Judicious Use of Antibiotics for Pediatric Infection
—Global Strategies to Prevent the Increase of Bacterial Resistance—

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Principle of antimicrobial therapy in children is to select and use the most appropriate antibiotics based on the inferred causative agent and with consideration given to the special characteristics of children. Resistant organisms have been increasing in recent years, so it is very important to use proper antibiotics based on a knowledge of antimicrobial susceptibility trends and Pharmacokinetics/Pharmacodynamics (PK/PD). We are careful to use antibiotics based on proper differential diagnosis using rapid diagnostic methods, Complete blood flow (CBC), C-reactive protein (CRP) and so on. The most practical means of judicious antibiotic use is to treat each patient based on the newly revised guidelines. As it is unlikely that many new antimicrobial agents will be developed in the future, we must maximize the efficacy and life span of current antimicrobial agents through judicious use.

Introduction

Drug resistant microbes have been increasing on a global basis in recent years, and it is frequently reported that antimicrobial agents such as NDM-1 in particular have lost efficacy not only in hospitals but in the community as well. This is truly a critical situation for humanity. The distribution of drug resistant microbes varies throughout the world, and it is reported that the occurrence of drug resistant microbes is high in countries that use a large quantity of antimicrobial agents.[1] Spain, France, the U.S.A., Portugal, and Greece use large quantities of antimicrobial agents, and have a high occurrence of drug resistant microbes. By contrast, Norway, the Netherlands, Denmark, Sweden, and Germany use much smaller quantities of antimicrobial agents, and have a low occurrence of drug resistant microbes. In general, East Asia and Southeast Asia, including Japan, have a high occurrence of drug resistant microbes.[2] (Figure 1) Infection prevention measures that are important in hospitals such as washing hands are meaningless against microbial drug resistance in the community, and only the judicious use of antimicrobial agents is important. (Figure 2) To confront this age of drug resistant microbes, we reexamined the appropriate use of antimicrobial agents, which is the fundamental strategy for the treatment of infection.

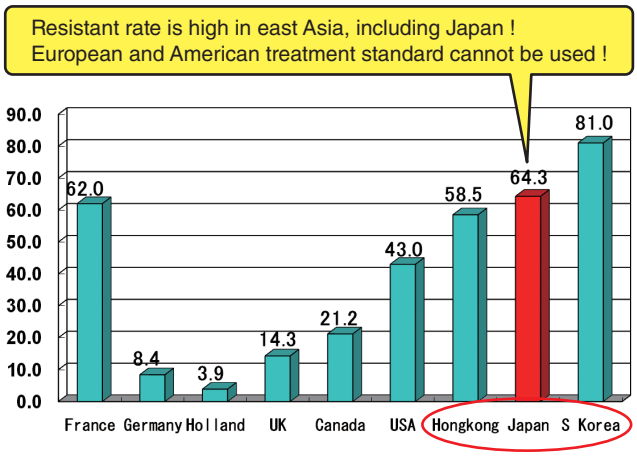

Figure 1 Rate of pneumococcus with reduced sensitivity to penicillin by country[1]
Penicillin G susceptibility interpretative criteria:
susceptible, =<0.06 mg/L; intermediate, 0.12-1mg/L; resistant, >=2mg/L
Felmingham D, et al. J AntiMicrob Chemother 2002; 50 (Suppl. S1): 25-37

Basic Points for Appropriate use of Antimicrobial Agents

Appropriate diagnosis of disease site and inference of causative agent

When considering antimicrobial treatment for infection in a child, the most important point is to appropriately diagnose the disease type that is suspected to involve

