An approach to the diagnosis of congenital infections

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Remarkable progress has been made in preventing nonbacterial congenital infection through the use of rubella and measles immunizations, hepatitis B immunoprophylaxis, zidovudine treatment of human immunodeficiency virus (HIV)-infected mothers, and prompt diagnosis and treatment of maternal syphilis. Intrauterine diagnosis and effective therapy are available for congenital toxoplasmosis, and intrauterine diagnosis of parvovirus B19 infection enables life-saving in utero transfusion when necessary. Further, serious fetal damage evident on fetal ultrasound can be attributed to cytomegalovirus by amniotic fluid cultures, and there is greater understanding of the risk of herpes simplex infections (1). Even with these major strides, the paediatrician continues to be called on and challenged to identify the rare, infected neonate.

One of the greatest challenges facing doctors is to decide when the diagnosis of congenital infection should be pursued. Few would argue with the need to investigate infants with the clinical findings noted in Table 1. Recommended clinical, microbiological and other investigations are described in Tables 2 and 3. Herpes simplex virus, usually acquired perinatally rather than congenitally, can present without skin lesions as 'neonatal sepsis' or pneumonitis (2). Consideration of appropriate diagnostic testing should be given to infants with these findings, noting that one of the earliest laboratory clues is elevated liver enzymes. As well, the infant whose mother has had no antenatal care needs evaluation for congenital syphilis (and preventive management of other infections), with appropriate follow-up as listed in Table 4.

Pathogens most frequently related to intrauterine infections – syphilis, toxoplasmosis, rubella, cytomegalovirus (CMV) and herpes simplex – are commonly grouped under the acronym STORCH. A more complete acronym, CHEAP TORCHES, has been suggested (3). This includes chicken pox, hepatitis (B, C and E), enterovirus, AIDS and parvovirus. The list of 'other' infections continues to grow with identification of new etiologies, ie, lymphocytic choriomeningitis virus (4) and Q fever (5), and the resurgence of others, ie, malaria and tuberculosis (6).

The futility of STORCH testing of a single serum has been demonstrated repeatedly (7). In preference to a single serum, every effort should be made to recover the organism from the neonate, to test paired maternal sera to document seroconversion during pregnancy, and to follow maternal and infant blood samples over several months.

Negative maternal and neonatal serology generally excludes the possibility of fetal infection except in very recent and HIV infections. Maternal serology, if positive, does not pinpoint the time of the mother's infection but simply indicates infection at some time in her life. The more important seroconversion may be demonstrated using stored blood from earlier in the pregnancy as well as from previous pregnancies, eg, blood banked in other screening programs. Passively acquired maternal antibody from those mothers with antibody confounds the infants's serological testing for a number of months. Serial titres taken postnatally that show a rise in titre at age two to four months or persistent titres at age six to eight months usually establish the diagnosis. Exceptions are CMV antibody, which may also be peri- or postnatally acquired, and HIV. Immunoglobulin (Ig) M-associated antibody in mother and neonate is notoriously unreliable except rubella-specific IgM and toxoplasmosis-specific IgM, the latter as a screen before reference laboratory testing or further review. Cord blood has yielded false positive and negative results for syphilis and other infections (8), and its use is not recommended.

Some infected infants, normal at birth, will have central nervous system and other manifestations of their

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TABLE 1: Findings in infants with congenital infection

