CHAPTER 12

GROUP B STREPTOCOCCAL INFECTIONS

Morven S. Edwards ❂ Victor Nizet

CHAPTER OUTLINE

Lancefield group B β-hemolytic streptococci were first recorded as a cause of human infection in 1938, when Fry [1] described three patients with fatal puerperal sepsis. Sporadic cases were reported during the next 3 decades, but this microorganism remained unknown to most clinicians until the 1970s, when a dramatic increase in the incidence of septicemia and meningitis in neonates caused by group B streptococci (GBS) was documented from geographically diverse regions. [2–4] Emergence of group B streptococcal infections in neonates was accompanied by an increasing number of these infections in pregnant women and nonpregnant adults. In pregnant women, infection commonly manifested as localized uterine infection or chorioamnionitis, often with bacteremia, and had an almost uniformly good outcome with antimicrobial therapy. In other adults, who typically had underlying medical conditions, infection often resulted in death [5]. The incidence of perinatal infection associated with GBS remained stable through the early 1990s. Case-fatality rates had declined by then, but remained substantial compared with case-fatality rates reported for other invasive bacterial infections in infants.

Several notable events have occurred in recent years. Capsular type IX has been proposed, bringing the number of types causing invasive human disease to 10 [6]. The complete genomes of types III and V GBS have been sequenced, opening new avenues for the identification of novel potential vaccine targets [7,8]. The discovery that surface-associated pili are widely distributed among GBS and that a vaccine based on combinations of the three pilus-island variants protects mice against lethal challenge with a wide variety of group B streptococcal strains paves the way for the design of pilus-based and perhaps other putative surface protein vaccines for testing in humans [9–11].

The implementation of 2002 consensus guidelines to prevent early-onset disease in neonates through universal antenatal culture screening at 35 to 37 weeks' gestation and intrapartum antibiotic prophylaxis (IAP) has been associated with a substantial decline in the incidence of neonatal infection for the first time in 3 decades [12]. Finally, testing of group B streptococcal candidate vaccines in healthy adults has been achieved, offering promise that immunization to prevent maternal and infant and perhaps adult invasive group B streptococcal disease could become a reality.

ORGANISM

Streptococcus agalactiae is the species designation for streptococci belonging to Lancefield group B. This bacterium is a facultative gram-positive diplococcus with an ultrastructure similar to that of other gram-positive cocci. Before Lancefield's classification of hemolytic streptococci in 1933 [13], this microorganism was known to microbiologists by its characteristic colonial morphology,

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its narrow zone of β-hemolysis surrounding colonies on blood agar plates, and its double zone of hemolysis that appeared when plates were refrigerated an additional 18 hours beyond the initial incubation [14]. Occasional strains (approximately 1%) are designated α-hemolytic or nonhemolytic. GBS are readily cultivated in various bacteriologic media. Isolation from certain body sites (respiratory, genital, and gastrointestinal tracts) can be enhanced by use of broth medium containing antimicrobial agents that inhibit growth of other bacterial species indigenous to these sites [15,16].

COLONIAL MORPHOLOGY AND IDENTIFICATION

Colonies of GBS grown on sheep blood agar medium are 3 to 4 mm in diameter, produce a narrow zone of β-hemolysis, are gray-white, and are flat and mucoid. β-hemolysis for some strains is apparent only when colonies are removed from the agar.

Tests for presumptive identification include bacitracin and sulfamethoxazole-trimethoprim disk susceptibility testing (92% to 98% of strains are resistant), hydrolysis of sodium hippurate broth (99% of strains are positive), hydrolysis of bile esculin agar (99% to 100% of strains fail to react), pigment production during anaerobic growth on certain media (96% to 98% of strains produce an orange pigment), and CAMP (Christie-Atkins-Munch-Petersen) testing (98% to 100% of strains are CAMP-positive) [17–19]. The CAMP factor is a thermostable extracellular protein that, in the presence of the β toxin of *Staphylococcus aureus*, produces synergistic hemolysis when grown on sheep blood agar. Hippurate hydrolysis is an accurate method for presumptive identification of GBS, but the requirement for 24 to 48 hours of incubation limits its usefulness. GBS can be differentiated from other streptococci by a combination of the CAMP test, the bile esculin reaction, and bacitracin sensitivity testing [17]. Biochemical micromethods identify GBS with reasonable accuracy after a 4-hour incubation period [20].

Definitive identification of GBS requires detection of the group B–specific antigen common to all strains through use of hyperimmune grouping antiserum. Lancefield's original method required acid treatment of large volumes of broth-grown cells to extract the group B antigen from the cell wall [21]. Supernatants were brought to neutral pH and mixed with hyperimmune rabbit antiserum prepared by immunization with the group B–variant strain (090R) (devoid of type Ia–specific antigen), and precipitins in capillary tubes were recorded. Less time-consuming serologic techniques are now employed, but all use group-specific antiserum to identify the group B antigen in intact cells, broth culture supernatants, or cell extracts. Commercial availability and simplicity make latex agglutination–based assays the most practical and frequently used methods by hospital laboratories [22]. Reverse transcriptase polymerase chain reaction (RT-PCR) methods have been developed more recently for grouping of clinical specimens, and PCR has been developed for genotyping of group B streptococcal isolates.

STRAINS OF HUMAN AND BOVINE ORIGIN

GBS were known to cause bovine mastitis before they were appreciated as pathogenic in humans [23]. Modern veterinary practices have largely controlled epidemics of bovine mastitis, but sporadic cases still occur. Substantial biochemical, serologic, and molecular differences exist between human and bovine isolates [24,25]. Among typable bovine strains, patterns of distribution distinct from the patterns of human isolates are noted. Other distinguishing characteristics for bovine strains include their unique fermentation reactions, their decreased frequency of pigment production, and their usual susceptibility to bacitracin. Protein X, rarely found in human strains, is commonly present in pathogenic bovine isolates [26].

CLASSIFICATION

Lancefield defined two cell wall carbohydrate antigens employing hydrochloric acid–extracted cell supernatants and hyperimmune rabbit antisera: the group B–specific or "C" substance common to all strains and the type-specific or "S" substance that allowed classification into types, initially types I, II, and III [27–29]. Strains designated as type I were later shown to have cross-reactive and antigenically distinct polysaccharides, and the antigenically distinct type Ia and type Ib polysaccharides were defined [28]. GBS historically designated type Ic were characterized when strains possessing type Ia capsular polysaccharide (CPS) were shown also to possess a protein antigen common to type Ib, most type II, and rarely type III strains [30]. This protein, originally called the "type Ib/c antigen," now is known as C protein. Rabbit antibodies directed against CPS protected mice against lethal challenge with homologous, but not heterologous, group B streptococcal types, and cross-protection was also afforded when antibodies against C protein were tested.

Current nomenclature designates polysaccharide antigens as type antigens and protein antigens as additional markers for characterization [31,32]. The former type Ic now is designated type Ia/c. Type IV was identified as a new type in 1979, when 62 strains were described that possessed type IV polysaccharide alone or with additional protein antigens [33]. Antigenically distinct types, V through IX, now are characterized. Strains not expressing one of the CPS-specific antigens are designated as nontypable by serologic methods, but often can be characterized by PCR-based methods.

Characterization of C protein showed that it is composed of two unrelated protein components, the trypsin-resistant α C protein and the trypsin-sensitive β C protein [34]. α C protein is expressed on many type Ia, Ib, and II strains [34]. Strains expressing α C protein are less readily opsonized, ingested, and killed by human polymorphonuclear leukocytes in the absence of specific antibody than are α C–negative strains [35]. α C protein consists of a series of tandem repeating units, and in naturally occurring strains, the repeat numbers can vary. The number of repeating units expressed alters antigenicity and influences the repertoires of antibodies elicited [36]. The use of one or two repeat units of α C proteins elicits antibodies that bind all α C proteins with equal affinity, suggesting its potential as a vaccine candidate [37,38].

β C protein is a single protein with a molecular mass of 124 to 134 kDa that is present in about 10% of isolates. β C protein binds the Fc region of human IgA [39–41]. Strains bearing α and β C proteins possess increased resistance to opsonization in vitro.

GBS express numerous additional surface proteins. Designation of additional α-like repetitive proteins (Alp) numerically (e.g., Alp2 and Alp3) is being considered. Most group B streptococcal strains have the gene for just one of the Alp family proteins. Genes encoding Alp1 (also designated "epsilon") are associated with type Ia, and genes encoding Alp3 are associated with type V strains [42]. Alp also are referred to as R proteins, of which R1 and R4 are the major ones found on clinical isolates [42]. Rib protein, expressed by most type III strains, has been shown to have an identical sequence to R4. The gene sequence of a protein initially designated R5 that is expressed by numerous clinically relevant group B streptococcal types has been sequenced and renamed group B protective surface protein [43]. Some GBS contain surface proteins designated as X antigens. These were first described by Pattison and coworkers [44], who introduced reagents for their detection in an attempt to classify nontypable strains further. The X and R antigens are immunologically cross-reactive. A laddering protein from type V GBS shares sequence homology with α C protein [45]. A protein designated Sip (for surface immunogenic protein) is distinct from other known surface proteins. It is produced by all serotypes of GBS and confers protection against experimental infection; its role in human infection is unknown [46].

Genome analysis has revealed that GBS produce long pilus-like structures. These structures extend from the bacterial surface and beyond CPS (Fig. 12–1) [9]. Formed by proteins with adhesive functions, these structures are implicated in host colonization, attachment, and invasion [47]. The pilus-like structures are encoded in genomic pilus islands that have an organization similar to that of pathogenicity islands. Three types of pilus island have been identified through genomic analysis; these are composed of partially homogeneous covalently linked proteins (pilus islands 1, 2a, and 2b). These pili proteins are highly surface-expressed and are involved in paracellular translocation through epithelial cells. At least one of these is present on all group B streptococcal clinical strains tested to date.

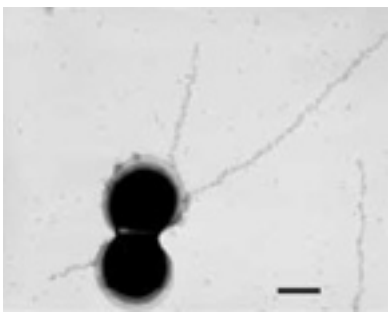


FIGURE 12–1 Immunogold labeling and transmission electron microscopy of group B streptococcal organisms showing long pilus-like structures extending from the cell surface. *(From Lauer P, et al. Genome analysis reveals pili in group B streptococcus. Science 309:105, 2005.).*

ULTRASTRUCTURE

Early concepts suggested a thick, rigid peptidoglycan layer external to the cytoplasmic membrane surrounded by concentric layers of cell wall antigens. The group-specific carbohydrate was thought to be "covered" by a type-specific CPS. Evidence now supports a model in which the group B carbohydrate and the CPS are linked independently to cell wall peptidoglycan [48].

Immunoelectron techniques reveal abundant CPS on Lancefield prototype strains Ia, II, and III, whereas less dense capsules are found on type Ib strains (Fig. 12–2) [49]. Similarly, incubation of the reference strains with homologous type-specific antisera reveals a thick capsular layer on types IV, V, and VI [50,51]. Ultrastructural studies show that the C protein also has a surface location [49]. CPS capsule expression can be regulated by altering cell growth rate [52]. Immunogold labeling and transmission electron microscopy show that the GBS pilus-like structures extend from the bacterial surface [9].

IMMUNOCHEMISTRY OF POLYSACCHARIDE ANTIGENS

Although Lancefield's initial serologic definition was achieved by extraction methods that employed 2N hydrochloric acid and heat treatment, these procedures resulted in degraded antigens of small molecular mass. When more gentle techniques were employed for extraction, large molecular mass or "native" polysaccharides were isolated that contained an additional antigenic determinant, *N*-acetylneuraminic acid or sialic acid. Human immunity has been shown to correlate with antibody to the sialic acid–containing type III structure [53]. The composition of the group B polysaccharide initially was determined using antigen extracted from whole cells of the Lancefield laboratory–adapted variant strain 090R, devoid of CPS. With the use of contemporary methods for determination, L-rhamnose, D-galactose, 2-acetamido-2-deoxy-D-glucose, and D-glucitol have been identified as its constituent monosaccharides. It is composed of four different oligosaccharides, designated I though IV, and linked by one type of phosphodiester bond to form a complex, highly branched multiantennary structure [54].

The repeating unit structures of the group B streptococcal CPS, determined by methylation analysis combined with gas-liquid chromatography/mass spectrometry, are schematically represented in Figure 12–3. CPS of types Ia, Ib, and III have a five-sugar repeating unit containing galactose, glucose, *N*-acetylglucosamine, and sialic acid in a ratio of 2:1:1:1 [53,55–57]. The type II and type V polysaccharides have a seven-sugar repeating unit; type IV and type VII polysaccharides have six-sugar repeats, and type VIII polysaccharide has a four-sugar repeating unit [50,58–62]. The molar ratios vary, but the component monosaccharides are the same among the polysaccharide types except that type VI lacks *N*-acetylglucosamine and type VIII contains rhamnose in the backbone structure [63].

Each antigen has a backbone repeating unit of two (Ia, Ib), four (II), or three (III, IV, V, VII, VIII) monosaccharides to which one or two side chains are linked. Sialic acid is the exclusive terminal side chain sugar except for

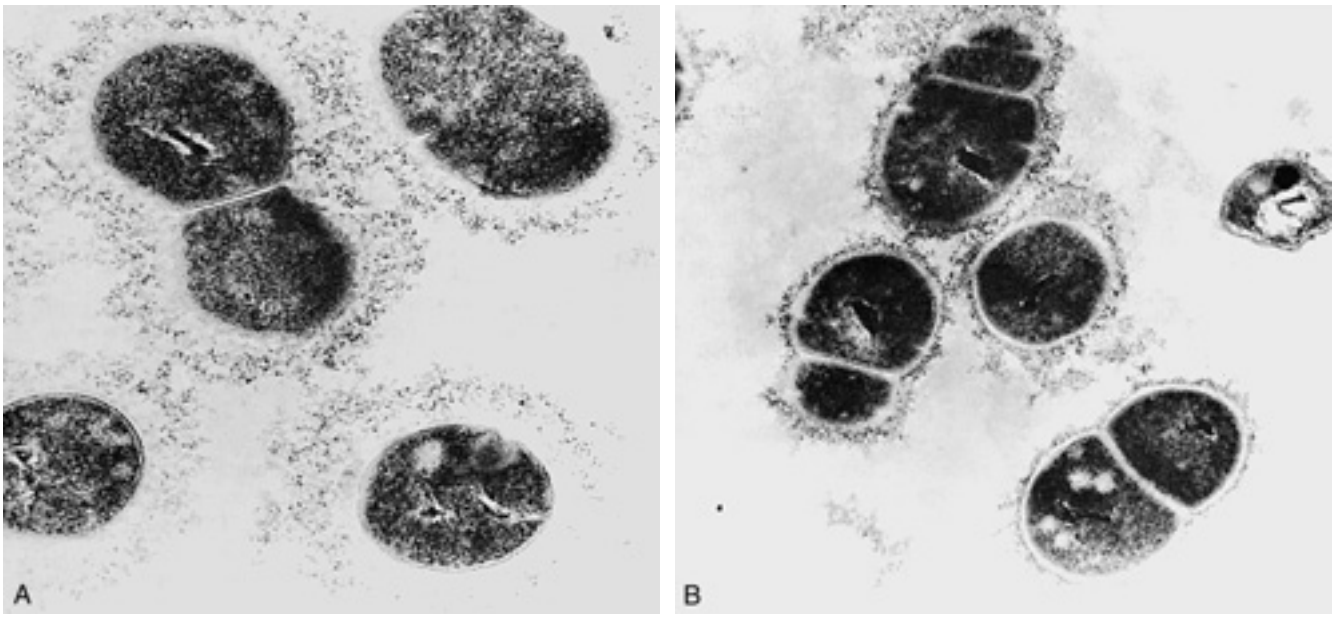


FIGURE 12–2 Electron micrographs of thin sections of type Ia group B streptococcal prototype strains. A, Strain 090. **B,** Strain A909. Both are stained with ferritin-conjugated type Ia–specific rabbit antibodies. The larger capsule is representative of those found also in Lancefield prototype II strain (18RS21) and type III isolates from infants with meningitis (M732), whereas the smaller capsule is representative of that also found on Lancefield prototype strain Ib (H36B). *(Micrographs courtesy of Dennis L. Kasper, MD.)*

the type II polysaccharide, which also has a terminal galactose. The structures of the type Ia and type Ib polysaccharides differ only in a single monosaccharide side chain linkage, although there are differences in the tertiary configuration of the molecules [64]. These monosaccharide linkages are critical to their immunologic specificity and explain their immunologic cross-reactivity [28,65]. The desialylated type III polysaccharide is immunologically identical to that of type 14 *Streptococcus pneumoniae* [66]. This observation stimulated investigations concerning the immunodeterminant specificity of human immunity to type III GBS and of antibody recognition of conformational epitopes as a facet of the host immune response [67,68]. The type III polysaccharide also can form extended helices. The position of the conformational epitope along these helices is potentially important to binding site interactions [69,70].

GROWTH REQUIREMENTS AND BACTERIAL PRODUCTS

GBS are quite homogeneous in their amino acid requirements during aerobic or anaerobic growth [71]. A glucose-rich environment enhances the number of viable GBS during stationary phase and the amount of CPS elaborated [72]. In a modified chemically defined medium, the expression of capsule during continuous growth is regulated by the growth rate [52]. Group B streptococcal invasiveness is enhanced by a fast growth rate and is optimal in the presence of at least 5% oxygen [73,74].

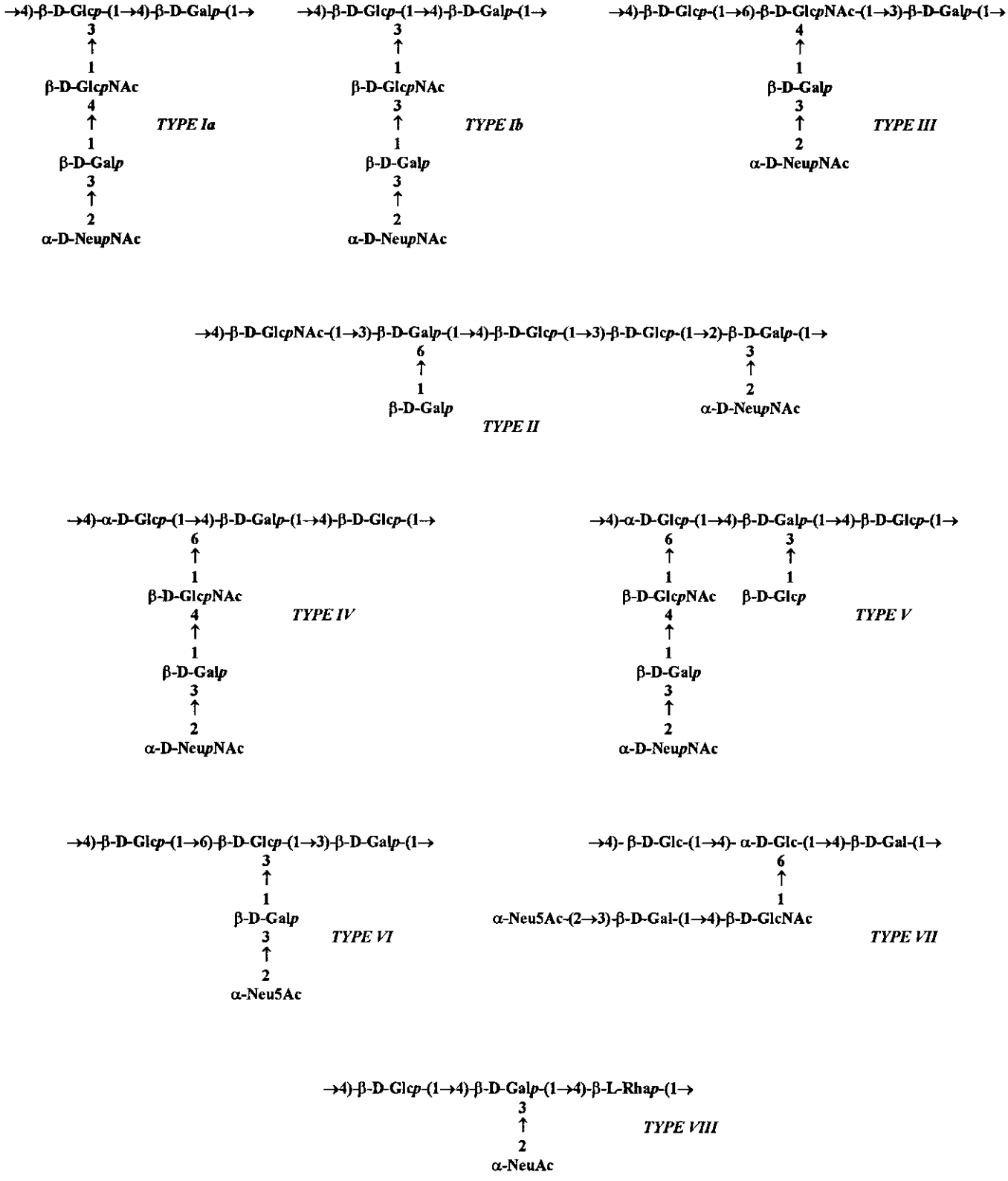
GBS elaborate many products during their growth, some of which contribute to virulence of the organism. Among these is the hemolysin that produces the β-hemolysis surrounding group B colonies on blood agar plates. Hemolysin is an extracellular product of almost all strains and is active against the erythrocytes from several mammalian species. It has been isolated and characterized and is known to function as a virulence factor [75]. Hemolysin is not detected in supernatants of broth cultures, suggesting either that it exists in a cell-bound form, or that it is released by cells and rapidly inactivated.

After growth to stationary phase, GBS produce two types of pigment resembling a β-carotenoid [76]. Pigment, similar to hemolysin, is formed and released by an active metabolic process, retaining its properties only in the presence of a carrier molecule. A potential role for pigment as a virulence factor is proposed, but to date has not been proved.

GBS can hydrolyze hippuric acid to benzoic acid and glycine, and this property has been useful historically to distinguish GBS from other β-hemolytic groups [77]. Ferrieri and coworkers [78] isolated and characterized the hippuricase of GBS. This enzyme is cell associated and is trypsin and heat labile. It is antigenic in rabbits, but its relationship to bacterial virulence, if any, has not been studied.

Most strains of GBS have an enzyme that inactivates complement component C5a by cleaving a peptide at the carboxyl terminus [79]. Group B streptococcal C5a-ase seems to be a serine esterase; it is distinct from the C5a-cleaving enzyme (termed *streptococcal C5a peptidase*) produced by group A streptococci [80], although the genes that encode these enzymes are similar [81]. C5a-ase contributes to the pathogenesis of group B streptococcal disease by rapidly inactivating the neutrophil agonist C5a, preventing the accumulation of neutrophils at the site of infection ~~(Table 12–1)~~ [82].

Another group of enzymes elaborated by nearly all GBS are the extracellular nucleases [83]. Three distinct nucleases have been physically and immunologically characterized. All are maximally activated by divalent cations of calcium plus manganese. These nucleases are immunogenic in animals, and neutralizing antibodies to them are detectable in sera from pregnant women known to be



f0020 **FIGURE 12–3** Repeating unit structures of group B streptococcal capsular polysaccharides type Ia [64], type Ib [64,65], type II [60,62], type III [56,57], type IV [61], type V [58], type VI [730], type VII [59], and type VIII [63].

TABLE 12–1 Group B Streptococcal Virulence Factors in Pathogenesis of Neonatal Infection

Virulence Factor	Molecular or Cellular Actions	Proposed Role in Pathogenesis
Host Cell Attachment and Invasion		
C surface protein	Binds cervical epithelial cells	Epithelial cell adherence, invasion
Fibrinogen receptor, FbsA	Binds fibrinogen in extracellular matrix	Epithelial cell attachment
Lipoteichoic acid	Binds host cell surfaces	Epithelial cell attachment
C5a peptidase, ScpB	Binds fibronectin in extracellular matrix	Epithelial cell adherence, invasion
Surface protein Lmb	Binds laminin in extracellular matrix	Epithelial cell attachment
Spb1 surface protein	Promotes epithelial cell uptake	Invasion of epithelial barriers
iagA gene	Alteration in bacterial cell surface (?)	Promotes blood-brain barrier invasion
Injury to Host Tissues		
β-Hemolysin/cytolysin	Lyses epithelial and endothelial cells	Damage and spread through tissues
Hyaluronate lyase	Cleaves hyaluronan or chondroitin sulfate	Promotes spread through host tissues
CAMP factor	Lyses host cells (cohemolysin)	Direct tissue injury
Resistance to Immune Clearance		
Exopolysaccharide capsule	Impairs complement C3 deposition and activation	Blocks opsonophagocytic clearance
C5a peptidase, ScpB	Cleaves and inactivates human C5a	Inhibits neutrophil recruitment
CAMP factor	Binds to Fc portion of IgG, IgM	Impairment of antibody function
Serine protease, CspA	Cleaves fibrinogen, coats GBS surface with fibrin	Blocks opsonophagocytosis
Fibrinogen receptor, FbsA	Steric interference with complement function (?)	Blocks opsonophagocytosis
C protein	Nonimmune binding of IgA	Blocks opsonophagocytosis
β-hemolysin/cytolysin	Lyses neutrophils and macrophages, proapoptotic	Impairment of phagocyte killing
Superoxide dismutase	Inactivates superoxide	Impairment of oxidative burst killing
Carotenoid pigment	Antioxidant effect blocks H_2O_2, singlet oxygen	Impairment of oxidative burst killing
Dlt operon genes	Alanylation of lipoteichoic acid	Interferes with antimicrobial peptides
Penicillin-binding protein 1a	Alteration in cell wall composition	Interferes with antimicrobial peptides
Activation of Inflammatory Mediators		
Cell wall lipoteichoic acid	Binds host pattern recognition receptors (TLRs)	Cytokine activation
Cell wall peptidoglycan	Binds host pattern recognition receptors (TLRs)	Cytokine activation
β-Hemolysin/cytolysin	Activation of host cell stress response pathways	Triggers iNOS, cytokine release

GBS, group B streptococci; iNOS, inducible nitric oxide synthase; TLRs, toll-like receptors.

genital carriers of GBS. Their role in the pathogenesis of human infection is unknown.

