Department of Infection Control

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Research Activities

Epidemiological research on sexually transmitted infections
From 2006 through 2008, a study group of the Ministry of Health, Labour and Welfare, "Research on progress of guidelines for the prevention of specified infections related to sexually transmitted infections," was active with Dr. Onodera as chief investigator.   The objectives of the study included research and development on preventing the onset and spread of sexually transmitted infections and on promoting countermeasures against sexually transmitted infections based on the contents of "Guidelines for prevention of specified infections related to sexually transmitted infections," revised in 2006.   The main items studied were: 1) epidemiological research on onset trends of sexually trans-mitted infections, 2) early detection of sexually transmitted infections in young people and trials related to treatment, 3) development of rapid and highly precise test methods for genital herpes and genital warts, and 4) surveillance of drug-resistant gonococci and development of diagnostic and therapeutic methods for gonococcal infections of the throat.   The main results are described.

According to a survey of onset trends of sexually transmitted infections, decreasing trends for sexual Chlamydia infection and gonococcal infections have been observed in both men and women in Japan since 2003, but the prevalence of genital herpes and genital warts remains largely unchanged in both men and women.   An epidemiological survey of all sexually transmitted infections was performed in model prefectures to verify the fixed-point survey.   Prefectures asked to cooperate in the survey were Chiba, Ishikawa, and Hyogo for 3 years from 2006 and Iwate, Ibaragi, and Tokushima for 2 years from 2007.   As a result, consistent trends in the trends survey on sexually transmitted infec-tions and the complete survey in this research differed by prefecture and disease, but the highest consistency was found for sexual Chlamydia infection, followed by genital herpes and genital warts.   The lowest consistency rate was for gonococcal infections.

As an event aimed at young people, Chlamydia self-testing kits (polymerase chain reaction ［PCR］ method) were distributed by post for 3 years.   During that period, the kits were sent to 6,121 persons, and the cooperation of 1,585 asymptomatic young persons was obtained.   The rates of Chlamydia infection were 5% in men and 6% in women.   In a sexual behavior questionnaire, more Chlamydia-positive persons than Chlamydia-negative persons replied that condoms were not for preventing infections but for avoiding pregnancy, suggesting that they regularly performed sex without using condoms.

These results showed the need to specify definite standards for fixed points and the methods for the design of fixed-point surveys in the future.   In addition to undertaking publicity on prevention and supplying information as measures against sexually trans-mitted infections in young people, the government must maintain smooth relations with

nongovernmental organizations and medical institutions from testing until medical examinations.

Clinical research

1. Clinical study of urosepsis

Patient characteristics and treatment results were examined in 55 adults with urosepsis examined at Kanagawa Prefecture Shiomidai Hospital from 2000 through 2007. Of the patients, 90% were elderly, both men and women, and 93% had underlying diseases, such as chronic renal failure, diabetes, and cerebrovascular disorders. The most common causative bacteria were *Escherichia coli,* and all patients in whom *Pseudomonas aeruginosa* or methicillin-resistant *Staphylococcus aureus* was detected had indwelling urethral catheters. Three patients died, and all of them had septic shock as a complication. In initial treatment, antibacterial agents, such as first- to third-generation cephems, carbapenems, and penicillins combined with beta-lactamase inhibitors, were used. The efficacy rate was 54.5%. An analysis of patients in whom initial treatment was ineffective showed errors in designation of the causative organism and in the selection of antibacterial agents because of an insufficient understanding of pathophysiology in more than half. Insufficient doses and numbers of treatments with antibacterial agents were confirmed in 44% of patients. These results indicate that in the treatment of urosepsis, an understanding of the clinical characteristics of patients and disease severity and the selection, based on this knowledge, of appropriate antibacterial agents at sufficient doses are essential.

2. Clinical study of poor prognostic factors in *P. aeruginosa* bacteremia

Because the mortality rate of *P. aeruginosa* bacteremia is extremely high, investigating prognostic factors and establishing effective treatment are essential. From April 2003 through December 2007 at hospitals affiliated with The Jikei University School of Medicine, age, underlying diseases, antibacterial agents used, and bacterial invasion routes were examined in 89 adults in whom *P. aeruginosa* was isolated in blood cultures. The mortality rate of *P. aeruginosa* bacteremia was 24.7%. The most common underlying disease was leukemia, and the most common invasion route was the urinary tract. As initial treatment, effective antibacterial agents were administered to 65.2% of the 89 patients, but the mortality rate was the same as in patients not given effective antibacterial agents. However, poor prognostic factors were thrombocytopenia, polymicrobial infections, and hypoalbuminemia. In our study, unlike in other studies, administration of appropriate antibacterial agents did not improve outcomes.

