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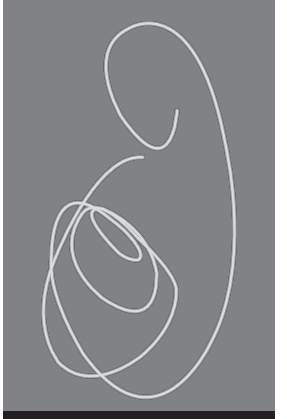

CHAPTER 13

Transmission of Infectious Diseases Through Breast Milk and Breastfeeding

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A large body of evidence clearly demonstrates the protective effects of breastfeeding and documents the transmission of specific infections to infants through breast milk. The fear and anxiety that arise with the occurrence of any infectious disease are even greater in the situation of the breastfeeding mother-infant dyad. Uncertainty and lack of knowledge often lead to proscribing against breastfeeding out of fear, which then deprives the infant of the potential protective, nutritional, and emotional benefits of breastfeeding exactly at the time when they are most needed (see the discussion of immunologic benefits of human milk in Chapter 5). Decisions concerning breastfeeding in a mother with an infectious illness should balance the potential benefits of breastfeeding versus the known or estimated risk for the infant acquiring a clinically significant infection via breastfeeding and the potential severity of the infection.

Documenting transmission of infection from mother to infant by breastfeeding requires not only the exclusion of other possible mechanisms of transmission but also the demonstration of the infectious agent in the breast milk and a subsequent clinically significant infection in an infant that was caused by a plausible infectious process. The first step is to establish the occurrence of a specific infection (clinically or immunologically evident) in a mother and demonstrate the persistence of the infectious agent such that it could be transmitted to the infant. Isolation or identification of the infectious agent from the colostrum, breast milk, or an infectious lesion of the breast is important but not necessarily proof of transmission to an infant. Epidemiologic evidence of transmission must be considered, including identifying characteristics of the organism that relate an isolate from an infant to the maternal isolate. Infectious organisms can reach the breast milk either by secretion in the fluid or cellular components of breast milk or by contamination of the milk at the time of or after expression. A reasonable mechanism of infection via breast milk should be evident and proved through either animal or human studies. Demonstration of a subclinical or clinically evident infection in an infant should follow these outlined steps.

Exclusion of other possible mechanisms of transmission (exposure to mother or other persons/animals via airborne, droplet, arthropod, or vector modes of transmission or through direct contact with other infectious fluids) would complete the confirmation of transmission of infection via breastfeeding. It is essential to exclude prenatal or perinatal transmission of infection to a fetus/infant, but doing this can often be difficult.

Clinical case reports or studies confirming the isolation of an infectious agent from the milk are important. To determine a reasonable estimate of the risk for infection via breast milk, larger epidemiologic studies are needed that compare infection rates in breastfed infants versus formula-fed infants,

addressing the issues just identified. Timing of breastfeeding is important relative to the timing of maternal infection and to the presence of a pathogen in colostrum or breast milk. The duration of breastfeeding is another important variable to consider in the estimate of risk because shedding of a pathogen in breast milk may be intermittent.

These considerations are only some of the variables to be taken into account, in general, to assess the risk for transmission of an infectious agent from mother to infant via breast milk or breastfeeding. Efforts to prove transmission of infection in a particular maternal-infant dyad can be just as difficult and must consider many of the same factors.

This chapter focuses on a discussion of specific, clinically relevant, infectious agents and diseases, with reasonable estimates of the risk for infection to infants from breastfeeding. The basic tenet concerning breastfeeding and infection is that breastfeeding is rarely contraindicated in maternal infection.[243] The few exceptions relate to specific infectious agents with strong evidence of transmission and to the association of an infant's illness with significant morbidity and mortality.

The risk or benefit of breastfeeding relative to immunization of a mother or infant is discussed for certain microorganisms. Appendix D addresses drugs in breast milk and includes Table D-1, on antiinfective agents, and Chapter 5 reviews how breastfeeding may protect against infection. Chapter 21 addresses specific concerns relating to banked breast milk and includes standards developed by the human Milk Banking Association of North America to guide the appropriate handling of banked human milk relative to possible infectious agents.

Infection Control Considerations

Isolation precautions have undergone some revisions in terminology and conceptualization.[143] Understanding that the transmission of microorganisms can occur with a known infection and with unrecognized sources of infection, recommendations have been made for standard precautions to be applied to all patients to protect health care workers from potentially infectious body fluids. Additionally, precautions based on the predominant modes of transmission have been recommended to protect against infection through the airborne route, direct contact, or contact with droplets. Although these precautions are intended to be used in clinical situations to protect health care workers, they may be applied in certain situations to the mother-infant dyad to prevent transmission of infectious agents from one to the other or to other hospitalized mothers and infants. These precautions are useful most often when a mother and infant are still hospitalized. The use of such precautions within the home is not meant to limit breastfeeding. They are intended to allow breastfeeding in the majority of cases and to facilitate the continuation of breastfeeding with some additional safeguards in certain situations, after short temporary periods of stopping breastfeeding, and when to safely use expressed breast milk (see Appendix F).

STANDARD PRECAUTIONS

Standard precautions include preventing contact with blood, all body fluids, secretions and excretions, nonintact skin, and mucous membranes by (1) careful handwashing before and after every patient contact; (2) use of gloves when touching body fluids, nonintact skin, or mucous membranes or any items contaminated with body fluids (linens, equipment, devices, etc.); (3) use of nonsterile gowns to prevent contact of clothing with body fluids; (4) use of masks, eye protection, or face shields when splashing with body fluids is possible; and (5) appropriate disposal of these materials. Standard precautions should be applied to all patients regardless of actual or perceived risks. The Centers for Disease Control and Prevention (CDC) does not consider breast milk a body fluid with infectious risks and thus these policies do not apply to breast milk. (See section on misadministration of breast milk later in this chapter as a possible exception to this concept.)

In considering breastfeeding infant-mother dyads and standard precautions, body fluids other than breast milk should be avoided, and only in specified situations should breast milk also be avoided. In general, clothing or a gown for the mother and bandages, if necessary, should prevent direct contact with nonintact skin or secretions. Avoiding infant contact with maternal mucous membranes requires mothers to be aware of and understand the risks and to make a conscious effort to avoid this type of contact. The use of gloves, gowns, and masks on infants for protection is neither practical nor appropriate. The recommendations concerning the appropriateness of breastfeeding and breast milk are addressed for specific infectious agents throughout this chapter. Human immunodeficiency virus (HIV) infection is an example of one infection that can be prevented by the use of standard precautions, including avoiding breast milk and breastfeeding. The recommendations concerning breastfeeding and HIV and the various variables and considerations involved are discussed later.

AIRBORNE PRECAUTIONS

Airborne precautions are intended to prevent transmission via droplet nuclei (dried respiratory particles smaller than 5 mcm that contain microorganisms and can remain suspended in the air for long periods) or dust particles containing microorganisms. Airborne precautions include the use of a private room with negative-air-pressure ventilation and masks at all times. In the case of pulmonary tuberculosis (TB), respiratory protective devices (requiring personal fitting and seal testing before use) should be worn. Airborne precautions are recommended with measles, varicella or disseminated zoster, and TB. Breastfeeding in the presence of these maternal infections is prohibited for the infectious period. This is to protect against airborne transmission of the infection from the mother and to allow the infant to be fed the mother's expressed breast milk by another individual. The exception to allowing breast milk would be local involvement of the breast by varicella-zoster lesions or *Mycobacterium tuberculosis,* such that the milk becomes contaminated by the infectious agent.

DROPLET PRECAUTIONS

Transmission via droplets occurs when an individual produces droplets that travel only a short distance in the air and then contact a new host's eyes, nose, mouth, or skin. The common mechanisms for producing droplets include coughing, sneezing, talking (singing or yelling), suctioning, intubation, nasogastric tube placement, and bronchoscopy. In addition to standard precautions applied to all patients, droplet precautions include the use of a private room (preferred) and a mask if within 3 feet (0.9 m) of the patient. Droplet precautions are recommended for adenovirus, diphtheria, respiratory infections, *Haemophilus influenzae, Neisseria meningitidis* or invasive infection, influenza, mumps, mycoplasma, parvovirus, pertussis, plague (pneumonic), rubella, and streptococcal pharyngitis, pneumonia, or scarlet fever. The institution of droplet precautions with a breastfeeding mother who has these infections should be specified for each particular infection. This may require some period of separation for the infant and mother (for duration of the illness, for short-term or complete treatment of the mother, for the infectious period) with use of expressed breast milk for nutrition in the interim. Prophylactic treatment of the infant, maternal use of a mask during breastfeeding or close contact combined with meticulous handwashing, and the mother's avoidance of touching her mucous membranes may be adequate and reasonable for certain infections.

CONTACT PRECAUTIONS

Contact precautions are meant to prevent transmission of infection via direct contact (contact between the body surfaces of one individual with another) and indirect contact (contact of a susceptible host with an object contaminated with microorganisms from another individual). Contact precautions include cohorting or a private room, gloves and gowns at all times, and handwashing after removal of gown and gloves. Contact precautions are recommended for a long list of infections, such as diarrhea in diapered or incontinent patients with *Clostridium difficile* infection, *Escherichia coli* O157:H7, *Shigella,* rotavirus, hepatitis A, respiratory illness with parainfluenza virus or respiratory syncytial virus (RSV), multidrug-resistant (MDR) bacteria (e.g., enterococci, staphylococci, gram-negative organisms), enteroviral infections, cutaneous diphtheria, impetigo, herpes simplex virus (HSV) infection, herpes zoster (disseminated or in immunocompromised individuals), pediculosis, scabies, *Staphylococcus aureus* skin infection, viral hemorrhagic fevers (e.g., Ebola, Lassa), conjunctivitis and abscesses, cellulitis, or decubitus that cannot be contained by dressings.[94] For a breastfeeding infant-mother dyad, implementation of precautions for each of these infections in a mother requires meticulous attention to gowning and handwashing by the mother and a specialized plan for each situation.

Each of these transmission-based precautions can be used together for organisms or illnesses that can be transmitted by more than one route. They should always be used in conjunction with standard precautions, which are recommended for all patients. The *Red Book: Report of the Committee on Infectious Diseases* by the American Academy of Pediatrics (AAP)[96] remains an excellent resource for infection control guidelines and recommendations to prevent transmission in specific situations and infections.

CULTURING BREAST MILK

Routine culturing of breast milk or culturing breast milk to screen for infectious agents is not recommended except when the milk is intended as donor milk to another mother's child directly or through human milk banks. See Chapter 21 for specific bacterial count standards for raw donor milk and for pasteurization of donor milk. Breastfeeding and the expression of or pumping of breast milk (referred to as expressed breast milk) for later use are not sterile activities.

In general expressed breast milk should not contain large numbers of microorganisms (less than 10^4 for raw milk and less than 10^6 for milk to be pasteurized), nor should it contain potential pathogens

such as *S. aureus*, β-hemolytic streptococci, *Pseudomonas* species, *Proteus* species, or *Streptococcus faecalis* or *faecium*. Few studies have examined "routine" culturing of milk and the significance of specific bacterial colony counts relative to illness in infants. The studies have been primarily concerned with premature or low-birth-weight (LBW) infants who remain hospitalized and are commonly fed via enteral tubes. A study from Canada tested 7610 samples of milk for use in 98 preterm infants.[242] The study did not identify any adverse events in the infants attributed to organisms growing in the milk samples, and routine bacteriological testing of expressed breast milk was not recommended. A study from Chicago examined gram-negative bacilli in the milk used in premature infants.[48] Samples were tested before feeding and from the nasogastric tubes during feeding. Milk samples from before feeding were less likely to contain gram-negative bacilli (36%) than milk samples from the nasogastric tubing (60%). Feeding intolerance was observed when there were more than 10^3 colony-forming units per milliliter (CFU/mL), and episodes of sepsis were identified when the bacterial counts in the milk were greater than or equal to 10^6 CFU/mL. This study recommended the routine bacteriologic testing of expressed breast milk. Another study from Arkansas focused on contamination of feeding tubes during administration of expressed breast milk or formula.[277] Ten infants in the neonatal intensive care unit (NICU) were exposed to greater than 10^5 gram-negative bacteria in their feeding tubes. The three infants who were fed expressed breast milk with contamination at greater than 10^5 organisms remained well, but the seven formula-fed infants with high levels of bacterial contamination in the feeding tubes developed necrotizing enterocolitis. The gram-negative bacteria with high level contamination in the feeding tubes were either *Enterobacter* or *Klebsiella* in all cases. Many NICUs consider 10^5 to 10^6 CFU/mL as the significant bacterial count for gram-negative bacilli in breast milk that places premature and LBW infants at greater risk for infection.

Even less data are available concerning specific bacterial colony counts for gram-positive organisms and the risk to the infant. Generally less than 10^3 gram-positive organisms per mL of milk is considered acceptable, with only case reports and no controlled trials to support this cutoff.

When the presence of an infectious illness in an infant and/or the breastfeeding mother's breast when breast milk is seriously considered as a possible mechanism of transmission to the infant, culturing breast milk to identify the organism may be warranted and useful. More important than hurrying to culture breast milk is the careful instruction of mothers on the proper technique for collecting expressed breast milk, storing it, and cleaning the collection unit. The reinforcement of proper technique from time to time, especially when a question of contamination arises, is equally important. Many small reports comment on the contamination of breast milk with different collection methods. Relative comparisons suggest decreasing contamination of expressed breast milk when collected by the following methods; drip milk, hand pumped milk, manual expression, modern electric pumped milk. One group from Malaysia published results showing no difference in contamination between milk collected by electric pump versus manual expression when collected in the hospital. Expressed breast milk collected at home by breast pump had higher rates of contamination with staphylococci and gram-negative bacteria.[46] Discussion continues about the need to discard the first few milliliters of milk to lower bacteria numbers in expressed breast milk without any evidence to suggest if this is truly necessary.[62,337] No evidence shows that cleansing the breast with anything other than tap water decreases the bacterial counts in cultured expressed breast milk.[414] If an infant is directly breastfeeding, collecting milk for culture by manual expression and trying to obtain a "midstream" sample (as is done with "midstream" urine collection for culture) is appropriate. If an infant is being fed expressed breast milk, collecting and culturing the milk at different points during collection (utilizing the same technique the mother uses [manual expression, hand pump, or electric pump]) and administration is appropriate. This might include a sample from immediately after collection, another of stored expressed breast milk, and a sample of milk from the most recent infant feeding at the time the decision to culture is made. Please see Box 13-1 for the basic steps in culturing expressed breast milk.

Interpretation of such culture results can be difficult and should involve a pediatric infectious disease expert, a microbiologist, and hospital epidemiologist. Additional organism identification is often required, utilizing antibiogram patterns or molecular fingerprinting by various techniques to correlate a bacterial isolate from breast milk with an isolate causing disease in infant or mother.

MISADMINISTRATION OF BREAST MILK

Misadministration of breast milk, also known as misappropriation, breast milk exposure, and accidental ingestion of breast milk, and other terms, is a medical-legal issue when it occurs in a hospital. This scenario occurs when one infant receives breast milk from another mother by mistake. This occurrence can be very distressing to the families (recipient patient, recipient parent, and donor mother) and medical staff involved. The actual risk

BOX 13-1. Culturing Breast Milk

1. Wash hands as per routine.
2. Wash breast with warm tap water and a clean washcloth.
3. Manually express breast milk ("midstream" collection is not required) or attach breast pump flange (previously cleaned as per routine) for collection and collect milk.
4. Place a 3 to 5 mL sample of expressed breast milk in a sterile container with a nonleakable top.
5. Deliver to the labatory in less than 1 hour or refrigerate at 4° C until delivery. Before sending samples to the viral lab or for nucleic acid/polymerase chain reaction (PCR) testing, confirm that the laboratory will accept and process the sample as requested and that the appropriate collection container and prelaboratory management of the specimen are utilized.
6. Processing of specimens:
   a. Direct examination by gram stain is not required.
   b. Culture on blood agar (BA) and MacConkey agar (MAC) media as per lab standards.
   c. Quantitate all isolates.
   d. Send separate samples for fungal culture, acid-fast bacilli, and viral culture as indicated, based on the clinical situation.
   e. Perform routine sensitivity testing on all potential pathogens. (This will require some discussion with the clinician and perhaps a pediatric infectious disease specialist.)

for transmission of an infectious agent to an infant via a single ingestion of expressed breast milk (the most common occurrence) from another mother is exceedingly low. In this scenario, the CDC recommends treating this as an accidental exposure to a body fluid, which could be infectious.[84] Bacterial, fungal, or parasitic infection from the one exposure is highly unlikely. The concern is about viral pathogens, known to be blood-borne pathogens, which have been identified in breast milk and include but are not limited to hepatitis B virus (HBV), hepatitis C virus (HCV), cytomegalovirus (CMV), West Nile virus, human T-cell lymphotropic virus (HTLV), and HIV.

Most hospitals have protocols for managing the situation from both the infection control/prevention and the medical-legal perspectives. These protocols advise informing both families about what occurred, discussing the theoretical risks of harm from the exposure, and reviewing test results and/or recommending testing to determine the infectious status of each mother relative to the above mentioned viruses. HCV is not a contraindication to breastfeeding and West Nile virus infection in lactating women is rare.[74,177] Neither infection has a documented effective form of prevention or acute treatment. Testing either mother (donor or of recipient infant) for these agents is not warranted. Prenatal testing for HIV is more commonplace throughout the world. The incidence of HIV among women of childbearing age is low, although it varies significantly by geographic location, and the hospital or locale-specific incidence would be important to know to estimate risk. Most women and medical staff are aware that HIV can be transmitted by breastfeeding; therefore breast milk from HIV-positive women is rarely if ever stored in hospitals. The risk for transmission of HIV via breastfeeding is due to the volume of feedings over months (estimated at 400 to 500 feedings in the first 2 months of life) compared with the small "dose of exposure" from one or two "accidental feedings." Transmission of HIV from a single breast milk exposure has never been documented. Immunologic components in breast milk, along with time and cold of storage, inactivate the HIV in expressed breast milk. For these reasons, the risk for transmission of HIV via expressed breast milk consumed by another child is thought to be extremely low. HTLV-I/II infection in childbearing women is uncommon except in certain geographic regions (Japan, Africa, the Caribbean, and South America). Transmission of HTLV via breast milk does occur and, like HIV, appears to be related to the volume and duration of breastfeeding. Limiting the duration of breastfeeding is effective in decreasing transmission.[407,409,446] Freezing and thawing expressed breast milk decreases the infectivity of HTLV-I.[11] In areas of low prevalence, a positive test in a mother should be suspected to be a false positive test, and retesting with both antibody and polymerase chain reaction (PCR) testing should be performed. For these reasons the transmission of HTLV-I/II via accidental expressed breast milk exposure is thought to be extremely low. Although the majority of women are CMV positive by childbearing age and CMV transmission occurs via breastfeeding, the risk for CMV in a full-term infant is low. Premature or LBW infants are at greater risk for developing disease with CMV infection. Freezing expressed breast milk (at −20° C) for 3 to 5 days significantly decreases the infectivity of CMV. Here again the risk for CMV transmission from a single accidental exposure to CMV-positive expressed breast milk is extremely low.

With a discussion of theoretical risk should be a discussion of possible preventive interventions, such as vaccination or antimicrobial postexposure prophylaxis. If donor mothers are positive for HBV, it is appropriate to give recipient infants hepatitis B virus immunoglobulin (HBIG) and HBV vaccines if they have not already received them. If a

donor mother is HIV or HTLV-I/II positive, the potential utility of postexposure prophylaxis with antiretroviral medications should be considered on a case-by-case basis. Clinicians participating in these decisions can refer to the AAP *Red Book* or the updated *United States Public Health Service Guidelines* for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis (available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5409al.htm).[324] It may also be appropriate to consult a pediatric infectious disease specialist.

Additional important components of the hospital-based protocols for managing accidental expressed breast milk exposure include ongoing psychosocial support for the families and staff, documentation of medical discussions with the families, investigative steps, consents and interventions, and the demonstration of ongoing infection control efforts to prevent additional events of misadministration of breast milk.

Clinical Syndromes and Conditions

Microorganisms produce a whole spectrum of clinical illnesses affecting mothers and infants. Many situations carry the risk for transmission of the involved organism from a mother to the infant, or vice versa; in general, however, infants are at greater risk because of such factors as inoculum size and immature immune response. As always, an infection must be accurately diagnosed in a timely manner. Empiric therapy and initial infection control precautions should begin promptly based on the clinical symptoms and the most likely etiologic agents. When dealing with a maternal infection, clarifying the possible modes of transmission and estimating the relative risk for transmission to the infant are essential first steps to decision-making about isolating a mother from her infant and the appropriateness of continuing breastfeeding or providing expressed breast milk. Breastfeeding infrequently is contraindicated in specific maternal infections.[243] Often the question of isolation and interruption of breastfeeding arises when symptoms of fever, pain, inflammation, or other manifestations of illness first develop in a mother and the diagnosis is still in doubt. A clinical judgment must be made based on the site of infection, probable organisms involved, possible or actual mechanisms of transmission of these organisms to the infant, estimated virulence of the organism, and likely susceptibility of the infant. Additionally, by the time the illness is clearly recognized or diagnosed in a mother, the infant has already been exposed. Given the dynamic nature of the immunologic benefits of breast milk, continuation of breastfeeding at the time of diagnosis or illness in a mother can provide the infant protection rather than continued exposure in most illnesses. Stopping breastfeeding is rarely necessary. Many situations associated with maternal fever do not require separation of mother and infant, such as engorgement of the breasts, atelectasis, localized nonsuppurative phlebitis, or urinary tract infections.

Appendix F lists a number of clinical syndromes, conditions, and organisms that require infection control precautions in hospitals. This appendix also includes short lists of possible etiologic agents for these conditions and appropriate precautions and recommendations concerning breastfeeding for different scenarios or organisms. This chapter considers specific infectious agents that are common, clinically significant, or of particular interest.

Bacterial Infections

ANTHRAX

Bacillus anthracis, a gram-positive, spore-forming rod, causes zoonotic disease worldwide. Human infection typically occurs due to contact with animals or their products. Three forms of human disease occur: cutaneous anthrax (the most common), inhalation anthrax, and gastrointestinal (GI) disease (rare). Person-to-person transmission can occur as a result of discharge from cutaneous lesions, but no evidence of human-to-human transmission of inhalational anthrax is available. No evidence of transmission of anthrax via breast milk exists. Standard contact isolation is appropriate for hospitalized patients or patients with draining skin lesions.

The issue of anthrax as a biologic weapon has exaggerated its importance as a cause of human disease. The primary concerns regarding anthrax and breastfeeding are antimicrobial therapy or prophylaxis in breastfeeding mothers and the possibility that infant and mother were exposed by intentional aerosolization of anthrax spores. The CDC published recommendations for treatment and prophylaxis in infants, children, and breastfeeding mothers.[72] The recommendations include the use of ciprofloxacin, doxycycline, amoxicillin, and several other agents without discontinuing breastfeeding. Little available is information on ciprofloxacin and doxycycline in breast milk for prolonged periods of therapy or prophylaxis (60 days) and possible effects on infants' teeth and bone/cartilage growth during that time period. Depending on the clinical situation and sensitivity testing of the identified anthrax strain, other agents can be substituted to complete the 60-day course. The CDC has approved the use of ciprofloxacin and doxycycline

for breastfeeding women for short courses of therapy (less than several weeks).

Simultaneous exposure of infant and mother could occur from primary aerosolization or from spores "contaminating" the local environment. In either case decontamination of the mother-infant dyad's environment should be considered.

Breastfeeding can continue during a mother's therapy for anthrax as long as she is physically well. Open cutaneous lesions should be carefully covered and, depending on the situation, simultaneous prophylaxis for the infant may be appropriate.

BOTULISM

Considerable justifiable concern has been expressed because of the reports of sudden infant death from botulism. Infant botulism is distinguished from food-borne botulism from improperly preserved food containing the toxin and from wound botulism from spores entering the wound. Infant botulism occurs when the spores of *Clostridium botulinum* germinate and multiply in the gut and produce the botulinal toxin in the GI tract.[17] The toxin binds presynaptically at the neuromuscular junction, preventing acetylcholine release. The clinical picture is a descending, symmetric flaccid paralysis. Not every individual who has *C. botulinum* identified in the stool experiences a clinical illness. The age of infants seems to relate to their susceptibility to illness. The illness is mainly in children younger than 12 months of age; the youngest patient described in the literature was 6 days old.[17] Most children become ill between 6 weeks and 6 months of age. The onset of illness seems to occur earlier in formula-fed infants compared with breastfed infants. When a previously healthy infant younger than 6 months of age develops constipation, then weakness and difficulty sucking, swallowing, crying, or breathing, botulism is a likely diagnosis. The organisms should be looked for in the stools, and electromyography may or may not be helpful.

In a group reviewed by Arnon et al,[19] 33 of 50 patients hospitalized in California were still being nursed at onset of the illness. A beneficial effect of human milk was observed in the difference in the mean age at onset, with breastfed infants being twice as old as formula-fed infants with the disease. The breastfed infants' symptoms were milder. Breastfed infants receiving iron supplements developed the disease earlier than those who were breastfed but unsupplemented. Of the cases of sudden infant death from botulism, no infants were breastfed within 10 weeks of death. All were receiving iron-fortified formulas. In most cases, no specific food source of *C. botulinum* can be identified, but honey is the food most often implicated, and corn syrup has been implicated in infants older than 2 months of age. Honey may contain botulism spores, which can germinate in the infant gut. However, botulin toxin has not been identified in honey. It has been recommended that honey not be given to infants younger than 12 months of age. This includes putting honey on a mother's nipples to initiate an infant's interest in suckling.

Arnon[18] reviewed the first 10 years of infant botulism monitoring worldwide. The disease has been reported from 41 of the 50 states in the United States and from eight countries on four continents. The relationship to breastfeeding and human milk is unclear. In general the acid stools (pH 5.1 to 5.4) of human milk fed infants encourage *Bifidobacterium* species. Few facultative anaerobic bacteria, or clostridia, existing as spores, are present in breastfed infants. In contrast, formula-fed infants have stool pHs ranging from 5.9 to 8.0, with few bifidobacteria, primarily gram-negative bacteria, especially coliforms and *Bacteroides* species. *C. botulinum* growth and toxin production decrease with declining pH and usually stops below pH 4.6. Breast milk also contains additional protective immunologic components, which purportedly have activity against botulinum toxin.[269]

The relationship between the introduction of solid foods or weaning in both formula-fed and breastfed infants and the onset of botulism remains unclear. For a breastfed infant, the introduction of solid food may cause a major change in the gut with a rapid rise in the growth of enterobacteria and enterococci followed by progressive colonization by *Bacteroides* species, clostridia, and anaerobic streptococci. Feeding solids to formula-fed infants minimally changes the gut flora as these organisms already predominate. Although more hospitalized infants have been breastfed, sudden-death victims are younger and have been formula fed, which supports the concept of immunologic protection in the gut of a breastfed infant.

Much work remains to understand this disease. Clinically, constipation, weakness, and hypotonicity in a previously healthy child constitute botulism until ruled out, especially with recent dietary changes. At this time, no reason exists to suspect breastfeeding as a risk for infant botulism, and some evidence suggests a possible protective effect from breastfeeding. Breastfeeding should continue if botulism is suspected in mother or infant.

BRUCELLOSIS

Brucella melitensis has been isolated in the milk of animals. Foods and animals represent the primary sources of infection in humans. Brucellosis demonstrates a broad spectrum of illness in humans, from subclinical to subacute to chronic illness with nonspecific signs of weakness, fever, malaise, body

aches, fatigue, sweats, arthralgia, and lymphadenitis. In areas where the disease is enzootic, childhood illness has been described more frequently. The clinical manifestations in children are similar to those in adults.[259] Infection can occur during pregnancy, leading to abortion (infrequently), and can produce transplacental spread, causing neonatal infection (rarely).

The transmission of *B. melitensis* through breast milk has been implicated in neonatal infection.[259,260] There have been eight cases of brucellosis in infants that were possibly associated with breastfeeding, but *Brucella* was not isolated from the breast milk in any of those cases.* One case of brucellosis in an infant caused by breast milk transmission, with *B. melitensis* isolated from the breast milk, before antibiotic treatment was given to the mother has been documented.[415] Additionally, *Brucella melitensis* has been cultured from women with breast lumps and abscesses.[295] Only one of six women described in this report was lactating at the time of diagnosis, and no information about the infant was given. Brucellosis mastitis or abscess should be considered in women presenting with appropriate symptoms and occupational exposure to animals, contact with domestic animals in their environment, or exposure to animal milk or milk products (especially unpasteurized products). The breast inflammation tends to be granulomatous in nature (without caseation) and is often associated with axillary adenopathy; occasionally systemic illness in the woman is evident. Treatment of brucellosis mastitis or abscess should be treated with surgery or fine needle aspiration as indicated and 4 to 6 weeks of combination antibiotic therapy with two or three medications. Temporary interruption of breastfeeding with breast pumping and discarding the milk to continue stimulation of milk production is appropriate. Breastfeeding should then continue after an initial period of 48 to 96 hours of therapy in the mother. Acceptable medications for treating the mother while continuing breastfeeding include gentamicin, streptomycin, tetracycline, doxycycline, trimethoprim-sulfamethoxazole, and rifampin (see Appendix D).

CHLAMYDIAL INFECTIONS

Chlamydial infection is the most frequent sexually transmitted disease (STD) in the United States and is a frequent cause of conjunctivitis and pneumonitis in an infant from perinatal infection. The major determinant of whether chlamydial infection occurs in a newborn is the prevalence rate of chlamydial infection of the cervix.[364] Specific chlamydial immunoglobulin A (IgA) has been found in colostrum and breast milk in a small number of postpartum women who were seropositive for *Chlamydia*. No information is available on the role of milk antibodies in protection against infection in infants.[389] It is not believed that *Chlamydia* is transmitted via breast milk. Use of erythromycin or tetracycline to treat mothers and oral erythromycin and ophthalmic preparations of tetracyclines, erythromycin, or sulfonamides to treat suspected infection in infants are appropriate during continued breastfeeding. Separating infants from mothers with chlamydial infections or stopping breastfeeding is not indicated. Simultaneous treatment of mothers and infants may be appropriate in some situations.

