TABLE 11–6
Borrelia burgdorferi (Bb) Tick Infection Rates, by Country and Tick Species

COUNTRY	REGION	TICK SPECIES	% OF TICKS POSITIVE FOR *Bb*[a]
U.S.	Northeast and Mid-Atlantic	*I. scapularis*[b, c]	24–61
	Northeast	*I. dentatus*	32
	Mid-Atlantic	*A. americanum*	6–22
	Mid-Atlantic	*I. cookei*	22
	Upper Midwest	*I. scapularis*	38–40
	South and Southeast	*A. americanum*	4
	South	*I. scapularis*	0–3
	West	*I. neotomae*	15
	West	*I. spinipalpis*	50–66
	West and Pacific Northwest	*I. pacificus*	1–14
Austria		*I. ricinus*	4–40
Belgium		*I. ricinus*	10–50
Bulgaria		*I. ricinus*	17
Bulgaria		*D. marginatus*	4
China	North Inner Mongolia, Heilongjiang, Jilin, Liaoning, Hebei, Xinjiang	*I. persulcatus*	20–40
Croatia		*I. ricinus*	45
Czech Republic	South Moravia	*I. ricinus*	15–23
Finland	Coastal islands	*I. ricinus*	40
France		*I. ricinus*	7
Germany		*I. ricinus*	19–44
Germany		*I. hexagonus*	12
Ireland	National parks (greatest in South)	*I. ricinus*	4–27
Japan	North to Central (Hokkaido, Nagano)	*I. persulcatus*	7–22
Japan	North (Hokkaido)	*I. ovatus*	10
Japan	Central to South (Nagano, Fukushima)	*I. ovatus*	26–27
Lithuania		*I. ricinus*	10
Netherlands		*I. ricinus*	2–27
Poland		*I. ricinus*	10–23
Russia		*I. ricinus*	4–27
Russia		*I. persulcatus*[d]	30
Slovenia		*I. ricinus*	>40
Spain	La Rioja	*I. ricinus*	11
Sweden	North	*I. ricinus*	3
Sweden	Northern Baltic Islands	*I. ricinus*	8–19
Sweden	South and Liso Peninsula	*I. ricinus*	23–30
Switzerland		*I. ricinus*	10–50
U.K.		*I. ricinus*	8
Yugoslavia (former)		*I. ricinus*	29
—	Eastern Europe	*I. ricinus*	0–50
—	Eastern Europe	*I. persulcatus*	21–58
—	Subarctic islands	*I. ricinus*	5
—	Subarctic islands	*I. uriae*[e]	2–6

[a] *Bb* positivity determined by microscopy, polymerase chain reaction, immunofluorescence, or other assay. Tick infection rates of adult ticks are generally higher than those of nymphal ticks,[181] with the exception of *I. pacificus*.
[b] *I. scapularis* from Lyme-endemic areas contains a median of 1900 *Bb* per tick.[432]
[c] *I. scapularis* from some Lyme-endemic areas may also contain *Babesia microti* and/or the agent of human granulocytic ehrlichiosis, in addition to *Bb*.[395, 396, 497]
[d] Co-infection of ticks with *Bb* and tick-borne encephalitis virus may occur.[405]
[e] 98% of museum specimens of British *I. uriae* were positive for *Bb*.[340]
Data from references 1, 123, 154–157, 161, 162, 170, 180, 181, 336, 344, 350, 351, 356, 362, 371, 378, 387, 394, 395, 403, 405, 409, 410, 412, 416, 420, 422, 424, 438, 449, 497, 503, 508, 513–515, 517, 522, 528, 535, 540, 549, and 579.

vector and *I. ovatus* another potential vector,[164, 351, 357, 374] although human Lyme disease has not been associated with *B. burgdorferi* strains from *I. ovatus*.[163, 374]

Lyme disease was first recognized in China in 1985, and in 1990, 132 cases of EM were reported from Hailin County in the Heilongjiang Province of northeastern China,[12, 344] adjacent to the Vladivostock focus of Lyme borreliosis in southeastern Russia.[448] Since then, it has become the most common tickborne disease in China, and hundreds of additional cases have been recognized. It has been reported from ten provinces and two autonomous areas, predominantly from the northeastern and northwestern regions, including the Heilonjiang, Jilin, Liaoning, Hebei, Inner Mongolia, Xinjiang, and Mudanjiang provinces[344, 349, 350, 449, 554] and the Beijing area.[388] *I. persulcatus* is the vector in most of these areas, but

Haemaphysalis longicornis has also been identified as a vector in the Beijing area.[388]

In 1998, the first case of Lyme disease, serologically confirmed but not culture-confirmed, was reported from Taiwan; although several strains of *Borrelia* have been isolated from indigenous rodents, and *I. ovatus* and *I. granulatus* occur locally, the vector has not been identified.[451] *B. burgdorferi* has been isolated from *Ixodes* ticks and rodents in Korea; Korea would therefore be considered an endemic area.[555]

In Central and South America, rare cases, not culture-confirmed, have been reported from Mexico,[556] Chile,[557] Brazil,[558] Argentina,[559] Puerto Rico, and Honduras.[560] In Chile, a case of confirmed Lyme neuroborreliosis was not considered autochthonous, and was attributed to imported German hamsters.[454] There are no ixodid ticks in Chile, and a large study of Chilean patients with suspected Lyme disease could not confirm any cases by either culture or Western blot; ELISA seropositivity in 5 patients was attributed to cross-reactivity, possibly with non-Lyme *Borreliae*.[505] Thirty-three clinical Lyme disease cases, most with serologic confirmation (including Western blot confirmation), have been reported from Rio de Janeiro and the nearby Cotia/Itapevi region of Brazil,[452, 506, 558] where several species of ixodid ticks occur; seroprevalence in blood donors was 3% in a low-risk area and 6.7% in the Cotia area; *Borreliae* were isolated by culture from human, tick, and wild animal sources in the Cotia region, but PCR could not confirm identity with either *B. burgdorferi sensu stricto*, *B. garinii*, or *B. afzelii*. Three patients with serologically confirmed suspected Lyme disease were reported from Mato Grosso do Sul, Brazil.[506] In Argentina, one clinical case has been reported,[559] and no culture-confirmed cases have been reported; three farm workers with arthritis were found to be seropositive.[453] It is uncertain whether reports of Lyme disease from Haiti,[560] Jamaica,[560] Peru,[373] and India[561] were due to cross-reacting non-Lyme *Borrelia* species such as those that cause relapsing fever, or to Lyme borreliosis originally acquired in an endemic country outside the country of reporting.

