รายงานผู้ป่วย

Penicillin resistant systemic pneumococcal infections in Thai children

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Strains of Streptococcus pneumoniae with decreased susceptibility to penicillin and other antimicrobial agents are increasing in many parts of the world, including Thailand. Three children with systemic penicillin-resistant S.pneumoniae infections were identified at Chulalongkorn Hospital over a 10-month period from August 1995 through June 1996. Clinical diagnosis included bacterial meningitis 2 and infective endocarditis 1. Two patients had underlying conditions (post splenectomy and congenital heart disease.) The minimal inhibtory concentrations (MICs) of penicillin ranged from 0.75 to 4 ug/ml and MICs of ceftriaxone ranged from 0.38 to 4 ug/ml. All were successfully treated with vancomycin. There were no deaths.

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เชื้อ Streptococcus pneumoniae ที่ดื้อต่อยาเพนิซิลลินและยาปฏิชีวนะอีกหลายๆ ขนาน ได้แพร่กระจายไปทั่วโลกรวมทั้งประเทศไทย ในระหว่างเดือนสิงหาคม 2538 ถึง เดือนมิถุนายน 2539 มีผู้ป่วยเด็กไทยที่มีการติดเชื้อ S.pneumoniae ในกระแสเลือดที่ดื้อต่อยาเพนิซิลลิน จำนวน 3 ราย 2 รายมีการติดเชื้อเยื่อหุ้มสมองอักเสบ และ 1 รายมีการติดเชื้อเยื่อบุหัวใจจอักเสบ (infective endocarditis) ผู้ป่วย 1 รายเคยถูกตัดม้าม อีก 1 ราย มีโรคหัวใจแต่กำเนิดทั้ง 3 สายพันธุ์ที่แยกได้จากผู้ป่วยดื้อต่อยาเพนิซิลลิน โดยมีค่า minimal inhibitory concentrations (MICs) ต่อยาเพนิซิลลินอยู่ระหว่าง 0.75 - 4 ไมโครกรัม/มิลลิลิตร และ MICs ต่อยา ceftriaxone ระหว่าง 0.38 - 4 ไมโครกรัม/มิลลิลิตร ทุกสายพันธุ์ไวต่อยา Vancomycin ผู้ป่วยทุกรายรอดชีวิต

Strains of Streptococcus pneumoniae with decreased susceptibility to penicillin and other antimicrobial agents are increasing worldwide.[1] Since the first pneumococcal strain resistant to penicillin was reported in 1967 by Hansman et al,[2] and the first multi-resistant strain was isolated in 1972 in Johannesburg,[3] penicillin resistant Streptococcus pneumoniae (PRSP) strains have been identified in many countries. The three countries with the greatest reported incidence of PRSP are South Africa, Spain, and Hungary.[1] In the United States, current levels are estimated to have reached 16%. Fifty four per cent of the intermediate penicillin resistant isolates and 59% of the high penicillin resistant isolates were from children 15 years old and younger.[4] To estimate the magnitude of this problem in our institute, clinical isolates of S.pneumoniae from peidatric patients recovered from January 1995 to February 1997 in the microbiology laboratory of Chulalongkorn Hospital were reviewed. There were 18 systemic isolates (12 blood, 6 CSF). Routine screening for penicillin susceptibility using a 1-ug oxacillin disc by the Kirby - Bauer disk diffusion method identified four isolates as PRSP. Resistance was confirmed by determination of the minimal inhibitory concentration (MIC) using the E test. Only three isolates were defined as PRSP (MIC > 0.1 ug/ml.)[5] These three cases of PRSP systemic infection were successfully treated with vancomycin.

Case I

The patient was a 2 year, 8 month old boy with homozygous-beta-thalassemia who had a splenectomy when he was 26-months old. He was presented with two days of high fever, cough, and loose stool. He was treated at a private clinic but without improvement. On the following day he was admitted to Chulalongkorn Hospital because of high fever, vomiting and generalized convulsions. On examination his temperature was 40°C, and he was pale, irritable and drowsy. His neck was stiff. The liver was enlarged 3 cm. below the costal margin. The remaining physical examination results were normal. He had been frequently treated with antibiotics for recurrent febrile illness during the month prior to admission. Laboratory results on admission were hemoglobin 9.2 gm/dl, white blood cell count 21,380/mm^3, 87% neutrophil, 11% lymphocytes, 2% monocytes, and platelets 92,000/mm^3. CSF examination revealed open pressure and closed pressure of 33,30 cm. water, respectively. There were 1920 red blood cell/mm^3 and 1000 white blood cell/mm^3, of which 80% were neutrophils and 20% were mononuclear cells. CSF protein was 820 mg/dl, glucose was 5 mg/dl, and blood glucose was 133 mg/dl. Gram-stained smears showed numerous gram positive diplococci. Blood and CSF cultures were obtained. Initial treatment included phenobarbital for convulsion control, penicillin 300,000 units/kg/day and

