Review

Campylobacter jejuni Infection during Pregnancy: Long-Term Consequences of Associated Bacteremia, Guillain-Barré Syndrome, and Reactive Arthritis†

JAMES L. SMITH

U.S. Department of Agriculture, Agricultural Research Service, Eastern Regional Research Center, 600 East Mermaid Lane, Wyndmoor, Pennsylvania 19038, USA

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ABSTRACT

Campylobacter jejuni infections are the main cause of foodborne gastroenteritis in the United States and other developed countries. Generally, C. jejuni infections are self-limiting and treatment is not necessary; however, infections caused by this organism can lead to potentially dangerous long-term consequences for some individuals. Bacteremia, Guillain-Barré syndrome (GBS; an acute flaccid paralytic disease), and reactive arthritis (ReA) are the most serious of the long-term consequences of C. jejuni infections. During pregnancy, foodborne infections may be hazardous to both the woman and the fetus. C. jejuni–induced bacteremia during pregnancy may lead to intrauterine infection of the fetus, abortion, stillbirth, or early neonatal death. Infection of a newborn by the mother during the birth process or shortly after birth may lead to neonatal enteritis, bacteremia, and/or meningitis. C. jejuni enteritis is the inducing antecedent infection in approximately 30% of cases of GBS. Thus, pregnant women infected with C. jejuni may contract GBS. GBS during pregnancy does not affect fetal or infant development and does not increase spontaneous abortion or fetal death; however, it may induce spontaneous delivery during the third trimester in severe cases. Reactive arthritis occurs in approximately 2% of C. jejuni enteritis cases and leads to the impaired movement of various joints. Pregnant women with C. jejuni–induced reactive arthritis can be expected to deliver a normal infant. A pregnant patient with GBS or ReA may be unable to care for a newborn infant because of the physical impairment induced by these diseases. Since C. jejuni infections put both fetuses and pregnant women at risk, pregnant women must take special care in food handling and preparation to prevent such infections.

Campylobacter jejuni–induced enteritis, a foodborne infection, can be an antecedent disease to extraintestinal illnesses such as Guillain-Barré syndrome (GBS), reactive arthritis (ReA), and bacteremia (142). Since there are no studies showing that pregnant women are at increased risk for C. jejuni–induced enteritis, it is assumed that the susceptibility of pregnant women to C. jejuni–induced GBS, ReA, or bacteremia is similar to that of the general population. It is important to note that when a pregnant woman suffers from a foodborne infection, the fetus or neonate also may be affected. Unfortunately, there is a paucity of information concerning the effect of C. jejuni–induced GBS, ReA, and bacteremia on pregnant women, fetuses, and neonates. Since there are approximately 6,000,000 pregnancies each year in the United States alone (Table 103 in U.S. Census Bureau (158)), there is a need to determine the incidence and consequences of C. jejuni–induced ReA, bacteremia, and GBS for pregnant women, fetuses, and neonates. In this review, the incidence, symptoms, treatment, and long-term sequelae of C. jejuni–induced bacteremia, GBS, and reactive arthritis are described in detail for both pregnant and nonpregnant populations.

C. JEJUNI INCIDENCE

While there are a number of species of Campylobacter, >99% of clinical Campylobacter isolates in the United States have been identified as C. jejuni (51). Campylobacter species are rarely involved in foodborne outbreaks in the United States, and as a result, 99% of Campylobacter infections are sporadic cases (4). In the United States during the 15-year period from 1983 through 1997, Campylobacter spp. were implicated in 4.1% of all foodborne outbreaks, 0.8% of all outbreak cases, and 1.9% of all outbreak deaths (14, 15, 106). In contrast, during the same period, Salmonella spp. accounted for 64.0% of all outbreaks, 66.8% of all outbreak cases, and 41.9% of all outbreak deaths (14, 15, 106). Nonetheless, except in 1999, Campylobacter spp. have been the most frequently isolated pathogens in infectious intestinal illnesses in the United States since 1996. In 1996, the U.S. Foodborne Diseases Active Surveillance Network reported 7,223 laboratory-confirmed cases of diarrhea from selected sentinel sites. Campylobacter spp. were isolated in 45.6% of these cases, whereas Salmonella spp. were isolated in 29.2% (30). In 1997, there were 8,576

* Author for correspondence. Tel: 215-233-6520; Fax: 215-233-6581; E-mail: jsmith@arserrc.gov.
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confirmed cases of diarrhea, with *Campylobacter* spp. being responsible for 46.3% of these cases and *Salmonella* spp. being responsible for 25.7% (31). In 1998, the trend continued: *Campylobacter* spp. were isolated in 4,031 of 9,787 (41.2%) cases of diarrhea, while *Salmonella* were isolated in 2,848 (29.1%) cases (32). There was a reversal of this trend in 1999 due to outbreaks of salmonellosis linked to unpasteurized orange juice, imported mangoes, and raw sprouts. *Salmonella* spp. were isolated in 42.4% of 10,697 laboratory-confirmed cases of diarrhea, whereas *Campylobacter* spp. were isolated in 35.5% of these cases (33). In 2000, there were 12,631 diagnosed cases of foodborne diarrhea. *Campylobacter* spp. accounted for 4,640 cases (36.7%), while *Salmonella* spp. accounted for 4,237 cases (33.5%) (34). *Campylobacter* spp. are also the most important cause of diarrheic diseases in a number of other countries. For example, *Campylobacter* spp. are the agent most often responsible for cases of infectious intestinal disease in Australia (150), Canada (155), England (167), Finland (63), The Netherlands (39), and New Zealand (83).

