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The same equation was applied to determine albumin concentration in BAL. Albumin was used as a marker of inflammation.

Dapsone concentration in plasma and BAL fluid was determined with a validated high performance liquid chromatography assay.<sup>6</sup> The standard curve in plasma was linear in the range of 12.5 to 3000 ng/ml. The sensitivity of the assay for determination of dapsone in BAL was enhanced by 10-fold concentration of the BAL samples and standards in saline solution. The standard curve was linear in the range of 2.5 to 300 ng/ml of unconcentrated standards. Interday and intraday variability determined at each point of both plasma and BAL standard curves was <10%. The lower limit of quantitation was 12.5 ng/ml in plasma and 2.5 ng/ml in BAL.

**Results.** BAL for Patient 1 was negative for *P. carinii* and acid-fast bacteria. The presence of fungal spores without mycelial forms was reported. Also rare colonies of viridans streptococci were cultured. The number of neutrophils, macrophages and lymphocytes in BAL sample was within normal range.

The specimen from Patient 2 was negative for *P. carinii*, fungi and acid-fast bacteria and positive for *Streptococcus pneumoniae*. The BAL sample was purulent with a high count of neutrophil cells.

The concentrations of dapsone in plasma and ELF are shown in Table 1. The concentration of albumin in ELF was 2% of the serum concentration in Patient 1 and 12% in Patient 2.

**Discussion.** Our data suggest that dapsone penetrates well into ELF. This observation was expected because dapsone is highly lipid-soluble with a small molecular weight. The difference in plasma concentrations reflects the high interpatient variability of dapsone pharmacokinetics reported in both adult and pediatric HIV-infected patients.<sup>6,9</sup> The fact that Patient 2 had signs of pulmonary inflammation and a higher penetration ratio may suggest that dapsone penetration into ELF is greater in the presence of inflammation. This may be clinically relevant because chronic inflammation in patients with a history of multiple pneumonias is a common finding in HIV-infected children. However, our observation regarding the effect of inflammation on dapsone penetration into ELF should be confirmed by further studies.

We studied the concentrations of dapsone at 24 h after administration; therefore we do not know the concentrations in the interval between doses. Dapsone half-life in the plasma of HIV-infected children has been reported to range from 18.2 to 35 h.<sup>6</sup> If no degradation of dapsone occurs in ELF, the half-life of dapsone in ELF should be comparable with or longer than the half-life in plasma. As a result the concentrations in ELF should be higher than the MIC of 0.1 mg/l<sup>10</sup> for most of the dosing interval when 2 mg/kg are administered three times weekly. To interpret our data correctly in terms of predicting clinical outcome, the pharmacodynamic aspects of dapsone against *P. carinii* should be elucidated. Such information is crucial to the design of a dosage regimen targeted to optimize peak and trough concentrations in relation to the MIC of *P. carinii*.

In conclusion additional studies are required to provide a sound pharmacokinetic basis for determining the optimal

dapsone regimen for *P. carinii* pneumonia prophylaxis in HIV-infected children.

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**TABLE 1.** Steady state concentrations of dapsone in the alveolar ELF and plasma of pediatric HIV-infected patients

| Patient | Time (h) | ELF (mg/l) | Plasma (mg/l) | ELF:Plasma Ratio |
|---------|----------|------------|---------------|------------------|
| 1       | 24       | 1.11       | 1.02          | 1.09             |
| 2       | 24       | 1.64       | 0.48          | 3.41             |

#### SEVERE NEONATAL ECHOVIRUS 20 INFECTION CHARACTERIZED BY HEPATIC FAILURE

Enteroviruses, small, single stranded RNA viruses, are a common cause of neonatal infection, especially in summer and fall.<sup>1-4</sup> The 66 known serotypes are grouped into 4 classes: polioviruses 1 to 3; Coxsackieviruses A 1 to 22 and 24; Coxsackieviruses B1 to B6 and echoviruses 1 to 7, 9, 11 to 27



nd 29 to 33. The more recently discovered serotypes are simply designated enteroviruses and numbered 68 to 71. More than 50% of enterovirus infections are caused by echoviruses.

