Lyme Disease in Women: Recognition, Treatment, and Prevention

Jonathan L. Temte, MD, PhD

Lyme disease is easily treated, but the elusive symptoms require a high index of suspicion and familiarity with local epidemiology.

Lyme disease is an uncommon, but not rare, condition that presents complex challenges. The likelihood of diagnosis is highly dependent on practice location and the patient's geographic history. Primary care physicians—especially those practicing in areas of increased Lyme prevalence—should have a basic understanding of this condition, including recognition, treatment, and prevention.

Lyme disease (ie, borreliosis) refers to the constellation of clinical findings associated with infection by the spirochete *Borrelia burgdorferi*. Humans infected with *B burgdorferi* are inadvertent hosts in the complex and intertwined life cycles of the spirochete and the deer ticks *Ixodes scapularis* in the northeastern and north-central United States and (less commonly) *I pacificus* in the western states.[1,2]

PRESENTATION

Asymptomatic Lyme Disease

Asymptomatic seroconversion may occur in approximately 7% of people infected with *B*

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CONTINUING MEDICAL EDUCATION

GOAL

To place the diagnosis and treatment of Lyme disease in women into perspective in the context of primary care clinical practice in endemic areas.

OBJECTIVES

1. To discuss the epidemiology of Lyme disease with regard to geographic area, time of year, and life cycle of the deer tick in women.
2. To describe symptoms and presentation at various disease stages, with appropriate diagnostic measures for each in women.
3. To present recommendations for treatment and prevention in women.

ACCREDITATION

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Albert Einstein College of Medicine and Quadrant HealthCom Inc. Albert Einstein College of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

This activity has been peer reviewed and approved by Brian Cohen, MD, professor of clinical OB/GYN, Albert Einstein College of Medicine. Review date: September 2005. It is designed for Primary Care Physicians.

The Albert Einstein College of Medicine designates this educational activity for a maximum of 1 category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only that credit that he/she spent in the educational activity.

Participants who answer 70% or more of the questions correctly will obtain credit. To earn credit, see the instructions on page 00 and mail your answers according to the instructions on page 00.

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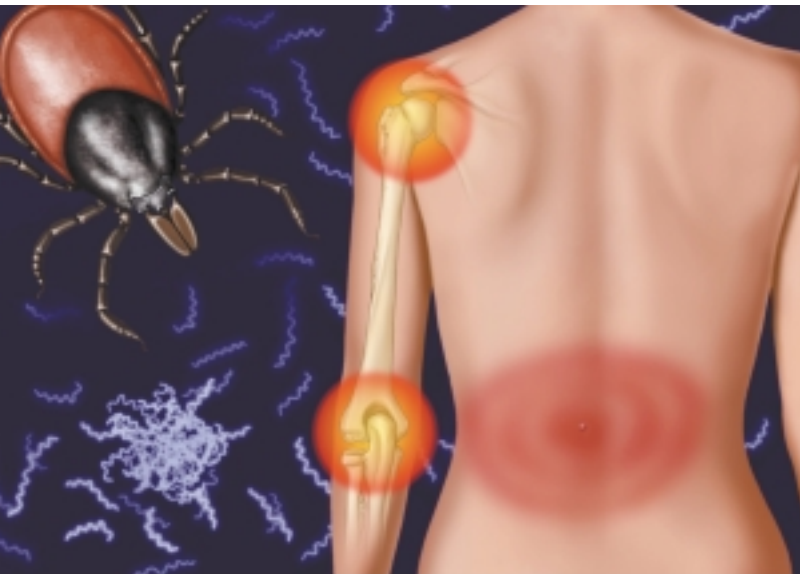


Stage 1 Lyme disease typically occurs 3 to 30 days after the tick bite. It is manifested by erythema migrans, a slowly expanding, erythematous, annular rash that occurs at the site of the original tick attachment.

burgdorferi.[3] The full clinical significance of asymptomatic seroconversion is not fully understood.