Tauxe (152) has estimated that 1 out of 100 individuals in the United States experiences a bout of campylobacteriosis each year. Thus, for the total population of approximately 270,000,000 in 1999 (Table 13 in U.S. Census Bureau (158)), an estimated 2,700,000 individuals had campylobacter enteritis ranging in severity from loose stools to dysentery. Although Buzby et al. (28) have estimated that 55 to 70% of all campylobacteriosis infections in the United States are foodborne, Mead et al. (93) have estimated that 80% of all *Campylobacter* infections are foodborne.

In industrialized countries like the United States, all age groups are susceptible to campylobacter infection. There is, however, a bimodal distribution of infection, with a peak of infection incidence in infants <1 year of age and another peak in adults aged 15 to 24 years (6, 14). In developing countries, the highest incidence of infection is in infants 6 to 12 months old, while most children by the age of 5 years and most adults are immune to campylobacter infection (6, 14).

There is evidence that certain immunocompromised groups are at increased risk for campylobacter infections. Patients with AIDS were found to be 39 times as likely as the population at large to have campylobacteriosis (147). Patients with AIDS and campylobacteriosis had an increased incidence of bacteremia and hospitalization, as well as a decreased survival time, compared with AIDS patients not infected with *Campylobacter* spp. (92, 109, 147). Patients with other diseases associated with defective cellular-mediated immunity and individuals taking drugs that suppress cellular immune function also may be at risk for campylobacteriosis (2, 13, 22, 76, 104). Gerba et al. (52) found that the fatality rate for *C. jejuni*–infected elderly people confined to nursing homes was 11 times as high as that for the general population. However, there is no evidence that healthy pregnant women or elderly individuals are predisposed to campylobacter infection, even though pregnant women and elderly people are potentially immunocompromised (144, 165).

**CAMPYLOBACTER-INDUCED ENTERITIS**

Campylobacter enteritis is variable in severity, ranging from asymptomatic excretion of the organism (25 to 50% of infected individuals may be asymptomatic) to an extremely severe disease ending in death. Only about 10% of infected persons are hospitalized (6). The infective dose is low: 50% of the volunteers in one study had positive stool cultures after ingesting 800 organisms (20). The mean incubation period for *C. jejuni* gastroenteritis is 3.2 days (range, 1.5 to 5.0 days). The illness usually begins abruptly with abdominal pain and diarrhea. Diarrhea can range from a few loose bowel movements to a profuse and prostrating watery diarrhea. Blood is present in the stools of approximately 14% of patients, and about half of the patients have fever. Nausea is common, but vomiting is not a major symptom in campylobacter enteritis (6, 141). Resolution of the disease usually occurs in 4 to 5 days, but the disease can resolve within 24 h in mild infections. Most campylobacter enteritis patients do not see a physician; however, some patients have a prolonged and severe illness lasting more than 10 days with a high fever and grossly bloody stools and must seek medical help. The mean duration of convalescent excretion of *Campylobacter* spp. is 37.6 days, but the period of excretion is longer for patients with immune deficiency diseases (6, 141). Death is rare; Mead et al. (93) estimated that the death rate from foodborne campylobacter infections is 0.001%.

Individuals who develop *C. jejuni* enteritis are at risk for bacteremia. Bacteremia resulting from campylobacteriosis is uncommon and transient in immunocompetent people (143). Bacteremia is more common in patients ≥65 years of age with a *C. jejuni* infection. The incidence of *C. jejuni*–induced bacteremia ranged from 0.3 cases per 1,000 patients aged 1 to 4 years to 5.9 cases per 1,000 patients ≥65 years of age. The average incidence of campylobacteriosis-induced bacteremia was found to be 1.5 cases per 1,000 patients (143). Skirrow et al. (143) reported that 25.8% (65 of 228) of immunocompromised patients with *C. jejuni* enteritis were bacteremic; therefore, underlying immunocompromising diseases predispose patients to *C. jejuni*–induced bacteremia. In addition, mortality from *C. jejuni* bacteremia is more likely for immunocompromised individuals (40, 143). In an outbreak of *C. jejuni*–induced bacteremia involving 11 immunocompetent individuals, Shandera et al. (132) found that all patients had a fever (with a mean maximal temperature of 102.6°F [39.2°C]), nine patients had diarrhea and a headache, and eight patients had abdominal pain and chills. Six patients had bloody stools, while only four experienced vomiting. The mean duration of bacteremic symptoms was 8 days, and all patients recovered (132). It is probable that symptoms of bacteremia for immunocompromised individuals are more severe than those described for immunocompetent patients.

Campylobacter enteritis has been associated with infection of the biliary tract leading to cholecystitis, pancreatitis, or obstructive hepatitis (141). *Campylobacter* spp. have been associated with cases of peritonitis for individuals on peritoneal dialysis and for individuals with urinary
tract infections, bacteremia, and nephritis (6, 141). Importantly, long-term complications, including ReA, uveitis, GBS, and erythema nodosum, have been associated with *Campylobacter enteritis* (141).