In northern Africa, 21 cases of serologically confirmed Lyme disease, with arthritis, lymphocytic meningitis, facial palsy, or pericarditis, were reported from Tunisia in 1998.[455] In South Africa, rare cases of Lyme disease[456, 562] have been reported, four potential tick vectors occur, and at least one has been found to be competent for *B. burgdorferi*.[456] From the rest of Africa, only sporadic cases have been reported, without culture confirmation, and several serosurveys have been done; it is uncertain whether these represent locally or non–locally acquired Lyme borreliosis, infection with other *Borreliae* producing Lyme-like illness, or cross-reacting infection with other prevalent bacteria. In southeastern Africa, a serosurvey in Zimbabwe found ELISA seropositivity rates of 1.6 to 5% in blood donors and healthy villagers, and 0% in dogs, cattle, and horses, and concluded that Lyme borreliosis was absent there[458]; a case of serologically confirmed probable Lyme disease with EM at a tick bite site from an autochthonous tick bite in Mozambique was reported in 1993,[563] but a serosurvey in Mozambique, reported in 1997, attributed 11% ELISA positivity in febrile patients to serologic cross-reactivity with leptospira, *Borrelia crocidurae*, and syphilis[564]; a serosurvey in Tanzania found very high ELISA seropositivity rates in blood donors, pregnant women, and arthritis and syphilis patients (30 to 55%) and noted that Lyme-like illness and tick bites occur, but that the seropositivity probably represents cross-reactions with leptospira, relapsing fever, and syphilis, which are prevelent.[565] A serosurvey of rural residents in Mali found no seropositivity by ELISA, but a survey of patients with neurologic disease identified six patients who were seropositive by both ELISA and Western blot; no ixodes ticks occur in Mali, and the authors conclude that *B. burgdorferi* does not exist in Mali, but that other cross-reacting *Borreliae*, such as *B. crocidurae*, transmitted by the soft tick *Alectorobius sonraai*, which causes tickborne meningoencephalitis in nearby Senegal, might cause a Lyme-like illness.[457]

From the Middle East, two serologically confirmed (IFA, ELISA, and/or Western blot), but not culture-confirmed, cases have been reported from Israel,[566, 567] but none has occurred in the absence of previous travel to known endemic areas. *B. burgdorferi* IFA and Western blot seropositivity of uncertain etiology have been reported from Fayoum, Egypt, and four ELISA serologically confirmed, but not culture-confirmed, cases have been reported from Alexandria, Egypt[568]; no information about travel to endemic areas was given. *I. ricinus* ticks have been found on migratory birds resting in Egypt during their fall migration from Europe and Asia to Africa.[376]

In southeastern Australia, between 1982 and 1986, nine cases of erythema migrans–like rashes were reported from the Hunter Valley and the New South Wales coast near Sydney; this area was initially considered a possible newly recognized endemic area.[391] In 1994, a case of ACA was reported in an Australian resident who had immigrated from Europe 25 years earlier, but it could not be considered an autochthonous case.[569] In 1998, the first case of an Australian patient with *B. garinii* culture–positive Lyme borreliosis (erythema migrans–like rash) associated with a locally acquired tick bite (from the New South Wales coastal area near Sydney) was reported[303]; however, because this patient had traveled to European endemic areas 17 months earlier, it could not be definitely proven that the case was acquired in Australia. Proof of Lyme endemicity will require additional culture-confirmed, locally acquired cases without previous travel to endemic areas.[391–392]

In the northern hemisphere, the Lyme borreliosis endemic and hyperendemic areas of Europe and Asia cluster in a definite band, which could be called the "Lyme Belt" (see Fig. 11–1); it is located approximately between 30 degrees North latitude and the Arctic Circle at 65 degrees North latitude (65° N). This region includes the majority of cases from Central Europe, Scandinavia, the former USSR, China, Japan, and northern Africa (Tunisia and Alexandria, Egypt). Israel is also located within this belt. In the western part of the northern hemisphere, the "Lyme Belt" extends from approximately 15° N to 50° N and includes the endemic areas of the United States and southern Canada, as well

as the cases from Mexico and the Caribbean. In the southern hemisphere, the cluster of Lyme or Lyme-like cases from southeastern Australia and Rio de Janeiro, Brazil, the cases from South Africa and Mozambique, and the *B. burgdorferi* seropositivity noted near Buenos Aires, Argentina, are all between 10 degrees South latitude (10° S) and approximately 40° S, but insufficient cases have been reported from the southern hemisphere to determine whether there is a similar southern hemisphere "Lyme belt." The presence of the migratory bird *B. burgdorferi* tick vector, *I. uriae*, has been demonstrated in the Falkland Islands at 51° S; the presence of this vector and *B. burgdorferi* has been demonstrated in Crozet Island at 46° S and in Campbell Island, New Zealand, between 45° S and 55° S in the southern hemisphere, placing the southern margin of the range of *B. burgdorferi* at least to the subantarctic region,[165] although no human Lyme disease cases have been reported from these islands.

EXPANSION OF LYME-ENDEMIC AREAS IN EUROPE, ASIA, AND OTHER CONTINENTS

In Europe, the geographic distribution of Lyme borreliosis correlates with the distribution of *I. ricinus*[4, 125] and the distribution of the deer population, and the number of deer has increased dramatically, as in North America.[144] Deer were initially abundant in Central Europe, but in the 1940s during and after World War II, deer were used for food and forests for fuel, resulting in almost complete destruction of the deer population and partial deforestation of the region. In the 1960s, regrowth of forests and return of deer began, and there has since been a deer population explosion, which has coincided with the increase in Lyme borreliosis in Central Europe. *B. burgdorferi* has been found in museum specimens of European ticks from the late nineteenth century.[340]

Several seroepidemiologic studies have reported the rates of *B. burgdorferi* seropositivity in the general population in Europe and Asia (Table 11–7).