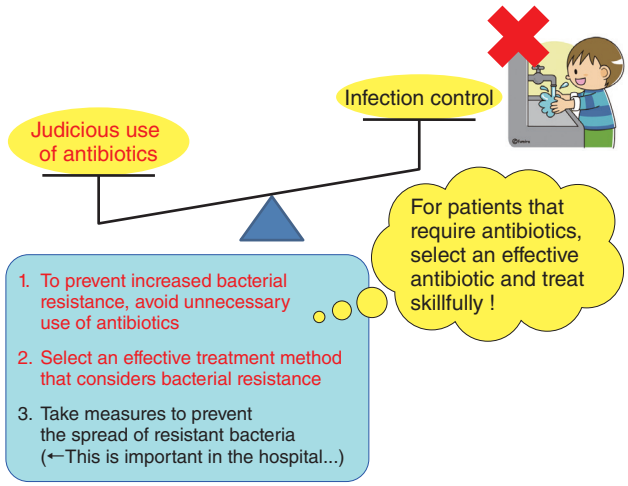

Figure 2 Community countermeasures for resistant bacteria

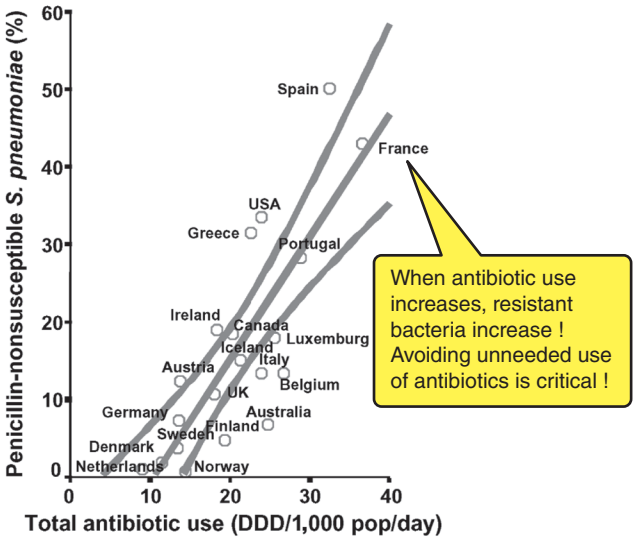

Figure 4 Antibiotic use and pneumococcus resistance[2]

microbial infection, and to infer the type of microbe that is the cause of the disease. It is also very important to use rapid diagnostic techniques as necessary. For example, a rapid testing kit enables selection of an antimicrobial agent that is effective for the cause, such as a penicillin antibiotic for Group A β-hemolytic streptococcus, or an anti-influenza agent for an influenza virus. If diagnosis is not possible using a rapid testing kit, testing for White blood cell (WBC) and CRP will allow a general determination of whether the infection is viral or bacterial, and thereby enable use of the appropriate antimicrobial agent.

The causative agent often varies by age in children, and thus the age of the patient must always be taken into consideration. It is also important not to administer antibacterial agents when not needed, such as for viral infections. For this purpose, an effort must be made to perform a differential diagnosis using such tests as CBC, CRP, and other parameters in order to differentiate bacterial and viral infections. In a bacterial infection, an increase in WBC and neutrophils in particular, and an increase in CRP are observed. In a viral infection, an increase in WBC, and in particular an increase in neutrophils and CRP are often observed relative to the healthy state; however, the values are often lower than the cutoff values of 13,000 /μL for WBC, 7,000 /μL for neutrophils, and 3 mg/dL for CRP, and thus it is possible to differentiate between a bacterial infection and a viral infection. (Figure 3)[3] In addition, by measuring the two parameters WBC and CRP, an inference can be made regarding the timing of the infection if it is bacterial. It is reported that when WBC is high and CRP is low, it can be inferred that the infection is at an early stage, and when WBC is low and CRP is high, it can be inferred that the infection is at a late stage.[4] This is because it takes about 12 hours after infection until CRP is produced, whereas

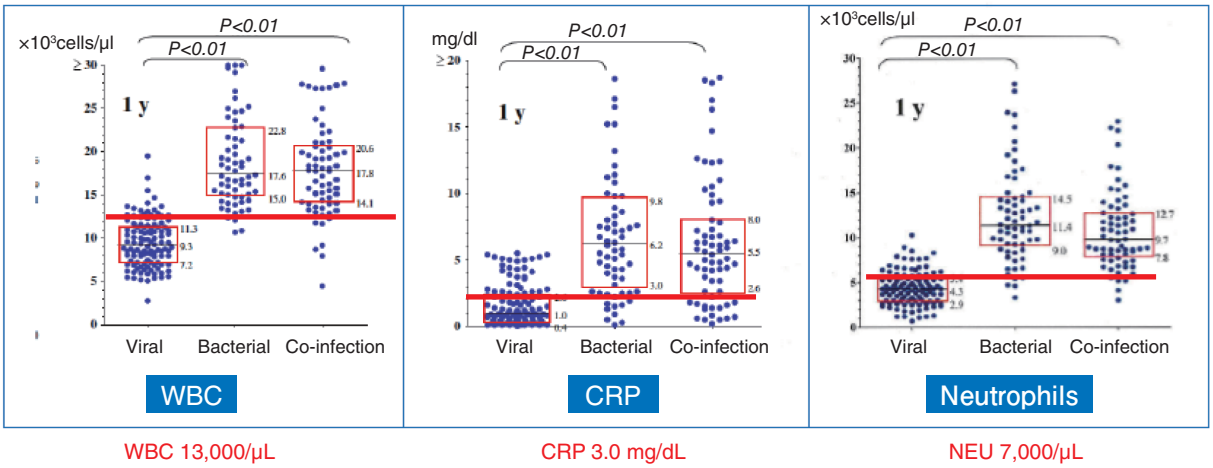

Figure 3 Differentiating viral infection from bacterial infection
T.Okada et.al, A practical approach estimating etiologic agents using real-time PCR in pediatric inpatients with community-acquired pneumonia. J Infect Chemother 18:832-840,2012