Early Localized (Erythema Migrans)

Stage 1 Lyme disease typically occurs 3 to 30 days after the tick bite. It is manifested by erythema migrans, a slowly expanding, erythematous, annular rash that occurs at the site of the original tick attachment.[3] This characteristic rash usually has no associated local symptoms, but is occasionally accompanied by localized pruritus or mild pain, and occurs in 70% to 80% of patients.[4] This period may also be marked by systemic symptoms such as malaise, fatigue, headache, fever, arthralgia, myalgia, and/or regional lymphadenitis.[1] In one series, however, 18% of serologically confirmed patients with Lyme disease presented with nonspecific, influenza-like symptoms, but without erythema migrans.[4]

Early Disseminated

Three to 12 weeks following the tick-bite manifestations of early Lyme disease, the disseminated stage may ensue.[3] Erythema migrans can initially occur at this point. Approximately 15% of untreated patients develop neuroborreliosis, which may present as lymphocytic meningitis, cranial neuropathy, encephalitis, radiculoneuritis, or ocular changes.[1] Chronic neuroborreliosis—with spinal radicular pain or distal paresthesias—may also develop. Cardiac manifestations (eg, atrioventricular block, myopericarditis, left ventricular dysfunction) occur in approximately 5% of untreated patients.[1]

Late Disease

Arthritis appears in approximately 60% of untreated patients as a late manifestation. Pain and swelling in large joints, particularly the knee, occur intermittently. A minority of patients progress to persistent joint inflammation.[1,3] Of patients prospectively identified with Lyme disease, only 3% presented with typical late manifestations involving the nervous system, heart, or joints.[5]

PREVALENCE AND EPIDEMIOLOGY

There were 21,273 cases of Lyme disease in the United States reported in 2003.[6] This total likely underestimates the disease burden, given the combined effects of misidentification and underreporting. The majority of cases were recorded in the northeastern and north-central states.

Estimates of Lyme disease prevalence vary widely depending on distribution and prevalence—both geographically and temporally—of the tick vector, as well as recognition and reporting by local physicians. For example, town-specific rates of Lyme disease in Connecticut range between 0 and 1,156 cases per 100,000 person-years.[7] Consequently, geographic prediction of Lyme disease transmission risk (Figure 1a) closely reflects the distribution of Ixodes ticks (Figure 1b).

In the context of clinical practice in an area of endemic Lyme disease, some worthwhile descriptive epidemiologic features emerge. Within the extended practices of the University of Wisconsin Department of Family Medicine, 276 diagnoses of Lyme disease were reported over a 3-year period (from a base of

758,208 total patient visits). Men comprised 58.5% of the diagnoses, which probably somewhat reflects gender differences in the likelihood of outdoor activities.[2] Many studies have demonstrated a higher incidence among children, and there appears to be some age-related differences in clinical presentation.[2] In Wisconsin, the peak of diagnosis occurs between ages 50 and 60 years (Figure 2)—possibly due to inadvertent detection of Lyme exposure in patients evaluated for unexplained arthritis and/or fatigue, complaints that are more common in this age group.

Although cases of Lyme disease have been reported with onset of symptoms in every month,[2] clinical diagnosis is highest in the summer and early fall. This is reflected in a primary care data set from Wisconsin (Figure 3), which demonstrates that most diagnoses are made between June and November.

The temporal trends found in Lyme disease diagnosis reflects the life cycle of the primary vectors[2,8] and timing of exposure, but are likely delayed by approximately 1 month due to the time factors involved in pathogenesis and diagnosis. The life cycle of *I scapularis* is illustrated in Figure 4. Notably, most tick-to-human transmission occurs during the blood meal needed for nymph-to-adult transformation, an event associated with late spring and summer.

PATHOGENESIS

Borrelia burgdorferi is delivered to the host through a tick bite. Lateral migration of spirochetes and perivascular inflammation explain the erythema migrans lesion at the site of tick attachment.[2] Hematogenous dissemination also occurs early, contributing to systemic symptoms. Distant organ involvement (eg, neurologic, cardiac, musculoskeletal) follows weeks to years after initial, untreated infection. Persistence of the spirochetes and the subsequent host inflammatory response appear to be the mechanisms of disease.[1,2]

In terms of immunoglobulin (Ig), IgM antibodies peak at 3 to 6 weeks postinfection, while IgG typically appears 4 to 6 weeks after infection and may remain elevated for years. Natural infection and recovery appears to confer immunity to subsequent reinfection.[2] This naturally acquired immunity is due to outer-surface lipoprotein-A (OspA) and OspB antibodies, which appear very late in the course of *B burgdorferi* infection.[9] Consequently, Lyme disease that is diagnosed early and appropriately treated may not result in immunity.

