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New Tricks for an Old Enterovirus

ABSTRACTS & COMMENTARY

Synopsis: *An outbreak of enterovirus 71 in Taiwan in 1998 resulted in more than 1 million cases of hand-foot-and-mouth disease or herpangina. Severe disease, especially rhombencephalitis, and fatalities from pulmonary edema and hemorrhage were observed, especially in young children.*

Sources: Ho M, et al. An epidemic of enterovirus 71 infection in Taiwan. *N Engl J Med* 1999;341:929-935; Huang CC, et al. Neurologic complications in children with enterovirus 71 infection. *N Engl J Med* 1999;341:936-942.

In 1998, an epidemic in taiwan of enteroviruses caused 129,106 cases of hand-foot-and-mouth disease or herpangina, which was estimated to represent less than 10% of the total number of cases. There were 405 cases of severe disease: aseptic meningitis, encephalitis, acute flaccid paralysis, pulmonary edema or hemorrhage, and myocarditis. There were 78 deaths, including 71 (91%) in children younger than 5 years of age, primarily resulting from pulmonary edema or hemorrhage. Enterovirus was isolated from 49% of outpatients with uncompleted hand-foot-and-mouth disease or herpangina, 75% of hospitalized patients who survived, and 92% of patients who died.

During the 1998 enterovirus epidemic in Taiwan, 41 children were hospitalized with culture-confirmed enterovirus infection and acute neurologic manifestations. The mean age of the patients was 2.5 years (range, 3 months to 8.2 years). Twenty-eight patients (68%) had hand-foot-and-mouth disease and six (15%) had herpangina. Three neurologic syndromes were observed: aseptic meningitis in three patients, rhombencephalitis (brain-stem encephalitis) in 37 patients, and acute flaccid paralysis in four patients, which followed rhombencephalitis in three patients. The most common symptoms were myoclonic jerks, and T_2-weighted magnetic resonance imaging (MRI) showed high-intensity lesions in the brain stem in 17 of 24 (71%) patients. Five patients with rhombencephalitis died.

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INSIDE

COMMENT BY HAL B. JENSON, MD, FAAP

Since enterovirus 71 was isolated in 1969, it has been recognized to cause sporadic cases and several large outbreaks in many parts of the world. Enteroviruses, as their name implies, are spread primarily by the fecal-oral route but the characteristics of this outbreak indicate potential respiratory spread.

The unusual complications of rhombencephalitis suggest that this enterovirus could represent a particularly virulent strain, with tropism for the rhombencephalon. Rhombencephalitis was manifest by: myoclonic jerks with tremor, ataxia, or both (Grade I); myoclonus with cranial nerve involvement, including ocular disturbances such as nystagmus, strabismus, or gaze paresis (Grade II); or transient myoclonus rapidly followed by loss of doll's eye reflex, and apnea (Grade III). This outbreak was also characterized by pulmonary edema and hemorrhage, another uncommon although recognized complication of enterovirus 71 infection, which was responsible for the majority of deaths.

We tend to consider enterovirus encephalitis as sporadic, self-limited, and generally without serious morbidity and with low mortality. This outbreak showed the epidemic and fatal aspects of enterovirus 71 infections. Patients with neurologic symptoms following hand-foot-and-mouth syndrome or herpangina, or with encephalitis of uncertain etiology, should be cultured for enteroviruses. This may hasten the diagnosis in sentinel patients and lead to earlier recognition of enteroviral outbreaks complicated by neurologic involvement. ❖

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In Utero Intervention for Obstructive Uropathy: Assessing the Benefits

ABSTRACT & COMMENTARY

Synopsis: *Antenatal surgical intervention in obstructive uropathy has been done for more than 15 years. The intent of this surgery is to divert urine from the fetal bladder to the amniotic space to prevent the pulmonary hypoplasia that results from oligohydramnios. The study group included 34 fetuses who underwent vesicoamniotic shunt placement over a nine-year period at the University of Michigan and Wayne State University. The object of the study was to assess the long-term outcome of these children. Freedman and colleagues conclude that the intervention may have benefited those with severe obstruction whose outcome is usually fatal.*

Source: Freedman AL, et al. Long-term outcome in children after antenatal intervention for obstructive uropathies. *Lancet* 1999;354:374-377.