The treatment of choice in most cases of *Campylobacter* enteritis is oral rehydration and electrolyte replacement. Antibiotic treatment is recommended in cases of prolonged (>1 week) or worsening symptoms such as high fever and bloody stools. Antibiotics are also indicated if patients experience complications or are immunocompromised (4, 6, 141). Since *Campylobacter* infections may have deleterious effects on fetuses, pregnant women should also receive antibiotic treatment (4, 6, 141). Antibiotics useful in treating *Campylobacter* enteritis include erythromycin and other macrolides, fluoroquinolones and other quinolines, tetracycline, and amoxicillin (100). Unfortunately, there are indications that *Campylobacter* species are becoming increasingly resistant to clinically useful antibiotics (47, 100). Multidrug resistance also has been reported (65, 88). There is a strong correlation between increased *Campylobacter* resistance to macrolides and quinolines and the use of these antibiotics in animal husbandry (47, 154).

**PREGNANT WOMEN AND *C. JEJUNI* ENTERITIS**

In 1996, there were 6,240,000 pregnancies in the United States (Table 103 in U.S. Census Bureau (158)). If 1 out of 100 persons has campylobacteriosis each year, then during 1999, assuming 6,000,000 women were pregnant, approximately 60,000 pregnant women had *C. jejuni*-induced enteritis. *C. jejuni* infections during pregnancy are generally mild and self-limiting, but an infection may have serious consequences for the fetus if the infection induces maternal bacteremia (139).

Blood cultures may not always be taken from patients who have acute gastroenteritis, and the sensitivity of the detection of *Campylobacter* in blood is low (141). Therefore, the incidence of 1.5 bacteremic cases per 1,000 cases of campylobacteriosis (143) probably represents a minimum number. If 60,000 pregnant women had *C. jejuni*-induced enteritis in 1999, it can be estimated that approximately 100 of those women also had bacteremia, but the actual number of bacteremic pregnant women was probably larger. However, the incidence of *C. jejuni*-induced bacteremia during pregnancy has not been reported.

Most women who are infected with *C. jejuni* during pregnancy do not experience any complications, and neither do their fetuses or newborn infants. However, infected mothers can transmit *C. jejuni* to their fetuses in utero or to their newborn infants during or shortly after the birth process (74, 108). An infected live baby usually shows signs of diarrhea and/or bacteremia (Table 1). Generally, neonatal *C. jejuni* infections are benign (141).

Maternal *C. jejuni* infections can lead to the death of the fetus, particularly if there is maternal bacteremia. *C. jejuni*-induced bacteremia during pregnancy can induce abortions, stillbirths, or early neonatal death (Table 1). Maternal bacteremia due to *C. jejuni* is normally associated with fetal or neonatal death but not with maternal death. However, Meyer et al. (95) reported a case in which *C. jejuni*-induced bacteremia in a pregnant woman led to the deaths of both the fetus and the mother.

*C. jejuni* is a placental pathogen. In vitro studies indicated that human clinical isolates of *C. jejuni* inoculated on the maternal side of an organ culture of human chorionamniotic membranes penetrated to the fetal side of the culture (41). Thus, the chorionamniotic membrane may not prevent the infection of the fetus by *C. jejuni*. Chicken fecal isolates were not able to penetrate the membrane (41). Both *C. jejuni* and *Campylobacter coli* grew and survived in human amniotic fluid (41, 60). The most probable route of *C. jejuni* infection of the fetus is through colonization of the placenta during the bacteremic stage of maternal infection (41). Therefore, a fetus is at risk when its mother has *C. jejuni* bacteremia. Denton and Clarke (38) have suggested that the placenta may be infected by organisms ascending from the vagina of a *C. jejuni*-infected pregnant woman.

Not all *C. jejuni* infections in neonates are caused by maternal infection. For example, Goossens et al. (56) described a hospital maternity ward outbreak of *Campylobacter* meningitis in 11 newborn infants (mean age, 9.6 days). A single strain of *C. jejuni*, isolated from the stools and blood of some of the neonates, was responsible for the outbreak. Interestingly, the source of infection was not the babies’ mothers but rather an asymptomatic caretaker physician infected with the outbreak strain. Recently, Wolfs et al. (169) reported a case of *C. jejuni*-induced bacteremia in a 3-week-old infant who had acquired the infection from a puppy. The strains isolated from the infant and from the puppy were shown to be identical by genetic analysis.

Thus, *C. jejuni*-induced enteritis with concurrent bacteremia during pregnancy can lead to fetal wastage by abortion, stillbirth, or premature labor (Table 1). The newborn infant can contact enteritis, bacteremia, or meningitis from *C. jejuni*-infected mothers or caretakers (Table 1). Information on the number of newborn infants infected by *C. jejuni* is poorly documented.

### TABLE 1. Consequences of maternal *C. jejuni* enteritis and/or bacteremia

<table>
<thead>
<tr>
<th>Consequence</th>
<th>Reference(s)</th>
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<tbody>
<tr>
<td>Death of mother and fetus</td>
<td>95</td>
</tr>
<tr>
<td>Abortion</td>
<td>1, 38, 73, 98, 112, 126, 157</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>49 (causative organism was <em>C. coli</em>), 54</td>
</tr>
<tr>
<td>Premature labor; bacteremic newborn infant died within 24 h of birth</td>
<td>139</td>
</tr>
<tr>
<td>Premature labor; bacteremic newborn infant required assisted ventilation and later died of respiratory arrest and cardiac failure</td>
<td>96</td>
</tr>
<tr>
<td>Diarrhea in newborn infant</td>
<td>64, 74, 163</td>
</tr>
<tr>
<td>Bloody diarrhea in newborn infant</td>
<td>54, 139, 161, 172</td>
</tr>
<tr>
<td>Bacteremia in newborn infant</td>
<td>80, 173</td>
</tr>
<tr>
<td>Blood diarrhea and bacteria in newborn infant</td>
<td>40, 82 (causative organism was <em>C. coli</em>).</td>
</tr>
</tbody>
</table>
jejuni or on the extent of fetal wastage due to maternal C. jejuni–induced enteritis and bacteremia is not readily available.

