

CLINICAL REPORT

Clinical Spectrum of Skin Manifestations of Lyme Borreliosis in 204 Children in Austria

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The spectrum of skin manifestations of Lyme borreliosis in children is not well characterized. We conducted a retrospective study to analyze the clinical characteristics, seroreactivity to *Borrelia burgdorferi* sensu lato, and outcome after treatment in 204 children with skin manifestations of Lyme borreliosis seen in 1996–2011. Solitary erythema migrans was the most common manifestation (44.6%), followed by erythema migrans with multiple lesions (27%), borrelial lymphocytoma (21.6%), and acrodermatitis chronica atrophicans (0.9%). A collision lesion of a primary borrelial lymphocytoma and a surrounding secondary erythema migrans was diagnosed in 5.9% of children. Rate of seroreactivity to *B. burgdorferi* sensu lato was lower in solitary erythema migrans compared to other diagnosis groups. Amoxicillin or phenoxymethylpenicillin led to complete resolution of erythema migrans within a median of 6 (solitary) and 14 days (multiple lesions), respectively, and of borrelia lymphocytoma within a median of 56 days. In conclusion, erythema migrans with multiple lesions and borrelial lymphocytoma appear to be more frequent in children than in adults, whereas acrodermatitis chronica atrophicans is a rarity in childhood. The outcome after antibiotic therapy was excellent in children, and appears to be better than in adults. Key words: pediatric Lyme borreliosis; erythema migrans; borrelial lymphocytoma; acrodermatitis chronica atrophicans.

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Lyme borreliosis (LB) is caused by an infection with spirochetes of the *Borrelia burgdorferi* sensu lato (s.l.) complex, which are transmitted to humans by *Ixodes* ticks (1). It is the most common tick-transmitted disease in the northern hemisphere and LB occurs in focal clusters with incidence rates of up to 350 cases per 100,000 per year (1, 2). A first incidence peak of this disease in the age of 5–14 years (3–5), and a seroprevalence rate of 3.2–4.8% among healthy children in LB endemic areas (6, 7) show that borrelial infections occur in children. Several organs

may be affected during the course of LB including the skin, nervous system, musculoskeletal system, and the heart (1). In Europe, several human pathogenic *B. burgdorferi* s.l. genospecies have been isolated from *I. ricinus* ticks and different clinical specimens from LB patients. For example, *B. afzelii* is the most common genospecies isolated from human skin samples, and is therefore associated with skin manifestations of LB, whereas *B. garinii* predominates in cerebrospinal fluid specimens from neuroborreliosis patients (8). Skin manifestations account for 79–90% of all LB cases in children and adults (3, 5, 9–11). There are 3 characteristic skin manifestations: erythema migrans (EM), borrelial lymphocytoma (BL), and acrodermatitis chronica atrophicans (ACA). EM is the hallmark of early LB and appears on average at 2 weeks after a tick bite. This occurs either as single or multiple, expanding, round-to-oval, red to bluish-red and sharply demarcated, macular or ring-like lesions (12, 13). BL is a B-cell pseudolymphoma that appears weeks to months after infection, usually as a soft, bluish-red nodule or plaque at the ear lobe, breast, axillary fold, or scrotum (14). ACA is the cutaneous manifestation of late stage LB that develops months to years after infection on the extensor surfaces of the distal extremities. It starts with an inflammatory stage characterized by a red to violaceous doughy swelling of the skin that evolves into a chronic atrophic stage with thinning and wrinkling of the skin due to loss of epidermal and dermal structures (15).

Most of the manifestations of LB may appear in both children and adults (1, 3, 5, 9), although differences in the prevalence and clinical characteristics of the various manifestations between both age groups have been described. For example, ACA typically affects elderly adults, whereas BL is primarily diagnosed in children (11, 14). Peripheral facial nerve palsy and aseptic meningitis are the most common neurologic manifestation of LB in children (3, 9, 10, 16, 17), whereas adults are commonly affected by radiculoneuritis (5). Data suggest that Lyme arthritis is more frequent in children than in adults (3, 18), but runs a more favorable course as 10% of adults but very few children develop chronic Lyme arthritis (3, 19). Therefore, prognostic data from adult study populations may not be applicable to children. Literature reports of comprehensive clinical examinations, especially of skin manifestations of LB in childhood,

are scarce. Most studies are only focused on a particular manifestation such as EM (18, 20, 21) or analyze only the serologic response (22). A recent survey among 52 pediatric infectious disease specialists investigated the management of 160 children with LB. This revealed major shortcomings in disease management, particularly of children with skin manifestations. Only half of the patients received appropriate antibiotic therapy, presumably because of a poor understanding of the nature of LB in children (23). Another study showed that only 72% of 106 general practitioners and 92% of 32 dermatologists correctly diagnosed typical EM lesions, with a better rate for those physicians who attended a CME course on LB (24). Therefore we conducted the present study to comprehensively describe the spectrum, clinical characteristics, serologic response, and therapy in 204 children with skin manifestations of LB.

