
Echovirus 11 Infections of Newborns With Mortality During the 1979 Enterovirus Season in Milwaukee, Wis.

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ECHOVIRUS type 11 (ECHO-11) has been implicated in severe neonatal infections that have resulted in death in nursery outbreaks (1,2). Other echoviruses, particularly types 3, 6, 9, and 14 have caused congenital and neonatal infections (3). The literature suggests that severe and fatal echovirus infections in newborns generally are confined to nursery epidemics and are acquired in the hospital (1).

Few attempts have been made to correlate these nursery outbreaks with community-acquired enterovirus disease. An opportunity to do this kind of correlation occurred during the summer and fall of 1979 when the city of Milwaukee experienced an outbreak of severe enteroviral disease in infants. Echovirus types 7, 11, and 30 were the predominant viruses isolated. ECHO-11, associated with three deaths, and Cocksackie B4, associated with one death, were thought to be late-pregnancy infections acquired after community exposure. ECHO-11 infections were associated with more severe symptoms in newborns than either ECHO-7 or ECHO-30, which caused comparatively mild, self-limiting illness.

We present data which indicate that ECHO-11 and other enteroviruses cross the placenta and infect the fetus, and they may be important causes of stillbirths that occur during enterovirus outbreaks. An epidemiologic description of the Milwaukee outbreak includes temporal association of community disease with severe infections in neonates, mortality risks of echovirus infection in premature infants, and a summary of 13 early-life infections—including those associated with the 4 fatalities.

Materials and Methods

The Milwaukee Health Department Virus Laboratory accepts specimens for viral isolation from hospitals within the Milwaukee County area, but mostly from hospitals within the city. For many of the neonates in this study, virus isolation specimens were submitted initially to rule out sepsis. Generally, brief histories or clinical data accompany the specimens. The laboratory processes 5,000 to 6,000 specimens a year.

During the outbreak, the laboratory recovered non-polio enteroviruses from 225 patients of local hospitals. The ages of 189 of these patients were known: 39 percent were under 60 days old, and 7 percent were under 7 days old.

St. Joseph's Hospital is a 571-bed, acute-care facility, and it has the largest obstetrical service in the city. The hospital's virus laboratory collects most specimens

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from obstetrical patients, from newborns in the nursery, from neonates in intensive care, and from patients receiving immunosuppressive therapy. Patients' histories are readily obtained for review from the hospital's medical records department. During the outbreak, the laboratory recovered nonpolio enteroviruses from 20 patients; 12 were under 28 days old, and 8 were under 1 week old.

For virus isolation and identification, specimens received at both laboratories were inoculated routinely into African green monkey kidney cells, HEp-2 cells, diploid human lung cells, and human foreskin fibroblast cells. Isolates were identified presumptively as enteroviruses by cytopathic effects in cells and typed by neutralization tests for which antibody pools were used according to the procedure of Lim and Benyesh-Melnick (4).