DIPHTHERIA

Corynebacterium diphtheriae causes several forms of clinical disease, including membranous nasopharyngitis, obstructive laryngotracheitis, and cutaneous infection. Complications can include airway obstruction from membrane formation and toxin-mediated central nervous system (CNS) disease or myocarditis. The overall incidence of diphtheria has declined even though immunization does not prevent infection but does prevent severe disease from toxin production. Fewer than five cases are reported annually in the United States.

Transmission occurs via droplets or direct contact with contaminated secretions from the nose, throat, eye, or skin. Infection occurs in individuals whether they have been immunized or not, but infection in those not immunized is more severe and prolonged. As long as the skin of the breast is not involved, no risk for transmission exists via breast milk. No toxin-mediated disease from toxin transmitted through breast milk has been reported in an infant.

Breastfeeding, along with chemoprophylaxis and immunization of affected infants, is appropriate in the absence of cutaneous breast involvement (see Appendix F).

GONOCOCCAL INFECTIONS

Maternal infection with *Neisseria gonorrhoeae* can produce a large spectrum of illness ranging from uncomplicated vulvovaginitis, proctitis, pharyngitis, conjunctivitis, or more severe and invasive disease, including pelvic inflammatory disease, meningitis, endocarditis, or disseminated gonococcal infection. The risk for transmission from mother to infant occurs mainly during delivery in the passage through the infected birth canal and occasionally from postpartum contact with the mother (or her partner). Risk for transmission from breast milk is negligible, and *N. gonorrhoeae* does not seem

*References 4, 27, 61, 260, 261, 320, 321, 427.

to cause local infection of the breasts. Infection in neonates is most often ophthalmia neonatorum and less often a scalp abscess or disseminated infection. Mothers with presumed or documented gonorrhea should be reevaluated for other STDs, especially Chlamydia trachomatis and syphilis, because some therapies for gonorrhea are not adequate for either of these infections.

With the definitive identification of gonorrhea in a mother, empiric therapy should begin immediately, and the mother should be separated from the infant until completion of 24 hours of adequate therapy. Treatment of the mother with ceftriaxone, cefixime, penicillin, or erythromycin is without significant risk to the infant. Single-dose treatment with spectinomycin, ciprofloxacin, ofloxacin, or azithromycin has not been adequately studied but presumably would be safe for the infant given the 24-hour separation and a delay in breastfeeding without giving the infant the expressed breast milk (pump and discard). Doxycycline use in a nursing mother is not routinely recommended.

Careful preventive therapy for ophthalmia neonatorum should be provided, and close observation of the infant should continue for 2 to 7 days, the usual incubation period. Empiric or definitive therapy against *N. gonorrhoeae* may be necessary depending on an infant's clinical status and should be chosen on the basis of the maternal isolate's sensitivity pattern. The mother should not handle other infants until after 24 hours of adequate therapy, and the infant should be separated from the rest of the nursery population, with or without breastfeeding.

HAEMOPHILUS INFLUENZAE

Haemophilus influenzae type B can cause severe invasive disease such as meningitis, sinusitis, pneumonia, epiglottitis, septic arthritis, pericarditis, and bacteremia. Shock can also occur. Because the increased utilization of the *H. influenzae* type B conjugate vaccines, invasive disease caused by *Haemophilus* has decreased dramatically, more than 95%, in the United States. Most invasive disease occurs in children 3 months to 3 years of age. Older children and adults rarely experience severe disease but do serve as sources of infection for young children. Children younger than 3 months of age seem to be protected because of passively acquired antibodies from the mothers, and some additional benefits may be received from breast milk.

Transmission occurs through contact with respiratory secretions, and droplet precautions are protective. No evidence suggests transmission through breast milk or breastfeeding. Evidence supports that breast milk limits the colonization of *H. influenzae* in the throat.[185]

In the rare case of maternal infection, an inadequately immunized infant in a household is an indication to provide rifampin prophylaxis and close observation for all household contacts, including the breastfeeding infant. Expressed breast milk can be given to an infant during the 24-hour separation after the mother's initiation of antimicrobial therapy, or if the mother's illness prevents breastfeeding, it can be reinitiated when the mother is able (see Appendix F).

LEPROSY

Although uncommon in the United States, leprosy occurs throughout the world. This chronic disease presents with a spectrum of symptoms depending on the tissues involved (typically the skin, peripheral nerves, and mucous membranes of the upper respiratory tract) and the cellular immune response to the causative organism, *Mycobacterium leprae.* Transmission occurs through long-term contact with individuals with untreated or multibacillary (large numbers of organisms in the tissues) disease.

Leprosy is not a contraindication to breastfeeding, according to Jeliffe and Jeliffe.[202] The importance of breastfeeding and urgency of treatment are recognized by experts who treat infants and mothers early and simultaneously. No mother-infant contact is permitted except to breastfeed. Dapsone, rifampin, and clofazimine are typically and safely used for infant and mother regardless of the method of feeding (see Appendix D).

LISTERIOSIS

Listeriosis is a relatively uncommon infection that can have a broad range of manifestations. In immunocompetent individuals, including pregnant women, the infection can vary from being asymptomatic to presenting as an influenza-like illness, occasionally with GI symptoms or back pain. Severe disease occurs more frequently in immunodeficient individuals or infants infected in the perinatal period (pneumonia, sepsis, meningitis, granulomatosis infantisepticum).

Although listeriosis during pregnancy may manifest as mild disease in a mother and is often difficult to recognize and diagnose, it is typically associated with stillbirth, abortion, and premature delivery. It is thought that transmission occurs through the transplacental hematogenous route, infecting the amniotic fluid, although ascending infection from the genital tract may occur.[122] Early and effective treatment of a woman can prevent fetal infection and sequelae.[206,257] Neonatal infection occurs as either early- or late-onset infection from transplacental spread late in pregnancy, ascending infection during labor and delivery, infection during passage

through the birth canal, or, rarely, during postnatal exposure.

No evidence in the literature suggests that *Listeria* is transmitted through breast milk. Treatment of the mother with ampicillin, penicillin, or trimethoprim-sulfamethoxazole is not a contraindication to breastfeeding as long as the mother is well enough. Expressed colostrum or breast milk also can be given if the infant is able to feed orally. The management of lactation and feeding in neonatal listeriosis is conducted supportively, as it is in any situation in which an infant is extremely ill, beginning feeding with expressed breast milk or directly breastfeeding as soon as reasonable.

MENINGOCOCCAL INFECTIONS

N. meningitidis most often causes severe invasive infections, including meningococcemia or meningitis often associated with fever and a rash and progressing to purpura, disseminated intravascular coagulation, shock, coma, and death.

Transmission occurs via respiratory droplets. Spread can occur from an infected, ill individual or from an asymptomatic carrier. Droplet precautions are recommended until 24 hours after initiation of effective therapy. Despite the frequent occurrence of bacteremia, no evidence indicates breast involvement or transmission through breast milk.

The risk for maternal infection to an infant after birth is from droplet exposure and exists whether the infant is breastfeeding or bottle feeding. In either case the exposed infant should receive chemoprophylaxis with rifampin, 10 mg/kg/dose every 12 hours for 2 days (5 mg/kg/dose for infants younger than 1 month of age), or ceftriaxone, 125 mg intramuscularly (IM) once, for children younger than 15 years of age. Close observation of the infant should continue for 7 days, and breastfeeding during and after prophylaxis is appropriate. The severity of maternal illness may prevent breastfeeding, but it can continue if the mother is able, after the mother and infant have been receiving antibiotics for 24 hours. A period of separation from the index case for the first 24 hours of effective therapy is recommended; expressed breast milk can be given during this period.

PERTUSSIS

Respiratory illness caused by *Bordetella pertussis* evolves in three stages: catarrhal (nasal discharge, congestion, increasing cough), paroxysmal (severe paroxysms of cough sometimes ending in an inspiratory whoop, i.e., whooping cough), and convalescent (gradual improvement in symptoms).

Transmission is via respiratory droplets. The greatest risk for transmission occurs in the catarrhal phase, often before the diagnosis of pertussis. The nasopharyngeal culture usually becomes negative after 5 days of antibiotic therapy. Chemoprophylaxis for all household contacts is routinely recommended. No evidence indicates transmission through breast milk, with similar risk to breastfed and bottle-fed infants.

In the case of maternal infection with pertussis, chemoprophylaxis for all household contacts, regardless of age or immunization status, is indicated. In addition to chemoprophylaxis of the infant, close observation and subsequent immunization (in infants older than 6 weeks of age) are appropriate. Despite chemoprophylaxis, droplet precautions and separation of mother and infant during the first 5 days of effective maternal antibiotic therapy are recommended. Expressed breast milk can be provided to the infant during this period.

STAPHYLOCOCCAL INFECTIONS

Staphylococcal infection in neonates can be caused by either *S. aureus* or coagulase-negative staphylococci (most often *S. epidermidis*) and can manifest in a wide range of illnesses. Localized infection can be impetigo, pustulosis in neonates, cellulitis, or wound infection, and invasive or suppurative disease includes sepsis, pneumonia, osteomyelitis, arthritis, and endocarditis. *S. aureus* requires only a small inoculum (10 to 250 organisms) to produce colonization in newborns, most often of the nasal mucosa and umbilicus.[193] By the fifth day of life, 40% to 90% of the infants in the nursery will be colonized with *S. aureus*.[126] The organism is easily transmitted to others from mother, infant, family, or health care personnel through direct contact.

Outbreaks in nurseries were common in the past. Mothers, infants, health care workers, and even contaminated, unpasteurized, banked breast milk were sources of infection.[298,326] Careful use of antibiotics, changes in nursery layout and procedures, standard precautions, and cohorting as needed decreased the spread of *S. aureus* in nurseries. Now the occurrence of methicillin-resistant *S. aureus* (MRSA) is again a common problem, requiring cohorting, occasionally epidemiologic investigation, and careful infection control intervention. There are numerous reports of MRSA outbreaks in NICUs.* The significance of colonization with *Staphylococcus* and the factors leading to development of disease in individual patients are not clear. The morbidity and mortality related to *S. aureus* infection in neonates is well described.[192,195,219] Management of such outbreaks has been reviewed.[147,250]

*References 37, 92, 216, 273, 292, 357, 362.

Little has been written about the role of breastfeeding in colonization with *S. aureus* in NICUs, well-baby nurseries, or at home.

MRSA is an important pathogen worldwide. Community-acquired MRSA is different from hospital-acquired MRSA. Community-acquired MRSA is usually defined as occurring in an individual without the common predisposing variables associated with hospital-acquired MRSA, lacking a MDR phenotype (common with hospital-acquired MRSA), frequently carrying multiple exotoxin virulence factors (such as Panton-Valentine leukocidin toxin), as well as carrying the smaller type IV staphylococcal cassette cartridge for the MecA gene on a chromosome (hospital-acquired MRSA carries types I-III staphylococcal cassette cartridge) and as being molecularly distinct from the common nosocomial strains of hospital-acquired MRSA. Community-acquired MRSA is most commonly associated with skin and soft tissue infections and necrotizing pneumonia and less frequently associated with endocarditis, bacteremia, necrotizing fasciitis, myositis, osteomyelitis, or parapneumonic effusions. Community-acquired MRSA is so common, it is now being observed in hospital outbreaks.[24,144,164,358] Community-acquired MRSA transmission to infants via breast milk has been reported.[34,144,210,253,286] Premature or small-for-gestational-age infants are more susceptible to and at increased risk for significant morbidity and mortality due to MRSA due in part to prolonged hospitalization, multiple courses of antibiotics, invasive procedures, and intravenous (IV) lines, their relative immune deficiency due to prematurity and illness, and altered GI tract due to different flora and decreased gastric acidity. Therefore colonization with MRSA may pose a greater risk to infants in NICUs in the long run. Full-term infants develop pustulosis, cellulitis, and soft tissue infections, but rarely has invasive disease been reported.[82,132,298] Fortunov et al[132] from Texas reported 126 infections in term or late-preterm previously well infants including 43 with pustulosis, 68 with cellulilitis or abscesses, and 15 invasive infections. Family history of soft tissue skin infections and male sex were the only variables associated with risk for infection; cesarean delivery, breastfeeding, and circumcision were not.[132] Nguyen et al[298] reported MRSA infections in a well-infant nursery from California. The eleven cases were all in full-term boys with pustular-vesicular lesions in the groin. The infections were associated with longer length of stay, lidocaine injection use in infants, maternal age older than 30 years, and circumcision. Breastfeeding was not an associated risk factor for MRSA infection.[298] The question of the role of circumcision in MRSA outbreaks was addressed by Van Howe and Robson.[426] They reported that circumcised boys are at greater risk for staphylococcal colonization and infection.[426]

Others report that *S. aureus* carriage in infants (and subsequent infection) is most likely affected by multiple variables including infant factors (antibiotics, surgical procedures [circumcision being the most common], duration of hospital stay as a newborn), maternal factors (previous colonization, previous antibiotic usage, mode of delivery, length of stay), and environmental factors (MRSA in the family or hospital, nursery stay versus rooming-in, hand hygiene).* Gerber et al[147] from the Chicago area published a consensus statement for the management of MRSA outbreaks in the NICU. The recommendations, which were strongly supported by experimental, clinical, and epidemiologic data, included using a waterless, alcohol-based hand hygiene product, monitoring and enforcing hand hygiene, placing MRSA-positive infants in contact precautions with cohorting if possible, using gloves and gowns for direct contact and masks for aerosol-generating procedures, cohorting nurses for care of MRSA-positive infants when possible, periodic screening of infants for MRSA using nares or nasopharyngeal cultures, clarifying the MRSA status of infants being transferred into the NICU, limiting overcrowding, and maintaining ongoing instruction and monitoring of health care workers in their compliance with infection control and hand hygiene procedures. Evaluation of the outbreak could include screening of health care workers and environmental surfaces to corroborate epidemiologic data and laboratory molecular analysis of the MRSA strains if indicated epidemiologically. The use of mupirocin or other decolonizing procedures should be determined on an individual basis for each NICU.

S. aureus is the most common cause of mastitis in lactating women.[317,394,395,436] Recurrence or persistence of symptoms of mastitis is a well described occurrence and an important issue in the management of mastitis. Community-acquired MRSA has been associated with mastitis as well.[342,358,395] (See Chapter 16 for a complete discussion of mastitis.)

Two studies, one from France and one from Brazil, investigated the occurrence of MRSA in expressed breast milk.[26,300] Barbe et al[26] cultured 9171 expressed breast milk samples from 378 women and tested 2351 samples before pasteurization and 6820 samples after pasteurization. MRSA and methicillin-susceptible *S. aureus* were identified respectively in eight samples (0.8%) from three mothers and 281 samples (19.3%) from 73 mothers of the tested expressed breast milk before pasteurization. After

*References 50, 88, 192, 201, 328, 357, 358.

pasteurization, *S. aureus* was not detected in any of the 6820 samples of expressed breast milk. Colonization of one infant with MRSA was identified, but no MRSA infections were identified in any of the hospitalized infants in the NICU during the 18 months of the study.[26] Novak et al[300] identified MRSA in 57 of 500 samples (11%) of expressed fresh-frozen milk from 500 different donors from five Brazilian milk banks. Only 3 of the 57 samples were positive with high-level bacterial counts of MRSA: greater than 10,000 CFU/mL. These were the only samples that would not have been acceptable by bacteriological criteria according to Brazilian or American criteria for raw milk use. They did not investigate other epidemiologic data to identify possible variables associated with low or high level contamination of expressed breast milk with MRSA.[300]

Management of an infant and/or mother with MRSA infection relative to breastfeeding or use of breast milk should be based on the severity of disease and whether the infant is premature, LBW, very-low-birth-weight (VLBW), previously ill, or full term.

Full-term infants who themselves or their mothers develop mild to moderate infections (impetigo, pustulosis, cellulitis/abscess, mastitis/breast abscess, or soft tissue infection) can continue breast feeding after a short period of interruption (24 to 48 hours). During this time, pumping to maintain the milk supply should be supported, an initial evaluation for other evidence of infection should be done in the maternal-infant dyad, the infected child and/or mother should be placed on "commonly" effective therapy for the MRSA infection, and ongoing observation for clinical disease should continue. The mother and infant can "room-in" together in the hospital, if necessary, with standard and contact precautions. Culturing the breast milk is not necessary. Empiric therapy for the infant may be chosen based on medical concerns for the infant and the known sensitivity testing of the MRSA isolate. Appropriate antibiotic choices include short-term use of azithromycin (erythromycin use during infancy [less than 6 weeks of age], or breastfeeding associated with an increased risk for hypertrophic pyloric stenosis), sulfamethoxazole-trimethoprim (in the absence of G6PD deficiency and older than 30 days of age), clindamycin, and perhaps linezolid for mild to moderate infections.

Infants in NICUs (premature, LBW, VLBW, and/or previously ill), who themselves or their mothers have a MRSA infection, should have the breast milk cultured and suspend breastfeeding or receiving breast milk from their mother until the breast milk is shown to be culture negative for MRSA. The infant should be treated as indicated for their infection or empirically treated if symptomatic (with pending culture results) and closely observed for development of new signs or symptoms of infection. Pumping to maintain the milk supply and the use of banked breast milk are appropriate. The infant should be placed on contact precautions, in addition to the routine standard precautions. The infant can be cohorted with other MRSA-positive infants with nursing care cohorted as well. For the mother with MRSA infection, she should be instructed concerning hand hygiene, the careful collection, handling, and storage of breast milk, contact precautions to be used with her infant, and the avoidance of contact with any other infants. The mother can receive several possible antibiotics for MRSA that are compatible with breastfeeding when used for a short period. If the mother remains clinically well, including without evidence of mastitis, but her breast milk is positive for MRSA greater than 10^4 CFU/mL, empiric therapy to diminish or eradicate colonization would be appropriate. Various regimens have been proposed to "eradicate" MRSA colonization, but none have been proven to be highly efficacious. These regimens usually include systemic antibiotics with one or two medications (rifampin added as the second medication), nasal mupirocin to the nares twice daily for 1 to 2 weeks with routine hygiene, with or without the usage of hexachlorophene (or similar topical agent or cleanser) for bathing during the 1 to 2 week treatment period. There is no clear information concerning the efficacy of using similar colonization eradication regimens for other household members or pets in preventing recolonization of the mother or infant. Before reintroducing the use of the mother's breast milk to the infant at least two to three negative breast milk cultures should be obtained after completion of therapy.

Routine screening of breast milk provided by mothers for their infants in NICUs for the presence of MRSA is not indicated in the absence of MRSA illness in the maternal-infant dyad, an MRSA outbreak in NICUs, or a high frequency of MRSA infection in a specific NICU.

TOXIN-MEDIATED *STAPHYLOCOCCUS* DISEASE

One case of staphylococcal scalded skin syndrome was reported by Katzman and Wald[208] in an infant breastfed by a mother with a lesion on her areola that did not respond to ampicillin therapy for 14 days. Subsequently the infant developed conjunctivitis with *S. aureus,* which produced an exfoliative toxin, and a confluent erythematous rash without mucous membrane involvement or Nikolsky sign. No attempt to identify the exfoliative toxin in the breast milk was made, and the breast milk was not cultured for *S. aureus*. The child responded to IV therapy with nafcillin. This emphasizes the importance of evaluating mother and infant at the time of a suspected infection and the need for continued

observation of the infant for evidence of a pyogenic infection or toxin-mediated disease, especially with maternal mastitis or breast lesions.

This case also raises the issue of when and how infants and their mothers become colonized with *S. aureus* and what factors lead to infection and illness in each. The concern is that *Staphylococcus* can be easily transmitted through skin to skin contact, colonization readily occurs, and potentially serious illness can occur later, long after colonization. In the case of staphylococcal scalded skin syndrome or toxic shock syndrome (TSS), the primary site of infection can be insignificant (e.g., conjunctivitis, infection of a circumcision, or simple pustulosis), but a clinically significant amount of toxin can be produced and lead to serious disease.

Toxic shock syndrome can result from *S. aureus* or *Streptococcus pyogenes* infection and probably from a variety of antigens produced by other organisms. TSS-1 has been identified as a "superantigen" that affects the T lymphocytes and other components of the immune response, producing an unregulated and excessive immune response and resulting in an overwhelming systemic clinical response. TSS has been reported in association with vaginal delivery, cesarean delivery, mastitis, and other local infections in mothers. Mortality rate in the mother may be as high as 5%.

The case definition of staphylococcal TSS includes meeting all four major criteria: fever greater than 38.9° C, rash (diffuse macular erythroderma), hypotension, and desquamation (associated with subepidermal separation seen on skin biopsy). The definition also includes involvement of three or more organ systems (GI, muscular, mucous membrane, renal, hepatic, hematologic, or central nervous system); negative titers for Rocky Mountain spotted fever, leptospirosis, and rubeola; and lack of isolation of *S. pyogenes* from any source or *S. aureus* from the cerebrospinal fluid (CSF).[368] A similar case definition has been proposed for streptococcal TSS.[451] Aggressive empiric antibiotic therapy against staphylococci and streptococci and careful supportive therapy are essential to decreasing illness and death. Oxacillin, nafcillin, first-generation cephalosporins, clindamycin, erythromycin, and vancomycin are acceptable antibiotics, even for a breastfeeding mother. The severity of illness in the mother may preclude breastfeeding, but it can be reinitiated when the mother is improving and wants to restart. Standard precautions, but allowing breastfeeding, are recommended.

Staphylococcal enterotoxin F has been identified in breast milk specimens collected on days 5, 8, and 11 from a mother who developed TSS at 22 hours postpartum.[428] *S. aureus* that produced staphylococcal enterotoxin F was isolated from the mother's vagina but not from breast milk. Infant and mother lacked significant antibody against staphylococcal enterotoxin F in their sera. The infant remained healthy after 60 days of follow-up. Staphylococcal enterotoxin F is pepsin inactivated at pH 4.5 and therefore is probably destroyed in the stomach environment, presenting little or no risk to the breastfeeding infant.[35] Breastfeeding can continue if the mother is able.

COAGULASE-NEGATIVE *STAPHYLOCOCCUS*

Coagulase-negative staphylococcal infection (the predominant isolate is *Staphylococcus epidermidis*) produces minimal disease in healthy, full-term infants but is a significant problem in hospitalized or premature infants. Factors associated with increased risk for this infection include prematurity, high colonization rates in specific nurseries, invasive therapies (e.g., IV lines, chest tubes, intubation), and antibiotic use. Illness produced by coagulase-negative staphylococci can be invasive and severe in high-risk neonates, but rarely in mothers. There are reports of necrotizing enterocolitis associated with coagulase-negative *Staphylococcus*. At 2 weeks of age, for infants still in the nursery, *S. epidermidis* is a frequent colonizing organism at multiple sites, with colonization rates as high as 75% to 100%. Serious infections with coagulase-negative staphylococci (e.g., abscesses, IV line infection, bacteremia/sepsis, endocarditis, osteomyelitis) require effective IV therapy. Many strains are resistant to penicillin and the semisynthetic penicillins, so sensitivity testing is essential. Empiric or definitive therapy may require treatment with vancomycin, gentamicin, rifampin, teicoplanin, linezolid, or combinations of these for synergistic activity. Transmission of infection in association with breastfeeding appears to be no more common than with bottle feeding. As with *S. aureus* infection control includes contact and standard precautions. Occasionally, during presumed outbreaks, careful epidemiologic surveillance may be required, including cohorting, limiting overcrowding and understaffing, surveillance cultures of infants and nursery personnel, reemphasis of meticulous infection control techniques for all individuals entering the nursery, and, rarely, removal of colonized personnel from direct infant contact.

S. epidermidis has been identified as part of fecal microbiota of breastfed infants.[203] *S. epidermidis* has also been identified in the breast milk of women with clinical evidence of mastitis.[107] Nevertheless, *S. epidermidis* is rarely associated with infection in full-term infants. Conceivably breast milk for premature infants could be a source of *S. epidermidis* colonization in the NICUs. The other factors associated with hospitalization in a NICU noted previously presumably play a significant role in both colonization and infection in premature infants.

The benefits of early full human milk feeding potentially outweigh the risk for colonization with *S. epidermidis* via breast milk.[348] Ongoing education and assistance should be provided to mothers about the careful collection, storage, and delivery of human breast milk for their premature infants.[353]

STREPTOCOCCAL INFECTIONS

Group A

S. pyogenes (β-hemolytic group A *Streptococcus* [GAS]) is a common cause of skin and throat infections in children, producing pharyngitis, cellulitis, and impetigo. Illnesses produced by GAS can be classified in three categories: (1) impetigo, cellulitis, or pharyngitis without invasion or complication; (2) severe invasive infection with bacteremia, necrotizing fasciitis, myositis, or systemic illness (e.g., streptococcal TSS); and (3) autoimmune-mediated phenomena, including acute rheumatic fever and acute glomerulonephritis. GAS can also cause puerperal sepsis, endometritis, and neonatal omphalitis. Significant morbidity and mortality rates are associated with invasive GAS infection; mortality rate is 20% to 50%, with almost half the survivors requiring extensive tissue débridement or amputation.[347] Infants are not at risk for the autoimmune sequelae of GAS (rheumatic fever or poststreptococcal glomerulonephritis). Transmission is through direct contact (rarely indirect contact) and droplet spread. Outbreaks of GAS in the nursery are rare, unlike with staphylococcal infections. Either mother or infant can be initially colonized with GAS and transmit it to the other.

In the situation of maternal illness (extensive cellulitis, necrotizing fasciitis, myositis, pneumonia, TSS, mastitis), it is appropriate to separate mother and infant until effective therapy (penicillin, ampicillin, cephalosporins, erythromycin) has been given for at least 24 hours. Breastfeeding should also be suspended and may resume after 24 hours of therapy for the mother.

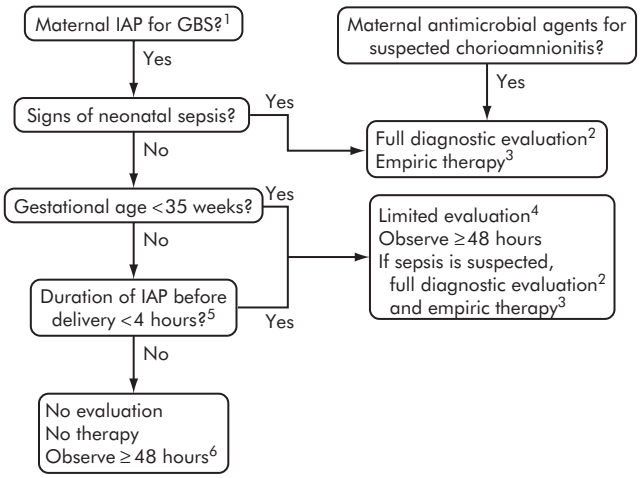
Group B

Group B *Streptococcus* (GBS, *Streptococcus agalactiae*) is a significant cause of perinatal bacterial infection. In parturient women, infection can lead to asymptomatic bacteriuria, urinary tract infection (often associated with premature birth), endometritis, or amnionitis. In infants, infection usually occurs between birth and 3 months of age (1 to 4 cases per 1000 live births). It is routinely classified by the time of onset of illness in the infant: early onset (0 to 7 days, majority less than 24 hours) and late onset (7 to 90 days, generally less than 4 weeks). Infants may develop sepsis, pneumonia, meningitis, osteomyelitis, arthritis, or cellulitis. Early-onset GBS disease is often fulminant, presenting as sepsis or pneumonia with respiratory failure; three quarters of neonatal disease is early onset. Type III is the most common serotype causing disease.

Transmission is believed to occur in utero and during delivery. Colonization rates of mothers and infants vary between 5% and 35%. Postpartum transmission is thought to be uncommon, although it has been documented. Risk factors for early-onset GBS disease include delivery before 37 weeks' gestation, rupture of membranes for longer than 18 hours before delivery, intrapartum fever, heavy maternal colonization with GBS, or low concentrations of anti-GBS capsular antibody in maternal sera.[95] The common occurrence of severe GBS disease before 24 hours of age in neonates has lead to prevention strategies. Revised guidelines developed by the AAP Committees on Infectious Diseases and on the Fetus and Newborn[95] have tried to combine various variables for increased risk for GBS infection (prenatal colonization with GBS, obstetric and neonatal risk factors for early-onset disease) and provide intrapartum prophylaxis to those at high risk (Figure 13-1) The utilization of these guidelines and intrapartum prophylaxis across the United States has decreased the incidence of early-onset disease by approximately 80%. In 2005, the incidence of early-onset disease was 0.35 cases per 1000 live births.[95]

Late-onset GBS disease is thought to be the result of transmission during delivery or in the postnatal period from maternal, hospital, or community sources. Dillon et al[112] demonstrated that 10 of 21 infants with late-onset disease were colonized at birth, but the source of colonization was unidentified in the others. Gardner et al[141] showed that only 4.3% of 46 children who were culture negative for GBS at discharge from the hospital had acquired GBS by 2 months of age. Anthony et al[15] noted that many infants are colonized with GBS, but the actual attack rate for GBS disease is low and difficult to predict.

Acquisition of GBS through breast milk or breastfeeding is uncommon. Cases of late-onset GBS disease associated with GBS in the maternal milk have been reported.[58,214,313,366,438] Some of the mothers had bilateral mastitis, at least one had delayed evidence of unilateral mastitis, and the others were asymptomatic. It was not clear when colonization of the infants occurred or when infection or disease began in the infants. The authors discussed the possibility that the infants were originally colonized during delivery, subsequently colonized the mothers' breasts during breastfeeding, and then became reinfected at a later time. Butter and DeMoor[56] showed that infants initially colonized on their heads at birth had GBS cultured from their throat, nose, or umbilicus 8 days later. Whenever they cultured GBS from the nipples of



[1] If no maternal IAP for GBS was administered despite an indication being present, data are insufficient on which to recommend a single management strategy.

[2] Includes complete blood cell (CBC) count with differential, blood culture, and chest radiograph if respiratory abnormalities are present. When signs of sepsis are present, a lumbar puncture, if feasible, should be performed.

[3] Duration of therapy varies depending on results of blood culture, cerebrospinal fluid findings (if obtained), and the clinical course of the infant. If laboratory results and clinical course do not indicate bacterial infection, duration may be as short as 48 hours.

[4] CBC including WBC count with differential and blood culture.

[5] Applies only to penicillin, ampicillin, or cefazolin and assumes recommended dosing regimens.

[6] A healthy-appearing infant who was ≥38 weeks' gestation at delivery and whose mother received ≥4 hours of IAP before delivery may be discharged home after 24 hours *if* other discharge criteria have been met and a person able to comply fully with instructions for home observation will be present. If any one of these conditions is not met, the infant should be observed in the hospital for at least 48 hours and until criteria for discharge are achieved.