Finding(s)	Possible congenital infections
Intrauterine growth retardation	• Rubella, cytomegalovirus (CMV), toxoplasmosis
Anemia with hydrops	• Parvovirus B19, syphilis, CMV, toxoplasmosis
Bone lesions	• Syphilis, rubella
Cerebral calcification	• Toxoplasmosis (widely distributed)
	• CMV and herpes simplex virus (HSV) (usually periventricular)
	• Parvovirus B19, rubella, human immunodeficiency virus (HIV)
	• Lymphocytic choriomeningitis virus
Congenital heart disease	• Rubella
Hearing loss (commonly progressive)	• Rubella, CMV, toxoplasmosis, syphilis
Hepatosplenomegaly	• CMV, rubella, toxoplasmosis, HSV, syphilis, enterovirus, parvovirus B19
Hydrocephalus	• Toxoplasmosis, CMV, syphilis, possibly enterovirus
Hydrops, ascites, pleural effusions	• Parvovirus B19, CMV, toxoplasmosis, syphilis
Jaundice with or without thrombocytopenia	• CMV, toxoplasmosis, rubella, HSV, syphilis, enterovirus
Limb paralysis with atrophy and cicatrices	• Varicella
Maculopapular exanthem	• Syphilis, measles, rubella, enterovirus
Microcephaly	• CMV, toxoplasmosis, rubella, varicella, HSV
Myocarditis/encephalomyocarditis	• Echovirus, coxsackie B, other enterovirus
Ocular findings	• CMV, toxoplasmosis, rubella, HSV, syphilis, enterovirus, parvovirus B19
Progressive hepatic failure and clotting abnormalities	• Echovirus, coxsackie B, other enterovirus, HSV, toxoplasmosis
Pseudoparalysis, pain	• Syphilis
Purpura (usually appears on first day)	• CMV, toxoplasmosis, syphilis, rubella, HSV, enterovirus, parvovirus B19
Vesicles	• HSV, syphilis, varicella, enterovirus

TABLE 2: Recommended clinical investigations for suspected congenital infections

1. Review maternal history (Table 5)
2. Assess the infant

Physical examination

- Gestational age, height, weight, head circumference
- Liver/spleen size
- Skin lesions
- Ophthalmological examination (paediatric expert)

Laboratory

- Complete blood count and smear, and platelet count
- Liver transaminase levels and bilirubin level (direct and indirect)
- Cerebrospinal fluid examination (cells, protein, microbiological [see Table 3])
- Maternal and infant sera for microbiological testing (not cord blood [see Table 3])
- Total serum immunoglobulin M
- Hold pretransfusion blood for possible additional tests

Other investigations

- Cranial computed tomographic scan with enhancement
- Long bone x-rays (if syphilis, rubella likely)
- Placental pathology

Follow-up

- Audiology assessment
- Serology

congenital infection later in childhood and adolescence. Obviously, early detection of all such infants would require comprehensive screening programs as is the case for syphilis and hepatitis B. To date, in Canada, this action has not been justified for toxoplasmosis or CMV infections. However, details in the maternal history, including exposures and illnesses during pregnancy, results of routine antenatal screening and results of fetal ultrasonography, can help dictate the need for further investigation. These details are summarized in Table 5.

Several points need emphasis. The majority of infected infants are born to mothers with asymptomatic infection, but maternal illness, if present, may be helpful to diagnosis. When reviewing the results of serological screening in pregnancy, it should be noted that the mothers of infants with congenital rubella syndrome may have positive serology and appear immune at the time of early pregnancy testing because the infection occurred during the first weeks of gestation. What is more useful are the results of earlier testing, eg, blood from a previous pregnancy showing rubella susceptibility. Findings on fetal ultrasonography associated with but not exclusive to congenital infection include intrauterine growth retardation, hydrops, placentamegaly, hydrocephalus, microcephalus, intracranial calcifications, myocarditis, hepatosplenomegaly, echogenic bowel, hepatic calcifications, meconium peritonitis, ascites and limb reduction (9).

Routine investigation for congenital infection of an infant with only prematurity or intrauterine growth retardation is unlikely to yield positive results and is, therefore, not recommended (10). To detect those infants in whom further clinical evaluation (ie, cranial computed tomography scan, opthalmology examination) or laboratory investigations may be worthwhile, the aforementioned review of maternal history (Table 5) may be useful.

Identification of a congenital infection as early as possible in life has both diagnostic and therapeutic advan-