Freedman and colleagues reviewed the course of follow-up of 34 patients who underwent antenatal vesicoamniotic shunt placement following diagnosis of obstructive uropathy by ultrasonography. These fetuses were considered to be at high risk for pulmonary hypoplasia, which is frequently fatal and is believed to result from oligohydramnios. There is also concern regarding the role that intrauterine obstruction plays in the development of renal dysplasia and insufficiency, as well as impaired bladder function. The intent of the study was to assess the clinical outcomes of the children two or more years after shunt procedures performed from 1987-1996. Twenty-one children survived, 17 were older than 2 years, and 14 were available for follow-up. The mean age at follow-up was 54.3 months (range, 25-114). None of the children had severe respiratory disease, although six had received diagnoses of either asthma or chronic bronchitis. Eight children had either end-stage renal disease or chronic renal insufficiency and six children had voiding dysfunction. Poor growth was com-

mon, with 86% of the children's height less than the 25th percentile and 50% less than the fifth percentile. Freedman et al conclude the intervention may have helped those fetuses with severe obstruction, achieving outcomes similar to children with less severe obstruction.

COMMENT BY THOMAS L. KENNEDY, MD, FAAP

Whenever fetal surgery is performed, it gets our attention. Such procedures seem dramatic, daring, and, pardon the expression, "cutting edge." In the case of surgery for obstructive uropathy to divert fetal urine to the amniotic cavity, intervention seems to make good sense for two reasons. First, relief of urinary tract obstruction (almost invariably posterior urethral valves in males) should reduce the risk of pressure-induced renal injury and/or developmental dysplasia. Second, oligohydramnios is associated with pulmonary hypoplasia and restoration of amniotic fluid should prevent it. But does it? How effective is surgical intervention? And what are the long-term outcomes of these children?

It was in search of answers to these questions that this follow-up study was conducted. It should be noted that definitive conclusions cannot be reached since there was no control group, intervention occurred at widely different times of gestation (14.5-31 weeks), and the numbers are small. Nevertheless, the intent was to determine the health of the 62% who survived the neonatal period.

Assessment of two most affected organ systems, that is, respiratory and renal, immediately come to mind. On the positive side, despite the fact that several of the children carry pulmonary "diagnoses," none has serious limitations. More concerning, end-stage renal failure and/or chronic renal insufficiency occurred in six of 14, but Freedman et al caution that, in the majority, ongoing voiding dysfunction and/or urinary tract infections appear to have contributed significantly to progressive renal injury. An important prognostic indicator seems to be the minimum serum creatinine in the first year of life; all children with a creatinine level that never got below 1.0 mg/dL eventually required dialysis or transplantation. Freedman et al do not comment on the incidence of other renal complications such as hypertension or renal tubular acidosis, but the significant problems with growth that were identified may be secondary to chronic acidosis.

At any rate, children who undergo antenatal relief of urinary tract obstruction are not home free. The surgery itself is difficult and may be associated with fetal demise, premature birth, or failure of the shunt to stay in place. Furthermore, the problems that predate the surgery may cause renal and pulmonary damage not reversed by the surgery. In those who survive, multiple surgical procedures are sometimes necessary and even then, ongoing voiding problems may persist and continue to cause renal injury.