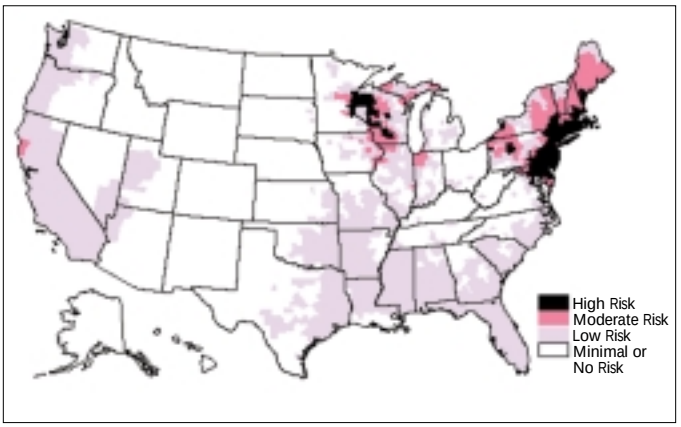
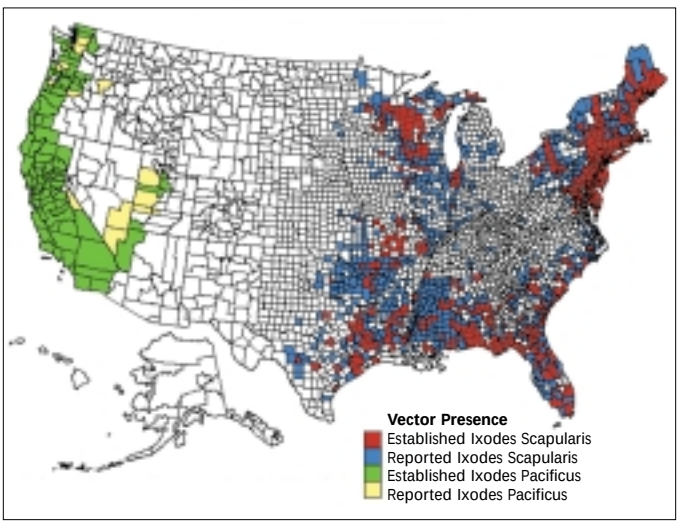


FIGURE 1a. National Lyme disease risk map demonstrating areas of predicted transmission.

Source: http://www.cdc.gov/epo/ mmwr/preview/ mmwrhtml/rr4807a2.htm.

FIGURE 1b. Distribution of Lyme disease tick vectors.

Source: http://www.cdc.gov/epo/mmwr/preview/ mmwrhtml/rr4807a2.htm.



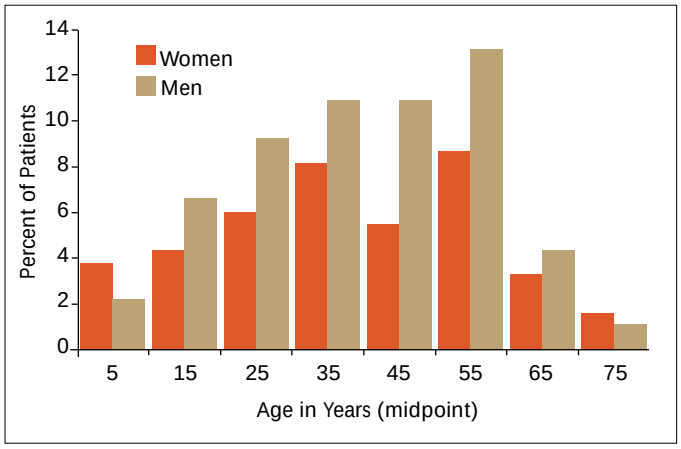
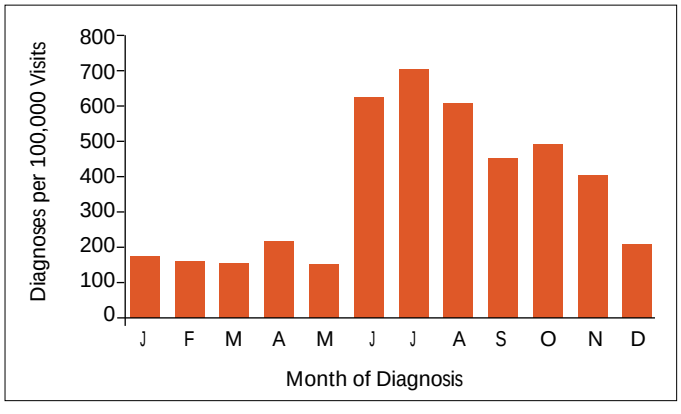