MATERIALS AND METHODS

All children included in this retrospective study lived in areas of eastern Austria, which are highly endemic for LB. They were seen between 1996 and 2011 at the Departments of Dermatology in Graz or Wiener Neustadt, where they were entered into a shared in-house LB database. All children enrolled suffered from one of the 4 defined dermatological manifestations of LB, i.e. solitary EM (SEM) or EM with multiple lesions (MEM), BL, or ACA. The diagnosis was made by a faculty dermatologist based on clinical case definitions (25). According to these definitions, SEM is an expanding round to oval, sharply demarcated, red to bluish-red erythema of at least 5 cm in diameter with or without central clearing. MEM is characterized by the appearance of multiple EM lesions in the same patient. BL is a non-tender, soft, well-circumscribed, bluish-red nodule or plaque of 1–5 cm, and ACA is a doughy bluish-red swelling with or without signs of atrophy, typically on the extensor surfaces of the extremities, including the hands and feet. A fifth group of patients comprised children in whom BL was surrounded by SEM (BLEM), and therefore represented a combination of skin manifestations of LB. The review of patient files revealed that a 4 mm punch biopsy of lesional skin for histopathologic examination had been obtained in 10 (11%) of SEM cases, 10 (18%) of MEM cases, 14 (31%) of BL cases, 4 (33%) of BLEM cases, and both patients with ACA. The findings had been supportive of the respective diagnosis according to published criteria (26). The following demographic and clinical parameters were used for analyses: Gender and age of patients, tick bite history, incubation period after a tick bite, duration of skin lesion before therapy, skin lesion-specific data including site, type, and size, presence of associated extracutaneous signs and symptoms, type and duration of antibiotic therapy, and the clinical course after initiation of therapy (duration of skin lesion and extracutaneous symptoms) during a follow-up period of 0–1,688 days (median 40 days). Fifty-three children (26%) were followed for at least 6 months after initiation of antibiotic therapy, 29 children (14%) for at least 12 months and 27 children (13%) were not available for follow-up. The presence of serum anti-*B. burgdorferi* s.l. IgG and IgM antibodies before therapy was assessed by a flagellin ELISA (Dako, Glostrup, Denmark) in 160 patients (78%). Each patient was allocated to one of 5 groups of dermatologic manifestations of LB (SEM, MEM, BL, BLEM, ACA). Clinical and serologic parameters were compared between the groups. Statistical analyzes were

performed using the package 'stats' of the R language (Version 2.15.3) (<http://www.r-project.org/>). Nonparametric distribution of data was confirmed by histograms, Q-Q plots, and Shapiro test. Parameters between diagnosis groups were compared with χ^2 or Wilcoxon rank sum test where applicable. Serologic results within a diagnosis group were compared by binominal test. *p*-values from multiple comparisons were corrected by the method of Benjamini & Hochberg (27). Two-tailed *p*-values < 0.05 were considered significant.

RESULTS

Clinical findings

The characteristics of patients are summarized in Tables SI¹ and SII¹. SEM was the most prevalent manifestation with 91 cases (44%), followed by MEM with 55 cases (27%). Forty-four children (22%) suffered from BL, and additional 12 patients (6%) had concomitant BL and EM lesions. Only two children (1%) were diagnosed with ACA, and were therefore not included in statistical analyses.

Sex and age. MEM and BLEM were more often found in boys compared to girls and the difference was statistically significant, while the sex ratio was equivalent in the other diagnosis groups. The median age of the children was between 6 and 9 years with no significant differences in the age distribution between the individual skin manifestations and sexes, but children with MEM and BL tended to be younger.

