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Chapter 10

FOCAL BACTERIAL INFECTIONS

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Infections of the Liver 347
Microbiology
Pathogenesis
Clinical Manifestations
Diagnosis
Prognosis
Treatment
Splenic Abscess 350
Infections of the Biliary Tract 350
Infections of the Adrenal Glands 351
Appendicitis 351
Microbiology
Pathogenesis
Clinical Manifestations
Diagnosis
Prognosis
Treatment
Peritonitis 354
Microbiology
Pathogenesis
Clinical Manifestations
Diagnosis
Prognosis
Treatment
Necrotizing Enterocolitis 358
Pathology and Pathogenesis
Microbiology
Clinical Manifestations
Diagnosis
Treatment
Prevention
Prognosis
Endocarditis 363
Pericarditis 364
Mediastinitis 365
Esophagitis 366
Infections of Endocrine Organs 366
Infections of the Salivary Glands 366
Infections of the Skin and Subcutaneous Tissue 367
Pathogenesis
Microbiology
Epidemiology
Clinical Manifestations
Diagnosis
Differential Diagnosis
Treatment
Prevention
Conjunctivitis and Other Eye Infections 372

INFECTIONS OF THE LIVER

Bacterial infection of the hepatic parenchyma frequently is recognized as multiple, small inflammatory foci (microabscesses) observed as an incidental finding in infants dying with sepsis. Diffuse hepatocellular damage, often in conjunction with infection of several organ systems, may be present after transplacental passage of microorganisms to the fetal circulation. On rare occasions, liver involvement may take the form of a solitary purulent abscess. Metastatic focal infections of the liver associated with bacteremia resolve with antimicrobial therapy, are not recognized, or are found only at postmortem examination. Rarely are they clinically apparent as solitary[1] or multiple[2] large abscesses diagnosed during life.

Although metastatic infections are rare, it is difficult to ascertain their true incidence. In a survey of more than 7500 autopsies of children performed between 1917 and 1967, Dehner and Kissane[3] found only three neonates with multiple, small, pyogenic hepatic abscesses, whereas a review of approximately 4900 autopsies[4] performed at Los Angeles Children's Hospital between 1958 and 1978 revealed 9 such infants.[5] Among 175,000 neonates admitted between 1957 and 1977 to Milwaukee Children's Hospital, 2 died with hepatic microabscesses[6]; 3 such patients were seen among 83,000 pediatric patients admitted to New York Hospital between 1945 and 1983,[7] and 1 was reported at the University of Texas Medical Branch in Galveston between 1963 and 1984.[8] Most reviewers who have discussed postmortem observations of infants dying with neonatal sepsis have not described the occurrence of such secondary sites of infection[9-16] or have presented them as an occasional ancillary finding.[17,18]

Similarly, solitary hepatic abscesses in the newborn have also been reported rarely. About 30 such cases have been described.[1,3,4,19-41] These infections frequently are associated with prematurity and umbilical vein catheterization,[5,6,21,22,25,28,32,34-41] whereas solitary abscesses may occur because of bacteremia. For example, Murphy and Baker[42] describe a solitary abscess after sepsis caused by *Staphylococcus aureus.*

Microbiology

Any bacteria that invade the bloodstream can cause multiple microabscesses in the liver. The etiologic agents in the infants described by Dehner and Kissane,[3] Moss and Pysher,[5] Chusid,[6] and Miedema and co-workers[7] included *Escherichia coli, S. aureus, Pseudomonas aeruginosa, Klebsiella* sp., *Enterobacter* sp., and *Listeria monocytogenes.* However, the causative bacteria of solitary abscesses are generally those colonizing the umbilical stump,[43] including *S. aureus* (11 cases); *E. coli* alone (3 cases); *E. coli* with *S. aureus* (2 cases) or enterococcus

(1 case); *Enterobacter* sp. (3 cases); *Klebsiella pneumoniae* alone (2 cases); *K. pneumoniae* with *Proteus* sp. (1 case); *P. aeruginosa* (1 case); *Staphylococcus epidermidis* with group F *Streptococcus* (1 case); and *Streptococcus pyogenes* (1 case). In three infants, the abscesses were described as "sterile."[19,28,31] Although one of these infants had received penicillin for 9 days before surgical drainage, it is possible that in all three cases the abscesses were caused by anaerobic bacteria that failed to grow under standard conditions of transport and culture. The presence of gas in seven abscesses[25,28,34,35,39] may indicate infection with anaerobes, a frequent cause of liver abscess in adults.[44]

The most common cause of intrauterine bacterial hepatitis, congenital listeriosis, characteristically involves the liver and adrenals (see Chapter 14). Typical lesions are histologically sharply demarcated areas of necrosis (miliary granulomatosis) or microabscesses containing numerous pleomorphic gram-positive bacilli.[15] Descriptions in the early 1900s of miliary necrosis of the liver related to "gram-positive argentophilic rodlike organisms" probably also represented infections with *L. monocytogenes*, which was not isolated and identified until 1926.[26]

Intrauterine tuberculosis results from maternal bacillemia with transplacental dissemination to the fetal bloodstream (see Chapter 19). Because the liver is perfused by blood with a high oxygen content[45] and is the first organ that encounters tubercle bacilli, it is often severely involved.[15,44,46] The presence of primary liver foci is considered prima facie evidence for the congenital nature of tuberculous lesions as a result of hematogenous spread through the umbilical vein.[47] However, closed-needle biopsy may be less accurate in the diagnosis of hepatic granulomas, and open biopsy may be required to confirm liver and regional node involvement.[48] Although generalized fetal infection may also arise through aspiration of contaminated amniotic fluid, the lesions acquired in this manner are usually most prominent in the lungs. In addition to hepatomegaly, a clinical picture of fever with elevated serum IgM and chorioretinitis (e.g., choroid tubercles) may be similar to that caused by other congenital infectious agents.[49] In a review by Abughal and co-workers,[49] positive sites of culture for tuberculosis included liver (8 of 9), gastric aspirate (18 of 23), tracheal aspirate (7 of 7), ear (5 of 6), and cerebrospinal fluid (3 of 10). Noncaseating granulomatous hepatitis, thought to be caused by a hypersensitivity reaction related to bacille Calmette-Guérin (BCG) vaccination, has also been described in a neonate,[50] but histologic and bacteriologic studies performed on liver biopsy specimens failed to identify the presence of acid-fast bacilli or BCG organisms.

On rare occasions, bacterial infection of the fetal liver has been reported in association with maternal tularemia,[51] anthrax,[52] typhoid fever,[53] and brucellosis.[54] It is uncertain whether the isolation of bacteria from the livers of stillborn fetuses is significantly associated with their clinical course.[55,56]

Treponema pallidum is the spirochete most commonly associated with transplacental hepatic infection (see Chapter 18). Pathologic changes in liver, found in up to 95% of infants dying with congenital syphilis,[57] may include those of diffuse hepatitis or focal areas of inflammation, both frequently accompanied by increased connective tissue and enlargement of the liver.[15,57-59] Involvement of liver has also been documented, on the basis of isolation of organisms or their identification in histologic sections, in newborns with intrauterine infection caused by various *Leptospira* species (*Leptospira icterohaemorrhagiae*,[60,61] *Leptospira pomona*,[62] *Leptospira canicola*,[63] *Leptospira kasman*[64]). Transplacental infection of the fetus with *Borrelia recurrentis* causes little or no inflammation of liver parenchyma or biliary epithelium despite the presence of large numbers of spirochetes in the sinusoids.[65-68] Congenital infection has been suggested with *Borrelia burgdorferi*[69] (cause of Lyme disease); hepatic, central nervous system, and cardiac lesions may be observed, and widely disseminated lesions were reported to occur in other tissues.

Pathogenesis

Infectious agents may reach the liver of the fetus or newborn by one of several pathways: transplacental or transorificial intrauterine infection; extension of thrombophlebitis of the umbilical vein; through the hepatic artery during the course of a systemic bacteremia; pylephlebitis due to a focus of infection in the drainage of the portal vein (mesenteric or splenic veins); direct invasion from contiguous structures or because of trauma or surgical inoculation; and extension up the biliary passages in cases of suppurative cholangitis. Abscesses with no apparent focus of infection seem to be relatively common in the newborn compared with older children.[30] Three such cases, all in infants with solitary hepatic abscesses, have been described.[23,24,31] Descriptions of the surgical findings, together with the nature of the lesions, suggest that an umbilical vein infection, obscured by the large collection of purulent material in the abscess, was the probable pathogenesis in all infants.

The mode of infection usually determines the pattern of hepatic involvement. Intense and prolonged seeding of the liver parenchyma, such as that which occurs in conjunction with intrauterine infection or neonatal sepsis, almost invariably results in diffuse hepatocellular damage or multiple small inflammatory lesions.[3,5,6] Umbilical vein thrombophlebitis, may cause an abscess of the falciform ligament[70] or extend into a single branch of the portal vein to produce a solitary pyogenic abscess,[6,21,22,26,29,32,33] or it can lead to disseminated foci of infection through dislodgment of septic emboli.[6,71-74]

The frequent use of umbilical catheters has been associated with an increase in the numbers of infants with solitary[5,6,20-22,32,34-40] or multiple[5,75,76] hepatic abscesses. In three large series, including almost 500 infants who died after placement of umbilical vein catheters, 29 infants were found to have purulent infections of hepatic vessels or parenchyma.[37,75,77] Use of venous catheters for infusion of hypertonic or acidic solutions may provide a necrotic focus for abscess formation,[21,32,34-36,76,77] and prolonged[5,22,32,77] or repeated[63] catheterization of a necrotic umbilical stump provides an ideal pathway for introduction of pathogenic organisms. It has been postulated that some hepatic abscesses have been caused by infusion of contaminated plasma[28] or by the use of nonsterile umbilical catheters.[75]

Although neonatal liver abscesses usually are caused by hematogenous dissemination of bacteria through the hepatic artery or umbilical vein, examples of infection arising from various other sources have been described. Solitary abscesses

have followed a presumed portal vein bacteremia caused by amebic colitis.[19,20] Direct invasion of adjacent liver parenchyma from purulent cholecystitis[24] or postoperative perihepatic abscesses[5] also has been observed. Ascending cholangitis, the most frequent cause of hepatic purulent infections in adults,[30] has not been implicated in the causes of newborn infections.

Disease due to embryonic anatomic errors is unique to newborns. Shaw and Pierog[78] described a newborn with umbilical herniation of a pedunculated supernumerary lobe of the liver; histologic examination showed numerous small foci of early abscess formation. Although signs and symptoms of sepsis appeared at 18 days of age, possibly the result of bacterial spread from the liver to the umbilical vein, the infant improved and ultimately recovered after removal of the polypoid mass on the 19th day of life.

Descriptions of "umbilical sepsis" and "acute interstitial hepatitis" recorded by Morison seem to indicate that his patients had acquired bacterial infections of umbilical vessels with widespread extension into portal tracts.[79] Although mild periportal parenchymal necrosis was observed in a few infants, hepatocellular damage was minimal or absent in most. Similar lesions have been found in infants dying with sepsis[80] and infantile diarrhea.[81]

Clinical Manifestations

Multiple hepatic abscesses and diffuse hepatitis related to neonatal sepsis or transplacental fetal infection are usually recognized only at autopsy. Very few clinical manifestations referable to hepatocellular damage are evident before death. The signs and symptoms associated with these conditions are those of the underlying sepsis or of secondary metastatic complications such as meningitis, pneumonitis, or peritonitis.[2,3,29,33,72,75]

Solitary abscesses are indolent in terms of their development and clinical presentation. Although the suppurative umbilical focus or umbilical catheterization responsible for the introduction of microorganisms can usually be traced to the first week of life, evidence of hepatic involvement is usually not apparent before the second or third week. The abscess frequently becomes a source for the hematogenous dissemination of microorganisms, so that most infants have signs and symptoms of a bacteremia. Despite intense infection of the underlying vessels, inspection of the umbilical stump usually shows no evidence of inflammation or purulent discharge. The presence of hepatomegaly, a finding commonly associated with neonatal sepsis, also offers little aid in establishing a definitive diagnosis. In one half of infants for whom physical findings are clearly described, a well-delineated, often fluctuant or tender mass could be palpated in the epigastrium or right upper quadrant. On a few occasions, this mass was noticed by the infant's mother several days before the onset of systemic symptoms. Abscesses occur in the right or left lobe of the liver with almost equal frequency and are generally 3 cm or more in diameter at the time of surgical exploration.

Diagnosis

Hematologic studies are of little value in establishing a diagnosis; leukocyte counts and sedimentation rates may be normal or elevated. The serum levels of liver enzymes may also be normal[25,38] or elevated.[5,23,36]

Abdominal radiographs are usually normal or show nonspecific displacement of the lower edge of the liver. In five infants, diagnosis was suspected from plain x-ray films by the presence of gas within the hepatic shadow.[28,32,34,39] Radiologic findings that commonly accompany hepatic abscess in older children, such as an altered contour of the diaphragm, right pleural effusion, and platelike atelectasis,[82] are rarely present in the neonate.

Ultrasonography should be the initial imaging study in newborns with clinical evidence of a hepatic abscess.[83-86] If negative, and the diagnosis is still strongly suspected, more sensitive techniques such as computed tomography (CT) or magnetic resonance imaging (MRI) should be performed.[83-88] Enhancement with contrast agents may increase the definition of smaller abscesses. Because congenital cysts, arteriovenous malformations, and tumors with central necrosis or hemorrhage can mimic hepatic abscess, the diagnosis should always be confirmed by aspiration of purulent material at laparotomy or by means of percutaneous drainage with ultrasound or CT guidance.[84,89,90]

Prognosis

The prognosis for infants with diffuse liver involvement related to fetal or neonatal sepsis is that of the underlying condition because hepatic function is rarely compromised sufficiently to determine the outcome. In most cases, pathologic changes in the liver are unsuspected before postmortem examination.

Of 24 infants with solitary hepatic abscesses whose course was described, 8 died. Two infants died before antibiotics were available,[26] and the death of another was ascribed to cecal perforation.[20] Four newborns died with sepsis caused by organisms that were identical to those isolated from the abscess.[21,25,33,34] Prematurity was undoubtedly a major contributing factor in two of these deaths.[21,25]

Treatment

Newborns with a solitary hepatic abscess have traditionally been treated with open surgical drainage in conjunction with antibiotic therapy. Developments in the therapy for pyogenic liver abscess during the past few years suggest that a reassessment of this approach may be in order.

Several investigators have described the use of percutaneous drainage of intrahepatic abscesses and cysts, guided by CT or ultrasonography, in neonates[41,75,90] and children.[7,84,89] When combined with antibiotic therapy and monitored by ultrasonography to ensure resolution, this treatment has been highly effective. It is questionable whether drainage contributed to recovery other than by aiding the selection of antibiotic coverage. Subsequently, patients have been successfully treated with empirical antibiotic therapy alone.[91,92] Conservative medical management in infants has been described in only two neonates and a 5-month-old infant.[33,37,78]

The risk of bacteremia and disseminated infection is high in neonates, and the need to identify infecting organisms to guide antibiotic coverage is of greater urgency in the first weeks of life. It is appropriate to ascertain a microbiologic

diagnosis with radiographically guided aspiration or drainage of any definable hepatic abscess in a newborn. When proper equipment (e.g., CT, ultrasonography) and experienced personnel are available, this can be attempted percutaneously.[89,90] When they are not available, open surgical drainage should be performed. Empirical antibiotic therapy should be reserved only for infants for whom it is believed that the risk of open or closed drainage would exceed the potential benefits.

If purulent material is obtained, initial antibiotic therapy can be selected on the basis of Gram staining results. In addition to *S. aureus* and the aerobic enteric organisms commonly associated with hepatic abscesses, anaerobic bacteria have been suspected as the cause of infection in a substantial number of patients.[25,28,32,33,35,39] If foul-smelling pus is aspirated or if Gram-stained smears show organisms with the characteristic morphology of anaerobes,[33] metronidazole, β-lactam and β-lactamase inhibitor combinations (e.g., piperacillin and tazobactam), clindamycin, or imipenem should be included in the initial regimen. Cultures of blood, cerebrospinal fluid, and urine should also be obtained before initiation of therapy.

If empirical antibiotic therapy is required, it must be adequate for infections caused by *S. aureus,* enteric organisms, and anaerobic bacteria. Oxacillin, gentamicin, and clindamycin is an appropriate combination. In nurseries where methicillin-resistant *S. aureus* or *S. epidermidis* infections have been a problem, substitution of vancomycin for oxacillin can provide coverage for these organisms. Gentamicin (and other aminoglycosides) and vancomycin levels must be monitored and dosages adjusted as necessary. Extended-spectrum cephalosporins (e.g., cefotaxime, cefepime, ceftazidime) may be used for enteric organisms and *Pseudomonas* sp., often obviating the need for aminoglycosides.

Definitive therapy is based on results of bacteriologic cultures that identify the bacteria and its antibiotic susceptibility. Adequate anaerobic transport and culture techniques must therefore be available if meaningful information is to be obtained. Duration of treatment is based on clinical response, cessation of drainage, and resolution of the abscess cavity as determined by serial ultrasonographic examinations. Parenteral therapy should be maintained for at least 2 weeks and may be individualized to longer therapy when necessary. In older children treated with multiple abscesses or in those for whom surgery is not feasible, therapy for up to 6 weeks or more has been recommended.

SPLENIC ABSCESS

Similar to hepatic abscesses, splenic abscesses have been rarely described in infants.[93] Only 1 of 55 splenic abscesses occurred in an infant younger than 6 months. *S. aureus, Candida* sp., and streptococci were the most frequent causes. In 20 of 48 cases, hepatic abscesses coexisted with splenic abscess. In the single infant case, torsion of the splenic vessels was present, whereas in older children, other distant infections of hematologic conditions (e.g., hemoglobinopathy, hematogenous malignancy) were the associated comorbid conditions.