Results

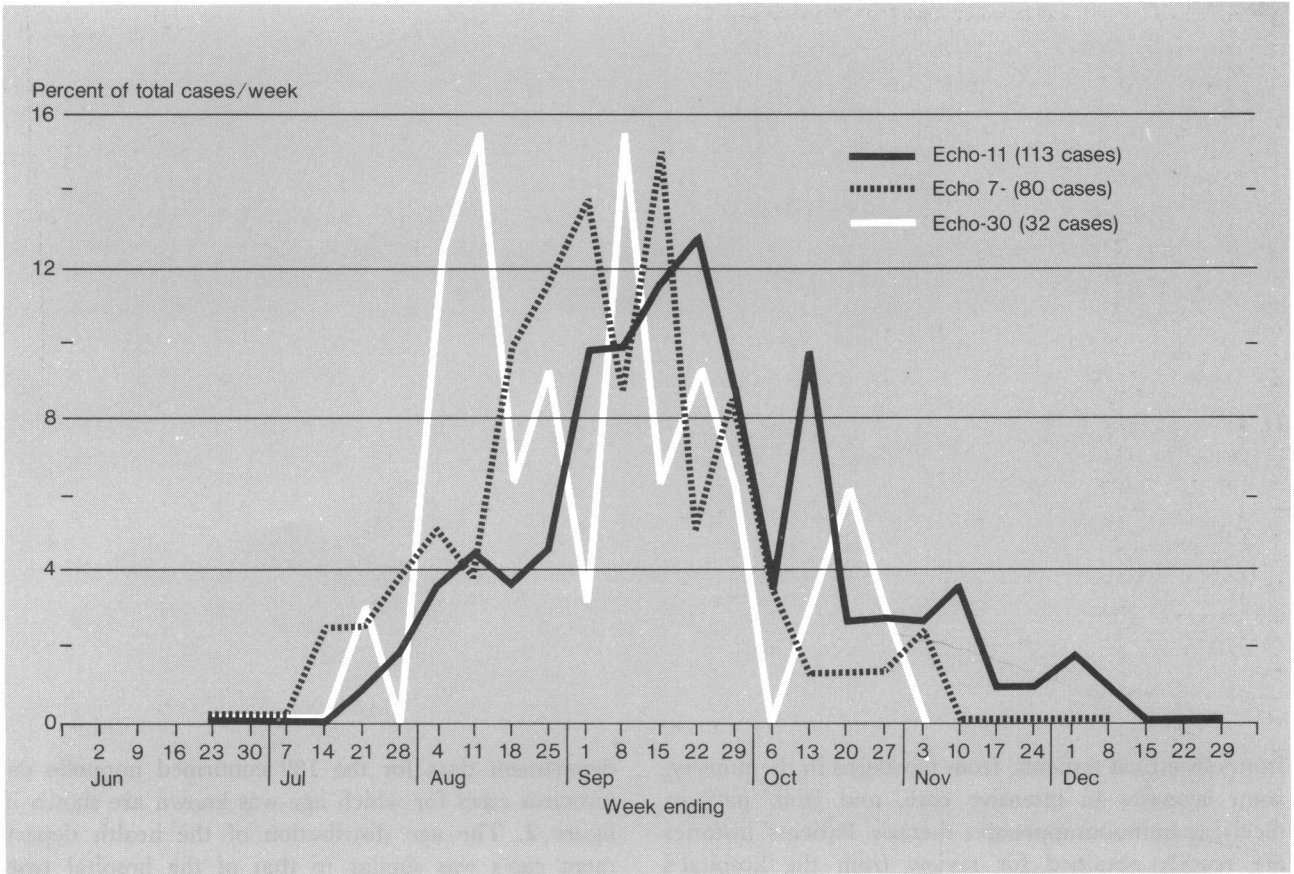
Monthly occurrence of echovirus cases. ECHO-7, ECHO-11, and ECHO-30 cases occurred in the community at essentially the same time during the summer and fall of 1979 (fig.1). ECHO-30 cases peaked first during August, ECHO-7 cases peaked in early September, and ECHO-11 cases peaked in the third week of September. Most of the echovirus cases were identified at St. Joseph's Hospital in September.

Age distribution of infected persons. The 1979 health

department data for the 189 confirmed nonpolio enterovirus cases for which age was known are shown in figure 2. The age distribution of the health department cases was similar to that of the hospital cases for the three echovirus types. Some 54-67 percent of all confirmed cases occurred in the under 1-year age group, 20-25 percent in the 1-to 10-year age group, and 13-25 percent in the 10-year and older age group. Significantly, 30-45 percent of all cases occurred in infants under 60 days old, regardless of echovirus type. Although ECHO-7 infections in the very young were nearly as common in the community as ECHO-11 infections, no ECHO-7 deaths were confirmed and ECHO-7 infections accounted for only 1 of 20 cases at St. Joseph's Hospital. In contrast, 13 of 16 echovirus infections in the intensive care unit of the hospital were caused by ECHO-11, and 7 of these were in infants under 1 week old.

All enterovirus cases confirmed by either the health department or the hospital are summarized in table 1. Although the proportions of ECHO-30 cases (14 and 10 percent) and ECHO-11 cases (50 and 65 percent) were similar for the health department and the hospital cases, ECHO-7 cases were 7 times more common (36 and 5 percent) in the health department cases than in the hospital cases. Since the age distribution for confirmed infections for all three echovirus types is similar (fig. 2) and the hospital cases re-

Figure 1. Monthly occurrence of predominant echovirus cases in Milwaukee, 1979



present serious infections of patients in the neonatal intensive care unit, ECHO-7 and ECHO-30 viruses seem to be less virulent than ECHO-11 for very young infants.

The overall mortality rate for laboratory-confirmed enterovirus infections for all ages was 1.7 percent (4 of 245 cases), but for infants whose infection occurred during the first week of life, the mortality rate was 19 percent (4 of 21), as the following data show.