An extracellular product that can contribute to virulence of GBS was originally defined as a neuraminidase and has been characterized more recently as a hyaluronate lyase [84]. Maximal levels are detected during late exponential growth in a chemically defined medium. Elaboration of large quantities can be a virulence factor for type III GBS. Musser and coworkers [85] identified a high neuraminidase–producing subset of type III strains that were responsible for most serious group B streptococcal infections. Later studies indicated that these were from a single clonal complex designated ST 17 that has been designated as "hypervirulent." ST 17 is almost exclusively found in type III strains.

GBS synthesize acylated (lipoteichoic) and deacylated glycerol teichoic acids that are cell associated and can be readily extracted and purified [86]. Strains from infants with early-onset or late-onset disease have higher levels of cell-associated and native deacylated lipoteichoic acid, and this product seems to contribute to attachment to human cells [87].

EPIDEMIOLOGY AND TRANSMISSION

The relationship between GBS strains of human and bovine origin has been queried for years. There is no compelling evidence to suggest that cattle serve as a reservoir for human disease, and transmission of GBS from cows to humans is exceedingly rare [25]. In addition, during the past decades when group B *Streptococcus* has been a dominant human pathogen in the United States, most of the population has lacked exposure to the two possible modes of transmission: (1) proximity to dairy cattle (direct contact) and (2) ingestion of unpasteurized milk. Application of molecular techniques to type III strains from bovine sources and strains infecting human neonates supports the assertion that these lineages are unrelated. Phylogenetic lineage determination does indicate, however,

that some clonal complexes of invasive or colonizing strains in humans are related to "ancestral" lineages of bovine GBS [88].

ASYMPTOMATIC INFECTION (COLONIZATION) IN ADULTS

Group B streptococcal infection limited to mucous membrane sites is designated as asymptomatic infection, colonization, or carriage. Comparisons of the prevalence of colonization are related to differences in ascertainment techniques. Factors that influence the accuracy of colonization detection include density of colonization, choice of bacteriologic media, body sites sampled, number of culture specimens obtained, and time interval of study.

Isolation rates are higher with use of broth rather than solid agar media, with media containing substances inhibitory for normal flora (usually antimicrobials), and with selective broth rather than selective solid agar media. Among selective broth media, Todd-Hewitt broth with gentamicin (4 to 8 μg/mL) or colistin (or polymyxin B) (10 μg/mL) and nalidixic acid (15 μg/mL) (Lim broth), with or without sheep red blood cells, has been useful for accurate detection of GBS from genital and rectal cultures [89]. Such media inhibit the growth of most gram-negative enteric bacilli and other normal flora that make isolation of streptococci from these sites difficult. Use of broth media enables detection of low numbers of organisms that escape detection when inoculation of swabs is directly onto solid agar.

Isolation rates also are influenced by body sites selected for culture. Female genital culture isolation rates double with progression from the cervical os to the vulva [90,91]. In addition, culture sampling of lower genital tract and rectal sites increases group B streptococcal colonization rates 10% to 15% beyond that found if a single site is cultured [92]. The urinary tract is an important site of group B streptococcal infection, especially during pregnancy, when infection is typically manifested as asymptomatic bacteriuria. To predict accurately the likelihood of neonatal exposure to GBS at delivery, maternal culture specimens from the lower vagina and rectum (not perianal area) should be collected.

In neonates, external auditory canal cultures are more likely to yield GBS than cultures from anterior nares, throat, umbilicus, or rectum in first 24 hours of life [3,93], and isolation of organisms from the ear canal is a surrogate for the degree of contamination from amniotic fluid and vaginal secretions sequestered during the birth process. After the first 48 hours of life, throat and rectal sites are the best sources for detection of GBS, and positive cultures indicate true colonization (multiplication of organisms at mucous membrane sites), not just maternal exposure [94]. Cultures from the throat and rectum are the best sites for detection during childhood and until the start of sexual activity, when the genitourinary tract becomes a common site of colonization [95,96].

The prevalence of group B streptococcal colonization is influenced by the number of cultures obtained from a site and the interval of sampling. Historically, longitudinal assessment during pregnancy defined vaginal colonization patterns as chronic, transient, intermittent, or indeterminant [97]. A longitudinal cohort study of nonpregnant young women in the 1970s found that among women who were culture-negative at enrollment, almost half acquired vaginal colonization during follow-up at three 4-month intervals [98]. The duration of any group B streptococcal colonization among college students was estimated by Foxman and colleagues [99] and is longer for women (14 weeks) than for men (9 weeks). Nearly half of women vaginally colonized at delivery have had negative antenatal culture results. In a more recent longitudinal study of pregnant women, the predictive value of a positive prenatal vaginal or rectal culture from the second trimester for colonization at delivery was 67% [100]. The predictive value of a positive prenatal culture result is highest (73%) in women with vaginal and rectal colonization and lowest (60%) in women with rectal colonization only. Cultures performed 1 to 5 weeks before delivery are fairly accurate in predicting group B streptococcal colonization status at delivery in term parturients. Within this interval, the positive predictive value is 87% (95% confidence interval 83 to 92), and the negative predictive value is 96% (95% confidence interval 95 to 98). Culture specimens collected within this interval perform significantly better than specimens collected 6 or more weeks before delivery [101].

The primary reservoir for GBS is the lower gastrointestinal tract [3,102]. The recovery of GBS from the rectum alone is three to five times more common than recovery from the vagina [92], the rectal-to-vaginal isolation ratio exceeds 1 [100], and the rectal site more accurately predicts persistence[92] or chronicity of carriage [103]. Fecal carriage or rectal colonization with GBS has been documented in individuals ranging in age from 1 day to 80 years [104]. Additional support for the intestine as the primary reservoir of colonization by GBS includes their isolation from the small intestine of adults [105] and their association with infections resulting from surgery of the upper or lower intestinal tract [106]. Rectal colonization also can contribute to the resistance of genital tract colonization to temporary decolonization by antibiotics [107].

Several factors influence genital carriage of GBS. Among healthy young men and women living in a college dormitory, sexually experienced subjects had twice the colonization rates of sexually inexperienced subjects [108]. In a longitudinal cohort study of nonpregnant young women, African American ethnicity, having multiple sex partners during a preceding 4-month interval, having frequent sexual intercourse within the same interval, and having sexual intercourse within the 5 days before a follow-up visit were independently associated with vaginal acquisition of GBS [98]. These findings suggest either that the organism is sexually transmitted or that sexual activity alters the microenvironment to make it more permissive to colonization. In another study of college women, GBS were isolated significantly more often from sexually experienced women, women studied during the first half of the menstrual cycle, women with an intrauterine device, and women 20 years old or younger [109]. Colonization with GBS also occurs at a high rate in healthy college students and is associated with having engaged in sexual activity, tampon use, milk consumption, and hand washing done four times daily or less [110]. Fish consumption increased the risk of acquiring some, but not all, capsular types [111].

A higher prevalence of colonization with GBS has been found among pregnant diabetic patients than among nondiabetic controls [112]. Carriage over a prolonged interval reportedly occurs more often in women who use tampons than women who do not [113]. Colonization is more frequent among teenage women than among women 20 years of age or older [97,109,114] and among women with three or fewer pregnancies than in women with more than three pregnancies [97,114,115]. Genital isolation rates are significantly greater in patients attending sexually transmitted disease clinics than in patients attending other outpatient facilities [90,116]. Ethnicity is related to colonization rates. In one large multicenter U.S. pregnancy study, colonization rates were highest in Hispanic women of Caribbean origin, followed by African Americans, whites, and other Hispanics [115]. In other assessments of geographically and ethnically diverse populations, the rate of colonization at delivery was significantly higher among African American women than in other racial or ethnic groups [98,117,118]. A large inoculum of vaginal group B streptococcal colonization also was more common among African American than among Hispanic or non-Hispanic white women [119]. Factors that do *not* influence the prevalence of genital colonization in nonpregnant women include use of oral contraceptives [109]; marital status; presence of vaginal discharge or other gynecologic signs or symptoms [109]; carriage of *Chlamydia trachomatis*, *Ureaplasma urealyticum*, *Trichomonas vaginalis*, or *Mycoplasma hominis* [115]; and infection with *Neisseria gonorrhoeae* [90,91].

Colonization with GBS can elicit an immune response. In a group of pregnant women evaluated at the time of admission for delivery, vaginal or rectal colonization with serotype Ia, II, III, or V was associated with significantly higher serum concentrations of IgG specific for the colonizing CPS type compared with noncolonized women [117]. Moderate concentrations of Ia, Ib, II, III, and V CPS-specific IgG also were found in association with colonization during pregnancy [120]. Maternal colonization with type III was least likely to be associated with these CPS-specific antibodies. In contrast to infection with organisms such as *N. gonorrhoeae* or genital mycoplasmas, genital infection with GBS is not related to genital symptoms [109,116,121].

GBS have been isolated from vaginal or rectal sites or both in 15% to 40% of pregnant women. These variations in colonization rates relate to intrinsic differences in populations (age, ethnicity, parity, socioeconomic status, geographic location) and to lack of standardization in culture methods employed for ascertainment. True population differences account for some of the disparity in these reported prevalence rates. When selective broth media are used, and vaginal and rectal samples are cultured, the overall prevalence of maternal colonization with GBS by region is 12% in India and Pakistan, 19% in Asia and the Pacific Islands, 19% in sub-Saharan Africa, 22% in the Middle East and North Africa, 14% in Central and South America, and 26% in the United States [117,122]. The reported rates of colonization among pregnant women range from 20% to 29% in eastern Europe, 11% to 21% in western Europe, 21% to 36% in Scandinavia, and 7% to 32% in the southern part of Europe [123]. The rate of persistence of group B streptococcal colonization in a subsequent pregnancy is higher compared with women negative for colonization in their prior pregnancy [124]. The prevalence rates of pharyngeal colonization among pregnant and nonpregnant women and heterosexual men are similar [3,125,126]; however, the rate approaches nearly 20% in men who have sex with men [127]. No definite relationship between isolation of GBS from throat cultures of adults or children and symptoms of pharyngitis has been proved [128], but some investigators have suggested that these organisms can cause acute pharyngitis [126].

ASYMPTOMATIC INFECTION IN INFANTS AND CHILDREN

Sites of colonization with GBS differ in children versus adults. In a study of 100 girls ranging in age from 2 months to 16 years, Hammerschlag and coworkers [95] isolated GBS from lower vaginal, rectal, or pharyngeal sites, or all three, in 20% of children. The prevalence of positive pharyngeal cultures resembled the prevalence of adults in girls 11 years or older (5%), but approached the prevalence reported for neonates in younger girls (15%). Rectal colonization was detected frequently in girls younger than 3 or older than 10 years of age (about 25%), but was uncommon in girls 3 to 10 years of age. Mauer and colleagues [96] isolated GBS from cultures of vaginal, anal, or pharyngeal specimens or all three in 11% of prepubertal boys and girls. Pharyngeal (5% each) and rectal (10% and 7%) isolation rates were similar for boys and for girls. Persson and coworkers [129] detected fecal group B streptococcal carriage in only 4% of healthy boys and girls, and Cummings and Ross [130] found that only 2% of English schoolchildren had pharyngeal carriage. Taken together, these findings indicate that the gastrointestinal tract is a frequent site for carriage during infancy and childhood in boys and girls, and genital colonization in girls is uncommon before puberty [131]. Whether this relates to environmental influences in the prepubertal vagina or to lack of sexual experience before puberty, or both, awaits further study.

TRANSMISSION OF GROUP B STREPTOCOCCI TO NEONATES

The presence of GBS in the maternal genital tract at delivery is the significant determinant of colonization and infection in the neonate. Exposure of the neonate to the organism occurs by the ascending route in utero through translocation through intact membranes, through ruptured membranes, or by contamination during passage via the birth canal. Prospective studies have indicated vertical transmission rates of 29% to 85%, with a mean rate of approximately 50% among neonates born to women from whom GBS were isolated from cultures of vagina or rectum or both at delivery. Conversely, only about 5% of infants delivered to culture-negative women become asymptomatically colonized at one or more sites during the first 48 hours of life.

The risk of a neonate acquiring colonization by the vertical route correlates directly with the density of colonization (inoculum size). Neonates born to heavily colonized women are more likely to acquire carriage at mucous

membrane sites than neonates born to women with low colony counts of GBS in vaginal cultures at delivery [132]. Boyer and associates [100] found that rates of vertical transmission were substantially higher in women with heavy than in women with light colonization (65% versus 17%) and that colonization at multiple sites and development of early-onset disease were more likely among infants born to heavily colonized mothers. The likelihood of colonization in a neonate born to a woman who is culture-positive at delivery is unrelated to maternal age, race, parity, or blood type or to duration of labor or method of delivery [100]. It is unclear whether preterm or low birth weight neonates are at higher risk for colonization from maternal sources than term infants.

Most neonates exposed through their mothers to GBS have infection that is limited to surface or mucous membrane sites (colonization) that results from contamination of the oropharynx, gastric contents, or gastrointestinal tract by swallowing of infected amniotic fluid or maternal vaginal secretions. Healthy infants colonized from a maternal source show persistence of infection at mucous membrane sites for weeks [133,134]. The distribution of CPS types in group B streptococcal isolates from mothers is comparable to that in isolates from healthy neonates.

Other sources for group B streptococcal colonization in neonates have been established. Horizontal transmission from hospital or community sources to neonates is an important, albeit less frequently proved, mode for transmission of infection [105,134]. Cross-contamination from maternally infected to uninfected neonates can occur from hands of nursery personnel [135]. In contrast to group A streptococci, which can produce epidemic disease in nurseries, GBS rarely exhibit this potential, and isolation of neonates with a positive culture result from skin, umbilical, throat, or gastric cultures is never indicated. An epidemic cluster of five infants with late-onset bacteremic infection related to type Ib GBS occurred among very low birth weight infants in a neonatal intensive care unit in the 1980s [136]. None of the index cases was colonized at birth, establishing that acquisition during hospitalization had occurred. Phage typing identified two overlapping patterns of susceptibility believed to represent a single epidemic strain. Epidemiologic analysis suggested infant-to-infant spread by means of the hands of personnel, although acquisition from two nurses colonized with the same phage–type Ib strain was not excluded. The infection control measures instituted prevented additional cases. This and other reports [135,137] indicate that cohorting of culture-positive infants during an outbreak coupled with implementation of strict hand hygiene for infant contact significantly diminishes nosocomial acquisition.

Community sources afford potential for transmission of GBS to the neonate. Indirect evidence has suggested that this mode of infection is infrequent [134]. Only 2 of 46 neonates culture-negative for GBS when discharged from the newborn nursery acquired mucous membrane infection at 2 months of age [138]. The mode of transmission likely is fecal-oral. Whether acquired by vertical or horizontal mode, colonization of mucous membrane sites in neonates and young infants usually persists for weeks or months [139].

SEROTYPE DISTRIBUTION OF ISOLATES

The differentiation of GBS into types based on CPS antigens has provided a valuable tool in defining the epidemiology of human infection. In the 1970s and 1980s, virtually all evaluations of GBS isolated from healthy neonates, children, or adults revealed an even distribution into types Ia or Ib, II, and III. This distribution also was reported for isolates from neonates with early-onset infection without meningitis and their mothers [140,141]. In 1990, types other than I, II, or III accounted for less than 5% of all isolates.

Beginning in the early 1990s, reports from diverse geographic regions documented type V as a frequent cause of colonization and invasive disease, first in neonates and later in adults [142–144]. The emergence of type V is not due to a single clone, but most type V isolates do have one pulse-field gel electrophoresis pattern that has been present in the United States since 1975 [145]. Type V now causes a substantial proportion of cases of early-onset disease and of infection among pregnant women. Type Ia has increased in prevalence and a corresponding decline has occurred in type II strains causing perinatal disease [143]. Type III strains, which account for about 70% of isolates from infants with meningitis, continue to be isolated from about two thirds of infants with late-onset disease [146,147]. Types VI, VII, VIII, and IX rarely cause human disease in the United States or the United Kingdom, but types VI and VIII are the most common serotypes isolated from healthy Japanese women [148,149].

The contemporary ~~COS~~ type distribution of GBS from different patient groups is shown in Figure 12–4. Prospective population-based surveillance through the Active Bacterial Core surveillance/Emerging Infections Program Network of the U.S. Centers for Disease Control and Prevention (CDC) defined the epidemiology of invasive group B streptococcal disease in the United States from 1999-2005 [150]. Serotyping was performed for greater than 6000 isolates. Among these, the group B streptococcal types represented in 528 early-onset disease cases were Ia (30%), III (28%), V (18%), and II (13%). The distribution for 172 pregnancy-associated cases was similar. The type distribution among 469 late-onset cases was Ia (24%), III (51%), and V (14%). Type V predominated among almost 5000 cases in nonpregnant adults, accounting for 31% of cases, followed by Ia (24%), II (12%), and III (12%).

MOLECULAR EPIDEMIOLOGY

In the 1970s and 1980s, epidemiologic investigation of group B streptococcal infections was hampered initially by the lack of a discriminatory typing system. Initial investigations employed phage typing in combination with serologic classification to discriminate between infant acquisition of GBS from maternal or nosocomial sources [151]. Although plasmids have been described in a few GBS [152], their use as epidemiologic markers is complex.

Tools such as multilocus enzyme electrophoresis [85,153,154], restriction enzyme fragment length polymorphism analysis, pulsed-field gel electrophoresis

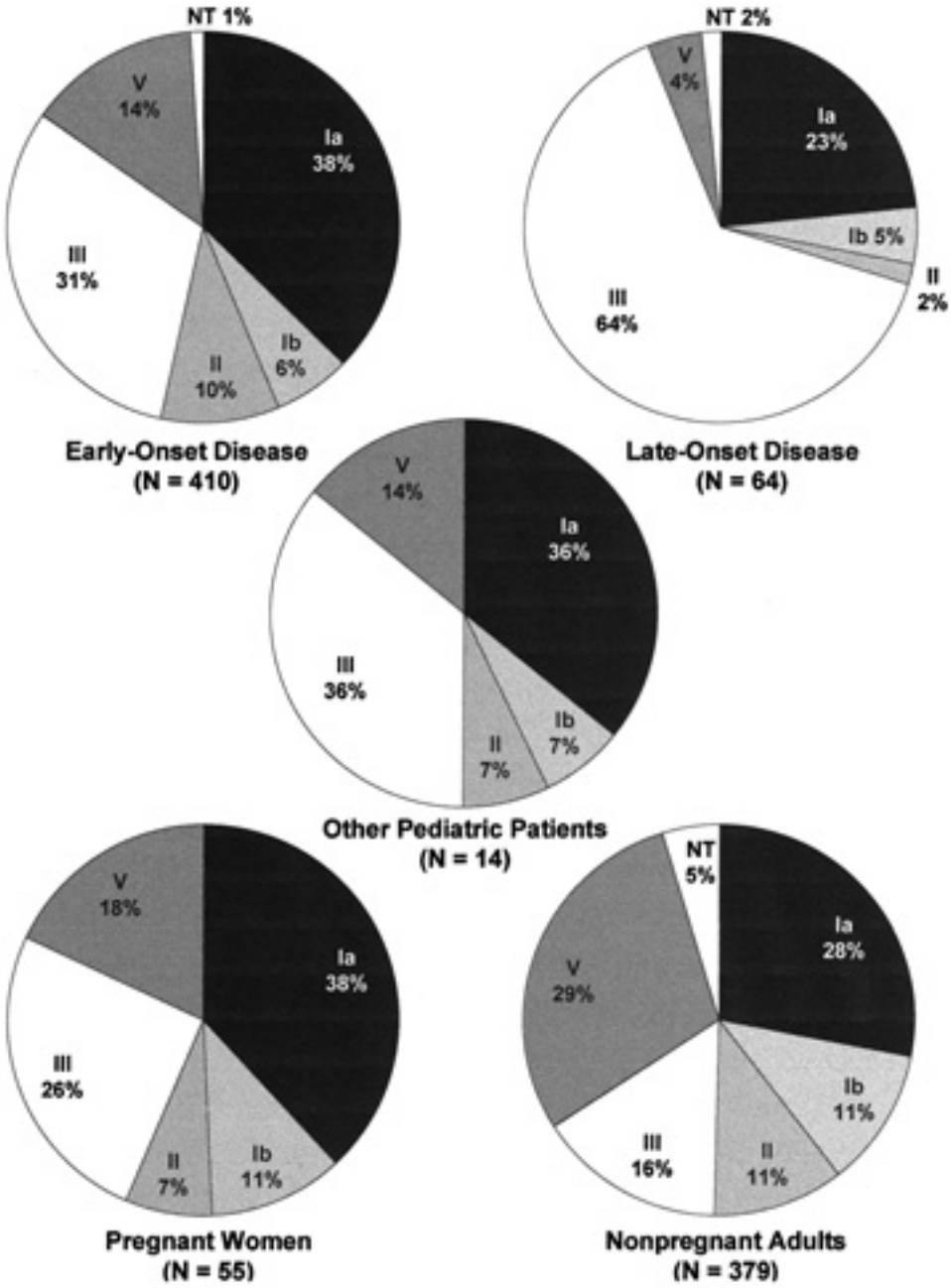


FIGURE 12–4 Schematic representation of group B streptococcal serotypes isolated from various patient groups. N, number of patient isolates studied; NT, nontypable strains. *(Data from references [142,143,699,731].)*

[155], and a random-amplified polymorphic DNA assay [156] have been employed for molecular characterization of group B streptococcal isolates associated with human disease. Restriction enzyme fragment length polymorphism analysis no longer is used because there are allelic variations within some CPS types. These techniques have indicated that some geographically and epidemiologically distinct isolates have identical patterns [157], suggesting dissemination of a limited number of clones in the United States; have shown the molecular relatedness of mother-infant and twin-twin strains [148,156]; and have documented mother-to-infant transmission associated with ingestion of infected mother's milk [157]. Molecular typing techniques have confirmed that sexual partners often carry identical strains. Multilocus sequence typing and capsular gene cluster (*cps*) genotyping has been used to investigate the dynamics of perinatal colonization. Changes in capsule expression and recolonization with antigenically distinct group B streptococcal clones were detected in culture-positive women over time by applying multilocus sequence typing [158].

Molecular characterization has been employed to explore the role of virulence clones in contributing to invasive disease. Type III GBS were classified into three major phylogenetic lineages on the basis of bacterial DNA restriction digest patterns [159]. Most cases of type III neonatal invasive disease seem to be caused by strains with the restriction digest pattern type III-3. The genetic

variation that distinguishes restriction digest pattern type III-3 strains seems to occur within localized areas of the genome that contain known or putative virulence genes [160–162]. Using genomic subtractive hybridization to identify regions of the genome unique to virulent restriction digest pattern type III-3 strains, a surface protein was identified that mediates epithelial cell invasion [163]. Using multilocus sequence typing, 10 allelic profiles were identified among type III isolates recovered from neonates with invasive disease and from colonized pregnant women [164]. The allelic profiles converged into three groups on concatenation. There was an equal distribution of these groups among colonizing and invasive isolates.

The finding that isolates with different capsular serotypes have the same sequence type suggests that capsular switching can occur [164,165]. One pulsed-field gel electrophoresis group bearing a gene from the capsular synthesis operon has been shown in type III strains causing neonatal meningitis, but not in type III colonizing strains [166]. Clustering of most invasive neonatal isolates into major pulsed-field gel electrophoresis groups has been noted [167]. Also, among type III strains evaluated by multilocus sequence typing, a single clone, ST 17, also called clonal complex 1 by other investigators, has been reported to be "hypervirulent," but this is controversial. Additional studies are required to elucidate the differences in virulence among clones identified by these techniques [168].

INCIDENCE OF INFECTION IN NEONATES AND PARTURIENTS

Two clinical syndromes occur among young infants with group B streptococcal disease that are epidemiologically distinct and relate to age at onset [2,3]. Historically, the attack rates for the first of these syndromes, designated early-onset because it occurs within the first 6 days of life (mean onset 12 to 18 hours), ranged from 0.7 to 3.7 per 1000 live births (Table 12–2). The attack rates for late-onset infection (mean onset 7 to 89 days of age) ranged from 0.5 to 1.8 per 1000 live births. Multistate active surveillance that identified cases of invasive disease in a population of 10.1 million in 1990 reported an incidence of 1.6 and 0.3 per 1000 live births for early-onset and late-onset disease [169]. Incidence of disease was significantly higher among African Americans than among whites. The crude incidence was higher among Hispanic whites than among non-Hispanic whites. These multistate surveillance findings are in accord with findings from a cohort study conducted in Atlanta indicating a higher risk for early-onset or late-onset disease among African American infants than among infants of other ethnic origins [170].