Tick bite. A tick bite was most often recalled by SEM patients (61%) and least often by BL patients (34%). It therefore appeared that the rate of recalled tick bites increased with a shorter incubation period of the skin lesion, which was one week in SEM but 3 weeks in BL. Sixteen percent of all children (or their parents) recalled multiple tick bites; multiple tick bites were most often reported in children with BLEM (26%) although it is a localized lesion. The rate of multiple tick bites in children with MEM (20%) was not significantly higher than in children with the localized lesions SEM (13%) or BL (14%). In those patients, who had localized lesions and in whom the exact site of the preceding tick bite was known, the location of the skin lesion and the tick bite corresponded in 79% of SEM (34/43 patients), in 60% of BL (6/10 patients), and in all BLEM patients (5/5 patients). In the remainder of cases, the site of the incriminated tick bite was located distantly to the respective skin lesion. Of 17 MEM patients who recalled only a single tick bite, 10 patients (59%) had an EM lesion at the site of the tick bite, while the other 7 patients (41%) did not develop an EM lesion at the site of a tick bite. Also in case of multiple tick bites in MEM patients, the tick bite sites and location of skin lesions were not strictly correlated.

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Disease duration. The median disease duration of ≤ 10 days before start of therapy in the characteristic manifestations of early LB (SEM and MEM) was significantly shorter than that of ≥ 42 days in BL or BLEM patients.

Localisation and lesional features. SEM was located in the head–neck region in most cases (Fig. 1), followed by the lower extremities. BL was preferentially found on the ear (Fig. 2), all other body sites were only rarely involved. The ear (and the abutting cheek) was the predilection site for BLEM as well, but almost as many such lesions were observed in the breast–shoulder area, a significant difference to sole BL lesions. SEM presented more often as annular (ring-like with central clearing) than as macular (homogenous) red rash. It was remarkably faint in 21 cases (23%), in particular in the face (see Fig. 1). Rare atypical lesions ($n=4$) included a partly hemorrhagic aspect, slightly elevated edge or scaling.

The diagnosis of SEM was made based on the clinical appearance. Histopathology was done in all patients with atypical SEM and substantiated the clinical diagnosis in all cases. SEM lesions were never itchy. SEM reached a median diameter of 10 cm with a growth rate (greatest diameter of SEM divided through its duration) of 0.2–4.5 cm/day (median 1.1 cm). Children with MEM had a median number of 5 (range 2–36), mostly annular, skin lesions per patient. They were irregularly disseminated over the extremities, the face, and trunk (Fig. 3). A clustered arrangement was seen in 5 patients (9%), especially in the gluteal region. In 5 of the 55 patients with MEM (9%), a primary erythema could be differentiated from secondary lesions, which were often smaller, less inflammatory and developed sequentially over a maximum of 12 days. BL lesions appeared as painless, soft and dark red to violaceous, sharply demarcated plaque or nodule of few centimeters in size (see Fig. 2). BLEM lesions were characterized by a primary central BL, around which an intense red EM developed after a median of 35 days (range 14–56 days), either spontaneously ($n=10$) or following a punching



Fig. 2. Solitary borrelial lymphocytoma of the earlobe in a 7-year-old boy.

trauma to the BL lesion ($n=2$). EM did not precede BL in any case. EM was either of ring-like or speckled morphology (Fig. 4) and had a median largest diameter of 12 cm. Extracutaneous signs and symptoms, which comprised headache, arthralgias, elevated temperature, fatigue, or malaise, were most common in children with EM (SEM 33%; MEM 40%). Fifty percent of these children with EM suffered from 2 or more symptoms. Only a minority of BL patients had extracutaneous symptoms, which included elevated temperature in one patient and regional lymphadenopathy in 2 others. In the quarter of BLEM cases with respective symptoms, they always occurred together with the development of the EM around the BL. Thus, BL lesions were only exceptionally associated with extracutaneous symptoms.

Therapy

At least one half of the patients in all diagnosis groups were treated with amoxicillin and around one third with phenoxymethylpenicillin. Doxycycline, cephalosporins (cefuroxime, ceftriaxone) and macrolides (azithromycin, clarithromycin, erythromycin) were only rarely



Fig. 1. Faint solitary annular erythema migrans on the left cheek in a 7-year-old girl.



Fig. 3. Erythema migrans with multiple faint annular lesions on the trunk and arms of a 5-year-old boy.



Fig. 4. Borrelial lymphocytoma at the right nipple surrounded by a speckled erythema migrans ("BLEM") in an 8-year-old boy.

used. The antibiotics were administered orally in body weight-adjusted doses (11, 28) for 2–4 weeks, with the shortest duration of therapy in SEM patients.

The only patient who was treated intravenously (2 weeks of ceftriaxone) was an 8-year-old girl with SEM on her left cheek, who developed headache. The presence of LB lymphocytic meningitis in this patient was substantiated by the results of a lumbar puncture, revealing intrathecal anti-*B. burgdorferi* s.l. IgM antibody production (index 3.6), pleocytosis (277 cells/ μ l; 84% lymphocytes, 2% neutrophils), moderately elevated protein (94 mg/dl) and normal glucose (42 mg/dl) concentration in the cerebrospinal fluid.