The existence of Lyme borreliosis in South America is uncertain, although its presence has been suspected. A 2% seropositivity rate was reported in agricultural workers in Peru, but this may be due to cross-reacting relapsing fever *Borrelia* organisms[373]; seropositive farmers with arthritis have been reported from Argentina,[453] and 7% seropositivity was reported in residents of Cotia, Brazil, which is suspected to be an endemic area.[452]

Lyme disease has been reported from northern Africa, where *I. ricinus* is prevalent, including Tunisia[455] and Egypt,[568] but its presence in the rest of Africa is uncertain, although suspected. An 11% seropositivity rate found in patients with nonspecific febrile illness in Mozambique, Africa, was considered due to cross-reactions with leptospirosis, non-Lyme borrelial relapsing fever, and syphilis.[564] However, one serologically confirmed case of Lyme disease with EM acquired from a Mozambique tick has been reported,[563] and its presence is suspected in South Africa.[456]

TABLE 11–7
Borrelia burgdorferi (Bb) Seropositivity Rates in Europe and Asia, by Country

COUNTRY	% OF PERSONS SEROPOSITIVE	
	General Population	High-Risk Population[a]
Austria	4–8	
Bulgaria		15–35 (forest workers, animal farmers)
China	1–12	26–53 (forest workers and rural northeastern residents)
Croatia	7	
Finland	3–6	12 (military recruits in Southwestern archipelago)
France		18–26 (forest workers)
Germany	5	18–34 (forest workers)
Greece	1	
Hungary	2–5	
Italy	0–13	8–18 (forest workers)
Ireland	5–15	
Japan	1	6–20 (forest workers)
Lithuania	4	14–32 (forest/field workers, veterinarians)
Netherlands	2–17	15 (hunters, military recruits)
Poland	19–24	50–71 (outdoor workers)
Russia	9	
Spain	3–13	31 (forest workers, farmers, cattle raisers)
Sweden	2–9	26–30 (Liso peninsula/Aspo Island residents)
Switzerland	4–6	19–60 (orienteers, sportsmen, forest workers, rural residents)
U.K./England	0–4	14–55 (forest workers, farmers, game keepers)
U.K./Scotland		16–27 (nature conservancy workers, Highlands residents)
Yugoslavia (former)	5	

[a]Persons with high frequencies of occupational, recreational, or residential exposure to tick-infested *Bb*-endemic geographic areas within these countries. Seropositivity rates increased with age and length of exposure in several longitudinal studies.

Data from references 162, 305, 344, 349, 388, 405, 406, 409, 437, 438, 450, 504, 508–510, 512, 514, 516, 517, 521–524, 526, 527, 529, 532, 533, 538, 539, 541–543, 548, 549, 551, 553, 554, 570, 571, and 573.

Lyme Borreliosis in Travelers to Endemic Areas

There are increasing reports of Lyme borreliosis in individuals who have acquired the infection during travel, often international, to Lyme-endemic areas in the recent or remote past.[9, 75, 454, 482, 569, 574–576] This may explain some of the cases that have been reported from areas such as Australia, which lack either the necessary tick vectors or *B. burgdorferi*.[303, 392, 566, 567] In Canada, where the incidence of Lyme disease is relatively low, half of all cases reported to the Laboratory Centre for Disease Control were acquired outside of Canada.[429] Pets that travel from endemic to nonendemic areas could be potential vehicles of transfer of infected ticks to their owners.[454]

Presentation with Lyme borreliosis in a nonendemic region may increase the risk of delayed diagnosis because the clinical presentations, although easily recognized by physicians in the endemic area, may be unrecognized by physicians in the nonendemic area who have little experience with the infection, or with its possibly different clinical manifestations in the area of acquisition.[482]

Travelers from nonendemic areas who engage in outdoor activities such as hiking, mountaineering, orienteering, or camping in endemic areas are at increased risk as they may be unaware of the local risk of tickborne infections, including the higher risk in hyperendemic areas, and may be less likely to use appropriate precautions, to recognize a tick bite, or to recognize early symptoms of infection. Vacationers, even when residing in endemic areas and knowledgeable about Lyme disease, are less likely to engage in tick-avoidance behaviors while on vacation.[577]

Borrelia burgdorferi Tick Infection Rates

In the United States, rates of *B. burgdorferi* infection of *I. scapularis* and *I. pacificus* in North America, and of *I. ricinus* and *I. persulcatus* in Europe and Asia, vary with geographic region, elevation, season, and stage of the tick, and are highest in the hyperendemic areas during early summer.[181, 411] *I. ricinus* infection rates were noted to increase significantly from Western to Eastern Europe.[181]

The distribution of the different genospecies of *B. burgdorferi sensu lato* in *I. ricinus* complex ticks varies with the global geographic location, and is more fully characterized in the northern hemisphere than the southern hemisphere. In Central Europe, the diversity is greatest, with four genospecies—*B. burgdorferi sensu stricto*, *B. garinii*, *B. afzelii*, and *B. valaisiana*—found in ticks.[53, 74] At the far western margin, in North America, only *B. burgdorferi sensu stricto* is indigenous.[53] At the far eastern margin of the range of its geographic distribution, in far eastern Russia and Japan, *B. burgdorferi sensu stricto* is absent but *B. garinii*, *B. afzelii*, and *B. japonica* are found[67, 69, 74, 163, 164]; in Japan, *B. tanukii* and *B. turdae* are also found.[58, 68] At the far northern, subarctic edge of the range in the northern hemisphere, only *B. garinii* has been found.[13, 152, 165] Co-infection of ticks with more than one genospecies has been reported from areas in which several genospecies occur.[74, 84, 160]

Borrelia burgdorferi Reservoir Animal Infection Rates

North American epidemiologic studies indicate that the white-footed mouse, *Peromyscus leucopus*, is reservoir-competent for *B. burgdorferi*[580] and is in fact the most important reservoir for *B. burgdorferi* infection in nature,[167, 182] and that the white-tailed deer *Odocoileus virginianus* is the reproductive host of the *I. scapularis* tick vector and is necessary for the maintenance of the tick, but not the spirochete, in nature.[411]

In the northeastern part of the United States, the enzootic cycle that maintains *B. burgdorferi* infection in nature is the white-footed mouse–*I. scapularis* cycle. The mice are reservoir-competent for *B. burgdorferi*[336, 378, 578, 580] because they have a high rate of infection, remain spirochetemic and highly infectious for all stages of *I. scapularis* ticks throughout the tick feeding season, do not develop immunity to the tick vector and therefore do not reject the tick, and serve as the reservoir of *B. burgdorferi* that infects the next cycle of ticks and results in high tick infection rates.