There has been a dramatic decline in the incidence of early-onset disease in the United States in association with implementation of universal antenatal culture screening and use of IAP. From 1993-1998, when risk-based and culture-based methods were in use, incidence of early-onset disease declined by 65%, from 1.7 to 0.6 per 1000 live births [12]. Comparison of the two approaches showed the superiority of the culture-based approach [171]. The incidence of early-onset disease has declined an additional 27% in association with implementation in 2002 of revised consensus guidelines advocating a culture-based approach for prevention of early-onset disease to a rate of 0.34 per 1000 live births in 2007 [150]. The burden of early-onset disease initially was disproportionately high in African American infants for reasons that were not well defined and then decreased in 2003-2005, but more recent data indicate reemergence of this disparity. Factors that might contribute to the disparity include higher maternal colonization rates and higher rates of preterm deliveries in African American women compared with white women, but additional study is needed [172]. In contrast to its impact on early-onset disease, use of IAP has had *no* impact on the incidence of late-onset disease, which has remained stable at 0.3 to 0.4 per 1000 live births since 2002 [150].

The male-to-female ratio for early-onset and late-onset group B streptococcal disease is equal at 1:1. Before 1996, 20% to 25% of all infants with group B streptococcal disease had onset after the first 6 days of life. In 200~~7~~, approximately ~~75~~% of all infants had disease with onset after 6 days of life [173]. Infants born prematurely constituted 23% of the total with early-onset disease and 52% of the total with late-onset disease.

The importance of group B *Streptococcus* as a common pathogen for the perinatal period relates to the pregnant woman as well as her infant. Postpartum endometritis occurs with a frequency of approximately 2%, and clinically diagnosed intra-amniotic infection occurs in 2.9% of women vaginally colonized with GBS at the time of delivery. The risk of intra-amniotic infection is greater in women with heavy colonization [174]. Implementation of intrapartum chemoprophylaxis has been associated with a significant decline in the incidence of invasive

TABLE 12–~~2~~ Fatality Rates in Early-Onset Group B Streptococcal Infection

	Case-Fatality Rate (%) by Birth Weight (g) or Gestational Age (wk)				
Study	**500-1000**	**1001-1500**	**1501-2000**	**2001-2500**	**>2500**
Boyer et al [708] (1973-1981)	90	25	29	33	3
Baker [613] (1982-1989)	60	25	26	18	5
Weisman et al [427] (1987-1989)	75	40	20	15	6
Schrag et al [12] (1993-1998)		30 (≤33 wk)		10 (34-36 wk)	2 (≥37 wk)
Phares et al [150] (1999-2005)		20 (<37wk)			3 (≥37 wk)

disease in pregnant women, from 0.29 per 1000 live births in 1993 to 0.23 per 1000 live births in 1998 and a further decline to 0.12 per 1000 live births in 1999-2005 [150,171]. Half of these infections were associated with infection of the upper genital tract, placenta, or amniotic sac and resulted in fetal death. Among the other infections, bacteremia without a focus (31%), endometritis without fetal death (8%), and chorioamnionitis without fetal death (4%) were the most common manifestations.

IMMUNOLOGY AND PATHOGENESIS

HOST-BACTERIAL INTERACTIONS RELATED TO PATHOGENESIS

The prevalence and severity of group B streptococcal diseases in neonates have stimulated intensive investigation to elucidate the pathogenesis of infection. The unique epidemiologic and clinical features of group B streptococcal disease pose several basic questions that provide a framework for hypothesis development and experimental testing: How does the organism colonize pregnant women and gain access to the infant before or during delivery? Why are newborns, especially infants born prematurely, uniquely susceptible to infection? What allows GBS to evade host innate immune defenses? How do these organisms gain entry to the bloodstream and then cross the blood-brain barrier to produce meningitis? What specific GBS factors injure host tissues or induce the sepsis syndrome?

Advances in knowledge of pathogenesis have been achieved through development of cell culture systems and animal models. Refinement of molecular genetic techniques has yielded isogenic mutant strains varying solely in the production of a particular component (e.g., CPS). Such mutants are important in establishing the biologic relevance of a given trait and its requirement for virulence in vivo. The sequencing of several complete GBS genomes has provided additional context for interpretation of experimental data and comparison with other well-studied pathogens [7,8].

Although GBS have adapted well to asymptomatic colonization of healthy adults, they remain a potentially devastating pathogen to susceptible infants. This section reviews the current understanding of virulence mechanisms, many of which are revealed or magnified by the unique circumstances of the birth process and the deficiencies of neonatal immune defense. The group B streptococcal virulence factors defined to date, with mode of action and proposed role in pathogenesis, are shown in Table 12–3. Key stages in the molecular, cellular, and immunologic pathogenesis of newborn infection are summarized schematically in Figure 12–5.

Maternal Colonization

The presence of GBS in the genital tract of the mother at delivery determines whether or not a newborn is at risk for invasive disease. Among infants born to colonized women, the risk of early-onset disease is approximately 30-fold that for infants born to women with a negative result on prenatal cultures [175]. A direct relationship exists between the degree (inoculum size) of group B streptococcal vaginal colonization, the risk of vertical transmission, and the likelihood of serious disease in the newborn [132,176]. Consequently, a crucial step in the pathogenesis of invasive disease in the newborn caused by GBS is colonization of pregnant women.

TABLE 12–3 Clinical Features of Group B Streptococcal Bone and Joint Infections*

Feature	Septic Arthritis without Osteomyelitis (20 Patients) [4,447,450,457, 709–711]	Osteomyelitis (45 Patients) [4,439–444,447, 448,451,454–456, 712–715]
Mean age at diagnosis (range)	20 days (5-37)	31 days (8-60)
Mean duration of symptoms (range)	1.5 days (<1-3)	9 days (1-28)
Male-to-female ratio	2:5	2:3
Site (%)	Hip (56) Knee (38) Ankle (6)	Humerus (56) Femur (24) Tibia, talus (4) Other† (16)
Group B streptococcal serotype (No. patients)	III (12)	III (15), Ib/c (3), Ia/c (1)
Mean duration of parenteral therapy (range)	2 wk (2-3)	3 wk (2-7)

**Includes authors' unpublished data for seven patients.*
†Ilium, acromion, clavicle, skull, digit, vertebrae; ribs—one patient each.

To establish colonization of the female genital tract, GBS must adhere successfully to the vaginal epithelium. Compared with other microorganisms, GBS bind very efficiently to exfoliated human vaginal cells or vaginal tissue culture cells [177,178], with maximal adherence at the acidic pH characteristic of vaginal mucosa [179,180]. A low-affinity interaction with epithelial cells is mediated by its amphiphilic cell wall–associated lipoteichoic acid, whereas higher affinity interactions with host cells are mediated by hydrophobic surface proteins. Soluble lipoteichoic acid competitively inhibits epithelial cell adherence [181,182] and decreases vaginal colonization of pregnant mice [183].

High-affinity protein-mediated interactions of GBS with epithelium are mediated largely through extracellular matrix components, such as fibronectin, fibrinogen, and laminin, which interact with host cell–anchored proteins such as integrins. Binding occurs to immobilized, but not soluble fibronectin, suggesting that this interaction requires close proximity of multiple fibronectin molecules and group B streptococcal adhesins [184]. More recently, a genome-wide phage display technique revealed a fibronectin-binding property associated with the surface-anchored group B streptococcal C5a peptidase, ScpB [185]. The dual functionality of ScpB was confirmed by decreased fibronectin binding of isogenic ScpB mutants and the direct interaction of recombinant ScpB with solid-phase fibronectin [185,186]. Similar targeted

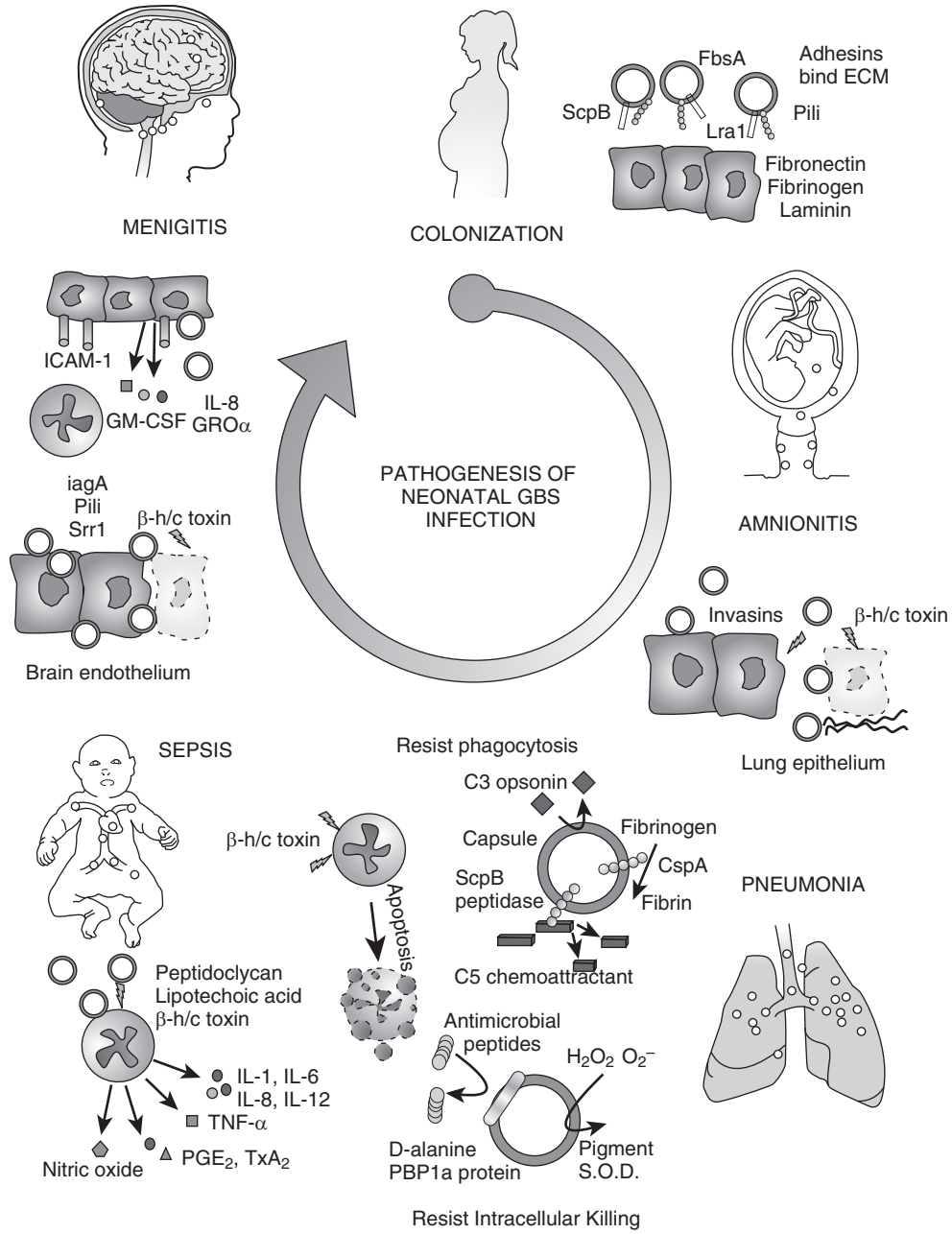


FIGURE 12–5 Pathologic mechanisms for different types of neonatal group B streptococcal (GBS) infection. ECM, extracellular matrix; GM-CSF, granulocyte-macrophage colony-stimulating factor; ICAM, intercellular adhesion molecule; IL-8, interleukin-8; PGE_2, prostaglandin E_2; SOD, superoxide dismutase; TNF-α, tumor necrosis factor-α; TxA_2, thromboxane A_2. *(Adapted from Doran KS, Nizet V. Molecular pathogenesis of neonatal group B streptococcal infection: no longer in its infancy. Mol Microbiol 54:23-31, 2004.)*

mutagenesis studies showed that adherence of GBS to laminin involves a protein adhesin called Lmb [187], attachment to fibrinogen is mediated by repetitive motifs within the surface-anchored protein FbsA [188], and binding to human keratin 4 is carried out by the serine-rich repeat domain protein Srr-1 [189].

More recently, GBS were revealed to express filamentous cell surface appendages known as pili [9]. Among eight sequenced GBS genomes, two genetic loci encoding pili were identified, although not all genomes contain both loci [190]. One of these islands includes genes encoding PilB, an LP(x)TG motif–containing protein that polymerizes to form a pilus backbone, along with accessory pilus proteins PilA and PilC [47,191]. Epithelial cell adherence was reduced in isogenic GBS mutants lacking PilA or PilC, but not mutants lacking the PilB backbone [191]. Solution of the crystal structure of PilC reveals a specific IgG-like fold domain (N2) required for epithelial cell binding [192].

Ascending Amniotic Infection

GBS can reach the fetus in utero through ascending infection of the placental membranes and amniotic fluid. Alternatively, the newborn may become contaminated

with the organism on passage through the birth canal. Infection by the ascending route plays a pivotal role in early-onset disease. A direct relationship exists between the duration of membrane rupture before delivery and attack rate for early-onset disease [193], whereas an inverse relationship exists between the duration of membrane rupture and the age at which clinical signs of early-onset pneumonia and sepsis first appear [194]. When the duration of membrane rupture was 18 hours or less, the attack rate was 0.7 per 1000 live births; when it was more than 30 hours, the attack rate increased to 18.3 per 1000 [193]. Histologic examination of placentas from women with group B streptococcal chorioamnionitis showed bacterial infiltration along a choriodecidual course, implying that ascending infection may be a primary trigger in many instances of premature rupture [195].

GBS may promote membrane rupture and premature delivery by several mechanisms. Isolated chorioamniotic membranes exposed to the organism have decreased tensile strength and elasticity and are prone to rupture [196]. The presence of GBS at the cervix activates the maternal decidua cell peroxidase–hydrogen peroxide–halide system, promoting oxidative damage to adjacent fetal membranes [197]. GBS also can modify the arachidonic acid metabolism of cultured human amnion cells, favoring production of prostaglandin E_2 [198,199], which is known to stimulate the onset of labor. Stimulation of chorionic cell release of macrophage inflammatory protein-lα and interleukin (IL)-8 from human chorion cells recruits inflammatory cells that may contribute to infection-associated preterm labor [200].

GBS occasionally seem to penetrate into the amniotic cavity through intact membranes. Clinically, this mechanism of entry is suggested by anecdotal reports of neonates with fulminant early-onset infection after delivery by cesarean section and no identifiable obstetric risk factors [133,201,202]. Migration of the organism through freshly isolated chorioamniotic membranes has been documented by scanning and transmission electron microscopy [203]. GBS invade primary chorion cells efficiently in vitro and are capable of transcytosing through intact chorion cell monolayers without disruption of intracellular junctions [204]. They also secrete an enzyme that degrades hyaluronic acid, an important component of the extracellular matrix that is abundant in placental tissues and may facilitate amniotic invasion [84,205].

Amniotic fluid supports the proliferation of GBS [206], such that when the organism gains access to the uterine cavity a large inoculum can be delivered to the fetal lung; this results in a continuum of intrapartum (stillbirth) to early postpartum infant death [176,207–211]. In utero infection probably accounts for the 40% to 60% of newborns with early-onset disease who have poor Apgar scores and in whom pulmonary signs develop within a few hours of birth because these infants almost invariably display clinical or histologic evidence of congenital pneumonia [193,208]. Conversely, when GBS are encountered in the immediate peripartum period or on passage through the birth canal, a lesser inoculum is delivered to the neonate. Although a small but meaningful risk of subsequent invasive disease exists, most of these newborns have asymptomatic colonization limited to mucosal surfaces and remain healthy.

Pulmonary and Bloodstream Entry

Early-onset group B streptococcal disease is heralded by respiratory symptoms, including tachypnea, hypoxia, cyanosis, and pulmonary hypertension [212]. One third to more than half of infants are symptomatic at birth or within 4 to 6 hours after delivery. Autopsies in fatal early-onset cases reveal that 80% have histologic evidence of lobar or multilobar pneumonia [211,213], characterized by dense bacterial infiltration, epithelial cell damage, alveolar hemorrhage, interstitial inflammatory exudate, and hyaline membrane formation [210,214]. When pneumonia develops in newborn primates exposed by intra-amniotic injection of GBS, bacterial density reaches 10^9 to 10^{11} organisms per gram of lung tissue [215]. As shown in rabbits, the poorer resolution of pneumonia in preterm versus term newborns reflects quantitative deficiency of pulmonary alveolar macrophages, mandating the recruitment of neutrophils as a secondary phagocytic defense mechanism [216].

Group B streptococcal disease rarely is limited to the initial pulmonary focus, but spreads to the bloodstream and is circulated through other organs and tissues. The capacity of GBS to cause disruption of the lung epithelial and endothelial barrier evidently involves the process of intracellular invasion, direct cytolytic injury, and damage induced by the inflammatory response of the newborn host. Intracellular invasion of alveolar epithelial and pulmonary endothelial cells by GBS was first noted in newborn macaques after intra-amniotic challenge [215] and later confirmed in human tissue culture lines derived from both cellular barriers [217,218]. In vivo and in vitro electron microscopy studies show that host cytoskeletal changes are triggered that lead to endocytotic uptake of the bacterium within a membrane-bound vacuole. Uptake requires induction of signal transduction pathways in the host cell that are mediated by Rho-family GTPases [219] and phosphatidylinositol-3 kinase [220].

Cellular invasion is correlated with virulence potential. Clinical isolates of GBS from infants with bloodstream infections invade epithelial cells better than strains from the vaginal mucosa of asymptomatic women [221]. FbsA, a group B streptococcal fibrinogen binding protein [222]; Lmb, which mediates laminin binding [223]; and ScpB, which interacts with fibronectin [186], each play a role in promoting efficient epithelial or endothelial cell invasion. Another GBS surface protein, Spb1, was identified by subtractive hybridization to play a specific role in serotype III GBS invasion of epithelial cells [163]. In addition, surface-anchored α C protein specifically interacts with host cell glycosaminoglycan on the epithelial cell surface to promote group B streptococcal internalization [224]. By contrast, CPS decreases intracellular invasion, presumably through steric interference of certain receptor-ligand interactions [225].

Although cellular invasion may play a principal role in bloodstream penetration in late-onset group B streptococcal infection, damage to the lung barrier often is

evident in severe early-onset infection. Alveolar exudate and hemorrhage in autopsy studies of infants with group B streptococcal pneumonia attest to significant pulmonary epithelial and endothelial cell injury [210,226]. The cellular damage seems to result largely from the actions of β-hemolysin/cytolysin. This toxin is responsible for the characteristic β-hemolytic phenotype displayed by the organism when grown on sheep's blood agar. Mutagenesis and heterologous expression studies have identified a single open reading frame, *cylE*, as necessary for group B streptococcal β-hemolysin/cytolysin expression and sufficient to confer β-hemolysis when cloned in *Escherichia coli* [227,228]. CylE is a predicted 79-kDa protein sharing no homology to the toxin, streptolysin S, that is responsible for β-hemolysis in group A, C, F, and G streptococci [229]. This pore-forming toxin lyses lung epithelial and endothelial cells and compromises their barrier function [230,231]. At subcytolytic doses, it promotes intracellular invasion and triggers the release of IL-8, the principal chemoattractant for human neutrophils [232]. Mutants lacking hemolysin expression are less virulent than the corresponding wild-type strains in mouse, rat, and rabbit models of group B streptococcal pneumonia [233–235].

The cytolytic, proinvasive, and proinflammatory effects of group B streptococcal β-hemolysin/cytolysin all are neutralized by dipalmitoyl phosphatidylcholine, the major phospholipid constituent of human lung surfactant [230,232]. This finding may partly explain the increased risk in premature, surfactant-deficient neonates for severe lung injury and invasive disease from group B streptococcal infection. Treatment with exogenous surfactant reduces histologic evidence of lung inflammation, improves lung compliance, and mitigates bacterial growth in preterm rabbits infected with GBS [236,237]. Clinical studies exploring the effect of surfactant administration on human infants with group B streptococcal sepsis also suggest a beneficial effect [238,239].

Capsular Polysaccharide and Immune Resistance

On penetration of GBS into the lung tissue or bloodstream of the newborn infant, an immunologic response is recruited to clear the organism. Central to this response are host phagocytic cells including neutrophils and macrophages. Effective uptake and killing by these cells require opsonization of the bacterium by specific antibodies in the presence of complement [240–242]. Neonates are particularly prone to invasive disease because of their quantitative or qualitative deficiencies in phagocytic cell function, specific antibody, or classic and alternate complement pathways. In addition to these newborn host susceptibilities, GBS possess numerous virulence determinants that seek to thwart each of the key components of effective opsonophagocytic killing. Chief among these factors is the sialylated group B streptococcal polysaccharide capsule.

The serotype-specific epitopes of group B streptococcal CPS are created by different arrangements of four monosaccharides (glucose, galactose, *N*-acetylglucosamine, and sialic acid) into a unique repeating unit (see "Immunochemistry of Polysaccharide Antigens" earlier), but unfailingly these structures contain a terminal sialic acid bound to galactose in an α2→3 linkage. The enzymatic machinery for capsule biosynthesis is encoded in the single long transcript of a 16-gene operon. More recent elegant experiments have shown that the heterologous expression of a single polymerase gene (*cpsH*) from this operon can cause a group B streptococcal type Ia strain to express type III capsule epitopes, and vice versa [243].

The conserved group B streptococcal terminal α2→3 sialic acid capsular component is identical to a sugar epitope widely displayed on the surface of all mammalian cells [244]. The terminal α2→3-linked sialic acid is overexpressed in humans, who in evolution have lost the genes to produce the alternative sialic acid, Neu5Gc. It is suggested that group B *Streptococcus* may be a particularly troublesome human pathogen because its sialylated capsule has undergone selection to resemble host "self" and avoid immune recognition. Compared with wild-type strains, isogenic capsule-deficient mutants of GBS elicit greater degrees of proinflammatory cytokine release from human cells [245]. It was shown more recently that GBS can use such molecular mimicry to engage a sialic acid–binding surface receptor, Siglec-9, expressed on human neutrophils, leading to negative cell signaling cascades that dampen the oxidative burst and bactericidal activities of phagocytic cell [246].

The properties of group B streptococcal CPS have been studied most thoroughly in serotype III organisms. Sialic acid is a critical element in the epitope of the type III capsule that confers protective immunity. After treatment with sialidase, the altered CPS fails to elicit protective antibodies against group B streptococcal infection. Protective antibodies derived from native type III capsule do not bind to the altered (asialo) capsule backbone structure [247]. Sialidase-treated type III GBS are opsonized more effectively by complement through the alternative pathway and are more readily phagocytosed by human neutrophils in vitro, and sialidase exhibits diminished lethality of the organism in neonatal rats [248,249].

More definitive evidence for the role of type III capsule in virulence is provided by the construction of isogenic capsule-deficient mutants by transposon mutagenesis or targeted allelic replacement [250–252]. Compared with the parent strains, isogenic capsule mutants are susceptible to opsonophagocytosis in the presence of complement and healthy adult neutrophils [253]. Opsonization by complement is a pivotal element in host defense against invasive infections; however, the extent of C3 deposition on GBS by the alternative complement pathway is inversely related to the size and density of their polysaccharide capsule present [253,254]. C3 fragments bound to the acapsular mutant are predominantly in the active form, C3b, whereas the inactive form, C3bi, is predominantly bound to the surface of the parent strain.

The type III group B streptococcal acapsular mutants also are significantly less virulent in animal models of infection. In a model of pneumonia and bacteremia, neonatal rats were inoculated with either the parent strain or an acapsular mutant by intratracheal injection. In animals that received the acapsular mutant, fewer GBS were recovered per gram of lung, more bacteria were associated with resident alveolar macrophages, and the animals became

significantly less bacteremic than animals that received the parent strain [255]. Subcutaneous injection of the acapsular mutants in neonatal rats resulted in LD_{50} values that were at least 100-fold greater than the values obtained with the parent strain [251,256]. Mouse passage of various serotypes of GBS was followed by increases in sialylated capsule content that correlated with increased virulence [257]. Taken together, these data provide compelling evidence that the capsule protects the organism from phagocytic clearance during the initial pulmonary phase and the later bacteremic phase of early-onset infection.

Noncapsular Factors That Interfere with Immune Clearance

The ability of GBS to avoid opsonophagocytosis is enhanced by surface proteins that can act in concert with CPS. Serotype II strains displaying both components of the C protein antigen are more resistant to phagocytic killing than are serotype II strains lacking C protein [258,259]. The b antigen of C protein binds human IgA [260,261], and IgA deposited nonspecifically on the bacterial surface probably inhibits interactions with complement or IgG [262]. A cell surface protease, CspA, targets host fibrinogen, producing adherent fibrin-like cleavage products that coat the bacterial surface and interfere with opsonophagocytic clearance [263]. The group B streptococcal BibA protein binds human C4bp, a component of the classical complement pathway, and increases resistance to phagocytic killing [264]. Finally, certain type Ia group B streptococcal strains can also use the surface anchored b protein to engage Siglec 5 on macrophages and neutrophils and downregulate their innate immune function, a unique example of protein-mediated subversion of a host lectin receptor [265].