INFECTIONS OF THE BILIARY TRACT

The development of ultrasonography has provided a safe and rapid means for evaluating the neonatal gallbladder. Consequently, an increasing number of reports have appeared within the past 10 years describing ultrasonographic changes seen in the first month of life, with hydrops,[94,95] cholelithiasis,[95-100] and transient distention of the gallbladder associated[94,95,99,101-104] or unassociated[99,102,103,105-108] with sepsis. Ultrasonographic criteria for separating normal from pathologically enlarged gallbladders and biliary tracts in neonates have also been described.[109,110]

Despite advanced technology and increased surveillance, cholecystitis in the neonate is observed infrequently. The literature has documented about 25 cases, of which 9 were seen in association with an epidemic of neonatal enteritis caused by *Salmonella enteritidis.*[111] Of the remaining infants, 16 were the subjects of isolated case reports[24,103,112-123] and 3 died of other causes with inflammatory changes in the gallbladder described as an incidental finding at autopsy.[81,95,124] A tissue diagnosis of "chronic cholecystitis" was established in an infant whose biliary disease apparently began at 6 days of age.[125]

The pathogenesis of this condition is uncertain; all but three cases[99,118,122] of cholecystitis in the newborn period have been acalculous. It is postulated that sepsis, dehydration, prolonged fasting (e.g., total parenteral nutrition), congenital obstruction, or a stone impacted in the cystic duct leads to biliary stasis and acute distention of the gallbladder. In most cases, resolution of the primary process permits restoration of the flow of bile and relief of distention. In some cases, prolonged obstruction leads to hydrops.[94] Cholecystitis rarely follows, perhaps because of a direct toxic effect of retained bile or because of ischemia related to elevated intraluminal pressure. Bacterial invasion by fecal flora is probably a secondary phenomenon.[114,115,126] Organisms that have been isolated from gallbladder contents or tissue include *E. coli,*[114-116,123] *Serratia marcescens,*[103,117] *Pseudomonas* sp.,[115] *Streptococcus faecalis,*[123] "*Streptococcus viridans,*"[121] *S. aureus,*[123] and *Clostridium welchii.*[123] "Gram-positive cocci" were identified by Gram stain in one patient.[113]

Infants with cholecystitis may become ill at any time during the first weeks of life; most cases are diagnosed in the third or fourth week. The typical clinical picture is one of sepsis together with signs of peritoneal inflammation and a palpable tender right upper quadrant or epigastric mass. Diarrhea frequently accompanies these findings. Although ultrasonography and radionuclide scintigraphy are helpful in suggesting the presence of gallbladder enlargement or inflammation, diagnosis can be confirmed only by surgical exploration.[94,102,103,106,108] Treatment consists of cholecystectomy or tube cholecystotomy, together with systemic antimicrobial therapy based on Gram stain, culture, and susceptibility studies. If a T tube is placed in the gallbladder, a cholangiogram should be done to confirm patency of the biliary system before the tube is removed.

Changes compatible with a diagnosis of ascending cholangitis have been described in histologic sections of liver specimens from infants who died with diarrhea accompanied by hepatocellular injury with cholestasis.[91] Bacteria were also identified in the biliary tree of 2 of 178 premature infants who died after placement of an umbilical venous catheter for

an exchange transfusion or for delivery of parenteral fluids.[75] The reasons for this association, if any, are unclear. An infant with spontaneous cholangitis caused by *Enterobacter agglomerans*, presenting as a fever of unknown origin at 3 weeks of age, has also been reported.[127]

Severe inflammation and fibrosis of extrahepatic bile ducts and diffuse changes in the portal tracts, resembling those found in biliary atresia, were found in a premature infant who died when 3 hours old of listeriosis.[128] The investigator postulated that occult prenatal infections with *L. monocytogenes* might be a rare cause of ascending cholangitis presenting as idiopathic biliary atresia at birth.

INFECTIONS OF THE ADRENAL GLANDS

Multiple adrenal microabscesses are occasionally found as metastatic lesions associated with neonatal sepsis. Such abscesses are particularly characteristic of neonatal listeriosis (see Chapter 14). Solitary adrenal abscesses, however, are rare, and only about 25 such cases have been described.[17,129-150]

The spectrum of organisms responsible for adrenal abscesses is the same as that seen in neonatal sepsis, including *E. coli* (seven cases),[17,129,130,135-138] streptococcus group B (four cases),[138-141] *Proteus mirabilis* (three cases),[131,132,144] *S. aureus*,[142,143] *Bacteroides* sp.,[133,145] and two cases each of *Streptococcus pneumoniae* with *Bacteroides* sp.[134]; *Peptostreptococcus* sp.[146] was recovered from one case. Drainage of foul-smelling pus at surgery suggests that anaerobic bacteria may have been present in two infants from whom *E. coli* and *S. aureus* were isolated.[136,142] Cultures were not obtained from four patients.[147-150]

Fourteen abscesses were located on the right side, seven were located on the left, and three[138,139,147] were bilateral. Three fourths of the infants were male. The same laterality and sex predominance are seen with adrenal hemorrhage in the newborn,[147,150-152] and it has been postulated that formation of an adrenal abscess requires a preexisting hematoma as a nidus for bacterial seeding.[137,138] This theory of pathogenesis is further supported by clinical observations,[134,135,139,146,147] and by objective evidence (e.g., curvilinear calcifications[130,132]) documenting the presence of hemorrhage before development of an abscess.[134,138,142,145,150]

Most infants with adrenal abscess have presented in the third or fourth week of life with signs of sepsis and an abdominal or flank mass. A history of difficult delivery or intrapartum asphyxia has been observed in about one half of these infants and significant maternal fever or infection during labor in about one fourth.[138,140,141,150] Although a few infants are afebrile when first evaluated, a palpable mass is almost always present. Abscesses are usually 6 to 8 cm in diameter, with some containing as much as 200 mL of pus[133] and measuring up to 12 cm in diameter[134] or crossing the midline.[146]

Laboratory studies are helpful in the evaluation of a possible adrenal abscess. Most infants demonstrate a leukocytosis; about one third are anemic with a history of prolonged neonatal jaundice, both of which are features associated with adrenal hemorrhage. Urinary excretion of catecholamines and their metabolites (particularly vanillylmandelic acid and homovanillic acid), which is usually increased with neuroblastoma, is normal. Because most infants with adrenal abscess are seen for evaluation of possible sepsis, a blood culture, lumbar puncture, urine culture, and chest radiograph should be obtained.

Ultrasonography has become a widely accepted modality for initial evaluation of all neonatal abdominal masses. With the presence of an adrenal abscess, ultrasound examination can help to define the extent and cystic nature of the lesion and often can demonstrate movable necrotic debris in the abscess cavity.[132,137,138,141,142,144-148] With serial examinations, abscesses can be distinguished from those masses associated with liquefying hematoma, adrenal cyst, hydronephrosis of an obstructed upper pole duplication, or necrotic neuroblastoma.[138,140,150,153-154] Intravenous pyelography demonstrates downward displacement of the kidney and compression of the upper calyces, which confirms the presence of a suprarenal mass.[130-132,134,136,138,141,142,144-146,149] A round, suprarenal, radiopaque halo or rim with central lucency, which is characteristic of adrenal abscess, may also be seen on early films[137,139,143] but is not pathognomonic.[138] Intravenous pyelography adds little diagnostic information to that provided by ultrasound studies. Experience with radionuclide scanning,[140,142,143] CT,[138,144] and MRI[126] in this condition is limited, but these modalities are likely to be as useful as ultrasonography.

Whatever diagnostic methods are used, concern about persisting signs of sepsis and the more than possible presence of an adrenal neoplasm usually encourage early efforts to establish a diagnosis. In the past, recommended management has been incision and drainage or resection of the abscess.[134,138,141,144,150] Needle aspiration under ultrasonographic guidance, combined with placement of a catheter for drainage and irrigation, has proved to be a useful alternative method[88,130,131,143] and probably will supplant open drainage as the preferred method. Antibiotic therapy should be based on Gram stain, culture, and susceptibility studies of abscess fluid and should be continued for 10 to 14 days provided drainage can be established.

The adrenals are infected in about 15% of infants with congenital syphilis.[57,58] In addition to the presence of spirochetes, the most frequent and characteristic change is an extraordinary amount of cellular connective tissue in the capsule.

APPENDICITIS

Acute appendicitis is extremely rare in infants younger than 4 weeks of age. Reviews of more than 25,000 cases of appendicitis in infants and children in Great Britain,[156] Ireland,[157] Norway,[158] Germany,[159] and the United States[160-165] revealed only eight infants who presented during the neonatal period. Pediatric surgery centers in Germany,[166] Boston,[167] Cleveland,[168] Chicago,[169] and Detroit[170] found only four cases of neonatal appendicitis during the past 15 to 20 years. Since the condition was first described by Albrecht in 1905[171,172] and Diess in 1908,[173] approximately 65 cases of neonatal suppurative appendicitis have been reported in the literature with sufficient details to permit characterization of the clinical features,[156,161,162,165,174-211] and the following discussion is based on a review of those cases. Only infants with acute intra-abdominal appendicitis were considered. Those with appendicitis caused by other conditions, such as

Hirschsprung's disease,[212,213] necrotizing enterocolitis (NEC),[214] or incarceration in an inguinal hernia,[215,216] have not been included. An additional 25 to 30 cases that have been reported with incomplete clinical observations, listed in series of patients with neonatal peritonitis (see "Peritonitis") or mentioned in other review articles but not available for analysis, are also not included.

Inflammation of the appendix is more common in male newborns than in female newborns. In those reports in which the sex was stated, 40 cases occurred in males and 17 in females. Prematurity also appears to be a predisposing factor: 23 of the 49 infants whose birth weights were recorded weighed less than 2500 g at birth. The incidence of appendicitis in infants of multiple births (six twins and one triplet) appears to be higher than would be expected on the basis of low birth weight alone.

Microbiology

Because obstruction of the appendiceal lumen is responsible for almost all cases of appendicitis,[167] it is intuitive that gram-negative enteric organisms resident in the bowel are usually isolated from the peritoneal fluid or periappendiceal pus of about 75% of infants. Specific etiologic agents have included *E. coli, Klebsiella, Enterobacter* sp., *Pseudomonas, Proteus* sp., untyped *Streptococcus, S. aureus,* and *Bacteroides* sp. These bacterial species have also been isolated from the peritoneal fluid of older children with appendicitis.[164,167,217] Attempts at isolation of anaerobic bacteria have been rarely described.

A single case of perforated amebic appendicitis with secondary bacterial peritonitis and multiple hepatic abscesses in a premature infant born in Great Britain has been reported. The *Entamoeba histolytica* observed in the wall of the necrotic appendix was presumably acquired from the infant's father, who was a carrier.[20]

A patient with gangrenous appendicitis associated with *Rhizopus oryzae* has also been reported.[218] It was postulated that the fungus colonized the infant's gut by transfer from an adhesive bandage used to secure an endotracheal tube.

Pathogenesis

Obstruction of the appendiceal lumen has been generally accepted as the primary cause of appendicitis in all age groups. The relative rarity of this condition in the first month of life is therefore probably related to factors that serve to decrease the likelihood of obstruction. Such factors include a wide-based, funnel-shaped appendix; the predominantly liquid and soft-solid diet given to infants; the absence of prolonged periods in the upright position; and the infrequency of infections that cause hyperplasia of the appendiceal lymphoid tissue.[164,219,220]

The causes of luminal obstruction in the newborn period, when recognized, are often extrinsic to the appendix itself. Reports of appendicitis caused by the presence of ectopic pancreatic tissue,[161] a fecalith,[175] or meconium plug[168] are unusual exceptions. In 1911, it was suggested that sharp angulation of the appendix, bent on itself in the narrow retrocolic space, may be an important cause of obstruction,[221] however, this anatomy, found in 11 neonates with inflammatory changes in the appendix and noted among 200 consecutive autopsies in infants younger than 3 months at death, has not been repeated in the past 80 years.

Inflammation of the appendix with perforation has been described as the presenting illness in several infants with neonatal Hirschsprung's disease.[212,214] The association of these two conditions has been attributed to functional obstruction, increased intraluminal pressure, and fecal trapping that occur proximal to aganglionic segments. Suppurative appendicitis related to incarceration and strangulation of the cecum within an inguinal or scrotal hernia has been found in a significant number of infants.[215,216]

Clinical Manifestations

The onset of neonatal appendicitis generally occurs during the first 2 weeks of life. Only 3 of 54 infants with this condition presented between the 21st and 20th days. The reasons for this phenomenon are unclear, particularly in view of the relatively even distribution of cases during the remainder of the first year of life.[165] Five cases of "prenatal" appendicitis have been described.[222-226] Of the four available for analysis, only one showed definite evidence of a suppurative process in the appendix and signs of bowel obstruction clearly present at birth[222]; however, cultures and Gram stain of the pus found at surgery were free of bacteria. Poisoning by mercuric chloride was suspected in one[224] of the remaining three cases, and the other two, who were said to have prenatal rupture of the appendix, were asymptomatic until the second[222] and twelfth[226] days of life.

The signs of neonatal appendicitis correspond to those of any of the various forms of intestinal obstruction that occur during the newborn period (Table 10-1).[226] Prominent early findings include abdominal distention, progressive and frequently bilious vomiting, and evidence of pain, as manifested by persistent crying, irritability, or "colic." Clinical features such as diarrhea, constipation, lethargy, or refusal to feed may also be evident but are too nonspecific to be helpful in establishing a diagnosis. The presence or absence of fever is an unreliable sign in appendicitis as in other forms of neonatal infection; temperature has been recorded as normal or subnormal in more than 50% of newborns with this condition. Abdominal tenderness and guarding are inconstant findings and, when present, are rarely localized to the appendiceal area. Physical signs of

Table 10–1 **Signs of Intra-abdominal Neonatal Appendicitis in 55 Infants**

Sign	Incidence (%)
Abdominal distention	90
Vomiting	60
Refusal of feedings	40
Temperature ≥ 38° C	40
Temperature 37° C to 38° C	30
Temperature ≤ 37° C	30
Pain (crying, restlessness)	30
Lethargy	30
Erythema/edema of right lower quadrant	25
Mass in right lower quadrant	20
Diarrhea	20
Passage of bloody stools	20

sufficient specificity to indicate acute inflammation of the appendix are generally absent until late in the course of the illness, when gangrene and rupture may result in the formation of a localized intra-abdominal abscess or cellulitis of the anterior abdominal wall. Erythema or edema, or both, of the right lower quadrant has been observed in several patients. The presence of this finding, particularly when accompanied by a palpable mass in the right iliac fossa, indicates bowel perforation with peritonitis and should suggest a preoperative diagnosis of NEC or appendicitis (see "Necrotizing Enterocolitis").

Diagnosis

The diagnosis of appendicitis in the neonate is usually determined at surgery performed for evaluation of abdominal distention and suspected peritonitis. With the high incidence of prematurity associated with early appendicitis, bowel perforation from NEC has been a common preoperative consideration.[207] The two conditions can coexist, and in some cases, the appendix may participate in the process of ischemic necrosis and perforation.[206,214]

Laboratory studies are of little value in establishing a diagnosis of appendicitis in the newborn. White blood cell counts of less than 10,000/mm^3 were found in 10 of 30 infants for whom this determination was performed. Urinalyses are usually normal, although ketonuria, which reflects diminished caloric intake, hematuria, and proteinuria may be seen. Because bacteremia may accompany appendiceal perforation and peritonitis, a blood culture and evaluation for metastatic infection with lumbar puncture and chest radiography should be performed. The value of paracentesis for diagnosis of bowel perforation and peritoneal infection is discussed later (see "Necrotizing Enterocolitis").

Radiologic examinations are occasionally helpful, but in most cases serve only to confirm a clinical impression of small bowel obstruction. The presence of an increased soft tissue density displacing loops of intestine from the right iliac fossa generally indicates appendiceal perforation with abscess formation and is perhaps the most reliable sign of acute appendicitis in the neonate. Extraluminal gas may be localized briefly to the right lower quadrant after rupture of the appendix.[212] The rapid development of an extensive pneumoperitoneum, however, obscures the site of origin of the escaping gas in most infants within a short time.[227] Ultrasonography may aid in detection of a periappendiceal abscess[83] but lacks sensitivity and specificity to be of assistance in establishing an early diagnosis of appendicitis.

Prognosis

The overall mortality rate from appendicitis in the newborn is high but is improving. Eight of the newborns in the last 12 reported cases have survived, whereas of 60 infants with this condition for whom the outcome was recorded, 38 (64%) died. Survival was unrelated to birth weight. Among factors responsible for mortalities, three appear to be of primary importance: delay in diagnosis, a high incidence of perforation, and the rapid onset of diffuse peritonitis after appendiceal rupture.

Perforation has been identified at surgery or autopsy in 70% of newborns with acute appendicitis. The relative frequency of this complication has been attributed to delays in establishing a diagnosis and to certain anatomic features of the appendix in young infants that predispose it to early necrosis and rupture. These features include a meager blood supply that renders the organ more vulnerable to ischemia; a cecum that is relatively smaller and less distensible than that of adults, thereby forcing a greater intraluminal pressure on the appendix; and the presence of a thin muscularis and serosa that readily lose their structural integrity under the combined effects of ischemia and increased internal pressure.[164,182,183,192]

After the appendix ruptures, infants are unable to contain infection efficiently at the site of origin. Rapid dissemination of spilled intestinal contents produces a diffuse peritonitis within hours because of the small size of the infant's omentum, which fails to provide an efficient envelope for escaping material; the relatively longer and more mobile mesenteries, which favor widespread contamination; and the small size of the peritoneal cavity, which also permits access of infected material to areas distant from the site of perforation.[161,167,182,183]

Peritonitis, accompanied by sepsis and by the massive outpouring of fluids, electrolytes, and proteins from inflamed serosal surfaces, is generally the terminal event in neonatal appendicitis. Deterioration of the infant's condition is often extremely rapid; failure to recognize the underlying illness and to institute appropriate therapy promptly is inevitably followed by a fatal outcome.

Treatment

Surgical intervention is essential for survival of young infants with appendicitis. Because vomiting, diarrhea, and anorexia frequently accompany this condition, restoration of fluid and electrolyte balance is a major factor in ensuring a favorable outcome. Loss of plasma into the bowel wall and lumen of the dilated intestine may require additional replacement with whole blood, plasma, or an albumin equivalent. Optimal preparation often necessitates a delay of several hours but remains a major determining factor in the success of any surgical procedure done during the neonatal period.

