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Pediatric Infections

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I. Introduction

Improvement in anaerobic microbiologic techniques has resulted in an increase in the isolation and identification of anaerobic organisms from a variety of infectious sites in children. The recent isolation of these organisms from children has led to increased appreciation of their role in pediatric infections. In general, the types of anaerobic infections and the infecting flora are similar to those seen in adults. However, the incidence of these infections varies because of the difference in predisposing conditions. While adults suffer more from ischemic and obstructive diseases, children tend to have more infections of the upper respiratory tract. Sites of anaerobic infections in children are the central nervous system (CNS), oral cavity, head and neck, chest, abdomen, skin, and soft tissue (1). Anaerobic infections tend to result in the formation of abscess,

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as evidenced by infections such as brain, tonsillar, lung, intraabdominal, and cutaneous abscesses.

Anaerobic bacteria colonize the newborn immediately after delivery. The bacteria have been recovered from such neonatal infections as cellulitis of the site of fetal monitoring, neonatal aspiration pneumonia, bacteremia, conjunctivitis, omphalitis, and infant botulism (1).

The fact that similar infections (such as pleuropulmonary or intraabdominal infections) in both adults and children have similar causative pathogens is no surprise. However, certain infections either are unique or are more frequently encountered in children. These infections include neonatal infections, acute and chronic otitis media, mastoiditis, peritonsillar and tonsillar infections, cervical lymphadenitis, periorbital infections, and paronychia. In many instances, the frequency of isolation of aerobic and anaerobic bacteria is unique among this age group.

This chapter presents the role of anaerobic bacteria in children. Since the infections mentioned above (except neonatal) are discussed at length in other chapters, these topics will be mentioned only briefly here, with particular reference to the typical features of these illnesses in childhood. Neonatal infections, which of course are unique to the pediatric group, will be discussed in detail.

II. Neonatal Infections

The incidence of infection in the fetus and the newborn infant is high. As many as 2% of fetuses are infected *in utero,* and up to 10% of infants are infected during delivery or in the first few months of life. Although the incidence of infections caused by anaerobes is small, the conditions predisposing to these infections are similar to those associated with other organisms.

Several factors have been associated with the acquisition of local or systemic infection in the newborn: premature and prolonged rupture of membranes (longer than 24 hr), maternal peripartum infection, premature delivery, low birth weight, depressed respiratory function of the infant at birth or fetal anoxia, and septic or traumatic delivery. The acquisition of infection while the newborn passes through the birth canal is the most frequent mode of transfer.

During pregnancy, the fetus is shielded from the flora of the mother's genital tract, although potentially pathogenic bacteria are found in the amniotic fluid. Inhibitory activity of the amniotic fluid restricts the growth of many bacteria (2), especially during the third trimester. However, colonization of the amniotic fluid occurs in labor with intact membranes (3). Increased perinatal morbidity was shown to be associated with

intraamniotic bacterial colonization with anaerobes (4). The relative sparsity of the *Bacteroides fragilis* population in the cervix at term labor and the added inhibitory effect of the amniotic fluid against this organism (2) at term may explain the relatively low incidence of *B. fragilis* infections at full term, compared to postabortal sepsis (5).

Following rupture of the membranes, colonization of the newborn is initiated, and is continued by further exposure to the cervical flora during the infant's passage through the birth canal (6). Potentially pathogenic aerobic and anaerobic bacteria can be found in the gastric contents of infants, which the baby acquires while passing through the birth canal (6). When premature rupture of the membranes occurs, the ascending flora can cause infection of the amniotic fluid with involvement of the fetal membranes, placenta, and umbilical cord (7). Aspiration of the infected amniotic fluid can cause aspiration pneumonia. Since anaerobic bacteria are the predominant organisms in the mother's genital flora (6), they become major pathogens in infections that follow early exposure of the newborn to that flora.

The immaturity of the immunologic system, which is manifested by decreased function of the phagocytes and decreased inflammatory reactions, may contribute to the susceptibility of infants to microbial infections (8). The presence of anoxia and acidosis in the newborn may also interfere with the defense mechanisms.

The support systems and procedures used in nurseries and intensive care units can contribute to the acquisition of infections. Offending instruments include umbilical catheters, arterial lines, and intubation devices. Contamination of equipment (such as humidifiers), contamination of supplies (such as intravenous solutions and infant formulas), and poor isolation techniques can result in outbreaks of bacterial or viral infections. Such spread is thought to contribute to the clustering of cases of necrotizing enterocolitis in newborns.

A. Conjunctivitis

The most common causes of infectious conjunctivitis (in descending order of frequency) are *Neisseria gonorrhoeae, Staphylococcus, Chlamydia trachomatis,* Streptococcus groups A and B, *Streptococcus pneumoniae, Haemophilus influenzae, Pseudomonas aeruginosa, Escherichia coli, Branhamella catarrhalis, Neisseria meningitidis, Corynebacterium diphtheriae,* herpes simplex virus, echoviruses, and *Mycoplasma hominis* (9).

Recent work also has implicated clostridia and peptostreptococci as probable causes of neonatal conjunctivitis (10). Newborn conjunctival cultures were obtained from 35 babies before the application of silver

nitrate and then 48 hr later. On initial culture, 46 facultative bacteria and 27 anaerobes were recovered. The organisms isolated in almost all of these cases were present also in the mother's cervical cultures and in the baby's gastric aspirates, taken concomitantly. Most of those organisms disappeared from the conjunctiva within 48 hr.

However, clostridial species were recovered from two infants who developed conjunctivitis on the second and third day postdelivery (10). *Clostridium perfringens* was recovered from one newborn, and *Clostridium bifermentans* with *Peptostreptococcus* spp. were recovered from the other. Similar organisms were recovered from the cervix of each mother immediately after delivery. In both infants, a profuse yellow–green discharge was noted in each eye. The conjunctivae were injected, and the examination revealed edematous eyelids, normal light reflex and pupillary reaction, and normal fundi. Local therapy with 2% penicillin eye drops for 5 days resulted in complete cure.