After phagocytic uptake of pathogens, neutrophils and macrophages seek to kill the engulfed bacteria by generation of reactive oxygen products and other antimicrobial substances. Streptococci are often thought of as "extracellular pathogens," but these organisms can survive for prolonged periods within the phagolysosome of macrophages [266,267]. Although GBS lack the neutralizing enzyme catalase, they are more than 10 times resistant to killing by hydrogen peroxide than is catalase-positive *S. aureus* [268]. Several mechanisms for enhanced intracellular survival have been identified. The organism possesses an endogenous source of the oxygen metabolite scavenger glutathione [268]. Another defense against oxidative burst killing is the enzyme superoxide dismutase (SodA), as evidenced by the fact that a SodA mutant is highly susceptible to macrophage killing and survives poorly in vivo [269]. Finally, GBS produce an orange carotenoid pigment, a property unique among hemolytic streptococci and genetically linked to the cyl operon encoding β-hemolysin/cytolysin. The free radical scavenging properties of the carotenoid neutralize hydrogen peroxide, superoxide, hypochlorite, and singlet oxygen, providing a shield against several elements of phagocyte oxidative burst killing [270]. The antioxidant effects of glutathione, SodA, and carotenoid pigment apparently compensate for the lack of catalase and explain the unexpected persistence of GBS within host phagolysosomes.

Cationic antimicrobial peptides, such as defensins and cathelicidins produced by host phagocytes, also are an important component of innate immune defense against invasive bacterial infection [271]. The group B streptococcal *ponA* gene codes for an extracytoplasmic penicillin-binding protein (PBP1a) that promotes resistance to phagocytic killing independent of capsule [272]. Group B streptococcal mutants with deletion of the PBP1a gene are less virulent after lung and systemic challenge, and this is correlated to an increased susceptibility to defensins and cathelicidins. Another way in which the organism avoids antimicrobial peptide clearance is through the D-alanylation of lipoteichoic acid in the bacterial cell wall; this requires activity of gene products that are encoded by the *dlt* operon. A *dlt*A mutant exhibits decreased negative surface charge that impedes cationic host defense peptides from reaching their cell membrane target of action [273]. Similarly, expression of the pilus backbone protein PilB renders GBS more resistant to killing by cathelicidins and is associated with enhanced phagocyte resistance and systemic virulence [274].

Direct cytotoxicity to host phagocytes represents another important virulence mechanism for immune resistance. The group B streptococcal β-hemolysin/cytolysin toxin produces direct cytolytic injury to macrophages and induces macrophage apoptosis over a longer interval. With highly hemolytic strains or with a large bacterial inoculum, killing of the phagocyte seems to outpace the phagocyte's microbicidal mechanisms, allowing bacterial proliferation in vitro in a murine bacteremia model [270]. Addition of an inhibitor of β-hemolysin/cytolysin blocks cytolysis and reduces apoptosis of macrophages, restoring phagocytic killing [270]. GBS-induced macrophage apoptosis can also occur by a β-hemolysin/cytolysin–independent mechanism regulated, at least in part, by glucose [275]. Signaling pathways involved in GBS-induced programmed cell death of macrophages seem to involve either caspase-3 or calpain activation [276,277].

Deficiencies in the neutrophil response to GBS have been documented in newborn infants. Neutropenia and depletion of the marrow neutrophil storage pool are frequent findings in infants with septicemia [278] and are correlated with poor clinical outcome [212]. Although neutrophilia and an increase in granulocytic stem cells develop in adult rats infected with GBS, severe neutropenia without a change in stem cell counts develops in neonatal rats [279]. Fatal infection in neonatal rats is associated with failure of recovery of depleted myeloid storage pools [280]. The explanation for this finding may be that the proliferative rate of neutrophils in noninfected neonatal animals already is maximal or near-maximal and cannot increase further in response to bacterial challenge [281].

GBS actively contribute to poor mobilization of neutrophils by production of an enzyme that cleaves and inactivates human C5a, a complement component that stimulates neutrophil chemotaxis [82]. Expression of C5a peptidase reduces the acute neutrophil response to sites of infection in C5a knockout mice reconstituted with human C5a [282]. Expression of group B streptococcal C5a peptidase is induced in normal human serum [283];

however, its enzymatic activity is often neutralized, in large part because of naturally occurring IgG antibodies present in many adults [82]. IgG also neutralizes C5a peptidase on the surface of a capsule-deficient group B streptococcal mutant, but fails to neutralize the enzyme on the surface of the intact encapsulated type III parent strain. The capsule serves to protect the cell-associated C5a peptidase from inactivation by naturally occurring antibodies.

Inflammatory Mediators and Sepsis

When failures in epithelial barrier function and immunologic clearance allow GBS to establish bacteremia in the neonate, sepsis or septic shock develops. Intravenous infusion of GBS in animal models produces similar pathophysiologic changes to human newborn infection, including hypotension, persistent pulmonary hypertension, tissue hypoxemia and acidosis, temperature instability, disseminated intravascular coagulation, neutropenia, and, ultimately, multiple organ system failure. These similarities have allowed in vivo experiments to elucidate the patterns in which the organism activates host inflammatory mediators to induce sepsis and circulatory shock.

Animal models in which GBS are infused intravenously exhibit a biphasic host inflammatory response [284–286]. The acute phase ($\leq$1 hour after infusion) is manifested by increased pulmonary artery pressure and decreased arterial oxygenation and is associated with an increase in serum levels of thromboxanes. Pulmonary hypertension and hypoxemia persist through the late phase (2 to 4 hours), in which a progressive pattern of systemic hypotension, decreased cardiac output, and metabolic acidosis develops together with hematologic abnormalities; organ system dysfunction; and increase in inflammatory markers, such as thromboxanes, tumor necrosis factor (TNF)-α, and prostacyclins. If production of thromboxane and prostacyclin is blocked by inhibition of the cyclooxygenase pathway in rabbits or lambs infused with GBS, decreased myocardial dysfunction and a significant increase in systemic blood pressure are observed [287–289].

Infusion of GBS produces pulmonary hypertension in piglets and isolated piglet lung preparations, suggesting a direct interaction of the organism with target cells in lung microvasculature [290,291]. GBS induce release of vasoactive eicosanoids prostacyclin and prostaglandin E_2 from lung microvascular cells [292] and stimulate the host inflammatory mediators leukotriene D_4 [293] and thromboxane A_2 [294].

The cytokine IL-12 has an important role in the systemic response to group B streptococcal infection. Elevation of IL-12 occurs 12 to 72 hours after challenge in the neonatal rat. Pretreatment with a monoclonal antibody against IL-12 results in greater mortality and intensity of bacteremia, whereas therapeutic administration of IL-12 is associated with a lower mortality rate and bloodstream replication of the organism [295]. By contrast, IL-1, a known stimulator of cyclooxygenase and lipoxygenase pathways, seems to occupy a proximal position in the deleterious cytokine cascade of septic shock [296]. Treatment with an IL-1 receptor antagonist improves cardiac output and mean arterial pressure, and increases duration of survival in piglets receiving a continuous infusion of GBS [297].

Controversy exists regarding the precise role of TNF-α in neonatal septicemia. TNF-α often is detected in the blood, urine, or cerebrospinal fluid (CSF) of infants with invasive disease [298]. Although infusion of GBS in piglets is associated with TNF-α release during the late phase of hemodynamic response, the TNF-α inhibitor pentoxifylline has only modest effects on pulmonary hypertension, hypoxemia, and systemic hypotension [299]. Marked improvement in these hemodynamic parameters is seen only when pentoxifylline treatment is combined with indomethacin inhibition of thromboxane and prostacyclin synthesis [300]. Serum TNF-α levels in the mouse and rat also increase after challenge; however, administration of polyclonal or monoclonal anti–TNF-α antibody does not affect overall mortality rate in these animal models [300,301].

Studies have sought to establish the components of GBS cell wall that trigger the host cytokine cascade. Host release of IL-l and IL-6 is stimulated by soluble cell wall antigens [302]. Cell wall preparations also cause nuclear factor κB (NF-κB) activation and TNF-α release from human monocytes in a manner requiring CD14 and complement receptor types 3 and 4 [303]. Group B polysaccharide and peptidoglycan are more effective stimulators of TNF-α release from monocytes than lipoteichoic acid or CPS [304]. Knockout mouse studies indicate that cell wall peptidoglycan-induced activation of p38 and NF-κB depends on the cytoplasmic toll-like receptor (TLR) adapter protein MyD88, but does not require the pattern recognition receptor TLR2 or TLR4 [305]. An additional, undefined secreted factor apparently activates phagocytes through TLR2 and TLR6 [306].

Inhibitor studies have shown that the mitogen-activated protein kinase/JNK signaling pathway is required for the NF-κB–dependent inflammatory response of phagocytes to GBS. Because neither phagocytosis nor oxidative killing of bacteria is affected by JNK inhibition, this pathway may represent a viable therapeutic target for group B streptococcal sepsis [307]. The nitric oxide pathway is implicated in overproduction of proinflammatory cytokines such as IL-6 and initiation of cellular injury during group B streptococcal lung infection [308]. Inducible cyclooxygenase-2 is also stimulated on group B streptococcal infection in human monocytes, likely through the mitogen-activated protein kinase pathway [309]. Infection also stimulates cyclooxygenase-2 and prostaglandin E_2 expression in lung tissue in vitro and in vivo. GBS-induced cyclooxygenase-2 and prostaglandin E_2 inflammatory response is reduced on treatment with an inducible nitric oxide synthase inhibitor and restored by addition of a nitric oxide donor, showing at least partial regulation by the nitric oxide pathway [310].

Another proinflammatory molecule contributing to the pathogenesis of group B streptococcal septicemia is β-hemolysin/cytolysin. This potent cytoxin acts to stimulate inducible nitric oxide synthase in macrophages, leading to release of nitric oxide [311]. In a mouse model of bacteremia and arthritis, β-hemolysin/cytolysin expression is associated with higher mortality, increased bacterial loads, greater degrees of joint injury, and release of the proinflammatory cytokines IL-6 and IL-1α systemically and intra-articularly [312]. Challenge of rabbits with

isogenic group B streptococcal mutants showed that β-hemolysin/cytolysin production was associated with significantly higher degrees of hypotension, increased mortality, and evidence of liver necrosis with hepatocyte apoptosis [313]. Partially purified β-hemolysin/cytolysin preparations produce significant hypotensive actions when infused in rats and rabbits, including death from shock [314]. β-hemolysin/cytolysin also contributes directly to cardiomyocyte dysfunction and apoptosis, which may magnify its role in the pathophysiology of group B streptococcal sepsis [315].

Blood-Brain Barrier Penetration and Meningitis

The pathophysiology of group B streptococcal meningitis varies according to age at onset. In early-onset disease, autopsy studies show little or no evidence of leptomeningeal inflammation, despite the presence of abundant bacteria, vascular thrombosis, and parenchymal hemorrhage [2,226]. By contrast, infants with late-onset disease usually have diffuse purulent arachnoiditis with prominent involvement of the base of the brain [316]. Similar age-related differences in central nervous system (CNS) pathology are evident in the infant rat model of invasive disease [317]. These histopathologic differences reflect underdevelopment of the host immunologic response in the immediate neonatal period, with a higher proportion of deaths resulting from overwhelming septicemia.

To produce meningitis, GBS must penetrate human brain microvascular endothelial cells, the single-cell layer constituting the blood-brain barrier. Intracellular invasion and transcytosis of human brain microvascular endothelial cell tissue culture monolayers have been shown in vitro [318]. Serotype III strains, which account for most of the isolates causing meningitis, invade more efficiently than strains of other common serotypes. A transposon mutant library of type III GBS was screened in tissue culture assays for alterations in invasiveness. Hypoinvasive mutants were identified with disruptions in *iag*A, sharing homology to genes encoding diglucosyldiacylglycerol synthase. Allelic replacement of *iag*A confirms the in vitro phenotype, and the *iag*A knockout mutant does not produce meningitis in mice [319].

In separate avenues of research, group B streptococcal mutants lacking the fibrinogen receptor FbsA, laminin-binding protein Lmb, or pilus backbone subunit protein PilB also showed reduced adherence or invasion of human brain microvascular endothelial cells in vitro [47,223,320]. More recently, a group B streptococcal mutant lacking the surface-anchored serine-rich repeat motif glycoprotein Srr-1 was attenuated for brain endothelial cell invasion and for production of meningitis in the murine model [321]. At high bacterial densities, invasion by GBS of brain microvascular endothelial cells is accompanied by evidence of β-hemolysin/cytolysin–induced cellular injury [245]. Correspondingly, β-hemolysin/cytolysin knockout mutants show decreased blood-brain barrier penetration and decreased lethality from meningitis in vivo [245].

The host inflammatory response to GBS contributes significantly to the pathogenesis of meningitis and CNS injury. The initiation of the inflammatory response is triggered through the sentinel function of the blood-brain barrier endothelium, which activates a specific pattern of gene transcription for neutrophil recruitment, including production of chemokines (e.g., IL-8, Groα), endothelial receptors (intercellular adhesion molecule-1), and neutrophil activators (granulocyte-macrophage colony-stimulating factor) [245]. A vascular distribution of cortical lesions in neonatal rats with group B streptococcal meningitis indicates that disturbances of cerebral blood flow contribute to neuronal damage [322]. Inflammation of individual brain vessels can lead to focal lesions, whereas diffuse alterations of cerebral blood flow could cause generalized hypoxic-ischemic injury and cerebral edema [322,323]. Arteriolar dysfunction is associated with the presence of oxygen free radicals thought to be a by-product of the phagocytic killing by infiltrating neutrophils [324]. Group B streptococcal β-hemolysin/cytolysin induces IL-8 and the neutrophil receptor intercellular adhesion molecule-1, promoting neutrophil migration across polar BMEC monolayers, suggesting that the toxin is crucial to this particular manifestation of CNS disease [245].

TNF-α production by astrocytes, microglial cells, and infiltrating leukocytes seems to contribute to apoptosis of hippocampal neurons [325], further increasing blood-brain barrier permeability during group B streptococcal meningitis [326]. Intraventricular inoculation of newborn piglets with GBS results in an early sharp increase in CSF TNF-α levels, followed shortly by prostaglandin release and neutrophil influx [327]. The magnitude of the observed TNF-α response and inflammatory cascade is markedly increased when an isogenic nonencapsulated mutant is tested in place of the type III parent strain [327], suggesting that a component of the underlying cell wall and not capsule is responsible for inducing the CNS inflammatory response. GBS signal through TLR2 to activate and stimulate nitric oxide production by microglia cells, resulting in neuronal destruction [328]. Simultaneous intracisternal administration of dexamethasone with GBS in the rat model leads to a marked reduction in subarachnoid inflammation, vasculopathy, and neuronal injury [322]. In the course of experimental group B streptococcal meningitis, microglial apoptosis is triggered via the cysteine protease caspase-8 and is hypothesized to represent a self-dampening mechanism that prevents overstimulation of brain inflammation [329].

HOST FACTORS RELATED TO PATHOGENESIS

Risk Factors for Early-Onset Infection

Infant and maternal factors that increase risk for early-onset group B streptococcal infection are listed in Table 12–4. The most obvious risk determinant is exposure through maternal colonization at delivery. Maternal race or ethnicity is correlated significantly with early-onset group B streptococcal disease, with enhanced risk for infants born to African American and Hispanic mothers compared with infants born to white mothers [117,143,330]. Risk correlates directly with density of maternal genital inoculum [132]. Symptomatic early-onset disease develops in 1% to 2% of infants born to

TABLE 12–4 Risk Factors for Early-Onset Group B Streptococcal Disease

Risk Factor	Representative Reference Nos.
Maternal colonization at delivery	[3,109,331]
High-density maternal colonization	[114,132,176]
Rupture of membranes before onset of labor	[176,330]
Preterm delivery <37 wk gestation	[330]
Prolonged rupture of membranes ≥18 hr	[330,706]
Chorioamnionitis	[679]
Intrapartum fever ≥38° C (≥100.4° F)	[330]
Intrauterine monitoring	[330,706]
Maternal postpartum bacteremia	[334]
Multiple pregnancy	[332,333]
Group B streptococcal bacteriuria or urinary tract infection	[330]
Cesarean section	[3,176]
Low level of antibody to infecting CPS type	[340]
Young maternal age (<20 yr)	[330,706]
Previous infant with invasive group B streptococcal infection	[707]
Maternal race/ethnicity	[110,170,143]

CPS, capsular polysaccharide.

colonized women who do not receive IAP, but this rate is considerably increased if there is premature onset of labor (before 37 weeks of gestation) (15%) [331], chorioamnionitis or interval between rupture of membranes and delivery longer than 18 hours (11%) [176,331], twin pregnancy (35%) [332,333], or maternal postpartum bacteremia (10%) [334].

Maternal group B streptococcal bacteriuria and urinary tract infection are predictive of high-inoculum colonization, which enhances infant risk for invasive infection [335]. Heavy group B streptococcal colonization in the second trimester of pregnancy also is associated with increased risk of delivering a preterm infant with low birth weight [336]. Among infants born to mothers with premature rupture of membranes at term gestation, maternal chorioamnionitis and colonization with GBS are strong predictors of neonatal infection [337]. Vaginal colonization with GBS is an independent risk factor for the development of chorioamnionitis [338].

Prolonged interval after rupture of membranes (>18 hours) before delivery and preterm delivery (<37 weeks' gestation) often are concomitant risk factors in neonates with early-onset group B streptococcal infection. The estimated incidence of early-onset group B streptococcal infection is 10 times higher in preterm than in term neonates [176,193]. Even with correction for preterm delivery, twin pregnancy is an independent risk factor for invasive early-onset group B streptococcal septicemia [332]. The explanation for the increased risk in twins likely relates to genetic factors regulating host susceptibility, lack of specific antibody to the infecting strain in the mother, similar density of maternal colonization, and virulence of disease-producing strains [332,333].

Antibody to Capsular Polysaccharide

Lancefield showed that antibodies directed against capsular type-specific surface antigens of GBS protected mice from lethal challenge [339]. Baker and Kasper [340] showed in 1976 that neonatal risk for type III group B streptococcal disease correlated with a deficiency of antibody to type III CPS in maternal sera. A low concentration of type III CPS-specific antibodies was shown in sera from 32 infants with invasive disease [341]. Women with type III group B streptococcal genital colonization at delivery whose infants remained well more often had antibody concentrations exceeding 2 μg/mL of type III–specific antibodies in their sera than women whose infants developed type III early-onset disease. Quantitative determination of antibodies to type III group B streptococcal polysaccharide by enzyme-linked immunosorbent assay (ELISA) indicated that these antibodies were predominantly IgG [342,343]. Gray and coworkers [344] noted a similar correlation between low concentrations of type II–specific antibodies in maternal delivery sera and susceptibility of infants to invasive infection. Approximately 15% to 20% of pregnant women have a concentration of IgG to CPS in their delivery serum presumed to protect against invasive disease. These higher concentrations are present significantly more often in sera of women colonized with the homologous group B streptococcal type than in noncolonized women [117,120,345].

Attempts have been made to quantify the concentration of antibody to group B streptococcal CPS in maternal serum conferring protection against invasive disease in infants. Using ELISA standardized by quantitative precipitation [346], 1 μg/mL, 0.2 μg/mL, and 1.3 μg/mL of IgG to serotypes Ia, Ib, and III were protective in experimental models of infection [347–350]. A prospective, multicenter, hospital-based, case-control study of mothers delivering infants with type Ia, III, or V early-onset sepsis and matched colonized control mothers delivering healthy infants quantified the maternal serum concentrations of type Ia, III, and V CPS-specific IgG at delivery that protected neonates from early-onset disease. For types Ia and III, maternal IgG concentrations of 0.5 μg/mL or greater corresponded to a 90% risk reduction. For type V, the same antibody concentration corresponded to 70% risk reduction [351]. The findings of Lin and colleagues [352,353] agreed in principle, but described a higher concentration of CPS-specific IgG as the correlate for protection against type Ia or III group B *Streptococcus*. Neonates whose mothers had at least a 5 μg/mL concentration of IgG to type Ia CPS in their sera had an 88% lower risk of developing early-onset disease compared with neonates whose mothers had concentrations less than 0.5 μg/mL. Neonates whose mothers had at least a 10 μg/mL concentration of IgG to type III CPS in their sera by ELISA had a 91% lower risk for early-onset disease compared with neonates whose mothers had concentrations less than 2 μg/mL. In contrast, antibody to the group B polysaccharide does not confer protection against invasive infant disease [354].

Low concentrations of IgG to type III CPS are uniformly found in acute sera of infants with late-onset type III infection [340,355–357]. In a study of 28 infants with late-onset bacteremia and 51 with meningitis, Baker and coworkers [341] detected low levels of antibodies to type III CPS in

acute sera from all infants. These low levels in term infants with late-onset type III group B streptococcal infection correlated with maternal levels at delivery [341,356].

It is important to employ antigens with "native" or intact type III polysaccharide specificity in evaluating human immunity to type III GBS [358,359]. Kasper and colleagues [247] used gently extracted (native) and hydrogen chloride–treated (core) type III group B streptococcal and pneumococcal type 14 antigens to study sera from infants with invasive type III infection and their mothers. Concentrations of type III–specific antibodies in sera of sick infants and their mothers had uniformly low binding to fully sialylated, type III polysaccharide. Opsonic immunity correlated with antibodies to fully sialylated, but not to desialylated type III polysaccharide or to type 14 pneumococcal antigen. Among infants recovering from type III disease in whom a significant increase in antibodies to the fully sialylated polysaccharide developed, no detectable increase in the acid-degraded or core antigen was seen. Human immunity to type III GBS relates to antibodies to capsular type III polysaccharide with an intact protective epitope.

An extension of this concept comes from studies in which adults have been immunized with either type III polysaccharide or pneumococcal polysaccharide vaccine [358]. Adults with low concentrations of type III antibodies in their sera before immunization responded to type III polysaccharide vaccine with a significant increase in type III–specific antibodies. This response was not observed when the structurally related type 14 pneumococcal polysaccharide was used as an immunizing agent. Among adults with moderate to high levels of antibodies to type III polysaccharide, however, significant increases in this antibody developed after pneumococcal polysaccharide vaccine. This finding suggests that the structurally similar antigen could elicit secondary B-cell proliferation in previously primed adults.

Mucosal Immune Response

Genital colonization with GBS may elicit specific antibody responses in cervical secretions. Women with group B streptococcal type Ia, II, or III rectal or cervical colonization have markedly elevated levels of IgA and IgG to the colonizing serotype in their cervical secretions compared with cervical secretions from noncolonized women. Elevated amounts of IgA and IgG to the protein antigen R4 also have been found in women colonized with type III strains (most type III strains contain R4 antigen) compared with noncolonized women [360,361]. These findings suggest that a mucosal immune response occurs in response to colonization with GBS. Induction of mucosal antibodies to surface group B streptococcal polysaccharide or protein antigens may prevent genital colonization, diminishing vertical transmission of infection from mothers to infants.

Complement and Antibody Interactions

Shigeoka and colleagues [240] showed that specific antibody was required and that the classical complement pathway maximized opsonization of types I, II, and III GBS [362]. Capsule-specific antibodies also facilitated alternative complement pathway–mediated opsonization and phagocytosis of type III GBS [248]. The relationship between antibody concentration and the rate constant of killing of type III strains was found to be linear and determined, at least in part, by the number of antibody molecules bound per organism [363,364]. IgG subclasses 1, 2, and 3 and IgM were shown to support opsonic activity in vitro [365–368], and an IgA monoclonal antibody activated C3 and conferred protection against lethal infection [369]. Encapsulated and genetically derived acapsular mutants of type III GBS deposit C3 and support its degradation, but an inverse correlation exists between extent of encapsulation and C3 deposition by the alternative pathway [253,370]. Among infants surviving type III group B streptococcal meningitis, transient development of type-specific antibodies, predominantly IgM, supported opsonophagocytosis during convalescence [371]. When specific IgM concentrations declined, and despite maturation of complement synthesis, opsonophagocytosis of type III organisms by these infant sera remained poor.

In contrast with these findings for type III strains, clinical isolates of type Ia GBS can be efficiently opsonized, phagocytosed, and killed by neutrophils from healthy adults by the classical complement pathway in the absence of antibodies [372]. Surface-bound CPS of type Ia strains mediates C1 binding and activation [373,374]. For type Ib GBS, a role for capsule size and density in modulating C3 deposition has been reported [254]. Variability among these strains in their capacity for C3 deposition by the alternative pathway also has been shown [375].

Type II strains possessing α C and β C proteins are more resistant to opsonization than strains lacking both proteins [258]. Strains lacking type II polysaccharide but having both C proteins are readily opsonized. R protein or an IgA-mediated blocking effect may modulate phagocytosis of some type II strains. Despite the complexity of type II opsonins, it is clear that complement is essential and that integrity of the classical complement pathway is critical. Evaluation of neutrophil-mediated killing of types IV and V GBS also reveals the importance of complement and CPS-specific antibodies [376,377]. When complement is limited, type-specific antibodies facilitate killing. In sufficient concentration, agammaglobulinemic serum promotes opsonization, phagocytosis, and killing of types IV and V GBS.

During the course of septic shock caused by GBS, complement components are consumed. Cairo and associates [378] found a significant association between low levels of total hemolytic complement and fatal outcome from neonatal bacterial sepsis, including GBS. A critical role for C3 activation through the alternative pathway has been shown for potent GBS-induced TNF-α release [379]. This finding and the observation that complement-dependent uptake of CPS by marginal zone B cells seems necessary for an effective immune response to CPS [380] may partially explain this finding. The β component of C protein also can bind human factor F, a negative regulator of complement activation, evading complement attack [381].