3. Clinical study of acquired immunodeficiency syndrome-related lymphomas

Treatment of acquired immunodeficiency syndrome-related lymphomas of ileocecal origin: Acquired immunodeficiency syndrome (AIDS)-related lymphomas show a more progressive course than do lymphomas in patients without AIDS and have a poorer prognosis. At present, a standard treatment has not been established. The significance of combination therapy with highly active antiretroviral treatment (HAART) remains unclear. We have used HAART combination chemotherapy to treat AIDS-related lymphomas of ileocecal origin. No severe adverse drug reactions have occurred, and good therapeutic effects against both the human immunodeficiency virus infection and

the malignant lymphomas were achieved, making long-term remission possible. In the future, it will be necessary to recruit more patients, but our study suggested the usefulness of HAART combination chemotherapy in the treatment of AIDS-related lymphomas. Treatment of AIDS-related esophageal primary lymphomas: AIDS-related lymphomas are aggressive and often refractory. In some of our patients with refractory esophageal primary AIDS-related lymphomas, salvage treatment was ineffective. Because the combination therapy of stavudine, amivudine, and fos-amprenavir with rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone (R-CHOP) was ineffective, it was replaced with rituximab, etopsoide, methylprednisolone, high-dose cytarabine, and cisplatin (R-ESHAP) therapy, which was also ineffective. In such patients, ultra-high-dose chemotherapy together with autologous peripheral stem cell transplantation will be necessary.

Basic research

1. A method of measuring minimum inhibitory concentrations of antibacterial agents using tetrazolium

The drug sensitivity test for bacteria (measurement of minimum inhibitory concentration [MIC]) assesses whether bacteria grow in a medium containing an antibacterial agent. The results showed that an incubation time of 18 to 24 hours is required. Therefore, we examined the MIC agreement rate between the standard method and a method in which evaluation was possible in 6 hours (rapid method) using the Tetracolor One reagent (Seikagaku Corp.) that combines a tetrazolium salt and an electron mediator. In the MIC measurement using a microplate, the agreement rate was high between the standard method and the rapid method except for some drugs (cephazolin, cefaclor, and minocycline). Because the MIC can be determined in 6 hours with the rapid method, it is useful for the rapid detection of resistant bacteria.

2. Typing analysis of *P. aeruginosa* in clinical isolates with PCR

Typing analysis of bacteria using molecular biology procedures is essential for testing of in-hospital propagation of resistant bacteria such as *P. aeruginosa* and *Acinetobacter*. We studied typing analysis with PCR to determine if it could be used to analyze clinical isolates of Gram-negative bacteria in our hospital. Nucleic acid was extracted from 17 clinical isolates of *P. aeruginosa* obtained in our hospital in 2008. Typing analyses with PCR and with pulsed-field gel electrophoresis (PFGE) were compared. PCR was performed with 2 primers, BOXAIR and ERIC2. The PCR products were subjected to agarose gel electrophoresis, and electroophoretic patterns were analyzed. With the PFGE method, electrophoresis of the DNA fragment after restriction enzyme Spe I treatment using a GenePath kit (Bio Rad Laboratories) was analyzed with a contour-clamped homogeneous electric field apparatus (CHEF DR2, Bio Rad). The typing analysis of clinical *P. aeruginosa* isolates using the BOXAIR and ERIC2 primers showed basic agreement with the results obtained by PFGE. Typing analysis with PCR is a rapid test that can be completed in 1 day, from extraction of the nucleic acids to electrophoresis, and the cost per strain of bacteria is also low. The identification capacity is slightly lower than that of PFGE, but these results showed that PCR is useful as a rapid and simple analytical method for outbreaks of *P. aeruginosa* infection.

Publications

Kato T, Sato F, Horino T, Nakazawa Y, Sakamoto M, Yoshida M, Onodera S, Hiroshi Kiyota H. Clinical features of 15 cases treated with linezolid. *Jpn J Chemother* 2008; **56:** 202–5.