Figure 13-1. Empiric management of neonate born to mother who received intrapartum antimicrobial prophylaxis (IAP) for prevention of early-onset group B streptococcal (GBS) disease. *CSF,* Cerebrospinal fluid; *CBC,* complete blood count. This algorithm is not an exclusive course of management. Variations that incorporate individual circumstances or institutional preferences may be appropriate. (From Committee on Infectious Diseases, American Academy of Pediatrics: *Red Book Report of the Committee on Infectious Disease, ed 26,* Elk Grove, Ill, 2003, American Academy of Pediatrics, p 590.)

mothers, the authors also found it in the nose or throat of the infants.

Byrne et al[58] presented a review of GBS disease associated with breastfeeding and made recommendations to decrease the risk for transmission of GBS to infants via breastfeeding or breast milk. Some of their recommendations included confirming appropriate collection and processing procedures for GBS cultures[370] in medical facilities to decrease false-negative cultures, reviewing proper hygiene for pumping, collection, and storage of expressed breast milk with mothers, reviewing the signs and symptoms of mastitis with mothers, and utilizing banked human milk as needed instead of mother's milk. When a breastfed infant develops late-onset GBS disease, it is appropriate to culture the milk. (See discussion of culturing breast milk earlier in this chapter.) Consider treatment of the mother to prevent reinfection if the milk is culture positive for GBS (greater than 10^4 CFU/mL), with or without clinical evidence of mastitis in the mother. Withholding the mother's milk until it is confirmed to be culture negative for a pathogen is appropriate and should be accompanied by providing ongoing support and instruction to the mother concerning pumping and maintaining her milk supply. Serial culturing of expressed breast milk after treatment of the mother for GBS disease or colonization would be appropriate to insure the ongoing absence of a pathogen in the expressed breast milk. There are reports of reinfection of the infant from breast milk.[23,225] Eradication of GBS mucosal colonization in the infant or the mother may be difficult. Some authors have recommended using rifampin prophylactically in both the mother and infant at the end of treatment to eradicate mucosal colonization.[23] (See Chapter 16 for management of mastitis in the mother.) A mother or infant colonized or infected with GBS should be managed with standard precautions[94] while in the hospital. Ongoing close evaluation of the infant for infection or illness and empiric therapy for GBS in the infant are appropriate until the child has remained well and cultures are subsequently negative at 72 hours. Occasionally, epidemiologic investigation in the hospital will utilize culturing medical staff and family members to detect a source of late-onset GBS disease in the nursery. This can be useful when more than one case of late-onset disease is detected with the same serotype. Cohorting in such a situation may be appropriate. Selective prophylactic therapy for colonized infants to eradicate colonization may be considered, but unlike GAS or *Staphylococcus* infection, GBS infection in nurseries has not been reported to cause outbreaks. No data support screening all breastfeeding mothers and their expressed breast

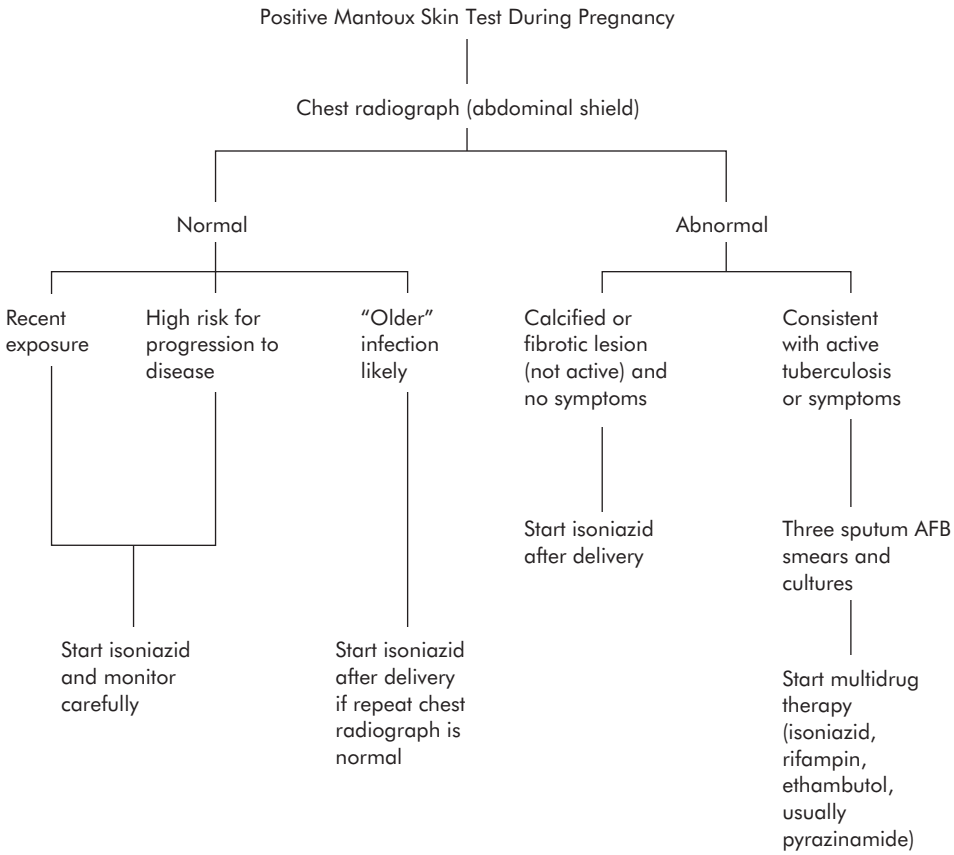


Figure 13-2. Evaluation and treatment of pregnant woman with positive tuberculin skin test. (From Starke JR: Tuberculosis, an old disease but a new threat to mother, fetus, and neonate, *Clin Perinatol* 24:107, 1997.)

milk for GBS as a reasonable method for protecting against spread of GBS infection via expressed breast milk. Selective culturing of expressed breast milk may be appropriate in certain situations.

TUBERCULOSIS

The face of tuberculosis (TB) is changing throughout the world. In the United States the incidence of TB rose during 1986 through 1993 and has been declining since then.[60] Increased rates of TB were noted in adults between 25 and 45 years of age, and because these are the primary childbearing years, the risk for transmission to children increased.

TB during pregnancy has always been a significant concern for patients and physicians alike.[340] It is now clear that the course and prognosis of TB in pregnancy are less affected by the pregnancy and more determined by the location and extent of disease, as defined primarily by chest radiograph, and by the susceptibility of the individual patient. Untreated TB in pregnancy is associated with maternal and infant mortality rates of 30% to 40%.[365] Effective therapy is crucial to the clinical outcome in both pregnant and nonpregnant women. TB during pregnancy rarely results in congenital TB.

Any individual in a high-risk group for TB should be screened with a tuberculin skin test (TST). No contraindication or altered responsiveness to the TST exists during pregnancy or breastfeeding. Interpretation of the TST should follow the most recent guidelines, using different sizes of induration in different-risk populations as cutoffs for a positive test, as proposed by the CDC.[68] Figure 13-2 outlines the evaluation and treatment of a pregnant woman with a positive TST.[398]

Treatment of active TB should begin as soon as the diagnosis is made, regardless of the fetus' gestational age, because the risk for disease to mother and fetus clearly outweighs the risks of treatment. Isoniazid, rifampin, and ethambutol have been used safely in all three trimesters. Isoniazid and pyridoxine therapy during breastfeeding is safe, although the risk for hepatotoxicity in the mother may be a concern during the first 2 months postpartum.[391]

Congenital TB is extremely rare if one considers that 7 to 8 million cases of TB occur each year worldwide and that less than 300 cases of congenital TB have been reported in the literature. As with

other infectious diseases presenting in the perinatal period, distinguishing congenital infection from perinatal or postnatal TB in infants can be difficult.

Postnatal TB infection in infancy typically presents with severe disease and extrapulmonary extension (meningitis, lymphadenopathy, and bone, liver, spleen involvement). Airborne transmission of TB to infants is the major mode of postnatal infection because of close and prolonged exposure in enclosed spaces, especially in their own household, to any adult with infectious pulmonary TB. Potential infectious sources could be the mother or any adult caregiver, such as babysitters, day care workers, relatives, friends, neighbors, and even health care workers.

The suspicion of TB infection or disease in a household with possible exposure of an infant is a highly anxiety-provoking situation (Figure 13-3). Although protection of an infant from infection is foremost in everyone's mind, separation of the infant from the mother should be avoided when reasonable. Every situation is unique, and the best approach will vary according to the specifics of the case and accepted principles of TB management. The first step in caring for the potentially exposed infant is to determine accurately the true TB status of the suspected case (mother or household contact). This prompt evaluation should include a complete history (previous TB infection or disease, previous or ongoing TB treatment, TST status, symptoms suggestive of active TB, results of most recent chest radiograph, sputum smears, or cultures), physical examination, a TST if indicated, a new chest radiograph, and mycobacterial cultures and smears of any suspected sites of infection. All household contacts should be evaluated promptly, including history and TST with further evaluation as indicated.[68] Continued risk to the infant can occur from infectious household contacts who have not been effectively evaluated and treated.

An infant should be separated temporarily from the suspected source if symptoms suggest active disease or a recent TST documents conversion, and separation should continue until the results of the chest radiograph are seen. Because of considerable variability in the course of illness and the concomitant infectious period, debate continues without adequate data about the appropriate period of separation.[278] This should be individualized given the specific situation. HIV testing and assessment of the risk for MDR TB should be done in every case of active TB. Sensitivity testing should be done on every *Mycobacterium tuberculosis* isolate. Table 13-1 summarizes the management of the newborn infant whose mother (or other household contact) has TB.

Initiation of prophylactic isoniazid therapy in the infant has been demonstrated to be effective in preventing TB infection and disease in the infant. Therefore continued separation of infant and mother is unnecessary after therapy in both mother and child has begun.[114] The real risk to an infant requiring separation is from airborne transmission. Separation of the infant from a mother with active pulmonary TB is appropriate, regardless of the method of feeding. However, in many parts of the world, after therapy in the mother and prophylaxis with isoniazid in the infant has begun, the infant and mother are not separated. With or without separation, the mother and infant should continue to be closely observed throughout the course of maternal therapy to ensure good compliance with medication by both mother and infant and to identify, early on, any symptoms in the infant suggestive of TB.

Tuberculous mastitis occurs rarely in the United States but does occur in other parts of the world* and can lead to infection in infants, frequently involving the tonsils. A mother usually has a single breast mass and associated axillary lymph node swelling and infrequently develops a draining sinus. TB of the breast can also present as a painless mass or edema. Involvement of the breast can occur with or without evidence of disease at other sites. Evaluation of extent of disease is appropriate, including lesion cultures by needle aspiration, biopsy, or wedge resection and milk cultures. Therapy should be with multiple anti-TB medications, but surgery should supplement this, as needed, to remove extensive necrotic tissue or a persistently draining sinus.[16] Neither breastfeeding nor breast milk feeding should be done until the lesion is healed, usually 2 weeks or more. Continued anti-TB therapy for 6 months in the mother and isoniazid for the infant for 3 to 6 months is indicated.

In the absence of tuberculous breast infection in the mother, transmission of TB through breast milk has not been documented. Thus even though temporary separation of infant and mother may occur pending complete evaluation and initiation of adequate therapy in the mother and prophylactic isoniazid therapy (10 mg/kg/day as a single daily dose) in the infant, breast milk can be expressed and given to the infant during the short separation. Breastfeeding can safely continue whether the mother, infant, or both are receiving anti-TB therapy. Anti-TB medications (isoniazid, rifampin, pyrazinamide, aminoglycosides, ethambutol, ethionamide, *p*-aminosalicylic acid) have been safely used in infancy, and therefore the presence of these medications in smaller amounts in breast milk is not a contraindication to breastfeeding.

Although conflicting, reports indicate that breastfeeding by TST-positive mothers does influence infants' responses to bacille Calmette-Guérin

*References 2, 160, 171, 200, 215, 381.

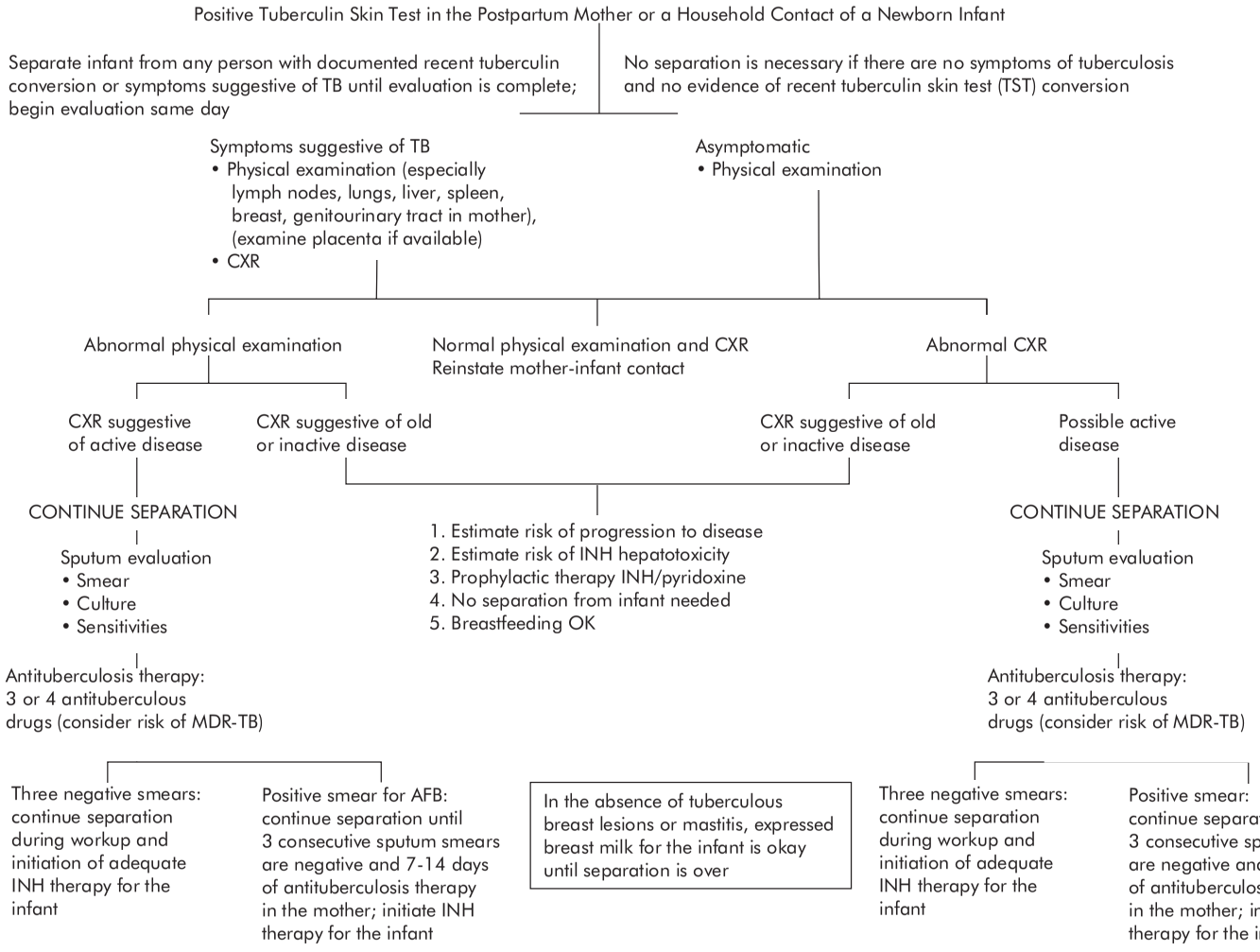


Figure 13-3. Management of newborn infant exposed to tuberculin-positive household contact. *CXR,* Chest x-ray film; *INH,* isoniazid; *MDR,* multidry-resistant; *TB,* tuberculosis.

TABLE 13-1 Management of Newborn Whose Mother (or Other Household Contact) Has Tuberculosis (TB)

Mother/Infant Status	Additional Workup Recommended[1]	Therapy For Mother/Contact	Therapy For Infant	Separation[2]	Breast Milk[3]	Breast-feeding[3]
1. TB infection, no disease[4]	None for mother/ contact	Prophylactic[5]	None	No	Yes	Yes
2. TB infection: Abnormal CXR not suggestive of active disease		Decide active vs. inactive disease				
a. Symptoms or physical findings suggestive of active TB	Aerosolized sputums (culture, smears)[6]	Active disease: empiric[5]	Isoniazid[7]	Yes	Yes	No[8]
		Inactive disease: prophylactic[5]	None	No	Yes	Yes
b. No symptoms or physical findings suggestive of active TB	Aerosolized sputums in select cases	Prophylactic[5]	None	No	Yes	Yes
3. TB infection: Abnormal CXR suggestive of active disease	Aerosolized sputums (culture, smears)[6]	Empiric therapy[5]	Isoniazid[7]	Yes	Yes	No[8]
4. Active pulmonary TB: Suspected MDR TB	Aerosolized sputums (culture, smears)[6]	Consult TB specialist for best regimen[9]	Consult pediatric TB specialist[9] Consider bacille Calmette-Guérin vaccine	Yes	Yes	No
5. TB disease: Suspected mastitis[10]	Aerosolized sputums (culture, smears)[6]	Empiric[5]	Isoniazid[7]	Yes	No[11]	No
6. TB infection: Status undertermined[12]	Perform/interpret CXR within 24 hours			Yes, until CXR interpreted (see a and b)	Yes	No
a. Abnormal CXR not suggestive of active disease	Proceed as in 2		As in 2	As in 2	As in 2	
b. Abnormal CXR suggestive of active disease	Proceed as in 3		As in 3	As in 3	As in 3	

Data from Committee on Infectious Diseases, American Academy of Pediatrics: *Red Book: Report of the Committee on Infectious Diseases,* ed 26, Elk Grove Village, Ill, 2003, American Academy of Pediatrics.

Notes:

[1]Further workup should always include evaluation of TB status of all other household (or close) contacts by tuberculin skin testing (TST), review of symptoms, physical examination, and chest x-ray (CXR). Sputum smears and cultures should be done as indicated.

[2]Separation should occur until interpretation of CXR film confirms absence of active disease, or, with active disease, separation should continue until individual is no longer considered infectious: three negative consecutive sputum smears, adequate ongoing empiric therapy, and decreased fever, cough, and sputum production. Separation means in a different house or location, not simply separate rooms in a household. Duration of separation should be individualized for each case in consultation with TB specialist.

[3]This assumes no evidence of breast involvement, suspected TB mastitis, or lesion (except in status 5, when breast involvement is considered). Risk to infant is via aerosolized bacteria in sputum from the lung. Expressed breast milk can be given even if separation of mother and infant is advised.

[4]TST positive, no symptoms or physical findings suggestive of TB, negative CXR film.

[5]*Prophylactic therapy:* Isoniazid 10 mg/kg/day, maximum 300 mg for 6 months; pyridoxine 25 to 50 mg/day for 6 months. *Empiric therapy:* Standard three- or four-drug regimens for 2 months, and treatment should continue for total of 6 months with isoniazid and rifampin when organism is shown to be sensitive. Suspected multidrug-resistant (MDR) TB requires consultation with TB specialist to select optimum empiric regimen and for ongoing monitoring of therapy and clinical response.

Continued

TABLE 13-1 Management of Newborn Whose Mother (or Other Household Contact) Has Tuberculosis (TB)

[6]Sensitivity testing should be done on any positive culture.

[7]Isoniazid 10 mg/kg/day for 3 to 9 months depending on mother's or contact's status; repeat TST at 3 months and obtain normal CXR in infant before stopping isoniazid. Before beginning therapy, workup of infant for congenital or active TB may be appropriate. This workup should be determined by clinical status of infant and suspected potential risk, and may include TST after 4 weeks of age, with CXR, complete blood count, and erythrocyte sedimentation rate, liver function tests, cerebrospinal fluid analysis, gastric aspirates, sonography/computed tomography of liver/spleen, and chest if congenital TB is suspected.

[8]Breastfeeding is proscribed when separation of mother and infant is indicated because of risk for aerosolized transmission of bacteria. Expressed breast milk given to infant via bottle is acceptable in absence of mastitis or breast lesions.

[9]Consult with TB specialist about MDR TB. Empiric therapy will be chosen based on the most recent culture sensitivities of index patient or perhaps suspected source case, if known, as well as medication toxicities and other factors.

[10]TB mastitis usually involves a single breast with associated axillary lymph node swelling and, infrequently, a draining sinus tract. It can also present as a painless mass or edema of breast.

[11]With suspected mastitis or breast lesion caused by TB, even breast milk is contraindicated until lesion or mastitis heals, usually 2 weeks or more.

[12]Patient has a documented, recent TST conversion but has not been completely evaluated. Evaluation should begin and CXR done and evaluated in less than 24 hours to minimize separation of this person from infant. Further workup should proceed as indicated by symptoms, physical findings, and CXR results.

vaccine, the TST, and perhaps the *M. tuberculosis* bacillus. Despite efforts to identify either a soluble substance or specific cell fractions (gamma/delta T cells) in colostrum and breast milk that affect infants' immune responsiveness, no unified theory explains the various reported changes and no evidence has identified a consistent, clinically significant effect.[39,213,319,367]

Viral Infections

ARBOVIRUSES

Arboviruses were originally a large collection of viruses grouped together because of the common mode of transmission through arthropods. They have now been reclassified into several different families: Bunyaviridae, Togaviridae, Flaviviridae, Reoviridae, and others. They include more than 30 human pathogens.

These organisms primarily produce either CNS infections (encephalitis, meningoencephalitis) or undifferentiated illnesses associated with fever and rash, severe hemorrhagic manifestations, and involvement of other organs (hepatitis, myalgia, polyarthritis). Infection with this array of viruses may also be asymptomatic and subclinical, although how often this occurs is uncertain. Some of the notable human pathogens include Bunyaviridae (California serogroup viruses), Hantavirus, Hantaan virus, Phlebovirus (Rift Valley fever), Nairovirus (Crimean-Congo hemorrhagic fever), Alphavirus (western, eastern, and Venezuelan equine encephalomyelitis viruses, chikungunya virus), Flavivirus (St. Louis encephalitis virus, Japanese encephalitis virus, dengue viruses, yellow fever virus, tick-borne encephalitis viruses), and Orbivirus (Colorado tick fever). Other than for Crimean-Congo hemorrhagic fever and for reported cases of Colorado tick fever associated with transfusion, direct person-to-person spread has rarely been described. Recent outbreaks of chikungunya virus infection in Reunion Island and in India described infection in young infants probably secondary to vertical spread from mother to infant transplacentally.[146,339,422] A few cases of early fetal deaths were associated with infection in pregnant women. The cases of vertical transmission occurred with near-term infection in the mothers, and the infants developed illness within 3 to 7 days of delivery.[146,339] No evidence for transmission via breast milk or breastfeeding is available.

Little evidence indicates that these organisms can be transmitted through breast milk. The exceptions to this include evidence of transmission of two Flaviviruses via breast milk, West Nile virus, and yellow fever vaccine virus. Standard precautions are generally sufficient. With any of these infections in a breastfeeding mother, the severity of the illness may determine the mother's ability to continue breastfeeding. Providing the infant with expressed breast milk is acceptable. (See the discussion of West Nile virus and yellow fever vaccine virus later in this chapter.)

In general, treatment for these illnesses is supportive. However, ribavirin appears to decrease the severity of and mortality from Hantavirus pulmonary syndrome, hemorrhagic fever with renal failure, and Crimean-Congo hemorrhagic fever. Ribavirin has been described as teratogenic in various animal species and is contraindicated in pregnant women. No information is available concerning ribavirin in breast milk, with little information available on the use of IV or oral ribavirin in infants.

ARENAVIRUSES

Arenaviruses are single-stranded ribonucleic acid (RNA) viruses that infect rodents and are acquired by humans through the rodents. The six major human pathogens in this group are (1) lymphocytic

choriomeningitis virus, (2) Lassa fever virus, (3) Junin virus (Argentine hemorrhagic fever), (4) Machupo virus (Bolivian hemorrhagic fever), (5) Guanarito virus (Venezuelan hemorrhagic fever), and (6) Sabia virus. The geographic distribution of these viruses and the illness they cause are determined by the living range of the host rodent (reservoir). The exact mechanism of transmission to humans is unknown and hotly debated.[25,69,131] Direct contact and aerosolization of rodent excretions and secretions are probable mechanisms.

Lymphocytic choriomeningitis virus is well recognized in Europe, the Americas, and other areas. Perinatal maternal infection can lead to severe disease in the newborn, but no evidence suggests transmission through breast milk.[28,224] Standard precautions with breastfeeding are appropriate.

Lassa fever (West Africa) and Argentine hemorrhagic fever (Argentine pampas) are usually more severe illnesses with dramatic bleeding and involvement of other organs, including the brain. These fevers more frequently lead to shock and death than do the forms of hemorrhagic fever caused by the other viruses in this group. Person-to-person spread of Lassa fever is believed to be common, and transmission within households does occur.[212] This may relate to prolonged viremia and excretion of the virus in the urine of humans for up to 30 days.[330] The possibility of persistent virus in human urine, semen, and blood after infection exists for each of the arenaviruses. The possibility of airborne transmission is undecided. Current recommendations by the CDC[69] are to use contact precautions for the duration of the illness in situations of suspected viral hemorrhagic fever. No substantial information describes the infectivity of various body fluids, including breast milk, for these different viral hemorrhagic fevers. Considering the severity of the illness in mothers and the risk to the infants, it is reasonable to avoid breastfeeding in these situations if alternative forms of infant nutrition can be provided.

As more information becomes available, reassessment of these recommendations is advisable. A vaccine is in clinical trials in endemic areas for Junin virus and Argentine hemorrhagic fever. Preliminary studies suggest it is effective, but data are still being accumulated concerning the vaccine's use in children and pregnant or breastfeeding women.

CYTOMEGALOVIRUS

Cytomegalovirus (CMV) is one of the human herpesviruses. Congenital infection of infants, postnatal infection of premature infants, and infection of immunodeficient individuals represent the most serious forms of this infection in children. The time at which the virus infects the fetus or infant and the presence or absence of antibodies against CMV from the mother are important determinants of the severity of infection and the likelihood of significant sequelae (congenital infection syndrome, deafness, chorioretinitis, abnormal neurodevelopment, learning disabilities).[234] About 1% of all infants are born excreting CMV at birth, and approximately 5% of these congenitally infected infants will demonstrate evidence of infection at birth (approximately five symptomatic cases per 10,000 live births). Approximately 15% of infants born after primary infection in a pregnant woman will manifest at least one sequela of prenatal infection.[96]

Various studies have detected that 3% to 28% of pregnant women have CMV in cervical cultures and that 4% to 5% of pregnant women have CMV in their urine.[120,172] Perinatal infection certainly occurs through contact with virus in these fluids but usually is not associated with clinical illness in full-term infants. The lack of illness is thought to result from transplacental passive transfer of protective antibodies from the mother.

Postnatal infection later in infancy occurs via breastfeeding or contact with infected fluids (e.g., saliva, urine) but, again, rarely causes clinical illness in full-term infants. Seroepidemiologic studies have documented transmission of infection in infancy, with higher rates of transmission occurring in daycare centers, especially when the prevalence of CMV in the urine and saliva is high. CMV has been identified in the milk of CMV-seropositive women at varying rates (10% to 85%) using viral cultures or CMV deoxyribonucleic acid (DNA) PCR.[172,301,397,430] CMV is more often identified in the breast milk of seropositive mothers than in vaginal fluids, urine, and saliva. The CMV isolation rate from colostrum is lower than that from mature milk.[172,396] The reason for the large degree of variability in identification of CMV in breast milk in these studies probably relates to the intermittent nature of reactivation and excretion of the virus in addition to the variability, frequency, and duration of sampling of breast milk in the different studies. Some authors have hypothesized that the difference in isolation rates between breast milk and other fluids is caused by viral reactivation in cells (leukocytes or monocytes) in the breast leading to "selective" excretion in breast milk.[301] Vochem et al[430] reported that the rate of virolactia was greatest at 3 to 4 weeks postpartum, and Yeager et al[455] reported significant virolactia between 2 and 12 weeks postpartum. Antibodies (e.g., secretory IgA) to CMV are present in breast milk, along with various cytokines and other proteins (e.g., lactoferrin). These may influence virus binding to cells, but they do not prevent transmission of infection.*

*References 5, 6, 234, 281, 301, 329, 452.

Several studies have documented increased rates of postnatal CMV infection in breastfed infants (50% to 69%) compared with bottle-fed infants (12% to 27%) observed through the first year of life[120,281,397,430] In these same studies, full-term infants who acquired CMV infection postnatally were only rarely mildly symptomatic at the time of seroconversion or documented viral excretion. Also, no evidence of late sequelae from CMV was found in these infants.

Postnatal exposure of susceptible infants to CMV, including premature infants without passively acquired maternal antibodies against CMV, infants born to CMV-seronegative mothers, and immunodeficient infants, can cause significant clinical illness (pneumonitis, hepatitis, thrombocytopenia).* In one study of premature infants followed up to 12 months, Vochem et al[430] found CMV transmission in 17 of 29 infants (59%) exposed to CMV virolactia and breastfed compared with no infants infected of 27 exposed to breast milk without CMV. No infant was given CMV-seropositive donor milk or blood. Five of the 12 infants who developed CMV infection after 2 months of age had mild signs of illness, including transient neutropenia, and only one infant had a short increase in episodes of apnea and a period of thrombocytopenia. Five other premature infants with CMV infection before 2 months of age had acute illness, including sepsis-like symptoms, apnea with bradycardia, hepatitis, leukopenia, and prolonged thrombocytopenia.[430] Vollmer et al[431] followed premature infants with early postnatal CMV infection acquired through breast milk for 2 to 4.5 years to assess neurodevelopment and hearing function. None of the children had sensorineural hearing loss. There was no difference between the 22 CMV-infected children and 22 matched premature control CMV-negative infants in terms of neurologic, speech and language, or motor development.[431] Neuberger et al[296] examined the symptoms and neonatal outcome of CMV infection transmitted via human milk in premature infants in a case-control fashion; 40 CMV-infected premature infants were compared with 40 CMV-negative matched premature infants. Neutropenia, thrombocytopenia, and cholestasis were associated with CMV infection in these infants. No other serious effects or illnesses were found directly associated with the infection including intraventricular hemorrhage, periventricular leukomalacia, retinopathy of prematurity, necrotizing enterocolitis, bronchopulmonary dysplasia, duration of mechanical ventilation or oxygen therapy, duration of hospital stay or weight, gestational age, or head circumference at the time of discharge.