TABLE 3: Recommended microbiological testing for suspected congenital infections

Specimen	Tests	Interpretation
Urine	Viral culture or detection* (CMV, HSV, rubella)	Urine for CMV must be obtained at younger than age two to three weeks. If positive, test is diagnostic for that infection.
Throat swab	Viral detection* (CMV, HSV, rubella, enteroviruses)	If positive, test is diagnostic for that infection.
Blood	Viral detection* (CMV, parvovirus B19)	If positive, test is diagnostic for that infection.
Neonatal serum (single specimen)	Rubella-specific IgM	If positive, test is diagnostic, although determination of status at 10 to 12 months of age is confirmatory.
Sequential neonatal, infant sera over six to 12 months	IgG antibody for etiological agents of concern	Passive maternal antibody in uninfected infant disappears at • four to nine months of age for CMV (unless peri- or postnatally transmitted); • eight months for *Toxoplasma gondii*; and • six months VDRL/rapid plasma reagent and 12 to 15 months treponemal test (eg, fluorescent treponemal antibody absorbed with nonpallidum treponemes). Positive specific antibody at eight to 12 months suggests congenital toxoplasmosis parvovirus B19, rubella or varicella zoster virus infection.
Single maternal serum at delivery	Toxo-specific IgM (or toxoplasmosis-specific)	If IgM-specific antibody is positive, reference laboratory testing of maternal and infant sera is recommended.
Serology of both mother and infant	IgG antibody for etiological agents of concern	Negative maternal serology rules out source of infection. Serial infant serology identifies passive maternal antibody (titres fall) and active infection (titres remain the same or rise over months).
Cerebrospinal fluid culture, detection	Detection* CMV, enteroviruses, HSV, toxoplasmosis (reference laboratory), parvovirus B19 Rubella-specific IgM antibody VDRL	If positive, usually diagnostic for that infection.
Skin lesions culture, detection	If vesiculated at birth: detection* of herpes, enteroviruses, varicella zoster virus and dark-field for *Treponema pallidum* (syphilis)	If positive, test is diagnostic for that infection.
Nasopharyngeal secretions	Dark-field for *T pallidum* (syphilis)	If positive, test is diagnostic for that infection.
Stool culture	Enteroviruses	If positive, test may be diagnostic for that infection.
Placenta	Pathology	Variable

**Detection refers to culture or polymerase chain reaction testing. CMV Cytomegalovirus; HSV Herpes simplex virus; Ig Immunoglobulin; VDRL Venereal Disease Research Laboratory test*

tages. The newborn period is often the only point at which laboratory testing and follow-up allow confirmation of a congenital infection. Thereafter, congenital infection can only be presumed because postnatal acquisition cannot always be ruled out. For example, it is only possible to detect congenital CMV infection by the presence of CMV in urine specimens obtained in the first two or three weeks of life. After that time, perinatal or postnatal acquisition cannot be excluded. Antimicrobial therapy is effective in preventing or minimizing the risk of sequelae in infants with syphilis and toxoplasmosis if initiated shortly after birth.

In summary, an appropriate index of suspicion, a reasonable clinical evaluation and judicious microbiological evaluation are the current best effort to identify infants with congenital infection at an opportune time, early in life. Unfortunately, many suspected infections remain undiagnosed. Prevention remains the goal, and guidelines for women planning pregnancy can be found in Table 6.

TABLE 4: Evaluation of mother and infant in the absence of antenatal care

Mother

- Genital examination for findings suggestive of venereal disease
- Cultures for *Chlamydia trachomatis*, gonorrhea
- Serological testing for hepatitis B surface antigen, hepatitis C, human immunodeficiency virus, syphilis (nontreponemal and treponemal testing) and rubella
- Adequate follow-up

Infant

- Prophylactic eye care
- Serological testing for hepatitis B surface antigen, hepatitis C, human immunodeficiency virus, syphilis (maternal nontreponemal and treponemal testing)
- First dose of hepatitis B vaccine and depending on maternal hepatitis B surface antigen status, hepatitis B immunoglobulin
- Adequate follow-up