Clinical presentations vary from benign nonspecific febrile illness to severe disseminated life-threatening disease. Although nearly all 30 echoviruses may cause neonatal disease, 7 serotypes have been reported to cause severe disease. The dominant serotype responsible for severe neonatal disease is echovirus 11.<sup>5</sup> The most common clinical presentation of serious echovirus disease in neonates is sepsis-like illness characterized by fever at onset. The differentiation from bacterial sepsis is a diagnostic problem.<sup>2-4</sup> Previous reviews have not identified echovirus 20 as a cause of severe neonatal disease. Recently four cases of severe neonatal disease caused by echovirus 20 occurred in the Netherlands within a period of 8 weeks. Liver failure was a dominant feature in 3 of 4 patients and the disease was fatal in one of them.

**Case 1.** On August 28, 1995, a 2640-g birth weight, 37½-week gestation female infant was born to a multigravida by cesarean section because of signs of infection of the mother (temperature of 39°C and abdominal pain). The Apgar scores were 8 and 9 at 1 and 5 min, respectively, and the examination was normal. On the fifth day of life the infant developed fever (temperature 38.8°C) but did not look ill. The laboratory results were normal. A blood sample was obtained for culture and antibiotics were given. Twenty-four hours later the patient became lethargic and developed feeding problems, with a distended, painful abdomen. The white blood cell (WBC) count decreased from  $14 \times 10^9/l$  to  $6.3 \times 10^9/l$  and the platelet count decreased from  $378 \times 10^9/l$  to  $20 \times 10^9/l$ , whereas C-reactive protein was normal. The liver function tests showed elevated levels of lactate dehydrogenase (LDH) at 7400 units/l (range, 26 to 334 units/l), serum aspartate aminotransferase (AST) at 944 units/l (range, 7 to 47 units/l) and serum alanine aminotransferase at 145 units/l (range, 3 to 47 units/l). The radiograph of the abdomen was normal. Ultrasound examination of the abdomen revealed ascites. Viral cultures of nasopharynx, stool and serologic tests were performed. There was laboratory evidence of disseminated intravascular coagulopathy (DIC). The patient was transferred to the neonatal intensive care unit (NICU) of the Academic Hospital Nijmegen on the eighth day of life. The physical examination on admission was normal except for some cutaneous hematomas. Cerebrospinal fluid (CSF) analysis showed no abnormalities. Viral cultures of CSF and blood were performed. Treatment consisted of antibiotics, acyclovir and fresh frozen plasma, platelet and red blood cell transfusions. Within the 3 following days the signs of DIC disappeared. All bacterial cultures were sterile. Viral culture of the stool and nasopharynx obtained on the eighth day of life and the viral culture of blood obtained on the ninth day of life yielded enterovirus later typed as echovirus 20. The viral culture of CSF was negative. Cultures taken from the mother were also negative. The serologic tests of the patient revealed a significant rise in titer of neutralizing antibodies to the patient's own virus isolate from 1:8 on Day 8 to 1:128 on Day 13. On the 23rd day of life the patient was discharged in good clinical condition.

**Case 2.** On October 10, 1995, a 3225-g birth weight, 39-week gestation male infant was born to a healthy multigravida by elective cesarean section. Apgar scores were 8 and 9 after 1 and 5 min, respectively, and the examination was normal. On the seventh day of life the infant developed fever (temperature 38.4°C) and anorexia and became lethargic. No focus of infection was detected. The laboratory results showed a hemoglobin of 7.8 mmol/l, a WBC count of  $4.7 \times 10^9/l$  with 14% band forms, a platelet count of  $103 \times 10^9/l$  and a