C. JEJUNI-INDUCED GBS

One of the most catastrophic consequences of a C. jejuni infection can be the induction of GBS in an infected person. GBS consists of a group of syndrome subtypes: acute inflammatory demyelinating polyradiculoneuropathy, acute motor axonal neuropathy, acute motor-sensory axonal neuropathy, and Miller-Fisher syndrome (12) (Table 2). The critical differences among these subtypes depend on how the pathologic and electrodiagnostic features of the diseases are expressed. At least 90% of the cases of GBS seen in developed countries involve the acute inflammatory demyelinating polyradiculoneuropathy subtype (12). GBS is the common cause of acute flaccid paralysis throughout the developed world. In industrialized countries, the annual incidence of GBS ranges from 1 to 4 cases per 100,000 people. Men are infected more commonly than women are by a ratio of 1.25:1 to 1.5:1. While all age groups are affected, the incidence of GBS increases steadily with age (61, 67, 99, 162).

The disease. GBS occurs sporadically, and outbreaks are rare (4). The syndrome can be mild, with only brief impairment of a patient’s lifestyle, or it can be a severe devastating paralysis. GBS is an autoimmune inflammatory disease of the peripheral nerves in which the myelin sheath surrounding the nerve cells is destroyed. The syndrome is acute and progresses rapidly with a loss of reflexes. The disease may start with tingling and numbness in the tips of the fingers and toes and weakness of the limbs. Limb, neck, shoulder, and back pain are characteristic of GBS. Weakness usually begins in the lower limbs and ascends to the upper limbs, the trunk, and the cranial nerves. Muscles that control facial and eye movements, speech, or swallowing may be affected. Approximately 25% of GBS patients have severe respiratory muscle weakness requiring assisted ventilation; around 40% are bedridden (61, 67, 99, 114). In addition, the autonomic nervous system may be affected. Effects on both hypertensive and hypotensive blood pressures, as well as cardiac arrhythmias, are seen as part of the dysautonomia (121). Only about 2% of patients with GBS die; patients on mechanical ventilation are more at risk for death than are patients who are less severely affected (27, 50).

There is much variation in the speed of recovery from GBS. In most cases, the median time from disease onset to the beginning of improvement is approximately 2 weeks. Approximately 2 months is required to regain the ability to walk unaided, and complete recovery is usually seen in 6 months. For severe GBS, especially for patients on mechanical ventilation, recovery is more gradual and may take years. Most patients recover physically, but about 20% have residual deficits (50, 61, 120). A prospective study involving 297 GBS patients indicated that the mean time to clinical recovery was 200 days (70). Patients over 55 years of age recovered more slowly, with a mean recovery time of 255 days, than did patients younger than 35 years, who had a mean recovery time of 157 days.

Most GBS patients develop psychological problems due to the nature of their illness (muscle paralysis, artificial respiration, slow recovery, etc.), and these problems may continue after recovery. Bernsen et al. (19) studied the psychosocial status of 122 patients 3 to 6 years after the onset of GBS and found that 77 of these patients had not returned to their predisease lifestyles due to real or imagined residual defects. Most of these patients (84 patients), however, showed signs of good recovery with only minor residual deficiencies or no residual deficiencies. The survey of Bernsen et al. (19) indicates that while the majority of GBS patients recovered clinically, they showed a persistent loss in physical performance. Merkies et al. (94) also noted that most GBS patients, despite good clinical improvement, were restricted in their work and social activities even 5 years after recovery. Most GBS patients listed fatigue as the most important cause of their physical dysfunction, and the fatigue symptoms did not improve over time (94).

Treatment. Since GBS can be life-threatening, it is necessary to provide maximum supportive care during the illness. Initially, the patient must be closely observed for signs of incipient respiratory failure, and mechanical ventilation should be provided if necessary. Diligent nursing care is essential. Bedridden patients must be turned frequently, and passive physical therapy should be initiated early in the illness. Pain is common, and patients are generally treated with mild analgesics (12, 61). Patients with GBS are often mentally depressed, and psychological sup-

<table>
<thead>
<tr>
<th>TABLE 2. Characteristics that differentiate the subtypes of GBS</th>
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<tbody>
<tr>
<td><strong>GBS subtype</strong></td>
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<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Acute inflammatory demyelinating polyradiculoneuropathy (AIDP)</td>
</tr>
<tr>
<td>Acute motor axonal neuropathy (AMAN)</td>
</tr>
<tr>
<td>Acute motor-sensory axonal neuropathy</td>
</tr>
<tr>
<td>Miller-Fisher syndrome</td>
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</table>
port and reassurance by friends, family members, and medical staff are necessary for the well-being of these patients (61).