WBC is stored in the reticuloendothelial system such as the spleen and is mobilized in the blood within several hours.[5]

Avoiding unnecessary administration of antibacterial agents

Because a positive correlation is observed between the quantity of antibacterial agents administered and the occurrence of resistant bacteria, it is clear that excessive use of antibacterial agents increases bacterial resistance. (Figure 4)[1] A basic rule for infection treatment is to administer antibacterial agents only to patients who require them. Antibacterial agents are administered for bacterial infections, but not for viral infections because of lack of efficacy. If a patient being treated for an ear infection catches cold or develops another condition and visits the other clinic, it is possible that the patient will be prescribed medicine from two clinics. There are cases where the medicines have the same clinical effect, and thus an overall evaluation must be made by the pharmacy or other clinic.

Taking Pharmacokinetics / Pharmacodynamics into Consideration in Antibiotic Therapy

As an indicator of the efficacy of antibiotic therapy, PK/PD, which combines Pharmacokinetics (PK) and Pharmacodynamics (PD), has been gaining attention in recent years. This is an attempt to clarify the markers that affect therapeutic value by means of an overall determination of antimicrobial activity, pharmacokinetics, tissue concentration, and drug sensitivity. PK/PD evaluation has identified medicines for which dosage is important, and medicines for which the number of doses is important. β-lactam medicines are widely used in pediatrics, and because the bactericidal effect is time-dependant the period of efficacy is short. As such, efficacy can be increased by reducing the dosage and increasing the number of doses. Quinolone antibacterial agents and aminoglycoside antibacterial agents have a concentration-dependant bactericidal effect and thus a long period of efficacy. Efficacy can therefore be increased by reducing the number of doses and increasing the dosage. (Table 1) It is reported that high-dose, short-term administration of amoxicillin results in a higher compliance and a lower resistance rate.[6] In both AMPC and cefditoren pivoxil, a higher dose shortens the time of exposure to concentrations that select resistant strains. This means that for β-lactam medicines as well, high-dose, short-term treatment suppresses selection of resistant strains.

Table 1 Efficacy prediction parameters of each antibiotic

Efficacy prediction parameter	T>MIC	AUC/MIC	Cmax/MIC
Antibiotic	Penicillin Cephem Carbapenem	Quinolone agent Linezolid Macrolide Ketolide Azithromycin	Quinolone agent Aminoglycoside
Antibacterial properties	Time dependent type	Concentration dependent type	Concentration dependent type
Objective of treatment	Maintain efficacious concentration over extended time	Maximization of exposure level	Maximization of exposure level

Drusano & Craig. J Chemother 1997;9:38–44Drusano et al. Clin Microbiol Infect 1998;4 (Suppl. 2):S27–41Vesga et al. 37th ICAAC 1997 Andes&Craig:Antimicrob Agents Chemother 2002:46 Vogelman et al:J Infect Dis 1988:158:831-847 (http://www.infectionacademy.org/downloads/AIM_educational_slide_resource_kit.ppt)

Adhering to the prescribed administration period

The approximate administration period required for each infection site has been determined in past comparative studies. By taking these periods into consideration in treatment, recurrence of the infection due to an excessively short administration period and an increase of resistant bacteria due to an unnecessarily long administration period can be avoided. However, patients often stop taking their medications when symptoms improve, such as when a fever abates, and the physician's expectations are not met. In countries such as the Netherlands where antimicrobial agents are rarely prescribed, the rate of medicine taken is high and only 10% of patients fail to take their medicine over the full administration period. In Japan, the percentage of patients who fail to take their medicine over the full administration period is high at 34%, and it can be inferred that a relapse occurs in many patients.[7]

Mixing different classes of antibacterial agents

It is reported that use of the same class of antimicrobial promotes the development of resistant bacteria. (Figure 5) Caution is particularly needed in the field of pediatrics, where useable antimicrobial agents are limited. When selecting an antimicrobial agent, it is important to consider the use of an antimicrobial agent with a mechanism of action that is different from the previously