A possible Jarisch Herxheimer reaction was observed in a 5-year-old boy with SEM who developed fever during the first day of cefuroxime treatment. The fever resolved within 24 h and the antibiotic therapy was continued for 14 days.

EM lesions resolved completely within a median of 1–2 weeks after initiation of therapy, regardless whether they were solitary (SEM), multiple (MEM), or associated with a BL lesion (BLEM). Clearance of BL lesions was clearly slower. In particular, the median time of 2 months until healing of BL was significantly longer than the time until healing of EM lesions. We found no significant difference in resolving of BL between the BL and the BLEM group. Extracutaneous signs and symptoms disappeared within a few days after start of therapy in the majority of children without significant difference between the diagnosis groups, although symptoms in children with BL were particularly short-lived. Headache and/or arthralgias persisted for up to 3 months after therapy in only 4 children with SEM and in one child with MEM who initially had 13 erythemas. None of the patients developed any later sequelae during a follow-up period of 6–24 months. Neither one of the various antimicrobials nor a longer duration of treatment was statistically significant superior in clearing dermatologic or extracutaneous signs and symptoms in any of the skin manifestations of LB.

Serology

Before start of therapy, 49% of the patients with SEM had antibodies to *B. burgdorferi* s.l., which was a smaller proportion than observed in MEM (69% seropositive), BL (76%), and BLEM (75%). IgG antibodies were the predominant antibody class in BL, which had the longest disease duration, whereas IgM antibodies were more common in the other groups (Fig. 5).

Acrodermatitis chronica atrophicans

Only 2/204 children, 2 girls aged 11 and 15 years, were diagnosed with ACA. Both have been published earlier (29, 30).

DISCUSSION

This is a large study of all pediatric patients seen in 2 hospital-based dermatologic centers in Eastern Austria between 1996 and 2011, which included the full spectrum of skin manifestations of LB published so far. The size of the study permitted assessment of the frequencies of different skin manifestations of LB. The health-care system in Austria allows for a direct access of all patients to hospital centers. However, the hospital-based accrual may lead to a bias of inclusion of more complex cases compared to the spectrum of what might be seen by a general dermatologist. SEM (44.6%) and MEM (26.9%) were most often observed in our patients (See Table S1¹). This is in accordance with previous reports in which SEM and MEM were also most prevalent in pediatric patients

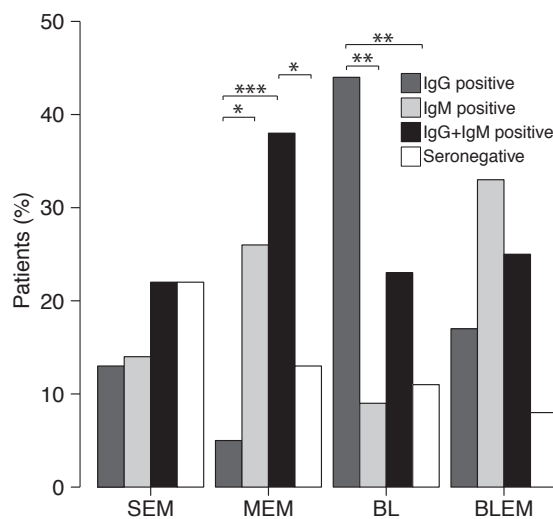


Fig. 5. Proportion of children seropositive or seronegative for anti-*B. burgdorferi* sensu lato antibodies. Information on serology was not available in 26 (29%) of children with solitary erythema migrans (SEM), 10 (18%) with erythema migrans with multiple lesions (MEM), 6 (13%) with borrelial lymphocytoma (BL), 2 (17%) with borrelial lymphocytoma plus erythema migrans (BLEM) * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ determined by binominal test and adjusted for multiple comparison by Benjamini & Hochberg (27) correction.

with skin manifestations of LB in Europe (75–77%) (3, 22), although these studies did not encompass the full spectrum of skin manifestations of LB. The rate of about 40% MEM among all EM patients found in our and in a previous study (20) may indicate a higher prevalence of MEM in children than in adults in Europe, where MEM is diagnosed in 4–7% (11). The 22% BL cases diagnosed in our study together with the previously reported 14% BL cases of children with skin manifestations (22) and the 7% BL cases of all children with LB (9) indicate that BL is seen more frequently in children than in adults, in which BL accounts for only 2% of all LB cases (9). In contrast, ACA is an extreme rarity in children with only 11 described cases (22, 29–35). In adults, ACA has an estimated prevalence of 1–2% among all LB patients with skin manifestations and preferentially affects elderly people in Europe (11).