Specific treatments for GBS include plasma exchange (plasmapheresis [PE]) and intravenous immunoglobulin (IVIG). Plasma exchange is a procedure involving the separation of cellular and plasma components of blood withdrawn from the patient followed by the dilution of blood cellular constituents with a plasma substitute. The patient’s circulatory system is then replenished with the plasma substitute—blood cell mixture. PE involves specialized equipment and trained technicians. IVIG is advantageous because it does not require special training or equipment. While both treatments are equally effective in expediting recovery from GBS (110), IVIG is more convenient and leads to fewer complications (24). In contrast to PE, there is less need for artificial ventilation when IVIG is used (105, 140). PE and IVIG are also effective in the treatment of pediatric GBS patients. Intravenous immunoglobulin is preferable for children, since PE is technically more difficult to perform because children have smaller veins (24, 78, 114, 131). However, IVIG is nephrotoxic for some patients. Levy and Pusey (87), in a study involving 119 patients on IVIG therapy, found that eight (6.7%) of these patients showed signs of renal failure. Levy and Pusey suggested that all patients undergoing treatment with IVIG should have their renal function monitored frequently.

IVIG therapy for 5 days costs the GBS patient $10,165, whereas PE therapy is less costly, at $6,204 for 6 days (101). Despite the high cost of IVIG therapy and PE therapy, these treatments decrease the total overall cost of GBS patient care, since untreated patients require a longer hospital stay (114). It is not completely clear why PE and IVIG are effective in treating GBS. The mechanism of action of PE may be the removal of autoantibodies or immune complexes from the circulatory system, resulting in the eventual alleviation of GBS symptoms (135). IVIG may act by modulating various immune responses of the recipient (148). A recent study indicated that clinical improvement in GBS patients was correlated with a reduction in the levels of circulating proinflammatory cytokines such as tumor necrosis factor-α and interleukin-1β with IVIG administration (133). The selective decrease in circulating proinflammatory cytokine levels, with the levels of circulating anti-inflammatory cytokines remaining unaffected, is likely the basis of the therapeutic action of IVIG.

**C. jejuni-induced GBS.** GBS is a postinfectious disease. Approximately two-thirds of GBS occurrences are preceded by viral or bacterial upper respiratory tract or gastrointestinal tract infections (61, 67, 114). *C. jejuni* enteritis is the infection that most commonly precedes GBS (4, 66, 67, 115). The results of several studies on the relationship between *C. jejuni* infections and GBS are summarized in Table 3. In 14 studies involving serology, stool cultures, or both, 28.6% of GBS patients tested positive for *C. jejuni* (67). In seven studies involving serology for *C. jejuni*, 27.8% of GBS patients had antibodies against the organism, whereas seven other studies involving only stool cultures indicated that 18.3% of GBS patients were *C. jejuni*-positive (4). Stool cultures may not always be effective in diagnosing *C. jejuni* infection because (i) the organism might have been cleared from the bowel by antimicrobial therapy; (ii) the patient might no longer be excreting the organism; (iii) enrichment techniques might not be used if the numbers in the stool are low; and (iv) multiple stool samples might not be used, since the detection rate for *C. jejuni* is increased greatly by daily sampling over a 3-day period (99).

Compared with individuals who have GBS that has not been induced by *C. jejuni*, most patients with *C. jejuni*-associated GBS have a more severe illness with long-lasting physical and neurological deficits; in addition, extensive axonal injury may be present (5, 36, 62). *C. jejuni* infection was significantly associated with a poor outcome for GBS patients (62). The time taken for a patient with *C. jejuni*-induced GBS to walk unaided was twice as long as that for GBS patients testing negative for *C. jejuni* infection (67, 116). Infected patients were more likely to require assisted ventilation and to have a longer recovery period, and recovery was often incomplete (62, 67). There is no correlation between the severity of the preceding *C. jejuni* infection and the development of GBS, since cases of GBS associated with asymptomatic *C. jejuni* infections also have been reported (5).

Molecular mimicry has been invoked as a hypothesis to explain the induction of GBS by a *C. jejuni* intestinal infection (97, 168). The core polysaccharides of certain *C. jejuni* lipopolysaccharides and a number of glycosphingolipids of the human neural ganglioside group are homologous. Thus, an immunological reaction against *C. jejuni* lipopolysaccharides may elicit an autoimmune-mediated attack against an infected individual’s neural tissue with the induction of GBS (55, 99, 102). A small number of studies involving only a few patients have indicated that infection by certain serotypes of *C. jejuni* are more likely to precede GBS. For example, serotype O:19 was more commonly isolated from GBS patients from Japan (127), whereas serotype O:41 was more frequently isolated from GBS patients from South Africa (84). However, Endtz et al. (46) did not find any particular *C. jejuni* serotype predominating in cases of GBS from France and Belgium. Dingle et al. (42) reported that *C. jejuni* genotypes associated with GBS and Miller-Fisher syndrome are of diverse genetic lineages, se-

### Table 3. Link between *C. jejuni* infections and GBS

<table>
<thead>
<tr>
<th>Type of assay for <em>C. jejuni</em></th>
<th>No. of <em>C. jejuni</em> infections and GBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of GBS patients</td>
<td>No. of patients positive for *C. jejuni (%)</td>
</tr>
<tr>
<td>Stool culture, serology, or both</td>
<td>14a 939 269 (28.6)</td>
</tr>
<tr>
<td>Serology</td>
<td>7b 410 114 (27.8)</td>
</tr>
<tr>
<td>Stool culture</td>
<td>7c 199 36 (18.3)</td>
</tr>
</tbody>
</table>

*From Table 1 of Hughes et al. (67).*

*From Table 1 of Allos (4).*

*From Table 2 of Allos (4).*
rotypes, and flagella types. No particular nucleotide sequence was correlated with neuropathy. It is not clear from these limited studies that particular serotypes of \textit{C. jejuni} predominate in the induction of GBS, and more extensive research is needed.