Since anaerobic bacteria have been recovered recently from children (11) and adults (12) suffering from bacterial conjunctivitis, the presence of these bacteria in neonatal conjunctivitis is not surprising. Although these organisms are not the most prevalent cause of inflammation of the eye in the neonatal age group, their presence should be suspected in children whose aerobic and chlamydial cultures are negative, in those who do not respond to conventional antimicrobial therapy, and in newborns at high risk of developing anaerobic infection.

B. Omphalitis

The umbilical stump becomes colonized with bacteria soon after delivery (13). The devitalized umbilical stump is an excellent medium that supports bacterial growth, and the umbilical vessels provide direct access to the bloodstream. The colonizing bacteria may invade the wound and spread through the blood vessels or the connective tissues to cause phlebitis or arteritis, and travel from there into the peritoneum or by emboli to various organs (14). Although infection of the cord stump is rare, its potential sequelae (such as cellulitis, peritonitis, septicemia, multiple hepatic abscesses, and portal vein thrombosis) may prove fatal.

Omphalitis manifests itself by drainage from the umbilical stump or from its base at its point of attachment to the abdominal wall or from the navel after the cord has separated. Secretions may be thin and serous, sanguineous, or frankly purulent, and at times they are foul smelling. Infection may remain restricted to the cord or may spread to the surrounding skin.

In studies that did not use techniques to identify anaerobes, the

predominant isolates have been *Staphylococcus aureus, E. coli, Klebsiella pneumoniae,* and *Proteus mirabilis.*

A recent study of 23 newborns with omphalitis demonstrated the polymicrobial aerobic and anaerobic etiology of neonatal omphalitis (14). Anaerobes were recovered from 39% of the patients. They included the *Bacteroides fragilis* group, anaerobic gram-positive cocci, and *Clostridium perfringens.* Maternal amnionitis caused by *B. fragilis* developed in three of the mothers whose newborns had omphalitis caused by these organisms.

Although anaerobic bacteria were reported as colonizers of noninfected ligated or nonligated umbilical cords (15), only a few reports described their isolation from cases of omphalitis (16). The anaerobes recovered in these cases were *Fusobacterium, Clostridium tertium, C. perfringens,* and *Clostridium sordellii.* Neonatal tetanus caused by *Clostridium tetani* usually results from contamination of the umbilical cord during improperly managed deliveries outside a medical facility. The disease is now rare in the United States (17); but it is still one of the most common causes of neonatal death in developing countries.

The recovery of anaerobes from umbilical infection is not surprising since, during vaginal delivery, the neonate is exposed to the cervical canal flora, including anaerobic bacteria (6).

Without evidence of spread, simple omphalitis responds readily to the local application of alcohol and drying of the infected area. Sometimes antibiotic compresses or ointments are applied. Bacitracin and neomycin, or a combination of these, are the local antibiotics of choice. Systemic antibiotic medication is indicated if the discharge is purulent or if any evidence of periumbilical spread appears. Such spread can cause generalized sepsis and metastatic infection. The final choice of antibiotic will depend on culture and sensitivity tests.

It is recommended that specimens from umbilical infection be routinely cultured for anaerobic organisms. Antimicrobial therapy effective against anaerobes should be considered. This is especially important in infants who are at high risk for developing anaerobic infection, such as those who have a foul-smelling secretion from the amniotic cord stump or those whose mothers had amnionitis.

C. Pneumonia

Pneumonia caused by anaerobes in the newborn can be classified according to the mode of acquiring the infection and the time when the infection began. The infection can be acquired *in utero* by the transplacental route or following intrauterine infection. The pneumonia can be acquired during delivery by inhaling the bacteria that colonize the birth

canal. The type of infection contracted after birth is influenced by environmental factors (e.g., a tracheostomy tube) or by human contact.

Anaerobic pneumonias tend to occur in association with aspiration, tissue anoxia, and trauma (16). Such circumstances usually are present in high-risk newborns, which make them more vulnerable to anaerobic pneumonia, especially in the presence of maternal amnionitis. The diagnosis of bacterial pneumonia usually has been achieved by cultures of tracheal aspirate, pleural fluid, needle aspirates of the lungs, and blood cultures.

Although the role of anaerobes as a cause of pulmonary infection in adults is well established (18), only two reports (19,20) describe the isolation of anaerobic organisms, namely *B. fragilis,* from children with perinatal pneumonia.

Harrod and Stevens (19) described two newborns who presented with neonatal aspiration pneumonia that developed following maternal amnionitis. *Bacteroides fragilis* was recovered from the blood of these children. Brook *et al.* (20) reported three newborns with neonatal pneumonia caused by organisms belonging to members of the *B. fragilis* group. The mothers of all three infants had premature rupture of their membranes and subsequent amnionitis. Organisms identical to those recovered from the newborns were recovered from the amniotic fluid of two of the mothers.

Isolation of the offending organisms should be performed using methods that bypass the oral flora, such as direct lung aspiration.

Antimicrobial therapy of anaerobic pneumonia should use agents effective against the β-lactamase-producing *Bacteroides* spp. These include agents such as clindamycin, chloramphenicol, metronidazole or the combination of a penicillin plus a β-lactamase inhibitor.

D. Infections following Intrauterine Fetal Monitoring (IFM)

Scalp electrodes are used frequently to monitor the fetal heart beat, thus providing useful data for maternal obstetric management and the reduction of risk to the infant.

A number of fetal complications related to application of the scalp electrodes have been observed, including minor ecchymoses and superficial lacerations, leakage of cerebrospinal fluid, osteomyelitis of the skull, sepsis, and scalp abscesses (21).