The take-away message is not that prenatal surgery for urinary tract obstruction should not be done, but that fetuses must be carefully selected, with intervention occurring in those with the most severe obstruction and as early in gestation as possible. However, identification of this group is not always easy, and relief of obstruction in these cases can lead to infant survival, although not always without significant post-natal problems. ❖

Long-Term Course of Hepatitis C Viral Infections in Children

ABSTRACTS & COMMENTARY

Synopsis: *Fourteen percent of German children who had undergone cardiac surgery before implementation of donor screening of blood donors were positive for antibodies against hepatitis C virus (HCV) and 55% of these antibody-positive children had circulating HCV. Liver function tests and liver biopsy of these children showed a small number of patients with significant liver disease. Children with hemophilia exhibited a high circulating HCV load but had less severe liver histopathology compared to children who had acquired HCV from blood transfusions or vertically.*

Sources: Vogt M, et al. Prevalence and clinical outcome of hepatitis C infection in children who underwent cardiac surgery before the implementation of blood-donor screening. *N Engl J Med* 1999;341:866-870; Zellos A, et al. High viral load and mild liver injury in children with hemophilia compared with other children with chronic hepatitis C virus infection. *J Pediatr Gastroenterol Nutr* 1999;29:418-423.

German children who underwent cardiac surgery before 1991, when routine blood donor screening for hepatitis C was introduced, were studied for hepatitis C virus (HCV). Sixty-seven of 458 patients (14.6%) had antibodies against HCV. The positive rate in normal age-matched controls was only 0.7%. At a mean follow-up time of 19.8 years, 37 of 67 antibody-positive patients (55%) had detectable HCV RNA in their blood. Only one of the HCV RNA-positive patients had elevated alanine aminotransferase (ALT). Seventeen of 37 patients had liver biopsy. Three of these had histologic signs of progressive liver damage, and these three patients had additional risk factors.

Zellos and associates evaluated whether the mode of transmission of HCV infection had an effect on subsequent liver injury and circulating viral load of children with HCV infections.

Thirty-nine children who had positive enzyme-linked immunoassay (ELISA) immune tests for HCV antibodies were divided into three groups reflecting their route of infection: blood transfusions, hemophilia factor replacement therapy, and vertical transmission from mother to infant. Serum HCV viral load was approximately five times higher in the hemophiliacs than in the other groups. However, and surprisingly, the degree of histologic liver injury (including inflammation and fibrosis) was significantly less severe in the hemophiliac boys compared to the other groups.

Group 1 consisted of nine children, 13.3 ± 0.9 years of age, who had a history of whole blood or red blood cell (RBC) transfusions. Group 2 consisted of 19 hemophiliac boys, 11.6 ± 0.8 years of age. Group 3 consisted of 10 children, aged 4.7 ± 1.1 years old, who presumably had vertically acquired HCV resulting from maternal to neonate transmission. Liver function tests (serum ALT), HCV viral load determined by polymerase chain reaction assay that measures the number of circulating viral copies per mL of blood, HCV genotype, and liver histology were assessed in all of these children and the results in the three groups were compared.

Despite a considerably shortened duration of infection, the children in group 3 with vertically acquired HCV infections had liver injury comparable to those in group 1. Genotype of the HCV infection did not influence either the level of viremia or histologic liver injury. Vogt and colleagues and Zellos et al conclude that children with hemophilia had higher levels of circulating HCV, but paradoxically had less evidence of hepatic damage than children who had acquired HCV by blood transfusions or vertical transmission at birth. Host resistance factors may have an important influence in the pathogenesis and expression of this disease.

COMMENT BY HOWARD A. PEARSON, MD, FAAP

There are few data on the prevalence and clinical outcome of HCV infections in children. These two papers examine this issue from somewhat different perspectives. In adults who have chronic HCV infections, the severity of subsequent hepatocellular disease may be influenced by the mode of transmission of the virus to the patient. This has not been studied in children. The report of Zellos et al showing a marked difference in the prevalence of persistent viremia in hemophiliac boys who were infected by virus contaminated Factor VIII but less severe hepatocellular damage compared to infections resulting from blood transfusions or vertical transmission suggest the possibility that host immune responses may affect the clinical expression of this disease. The finding of such a large group of HCV-infected hemophiliac boys is distressing, following as it does the 1980-1985 infection of about 70% of these boys with HIV that has virtually wiped out a generation of them. The present replacement therapies for hemophilia A are increasingly produced *in vitro* by recombinant DNA technologies and should be free of virus.