We found that SEM affects boys and girls equally as the most typical skin manifestation of early LB with a median incubation period and disease duration of one week, which is comparable with prior literature (11–16 days) (20, 21, 36). The majority of SEM in our children (79%) and in previous European studies (46–58%) (20, 21) occurred at the site of a recalled tick bite. Presumably due to the shorter stature, the predilection site of SEM is therefore the head–neck region. This and the prevalence of annular versus macular lesions, which has also been observed earlier (20, 21, 36) are important differences from adults. Transient extracutaneous signs and symptoms were present in one third of our patients, which is about the same percentage as previously described in children (21–33%) (20, 36) and similar to the rate in adults (36%) (37). MEM patients were significantly more often male and tended to be younger. Less than a quarter of MEM patients in the present study had a history of multiple tick bites, and the site of tick bites in general did not regularly correspond to the localization of skin lesions. The median incubation period reported in the literature (10.5–22 days) (20, 21, 38) and in our patients series (median 15 days) was longer than in SEM, as was the disease duration. Previous reports on the predominance of annular MEM lesions (99%), the low median number of lesions per patient (median, 4.5–5.5), and the frequent affection of the limbs (46%) (20, 21, 38) are substantiated by this study. Only a minority (5%) of our patients had a primary EM with sequential development of further lesions. The percentage of patients with MEM who had extracutaneous symptoms was only slightly higher than with SEM (40% vs. 33%), which is in accordance with Arnez et al. (20) (28% versus 26%). The spectrum of symptoms was the same in SEM and MEM patients in this and other studies (20), and usually included non-specific flu-like symptoms and regional lymphadenopathy. Persistence of such symptoms has not been observed in SEM and MEM patients.

While BL is only rarely observed in children and adults in North America, it is more commonly seen in European children (11, 18). This may be explained by the fact that BL is mostly caused by *B. afzelii* and *B. garinii*, borrelia genospecies which are predominant in Europe (39). We have shown that BL developed after a longer incubation period and the disease duration was significantly longer than in SEM or MEM. The clinical appearance of BL is similar in children and adults, but local symptoms such as itching are less common in children (40). The vast majority of BL lesions (84%) in children in the present study were localized on the ear, which is in accordance with Pohl-Koppe et al. (88%) (41). On the contrary, the predilection site for BL in adults is the breast (14, 40, 42) (Table SIII¹). Considering the concordance of 60% between the site of tick bites and BL lesions, we suggest that, as with SEM, the shorter stature of children may be responsible for this difference. We did not observe multiple BL in 44 children. The only patient with more than one simultaneous BL lesions described in the literature so far was a 3-year-old boy without any other notable peculiarities. He developed 3 BL lesions at his breast and both ears 4 weeks after a tick bite, had no extracutaneous symptoms and was tested positive for anti-*B. burgdorferi* s.l. IgG antibodies (41). In contrast to SEM and MEM, we and others (41) have only seen extracutaneous symptoms in children with BL rarely. They are more common in adults (40) (see Table SIII¹). We propose that BL is a localized, early subacute skin manifestation of LB because it is usually a solitary skin lesion without extracutaneous symptoms.

In this study we describe a group of 12 children with BLEM, a collision lesion (43) of BL and a surrounding EM. The concomitant appearance of BL with EM at the same body site has been described in several pediatric and adult patients (22, 40–42, 44). For example, 13/25 (52%) children and adults with BL at the ear (40) and 59/83 (71%) adults with BL at the breast (40, 42) had a concomitant EM at the site of BL. The majority of these patients developed EM before the onset of BL, whereas only a 58-year-old woman was described to develop EM one month after onset of BL at the breast (40). This is in stark contrast to the BLEM patients in our study, in all of which BL developed a minimum of 14 days before the onset of EM. The appearance of EM around BL was associated with the onset of extracutaneous symptoms in 25% of BLEM patients, which is noticeably higher than in pediatric patients with BL only (40, 41). We hypothesize that the spread of viable spirochetes from an untreated BL lesion causes the development of EM and extracutaneous symptoms. This has been observed in about 20% (12/56) of children with BL, which suggests that it is important to treat any LB manifestation as soon as possible.

Testing for anti-*B. burgdorferi* s.l. specific IgG and IgM antibodies is the most common laboratory test.