1. Predisposing Factors

Several factors have been associated with predisposition to scalp infection, including duration of the monitoring and ruptured membranes,

presence of high-risk indications for monitoring, and presence of amnionitis (22). Introduction of the electrode into the scalp can permit the vaginal flora to enter the subcutaneous tissues. The electrode is a nidus for infection, and the longer it is in place, the greater the risk of infection.

The higher infection rate among high-risk infants suggests that these fetuses may be somewhat compromised and therefore are more susceptible to infection. Infants born after normal pregnancies and monitored electively are at lower risk for developing scalp infections (22).

2. Incidence

The rate of scalp infection associated with fetal heart monitoring was estimated to be between 0.4 and 5.2%, and was not found to be related to the type of scalp electrode used (22). Osteomyelitis and bacteremia occasionally have been reported (22,23).

3. Bacteriologic Etiology and Complications

Several case reports describe the recovery of *Neisseria gonorrhoeae, E. coli, Haemophilus influenzae,* and groups A and B streptococci from scalp abscesses (21).

Okada *et al.* (22) studied 42 infants with scalp abscess following fetal monitoring. Anaerobic microorganisms mixed with aerobes were recovered in 58% of the children, aerobes alone in 33%, and anaerobes alone in 9%. The most common anaerobic organisms were *Peptostreptococcus* spp. and *Bacteroides* spp. *Bacteroides fragilis* was also recovered in a case with scalp abscess, osteomyelitis, and bacteremia (23).

4. Clinical Manifestations

A local lesion generally develops within 2 to 3 days after delivery. The lesion usually is localized around the area where the electrode was installed. Sometimes the abscess drains spontaneously, and in some cases osteomyelitis of the occipital bone develops. If a cephalhematoma is present, it also can become infected. As the infection progresses, the skin can become necrotic and slough. The infection can extend and cause meningitis and ventriculitis, or spread systemically in the form of sepsis (23).

5. Diagnosis

Aspiration of the purulent fluid followed by inoculation of the aspirate into adequate aerobic and anaerobic cultures is essential. Blood cultures and cultures of other sites should be performed when indicated.

6. Management

Local management of the abscess may require aspiration or leaving a drain in place. For patients whose skin has sloughed or become necrotic,

extensive debridement may be required, with subsequent covering of the wound site by skin graft. For patients whose abscess is large or in whom an extension of the infection is suspected, parenteral antimicrobial therapy should be started. The choice of the antimicrobial agents depends on the bacteria isolated. When *N. gonorrhoeae* is recovered, penicillin therapy is adequate, but when aerobic gram-negative enteric organisms are recovered, aminoglycosides should be administered. Usually penicillin is adequate for the treatment of most anaerobic organisms, except for the β-lactamase-producing *Bacteroides* spp. Since these organisms frequently were recovered from the infected sites, appropriate coverage with agents active also against these organisms should be used.

7. Prevention

Caution should be used in selecting the infants for the procedure. Intrauterine fetal monitoring should be avoided in infants whose mothers are known to be infected with *N. gonorrhoeae* or who have amnionitis; however, when IFM is essential, the infants should be watched carefully for the development of such a complication.

E. Ascending Cholangitis following Portoenterostomy

Atresia of the extrahepatic bile ducts is associated with an extremely poor prognosis. Kasai *et al.* (24) devised a procedure, hepatic portoenterostomy, that may improve this outlook. Infection of the biliary tract is a frequent complication after this procedure. Anaerobic, as well as aerobic, bacteria are implicated in these infections.

Hitch and Lilly (25) obtained 283 cultures from 19 patients, and recovered aerobic and anaerobic bacteria from the bilioenteric conduits within the first postoperative month and during episodes of cholangitis. *Escherichia coli, Klebsiella* species, group D streptococci, *Pseudomonas* species, *Proteus* species, and *Enterobacter* species were the predominant aerobic isolates. *Bacteroides* species, including *B. fragilis,* were recovered in 11% of the cultures.

Brook and Altman (26) recovered anaerobes from three of six children with cholangitis after hepatic portoenterostomy (Kasai's procedure). These included two isolates of *B. fragilis* and one isolate of *C. perfringens.*

The anaerobes recovered in children with ascending cholangitis are part of the normal gastrointestinal flora in infants. The initial sterile meconium becomes colonized within 24 hr with aerobic and anaerobic bacteria, predominantly micrococci, *E. coli, Clostridium* species, *B. fragilis,* and streptococci (27). The isolation rate of *B. fragilis* and other anaerobic

bacteria in the gastrointestinal tract of term babies approaches that of adults within 1 week (27).

Although the number of infants studied is small, the data suggest that anaerobes play a major role in cholangitis after Kasai's procedure, and that specimens obtained from these patients should be cultured routinely for anaerobic as well as aerobic bacteria. The route by which both aerobic and anaerobic bacteria reach the bile ducts in patients who have undergone Kasai's procedure is probably an ascending one from the gastrointestinal tract. This mode of spread is favored by the surgical procedure that approximates a part of the jejunum to the bile system, by the lack of the normal choledochal sphincter action, and by the stasis that can develop after the surgery. Other mechanisms of development of cholangitis are transhepatic filtration of bacteria from the portal venous blood into the cholangiole and periportal lymphatic infection.

F. Bacteremia and Septicemia

It is difficult to ascertain the true incidence of neonatal anaerobic bacteremia because anaerobic blood cultures were not used in the major series of neonatal sepsis. The incidence of anaerobic bacteremia in newborns varied between 1 and 18 cases per 1000 live births (28,29); anaerobes account for up to 26% of all instances of neonatal bacteremia (29).

A total of 126 cases of anaerobic neonatal bacteremia have been reported in the literature (30). The predominant organisms were *Bacteroides* spp. (53 cases). Among these, *B. fragilis* was predominant. The other organisms were *Clostridium* spp. (33 instances), anaerobic gram-positive cocci (32 cases), *Propionibacterium acnes* (4 cases), *Veillonella* spp. (3 cases), and *Fusobacterium* spp. (1 case).