chloramphenicol 100 mg/kg/day intravenously. CSF and blood cultures grew S. pneumoniae which were resistant to penicillin by 1-ug oxacillin disk. A repeat lumbar puncture 24 hours after treatment showed few gram positive diplococci on a Gram-stained smear and slight growth of PRSP from the CSF culture. The MICs for penicillin and ceftriaxone were 0.75 and 0.38 ug/ml, respectively. Vancomycin 60 mg/kg/day in 4 divided doses was substituted for the penicillin and chloramphenicol. A repeat blood culture before the vancomycin therapy was sterile. Fever persisted during the 4-day treatment of penicillin and chloramphenicol in spite of improvement of general well being. He became afebrie in day 8 of the vancomycin treatment. On day 10 of the therapy fever returned but clinical evaluation failed to identify an additional site of infection, but the patient was doing well. Vancomycin was discontinued after 14 days of treatment in spite of the fever. Four days after completing the antibiotic, a repeat lumbar puncture showed clear CSF with 60 white blood cell/mm^3 of which 67% were neutrophils and 33% were mononuclear cells. CSF protein was 60 mg/dl, glucose 44 mg/dl, blood glucose 94 mg/dl, and CSF culture was sterile. He became afebrile in the next 2 days and remained well thereafter.

Case II

A 10 month old boy was admitted to a private hospital in Bangkok with a one day history of fever, diarrhea and tonic-clonic convulsions for three minutes. He also had a history of recurrent upper respiratory tract infections during the prior 3 weeks which was treated with antibiotics. On admission, the white blood cell count was 48,000/mm^3 with 84% neutrophils and 16% lymphocytes. The platelet count was 432,000/mm^3 and hematocrit was 34.7%. Cerebrospinal fluid (CSF) examination revealed 2 white blood cells/mm^3. All were mononuclear cells. CSF protein was 12 mg/dl and glucose was 90 mg/dl. The blood and CSF were cultured. Therapy was started with intravenous ampicillin 100 mg/kg/day and oral Co-trimoxazole (40 mg of trimethoprim twice dialy) and changed to cefotaxime 100 mg/kg/day plus norfloxacin (100 mg twice daily) on the following day which he received for 3 days. The blood and CSF cultures grew S.pneumoniae sensitive to penicillin by the penicillin disk. Penicillin G 200,000 unit/kg/day was started two days before the child was referred to our hospital. On examination his temperature was 39.5°C and he was irritable. The head and neck examination revealed a stiff neck. The rest of the examination was unremarkable. Initial laboratory studies revealed hemoglobin 10.5 g/dl, hematocrit 30.6%, white blood cell count 24,000/mm^3, 73% neutrophils, 24% lymphocytes, 3% monocytes, and the platelet count was 631,000/$mm.^3$ CSF examination showed 740 white blood cell/mm^3 of which 12% were neutrophils, and 88% were mononuclear cells. CSF protein was 158 mg/dl glucose was 34 mg/dl and blood glucose was 115 mg/dl. No organisms were seen on a Gram-stained smear.

Blood and CSF cultures were obtained and cefotaxime 200 mg/kg/day was administered intravenously. The CSF culture was positive for S. pneumoniae which was resistant to penicillin by a 1-ug oxacillin disk and confirmed by determination of MIC by E test. The MICs for each antibiotic were penicillin 4 ug/ml, ceftriaxone 4 ug/ml, and vancomycin 0.5 ug/ml. The blood culture was sterile. Cefotaxime dosage was increased to 300 mg/kg/day and vancomycin 60 mg/kg/day intravenous divided every 6 hours was added. A repeat lumbar puncture before this combination therapy yielded traumatic CSF and a sterile culture. The patient defervesed within 4 days. Both medications were given in these doses for 6 days and then the cefotaxime was stopped. Only the vancomycin was continued for a total of 15 days. A final CSF after discontinunce of the antibiotics was clear with a white blood cell count of 4/mm^3, all were mononuclear cells. The CSF protein was 31 mg/dl and glucose was 42 mg/dl. Blood glucose was 98 mg/dl. A CSF culture was sterile. He was subsequently followed for eight months and has had normal growth and development.

Case III

A 4-year old boy with a double-outlet right ventricle, pulmonary stenosis and a functioning Blalock-Taussig shunt was presented after 3 days of fever and chest pain. Physical examination revealed central cyanosis, heart murmur, and clubbing of the fingers, but without evidence of embolic phenomenon. Six out of eight specimens of blood culture grew S.pneumoniae that were resistant to penicillin and sensitive to cefazolin, ceftriaxone and vancomycin. An echocardiogram could not demonstrate vegetations. The diagnosis of infective endocarditis was proposed, Cefazolin was adminstered intravenously. The patient responsed well and became afebrile a few days after treatment. Hemoculture was negative at the end of first week of cefazolin therapy. At the beginning of the third week of treatment, the patient developed fever and jaun-dice of unknown etiology. Fever persisted and blood culture obtained at the end of third week grew S.pneumoniae with an MIC for penicillin of 3 ug/ml. Cefotaxime 200 mg/kg/day was replaced with good clinical response in the following days. A blood culture was sterile after 72 hours of cefotaxime therapy. The patient remained afebrile until two weeks later when the fever recurred and a blood culture was positive for S. pneumoniae with an MIC for ceftriaxone of 1.5 ug/ml. Cefotaxime was discontinued and vancomycin was administered for four weeks resulting in a successful outcome. A detailed report had been described by Pancharoen et al.[6]