FIGURE 2. Age and sex distribution of Lyme disease diagnosed in the University of Wisconsin Department of Family Medicine clinics.

DIAGNOSIS

A straightforward case definition has been established for Lyme disease.[10] Diagnosis is based on the presence of either erythema migrans as observed by a clinician, or of at least one manifestation (neurologic, cardiovascular, musculoskeletal system) and laboratory evidence of infection. Many serologic Lyme disease tests are ordered inappropriately[11]; these tests should only be used in symptomatic patients with potential exposure in a Lyme-endemic region. They should not be used in patients with clinician-observed erythema migrans alone, as serodiagnostic testing is insensitive in the first several weeks of infection.[1]

FIGURE 3. Months of Lyme disease diagnosis in Wisconsin.



Serologic diagnosis is based on initial testing using enzyme immunoassay or immunofluorescent assay. Positive or equivocal results should be tested further using Western blot immunoassay.[12] This two-step approach provides an estimated sensitivity of 0.77 and a specificity of 0.93.[13] However, the positive predictive value of testing depends on the prevalence of Lyme disease in the target population. Accordingly, clinicians should know the background risk in their patient population to properly interpret positive and negative results.[14] Clinicians must also appraise the validity of the testing available to their practices; the US Centers for Disease Control and Prevention recently issued a warning regarding the wide availability of inappropriate and inadequately validated testing.[12]

Western blot testing for Lyme disease evaluates three IgM bands and 10 IgG bands. The IgM results are considered positive if at least two of the three bands are positive; IgG results are positive if at least five of the 10 bands are positive.[1] Only the IgG results should be used after the first month following the onset of symptoms.

TREATMENT

Concise guidelines have been developed for the appropriate management of Lyme borreliosis,[15] and are divided by disease stage. Although no antimicrobial prophylaxis is advised for tick bites, persons developing a skin lesion or other illness consistent with early Lyme disease should seek medical attention. Adult patients found to have early Lyme disease with no neurologic findings or third-degree atrioventricular block should receive doxycycline (100 mg twice daily) or amoxicillin (500 mg three times daily) for 14 to 21 days. Children can receive amoxicillin (or doxycycline if ≥ age 8 years) in weight-adjusted dosages. Ceftriaxone (2 g once daily intravenously [IV] for 14 to 28 days) is recommended for adults with acute neurologic disease; children should receive weight-adjusted dosages of ceftriaxone (75 to 100 mg/kg once daily IV for 14 to 28 days).

Late Lyme arthritis is treated similarly to cases with early manifestations in the absence of neu-