Multiple organisms, aerobic and anaerobic, were isolated from eight patients reported in one study (29). Simultaneous isolation of the anaerobes from other sites was reported by several authors (29,30). This was especially common with *B. fragilis*. Predisposing and associated infections were noted by various investigators. Brook *et al.* (31) reported the recovery of *B. fragilis* from lung aspirates of two patients with pneumonitis, Harrod and Stevens (19) recovered *B. fragilis* from the inflamed placenta, and Dysant and associates (32) and Brook *et al.* (20) recovered *B. fragilis* from the cerebrospinal fluid of one patient each with meningitis. Brook (23) recovered *B. fragilis* from an occipital abscess that developed after neonatal monitoring with scalp electrodes. Ahonkhai and colleagues (33) reported the concomitant isolation of *C. perfringens* from the placenta of a newborn.

1. Diagnosis

The diagnosis of septicemia can be made only by recovery of the organism from blood cultures. Blood should be obtained from a peripheral vein rather than from the umbilical vessels, which frequently are colonized by bacteria. Femoral vein aspiration may result in cultures contaminated with organisms from the perineum such as *Bacteroides* spp. and coliforms. In many cases, organisms identical to those found in the newborn's blood can be recovered from the mother's blood or amniotic fluid. The examination of gastric aspirates generally is not helpful in the prediction of anaerobic bacteria that were ingested during delivery (6). Examination of the gastric aspirate for white blood cells may reveal the presence of maternal amnionitis.

2. Predisposing Conditions

The factors predisposing to anaerobic bacteremia were found to be similar to those for aerobic bacteremia. Prematurity was reported in about one-third of the newborns with anaerobic bacteremia, and the male-to-female ration was 1.6 : 1. Several investigators (28,29) had demonstrated a relationship between premature rupture of fetal membranes, foul-smelling amniotic fluid, and neonatal bacteremia. Prolonged rupture of fetal membranes often is associated with amnionitis, and it is generally accepted that an important pathway for fetal infection is the ascending route through the membranes from the cervix.

Of interest is the correlation between certain predisposing conditions and some bacterial isolates. Neonatal pneumonia and abscesses were reported in association with the recovery of *B. fragilis* and necrotizing enterocolitis with the recovery of clostridia (34–36).

The clinical manifestations of neonatal anaerobic bacteremia are not different from those seen in aerobic bacteremia (29). Over half of the infants had evidence of fetal distress, and three-fourths had a low Apgar score. A positive correlation between the presence of foul-smelling discharge at birth and bacteremia caused by *Bacteroides* spp. was noted (29). About two-thirds of the infants may manifest respiratory distress, with tachypnea and/or cyanosis shortly after birth. Chest films may reveal pneumonitis, indicating prenatal aspiration of infected amniotic fluid and subsequent development of pneumonia.

Other clinical manifestations are nonspecific, and include poor sucking and feeding activity, lethargy, hypotonia, irritability, and tonic-clonic seizures.

3. Prognosis

Mortality depends on such factors as age of the patient, underlying disease, nature of the infecting organism, speed of diagnosis, and type of

surgical or medical therapy. The overall mortality from anaerobic bacteremia in the 126 patients reported in the literature is 18.3% (30). The highest mortality occurred in *Bacteroides* infections (36%), while the mortality from other organisms was generally below 10%.

Spontaneous recovery from anaerobic bacteremia has been reported (29,37), but most reports state the need to adequately treat such patients (31) and also describe infants who were inappropriately treated and died (20). Complete recovery generally follows appropriate therapy in the absence of complicating factors such as other sites of infections (meningitis, abscesses).

4. Therapy

Antimicrobial therapy must be started as soon as possible in infants suspected of bacteremia. In most cases, this should be done before the recovery of organisms. The clinician cannot wait for this information because of the vulnerability of newborns to bacterial infections.

In most instances, a penicillin derivative and an aminoglycoside are used to treat newborns. Although most anaerobic organisms are susceptible to penicillin G, members of the *B. fragilis* group and some strains of other *Bacteroides* are resistant to that agent. Therefore, such therapy can be inappropriate for the eradication of β-lactamase-producing *Bacteroides* (20). Antimicrobials that are effective against these organisms should be used, including clindamycin, metronidazole, cefoxitin, chloramphenicol, imipenem, and the combination of a β-lactamase inhibitor and a penicillin.

Since clindamycin does not penetrate the blood–brain barrier in sufficient quantities, it is not recommended for the treatment of meningitis. Other antimicrobial agents such as chloramphenicol or metronidazole, which are known to penetrate the central nervous system, should be administered in the presence of meningitis. Although the experience in newborns is limited, metronidazole has been used successfully in the treatment of neonatal bacteremia (38).

The length of treatment for anaerobic infections is not established. However, it is apparent from data derived from older children (31) that prolonged therapy of at least 14 days is adequate to eliminate the infection.

Surgical drainage is essential when pus has collected. Organisms identical to those causing anaerobic bacteremia have been recovered from other infected sites in many patients. In some cases, these extravascular sites undoubtedly serve as a source of persistent bacteremia.

The early recognition of anaerobic bacteremia and the administration of appropriate antimicrobial and surgical therapy play significant roles in preventing mortality and morbidity in newborns.

G. Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC) is a relatively common disease in the newborn, occurring in 1 to 2%. The term NEC has been applied to a clinical syndrome that probably has multiple etiological factors. The type of feeding, prematurity, low birth weight, umbilical catheterization, hypoxemia, and other conditions that inhibit oxygen delivery to the gut may predispose the newborn to develop NEC (39). The role of bacteria such as *E. coli, K. pneumoniae,* and other organisms in NEC has been suggested because they have been isolated in various epidemics (39). However, the role of anaerobic bacteria in NEC has been studied only recently (40).