Data source	Number of cases	Number of deaths
St. Joseph's Hospital	8	2
Milwaukee Health Department	13	2
Total	21	4

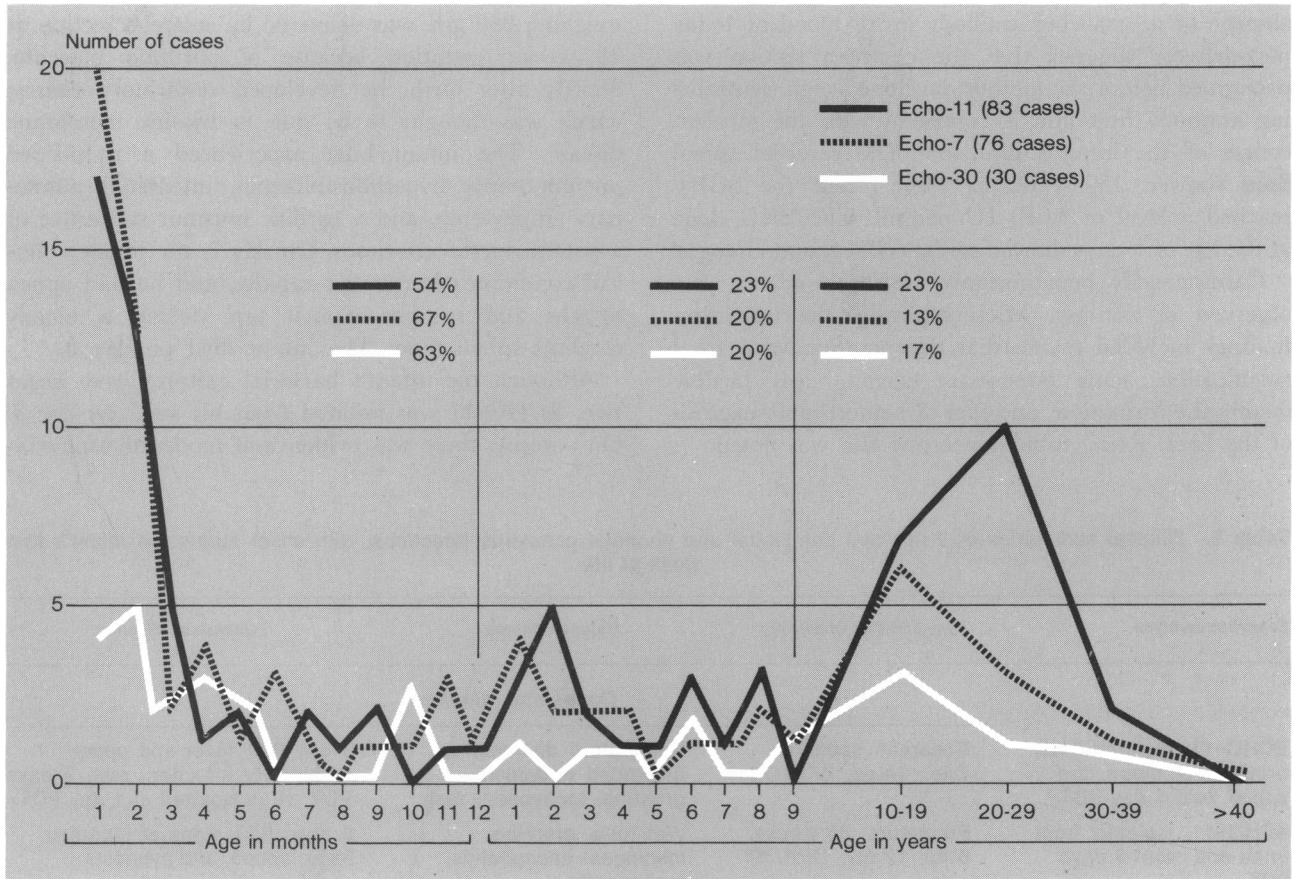
Clinical Histories of 13 Cases

Remington and Klein (5)—who recognized the difficulty of determining whether the infection in the new-

Table 1. Enterovirus cases and deaths confirmed by the Milwaukee, Wis., Health Department or St. Joseph's Hospital, 1979