*References 57, 103, 168, 169, 244, 267.

Exposure of CMV-seronegative or premature infants to CMV-positive milk (donor or natural mother's) should be avoided.[379] Various methods of inactivating CMV in breast milk have been reported, including Holder pasteurization, freezing (–20° C for 3 days), and brief high temperature (72° C for 10 seconds).[120,135,155,393,455] One small, prospective study suggests that freezing breast milk at –20°C for 72 hours protects premature infants from CMV infection via breast milk. Sharland et al[379] reported on 18 premature infants (less than 32 weeks) who were uninfected at birth and exposed to breast milk from their CMV seropositive mothers. Only one of 18 (5%) infants became positive for CMV at 62 days of life, and this infant was clinically asymptomatic. This transmission rate is considerably lower than others reported in the literature. CMVseronegative and leukocyte-depleted blood products were used routinely. Banked breast milk was pasteurized and stored at –20° C for various time periods and maternal expressed breast milk was frozen at –20° C before use whenever possible. The infants received breast milk for a median of 34 days (range 11 to 74 days) and they were observed for a median of 67 days (range 30 to 192 days). Breast milk samples pre- or postfreezing were not analyzed by PCR or culture for the presence of cytomegalovirus.[379] Buxmann et al[57] demonstrated no transmission of CMV in 23 premature infants receiving thawed frozen breast milk until 33 weeks (gestational age + postnatal age) (less than or equal to 31 weeks gestational age) born to 19 mothers who were CMV-IgG negative. CMV infection was found in five premature infants of 35 infants born to 29 mothers who were CMV-IgG positive and who provided breast milk for their infants. Three of the five children remained asymptomatic. One child development a respirator-dependent pneumonia and the second developed an upper respiratory tract infection and thrombocytopenia in association with their CMV infections.[57] Yasuda et al[454] reported on 43 preterm infants (median gestational age 31 weeks) demonstrating a peak in CMV DNA copies, detected by a real-time PCR assay, in breast milk at 4 to 6 weeks postpartum. Thirty of the 43 infants received CMV DNA-positive breast milk. Three of the 30 had CMV DNA detected in their sera, but none of the three had symptoms suggestive of CMV infection. Much of the breast milk had been stored at –20° C before feeding, which the authors propose is the probable reason for less transmission in this cohort.[454] Lee et al[248] reported on the use of maternal milk frozen at –20°C for a minimum of 24 hours before feeding to premature infants in a NICU; 23 infants had CMV-seropositive mothers and 39 infants had CMV-seronegative mothers. Two infants developed CMV infection, which was symptomatic. They were both fed frozen

thawed milk from CMV-seropositive mothers.[248] Others have reported individual cases of CMV infection in premature infants despite freezing and thawing breast milk.[268,314] Simple freezing and thawing of breast milk does not completely prevent transmission of CMV to premature infants. The efficacy of freezing and thawing breast milk for varying lengths of time to prevent CMV infection in premature infants has not been studied prospectively in a randomized controlled trial. Eleven of 36 neonatal units in Sweden (27 of which have their own milk banks) freeze maternal milk to reduce the risk for CMV transmission to premature infants.[314]

A prominent group of neonatologists and pediatric infectious disease experts in California who recognize the significant benefits of providing human milk to premature and LBW infants recommend screening mothers of premature infants for CMV IgG at delivery and, when an infant's mother is CMV IgG positive at delivery, using either pasteurized banked human milk or frozen then thawed maternal breast milk for premature infants until they reach the age of 32 weeks.[445] In consideration of the low rates of CMV virolactia in colostrum[169,397] and the predominant occurrence of virolactia between 2 and 12 weeks (peak at 3 to 4 weeks) postpartum,[430,455] they reasonably propose beginning colostrum and breast milk feedings for all infants until the maternal CMV serologic screening is complete. They appropriately recommend close observation and follow-up of premature infants older than 3 weeks of age for signs, symptoms, and laboratory changes of CMV infection until discharge from the hospital.[445]

CMV-seropositive mothers can safely breastfeed their full-term infants because, despite a higher rate of CMV infection than in formula-fed infants observed through the first year of life, infection in this situation is not associated with significant clinical illness or sequelae.

DENGUE DISEASE

Dengue viruses (serotypes dengue 1 to 4) are flaviviruses associated primarily with febrile illnesses and rash; dengue fever, dengue hemorrhagic fever, and dengue shock syndrome. The mosquito *Aedes aegypti* is the main vector of transmission of dengue virus in countries lying between latitudes 35 degrees north and 35 degrees south. More than 2.5 billion people live in areas where transmission occurs; dengue virus infects over 100 million individuals a year and casuses approximately 24,000 deaths a year.[159,163] Although dengue hemorrhagic fever and dengue shock syndrome occur frequently in children younger than 1 year of age, they are infrequently described in infants younger than 3 months of age.[167] There are also differences in the clinical and laboratory findings of dengue virus infection in children compared with adults.[222] Boussemart et al[49] reported on two cases of perinatal/prenatal transmission of dengue and discussed eight additional cases in neonates from the literature. Prenatal or intrapartum transmission of the same type of dengue as the mother was confirmed by serology, culture, or PCR. Phongsamart et al[333] described three additional cases of dengue virus infection late in pregnancy and apparent transmission to two of the three infants with passive acquisition of antibody in the third infant. Sirinavin et al[386] reported on 17 cases in the literature of vertical dengue infection, all presenting at less than 2 weeks of age, but no observations or discussion of breast milk or breastfeeding as a potential source of infection were published. Watanaveeradej et al[439] presented an additional three cases of dengue infection in infants documenting normal growth and development at follow-up at 12 months of age.

It has been postulated that more severe disease associated with dengue disease occurs when an individual has specific IgG against the same serotype as the infecting strain in a set concentration, leading to antibody-dependent enhancement of infection. The presence of preexisting dengue serotype specific IgG in an infant implies either previous primary infection with the same serotype, passive acquisition of IgG from the mother (who had a previous primary infection with the same serotype), or perhaps acquisition of specific IgG from breast milk. Watanaveeradej et al[439] documented transplacentally transferred antibodies against all four serotypes of dengue virus in 97% of 2000 cord sera at delivery. Follow-up of 100 infants documented the loss of antibodies to dengue virus over time with losses of 3%, 19%, 72%, 99%, and 100% at 2, 4, 6, 9, and 12 months of age, respectively.

No evidence is available in the literature about more severe disease in breastfed infants compared with formula-fed infants. No interhuman transmission of dengue virus in the absence of the mosquito vector and no evidence of transmission via breast milk are known. Only one report of a factor in the lipid portion of breast milk, which inhibits the dengue virus, is available, and no evidence for antibody activity against dengue virus in human breast milk is known.[127] Breastfeeding during maternal or infant dengue disease should continue as determined by the mother's or infant's severity of illness.

EPSTEIN-BARR VIRUS

Epstein-Barr virus (EBV) is a common infection in children, adolescents, and young adults. It is usually asymptomatic but most notably causes infectious mononucleosis and has been associated with chronic fatigue syndrome, Burkitt lymphoma, and

nasopharyngeal carcinoma. Because EBV is one of the human herpesviruses, concern has been raised about lifelong latent infection and the potential risk for infection to a fetus and neonate from the mother. Primary EBV infection during pregnancy is unusual because few pregnant women are susceptible.[149,189] Although abortion, premature birth, and congenital infection from EBV are suspected, no distinct group of anomalies is linked to EBV infection in fetus or neonate. Also, no virologic evidence of EBV as the cause of abnormalities was found in association with suspected EBV infection.

Culturing of EBV from various fluids or sites is difficult. The virus is detected by its capacity to transform B lymphocytes into persistent lymphoblastoid cell lines. PCR and DNA hybridization studies have detected EBV in the cervix and in breast milk. One study, which identified EBV DNA in breast milk cells in more than 40% of women donating milk to a breast milk bank, demonstrated that only 17% had antibody to EBV (only IgG, no IgM).[204] Another study examining serologic specimens from breastfed and bottle-fed infants showed similar seroprevalence of EBV at 12 to 23 months of age (36/66 [54.5%] and 24/43 [55.8%]) in the breastfed and bottle-fed children, respectively.[236]

The question of the timing of EBV infection and the subsequent immune response and clinical disease produced requires continued study. Differences exist among the clinical syndromes that manifest at different ages. Infants and young children are asymptomatic, have illness not recognized as related to EBV, or have mild episodes of illness, including fever, lymphadenopathy, rhinitis and cough, hepatosplenomegaly, or rash. Adolescents or young adults who experience primary EBV infection more often demonstrate infectious mononucleosis syndrome or are asymptomatic. Chronic fatigue syndrome is more common in adolescents and young adults. Burkitt lymphoma, observed primarily in Africa, and nasopharyngeal carcinoma, seen in southeast Asia, where primary EBV infection usually occurs in young children, are tumors associated with early EBV infection.[246] These tumors are related to "chronic" EBV infection and tend to occur in individuals with persistently high antibody titers to EBV viral capsid antigen and early antigen. The questions of why these tumors occur with much greater frequency in these geographic areas and what cofactors (including altered immune response to infection associated with coinfections, immune escape by EBV leading to malignancy, or increased resistance to apoptosis secondary to EBV gene mutations) may contribute to their development remain unanswered.[21,289]

It also remains unknown to what degree breast milk could be a source of early EBV infection compared with other sources of EBV infection in an infant's environment. Similar to the situation of postnatal transmission of CMV in immunocompetent infants, clinically significant illness rarely is associated with primary EBV infection in infants. More data concerning the pathogenesis of EBV-associated tumors should be obtained before proscribing against breastfeeding is warranted, especially in areas where these tumors are common but the protective benefits of breastfeeding are high. In areas where Burkitt lymphoma and nasopharyngeal carcinoma are uncommon, EBV infection in mother or infant is certainly not a contraindication to breastfeeding.

FILOVIRIDAE

Marburg and Ebola viruses cause severe and highly fatal hemorrhagic fevers. The illness often presents with nonspecific symptoms (conjunctivitis, frontal headache, malaise, myalgia, bradycardia) and progresses with worsening hemorrhage to shock and subsequent death in 50% to 90% of patients. Person-to-person transmission through direct contact, droplet spread, or airborne spread is the common mode of transmission. However, the animal reservoir or source of these viruses in nature for human infection has not been identified. Attack rates in families are 5% to 16%.[330] No postexposure interventions have proved useful in preventing spread, and no treatment other than supportive is currently available.

A recent report documented the presence of Ebola virus in numerous body fluids including in breast milk. One acute breast milk sample on day 7 after the onset of illness and a "convalescent" breast milk sample on day 15 from the same woman were positive for Ebola virus by both culture and PCR testing.[30] In the same study, saliva remained virus positive for a mean of 16 days after disease onset, urine was positive for a mean of 28 days, and semen for a mean of 43 days after the onset of disease.

No information is available concerning the risk for transmission of these viruses in breast milk or additional risks or benefits from breastfeeding. Contact precautions are recommended for Marburg virus infections and contact and airborne precautions for Ebola virus infection. Given the high attack and mortality rates, these precautions should be carefully instituted and breastfeeding not allowed. If any other suitable source of nutrition can be found for an infant, expressed breast milk should also be proscribed for the infant of a mother with either of these infections for at least 3 weeks postrecovery.

HEPATITIS IN THE MOTHER

The diagnosis of hepatitis in a pregnant woman or nursing mother causes significant anxiety. The first issue is determining the etiology of the hepatitis,

which then allows for an informed discussion of risk to the fetus/infant. The differential diagnosis of acute hepatitis includes (1) common causes of hepatitis, such as hepatitis A, B, C, and D; (2) uncommon causes of hepatitis, such as hepatitis E and G, CMV, echoviruses, enteroviruses, EBV, HSV, rubella, varicella-zoster virus, yellow fever virus; (3) rare causes of hepatitis, such as Ebola virus, Junin virus, and Machupo virus (cause hemorrhagic fever), Lassa virus, and Marburg virus; and (4) nonviral causes, such as hepatotoxic drugs, alcoholic hepatitis, toxoplasmosis, autoimmune hepatitis, bile duct obstruction, ischemic liver damage, Wilson disease, α_1-antitrypsin deficiency, and metastatic liver disease. The following sections focus on hepatitis viruses A to G. Other infectious agents that can cause hepatitis are considered individually in other sections. Box 13-2 provides hepatitis terminology.

Martin et al[266] outline a succinct diagnostic approach to a patient with acute viral hepatitis and chronic viral hepatitis (Figures 13-4 and 13-5). The approach involves using the four serologic markers (IgM anti-hepatitis A virus, hepatitis B surface antigen [HBsAg], IgM anti-HBcAg, anti-HCV) as the initial diagnostic tests. Simultaneous consideration of other etiologies of acute liver dysfunction is appropriate depending on a patient's history. If the initial diagnostic tests are all negative, subsequent additional testing for anti-hepatitis D virus (HDV), HCV RNA, hepatis G virus (HGV) RNA, anti-hepatis E virus (HEV), or HEV RNA may be necessary. If initial testing reveals positive HBsAg, testing for anti-HDV, HBeAg, and HBV DNA is appropriate. These additional tests are useful in defining the prognosis for a mother and the risk for infection to an infant. During the diagnostic evaluation, it is appropriate to discuss with the mother or parents the theoretic risk for transmitting infectious agents that cause hepatitis via breastfeeding. The discussion should include an evaluation of the positive and negative effects of suspending or continuing breastfeeding until the exact etiologic diagnosis is determined. The relative risk for transmission of infection to an infant can be estimated and specific preventive measures provided for the infant (Table 13-2).

BOX 13-2. Terminology for Hepatitis

Hepatitis A Virus (HAV)	
IgM anti-HAV	Immunoglobulin M (IgM) antibody against HAV
HAV RNA	HAV ribonucleic acid
Hepatitis B Virus	
HBsAg	Hepatitis B surface antigen
HBeAg	Hepatitis Be antigen
HBcAg	Hepatitis B core antigen
Anti-HBe	Antibody against hepatitis Be antigen
IgM anti-HBcAg	IgM antibody against hepatitis B core antigen
HBV DNA	HBV deoxyribonucleic acid
HBIG	Hepatitis B immunoglobulin
Hepatitis C Virus (HCV)	
Anti-HCV	Antibody against HCV
HCV RNA	HCV ribonucleic acid
Hepatitis D Virus (HDV)	
Anti-HDV	Antibody against HDV
Hepatitis E Virus (HEV)	
HEV RNA	HEV ribonucleic acid
Hepatitis G Virus (HGV)	
HGV RNA	HGV ribonucleic acid
TT Virus (TTV)	
TTV DNA	TT virus deoxyribonucleic acid
Other	
NANBH	Non-A, non-B hepatitis
ISG	Immune serum globulin

HEPATITIS A

Hepatitis A virus (HAV) is usually an acute self-limited infection. The illness is typically mild, and generally subclinical in infants. Occasionally, HAV infection is prolonged or relapsing, extending 3 to 6 months, and rarely it is fulminant, but HAV infection does not lead to chronic infection. The incidence of prematurity after maternal HAV infection is increased, but no evidence to date indicates obvious birth defects or a congenital syndrome.[372,464] HAV infection in premature infants may lead to prolonged viral shedding.[349] Transmission is most often person to person (fecal-oral), and transmission in food-borne or water-borne epidemics has been described. Transmission via blood products and vertical transmission (mother to infant) are rare.[440] Transmission in daycare settings has been clearly described.

Infection with HAV in newborns is uncommon and does not seem to be a significant problem. The usual period of viral shedding and presumed contagiousness lasts 1 to 3 weeks. Acute maternal HAV infection in the last trimester or in the postpartum period could lead to infection in an infant. Symptomatic infection can be prevented by immunoglobulin (Ig) administration, and 80% to 90% of disease can be prevented by Ig administration

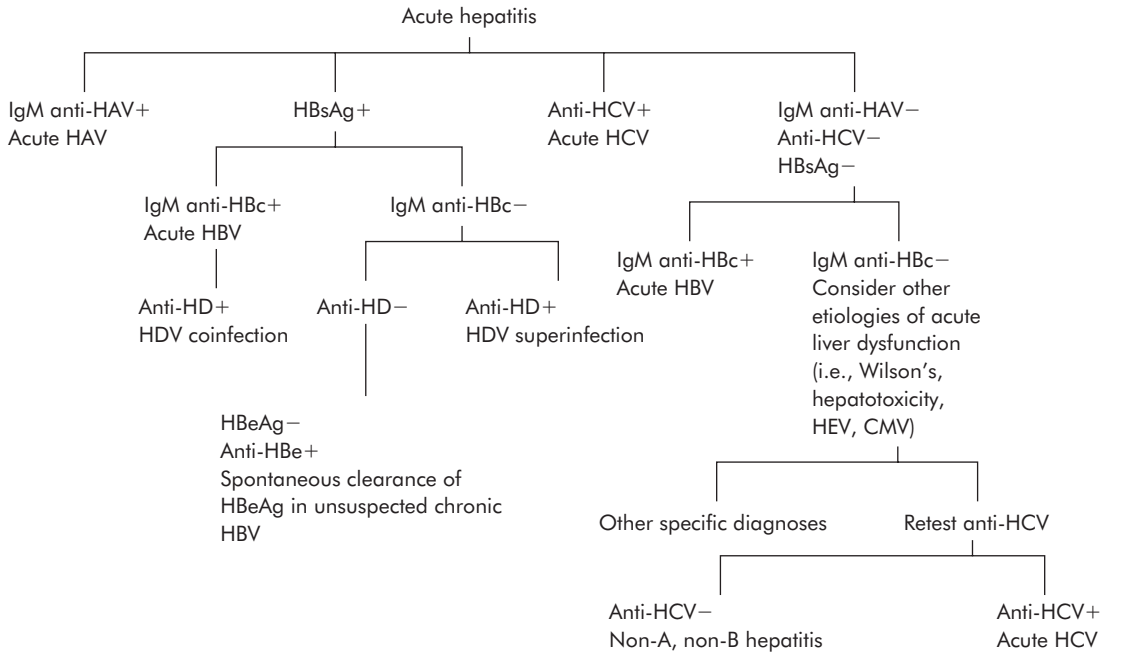


Figure 13-4. Diagnostic approach to patient with acute viral hepatitis. See Box 13-2 for definitions of abbreviations. (From Martin P, Friedman L, Dienstag J: Diagnostic approach. In Zuckerman A, Thomas H, editors: *Viral Hepatitis: Scientific Basis and Clinical Management,* Edinburgh, 1993, Churchill Livingstone.)

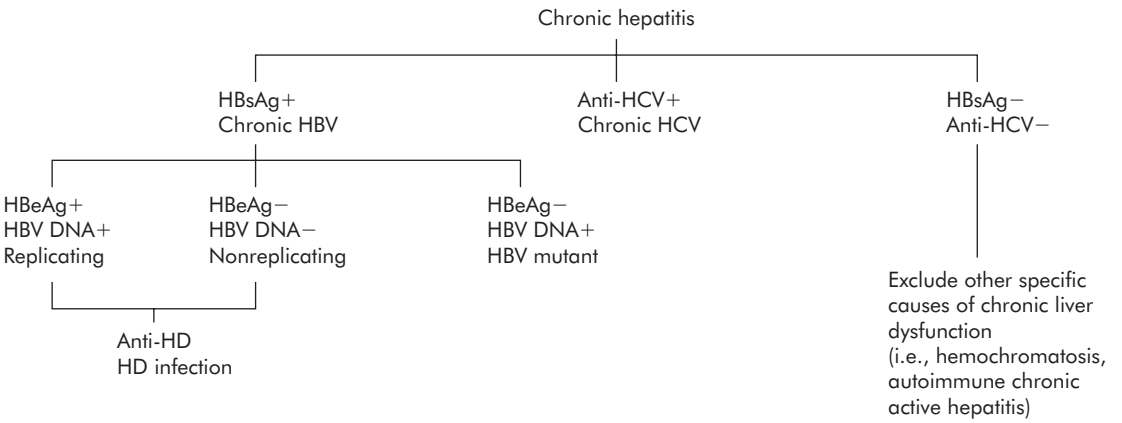


Figure 13-5. Diagnostic approach to patient with chronic viral hepatitis. See Box 13-2 for definitions of abbreviations. (From Martin P, Friedman L, Dienstag J: Diagnostic approach. In Zuckerman A, Thomas H, editors: *Viral Hepatitis: Scientific Basis and Clinical Management,* Edinburgh, 1993, Churchill Livingstone.)

within 2 weeks of exposure. HAV vaccine can be administered simultaneously with Ig without affecting the seroconversion rate to produce rapid and prolonged HAV serum antibody levels.

Transmission of HAV via breast milk has been implicated in one case report, but no data exist on the frequency of isolating HAV from breast milk.[440] Because HAV infection in infancy is rare and usually subclinical without chronic disease and because exposure has already occurred by the time the etiologic diagnosis of hepatitis in a mother is made, no reason exists to interrupt breastfeeding with maternal HAV infection. The infant should receive Ig and HAV vaccine, administered simultaneously.

HEPATITIS B

Hepatitis B virus (HBV) infection leads to a broad spectrum of illness, including asymptomatic seroconversion, nonspecific symptoms (fever, malaise, fatigue), clinical hepatitis with or without jaundice, extrahepatic manifestations (arthritis, rash, renal

TABLE 13-2 Viral Hepatitis in Association With Breastfeeding*

Hepatitis	Virus	Identified in Breast Milk	Factors for Perinatal/ Postnatal Transmission	Prevention	Breastfeeding†
A	Picornaviridae (RNA)	?	Vertical transmission uncertain or rare	ISG	Limited evidence of transmission via breastfeeding or of serious disease in infants
			HAV in pregnancy associated with premature birth	HAV vaccine	Breastfeeding permissible after ISG and vaccine
B	Hepadnaviridae (DNA)	HBsAg	Increased risk for vertical transmission with HBeAg+, in countries where HBV is endemic, or early in maternal infection, before Ab production	HBIG	Low theoretic risk
		HBV DNA		HBV vaccine	Virtually no risk after HBIG and HBV vaccine Breastfeeding OK after HBIG and vaccine
C	Flavivirus (RNA)	HCV RNA detected	Increased risk when mother HIV+ and HCV+ or with increased HCV RNA titers	None	Positive theoretic risk Inadequate data on relative risk Breastfeeding OK after informed discussion with parents
			Vertical transmission uncommon		
D	Delavirdine (RNA negative strand, circular)	?	Requires coinfection/ superinfection with HBV	None (except to prevent HBV infection, give HBIG/HBV vaccine)	Prevent HBV infection with HBIG and vaccine
			Vertical transmission rare		Breastfeeding OK after HBIG and vaccine
E	Caliciviridae (RNA)	+	Severe disease in pregnant women (20% mortality)	ISG and subunit vaccine being tested	Usually subclinical infection in children Breastfeeding OK
G	Related to calicivirus and flavivirus (RNA)	?	Vertical transmission occurs	None	Inadequate data
TT	TT virus (DNA, circular, single stranded)	TTV DNA detected	Vertical transmission occurs	None	Inadequate data

Data from Committee on Infectious Diseases, American Academy of Pediatrics: *Red Book: Report of the Committee on Infectious Diseases, ed 26,* Elk Grove, Ill, 2003, American Academy of Pediatrics.

*See Box 13-2 for abbreviations. *Ab,* Antibody; *HIV,* human immunodeficiency virus.

†With any type of infectious hepatitis, discussion of what is known and not known concerning transmission should be related to the mother/parents, and together an informed decision can be made concerning breastfeeding.

involvement), fulminant hepatitis, and chronic HBV infection. Chronic HBV infection occurs in up to 90% of infants infected via perinatal and vertical transmission and in 30% of children infected between 1 to 5 years of age. Given the increased risk for significant sequelae from chronic infection (chronic active hepatitis, chronic persistent hepatitis, cirrhosis, primary hepatocellular carcinoma), prevention of HBV infection in infancy is crucial. Transmission of HBV is usually through blood or body fluids (stool, semen, saliva, urine, cervical secretions).[94]

Vertical transmission either transplacentally or perinatally during delivery has been well described throughout the world. Vertical transmission rates in areas where HBV is endemic (Taiwan and Japan) are high, whereas transmission to infants from HBV carrier mothers in other areas where HBV carrier rates are low is uncommon.[399] Transmission of HBV to infants occurs in up to 50% of infants when the mothers are acutely infected immediately before, during, or soon after pregnancy.[462]

HBsAg is found in breast milk, but transmission by this route is not well documented. Beasley[31] and

Beasley et al[32] demonstrated that although breast milk transmission is possible, seroconversion rates are no different between breastfed and nonbreastfed infants in a long-term follow-up study of 147 HBsAg-positive mothers. Hill et al[176] followed 101 breastfed infants and 268 formula-fed infants born to women who were chronically HBsAg positive. All infants received hepatitis B immunoglobulin at birth and a full series of hepatitis B vaccine. None of the breastfed infants and nine of the formula-fed infants were positive for HBsAg after completion of the HBV vaccine series. Breastfeeding had occurred for a mean of 4.9 months (range 2 weeks to 1 year). Transmission, when it does happen, probably occurs during labor and delivery. Another report from China followed 230 infants born to HBsAg-positive women. The infants received appropriate dosing and timing of HBIG and HBV vaccine. At 1 year of age, anti-HBs antibody was present in 90.9% of the breastfed infants and 90.3% of the bottle-fed infants.[437] Risk factors associated with immunoprophylaxis failure against vertical transmission of HBV include HBeAg-seropositive mothers and elevated HBV DNA "viral loads" in the mothers.[392] In 2009 the AAP Committee on Infectious Diseases stated that "that breastfeeding of the infant by a HBsAg-positive mother poses no additional risk for acquisition of HBV infection by the infant with appropriate administration of hepatitis B vaccine and HBIG."[96]

Screening of all pregnant women for HBV infection is an essential first step to preventing vertical transmission. Universal HBV vaccination at birth and during infancy, with administration of hepatitis B immunoglobulin (HBIg) immediately after birth to infants of HBsAg-positive mothers, prevents HBV transmission in more than 95% of cases. Breastfeeding by HBsAg-positive women is not contraindicated, but immediate administration of HBIG and HBV vaccine should occur. Two subsequent doses of vaccine should be given at appropriate intervals and dosages for the specific HBV vaccine product. This decreases the small theoretic risk for HBV transmission from breastfeeding to almost zero.

When acute peripartum or postpartum hepatitis occurs in a mother and HBV infection is a possibility, with its associated increased risk for transmission to the infant, a discussion with the mother or parents should identify the potential risks and benefits of continuing breastfeeding until the etiology of the hepatitis can be determined. If an appropriate alternative source of nutrition is available for the infant, breast milk should be withheld until the etiology of the hepatitis is identified. HBIG and HBV vaccine can be administered to the infant who has not already been immunized or has no documented immunity against HBV.[400] If acute HBV infection is documented in a mother, breastfeeding can continue after immunization has begun.

HEPATITIS C

Acute infection with HCV can be indistinguishable from hepatitis A or B infection; however, it is typically asymptomatic or mild. HCV infection is the major cause of blood-borne non-A, non-B hepatitis (NANBH). Chronic HCV infection is reported to occur 70% to 85% of the time regardless of age at time of infection. Sequelae of chronic HCV infection are similar to those associated with chronic HBV infection. Bortolotti et al[47] described two groups of children with HCV infection whom they observed for 12 to 48 months. The first group of 14 children, who acquired HCV infection early in life, presumably from their mothers, demonstrated biochemical evidence of liver disease in the first 12 months of life. Two of these children subsequently cleared the viremia and had normal liver function, an additional three children developed normal liver function despite persistent HCV viremia, and the remaining children had persistent viremia and abnormal liver function. The second group of 16 children, with chronic HCV infection, remained free of clinical symptoms of hepatitis, but 10 (62%) of them had mild alanine aminotransferase elevations, and 7 of the 16 (44%) who had liver biopsies had histologic evidence of mild to moderate hepatitis.

The two commonly identified mechanisms of transmission of HCV are transfusions of blood or blood products and IV drug use. However, other routes of transmission exist because HCV infection occurs even in the absence of obvious direct contact with significant amounts of blood. Other body fluids contaminated with blood probably serve as sources of infection. Transmission through sexual contact occurs infrequently and probably requires additional contributing factors, such as coinfection with other sexually transmitted agents or high viral loads in serum and other body fluids. Studies of transmission in households without other risk factors have demonstrated either low rates of transmission or no transmission.

The reported rates of vertical transmission vary widely. In mothers with unknown HIV status or known HIV infection, the rates of vertical transmission were 4% to 100%, whereas the rates varied between 0% and 42% in known HIV-negative mothers.[113] These same studies suggest that maternal coinfection with HIV, HCV genotype, active maternal liver disease, and the serum titer of maternal HCV RNA may be associated with increased rates of vertical transmission.[263,307,461] The correlation between HCV viremia, the HCV viral load in

a mother, and vertical transmission of HCV is well documented.[288,355,406,456] The clinical significance and risk for liver disease after vertical transmission of HCV are still unknown. The timing of HCV infection in vertical transmission is also unknown. In utero transmission has been suggested by some studies,[125] whereas intrapartum or postpartum transmission was proposed by Ohto et al[308] when they documented the absence of HCV RNA in the cord blood of neonates who later became HCV RNA positive at 1 to 2 months of age. More recently, Gibb et al[150] reported two pieces of data supporting the likelihood of intrapartum transmission as the predominant time of vertical transmission: (a) low sensitivity of PCR for HCV RNA testing in the first month of life with a marked increase in sensitivity after that for diagnosing HCV infection in infants and (b) a lower transmission risk for elective cesarean delivery (without prolonged rupture of membranes) compared with vaginal or emergency cesarean delivery.[150] Another group, McMenamin et al,[275] analyzed vertical transmission in 559 mother-infant pairs. The overall vertical transmission rate was 4.1% (18/441), with another 118 infants not tested or lost to follow-up. Comparison of the vertical transmission rate was no different for vaginal delivery or emergency cesarean in labor versus planned cesarean (4.2% vs. 3.0%). This held true even when mothers had hepatitis C RNA detected antenatally (7.2% vs. 5.3%). The authors did not support planned cesarean delivery to decrease vertical transmission of hepatitis C infection. No prospective, controlled trials of cesarean versus vaginal delivery and the occurrence of vertical hepatitis C transmission are available.