1. Predisposing Conditions

Certain infants have been identified as being at high risk. Many of these infants are premature, some are small for gestational age, and almost all have sustained a period of stress or hypoxemia. Hyaline membrane disease, sepsis, congenital heart disease, hypothermia, and hypoglycemia have all been associated with development of NEC. Maternal complications that are associated with fetal distress and shock (such as prolonged rupture of membranes and maternal infection) frequently are observed in these infants.

2. Etiology

Two sequential conditions are significant in the development of NEC. The first is injury to the intestinal mucosa caused by ischemia, which is followed by the detrimental activity of intestinal bacteria.

Damage to the intestinal mucosa can be due to various factors that may be synergistic. In shock and hypoxia, there is a shunting of blood to the heart and brain and reduction in the blood supply to the intestinal tract and kidney. This "diving reflex" can cause intestinal ischemia and permanent damage to the mucosa, including initial thrombosis of the vascular canal and local infarction of the bowel.

Some procedures that may cause gut ischemia have been associated with NEC, including the use of umbilical and venous catheters. The possibility exists that interruption of portal venous flow during the use of the catheters may result in compromise of the gut mucosa.

Diet also has been associated with the etiology of mucosal damage. It was noted that NEC rarely occurs before feeding, and it is especially prevalent in infants fed with hyperosmolar formulas. Since premature infants are relatively unable to handle large loads of water and electrolytes, severe fluid loss with damage to the mucosa can occur when these solutions are given.

The intestinal bacteria exploit the break in the integrity of the mucosa. Adynamic ileus and stasis develop and bacteria colonize and multiply in the fed infant whose immunologic defenses are deficient. Gas-forming organisms that generate pneumatosis may accumulate and rupture the intestinal wall, producing pneumoperitoneum and peritonitis. Further invasion of the lumen takes place, and bacterial proliferation extends into the lymphatics and radicles of the portal circulation and reaches the liver. Finally, overwhelming sepsis and death occurs.

Numerous reports have implied that the fecal microflora may contribute to the pathogenesis of NEC. A broad range of organisms generally found in the distal gastrointestinal tract have been recovered from the peritoneal cavity and blood of infants with NEC.

Among the various organisms isolated from infants with NEC, and thus implicated in the etiology of NEC, are the acknowledged enteric pathogens (rotavirus, coronavirus, coxsackie B_2 and *Salmonella,* and members of the normal flora of the neonatal gut such as *E. coli* and *K. pneumoniae*) and nonenteropathogenic organisms (*Enterobacter cloacae* and clostridia) (41).

Clostridia may be pathogenic in certain cases of NEC (34, 40, 41). Pedersen *et al.* (40) isolated *C. perfringens* from an infant with fulminant NEC, and postulated that the disease might be gas gangrene of the bowel. In other investigations, *C. perfringens* (34, 42), *Clostridium butyricum* (43, 44), *Clostridium difficile* (45), and other clostridia have been isolated from infants with NEC. All these clostridial species also have been recovered from the blood of newborns with NEC (35, 36, 43). The toxin of *C. difficile,* the agent of antibiotic-associated colitis, has been found in the stools of infants with NEC (46) and also in stools of normal infants (47). Because clostridia are normal inhabitants of the neonatal gastrointestinal tract, their role as primary pathogens of NEC has been challenged (42). The clostridia may act as secondary invaders of an already existing necrotic focus. The mechanism may be similar to that postulated for a type of necrotic enteritis occurring in children and adults in China and Sri Lanka, in which *C. perfringens* invades an intestinal wall previously damaged by parasitic infestation (48).

The hypoxia and circulatory disturbances in small premature infants at risk for NEC may lead to ischemic segments of bowel, in which the multiplication of clostridia and the production of toxin may result in bowel ulceration, infarction, pneumatosis, and the clinical picture of enterocolitis.

Clostridia in the gastrointestinal tract do not cause illness unless they invade the tissues and/or produce exotoxins. A low oxidation–reduction potential, which occurs in the presence of devitalized tissue, is essential for toxin production. Therefore, those infants who are colonized by

clostridia and who have an episode of intestinal ischemia may be at risk of clostridial invasion of the devitalized portions of their own intestines.

The gas-forming capability of certain clostridia may explain the more extensive pneumatosis intestinalis and the higher incidence of portal venous gas among the infants with clostridia. The production of clostridia exotoxins, which cause cell lysis and tissue necrosis, may explain the more rapid progression to gangrene and the more extensive gangrene found in infants with clostridia (49).

The anaerobic bacteria, including clostridia, are considered to be members of the normal flora of infants of this age. Long and Swenson (27) showed that most newborns were colonized by 10 days of age with aerobic gram-negative rods as well as by an anaerobic flora. Various species of clostridia were found in one-third of the infants. The sources of the neonatal intestinal flora are (a) the unsterile environment to which the infant is exposed from the moment he or she leaves the uterus, and (b) the normal flora of the cervix and vagina, which contains many anaerobes, including clostridia (6). Differences among neonates in gestational age, route of delivery, and type of feeding are associated with different colonization patterns of aerobic and anaerobic bacteria (27).

3. Clinical Manifestations

The onset of NEC generally is in the first week of life, but in some patients it may be delayed to the second or third week. The typical infant with NEC is premature and recovering from some form of stress, but is well enough to begin gavage feedings. He or she develops temperature instability, lethargy, and moderate abdominal distention. The stools show traces of occult blood, and diarrhea may be present. As abdominal distention progresses, the gastric residue rises, the urine volume decreases, and osmolarity rises. The gastric aspirate then becomes bile stained, hypotension develops, and gross blood appears in diarrheal stools. If untreated, the patient will progress to massive abdominal distention, acidosis, disseminated intravascular coagulation, peritonitis, and vasomotor collapse.