The study of \textit{C. jejuni}-induced GBS is hampered by the lack of an adequate animal model. Lewis rats injected with proteins or peptides derived from bovine peripheral nervous system myelin develop experimental allergic neuritis (EAN), which is T cell mediated. Experimental allergic neuritis is a paralytic disease that demonstrates clinical, histologic, and electrophysiologic features similar to those of human GBS \cite{122, 164}. Unfortunately, experimental allergic neuritis cannot be induced in the Lewis rat by \textit{C. jejuni} \cite{164}. When Li et al. \cite{89} orally infected chickens with a \textit{C. jejuni} strain isolated from a GBS patient, a number of the chickens showed clinical signs similar to those of human GBS. However, further reports on the use of this chicken model for human GBS have not been forthcoming.

The National Hospital Discharge Survey for the United States indicates that for 1979 through 1993, a yearly average of 9,575 individuals (range, 6,618 to 15,417 individuals) developed GBS \cite{27}. Thus, with the United States population of 270,000,000 in 1999, the expected incidence of GBS would be 3.5 cases per 100,000 people. Nachamkin et al. \cite{99} have assumed that 30% of occurrences of GBS are preceded by a \textit{C. jejuni} infection; thus, 2,873 of these 9,575 GBS cases would be induced by \textit{C. jejuni} enteritis. One case of GBS would be expected for every 940 cases of campylobacteriosis, which agrees well with the assertion of Hughes et al. \cite{66} that approximately one case of GBS occurs for each 1,000 cases of symptomatic \textit{C. jejuni} enteritis.

Buzby et al. \cite{27} estimated that the cost of \textit{Campylobacter}-associated GBS in the United States ranges from $247,000,000 to $1,799,000,000 (1995 dollars) per year. These estimates include medical costs and costs due to loss in productivity. Buzby et al. \cite{27} estimated that the medical cost to each patient with \textit{C. jejuni}-induced GBS is approximately $110,000. When medical costs are combined with a loss in productivity, each case of GBS due to a \textit{C. jejuni} infection costs approximately $470,000.

\section*{GBS DURING PREGNANCY}

A number of investigators have reported that the incidence of GBS during pregnancy is similar to that seen in the general population \cite{37, 113, 119}. Therefore, assuming that 6,000,000 pregnancies occurred in the United States in 1999, at least 210 cases of GBS would be expected for pregnant women, assuming a rate of 3.5 cases per 100,000 people. However, by the mid-1990s, a total of only 40 to 50 cases of GBS in pregnant women had been described worldwide in the medical literature \cite{21, 119, 170}. The small number of reports suggests that most cases of GBS during pregnancy are uncomplicated and are not interesting enough to describe.

During pregnancy, mild cases of GBS may be misdiagnosed, since pregnant women may normally complain of muscle weakness, general malaise, paresthesia (numbness or tingling in the tips of the fingers and toes), respiratory discomfort, urinary incontinence, and unsteady gait. These normal physiologic changes experienced by pregnant women mimic the early signs of GBS and further impede a proper diagnosis of the disease \cite{44, 81, 85}. Kuller et al. \cite{81} described a case of GBS diagnosed during late pregnancy (~36 weeks) in an individual who had shown signs of GBS for at least 3 months previously. The GBS symptoms, however, were attributed to “normal changes of pregnancy” by her physician, resulting in a lengthy delay in diagnosis and treatment.

GBS may occur at any time during pregnancy, but there is a peak incidence in the third trimester \cite{21}. There is even a risk of postpartum GBS, especially during the first 30 days after the birth of a child \cite{35, 71}. The likelihood of severe complications with GBS during the first or second trimester is low, but severe respiratory compromise with premature labor may result from GBS contacted during the third trimester \cite{21, 85, 118}. The average duration of illness is 3 to 6 months, and 80% of pregnant women recover completely \cite{21}. Since most babies born to women with GBS are normal, therapeutic abortion is not recommended \cite{21, 44, 103, 118}.

GBS does not influence pregnancy, nor does pregnancy modify the expression of GBS symptoms \cite{21, 44, 118}. GBS during pregnancy does not impair fetal or infant development and does not lead to an increase in spontaneous abortion or fetal death \cite{21, 44, 118}. The risk of premature delivery in the third trimester is increased for severe GBS.

The majority of pregnant patients with GBS during the third trimester who require assisted ventilation have experienced premature labor, and the onset of labor is closely related to respiratory distress \cite{21, 44, 113, 118}.

The death rate for GBS in pregnant patients has been reported to be 10%, which is much higher than the 2% death rate for nonpregnant GBS patients \cite{21, 37, 44, 68}. However, the higher death rate is probably a false finding resulting from the limited literature available on GBS during pregnancy. The inflated death rates indicated in these reports probably reflect more severe and complicated cases.

Neonates and children younger than 2 years of age rarely develop GBS \cite{7}. Recently, however, a case of neonatal GBS occurring 12 days postpartum in a child born to a mother with GBS was reported \cite{91}. The baby exhibited typical GBS symptoms and required mechanical ventilation. Treatment with IVIG was initiated, and the child returned to normal within 2 weeks \cite{91}.