However, only 31–64% of children and adults with SEM have a positive serology before therapy, without a notable difference between both age groups (3, 22, 37, 45, 46). In MEM, the percentage in this and other studies tends to be higher for children (46–89%) (20) and adults (52–89%) (37, 47). Thus, serologic testing is not sensitive enough to substantially contribute to the diagnosis of SEM or MEM. Except for ACA, where anti-*B. burgdorferi* s.l. antibodies are mandatory for the diagnosis, the proportion of patients with a positive serologic result is highest among adult (70–95%) (11) and pediatric patients with BL or BLEM (75–88%) as demonstrated by Pohl-Koppe et al. (41) and in the present study. Serologic testing is therefore more helpful in these LB manifestations. Skin biopsies from lesional skin for histopathology and/or direct detection of *B. burgdorferi* s.l. (-specific DNA) by culture or PCR may yield important information but is usually only employed in challenging cases (14).

All children in this study responded well to antibiotic therapy. SEM and MEM as well as the EM component in BLEM completely cleared within days to weeks. BL lesions took longer to resolve. These results compare well with earlier reports, in which the median time until clearing was 4–7 days in SEM and MEM (36) and 18 days in BL (40). Extracutaneous symptoms disappear faster than skin lesions, for the most part in only a few days, and rarely last longer than 3 months (20, 22), which is also shown in the present study. No long-term data on SEM or MEM are available for European children. In the 40 patients with SEM or MEM and the 13 patients with BL or BLEM, who were followed for at least 6–12 months in our study, sequelae were not observed. This is consistent with a North American study that observed children with SEM or MEM for 2 years (18) and a European study that observed adult and pediatric BL patients for up to one year (40). In contrast, <10–20% of adult patients with SEM or MEM report persistence or recurrence of extracutaneous symptoms, most commonly arthralgias (11). No late sequelae occur after BL (42). Therefore the outcome after therapy appears to be more favorable in children than in adults. The antibiotics used in our children were primarily amoxicillin and phenoxymethylpenicillin as in earlier studies (28), and there were no significant differences in the efficacy between the drugs.

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REFERENCES

1. Stanek G, Wormser GP, Gray J, Strle F. Lyme borreliosis. *Lancet* 2012; 379: 461–473.
2. Rizzoli A, Hauffe H, Carpi G, Vourc HG, Neteler M, Rosa R. Lyme borreliosis in Europe. *Euro Surveill* 2011; 16: 19906.
3. Huppertz HI, Bohme M, Standaert SM, Karch H, Plotkin SA. Incidence of Lyme borreliosis in the Wurzburg region of Germany. *Eur J Clin Microbiol Infect Dis* 1999; 18: 697–703.
4. Bacon RM, Kugeler KJ, Mead PS. Surveillance for Lyme disease – United States, 1992–2006. *MMWR Surveill Summ* 2008; 57: 1–9.
5. Fulop B, Poggensee G. Epidemiological situation of Lyme borreliosis in Germany: surveillance data from six Eastern German States, 2002 to 2006. *Parasitol Res* 2008; 103 Suppl 1: S117–S120.
6. Dehnert M, Fingerle V, Klier C, Talaska T, Schlaud M, Krause G, et al. Seropositivity of Lyme borreliosis and associated risk factors: a population-based study in children and adolescents in Germany (KiGGS). *PLoS One* 2012; 7: e41321.
7. Skogman BH, Ekerfelt C, Ludvigsson J, Forsberg P. Seroprevalence of Borrelia IgG antibodies among young Swedish children in relation to reported tick bites, symptoms and previous treatment for Lyme borreliosis: a population-based survey. *Arch Dis Child* 2010; 95: 1013–1036.
8. Fingerle V, Schulte-Spechtel UC, Ruzic-Sabljić E, Leonhard S, Hofmann H, Weber K, et al. Epidemiological aspects and molecular characterization of Borrelia burgdorferi s.l. from southern Germany with special respect to the new species Borrelia spielmanii sp. nov. *Int J Med Microbiol* 2008; 298: 279–290.
9. Berglund J, Eitrem R, Ornstein K, Lindberg A, Ringer A, Elmud H, et al. An epidemiologic study of Lyme disease in southern Sweden. *N Engl J Med* 1995; 333: 1319–1327.
10. Esposito S, Bosis S, Sabatini C, Tagliaferri L, Principi N. Borrelia burgdorferi infection and Lyme disease in children. *Int J Infect Dis* 2013; 17: e153–e158.
11. Mullegger RR, Glatz M. Skin manifestations of Lyme borreliosis: diagnosis and management. *Am J Clin Dermatol* 2008; 9: 355–368.
12. Smith RP, Schoen RT, Rahn DW, Sikand VK, Nowakowski J, Parenti DL, et al. Clinical characteristics and treatment outcome of early Lyme disease in patients with microbiologically confirmed erythema migrans. *Ann Intern Med* 2002; 136: 421–428.
13. Strle F, Videcnik J, Zorman P, Cimperman J, Lotric-Furlan S, Maraspin V. Clinical and epidemiological findings for patients with erythema migrans. Comparison of cohorts from the years 1993 and 2000. *Wien Klin Wochenschr* 2002; 114: 493–497.
14. Colli C, Leinweber B, Mullegger R, Chott A, Kerl H, Cerroni L. Borrelia burgdorferi-associated lymphocytoma cutis: clinicopathologic, immunophenotypic, and molecular study of 106 cases. *J Cutan Pathol* 2004; 31: 232–240.
15. Asbrink E, Hovmark A. Early and late cutaneous manifestations in Ixodes-borne borreliosis (erythema migrans borreliosis, Lyme borreliosis). *Ann N Y Acad Sci* 1988; 539: 4–15.
16. Tveitnes D, Natas OB, Skadberg O, Oymar K. Lyme meningitis, the major cause of childhood meningitis in an endemic area: a population based study. *Arch Dis Child* 2012; 97: 215–220.
17. Dhote R, Basse-Guerineau AL, Beaumesnil V, Christoforov B, Assous MV. Full spectrum of clinical, serological, and epidemiological features of complicated forms of Lyme borreliosis in the Paris, France, area. *Eur J Clin Microbiol Infect Dis* 2000; 19: 809–815.
18. Gerber MA, Shapiro ED, Burke GS, Parcels VJ, Bell GL. Lyme disease in children in southeastern Connecticut.