Vogt et al show that although there was a substantial risk of acquiring HCV infection from nonscreened blood transfusions, after about 20 years the virus had spontaneously cleared in many patients, and the clinical course in those still infected appeared more benign than would be expected in persons infected in adult life.

Even today, when extensive testing of blood has essentially eliminated most of the diseases that are now known to be transmissible, such as HIV and hepatitis A, B, and C, there could well be currently unknown viruses that are lurking or could enter the blood supply in the future. Only when these viruses and the diseases that they produce are recognized and appropriate testing is developed to detect them, there is at least a theoretical risk of repetition of the hepatitis C and HIV disasters of the last 25 years. As a hematologist, I would be the last person to argue against the appropriate use of blood products. However, transfusion of blood products has at least a theoretical risk of transmitting serious and even fatal diseases and they should not be administered for trivial or unnecessary indications. ❖

Intellectual Outcome at 12 Years of Age in Children with Congenital Hypothyroidism

ABSTRACT & COMMENTARY

Synopsis: *Children with congenital hypothyroidism have intellectual defects that may be related to the severity of the disease at birth and inadequate replacement therapy.*

Source: Salerno M, et al. Intellectual outcome at 12 years of age in congenital hypothyroidism. *Eur J Endocrinol* 1999; 141:105-110.

The intelligence quotient (iq) of 40 children diagnosed as having congenital hypothyroidism by

neonatal genetic screening was determined in follow-up studies when they reached 12 years of age using the Wechsler Intelligence Scale for Children-Revised and compared with a control group made up of their healthy siblings. The mean IQ score of the hypothyroid children was not significantly different from the control group (88.4 ± 13 vs 93.4 ± 10.7). However, 13 patients showed subnormal IQ scores that were significantly lower when compared with their siblings (72 ± 4.9 vs 86.7 ± 9.6; $P < 0.0001$). The low IQ scores were associated with lower serum concentrations of thyroxine at diagnosis, poor treatment compliance during follow-up, and lower familial IQ. Even though the mean IQ scores in patients with congenital hypothyroidism fall within the norm for a carefully selected, related control group, low performance on IQ testing may be present in infants with more severe hypothyroidism and in those with inadequate compliance with replacement therapy.

COMMENT BY MYRON GENEL, MD, FAAP

Without question, one of the public health triumphs of the past 25 years has been the development and widespread application of newborn screening for congenital hypothyroidism. Early identification and the provision of appropriate replacement therapy with levothyroxine prevents the profound mental retardation that often occurred when the diagnosis relied on clinical symptoms and a high index of suspicion. While the advent of universal neonatal screening programs makes possible early diagnosis, optimal outcomes are dependent upon a number of other factors, as is illustrated by this Italian report of the intellectual outcome at 12 years of age in 40 children detected by a regional screening program. Of these 40 children, 13 had IQs less than 80; for the most part, these were infants with the most profound chemical hypothyroidism when detected. Overall performance IQs were less in the hypothyroid children compared to their siblings, even though, as a group, full-scale and verbal IQs were not significantly different. It is useful to note that therapy was not begun until a mean age of 28 days; optimally, this should be accomplished in half of this time. The starting dosage of levothyroxine, as recognized by Salerno and colleagues, was low, averaging 6.8 mcg/kg/d, whereas current recommendations are for dosages of 10-15 mcg/kg/d. Additional factors include compliance to a daily treatment regimen and the pervasive effect on child rearing of having a child with a chronic and potentially disabling condition. Operationally, screening programs have improved significantly in the past two decades. Even so, only with prompt treatment, adequate therapy, and compliance with a daily treatment program can the full benefits be achieved. ❖

Brief Reports

Frequency of Serious Infections in Infants Younger than 8 Weeks with Otitis Media

Source: Nozicka CA, et al. Otitis media in infants aged 0-8 weeks: Frequency of associated serious bacterial disease. *Pediatr Emerg Care* 1999;15:252-254.