The white-footed mouse is the most important reservoir for *B. burgdorferi* infection in nature, and it maintains the horizontal transmission of infection from nymphal to larval ticks. Because ticks are already infected with *B. burgdorferi* before deer attachment, the white-tailed deer does not appear to be important for transmission and maintenance of *B. burgdorferi* infection in nature, although they are important for maintenance and geographic dissemination of the tick.[167]

B. burgdorferi has been isolated from the blood of asymptomatic, wild, white-footed mice and white-tailed deer from the Lyme-endemic coastal islands of northeastern United States.[413, 578] The geographic distribution of infected mice has been noted to correlate with the areas of Lyme endemicity.[384] Mice were found to be chronically spirochetemic in nature during the spring, summer, and fall,[578] and were spirochetemic and infectious for ticks for more than 200 days after experimental infection with *B. burgdorferi*.[580] Deer were heavily infested by adult but not immature *I. scapularis* during the winter, suggesting that deer were important wintertime hosts for adult *I. scapularis*.[578] Although the deer were spirochetemic during summer, fall, and winter, and may be reservoirs for *B. burgdorferi*,[578] they are not major reservoirs for maintenance of *B. burgdorferi* in nature because they host mainly adult ticks that have a very low rate of transovarial transmission of the spirochete.[154, 167, 354]

In northwestern United States, the *I. pacificus* tick transmits Lyme borreliosis to humans, but the enzootic transmission cycle is different from that in northeastern United States.[378, 420] Because the preferred host of immature *Ixodes pacificus* is the fence lizard, which is not a competent reservoir for *B. burgdorferi*, the infection rate of *I. pacificus* is low (1 to 2%) and the *I. pacificus*–*Peromyscus* mouse cycle is unable to maintain transmission of the *B. burgdorferi* infection in nature; this is

accomplished instead by *Ixodes neotomae*, a non-*ricinus* complex tick that has a 15% infection rate, and the dusky-footed woodrat, *Neotoma fuscipes*. *I. neotomae* and *I. pacificus* are both competent vectors for *B. burgdorferi*, but *I. neotomae* rarely bites humans and is needed only for maintenance of *B. burgdorferi* infection in the woodrat reservoir, which remains spirochetemic and is able to infect feeding ticks. *I. pacificus* nymphs and adult ticks are commonly associated with human tick bites, and they are needed to transfer infection from the woodrat to humans. These two ticks and the woodrat have the same geographic distribution, which extends from Oregon to Southern California and into the Sierra Nevada foothills, from sea level to 2100 meters elevation, where Lyme disease is endemic. The infection rate in woodrats in California was 44% and in *I. neotomae* was 15%.[378]

In some geographic areas of North America, other mammalian reservoir-tick cycles in addition to or instead of the mouse–*I. scapularis* cycle may contribute to maintenance of *B. burgdorferi* infection in nature, such as the cottontail rabbit–*I. dentatus* cycle in Nantucket[170] and New York,[100] the Norway rat–*I. scapularis* cycle on Monhegan Island, Maine (where no mice occur),[415] the *Peromyscus maniculatus*–*I. scapularis* cycle on Isle au Haut, Maine (where no *P. leucopus* occur),[414] the chipmunk–*I. scapularis* cycle in Wisconsin and Illinois,[416, 417] the squirrel–*I. scapularis* cycle in Connecticut and Wisconsin,[416] the woodrat–*I. neotomae* cycle in California,[378] the Mexican woodrat–*I. spinipalpis* cycle in Colorado,[362] the meadow vole–*I. scapularis* cycle in the Northeast,[168] and the cotton mouse–*Peromyscus gossypinus* cycle on Sapelo Island, Georgia.[361] The *B. burgdorferi* infection rate in some of these reservoir hosts may be as high as 90 to 100%, depending on the host species and geographic location. Seroepidemiologic studies found the rates of *B. burgdorferi* seropositivity in wild and domestic host animals in various geographic areas of the United States to be 10 to 100% in the northeastern states,[154, 169, 578] 5 to 60% in Wisconsin,[169, 416] 11% in North Carolina,[169] and 14 to 99% in Texas.[169, 382]

In Europe, in addition to the woodmouse–and yellow-necked mouse–*I. ricinus* cycle, which is considered to maintain *B. burgdorferi* infection in nature, other cycles such as the edible dormouse *Glis glis*–*I. ricinus* cycle in Germany,[581] the hedgehog–*I. hexagonus* cycle in Germany,[336] and the mouse–*I. trianguliceps* cycle in Central Europe[168] may be important. In a highly Lyme-endemic area of Germany, the edible dormouse is the preferred host of *I. ricinus*, even though the woodmouse and yellow-necked mouse are abundant, and it is considered more important in amplification of the human Lyme disease risk because these mice have a peridomestic rather than sylvan habitat.[581]

In Japan, the *I. persulcatus*–rodent (woodmouse and vole) and *I. persulcatus*–migratory bird enzootic cycles are responsible for maintenance of the *B. burgdorferi* infection in nature; *B. burgdorferi* has been isolated from woodmice[163] and voles,[68, 163] and from larval ticks that fed on migratory birds of the genera *Emberiza* and *Turdus*.[163]

B. burgdorferi infection has been demonstrated in 24 different species of mammals and birds.[167] It has even been found in migratory European seabirds, which may play a role both in transhemispheric transfer of infection and in maintenance of *B. garinii* in enzootic cycles of remote high-latitude northern and southern hemisphere islands and peninsulas.[165]

Serosurveys for the presence of *B. burgdorferi* antibody in sentinel animals such as white-tailed deer,[154, 578, 582] which usually have a travel range of less than 10 kilometers, and cattle[583] are useful in the definition of geographic areas of *I. scapularis* occurrence and *B. burgdorferi* endemicity.

PATHOLOGY AND PATHOGENESIS

Immunopathogenesis

Tissue damage or dysfunction is the result of either direct tissue invasion by *B. burgdorferi* or the immunopathologic immune response to the infection.[148, 149, 151, 204–207] Infection elicits a sequence of immunologic, B and T lymphocyte, and other cellular responses in activated antigen-presenting cells, and in various host tissues and organs, as is discussed in the section on Interactions with the Immune System, earlier in this chapter. These responses are the reaction to either live *B. burgdorferi*, degenerated dead organisms, degraded antigens, or even membrane-bound blebs (containing *B. burgdorferi* antigens on their surfaces and DNA fragments inside),[102, 103, 215] and they result in characteristic histopathologic findings.