- Pediatric Lyme Disease Study Group. *N Engl J Med* 1996; 335: 1270–1274.
19. Steere AC, Glickstein L. Elucidation of Lyme arthritis. *Nat Rev Immunol* 2004; 4: 143–152.
 20. Arnez M, Pleterski-Rigler D, Luznik-Bufon T, Ruzic-Sabljić E, Strle F. Solitary and multiple erythema migrans in children: comparison of demographic, clinical and laboratory findings. *Infection* 2003; 31: 404–409.
 21. Arnez M, Ruzic-Sabljić E. *Borrelia burgdorferi* sensu lato bacteremia in Slovenian children with solitary and multiple erythema migrans. *Pediatr Infect Dis J* 2011; 30: 988–990.
 22. Aberer E, Kehldorfer M, Binder B, Schaperi H. The outcome of Lyme borreliosis in children. *Wien Klin Wochenschr* 1999; 111: 941–944.
 23. Esposito S, Baggi E, Villani A, Norbedo S, Pellegrini G, Bozzola E, et al. Management of paediatric Lyme disease in non-endemic and endemic areas: data from the Registry of the Italian Society for Pediatric Infectious Diseases. *Eur J Clin Microbiol Infect Dis* 2013; 32: 523–529.
 24. Lipsker D, Lieber-Mbomeyo A, Hedelin G. How accurate is a clinical diagnosis of erythema chronicum migrans? Prospective study comparing the diagnostic accuracy of general practitioners and dermatologists in an area where Lyme borreliosis is endemic. *Arch Dermatol* 2004; 140: 620–621.
 25. Stanek G, O'Connell S, Cimmino M, Aberer E, Kristofersitsch W, Granstrom M, et al. European Union Concerted Action on Risk Assessment in Lyme Borreliosis: clinical case definitions for Lyme borreliosis. *Wien Klin Wochenschr* 1996; 108: 741–747.
 26. Weger W, Mülleger RR. Histopathology and immunohistochemistry of dermatoborreliosis. *Acta Dermatoven APA* 2001; 10: 135–142.
 27. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J Royal Statistic Soc (Series B)* 1995; 57: 289–300.
 28. Wormser GP, Dattwyler RJ, Shapiro ED, Halperin JJ, Steere AC, Klempner MS, et al. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2006; 43: 1089–1134.
 29. Mülleger RR, Schlupe EM, Millner MM, Soyer HP, Volkenandt M, Kerl H. Acrodermatitis chronica atrophicans in an 11-year-old girl. *Br J Dermatol* 1996; 135: 609–612.
 30. Zalaudek I, Leinweber B, Kerl H, Mülleger RR. Acrodermatitis chronica atrophicans in a 15-year-old girl misdiagnosed as venous insufficiency for 6 years. *J Am Acad Dermatol* 2005; 52: 1091–1094.
 31. Andres C, Ziai M, Bruckbauer H, Ring J, Hofmann H. Acrodermatitis chronica atrophicans in two children. *Int J Dermatol* 2010; 49: 180–183.
 32. Brzonova I, Wollenberg A, Prinz JC. Acrodermatitis chronica atrophicans affecting all four limbs in an 11-year-old girl. *Br J Dermatol* 2002; 147: 375–378.
 33. Gellis SE, Stadecker MJ, Steere AC. Spirochetes in atrophic skin lesions accompanied by minimal host response in a child with Lyme disease. *J Am Acad Dermatol* 1991; 25: 395–397.
 34. Menni S, Pistrutto G, Piccinno R, Trevisan G. Acrodermatitis chronica atrophicans in an Italian child. *Acta Derm Venereol* 1996; 76: 243.