Serotype	Milwaukee Health Department			St. Joseph's Hospital			Age in weeks		
	Number of cases	Percent of cases	Number of deaths	Number of cases	Percent of cases	Number of deaths	1	2-4	≥60
ECHO-7	80	36	0	1	5	0	1
ECHO-11	113	50	2	13	65	1	7	1	5
ECHO-30	32	14	0	2	10	0	2
Coxsackie B2	1	5	0	..	1	..
Coxsackie B4	2	10	1	1	1	..
Not typed	1	5	0	..	1	..
Total	225	..	2	20	..	2	8	4	8

Figure 2. Distribution of confirmed enterovirus cases in Milwaukee, summer through fall 1979, by ages of patients



born was acquired in utero, during the delivery process, or postpartum—stated: “If the onset of clinical signs and symptoms after birth is within the minimum incubation period for the disease (3 days for enteroviruses), it is likely that the infection was acquired prior to delivery.” Their assumption was borne out in one instance of an ECHO-11 nursery outbreak (1), where it was possible to estimate the incubation period (4–7 days) in newborns after contact with an infected baby, the index case.

Clinical signs previously observed in newborns with probable congenital enterovirus infection were hepatosplenomegaly, jaundice, adenopathy, pneumonitis, rash, meningoencephalitis, paralysis, myocarditis, and keratoconjunctivitis (5). Considering these guidelines, we categorized our 13 cases of confirmed enterovirus infections as group 1, fatal congenital infections; group 2, nonfatal congenital infections; and group 3, nonfatal neonatal infections.

Group 1, Fatal Congenital Infections

Case 1: Coxsackie virus type B4. On January 25,

1979, a male was delivered by cesarean section at 37 week’ gestation because of abruptio placenta. His birth weight was 3,360 gm. The mother had a familial history of spherocytosis, and she had had a splenectomy. Ten days before the birth, the mother contracted a “flu-like” febrile illness. The results of extensive bacterial and viral studies were negative, but serums drawn on the 9th and 21st days after delivery showed Coxsackie virus type B4 neutralization titers of 1:1,280. The infant appeared normal at birth, except for a mild lymphadenopathy in the groin and axilla. A fine vesiculopapular rash, which cleared spontaneously, was seen 6 hours after birth. At the age of 5 days he became febrile, hyperbilirubinemic, lethargic, and developed a progressive metabolic acidosis. The next day, he experienced seizures and congestive cardiac failure. At the age of 10 days, the infant died.

Many bacterial cultures were performed, and all were negative. However, Coxsackie virus type B4 was isolated from the infant’s spinal fluid on day 5 and from kidney, heart, liver, and brain specimens at autopsy. The serum drawn from the infant at age 1 day gave a Coxsackie virus type B4 neutralization titer

of 1:2. The infant's IgM was 5 mg per dl. The absence of neutralizing antibody in his blood at 1 day post-delivery suggests that the cesarean section was performed before the mother developed high neutralizing antibody titer and is consistent with the virulent course of the infant's infection. The cerebral spinal fluid showed 150 WBC per mm³, and the SGPT reached a level of 3,010 IU per ml. The EKG done at the age of 5 days showed severe ST segment changes.

Cardiomegaly, hepatomegaly, and brain edema were observed at autopsy. Microscopically, the important findings included myocardial degeneration with focal calcification, acute pulmonary edema, early hyaline membrane formation, and foci of hemorrhagic necrosis of the liver. Renal tubular necrosis also was noted.

Case 2: ECHO-11. On September 6, 1979, a male weighing 960 gm. was delivered by cesarean section at 28 weeks' gestation because of abruptio placenta. Shortly after birth, he developed respiratory distress which was thought to be due to hyaline membrane disease. The infant later experienced a right-sided pneumothorax hyperbilirubinemia, interstitial pulmonary emphysema, and a cardiac murmur suggestive of a patent ductus arteriosus. On day 7, the infant's clinical condition deteriorated rapidly, and he had apnea attacks and seizures. Spinal tap yielded a bloody cerebral spinal fluid. The infant died on day 8.