The preoperative use of antibiotics has been recommended in infants with intestinal obstruction to achieve therapeutic blood levels of drug before the time of incision and possible contamination.[168,228,229] Although there are few data to support such a recommendation in neonates, any controversy regarding the need for prophylactic antibiotics is generally moot. Perforation, fecal spillage, and peritonitis occur so early in the course of neonatal appendicitis that almost all infants with this condition require treatment before the time of surgery. After the diagnosis of gangrenous or perforated appendicitis has been established and surgery performed, parenteral antibiotic therapy should be continued for 10 days. The combination of clindamycin (or metronidazole), gentamicin (or extended-spectrum cephalosporins), and ampicillin provides adequate coverage against most enteric pathogens and can be used for initial empirical therapy. Alternatively, β-lactam and β-lactamase inhibitor combinations such as ticarcillin plus clavulanate or piperacillin plus tazobactam or carbapenem antibiotics (e.g., imipenem) can be used alone to broadly cover enteric bacteria, *Pseudomonas* sp., and anaerobic bacteria. Until the infant is able to tolerate

alimentation, careful attention to postoperative maintenance of body fluids, electrolyte balance, nutrition, and correction of blood and plasma losses is vital to survival (see "Peritonitis" and "Necrotizing Enterocolitis").

PERITONITIS

Peritonitis in the newborn is most commonly associated with perforation of the gastrointestinal tract, ruptured omphaloceles, or wound infections that follow abdominal surgery.[230,231] For this reason, diagnosis and treatment of neonatal peritonitis are less frequently the responsibility of the pediatrician or neonatologist than of the surgeon. It has been estimated that as many as 20% to 40% of gastrointestinal surgical problems in the neonatal period are complicated by bacterial peritonitis (see "Necrotizing Enterocolitis").[186,232] Between 1 and 10 cases per year have been reported in retrospective analyses of peritonitis diagnosed during the first month of life at pediatric surgical centers in the United States,[232-234] Great Britain,[231,235] Hungary,[236] Germany,[237,238] France,[239] and Zimbabwe.[240] Among almost 3000 infants admitted to a neonatal intensive care unit in Liverpool in 1981 to 1982, there were six cases of peritonitis, all from NEC perforation of the gastrointestinal tract.[241] Peritonitis was present in 4 (all of low birth weight) of 501 infants on whom consecutive autopsies were performed from 1960 through 1966 at St. Christopher's Hospital for Children in Philadelphia. These cases represented approximately 3% of all patients with inflammatory lesions associated with death in this age group.[242] Potter considered the peritoneum "one of the most frequent points of localization" in infants dying with sepsis.[15] Among 121 such infants autopsied from 1976 to 1988 at St. Mary's Hospital in Manchester, England, generalized peritonitis was found in 9 (7.4%).[231]

A preponderance of males (2.5:1)[191,240,241] and a high incidence of prematurity (33%)[232,235-237] have been found in unselected series of infants with this condition. These features are probably less a characteristic of bacterial peritonitis in the newborn than of the primary surgical and septic conditions that are responsible for its occurrence (particularly NEC). Among newborns with primary peritonitis, there appears to be a female preponderance.[236,244] A high incidence of congenital anomalies not involving the intestinal tract has also been observed among neonates with peritonitis.[232,237,243,245]

Microbiology

The condition that permits bacteria to colonize the peritoneal surface determines the nature of the infecting organisms. Most infants in whom rupture of a viscus and fecal spillage have caused peritonitis are infected by bacteria considered to be part of the normal enteric microflora; however, prior use of antimicrobial agents and colonization patterns within a nursery are important factors in determining which organisms predominate. Although a mixed flora of two to five species can often be recovered,[243] single isolates have been reported in as many as a third of infants with peritonitis.[246,247] The predominant aerobic organisms usually include *E. coli, Klebsiella* sp., *Enterobacter* sp., *Pseudomonas* sp., *Proteus* sp., coagulase-negative and coagulase-positive staphylococci, ungrouped streptococci, *Enterococcus,* and *Candida.*[231,232,238,240,247-249]

Techniques adequate for the isolation of anaerobic organisms have been used infrequently. In a series of 43 consecutive infants with gastrointestinal perforation and bacterial growth from peritoneal fluid, a mixed aerobic-anaerobic flora was isolated with *Bacteroides* sp. as the predominant anaerobes[243]; remaining specimens grew aerobic or facultative organisms alone and no culture yielded only anaerobes. In that series and others, the same organisms were frequently isolated from the peritoneal cavity and blood.[233,243,245,249]

In contrast to fecal flora isolated from infants with gastrointestinal perforation, gram-positive organisms predominated among neonates with "idiopathic primary peritonitis." This condition is caused by sepsis in most cases, but it also has often been associated with omphalitis. Specific organisms in one representative series included *S. pneumoniae* (three cases), ungrouped β-hemolytic *Streptococcus* (three cases), and *S. aureus, Pseudomonas* sp., and *E. coli* (one case each).[232] Gram-positive cocci were also the major isolates in other series of peritonitis associated with hematogenous dissemination of organisms or extension from a peripheral suppurative focus.[10,26,33,71,244-254] Many of the cases caused by *S. aureus* occurred before the advent of antibiotics or during the worldwide pandemic of staphylococcal disease in the late 1950s, whereas streptococci, particularly group B, have been a prominent cause in recent years.[244,250-254]

Rarely, peritonitis may be caused by *Candida albicans* in pure culture or mixed with gram-negative enteric organisms.[231,255] Because clinical findings in this condition are not different from those of bacterial peritonitis, the diagnosis is usually established by blood or peritoneal fluid culture. Severe hypothermia has been described as a possible predisposing cause of bowel perforation and peritonitis due to *Candida.*[256] In addition to well-recognized risk factors, such as prematurity, antibiotic therapy, and parenteral nutrition with deep venous catheters, NEC may also be a significant risk factor for systemic candidiasis, in which it was observed in 37% of 30 infants.[257] However, only a single infant in this series had a positive culture for *Candida* species from the peritoneum. Peritoneal catheters or peritoneal dialysis may also be a risk for direct inoculation of *Candida* organisms into the peritoneal space, which occurred in 1 of 26 children[258] (see Chapter 34).

Pathogenesis

Acute bacterial peritonitis may occur whenever bacteria gain access to the peritoneal cavity, through intestinal perforation, by extension from a suppurative focus, or by the hematogenous route. Intrauterine peritonitis due to *L. monocytogenes* has been reported[231]; however, cases of "fetal peritonitis" described in earlier reports were actually examples of meconium peritonitis caused by intrauterine intestinal perforation.[259,260] Although bacterial colonization of the gastrointestinal tract in the first days of life may lead to infection in this condition, it is an aseptic peritonitis in its initial stages. A similar condition with focal perforation of the ileum or colon occurring postnatally has been described in very low birth weight infants. Blue-black discoloration of the abdomen, caused by meconium staining of the tissues of

Table 10–2 Etiology of Bacterial Peritonitis in the Neonatal Period

Gastrointestinal perforation[191,231,232,235–240,243,245,249,262,263]
Necrotizing enterocolitis
Ischemic necrosis
Spontaneous focal gastrointestinal perforation[233,246,249,261,262,264]
Volvulus
Hirschsprung's disease
Meconium ileus (cystic fibrosis)[231,266]
Postoperative complications
Congenital anomalies
Internal hernia
Catheter-associated vascular thrombosis[231]
Indomethacin therapy (enteral or parenteral)[267,268]
Trauma
Feeding tubes[269]
Rectal thermometers, catheters, enema[279–275]
Intrauterine exchange transfusion[231,273]
Paracentesis of ascites fluid
Meconium peritonitis with postnatal bacterial contamination[243,259,260]
Peptic ulcer: stomach, duodenum, ectopic gastric mucosa
Acute suppurative appendicitis
Infection
Shigella or salmonella enterocolitis[274–276]
Congenital luetic enteritis with necrosis[58]
Ruptured omphalocele or gastroschisis
Postoperative: anastomotic leaks, wound dehiscence, wound contamination
Primary peritonitis
Prenatal sepsis: *listeriosis, syphilis,*[58] *tuberculosis*[46–49]
Neonatal sepsis[10,33,231,232,240,252–254,263,278]
Suppurative omphalitis[26,72,240,244,250,251,263,277]
Transmural migration (theory)[265,279]

the underlying skin, may be the first striking physical finding in these infants. Clinical, radiographic, and histopathologic evidence of infection or inflammation was notably absent in most cases.[229]

The various conditions that predispose to neonatal peritonitis are outlined in Table 10-2. The relative importance of each in the cause of this condition can be estimated from data collected in several large series. Among almost 400 newborns with peritonitis studied between 1959 and 1978, perforation of the intestinal tract was responsible for 72% of cases, with ruptured omphaloceles or gastroschisis responsible for 12%, hematogenous dissemination or "primary" peritonitis for 12%, and omphalitis and postoperative complications for 2% each.[191,230,231,237,262,263] A comprehensive review of neonatal peritonitis by Bell describes common sites and causes of gastrointestinal perforation and their relative frequencies (Figs. 10-1 and 10-2).[230,243]

No recent cases of neonatal peritonitis have been attributed to microorganisms entering the peritoneal cavity by traversing the bowel wall through the lymphatics or within macrophages (i.e., transmural migration). Evidence for the existence of this pathway is theoretical and is based primarily on retrospective analyses of pathologic data in humans, together with supporting observations made on laboratory animals.[265,279] Further confirmation is necessary before the transmural pathway can be accepted as an established source of peritoneal colonization by bacteria.

Clinical Manifestations

Neonatal peritonitis is a disease primarily of the first 10 days of life; a significant number of infants have evidence of

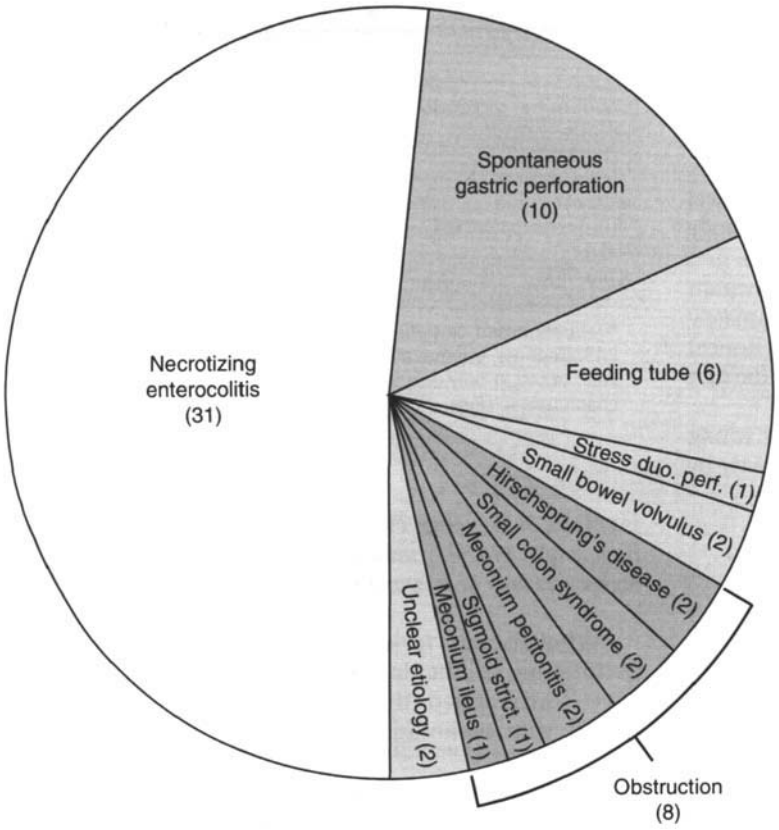

Figure 10–1 Causes of perforation in 60 neonates. (From Bell MJ. Peritonitis in the newborn—current concepts. duo. perf., duodenal perforation; strict., stricture. Pediatr Clin North Am 32:1181, 1985.)

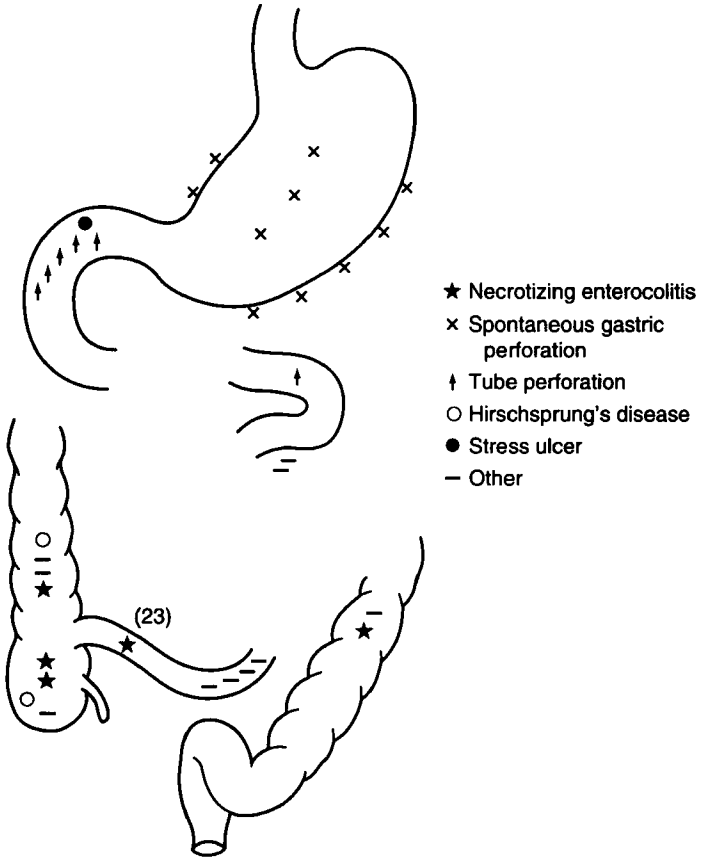

Figure 10–2 Sites of perforation in 60 neonates. (From Bell MJ. Peritonitis in the newborn—current concepts. Pediatr Clin North Am 32:1181, 1985.)

peritoneal infection within the first 24 hours.[232,233,240,245] An analysis of etiologic factors responsible for peritonitis in the newborn provides a ready explanation for this observation (see Table 10-2). Most cases of NEC[243,280] and spontaneous gastric perforation[233,243,249,262] occur within the first week. Ruptured omphaloceles and gastroschisis often develop early infections, and in infants with congenital obstruction, the onset of alimentation during the first 12 to 24 hours accentuates distention and ischemic necrosis of the bowel wall, which leads to early intestinal perforation. Exchange transfusions are performed most frequently within the first 1 or 2 days of life and may be followed by enterocolitis within 4 to 24 hours in infants in whom perforation ultimately occurs.[281,282] Neonatal sepsis, with potential peritoneal seeding of microorganisms, is more frequent during the first 48 hours of life than during any subsequent period.[283]

The variety of signs and symptoms present in a young infant with peritonitis were summarized most succinctly by Thelander[249] in 1939:

The little patient looks sick. He is cyanotic; the respirations are rapid and grunting; the abdomen is distended, and the abdominal wall, the flanks and the scrotum or vulva are usually edematous. Frequently brawny induration of the edematous area, which may resemble erysipelas, is also present. Food is taken poorly or not at all. Vomiting is frequent and persistent. The vomitus contains bile and may contain blood. The stools are either absent or scant; some mucus or blood may be passed. The temperature may be subnormal, but varying degrees of fever have been reported. The blood count is of little or no value. The hemoglobin content may be very high, which probably indicates only dehydration. The leukocytes may or may not respond with a rise.

Table 10–3 Signs of Bacterial Peritonitis in the Neonate[a]

Sign	Incidence (%)
Abdominal distention	85
Shock	80
Vomiting	70
Constipation	60
Hypothermia	60
Respiratory distress	55
Fever	15
Diarrhea	15

[a]Data are based on patients described in references 232, 240, and 243. Redness, edema, and induration of the anterior abdominal wall, noted in only one series,[243] are also recognized as characteristic signs.

Although this review was limited to neonates with perforation of the intestinal tract, subsequent reports have corroborated the presence of these findings in infants with peritonitis resulting from a wide variety of causes.[191,232,234-236,240,243,249] Not all of the symptoms described may be encountered in any one patient; however, some are always present (Table 10-3).

The large overlap between signs of neonatal peritonitis and sepsis can make it difficult to differentiate the two on the basis of clinical findings. Signs of intestinal obstruction such as abdominal distention and vomiting, which are seen in 10%to 20% of newborns with sepsis,[9,17,245] may reflect a coexistent unrecognized peritonitis. Because the early use of antibiotics often cures hematogenous peritonitis in infants with septicemia, the diagnosis may be missed in infants who survive. It is noteworthy that peritonitis unassociated with perforation was found at postmortem examination in 4 of 20 infants with sepsis in 1933,[10] 9 of 73 premature infants dying with septicemia between 1959 and 1964,[9] and 9 of 121 such infants dying between 1976 and 1988.[230]

Diagnosis

Demonstration of free intraperitoneal fluid by ultrasonography[284] or abdominal radiographs taken in the erect and recumbent positions can be helpful in the diagnosis of peritonitis, and is sometimes the only evidence of perforation. Absence of definition of the right inferior hepatic margin, increased density of soft tissue, and the presence of "floating" loops of bowel have been recorded as positive signs of ascites.[227,285] Diagnostic paracentesis can be useful in determining whether the fluid is caused by bacterial peritonitis,[244,252,286,287] hemoperitoneum, chylous ascites,[288] or bile peritonitis.[289]

The left lateral ("left-side down") decubitus film is of great value in showing small amounts of intraperitoneal gas.[243] Although pneumoperitoneum can be caused by mediastinal air dissecting from the chest into the abdomen,[290,291] free gas in the peritoneal cavity usually *indicates intestinal* perforation. An associated pneumatosis intestinalis should strongly suggest the diagnosis of NEC, but is not necessarily specific for this condition. Several patterns of intraperitoneal gas distribution have been described[281-293]: the air-dome sign, falciform ligament sign, football sign, lucent-liver sign, saddlebag sign, and gas in the scrotum. Absence of a gastric air-fluid level on an erect abdominal radiograph, together with a normal or decreased amount of gas in the small and large bowel, strongly favors a diagnosis of gastric perforation.[293] This finding is almost always accompanied by pneumoperitoneum.