4. Diagnosis

The earliest radiographic finding may be dilation of the small bowel. The pattern suggests mechanical or aganglionic obstruction, most frequently in the form of multiple dilated loops of small bowel, but sometimes at isolated loops. Air–fluid levels often are observed in the erect position. Commonly, intestinal loops will appear separated because of the presence

of mural edema or peritoneal fluid. This progresses to pneumatosis intestinalis in about 30% of infants, and about one-third of those also will have gas within the liver's portal venous system.

Common findings are thickened bowel wall, bubbly appearance of the intestinal wall and contents, and loops of unequal size. Free air ultimately will be identified within the peritoneal cavity of all infants with NEC who are not successfully treated. Often the site of perforation is walled off, and the intestinal wall may be intact in some infants with gas under the diaphragm.

Stool cultures are consistently negative for pathogens, but blood cultures yield organisms in about one-fourth of the patients. The white blood count may be low or high, and the platelet count usually falls. At least 50% of infants with NEC have platelet counts of 50,000/mm^3 or less. Prothrombin time and partial thromboplastin times are elevated. Hyponatremia is common at the outset of NEC.

5. Management

Medical management consists of withholding oral feeding, placement of an asogastric tube, vigorous intravenous hydration with fluids containing electrolytes and calories, support of the circulation with plasma, blood, or dextran, and administration of oral and systemic antibiotics for the prevention and treatment of sepsis.

The acutely ill neonate presenting with a septic shock-like condition requires immediate attention. Antibiotics appropriate for the known sensitivities of the nursery patient's enteric flora should be started immediately; ticarcillin and gentamicin or clindamycin and an aminoglycoside are satisfactory. White cell transfusions may be effective in infants with sepsis whose bone marrow reserves are depleted, but there is no agreement on this point. Orally administered aminoglycosides are not indicated since they do not prevent intestinal perforation or alter the course of the disease (50).

Penicillin and metronidazole, which are effective against most clostridia should be used in the treatment of infections by these organisms. Because of the resistance of many *Clostridium* spp. to clindamycin, this drug should not be used for these organisms.

When NEC has been detected early and appropriate therapy instituted promptly, only a small percentage of infants will require surgical intervention. Of the many indications for surgery in NEC, the most common is intestinal perforation (51). This acute emergency usually develops between 12 and 48 hr after the onset of colitis, although it has been noted as late as 1 week. Additional surgical indications include a right lower quadrant mass, a persisting isolated dilated loop of bowel, abdominal wall

erythema, thrombocytopenia, acidosis, ascites, and failure to respond to medical therapy.

6. Prevention

Prophylaxis with oral kanamycin or gentamicin has been shown to either lower the incidence of the disease or have no appreciable effect (52). Nevertheless, multiple antibiotic-resistant organisms may produce severe morbidity (52), and NEC can develop despite the suppression of gram-negative stool flora (52). Superinfection with *Staphylococcus aureus* or *Candida* may develop. Direct gastrointestinal injury may be induced by aminoglycosides (53). The systemic absorption of gentamicin may also have an adverse effect (50). Aminoglycosides are not effective against clostridial organisms, and the use of oral vancomycin may be indicated if clostridia are cultured (45). At present, endemic NEC occurs too infrequently and unpredictably to warrant the administration of oral antibiotics. Nevertheless, during epidemics of this disorder, especially those associated with a specific organism, appropriate antimicrobial prophylaxis may be warranted. Infection control measures are indicated.

Infant botulism is presented in Chapter 28.

III. Infection in Childhood

A. Central Nervous System Infections

Anaerobes are frequently isolated from brain abscesses in children. The seeding of anaerobic bacteria into the central nervous system occurs either through contiguous spread from chronic mastoiditis, otitis media, or sinusitis, or through hematogenous seeding from a distant site (e.g., lung or abdomen).

Brain abscesses occur most frequently in the first 20 years of life and between the ages of 50 and 70 (54). The most common anaerobic organisms found are gram-positive anaerobic cocci, *Bacteroides* species (including *B. fragilis*), *Fusobacterium,* and *Actinomyces.*

In a recent study of 19 children with brain abscesses, 14 were found to have sinusitis and 2 others had dental infections (54). Anaerobic organisms were recovered alone in 63% of the specimens, mixed anaerobic and aerobic organisms were recovered in 26% of the specimens, and aerobes alone were recovered in two patients (11%). The experience emphasizes the importance of anaerobes in the pathogenesis of intracranial abscesses.

Cases of anaerobic meningitis are rare; however, when reported, they are usually associated with chronic otitis media or as a complicaton of a surgical procedure such as lumboperitoneal shunts (55).

B. Head and Neck Infections

1. Chronic, Recurrent Pharyngotonsillitis

Group A β-hemolytic streptococci (GABHS), *S. aureus,* and *S. pneumoniae* are traditionally associated with tonsillar and peritonsillar infections. However, anaerobes also have been isolated from the tonsils of children with chronic recurrent tonsillitis (56) and peritonsillar abscess (57). β-Lactamase-producing strains of *B. fragilis, Fusobacterium* spp., and *S. aureus* were isolated from the tonsils of about three-fourths of children with recurrent tonsillitis (58–60).

A recent study demonstrated an association between the presence of β-lactamase-producing organisms (BLPO) and the outcome of 10-day oral penicillin therapy (60). Of 98 children with acute GABHS tonsillitis, 36 failed to respond to therapy. Before therapy, 17 isolates of BLPO were detected in 16 (26%) of those cured. After therapy, 30 such organisms were recovered in 19 (30%) of the children. In contrast, before therapy, 40 BLPO were recovered from 25 (69%) of the children who failed, and after therapy, 62 such organisms were found in 31 (86%) of the children in that group. Brook and Gober (61) have demonstrated the rapid emergence of BLPO after one course of penicillin. The organisms were members of the *Bacteroides melaninogenicus* group, *S. aureus, B. catarrhalis,* and *H. influenzae.* These organisms also were isolated from the household contacts of children repeatedly treated with penicillin, suggesting their possible transfer between family members.