Nozicka and associates at the children's hospital of Wisconsin emergency department (ED) in Milwaukee studied 40 nontoxic-appearing small infants with otitis media (OM) confirmed by a pediatric otolaryngologist using a binocular operating microscope. Thirty-eight percent (15/40) had rectal temperatures equal to or greater than 38°C. All infants had typanocentesis with middle ear fluid (MEF) culture and complete sepsis evaluation including complete blood count (CBC), blood culture, catheter urine culture, and lumbar puncture with cerebrospinal fluid (CSF) culture. All infants were treated with parenteral ampicillin and either gentamicin or cefotaxime and admitted to the hospital.

Bacterial pathogens were recovered from the MEF in 25/40 (62.5%) infants and 15 infants had negative cultures of the MEF. All infants who were afebrile on admission to the ED had negative blood, urine, and CSF cultures. Only two of 15 febrile infants had positive cultures from sites other than the MEF.

Nozicka et al conclude that previously healthy, nontoxic-appearing, afebrile, nontoxic infants aged 2-8 weeks of age with OM infrequently have an associated serious bacterial infection and the oral antibiotic therapy with close follow-up may be a reasonable therapeutic option. However, infants younger than 2 months of age with OM who are febrile and toxic and who have signs of systemic illness require a full septic workup and consideration of parenteral antibiotic therapy. —**lmb**

Breath-Holding Spells and Iron Deficiency

Source: Mocan H, et al. Breath holding spells in 91 children and response to treatment with iron. *Arch Dis Child* 1999;81: 261-262.

Breath-holding spells are a frequent complaint in pediatric practice. They are clinical

episodes based upon history given by the family as well as direct observation of the spells. Spells are usually defined as stopping of the child's breathing during expiration after a deep inspiration during crying. Spells are classified as cyanotic, pallid, and mixed according to the color of the patient's skin during the spell. It has been estimated that as many as 27% of otherwise healthy children experience breath-holding spells.[1] The cause of breath-holding spells has not been defined[2]; however, an association with iron deficiency anemia has been suggested and reports have described correction of these spells coincident with iron medication.[3]

Mocan and associates from Turkey studied 91 children, 6-31 months of age, with typical breath-holding spells. Studies of iron status included hemoglobin, mean cell volume (MCV) serum iron, and total iron-binding capacity. Other studies included blood sugar serum calcium, ECG, EEG, and skull x-rays. Sixty-three patients with breath-holding spells had concomitant iron deficiency anemia and were treated with oral iron, 6 mg/kg/d for three months. The remaining 28 patients were not treated. Frequency of the spells were assessed. Fifty percent (32/68) patients treated with iron had complete cessation of spells and another 33.3% (21/68) had partial remissions, with at least a 50% decrease in the frequency of spells. In contrast, only 6/28 (21%) of the non-iron-deficient, nontreated patients had complete or partial improvement during three months of observation. Mocan et al acknowledge that they did not measure serum ferritin levels in these children, and it is possible that some of their "non-iron-deficient" children may have had a degree of iron deficiency.

Breath-holding spells are most frequent in children of the same age group in which iron deficiency is most prevalent. It would seem prudent that children experiencing repetitive breath-holding spells should be studied for iron deficiency and given appropriate therapy for this when present. One might consider a short course of empiric iron therapy even without blood studies. Mocan et al conclude that anticonvulsants are not the treatment of choice for breath-holding spells in infancy. —**hap**

References

1. Bridge EM, et al. Breath holding spells; their relationship to syncope, convulsions and other phenomena. *J Pediatr* 1943;23:539-561.
2. Dimaro FJ, et al. Pallid breath holding spells; evaluation of the autonomic nervous system. *Clin Pediatr* 1990;29:17-24.
3. Daoud AS, et al. Effectiveness of iron therapy on breath-holding spells. *J Pediatr* 1997;130:547-550.