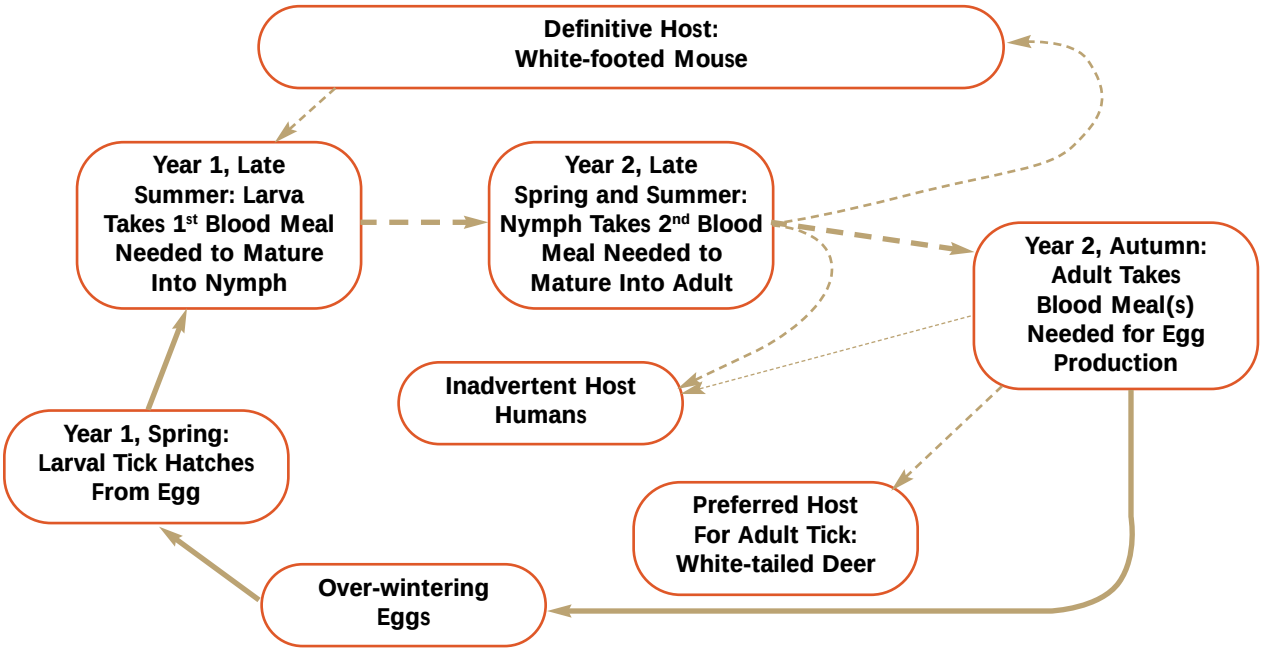


FIGURE 4. Life cycle of *Ixodes scapularis*. Dotted lines demonstrate the transmission of *Borrelia burgdorferi*.

rologic disease, but for 28 days. Patients with persistent or recurrent joint swelling after the recommended antibiotic course should receive a second 28-day course of oral antibiotics or 2 to 4 weeks of IV ceftriaxone. For patients with late neuroborreliosis, ceftriaxone (2 g daily IV for 14 to 28 days) is recommended.[15] Treatment failures occur predominantly in patients with unrecognized or unapparent neuroborreliosis who are treated with oral antibiotics for erythema migrans.[16]

PROGNOSIS, COMPLICATIONS, AND SEQUELAE

When Lyme disease is recognized early and treated appropriately, most patients have good clinical outcomes. Most signs and symptoms dissipate within 3 weeks of initiating treatment, but symptoms may persist for more than 30 days or even 60 days in 11% and 5% of patients, respectively.[17]

The complications and sequelae of Lyme disease are closely related to early management. Patients with initial arthritis (with or without facial palsy) are more likely to have chronic or episodic knee pain 10 to 20 years after initial diagnosis.[18] Patients with initial facial palsy who did not receive antibiotics for acute neuroborreliosis tend to have persistent joint pain, sleep disturbance, and poorer health status.[18]

PREVENTION

Tick Avoidance

The key to Lyme disease management is prevention of Ixodes tick exposure and attachment.[15] Central principles include:

- Avoidance of tick-infested areas
- Use of protective clothing (eg, shirt tucked into pants, pants tucked into socks), increasing time for ticks to encounter skin
- Use of light-colored clothing in tick-infested areas to facilitate tick location and removal
- Daily inspection of entire body and removal of any ticks with forceps
- Use of chemical tick repellents.

Insect repellents containing N,N-diethyl-m-toluamide (DEET) are available in more than 230 formulations worldwide, and have been shown to be effective in reducing tick attachment.[19] Moreover, DEET-containing insect

CASE HISTORY

A 56-year-old woman presented to her family physician with complaints of musculoskeletal discomfort. She had been using pravastatin for hypercholesterolemia, but had discontinued this medication due to concern about possible side effects. The discomfort persisted postdiscontinuation, however. The patient's symptoms included soreness and intermittent fluid collection in the knees and elbows, tenderness in the hands, wrists and fingers, occasional pain in the jaw and hips, and neck stiffness. Of note was a history of right facial palsy 2 years previously that was diagnosed elsewhere as Belle's palsy.