PE has been used successfully in the treatment of GBS during pregnancy \cite{21, 37, 68, 81, 118, 170}. Plasma exchange does not affect pregnancy or fetal development \cite{21, 118}. While complications are rare, Hurley et al. \cite{68} recommend that PE be reserved for pregnant women with rapidly progressing GBS who are most likely to require respiratory assistance. Recent studies have indicated that IVIG also is effective in the treatment of pregnant GBS patients \cite{25, 130}.

The literature indicates that most pregnant women with GBS recover and that in the majority of cases the delivery is normal. However, the physical and psychological con-
Campylobacter-induced GBS during pregnancy. While there is no supporting literature, it is probable that C. jejuni enteritis contributes to GBS during pregnancy. If 60,000 pregnant women in the United States were infected with C. jejuni during 1999, then at least 64 of these women would be expected to develop Campylobacter-induced GBS, assuming an incidence of 1 GBS patient for every 940 campylobacteriosis cases. GBS induced by C. jejuni is reportedly more severe than GBS induced by other agents (67, 116). It is probable that C. jejuni--induced GBS is more severe in pregnant women, but information is lacking.

C. JEJUNI AND REACTIVE ARTHRITIS

Another important long-term consequence of C. jejuni--induced enteritis is ReA. In the older literature, ReA and Reiter's syndrome were regarded as separate disease entities, but at present, ReA and Reiter's syndrome are considered synonymous terms because of overlapping clinical, epidemiological, and genetic features (8, 11, 138).

Reactive arthritis is a syndrome characterized by sterile inflammation of the joints due to an infection originating at a nonarticular site (29). The infections that precipitate ReA may have an origin in either the genitourinary tract or the gastrointestinal tract. Enteric organisms that are known to induce ReA include species of Campylobacter, Salmonella, Shigella, and Yersinia (48, 77, 156). The linkage between ReA and C. jejuni enteritis is documented in Table 4.

Even though enteric bacteria induce ReA, viable bacteria have not been cultured from the joint fluid of infected individuals. Antigens from triggering enteric bacteria, but not bacterial DNA or RNA, have been detected in synovial fluid and synovial membranes (58, 136). The mechanism(s) by which enteric bacterial antigens reach the affected joints is unknown. There is a hereditary disposition for the acquisition of ReA. Individuals carrying the gene for human leukocyte antigen-B27 (HLA-B27) are more likely to acquire ReA if they are infected by a triggering organism.

The HLA system is the human major histocompatibility complex that plays an important role in the immunological defense of the body. It is through the HLA system that self is differentiated from nonself. When the immune system senses the presence of foreign tissue (such as a transplant from another individual) or other foreign bodies (such as microbial pathogens), the HLA system induces an immune response to eliminate the foreign material. Certain autoimmune diseases are associated with particular antigens of the HLA system. While HLA-B27 positivity predisposes an individual to ReA, virtually the same clinical disease is seen in HLA-B27-negative ReA patients (151). However, HLA-B27-positive patients tend to have a prolonged and more severe clinical course (45, 77). It is unclear why HLA-B27-positive individuals are more prone to ReA. While there have been numerous studies concerning the role that HLA-B27 might play in ReA acquisition or in the

### Table 4. Linkage between ReA and C. jejuni enteritis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sex, a age (yr)</th>
<th>HLA-B27 status</th>
<th>Arthritis</th>
<th>Urethritis</th>
<th>Conjunctivitis</th>
<th>Presence of C. jejuni</th>
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<tbody>
<tr>
<td>18</td>
<td>M, 20</td>
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<td>-</td>
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<tr>
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<td>-</td>
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<tr>
<td>16</td>
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<td>-</td>
<td>+</td>
<td>-</td>
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<tr>
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<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>111</td>
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<td>-</td>
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<td>-</td>
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<td>-</td>
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</tr>
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<td>M, 76</td>
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<td>+</td>
<td>-</td>
<td>-</td>
<td>+ (stool)</td>
</tr>
</tbody>
</table>

a M, male; F, female.
b The patient was receiving antibiotics.
c The stool culture was identified as Campylobacter lari.
In a study of post-ReA patients, the joint manifestations of ReA are asymmetric and oligoarticular, affecting an average of four joints. Lower-limb joints are more commonly affected than upper-limb joints. The affected joints are swollen, warm, and tender and are painful when moved. If fingers or toes are affected, the entire digit is swollen (sausage digits). In addition, there is enthesitis, which is an inflammation of the bony sites where tendons, ligaments, or fascia have their insertions (11, 77, 138). Other manifestations that may occur with ReA include mucocutaneous lesions (painless, small superficial ulcers) that develop on the oral mucosa, tongue, lips, palate, or pharynx. In addition, there may be skin lesions on the palms and soles. Cardiac involvement is seen in 1 to 2% of ReA patients (11, 77).

Most ReA patients experience an acute self-limited illness lasting 3 to 12 months. However, symptoms do not subside in 15 to 20% of patients, and these individuals suffer chronic and disabling arthritis and enthesitis for about 10% of ReA patients. Death from ReA is infrequent and generally occurs in patients with cardiac involvement (11).