These BLPO may be responsible for protecting streptococci from penicillin. This protective action has been demonstrated *in vitro* and *in vivo* (62–64). A 200-fold increase in resistance of GABHS to penicillin was observed when it was inoculated with *S. aureus* (62). When mixed with cultures of *B. fragilis,* the resistance of GABHS to penicillin increased 8500-fold (63).

Using a subcutaneous abscess model in mice, Brook *et al.* (64) demonstrated the protection of GABHS from penicillin by *B. fragilis,* and *B. melaninogenicus.* Either clindamycin or the combination of penicillin and clavulanic acid (a β-lactamase inhibitor), which are active against both GABHS and *Bacteroides,* were the most effective in eradicating the infection.

Under these circumstances, therapy directed at both the BLPO and the streptococci may be required for the eradication of infection. Several studies have described the efficacy of clindamycin and its parent compound, lincomycin, in the treatment of recurrent streptococcal illness or the streptococcal carrier state (65–69). The superiority of these drugs may be due to not only their effectiveness against GABHS but also the

sensitivity of other aerobic and anaerobic organisms that may "protect" the pathogenic streptococci by producing β-lactamase.

The most recent of these studies is a prospective randomized study comparing penicillin, erythromycin, and clindamycin therapies (69). β-Lactamase-producing aerobic and anaerobic bacteria were present in 43 of the 45 (93%) tonsillar cultures before therapy. The administration of penicillin eradicated GABHS in 2 of 15 patients, erythromycin in 6 of 15, and clindamycin in 14 of 15.

2. Suppurative Thyroiditis and Parotitis

Suppurative thyroiditis and parotitis generally have been regarded to be due primarily to *S. aureus*. However, anaerobic bacteria, including *Bacteroides* spp. and *Peptostreptococcus* spp., recently have been identified as causative organisms (70–72).

3. Chronic Sinusitis

When appropriate microbiological techniques for anaerobes are applied, anaerobes frequently are recovered in chronic sinusitis. In one study (73), 43% of the patients harbored anaerobes in mixed culture; in 9%, anaerobes were found to be the only isolate. The predominant anaerobes isolated were *Peptostreptococcus* spp., *Bacteroides* ssp., and *Veillonella* spp. In a study of 40 children with chronic sinusitis, anaerobes were isolated from all 37 culture-positive patients (74). Anaerobes were the only isolate in 23 patients (62%), and were recovered with aerobes in the remaining 14 patients (38%). An average of almost three anaerobes per specimen was found. *Bacteroides* spp. (including *B. melaninogenicus*), anaerobic gram-positive cocci, *Fusobacterium* spp., β-hemolytic streptococci, *S. aureus*, and *Haemophilus* spp. were the organisms isolated, in descending frequency. *Bacteroides fragilis*, which has been isolated from chronically inflamed sinuses of adults, was not isolated in this group of pediatric patients.

The fact that anaerobes have been isolated in brain abscess and meningitis occurring after sinusitis (54) emphasizes the urgency of appropriate therapy. Therapy should include the early use of effective agents directed at the likely pathogens and also surgical intervention, if necessary.

4. Dental Infections

Anaerobes are responsible for periodontal infections in children. *Fusobacterium* spp., pigmented *Bacteroides*, anaerobic gram-positive cocci, and *Actinomyces* spp. are the significant pathogens associated with dental infections such as periodontitis and periodontal abscess (75).

5. Otitis Media

The more chronic the nature of otitis or mastoiditis, the more frequently anaerobes are isolated. For example (76), in acute otitis, anaerobic gram-positive cocci were isolated from 15% of the aspirates, whereas another study (77) recovered anaerobes from 56% of the aspirates in patients with chronic otitis media. Chronic ear infections are usually polymicrobial. The predominant aerobes are enteric gram-negative rods and *S. aureus*, and the predominant anaerobes are *Bacteroides* spp., gram-positive anaerobic cocci, and *F. nucleatum*. Many of the organisms recovered from the chronically infected ear produce the enzyme β-lactamase.

In a study of 22 children undergoing mastoidectomy for chronic mastoiditis (78), anaerobes were isolated alone or in combination with aerobes in 21 (95%). An average of 3.5 organisms per specimen (2.2 anaerobes and 1.3 aerobes) were isolated; the most prevalent organisms were *Bacteroides* spp. (including *B. fragilis* and *B. melaninogenicus* groups), *S. aureus*, *Pseudomonas aeruginosa*, and *E. coli*. Antibiotics effective against a polymicrobial flora can provide effective therapy in chronic otitis media. Further studies are needed to define the optimal antibiotic and surgical treatment.

C. Intraabdominal Infections

Anaerobic bacteria have been more closely linked to intraabdominal infection than perhaps any other infection in the body. This is not surprising because anaerobes outnumber aerobes in the gastrointestinal tract by 1000 to 1 (16). With the introduction of improved anaerobic bacteriology, anaerobes have been isolated from nearly all specimens obtained from abdominal infections, such as those following trauma or perforated appendicitis.

Bacteroides fragilis is the most important pathogen in appendicitis-related infections (79). One study (80) of 100 peritoneal fluid specimens from children who had undergone appendectomy reported anaerobic organisms in 88% (14% alone and 74% in mixed culture) of the specimens. *Bacteroides* spp. were the predominant (157 isolates) anaerobes, including 92 in the *B. fragilis* group and 26 in the *B. melaninogenicus* group. All of the *B. fragilis* and 25% of the other *Bacteroides* isolates were β-lactamase producers. The principal aerobic organism isolated was *E. coli* (57 isolates). *Bacteroides fragilis* and *E. coli* were also primary organisms isolated from postsurgery draining wounds.