Although the infant's bacterial cultures were negative, ECHO-11 was isolated from his stool on day 3. On autopsy, there was evidence of moderate asphyxia-

Table 2. Clinical summaries of 9 nonfatal congenital and neonatal echovirus infections, with onset during the infant's first week of life

<i>Echovirus serotype</i>	<i>Type and date of delivery</i>	<i>Major symptoms</i>	<i>Evidence of Infection</i>
<i>Congenital infection</i>			
ECHO-11, isolated from urine, stool, blood, and spinal fluid 1 day PDT ¹	Cesarean section, 7 lb., 14 oz., 8/30/79	Respiratory distress, distended abdomen, grunting, tachypnea, rash	1 day PDT fever and upper respiratory infection, rash 3 days PDT, virus isolated at 1 day PDT
ECHO-11, isolated from urine and stool 5 days PDT	Premature, 36 weeks, 6 lb., 12 oz., 12/6/79	Wet lung, grunting, meningeal encephalitis, tachycardia	3 days PDT signs of jaundice, fever, apnea, and cyanosis
ECHO-11, isolated from spinal fluid and rectum 7 days PDT	Vaginal, 9/11/79	Meningitis, rash, fever	100.5° temperature 3 days PDT, rash 6 days PDT
ECHO-7, isolated from rectum of baby 1 day PDT and from rectum of mother 2 days PDT	Cesarean section, 9/7/79	Respiratory distress, rash, and 102° temperature	Respiratory distress 1 day PDT, 102° temperature and rash 4 days PDT. ECHO-7 isolated 1 day PDT from rectum of baby and 1 day from rectum of mother. Mother had rash before delivery and sibling had flu 2 days earlier
ECHO-7, isolated from spinal fluid and rectum	Cesarean section, 8/11/79	Loose stools, irritability, and tense extremities—temperature elevated for 7 days	ECHO-7 isolated from baby 2 days PDT. Mother with fever 2 days before delivery
ECHO-7, isolated from rectum	Vaginal, 10/28/79	Fever at birth	ECHO-7 isolated 1 day PDT from baby
<i>Neonatal infection</i>			
ECHO-11, isolated from throat and rectum	Vaginal, 38-39 weeks, 2/8/80	Aseptic meningitis, idiopathic hyperbilirubinemia, fever	Icteric skin and 5 days PDT fever 100.7°, ECHO-11 isolated 6 days PDT
ECHO-11, isolated from stool	Cesarean section, 7 lb., 8 oz., 9/4/79	Viral meningitis	Fever 101.2° 4 days PDT, ECHO-11 isolated 8 days PDT
ECHO-11, isolated from urine 41 days PDT	Premature, 32 weeks, 7/29/79	Viral meningitis, severe hyaline membrane disease, brachycardia, anemia, hyperbilirubinemia, apnea	Icteric at 7 days PDT, brachycardia and apnea 30 days PDT

¹ Post-delivery time.

Table 3. Association of enterovirus serotypes with prematurity and mortality for 13 cases that occurred during the first week of life, Milwaukee, 1979

Serotype	Total cases	Number of deaths	Percent mortality	Premature cases	Number of deaths	Percent mortality
Coxsackie B4	1	1	100	1	1	100
ECHO-11	9	3	(A) 33	4	3	(B) 75
ECHO-7	3	0	(C) 0	2	0	(D) 0
Total	13	4	30	7	4	57

NOTE: Statistical analysis by *t* test for small numbers: A:B, $P = > .1 < .2$, not significant; A:C, $P = > .05 < .1$, not significant; B:D, $P = < .01$, highly significant.

tion, severe hyaline membrane disease, patent ductus arteriosus with congestive cardiac failure, interstitial pneumonia, edema, severe anemia, and interventricular cerebral hemorrhage.

Case 3: ECHO-11. On September 3, 1979, a male was delivered by cesarean section at 35 weeks' gestation. Shortly after birth, he exhibited respiratory distress, and he was placed in the neonatal intensive care unit. At age 2 days, the infant's temperature rose to 101.4° F. He developed a pneumothorax on the next day, and he died on day 4.

The mother had no signs or symptoms of febrile illness during pregnancy or delivery, but 3 days before the infant's birth his sibling had signs of a flu-like syndrome. Throat, rectal, and urine cultures were positive for ECHO-11 shortly after his birth.

Case 4: ECHO-11. A full-term female became febrile and irritable at age 3 days in mid-October 1979. She died on day 7. ECHO-11 was isolated from day 4 cultures of throat, cerebrospinal fluid, and stool; it was also isolated from blood drawn at autopsy. Serum specimens drawn from the mother at 3 and 11 weeks after delivery showed an unchanged neutralization antibody titer of 1:160 for ECHO-11.