C-reactive protein level of 17 mg/l. CSF analysis was not possible because of a traumatic tap. After samples were obtained for cultures, antibiotics and acyclovir were given. The patient was transferred to the NICU of the University Children's Hospital Utrecht. On admission the infant was lethargic, with a distended, painful abdomen without organomegaly and required ventilatory support. There were no radiographic signs of pneumonia. Laboratory tests revealed a WBC count of  $2.5 \times 10^9/l$  with 18% band forms, a platelet count of  $42 \times 10^9/l$ , a slightly increased serum AST of 160 units/l and markedly elevated LDH of 1456 units/l. During the following hours the infant developed marked edema, ascites and pleural and pericardial effusion. Ultrasound examination of the abdomen revealed ascites and an enlarged liver and spleen. There was evidence of DIC and progressive deterioration of the liver function. The patient became hypotensive, developed seizures and pulmonary function progressively worsened. Despite all therapeutic measures the infant died on the fourth day after onset of the first symptoms. All bacterial cultures remained sterile. The viral cultures of stool, throat and cerebrospinal fluid obtained on the eighth day of life yielded enterovirus, later typed as echovirus 20. Postmortem cultures of brain, liver and lungs yielded echovirus 20.

**Case 3.** On October 19, 1995, a 2720-g birth weight, 36-week gestation female infant was born to a healthy multigravida by cesarean section because of abruptio placentae. The Apgar scores were 9 and 10 at 1 and 5 min, respectively. Because of prematurity the infant was admitted to the neonatal nursery. On the fourth day of life the infant developed fever (38.2°C), anorexia and lethargy. The initial blood and CSF analysis were normal and after samples for culture were obtained, antibiotics were given. Within 24 h the patient became irritable with a painful, slightly distended abdomen. Ultrasound examination of the abdomen revealed minimal ascites. Blood analysis showed marked leukopenia with a WBC count of  $4.6 \times 10^9/l$  with 26% band forms, thrombocytopenia of  $53 \times 10^9/l$  and liver dysfunction (LDH, 2125 units/l; AST, 139 units/l). The patient was transferred to the NICU of the University Children's Hospital Utrecht.

During the following days hepatosplenomegaly developed and the ascites increased. Blood chemistry showed evidence of DIC and deterioration of liver function. Treatment consisted of vitamin K, fresh frozen plasma, red blood cell and platelet transfusions. Bacterial cultures remained sterile. Viral cultures from stool and ascites fluid obtained on the seventh day of life yielded enterovirus later typed as echovirus 20. From the second week of illness the infant's clinical condition gradually improved and after 27 days the patient was discharged in good clinical condition, but still with signs of cholestasis.

**Case 4.** On October 18, 1995, a 2230-g birth weight, 37-week gestation female infant was born to a healthy multigravida by vaginal delivery as the second of twins. The delivery was induced because of placental insufficiency and growth retardation of both fetuses. The Apgar scores were 6 and 8 at 1 and 5 min, respectively. Because of low birth weight the infant was admitted to the neonatal nursery. On the fifth day of life the infant developed fever (38.4°C) and poor feeding. Physical examination showed prolonged capillary refill, lethargy and a slightly distended abdomen, prompting evaluation for possible sepsis. Laboratory results, however, were normal. After samples were obtained for bacterial culture sepsis therapy was initiated. The clinical condition of the patient improved during the next 24 h, although the platelet count dropped to  $95 \times 10^9/l$ . Liver function tests were not performed. All bacterial cultures remained sterile. Because during the same period another infant (Case 3) in the



nursery had to be transferred to the NICU with clinical manifestations suggesting viral disease, stool was collected on the ninth day of life for viral culture, which yielded an enterovirus, typed as echovirus 20.

On the 18th day of life the patient was discharged in good clinical condition. The twin sister of the patient showed no signs of illness and viral cultures were not obtained.

The selected laboratory values and demographic data of the four patients are summarized in Tables 1 and 2, respectively.