The risk for HCV transmission via breast milk is uncertain. Anti-HCV antibody and HCV RNA has been demonstrated in colostrum and breast milk, although the levels of HCV RNA in milk did not correlate with the titers of HCV RNA in serum.[36,162,256,355] Nevertheless, transmission of HCV via breastfeeding (and not in utero, intrapartum, or from other postpartum sources) has not been proven in the small number infants studied. Transmission rates in breastfed and nonbreastfed infants appear to be similar, but various important factors have not been controlled, such as HCV RNA titers in mothers, examination of the milk for HCV RNA, exclusive breastfeeding versus exclusive formula feeding versus partial breastfeeding, and duration of breastfeeding.* Zanetti et al[461] documented the absence of HCV transmission in 94 mother-infant pairs when the mother had only HCV (no HIV) infection and no transmission in 71 mother-infant pairs who breastfed, including 23 infants whose mothers were seropositive for HCV RNA. Eight infants in that study were infected with HCV, their mothers had both HIV and HCV, and three of these eight infants were infected with both HIV and HCV. The HCV RNA levels were significantly higher in the mothers coinfected with HIV compared with those mothers with HCV alone.

Overall, the risk for HCV infection via breastfeeding is low, the risk for HCV infection appears to be more frequent in association with HIV infection and higher levels of HCV RNA in maternal serum, no effective preventive therapies (Ig or vaccine) exist, and the risk for chronic HCV infection and subsequent sequelae with any infection is high. It is therefore appropriate to discuss the theoretic risk for breastfeeding in HCV-positive mothers with the mother or parents and to consider proscribing breast milk when appropriate alternative sources of nutrition are available for the infants. HIV infection is a separate contraindication to breastfeeding. Additional study is necessary to determine the exact role of breastfeeding in the transmission of HCV, including the quantitative measurement of HCV RNA in colostrum and breast milk, the relative risk for HCV transmission in exclusively or partially breastfed infants versus the risk in formula-fed infants, and the effect of duration of breastfeeding on transmission.

The current position of the CDC is that no data indicate that HCV virus is transmitted through breast milk.[83] Therefore breastfeeding by a HCV-positive, HIV-negative mother is not contraindicated.

Infants born to HCV RNA-positive mothers require follow-up through 18 to 24 months of age to determine infants' HCV status, regardless of the mode of infant feeding. Infants should be tested for alanine aminotransferase and HCV RNA at 3 months and 12 to 15 months of age. Alanine aminotransferase and anti-HCV antibody should be tested at 18 to 24 months of age to confirm an infant's status: uninfected, ongoing hepatitis C infection, or past HCV infection.

HEPATITIS D

Hepatitis D virus (HDV) is a defective RNA virus that causes hepatitis only in persons also infected with HBV. The infection occurs as either an acute coinfection of HBV and HDV or a superinfection of HBV carriers. This "double" infection results in more frequent fulminant hepatitis and chronic hepatitis, which can progress to cirrhosis. The virus uses its own HBV RNA (circular, negative-strand RNA) with an antigen, HDAg, surrounded by the surface antigen of HBV, HBsAg. HDV is transmitted in the same way as HBV, especially through the

*References 150, 256, 263, 284, 288, 307, 308, 461.

exchange of blood and body fluids. HDV infection is uncommon where the prevalence of HBV is low. In areas where HBV is endemic, the prevalence of HDV is highly variable. HDV is common in tropical Africa and South America as well as in Greece and Italy but is uncommon in the Far East and in Alaskan Inuit despite the endemic occurrence of HBV in these areas.[390]

Transmission of HDV has been reported to occur from household contacts and, rarely, through vertical transmission. No data are available on transmission of HDV by breastfeeding. HDV infection can be prevented by blocking infection with HBV; therefore HBIG and HBV vaccine are the best protection. In addition to HBIG and HBV vaccine administration to the infant of a mother infected with both HBV and HDV, discussion with the mother or parents should include the theoretic risk for HBV and HDV transmission through breastfeeding. As with HBV, once HBIg and HBV vaccine have been given to the infant, the risk for HBV or HDV infection from breastfeeding is negligible. Therefore breastfeeding after an informed discussion with the parents is acceptable.

HEPATITIS E

Hepatitis E virus (HEV) is a cause of sporadic and epidemic, enterically transmitted NANBH, which is typically self-limited and without chronic sequelae. HEV is notable for causing high mortality rate in pregnant women. Transmission is primarily via the fecal-oral route, commonly via contaminated water or food. High infection rates have been reported in adolescents and young adults (ages 15 to 40 years). Tomar[416] reported that 70% of cases of HEV infections in the pediatric population in India manifest as acute hepatitis. Maternal-neonatal transmission was documented when the mother developed hepatitis E infection in the third trimester. Although HEV was demonstrated in breast milk, no transmission via breast milk was confirmed in the report. Five cases of transfusion-associated hepatitis E were reported.[416] Epidemics are usually related to contamination of water. Person-to-person spread is minimal, even in households and day care settings. Although Ig may be protective, no controlled trials have been done. Animal studies suggest that a recombinant subunit vaccine may be feasible.[344]

HEV infection in infancy is rare, and no data exist on transmission of HEV by breastfeeding. No evidence of clinically significant postnatal HEV infection in infants or of chronic sequelae in association with HEV infection and no documented HEV transmission through breast milk is available. Currently no contraindication exists to breastfeeding with maternal HEV infection. Ig has not been shown to be effective in preventing infection, and no vaccine is available for HEV.

HEPATITIS G

Hepatitis G virus (HGV) has recently been confirmed as a cause of NANBH distinct from hepatitis viruses A through E. Several closely related genomes of HGV, currently named GBV-A, -B, and -C, appear to be related to HCV, the pestiviruses, and the flaviviruses. Epidemiologically, HGV is most often associated with transfusion of blood, although studies have identified nontransfusion-related cases. HGV genomic RNA has been detected in some patients with acute and chronic hepatitis and a small number of patients with fulminant hepatitis. GBV-C/HGV has also been found in some patients with inflammatory bile duct lesions, but the pathogenicity of this virus is unconfirmed. HGV RNA has been detected in 1% to 3% of healthy blood donors in the United States.[8] Feucht et al[128] described maternal-to-infant transmission of HGV in three of nine children. Two of the three mothers were coinfected with HIV and the third with HCV. None of these infants developed signs of liver disease. Neither the timing nor the mode of transmission was clarified. Lin et al[255] reported no HGV transmission in three mother-infant pairs after cesarean delivery and discussed transplacental spread via blood as the most likely mode of HGV infection in vertical transmission. Wejstal et al[442] reported on perinatal transmission of HGV to 12 of 16 infants born to HGV viremic mothers, identified by PCR. HGV did not appear to cause hepatitis in the children.[442]

Fischler et al[130] followed eight children born to HGV-positive mothers and found only one to be infected with HGV. That child remained clinically well, while his twin, also born by cesarean delivery and breastfed, remained HGV negative for 3 years of observation. Five of the other six children were breastfed for variable periods without evidence of HGV infection. Ohto et al[309] examined HGV mother-to-infant transmission. Of 2979 pregnant Japanese women who were screened, 32 were identified as positive for GBV-C/HGV RNA by PCR; 26 of 34 infants born to the 32 HGV positive women were shown to be HGV RNA positive. Reportedly, none of the infants demonstrated a clinical picture of hepatitis, although two infants had persistent mild elevations (less than two times normal) of alanine aminotransferase. The viral load in mothers, who transmitted HGV to their infants, was significantly higher than in nontransmitting mothers. Infants born by elective cesarean delivery had a lower rate of infection (3 in 7) compared with infants born by emergency cesarean delivery (2 of 2) or born

vaginally (21 of 25). In this study, HGV infection in breastfed infants was four times more common than in formula-fed infants, but this difference was not statistically significant because only four infants were formula fed. The authors report no correlation between infection rate and duration of breastfeeding was seen. Testing of the infants was not done frequently and early enough routinely through the first year of life to determine the timing of infection in these infants.[309] Schröter et al[371] reported transmission of HGV to 3 of 15 infants born to HGV RNA positive mothers at 1 week of age. None of 15 breast milk samples were positive for GBV-C/HGV RNA, and all of the children who were initially negative for HGV RNA in serum remained negative at follow-up between 1 to 28 months of age.[371]

The foregoing data suggest that transmission is more likely to be vertical, before, or at delivery rather than via breastfeeding. The pathogenicity and the possibility of chronic disease due to HGV infection remain uncertain at this time. Insufficient data are available to make a recommendation concerning breastfeeding by HGV-infected mothers.

HERPES SIMPLEX VIRUS

Herpes simplex virus types 1 and 2 (HSV-1, HSV-2) can cause prenatal, perinatal, and postnatal infections in fetuses and infants. Prenatal infection can lead to abortion, prematurity, or a recognized congenital syndrome. Perinatal infection is the most common form of infection (1 in 2000 to 5000 live births, 700 to 1500 cases per year in the United States) and is often fatal or severely debilitating. The factors that facilitate intrapartum infection and predict the severity of disease have been extensively investigated. Postnatal infection is uncommon but can occur from a variety of sources, including oral or genital lesions and secretions in mothers or fathers, hospital workers and home caregivers, and breast lesions in breastfeeding mothers. A number of case reports have documented severe HSV-1 or HSV-2 infections in infants associated with HSV-positive breast lesions in the mothers.[116,161,338,403] Cases of infants with HSV gingivostomatitis inoculating the mothers' breasts have also been reported.

In the absence of breast lesions breastfeeding in HSV-seropositive or culture-positive women is reasonable when accompanied by careful handwashing, covering the lesions, and avoiding fondling or kissing with oral lesions until all lesions are crusted. Breastfeeding during maternal therapy with oral or IV acyclovir can continue safely as well. Inadequate information exists concerning valacyclovir, famciclovir, ganciclovir, and foscarnet in breast milk to make a recommendation at this time. Breastfeeding by women with active herpetic lesions on their breasts should be proscribed until the lesions are dried. Treatment of the mothers' breast lesions with topical, oral, and/or IV antiviral preparations may hasten recovery and decrease the length of viral shedding.

HUMAN HERPESVIRUS 6 AND HUMAN HERPESVIRUS 7

Human herpesvirus 6 (HHV-6) is a cause of exanthema subitum (roseola, roseola infantum) and is associated with febrile seizures. HHV-6 appears to be most similar to CMV based on genetic analysis. No obvious congenital syndrome of HHV-6 infection has been identified, although prenatal infection has been reported.[118] Seroepidemiologic studies show that most adults have already been infected by HHV-6. Therefore primary infection during pregnancy is unlikely, but reactivation of latent HHV-6 infection may be more common. No case of symptomatic HHV-6 prenatal infection has been reported. The significance of reactivation of HHV-6 in a pregnant woman and the production of infection and disease in the fetus and infant remains to be determined. Primary infection in children occurs most often between 6 and 12 months of age, when maternally acquired passive antibodies against HHV-6 are waning. Febrile illnesses in infants younger than 3 months of age have been described with HHV-6 infection, but infection before 3 months or after 3 years is uncommon.

Various studies involving serology and restriction enzyme analysis of HHV-6 isolates from mother/infant pairs support the idea that postnatal transmission and perhaps perinatal transmission from the mothers are common sources of infection. One study was unable to detect HHV-6 in breast milk by PCR analysis in 120 samples, although positive control samples seeded with HHV-6-infected cells did test positive.[119]

Given the limited occurrence of clinically significant disease and the absence of sequelae of HHV-6 infection in infants and children, the almost universal acquisition of infection in early childhood (with or without breastfeeding) and the absence of evidence that breast milk is a source of HHV-6 infection, breastfeeding can continue in women known to be seropositive for HHV-6.

Human herpesvirus 7 (HHV-7) is closely related to HHV-6 biologically. Primary infection with HHV-7 occurs primarily in childhood, usually later in life than HHV-6 infection. The median age of infection is 26 months, with 75% of children becoming HHV-7 positive by 5 years of age.[63] Seroprevalence of HHV-7 antibody has been reported to be 80% to 98% in adults, and passive antibody is present in almost all newborns.[306,408] Like HHV-6, HHV-7 infection can be associated with acute febrile illness, febrile seizures, and irritability, but in

general it is a milder illness than with HHV-6 with fewer hospitalizations. Virus excretion of HHV-7 occurs in saliva, and PCR testing of blood cells and saliva are frequently positive in individuals with past infection.[463] Congenital infection of HHV-6 was detected via DNA PCR testing in 57 of 5638 of cord blood samples (1%), but HHV-7 was not detected in any of 2129 cord blood specimens.[165]

HHV-7 DNA was detected by PCR in 3 of 29 breast milk mononuclear cell samples from 24 women who were serum positive for HHV-7 antibody.[137] In the same study, small differences were seen in the HHV-7 seropositive rates between breastfed infants and bottle-fed infants at 12 months of age (21.7% versus 20%), at 18 months of age (60% versus 48.1%), and at 24 months of age (77.3% versus 58.3%, respectively,). None of these differences were statistically significant. Given that, in general, HHV-6 infection occurs earlier than HHV-7 infection in most infants and that HHV-6 is rarely found in breast milk, it seems unlikely that HHV-7 in breast milk is a common source of infection in infants and children. The infrequent occurrence of significant illness with HHV-7 infection, with the absence of sequelae except in patients who had transplantation surgery at older ages and the common occurrence of infection in childhood argue, that no reason to proscribe against breastfeeding for HHV-7 positive women exists.

Human Papillomavirus

Human papillomavirus (HPV) is a DNA virus with at least 100 different types. These viruses cause warts, genital dysplasia, cervical carcinoma (types 6 and 11), and laryngeal papillomatosis. Transmission occurs through direct contact and sexual contact. Laryngeal papillomas are thought to result from acquiring the virus in passage through the birth canal. Infection in pregnant women or during pregnancy does not lead to an increase in abortions or the risk for prematurity, and no evidence indicates intrauterine infection. HPV is one of the most common viruses in adults and one of the most commonly sexually transmitted infections.

Diagnosis is usually by histologic examination or DNA detection. Spontaneous resolution does occur, but therapy for persistent lesions or growths in anatomically problematic locations is appropriate. Therapy can be with podophyllum preparations, trichloroacetic acid, cryotherapy, electrocautery, and laser surgery. Interferon is being tested in the treatment of laryngeal papillomas, with mixed results.[109] Prevention against transmission means limiting direct or sexual contact, but this may not be sufficient because lesions may not be evident and transmission may still occur.

Rintala et al[346] examined the occurrence of HPV DNA in the oral and genital mucosa of infants during the first 3 years of life. HPV DNA was identified in 12% to 21% of the oral scrape samples and in 4% to 15% of the genital scrape samples by PCR. Oral HPV infection was acquired by 42% of children, cleared by 11%, and persisted in 10% of children; 37% of the children were never infected. They did not report on breast milk or breastfeeding in that study. The question of the source of the infection remains undetermined.

The breast is a rare site of involvement.[110] HPV types 16 and 18 can immortalize normal breast epithelium in vitro.[441] HPV DNA has been detected in breast milk in 10 of 223 (4.5%) of milk samples from 223 mothers, collected 3 days postpartum.[361] No attempt was made to correlate the presence of HPV DNA in breast milk with the HPV status of an infant or to assess the "viral load" of HPV in breast milk or its presence over the course of lactation. A second study found DNA of cutaneous and mucosal HPV types in 2 of 25 human milk samples and 1 of 10 colostrum samples.[64] No reports of HPV lesions of the breast or nipple and documented transmission to an infant secondary to breastfeeding are available.

No increased risk for acquiring HPV from breast milk is apparent, and breastfeeding is acceptable. Even in the rare occurrence of an HPV lesion of the nipple or breast, no data suggest that breastfeeding or the use of expressed breast milk is contraindicated.

MEASLES

Measles is another highly communicable childhood illness that can be more severe in neonates and adults. Measles is an exanthematous febrile illness following a prodrome of malaise, coryza, conjunctivitis, cough, and often Koplik spots in the mouth. The rash usually appears 10 to 14 days after exposure. Complications can include pneumonitis, encephalitis, and bacterial superinfection. With the availability of vaccination, measles in pregnancy is rare (0.4 in 10,000 pregnancies),[148] although respiratory complications (primary viral pneumonitis, secondary bacterial pneumonia), hepatitis, or other secondary bacterial infections often lead to more severe disease in these situations.

Prenatal infection with measles may cause premature delivery without disrupting normal uterine development. No specific group of congenital malformations have been described in association with in utero measles infection, although teratogenic effects of measles infection in pregnant women may rarely manifest in the infants.

Perinatal measles includes transplacental infection when measles occurs in an infant in the first 10 days of life. Infection from extrauterine exposure

usually develops after 14 days of life. The severity of illness after suspected transplacental spread of virus to an infant varies from mild to severe and does not seem to vary with the antepartum or postpartum onset of rash in the mother. It is uncertain what role maternal antibodies play in the severity of an infant's disease. More severe disease seems to be associated with severe respiratory illness and bacterial infection. Postnatal exposure leading to measles after 14 days of life is generally mild, probably because of passively acquired antibodies from the mother. Severe measles in children younger than 1 year of age may occur because of declining passively acquired antibodies and complications of respiratory illness and rare cases of encephalitis.

Measles virus has not been identified in breast milk, whereas measles-specific antibodies have been documented.[1] Infants exposed to mothers with documented measles while breastfeeding should be given immunoglobulin (Ig) and isolated from the mother until 72 hours after the onset of rash, which is often only a short period after diagnosis of measles in the mother. The breast milk can be pumped and given to the infant because secretory IgA begins to be secreted in breast milk within 48 hours of onset of the exanthem in the mother. Table 13-3 summarizes management of the hospitalized mother and infant with measles exposure or infection.[148]

MUMPS

Mumps is an acute transient benign illness with inflammation of the parotid gland and other salivary glands and often involves the pancreas, testicles, and meninges. Mumps occurs infrequently in pregnant women (1 to 10 cases in 10,000 pregnancies) and is generally benign. Mumps virus has been isolated from saliva, respiratory secretions, blood, testicular tissue, urine, CSF in cases of meningeal involvement, and breast milk. The period of infectivity is believed to be between 7 days before and 9 days after the onset of parotitis, with the usual incubation period being 14 to 18 days.

Prenatal infection with the mumps virus causes an increase in the number of abortions when infection occurs in the first trimester. A small increase in the number of premature births was noted in one prospective study of maternal mumps infection.[383] No conclusive evidence suggests congenital malformations are associated with prenatal infection, not even with endocardial fibroelastosis, as originally reported in the 1960s.

Perinatal mumps (transplacentally or postnatally acquired) has rarely if ever been documented. Natural mumps virus has been demonstrated to infect the placenta and infect the fetus, and live attenuated vaccine virus has been isolated from the placenta but not from fetal tissue in women vaccinated 10 days before induced abortion. Antibodies to mumps do cross the placenta.

Postnatal mumps in the first year of life is typically benign. No epidemiologic data suggest that mumps infection is more or less common or severe in breastfed infants compared with formula-fed infants. Although mumps virus has been identified in breast milk and mastitis is a rare complication of mumps in mature women, no evidence indicates that breast involvement occurs more frequently in lactating women. If mumps occurs in the mother breastfeeding can continue because exposure has already occurred throughout the 7 days before the development of symptoms in the mother and secretory IgA in the milk may help to mitigate the symptoms in the infant.

PARVOVIRUS

Human parvovirus B19 causes a broad range of clinical manifestations, including asymptomatic infection (most frequent manifestation in all ages), erythema infectiosum (fifth disease), arthralgia and arthritis, red blood cell (RBC) aplasia (less often decreased white blood cells or platelets), chronic infection in immunodeficient individuals, and rarely myocarditis, vasculitis, or hemophagocytic syndrome.

Vertical transmission can lead to severe anemia and immune-mediated hydrops fetalis, which can be treated, if accurately diagnosed, by intrauterine transfusion. Inflammation of the liver or CNS can be seen in the infant, along with vasculitis. If the child is clinically well at birth, hidden or persistent abnormalities are rarely identified. No evidence indicates that parvovirus B19 causes an identified pattern of birth defects.

Postnatal transmission usually occurs person to person via contact with respiratory secretions, saliva, and rarely blood or urine. Seroprevalence in children at 5 years of age is less than 5%, with the peak age of infection occurring during the school-age years (5% to 40% of children infected). The majority of infections are asymptomatic or undiagnosed seroconversions.[417] Severe disease, such as prolonged aplastic anemia, occurs in individuals with hemoglobinopathies or abnormal RBC maturation. Attack rates have been estimated to be 17% to 30% in casual contacts but up to 50% among household contacts. In one study of 235 susceptible pregnant women, the annual seroconversion rate was 1.4%.[223]

No reports of transmission to an infant through breastfeeding are available. Excretion in breast milk has not been studied because of limitations in culturing techniques. Rat parvovirus has been demonstrated in rat milk. The very low seroconversion rate in young children and the absence of chronic

TABLE 13-3 Guidelines for Preventive Measures After Exposure to Measles in Nursery or Maternity Ward

Type of Exposure or Disease	MEASLES (PRODROME OR RASH) PRESENT*		Disposition
	Mother	Neonate	
A. Siblings at home have measles* when neonate and mother are ready for discharge from hospital.	No	No	1. Neonate: Protective isolation and immunoglobulin (IG) indicated unless mother has unequivocal history of previous measles or measles vaccination.† 2. Mother: With history of previous measles or measles vaccination, she may either remain with neonates or return to older children. Without previous history, she may remain with neonate until older siblings are no longer infectious, or she may receive IG prophylactically and return to older children.
B. Mother has no history of measles or measles vaccination exposure 6 to15 days antepartum.‡	No	No	1. Exposed mother and infant: Administer IG to each and send home at earliest date unless siblings at home have communicable measles. Test mothers for susceptibility if possible. If susceptible, administer live measles vaccine 8 weeks after IG. 2. Other mothers and infants: Same unless clear history of previous measles or measles vaccination in the mother. 3. Hospital personnel: Unless clear history of previous measles or measles vaccination, administer IG within 72 hours of exposure. Vaccinate 8 weeks or more later.
C. Onset of maternal measles occurs antepartum or postpartum.§	Yes	Yes	1. Infected mother and infant: Isolate together until clinically stable, then send home. 2. Other mothers and infants: Same as B-3 except infants should be vaccinated at 15 months of age. 3. Hospital personnel: Same as B-3.
D. Onset of maternal measles occurs antepartum or postpartum.§	Yes	No	1. Infected mother: Isolate until no longer infectious.§ 2. Infected mother's infant: Isolate separately from mother. Administer IG immediately. Send home when mother is no longer infectious. Alternatively, observe in isolation for 18 days for modified measles,¶ especially if IG administration was delayed more than 4 days. 3. Other mothers and infants: Same as C-2. 4. Hospital personnel: Same as B-3.

From Gershon AA: Chickenpox, measles and mumps. In Remington JS, Klein JO, editors: *Infectious Diseases of the Fetus and Newborn Infant, ed 4,* Philadelphia, 1995, WB Saunders.

*Catarrhal Stage or less than 72 hours after onset of exanthem.

†Vaccination with live attenuated measles virus.

‡With exposure less than 6 days antepartum, mother would not be potentially infectious until at least 72 hours postpartum.

§Considered infectious from onset of prodrome until 72 hours after onset of exanthem.

¶Incubation period for modified measles may be prolonged beyond the usual 10 to 14 days.

or frequent severe disease suggest that the risk for parvovirus infection via breast milk is not significant. The possibility of antibodies against parvovirus or other protective constituents in breast milk has not been studied. Breastfeeding by a mother with parvovirus infection is acceptable.

POLIOVIRUSES

Poliovirus infections (types 1, 2, and 3) cause a range of illness, with 90% to 95% subclinical, 4% to 8% abortive, and 1% to 2% manifest as paralytic poliomyelitis. A review by Bates[29] from 1955 of 58 cases of poliomyelitis in infants younger than 1 month of age demonstrated paralysis or death in more than 70% and only one child without evidence of even transient paralysis. More than half the cases were ascribed to transmission from the mothers, although no mention was made of breastfeeding. Breastfeeding rates at the time were approximately 25%.

Prenatal infection with polioviruses does cause an increased incidence of abortion. Prematurity and stillbirth apparently occur more frequently

in mothers who developed paralytic disease versus inapparent infection.[188] Although individual reports of congenital malformations in association with maternal poliomyelitis exist, no epidemiologic data suggest that polioviruses are teratogenic. Also, no evidence indicates that live attenuated vaccine poliovirus given during pregnancy is associated with congenital malformations.[89,170]

Perinatal infection has been noted in several case reports of infants infected in utero several days before birth who had severe disease manifesting with neurologic manifestations (paralysis) but without fever, irritability, or vomiting. Additional case reports of infection acquired postnatally demonstrate illness more consistent with poliomyelitis of childhood. These cases were more severe and involved paralysis, which may represent reporting bias.[89]

No data are available concerning the presence of poliovirus in breast milk, although antibodies to poliovirus types 1, 2, and 3 have been documented.[270] In this era of increasing worldwide poliovirus vaccination, the likelihood of prenatal or perinatal poliovirus infection is decreasing. Maternal susceptibility to poliovirus should be determined before conception and poliovirus vaccine offered to susceptible women. An analysis of the last great epidemic in Italy in 1958 was done using a population-based case-control study.[336] In 114,000 births, 942 infants were reported with paralytic poliomyelitis. A group of matched control subjects was selected from infants admitted to the hospital at the same time. Using the dichotomous variable of never breastfed and partially breastfed, 75 never-breastfed infants were among the cases and 88 among the control group. The authors determined an odds ratio of 4.2, with 95% confidence interval of 1.4 to 14, demonstrating that the risk for paralytic poliomyelitis was higher in infants never breastfed and lowest among those exclusively breastfed. Because by the time the diagnosis of poliomyelitis is made in a breastfeeding mother, the exposure of the infant to poliovirus from maternal secretions has already occurred, and because the breast milk already contains antibodies that may be protective, no reason exists to interrupt breastfeeding. Breastfeeding also does not interfere with successful immunization against poliomyelitis with oral or inactivated poliovirus vaccine.[71]

Retroviruses

HUMAN T-CELL LEUKEMIA VIRUS TYPE I

The occurrence of human T-cell leukemia virus type I (HTLV-I) is endemic in parts of southwestern Japan,[66,105,207,450] the Caribbean, South America,[156] and sub-Saharan Africa. HTLV-I is associated with adult T-cell leukemia/lymphoma and a chronic condition with progressive neuropathy. The progressive neuropathy is called HTLV-I associated myelopathy or tropical spastic paraparesis.[136] Other illnesses have been reported in association with HTLV-I infection including dermatitis, uveitis, arthritis, Sjögren syndrome in adults, and infective dermatitis and persistent lymphadenitis in children. Transmission of HTLV-I occurs most often through sexual contact, via blood or blood products, and via breast milk. Infrequent transmission does occur in utero or at delivery and with casual or household contact.[291]

Seroprevalence generally increases with age and varies widely in different regions and in populations of different backgrounds. In some areas of Japan, seropositivity can be as high as 12% to 16%, but in South America, Africa, and some Caribbean countries the rates are 2% to 6%. In Latin America seropositive rates can be as high as 10% to 25% among female sex workers or attendees to STD clinics.[156] In blood donors in Europe, the seroprevalence of HTLV-I has been reported at 0.001% to 0.03%. The seroprevalence in pregnant women in endemic areas of Japan is as high as 4% to 5% and in nonendemic areas as low as 0.1% to 1.0%. HTLV-1 is not a major disease in the United States. In studies from Europe the seroprevalence in pregnant women has been noted to be up to 0.6%. These pregnant women were primarily of African or Caribbean descent.[138]

HTLV-I antigen has been identified in breast milk of HTLV-I positive mothers.[220] Another report shows that basal mammary epithelial cells can be infected with HTLV-I and can transfer infection to peripheral blood monocytes.[254] Human milk from HTLV-I positive mothers caused infection in marmosets.[221,453] HTLV-I infection clearly occurs via breastfeeding and a number of reports document an increased rate of transmission of HTLV-I to breastfed infants compared with formula-fed infants.* Ando et al[12,13] in two separate reports demonstrated a parallel decline in antibodies against HTLV-I in both formula-fed and breastfed infants to a nadir at approximately 1 year of age and a subsequent increase in antibodies from 1 to 2 years of age. The percentage of children seropositive at 1 year of age in the breastfed and formula-fed groups, respectively, was 3.0% and 0.6%, at 1.5 years of age it was 15.2% and 3.9%, and at 2 years of age it was 41.9% and 4.6%. A smaller group of children followed through 11 to 12 years of age demonstrated no newly infected children after 2 years of age and

*References 9, 10, 12, 13, 178-180, 407.

TABLE 13-4 HTLV-I Transmission Related to Duration of Breastfeeding

Author (Reference)	Duration (mo)	Seroconversion Rate (%)	Number of Children*
Takahashi[407]	≤6	4.4	4/90
	≥7	14.4	20/139
	(bottle-fed)	5.7	9/158
Takezaki[409]	≤6	3.9	2/51
	>6	20.3	13/64
Wiktor[446]	<12	9.0	8/86
	≥12	32.%	19/60

HTVL, Human T-cell leukemia virus.
*Number of children positive for HTLV-I over the number of children examined.

no loss of antibody in any child who was seropositive at 2 years of age.[12,13]

Transmission of HTLV-I infection via breastfeeding is also clearly associated with the duration of breastfeeding.[407,409,446,447] It has been postulated that the persistence of passively acquired antibodies against HTLV-I offers some protection through 6 months of life (Table 13-4).

Other factors relating to HTLV-I transmission via breast milk have been proposed. Yoshinaga et al[460] presented data on the HTLV-I antigen producing capacity of peripheral blood and breast milk cells and showed an increased mother-to-child transmission rate when the mother's blood and breast milk produced large numbers of antigen-producing cells in culture.[460] Hisada et al[183] reported on 150 mothers and infants in Jamaica, demonstrating that a higher maternal provirus level and a higher HTLV-I antibody titer were independently associated with HTLV-I transmission to the infant. Ureta-Vidal et al[421] reported an increased seropositivity rate in children of mothers with a high proviral load and elevated maternal HTLV-I antibody titers.

