Differences between Japan and the U.S. in Test and Treatment Strategies in Pediatrics

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Abstract
The differences between Japan and the U.S. regarding the treatment strategies in pediatrics are discussed. In Japan, serum CRP measurement is considered an important screening test for serious bacterial infection and evaluating the effectiveness of treatment, antibiotics are used frequently for bacterial gastrointestinal infection, and theophylline is administered often to children with bronchitis or bronchial asthma. Theophylline is also given to children with asthmoid bronchitis. On the other hand, these tests and therapies are not frequently used in the U.S. These are preferred in Japan based on the physicians' experience and wishful thinking.

Key words Pediatrics in Japan and the U.S., CRP, Antibiotics, Bacterial gastrointestinal infection, Theophylline

Introduction
Each country has a distinct style in the practice of health care and medical sciences reflecting the tradition of the country. Japan has come through more than 130 years since the introduction of Western medicine and experienced strong influence of the U.S. medicine after the World War II. Despite this fact, there are several important differences between Japan and the U.S. in the test and treatment policies regarding the clinical findings and diseases in children.

The Use of Serum CRP
The first difference is the inclination of Japanese pediatricians toward the use of serum CRP (C-reactive protein) measurement in estimating the cause and evaluating the severity of infections. CRP was first recognized as the protein produced in the liver binded to and precipitated pneumococal C-polysaccharide.

While CRP has various physiological functions, it is generally understood as a marker for inflammatory response. I am not going to argue against this understanding, but more exactly, it should be considered as a protein that is called to action as a result of tissue damage. When tissue damage brings cells into direct contact with blood, the nuclei and DNA in such cells are quickly opsonized and processed in the reticuloendothelial system. Many Japanese physicians measure serum CRP as a marker for inflammatory response without recognizing the meaning of the important biological roles of CRP.

On the other hand, physicians in the U.S. do not measure CRP as frequently as in Japan. There are several reasons discouraging the measurement of CRP in patients with infection. Even in the case of bacterial infection, serum CRP is not elevated much in the early stage of infection. A patient with high fever due to bacterial brain abscess does not show elevated serum CRP because the presence of the blood-brain barrier prevents the transmission of the CRP production stimulus to the liver. Serum CRP may be elevated even in the case of viral infection, because EB virus, adeno-
virus, and some other viruses cause tissue damage. Hence, serum CRP by itself is not a definitive means for discriminating bacterial infection from viral infection. Because of these reasons, American physicians use blood cultures more frequently than Japanese physicians when serious bacterial infection is suspected, in particular when the focus of infection is not identified. This attitude of American physicians seems to reflect their philosophy of placing more emphasis on evidence. Recently, serum CRP is measured in the U.S. for research purposes. For example, obesity is considered a condition involving chronic inflammation, and this theory is supported by the small increase in blood CRP in obese persons.

The Use of Antibiotics for Bacterial Gastroenteritis

The second peculiarity of Japanese practice is the use of antibiotics for bacterial gastroenteritis. All physicians in Japan and in the U.S. know that enterohemorrhagic *E. coli* such as O157:H7 is the causative agent of bacterial gastroenteritis occurring frequently in the period from June to September. When a child is presented with diarrhea followed by bloody stool in summer, Japanese physicians use an antibiotic therapy typically with fosfomycin after a stool culture is done. A report from Japan demonstrated that the use of fosfomycin within 3 days after the onset of diarrhea was effective for the prevention of hemolytic uremic syndrome (HUS) secondary to enterohemorrhagic *E. coli* infection in a study comparing the groups with and without the use of fosfomycin. However, American physicians do not use antibiotics except for severe cases. To begin with, fosfomycin is not commercially available in the U.S. It should be noted that even in Japan, antibiotics are not given to patients with gastroenteritis, if *Salmonella* is considered to be the causative bacteria.