 35. Nadal D, Gundelfinger R, Flueller U, Boltshauser E. Acrodermatitis chronica atrophicans. *Arch Dis Child* 1988; 63: 72–74.
 36. Nizic T, Velikanje E, Ruzic-Sabljić E, Arnez M. Solitary erythema migrans in children: comparison of treatment with clarithromycin and amoxicillin. *Wien Klin Wochenschr* 2012; 124: 427–433.
 37. Eriksson P, Schroder MT, Niiranen K, Nevanlinna A, Pannelius J, Ranki A. The many faces of solitary and multiple erythema migrans. *Acta Derm Venereol* 2013; 93: 693–700.
 38. Arnez M, Pleterski-Rigler D, Ahcan J, Ruzic-Sabljić E, Strle F. Demographic features, clinical characteristics and laboratory findings in children with multiple erythema migrans in Slovenia. *Wien Klin Wochenschr* 2001; 113: 98–101.
 39. Lenormand C, Jaulhac B, De Martino S, Barthel C, Lipsker D. Species of *Borrelia burgdorferi* complex that cause borrelial lymphocytoma in France. *Br J Dermatol* 2009; 161: 174–176.
 40. Strle F, Pleterski-Rigler D, Stanek G, Pejovnik-Pustinek A, Ruzic E, Cimperman J. Solitary borrelial lymphocytoma: report of 36 cases. *Infection* 1992; 20: 201–206.
 41. Pohl-Koppe A, Wilske B, Weiss M, Schmidt H. Borrelial lymphocytoma in childhood. *Pediatr Infect Dis J* 1998; 17: 423–426.
 42. Maraspin V, Cimperman J, Lotric-Furlan S, Ruzic-Sabljić E, Jurca T, Picken RN, et al. Solitary borrelial lymphocytoma in adult patients. *Wien Klin Wochenschr* 2002; 114: 515–523.
 43. Leinweber B, Ambros-Rudolph CM, Glatz M, Mülleger RR. Concurrence of erythema migrans and herpes simplex: first description of a highly unusual dual skin infection. *J Eur Acad Dermatol Venereol* 2009; 23: 452–454.
 44. Weisshaar E, Schaefer A, Scheidt RR, Bruckner T, Apfelbacher CJ, Diepgen TL. Epidemiology of tick bites and borreliosis in children attending kindergarten or so-called “forest kindergarten” in southwest Germany. *J Invest Dermatol* 2006; 126: 584–590.
 45. Wormser GP, Schriefer M, Aguero-Rosenfeld ME, Levin A, Steere AC, Nadelman RB, et al. Single-tier testing with the C6 peptide ELISA kit compared with two-tier testing for Lyme disease. *Diagn Microbiol Infect Dis* 2013; 75: 9–15.
 46. Hofhuis A, Herremans T, Notermans DW, Sprong H, Fonville M, van der Giessen JW, et al. A prospective study among patients presenting at the general practitioner with a tick bite or erythema migrans in The Netherlands. *PLoS One* 2013; 8: e64361.
 47. Philipp MT, Wormser GP, Marques AR, Bittker S, Martin DS, Nowakowski J, et al. A decline in C6 antibody titer occurs in successfully treated patients with culture-confirmed early localized or early disseminated Lyme borreliosis. *Clin Diagn Lab Immunol* 2005; 12: 1069–1074.
 48. Strle F, Nelson JA, Ruzic-Sabljić E, Cimperman J, Maraspin V, Lotric-Furlan S, et al. European Lyme borreliosis: 231 culture-confirmed cases involving patients with erythema migrans. *Clin Infect Dis* 1996; 23: 61–65.
 49. Oksi J, Marttila H, Soini H, Aho H, Uksila J, Viljanen MK. Early dissemination of *Borrelia burgdorferi* without generalized symptoms in patients with erythema migrans. *Apms* 2001; 109: 581–588.