Phagocyte Function

Smith and associates [382] examined the role of complement receptors CR1 and CR3 in the opsonic recognition of types Ia and III GBS by neutrophils from healthy

neonates and adults. Selective blockade of CR3 or of CR1 and CR3 inhibited killing for each serotype by neutrophils from neonates. These experiments indicated the importance of complement receptor function to opsonization, phagocytosis, and killing of GBS by neutrophils. Whether deficient complement receptor function contributes to susceptibility of neonates to invasive infection is unknown. A role for CR3 also has been shown in nonopsonic recognition of GBS by macrophages [383].

Yang and coworkers [384] performed selective blockade of neutrophil receptors in experiments with type III GBS opsonized with immunoglobulin. Antibodies to neutrophil Fc receptor III (FcR III) inhibited phagocytosis of opsonized bacteria to an extent exceeding that of CR3. Noya and colleagues [385] showed a substantial role for neutrophil FcR II in mediating ingestion of type III GBS opsonized in complement-inactivated serum. When complement receptor function was allowed, FcR II participation no longer was requisite for occurrence of phagocytosis. Participation by FcR and complement receptor in phagocytosis of GBS by peritoneal macrophages also has been reported [386].

Christensen and coworkers [279,281] and others [278] have addressed the explanations for the profound neutropenia often observed in fulminant group B streptococcal infection in neonates. The nearly maximal proliferative rate of granulocytic stem cells in noninfected neonatal animals led to the suggestion that neutrophil transfusion might improve the survival of human neonates with group B streptococcal infection in whom neutrophil storage pool depletion was documented [278,378]. In experimental infection with type III GBS, monoclonal IgM antibody to type III polysaccharide stimulated the release of neutrophils from storage pools into the bloodstream and improved neutrophil migration to the site of infection [387]. This facilitation of neutrophil function by type III–specific antibody improved survival in animals only if the antibody was administered when neutrophil reserves were intact (very early in infection) [388]. Antibody recipients did not become neutropenic and did not experience depletion of their neutrophil reserves. These and similar in vitro and in vivo studies using commercial preparations of immunoglobulin for intravenous administration [389–391] emphasize the importance of IgG in facilitating the neutrophil inflammatory response.

Reticuloendothelial clearance of opsonized GBS also is less efficient in experimental infection of young animals [392,393], as are lung macrophage postphagocytic oxidative metabolic responses [394]. An age-related impairment in clearance of GBS from the lungs has been reported for infant compared with adult rats and for preterm compared with term animals [395,396]. Animal age is a more important determinant of bacterial elimination from the lung than amount of polysaccharide capsule, although encapsulated strains are ingested less efficiently and in fewer numbers in infant rats than in adult rats [255].

Other Factors Related to Pathogenesis

Fibronectin is a high-molecular-weight glycoprotein that participates in adherence and functions as a nonspecific opsonin. The observation that septic neonates have significantly lower fibronectin levels than healthy age-matched controls stimulated evaluation of the possible role of fibronectin in the pathogenesis of group B streptococcal infection [397]. Soluble fibronectin binds poorly to GBS in the absence of other opsonins [398]. GBS do adhere to immobilized fibronectin, however. Fibronectin also enhances ingestion by neutrophils, monocytes, or macrophages of GBS opsonized with type-specific antibody [399–401] and may promote TNF-α production by macrophages [402]. It also has been shown that interaction of type III CPS with the lectin site of CR3 effectively triggers phagocytosis of type III organisms by nonimmune serum. Use of this mechanism provides a potential explanation for the infrequency with which invasive infection develops in susceptible individuals exposed to GBS [403].

It has been hypothesized that some individuals may have a genetically based predisposition to infection with GBS. Among 34 Swedish mothers of infants with group B streptococcal disease, Grubb and coworkers [404] identified a surplus of individuals possessing G3m(5) and a deficit of individuals with G1m(1). Thom and colleagues [405] found deficits of G1m(1) and Km(1) and an increased incidence of G2m(23) among mothers of infected infants. The distribution of allotypic markers may influence responses to protein and polysaccharide antigens. G2m(23) is a marker of IgG_2, the subclass most often associated with brisk immune responses to polysaccharide antigens. There could be genetically determined explanations for the deficiency of IgG subclasses [406], high IgM concentration with divergent ratio of IgG to IgM [407,408], and chronic colonization state without immunologic response [409] described in Swedish mothers of infants with group B streptococcal disease. In a study of women in the United States who delivered infants with invasive type III group B streptococcal disease, postpartum immunization with type III group B streptococcal polysaccharide elicited immune responses similar to those in control women [410].

PATHOLOGY

Pathologic findings in early-onset infection depend on the duration of exposure to GBS before or during birth. Intrauterine death has been attributed to group B streptococcal infection [209,409,411] and is considered to be a common cause of mid-gestational fetal loss in women who have experienced either vaginal hemorrhage or septic abortion [411,412]. Fetal membrane infection with GBS can result in spontaneous abortion or premature rupture of membranes or both, as suggested by Hood and associates in 1961 [413–415].

Becroft and colleagues [416] noted histologic changes consistent with congenital pneumonia in live-born neonates whose autopsy lung cultures yielded GBS. Numerous placentas showed amnionitis in mothers whose infants had fulminant pneumonia and died within 36 hours after birth. Findings were sufficient in stillborn infants to indicate that death occurred as a direct consequence of group B streptococcal intra-amnionitis infection and intrauterine pneumonia. deSa and Trevenen [412] described pneumonitis with pulmonary interstitial and intra-alveolar inflammatory exudates in 15 infants

weighing less than 1000 g who had intra-amniotic infection; 6 infants were stillborn, and 9 died within hours of birth. Placental examination revealed chorioamnionitis. In a primate model of infection, intra-amniotic inoculation of GBS elicited fulminant early-onset neonatal infection [215]. Microscopy of lung tissue revealed organisms within membrane-bound vacuoles of alveolar epithelial cells; interstitial fibroblasts; and organisms present within tissue macrophages of the liver, spleen, and brain, documenting their rapid dissemination.

Amnionitis in association with early-onset group B streptococcal sepsis (1) is more frequently detected when death occurs shortly after birth, (2) is a common finding when membranes have been ruptured 24 hours or longer before delivery [211,412,413], and (3) can be clinically silent in some women. GBS can enter the amniotic fluid cavity through ruptured or intact membranes [417], allowing fetal aspiration of infected fluid and subsequent pulmonary lesions or bacteremia, without eliciting a local inflammatory response or maternal signs of intra-amniotic infection.

Among neonates with fatal early-onset group B streptococcal disease, pulmonary lesions are the predominant pathologic feature. The association between pulmonary inflammation and formation of hyaline membranes was first noted by Franciosi and coworkers [2]. Subsequently, autopsy findings in early-onset disease cases revealed "atypical" pulmonary hyaline membranes in most [2,210,211], and these corresponded with radiographic features consistent with respiratory distress syndrome in some neonates [133]. GBS were frequently present within these membranes, and in some infants these were composed almost entirely of streptococci, rendering them basophilic in hematoxylin and eosin preparations [214]. Katzenstein and colleagues [214] postulated that invasion of alveolar cells and capillary endothelial cells by GBS resulted in exudation of plasma proteins into the alveoli, deposition of fibrin, and hyaline membrane formation. Immune complex–mediated injury to the lung was proposed by Pinnas and associates [418] as a mechanism for this hyaline membrane formation.

Histologic evidence for pneumonia was found historically in approximately 80% of patients with fatal early-onset group B streptococcal pneumonia [210,418,419]. The associated radiographic pattern could be focal, extensive, lobular, or bronchial, involving one or more lobes. The typical histologic features of congenital pneumonia (i.e., alveolar exudates composed of neutrophils, erythrocytes, and aspirated squamous cells, with edema and congestion) were observed either independently or in association with hyaline membrane formation. In neonates with fulminant, rapidly fatal group B streptococcal infection, the cellular inflammatory response was less pronounced. An interstitial inflammatory exudate is a consistent feature of fatal infection, as is pulmonary hemorrhage, which can range from focal interstitial to extensive intra-alveolar bleeding.

In CNS infection, age at onset predicts distinctive morphologic findings in the brain and meninges. In early-onset meningitis, little or no evidence of leptomeningeal inflammation is seen in three quarters of infants [2,176,226], although purulent meningitis can be observed occasionally. This lack of inflammatory response can be the result of rapidly progressive infection, with an interval of only a few hours from onset of clinical illness until death, or can reflect inadequate host response to infection, or both. Bacteria generally are found in large numbers, and perivascular inflammation, thrombosis of small vessels, and parenchymal hemorrhage frequently are noted [226]. In some preterm infants surviving septic shock caused by early-onset group B streptococcal infection, periventricular leukomalacia, a condition characterized by infarction of the white matter surrounding the lateral ventricles, develops [420]. Infants with fatal late-onset meningitis almost always have a diffuse purulent leptomeningitis, especially prominent at the base of the brain, with or without perivascular inflammation and hemorrhage [2,421]. Infants surviving severe meningitis have multiple areas of necrosis, and abscess formation can be found throughout the brain by neuroimaging or later at autopsy.

This age-related inflammatory response in infants with group B streptococcal infection has a parallel in the infant rat model of meningitis [317]. Young infant rats 5 to 10 days of age have numerous bacteria distributed in a perivascular pattern, and organisms can extend transmurally into vessel lumina. These animals generally have no evidence of acute leptomeningeal inflammation or edema. By contrast, 11- to 15-day-old animals have leptomeningitis and cerebritis with a pronounced infiltration of neutrophils and macrophages around meningeal vessels and in perivascular spaces within the cerebral cortex. Because response to infection becomes more efficient within a few weeks after birth, the absence of inflammation in the brain and meninges of infant rats and of human neonates with early-onset group B streptococcal infection may relate to chemotactic defects [241], exhaustion of neutrophil stores [280,281], reticuloendothelial system immaturity [392], or to other deficits in the host response to infection.

CLINICAL MANIFESTATIONS AND OUTCOME

EARLY-ONSET INFECTION

When the incidence of neonatal infection caused by GBS increased dramatically in the 1970s [422], a bimodal distribution of cases according to age at onset of signs became apparent. Two syndromes related to age were described in 1973 by Franciosi and associates [2] (acute and delayed) and by Baker and colleagues [3] (early and late). Early-onset infection typically manifests within 24 hours of birth (an estimated 85% of cases; median age 12 hours), but it can become evident during the second 24 hours of life (an estimated 10% of cases) or at any time during the subsequent 5 days. Premature infants often experience onset at or within 6 hours of birth; infants with onset after the first 24 hours of life usually are of term gestation [208]. Late-onset infections occur at 7 to 89 days of age (median age 37 days). Classification of syndromes by age at onset is useful, but there also is a continuum in age at onset. A few patients with early-onset disease can present at 5 or 6 days of age, and late late-onset infection can affect 3- to 6-month-old infants,

especially infants with gestational age of less than 28 weeks [150]. Onset beyond 6 months of age can herald the presentation of human immunodeficiency virus (HIV) infection or other immune system abnormalities [423].

Early-onset group B streptococcal infection often affects neonates whose mothers have obstetric complications associated with risk for neonatal sepsis (onset of labor before 37 weeks of gestation, prolonged interval at any gestation between rupture of membranes and delivery, rupture of membranes ≥18 hours before delivery, intrapartum fever >38° C [>100.4° F], intra-amniotic infection, early postpartum febrile morbidity, and twin births) (Table 12–5). A nearly threefold risk of early-onset group B streptococcal disease has been observed when six or more vaginal examinations are performed before delivery [424]. The incidence of infection correlates inversely with the degree of preterm birth, and group B *Streptococcus* is the most frequent pathogen associated with early-onset sepsis in neonates with very low birth weight (<1500 g) [425]. One fourth of infants with early-onset disease historically were born before 37 weeks' gestation, but this number has increased since the introduction of routine prenatal culture screening and IAP for women colonized with GBS [150].

Early-onset group B streptococcal infection can occur in term neonates with no defined maternal risk factors other than colonization. In such cases, recognition is often delayed until the appearance of definite signs of sepsis (e.g., tachypnea, apnea, hypotension), but more subtle signs usually precede these overt manifestations. One report found that one third of healthy term neonates with early-onset group B streptococcal infection were identified solely on the basis of evaluation for maternal intrapartum temperature exceeding 38° C (100.4° F) [426].

The three most common expressions of early-onset infection are bacteremia without a defined focus of infection, pneumonia, and meningitis. In the 21st century, bacteremia without a focus occurs in 80% to 85%, pneumonia occurs in 10% to 15%, and meningitis occurs in 5% to 10% of infants [150]. Bacteremia is often detected in neonates with the latter two presentations, but not always. Regardless of site of involvement, respiratory signs (apnea, grunting respirations, tachypnea, or cyanosis) are the initial clinical findings in more than 80% of neonates. Hypotension is an initial finding in approximately 25%. Infants with fetal asphyxia related to group B streptococcal infection in utero can have shock and respiratory failure at delivery [427]. Additional signs include lethargy, poor feeding, hypothermia or fever, abdominal distention, pallor, tachycardia, and jaundice.

Pneumonia occurs in 10% to 15% of infants with early-onset infection, and virtually all of these infants have acute respiratory signs. Most have these respiratory findings in the first few hours of life (many at birth) or within the first 24 hours of life [210]. Among 19 infants with group B streptococcal congenital pneumonia at autopsy, 89% had 1-minute Apgar scores of 4 or less, indicating in utero onset of infection [208]. Radiographic features consistent with and indistinguishable from those of surfactant deficiency are present in more than half of these neonates (Fig. 12–6). Treatment with surfactant improves gas exchange in most, although the response is slower than in noninfected infants, and repeated surfactant doses often are needed [239]. Infiltrates suggesting congenital pneumonia (Fig. 12–7) are present in one third of infants. Increased vascular markings suggesting the diagnosis of transient tachypnea of the newborn or pulmonary edema can occur. Occasionally, respiratory distress is present in the absence of radiographic abnormalities, appearing as persistent fetal circulation and pulmonary hypertension [419,428]. Small pleural effusions and cardiomegaly can occur.

Meningitis occurs in 5% to 10% of neonates with early-onset infection. Neonates with meningitis often have a clinical presentation early in the course that is identical to presentation of neonates without meningeal involvement. Respiratory distress can be the most common initial sign, and in 27 infants with early-onset meningitis, seizures were never a presenting feature [429]. Examination of CSF is the only means to exclude meningitis, a finding that requires modification of supportive and specific chemotherapy (see "Treatment" later on).

TABLE 12–5 Features of Group B Streptococcal Disease in Neonates and Infants

Feature	Early-Onset (<7 Days)	Late-Onset (7-89 Days)	Late Late-Onset (>89 Days)
Median age at onset	1 day	37 days	>3 mo
Incidence of prematurity	Increased	Increased	Common
Maternal obstetric complications	Frequent (70%)	Preterm delivery	Varies
Common manifestations	Septicemia (80%-85%)	Meningitis (25%-30%)	Bacteremia without a focus (common)
	Meningitis (5%-10%)	Bacteremia without focus (65%)	Bacteremia with a focus (uncommon)
	Pneumonia (5%-10%)	Soft tissue, bone, or joint pneumonia (5%-10%)	
CPS types isolated	Ia (~30%)	III (~60%)	Several
	II (~15%)	Ia (~25%)	
	III (30%)	V (~15%)	
	V (20%)		
Case-fatality rate	3%-10%	2%-6%	Low

CPS, capsular polysaccharide.

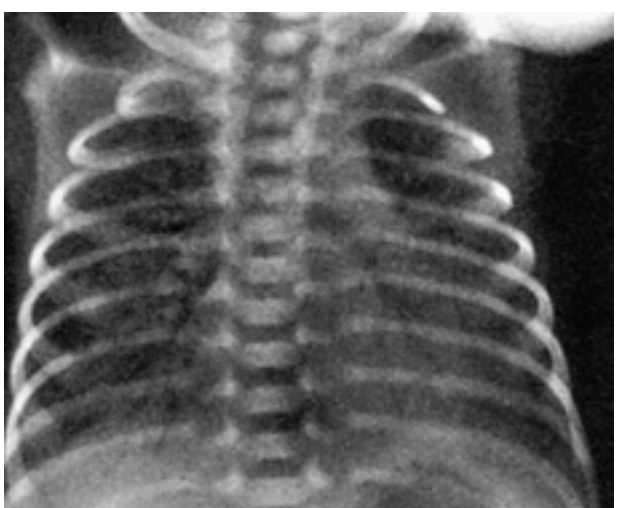


FIGURE 12–6 Chest radiograph from an infant with early-onset group B streptococcal septicemia shows features consistent with respiratory distress syndrome of the newborn.

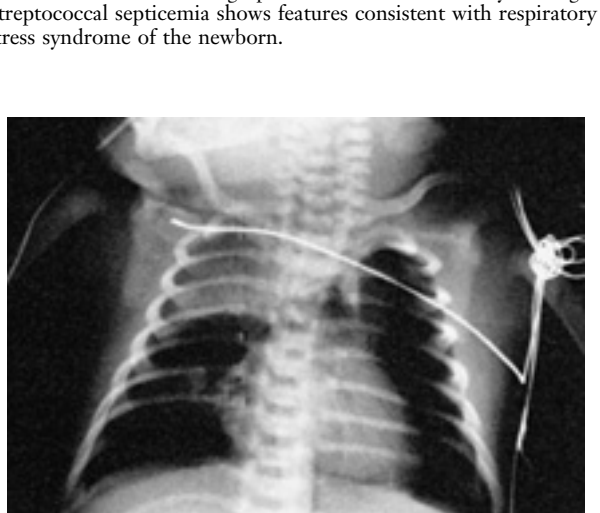


FIGURE 12–7 Chest radiograph shows right upper and lower lobe infiltrates as manifestations of early-onset group B streptococcal pneumonia in an infant.

Seizures occur during the first 24 hours of therapy in nearly 50% of infants with meningitis. Persistent seizures, semicoma or coma, and a CSF protein concentration greater than 300 mg/dL are associated with a poor prognosis [430–432].

The case-fatality rate for the nearly 300 neonates with early-onset infection summarized by Anthony and Okada [422] in 1977 was 55%. Current data indicate much lower rates of 2% to 10%. Features associated with fatal outcome include a low 5-minute Apgar score, shock, neutropenia, pleural effusion, apnea, and delay in treatment after onset of symptoms [170,212,427]. Fatal infection also occurs significantly more often among premature than among term neonates (see Table 12–2). In 1981, Pyati and colleagues[433] reported a case-fatality rate of 61% among 101 preterm neonates who had early-onset group B streptococcal infection. Infants with a birth weight greater than 1500 g had a fatality rate of 14%, however. Contemporary data document that the risk of death among preterm cases is 20%—nearly 8-fold that of term infants for whom infection was fatal in 3% of cases [150].

LATE-ONSET INFECTION

Late-onset group B streptococcal infection historically affected term infants 7 to 89 days of age who had had an unremarkable maternal obstetric and early neonatal history. Contemporary data indicate that at least half of infants with late-onset disease now are born before 37 weeks of gestation [150]. Late-onset disease has a lower fatality rate (1% to 6%) than early-onset disease. Clinical expressions of late-onset disease include bacteremia without a focus of infection (65% of infants), meningitis (25%), bacteremic cellulitis or osteoarthritis (2% to 3% each), and pneumonia (3%) (see Table 12–5) [150].

Bacteremia without a detectable focus of infection is the most common clinical expression of late-onset group B streptococcal disease [434]. Bacteremia without a focus typically manifests with nonspecific signs (i.e., fever, poor feeding, irritability). Diagnosis results from the practice of obtaining routine blood cultures in febrile infants during the first few weeks of life to exclude serious bacterial infection as an underlying cause. These infants often are mildly ill, but failure to initiate antimicrobial therapy in a timely manner can result in progression to shock, especially in preterm infants, or extension of infection to distant sites such as the CNS. Either transient or persistent bacteremia can occur. Approximately 3% of infants with late-onset bacteremia without a focus die; survivors typically recover without sequelae after treatment.

The presenting signs in infants with late-onset meningitis almost always include fever, irritability or lethargy or both, poor feeding, and tachypnea. Upper respiratory tract infection precedes late-onset meningitis in 20% to 30% of infants, suggesting that alteration of mucosal barrier by respiratory viral illness might facilitate entry of GBS into the bloodstream [2,3,430]. In contrast to early-onset infection, grunting respirations and apnea are less frequent initial findings, and their presence suggests rapidly progressive, fulminant infection. Apnea or hypotension is observed in less than 15% of patients, but there is a spectrum in clinical severity of illness at presentation. Some infants appear clinically well a few hours before initial evaluation and present with seizures, poor perfusion, neutropenia, and large numbers of gram-positive cocci in the CSF. These patients often have a rapidly fatal course, or if they survive, they are left with devastating neurologic sequelae. Leukopenia or neutropenia at the time of diagnosis has been correlated with fatal outcome in these infants [212].

Other initial findings associated with increased risk for fatal outcome or permanent neurologic sequelae include hypotension, coma or semicoma, status epilepticus, absolute neutrophil count less than 1000/mm^3, and CSF protein level greater than 300 mg/dL [212,422,430].

These findings most likely reflect a high bacterial inoculum in the CSF and cerebritis. Subdural effusions, which usually are small, unilateral, and asymptomatic, are found in 20% of patients with late-onset meningitis. These are not associated with any permanent sequelae. Subdural empyema, obstructive ventriculitis, large infarctions, and encephalomalacia are uncommon complications.

LATE LATE-ONSET INFECTION

Infections in infants older than 89 days of age can account for 20% of cases of late-onset disease [435]. The terms *very late onset*, *late late-onset*, and *beyond early infancy* have been applied to disease in these infants. Most of these infants have a gestational age of less than 35 weeks. The need for prolonged hospitalization and the immature host status in these infants probably contributes to infection beyond the interval for term neonates. Bacteremia without a focus is a common presentation. Occasionally, a focus for infection, such as the CNS, intravascular catheter, or soft tissues, is identified (see Table 12–5). In the outpatient setting, infants older than 89 days of age are likely to have a temperature greater than 39° C (>102.2° F) and a white blood cell count exceeding 15,000/mm^3 [434]. A viral infection can precede the onset of bacteremia [436]. When there are no other apparent risk factors for late late-onset infection in a term infant, immunodeficiency including HIV infection should be considered [437,438].

SEPTIC ARTHRITIS AND OSTEOMYELITIS

The clinical features of 20 infants with group B streptococcal septic arthritis alone and 45 infants with osteomyelitis (with or without concomitant septic arthritis) are shown in Table 12–3. The mean age at diagnosis of osteomyelitis (31 days) is greater than that for septic arthritis (20 days). The mean duration of symptoms is shorter for septic arthritis than for osteomyelitis (1.5 days versus 9 days). In some infants with osteomyelitis, failure to move the involved extremity since hospital discharge after birth, or shortly thereafter, may be noted; this lack of movement can persist for 4 weeks before the diagnosis is made [439].

Decreased motion of the involved extremity and evidence of pain with manipulation, such as lifting or diaper changing, are common signs of bone infection. Warmth or erythema can occur occasionally [440,441]; a history of fever is reported in only 20% of infants. The paucity of signs suggesting infection and the finding of pseudoparalysis have led to an initial diagnosis of Erb palsy and to assessment for possible child abuse [439,442,443]. In several infants, osteomyelitis of the proximal humerus has been associated with findings on nerve conduction studies consistent with brachial plexus neuropathy [444,445], and in one infant, sciatic nerve injury at the level of the pelvis caused footdrop in association with iliac osteomyelitis [446].

Physical findings include fixed flexion of the involved extremity, mild swelling, evidence of pain with passive motion, decreased spontaneous movement, and, in a few infants, erythema and warmth. Lack of associated systemic involvement is the rule, although osteomyelitis in association with meningitis, peritonitis, and overwhelming sepsis with congestive heart failure has been reported [441,442,447–449].

When infants with septic arthritis alone are compared with infants with osteomyelitis, infants with septic arthritis more often have lower extremity involvement, with the hip joint predominating [447,450]. By contrast, more than half of the reported infants with osteomyelitis have had involvement of the humerus, and in infants for whom the location was specified, the proximal humerus predominated [439,442,447,451]. Osteomyelitis involving both proximal humeri has been described [448]. Involvement of the femur, vertebrae, or small bones occurs occasionally [452,453]. Usually, only one bone is affected, although infection involving two adjacent bones or multiple nonadjacent bones can occur rarely [448,454,455]. Although most infants with humeral osteomyelitis have had concomitant infection in the shoulder joint, isolated septic arthritis of the shoulder joint has not been reported.

Group B streptococcal bone and joint infections have a good prognosis. At evaluation 6 months to 4 years after diagnosis, 17 (90%) of 19 infants with osteomyelitis had normal function in the affected extremity.* Residual shortening and limitation of motion of the humerus were noted in a patient who had overwhelming sepsis of acute onset, with congestive heart failure and osteomyelitis involving noncontiguous sites [447]. Growth disturbance can result as a consequence of subluxation of the hip joint after septic arthritis.

Although septic arthritis and osteomyelitis are considered manifestations of late-onset disease, osteomyelitis seems to represent a clinically silent early-onset bacteremia with seeding of a bone and then later onset of clinical expression of infection. An episode of asymptomatic bacteremia with a birth trauma–induced nidus in the proximal humerus could allow localization of bacteria to the bone. Because lytic lesions take more than 10 to 14 days to become radiographically visible, the presence of such lesions on radiographs obtained at hospital admission suggests long-standing infection (Fig. 12–8). Non–type III strains are overrepresented among infants with osteomyelitis, which is consistent with the hypothesis that, in at least some patients, early-onset bacteremia with bony localization of infection may have occurred.