It is generally believed in the U.S. that there is no evidence that the use of antibiotics improves the course of bacterial gastroenteritis. On the final day of the international conference on verotoxin-producing *E. coli* (VTEC) in Washington DC, 1999, bacteriologists and pediatricians form Japan and the U.S. held a one-day conference sponsored by the Ministry of Health and Welfare. This conference only underscored the disagreement of opinions concerning the use of antibiotics. Bacteriologists from Japan alone argued for the usefulness of antibiotics. The report of the effectiveness of early fosfomycin therapy has not been a subject of serious consideration in the U.S., because it was not a controlled study.

Furthermore, the common opinion of pediatricians in the U.S. is represented by the report from Seattle claiming that the use of antibiotics increases the risk of HUS. Although the result of this study was statistically significant and should be respected, it should be interpreted with caution because the study might have been biased by two facts: the patients who received antibiotics were much fewer than those who did not and the HUS occurrence rate was much higher than that in Japan. We need to see some more evidence before concluding that antibiotics are detrimental, but experience in Japan has also shown that the early use of antibiotics cannot always prevent severe HUS. When Verotoxin has been absorbed from the small intestines before the onset of diarrhea in VTEC infection, it is impossible to prevent encephalopathy and nephropathy by the early use of highly bactericidal antibiotics.

The Use of Theophylline for Bronchitis and Bronchial Asthma

The third point is the use of theophylline for bronchitis and bronchial asthma. Formerly in the U.S., the round-the-clock (RTC) therapy with theophylline was used commonly for the prevention of acute bronchial asthma in children, but this therapy is rarely used at the present. Theophylline is also going out of use for the treatment of acute bronchial asthma. This change reflects the facts that the effectiveness of inhaled steroids for the prevention of acute bronchial asthma was proved, several new drugs for the treatment of acute bronchial asthma were developed, and the risk of theophylline intoxication has become widely known to people. As a result, the convenient kit for the bedside measurement of blood theophylline is no longer produced in the U.S. In the U.S., relatively inexpensive theophylline is regarded as an antiasthmatic drug for developing countries.

In Japan, the 2005 version of the guidelines for the treatment of bronchial asthma (“Japanese Pediatric Guideline for the Treatment and Management of Asthma 2005” [JPGL 2005]) was published by the Japanese Society of Pediatric Allergy and
Clinical Immunology. The new version advises increased caution regarding the use of theophylline for the treatment of acute bronchial asthma. However, theophylline is still used in Japan, often on an outpatient basis, not only for bronchial asthma but also for bronchiolitis, bronchitis, and asthmatoid bronchitis in children.

The margin between the therapeutic range and the toxic range of theophylline is small, and theophylline intoxication may occur unless the blood level is monitored. There also have been cases of younger children developing so-called theophylline-associated convulsions, in which serious convulsions take place even when the blood level is lower than the toxic range. Convulsions due to theophylline intoxication and convulsions associated with the nontoxic blood levels of theophylline are often refractory, responding poorly to anticonvulsants and persisting for a long time. Such convulsions frequently leave aftereffects such as central nervous system (CNS) damages.

Recently, there have been an increasing number of lawsuits in Japan concerning the cases in which high blood levels of theophylline caused convulsions and CNS aftereffects. In most cases, the disputes have been settled through reconciliation. Japanese pediatricians should recognize the fact that the court often acknowledges the fault on the side of medical providers.

The decreased rate of theophylline metabolism during fever may cause the elevation of the blood level to reach the toxic range. To prevent CNS damages due to theophylline intoxication and those due to theophylline-associated encephalopathy, pediatricians should basically avoid the use of theophylline for bronchiolitis, bronchitis, and asthmatoid bronchitis in children under the age of 5. If theophylline must be prescribed, parents should be fully informed about potential side effects of theophylline and consent should be obtained. Revision of the current indications for theophylline is also needed regarding the fact that they include asthmatoid bronchitis.

References