Various interventions have been proposed to decrease HTLV-I transmission via breastfeeding. Complete avoidance of breastfeeding was shown to be an effective intervention by Hino et al[180,181] in large population of Japanese in Nagasaki. Avoiding breastfeeding led to an 80% decrease in transmission. Breastfeeding for a shorter duration is another effective alternative. Ando et al[11] showed that freezing and thawing breast milk decreased the infectivity of HTLV-I. Sawada et al[363] demonstrated in a rabbit model that HTLV-I immunoglobulin protected against HTLV-I transmission via milk. It is reasonable to postulate that any measure that would decrease the maternal provirus load or increase the anti-HTLV-I antibodies available to infants might decrease the risk for transmission. The overall prevalence of HTLV-I infection during childhood is unknown because the majority of individuals do not manifest illness until much later in life. The timing of HTLV-I infection in a breastfeeding population has been difficult to assess because of passively acquired antibodies from the mother and issues related to testing. Furnia et al[139] estimated the time of infection for a cohort of 16 breastfed infants in Jamaica. The estimated median time of infection was 11.9 months as determined by PCR compared with the estimated time of infection, based on whole virus Western blot, of 12.4 months.

In areas where the prevalence of HTLV-I infection (in the United States, Canada, or Europe) is rare, the likelihood that a single test for antibody against HTLV-I would be a false positive test is high compared with the number of true positive tests. Repeat testing is warranted in many situations.[66] Quantification of the antibody titer and the proviral load is appropriate in a situation when mother-to-child transmission is a concern. A greater risk for progression to disease in later life has not been shown for HTLV-I infection through breast milk, but early-life infections are associated with the greatest risk for adult T-cell leukemia.[402] The mother and family should be informed about all these issues. If the risk for lack of breast milk is not too great and formula is readily available and culturally acceptable, then the proscription of breastfeeding, or at least a recommendation to limit the duration of breastfeeding to 6 months or less, is appropriate to limit the risk for HTLV-I transmission to the infant. Freezing and thawing breast milk before giving it to an infant might be another reasonable intervention to decrease the risk for transmission, although no controlled trials document the efficacy of such an intervention. Neither Ig nor antiviral agents against HTLV-I are available at this time.

HUMAN T-CELL LEUKEMIA VIRUS TYPE II

Human T-cell leukemia virus type II (HTLV-II) is endemic in specific geographic locations, including Africa, the Americas, the Caribbean, and Japan. Transmission is primarily through intravenous drug use, contaminated blood products, and breastfeeding. Sexual transmission occurs but its overall contribution to the prevalence of HTLV-II in different populations remains uncertain. Many studies have examined the presence of HTLV-I and II in blood products. PCR testing and selective antibody tests suggest that about half of the HTLV seropositivity in blood donors is caused by HTLV-II.

HTLV-II has been associated with two chronic neurologic disorders similar to those caused by HTLV-I, tropical or spastic ataxia.[258] A connection between HTLV-II and glomerulonephritis, myelopathy, arthritis, T-hairy cell leukemia, and large granulocytic leukemia has been reported.

Mother-to-child transmission has been demonstrated in both breastfed and formula-fed infants.

It appears that the rate of transmission is greater in breastfed infants.* HTLV-II has been detected in breast milk.[174] Nyambi et al[304] reported that HTLV-II transmission did correlate with the duration of breastfeeding. The estimated rate of transmission was 20%. The time to seroconversion (after the initial loss of passively acquired maternal antibodies) for infected infants seemed to range between 1 and 3 years of age.[304] At this time avoidance of breastfeeding and limiting the duration of breastfeeding are the only two possible interventions with evidence of effectiveness for preventing HTLV-II mother-to-child transmission.[207]

With the current understanding of retroviruses, it is appropriate in cases of documented HTLV-II maternal infection to recommend avoiding or limiting the duration of breastfeeding and provide alternative nutrition when financially practical and culturally acceptable. Mothers should have confirmatory testing for HTLV-II and measurement of the proviral load. Infants should be serially tested for antibodies to HTLV-II and have confirmatory testing if seropositive after 12 to 18 months of age. Further investigation into the mechanisms of transmission via breast milk and possible interventions to prevent transmission should occur as they have for HIV-1 and HTLV-I.

HUMAN IMMUNODEFICIENCY VIRUS TYPE 1

Human immunodeficiency virus type 1 (HIV-1) is transmitted through human milk. Refraining from breastfeeding is a crucial aspect of preventing perinatal HIV infection in the United States and many other countries. The dilemma is the use of replacement feeding versus breastfeeding in countries where breastfeeding provides infants with significant protection from illness and death due to malnutrition or other infections.

Breastfeeding and HIV Transmission

The question of the contribution of breastfeeding in mother-to-child HIV-1 transmission is not a trivial one when one considers the following:

1. The World Health Organization (WHO) has estimated that 33.2 million people (estimate range 30.6 to 36.1) were living with HIV-1 in 2007.[419]
2. More than 90% of children younger than 13 years old infected with HIV-1 have been infected by mother-to-child transmission. The number of children estimated to be living with HIV increased to 2 million in 2007 (estimate range 1.9 to 2.3 million).[419]
3. The WHO estimates that 2.7 million people were newly infected with HIV-1 in 2007, with children younger than 14 years old making up 370,000 of that 2.7 million. (This number has declined due to increasing access to interventions to prevent mother-to-infant transmission. Availability of antiretroviral therapy for prevention of mother-to-child HIV transmission in developing countries in 2007 was estimated to reach 33% of the mothers who needed it.)[419]
4. Breastfeeding contributes an estimated 10% to 20% increase in the overall mother-to-child transmission rates, over and above intrauterine and intrapartum transmission, when no specific interventions to prevent transmission via breastfeeding are utilized.
5. Despite a dramatic increase in the number of people receiving antiretroviral therapy in developing countries (3 million), this represented only 31% of the individuals who needed treatment.[419]

The evidence of HIV transmission via breastfeeding is irrefutable. Multiple publications summarize the current evidence for HIV transmission via breastfeeding in the literature.[232,341,420] Since 1985, case reports have documented HIV transmission via breast milk to children around the world.[182,198,249,465] Primary HIV infection in breastfeeding mothers, with the concomitant high viral load, is associated with a particularly high rate of HIV transmission via breast milk. Palasanthiran et al[322] estimated that risk at 27%.Large observational studies have demonstrated higher rates of HIV transmission in breastfed infants of mothers with chronic HIV infection compared with formula-fed infants.[43,108,124] A systematic analysis of published reports estimated the additional risk for perinatal HIV transmission due to breastfeeding to be 14% (95% confidence interval 7% to 22%).[117] More recently published cohort studies similarly attributed additional risk for HIV transmission due to breastfeeding at 4% to 22% over and above the risk from prenatal and intrapartum transmission.[38,104,121] Laboratory reports demonstrate the presence of cell-free virus and cell-associated virus in breast milk as well as various immunologic factors that could block or limit infection.* A dose-response relationship has been observed, correlating the HIV viral load in human milk as well as a mother's plasma viral load with an increased transmission risk for the breastfed infant.[335,345,351,373]

Many of the potential risk factors associated with human milk transmission of HIV have been described. The cumulative risk for HIV transmission

*References 139, 174, 196, 237, 238, 304, 425, 429.

*References 55, 158, 228, 293, 297, 316, 354, 412, 423, 434, 435.

is higher the longer the duration of breastfeeding.[108,251,282,290,424] Maternal characteristics related to transmission of HIV via human milk include younger maternal age, higher parity, lower CD4+ counts, higher plasma viral loads, and breast abnormalities (mastitis, abscess, or nipple lesions). Characteristics of human milk that relate to a higher risk for transmission include higher viral load in the milk, lower concentrations of antiviral substances (lactoferrin, lysozyme), and lower concentrations of virus-specific cytotoxic T-lymphocytes, levels of various interleukins (IL-7, IL-15),[434,435] secretory IgA, and IgM. Mixed breastfeeding is also associated with a higher risk for HIV transmission compared with exclusive breastfeeding.[99,100,410] The measurable benefits of breast milk versus the relative risk for HIV transmission to the infant due to exclusive breastfeeding (with optimization of other factors to decrease HIV transmission) have been reported in a couple of studies.[97,229] The measurable benefits of receiving breast milk versus the relative increased risk for HIV transmission will need to be determined in a prospective fashion in different locales.[247]

Interventions to Prevent Breastfeeding-Related Transmission

A number of potential interventions to prevent breastfeeding transmission of HIV-1 can be utilized (Box 13-3). The simplest and most effective is the compete avoidance of human milk. This is a practical solution in places like the United States and other countries where replacement feeding as well as other strictly medical interventions are feasible and reasonable, and the risk for not providing breast milk to the infant is negligible. In resource-poor situations, where the risk for other infections is high without the benefits of breast milk, exclusive breastfeeding is appropriate, with any other reasonable and culturally acceptable interventions to decrease HIV transmission via breast milk.

Potentially effective interventions include exclusive breastfeeding, early weaning versus breastfeeding for longer durations, education, and support to decrease the likelihood of mastitis or nipple lesions.[191] Other possible interventions include treating a mother with antiretroviral therapy for her own health (CD4 counts less than 350) or prophylactically to decrease the human milk viral load, treating an infant prophylactically for a prolonged period of time (6 weeks to 6 months) to protect against transmission via breastfeeding, treating the milk itself to decrease the viral load (by pasteurization or other methods),[316,318] treating acute conditions in mothers and infants (e.g., mastitis, breast lesions, infant candidiasis), and enhancing an infant's own defenses via vitamins, immunization, or antiretroviral therapy. Some of these may not be feasible in certain settings such as pasteurization or maternal antiretroviral therapy. Others may not be culturally acceptable, such as treating expressed breast milk before giving it to an infant or even exclusive breastfeeding.

Advantages of Breastfeeding

Significant data demonstrate the advantage of breastfeeding, even for HIV-infected or HIV-exposed infants. The complete avoidance of breastfeeding in certain situations may lead to increased risk for illness and death due to other reasons besides HIV transmission.[106] A study from Kenya showed improved HIV-1-free survival rates in a formula-fed group of children born to HIV-positive mothers, but the breastfed and formula groups had similar mortality rates (24.4% versus 20.0%, respectively) and similar incidences of diarrhea and pneumonia in the first 2 years of life.[272] No difference in the two groups was seen in the prevalence of malnutrition, but the breastfed infants had better nutritional status in the first 6 months of life. Arpadi et al[20] recommend additional nutritional interventions to complement breastfeeding in this population after 6 months of age. Two reports from Zambia document the benefit of exclusive breastfeeding for decreasing late HIV transmission and the lower mortality at 12 months in infants who had continued breastfeeding rather than had discontinued breastfeeding at 4 months of age.[229,385] In Malawi, HIV-infected and HIV-exposed infants who were breastfed (exclusive breastfeeding for 2 months and mixed feeding after that) had lower mortality at 24 months than those who were not breastfed.[405] A report from Botswana examined breastfeeding plus infant zidovudine prophylaxis for 6 months versus formula feeding plus infant zidovudine for 1 month; this study showed a decreased risk for vertical transmission with formula feeding, but also increased cumulative mortality for the HIV-infected infants at 7 months of age who were in the formula-fed group.[411] A study from South Africa examining the use of vitamin A also demonstrated less morbidity in HIV-infected children who were breastfed than not breastfed.[102] Other abstract reports have shown increased morbidity in HIV-infected children due to diarrhea, gastroenteritis, and hospitalization after weaning from breastfeeding.[205,226,315,413]

Exclusive Breastfeeding

Exclusive breastfeeding in most areas of the world is essential to infant health and survival, even in the situation of maternal HIV infection.[97,99,100,229] The duration of exclusive breastfeeding is crucial to decreasing the risk for HIV infection in infants

BOX 13-3. Recommendations on Breastfeeding and Transmission of Human Immunodeficiency Virus (HIV)

- Women and their health care providers need to be aware of the potential risk for transmission of HIV infection to infants during pregnancy and in the peripartum period and through breast milk.
- Documented, routine HIV education and routine testing with the consent of women seeking prenatal care are strongly recommended so that each woman knows her HIV status and the methods available both to prevent the acquisition and transmission of HIV and to determine whether breastfeeding is appropriate.
- At delivery, education about HIV and testing with the consent of women whose HIV status during pregnancy is unknown are strongly recommended. Knowledge of a woman's HIV status assists in counseling on breastfeeding and helps each woman understand the benefits to herself and her infant of knowing her serostatus and the behaviors that would decrease the likelihood of acquisition and transmission of HIV.
- Women who are known to have HIV infections must be counseled not to breastfeed or provide their milk for the nutrition of their own or other's infants.
- In general, women who are known to be HIV seronegative should be encouraged to breastfeed. However, women who are HIV seronegative but at particularly high risk for seroconversion (e.g., injection drug users and sexual partners of known HIV-positive persons or active drug users) should be educated about HIV with an individualized recommendation concerning the appropriateness of breastfeeding. In addition, during the perinatal period, information should be provided on the potential risk for transmitting HIV through breast milk and about methods to reduce the risk for acquiring HIV infection.
- Each woman whose HIV status is unknown should be informed of the potential for HIV-infected women to transmit HIV during the peripartum period and through breast milk and the potential benefits to her and her infant of knowing her HIV status and how HIV is acquired and transmitted. The health care provider needs to make an individualized recommendation to assist the woman in deciding whether to breastfeed.
- Neonatal intensive care units should develop policies that are consistent with these recommendations for the use of expressed breast milk for neonates. Current standards of the U.S. Occupational Safety and Health Administration (OSHA) do not require gloves for the routine handling of expressed human milk. However, health care workers should wear gloves in situations in which exposure to breast milk might be frequent or prolonged, such as in milk banking.
- Human milk banks should follow the guidelines developed by the U.S. Public Health Service, which include screening all donors for HIV infection, assessing risk factors that predispose to infection, pasteurizing all milk specimens.

From Lawrence RA: A review of the medical benefits and contraindications to breastfeeding in the United States. In *Maternal and Child Health Technical Information Bulletin,* Washington, DC, 1997, U.S. Health Resources and Services Administration.

versus the risk for malnutrition and other infections with early weaning. In the Mashi Study in Botswana, Thior et al[411] evaluated infants randomized to breastfeeding plus infant zidovudine for 6 months or formula feeding plus 1 month of infant zidovudine. The cumulative infant mortality was significantly higher at 7 months for the formula-fed group but at 18 months it was similar between the two groups. The breastfed infants were more likely to become HIV infected despite the 6 months of zidovudine prophylaxis.[411] Becquet et al[33] analyzed data from Cote d'Ivoire for 2001 to 2005; 47% of the HIV-exposed infants were breastfed for a median of 4 months, and 53% were formula fed and observed for 2 years. No significant difference in the rate of HIV infection was seen in the two groups, and no significant difference between the two groups was seen for morbid events (diarrhea, acute respiratory infections or malnutrition) or hospitalization or death. The authors attributed these good outcomes to effective nutritional counseling and care, access to clean water, and the provision of a safe and continuous supply of breast milk substitute.[33] Coovadia et al[97] studied exclusive breastfeeding in the first 6 months of life as an intervention in South Africa. Of the exclusively breastfed infants, 14.1% at 6 weeks of age and 19.5% at 6 months of age were HIV infected. Breastfed infants who also were fed solids or formula milk were more likely to acquire infection than exclusively breastfed infants. The cumulative mortality at 3 months of age was markedly lower for exclusively breastfed infants (6.1%) versus 15.1% in the infants receiving mixed feedings.

Early Weaning

Kuhn et al[230] examined the effects of early, abrupt weaning on HIV-free survival of 958 children in Zambia. Infants were randomly assigned to two different counseling programs that advised either abrupt weaning at 4 months or prolonged breastfeeding. In the weaning intervention group, 69% of mothers stopped breastfeeding by 5 months compared with a median duration of breastfeeding of 16 months in the control group. The study found no significant difference in HIV-free survival at

24 months in the two groups (83.9% versus 80.7%). Children already infected by 4 months of age had a higher mortality if they were assigned to the early weaning group (73.6% versus 54.8%). Additional analysis showed that in mothers with less severe HIV disease early weaning was clearly harmful to the infant.[231] Arpadi et al[20] studied the growth of HIV-exposed, uninfected children who were exclusively breastfed for 4 months with rapid weaning to replacement foods or exclusively breastfed until 6 months and then continued breastfeeding with complementary foods. Weight-for-age z scores dropped markedly in both groups from 4 to 15 months of age but less so in the continued breastfeeding group. Length-for-age z score also dropped dramatically, but was not influenced by continued breastfeeding. Even in this HIV-exposed, uninfected group of children, additional nutritional interventions are essential to complement breastfeeding beyond 6 months of age.[20]

Antiretroviral Prophylaxis With Breastfeeding

In recent years the discussion around preventing HIV transmission via breastfeeding and in the number of studies examining the important issues have increased.[98,233,283] The fact that intrapartum and perinatal transmission of HIV from mothers to infants has decreased markedly due to the increased utilization of antiretroviral therapy during pregnancy, delivery, and postnatally for prevention emphasizes the importance of now working harder to decrease breast milk transmission of HIV. In considering different possible interventions to decrease mother-infant HIV transmission, it is crucial to reemphasize the goals of optimizing maternal health and survival and optimizing infant health and survival at the same time.

A laboratory report shows that mothers receiving highly active antiretroviral therapy (HAART) while breastfeeding do have decreased whole breast milk HIV-1 viral loads (23/26 mothers had less than 50 copies/mL) compared with mothers who did not receive HAART (9/25 with less than 50 copies/mL). However, the whole milk HIV-1 DNA load (measured as "undetectable" at less than 10 copies/10^6 cells) was not significantly different in the HAART (13 of 26 mothers)] and non-HAART (15 of 23) groups.[378] HIV-1 DNA is incorporated into cells found in breast milk. Another group showed significantly lower HIV RNA levels in the breast milk of women treated with nevirapine, zidovudine, and lamivudine compared with women not receiving antiretroviral therapy.[152]

The use of maternal HAART seems to decrease HIV-1 transmission via breastfeeding. One group working in Mozambique, Malawi, and Tanzania working with mother-infants pairs receiving HAART as prevention during pregnancy compared one cohort (809 mother-infant pairs) who received supplementary formula and water filters for the first 6 months of life with a second cohort (251 mother-infant pairs) breastfeeding exclusively and the mothers receiving HAART for the first 6 months. The cumulative incidence rate of HIV infection at 6 months of age was 2.7% for the formula-fed infants and 2.2% for breastfed infants. Through 6 months of age no apparent additional risk for late postnatal transmission of HIV was observed.[323] The Petra study team working in Tanzania, South Africa, and Uganda examined the efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late HIV transmission in this predominantly breastfeeding population.[332] There were four regimens: A, zidovudine and lamivudine starting at 36 weeks' gestation plus intrapartum medication and 7–days' postpartum treatment; B, same as A without the prepartum component; C, intrapartum zidovudine and lamivudine only; D, placebo. At week 6 the HIV transmission rates were 5.7% in group A, 8.9% in group B, 14.2% in group C, and 15.3% in group D. At 18 months the HIV infection rates were 15% in group A, 18% in group B, 20% in group C, and 22% in group D. Although a measurable decrease in transmission at 6 weeks of age was observed, limited protection was seen at 18 months of age. An observational study from Tanzania compared maternal HAART for 6 months with exclusive breastfeeding and abrupt weaning at 5 to 6 months of age with a historical control of the same feeding schedule without the postnatal maternal HAART. In the treatment group the cumulative HIV transmission was 4.1% at 6 weeks, 5.0% at 6 months, and 6.0% at 18 months of age. The cumulative HIV infection or death rate was 8.6% at 6 months and 13.6% at 18 months of age. The cumulative risk for HIV transmission was 1.1% between 6 and 18 months. The HIV transmission in this treatment group was half the transmission rate in the historical control group.[218] Another study in sub-Saharan Africa with 6 months of maternal HAART and exclusive breastfeeding for 6 months demonstrated 94% HIV-free survival at 12 months of age; the maternal and infant mortality rates for the treated mother-infant pairs were significantly lower than the country's maternal and infant mortality rates.[264]

Antiretroviral therapy prophylaxis for infants is another investigated intervention to decrease HIV transmission via breastfeeding. In a study from Cote d'Ivoire comparing different groups over time, infants received zidovudine (ZDV) alone as ZDV prophylaxis, a single dose of nevirapine (NVP), and 7 days of zidovudine (ZDV) as NVP/ZDV prophylaxis, or a single dose of nevirapine

plus zidovudine and lamivudine (3TC) for 7 days as NVP/ZDV/3TC prophylaxis. Formula feeding (FF) was compared with exclusive shortened breastfeeding (ESB) upto 4 months of age and prolonged breastfeeding (PB). The cumulative transmission rates at 18 months were 22.3% in 238 infants in the ZDV + PB group, 15.9% in 169 infants in the NVP/ZDV + ESB group, 9.4%, in the 195 infants in the NVP/ZDV +FF group, 6.8% in the 198 infants in the NVP/ZDV/3TC + ESB group, and 5.6% in the 126 infants in the NVP/ZDV/3TC + FF group.[252] Kumwenda et al[235] working in Malawi demonstrated decreased HIV transmission with breastfeeding and two different infant prophylaxis regimens. At 9 months of age, they observed a 10.6% occurrence of HIV transmission for infants receiving a single dose of nevirapine plus 1 week of zidovudine compared with 5.2% in the group receiving a single dose of nevirapine plus 1 week of zidovudine plus 14 weeks of daily nevirapine, and 6.4% in the group receiving a single dose of nevirapine plus 1 week of zidovudine plus 14 weeks of nevirapine and zidovudine.[235] In the Mitra Study in Tanzania in which the median time of breastfeeding was 18 weeks, the HIV transmission rate at 6 months in the infants who received zidovudine plus 3TC for 1 week plus 3TC alone for breastfeeding through 6 months of age was less than 50% of the transmission rate for those infants receiving only 1 week of zidovudine plus 3TC.[217] A summary of three trials in Ethiopa, India, and Uganda compared a single dose of nevirapine at birth for infants with 6 weeks of daily nevirapine in predominantly breastfed infants whose mothers were counselled regarding feeding per the WHO/UNICEF guidelines. At 6 months 87 of 986 infants in the single-dose group and 62 of 901 in the extended-dose group were HIV infected, which was not statistically significant. The authors suggested that a longer course of infant antiretroviral prophylaxis might be more effective.[388]

Human Immune Deficiency Virus in Maternal Health and Breastfeeding

The potential effect of breastfeeding on the HIV-positive mother needs to be adequately assessed in relation to the mother's health status. From Uganda and Zimbabwe Mbizvo et al[271] reported no difference in the number of hospital admissions or mortality between HIV-positive and HIV-negative women during pregnancy. In the 2 years after delivery the HIV-positive women had higher hospital admission (approximately two times increased risk) and death rates (relative risk greater than 10) than HIV-negative women.[271] Chilongozi et al[90] reported on 2292 HIV-positive mothers from four sub-Saharan sites followed for 112 months. Serious adverse events occurred in 166 women (7.2%); 42 deaths occurred in the HIV-positive women, and no deaths occurred in 331 HIV-negative women.[90]

Several studies have examined breastfeeding relative to mothers' health and reported conflicting results. The first study from Kenya demonstrated a significantly higher mortality rate in breastfeeding mothers compared with a formula-feeding group in the 2 years after delivery. The hypothesized explanation offered by the authors for this difference was increased metabolic demands, greater weight loss, and nutritional depletion.[294] A second study from South Africa showed an overall lower mortality rate in the two groups with no significant difference in mortality rate in the 10 months of observation.[101] Kuhn et al[227] reported no difference in mortality at 12 months after delivery between 653 women randomly assigned to a short breastfeeding group (326 women, median breastfeeding duration 4 months, 21% still breastfeeding at 12 months) and a long breastfeeding group (327 women, 90% breastfeeding at 5 months, 72% breastfeeding at 12 months, median 15 months). The HIV-related mortality rates were high (4.9%), but not associated with prolonged lactation.[227] Walson et al[433] followed 535 HIV-positive women for 1 to 2 years in Kenya. The mortality risk was 1.9% at 1 year and 4.8% at 2 years of follow-up. Although less than 10% of women reported a hospitalization during the 2 years, they experienced various common infections (pneumonia, diarrhea, TB, malaria, STDs, urinary tract infections, mastitis). Breastfeeding was a significant cofactor for diarrhea and mastitis but not for pneumonia, TB, or hospitalization.[433]

In summary, breastfeeding of infants by HIV-positive mothers does lead to an increased risk for HIV infection in the infants. Much remains to be understood about the mechanisms of HIV transmission via breast milk and the action and efficacy of different interventions to prevent such transmission. The complete avoidance of breastfeeding is a crucial component for the prevention of perinatal HIV infection in the United States and many other countries.

In resource-poor settings, where breastfeeding is the norm and where it provides vital nutritional and infection protective benefits, the WHO, UNICEF, and the Joint United Nations Programme on HIV/AIDS (UNAIDS) recommend education, counseling, and support for HIV-infected mothers so they can make an informed choice concerning infant feeding. Mothers choosing to breastfeed should receive additional education, support, and medical care to minimize the risk for HIV transmission and to optimize their own health status during and after breastfeeding. Mothers choosing to use replacement feedings should receive parallel education,

support, and medical care for themselves and their infants to minimize the effect of the lack of breastfeeding.

Good evidence now shows that antiretroviral prophylactic regimens for mothers or infants while continuing breastfeeding does decrease postnatal HIV transmission. Early weaning is associated with increased morbidity and mortality. Further carefully controlled research is indicated to adequately assess the risks and benefits to infants and mothers of prolonged breastfeeding with antiretroviral prophylaxis for either or both mothers and infants. Along with this, HIV testing rates must be improved at the same time as increased availability and access to antenatal care, HIV prevention services, and HIV medical care for everyone must be increased. The availability and free access to antiretroviral medications must also improve.

The decision about infant feeding for HIV-positive mothers remains a difficult one, but this is slowly changing with increasing options. The goals remain 100% HIV transmission prevention, optimal maternal health and survival, and long-term infant health and survival.

HUMAN IMMUNODEFICIENCY VIRUS TYPE 2

Human immunodeficiency virus type 2 (HIV-2) is an RNA virus in the nononcogenic, cytopathic lentivirus genus of retroviruses. It is genetically closer to simian immunodeficiency virus than to HIV-1. The clinical disease associated with HIV-2 has similar symptoms to HIV-1 infection but progresses at a slower rate to severe immunosuppression.

HIV-2 is endemic in western Africa and parts of the Caribbean and found infrequently in Europe and North and South America.[190,305] It is transmitted via sexual contact, blood, or blood products and from mother to child.

Routine testing for HIV-2 is recommended in blood banks. Antibody tests used for HIV-1 are only 50% to 90% sensitive for detecting HIV-2.[65] Specific testing for HIV-2 is appropriate whenever clinically or epidemiologically indicated.

Vertical transmission occurs infrequently. Ekpini et al[121] followed a large cohort of west African mothers and infants: 138 HIV-1 positive women, 132 HIV-2 positive women, 69 women seropositive for both HIV-1 and 2, and 274 HIV seronegative women. A few cases of perinatal HIV-2 transmission occurred, but no case of late postnatal transmission was observed.[121]

It is probable that HIV-2 transmission via breast milk is less common than with HIV-1, but insufficient data support that the risk for transmission is zero. Mothers who test positive for HIV-2 should be tested for HIV-1, and guidelines for breastfeeding should follow those for HIV-1 until additional information is available.

RABIES

Rabies virus produces a severe infection with progressive CNS symptoms (anxiety, seizures, altered mental status) that ultimately proceeds to death; few reports of survival exist. Rabies occurs worldwide except in Australia, Antarctica, and several island groups. In 1992 more than 36,000 cases of rabies were reported to the WHO, a number that is probably a marked underestimate of the actual cases.[67] Between 1990 and 2003, 37 cases of human rabies were reported in the United States.[70,78] Postexposure prophylaxis is given to thousands of patients each year.

Rabies virus is endemic in various animal populations, including raccoons, skunks, foxes, and bats. Because of aggressive immunization programs, rabies in domesticated dogs and cats in the United States is uncommon. The virus is found in the saliva and tears and nervous tissue of infected animals. Transmission occurs by bites, licking, or simply contact of oral secretions with mucous membranes or nonintact skin. Many cases of rabies in humans now lack a history of some obvious contact with a rabid animal. This may be a result of the long incubation period (generally 4 to 6 weeks, but can be up to 1 year, with reports of incubation periods of several years), a lack of symptoms early in an infectious animal, or airborne transmission from bats in enclosed environments (caves, laboratories, houses).

Person-to-person transmission via bites has not been documented, although it has occurred in corneal transplants.[44] Rabies viremia has not been observed in the spread of the virus. No evidence exists indicating transmission through breast milk.

In the case of maternal infection with rabies, many scenarios can occur before the onset of progressive, severe CNS symptoms. The progression and severity of maternal illness can preclude breastfeeding, but separation of an infant from the mother is appropriate regardless of the mother's status and method of infant feeding (especially to avoid contact with saliva and tears). Breastfeeding should not continue when the mother has symptoms of rabies, and the infant should receive postexposure immunization and close observation. An infant may received expressed breast milk, but the expression must occur without possible contamination with saliva or tears from the mother.

Depending on the scenario, the nature of a mother's illness, the possible exposure of an infant to the same source as the mother, and the exposure of a child to the mother, postexposure immunization of an infant may be appropriate.

A more common scenario is a mother's apparent exposure to rabies (without exposure for the infant), necessitating postexposure immunization of the mother with rabies vaccine. In the majority of cases, in the absence of maternal illness, breastfeeding can reasonably continue during the mother's five-dose immunization series in 28 days. In a rare situation in which apparent exposure of mother and infant to rabies occurs together, postexposure treatment of both mother and infant should be instituted, and breastfeeding can continue.

RESPIRATORY SYNCYTIAL VIRUS

Respiratory syncytial virus (RSV) is a common cause of respiratory illness in children and is relatively common in adults, usually producing milder upper respiratory tract infection in adults. No evidence indicates that RSV causes intrauterine infection, adversely affects the fetus, or causes abortion or prematurity. RSV does produce infection in neonates, causing asymptomatic infection, afebrile upper respiratory tract infection, bronchiolitis, pneumonia, and apnea. Mortality rate can be high in neonates, especially in premature infants and ill full-term infants, particularly those with preexisting respiratory disease (hyaline membrane disease, bronchopulmonary dysplasia) or cardiac disease associated with pulmonary hypertension.

RSV is believed to be transmitted via droplets or direct contact of the conjunctiva, nasal mucosa, or oropharynx with infected respiratory secretions. Documentation of RSV infection is rarely made in adults, and spread from a mother or other household contacts probably occurs before a diagnosis can be made. Therefore risk for RSV transmission from breast milk is probably insignificant compared with transmission via direct or droplet contact in families. In nurseries, however, it is appropriate to make a timely diagnosis of RSV infection in neonates to isolate infants from the others and prevent spread in the nursery. Ribavirin is not recommended for routine use. It is infrequently used in patients with potentially life-threatening RSV infection.