CELLULITIS OR ADENITIS

The manifestation of late-onset group B streptococcal infection designated as facial cellulitis [458], submandibular cellulitis [459], cellulitis/adenitis syndrome [460], or lymphadenitis [461] has been reported in at least 25 infants [462–465]. Presenting signs include poor feeding; irritability; fever; and unilateral facial, preauricular, or submandibular swelling, usually, but not always, accompanied by erythema. The mean age at onset is 5 weeks (range 2 to 11 weeks), and in contrast to all other expressions of late-onset infection, there is a striking male predominance (72%). The most common sites are the submandibular and parotid, and enlarged adjacent nodes become palpable within 2 days after onset of the soft

*References [4,439,440,444,447,448,456,457].

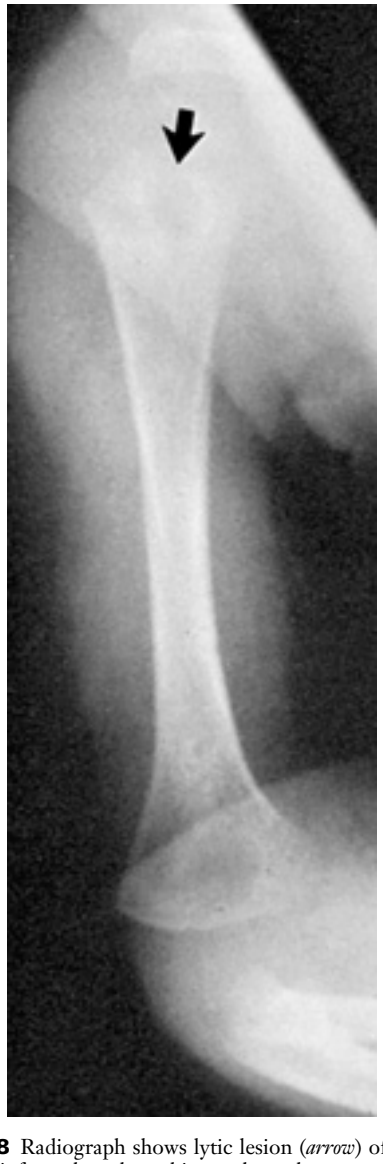


FIGURE 12–8 Radiograph shows lytic lesion (*arrow*) of the proximal humerus in an infant whose bone biopsy showed osteomyelitis caused by type III group B streptococci.

tissue infection. Four of the five infants with facial or submandibular cellulitis described by Baker [460] had ipsilateral otitis media at the time of diagnosis. Less common sites of involvement with cellulitis are the face, preauricular or inguinal areas, scrotum, anterior neck region, and prepatellar spaces (Fig. 12–9) [460,464,465]. In one patient, cellulitis of the neck occurred in association with an infected thyroglossal duct cyst [460].

Bacteremia almost always is detected in these infants (92%), and cultures of soft tissue or lymph node aspirates have yielded GBS in 83% of the infants in whom this procedure was performed. These infants usually are not seriously ill, few have associated meningitis, and recovery within a few days of initiation of appropriate antimicrobial therapy is the rule. Fulminant and fatal facial cellulitis has been described in a 7-hour-old neonate [4], however, and associated meningitis has been described in two infants [466].

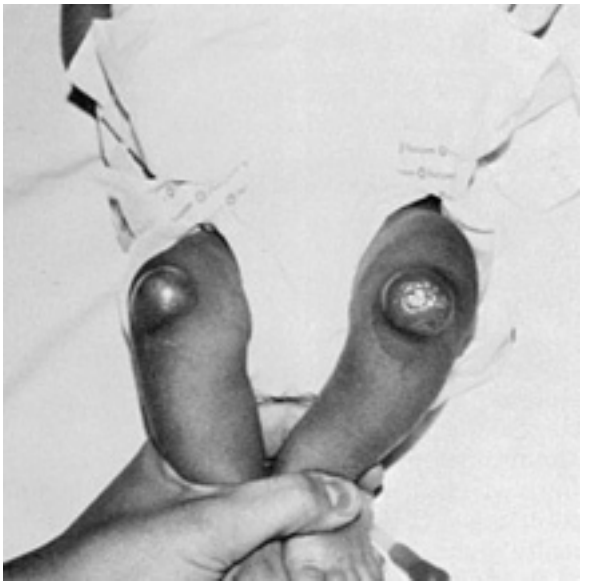


FIGURE 12–9 Prepatellar bursitis of both knees in an infant who had abraded his knees on the bed sheets. Aspiration of purulent material from the prepatellar space yielded type III group B streptococci. The knee joints were not affected.

UNUSUAL MANIFESTATIONS OF INFECTION

Numerous uncommon clinical manifestations of early-onset and late-onset group B streptococcal infection have been recorded (Table 12–6). Peritonitis [467] and adrenal abscess [468–470] have been described as abdominal manifestations of early-onset and late-onset infection. Adrenal abscess is thought to result from bacteremic seeding associated with adrenal hemorrhage and subsequent abscess formation. One neonate thought to have neuroblastoma underwent en bloc resection of a large mass with nephrectomy before the diagnosis of adrenal abscess was established [469]. Gallbladder distention is a nonspecific manifestation of early-onset sepsis that usually resolves with medical management of the infection [471]. Late-onset bacteremia can occur in association with jaundice, elevated levels of liver enzymes, and increased direct-reacting bilirubin fraction. Hemolysis and hepatocellular inflammation possibly contribute to the development of jaundice.

Brain abscess rarely occurs in association with recurrence of group B streptococcal meningitis. One infant recovered after craniotomy and excision of a well-encapsulated frontal mass, but had neurologic sequelae [472]. Sokol and colleagues [473] described a 5-week-old infant with a cerebellar cyst believed to represent an astrocytoma. This infant proved to have obstructive hydrocephalus and chronic group B streptococcal ventriculitis. Rarely, anterior fontanelle herniation can complicate severe meningitis. The presence of a noncystic doughy mass over the fontanelle indicates that brain herniation may have occurred, and cranial ultrasonography or computed tomography (CT) can be obtained to confirm this diagnosis. One patient with cervical myelopathy initially had absence of extremity movement, but made a good recovery and was able to walk at age 3 years [474].

Another unusual complication of group B streptococcal meningitis is subdural empyema, which has been

TABLE 12–6 Unusual Clinical Manifestations of Group B Streptococcal Infections

Site and Manifestation	Associated with Early-Onset or Late-Onset Infection	Reference No.
Abdomen		
Peritonitis	Both	[467]
Adrenal abscess	Both	[468–470]
Gallbladder distention	Early	[471]
Brain		
Abscess	Late	[472]
Anterior fontanelle herniation	Both	[716]
Chronic meningitis	Late	[473]
Subdural empyema	Both	[475,476]
Cerebritis	Late	[478]
Myelopathy/myelitis	Early	[474,717]
Ventriculitis complicating myelomeningocele	Both	[718]
Oculomotor nerve paralysis	Late	[719]
Ventriculoperitoneal shunt infection	Late	[720]
Cardiovascular		
Asymptomatic bacteremia	Both	[4,721,722]
Endocarditis	Both	[136,449,479]
Pericarditis	Not specified	[481]
Myocarditis	Late	[456]
Mycotic aneurysm	Late	[482]
Ear and sinus		
Ethmoiditis	Late	[4]
Otitis media/mastoiditis	Both	[460,483–486]
Eye		
Conjunctivitis/ophthalmia neonatorum	Early	[2,487,723]
Endophthalmitis	Late	[488]
Retrobulbar abscess	Early	[724]
Respiratory tract		
Diaphragmatic hernia	Both	[493]
Supraglottitis	Late	[489]
Pleural empyema	Both	[4,491,492]
Tracheitis	Late	[490]
Skin and soft tissue		
Abscess of cystic hygroma	Late	[506]
Breast abscess	Late	[509,725]
Bursitis	Late	[726]
Cellulitis/adenitis	Both	[4,458–462, 496,727]
Dactylitis	Late	[728]
Fasciitis	Late	[499–501]
Impetigo neonatorum	Early	[502,503]
Purpura fulminans	Both	[497,498]
Omphalitis	Both	[421]
Rhabdomyolysis	Late	[729]
Retropharyngeal cellulitis	Late	[507,508]
Scalp abscess	Both	[505]
Urinary tract infection	Both	[435,510]

described in patients with early-onset and late-onset infections [475,476]. The diagnosis was established by needle aspiration of the subdural space at the time of hospital admission [476] or within the first 5 days of treatment. Irritability, vomiting, seizures, increasing head circumference, focal neurologic signs, a tense anterior fontanelle, or a combination of these prompted evaluation [475,477]. Sterilization of the subdural space was accomplished by open or closed drainage in conjunction with antimicrobial therapy. Basal ganglia and massive cerebral infarction also have been described [478].

Cardiovascular manifestations of group B streptococcal infection are rare. Endocarditis [136,449,479,480], pericarditis [481], myocarditis [456], and mycotic aneurysm of the aorta [482] have been documented. Echocardiography can be useful in delineating the nature of cardiac involvement, and this technique was employed successfully to detect a 0.7-cm vegetation on the anterior leaflet of the mitral valve in a 4-week-old infant with endocarditis caused by a type III strain [449]. Paroxysmal atrial tachycardia can be a presenting feature of group B streptococcal septicemia in the absence of focal infection of the heart [133].

GBS are an uncommon cause of otitis media in the first few weeks of life (2% to 3% of cases) [483]. Otitis media is more often associated with late-onset disease manifesting as meningitis or submandibular cellulitis [484–486]. The finding of acute mastoiditis at autopsy in one infant with otitis media and meningitis suggests that the middle ear can serve as a portal of entry in a few patients [486].

Conjunctivitis related to GBS occurs with such rarity that no cases were identified among 302 neonates with ophthalmia neonatorum described by Armstrong and associates [487]. Exudative conjunctivitis has been reported, however, in association with early-onset bacteremia [487]. More severe ocular involvement is rare, but endophthalmitis has been noted in infants with septicemia and meningitis [488]. As is the case for other agents producing endophthalmitis, high-grade bacteremia is a likely prelude to this unusual metastatic focus of group B streptococcal infection.

Supraglottitis was described in a 3-month-old infant with acute onset of stridor [489]. Swelling of the left aryepiglottic fold, but not the epiglottis, was noted at laryngoscopy. An infant with bacterial tracheitis had a similar presentation [490]. Although pulmonary infection caused by GBS is common, pleural involvement is rare, but it has been reported as a complication of early-onset [491] and late-onset [492] pneumonia. An interesting but unexplained association is delayed development of right-sided diaphragmatic hernia and early-onset group B streptococcal sepsis [493]. In affected infants, the onset of respiratory distress invariably occurs at or within 48 hours after birth, whereas the mean age at diagnosis of right-sided diaphragmatic hernia in the 40 reported cases is 11 days (range 4 to 91 days). One speculation is that group B streptococcal pneumonia causes necrosis of the adjacent diaphragm and results in herniation of viscera into the pleural space. Another is that ventilation increases intrathoracic pressure to mask or delay herniation through a congenital diaphragmatic defect. This phenomenon should be a consideration in an infant whose condition

deteriorates despite appropriate management for early-onset disease. Radiographic features include increased density in the right lower lung or irregular aeration or both, followed by progression to elevation of right bowel gas and liver shadow.

In addition to cellulitis and adenitis, GBS uncommonly can produce various unusual skin and soft tissue manifestations, including violaceous cellulitis [494], perineal cellulitis and septicemia after circumcision [495], scrotal ecchymosis as a sign of intraperitoneal hemorrhage [496], purpura fulminans [497,498], necrotizing fasciitis [499–501], impetigo neonatorum [502,503], omphalitis [421,504], scalp abscess secondary to fetal scalp electrode [505], abscess complicating cystic hygroma [506], retropharyngeal cellulitis [507,508], and breast abscess [509]. In patients with impetiginous lesions and abscess formation, bacteremia is unusual, but it is a frequent accompaniment to omphalitis and necrotizing fasciitis.

Among infants with early-onset bacteremia, isolation of GBS from the urine is frequent when this body fluid is cultured, but primary urinary tract infection with these organisms is rare. An infant with severe bilateral ureterohydronephrosis and GBS in his urine has been described [510]. The isolation of GBS from a urine culture of a patient without bacteremia is an indication for evaluation for possible structural anomalies of the genitourinary tract.

Sudden death occurred in three infants ranging from 3 to 8 months of age. The deaths were attributed at the time of autopsy to group B streptococcal infection [409].

RELAPSE OR RECURRENCE OF INFECTION

Relapse or recurrence of group B streptococcal infection occurs in an estimated 0.5% to 3% of infants. Signs can develop during treatment for the initial episode or at an interval of 3 days to 3 months after completion of therapy [511–513]. In one review, eight of nine infants with a recurrence were born at 25 to 36 weeks of gestation, and male infants predominated [512]. The first episode occurred at a mean age of 10 days (range 1 to 27 days) and the recurrence at a mean age of 42 days (range 23 to 68 days) of life. In another report that included a set of fraternal twins, seven of eight infants were preterm (mean 30 weeks of gestation), each had a birth weight of less than 2500 g, and all infections were late-onset [513]. The mean age at initial presentation was 38 days (range 13 to 112 days), and at recurrence it was 57 days (range 34 to 130 days). Two relapses in one infant have been documented [514,515].

Relapse or recurrence of infection can be the result of an undrained focus of infection, such as a brain abscess, or can occur in association with congenital heart disease. Identical isolates recovered from maternal genital and breast milk cultures suggest that breast milk can serve as a source of repeated infant exposure [516,517]. Recurrent infection can have a clinical expression similar to that of the initial episode or can involve new sites (meninges, ventricular or subdural fluid, or both; brain parenchyma; and soft tissue). In most instances, the second episode of group B streptococcal disease responds to retreatment with penicillin or ampicillin, but typically the duration of treatment for the recurrence is extended empirically; evidence for longer duration of therapy in this circumstance is lacking [513].

Because infants who receive treatment for invasive infection often remain colonized with GBS at mucous membrane sites, pharyngeal or gastrointestinal colonization can be the source for recurrence. In addition, infants recovering from invasive infection with type III strains usually lack protective levels of antibody during convalescence. Moylett and colleagues [513] and others [514] used pulsed-field gel electrophoresis to document that isolates from patients with recurrent episodes were identical and were derived from a single clone. Sets of isolates analyzed from first and second episodes and from maternal and infant colonizing and invasive strains were genotypically identical [512,513]. Recurrent infection in most infants likely is a consequence of reinvasion from persistently colonized mucous membrane sites or from reexposure to a household carrier. The timing of the recurrence or relapse in Moylett's series was 4 days after discontinuation of appropriate therapy. Uncommonly, infants have had a second infection with a strain that is genetically unrelated to the original isolate.

MATERNAL INFECTIONS

In 1938, Fry [1] described three fatal cases of endocarditis in postpartum women. This was the initial insight that group B *Streptococcus* was a human pathogen and could cause puerperal infection. Postpartum infections including septic abortion, bacteremia, chorioamnionitis, endometritis, pneumonia, and septic arthritis were recorded sporadically thereafter, but group B streptococcal infections in postpartum women, as in neonates, were uncommonly reported before 1970 [413,518,519]. The dramatic increase in incidence of neonatal infections in the 1970s was paralleled by an increased incidence of infections in pregnant women.

Before the institution of IAP in the 1990s, GBS accounted for 10% to 20% of blood culture isolates from febrile women on obstetric services [520]. These women had a clinical picture characterized by fever, malaise, uterine tenderness with normal lochia, and occasionally chills. Faro [334] described 40 women with group B streptococcal endometritis and endoparametritis among 3106 women giving birth over a 12-month interval, an incidence of 1.3 per 1000 deliveries. GBS were isolated from the endometrium in pure culture in one third of cases or in addition to other organisms in the remainder; one third of the women had concomitant bacteremia. In most, signs of infection developed within the first 24 hours after cesarean section. Clinical features included chills; tachycardia; abdominal distention; and exquisite uterine, parametrial, or adnexal tenderness. Higher fever correlated with risk for concomitant bacteremia. Recovery was uniform after administration of appropriate antimicrobial agents. Six infants born to these women developed group B streptococcal septicemia, however, and infection was fatal was three. The observation that maternal febrile morbidity could serve as an early clue to bacteremic neonatal infection is important, and infants of such women should be carefully evaluated.

The contemporary incidence of invasive disease in pregnant women is 0.12 per 1000 live births [150]. This incidence has declined significantly in association with implementation of IAP to prevent early-onset neonatal disease [12,143]. Half of the 409 pregnancy-associated disease cases identified in the United States from 1999-2005 by an active population-based surveillance system were associated with infection of the upper genital tract, placenta, or amniotic sac and resulted in fetal death. Among the remainder, manifestations of disease included bacteremia without a focus (31%), endometritis without fetal death (8%), chorioamnionitis without fetal death (4%), pneumonia (2%), and puerperal sepsis (2%). Isolates in pregnancy-associated infections were obtained from blood in 52% of women and from the placenta, amniotic fluid, or conceptus in most of the remainder. When pregnancy outcome was known, most of the women (61%) had a spontaneous abortion or stillborn infant, 5% had infants who developed clinical infection, 4% had induced abortions, and 30% had infants who remained clinically well.

Most obstetric patients with group B streptococcal infection, even in the presence of bacteremia, show a rapid response after initiation of antimicrobial therapy. Potentially fatal complications can occur, however, including meningitis [521], ventriculoperitoneal shunt infection [522], abdominal abscess [523], endocarditis [142,524–526], vertebral osteomyelitis [527], epidural abscess [528], or necrotizing fasciitis [529].

Group B streptococcal bacteriuria during pregnancy is a risk factor for intrauterine or neonatal infection. Asymptomatic bacteriuria, cystitis, or pyelonephritis occurs in 6% to 8% of women during pregnancy. In women with asymptomatic bacteriuria, approximately 20% are caused by GBS [530]. Group B streptococcal bacteriuria is a marker for heavy vaginal colonization, so the finding of bacteriuria indicates enhanced risk for maternal and neonatal infection [100]. In the series reported by Moller and associates [414] that predated IAP, a cohort of 68 women with asymptomatic group B streptococcal bacteriuria had significantly increased risk of preterm delivery compared with nonbacteriuric controls. Stillbirth because of congenital group B streptococcal infection can occur even in the current era, and a woman with any quantity of group B streptococcal bacteriuria during pregnancy should receive IAP [531].

DIAGNOSIS

ISOLATION AND IDENTIFICATION OF THE ORGANISM

The definitive diagnosis of invasive group B streptococcal infection is established by isolation of the organism from culture of blood, CSF, or a site of suppurative focus (e.g., bone, joint fluid, empyema fluid). Isolation of GBS from surfaces, such as the skin or umbilicus or from mucous membranes, is of no clinical significance.

Lumbar puncture is required to exclude meningeal involvement in infants with invasive group B streptococcal infection because clinical features cannot reliably distinguish between meningeal and nonmeningeal involvement. GBS often are isolated from blood at the time of initial evaluation of infants with meningitis, but the blood culture is sterile in 20% to 30%. Wiswell and colleagues [532] found that if lumbar puncture were omitted as part of the sepsis evaluation, the diagnosis of meningitis was missed or delayed in more than one third of infants. Infants with late-onset infection can have meningitis even when focal infection, such as cellulitis, is apparent [466]. If lumbar puncture must be deferred because an infant is clinically unstable, penicillin G or ampicillin at the doses recommended for treatment of group B streptococcal meningitis (see "Treatment" later on) should be administered until meningeal involvement can be assessed.

Antigen Detection Methods

Antigen detection is not a substitute for appropriately performed bacterial cultures and now is rarely used to establish a provisional diagnosis of group B streptococcal infection. A positive result indicates that group B streptococcal antigen is detectable, but not that viable organisms are present. Serum and CSF are the only specimens recommended for testing [533]. In neonates with meningitis, the sensitivity of antigen detection is 72% to 89%. The estimated sensitivity for serum is 30% to 40%. False-positive results have been encountered. The estimated specificity of commercial assays ranges from 95% to 98%. Antigen assays should not be employed to assess treatment efficacy.

RT-PCR has been evaluated in a research setting to assess group B streptococcal exposure in infants born to women whose colonization status is unknown at delivery. The rates of colonization detected by culture and PCR were 17% and 51%. The authors suggest that a negative PCR test could be useful in allowing early discharge of infants born to mothers with a negative RT-PCR [534]. A fluorescent RT-PCR assay was shown to be sensitive and specific for early detection within 4 hours of incubation of GBS in neonatal blood cultures, but at the present time this test is not available commercially [535].

Other Laboratory Tests

Acute-phase reactants, such as C-reactive protein, can be elevated during group B streptococcal infection, but the usefulness for establishing a provisional diagnosis of infection is limited. The return to normal of the C-reactive protein level could be helpful, however, in minimizing antibiotic exposure in the nursery setting [536]. Levels of inflammatory cytokines such as IL-6 are elevated acutely during group B streptococcal sepsis. In one report, production of IL-6 was noted in all 16 neonates with bacteremic early-onset or late-onset group B streptococcal infection when samples were collected within 48 hours of initiation of antimicrobial therapy [537]. These assays generally are not available in clinical laboratories, however.

Abnormalities in the white blood cell count, including leukopenia, neutropenia, leukocytosis, increase in band forms, or decline in the total white blood cell count in the first 24 hours of life, can be suggestive of group B streptococcal infection. Greenberg and Yoder [538] cautioned that repeat testing at 12 to 24 hours of age can enhance sensitivity compared with testing at 1 to 7 hours

of age. Fatal early-onset group B streptococcal sepsis can occur with a normal leukocyte count, however [539]. Measurements of peripheral blood leukocytes or inflammatory mediators generally are nonspecific and should be employed only as adjunctive to results from blood and CSF cultures.

DIFFERENTIAL DIAGNOSIS

The clinical features in neonates with early-onset group B streptococcal infection mimic the features in infants with sepsis caused by other etiologic agents and by some noninfectious illnesses. Radiographic findings of pneumonia are present in some neonates with early-onset group B streptococcal sepsis. Neonates with early-onset group B streptococcal pneumonia can have apnea and shock within the first 24 hours of life, a 1-minute Apgar score of 5 or less, and an unusually rapid progression of pulmonary disease [208]. Infection also should be considered in neonates with persistent fetal circulation associated with respiratory distress, neutropenia, and systemic hypotension [212].

The differential diagnosis for late-onset group B streptococcal infection depends on the clinical presentation. For infants with meningitis, the characteristic CSF Gram stain findings can provide a presumptive diagnosis. When this method is inconclusive usually in the setting of partial treatment, other organisms, including viruses, *E. coli*, *Neisseria meningitidis*, *S. pneumoniae*, and nontypable *Haemophilus influenzae*, must be considered. Fever usually is a presenting feature in term infants, and empirical therapy with broad-spectrum antibiotics customarily is employed until results of cultures permitting a specific diagnosis of bacteremia or focal infection are available. The paucity of signs characteristic of group B streptococcal osteomyelitis and the history that signs have been present since birth have caused confusion with Erb palsy and neuromuscular disorders. The characteristic bony lesion; tenderness of the extremity when a careful examination is performed; and isolation of the organism from blood, bone, or joint fluid usually provide a definitive diagnosis [439]. Finally, the lengthy list of uncommon manifestations of infection between 1 week and 3 months of age and beyond indicates that GBS should be suspected as an etiologic agent, regardless of site of infection, for infants in this age group.

TREATMENT

GBS have been a frequent cause of infection in neonates for 4 decades, resulting in increased awareness of associated risk factors and need for prompt and aggressive therapy. Despite striking declines, however, death and disability from these infections still occur. In addition, relapses or reinfections, although uncommon, occur in the face of optimal therapy. These facts should prompt efforts to develop improved treatment modalities.

IN VITRO SUSCEPTIBILITY

Uniform susceptibility of GBS to penicillin G has continued for more than 50 years of usage [540–545]. More recently, reduced susceptibility of certain strains of GBS to penicillin and other β-lactam antibiotics has been documented in the United States [546] and Japan [547] and experimentally traced to point mutations in penicillin-binding proteins (e.g., PbP2x) reminiscent of first-step mutations in the evolution of pneumococcal penicillin resistance decades ago. The clinical implications of this finding are as yet unclear. Efforts should be continued, however, to monitor clinical isolates for mutations that would suggest the evolution of penicillin-resistant strains. In vitro susceptibility of GBS to ampicillin; semisynthetic penicillins; vancomycin; teicoplanin; linezolid; quinopristin/dalfopristin; gatifloxacin; levofloxacin; and first-generation, second-generation (excluding cefoxitin), and third-generation cephalosporins also is the rule, although the degree of in vitro activity varies [543,544,548–554]. Ceftriaxone is the most active of the cephalosporins in vitro. Imipenem and meropenem are highly active [541,548]. Resistance to quinolones can occur through mutations in the gyrase and topoisomerase IV genes, usually in patients who have received prior quinolone therapy [555].

Resistance to erythromycin and clindamycin is increasing. Contemporary data from multiple studies indicate that 20% to 30% of isolates are erythromycin-resistant, and 10% to 20% are resistant to clindamycin [543,544,556]. Rates of resistance in colonizing isolates can be 40% for erythromycin and clindamycin [557]. These high rates of resistance are reported from geographically diverse regions [558–561].