The polymicrobic nature of infection associated with a perforated appendix is emphasized by this report. In addition, the presence of

β-lactamase-producing organisms in 75% of the patients has important therapeutic implications.

D. Pleuropulmonary Infection

Anaerobes commonly have been identified as causative organisms in adult pleuropulmonary infections such as aspiraton pneumonia, lung abscess, necrotizing pneumonia, and empyema (16). Organisms isolated from these pleuropulmonary infections generally reflect the normal oral flora.

Studies (81, 82) in children have yielded findings that parallel the adult experience. Anaerobic bacteria were isolated from 92% of 52 children with aspiration pneumonia (81) and 12% of children with necrotizing pneumonia and in all 10 children with lung abscesses (82). The preponderant anaerobes isolated were anaerobic gram-positive cocci, *Bacteroides* spp. (including *B. fragilis* and *B. melaninogenicus* groups), *Fusobacterium* spp., and *Veillonella* spp. Anaerobes and aerobes (2.7 and 2.2 per specimen, respectively) were almost always isolated together, emphasizing the polymicrobic nature of these infections. *Bacteroides fragilis* resistant to penicillin was isolated in 15% of the patients, a recovery rate similar to that found in adults. Anaerobes also were recovered from four of six children with cystic fibrosis, when cultures were obtained by transtracheal aspiration (83). These organisms included *B. melaninogenicus* and *B. fragilis*, and were mixed with aerobic and facultative bacteria. Anaerobes are involved in the colonization of the tracheobronchial tree and the subsequent tracheitis and pneumonia that follow tracheal intubation after tracheostomy (84). Serial tracheal cultures from 27 intubated patients yielded an average of 2.2 aerobes and 1.2 anaerobes per specimen. The organisms recovered were similar to those found in patients with aspiration pneumonia.

E. Skin and Soft Tissue Infections

Cutaneous abscesses are commonly encountered in children. *Staphylococcus aureus* and GABHS are the organisms previously implicated in these infections. Anaerobes, chiefly the *B. fragilis* group, have been associated with cutaneous abscesses of the buttock, perirectal, vulvovaginal, head, and finger (paronychia) areas more frequently than other sites of the body (85).

Surgical drainage is the therapy of choice. However, the fact that the β-lactamase producers *S. aureus* and *B. fragilis* are frequently isolated from the abscesses supports the selection of an antibiotic that is resistant to β-lactamases.

Decubitus ulcers are a complication of prolonged hospitalization in both adults and children. A study (86) of 42 children with decubiti reported the isolation of anaerobes, primarily in mixed culture, in 50% of the ulcers. Anaerobic gram-positive cocci, *B. fragilis,* and *F. nucleatum* were the most common anaerobes isolated, and *S. aureus,* GABHS, *H. influenzae,* and *Enterobacter* spp. were the most common aerobes.

F. Bacteremia

Anaerobes are rarely isolated from the blood cultures of pediatric patients. However, in a survey of anaerobic infections in children, blood cultures were the second most frequent source of anaerobic organisms (87). The predominant isolate from blood cultures (56 to 65%) was *Propionibacterium acnes,* an organism that is a normal inhabitant of the skin. No doubt many of these isolates reflect contamination of the blood culture with skin flora. However, *P. acnes* can act, on occasion, as a true cause of bacteremia, such as in the contamination of ventriculoperitoneal shunts (87). The other anaerobic organisms most commonly isolated from blood are *B. fragilis,* anaerobic gram-positive cocci, and *Fusobacterium* (28, 31, 87). Anaerobic bacteremia usually occurs in patients with chronic debilitating disorders such as malignancy, immunodeficiency, or chronic renal insufficiency, and it usually carries a poor long-term prognosis. *Bacteroides* spp. also were frequently isolated following perforation of an abdominal viscus and appendicitis (88).

A recent report summarized 28 children with bacteremia (31). Twenty-nine anaerobic isolates were recovered; of these, 14 were *Bacteroides* spp., 4 anaerobic gram-positive cocci, 4 *P. acnes,* and 3 *Fusobacterium* spp.

Some predisposing conditions were noted in these patients. Two had malignancies, two suffered from hematologic abnormality, and one had an immune deficiency. Certain serious complications associated with bacteremia were noted in the patients. The most frequent complication was meningitis, which occurred in five patients. Peritonitis occurred in three patients, subdural empyema in two, and septic shock in one. Early recognition and treatment with appropriate antimicrobial and surgical therapies were the most important factors in reducing the mortality and morbidity of these patients.

As reported in adults, the strains of anaerobic organisms recovered from the blood of children depended to a large extent on the portal of entry and the underlying disease. *Bacteroides* spp., including the *B. fragilis* group, were the predominant isolates from patients in whom the gastrointestinal tract was the probable portal of entry. Infections of the ear, sinus, and oropharynx predisposed to bacteremia by *Peptostrep-*

tococcus spp. and *Fusobacterium* spp. This is not surprising since these organisms are part of the normal flora of such anatomical sites and can be involved in local infections.

IV. Conclusions

Many infections in children are produced by anaerobic bacteria. In the upper respiratory passage and lungs, the major anaerobic pathogens are *Peptostreptococcus* species, the *B. melaninogenicus* group, and *Fusobacterium* species. In intraabdominal infections and infections of the female genital tract, the most frequent isolates are of the *B. fragilis* group, *Clostridium* species, and anaerobic gram-positive cocci.

Recognition of the pattern of infectivity of the various anaerobic organisms at different body sites, the pathogenic features of the organisms, and the increased number of β-lactamase-producing *Bacteroides* species allow the earlier identification of these organisms and the initiation of appropriate management of these infections.

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