RSV infection should be suspected in any infant with rhinorrhea, nasal congestion, or unexplained apnea, especially in October through March in temperate climates. Prophylaxis against RSV with RSV-specific immunoglobulin IV (RSV-IGIV) during this season for infants at highest risk for severe disease is appropriate.

Debate surrounds the topic of the effect of passively acquired antibodies (in infants from mothers before birth) against RSV on the occurrence and severity of illness in neonates and infants. It appears that a higher level of neutralizing antibody against RSV in neonates decreases the risk for severe RSV disease.[153,239] Some controversy remains concerning the measurable benefit of breastfeeding for preventing serious RSV disease.[3,54,115] Some studies have shown benefit and others no effect. Controlling for possible confounding factors (e.g., smoking, crowded living conditions) in these studies has been difficult. At this point, no reason exists to stop breastfeeding with maternal RSV infection; a potential exists for benefit from nonspecific factors in breast milk against the RSV. Infants with RSV infection should breastfeed unless their respiratory status precludes it.

ROTAVIRUSES

Rotavirus infections usually result in diarrhea, accompanied by emesis and low-grade fever. In severe infections the clinical course can include dehydration, electrolyte abnormalities, and acidosis and can contribute to malnutrition in developing countries. Generally, every child will have at least one episode of rotavirus infection by 5 years of age.[157] In developed countries, rotavirus is often associated with diarrhea requiring hospitalization in children younger than 2 years of age, but rarely associated with death. Worldwide rotavirus is the leading cause of diarrhea-related deaths in children younger than 5 years old. Estimates suggest that in children younger than 5 years old rotavirus infection leads to more than 100 million occurrences of diarrhea, 2 million hospital admissions, and 500,000 deaths each year.[157] Fecal-oral transmission is the most common route, but fomites and respiratory spread may also occur. Spread of infection occurs most often in homes with young children or in daycare centers and institutions. In hospitalized infants or mothers with rotavirus infection, contact precautions are indicated for the duration of the illness. No evidence indicates prenatal infection from rotavirus, but perinatal or postnatal infection from contact with the mother or others can occur.

No case of transmission of rotavirus via breast milk has been documented. Breast milk does contain antibodies to rotavirus for up to 2 years. Human milk mucin has been demonstrated to inhibit rotavirus replication and prevent experimental gastroenteritis.[457] The mechanisms of rotavirus immunity are not well understood. They are thought to be multifactorial with cell-mediated immunity limiting severity and the course of infection, while humoral immunity protects against subsequent infections. Innate and adaptive responses at the level of the mucosa are probably the most important.[134]

Exclusive breastfeeding may decrease the likelihood of severe rotavirus-related diarrhea by as much as 90%.[93,377] Although breastfeeding does not prevent infection with rotavirus, it seems to decrease the severity of rotavirus-induced illness in children younger than 2 years old.[93,123,184] At least one study

suggested that this may represent simply the postponement of severe rotavirus infection until an older age.[93] One study suggested that protection against rotavirus rapidly declines upon discontinuation of breastfeeding.[356] This delay in rotavirus infection until the child is older may be beneficial in that the older child may be able to tolerate the infection or illness with a lower likelihood of becoming dehydrated or malnourished. Continuing breastfeeding during an episode of rotavirus illness with or without vomiting is appropriate and often helpful to the infant. No reason to suspend breastfeeding by a mother infected with rotavirus is apparent.

Two rotavirus vaccines (RotaTeq and Rotarix) have been licensed for use in more than 90 countries, but less than 20 countries have routine immunization programs. Additional types of rotavirus vaccines are undergoing study in various countries, specifically examining the efficacy of the vaccines in low and medium income countries.[444] Some of the explanations for the slow implementation of an effective vaccine globally include differences in protection with specific vaccines in high income countries compared with low or medium income countries, the unfortunate association with intussusception in the United States, the delayed recognition of the significant rotavirus-related morbidity and mortality, and the cost of the new vaccines. The question of variable efficacy of the specific rotavirus vaccines in developed and developing countries remains an important one. Several trials are examining this issue and attempting to address factors such as maternal transplacentally transferred antibodies, breastfeeding practices (especially immediately before immunization with a live oral rotavirus vaccine), stomach acid, micronutrient malnutrition, interfering gut flora, and differences in the epidemiology of rotavirus in different locations.[327] Evidence indicates that maternal immunization with rotavirus vaccine can increase both transplacental acquisition of antibodies and secretory IgA in breast milk.[334] Additionally, oral rotavirus vaccines have been able to stimulate a good serologic response in both formula-fed and breastfed infants, although the antigen titers may need to be modified to create an optimal response in all infants.[86] The actual protective effect of these vaccines in different situations and strategies will require measurement in ongoing prospective studies.

RUBELLA VIRUS

Congenital rubella infection has been well described, and the contributing variables to infection and severe disease have been elucidated. The primary intervention to prevent congenital rubella has been to establish the existence of maternal immunity to rubella before conception, including immunization with rubella vaccine and reimmunization if indicated. Perinatal infection is not clinically significant. Postnatal infection occurs infrequently in children younger than 1 year of age because of passively acquired maternal antibodies. The predominant age of infection is 5 to 14 years old, and more than half of those with infections are asymptomatic. Postnatal rubella is a self-limited, mild viral infection associated with an evanescent rash, shotty adenopathy, and low-grade transient fever. It most often occurs in the late winter and spring. Infants with congenital infection shed the virus for prolonged periods from various sites and may serve as a source of infection throughout the year. Contact isolation is appropriate for suspected and proved congenital infection for at least 1 year, including exclusion from day care and avoidance of pregnant women, whereas postnatal rubella infection requires droplet precautions for 7 days after the onset of rash.

Rubella virus has been isolated from breast milk after natural infection (congenital or postnatal) and after immunization with live attenuated vaccine virus. Both IgA antibodies and immunoreactive cells against rubella have been identified in breast milk. Breastfed infants can acquire vaccine virus infection via milk but are asymptomatic. Because postpartum infection with this virus (natural or vaccine) is not associated with clinically significant illness, no reason exists to prevent breastfeeding after congenital infection, postpartum infection with this virus, or maternal immunization with rubella vaccine.

SEVERE ACUTE RESPIRATORY SYNDROME

Severe acute respiratory syndrome (SARS) is a term that could be applied to any acute serious respiratory illness caused by or associated with a variety of infections agents; since 2003, however, it has been linked with SARS-associated coronavirus (SARS-CoV). In the global outbreak of 2002 to 2003, more than 8400 probable cases of SARS and more than 800 deaths occurred. More than the actual number of affected individuals or its associated mortality rate (approximately 10% overall, and closer to 50% in persons older than 65 years of age), it was what we did not know about this new unusual illness, and the tremendous publicity surrounding it, that made SARS such a sensation. We now know the cause of this illness, known as the SARS-CoV. SARS-CoV was shown not to be closely related to the previously characterized coronavirus groups.[265,350] Despite intense international collaboration to study the illness and the virus, many things are not known, such as the degree of infectiousness, the actual period of transmissibility, all the modes of transmission, how many people have an asymptomatic infection compared with those with symptoms

or severe illnesses, how to make a rapid diagnosis of confirmed cases, and where it originated.

At least 21 cases of probable SARS in children have been described in the literature.[42,187,380,387] In general, the illness in children is a mild, nonspecific respiratory illness, but in adolescents and adults it is more likely to progress to severe respiratory distress. It has been reported that children are less likely to transmit SARS than adults.[187] The overall clinical course, the radiologic evolution, and the histologic findings of these illness are consistent with the host's immune response playing a significant role in disease production.

Five infants were born to mothers with confirmed SARS. The infants were born prematurely (26 to 37 weeks), presumably due to maternal illness. Although two of the five infants had serious abdominal illnesses (other coronaviruses have been associated with reported outbreaks of necrotizing enterocolitis), the presence of SARS-CoV could not be demonstrated in any of these infants.[380] No evidence of vertical transmission of SARS is available.

The mode of feeding for any of the reported cases of young children with SARS or the infants born to mothers with SARS was not mentioned. As with other respiratory viruses predominantly transmitted by droplets, transmission via breast milk is an insignificant mode of transmission, if it occurs at all. The benefits of breastfeeding being what they are, mothers with SARS should continue breastfeeding if they are able, or expressed breast milk can be given to an infant until the mother is able to breastfeed.

SMALLPOX

In this era of worry about biologic terrorism, smallpox is an important concern. The concern for infants (breastfed or formula-fed) is direct contact with mothers or household members with smallpox. Smallpox is highly contagious in the household setting due to person-to-person spread via droplet nuclei or aerosolization from the oropharynx and direct contact with the rash. Additional potential exposures for infants include the release of a smallpox aerosol into the environment by terrorists, contact with a smallpox-contaminated space or the clothes of household members exposed to an aerosol, and infection via contact with a mother's or a household member's smallpox vaccination site. These risks are the same for breastfed and formula-fed infants. No evidence for transmission of the smallpox virus via breast milk exists.

A contact is defined as a person who has been in the same household or had face-to-face contact with a patient with smallpox after the onset of fever. Patients do not transmit infection until after progression from the fever stage to the development of the rash. An exposed contact does not need to be isolated from others during the post-contact observation period (usually 17 days) until the person develops fever. Temperature should be monitored daily in the exposed contact. Personal contact and breastfeeding between mother and infant can continue until the onset of fever, when immediate isolation (at home) should begin. Providing expressed breast milk for the infant of a mother with smallpox should be avoided because of the extensive nature of the smallpox rash and the possibility of contamination (from the rash) of the milk during the expression process. No literature documents transmission of the smallpox virus via expressed breast milk.

The other issue for breastfeeding infants is the question of maternal vaccination with smallpox in a preexposure event vaccination program. Children older than 1 year of age can be safely and reasonably vaccinated with smallpox in the face of a probable smallpox exposure. Smallpox vaccination of infants younger than 1 year of age is contraindicated. Breastfeeding is listed as a contraindication to vaccination in the preevent vaccination program. It is unknown whether vaccine virus or antibodies are present in breast milk. The risk for infection due to contact or aerosolization of virus from a mother's smallpox vaccination site is the same for breastfed and formula-fed infants. The Advisory Committee on Immunization Practices also does not recommend preevent smallpox vaccination of children younger than 18 years old.[443]

A report documents tertiary contact vaccinia in a breastfeeding infant.[140] A United States military person received a primary smallpox vaccination and developed a local reaction at the inoculation site. Despite reportedly observing appropriate precautions, the individual's wife developed vesicles on both areolae (secondary contact vaccinia). Subsequently, the breastfeeding infant developed lesions on her philtrum, cheek, and tongue. Both the mother and infant remained well and the infections resolved without therapy. Culture and PCR testing confirmed vaccinia in both the mother's and the infant's lesions. The breast milk was not tested.[140]

In a review from 1931 to 1981, Sepkowitz[375] reported on 27 cases of secondary vaccinia in households. The CDC reported 30 suspected cases of secondary/tertiary vaccinia with 18 of those cases confirmed by culture or PCR. The 30 cases were related to 578,286 vaccinated military personnel. This is an incidence of 5.2 cases per 100,000 vaccinees and 7.4 cases per 100,000 primary vaccinees.[79] In a separate report on the civilian preevent smallpox vaccination program, 37,802 individuals were vaccinated between January and June 2003, and no cases of contact vaccinia were reported.[77]

The risk for contact vaccinia is low. The risk is from close or intimate contact. In the

above-mentioned case, the risk for the infant was contact with the mother's breasts, the inadvertent site of her contact vaccinia. Breastfed and formula-fed infants are equally at risk from close contact in the household of a smallpox vaccinee or a case of secondary vaccinia, and separation from the individual is appropriate in both situations. If the breast of the nursing mother is not involved, expressed breast milk can be given to the infant.

TT VIRUS

TT virus (TTV) is a recently identified virus found in a patient (TT) with posttransfusion hepatitis not associated with the other hepatitis-related viruses A through G. TTV has been described as an unenveloped, circular, single-stranded DNA virus.[311] This virus is prevalent in healthy individuals, including healthy blood donors, and has been identified in patients with hepatitis. TTV DNA has been detected in infants of TTV-positive and TTV-negative mothers. Ohto et al[310] reported no TTV DNA was detected in cord blood from 38 infants, and it was detected in only 1 of 14 samples taken at 1 month of age. They noted an increasing prevalence from 6 months (22%) to 2 years (33%), which they ascribed to acquisition via nonparenteral routes. In comparisons of the TTV DNA in TTV-positive mothers and their TTV-positive infants, 6 of 13 showed high level nucleotide sequence similarity, and 7 of 13 differed by greater than 10%.[310]

Schröter et al[371] reported on TTV DNA in breast milk examined retrospectively. Notably, TTV DNA was detected in 22 of 23 serum samples of infants at 1 week of age, who were born to 22 women viremic for TTV DNA. Twenty-four women who were negative for TTV DNA gave birth to 24 children who were initially negative for TTV DNA and remained negative throughout the observation period (mean 7.5 months, range 1 to 28 months). TTV DNA was detected in 77% of breast milk samples from TTV viremic women and in none of the breast milk samples from TTV-negative women. No clinical or laboratory evidence of hepatitis was found in the 22 children who were observed to be TTV DNA positive during the period of the study.[371] Other authors have reported TTV in breast milk detected by PCR. They describe the absence of TTV DNA in infants at 5 days and 3 months of age, and 4 of 10 infants were positive for TTV DNA at 6 months of age, suggesting the late acquisition of infection via breastfeeding.[197]

TT virus is transmitted in utero and is found in breast milk. No evidence of clinical hepatitis in infants related to TTV infection and no evidence for a late chronic hepatitis exist. Given the current available information, no reason to proscribe breastfeeding by TTV-positive mothers is compelling. Certainly more needs to be understood concerning the chronic nature of this infection and the possible pathogenesis of liver disease.

TUMOR VIRUS IN BREAST MILK

No documented evidence indicates that women with breast cancer have RNA of tumor virus in their milk. No correlation between RNA-directed DNA polymerase activity has been found in women with a family history of breast cancer. RNA-directed DNA polymerase activity, a reserve transcriptase, is a normal feature of the lactating breast.[91,129,352]

Epidemiologic data conflict with the suggestion that the tumor agent is transmitted through the breast milk. The incidence of breast cancer is low among groups who had nursed their infants, including lower economic groups, foreign-born groups, and those in sparsely populated areas.[262] The frequency of breast cancer in mothers and sisters of a woman with breast cancer is two to three times that expected by chance. This could be genetic or environmental. Cancer actually is equally common on both sides of the family of an affected woman. If breast milk were the cause, it should be transmitted from mother to daughter. When mother-daughter incidence of cancer was studied, no relationship was found to breastfeeding.

Sarkar et al[360] reported that human milk, when incubated with mouse mammary tumor virus, caused degradation of the particular morphology and decreased infectivity and reverse transcriptase activity of the virions. They suggest that the significance of this destructive effect of human milk on mouse mammary tumor virus may account for the difficulty in isolating the putative human mammary tumor agent. Sanner[359] showed that the inhibitory enzymes in milk can be removed by special sedimentation technique. He ascribes the discrepancies in isolating virus particles in human milk to these factors, which inhibit RNA-directed DNA polymerase.

The fear of cancer in breastfed female offspring of a woman with breast cancer does not justify avoiding breastfeeding. Breastfed women have the same breast cancer experience as nonbreastfed women, and no increase is seen in benign tumors. Daughters of breast cancer patients have an increased risk for developing benign and malignant tumors because of their heredity, not because of their breastfeeding history.[280,287]

Unilateral breastfeeding (limited to the right breast) is a custom of Tanka women of the fishing villages of Hong Kong. Ing et al[194] investigated the question, "Does the unsuckled breast have an altered risk for cancer?" They studied breast cancer data from 1958 to 1975. Breast cancer occurred equally in the left and the right breasts.

Comparison of patients who had nursed unilaterally with nulliparous patients and with patients who had borne children but not breastfed indicated a highly significantly increased risk for cancer in the unsuckled breast. The authors conclude that in postmenopausal women who have breastfed unilaterally, the risk for cancer is significantly higher in the unsuckled breast. They thought that breastfeeding may help protect the suckled breast against cancer.[194]

Others[274] have suggested that Tanka women are ethnically a separate people and that left-sided breast cancer may be related to their genetic pool and not to their breastfeeding habits. No mention has been made of other possible influences, such as the impact of their role as "fishermen" or any inherent trauma to the left breast.[274]

In 1926, Lane-Claypon[240] stated that a breast that had never lactated was more liable to become cancerous. Nulliparity and absence of breastfeeding had been considered important risk factors for breast cancer. MacMahon et al[262] reported in 1970 that age at first full-term pregnancy was the compelling factor, and the younger the mother, the less the risk.

In a collective review of the etiologic factors in cancer of the breast in humans, Papaioannou[325] concludes, "Genetic factors, viruses, hormones, psychogenic stress, diet, and other possible factors, probably in that order of importance, contribute to some extent to the development of cancer of the breast."[325]

Wing[449] concluded in her 1977 review on human milk and health that "in view of the complete absence of any studies showing a relationship between breastfeeding and increased risk of breast cancer, the presence of virus-like particles in breast milk should not be a contraindication to breastfeeding." Henderson et al[173] made a similar statement in 1974, whereas Vorherr[432] concluded in 1979 that the roles of pregnancy and lactation in the development and prognosis of breast cancer had not been determined.

Gradually, studies have appeared challenging the dogma. Brinton et al,[52] McTiernan and Thomas,[276] and Layde et al[245] showed the clearly protective effects of breastfeeding. Another example is a study conducted to clarify whether lactation has a protective role against breast cancer in an Asian people, regardless of confounding effects of age at first pregnancy, parity, and closely related factors.[458] In a hospital-based case-control study of 521 women without breast cancer, statistical adjustment for potential confounders and a likelihood ratio test for linear trend were done by unconditional logistic regression. Total months of lactation regardless of parity was the discriminator. Regardless of age of first pregnancy and parity, lactation had an independent protective effect against breast cancer in Japanese women.[458] Although breast cancer incidence is influenced by genetics, stress, hormones, and pregnancy, breastfeeding clearly has a protective effect. "There is a reduction in the risk of breast cancer among premenopausal women who have lactated. No reduction in the risk of breast cancer occurred among postmenopausal women with a history of lactation," according to Newcombe et al,[299] reporting a multicenter study in 1993.

VARICELLA-ZOSTER VIRUS

Varicella-zoster virus infection (varicella/chickenpox, zoster/shingles) is one of the most communicable diseases of humans, in a class with measles and smallpox. Transmission is thought to occur via respiratory droplets and virus from vesicles. Varicella in pregnancy is a rare event, although disease can be more severe with varicella pneumonia, and can be fatal.

Congenital varicella-zoster virus infection occurs infrequently, causing abortion, prematurity, and congenital malformations. A syndrome of malformations has been carefully described with congenital varicella-zoster virus infection, typically involving limb deformity, skin scarring, and nerve damage, including to the eye and brain.[148]

Perinatal infection can lead to severe infection in infants if maternal rash develops 5 days or less before delivery and within 2 days after delivery. Illness in infants usually develops before 10 days of age and is believed to be more severe because of the lack of adequate transfer of antibody from the mother during this period and transplacental spread of virus to the fetus and infant during viremia in the mother. Varicella in a mother occurring before 5 days before delivery allows sufficient formation and transplacental transfer of antibodies to the infant to ameliorate disease even if the infant is infected with varicella-zoster virus. Mothers who develop varicella rash more than 2 days after delivery are less likely to transfer virus to the infant transplacentally; they pose a risk to the infants from postnatal exposure, which can be diminished by the administration of varicella-zoster Ig to the infant. Postnatal transmission is believed to occur through aerosolized virus from skin lesions or the respiratory tract entering the susceptible infant's respiratory tract. Airborne precautions are therefore appropriate in the hospital setting. Infants infected with varicella-zoster virus in utero or in the perinatal period (younger than 1 month of age) are more likely to develop zoster (reactivation of latent varicella-zoster virus) during childhood or as young adults. Table 13-5 summarizes management of varicella in the hospitalized mother or infant.[148]

TABLE 13-5 Guidelines for Preventive Measures After Exposure to Chickenpox in Nursery or Maternity Ward

Type of Exposure or Disease	CHICKENPOX LESIONS PRESENT		Disposition
	Mother	Neonate	
A. Siblings at home have active chickenpox when neonate and mother are ready for discharge from hospital.	No	No	1. Mother: If she has a history of chickenpox, she may return home. Without a history, she should be tested for varicella-zoster virus antibody titer.* If test is positive, she may return home. If test is positive, she may return home. If test is negative, varicella-zoster Ig† is administered and she is discharged home. 2. Neonate: May be discharged home with mother if mother has history of varicella or is varicella-zoster virus-antibody positive. If mother is susceptible, administer varicella-zoster Ig to infant and discharge home or place in protective isolation.
B. Mother has no history of chickenpox; exposed during period 6-20 days antepartum.‡	No	No	1. Exposed mother and infant: Send home at earliest date unless siblings at home have communicable chickenpox.§ If so, may administer varicella-zoster Ig and discharge home, as above. 2. Other mothers and infants: No special management indicated. 3. Hospital personnel: No precautions indicated if there is a history of previous chickenpox or zoster. In absence of history, immediate serologic testing is indicated to determine immune status.* Nonimmune personnel should be excluded from patient contact until 21 days after an exposure. 4. If mother develops varicella 1 to 2 days postpartum, infant should be given varicella-zoster Ig.
C. Onset of maternal chickenpox occurs antepartum‡ or postpartum.	Yes	No	1. Infected mother: Isolate until no longer clinically infectious. If seriously ill, treat with acyclovir.¶ 2. Infected mother's infant: Administer varicella-zoster Ig† to neonates born to mothers with onset of chickenpox less than 5 days before delivery and isolate separately from mother. Send home with mother if no lesions develop by the time mother is noninfectious. 3. Other mothers and infants: Send home at earliest date. varicella-zoster Ig may be given to exposed neonates. 4. Hospital personnel: Same as B-3.
D. Onset of maternal chickenpox occurs antepartum.§			1. Mother: Isolation unnecessary. 2. Infant: Isolate from other infants but not from mother. 3. Other mothers and infants: Same as C-3 (if exposed). 4. Hospital personnel: Same as B-3 (if exposed).
E. Congenital chickenpox	No	Yes	1. Infected infant and mother: Same as D-1 and D-2. 2. Other mothers and infants: Same as C-3. 3. Hospital personnel: Same as B-3.

From Gershon AA: Chickenpox, measles and mumps. In Remington JS, Klein JO, editors: *Infectious Diseases of the Fetus and Newborn Infant, ed 4,* Philadelphia, 1995, WB Saunders.

*Send serum to virus diagnostic laboratory for determination of antibodies to varicella-zoster virus by a sensitive technique (e.g., FAMA, LA, ELISA). Personnel may continue to work for 8 days after exposure pending serologic results because they are not potentially infectious during this period. Antibodies to varicella-zoster virus greater than 1:4 probably are indicative of immunity.

†Varicella-zoster Ig is available as VariZIG under an investigational new drug (IND) application from the Food and Drug Administration. It is obtainable through FFF Enterprises at 800-843-7477. The dose for a newborn is 1.25 mL (1 vial). The dose for a pregnant woman is conventionally 6.25 mL (5 vials).

‡If exposure occurred less than 6 days antepartum, mother would not be potentially infectious until at least 72 hours postpartum.

§Considered noninfectious when no new vesicles have appeared for 72 hours and all lesions have crusted.

¶Dosage of acyclovir for pregnant woman is 30 mg/kg/day; for seriously ill infant with varicella, 750 to 1500 mg/m^2/day.

ELISA, Enzyme-linked immunosorbent assay; *FAMA,* fluorescent antibody to membrane antigen; *LA,* latex agglutination.

Postnatal varicella from nonmaternal exposure can occur but is generally mild when it develops after 3 weeks of age or when a mother has passed on antibodies against varicella-zoster virus via the placenta. Severe postnatal varicella does occur in premature infants or infants of varicella-susceptible mothers. When a mother's immune status relative to varicella-zoster virus is uncertain and measurement of antibodies to varicella-zoster virus in mother or infant cannot be performed promptly (less than 72 hours), administration of VZIG[81] or IVIG to the infant exposed to varicella or zoster in the postnatal period is indicated. Ideally a mother's varicella status should be known before pregnancy, when varicella virus vaccine could be given if indicated.

Varicella-zoster virus virus has not been cultured from milk, but varicella-zoster virus DNA has been identified in breast milk.[459] Antibody against varicella-zoster virus has also been found in breast milk.[270] Breast milk from mothers who had received the varicella vaccine in the postpartum period was tested for varicella-zoster virus DNA. Varicella DNA was not detected in any of the 217 breast milk samples from the 12 women, all of whom seroconverted after vaccination.[45] One case of suspected transfer of varicella-zoster virus to an infant via breastfeeding has been reported, but virus may have been transmitted by respiratory droplet or exposure to rash before the mother began antiviral therapy.[459]

Isolation of an infant from the mother with varicella and interruption of breastfeeding should occur only while the mother remains clinically infectious, regardless of the method of feeding. As soon as the infant has received varicella-zoster Ig, expressed breast milk can be given to an infant if no skin lesions involve the breasts. Persons with varicella rash are considered noninfectious when no new vesicles have appeared for 72 hours and all lesions have crusted, usually in 6 to 10 days. Immunocompetent mothers who develop zoster can continue to breastfeed if the lesions do not involve the breast and can be covered because antibodies against varicella-zoster virus are provided to the infant via the placenta and breast milk and will diminish the severity of disease, even if not preventing it. Conservative management in this scenario would include giving an infant varicella-zoster Ig as well (see Table 13-5).

WEST NILE VIRUS

West Nile virus disease in the United States is one of the best examples of an emerging infectious disease taking on new importance in public awareness about health issues. In 2003 9136 human cases of West Nile infection were reported to the CDC (through 2/11/2004). Cases were reported from 45 states, including 6256 cases (68%) of West Nile fever (milder cases), 2718 cases (30%) of West Nile meningoencephalitis, and 228 deaths related to West Nile disease.[80] West Nile virus is endemic in Israel and parts of Africa. Outbreaks have been reported from Romania (1996), Russia (1999), Israel (2000), and Canada (2002) as well as the United States (1999 to 2003).[331]

It is estimated that 150 to 300 asymptomatic cases of West Nile infection occur for every 20 febrile illnesses and for every one case of meningoencephalitis associated with West Nile virus. West Nile fever is usually a mild illness of 3 to 6 days' duration. The symptoms are relatively nonspecific, including malaise, nausea, vomiting, headache, myalgia, lymphadenopathy, and rash. West Nile disease is characterized by severe neurologic symptoms (e.g., meningitis, encephalitis, or acute flaccid paralysis, and occasionally optic neuritis, cranial nerve abnormalities, and seizures). Children are infrequently sick with West Nile virus infection and infants younger than 1 year of age have rarely been reported.[331] The case-fatality rate for 2003 in the United States was approximately 2.5%, but has been reported as high as 4% to 18% in hospitalized patients. The case-fatality rate for persons older than 70 years of age is considered to be higher, 15% to 29% among hospitalized patients in outbreaks in Romania and Israel.[331]

The primary mechanism of transmission is via a mosquito bite. Mosquitoes from the genus *Culex* are primary vectors. The bird-mosquito-bird cycle serves to maintain and amplify the virus in the environment. Humans and horses are incidental hosts. The pathogenesis of the infection is believed to occur via replication of the virus in the skin and lymph nodes, leading to a primary viremia that seeds secondary sites before a second viremia causes the infection of the CNS and other affected organs.[59,111] Transmission has been reported in rare instances during pregnancy[7,73] via organ transplant[199] and percutaneously in laboratory workers.[75]

A study of West Nile virus infection in pregnancy documented four miscarriages, two elective abortions, and 72 live births. Cord blood samples were tested in 55 infants and 54 of 55 were negative for anti-West Nile virus IgM. Three infants had West Nile virus infection, which could have been acquired congenitally. Three of 7 infants who had congenital malformations might have been caused by maternal West Nile virus infection based on timing in pregnancy, but no evidence of West Nile virus etiology is conclusive.[312] West Nile virus transmission occurs via blood and blood product transfusion,[186] and the incidence has been estimated to be as high as 21 per 10,000 donations during epidemics in specific cities.[40] No evidence

of direct person-to-person transmission without the mosquito vector has been found.

One case of possible West Nile virus transmission via breastfeeding has been documented.[74] The mother acquired the virus via packed RBC transfusions after delivery. The second unit of blood she received was associated with other blood products from the same donation causing West Nile infection in another transfusion recipient. Eight days later the mother had a severe headache and was hospitalized with fever and a CSF pleocytosis on day 12 after delivery. The mother's CSF was positive for West Nile virus-specific IgM antibody. The infant had been breastfed from birth through the second day of hospitalization of the mother. Samples of breast milk were West Nile virus–specific IgG and IgM positive on day 16 after delivery and West Nile virus-specific IgM positive on day 24. The same milk was West Nile virus RNA positive by PCR testing on day 16, but not on day 24 after delivery. The infant tested positive for West Nile virus-specific IgM in serum at day 25 of age, but remained well without fever. No clear-cut exposure to mosquitoes for the infant were reported. The cord blood and placenta were not available to be tested. IgM antibodies can be found in low concentrations in breast milk, but this is not common or as efficient as the transfer of IgA, secretory IgA, or IgG into breast milk.

A review of West Nile virus illness during the breastfeeding identified six occurrences of breastfeeding during maternal West Nile virus illness.[177] Five of the six infants had no illness or detectable antibodies to West Nile virus in their blood. One infant developed a rash and was otherwise well after maternal West Nile virus illness, but was not tested for West Nile virus infection. Two infants were identified who developed West Nile virus illness while breastfeeding, but no preceding West Nile virus infection was demonstrated in their mothers. Two other breastfeeding infants developed West Nile virus-specific antibodies after their mothers acquired West Nile virus illness in the last week of pregnancy, but congenital infection could not be ruled out. Live virus was not cultured from 45 samples of breast milk from mothers infected with West Nile virus during pregnancy, but West Nile virus RNA was detected in two samples and 14 samples had IgM antibodies to West Nile virus.[177]

The above data suggest that West Nile virus infection through breastfeeding is rare. To date evidence of significant disease due to West Nile virus infection in young breastfeeding children is lacking. At this time, no reason exists to proscribe breastfeeding in the case of maternal West Nile virus infection if a mother is well enough to breastfeed. As with many other maternal viral illnesses, by the time the diagnosis is made in a mother, the infant may have already been exposed during maternal viremia and possible virolactia. The infant can and should continue to receive breast milk for the potential specific and nonspecific antiviral immunologic benefits.