Macrolide resistance mechanisms include ribosomal modification by a methylase encoded by *erm* genes and drug efflux by a membrane-bound protein encoded by *mef* gene [556]. The presence of *erm* genes results in the macrolide–lincosamide–streptogramin B resistance phenotype [562]. Erythromycin-resistant isolates that are constitutively resistant, inducibly resistant, or susceptible to clindamycin are described [563]. Alone or in combination, *erm*(A), *erm*(B), and *mef*(A) genes are responsible for resistance in GBS. An *erm*(T) gene has been identified in a few strains of GBS inducibly resistant to clindamycin [564]. The presence of a composite transposon in GBS and pneumococci suggests that *erm*(B)-mediated macrolide resistance could be due to the horizontal transfer of a mobile transposable element [565]. A particularly high proportion of strains resistant to erythromycin has been reported for type V [544,566]. Tigecycline and telithromycin are active in vitro against macrolide-resistant GBS, but data confirming their clinical effectiveness are scant [567,568]. The percentage of tetracycline-resistant strains is 75% to nearly 90% [549]. Resistance of GBS to bacitracin, nalidixic acid, trimethoprim-sulfamethoxazole, metronidazole, and aminoglycosides is uniform.

Despite resistance of most group B streptococcal strains to aminoglycosides, synergy often is observed when an aminoglycoside (especially gentamicin) and penicillin or ampicillin are used in combination [553,569]. The best combination theoretically to accelerate the killing of GBS in vivo is penicillin or ampicillin plus gentamicin. Therapeutic concentrations of gentamicin in the serum are not required to achieve synergy. By contrast, the rapid and predictable bactericidal effect of penicillin or ampicillin on GBS in vitro is ablated by the addition

of rifampin [570]. Although in vivo data are lacking, the in vitro antagonism of rifampin when combined with penicillins suggests that they should not be employed concurrently in the treatment of proven or suspected group B streptococcal disease.

Among the newer β-lactam antibiotics reputed to attain high concentrations of drug in the CSF, only cefotaxime, ceftriaxone, meropenem, and imipenem achieve minimal bactericidal concentrations (MBCs) comparable with MBCs of penicillin G and ampicillin (0.01 to 0.4 μg/mL) [541,549,553,556], and limited data suggest that their efficacy is equivalent to that of penicillin G [553,571,572]. Despite their uniform susceptibility to penicillin G, GBS require higher concentrations for growth inhibition in vitro than strains belonging to group A. The minimal inhibitory concentration (MIC) of penicillin G to GBS is 4-fold to 10-fold greater than the MIC for group A strains (range 0.003 to 0.4 μg/mL) [540,549,573]. This observation, combined with the observation indicating the significant influence of inoculum size on in vitro susceptibility to penicillin G, may have clinical relevance [540,574].

When the inoculum of group B *Streptococcus* is reduced from 10^5 to 10^4 colony-forming units (CFU)/mL, a twofold lower concentration of penicillin G is sufficient to inhibit in vitro growth. Similarly, if the inoculum is increased from 10^4 to 10^7 CFU/mL, the MBC of ampicillin is increased from 0.06 to 3.9 μg/mL. Such in vitro observations may have in vivo correlates because some infants with group B streptococcal meningitis have CSF bacterial concentrations of 10^7 to 10^8 CFU/mL [574]. At the initiation of therapy for meningitis, achievable CSF levels of penicillin G or ampicillin may be only one tenth of serum levels. This inoculum effect also has been noted with cefotaxime and imipenem [549]. The dose chosen to treat group B streptococcal meningitis can be crucial to the prompt sterilization of CSF.

Although GBS are susceptible to penicillin G, in vitro tolerance among 4% to 6% of strains has been noted [575]. Defined as MBC in excess of 16 to 32 times the MIC, tolerance in vitro corresponds with delayed bacterial killing, additive rather than synergistic effects when gentamicin is used in combination with penicillin G, and possibly an autolytic enzyme defect in such strains [576]. Detection of tolerance depends, however, on choice of growth medium, growth phase of bacterial inoculum, and definition of MBC employed for testing.

ANTIMICROBIAL THERAPY

Penicillin G is the drug of choice for treatment of group B streptococcal infections. The recommended dosage for treatment of meningitis is high because of (1) the relatively high MIC of penicillin G for GBS (median 0.06 μg/mL) with respect to attainable levels of this drug in the CSF, (2) the high inoculum in the CSF of some infants [574], (3) reports of relapse in infants with meningitis treated for 14 days with 200,000 U/kg/day of penicillin G, and (4) the safety of high doses of penicillin G in the newborn. To ensure rapid bactericidal effects, particularly in the CSF, we recommend penicillin G (450,000 to 500,000 U/kg/day) or ampicillin (300 to 400 mg/kg/day) for the treatment of meningitis (Table 12–7). There is no evidence to suggest increased risk for adverse reactions at these higher doses even in premature infants.

In the usual clinical setting, antimicrobial therapy is initiated before definitive identification of the organism. Initial therapy should include ampicillin and an aminoglycoside appropriate for the treatment of early-onset neonatal pathogens including GBS. Such a combination is more effective than penicillin G or ampicillin alone for killing of GBS [569,573]. We continue combination therapy until the isolate has been identified as GBS and, in patients with meningitis, until a CSF specimen obtained 24 to 48 hours into therapy is sterile. Kim [576] suggests that MIC and MBC determinations be considered in the following settings: (1) a poor bacteriologic response to antimicrobial therapy, (2) relapse or recurrence of infection without a discernible cause, and (3) infections manifested as meningitis or endocarditis. If tolerance is shown, therapeutic choices include using penicillin G or ampicillin alone or employing cefotaxime. No data are available to indicate the better of these choices [577].

For an infant with late-onset disease in whom CSF reveals gram-positive cocci in pairs or short chains, initial therapy should include ampicillin and gentamicin or

TABLE 12–7 Antimicrobial Regimens Recommended for Treatment of Group B Streptococcal Infections in Infants*

Manifestation of Infection	Drug	Daily Dose (Intravenous)	Duration
Bacteremia without meningitis	Ampicillin plus gentamicin	150-200 mg/kg plus 7.5 mg/kg	Initial treatment before culture results (48-72 hr)
	Penicillin G	200,000 U/kg	Complete a total treatment course of 10 days
Meningitis	Ampicillin plus gentamicin	300-400 mg/kg plus 7.5 mg/kg	Initial treatment (until cerebrospinal fluid is sterile)
	Penicillin G	500,000 U/kg	Complete a minimum total treatment course of 14 days†
Septic arthritis	Penicillin G	200,000 U/kg	2-3 wk
Osteomyelitis	Penicillin G	200,000 U/kg	3-4 wk
Endocarditis	Penicillin G	400,000 U/kg	4 wk‡

**No modification of dose by postnatal age is recommended. Oral therapy is never indicated.*
†Longer treatment (up to 4 wk) may be required for ventriculitis.
‡In combination with gentamicin for the first 14 days.

cefotaxime, rather than penicillin G alone, because (1) GBS are a frequent cause of meningitis in infants 1 to 8 weeks of age, and combination therapy can improve efficacy early in the course of infection, and (2) *Listeria monocytogenes* can be confused by CSF Gram stain with group B *Streptococcus*, and ampicillin and gentamicin are synergistic in vitro against most strains of *Listeria*. If pneumococcal meningitis is a consideration, cefotaxime and vancomycin would be a reasonable empirical regimen pending culture confirmation. Because group B streptococcal meningitis is uncommon beyond 8 weeks of age, no change is suggested from the use of conventional agents as the initial treatment of meningitis in term infants older than 2 months. For preterm infants remaining hospitalized from birth, empirical therapy can include vancomycin and an aminoglycoside. If meningitis is suspected, ampicillin or cefotaxime should be included in the regimen because vancomycin achieves low CSF concentrations and has a substantially higher MBC against GBS and *L. monocytogenes* than ampicillin.

When the diagnosis of group B streptococcal infection is confirmed, and CSF for patients with meningitis obtained 24 to 48 hours into therapy is sterile, treatment can be completed with penicillin G monotherapy. Good outcomes have been achieved when parenteral therapy is given for 10 days for bacteremia without a focus or with most soft tissue infections, 2 to 3 weeks for meningitis or pyarthrosis, and 3 to 4 weeks for osteomyelitis or endocarditis (see Table 12–7). Limited evidence suggests that a 7-day course of therapy can suffice for uncomplicated bacteremia, but additional data would be required to support a change in current recommendations [578]. For infants with meningitis, failure to achieve CSF sterility suggests an unsuspected suppurative focus (subdural empyema, brain abscess, obstructive ventriculitis, septic thrombophlebitis) or failure to administer an appropriate drug in sufficient dosage.

At the completion of therapy (minimum 14 days), a lumbar puncture should be considered to evaluate whether the CSF findings are compatible with resolution of the inflammatory process or are of sufficient concern to warrant extending treatment or additional diagnostic evaluation. Neutrophils greater than 30% of the total cells or a protein concentration greater than 200 mg/dL warrants consideration for a neuroimaging study of the brain. These findings can be observed in patients with a fulminant course manifested by severe cerebritis, extensive parenchymal destruction with focal suppuration, or severe vasculitis with cerebral infarctions.

Infants with septic arthritis should receive at least 2 weeks of parenteral therapy; infants with bone involvement require 3 to 4 weeks of therapy to optimize an uncomplicated outcome. Drainage of the suppurative focus is an adjunct to antibiotic therapy. In infants with septic arthritis excluding the hip or shoulder, one-time needle aspiration of the involved joint usually achieves adequate drainage. With hip or shoulder involvement, immediate open drainage is warranted. For most infants with osteomyelitis, some type of closed or open drainage procedure is required for diagnosis because blood cultures typically are sterile. These procedures must be performed before or early in the course of therapy to ensure successful isolation of the infecting organism.

With recurrent infection, three points should be considered. First, appropriate antimicrobial therapy fails to eliminate mucous membrane colonization with GBS in 50% of infants [579]. Second, community exposure can result in colonization with a new strain that subsequently invades the bloodstream. Systemic infection in neonates does *not* result in protective levels of CPS type–specific antibodies [341]. Recurrent infections do occur in healthy infants. In this event, an evaluation to exclude an immune abnormality, such as HIV infection or hypogammaglobulinemia, can be considered, but detection of abnormalities is rare. Therapy for recurrent infection need not be extended beyond that appropriate to the clinical expression of the recurrent infection. Finally, although it is desirable to eliminate colonization, an efficacious regimen has not been identified. One small prospective study revealed that administration of oral rifampin (20 mg/kg/day for 4 days) to infants after completion of parenteral therapy eliminated mucous membrane colonization in some subjects [580]. Further study is needed to identify a more reliable approach to eliminating colonization.

SUPPORTIVE MANAGEMENT

Prompt, vigorous, and careful supportive care is important to the successful outcome of most group B streptococcal infections. When early-onset disease is accompanied by respiratory distress, the need for ventilatory assistance should be anticipated before onset of apnea. Early treatment of shock, often not suspected during its initial phase, when systolic pressure is maintained by peripheral vasoconstriction, is crucial. Persistent metabolic acidosis and reasonably normal color are characteristic of this early phase. Persistent perfusion abnormalities after initial attempts to achieve adequate volume expansion warrant placement of a central venous pressure monitoring device and treatment with appropriate inotropic agents. This concept applies also to patients with late-onset meningitis. Fluid management should include packed red blood cell transfusions to optimize oxygen-carrying capacity. In patients with meningitis, effective seizure control is required to achieve proper oxygenation, to decrease metabolic demands, prevent additional cerebral edema, and optimize cerebral blood flow. Monitoring of urine output and attention to electrolyte balance and osmolality are needed to detect and manage the early complications of meningitis, such as inappropriate secretion of antidiuretic hormone and increased intracranial pressure. Such intense and careful supportive management requires treatment in an intensive care unit of a tertiary care facility.

Extracorporeal membrane oxygenation (ECMO) has been suggested as rescue therapy for overwhelming early-onset group B streptococcal sepsis. Hocker and coworkers [581] compared conventional treatment with ECMO for neonates with early-onset disease. Survival was not improved significantly with use of ECMO when all infants or only hypotensive infants were compared. LeBlanc [582] emphasized the difficulty of interpreting this study, citing the retrospective design and the fact that the sickest infants die before ECMO can be initiated. Until a prospective, controlled trial is performed, ECMO therapy should be considered controversial.

ADJUNCTIVE THERAPIES

Despite prompt initiation of antimicrobial therapy and aggressive supportive care, death or sequelae can result from group B streptococcal infection. Considerable investigative efforts have been directed toward adjunctive therapy. High mortality rates for neutropenic neonates prompted clinical evaluation of granulocyte transfusions as adjunctive therapy for early-onset group B streptococcal sepsis. In three trials, 13 infants with neutrophil storage pool depletion were assessed [278,378,583]. The results seemed promising, but the logistics of providing timely transfusion and the concern for adverse effects, such as graft-versus-host reaction, transmission of viral agents, and pulmonary leukocyte sequestration, render this approach to therapy impractical.

Recombinant human cytokine molecules such as granulocyte colony-stimulating factor promote granulocyte proliferation, enhance chemotactic activity and superoxide anion production, and increase expression of neutrophil C3bi receptors. Results in experimental infection suggest that granulocyte colony-stimulating factor might be a useful adjunct in the treatment of group B streptococcal neonatal sepsis, possibly in combination with intravenous immunoglobulin (IVIG) [584–586]. Specific recommendations must await evaluation of their safety and efficacy in controlled clinical trials.

Human immunoglobulin modified for intravenous use could provide specific antibodies to enhance opsonization and phagocytosis of GBS [587–593]. IVIG has been shown in experimental models [594] and septic neonates [595] to improve complement activation and chemotaxis by neonatal sera and to hasten resolution of neutropenia. Administration of sufficient human type-specific antibodies against CPS to animals before lethal challenge with GBS of the homologous serotype is protective [350,587–591]. Despite this sound theoretical rationale, commercial preparations of IVIG contain relatively low concentrations of antibodies to group B streptococcal polysaccharides [590–593,595–600], suggesting that prohibitively large doses would be required and raising concern for reticuloendothelial blockade [589,592]. In addition, functional activity of licensed IVIG preparations can vary by manufacturer and lot [588,589,595–601], and any increase in antibodies after infusion would be transient only [596,602]. Christensen and colleagues [603] administered either IVIG (750 mg/kg) or albumin to 22 neonates with severe, early-onset sepsis, however, and all infants survived. Eleven patients had neutropenia, but in IVIG recipients, this abnormality resolved within 24 hours of infusion, whereas it persisted in placebo recipients.

A hyperimmune group B streptococcal globulin or human-human monoclonal antibodies would theoretically circumvent many potential problems. Raff and coworkers [604] developed a human IgM monoclonal antibody specific for the group B cell wall polysaccharide. This antibody reacted with all group B streptococcal types tested and was shown to be safe and protective in newborn, nonhuman primates [605]. A hyperimmune globulin [599] prepared by vaccinating healthy adults with polysaccharides from types Ia, Ib, II, and III GBS was protective against experimental challenge with types I, II, and III strains ~~in doses of 4 to 20 mg/kg~~ [606]. To date, no commercial preparation of IVIG hyperimmune for IgG directed against type-specific CPS is available, however, for testing in appropriately designed clinical trials.

PROGNOSIS

Several clinical scoring systems have been developed to predict at the time of initial evaluation infants likely to die as a consequence of neonatal group B streptococcal infection [212,432,607]. Payne and colleagues [212] described a score derived from five variables that, together with an initial blood pH less than 7.25, enabled prediction of outcome accurately in 93% of infants with early-onset group B streptococcal infection. These features were birth weight less than 2500 g, absolute neutrophil count less than 1500 cells/mm^3, hypotension, apnea, and pleural effusion seen on the initial chest radiograph.

A fatal outcome can be predicted with reasonable accuracy, but little information is available concerning the long-term prognosis for survivors of neonatal group B streptococcal sepsis. One group at potential risk for sequelae are preterm infants with septic shock, who can develop periventricular leukomalacia. Among these survivors, substantial neurodevelopmental sequelae have been identified at evaluation during the second year of life. The correlates of severity and duration of shock with periventricular leukomalacia and with long-term morbidity from group B streptococcal disease have not been assessed. Prospective, active surveillance of neonatal group B streptococcal infections in Germany conducted from 2001-2003 found that 14% of 347 infants had neurologic sequelae of infection at the time of discharge from the hospital [608].

Long-term outcomes for survivors of group B streptococcal meningitis are guarded. Among 41 survivors from a cohort born in 1996-1997 in England and Wales, 34% had moderate or severe disability, 27% had mild disability, and 39% were functioning normally at 5 years of age [609]. Stoll and colleagues [610] showed for extremely low birth weight infants that meningitis with or without sepsis was associated with poor neurodevelopmental and growth outcomes and impairment of vision and hearing in early childhood.

Among 200 neonates with early-onset or late-onset meningitis cared for in the 1970s and 1980s, one quarter died in the hospital as the direct consequence of meningitis [429,431,432]. Among 112 survivors assessed at mean intervals 2 to 8 years after diagnosis, 20% had major neurologic sequelae. The most serious of these were profound mental retardation, spastic quadriplegia, cortical blindness, deafness, uncontrolled seizures, hydrocephalus, and hypothalamic dysfunction with poor thermal regulation and central diabetes insipidus [429,432,476,611]. Mild or moderate sequelae persisted in an additional 20% of survivors evaluated at a mean of 6 years after diagnosis. These sequelae included profound unilateral sensorineural hearing loss, borderline mental retardation, spastic or flaccid monoparesis, and expressive or receptive speech and language delay.

In a sibling-controlled follow-up study, 12% of survivors had major neurologic sequelae when evaluated at

3 to 18 years of age. When these nine children were excluded, there were no significant differences, as rated by parents, between the children with meningitis and their siblings for academic achievement, measures of intelligence quotient, fine motor dexterity, or behavior difficulties [611]. Meningitis survivors were more likely than siblings to have seizure disorders and hydrocephalus. More subtle deficits, such as delayed language development and mild hearing loss, may not be detected by routine examination [432], and meningitis survivors should undergo audiometric testing during convalescence and careful long-term neurologic and developmental assessments.

PREVENTION

Theoretically, early-onset and late-onset group B streptococcal disease could be prevented if susceptible hosts were not exposed to the microorganism or if exposure occurred in the setting of protective immunity. Several approaches to prevention have been advocated; conceptually, these are directed at eliminating exposure or enhancing host resistance by chemoprophylaxis or immunoprophylaxis. Both strategies have limitations with respect to implementation, but could be targeted for the prevention of maternal and neonatal infections and are theoretically achievable [612,613].

CHEMOPROPHYLAXIS

Historical Precedents

Chemoprophylaxis was suggested as a means to prevent early-onset group B streptococcal infection by Franciosi and coworkers in 1973 [2]. Because maternal genital colonization was recognized to expose infants to the organism, oral penicillin treatment for colonized women was subsequently proposed. Carriers of GBS identified by third-trimester vaginal culture received a course of an oral antimicrobial. Approximately 20% to 30% remained colonized after treatment, and in most of these women, GBS were isolated from vaginal cultures at delivery [614–616]. Reacquisition from colonized sexual partners was suggested as an explanation for these high failure rates, but failure rates remained high when colonized pregnant women and their spouses received concurrent treatment with penicillin by the oral or the parenteral route [2,614,617]. One explanation cited for failure of this approach was the difficulty in eradicating a constituent of the normal bowel flora [614].

Yow and colleagues [618] gave intravenous ampicillin at hospital admission to 34 women in labor and vaginally colonized with GBS and successfully interrupted vertical transmission of colonization in all. Boyer and Gotoff [619,620] provided in 1986 the first documentation that IAP could prevent invasive early-onset neonatal infection. Women colonized with GBS who had risk factors for early-onset infection were randomly assigned to receive routine labor and delivery care or intrapartum ampicillin intravenously until delivery. Group B streptococcal sepsis developed in 5 of 79 neonates in the routine care group, 1 of whom died, whereas 85 infants born to women in the ampicillin treatment group remained well. Intrapartum ampicillin prophylaxis for group B streptococcal carriers also resulted in reduced maternal morbidity [621]. These data established the efficacy of IAP for prevention of early-onset neonatal disease and reduction of group B *Streptococcus*–associated febrile maternal morbidity. The cost-effectiveness of this approach subsequently was validated [622,623].

In 1992, the American College of Obstetricians and Gynecologists (ACOG) [624] and the American Academy of Pediatrics (AAP) [625] published separate documents regarding maternal IAP for the prevention of early-onset group B streptococcal infection. The ACOG technical bulletin was educational, whereas the AAP guidelines were directive. The AAP guidelines specified that if culture screening was performed antenatally, specimens should be obtained from lower vaginal and rectal sites, and culture-positive women with one or more risk factors and group B streptococcal colonization should be given intrapartum intravenous penicillin G or ampicillin. The ACOG proposed that culture screening could be avoided by providing treatment for all women with risk factors. Neither the AAP nor ACOG approach was implemented widely, and invasive disease rates remained unacceptably high.

Rapid Assays for Antenatal Detection of Group B Streptococci

There are difficulties inherent to ascertainment of group B streptococcal colonization status rapidly even when assays can be processed 24 hours a day. Latex particle agglutination and enzyme immunoassays for detection of group B streptococcal antigen in cervical or lower vaginal swab specimens are not sufficiently sensitive to determine colonization status accurately at hospital admission, especially for women with a low density of organisms [626]. An optical immunoassay (Strep B OIA test; Biostar, Boulder, CO) was considerably more sensitive than earlier assays for detecting light (13% to 67%) and heavy (42% to 100%) or overall (81%) colonization and has outperformed enzyme immunoassays in direct comparisons [626–630]. Assays using a DNA hybridization methodology have shown variable sensitivity [631,632].

Bergeron and colleagues [633] described a fluorogenic RT-PCR technique for rapid identification of women colonized with GBS at admission for delivery. The sensitivity of RT-PCR and of conventional PCR was 97%, the negative predictive value was 99%, and the specificity and positive predictive value were 100%. Results were available from RT-PCR in 45 minutes; by comparison, conventional PCR required 100 minutes, and conventional cultures required 36 hours minimum. Field testing of commercially available assays such as the Xpert GBS Assay (Cepheid, Sunnyvale, CA) that uses automated RT-PCR technology and IDI-StrepB (Infectio Diagnostic, Quebec, Canada) that uses a PCR assay to amplify group B streptococcal target has been conducted [634–636]. The performance of RT-PCR and optical immunoassay is sufficiently robust for use in point-of-care settings [637]. A cost-benefit analysis suggests that widespread implementation would afford benefit over the current culture-based strategy, but, to date, these newer methods should be considered as adjunctive tests to antenatal culture-based methods for detection of GBS [638].

Intrapartum Antibiotic Prophylaxis

The current era of IAP dates from 1996, when consensus recommendations for the prevention of early-onset group B streptococcal disease were endorsed by the CDC, AAP, and ACOG [533,639,640]. These recommendations indicated that obstetric care providers and hospitals should adopt a culture-based or a risk-based policy to identify women to receive IAP. The culture-based approach employed lower vaginal and rectal cultures obtained at 35 to 37 weeks of gestation to identify candidates for IAP. The risk-based strategy identified IAP recipients by factors known to increase the likelihood of neonatal group B streptococcal disease: labor onset or membrane rupture before 37 weeks of gestation, intrapartum fever greater than or equal to 38° C (≥100.4° F), or rupture of membranes 18 or more hours before delivery. In both strategies, women with group B streptococcal bacteriuria or previous delivery of an infant with group B streptococcal disease were to receive IAP. These strategies each resulted in the administration of IAP to approximately one in four pregnant women [639].

The incidence of early-onset disease declined by 70% from 1.7 per 1000 live births to 0.5 per 1000 live births by 1999 in association with implementation of one of these two IAP methods (Fig. 12–10) [612,641]. A resulting 3900 to 4500 early-onset infections and 200 to 225 neonatal deaths were estimated to be prevented annually [612,642]. By contrast, the rate of late-onset disease remained constant at 0.5 to 0.6 per 1000 live births. Also, the incidence of invasive group B streptococcal disease, primarily bacteremia with or without intra-amniotic infection or endometritis among pregnant women declined significantly, from 0.29 per 1000 live births in 1993 to 0.23 in 1998 [612,642]. By 1999, two thirds of U.S. hospitals in a multistate survey had a formal prevention policy, and numerous individual practitioners had adopted one of the two strategies proposed in 1996 [612,643].

By 2002, it was evident that further reduction in the incidence of early-onset disease could be accomplished by adoption of universal culture screening. A direct comparison in 5144 births showed that the culture-based strategy was 50% more effective than the risk-based strategy in preventing early-onset disease in neonates [171]. Culture-based screening more often resulted in administration of IAP for at least 4 hours before delivery. The 2002 revised CDC guidelines recommending a universal culture-based approach to prevention of perinatal group B streptococcal disease are endorsed by the AAP and the ACOG [612,644,645]. Early-onset disease incidence declined an additional 29% after issuance of the revised guidelines in 2002, to 0.34 cases per 1000 live births from 2003-2007 [172].