In equivocal cases, metrizamide contrast studies of the bowel can be helpful in establishing a diagnosis of intestinal perforation.[246,290] Serial abdominal transillumination with a bright fiberoptic light is a useful bedside method for the early detection of ascites or pneumoperitoneum in the newborn.[294]

Failure to demonstrate free air in the peritoneal cavity does not, however, rule out a diagnosis of perforation, particularly if air swallowing has been reduced or prevented through orotracheal intubation, nasogastric suction, or use of neuromuscular blocking agents.[286,290,295] In some cases, the amount of gas in the bowel lumen is so small that even if perforation occurs the gas could escape detection. Alternatively, small leaks may become walled off and the free air reabsorbed.[290,296,297] In three large series of infants with peritonitis in whom a patent site of perforation was found at surgery, pneumoperitoneum was absent in 35% to 75%.[232,243,245]

Radiographic evidence of intestinal obstruction, although a common cause or consequence of peritonitis, lacks sufficient specificity to be a consistent aid to diagnosis. A diffuse granular appearance of the abdomen, with one or more irregular calcific densities lying within the bowel lumen or in the peritoneal cavity, should suggest a diagnosis of meconium peritonitis with possible bacterial superinfection.[260]

Prognosis

Prematurity, pulmonary infections, shock, and hemorrhage related to perforation of the intestinal tract, sepsis, and disseminated intravascular coagulopathy are often the factors responsible for the death of neonates, who may concurrently have peritonitis diagnosed at surgery or at postmortem examination. For this reason, case-fatality rates often represent the mortality rate among newborns dying with, rather than because of, infection of the peritoneal cavity.[231,237,243]

Before 1970, the incidence of fatalities was exceedingly high when peritonitis was associated with gastrointestinal perforation; mortality rates of 70% were observed in large series.[191,232,235,236,238-240,245,297] Heightened awareness of conditions associated with perforation, more rapid diagnosis, and improved surgical management have led to a doubling of survivors in recent years.[237,238] The cause of perforation appears to influence the likelihood of survival, with spontaneous gastric perforation having the lowest mortality rate (10%) and perforation of the duodenum caused by a feeding tube the highest (50%); NEC (40%) and all other causes (25%) occupy intermediate positions.[243]

As survival rates have improved, the number of nonlethal complications after perforation has risen proportionally. In one review, two thirds of surviving infants had significant postoperative complications pertaining to infection (e.g., bacteremia, wound infection, intra-abdominal abscess) or gastrointestinal tract dysfunction (e.g., esophageal reflux, obstruction, stomal stenosis).[243] Secondary surgical procedures to correct these problems were required in more than one half of the infants. Sixty percent required parenteral hyperalimentation for nutritional support during their recovery period.

The mortality rate among neonates with peritonitis from causes other than perforation of the bowel, such as sepsis,[191,232,236,240] omphalitis,[240,277] or a ruptured omphalocele,[232,237,240] although high in the past, has not been reassessed in the past few years.[243]

Early diagnosis and institution of appropriate surgical therapy are major factors in reducing the mortality rate.[243] It has been shown that infants operated on within 24 hours after the onset of symptoms have survival rates almost double those operated on between 24 and 48 hours and two and one half times higher than the rate for those whose surgery was delayed more than 48 hours.[245] Factors with an apparent adverse influence on prognosis include low birth weight,[232,237,240,243,263] low birth weight for gestational age,[230] congenital malformations,[237] male sex,[231] and initial serum pH of less than 7.30.[231]

Treatment

The treatment of bacterial peritonitis is directed primarily toward correction of the causative condition.[231] Careful attention to preoperative preparation of the infant is

essential to survival. As soon as bowel obstruction or perforation is diagnosed, continuous nasogastric suction should be instituted for decompression and prevention of aspiration pneumonitis. Diagnostic needle paracentesis is also useful for relief of pneumoperitoneum and may facilitate exchange of gas by reducing the intra-abdominal pressure. Shock, dehydration, and electrolyte disturbances should be corrected through parenteral administration of appropriate electrolyte solutions, plasma, or plasma substitutes. If blood is discovered in fluid recovered by gastric suction or abdominal paracentesis, use of whole blood, packed red blood cells, or other fluids may be necessary to correct hypovolemia. Persistent bleeding must be evaluated for disseminated intravascular coagulation or thrombocytopenia, or both, and treated accordingly. Hypothermia, which frequently accompanies neonatal peritonitis, should be corrected before induction of anesthesia. Infants who are unable to tolerate oral or tube feedings within 2 or 3 postoperative days should be started on parenteral hyperalimentation.

If a diagnosis of peritonitis is established at the time of paracentesis or surgery, aerobic and anaerobic cultures of peritoneal contents should be taken before initiation of antibiotic therapy. Parenteral administration of a combination of gentamicin or an extended-spectrum cephalosporin with clindamycin and ampicillin should be continued for 7 to 10 days.[216,229] Other antibiotics that provide a broad spectrum against the enteric organisms, *Pseudomonas* sp., enterococci, and anaerobic organisms include the β-lactam and β-lactamase inhibitor compounds and the carbapenems. In the event of a poor clinical response, culture and susceptibility studies of the infecting organisms should be used as guides for modifying therapy.

Leakage of intestinal contents sometimes results in formation of a localized abscess rather than contamination of the entire peritoneal cavity. Management of infants with such an abscess should include antimicrobial therapy and surgical drainage of the abscess by the most convenient route.

NECROTIZING ENTEROCOLITIS

NEC with necrosis of the bowel wall is a severe, often fatal, disease occurring with increasing frequency in recent years. The average annual NEC mortality rate is 13.1 per 100,000 livebirths; black infants, particularly males, are three times more likely to die of NEC than are white infants, and mortality rates are highest in the southern United States.[298-308] NEC occurs in about 5% of infants admitted to neonatal intensive care units; however, the incidence varies widely among centers and even from year to year at the same institution.[309-322] NEC predominantly affects infants with birth weights below 2000 g[298,300,315,323-330]; in several series, the frequency in infants younger than 1500 g was as high as 10% to 15%.[298-301,316,317,321,329,331-335] Only 5% to 10% of all cases of classic NEC occur in term infants.[308,336-338] It has been stated that occasional cases of NEC may be the price to be paid for the benefits of modern neonatal intensive care.[339] Although most reports of NEC emanate from the United States, Canada, and Great Britain, the condition occurs worldwide in countries maintaining neonatal intensive care units. In a review of NEC in two neonatal intensive care units of academic centers, NEC increased the risk for death (OR = 24.5), infections (OR = 5.7), and the need for central line placement (OR = 14.0).[340] Infants with surgical and medical NEC had lengths of stay of 60 and 22 days greater, respectively, than infants without NEC with additional costs of $186,200 and $73,700, respectively, resulting in additional hospital charges of $216,666 per surviving infant.

Pathology and Pathogenesis

Bowel wall necrosis of variable length and depth is the characteristic feature of NEC, with perforation in up to one third of affected infants generally in the terminal ileum or cecum, where microcirculation is poor.[243,303,307,327,336,341-343] The pathogenesis of NEC is not established, but most investigators agree that the initiating event is some form of stress to the immature gastrointestinal tract, which leads to disruption of the mucosal barrier, bacterial invasion and proliferation, and gas formation within the bowel wall (Fig. 10-3).[315,323,324,345] Surgical specimens from early stages of the disease show mucosal edema, hemorrhage, and superficial ulceration with very little inflammation or cellular response. By the second or third day, after progression to pneumatosis and transmural necrosis of the bowel wall, bacterial proliferation and the acute inflammatory reaction become more prominent.[303,327]

There has been much investigation and little agreement on the importance of various perinatal events in the causation of NEC.[315,323,324,344] Except for immaturity and possibly polycythemia, other factors originally thought to predispose to NEC have, on further study, occurred with equal frequency in control populations of infants.[316,321,324,328,329,338,346,347] Maternal complications of pregnancy, labor, and delivery and neonatal respiratory distress syndrome are thought to be unrelated to the development of NEC, whereas evidence linking NEC to birth asphyxia, hypotension, hypothermia, use of vascular catheters, exchange transfusion, feeding history, abnormalities of gut motility, neonatal achlorhydria, and the presence of patent ductus arteriosus is often contradictory. Each of these conditions, singly or together, may act as a stress leading to mucosal injury, but none has been consistently associated with NEC.[348,349] NEC has occurred among apparently healthy infants with no known predisposing risk factors.[298,307,336,345] Several studies (discussed later) suggest that early feeding of premature neonates may play a causal role in NEC. Dvorak and coinvestigators[344] have shown that maternal milk may be protective compared with artificial formulas in a neonatal rat model of NEC; similar to human NEC, artificial feeding of maternal milk reduced the incidence and severity of NEC injury and IL-10 expression was significantly increased when neonates were fed maternal milk.

Some epidemiologic observations suggest that NEC is an infectious contagious disease of nosocomial origin. The temporal clustering of cases at institutions, the association of some outbreaks with single infectious agents or alterations in bowel flora, and the possible beneficial effects of breastfeeding, oral nonabsorbable antibiotics, or infection control measures in reducing the incidence of disease suggest a possible nosocomial cause. Unfortunately, the evidence linking NEC to a specific infectious agent is often circumstantial or open to alternative interpretation. Evidence suggests that

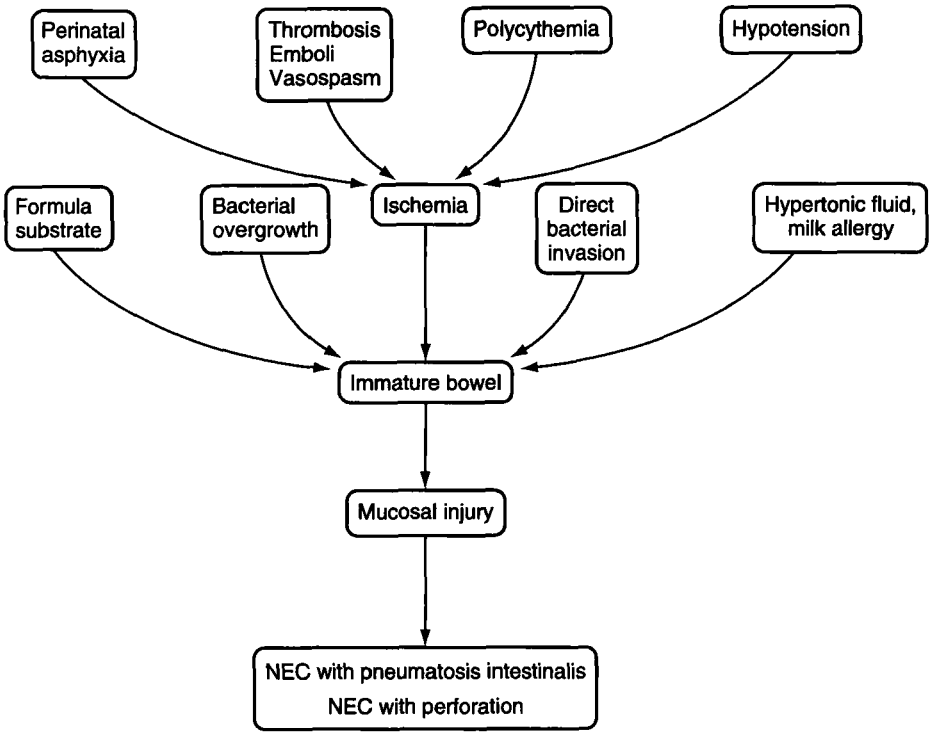

Figure 10–3 Pathogenesis of mucosal injury leading to necrotizing enterocolitis (NEC). (Adapted from Walsh MC, Kliegman RM. Necrotizing enterocolitis. Pediatric Basics 40:5, 1985.)

NEC is the end response of the immature gastrointestinal tract to multiple factors acting alone or in concert to produce mucosal injury, with colonization or invasion by the microorganisms representing only one part of the continuum of that disease process.[282,289,290,307]

Microbiology

Descriptions of sporadic outbreaks of NEC in neonatal intensive care units have led to a search for transmissible agents, including bacterial, viral, and fungal pathogens.[304,315,323,324,345,350-355] Predominance of a single organism in stool, blood, bowel wall, or peritoneal cavity of infants during epidemics of NEC has implicated a number of agents including *Klebsiella* sp.,[301,312,330,343,356-358] *Enterobacter* sp.,[359] *E. coli*,[360,361] *Pseudomonas* sp.,[362,363] *Salmonella* sp.,[364] *S. epidermidis* and other coagulase-negative staphylococci,[365] *S. aureus*,[366] rotavirus,[367,368] coronavirus,[369] coxsackievirus B2,[370] and *Torulopsis glabrata*.[371]

The analogous pathology of necrotizing enteritis caused by *Clostridium septicum*[367,2]and *Clostridium perfringens* in domestic animals,[314,358,373] older children, and adults[374] favored suggestions that *Clostridium* species might act as a primary pathogen in NEC.[315,323,324,345,355,375] Several reports provided evidence that *C. perfringens*,[314,376-379] *Clostridium difficile*,[347,380] or *Clostridium butyricum*, acting alone[381,382] or synergistically with *Klebsiella*,[383] was able to evoke NEC. Subsequent studies, however, indicated that these species were often acquired from the nursery environment[385,386] and could frequently be recovered from healthy neonates.[374,386-392] Clostridial cytotoxin, which had been recovered from the stool of infants involved in an outbreak of NEC,[347,380] has also been found in the stool of up to 90% of normal infants.[347,379,385,391-393] The role of *Clostridium* sp. in NEC remains unclear.[355,375]

The δ-toxins, hemolysins of coagulase-negative staphylococci[394] and *S. aureus*, have also been proposed as possible primary toxins capable of producing NEC in infants. Frequent colonization by δ-toxin staphylococci and higher levels of toxin production by associated strains causing NEC have been reported,[395] as well as one outbreak with δ-toxin–producing *S. aureus* strains.[366] Prospective studies have documented significant shifts in aerobic bacterial bowel flora within 72 hours before onset of clinical NEC[396]; the observed shift results from preclinical changes in the intestinal environment. This suggests that bacteria isolated at the time of onset were present because of possible intraluminal changes and are not directly involved in NEC.

Pending further experimental or epidemiologic observations, the weight of evidence indicates that although bacteria or bacterial toxins may play a primary or secondary role in the pathogenesis of NEC, the occasional association of this condition with a single organism probably reflects patterns of intestinal colonization prevalent in the nursery at the time of an outbreak.[315,323,324,345] Despite intensive efforts to identify a specific infectious agent or toxin in the cause of NEC, there have yet to be convincing reports implicating the same pathogen in more than one outbreak.[355]

Clinical Manifestations

Signs of NEC usually develop in the first 7 days of life,[308,336,397] and 50% or more cases are recognized within 5 days of birth.[298,327,330,398,399] Small, immature newborns often develop illness later, during the second to the eighth week,[332,334] whereas low-risk, term infants may become ill shortly after delivery, as early as the first 24 hours.[337]

NEC is a disease with a wide spectrum of manifestations, ranging from a mild gastrointestinal disturbance to a fulminant course characterized by early bowel perforation,

Table 10–4 Modified Bell's Staging Criteria and Recommendations for Therapy for Necrotizing Enterocolitis

Stage	Signs			Treatment
	Systemic	*Intestinal*	*Radiologic*	
IA (suspected)	Temperature instability apnea, bradycardia, lethargy	Elevated residuals, mild abdominal distention emesis guaiac-positive stools	Normal, mild ileus	NPO, antibiotics for 3 days
IB (suspected)	Same as IA	Frank rectal blood	Same as IA	Same as IA
IIA (definite), mild	Same as IB	Same as IB plus absent bowel sounds ± abdominal tenderness	Dilatation, ileus, pneumatosis intestinalis	NPO, antibiotics for 7-14 days if examination is normal in 24-48 hr
IIB (definite), moderate	Same as IIA with mild metabolic acidosis, mild thrombocytopenia	Same as IIA with definite abdominal tenderness ± abdominal cellulitis or right lower quadrant mass	Same as IIA plus portal gas ± ascites	NPO, antibiotics for 14 days
IIIA (advanced), bowel intact	Same as IIB plus hypotension, bradycardia, severe apnea, respiratory/ metabolic acidosis, disseminated intravascular coagulation, neutropenia	Same as IIB plus peritonitis, marked tenderness, abdominal distention	Same as IIB with ascites	Same as IIB plus 200 mL/kg fluid, inotropic agents, assisted ventilation, paracentesis
IIIB (advanced), bowel perforated	Same as IIIA	Same as IIIA	Same as IIIA plus pneumoperitoneum	Same as IIIA plus surgery

NPO, nothing by mouth.
Adapted from Walsh MC, Kliegman RM. Necrotizing enterocolitis: treatment based on staging criteria. *Pediatr Clin North Am* 33:179, 1986.

peritonitis, sepsis, and shock.[323,400,402] A staging system (Table 10-4) taking these clinical variations into account may be useful in guiding patient evaluation and therapy.[323,403] The apparent stage of disease for an individual infant disease usually can be defined on the second day of illness. An infant who exhibits only mild systemic and intestinal signs 24 to 48 hours after onset is unlikely to develop a more serious illness.[323]

The classic presentation of NEC includes a triad of abdominal distention, retention of gastric contents, and gastrointestinal bleeding.* These findings are often preceded or accompanied by signs consistent with sepsis, such as lethargy, poor feeding, temperature instability, apnea, and bradycardia. Diarrhea is variable, rarely observed in some series[323] but common in others.[334,361] Progression of bowel wall necrosis leading to perforation, peritonitis, and sepsis is reflected in deteriorating vital signs accompanied by persistent acidosis,[404] clotting disorders, and circulatory collapse. Redness, induration, and edema of the anterior abdominal wall are commonly described in the advanced stages of NEC. In the absence of aggressive medical and surgical intervention, the course is rapidly downhill once late signs appear.

*See references 292, 303, 316, 318, 320, 325, 333, 338, 387, 392.

Diagnosis

Radiographic signs of NEC are largely nonspecific,[402] and interobserver variability in the interpretation of films is substantial.[404] However, roentgenographic examination of the abdomen remains the most reliable aid in establishing a diagnosis of NEC.[298,319,327,404,405] Ileus with generalized bowel dilatation and abdominal distention are the earliest radiologic findings. Increasing distention, separation of loops by peritoneal fluid or edema of the bowel wall, a gasless abdomen, pneumatosis intestinalis, and hepatic or portal air occur as NEC worsens. A persistent single dilated loop of bowel remaining relatively unchanged in shape and position in serial films is strongly suggestive[406-408] but not diagnostic[407,409] of localized bowel ischemia with impending perforation.