Adhesion of *B. burgdorferi* to different host tissues and cells may be involved in tropism for various tissues and organs, and in the pathogenesis of the manifestations of Lyme disease in various organs.[150, 204, 297, 298, 585–587] Several different strains of all three genospecies, *B. burgdorferi sensu stricto*, *B. garinii*, and *B. afzelii*, bind to at least one of three mammalian cell integrins, $\alpha_{IIb}\beta_3$ (the fibrinogen receptor located on platelets), $\alpha_V\beta_3$ (the vitronectin receptor located on platelets, osteoclasts, smooth muscle, endothelial cells, and some lymphocytes), and $\alpha_5\beta_1$ (the fibronectin receptor located on epithelial cells, endothelial cells, fibroblasts, lymphocytes, and platelets); each strain has a distinct integrin recognition pattern.[585]

B. burgdorferi, Osp A, and even *B. burgdorferi* membrane blebs induce T lymphocyte proliferation in immune individuals,[208, 209, 211–213] and some groups have reported a nonspecific T lymphocyte proliferative effect even in nonimmune individuals.[217] T lymphocyte populations in peripheral blood, synovial fluid, and CSF of patients with Lyme borreliosis are mainly of the type 1 helper (Th1) subset.[205, 214, 393] The responding T lymphocytes form inflammatory infiltrations in the synovium,[323, 370, 372, 393] central nervous system,[295, 592] and other tissues.

B. burgdorferi, Osp A, and membrane blebs also induce polyclonal B lymphocyte stimulation in immune and even in nonimmune individuals.[215, 216] The responding B lymphocytes differentiate into plasma cells and produce perivascular lymphoplasmacytic infiltrations and hypercellular vascular occlusive damage, resembling syphilitic endarteritis obliterans, in many involved tissues but primarily in the skin and soft tissues, heart, synovium, reticuloendothelial system, and peripheral nervous sys-

tem. *B. burgdorferi* also induces macrophage production of cytokines (IL-6 and TNF-α)[216] and nitric oxide,[216, 296] as well as peripheral blood mononuclear cell production of IL-10.[217] The histopathology of Lyme borreliosis includes inflammatory infiltrates consisting of neutrophils, lymphocytes, plasma cells, and macrophages.

Changes in the expression of *B. burgdorferi* outer surface proteins (such as the downregulation of Osp A and B expression and the upregulation of Osp C, E, and F) and in Erp protein expression that occur either during tick feeding, with transmission of the spirochete to the bite site, or after entry of the spirochete into the mammalian host are important in the pathogenesis of the infection.[119, 121, 127, 128, 138–142] *B. burgdorferi* does not produce proteolytic enzymes, but its outer surface protein A is able to bind host blood meal–derived plasmin, plasminogen, and urokinase-type plasminogen activator, creating a host-derived bioactive surface protease, which is involved in dissemination of *B. burgdorferi* from the tick midgut to the tick salivary glands for transmission, and which is necessary for spirochetemia in mice after tick-transmitted infection.[146] It also presumably digests extracellular matrix and facilitates spirochetal spread in the skin after inoculation by the tick. Because of these bound host-derived enzymes, the spirochete is invisible to, and able to evade, the host immune response, in a mechanism referred to as "stealth pathogenesis."[144–146] This may explain the paradox of the ability of *B. burgdorferi* to persist in skin or other tissues for long periods of time with only minimal mononuclear cell infiltration, despite eliciting a strong immune response that, in vitro, is capable of killing it.

B. burgdorferi is introduced into the deep dermis via the bite of an infected tick, which produces a "tick papule" at the bite site. The spirochete induces expression of adhesion molecules by endothelial cells, which facilitate the spirochete's ability to cross endothelial cell layers and extravasate into tissues; this also leads to recruitment of inflammatory cells to areas of spirochetal infection.[145] Within several days to a few weeks, the organism migrates centrifugally in the skin, produces a local skin lesion (EM), and also enters the skin vasculature and disseminates hematogenously[280, 591] throughout the body to the skin, where it may produce secondary EM lesions, and to the organs and reticuloendothelial system, where it may produce a generalized flulike illness with fever, headache, myalgias, arthralgias, conjunctivitis, pharyngitis, adenopathy, tender hepatosplenomegaly, pneumonitis, and orchitis.[145, 393, 592] Some of the nonspecific symptoms occuring during infection, such as myalgia, arthralgia, fatigue, malaise, and fever, may be due to spirochetal triggering of host cell cytokine release.[151] Four to nine weeks after the initial hematogenous dissemination, spirochetal invasion of heart, central nervous system (CNS), and presumably peripheral nervous system may occur, producing myocarditis, meningoencephalitis, cranial nerve paresis, stupor, and personality changes.[588, 592] Months to years after infection, late manifestations of *B. burgdorferi* infection may develop as a result of the initial dissemination of *B. burgdorferi* to various organs, especially the skin, eye, joints, and nervous system.[592]

The manifestations of acute Lyme borreliosis are related to direct spirochetal invasion of the involved tissues and the resulting local immunohistopathologic response, and they are generally responsive to antibiotic therapy. The manifestations of late disease, if not previously treated with adequate antibiotic therapy, may be related to a combination of persistence of infection and the host immunohistopathologic response; these may respond to antibiotic therapy if the presence of active ongoing infection is the essential trigger of the pathologic response. The manifestations of late chronic disease, if resistant to repeated courses of antibiotic therapy considered adequate by current standards, are considered related to previous damage or to ongoing autoimmune immunopathologic responses induced by the initial infection.

Immunopathologic mechanisms, based on autoimmunity and molecular mimicry, may be involved in the pathogenesis of Lyme peripheral neuropathy and chronic Lyme arthritis, even after elimination of active *B. burgdorferi* infection.[126, 151, 204, 256, 323, 587, 589] An epitope of flagellin that cross reacts with an epitope at the N-terminal end of human axonal HSP 60 may be involved in the immunopathogenesis of peripheral nerve damage.[113, 151, 265] An arthritogenic epitope of Osp A, which cross reacts and shares homology with an epitope of human leukocyte function–associated antigen-1 (LFA-1), is a candidate autoantigen for chronic treatment-resistant Lyme arthritis in patients with HLA-DR4 specificity.[126, 323, 593] The phenomenon of epitope spreading, in which T cells initially recognize a single immunodominant epitope, and then progressively recognize an increasing number of nearby epitopes, could play a role in the immunopathogenesis of Lyme arthritis, if an arthritogenic epitope is eventually recognized, which results in overcoming of self-tolerance.[323]

Small numbers of *B. burgdorferi* may be visualized in some infected tissue samples, particularly skin biopsy specimens. Organisms are most easily found in early infection, but persistence of live *B. burgdorferi* for several years after onset of infection has also been demonstrated.[19, 200, 284, 304, 306, 594] *B. burgdorferi* PCR has also demonstrated *B. burgdorferi* DNA in tissue samples and body fluids but does not confirm the presence of viable spirochetes, as PCR will detect even *B. burgdorferi* DNA fragments in cystic blebs arising from spirochetal outpouchings.[102, 103, 186]

The histopathology of the various manifestations of Lyme borreliosis has been extensively studied, but only sparse data are available on the histopathology of congenital Lyme borreliosis. This section includes a description of the pathology of Lyme borreliosis by organ system, followed by a discussion on the pathology of the placenta and the congenitally infected fetus or infant.