Special Report

Spontaneous Closure of Atrial Septal Defects

By Alan Friedman, MD, FAAP

It is well known that atrial septal defects (ASD) frequently close spontaneously during childhood, especially secundum ASDs, which are small. Large ASDs and primum or sinus venosus ASDs close less frequently and often require surgical or interventional transcatheter closure. A recent large study from Iceland evaluated the rate of ASD spontaneous closure, the closure rate for different sizes of ASDs, and determined the probability of intervention in relation to the size of the ASD at diagnosis.[1] This was a cross-sectional study of all children born in Iceland between 1984 and 1993 who were diagnosed with an ASD. Patients who had an ASD associated with another congenital heart disease were excluded. An ASD was found in 91 patients, with an inci-

dence of 2.1 per 1000 births and a male:female ratio of 1:2.2. The age at diagnosis ranged from 1 week to 10 years, with a mean age of 12.1 ± 13 months. Eighty patients with secundum ASDs were included in the study.

There were 29 children with defects less than 4 mm and spontaneous closure occurred in 62% at mean follow-up of 36 ± 12 months. Another 28% demonstrated a decrease in size to what was considered a patent foramen ovale. One defect got larger with time.

There were 17 children with ASDs measuring 5-6 mm in diameter and like the small defects, 64% demonstrated spontaneous closure during a follow-up period of 38 ± 16 months. Another 29% demonstrated smaller defects at follow-up. One defect got larger with time.

There were eight children with ASDs measuring 7-8 mm and only one of these spontaneously closed. However, 50% demonstrated a decrease in size. One defect got larger with time.

There were 26 children who were found to have an ASD of 8 mm or more at diagnosis and none of these demonstrated spontaneous closure over the 35 ± 12 months of follow-up. Two patients (8%) did have a decrease in ASD size to 4 mm. The necessity for surgical closure was low in the 4 mm group but was more than 90% in the 8 mm group.

ASD is the second most common cardiac defect in children and adults. It is not uncommon for ASDs to have minimal symptoms and findings that often include a soft murmur that may be interpreted as functional in nature. As a result, children with ASDs are often diagnosed after infancy and in the school-age years.

ASDs are classified by their anatomic position in the atrial septum. Primum ASDs are part of the endocardial cushion defect family often seen in children with trisomy 21. Sinus venosus ASDs are located in the region of the superior vena cava's entrance to the right atrium and are frequently associated with anomalous return of the right pulmonary veins. Both of these defects typically require surgical repair, as they often result in right ventricular volume overload.

The most common defect is referred to as the secundum ASD because it is a defect in the embryological secundum atrial septum. These defects often occupy the central portion of the septum in the region of the fossa ovalis and can be further classified as small (< 4 mm), moderate (4-8 mm), or large (> 8 mm) in diameter. A clinical diagnosis of an ASD and its type can be determined by routine echocardiography, which is used to define both the location and size of the ASD.

It is known that secundum ASDs can undergo a spontaneous decrease in size or even demonstrate complete spontaneous closure. The necessity for surgical or transcatheter closure of a secundum ASD is dependent on its size, associated symptoms, and the degree of right ventricular volume overload. Small secundum ASDs rarely lead to the latter and so often don't require closure, while large defects often need to be closed. Typically, closure is undertaken prior to school age (i.e., 3-6 years) or following diagnosis in the older child or adolescent who is diagnosed in later life.