If free air or ascites is absent on initial abdominal examination, supine and left lateral decubitus films should be obtained every 6 to 8 hours until improvement or definitive surgery or invasive diagnostic measures have ruled out the presence of perforation. When perforation occurs, it is usually within the first day after diagnosis[341] but may be delayed for as long as 5 or 6 days.[410] Although the presence of pneumoperitoneum[245,281,292] or intraperitoneal fluid generally indicates perforation, its absence does not exclude perforation.[222,243,245] In one study,[341] only 63% of infants with NEC and proven perforation had free air, 21% had ascites, and 16% had neither.

When plain films are normal or equivocal, other studies may be diagnostic. A metrizamide gastrointestinal series may demonstrate intestinal perforation or abnormalities of the bowel wall, mucosa, or lumen.[246,290,411] Real-time ultrasonography may reveal portal venous and hepatic parenchymal gas in standard radiographs.[341,412,413] Serial abdominal transillumination with a fiberoptic light has been described as a bedside method for early detection of ascites or pneumoperitoneum, although its sensitivity when compared with standard radiographic methods has not been determined.[294]

A rapid and direct means of establishing the presence of intestinal necrosis or perforation is by abdominal paracentesis.[414-416] Use of the procedure is unnecessary in infants to rule out NEC or in those improving on medical therapy. It is generally reserved for infants suspected, on the basis of clinical, radiographic, and laboratory findings, of having intestinal gangrene. When performed properly, paracentesis is safe and accurate, as described by Kosloske[416]: The abdomen is palpated to locate any masses or enlarged viscera. After an antiseptic skin preparation, a small needle (22 or 25 gauge) is inserted carefully in the flank, at a 45-degree angle. It is advanced slowly and aspirated gently until free flow of 0.5 mL or more of peritoneal fluid is obtained. Any volume less than 0.5 mL is considered a dry tap and cannot be accurately interpreted. The color and appearance of the fluid are noted, and the fluid is transported immediately to the laboratory—preferably in the syringe with air expelled and the needle covered with a cork or rubber stopper—for Gram staining and for aerobic and anaerobic cultures. A positive paracentesis consists of brown fluid or bacteria on the unspun fluid.

The accuracy of paracentesis in determining the need for an operation is between 90% and 95%.[415,416] False-positive results are rare; false-negative results are quite common. Patients with a dry tap should be closely observed under medical therapy with continuing serial paracenteses until indications for or against surgical intervention are clearly defined. Infants with a positive result should undergo exploratory surgery immediately.

Thrombocytopenia and disseminated intravascular coagulation are the most common hematologic complications,[298,330,354,414,417-419] particularly in the presence of bowel gangrene or perforation.[303,419,420] Platelet-activating factor (PAF) has been used to assist in the staging of NEC[421]; a cut-off level of 10.2 ng/mL had a positive predictive value of 100% in identifying infants with stage II or III NEC. Leukopenia and absolute granulocytopenia, apparently caused by margination of white blood cells rather than bone marrow depletion,[422] also have occurred during early stages of the illness.[417,418] A low absolute granulocyte count persisting for 2 to 3 days is associated with a poor prognosis. Hemolytic anemia has been reported in association with NEC related to *C. perfringens.*[378] No consistent urinary abnormalities have been described for NEC, although increased D-lactate excretion, reflecting heightened enteric bacterial activity, may occur.[423] Increased amounts of fecal-reducing substances have been found in almost three fourths of formula-fed premature infants during early stages of NEC, before the onset of abdominal distention, poor feeding, or emesis.[424] Although not readily available, levels of growth factors in urine have been found to be much higher in children with stage II and III NEC[425]; such an analysis might identify children at higher risk of complications and the need for surgical intervention.

The evaluation of patients with NEC should include culture of blood, cerebrospinal fluid, urine, and stool. The likelihood of bacteremia accompanying NEC depends on the severity of bowel involvement; the reported incidence has varied from 10% to 67% among symptomatic infants. Combined data from several large studies showed positive blood cultures in about one third of newborns with NEC.[303,304,353,410] The usual organisms have been *E. coli, Klebsiella* sp., *S. aureus,* and *Pseudomonas* sp., whereas enterococci and anaerobic bacteria were isolated occasionally. A spectrum of organisms similar to those causing sepsis have been isolated from the peritoneal fluid.[303,312,334,354,410] Meningitis may accompany bacteremia, occurring in approximately 1% of NEC cases.[337,426]

Treatment

Early and aggressive treatment must be initiated for any infant suspected of having NEC.[315,323] The modified Bell staging system of NEC may guide diagnostic studies, management, antibiotics, and surgical consultation and intervention (see Table 10-4). Umbilical catheters should be removed whenever possible, oral feedings should be stopped, and nasogastric tube drainage should be instituted. Fluid and electrolyte deficits and maintenance require rigorous attention; blood, plasma, or colloid infusions are often necessary for volume expansion and maintenance of tissue perfusion.

After appropriate cultures (i.e., blood, cerebrospinal fluid, urine, and stool) are obtained, parenteral antibiotic therapy should be started with clindamycin and gentamicin or an extended-spectrum cephalosporin and ampicillin. In nurseries where coagulase-negative staphylococcal colonization or infection is prevalent, initial therapy with vancomycin may replace ampicillin.[427] The β-lactamase and β-lactamase inhibitor combinations (e.g., piperacillin plus tazobactam), can replace gentamicin, ampicillin, and clindamycin, covering anaerobic, gram-negative enteric aerobic, and many gram-positive pathogens. Gentamicin and vancomycin dosages should be modified as necessary on the basis of serum levels. Despite anecdotal evidence that oral nonabsorbable aminoglycosides prevent gastrointestinal perforation in infants with NEC,[428] later controlled studies did not corroborate this finding[429]; their use is not routinely recommended. The need for inclusion of clindamycin to provide activity against anaerobic bacteria in the management of NEC has been questioned.[430]

After immediate treatment has been started, follow-up studies should be instituted. These include serial examinations with measurement of abdominal girth; testing of stools for blood; levels of serum electrolytes, blood glucose, and arterial blood gases; complete blood cell count and platelet count; urine-specific gravity; and supine and left lateral decubitus abdominal radiographs. These tests should be considered as often as every 6 to 8 hours until the infant's clinical condition stabilizes. Attention to vital functions should be provided as necessary on the basis of clinical, laboratory, or radiographic studies. Parenteral nutritional support through a central or peripheral vein must be started as soon as possible.

Early recognition and prompt initiation of medical therapy may reduce the need for surgery. Generally accepted criteria for surgical exploration are a deteriorating clinical condition despite appropriate medical therapy, signs of peritonitis, presence of free air within the abdomen, or a positive paracentesis result. The principles of surgical preparation and management have been discussed by several investigators.[305,416,431,432] In addition to laparotomy with removal of necrotic bowel, closed peritoneal drainage has been proposed as an alternative in very small infants, with a resultant survival of more than 50%.[433]

Prevention

The first observations implicating bacterial proliferation as a factor in pathogenesis of NEC prompted efforts at suppression of gut flora with topical antibiotics in the hope of preventing NEC. Attempts to prevent NEC by giving oral kanamycin or gentamicin prophylactically in the first hours of life, before any signs of bowel involvement are recognized, have generated contradictory data. In controlled clinical trials, a significant reduction in the incidence of NEC in treated premature infants was shown in some,[331,434-437] whereas in others, investigators were unable to demonstrate any protective effect.[437,438] Studies of vancomycin[439] have shown a significant reduction in NEC in high-risk infants. Previous studies revealed selective growth of resistant organisms in bowel flora[331,438,440] and evidence of significant systemic absorption of aminoglycoside antibiotics,[429,441,442] suggesting that oral aminoglycoside prophylaxis is not free of potential risks. Potential risk factors, however, have not been examined in vancomycin trials. Until additional evidence is presented indicating clear-cut benefits from the use of oral aminoglycosides or vancomycin, it does not appear that either should be used routinely for prevention of NEC in premature infants. Epidemiologic evidence that early use of parenteral ampicillin and aminoglycoside therapy may delay or decrease the risk of NEC has not been confirmed in controlled studies.[343] Oral probiotics have been suggested to alter the bowel flora of the infant to reduce the incidence and severity of NEC. Infants fed breast milk and a product including *Lactobacillus acidophilus* and *Bifidobacterium infantis* had a reduced incidence and severity of NEC compared with those of infants fed breast milk alone.[343a]

Excessive or accelerated feedings have been associated with increased frequency of endemic NEC,[443] and some have recommended a schedule of slow advancement of daily feeding volumes limited to about 20 mL/kg/day. NEC infants are more likely to have been fed earlier, to have received full-strength formulas sooner, and to have received larger feeding volumes and increments, and stress and associated respiratory problems may make such infants more vulnerable to NEC.[245,309-314,444] Prior studies of the use of a feeding regimen employing prolonged periods of bowel rest in high-risk infants has been successful in preventing NEC in some nurseries[315] but totally without value in others.[317,324] Later studies have added additional support for standardized feeding schedules in low-birth-weight infants (500 to 2500 g); all have used maximum volumes no greater than 20 mL/kg/day, with feeding beginning at 24 to 72 hours after birth, depending on birth weight and gestational age.[325,326] Both synthetic formulas and breast milk have been successful. Carrion and Egan[445] have suggested that relative hypochlorhydria of the neonate may contribute to NEC and found that hydrochloric acid supplements (0.01 to 0.02 1.0 N HCl/mL of formula) significantly reduced NEC rates and lowered gastric pH. Additional studies have shown that standardized feedings begun at a median of 4 days after onset of NEC can be associated with an abbreviated time until institution of full enteral feedings, a reduced incidence of the use of central catheters and catheter infections, and ultimately, a shorter hospital stay.[446]

Many NEC "epidemics" in neonatal intensive care units, lasting 2 weeks to 7 months, have been reported from centers worldwide.[343,354,355,447,448] Although the microbiologic agents associated with these outbreaks have varied, institution of strict infection control measures was often useful in bringing about a significant decrease in the incidence of NEC; the reasons for success are less clear. However, results have been sufficiently impressive to recommend that enforcement of bedside enteric precautions, together with cohorting of infants and staff, be instituted when two or more cases of NEC occur in a nursery.[323,355,449]

The use of human breast milk has been claimed, largely on the basis of experimental evidence, to exert a protective effect against the development of NEC. Unfortunately, there are no prospective, controlled studies demonstrating any benefit from the feeding of colostrum or breast milk to human neonates. A study demonstrating the protective effect of an orally administered IgA-IgG preparation suggests a possible way to provide benefits of high levels of functionally active antibodies in the gastrointestinal tract.[450]

Prognosis

The mortality rate of NEC is difficult to determine because mild cases of suspected NEC are probably more common than is recognized.[323,400,401] In studies in which analysis has been limited to infants with "definite NEC," mortality figures vary from 20% to 40%.[308,315,324,334-338,397,402,404,415] Several longitudinal studies have shown a significant improvement in outcome.[308,319,404,451] A poor prognosis has been linked with very low birth weight, associated congenital defects, bacterial sepsis, disseminated intravascular coagulation, intestinal perforation, and persistent hemodynamic or respiratory instability.[329,350,397,410] Surgical intervention, generally reserved for the sickest infants with more extensive bowel involvement, is also associated with higher mortality rates.[329,397,401,404,416]

Infants who survive the acute phase of illness generally do well, although NEC may recur in 5% to 10%.[308,334,451,452] In addition to surgical complications (e.g., short-bowel syndrome, anastomotic leaks, fistula formation), enteric strictures are probably the most common delayed complication in surviving infants, occurring in 4% to 20%. Usually found at sites of ischemia and necrosis in terminal ileum or colon,[298,327,453] these strictures often become apparent within a few weeks but may be delayed as long as 18 months. When multiple strictures occur, the intervening normal bowel may form an enterocyst.[405,454] Clinically, strictures present as frequent episodes of abdominal distention, often with vomiting, obstipation, or hematochezia. Diagnosis is confirmed by gastrointestinal contrast studies. Surgery with removal of the stenotic site is necessary to effect a cure.

Long-term follow-up of low-birth-weight infants with severe NEC (i.e., Bell's stages II and III) has documented higher rates of subnormal body weight (15% to 39%) and head circumference (30%) in addition to significant neurodevelopmental impairment (83%).[455] Clinical observations suggest that infants with bowel resection for NEC are at increased risk of sepsis, occurring from 1 week to 3 years (mean, 4 months) later. Almost all had had a central venous catheter in place for parenteral nutrition at the time of infection. Enteric bacilli were responsible for more than 40% of the bacteremias, whereas only 20% were caused by staphylococcal species, which are the usual causes of catheter sepsis. Several infants had two or more episodes of sepsis, and 2 of 19 died as a direct consequence of infection.[445]

ENDOCARDITIS

Neonatal bacterial endocarditis, previously uncommon, has been recognized more frequently in recent years. About 60 cases that meet clinical and bacteriologic criteria sufficient to establish this diagnosis have been reported in the literature[457-485]; 35 have been reported in the past 2 decades. The prolonged survival of critically ill infants and the increased use of intravascular catheters, together with advances in the diagnostic sensitivity and availability of echocardiography, may be responsible for rising recognition of endocarditis. In a 35-year review of 76 cases of endocarditis in children, 10% of patients were younger than 1 year; the youngest patient was 1 month old.[486] Sixty-two (83%) had congenital heart disease, and 77% had had prior surgery. Central venous catheters were additional significant risk factors. For example, at the University of New Mexico in a level III nursery with 3200 to 3500 admissions annually, 12 cases of endocarditis occurred in children younger than 3 months.[487] Organisms isolated from these 10 cases included *S. aureus* (6 cases), *Klebsiella pneumoniae* (1 case), *Enterobacter cloacae* (2 cases), *Candida* sp. (1 case), alpha-streptococci (1 case), and coagulase-negative staphylococci (1 case). Three patients had congenital heart disease with early surgical intervention; all had surgically implanted catheters or intravenous access devices, one had NEC, and one had an associated osteomyelitis.

Etiologic agents of bacterial endocarditis in the newborn have been identified by isolation from blood cultures or morphologic characteristics of organisms entrapped within valvular vegetations examined at autopsy. On this basis, the causative organisms have included *S. aureus* in 36 infants*; streptococci in 6 infants[443,460,489]; *S. epidermidis*[468,469,488] and streptococcus group B[462,472,476] each in 5 infants; *S. pneumoniae*,[460,489] *P. aeruginosa*,[461,467] and *S. marcescens*[465,477] in 2 each; and *Neisseria gonorrhoeae*,[460] *S. faecalis*,[490] *Streptococcus salivarius*,[71] and mixed alpha-hemolytic *Streptococcus*, *K. pneumoniae*, and *P. mirabilis*[468] in 1 each. Despite widespread cardiovascular involvement associated with congenital syphilis, there is no conclusive evidence that this disease produces valvular heart lesions in infected infants.[58] *Candida* endocarditis has become increasingly prevalent, particularly associated with the use of central venous catheters.

*See references 445-447, 450, 453-455, 457, 458, 465-477, 479-500.

Factors that predispose a newborn to endocarditis are not well understood, although intravascular catheters are certainly associated with endocarditis. Unlike older children, in whom congenital heart disease is often associated with endocarditis,[492] cardiac anomalies were found in only nine of the reported cases in neonates in series before 1994.[458,463,465,468,472,473,478,494] Bacteremia arising from an infected umbilical stump,[459-461] conjunctivitis,[460] and skin lesions[460,482] were the presumed sources of valvular involvement in six infants; the invasive organisms associated with these conditions and with neonatal endocarditis in general can infect normal heart valves.[495] Nevertheless, the greater frequency of bacterial and fungal[481,493,496-502] endocarditis in newborns in recent years, particularly in association with prematurity or placement of central vessel catheters or both, indicates that other, more complex mechanisms may also be operative in some cases.[467-470,484,488,493,503]

Observations in laboratory animals and autopsy studies of adults have shown that damage to the intracardiac endothelium with formation of a sterile platelet-fibrin thrombus at the site of the injury is often the initiating event in a patient with endocarditis.[504] Endocardial trauma caused by placement of cardiac catheters, disseminated intravascular coagulation, and various nonspecific stresses associated with prematurity such as hypotension and hypoxia has been implicated in the genesis of thrombi.[468,484,488,495,505,506] Nonbacterial thrombotic endocarditis or verrucous endocarditis usually remains uninfected and is described as an incidental finding at autopsy.[467,484,506,507] With bacteremia, however, implantation of organisms may lead to valvular infection. Whether this mechanism or that of direct bacterial invasion is primarily responsible for valvulitis is not known. A similar pathogenesis has been postulated for formation of mycotic aortic aneurysms in newborns.[480,510,511]

Endocarditis should be suspected in any neonate, particularly a premature infant, with an indwelling vascular catheter, evidence of sepsis, and new or changing heart murmurs. When these findings are accompanied by persistent bacteremia or signs of congestive heart failure in the absence of underlying heart disease, the diagnosis must be considered seriously. Although Janeway's lesions,[484] a generalized petechial rash,[479,490,493] and splinter hemorrhages[490] have been seen, murmurs characteristic of semilunar valve insufficiency, Osler's nodes, Roth's spots, arthritis, and other findings typical of valvular infection in adults and older children have not been observed in neonates. However, multiple septic emboli with involvement of the skin, bones, viscera, and central nervous system are relatively common findings.*

Two-dimensional echocardiography has proved to be an invaluable rapid, noninvasive method for diagnosing endocarditis.[469-472,478,504,515] Although it cannot differentiate between infected and sterile vegetations and other valvular lesions (discussed later), imaging is quite specific, and false-positive readings are uncommon. Unfortunately, less certainty can be placed on a negative report. Despite detection of vegetations with echocardiography as small as 2 mm, the number of false-negative examinations is significant[478,484,516]; in one series, two of three infants with thrombotic valvular lesions 3 to 7 mm in diameter had normal two-dimensional

*See references 445, 447, 449, 450, 454-456, 458-464, 468, 469, 471, 475, 477, 479, 498-500.

echocardiograms.[484] A diagnosis of bacterial endocarditis should be considered in any infant with a compatible history and physical findings regardless of the results obtained by echocardiography. Widespread use of new techniques such as transesophageal echocardiography, which provides detailed views of the mitral and tricuspid valves, and color flow Doppler imaging, which can identify areas of turbulence as blood passes over vegetations or through narrowed valve leaflets, may greatly improve diagnostic accuracy in the future.[515]

When endocarditis is suspected, specimens of blood, cerebrospinal fluid, and urine obtained by catheterization or suprapubic aspiration should be sent for bacterial and fungal culture. Because blood drawn from a central catheter often contains organisms colonizing the line but not necessarily present in the systemic circulation, at least two *peripheral* venous blood cultures should be obtained before antimicrobial therapy is initiated. Volumes of 1 to 5 mL, depending on the infant's size, should be adequate.[504]

Routine laboratory studies are helpful in supporting a diagnosis of endocarditis in the newborn. The leukocyte count, differential count, and platelet count are usually indicative of sepsis rather than cardiac valve infection in particular. Microhematuria has been reported, although rarely.[484,490] A chest radiograph should be obtained to determine signs of cardiac failure or pulmonary or pleural space infection. CT or MRI of the brain can be helpful in an infant with neurologic signs, particularly if left-sided endocarditis or a right-to-left shunt exists. Baseline determinations of inflammatory markers are useful and can be used for assessing the efficacy of the therapy; both the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level have been used.