Lyme Borreliosis in Pregnant and Nonpregnant Women

CUTANEOUS

A "tick papule" develops at the tick bite site, which consists of an ulcerated papule of partially denuded hyperplastic epithelium above a lymphocytic, plasmacytic,

macrophage, and mast cell inflammatory infiltrate.[590] During an ixodid (hard) tick bite, the tick's salivary glands secrete a latex-like material that hardens to a tough tissue-like material and cements the mouthparts to the skin; the mouthparts have rows of "teeth" called *denticles*, which become embedded in the skin and the cement.[880] *B. burgdorferi* spirochetes have been detected in skin surrounding the bite site.

Erythema migrans (EM)[82, 148, 338, 592, 596, 597] occurs during early infection as either single (localized) or multiple (disseminated) skin lesions. The skin lesion contains upper and deep dermal perivascular and interstitial mononuclear cell infiltration. Spirochetes are found most often in the peripheral advancing edge of the EM lesion in areas with plasma cell infiltration, around and in small vessels, in collagen fibers, in the upper dermis, or at the dermal-epidermal junction.

Borrelial lymphocytoma (BL),[82, 592, 597] also known as lymphadenosis benigna cutis or B cell pseudolymphoma, occurs during early infection as either single (solitaria) or multiple (dispersa) skin lesions, usually on the earlobe or areola, and more often in Europe than the United States. The histopathology consists of hyperplastic and crowded, well-defined lymphoid follicles composed of dense, diffuse polyclonal lymphocytic (polyclonal B cells, helper T cells, or suppressor T cells), plasmacytic, macrophage, and occasionally eosinophilic infiltration in the dermis or subcutaneous tissue (sometimes with formation of germinal centers) that is similar in appearance to tonsillar tissue. Spirochetes are found in the subepidermal zone, in and around small blood vessels, and in collagen fibers in areas of inflammatory infiltration.

Acrodermatitis chronica atrophicans (ACA)[148, 592, 600–602] occurs during late chronic infection as either unilateral or symmetrical bilateral distal extremity skin lesions, more often in Europe than in the United States. The histopathology in the infiltrative phase shows epidermal loss of rete ridges, a subepidermal bandlike infiltrate, a dense patchy or interstitial mononuclear infiltration of the dermis and subcutaneous fat around and between blood vessels and skin appendages, a small fibrotic zone between the epidermis and the infiltrate, panniculitis, prominent dilated dermal blood vessels, endothelial proliferation, telangiectasia, and disappearance of elastin fibers; this progresses to eventual epidermal atrophy. Spirochetes can be found easily in these nodules and sparsely in ACA skin lesions.

RETICULOENDOTHELIAL

Splenitis,[590, 592, 604] hepatitis,[590, 605] and lymphadenitis[590, 592, 606] may occur during early infection.

Lymphadenopathy occurs in early infection, and lymph node histopathology ranges from perifollicular mononuclear cell (lymphocytic, plasmacytic, macrophage, and occasionally eosinophilic) infiltration and follicular hypertrophy, to focal necrotizing microabscesses with thrombosed capillaries; rare spirochetes may be seen.

Splenomegaly occurs in early infection, and splenic histopathology ranges from perifollicular lymphoplasmacytic infiltration with prominent germinal centers, to necrotizing splenitis with patchy subcapsular inflammation and suppuration, inflammation and acute central necrosis of splenic follicles, occasional destruction of blood vessels, and the presence of many spirochetes.

Hepatomegaly and hepatitis may occur in early infection and may be either transient or severe. Histopathology ranges from mild granulomatous hepatitis or lymphocytic portal triaditis to severe hepatocellular damage with ballooned hepatocytes, fat microvesicles, mononuclear (including plasmacytic) and granulocytic sinusoidal infiltration, Kupffer cell hyperplasia, marked hepatocyte mitotic activity, and sparse spirochetes in the hepatic sinusoids and parenchyma.

CARDIAC

Cardiac involvement[590, 592, 607] in early disseminated infection consists of tachycardia, varying degrees of heart block, or myocarditis. Histopathologic examination of endomyocardial biopsy (or autopsy) specimens shows perivascular and interstitial mononuclear cell (lymphocytic, plasmacytic, and macrophage) bandlike endocardial infiltration, myocardial infiltration, and occasionally pericardial infiltration, as well as vascular changes suggestive of early obliterative vasculopathy. Spirochetes may be seen in endocardium and myocardium near interstitial infiltrations and in intramyocardial vessels.[308]

NEUROLOGIC

The meningoencephalitis and meningoradiculoneuritis of early infection, which include meningitis, encephalopathy, psychoneurosis, cranial neuritis, radiculoneuritis, and the triad of cranial neuritis–meningitis–radiculoneuritis (Bannwarth's syndrome), have a common basic histopathology consisting of lymphoplasmacytic infiltration around epineural blood vessels,[82, 311, 590, 592, 609–611] which suggests vasculitis as a major pathophysiologic mechanism in neuroborreliosis. Rare spirochetes may be seen in brain tissue. Demonstration of spirochetes in CSF is very unusual.

The peripheral neuropathy of late chronic borreliosis[590, 592, 612] is more common in Europe than in the United States and is often associated with ACA. The histopathology of chronic peripheral neuropathy is similar to that of acute meningoradiculoneuritis but is more severe. Spirochetes have not been demonstrated in these biopsy specimens.

Acute focal encephalitis[267, 311, 610] with focal contrast-enhancing central nervous system lesions may develop during either early disseminated or late chronic infection. The histopathology of brain biopsy or autopsy specimens shows sharply demarcated areas of lymphocytic (and occasionally eosinophilic) perivascular cuffing, increased cellularity as a result of foamy macrophages and astrocytes, spongiform change with reactive astrocytes, and areas of necrosis and subcortical and periventricular loss of myelinated fibers, similar to an acute demyelinating process; only rare spirochetes are seen.