**Epidemiology.** The virus diagnostic laboratories that participate in the Netherlands Working Group on Clinical Virology report on a monthly basis infections that are diagnosed throughout the country. This database showed that echovirus 20 infections have been relatively rare in the Netherlands during the past decades but that their number rose significantly in 1994 and 1995. From 1986 to 1993 the annual average number of cases of enterovirus infection was 264 (range, 118 to 509), of which 1% were echovirus 20 (average annual number, 3; range, 1 to 8). In 1994 the percentage of echovirus 20 increased to 10% (28 of 272 enterovirus cases); in 1995 the contribution of echovirus 20 increased further to 14% (30 of 207 enterovirus cases). In addition we sent a questionnaire to the virus diagnostic laboratories, with special emphasis on neonatal infection by echovirus 20. Three additional neonatal cases were found, all in 1994, 2 of whom had severe illness. One had sepsis-like illness and the other meningoencephalitis. The third case had gastroenteritis only. These cases were reported by laboratories in Rotterdam and Delft.

**Discussion.** Sepsis-like illness in neonates can be caused by bacteria and some viruses. Severe echovirus infection in neonates is such a viral disease characterized by a sepsis-like illness at onset. Approximately two-thirds of the patients with severe echovirus disease have a systemic manifestation and one-third of the patients have meningoencephalitis.<sup>5</sup> To our knowledge this is the first detailed description of severe neonatal infection by echovirus 20. One report, the epidemiologic study of 233 infants younger than 3 months of age and admitted with clinical signs of sepsis, described the isolation of this serotype four times. The age of the patients, clinical course of the illness, laboratory results and outcome were not separately described.<sup>4</sup> In another report dated from 1960 echovirus 20 was isolated from asymptomatic infants.<sup>6</sup>

All four cases described in this report occurred within a 60-day period in two areas approximately 60 km apart (Utrecht and Nijmegen). Three of the infants were admitted within a 6-day period from inside the metropolitan area of Utrecht (Cases 2, 3 and 4). There were no other relationships among the patients. However, Cases 3 and 4 were admitted in the same period to the same neonatal unit. In retrospect three additional cases were found that occurred in 1994. From the epidemiologic data collected by the Netherlands Working Group on Clinical Virology, it became evident that there was an increased circulation of echovirus 20 in 1994 and 1995. Waning of immunity with time passed after a previous echovirus 20 epidemic may explain an increased circulation in

1994 and 1995, but not an altered pathogenicity of echovirus 20 infection in the neonate. Increased virulence of the serotype can offer a more likely explanation. This may result in an increased awareness of clinically significant infections, occurring also after the neonatal period. Enteroviruses, being RNA viruses, have a high mutational frequency that may lead to changes in pathogenicity, virulence and antigenicity.<sup>7-9</sup> Such factors might have been responsible for a newly circulating strain of echovirus 20 causing sepsis-like illness in neonates. The patients with neonatal echovirus 20 infection described here developed a bacterial sepsis-like illness with fever, poor feeding and lethargy. The differentiation from bacterial infection was the main diagnostic problem at onset. Clinical chemistry and hematologic findings were not very helpful in the differentiation. The temperature was only moderately elevated for 1 to 2 days. Signs of liver failure and hepatomegaly developed within the first week of the illness. Severe liver failure with DIC characterized three of the four cases. Encephalitis and severe capillary leak followed by respiratory and circulatory failure were observed in the fulminant course of the disease in the case with a fatal outcome.

A nearly identical clinical illness with fulminant liver necrosis has been described in neonates with perinatally acquired herpes simplex virus, echovirus 11 and Coxsackievirus B infections.<sup>5, 10, 11</sup> Myocarditis, described in other neonatal echovirus infections, was not observed in the cases reported here.

The previously reported risk factors for severe neonatal echovirus disease as prematurity, male sex and maternal disease, were not evident in our cases.<sup>4, 12, 13</sup> Another important risk factor, frequently described in the literature, is cesarean section performed because of abdominal illness of the mother.<sup>2, 5, 13</sup> Three of our patients had been delivered by cesarean section, but only in Case 1 because of maternal disease.