Intravenous therapy with a penicillinase-resistant penicillin and an aminoglycoside should be started after appropriate cultures have been obtained. In nurseries where methicillin-resistant *S. aureus* or *S. epidermidis* infections have been a problem, vancomycin should be substituted initially for the penicillin antibiotic.[504,515,516] If endocarditis caused by *Enterococcus* sp. is suspected, ampicillin should be added or substituted for the penicillinase-resistant penicillin. After the infecting organism is isolated and antibiotic susceptibilities have been determined, specific antimicrobial therapy can be instituted. Between 4 and 8 weeks of parenteral treatment is usually adequate, depending on the susceptibility of the organism, response to therapy assessed clinically by reduction or elimination of the observed vegetations, and laboratory response. The CRP level often normalizes 2 to 3 weeks before the ESR, and blood cultures are usually sterile after 3 to 5 days of effective therapy. However, *Candida* sp. may persist for weeks despite the use of active antifungal drugs. Dosage and efficacy should be monitored weekly with clinical and bacteriologic response with or without serum antibiotic and bactericidal levels.[515,517] Determination of serum bactericidal titers (Schlichter's assay) is of uncertain value and has never been validated in neonatal endocarditis.[504,515,518] Efficacy of treatment may also be monitored with serial echocardiograms taken until vegetations remain stable in size or disappear.[478,479,481,488,493]

Intravascular catheters must be removed whenever possible and the tip of the removed catheter should be cultured.[504,519] Extremely large or mobile vegetations occluding an outflow tract or posing a high risk of embolism may have to be removed surgically.[476,478,481] In infants with right-sided endocarditis, demonstration of decreased pulmonary blood flow through the use of ventilation-perfusion scan can be of value in confirming the presence of emboli, particularly if there is clinical evidence of increasing respiratory effort and diminished peripheral oxygen saturation.[476]

With the availability of echocardiography, improved clinical awareness, and early diagnosis, prognosis has improved. Although there were infrequent survivors before 1973,[495] the first survivors with proven endocarditis were reported in 1983.[478,479,484] Approximately two thirds of subsequent cases have been cured. Death is usually the result of overwhelming sepsis, often in conjunction with cardiac failure. Early reconstructive surgery for infants who fail medical management may be helpful but has been reported in only a limited number of cases.[520,521]

Inspection of the heart at autopsy has shown the mitral valve to be infected, alone or in combination with other valves, in about one half the patients. The tricuspid valve was involved in 12 infants, pulmonary valve in 7, aortic valve in 6, infected mural thrombi in 12, and an unspecified site in 3. Microscopic examination of valve cusps has revealed the characteristic lesions of endocarditis, with multiple small, confluent, friable vegetations composed principally of bacteria and thrombi surrounded by inflammatory exudate.[458,482,484] On gross inspection, these vegetations are easily confused with noninflammatory lesions such as those of nonbacterial thrombotic endocarditis, blood cysts,[522] developmental valvular defects,[523] or hemangiomas or other vascular anomalies.[524] Cases described as fetal endocarditis in the literature are almost certainly examples of these types of lesions.[508,523,525]

PERICARDITIS

Purulent pericarditis is a very unusual complication of neonatal sepsis. Approximately 20 cases of proven bacterial origin have been reported within the past 50 years.[512,527-538] No single causative agent has predominated. *S. aureus* was responsible for seven cases,[512,527-529] *E. coli* was isolated from three patients,[529,534,535] *Haemophilus influenzae* was found in two,[530,537] and *Salmonella wichita*,[531] *Klebsiella*,[538] and *P. aeruginosa*[536] were isolated from single cases. One early review of *Pseudomonas* sepsis described suppurative pericarditis in four neonates.[532] Another report on the recovery of *Pseudomonas* from the pericardium of premature infants dying of septicemia and meningitis during a nursery outbreak is difficult to evaluate because details of clinical and autopsy findings were not given.[539] Cases caused by *Candida* sp. and *Mycoplasma hominis* have also been described.[493,499,540] The causes of a pericardial effusion in three fetuses with multiple congenital anomalies, myocardial hypertrophy, and pericarditis are uncertain. Although the inflammatory exudate found at autopsy contained polymorphonuclear leukocytes in addition to lymphocytes, no evidence of bacterial infection was found.[541]

Virtually every infant with pericarditis has associated septic foci; pneumonia and multiple pulmonary abscesses are the most common sites. Involvement of pericardium may occur by direct extension from adjoining lung abscesses or by hematogenous spread of bacteria.[527] The presence of infectious processes elsewhere is sufficiently frequent to

warrant the suggestion that pericarditis should be suspected in all infants who develop clinical signs of "heart failure" or a sudden increase in the size of the cardiac silhouette during the course of a purulent infection such as meningitis, pneumonia, or omphalitis.[530,542]

Neonates with bacterial pericarditis generally present with signs and symptoms suggesting sepsis and respiratory distress. Poor feeding, listlessness, emesis, or abdominal distention may be seen in the presence of tachypnea, tachycardia, and cyanosis of various degrees. More specific signs of cardiac involvement became apparent with the accumulation of increasing amounts of pericardial effusion. Unfortunately, the clinical findings of cardiac tamponade are extremely subtle and difficult to differentiate from those of myocardial disease with right-sided heart failure. A rapid pulse, quiet precordium, muffled heart sounds, neck vein distention, and hepatomegaly are findings common to both entities. More specific signs of tamponade, such as narrow pulse pressure or respiratory variations in pulse volume of more than 20 mm Hg (i.e., pulsus paradoxus), are technically difficult to obtain in neonates without an arterial catheter in place. A pericardial friction rub is absent in more than 50% of older infants and children and in most neonates with purulent pericarditis.

Rapid enlargement of the cardiac silhouette, a globular heart shape with widening of the base on tilting, and diminished cardiac pulsation on fluoroscopic examination are of little value in differentiating pericardial effusion from cardiac dilation.[543] The early ST segment elevation and subsequent T wave inversion seen on the electrocardiogram reflect subepicardial damage or inflammation and are similar to changes seen with primary myocarditis. Diminution in the amplitude of the QRS complex by fluid surrounding the heart is not a constant finding. Confirmation of the presence of a pericardial effusion is usually obtained by two-dimensional echocardiography.[512,543] In some cases, CT scan can also be helpful in delineating the extent of a pericardial effusion.[544]

The causes of neonatal pericardial effusion include viral pericarditis,[545] intrapericardial teratoma,[546] maternal lupus,[547] immune and nonimmune[548] fetal hydrops, congenital diaphragmatic defects,[549] chylopericardium,[550] and central venous catheter perforation of the right atrium.[551]

A definitive diagnosis of purulent pericarditis can be made only by obtaining fluid at surgery or through needle aspiration. Care and experience are necessary to facilitate aspiration while avoiding the risks of cardiac puncture or laceration.[541] Accurate monitoring of needle position can usually be obtained through CT guidance, with echocardiographic or fluoroscopic imaging, or by attaching the exploring electrode (V lead) of an electrocardiograph to the needle and by looking for injury current if contact is made with the epicardial surface of the heart.

When fluid is obtained, it should be sent for analysis to the laboratory in the aspirating syringe with the air expelled and the needle covered with a cork or rubber stopper. In addition to cell count and protein and glucose levels, Gram and acid-fast stains should be performed together with cultures for bacteria, viruses, mycobacteria, and fungi. Rapid identification of bacterial antigens by latex agglutination or by counterimmunoelectrophoresis of pericardial fluid, urine, or serum may also help to establish an etiologic diagnosis.[552]

Purulent pericarditis is a medical and surgical emergency. Therapy must be directed toward relief of the cardiac tamponade through adequate pericardial drainage and toward resolution of the infection. Both modes of treatment are essential for successful therapy for bacterial pericarditis in the newborn. Not a single infant with suppurative pericarditis has recovered when treated by antibiotics alone.[527] Although repeated needle aspirations or catheter drainage[553] may be sufficient, the frequent occurrence of loculations of pus, particularly with staphylococcal infection, suggests that open surgical pericardiostomy is the method of choice to achieve adequate drainage.

Cultures of blood, cerebrospinal fluid, and urine should be obtained before instituting antimicrobial therapy. Initial therapy should be based on results of Gram stain or antigen detection tests of the pericardial fluid. If no organisms can be identified, treatment can be started with penicillinase-resistant penicillin and an aminoglycoside (or extended-spectrum cephalosporin) until definitive culture and susceptibility data are available. In nurseries where methicillin-resistant *S. aureus* infection has been a problem, vancomycin should be substituted for penicillin.[517]

The prognosis of neonatal purulent pericarditis is very poor; only three survivors have been reported[512,529,538] before the last decade of the 20th century. Treatment of these patients consisted of needle aspirations, drainage, and systemic antibiotic therapy, and in one case, treatment was combined with local instillation.

MEDIASTINITIS

Purulent mediastinitis has been reported in 11 infants younger than 6 weeks, although it is likely that a great many more cases occur than have been reported in the literature and that it is a frequent complication of cardiothoracic surgery performed in the neonatal period. Six of the reported patients acquired their mediastinal abscess through blood-borne dissemination of organisms[554-556] or by extension from a focus of infection in an adjacent retropharyngeal abscess,[557] pleural or pulmonary abscess,[527,555] or vertebral osteomyelitis.[558] One infant developed infection as a complication of surgery for esophageal atresia.[555] *S. aureus* was the causative organism in four infants, and *S. pneumoniae, Clostridium* sp., and mixed *S. aureus* and *E. coli* were causative in one infant each. Organisms were not identified in four cases.

Traumatic perforation of the posterior pharynx or esophagus, often the result of resuscitative efforts in infants involving endotracheal or gastric intubation, produces a potential site for entry of microorganisms.[559-566] Although retropharyngeal abscess,[567] an infected pseudodiverticulum, or pyopneumothorax may occur as a consequence, purulent mediastinitis has been reported only three times as a complication,[556,560,561] but it is probably more common than is reported. At least one case of mediastinitis has occurred as the result of overly vigorous passage of a nasogastric tube through an atretic esophageal pouch.[560] Low (intrathoracic) perforations are said to have a higher risk of mediastinitis and abscess formation than those in the cervical region.[562]

Early symptoms are nonspecific and are similar to those of any septic process in a neonate. As purulent fluid accumulates in the mediastinum, it places increasing pressure

on the esophagus, trachea, and tributaries of the superior vena cava and thoracic duct, bringing about rapid development of dysphagia, dyspnea, neck vein distention, and facial cyanosis or edema. To maintain a patent tracheal airway, an afflicted infant will lie in an arched position with head extended in a manner very similar to that seen in neonates with congenital vascular ring. A halting, inspiratory, staccato type of breathing, probably because of pain, is also characteristic. Ultimately, the abscess may point on the anterior chest wall or in the suprasternal notch.

Usually, mediastinitis is first suspected when widening of the mediastinum is observed on a chest radiograph obtained for evaluation of respiratory distress. Forward displacement of the trachea and larynx may accompany these findings when retropharyngeal abscess is associated with mediastinitis. Infection after traumatic perforation of the esophagus or pharynx is often accompanied by pneumomediastinum with or without a pneumothorax.[560,562]

Contrast studies performed to define the cause of respiratory or feeding difficulties in infants with mediastinitis may result in flow of radiopaque fluid into an esophageal laceration, mimicking the findings of an atresia, duplication, or diverticulum of the esophagus.[562,563] In such cases, endoscopy often demonstrates a mucosal tear confirming the diagnosis.[563,564]

Treatment should be directed toward establishment of drainage and relief of pressure on vital structures through a mediastinotomy and placement of drainage tubes. The use of a tracheostomy or endotracheal tube may be necessary for maintenance of an adequate airway.

Initial empirical antimicrobial therapy with clindamycin (or metronidazole), ampicillin, and an aminoglycoside (or extended-spectrum cephalosporin) should be started after cultures of the blood and cerebrospinal fluid have been obtained. More limited empirical antibiotic therapy could be provided with a β-lactam and β-lactamase inhibitor combination alone, such as piperacillin plus tazobactam, ampicillin plus sulbactam, or ticarcillin plus clavulanate. Specific therapy can subsequently be determined by the results of bacteriologic studies of these sources or purulent fluid obtained at surgery.

ESOPHAGITIS

The esophagus is infrequently a focus for infection of the fetus or newborn.[568] Esophageal atresia is associated with congenital rubella (see Chapter 28). Severe esophagitis has also been reported in neonates with congenital cytomegaloviral infection.[569] The esophagus may be involved in infants with congenital Chagas' disease identified by signs of dysphagia, regurgitation, and megaesophagus.[570] Esophageal disease may follow mediastinitis in the neonate (discussed earlier). Only occasional cases of bacterial esophagitis in a neonate have been reported; for example, a 940-g male infant developed signs of sepsis on the fifth day of life and died 5 hours later.[569] Premortem blood cultures were positive for *Bacillus* sp. Examination at autopsy revealed histologic evidence of esophagitis with pseudomembranous necrosis of squamous epithelium and many gram-positive bacilli. No other focus of infection was evident.

INFECTIONS OF ENDOCRINE ORGANS

Endocrine glands other than the adrenal are rarely involved in fetal or neonatal infection. Neonatal suppurative thyroiditis in a term Laotian infant was reported by Nelson.[571] The infant presented with a left anterior neck mass at 3 days of age. At surgery, a cystic mass within the left lobe of the thyroid was identified. Purulent material within the mass grew *S. viridans* and nonhemolytic streptococci.

Orchitis has been described in a 10-week-old neonate caused by *S. enteridis*.[572] This infant presented with symptoms of sepsis and diarrhea, subsequently developing unilateral scrotal swelling and erythema on the fifth day after onset of illness. Ultrasound examination of the testis showed a patchy increased echo intensity; the diagnosis was confirmed at exploratory surgery to rule out testicular torsion. Three other cases of infection of the testes caused by *Salmonella* sp. in infants younger than 3 months have been described.[572]

INFECTIONS OF THE SALIVARY GLANDS

Neonatal infections of salivary glands are uncommon, but when such infections occur, involvement of the parotid is the most frequent,[573-578] and submandibular gland infection is infrequent.[574-579] Most infections are caused by *S. aureus*,[573-576] but *E. coli*,[576] *P. aeruginosa*,[576] and group B streptococci (see Chapter 13) have also been implicated in suppurative parotitis. Not surprisingly, oral anaerobic bacteria, including *Bacteroides* sp. and *Peptostreptococcus* sp., may be found in mixed or isolated infections in more than one half of the cases.[577] Infections of the salivary glands occur more frequently in premature and male infants[576,579] and most commonly present during the second week of life. The oral cavity is the probable portal of entry for the infecting organism. However, blood-borne bacteria may invade the salivary glands. Dehydration with resultant decreased salivary flow may be a predisposing cause in some infants.

The clinical manifestations of salivary gland infection include fever, anorexia, irritability, and failure to gain weight. There may be swelling, tenderness, or erythema over the involved gland. Purulent material may be expressed from the ductal opening with or without gentle pressure over the gland.

The diagnosis is made by culture, Gram stain, or both, of the pus exuding from the duct or by percutaneous aspiration of a fluctuant area. If microscopic examination of the Gram stain does not suggest a responsible pathogen, initial antibiotic therapy should be directed against *S. aureus, E. coli,* and *P. aeruginosa* (i.e., penicillinase-resistant penicillin or vancomycin plus an aminoglycoside or extended-spectrum cephalosporin with activity against *Pseudomonas* organisms). If there is a strong suspicion of involvement with anaerobic bacteria (i.e., negative aerobic cultures or failure to respond to therapy directed at aerobic pathogens), consideration should be given to adding or substituting antibiotics appropriate for anaerobic bacteria (e.g., clindamycin, metronidazole in combination with other antibiotics or a β-lactam and β-lactamase antibiotic alone). The duration of therapy should extend throughout the period of inflammation, continuing 3 to 5 days after signs of local inflammation have disappeared. Incision and drainage often may be required; surgical drainage should be considered if there is not a

prompt response to therapy within 72 hours or if fluctuance of the gland becomes apparent. Careful attention to preservation of the function of the seventh cranial nerve is important when considering incision and drainage.

INFECTIONS OF THE SKIN AND SUBCUTANEOUS TISSUE

Bacterial infections of the skin of the newborn may manifest as maculopapular rash, vesicles, pustules, bullae, abscesses, cellulitis, impetigo, erythema multiforme, and petechiae or purpura. In a review of 2836 neonatal infections in Finland, only 6 were characterized as cellulitis.[579a] Most infections of skin are caused by *S. aureus;* such staphylococcal diseases include bullous impetigo, chronic furunculosis, scalded skin syndrome, and breast abscesses (see Chapter 17). Cellulitis frequently accompanied by adenitis and bacteremia may be caused by group B streptococci (see Chapter 13). Cutaneous infections caused by many other bacteria are discussed in this section; however, most microorganisms that cause disease in the neonate may produce cutaneous infections, and when relevant, those infections are discussed in other chapters. For additional information on bacterial infections of the skin, the reader is referred to the text by Solomon and Esterly[580] and the reviews by Swartz and Weinberg[581] and Frieden.[582] Excellent color photographs are included in the *Color Atlas of Pediatric Dermatology* by Weinberg and co-workers.[583]

Pathogenesis

The skin of the newborn has unique characteristics, including absent microflora at birth; the presence of vernix caseosa; a less acid pH than that of older children; and often the presence of surgical wounds, including the severed umbilical cord, a circumcision site, and catheter wounds. The infant is immediately exposed to other infants, personnel, and the nosocomial environment. After the staphylococcal pandemic of the 1950s, information on the colonization of the skin, predisposing factors responsible for neonatal skin infection, bacterial transmission in the nursery, the inflammatory response of the skin to bacterial invasion, virulence factors of staphylococci, and methods of prevention of cross-infection became available. These studies are described in part in Chapters 17 and 35 and have been reviewed elsewhere.[584]

Cutaneous bacterial infection may be a primary event or the result of systemic infection. Septicemic embolic infection may occur at widely separated sites, whereas local infections often occur at a site with an identifiable predisposing cause. Procedures resulting in breaks in the cutaneous continuity, such as forceps abrasions or wounds at fetal electrodes or at venipuncture sites, may be readily identified. The necrotic umbilical cord is a site for proliferation of microorganisms that may invade local tissues.