The pathogenesis of neuroborreliosis probably in-

volves a small number of spirochetes, adhering to oligodendroglia in neural tissue, which elicit an intense local inflammatory immune response that produces the actual tissue damage; molecular mimicry may also be involved, as *B. burgdorferi* and axonal proteins have cross-reactive epitopes.[113, 151, 265]

Vasculitis is one of the major mechanisms involved in the pathogenesis of central nervous system neuroborreliosis.[311]

MUSCULOSKELETAL

Myositis,[592, 614–616] especially of proximal muscles, may occur in early disseminated infection, and localized myositis may occur adjacent to areas of cutaneous, articular, or neuropathic involvement.

Arthritis[82, 177, 205, 590, 618, 620] may be a manifestation of either early or late chronic infection. Histopathology consists of hypertrophy and hyperplasia of synovial lining cells; deposition of fibrin and neutrophils on synovial surfaces and villous stroma; synovial villous hypertrophy; diffuse or perivascular subsynovial mononuclear cell infiltration; subsynovial vascular proliferation; endarteritis obliterans; and even synovial pannus formation and cartilage erosion. Rare spirochetes are found in areas of heavy perivascular and subsynovial inflammatory infiltration but not in synovial fluid. The small number of spirochetes present is similar to tertiary syphilis or tuberculoid leprosy, in which a small number of organisms elicit an intense immunologic response.

The synovial histopathology of Lyme arthritis and other chronic inflammatory arthritides, including rheumatoid arthritis, is similar, but endarteritis obliterans is seen only in Lyme arthritis and syphilis, and not in other non-Lyme arthritis synovial biopsy specimens. There has also been evidence of active vascular injury consistent with repeated microvascular injuries, probably occurring with each episode of arthritis.[620]

The histopathology of the chronic arthritis associated with ACA[600] shows degenerative arthritis, joint capsule atrophy, bony atrophy, and cortical thickening.

Lyme Borreliosis in the Fetus and Newborn Infant

Although there have been a relatively small number (only 66) of reported cases that could be considered congenital Lyme borreliosis,[25, 27, 29–38, 41–48, 621] there are several reports of the pathologic findings. There are 13 descriptions of pathologic or culture findings in gestational Lyme disease placentas or decidua,[33–36, 41, 690, 622, 623] 19 descriptions of fetal or neonatal pathologic findings in congenital Lyme borreliosis, 2 descriptions of skin biopsies in congenital Lyme borreliosis, and 2 descriptions of brain pathologic and culture findings in sudden infant death syndrome of suspected Lyme borrelial etiology. Spirochetes have been found by culture, silver stain, or *B. burgdorferi*–specific IFA in autopsied organs (liver, spleen, bone marrow, heart, brain, kidney) of congenitally infected fetuses and neonates by Schlesinger and associates,[25] MacDonald and colleagues,[33–35] Lavoie and co-workers,[32] and Weber and associates,[38, 39] as well as in the skin biopsy of a congenitally infected infant by Trevisan and colleagues.[43]

It is striking that many of the late stillbirths and perinatal deaths occurred in infants with cardiac abnormalities and generalized spirochetosis involving the kidneys, reticuloendothelial system, and central nervous system, after first-trimester gestational Lyme disease, and that most of the miscarriages studied pathologically occurred late, between 15 and 25 weeks. The lack of inflammatory findings even when spirochetes were present has been remarkable, and could be related to the immunopathogenetic features of *B. burgdorferi* infection, in which the spirochete is able to spread and persist in tissues without eliciting a prominent host immune response (discussion of this is in the sections Pathology and Pathogenesis: Immunopathogenesis, and The Organism: Interactions with the Immune System: Evasion of Host Defenses and Persistence in Tissue).

Although relatively few cases of congenital Lyme borreliosis have been studied pathologically, comparisons with congenital syphilis may be appropriate, particularly as congenital syphilis causes late abortion, stillbirth, and early perinatal death, and the histopathology shows perivascular and interstitial inflammation, including endarteritis obliterans, of the reticuloendothelial system, nervous system, skeletal system, and placenta.

The histopathologic findings of patients with congenital Lyme borreliosis listed in Table 11–8 in the section Clinical Manifestations are described by organ system in Table 11–9.

CUTANEOUS

There are no reports on the histopathology of the skin of fatal cases of early congenital Lyme disease, but skin biopsy of a patient with infantile multisystem inflammatory disease who was considered to have congenital Lyme disease showed vasculitis with stromal edema and marked eosinophilia (patient 40, see Table 11–8).[31] Biopsy of a skin lesion of a 9-year-old child with congenital Lyme borreliosis (patient 51, see Table 11–8), with a history of recurrent multiple EM lesions since 3 weeks of age, showed a normal epidermis; superficial and deep perivascular, periadnexal, and interstitial lymphocytic infiltrates with sparse plasma cells and some neutrophils; and numerous *Borreliae* by Warthin-Starry silver stain visible in the epidermis and dermis; *B. burgdorferi* PCR of the biopsy material was positive.[43]

RETICULOENDOTHELIAL

Spirochetes have been found in liver, spleen, or bone marrow of six fetuses or infants with congenital Lyme borreliosis in the absence of inflammation, necrosis, or granuloma formation. Spirochetes were seen by silver stain, *B. burgdorferi*–specific IFA stain, or culture in the livers of two term infants (patients 2 and 22, see Table 11–8) and in the spleen and bone marrow of one 35-week, slightly premature infant (patient 1, see Table 11–8) with severe fatal early congenital Lyme borreliosis after first-trimester gestational Lyme disease.[25, 33–35, 38, 39] The spirochetes were seen in the lumen of a large

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TABLE 11–8
Congenital Lyme Borreliosis: 66 Adverse Outcomes of Pregnancies Complicated by Lyme Borreliosis (LB)