Groups 2 and 3, Nonfatal Congenital and Neonatal Infections

Clinical summaries of nine nonfatal congenital and

neonatal echovirus infections are presented in table 2. The three ECHO-7 infections were associated primarily with fever, sometimes with rash or respiratory signs, but no jaundice or central nervous system signs were present. These ECHO-7 infections differed markedly from the central nervous system and liver complications seen in a majority of the ECHO-11 and Coxsackie B4 infections. Fever was a common symptom in all of the enterovirus cases, but rash occurred in only five.

Association of enterovirus type, prematurity, and type of delivery with mortality. Since 7 of the 13 cases were associated with prematurity, and case histories were studied to determine if any association existed between mortality and enterovirus type, delivery process, and prematurity.

Table 3 shows the 13 cases in terms of overall mortality and mortality among infants delivered prematurely. During the first week of life, 12 infants had either ECHO-7 or ECHO-11 infection and 1 had a Coxsackie B4 infection. Of the 13 cases, 7 were in premature infants delivered by cesarean section, and all 4 deaths occurred in this group. ECHO-11 was isolated from 3 infants who died and Coxsackie B4 virus from 1—a mortality rate of 75 percent in premature infants with ECHO-11 infection and an overall enterovirus mortality rate of 57 percent in premature infants. Five infants infected with ECHO-11 virus during the first week of life, who were not premature, survived.

In table 4, fatal cases of ECHO-11 and ECHO-7

Table 4. Association of enterovirus serotypes with type of delivery and mortality, Milwaukee, 1979

Serotype	Number of cases with cesarean section	Number of deaths	Percent mortality	Number of cases with vaginal delivery	Number of deaths	Percent mortality
ECHO-11	4	2	(E) 50	5	1	(F) 20
ECHO-7	2	0	(G) 0	1	0	0

NOTE: Statistical analysis by *t* test for small numbers: E:F, $P = > .2 < .5$, not significant; E:G, $P = .05$, significant.

Table 5. Summary of idiopathic stillbirths and enterovirus confirmed cases at St. Joseph's Hospital, Milwaukee, by month, 1979-80

Month	Total enterovirus Isolations	Total enterovirus cases	Enterovirus cases, age < 4 weeks	Number of Idiopathic stillbirths
1979				
January	1	1	1	0
February	0	0	0	0
March	0	0	0	1
April	0	0	0	1
May	0	0	0	1
June	0	0	0	1
July	1	1	0	1
August	8	4	1	5
September ..	17	11	7	2
October	1	1	1	4
November ...	0	0	0	1
December ...	2	1	1	2
1980				
January	0	0	0	1
February	3	1	1	1
Total ..	33	20	12	19

are compared by type of delivery—vaginal or cesarean section. Infants with ECHO-7 infection survived regardless of type of delivery. Of 4 ECHO-11 infected infants delivered by cesarean section, 2 died, whereas 1 death occurred among 5 ECHO-11 infants delivered vaginally.

The results of the statistical analysis by the *t* test suggested that ECHO-11, not ECHO-7, was significant in the mortality that occurred among the premature infants (B:D and E:G, tables 3 and 4).

Association of enterovirus disease and stillbirths. Epidemiologic data for the 20 enterovirus cases diagnosed at St. Joseph's Hospital were examined for temporal relationship between stillbirths at the hospital and enterovirus infections. The numbers of stillbirths and enterovirus cases for each month of 1979 and the first 2 months of 1980 are shown in table 5. One stillbirth in February, 2 in April, and 1 in June are omitted from the table because the cause of death for 3 was knots in the cord, and 1 death was caused by severe hypertension in the mother.

The majority of cases occurred from July through October—12 of 19 stillbirths, 9 of 12 enterovirus infections in infants under 1 month old, and 16 of 20 cases seen at the hospital. In September, 8 of 11 cases were due to ECHO-11 infections. Thus, this coincidence of peaks in cases tends to support an association between the increased number of stillbirths in the summer and fall of 1979 and the presence of enteroviruses in the community, especially ECHO-11.

Discussion

Our report of 3 deaths of premature infants infected with ECHO-11 is similar to Modlin's report (6) of 4 ECHO-11 associated deaths of premature infants in Boston during an enterovirus outbreak in 1979. The clinical course in our group consisted of vague, early signs of respiratory distress leading to severe jaundice and generalized infections; death occurred within 4-8 days. We believe that our cases were acquired congenitally because symptoms appeared well within the 3-day incubation period of the disease and because 2 of the 3 infants who died had been delivered by cesarean section. Although other echovirus types were active in the community outbreak, only type 11 was associated with the 3 fatalities.