Infection of the circumcision site remains a concern, because it is the most common surgical procedure in children in the United States. Speert[585] found that cleanliness was frequently disregarded by professional circumcisers as late as the 19th century. Operators were frequently uneducated, were dirty, and often spat on their instruments. Erysipelas, tetanus, and diphtheria have long been recognized as complications of unsterile surgical technique performed on newborns. In a now obsolete and prohibited part of the Orthodox Jewish circumcision ritual, the operator applied his lips to the fresh circumcision wound and sucked a few drops of blood. Such practices were responsible for transmission of syphilis and tuberculosis in neonates in the past. In one report,[586] a 4-month-old infant presented with a penile ulcer, bilateral inguinal adenopathy, and a draining inguinal sinus caused by *Mycobacterium tuberculosis* after the "barber" spat on his razor before circumcision. Reports of 43 cases of tuberculosis associated with circumcision had been published by 1916.[585] Subsequent case reports of severe infection after circumcision include bacteremia related to group B streptococci,[587] local infection and fatal staphylococcal pneumonia,[588] staphylococcal scalded skin syndrome,[589,590] necrotizing fasciitis,[591] and bullous impetigo.[592] Two reports of necrotizing fasciitis after Plastibell circumcision emphasize severe infection as a potential risk of this procedure.[593] One infection caused by *S. aureus* and *Klebsiella* sp. was associated with prolonged convalescent and multiple surgical repairs, whereas a second infant survived staphylococcal necrotizing fasciitis after 14 days of intravenous antibiotic treatment.

The incidence of infection after elective circumcision was investigated at the University of Washington Hospital[594] during the period 1963 to 1972. Infection, defined as the presence of pus or erythema, occurred in 0.41% of 5521 infants and was more frequently associated with the use of a disposable plastic bell (Plastibell, 0.72%) than with the use of a metal clamp (Gomco, 0.14%). Wound cultures were infrequently available, and the microbiologic diagnosis was uncertain for most infants. It is clear that circumcision infection is uncommon, but local spread of infection may be devastating and lead to systemic infection.

Intrapartum fetal monitoring with scalp electrodes and intrauterine pressure catheters and measurements of fetal blood gases through scalp punctures have been associated with infections related to herpesvirus (see Chapter 26), *Mycoplasma* (see Chapter 16), and a variety of aerobic and anaerobic bacteria. Bacterial infections have varied from pustules to abscesses or fasciitis.[578-581] Infection rates are relatively low, varying from 0.1% to 4.5%[597,598]; however, severe infections, including fasciitis, meningitis, and osteomyelitis have occurred as severe complications. A review[599] of causative organisms in fetal scalp monitor infections found that 61% of infections were polymicrobial, involving anaerobic bacteria, aerobic gram-positive cocci, and gram-negative bacilli.

A multitude of specific virulence factors may be important determinants of disease. Some phage types of *S. aureus* are responsible for local tissue damage and systemic disease; other staphylococci elaborate toxins that result in bullae and other cutaneous pathology. Groups A and B streptococci are responsible for cellulitis and impetigo in the infant. *P. aeruginosa* may invade and proliferate in small blood vessels, thereby causing local necrosis and eschar formation (i.e., ecthyma gangrenosum). Infections with *Clostridium* sp. cause disease in devitalized tissues such as the umbilical stump.[600] Similarly, organisms usually considered commensals, such as diphtheroids, *might* be responsible for infection of the cord and fetal membranes.[601]

Microbiology

The skin of the infant is colonized initially by microorganisms present in the maternal birth canal. The skin of infants delivered by cesarean section is usually sterile at birth. After birth, microorganisms may be transferred to the skin during handling by the parents and nursery personnel. The prevalent organisms on the skin during the first few days of life include coagulase-negative staphylococci, diphtheroids, and gram-negative enteric bacilli (including *E. coli*).[602,603] The umbilicus, genitalia, and adjacent skin areas (groin and abdomen) are colonized first; and organisms then spread to the nose, throat, conjunctivae, and other body sites. Organisms present in the nursery environment colonize neonatal skin after a few days in the nursery. *S. aureus*, group B streptococci, and various species of gram-negative bacilli may be present, but the microbiologic flora differs among nurseries and from time to time in the same nursery. Use of soaps and antiseptic solutions modifies the flora on the skin of the newborn. Hexachlorophene decreases colonization with staphylococci and diphtheroids, but gram-negative organisms are unaffected or may increase after use of this agent.[604]

Epidemiology

Male infants are more susceptible to skin infections caused by *S. aureus* than are female infants. Thompson and co-workers[605] demonstrated that males were colonized more frequently in every body site cultured, including the nose, groin, rectum, and umbilicus. Their review of studies indicated that in England, the United States, and Australia, approximately 50% more males had skin lesions than did females. Although the incidence of breast abscesses is equal in males and females during the first 2 weeks of life, such abscesses are more frequent thereafter in females.[606] The reason for this pattern is unclear, but Rudoy and Nelson[606] hypothesized that physiologic breast enlargement may play a role. Hormone production in the female infant after the second week might account for the increase in abscesses of the breast.

Infections caused by methicillin-resistant *S. aureus* (MRSA) involving the skin of children and neonates have markedly increased. The *mecA* gene responsible for resistance to oxacillin and nafcillin is often closely linked to a gene responsible for skin invasion. Before 1997, epidemic MRSA infections occurred in neonatal units involving infections of the respiratory tract, nasopharynx, gastrointestinal tract, eye, blood, wounds or umibilicus[607]; these infections were usually restricted to single nurseries and involved a single genetic variant of MRSA. Since 1990, MRSA infections acquired in the community have been reported with increased frequency,[608] including in infants as young as 2 weeks old. Up to 91% of these infections have involved the skin and soft tissues and, unlike typical nosocomial MRSA, community-acquired MRSA organisms have frequently remained susceptible to trimethoprim-sulfamethoxazole and clindamycin. At the University of New Mexico, continued surveillance of MRSA-colonized and -infected infants in the neonatal intensive care units has shown that by 2003, more than one half of all isolates are now community acquired.

Seasonal variation in the frequency of neonatal skin infections has been reported by Evans and co-workers, who conducted a series of studies at Harlem Hospital (New York).[609] The prevalence of *S. aureus, E. coli,* and streptococci in the nares and umbilicus of infants was lowest in the autumn and usually highest in the summer or spring. No seasonal variation was observed for *S. epidermidis* or *Enterobacter* sp. The investigators concluded that seasonal differences must be considered in investigations of bacterial colonization of the newborn skin and that high humidity may favor gram-negative colonization.

The time of onset of skin lesions associated with sepsis may be early (during the first week of life) or late (up to several weeks or months after birth). Disease acquired in the nursery usually becomes apparent after 5 days of age. Many skin lesions do not appear until after the infant has left the nursery; the observed incidence of skin disease caused by bacteria should include surveillance of infants in the home during the first month of life. Physicians responsible for neonatal care must be alert to the unusual occurrence of skin lesions. The introduction of a new and virulent bacterium, an alteration in technique, or the use of contaminated materials must be considered as possible causes of an increased incidence of such infections.

Clinical Manifestations

Infants who have skin infections that remain localized that are not invasive or part of a systemic infection have few general signs of disease, such as fever, alteration in feeding habits, vomiting, or diarrhea. These signs may be present when significant tissue invasion occurs, as in abscesses or extensive cellulitis. The various cutaneous manifestations that result from infectious diseases are listed in Table 10-5.

Among the common and least specific lesions are maculopapular rashes; these rashes may be caused by viruses (measles, rubella, or enteroviruses), fungi (*Candida* sp.), or bacteria (streptococci or staphylococci), or they may be unassociated with any infectious process. Erythema multiforme lesions have been observed in cases of sepsis related to *S. aureus*,[610] streptococci,[580] and *P. aeruginosa*.[611] Virtually any rash may be associated with bacterial infection. In an outbreak of sepsis caused by *Achromobacter* in premature infants,[612] illness was marked by respiratory distress, including apnea and cyanosis, but was characterized by a rash consisting of indurated, erythematous lesions with sharply defined borders that began on the cheeks or chest and spread rapidly to adjacent areas.

Cellulitis, erysipelas, and impetigo are usually associated with streptococcal infection (group A or B),[613] although impetigo caused by *S. aureus* or *E. coli* has also been reported in infants.

Vesicles, commonly associated with infections by herpesviruses, also are seen on occasion during early stages of skin lesions caused by *S. aureus, H. influenzae,*[614] *L. monocytogenes,*[615] and *P. aeruginosa. Streptococcus* group B,[616] *S. aureus, P. aeruginosa,* herpes simplex virus, and *T. pallidum* may also be responsible for bullous lesions. Pustules commonly occur in staphylococcal diseases but also occur in infections caused by *L. monocytogenes* and, rarely, in skin infections with *H. influenzae*.[617]

Ecthyma gangrenosum is a local manifestation of infection with *P. aeruginosa*.[618,619] Lesions begin as a vesicular eruption on a wide erythematous base. Vesicles

Table 10–5 Manifestations and Etiologies of Some Infections of the Skin in Newborns

Clinical Manifestation	Etiologic Agent[a]	
	Bacterial	*Nonbacterial*
Maculopapular rash	*Treponema pallidum*[b,c] *Listeria monocytogenes* *Streptococcus*[b] *Staphylococcus*[b]	Measles virus[b] Rubella virus[b] Enteroviruses[b] Molluscum contagiosum (639) *Candida* sp.[b]
Cellulitis (erysipelas)	Groups A and B streptococci *Achromobacter* sp. (612)	
Impetigo	Groups A and B streptococci (613)[b] *Staphylococcus aureus*[b] *Escherichia coli*	
Erythema multiforme	Beta-hemolytic *Streptococcus* (610) *Staphylococcus aureus*[b] *Pseudomonas aeruginosa* (611)	
Vesicular or bullous lesions	*Staphylococcus aureus* *Pseudomonas aeruginosa* *Treponema pallidum* *Haemophilus influenzae* type b (614) *Listeria monocytogenes* (615)	Herpes simplex virus[b,c] Cytomegalovirus[b] Varicella virus[b,c] Variola virus[c] Coxsackieviruses[b] *Candida* sp[b] *Aspergillus* sp.[b] *Drosophila* larvae (640) *Sarcoptes scabei* (641)
Pustular rashes	*Staphylococcus aureus*[b] *Listeria monocytogenes*[b] *Haemophilus influenzae* (617)	
Ecthyma gangrenosa	*Pseudomonas aeruginosa* (618-620)	
Abscesses and wound infections	*Staphylococcus aureus*[b] *Staphylococcus epidermidis*[b] Beta-hemolytic streptococci (623) Group B streptococci (624) *Escherichia coli* (625-627) *Klebsiella* sp. (628) *Proteus mirabilis* (629) *Pseudomonas aeruginosa* (630) *Salmonella* sp. (631) *Serratia marcescens* (633) *Haemophilus influenzae* (634) *Haemophilus parainfluenzae* (635) *Corynebacterium vaginalis* (636) *Neisseria gonorrhoeae* (644) *Gardnerella vaginalis* (637) *Bacteroides* sp. (638)	*Mycoplasma hominis*[b] *Candida albicans* (642)
Petechiae, purpura, and ecchymoses	Gram-positive cocci[b] and gram-negative bacilli[b] associated with sepsis *Listeria monocytogenes* (615) *Streptococcus pneumoniae* (615) *Treponema pallidum*[b,c]	Rubella virus[b,c] Cytomegalovirus[b,c] Herpes simplex virus[b,c] Coxsackievirus B[b,c] *Toxoplasma gondii*[b,c]

[a]Numbers in parentheses refer to references.
[b]See appropriate chapter for further discussion.
[c]Including infections acquired in utero.

rupture and form an indurated black eschar followed by larger sharply demarcated, painless necrotic areas, resulting from a small vessel vasculitis with necrosis of the adjacent tissue. The organisms are present in purulent material underlying the necrotic membrane. These lesions are particularly more common adjacent to nose, lip, ear, mouth, and perineum, resulting in avascular necrosis and loss of tissue. *P. aeruginosa* may be grown in pure culture from blood and lesions. Among 48 infants described in one outbreak, lesions appeared within the first 2 weeks of life; most infants died within 3 days of onset.[620] Ecthyma is relatively specific for *Pseudomonas* infections, but similar or identical lesions have rarely been described in infections due to *S. aureus, Aeromonas hydrophila, S. marcescens, Aspergillus* sp., or *Mucor* sp.[621]

Many infants with *Candida* infections have cutaneous manifestations. In a report by Baley and Silverman,[622] 18 infants with systemic candidiasis were described; 8 had a burnlike truncal erythema, and 9 other infants had typical candidal diaper rashes or maculopapular rashes of the axillae or neck.

Abscesses of the skin and subcutaneous tissue are usually caused by *S. aureus* and, less frequently, by streptococci of groups A or B[623,624] or by gram-negative enteric bacilli.[625-633] Community-acquired MRSA organisms are even more likely to produce skin infections with abscess formation. Organisms

that colonize the skin over an area that has been disrupted by an abrasion or other wound may invade the subcutaneous tissue and produce an abscess. *Haemophilus* sp.,[634-636] *Gardnerella vaginalis*,[637] *Bacteroides* sp.,[638] molluscum contagiosum,[639] *Drosophila myiasis*,[640] scabies,[641] and *Candida*[642] are examples of diverse causes of cutaneous abscesses; virtually any bacterial, fungal, or parasitic agent that is normally or transiently on skin may become a pathogen. *E. coli*, *Klebsiella* sp., *P. aeruginosa*,[623,628,643] *N. gonorrhoeae*,[644] and *Bacteroides fragilis*[645] have caused wound infections in infants whose scalps were lacerated by forceps, fetal electrodes, or instruments used for obtaining blood from the scalp in utero. An extensive outbreak of systemic disease caused by *S. marcescens* in a neonatal intensive care nursery in Puerto Rico included wound infections at the site of intravenous infusions.

A cephalohematoma may become infected during sepsis or from manipulation of the cephalohematoma, such as through diagnostic or therapeutic needle puncture[646] or by puncture from a fetal monitor. Infections may be caused by *Bacteroides* sp.,[638] *E. coli*,[625,626] and *P. aeruginosa*.[647] The infection may be associated with meningitis[647] or with osteomyelitis of the underlying skull.[625,626]

S. aureus is the most frequent etiologic agent in breast abscess, but gram-negative enteric bacilli may becoming more common.[627,631,632] Of 36 cases with mastitis seen in Dallas during a 16-year period, 32 cases were caused by *S. aureus*, 1 was caused by *E. coli*, and 2 were caused by *Salmonella* sp.; and both *E. coli* and *S. aureus* were isolated from one abscess.[648] Forty-one cases of mastitis in neonates were managed at Children's Hospital (Boston) from 1947 to 1983.[649] *S. aureus* was responsible for 29 of 34 cases with an identifiable bacterial pathogen. All cases occurred in term infants during weeks 1 to 5 of life. Bilaterality and extramammary foci were rare. One third of infants were febrile, and most had elevated white blood cell counts (>15,000 cells/mm^3). Other reports have identified group B streptococci[624] and *P. mirabilis*[629] as causes of breast abscesses. Brook[632] found that 5 of 14 breast abscesses contained anaerobic bacteria (i.e., *Bacteroides* sp. and *Peptostreptococcus*), but *S. aureus*, group B streptococci, or enteric bacteria predominated; anaerobic bacteria occurred alone in only 2 of 14 cases.

Paronychia may occur in neonates after injury to the cuticle. The lesion is usually caused by *S. aureus* or β-hemolytic streptococci.[650] The authors of a report on an outbreak of paronychia in a Kuala Lumpur nursery suggest but do not prove that the lesions were caused by an anaerobic *Veillonella* sp.[651]

Omphalitis is defined by the presence of erythema or serous or purulent discharge from the umbilical stump or periumbilical tissues. A review by Cushing[652] provided a useful discussion of the pathophysiology, microbiology, diagnosis, and management of omphalitis. The incidence of infection is more frequent in low-birth-weight infants and in those with complications of delivery. A survey of infants born at the Royal Woman's Hospital in Brisbane[653] identified an incidence of approximately 2% among term infants. The mean age of presentation of omphalitis was 3.2 days. Perhaps because hexachlorophene bathing was used, gram-negative bacilli were more frequently associated with infection than were gram-positive cocci. However, microbiologic results are difficult to interpret because swabs of the site of infection do not exclude surface contaminants unless cultures are taken with extreme care and precision.

A series from the United States[654] found that periumbilical fasciitis was more frequent in males but did not find that umbilical catheterization, low birth weight, or septic delivery was associated with a high risk; overall, the incidence of omphalitis was equal in males and females. In this series, omphalitis presented as discharge, cellulitis, or fasciitis; gram-positive organisms were found in 94% of cultures, and gram-negative bacteria were found in 64%. *S. aureus* was the most frequent isolate, with *E. coli* and *Klebsiella* sp. the next most common. Group A streptococci have been responsible for nursery outbreaks that may include an indolent form of omphalitis characterized by erythema and oozing of the umbilical stump for days to weeks, accompanied by pustular lesions of the abdominal wall in some cases.[655] Neonatal tetanus usually occurs as a result of contamination of the umbilical wound by *Clostridium tetani* at delivery.