Discussion

Reports of penicillin resistance worldwide indicate that resistance is an increasing problem. From 1990-1994, 20 of 81 strains (24.1%) of S.pneumoniae were identified as PRSP from the

microbiology laboratory of Chulalongkorn Hospital.[7] Screening for penicillin resistance with the oxacillin disk is now a standard laboratory procedure, but false resistance results in up to 40% of the tests, and quantitative confirmation is advised.[4] Our experience demonstrated that 1 of 4 isolates identified as PRSP by oxacillin disk to be false resistance.

Several studies have implicated certain risk factors in the development of penicillin-resistant pneumococcal infections. Pallares, et al[8] retrospectively studied 24 adults with PRSP bacteremic pneumonia compared with 48 control patients with penicillin sensitive S. pneumoniae (PSSP) bactermic pneumonia. Patients with PRSP infection had a significantly greater incidence of beta-lactam antibiotic use during the previous 3 months, a greater incidence of hospitalization during the previous 3 months, a greater incidence of nosocomial pneumonia, more episodes of pneumonia during the previous year, more clinical factors associated with a poor prognosis on presentation, and an over all mortality rate significantly greater than the control group. Tan, et al[9] compared 43 children with systemic PRSP infections with 66 controls with PSSP infection. The only identified associated risk factor in children who developed a systemic PRSP infection appeared to have been the use of antibiotics during the month prior to their infection. A history of antibiotic use before admission was identified in 2 patients in our study.

The increase in the frequency of systemic infections due to PRSP has led to questions regarding optimal therapy. Although beta lactam therapy of sepsis and pneumonia caused by pneumococci with intermediate penicillin resistance (MIC 0.1-1 ug/ml) is effective,[8,10,11] there have been reports of a small number of adults with highly penicillin resistant infections who did not respond to this therapy,[8,12] Therapy with more active beta-lactam agents (e.g. as imipenem, cefotaxime, ceftriaxone), or non betalactam agents (e.g. vancomycin, clindamycin) for high level PRSP infections or in critically ill patients is recommended.[8,12] Endocarditis caused by S.pneumoniae is uncommon,[13] and optimal treatment for PRSP endocarditis is unknown. The treatment of experimental endocarditis in rabbits due to PRSP (MIC of penicillin 1, 4 ug/ml) by different dosages of penicillin, cefotaxime, teicoplanin showed that only regimens of drugs that provided concentrations in serum several fold above the MIC throughout the interval between doses provided constant sterilization of the cardiac vegetations.[14] The failure of cefotaxime therapy in our patient with endocarditis caused by high-level penicillin resistant S. pneumoniae may have been due to inadequate serum concentrations of the drug which need to be several fold above the MIC throughout the interval between doses.

Multiple regimens have been suggested for the therapy of meningitis due to penicillin - resistant pneumococci. Chloramphenicol which is wildly used to treat meningitis in developing

countries, is no longer recommended due to adverse experience in South Africa and its bacteriocidal activity against many penicillin - resistant strains is poor.[15,16] Despite susceptibility on conventional disk testing, the minimal bactericidal concentrations (MBCs) of chloramphenicol against penicillin-resistant pneumococcal isolates were significantly higher than for the penicillin-sensitive isolates, resulting in subtherapeutic bactericidal-activity and treatment failure.

Third-generation cephalosporins (cefotaxime, ceftriaxone) have been considered the treatment of choice in penicillin-resistant pneumococcal meningitis.[17] However, failure of cephalosporin therapy is increasingly being reported.[18,19] Recently, Florez, et al[20] reported cefotaxime failure in pneumococcal menininingitis caused by a strain for which the MIC of cefotaxime was 0.5 ug/ml. More clinical data are needed before firm recommendation can be made about the cephalosporin resistance breakpoint for S. pneumoniae. Some authors[21] suggest strategy of increasing the dose of cefotaxime from 200 mg/kg/day to 250 to 300 mg/kg/day to achieve higher CSF concentrations to overcome some degree of the cephalosporin resistance.

Cefotaxime or ceftriaxone and vancomycin combination therapy has been proposed for the treatment of meningitis caused by PRSP.[17,21] Studies of experimental animals with cephalosporin-resistant pneumococcal meningitis suggest that the combination of ceftriaxone and vancomycin is more effective than either drug alone.[22] Repeated examination and culture of the cerebrospinal fluid 24 to 36 hours after the start of therapy is advised in evaluating whether therapy is effacacious.[17,21]

With the increasing incidence of beta-lactam resistance, epidemiologic, clinical and bacteriologic data should be gathered with the greatest care in order to determine the risk factors, and to better define the optimum therapy of infections due to strains of varying levels of beta-lactam resistance.

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