The course of neonatal echovirus 20 infection in our four patients was quite variable. Complete uneventful recovery, hepatitis followed by chronic liver disease and fulminant hepatic necrosis with fatal outcome were observed.

Specific antiviral therapy of neonatal echovirus infection is not yet possible. Because the disease is usually self-limiting, supportive care is sufficient in most cases.<sup>1-3</sup> Treatment with intravenous immunoglobulin is another option.<sup>2, 10, 12, 14</sup> Previously one patient with an echovirus 11 infection has been described who recovered after transfusions with maternal plasma<sup>15</sup> and another has been described after liver transplantation.<sup>16</sup>

The diagnosis can be made by virus isolation from stool, CSF, blood or a nasopharyngeal swab.<sup>1-3, 12</sup> In some cases the diagnosis can be obtained only by PCR and not by culture.<sup>17</sup> Virus isolation took 2 to 7 days in our patients.

The transmission of echoviruses may occur *in utero*, at delivery or postnatally.<sup>1, 3, 4, 13</sup> The source and the mode of transmission of the echovirus 20 infection in our cases remained unclear. Only one of the mothers had symptoms of a virus-like illness before delivery. After cesarean section she promptly recovered and viral cultures of her throat and stool

TABLE 1. Extremes of laboratory abnormalities in four neonates with echovirus 20 infection

| Patient | WBC<br>( $\times 10^9/l$ ) | Platelets<br>( $\times 10^9/l$ ) | AST<br>(Units/l) | ALT<br>(Units/l) | LDH<br>(Units/l) | PTT (s) | PT (s) |
|---------|----------------------------|----------------------------------|------------------|------------------|------------------|---------|--------|
| 1       | 6.3                        | 12                               | 2650             | 1440             | 13 500           | 94      | 62     |
| 2       | 2.5                        | 9                                | 2100             | 410              | 10 244           | 96      | 180    |
| 3       | 4.6                        | 15                               | 1757             | 405              | 9008             | 72      | 35     |
| 4       | 6.1                        | 95                               | NA               | NA               | NA               | NA      | NA     |

ALT, alanine aminotransferase; NA, not available; PTT, partial thromboplastin time; PT, prothrombin time.

TABLE 2. Demographic data of patients with echovirus 20 infection

| Patient | Gestational Age (Weeks) | Birth Weight (g) | Sex | Age at Onset | Maternal Disease      | Outcome     |
|---------|-------------------------|------------------|-----|--------------|-----------------------|-------------|
| 1       | 37½                     | 2640             | F   | 5            | Fever, abdominal pain | Recovery    |
| 2       | 39                      | 3225             | M   | 7            | None                  | Died        |
| 3       | 36                      | 2720             | F   | 4            | None                  | Cholestasis |
| 4       | 37                      | 2230             | F   | 5            | None                  | Recovery    |

taken on the eighth day after delivery were negative. Viral cultures of the parents of other patients were not obtained.

Many outbreaks of echovirus infection in nurseries have been described in the literature.<sup>5, 12, 13</sup> Echoviruses may be introduced into the nursery by an infected adult, but a vertically infected neonate may also be the source of transmission to other infants in the nursery. Good hygienic practices such as hand washing, mouth care and cohorting of the patients may prevent transmission of the virus within the neonatal care unit. As far as we could ascertain there was no transmission of echovirus 20 from the patients to other infants.

In conclusion echovirus 20 may cause a severe neonatal disease characterized by a sepsis-like presentation at onset, development of severe hepatitis with DIC in the course of illness which can lead to a massive hepatic necrosis and death.

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#### **CLOSTRIDIUM TERTIUM MENINGITIS AS THE PRESENTING SIGN OF A MENINGOCELE IN A TWELVE-YEAR-OLD CHILD**

Anaerobic bacterial meningitis is a rare entity, usually seen as a complication of anaerobic brain abscesses.<sup>1</sup> Clos-