She denied recent exposure to ticks or tick bites, and reported no history of rashes consistent with erythema migrans. She had extensive outdoor exposure in areas of Lyme disease prevalence, however.

Physical findings were normal. No joint deformity or effusion was noted. There was no discernable facial weakness or other neurologic abnormalities. Laboratory studies included Westergren erythrocyte sedimentation rate (normal at 5 mm/hr), C-reactive protein testing (slightly elevated at 1.1 mg/L), arthritic panel (positive antinuclear antibody titer at 1:40, nonspecific finding) and a Lyme disease Western blot that was positive for nine of 10 IgG bands and one of three IgM bands. These findings were consistent with a diagnosis of late Lyme disease.

Amoxicillin, 500 mg three times daily, was given for an initial period of 28 days. The patient reported a 30% reduction in symptoms at her 1-month follow-up visit, and elected to continue antibiotic therapy for an additional 28-day period. Resolution of 80% of her joint symptoms was achieved at follow-up.

repellents are considered relatively safe for children and pregnant/lactating women when used as recommended.[20]

Vaccine

A vaccine containing recombinant OspA was licensed by the US Food and Drug Administration in 1998. This vaccine had an estimated efficacy of 76% following a three-dose schedule (0, 1-, and 12-month).[21] The incidence of adverse events is relatively low, and comprising arthralgia, myalgia, and pain.[22] The vaccine was limited in use, and was deemed cost-effective only for individuals living in areas of endemic Lyme disease who are frequently exposed to ticks.[23] Consequently, vaccine production was halted in early 2002—presumably due to low utilization.[6,24]

CONCLUSION

Lyme disease can be successfully identified and managed in the primary care setting. When appropriately managed, outcomes are good. Nevertheless, efforts to educate patients about preventive measures represent an essential aspect of care in endemic regions.

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Coding for Lyme Disease

Frank Vidal, MMC

The key coding elements in this analysis of Lyme disease is to differentiate between the presentation of symptoms that initiate the diagnostic process toward Lyme disease and the verfication of the diagnosis itself, as it relates to coding communications. Patients with symptoms of Lyme disease who have not had the disease confirmed as per the protocol indicated in the study should be coded with the *International Classification of Diseases, 9th revision* (ICD-9) code for the presenting symptom until confirmaton. As with all infectious diseases, the reporting of ICD-9 code **088.81** should only be used when Lyme disease has been confirmed.

PROCEDURAL ELEMENTS

Evaluation and Management Services

- **99201-99205 –** New patient in office or other outpatient setting
- **99211-99215 –** Established patient in office or other outpatient setting

The following immunoassay is listed as a Clinical Laboratory Improvement Amendments (CLIA) waived test, and can be coded if performed at a physician's office with the appropriate CLIA waiver license.

- **86618 –** Qualitative or semiquantitative immunoassays (antibody, *Borrelia burgdorferi* [Lyme disease])

DIAGNOSTIC ELEMENTS

Presenting symptoms indicated in the study prior to confirmation:

- **088.81 –** Lyme disease (erythema chronicum migrans)
- **690.8 –** Other erythematosquamous dermatosis
- **695.9 –** Unspecified erythematous condition
- **049.0 –** Lymphocytic choriomeningitis
  - – Lymphocytic (meningitis, serous, benign; meningoencephalitis, serous, benign)
- **729.2 –** Neuralgia, neuritis, and radiculitis, unspecified (cranial neuropathy)
- **323.9 –** Unspecified cause of encephalitis
- **719.0X –** Effusion of joint
  - – Hydrarthrosis (Swelling of joint, with or without pain)

  Fifth digit ranges:

  0 site unspecified
  1 shoulder region
  2 upper arm
  3 forearm
  4 hand
  5 pelvic region and thigh
  6 lower leg
  7 ankle and foot
  8 other specified sites
  9 multiple sites

Frank Vidal, MMC, is chairman, International Academy of Medical Coding, United States Chapter.

Infectious Diseases Society of America. *Clin Infect Dis*. 2000;31(suppl 1):S1-S14.
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