The Icelandic study, which included virtually every child diagnosed in that small country over a decade, nicely documents the natural history of ASDs. Small defects particularly tend to spontaneously resolve to complete closure or to decrease to an insignificant flow comparable to that of a patent foramen ovale. In fact, 90% of defects that measure less than 4 mm at diagnosis will follow such a course and these children should not require surgical intervention. However, it was shown that a small number of these small defects actually increased in size over time, indicating that even small ASDs must be followed to verify that they have not become significantly larger.

Conversely, it is clear that an ASD that is large at diagnosis is likely to remain so, and often requires intervention at an appropriate age. Counseling of these families and patients at the time of diagnosis should include advising them of the probable necessity of intervention by either surgical or transcatheter technique at some time. Not surprisingly, moderately sized ASDs (4-8 mm) remain problematic because although most will resolve or become hemodynamically insignificant, some will require intervention. Again, a few ASDs in this intermediate group appear to increase in size.

The phenomenon of spontaneous closure is real in patients with an ASD and usually occurs during the preschool-age period. It continues to be unclear as to how this process occurs, although it may be related to postnatal growth of the septum secundum. Alternatively, tissue reaction to flow at the edges of the defects may lead to "filling in of the defect." What is perplexing is the apparent growth of some defects. Perhaps this is related to an elliptical shape of the secundum ASD and its relative stretching with cardiac growth. Whatever the reason, it is clear that a child found to have an ASD early in life should be followed according to their age, with repeat imaging study before the age of 4 years. ❖

Reference

1. Helgason H, Jonsdottir G. Spontaneous closure of atrial septal defects. *Pediatr Cardiol* 1999;20:195-199.

CME Questions

23. True statements concerning atrial septal defects include all of the following *except*:
a. a defect size of less than 4 mm often closes spontaneously.
b. a defect size of more than 8 mm often closes spontaneously.
c. a defect of the embryologic secundum atrial septum often closes spontaneously.
d. a defect in the region of the sinus venosus infrequently closes spontaneously.

24. True statements concerning enterovirus 71 include all of the following *except*:
a. it is an etiologic agent in some cases of herpangina and hand-foot-and-mouth disease.
b. severe complications occur more in young children than in adults.
c. it may produce lesions in the brain stem demonstrated by MRI.
d. they are exclusively spread by the fecal-oral route.

25. Fetal urinary tract obstructions:
a. can often be relieved antenatally but surgery is associated with a 62% neonatal demise.
b. is most often caused by posterior uretheral valves.
c. require antenatal surgery, which is almost universally successful with few long-term sequellae.
d. should not be considered in fetuses with severe obstruction.

26. Neonates with proven otitis media:
a. frequently have bacterial pathogens cultured from MEF.
b. frequently have bacterial pathogens cultured from other sites than the MEF.
c. have other positive bacterial cultures more frequently if they are febrile/toxic.
d. should always be hospitalized for a septic workup and parenteral antibiotics.

27. Breath-holding spells of infancy:
a. can be diagnosed by appropriate laboratory studies and EEG.
b. are characterized by a cessation of breathing during inspiration.
c. are usually diagnosed by the family history coupled with direct observation when possible.
d. do not usually repond to iron therapy and often require anticonvulsant therapy.

28. True statements about hepatitis C viral infections in children who had undergone cardiac surgery in infancy before implementation of donor screening include all of the following *except*:
a. infections occurred in more than half of these children.
b. there was a high prevalence of detectable HCV in their blood one to three decades later.
c. infections caused severe, long-term hepatocellular disase.
d. the course was considerably less severe than observed in patients infected as adults.

29. Children with congenital hypothyroidism diagnosed in the neonatal period:
a. have much lower mean IQ scores compared to the mean IQ of a control group consisting of their healthy siblings.
b. have significantly lower IQs when compared individually to their healthy siblings.
c. IQ scores were lowest in children with relatively mild chemical indicators of hypothyroidism.
d. should be treated with 6 mcg/kg/d of levothyroxine.

Readers are Invited

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