Acute necrotizing fasciitis is a bacterial infection of subcutaneous tissue and fascial sheath.[630,656,657] Infection can arise in an operative wound or in a focal infection such as a breast abscess, or there may be no apparent predisposing cause. Necrotizing fasciitis has been reported after circumcision[591] and as a complication of insertion of a fetal monitor.[595] The trunk and extremities are the areas most commonly involved; inflammation spreads rapidly along fascial planes, producing thrombosis and extensive necrosis, with infarcts developing in overlying skin. Vesicles and bullae appear, and the skin may become blue-gray or black. Myositis and bacteremia may accompany fasciitis. Staphylococci, group B streptococci,[658] *E. coli*, *P. aeruginosa*, anaerobic bacteria,[596] and mixtures of gram-positive and gram-negative bacteria have been associated with this disease. The bacteria are present in skin lesions, deep fascia, and in some cases, blood. The mortality is high despite the use of fasciotomy, wide debridement, and antibiotics.

Perirectal abscesses may occur in newborns. Unlike older children, most newborns with perirectal abscess do not have underlying immunodeficiency, although infants with acquired or congenital immunodeficiency often present with this condition. The most common cause of perirectal abscess is *S. aureus*, *E. coli*, or other enteric bacilli[659,660]; however, anaerobic bacteria can also be involved. *S. aureus* and enteric bacilli may be more common in infants and newborns.[660] Recent rectal surgery for conditions such as Hirschsprung's disease or imperforate anus (myotomy or rectal dilatation) may be predisposing causes in infants; as in older children, neutropenia may be associated with an increased risk for perirectal abscess.

Otitis externa is uncommon in the newborn. Victorin[661] described an outbreak of neonatal infections in which *P. aeruginosa* was cultured from seven infants with suppuration of the auditory canal. The author suggested that this outbreak was caused by contaminated bath water used in the nursery.

Diagnosis

The appearance of a skin lesion alone may be sufficiently typical to suspect certain etiologic agents (e.g., ecthyma gangrenosum), but more often, the appearance is nonspecific. A microbiologic diagnosis should be sought to

provide specific therapy. The lesion and the surrounding tissue should be cleaned with 70% ethanol to prevent contamination from organisms that colonize the surface. If crusts are present, they should be lifted with a sterile swab to provide drainage, and cultures should be obtained from the base of the lesion. Vesicles and pustules can be aspirated with a needle (20 to 25 gauge) attached to a syringe, or they can be opened and exudate collected on a sterile swab. In general, swabs are not preferred for specimen collection because swab materials bind or inactivate bacterial organisms. Aspiration of abscesses is important; more than one aspiration may be required because the suppurative focus may not be easily distinguished from the surrounding inflammatory tissue. Aspiration of the leading edge or point of maximal inflammation of an area of cellulitis may be of value and should be performed if no other suppurative or purulent sites are available for culture. A small needle (25 or 26 gauge) should be attached to a tuberculin or other small-volume syringe filled with 0.25 to 0.50 mL of sterile non-bacteriostatic saline; the needle should be inserted into the area of soft tissue to be sampled, with continuous, gentle aspiration applied to the syringe. If no fluid is returned to the syringe, a small amount of fluid should be injected and immediately aspirated back into the syringe. Collected material may be sent to the laboratory in the syringe for Gram stain and culture, or, alternatively, the contents may be washed into a tube of bacteriologic broth medium for transport and subsequent culture.

If swabs are used, care must be taken that the material does not dry before it is plated on bacteriologic media. Swabs preferentially should be directly inoculated or rinsed in bacteriologic media and immediately transported to the microbiology laboratory. Alternatively, they may be refrigerated or placed in appropriate transport media if more than a few hours will elapse before inoculation of media in the laboratory. Whenever sufficient material is available (on swabs or in liquid), several slides should be prepared for Gram staining.

It is often difficult to distinguish petechiae from vascular dilatation. Pressure with a glass slide on the border of the lesion is a simple and reliable method for detecting extravasation of red blood cells. If the lesion disappears on pressure, it is probably caused by dilatation of small vessels, whereas persistence of the lesion after application of pressure indicates extravasation of red blood cells. Bacteria may be present in petechial lesions that occur in infants with bacterial sepsis. Blood obtained by aspiration or gentle scraping with a scalpel at the center of the petechiae may reveal the causative organism on Gram stain or culture.

Differential Diagnosis

Sclerema neonatorum, milia, and erythema toxicum are noninfectious lesions that are often confused with infections of the skin.[662] Bullous and purpuric lesions may be caused by noninfectious disorders, including mast cell diseases (e.g., urticaria pigmentosa), histiocytosis X, acrodermatitis enteropathica, dermatitis herpetiformis, epidermolysis bullosa, congenital porphyria,[580] and pemphigus vulgaris.[663] A syndrome of generalized erythroderma, failure to thrive, and diarrhea has been associated with various forms of immunodeficiency.[664]

Sclerema neonatorum is a diffuse, spreading, waxy hardness of the skin and subcutaneous tissue that occurs during the first weeks of life.[646,666] The subcutaneous tissue seems to be bound to underlying muscle and bone. This condition is usually seen on the thighs, buttocks, and trunk. Although associated with sepsis in some infants, sclerema also afflicts infants with dehydration, acidosis, and shock. Most evidence supports the hypothesis that sclerema is a manifestation of shock and insufficiency of the peripheral circulation. When it occurs in infants with generalized infection, sclerema is associated with a poor prognosis. In a review of cases of sepsis at The New York Hospital, sclerema was detected in 6 of 71 infants, 5 of whom died.[667]

Milia are yellow or pearly white papules that are 1 mm in diameter and usually found scattered over the cheeks, forehead, and nose.[662,668] The lesion is a small cyst formed from retention of sebum in sebaceous glands. Because the cyst is capped by a shiny surface of epidermis, it may be confused with a small pustule. Milia are common; Gordon[668] estimated that 40% of healthy newborns have milia. The lesions are common in the first few weeks of life. These cysts may be distinguished from staphylococcal pustules by aspiration and Gram stain of the material.

Erythema toxicum consists of several types of lesions, including 1- to 3-mm, yellow-white papules or pustules on an erythematous base, erythematous macules, or diffuse erythema. These lesions are usually present on the trunk but may involve the head and neck and extremities as well. Most lesions appear within the first hours of life and are uncommon after 2 days of age. Erythema toxicum is uncommon in low-birth-weight or premature infants.[669] The affected infants have no signs of systemic illness or local irritation. A smear of the contents of pustules reveals the presence of eosinophils and an absence of bacteria. Other noninfectious pustular lesions of newborns include neonatal pustular melanosis, which is marked by a mixed infiltrate that has a predominance of neutrophils,[670] and infantile acropustulosis, which is characterized by an eosinophilic infiltration of the skin.[671,672]

Bullae may occur on the skin of the wrist or forearm and usually are caused by trauma.[673] Sucking of the extremity by the infant is believed to cause the bullae, which contain sterile serous fluid.

Purpura may be caused by noninfectious causes, including trauma, erythroblastosis fetalis, or less frequently, coagulation disorders, maternal drug ingestion, congenital leukemia, and congenital Letterer-Siwe disease.

Diaper rash is primarily a contact dermatitis associated with soilage of the skin by urine and stool.[674-676] The rash may occur as a mild erythema or scaling, a sharply demarcated and confluent erythema, or discrete shallow ulcerations. A beefy red, confluent rash with raised margins, satellite (e.g., folliculitis) oval lesions, or discrete vesicular-pustular lesions indicates secondary invasion by *C. albicans* or *S. aureus.* Systemic infectious illnesses that manifest as disseminated rashes (e.g., herpes, varicella, syphilis) may be characterized by early typical lesions in the diaper area.

Treatment

The treatment of localized skin lesions consists of the use of local antiseptic materials, systemic antimicrobial

agents, and appropriate incision and drainage or debridement.

Hexachlorophene (3% detergent emulsion) and chlorhexidine (4% solution) are of value in cleaning small, abraded areas and discrete pustular lesions. Because of the concern over its neurotoxicity and cutaneous absorption, hexachlorophene should not be used on large open areas of skin (see Chapter 17).

Systemic antibiotics should be considered for therapy whenever there is significant soft tissue infection with abscess or cellulitis. The specific antibiotic choice should be made on the basis of the microbiology of the lesion; streptococci may be treated effectively with penicillin G, ampicillin, or extended-spectrum cephalosporins (i.e., cefotaxime or ceftriaxone), whereas staphylococci generally must be treated with penicillinase-resistant penicillins or vancomycin. Infections due to gram-negative enteric bacilli may be treated with aminoglycosides or extended-spectrum cephalosporins based on the results of susceptibility testing. Infections due to *Pseudomonas* organisms can be effectively treated with aminoglycosides or ceftazidime.

Local heat and moist dressings over areas of abscess formation may facilitate localization or spontaneous drainage. Indications for incision and drainage of abscesses in infants are the same as for those in older children and adults.

Prevention

Prevention of local skin infections is best provided by appropriate routine hygiene, maintenance of the integrity of skin (i.e., avoidance of drying, trauma, or chemical contact), frequent diaper changes, and hygienic care of the umbilicus or other wounds or noninfectious skin inflammation. The following measures of skin care are recommended by the Committee of the Fetus and Newborn of the American Academy of Pediatrics[676] to prevent infection:

1. The first bath should be postponed until the infant is thermally stable.
2. Nonmedicated soap and water should be used; sterile sponges (not gauze) soaked in warm water may be used.
3. The buttocks and perianal should be cleaned with fresh water and cotton or with mild soap and water at diaper changes.
4. Ideally, agents used on the newborn skin should be dispensed in single-use containers.
5. No single method of cord care has proved to be superior, and none is endorsed.[676]

Cord care may include application of alcohol, triple dye (i.e., brilliant green, proflavine hemisulfate, and crystal violet) or antimicrobial agents such as bacitracin. Alcohol hastens drying of the cord but is probably not effective in preventing cord colonization and omphalitis. A randomized study of triple dye, povidone-iodine, silver sulfadiazine, and bacitracin ointment showed comparability in antimicrobial control.[677]

During nursery outbreaks, the Centers for Disease Control and Prevention recommend the judicious use of hexachlorophene bathing.[678] Daily hexachlorophene bathing of the diaper area[679] and umbilical cord care with 4% chlorhexidine solution[680] have demonstrated efficacy for prevention of staphylococcal disease (see Chapter 17).

CONJUNCTIVITIS AND OTHER EYE INFECTIONS

Conjunctivitis in the newborn usually results from one of four causes: infection with *N. gonorrhoeae,* infection with *S. aureus,* inclusion conjunctivitis caused by *Chlamydia trachomatis,* or chemical conjunctivitis induced by silver nitrate solution.[681,682] Less commonly, other microorganisms have been implicated as a cause of conjunctivitis, including group A and B streptococci, *S. pneumoniae, H. influenzae* (nontypeable[609] and group b[683]), *P. aeruginosa, Moraxella (Neisseria) catarrhalis,*[684] *Neisseria meningitidis,*[685] *Corynebacterium diphtheriae,*[686] *Pasteurella multocida,*[687] *Clostridium* sp.,[688] herpes simplex virus, echoviruses, *M. hominis,* and *Candida* sp. In addition to meningococcal infections, other neisserial species can be confused with gonococcal infections; *Neisseria cinerea* has been reported to cause conjunctivitis that was indistinguishable from gonococcal infection.[689] An epidemic of erythromycin-resistant *S. aureus* conjunctivitis affected 25 of 215 newborns during a 10-month period; control of the epidemic was achieved by identification of staff carriers and substitution of silver nitrate prophylaxis for erythromycin.[690] The major causes of conjunctivitis in the neonate are discussed in Chapter 12 and Chapter 17. Cultures of the conjunctivae of neonates with purulent conjunctivitis and from the comparable eyes of a similar number of infants chosen as controls revealed significant differences, suggesting causality for *S. viridans, S. aureus, E. coli,* and *Haemophilus* sp.[691,692]

Compared with chemical (e.g., silver nitrate) conjunctivitis, other noninfectious causes for conjunctivitis occur only rarely. Eosinophilic pustular folliculitis has been described since 1970[693]; although this disease usually occurs after 3 months of age, some infants younger than 4 to 6 weeks have been described. These infants present with recurrent crops of pruritic papules primarily affecting the scalp and brow. Biopsy specimens reveal folliculitis with a predominant eosinophilic infiltrate; most infants also have a leukocytosis and eosinophilia. Other acute or chronic cutaneous conditions may also manifest as conjunctival or periorbital inflammation, such as seborrhea, atopic dermatitis, acropustulosis of infancy, and erythema toxicum (see "Infections of the Skin and Subcutaneous Tissue").

In a review by Hammerschlag,[694] the incidence of the two major pathogens ranged from 17% to 32% for *C. trachomatis* and 0% to 14.2% for *N. gonorrhoeae* in four United States studies. In other developed countries such as England,[695] investigators found 8 cases of gonococcal infection and 44 cases of chlamydial infection among 86 newborns with ophthalmia neonatorum; in Denmark,[696] investigators found that 72% of infants with conjunctivitis at 4 to 6 days after birth had positive cultures, but 70% were caused by staphylococci (both *S. aureus* and *S. epidermidis*), and that chlamydiae were isolated from only 2 of 300 newborns. The incidence and microbiology of neonatal conjunctivitis is dependent on the incidence of transmissible infections in the maternal genital tract or the nursery and the use and efficacy of chemoprophylaxis. In Nairobi, Kenya, in a hospital where ocular prophylaxis had been discontinued, the incidence of gonococcal and chlamydial ophthalmitis was 3.6 and 8.1 cases per 100 livebirths, respectively[697]; whereas in Harare, Zimbabwe, in a hospital where prophylaxis

also was not used, the most common cause of conjunctivitis was *S. aureus.*[698] The introduction of tetracycline ointment for prophylaxis at Bellevue Hospital (New York City) led to an overall increase in conjunctivitis associated with an increase in the incidence of gonococcal infection[699] because of the emergence of tetracycline resistance among gonococci.

Infections related to *P. aeruginosa* deserve special attention. Although uncommon, pseudomonal conjunctivitis may be a devastating disease if not recognized and treated appropriately.[699] The infection is usually acquired in the nursery, and the first signs of conjunctivitis appear between the 5th and 18th days of life. At first, the clinical manifestations are localized to the eye and include edema and erythema of the lid and purulent discharge. In some children, the conjunctivitis progresses rapidly, with denuding of the corneal epithelium and infiltration with neutrophils. With extension of the corneal infiltration, perforation of the cornea may occur. The anterior chamber may fill with fibrinous exudate, and the iris can adhere to the cornea. Subsequent invasion of the cornea by small blood vessels (pannus) is characteristic of pseudomonal conjunctivitis. The late ophthalmic complications may be followed by bacteremia and septic foci in other organs.[700]

Pseudomonal eye infections in neonates can occur in epidemic form, with subsequent high rates of mortality and ophthalmic morbidity. Burns and Rhodes[700] reported a series of eye infections caused by *P. aeruginosa* in premature infants with purulent conjunctivitis rapidly progressing to septicemia, shock, and death in four infants. Five other children with conjunctivitis alone survived, but one child required enucleation. Drewett and co-workers[701] described a nursery outbreak of pseudomonal conjunctivitis believed to be caused by contaminated resuscitation equipment; of 14 infected infants, 1 became blind, and another had severe corneal opacities. Rapidity of the course of this infection is indicated in a case report of a 10-day-old infant who developed a corneal ulcer with perforation within 2 days after first observation of a purulent discharge.[702] An outbreak of four cases of *Pseudomonas* conjunctivitis in premature infants occurred within a period of 2 weeks at the American University of Beirut Medical Center[703]; no cause for the outbreak was found.

A review by Lohrer and Belohradsky[704] of bacterial endophthalmitis in neonates underlines the importance of *P. aeruginosa* in invasive bacterial eye infections ranging from keratitis to panophthalmitis. The literature review included 16 cases of invasive eye infections in neonates; 13 were caused by *P. aeruginosa,* and the others were cases of endophthalmitis caused by group B streptococci and *S. pneumoniae.* Other opportunistic gram-negative pathogens associated with outbreaks of infections in nurseries may also include conjunctivitis as a part of the infection syndrome. In a report by Christensen and co-workers,[705] a multiply antibiotic-resistant *S. marcescens* was responsible for 15 cases of pneumonia, sepsis, and meningitis and for 20 cases of conjunctivitis, cystitis, and wound infection over a 9-month period in a neonatal intensive care unit.

Dacryocystitis may complicate a congenital lacrimal sac distention (i.e., dacryocystocele). Harris and DiClementi[706] described an infant who presented on day 4 of life with edema and erythema of the lower lid. Purulent material emerged from the puncta after moderate pressure over the lacrimal sac; *S. marcescens* was grown from the material.

The physician responsible for management of the child with purulent conjunctivitis must consider the major causes of the disease and must be alert to the rare pathogen. In hospitals that practice Credé's method (i.e., silver nitrate application), purulent conjunctivitis during the first 48 hours of life is almost always caused by chemical toxicity.[707] After the first 2 days, the pus of an exudative conjunctivitis must be carefully examined by Gram stain for the presence of gram-negative intracellular diplococci, gram-positive cocci in clusters, and gram-negative bacilli. Appropriate cultures should be used for isolation of the organisms concerned. If the smears are inconclusive and no pathogens are isolated on appropriate media and if the conjunctivitis persists, a diagnosis of inclusion or chlamydial infection is likely.[706,798,709]

The treatment of gonococcal and staphylococcal conjunctivitis is discussed in Chapters 12 and 17. Chlamydial conjunctivitis is reviewed in Chapter 11.

If infection with *Pseudomonas* species is suspected, treatment should be started at once with an effective parenteral antibiotic such as an aminoglycoside (e.g., tobramycin, amikacin, or gentamicin) with or without an antipseudomonal penicillin or ceftazidime (see Chapter 35) and with a locally applied ophthalmic ointment. The use of subconjunctival gentamicin or other antipseudomonal aminoglycoside is of uncertain value; however, if the cornea appears to be extensively involved, there is a risk of rapid development of endophthalmitis, and the subconjunctival injection of antibiotics should be considered in consultation with an ophthalmologist. If the diagnosis is confirmed, this regimen is continued until the local signs of *Pseudomonas* infection resolve.

Recommendations for ocular chemoprophylaxis are discussed in chapter 12 on gonococcal and Chapter 11 on chlamydial infections. Additional information is available in the 2000 edition of the Report of the Committee on Infectious Diseases published by the American Academy of Pediatrics.[710]

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Necrotizing Enterocolitis

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Endocarditis

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Conjunctivitis and Other Eye Infections

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