YELLOW FEVER VIRUS

Yellow fever virus is a flavivirus which is transmitted to humans by infected *Aedes* and *Haemogogus* mosquitos in tropical areas of South America and Africa. Large outbreaks occur when mosquitos in a populated area become infected from biting viremic humans infected with yellow fever virus. Transmission from the mosquitos to other humans occurs after an incubation period in the mosquito of 8 days. Direct person-to-person spread has not been reported. Illness due to yellow fever virus usually begins after an incubation period of 3 to 6 days, with acute onset of headache, fever, chills, and myalgia. Photophobia, back pain, anorexia, vomiting, and restlessness are other common symptoms. The individual is usually viremic for the first 4 days of illness until the fever and other symptoms diminish. Liver dysfunction and even failure can develop as can myocardial dysfunction. CNS infection is uncommon but symptoms can include seizures and coma. Medical care should include intensive supportive care and fluid management.

One case of congenital infection after immunization of a pregnant woman with the attenuated vaccine strain has been reported. One of 41 infants whose mothers had inadvertently received the yellow fever virus vaccine during pregnancy developed IgM and elevated neutralizing antibodies against the yellow fever virus without any evidence of illness or abnormalities.[418] A more recent study[404] from Brazil examined inadvertent yellow fever virus immunization during pregnancy during a mass vaccination campaign in 2000; 480 pregnant women received the yellow fever virus at a mean of 5.7 weeks' gestation, the majority of whom did not know their pregnancy status at the time. Seroconversion occurred in 98.2% of the women after at least 6 weeks after vaccination. Mild postvaccination illness (headache, fever, or myalgia) was reported by 19.6% of the 480 women. The frequency of malformations, miscarriages, stillbirths, and premature deliveries was similar to that found in the general population. At the 12-month follow-up point, 7% of the infants still demonstrated neutralizing antibodies against yellow fever virus, but after 12 months only one child was still seropositive.[404]

Transmission of the yellow fever vaccine virus through breastfeeding was recently reported from Brazil.[85] The mother was immunized during a yellow

fever epidemic in a nonendemic area in Brazil; 15 days after delivering a healthy female infant (39 weeks' gestational age) the mother received the 17DD yellow fever vaccine, and 5 days later the mother reported headache, malaise, and low-grade fever that persisted for 2 days. The mother continued breastfeeding and did not seek medical care for herself. At 23 days of age the infant became irritable, developed fever, and refused to nurse. The infant developed seizures and subsequent evaluation of the infant demonstrated an abnormal CSF and CT of the brain showed bilateral areas of diffuse low density suggestive of inflammation and consistent with encephalitis. Yellow fever-specific IgM antibodies were identified in the infant's serum and CSF. Reverse-transcriptase polymerase chain reaction (RT-PCR) testing of the CSF also demonstrated yellow fever virus RNA identical to the 17DD yellow fever vaccine virus. Breast milk and maternal serum were not tested for yellow fever virus.[85]

Yellow fever virus, wild or vaccine type, has not been identified in human breast milk, although another flavivirus, West Nile virus, has been detected in milk from a few lactating women with West Nile virus infection.[177] (See the section on West Nile virus.) Yellow fever vaccine–associated neurologic disease occurs at different rates in different age-groups, including 0.5 to 4.0 cases per 1000 infants younger than 6 months of age.[285] The 17D-derived yellow fever vaccines are contraindicated in infants younger than 6 months of age. Since 2002, the Advisory Committee on Immunization Practices has recommended, based on theoretical risk, that yellow fever vaccine be avoided in nursing mothers, except when exposure in high-risk yellow fever endemic areas is likely to occur.[76] No case of transmission of yellow fever virus from an infected mother to her infant via breastfeeding or breast milk has been reported. Published information on the severity of yellow fever virus infection in infants younger than 1 year of age, potential protection from passively acquired antibodies, or protection from breast milk is limited. No information on a differential risk in breastfed versus formula-fed infants is available. Given the well documented method of transmission of yellow fever virus via mosquitos, and the lack of evidence of transmission via breast milk, it makes more sense to protect all infants against mosquito bites than to proscribe breastfeeding, even in the mother infected with yellow fever virus. Continued breastfeeding or use of expressed breast milk will depend on a mother's health status and ability to maintain the milk supply while acutely ill. If another source of feeding is readily available then temporarily discarding expressed breast milk for at least 4 days of acute illness in the mother is a reasonable precaution.

SPIROCHETES

Lyme disease

Lyme disease, as with other human illnesses caused by spirochetes, especially syphilis, is characterized by a protean course and distinct phases (stages) of disease. Lyme borreliosis was described in Europe in the early twentieth century. Since the 1970s, tremendous recognition, description, and investigation of Lyme disease have occurred in the United States and Europe. Public concern surrounding this illness is dramatic.

Lyme disease is a multisystem disease characterized by involvement of the skin, heart, joints, and nervous system (peripheral and central). Stages of disease are identified as early localized (erythema migrans, often accompanied by arthralgia, neck stiffness, fever, malaise, and headache), early disseminated (multiple erythema migrans lesions, cranial nerve palsies, meningitis, conjunctivitis, arthralgia, myalgia, headache, fatigue, and, rarely, myocarditis), and late disease (recurrent arthritis, encephalopathy, and neuropathy). The varied manifestations of disease may relate to the degree of spirochetemia, the extent of dissemination to specific tissues, and the host's immunologic response.

The diagnosis of Lyme disease is often difficult in part because of the broad spectrum of presentations, inapparent exposure to the tick, and the lack of adequately standardized serologic tests. Culture of the spirochete, *Borrelia burgdorferi,* is not readily available. Enzyme-linked immunosorbent assay (ELISA), immunofluorescent assay, and immunoblot assay are the usual tests. PCR detection of spirochetal DNA requires additional testing in clinical situations to clarify and standardize its utility.

Gardner[142] reviewed infection during pregnancy, summarizing a total of 46 adverse outcomes from 161 cases reported in the literature. The adverse outcomes included miscarriage and stillbirth (11% of cases), perinatal death (3%), congenital anomalies (15%), and both early- and late-onset progressive infection in the infants. Silver[384] reviewed 11 published reports and concluded that Lyme disease during pregnancy is uncommon, even in endemic areas. Although the spirochete can be transmitted transplacentally, a significant immune response in the fetus is often lacking, and the association of Lyme infection with congenital abnormalities is weak.[401,448]

Little published information exists on whether *B. burgdorferi* can be transmitted via breast milk. One report showed the detection of *B. burgdorferi* DNA by PCR in the breast milk of two lactating women with untreated erythema migrans, but no evidence of Lyme disease or transmission of the spirochete in the one infant followed for 1 year.[369] No attempt to culture the spirochete was made, so it is not possible to determine if the detectable DNA was from

viable spirochetes or noninfectious fragments. In that same study of 56 women with untreated erythema migrans who had detectable *B. burgdorferi* DNA in the urine, 32 still had detectable DNA in the urine 15 to 30 days after starting treatment, but none had it 6 months after initiating therapy. Ziska et al[466] reported on the management of nine cases of Lyme disease in women associated with pregnancy; seven of the nine women were symptomatic at conception and six received antibiotics throughout pregnancy. Follow-up of the infants showed no transmission of Lyme disease, even in the seven infants who had been breastfed.[466]

The lack of adequate information on transmission of *B. burgdorferi* via breast milk cannot be taken as proof that it is not occurring. If one extrapolates from data on syphilis and the *Treponema pallidum* spirochete, it would be prudent to discuss the lack of information on the transmission of *B. burgdorferi* via breast milk with the mother or parents and to consider withholding breast milk at least until therapy for Lyme disease has begun or been completed. If the infection occurred during pregnancy and treatment has already been completed, an infant can breastfeed. If infection occurs postpartum or the diagnosis is made postpartum, infant exposure may have already occurred. Again, discussion with the mother or parents about withholding versus continuing breastfeeding is appropriate.

After prenatal or postnatal exposure, an infant should be closely observed and empiric therapy considered if the infant develops a rash or symptoms suggestive of Lyme borreliosis. Treatment of mother and infant with ceftriaxone, penicillin, or amoxicillin is acceptable during breastfeeding relative to the infant's exposure to these medications. Doxycycline should not be administered for more than 14 days while continuing breastfeeding because of possible dental staining in the neonate. Continued surveillance for viable organisms in breast milk and evidence of transmission through breastfeeding is recommended.

A large body of information is available on various "Lyme vaccines" used in dogs, but these vaccines are only partially protective and must be repeated yearly. Preliminary information suggests that a vaccine for use in humans safely produces good serologic responses, but protective efficacy has not been demonstrated, and no information exists on its use during pregnancy or breastfeeding.

Syphilis

Syphilis is the classic example of a spirochetal infection that causes multisystem disease in various stages. Both acquired syphilis and congenital syphilis are well-described entities. Acquired syphilis is almost always transmitted through direct sexual contact with open lesions of the skin or mucous membranes of individuals infected with the spirochete, *Treponema pallidum*. Congenital syphilis occurs by infection across the placenta (placentitis) at any time during the pregnancy or by contact with the spirochete during passage through the birth canal. Any stage of disease (primary, secondary, tertiary) in a mother can lead to infection of the fetus, but transmission in association with secondary syphilis approaches 100%. Infection with primary syphilis during pregnancy, without treatment, leads to spontaneous abortion, stillbirth, or perinatal death in 40% of cases. Similar to acquired syphilis, congenital syphilis manifests with moist lesions or secretions from rhinitis (snuffles), condylomata lata, or bullous lesions. These lesions and secretions contain numerous spirochetes and are therefore highly infectious.

Postnatal infection of an infant can occur through contact with open, moist lesions of the skin or mucous membranes of the mother or other infected individuals. If the mother or infant has potentially infectious lesions, isolation from each other and from other infants and mothers is recommended. If lesions are on the breasts or nipples, breastfeeding or using expressed milk is contraindicated until treatment is complete and the lesions have cleared. Spirochetes are rarely identified in open lesions after more than 24 hours of appropriate treatment. Penicillin remains the best therapy.

Evaluation of an infant with suspected syphilis should be based on the mother's clinical and serologic status, history of adequate therapy in the mother, and the infant's clinical status. Histologic examination of the placenta and umbilical cord, serologic testing of the infant's blood and CSF, complete analysis of the CSF, long bone and chest radiographs, liver function tests, and a complete blood cell count are all appropriate given the specific clinical situation. Treatment of the infant should follow recommended protocols for suspected, probable, or proven syphilitic infection.[96]

No evidence indicates transmission of syphilis via breast milk in the absence of a breast or nipple lesion. When a mother has no suspicious breast lesions, breastfeeding is acceptable as long as appropriate therapy for suspected or proven syphilis is begun in the mother and infant.

PARASITES

Giardia lamblia

Giardiasis is a localized infection limited to the intestinal tract, causing diarrhea and malabsorption. Immunocompetent individuals show no evidence of invasive infection, and no evidence exists that documents fetal infection from maternal infection during pregnancy. Giardiasis is rare in children

younger than 6 months of age, although neonatal infection from fecal contamination at birth has been described.[22] Human milk has an in vivo protective effect against *Giardia lamblia* infection, as documented by work from central Africa, where the end of breastfeeding heralds the onset of *Giardia* infection.[145] This has been reaffirmed in undeveloped countries around the world.

The protective effect of breast milk has been identified in the milk of noninfected donors.[151] The antiparasitic effect does not result from specific antibodies but rather from lipase enzymatic activity. The lipase acts in the presence of bile salts to destroy the trophozoites as they emerge from their cysts in the GI tract. Hernell et al[175] demonstrated that free fatty acids have a marked giardiacidal effect, which supports the conclusion that lipase activity releasing fatty acids is responsible for killing *G. lamblia.*

G. lamblia have also been reported to appear in the mother's milk, and the parasite has been transmitted to newborns via that route. The exact relationship of breastfeeding to transmission of *G. lamblia* and the effect on infants continue to be studied, even though symptomatic infection in breastfed infants is rare.[151] One report from the Middle East suggests that even partial breastfeeding is protective against infection with intestinal parasites, including *Cryptosporidium* and *Giardia lamblia.*[41]

Breastfeeding by mothers with giardiasis is problematic mainly because of the medications used for therapy. Metronidazole's safety in infants has not been established, and little information is available on quinacrine hydrochloride and furazolidone in breast milk. Paromomycin, a nonabsorbable aminoglycoside, is a reasonable alternative recommended for treatment of pregnant women. Breastfeeding by a mother with symptomatic giardiasis is acceptable when consideration is given to the presence of the therapeutic agents in the breast milk.

Hookworm Infection

Hookworm infection, most often caused by *Ancylostoma duodenale* and *Necator americanus,* is common in children younger than the age of 4 years, and there is at least one report on infantile hookworm disease from China.[374] This publication from the Chinese literature reports hundreds of cases of infantile hookworm disease that include the common symptoms of bloody stools, melena, anorexia, listlessness, and edema. Anemia, eosinophilia and even leukemoid reactions occur as part of the clinical pictures in young children. They also note at least 20 cases of hookworm diseases in newborn infants younger than 1 month of age. In the discussion of infantile hookworm infection, they note four routes of infection: direct contact with contaminated soil, "sand-stuffed" diapers, contaminated "washed/wet" diapers, and vertical equal to transmammary transmission or transplacental transmission. They postulated that infection of infants before 40 to 50 days of age would most likely be due to transplacental transmission and infection before environmental contact would most likely be due to transmammary transmission. Ample evidence is available in veterinary medicine of transmammary spread of helminths.[302,382] At least two reports suggest the possibility of transmammary transmission of hookworms in humans. Setasuban et al[376] described the prevalence of *Necator americanus* in 128 nursing mothers as 61% and identified *N. americanus* in breast milk in one case. Nwosu[303] documented positive stool samples for hookworms in 33 of 316 neonates (10%) at 4 to 5 weeks of age in southern Nigeria. The majority of neonatal infections were due to *Ancylostoma duodenale* although *Necator americanus* is more prevalent in that area of Nigeria. Examination of colostral milk did not demonstrate any hookworm larvae.[303]

Additional epidemiologic work is necessary to determine the potential significance of transmammary spread of helminths in humans, and more careful examination of breast milk as a source of hookworm infection is required before reasonable recommendation are possible.

Malaria

Malaria is recognized as a major health problem in many countries. The effect of malaria infection on pregnant and lactating women and thus on the developing fetus, neonate, and growing infant can be significant. The four species of malaria, *Plasmodium vivax, P. ovale, P. malariae,* and *P. falciparum,* vary in the specific aspects of the disease they produce. *P. vivax* exists throughout the world, but *P. falciparum* predominates in the tropics and is most problematic in its chloroquine-resistant form. Malaria in the United States is most often seen in individuals traveling from areas where malaria is endemic. The parasite can exist in the blood for weeks, and infection with *P. vivax* and *P. malariae* can lead to relapses years later. Transmission occurs through the bite of the anopheline mosquito and can occur via transfusion of blood products and transplacentally.

Congenital malaria is rare but seems to occur more often with *P. vivax* and *P. falciparum.* It usually presents in the first 7 days of life (range 1 day to 2 months). It may resemble neonatal sepsis, with fever, anemia, and splenomegaly occurring in the most neonates and hyperbilirubinemia and hepatomegaly in less than half.

Malaria in infants younger than 3 months of age generally manifests with less severe disease and death than in older children. Possible explanations include the effect of less exposure to mosquitoes,

passive antibody acquired from the mother, and the high level of fetal hemoglobin in infants at this age.[22] The variations in the infection rates in children younger 3 months of age during the wet and dry seasons support the idea that postnatal infection is more common than congenital infection. No evidence indicates that malaria is transmitted through breast milk. The greatest risk to infants is exposure to the anopheline mosquito infected with malaria.

The main issues relative to malaria and breastfeeding are how to protect both mothers and infants effectively from mosquitoes and what drugs for treating malaria in mothers are appropriate during lactation. Protection from mosquito bites includes screened-in living areas, mosquito nets while sleeping, protective clothing with or without repellents on the clothes, and community efforts to eradicate the mosquitoes. Chloroquine, quinine, and tetracycline are acceptable during breastfeeding. Sulfonamides should be avoided in the first month of an infant's life, but pyrimethamine-sulfadoxine (Fansidar) can be used later.

Mefloquine is not approved for infants or pregnant women. However, the milk/plasma ratio for mefloquine is less than 0.25, there is a large volume of distribution of the drug, high protein binding of the drug limits its presence in breast milk, and the relative importance of breastfeeding in areas where malaria is prevalent shifts the risk/benefit ratio in favor of treatment with mefloquine. The single dose recommended for treatment or the once-weekly dose for prevention allows for continued breastfeeding with discarding of the milk for short periods after a dose (1 to 6 hours). Maternal plasma levels of primaquine range from 53 to 107 ng/mL, but no information is available on levels in human milk. Primaquine is used in children, and once daily dosing in the mother would allow discarding milk with peak levels of drug. Therefore breastfeeding during maternal malaria even with treatment is appropriate with specific medications.

Strongyloides

Strongyloides stercoralis is a nematode (roundworm). Most infections are asymptomatic, but clinically significant infection in humans can include larval skin invasion, tissue migration, intestinal invasion with abdominal pain and GI symptoms, and a Loeffler-like syndrome due to migration to the lungs. Immune-compromised individuals can develop dissemination of larvae systemically, causing various clinical symptoms. Humans are the principal hosts, but other mammals can serve as reservoirs. Infection via the skin by filariform larvae is the most common form of transmission; ingestion is an uncommon occurrence. Transmammary transmission of *Strongyloides* species has been described in dogs, ewes, and rats.[211,302,382] Only one report of transmammary passage of *Strongyloides* larvae in humans is available. In 76 infants younger than 200 days of age, 34% demonstrated the presence of *Strongyloides fuelleborni* on stool examination. The clinical significance of this was not elucidated. Strongyloides larvae was identified in only one sample of milk from 25 nursing mothers.[53]

In the absence of an understanding of the clinical significance of *Strongyloides* in the stools of young infants, given the lack of exclusion of the most common mechanism of transmission (through the skin) in the single report and the apparent infrequent evidence of these larvae in human milk, it is difficult to make any recommendations concerning breastfeeding and *Strongyloides*.

Toxoplasmosis

Toxoplasmosis is one of the most common infections of humans throughout the world. The infective organism, *Toxoplasma gondii,* is ubiquitous in nature. The prevalence of positive serologic test titers increases with age, indicating past exposure and infection. The cat is the definitive host, although infection occurs in most species of warm-blooded animals.

Postnatal infection with toxoplasmosis is usually asymptomatic. Symptomatic infection typically manifests with nonspecific symptoms, including fever, malaise, myalgia, sore throat, lymphadenopathy, rash, hepatosplenomegaly, and occasionally a mononucleosis-like illness. The illness usually resolves without treatment or significant complications.

Congenital infection or infection in an immunodeficient individual can be persistent and severe, causing significant morbidity and even death. Although most infants with congenital infection are asymptomatic at birth, visual abnormalities, learning disabilities, and mental retardation can occur months or years later. The syndrome of congenital toxoplasmosis is clearly defined, with the most severe manifestations involving the CNS, including hydrocephalus, cerebral calcifications, microcephaly, chorioretinitis, seizures, or simply isolated ocular involvement. The risk for fetal infection is related to the timing of primary maternal infection, although transmission can occur with preexisting maternal toxoplasmosis.[241] In the last months of pregnancy the protozoan is more readily transmitted to the fetus, but the infection is more likely to be subclinical. Early in pregnancy the transmission to a fetus occurs less frequently but does result in severe disease. Treatment of documented congenital infection is currently recommended, although duration and optimal regimen have not been determined, and reversal of preexisting sequelae generally does not occur.[343]

Prevention of infection in susceptible pregnant women is possible by avoiding exposure to cat feces or the organism in the soil. Pregnant or lactating women should not change cat litter boxes, but if they must, it should be done daily and while wearing gloves. The oocyst is not infective for the first 24 to 48 hours after passage. Mothers can avoid ingestion of the organism by fully cooking meats and carefully washing fruits, vegetables, and food preparation surfaces.[94]

In various animal models, *T. gondii* has been transmitted through the milk to the suckling young. The organism has been isolated from colostrum as well. The newborn animals became asymptomatically infected when nursed by an infected mother whose colostrum contained *T. gondii*. Only one report has identified *T. gondii* in human milk, and some question surrounds the reliability of that report.[241] Transmission during breastfeeding in humans has not been demonstrated. Breast milk may contain appropriate antibodies against *T. gondii*. Given the benign nature of postnatal infection, the absence of documented transmission in human breast milk, and the potential antibodies in breast milk, no reason exists to proscribe breastfeeding by a mother known to be infected with toxoplasmosis.

Trichomonas vaginalis

Trichomonas vaginalis is a flagellated protozoan that can produce vaginitis (see Chapter 16 for a discussion of vaginitis) but frequently causes asymptomatic infection in both men and women. The parasite is found in 10% to 25% of women in the childbearing years. It is transmitted predominantly by sexual intercourse, but it can be transmitted to the neonate by passage through the birth canal. This parasite often coexists with other STDs, especially gonorrhea.

Infection during pregnancy or while taking oral contraceptives is more difficult to treat. Some evidence suggests that infection with and growth of the parasite are enhanced by estrogens or their effect on the vaginal epithelium. No evidence indicates adverse effects on the fetus in association with maternal infection during pregnancy. Occasionally female newborns have vaginal discharge during the first weeks of life caused by *T. vaginalis*. This is thought to be influenced by the effect of maternal estrogen on the infant's vaginal epithelium and acquisition of the organism during passage through the birth canal. The organism does not seem to cause significant disease in a healthy infant. No documentation exists on transmission of *T. vaginalis* via breast milk.

The difficulty encountered with maternal infection during lactation stems from metronidazole (Flagyl), the drug of choice, being contraindicated for infants. Case reports describe treatment of neonates with metronidazole without adverse effect. Although topical agents containing povidone-iodine (Betadine) or sodium lauryl sulfate (Trichotine) can be effective when given as douches, creams, or suppositories, metronidazole remains the treatment of choice. The AAP advises using metronidazole only with a physician's discretion and considers its effect on a nursing infant unknown but possibly a concern. The potential concerns are metronidazole's disulfiram-like effect in association with alcohol, tumorigenicity in animal studies, and leukopenia and neurologic side effects described in adults. On the other hand, metronidazole is given to children beyond the neonatal period to treat serious infections with various other parasites, such as *Entamoeba histolytica*.

The current recommendation for lactating women is to try local treatment first, and if these fail, then to try metronidazole. A 2-g single-dose treatment produces peak levels after 1 hour, and discarding expressed breast milk for the next 12 to 24 hours is recommended. If this treatment also fails, a 1-g twice-daily regimen for 7 days or a 2-g single daily dose for 3 to 5 days is recommended, with discarding of breast milk close to the dose and timing of feedings distant from the dose. Infants who exclusively breastfeed are presumed at greater risk from exposure to metronidazole than those who are only partially breastfed.

Candida *Infections*

Candida consists of multiple species. The most common species affecting humans include *C. albicans* as the dominant agent and *C. tropicalis*, *C. krusei*, and *C. parapsilosis*, as well as many other uncommon species. In general, *Candida* exists as a commensal organism colonizing the oropharynx, GI tract, vagina, and skin without causing disease until some change disrupts the balance between the organism and the host. Mild mucocutaneous infection is the most common illness, which can lead to vulvovaginitis, mastitis, or, uncommonly, oral mucositis in a mother, and thrush (oral candidiasis) and candidal diaper rash in an infant.

Invasive candidal infection occurs infrequently, usually when a person has other illness, impaired resistance to infection (HIV, diabetes mellitus, neutropenia; decreased cell-mediated immunity in premature infants or LBW or VLBW infants), or disrupted normal mucosal and skin barriers and has received antibiotics or corticosteroids. Invasive disease can occur through local spread, and may occur more often in the genitourinary tract (urethra, bladder, ureters, kidneys), but usually develops in association with candidemia. The bladder and kidney

are more frequently involved, but when dissemination occurs via candidemia, a careful search for other sites of infection should be made (e.g., retina, liver, spleen, lung, meninges).[279]

Transmission usually occurs from healthy individuals colonized with *Candida* through direct contact with them or through contact with their oral or vaginal secretions. Intrauterine infection can occur through ascending infection through the birth canal but is rare. No distinct syndrome of congenital candidal infection exists. Most often an infant is infected in passing through the birth canal and remains colonized. Postnatal transmission can occur through direct contact with caregivers.

The mother and infant serve as an immediate source of recolonization for each other, especially during the direct contact of breastfeeding. For this reason, an infant and breastfeeding mother should be treated simultaneously when treating thrush, vulvovaginitis, diaper candidiasis, or mastitis. Colonization with this organism usually occurs in the absence of any clinical evidence of infection. Simultaneous treatment should occur even in the absence of any clinical evidence of *Candida* infection or colonization in the apparently uninvolved individual of the breastfeeding dyad.

No well-controlled clinical trials define the most appropriate or most effective method(s) of treatment for candidal infection in breastfeeding mother-infant pairs. The list of possible treatment products is extensive and includes many anecdotal and empirical regimens. In the face of this absence of data, Brent[51] conducted a survey of members of The Academy of Breastfeeding Medicine concerning the respondents' approach to diagnosis and treatment of thrush in the breastfeeding dyad. Most of the respondents relied on the history and physical examination of the infant, but only a third rated the examination of the mother as very important in making a diagnosis. Only 7% reported using laboratory testing to make the diagnosis. Twenty-one percent of the respondents reported using only oral nystatin for the infant when the mother was asymptomatic. Almost half treated the infant and the mother with topical nystatin, and 13% used oral nystatin for the infant and oral fluconazole for the mother when the mother had breast pain. Less than 5% used oral fluconazole for both infant and mother, and other therapies were used by about 15% of the respondents. For recurrence of persistence of the thrush, more respondents reported treating the mother or both the infant and mother with fluconazole, and almost a quarter reported using other therapies.

Considerable discussion of mammary candidosis/candidiasis, the clinical diagnosis of candidal involvement of the breast, the significance of pain with breastfeeding, and the presence or absence of *Candida albicans* in milk samples is ongoing.[14,133,166] This topic will continue to be debated because additional prospective studies are necessary to clarify specific issues. Data are inadequate to make specific recommendations about various clinical situations regarding candida and breastfeeding. Clinical practice will vary with experience, especially for the more problematic clinical situations. Some general guidelines follow. (See Chapter 16 for a discussion of mastitis.)

The treatment of mucocutaneous candidiasis should probably begin with a topical agent, such as nystatin, clotrimazole, miconazole, econazole, butaconazole, terconazole, or ciclopirox. Treatment should continue for at least 2 weeks, even with obvious improvement in 1 or 2 days. Failures most often result from inadequate therapy involving the frequency of application, careful washing and drying before application, or, in the case of diaper candidiasis, decreasing the contact of the skin with moisture. Nystatin oral suspension is less effective for the treatment of oral candidiasis in infants, now compared with the past, supposedly due to increasing resistance.[154] Gentian violet (diluted to 0.25% to 1.0%) applied to the breast or painted onto an infant's mouth is being recommended more frequently. Other topical preparations have been recommended for the mother's breast including mupirocin, grapefruit seed extract, or mixtures of mupirocin, betamethasone ointments, and miconazole powder. Controlled clinical trials for efficacy and toxicity are not available.

When good adherence to the proposed regimen with topical agents fails, or when infant or mother are severely affected by pain and decreased breastfeeding, systemic therapy is appropriate. Fluconazole and ketoconazole are the most commonly used systemic agents for oral or diaper candidiasis and vulvovaginitis or mastitis. Fluconazole has a better side effect profile than ketoconazole, and more data are available concerning its safe use in children younger than 6 months of age and even neonates and premature infants.[87,154,209] Fluconazole is not currently approved for use in infants younger than 6 months of age. For severe invasive infections in infants, amphotericin B with or without oral flucytosine, IV fluconazole, voriconazole or caspofungin are reasonable choices in different situations. Use of itraconazole in infants has not been adequately studied to date. Maternal use of fluconazole during breastfeeding is not contraindicated because only a small amount of medicine compared with the usual infant dose reaches the infant through breast milk. Amphotericin or caspofungin therapy in mothers is also not contraindicated because these are both poorly absorbed from the GI tract. Whenever a mother is treated for candidal mastitis or vulvovaginitis, the infant should be treated simultaneously,

at least with nystatin oral suspension as the first choice of medication.

Any predisposing risk factors for candidal infection in mothers and infants should be reduced or eliminated to improve the chance of rapid, successful treatment and to decrease the likelihood of chronic or recurrent disease. For mothers, such interventions might include decreasing sugar consumption, stopping antibiotic use as soon as possible, and consuming some form of probiotic bacteria, such as acidophilus (in yogurt, milk, or pill form), to reestablish a normal colonizing bacterial flora. For infants, breastfeeding can enhance the growth of specific colonizing bacterial flora such as lactobacillus, which can successfully limit fungal growth. Breastfeeding should continue with appropriate support and problem-solving with a professional who is knowledgeable about breastfeeding.

Summary

HIV-1, HIV-2, HTLV-I, and HTLV-II are the only infectious diseases that are considered absolute contraindications to breastfeeding in developed countries. When the primary route of transmission is via direct contact or respiratory droplets/particles, temporary separation of mother and infant may be appropriate (whether the infant is breastfed or formula fed), but expressed breast milk should be given to the infant for the organism-specific immunologic benefits in the mother's milk. In most instances, by the time a specific diagnosis of infection is made for a mother, the infant has already been exposed to the organism and providing expressed breast milk to the infant should continue. (Refer to Appendix F for specific exceptions, such as Lassa fever.) Regarding antimicrobial therapy for mothers and continued breastfeeding, the majority of the medications commonly used in adults can be used to treat the same infection in infants. The additional amount of medication received by infants via breast milk is usually insignificant. In almost all instances, an appropriate antimicrobial agent for treating mothers that is also compatible with breastfeeding can be chosen.

Unless the risk to infants for transmission of an infectious agent via breast milk that leads to a clinically significant illness in the infants is documented, breastfeeding should continue.

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