In a study of post-\textit{Salmonella} ReA in 27 patients, Thompson et al. (153) found that after 5 years, chronic ReA with mild symptoms persisted in a majority of patients. Joint damage was severe enough in four ReA patients (14.8%) to lead to a change in employment status. Glennås et al. (53), in a study involving a group of 27 postenteric ReA patients, found that 20% and 5% of the patients still had signs of arthritis after 1 and 2 years, respectively. Even though arthritis symptoms disappeared in most of the patients, approximately 20% still had joint pain and back pain or stiffness after 2 years (53). Thus, the aftereffects of ReA may be long-lasting in some patients.

Joint inflammation in ReA patients improves with the administration of a nonsteroidal anti-inflammatory agent. There are no experimental data to indicate that antibiotics active against postenteric ReA-triggering microorganisms play a role in relieving symptoms of ReA (171). Antibiotics are generally not recommended. Antibiotics may be indicated, however, if a patient’s diarrheic illness is severe (69, 123).

Keat (75) stated that ReA occurs in 2 to 3% of all patients with \textit{Shigella}, \textit{Salmonella}, and Campylobacter infections, but the proportion is higher for patients with yersiniosis. Data obtained from foodborne outbreaks indicate that the incidence of postenteric ReA is approximately 2%. In a massive outbreak of salmonellosis traced to contaminated pasteurized milk, there were 16,000 culture-confirmed cases; however, the actual number of diarrheic cases was estimated to be at least 10- to 12-fold higher (124). The reported incidence of ReA for that outbreak was 2.3% (10). In a discussion of four \textit{Shigella} outbreaks involving hundreds of cases, Burmester et al. (26) reported that the incidence of \textit{Shigella}-induced ReA ranged from 1.5 to 4%, with a mean of 1.8%. \textit{C. jejuni} is rarely involved in outbreaks, and data such as those obtained for \textit{Salmonella} spp. and \textit{Shigella} spp. are not available; however, Kosunen et al. (79) found that 2.3% (8 of 342) of hospital patients with \textit{C. jejuni} infections developed ReA.

Assuming that 2% of the individuals with \textit{Campylobacter} enteritis develop ReA, 54,000 of the estimated 2,700,000 cases of \textit{C. jejuni}-induced diarrhea in 1999 would be expected to develop into ReA. However, Skirrow and Blaser (141) caution that the frequency of \textit{Campylobacter}-induced ReA that is actually seen depends on the prevalence of the HLA-B27 gene in the infected population, since 60 to 80% of ReA victims are HLA-B27 positive. Since most cases of diarrhea from \textit{C. jejuni} are sporadic (4), the appearance ReA would also be sporadic. Therefore, many cases of \textit{C. jejuni}-induced ReA are probably not recognized as such and are not reported.

**PREGNANCY AND REACTIVE ARTHRITIS**

In 1999, the expected number of cases of \textit{C. jejuni}-induced ReA during pregnancy would be 1,200, assuming a 2% occurrence in the expected 60,000 cases of \textit{C. jejuni}-induced enteritis in pregnant women. There is a lack of information concerning the course of ReA during pregnancy. This lack of information suggests that pregnancy does not predispose a woman to ReA and that women with ReA will have the same rate of fertility, the same course of pregnancy, and the same normal delivery as healthy females. It is likely that ReA for pregnant women is not much different from the disease for nonpregnant women. However, the pregnant patient with unresolved ReA after delivery will experience physical difficulties in caring for her infant.

**PERSPECTIVES**

Since a \textit{C. jejuni} infection during pregnancy can have serious consequences for the mother and/or the fetus, it is imperative that health care workers make pregnant women aware that the organism is commonly present in foods and...
the environment. Pregnant women should be given instruction regarding the precautions that can be taken to prevent infection. Several key points should be highlighted. First, it should be pointed out that the primary line of defense against Campylobacter spp. is proper food hygiene, since the majority of campylobacteriosis cases have foodborne origins (28, 93). Epidemiological studies have indicated that the improper handling of raw poultry and the consumption of undercooked poultry account for 50 to 70% of all Campylobacter infections (5, 152). The presence of C. jejuni in chickens should not be surprising, since Campylobacter is a normal constituent of the indigenous intestinal flora of the chicken and is commonly present in chicken flocks (159). While poultry is the most commonly identified source of Campylobacter infections, other foods that may be contaminated include pork, beef, milk, mutton, and lamb (149). Additionally, C. jejuni present in run-off water from stock-raising farms or raw sewage may contaminate water supplies or irrigation waters, resulting in the contamination of vegetables and fruits. The importance of practicing safe and sound food hygiene in the care, preparation, and serving of foods, especially chicken or other poultry, must be stressed to food handlers so that pregnant women can avert infection. General recommendations for safe handling of foods for pregnant women are given in Smith (145). Second, in addition to foods, other household sources of infection can include pets (particularly kittens, puppies, and some exotic pets), rodents, and insects (149).

Vaccination may eventually prove to be a means of protecting pregnant women and other individuals at increased risk of Campylobacter infection. Unfortunately, at the present time, there are no anti-Campylobacter vaccines available for humans, but studies are under way to develop suitable vaccines (107, 129). An ideal vaccine against C. jejuni should be highly protective and long-lasting; should be safe, with no adverse reactions (e.g., neurologically mimicking epitopes that might invoke GBS should be absent); and should elicit both cellular and humoral immunity. It is important for the vaccine to stimulate production of mucosal antibodies (i.e., secretory immunoglobulin A); specific secretory immunoglobulin A against C. jejuni could possibly prevent the attachment to and colonization of the intestinal tract by the organism. A vaccine that could be administered orally would have an added advantage.

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