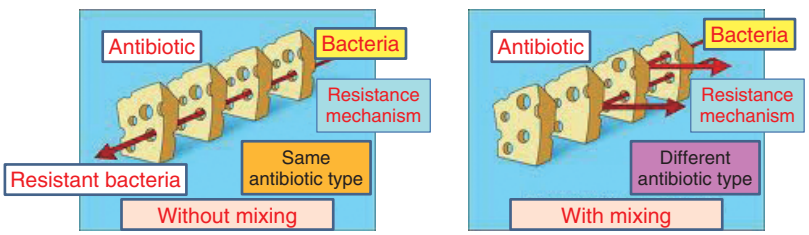

Figure 5 Mechanism of resistant bacteria suppression by mixing

used agent (referred to as "mixing"). For example, if only antimicrobial agents of the same class are used, such as penicillin and cephem, bacterial resistance will be promoted, but if different types such as quinolone and tetracycline are suitably incorporated, the incidence of resistant bacteria will be reduced. If a lack of efficacy is observed when treating mycoplasma pneumonia infection with macrolide agent, it is best to change to a tosufloxacin, a new quinolone agent, for pediatric use rather than another macrolide agent.

Consulting guidelines

Even for a pediatrician who specializes in infection, it is difficult to maintain a detailed knowledge of trends in resistant bacteria that vary from year to year, new antimicrobial agents, PK/PD, and mixing. The most reasonable approach is to refer to guidelines that are created and frequently revised by a group of infection specialists who organize and review the evidence, and have a thorough knowledge of the information. At Kawasaki Medical School Hospital, the rate of inappropriate use of antimicrobial agents was about 10% prior to introduction of guidelines. After introduction, the rate fell to 0%. Treatment based on the guidelines reduces treatment failure, and thus we also recommend that physicians who are not specialists in infection use these guidelines in routine medical care.

We compared the guidelines of developed countries for treatment of pneumonia in children. A problematic point in the guidelines of Great Britain and the U.S.A. was evaluation using a blood culture but no sputum culture. In Great Britain, medical expenses are low, and thus an antimicrobial agent is administered immediately. X-ray, CRP, CBC, and other tests are not recommended. In the U.S.A., these tests are run, however, the treatment plan is decided based on the result of a blood culture. The results of a blood culture and a sputum culture are completely different, and thus deciding the treatment plan based only on the result of a blood culture is problematic. In Japan, the sputum collection method developed by Dr. Suzuko Uehara of Chiba University is used, and thus it may be asserted that the guidelines of Japan are better.

The pediatric respiratory treatment guidelines of Japan were updated in 2004, 2007, and 2011. In the 2007 guidelines, CRP and neutrophils were used in the severity levels of community-acquired pediatric pneumonia, however, WBC and CRP were deleted from the severity levels in the 2011 guidelines. This was because there were few facilities that could test for neutrophils and CRP at night. Recently the use of instruments that can simultaneously measure CBC and CRP has spread in community clinics, and we think it is time to reconsider the value of CBC and CRP. The Japanese septicemia treatment guidelines indicate that delays in the administration of antimicrobial agents lead to a rise in the death rate,[8] and thus delaying administration of an antimicrobial agent to a patient that truly requires this treatment due to concerns about appropriate use of antimicrobial agents is also seen as problematic. The Japanese septicemia treatment guidelines also recommend the use of a white cell count in the diagnosis of SRIS, and CRP is included as a supplementary indicator. In cases where it is difficult to determine the cause of a patient's fever from clinical observation alone and there is a long interval from blood sample collection until reporting of measurement results, as is the case with immunological test parameters such as procalcitonin, the utilization of an instrument that provides quick test results and allows easy bedside use by a nurse or doctor is desirable.

Conclusions

To enable the maximum use of antimicrobial agents, it is important that physicians use antibiotic therapy effectively in a way that does not increase resistant bacteria. In other words, antimicrobial agents should be used judiciously. For this purpose, physicians should follow the treatment guidelines for the particular case, while always giving consideration to: 1. appropriate diagnosis of disease type and inference of the causative agent, 2. avoidance of unnecessary administration of antimicrobial agents, 3. Setting the dosage and number of doses based on (PK) / (PD), 4. Follow the set administration period and 5. Be aware of mixing any of antimicrobial agents.

To diagnose the disease site appropriately and infer the causative agent, it is important to determine whether the infection is bacterial or viral. For this purpose, an effort must be made to employ CBC, CRP, and other simple tests to perform a differential diagnosis. In recent years the use of instruments that can measure CBC and CRP simultaneously has spread in community clinics, and in this age where fewer new antimicrobial agents are being developed and judicious use of existing agents is required, the ability to perform the necessary tests for appropriate antimicrobial agent use at the bedside is truly welcome.

References

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