not be beneficial in treating these patients, even those with a high CRP level. Clinicians should be more prudent in antibiotic use when no obvious evidence of bacterial infection is found.

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1. Introduction

There is a high prevalence and morbidity of diseases caused by enterovirus and coxsackievirus every year in Taiwan and Southeast Asia.^{1–5} They can be diagnosed easily by their clinical presentations of herpangina and hand, foot and mouth disease (HFMD). Most patients have a self-limiting illness that resolves within a few days without active intervention. A higher incidence and a possible

association with neurological sequelae and death have been shown in a few cases with laboratory risk factors such as a high leukocyte count and hyperglycemia. Previous studies have mainly focused on serious complications.³ However in a literature review, approximately 6% of uncomplicated cases were noted to have elevated C-reactive protein (CRP >80 mg/l).^{1,6} The implication of the CRP level and the subsequent indication for antibiotics in these patients have rarely been discussed.

CRP is produced by hepatocytes and is elevated at around 12 h after a viral or bacterial infection. It is a very convenient and readily available tool in clinical practice for infectious diseases, although the cut-off level is not always reliable.⁷ It rises in response to both

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infectious and inflammatory diseases and shows greater elevations in serious bacterial infections than in nearly all viral infections.^{6,8–11} Clinicians may distinguish those children who have a serious bacterial infection and who may benefit from antibiotics by a higher CRP level.

Therefore, a high CRP level in these cases remains a challenge for pediatricians.¹² Both doctors and parents are aware of the potential benefits of antibiotics for some patients and the potential risks of not treating a life-threatening infection in a small minority. Therefore, there is a relatively high motivation to prescribe antibiotics, despite the costs, adverse effects, and increasing potential antibiotic resistance resulting from this practice.

The present study had two specific aims. The first was to determine whether a higher CRP level in patients was associated with a higher proportion of antibiotic prescriptions. The second was to evaluate the potential benefits of antibiotics for herpangina or HFMD in those infants and children with a high CRP level (≥ 80 mg/l).

2. Materials and methods

2.1. Study population and definitions

We identified infants and children hospitalized with herpangina (074.0) or HFMD (074.3) by International Classification of Diseases Ninth Revision (ICD-9) code from our hospital database. Medical information including antibiotic prescriptions and laboratory data including serum CRP level and total white blood cell (WBC) count during the hospitalization were collected and analyzed. The laboratory data in this study were obtained at the time of the patient's first clinical evaluation. Initially, in accordance with previous studies,^{1,6} we divided the patients into three groups by CRP level: A < 40 mg/l, B 40–80 mg/l, and C ≥ 80 mg/l.

Patients enrolled in group C met the following criteria: (1) chief complaints of fever with or without a poor appetite; (2) all had both an initial impression and final diagnosis associated with herpangina or HFMD during this hospitalization; (3) all had a high CRP level, defined as no less than 80 mg/l (≥ 80 mg/l); and (4) none had suffered from herpangina or HFMD in the 2 weeks prior to this hospitalization. All cases had to fulfill these criteria. Institutional approval to carry out this study was received. Ethics review board approval was not required for this retrospective analysis.

The medical records of the cases were reviewed retrospectively for demographic data, underlying diseases, clinical manifestations, laboratory data, clinical outcome, and antibiotic therapy. Antibiotic therapy was defined as a prescription of antibacterial agents for more than 24 h during the admission. In the present study, septic workup for urinary tract infection included all urinalysis and urine culture. All patient urine specimens were collected by sterile plastic bag or midstream urine collection. If there was neither obvious pyuria (WBC $> 15 \times 10^6$ /l), as assessed by hemocytometer with an enhanced urinalysis, nor a single uropathogenic organism on urine culture ($> 10^5$ CFU/ml), this was recorded as a negative result of urine examination for the septic workup.

2.2. Analysis of the benefits of antibiotics by case-control study of group C

We conducted a case-control study to further analyze the effectiveness of antibiotics in our enrolled patients with high CRP levels (group C). The case group comprised those who were given antibiotic therapy for more than 24 h. The control group comprised those cases who did not receive antibiotic therapy. In general, fever is an objective symptom for the evaluation of infectious diseases. For the analysis of the potential benefits of antibiotics, we recorded the duration of hospitalization and the patient's clinical course

related to fever, including the number of febrile days before and after admission.

2.3. Statistical analysis

SPSS for Windows (version 17.0; SPSS Inc., Chicago, IL, USA) was used for the data analysis. Descriptive statistics were performed, with continuous variables summarized as the median and range, and categorical variables summarized as the frequency and proportion. The Chi-square test or Fisher's exact test, or a non-parametric test was used to assess differences between two groups. The prevalence of the samples was compared with the Chi-square test for linear trend. Statistical significance was set at $p < 0.05$.

3. Results

This retrospective cross-sectional study was conducted at Kaohsiung Chang Gung Memorial Hospital, a medical center with 170 pediatric ward beds and 53 intensive care unit beds, providing primary and tertiary care for infants and children in southern Taiwan. The annual emergency department census in this hospital is approximately 55 000 visits. The clinical microbiology laboratory and medical records center databases were reviewed in order to identify patients with enterovirus infections during the period January 1, 2008 to December 31, 2012.

During this period, there were 3664 admission episodes for infants and children with herpangina and HFMD. The laboratory data including CRP level and total WBC count were available for 3566 out of 3664 episodes; thus 98 of 3664 episodes were excluded from this study due to a lack of clinical and laboratory information. Antibiotics were prescribed in 537 of the 3566 episodes (15%). Finally, a total of 214 episodes (6%) were enrolled in group C on the basis of our criteria and were then evaluated further in a demographic and descriptive study. Although group C was the least populated group in our study, it had the highest

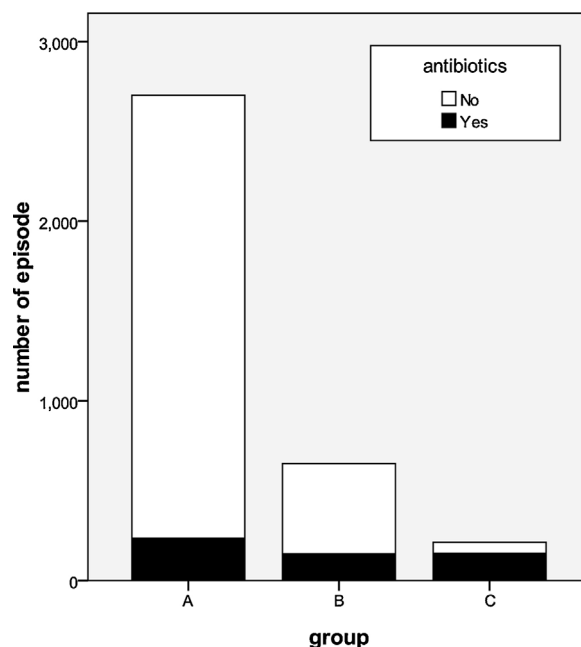


Figure 1. The proportion of antibiotic prescriptions is illustrated in groups A (8.7%), B (22.9%), and C (71.0%) according to the CRP level (< 40 , 40–80, and ≥ 80 mg/l, respectively). The black column shows the number of episodes with an antibiotic prescription in each group (A 236, B 149, and C 152); the white column shows the number of episodes without an antibiotic prescription in each group (A 2465, B 502, and C 62).

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