	MATERNAL GESTATIONAL				FETAL/NEONATAL				
PATIENT NO.	Trimester of LB	Clinical History[b]	Antibiotic Therapy No. Days[c]	LB Serology[d]	Gestational Age (wk)	Weight (g)	Antibiotic Therapy No. Days[c]	LB Serology[d]	Tissue *Borrelia*[f]
1	1	EM,Fl,Ar	–	+	35	3000	–		+H,S,K,BM
2	1	EM,Ar	–	+	40	2500			+L,H,K,AB
3	≤2	Tx	–	–	19	514			+L,P
4	≤2	Tx,Ar	–	–	23	490			+L,K
5	≤2	O	–	–	15	85			+L,P
6	≤1	VB	NA[a]	NA	39	2250	NA		+F
7	NA	O	NA	NA	40	1950	NA		+F
8	≤2	VB	NA	–	17	30			+B
9	≤2	VB	NA	–	16	150			+B
10	≤1	O	NA	NA	12	294			+K
11	≤2	Ar	–	–	25	NA			+F
12	NA	O	–	NA	~40	3746	+ IV		+P
13	NA	Tx	–	NA	37	2157	+ IVPN, IVMT		+P
14	1	EM,Ar	+ PO PN 10 d	+	20	NA			–
15	1	BP,Ar	–	NA	36	2100	NA		
16	2	EM,Ar	+ PO ER 10 d PO PN 10 d	NA	NA	NA	NA		
17	2	EM	+ PO PN 10 d	NA	40	NA	NA	–	
18	3	EM,Me	–	NA	40	NA	+ IVPN 10 d		
19	1	LB	+	+	13	NA			–
20	1	LB	+	+	NA	NA	NA		
21	≤1	Ar	–	–	~40	NA	NA		+B,H
22	1	EM	+ PO PN 7 d	+	40	3400	NA		+L,B
23	1	EM,Fl	+ IV CTX 2 d, PO PN 12 d	+(+LPA[e])	40	3461	+ IVCTX 14 d	–(+LPA)[g]	
24	2	Fl	+ PO AM 10 d	–(–LPA[e])	34	1050	+ IVAM 6 d, IVCTX 7 d	+(+LPA)[g]	
25	1	EM,Pn,Ar	+ PO ER 10 d, IV CFX 5 d, PO CFC/CEP/ CFM 39 d	+(+LPA[e])	37	3490	+ IVAM 5 d, IVCFT/CTX 3 d	–(+LPA)[g]	
26	2	EM,Ar	+ PO ER 10 d, PO CFM 49 d	–(+LPA[e])	40	3461	+ IVCTX 28 d	–(+LPA)[g]	
27	1	EM,Ar	–	+	NA	NA	NA	–	
28	NA	NA	NA	+	NA	NA	NA	–	
29	NA	NA	NA	+	NA	NA	NA	–	
30	NA	NA	NA	+	NA	NA	NA	–	
31	NA	NA	NA	+	NA	NA	NA	–	
32	NA	NA	NA	+	NA	NA	NA	–	
33	NA	NA	NA	+	NA	NA	NA	–	

[a]NA, information not available.

[b]O = unremarkable; EM = erythema migrans; FI = flulike illness; Ar = arthralgia/arthritis; BP = Bell's palsy; Me = meningoencephalitis; Cr = cranial neuritis; Ra = radiculitis; HA = headache; LB = Lyme borreliosis, unspecified; Pn = pneumonia; Tx = toxemia; VB = vaginal bleed.

[c]PO = oral; IV = intravenous; PN = penicillin; ER = erythromycin; CTX = cefuriaxone; CFX = cefuroxime; CFC = cefaclor; CEP = cephalexin; CFM = cefixime; CFT = cefotaxime; CDX = cefadroxil; MT = metronidazole; AM = ampicillin; NA = not available (use of antibiotic therapy could not be definitively established for the individual patient, although in some reports, some patients in the group may have been treated).

[d]*Borrelia burgdorferi* antibody detected either by IFA (immunofluorescence assay), ELISA (enzyme-linked immunosorbent assay), or WB (Western immunoblot).

[e]LPA = in vitro lymphocyte proliferative assay for *B. burgdorferi*.

[f]*Borrelia* detected in tissue samples by IFA, silver stain, culture, or PCR (polymerase chain reaction); H = heart; S = spleen; K = kidney; BM = bone marrow; L = liver; A = adrenal; B = brain; Sk = skin; P = placenta; F = fetal tissue unspecified; D = decidua.

[g]CoA = coarctation aorta; EFE = endocardial fibroelastosis; AS = aortic stenosis; LSVC = left superior vena cava; PDA = patent ductus arteriosus; VSD = ventricular septal defect; ASD = atrial septal defect; RD = respiratory distress; IUGR = intrauterine growth retardation; GR = growth retardation; DD = developmental delay; GER = gastroesophageal reflux; TEF = tracheoesophageal fistula; BIH = bilateral inguinal hernia.

[h]21 of 23 (91.3%) of patients with LB in this subgroup received antibiotic therapy, but individual outcomes of the two untreated pregnancies were not specifically identified.

CLINICAL OUTCOME[a]	REFERENCE
CoA, EFE, AS, LSVC, PDA, cardiac dysfunction, RD, death 39 hours	25, 33
IUGR, VSD, stillbirth	33–35
ASD, stillbirth	33, 34
CoA, stillbirth	33, 34
Miscarriage	33, 34
VSD, hydrocephalus, omphalocele, clubfoot, meningomyelocele, RD, death 4 hours	33
IUGR, absent hemidiaphragm, RD, cardiac dysfunction, VSD, death 30 min	33
Hydrocephalus, miscarriage	33
Miscarriage	33
Miscarriage	33
VSD, miscarriage	33
R/O sepsis, RD	33
R/O sepsis, RD, hypoglycemia, fever	33
Miscarriage	36
Prematurity, hyperbilirubinemia	36
Syndactyly	36
DD, cortical blindness	28, 36
Rash, hyperbilirubinemia	36
Miscarriage	29
Syndactyly	29
Cardiac dysfunction, aortic thrombosis, lethargy, hypertension, acidosis, death 8 days	32
RD, death 23 hours	38, 39
Rash, adenopathy	621
IUGR, cardiomyopathy, PDA, R/O sepsis, RD, rash, adenopathy, hepatomegaly, hyperbilirubinemia, meconium ileus, metaphyseal bands, joint contractures, R/O encephalitis	621
R/O sepsis, rash, hepatomegaly, hyperbilirubinemia, metaphyseal bands, pectus excavatum, R/O encephalitis, hypotonia, hemiparesis, eso/exotropia, dysphagia, GER, BIH, facial/ear dysmorphia, unilateral simian crease, GR, DD, dental anomalies	621
Hyperbilirubinemia, retinal lesions, R/O meningoencephalitis	621
VSD	37
Hyperbilirubinemia	37
Hyperbilirubinemia	37
Hypotonia	37
IUGR	37
Macrocephaly	37
Supraventricular extrasystoles	37

Table continued on following page