TABLE 5: Maternal history suggestive of congenital infection

History	Infection
Exposure	
Season	Parvovirus B19 (winter, spring) Rubella (winter, spring) Enterovirus (summer, autumn)
Handling or ingestion of raw meat that has never been frozen	Toxoplasmosis
Contact with diapered children in daycare, household or school	Cytomegalovirus (CMV), parvovirus
Exposure in travel to certain geographic regions	Toxoplasmosis (ie, through culinary practices), tuberculosis, malaria, trypanosomiasis, hepatitis B virus (HBV)
Kitten or cat feces in 21 days after the animal's primary infection (handling animal or kitty litter, gardening)	Toxoplasmosis
Number of sexual partners, sex industry worker/partner, illicit drug use	Syphilis, herpes simplex virus (HSV), HBV, hepatitis C virus, human immunodeficiency virus (HIV)
Sexually active adolescents	CMV, HSV, HBV, HIV
Unimmunized (eg, immigrant from developing world*)	Rubella
Illness	
Rash	Syphilis, rubella, parvovirus B19, enterovirus
Arthritis	Parvovirus B19, rubella
Mononucleosis-like fatigue, lymphadenopathy	CMV, toxoplasmosis, HIV
Screening in pregnancy	HBV, rubella, syphilis, HIV
Fetal ultrasonography	Variable

**Note that the World Health Organization immunization program does not include rubella*

TABLE 6: General information about infections for women planning pregnancy

- Keep all adult immunizations up to date.
- Ensure that you are immune to rubella by blood test. If you are not, you require immunization.
- During pregnancy, your doctor routinely tests for rubella immunity, hepatitis B and syphilis infections and, with your consent, human immunodeficiency virus.
- Follow the procedure outlined below to reduce the risk of toxoplasma and other foodborne infection.

  Avoid eating undercooked meat in pregnancy. Previously frozen meat is free of toxoplasmosis. Wash hands thoroughly after handling, and keep cooking utensils thoroughly cleaned, separating those used for raw and cooked foods. Avoid contact with materials potentially contaminated with cat excrement, including kitty litter boxes. Wash raw fruit and vegetables thoroughly before eating; wash hands after handling. Wear gloves when gardening. Use foods before the expiry date.
- If you are exposed to erythema infectiosum (Fifth Disease, human parvovirus B19), chicken pox or shingles during your pregnancy, inform your physician promptly.
- If your partner is diagnosed with an infection other than a cold or influenza, inform your physician who can evaluate any risk.
- There is currently no effective method of preventing the uncommon complications of infections during pregnancy with cytomegalovirus (CMV) or enterovirus. While women who regularly handle the respiratory secretions or diapers of young children may wish to be tested for CMV immunity before pregnancy, the only current preventive strategy for susceptible women is good hygiene when they are with young children in their home or in the group child care environment.
- Symptoms of genital herpes may occur years after the original infection. It is almost always the *first* infection that occurs without any symptoms (asymptomatic primary) in a mother that affects the infant; such infections are very, very rare and cannot be identified.
- Because of the difficulty in interpreting blood tests for infection during pregnancy, testing for immunity before pregnancy is preferable.

REFERENCES

1. Duff P. Perinatal infectious disease. Semin Perinatol 1998;22:241.
2. Pass R. Viral infections in the fetus and neonate. In: Long S, Pickering PC, Prober CG, eds. Principles and Practice of Pediatric Infectious Diseases. New York: Churchill Livingstone, 1997:614-8.
3. Ford-Jones E, Kellner J. "CHEAP TORCHES": A better acronym when considering congenital and perinatal infections. Pediatr Infect Dis 1995;14:638-40.
4. Wright R, Johnson D, Neumann M, et al. Congenital lymphocytic choriomeningitis virus syndrome: a disease that mimics congenital toxoplasmosis or cytomegalovirus infection. Pediatrics 1997;100:E9.
5. Stein A, Raoult D. Q fever during pregnancy: a public health problem in southern France. Clin Infect Dis 1998;27:592-6.
6. Lee LH, LeVea CM, Graman PS. Congenital tuberculosis in a neonatal intensive care unit: case report, epidemiologic information, and management of exposures. Clin Infect Dis 1998;27:274-7.
7. TORCH syndrome and TORCH screening. Lancet 1990;i:1559-61.
8. Chabra RS, Brion LP, Casta M, et al. Comparison of maternal sera, cord blood and neonatal sera for detecting presumptive congenital syphilis: relationship with maternal treatment. J Pediatr 1993;91:88-91.
9. Ford-Jones E, Ryan G. Implications for the fetus of maternal infections in pregnancy. In: Armstrong D, Cohen J, eds; Ronald A, section ed. Infectious Diseases. London: Mosby International, 1999. (In press)
10. Greenough A. The TORCH screen and intrauterine infections. Arch Dis Child 1994;70:F163-5.