Currently, all pregnant women should be screened in each pregnancy for group B streptococcal carriage at 35 to 37 weeks of gestation. The risk-based approach is an acceptable alternative only in circumstances in which the culture has not been performed or results are unavailable before delivery. Culture specimens should be obtained from the lower vagina and the rectum using the same or two different swabs. These swabs should be placed in a non-nutritive transport medium, transferred to and incubated overnight in a selective broth medium, and subcultured onto 5% sheep blood agar medium or colistin–nalidixic acid medium for isolation of GBS. At the time of labor or rupture of membranes, IAP should be given to all pregnant women identified antenatally as carriers of GBS. The indications for IAP are shown in Figure 12–11. Group B streptococcal bacteriuria during the current pregnancy or prior delivery of an infant with invasive group B streptococcal disease always is an indication for IAP, so antenatal screening is unnecessary for these women. If culture results are unknown at the onset of labor or rupture of membranes, the risk factors listed in Figure 12–11 should be used to determine the need to institute IAP. Women who present with preterm labor before antenatal group B streptococcal screening should have cultures obtained and IAP initiated. If labor ceases and cultures are negative, IAP is discontinued, and antenatal screening is performed at 35 to 37 weeks of gestation. If labor ceases and cultures are positive, some experts recommend oral amoxicillin for another 5 to 7 days.

Planned cesarean section before rupture of membranes and onset of labor constitute exceptions to the need for IAP for women colonized with GBS. These women are at extremely low risk for having an infant with early-onset disease. Culture-negative women who are delivered at 37 weeks of gestation or later need not receive IAP routinely, even when a risk factor is present. Therapeutic use of broad spectrum antibiotics in labor should be employed

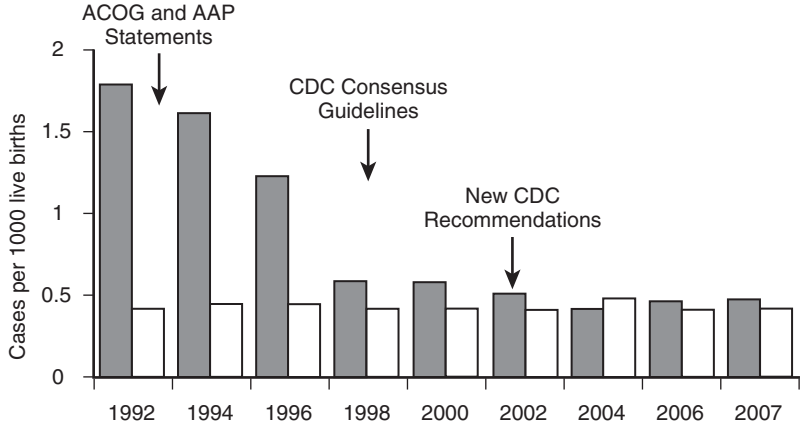


FIGURE 12–10 Incidence of early-onset (*gray bars*) and late-onset (*white bars*) group B streptococcal disease from 1992-2007. The dates of the initial prevention statements from the American College of Obstetricians and Gynecologists (ACOG) and the American Academy of Pediatrics (AAP) [624,625], the 1996 consensus guidelines from the Centers for Disease Control and Prevention (CDC) [639], and the revised 2002 CDC guidelines [612] are shown.

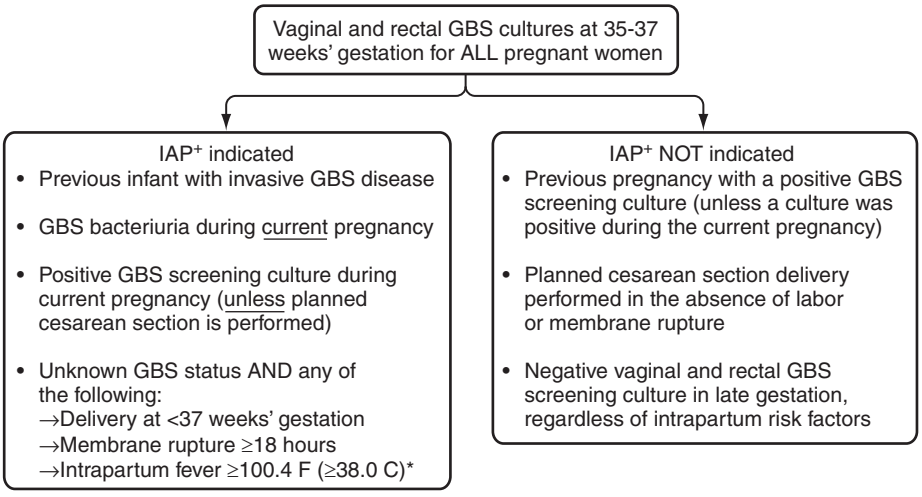


FIGURE 12–11 Revised recommendations for culture-based screening for maternal colonization with group B streptococci (GBS) and administration of intrapartum antibiotic prophylaxis (IAP). *(Adapted from Centers for Disease Control and Prevention. Prevention of perinatal group B streptococcal disease: revised guidelines from CDC. MMWR Morb Mortal Wkly Rep 51[RR-11]:1-22, 2002.)*

as is appropriate for maternal indications, such as intra-amniotic infection.

The recommended maternal intrapartum chemoprophylaxis regimen consists of penicillin G (5 million U initially and ~~2.5~~ million U every 4 hours thereafter until delivery) [612]. Penicillin or ampicillin given 4 or more hours before delivery reliably prevents vertical transmission and early-onset disease. Ampicillin administered as a 2-g intravenous loading dose and then 1 g every 4 hours until delivery is an alternative to penicillin [612]. The rationale for the high initial dose of the β-lactam antibiotic relates to the desired drug concentrations needed in the amniotic and vaginal fluids (peak approximately 3 hours after completion of the initial dose) to reduce substantially the number of GBS at either site. IAP "failures" typically occur when penicillin or ampicillin has been initiated 2 or less hours before delivery; clindamycin has been given without susceptibility testing, and clindamycin-resistant early-onset group B streptococcal neonatal sepsis ensued; or appropriate IAP is given in the setting of clinically apparent or silent intra-amniotic infection.

Prophylaxis for penicillin-allergic women must take into account increasing resistance among GBS to erythromycin and clindamycin. Women *not* at high risk for anaphylaxis (e.g., a rash without anaphylaxis or respiratory compromise) should receive cefazolin, 2 g intravenously as an initial dose and then 1 g every 8 hours until delivery. Cefazolin has pharmacokinetics similar to penicillin with respect to peak concentrations in serum and amniotic fluid of pregnant women. Women whose group B streptococcal isolates are tested and found to be clindamycin susceptible and who are at high risk for anaphylaxis with penicillin can receive clindamycin at a dose of 900 mg every 8 hours. If susceptibility testing is unavailable or the results are unknown, or when isolates are resistant to clindamycin, vancomycin, 1 g intravenously every 12 hours until delivery, is an alternative for women with serious penicillin hypersensitivity reactions. Neither the pharmacokinetics of vancomycin in amniotic or vaginal fluids nor its efficacy in preventing early-onset disease has been investigated.

The risk of anaphylaxis from administration of penicillin is low. Estimates range from 4 events per 10,000 to 4 per 100,000 patients. Anaphylaxis associated with administration of a β-lactam antibiotic as IAP for the prevention of early-onset group B streptococcal infection has been reported, but is rare [171,646–648]. Most pregnant women reporting a penicillin allergy that is not anaphylaxis have negative skin test on hypersensitivity testing and are able to receive IAP with penicillin safely [649]. A fetal demise in association with new-onset penicillin allergy during IAP has been reported in a woman with rheumatoid arthritis [650]. No adult fatalities in association with IAP are reported, and the risk of a fatal event is low because the antimicrobials are administered in a hospital setting where medical intervention is readily available.

Numerous residual problems, barriers to implementation, and missed opportunities must be overcome to achieve maximal benefit from IAP [651–653]. Procedural issues, such as suboptimal culture processing and collection of cultures earlier than 5 weeks before delivery, constitute one set of problems. Laboratories may not adhere to recommended methods for isolation of GBS, a problem that remains despite the 2002 consensus recommendations and one that results in colonized women delivering infants with early-onset disease. Even optimal antenatal culture methods miss some women who are colonized at delivery, exposing their neonate to GBS and resulting in colonization or illness. Another problem is that women who are not screened adequately more often are medically underserved; women in their teens, blacks, and Hispanics are more likely than whites to receive inadequate prenatal care and prenatal testing, and are less likely to receive recommended prevention interventions.

Problems surround lack of recommended IAP in certain circumstances. The most prominent is lack of adherence to the 2002 recommendation for routine IAP in

women who deliver before antenatal screening occurs (i.e., 35 to 37 weeks of gestation). These women should have vaginal and rectal cultures performed and routinely receive IAP, but this recommendation is the one least commonly implemented. Whether this is because delivery ensues too quickly to administer IAP, or the recommendation is unclear to obstetric providers, or both, is unknown. Also, adherence to guidelines in penicillin-allergic women is suboptimal, and cefazolin as the appropriate IAP for women with a nonserious penicillin allergy is administered uncommonly [654]. Reliance on clindamycin as the alternative agent in women without serious penicillin allergy results in inadequate IAP in at least 20% of patients when antimicrobial susceptibility testing of colonizing isolates is not performed antenatally.

A final issue is a need for increased awareness of perinatal group B streptococcal infection. In one report, only 47% of women younger than 50 years of age reported having heard of group B *Streptococcus* [655]. Women with a high school education or less; with low household income; or reporting black, Asian/Pacific Islander, or "other" race had lower awareness than that noted in other women. Efforts to raise awareness should target women from groups that traditionally are medically underserved. Hospital infection control teams can contribute to these efforts by spearheading educational efforts toward effective implementation among hospital obstetric staff and laboratory personnel [642].

Impact of Intrapartum Antibiotic Prophylaxis on Neonatal Sepsis

The efficacy of IAP in preventing early-onset group B streptococcal infection has been shown in numerous observational studies and in countries other than the United States when guidelines have been implemented [171,424,656–658]. The impact of increased use of IAP on the occurrence of sepsis caused by organisms other than GBS is a subject of ongoing evaluation. Concern exists that neonatal sepsis caused by organisms other than group B *Streptococcus* is increasing while group B streptococcal sepsis is decreasing and that the organisms causing non–group B streptococcal sepsis are likely to be ampicillin-resistant [659]. Surveillance trends are insufficient to establish a relationship between IAP for group B *Streptococcus* and *E. coli* sepsis risk, but single hospital–reported increases in *E. coli* sepsis that have occurred in preterm and very low birth weight infants are of concern [660]. A significant increase in the rate of early-onset sepsis caused by *E. coli* has been observed in multicenter studies, but only infants of very low birth weight (<1500 g birth weight) were evaluated [661]. In a multisite surveillance of trends in incidence and antimicrobial resistance of early-onset sepsis, stable rates of sepsis caused by other organisms were found, but an increase in ampicillin-resistant *E. coli* was observed among preterm but not term infants [662].

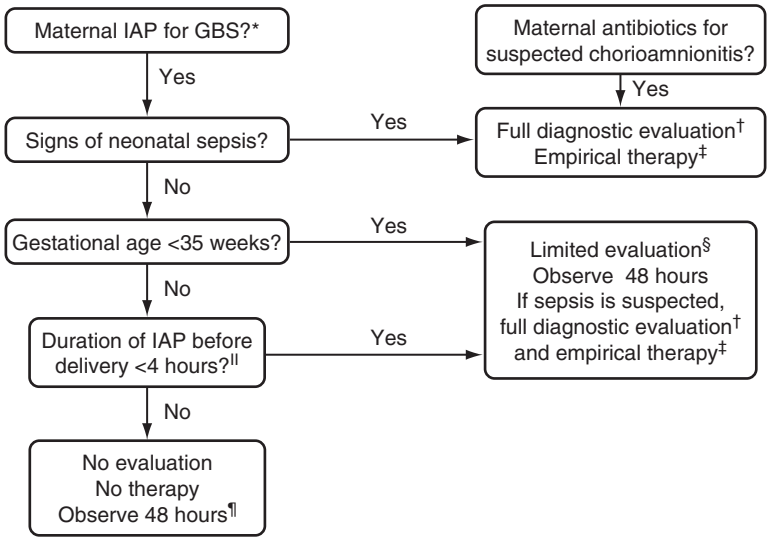
A relationship between neonatal death caused by ampicillin-resistant *E. coli* and prolonged antepartum exposure to ampicillin was noted by Terrone and colleagues [663]. In another report, the frequency with which ampicillin-resistant Enterobacteriaceae were isolated was similar after exposure to ampicillin or penicillin [664]. Repeat cultures 6 weeks postpartum revealed no increase in antibiotic resistance in either GBS or *E. coli* from women who had received IAP [665]. Ongoing population-based surveillance is required to monitor these trends and to identify possible reasons for the increase in ampicillin-resistant *E. coli* infections in preterm neonates, in particular, the use of antenatal antimicrobial agents other than IAP [666,667].

Management of Neonates Born to Mothers Receiving Intrapartum Antimicrobial Prophylaxis

Management of infants born to mothers given IAP is based on the neonate's clinical status and gestational age, if the mother had chorioamnionitis, and duration of IAP before delivery (Fig. 12–12) [612]. If an infant has any signs of sepsis, a full diagnostic evaluation, including complete blood cell count and differential, blood culture, and chest radiograph if the neonate has respiratory signs, and empirical therapy should be initiated pending laboratory results. A lumbar puncture, if feasible, should be performed. Although published reports vary, a minimum of 10% and a maximum of nearly 40% of infants with meningitis have a negative blood culture [532]. If lumbar puncture is deferred and therapy is continued for more than 48 hours because of suspected infection, CSF should be obtained for routine studies and culture. Depending on the CSF results, therapy appropriate for sepsis or presumed meningitis is given.

If a woman receives broad-spectrum antibiotics for suspected chorioamnionitis, her healthy-appearing infant should have a full diagnostic evaluation excluding a lumbar puncture, and most experts would initiate empirical therapy pending culture results regardless of the clinical condition at birth, gestational age, or duration of antibiotics before birth. This approach is based on the infant's exposure to suspected or established infection. The duration of therapy is based on results of cultures and the infant's clinical course (see "Treatment" section). If the infant is healthy-appearing, but has a gestational age of less than 35 weeks, some experts would perform a limited evaluation that includes complete blood count and blood culture, without regard to the duration of maternal IAP. Empirical therapy need not be initiated, unless signs of sepsis develop or the infant is very immature. Healthy-appearing infants with a gestational age of at least 35 weeks whose mothers received intravenous penicillin, ampicillin, or cefazolin less than 4 hours before delivery should be observed closely without a diagnostic evaluation. If the infant is healthy-appearing and has a gestational age of 35 weeks or more, and the mother received penicillin, ampicillin, or cefazolin 4 hours or more before delivery, routine care is advised.

The recommended interval of observation for neonates undergoing a limited evaluation is 48 hours. The approach presented in Figure 12–12 is not to be taken as an exclusive management pathway. Hospital discharge at 24 hours of age can be reasonable under certain circumstances, specifically when the infant is born after the mother has received a β-lactam as IAP for 4 hours or



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

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

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

§ CBC with differential and blood culture.

|| Applies only to penicillin, ampicillin, or cefazolin and assumes recommended dosing regimens.

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

FIGURE 12–12 Recommended management of newborn infants exposed to maternal intrapartum antibiotic prophylaxis (IAP) for group B streptococcal (GBS) infection. *(Adapted from Centers for Disease Control and Prevention. Prevention of perinatal group B streptococcal disease: revised guidelines from CDC. MMWR Morb Mortal Wkly Rep 51[RR-11]:1-22, 2002.)*

longer before delivery, has a gestational age of 38 weeks or more, and is healthy-appearing. Other discharge criteria should be met, and the infant should be under the care of a person able to comply with instructions for home observation [612,668]. The risk of bacterial infection in healthy-appearing newborns is low. Outcomes among infants whose mothers receive IAP are better than among infants whose mothers do not receive IAP. Rehospitalization is uncommon among these latter infants, however [669].

The influence of maternal IAP on the clinical spectrum of early-onset infection in term infants has been evaluated [669–671]. Exposure to antibiotics in labor does not change the clinical spectrum of disease or the onset of clinical signs of infection within 24 to 48 hours of birth for infants with early-onset group B streptococcal infection. Infants whose mothers have received IAP are less likely to be ill, to require assisted ventilation, or to have proven bacterial infection [669]. These infants are not more likely to undergo invasive procedures or to receive antibiotics [670]. The number of infants undergoing evaluation for sepsis has decreased in association with implementation of IAP guidelines, and among group B *Streptococcus*–negative women, ordering of laboratory tests has diminished by almost 40% [672].

Chemoprophylaxis for the Neonate

Chemoprophylaxis for neonates at birth continues to be advocated by some investigators. Three decades ago, Steigman and colleagues [673] found no cases of early-onset group B streptococcal infection among 130,000 newborns who received a single intramuscular injection of penicillin G (50,000 U) at birth as prophylaxis for gonococcal infection. Neonates with possible in utero acquisition of infection who were ill at birth did not receive prophylaxis and were excluded from the analysis. Pyati and coworkers [674] evaluated more than 1000 neonates with birth weights of less than 2000 g in whom a blood culture was obtained before penicillin was administered. In these high-risk infants, penicillin prophylaxis at birth was ineffective in preventing group B streptococcal bacteremia or in altering the mortality rate associated with infection.

A few centers use a combined maternal and neonatal protocol that advocates a risk-based maternal IAP approach coupled with administration of a single dose of intramuscular penicillin to all infants within 1 hour of birth [675–677]. Observational studies showed a 76% reduction in early-onset infection to 0.47 per 1000 live births when rates for the 5 years from 1986-1994 were compared with rates from 1994-1999.

In the special circumstance of an apparently nonaffected sibling in a twin or multiple birth with early-onset [332,333] or late-onset [333] group B streptococcal disease, the well-appearing sibling of a neonate with invasive infection is at increased risk of developing group B streptococcal disease. At the time of diagnosis of group B streptococcal disease in the index patient of a multiple birth, the other infant or infants should be assessed clinically [333]. If signs of infection are noted, cultures of blood and CSF should be obtained, and empirical antimicrobial treatment should be initiated until laboratory results become available. If cultures yield group B *Streptococcus*, a full course of treatment is appropriate. If findings from the clinical assessment are unremarkable, management should be undertaken on a case-by-case basis. The risk for a poor outcome when the second of twin is not evaluated until clinical signs of infection are apparent warrants caution in this circumstance. Even when empirical therapy is given and invasive infection is excluded, later onset is possible [678].

IMMUNOPROPHYLAXIS

The most promising approach to prevention of group B streptococcal disease is immunoprophylaxis [613,679]. The underlying principle is that IgG directed against CPS of GBS, critical for protection against invasive disease, are provided by passive or active immunization. Human sera containing a sufficient concentration of CPS-specific antibody have been shown in animal models of infection to protect against lethal challenge with each of the major group B streptococcal types [350,680]. Provision of protective levels of type-specific immunity to the newborn theoretically can be achieved by passive or active maternal immunization. Passive immunotherapy for the mother would require development of hyperimmune preparations of human immunoglobulin for intravenous use, would be expensive, and would require many hours of infusion before delivery to provide fetal serum levels, but animal studies indicate the potential usefulness of such an approach [681,682].

The first candidate group B streptococcal vaccine, a purified type III CPS, underwent testing in healthy adults in 1978 [359]. Subsequently, types Ia and II CPS vaccines were studied [683]. Although these vaccines were well tolerated and elicited primarily IgG class response within 2 to 4 weeks, the immunogenicity was variable. It was discovered that nearly 90% of adults had very low preimmunization serum concentrations of CPS-specific antibodies in association with presumed immunologic naïvete. These low levels predicted a poor immune response in many, so that only 40% and 60% developed significant type-specific antibody responses after immunization with type Ia and type III CPS vaccines. By contrast, 88% of adults immunized with type II CPS vaccine responded with fourfold or greater increases in type II CPS–specific antibodies.

These early trials verified the feasibility of immunization as an approach to prevent group B streptococcal disease and revealed the need to develop candidate vaccines with enhanced immunogenicity. The first study conducted in pregnant women was an encouragement to the ultimate potential success of a group B streptococcal vaccine program [410]. Among 25 pregnant responders to a type III CPS group B streptococcal vaccine, 90% delivered infants with substantial levels of specific antibody to the type III CPS in cord sera that promoted functional activity in vitro throughout the first 3 months of life in most instances.

Development of the first group B streptococcal CPS conjugate vaccine, type III CPS–tetanus toxoid, was driven by the prominence of type III among infants with early-onset and late-onset disease and by its dominance as a cause of meningitis. Type III CPS was linked covalently to monomeric tetanus toxoid by reductive amination coupling chemistry [684]. Group B streptococcal CPS–protein conjugate vaccines of all clinically important types subsequently were developed and found to be immunogenic and protective in experimental animals [52,684–689]. The first clinical evaluation of the type III CPS–tetanus toxoid conjugate showed greater than fourfold increases in postimmunization CPS-specific IgG in 90% of healthy nonpregnant women [690]. The vaccine was well tolerated, and the antibodies, predominantly of the IgG class, were functional in vitro and protective in a murine model of infection.

Conjugate vaccines to each of the clinically relevant group B streptococcal CPS types causing invasive disease have been tested in nearly 500 healthy adults 18 to 50 years old [688,690–692]. Systemic responses, such as low-grade fever, chills, headache, or myalgias, always short-lived, were observed in less than 2% of volunteers. Local reactions were frequent but mild, typically consisting of pain without erythema or swelling, and resolved within 48 to 72 hours. Immune responses to each of the conjugate vaccines, with the exception of type V, are dose-dependent. Doses of 4 to 15 μg of the CPS component have elicited greater than fourfold increases in CPS-specific IgG in 80% to 93% of recipients of type Ia, Ib, II, III, and V conjugates at 8 weeks after immunization. Evaluation of a vaccine combining type II and type III CPS, each conjugated to tetanus toxoid, showed no immune interference compared with response after administration of one of the monovalent vaccines [693].

A phase 1 randomized placebo-controlled, double-blinded trial of type III CPS–tetanus toxoid conjugate vaccine was conducted in 30 healthy pregnant women at 30 to 32 weeks of gestation [693]. Immunization was well tolerated. Geometric mean concentrations of IgG to type III CPS from immunized women were significantly increased from preimmunization values and correlated well with infant cord values. Sera from the infants of vaccinated women collected at 1 and 2 months of age promoted in vitro opsonization and killing of type III GBS by human neutrophils.

One alternative strategy for the preparation of group B streptococcal conjugate vaccines is to construct "designer" glycoconjugate vaccines with size-specific antigens and site-controlled coupling that optimizes the magnitude and specificity of the antipolysaccharide response [694]. An oligosaccharide-based tetanus toxoid conjugate vaccine against type III GBS was synthesized to retain the antigenic specificity of the native polysaccharide and has been shown to be immunogenic in mice [695].

Conjugate vaccine size, CPS molecular weight, and the degree of polysaccharide-protein cross-linking all are important considerations in optimizing immunogenicity of candidate vaccines [67].

Use of proteins that are conserved across most group B streptococcal serotypes offers another strategy for vaccine development. The C protein could be an alternative to tetanus toxoid as the protein component of a conjugate vaccine [680,687,696]. Invasive disease, but not colonization, elicits α C–specific and β C–specific IgM and IgG in adults [697,698]. A type III polysaccharide–C protein conjugate vaccine theoretically could prevent most systemic infections [699]. A recombinant β C protein modified to eliminate its IgA-binding site conjugated to type III CSP has been shown to be immunogenic in mice, inducing polysaccharide and protein-specific functional IgG [700]. The group B streptococcal surface proteins, Rib, Sip, and C5a peptidase, each have been shown to elicit antibodies that are protective in experimental models of group B streptococcal infection [701–703]. Their roles in human infection are not established.

The discovery that surface-associated pilus-like islands are distributed widely among group B streptococcal clinical isolates potentially paves the way for the development of pilus island–based vaccines. An entire pilus island has been transferred from group B *Streptococcus* to a nonpathogenic species. Mucosally delivered *Lactococcus*-expressing pilus island 1 protected mice from challenge with pilus 1–containing group B streptococcal strains [10]. Pilus islands 1, 2a, and 2b, alone or in combination, were identified on each of 289 group B streptococcal isolates from infants and adults with invasive disease, and most were highly surface expressed [11]. A combination of the three pilus-island components conferred protection against all tested group B *Streptococcus* challenge strains. A vaccine exclusively constituted by pilus components in concept could be broadly efficacious in preventing infections caused by GBS [11].

Because most pregnant women have low concentrations of type-specific IgG in their sera, a practical approach to immunoprophylaxis would be immunization of women during adolescence, before pregnancy, or in late in pregnancy (i.e., early third trimester) [593]. In view of the substantial disease burden in nonpregnant adults, targeted adult immunization (e.g., diabetics or adults ≥65 years old) also is an attractive prevention strategy. Types Ia, III, and V GBS account for 75% to 85% of infections and, together with types Ib and II, for most invasive disease in infants and adults [143,146,699,704]. The production of a trivalent or a pentavalent conjugate vaccine is technically achievable. Physicians and their patients and pharmaceutical industry leaders must perceive this mode of prevention to be of high benefit and negligible risk, especially if pregnant women are to be included in the target population. The cost of developing suitable vaccines, although substantial, is considerably less than the death, disability, and treatment associated with these infections [623,705]. If the prevention of group B streptococcal disease is to become a reality, however, physicians, public health officials, parents, and patients must join together as advocates for pregnant women, neonates and young infants, and at-risk adults.

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