Previously reported early-life ECHO-11 infections were attributed to nursery outbreaks (1,2). In one of these outbreaks, three infants died after the infection was spread from the index case to staff members and then to the nursery in November 1978. The histories for the 13 early-life cases in our group indicate that these infections were probably acquired in the community during the outbreak and were treated at St. Joseph's Hospital as well as elsewhere in the city. We reached this conclusion because both the community-confirmed cases and the cases at St. Joseph's Hospital peaked during September. Also, the hospital cases were not associated with a sharp epidemic curve; rather, they were in infants admitted at various times during July, August, and September.

In the Milwaukee outbreak, echovirus infections of newborns in nurseries were acquired in the community rather than in the hospital. These infections were commonly seen in nurseries during 1979 because community-acquired echovirus infections, particularly ECHO-11, of pregnant women and newborns are more likely to require hospitalization than the milder infections of older children and adults.

We attempted to assess the effect of prematurity and delivery by cesarean section on the enterovirus mortality associated with the 13 early-life infections (table 3). Although the number of cases is small, the data nonetheless indicate that the virulence and serotype of the enterovirus are important factors because ECHO-7 was not associated with prematurity and deaths, although ECHO-7 infections did occur in premature infants ($P < .01$). Cesarean section alone did not appear to be a predisposing factor, because two infants with ECHO-7 infections who were delivered by cesarean section had mild cases and recovered rapidly (table 4).

Congenital enterovirus infection has been firmly established for polioviruses, Coxsackie type B viruses,

and echoviruses (7). However, intrauterine death due to echoviruses has not been proved. Establishment of intrauterine death as a result of enteroviruses would require isolation of the virus from fetal tissues at autopsy. ECHO-11 was isolated from a mother with a history of infection before delivery of an aborted fetus, but virus was not recovered from the fetus (8). Our finding of a temporal association between idiopathic stillbirths and ECHO-11 infections supports the premise that this virus may cause intrauterine death.

Speculation and Relevance

It is likely that during enterovirus outbreaks which occur in the summer and fall months certain echoviruses, including types 7 and 11, commonly cross the placental barrier and initiate intrauterine infections. These infections may be mild or severe, depending on the echovirus type and the gestational age of the fetus. If the infection is mild, the newborn may recover promptly and completely; if it is severe, the pregnancy may terminate in a stillbirth or the birth of a baby who has generalized severe symptoms of disease that may lead to death. If the outcome is not death, the infant may experience a prolonged, stormy clinical course and either complete recovery or permanent neurological or possibly myocardial deficit (9,10). Obviously, all aspects of intrauterine echovirus infection must be further explored and evaluated.

Finally, ECHO-11 has unusual virulence for the very young, and it can produce a wide range of clinical manifestations—from mild cases of aseptic meningitis, mild transient paralysis, and myocarditis to severe infections of the central nervous system, including fatal

bulbospinai paralytic poliomyelitis (11). The full impact of clinical disease caused by ECHO-11 in the very young needs to be examined thoroughly.

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SYNOPSIS

PIRAINO, FRANK F. (St. Joseph's Hospital, Milwaukee), SEDMAK, GERALD, and RAAB, KARLO: *Echovirus 11 infections of newborns with mortality during the 1979 enterovirus season in Milwaukee, Wis. Public Health Reports, Vol. 97, July-August 1982, pp. 346-353.*

Echovirus serotype 11 (ECHO-11) was implicated in three neonatal deaths during an enterovirus outbreak

from July through October 1979 in Milwaukee. The deaths followed congenital infections acquired in the community during late pregnancy. Two of the three ECHO-11 and one Coxsackie B4 deaths of infants occurred after cesarean section deliveries.

Of 225 confirmed echovirus infections, 30 to 45 percent occurred in infants under 60 days old, 54 to 67 percent in the first year of life, and 13 to 25 percent in the over-10 age groups. In 13 cases with onset of

symptoms in the first week of life, 8 (including the 4 fatalities) were acquired congenitally; 6 of the 8 were associated with ECHO-11, 2 with ECHO-7, and 1 with Coxsackie B4.

ECHO-7 and 30 other predominant strains were isolated during the outbreak, but none was associated with mortality or severe disease in neonates. At a Milwaukee hospital, a temporal association was observed between echovirus infection, particularly ECHO-11, and increased numbers of stillbirths.