Clinical Presentation and Medical Management of Melioidosis in Children: A 24-Year Prospective Study in the Northern Territory of Australia and Review of the Literature

Charlie McLeod,1 Peter S. Morris,1 Paul A. Bauert,1 Charles J. Kilburn,1 Linda M. Ward,2 Robert W. Baird,3,4 and Bart J. Currie2,3

1Pediatric Department, Royal Darwin Hospital; 2Global and Tropical Health Division, Menzies School of Health Research; 3Infectious Diseases Department, and 4Pathology Department, Royal Darwin Hospital, Australia

Background. Melioidosis is less common in children than adults. The clinical spectrum of disease varies greatly between the 2 groups. Treatment guidelines are currently based on adult studies, and revision of existing guidelines is necessary to instruct specific pediatric management.

Methods. Culture-confirmed cases of melioidosis in the Northern Territory between 1989 and 2013 were identified from the Prospective Melioidosis Study. The epidemiology and clinical spectrum of disease for children aged ≤16 years were analyzed and compared with the adult data.

Results. Forty-five pediatric patients were identified, representing 5% of the total 820 melioidosis cases over 24 years. Most children (84%) had no recognized risk factors for melioidosis, and 80% presented during the wet season. Primary cutaneous melioidosis was the commonest presentation in children (60% vs 13%; \( P < .001 \)), whereas pneumonia predominated in adults (54% vs 20%; \( P < .001 \)). Bacteremia was less common in children than in adults (16% vs 59%; \( P < .001 \)). Brainstem encephalitis occurred in 3 children without risk factors. Children were more likely to report an inoculating event (42%; \( P < .001 \)). There was no difference in mortality between the groups (\( P = .178 \)), with 3 children dying (7%); all had identifiable risk factors. Four children with cutaneous melioidosis were successfully treated with oral therapy alone, while 2 had skin lesions that resolved spontaneously.

Conclusions. Pediatric melioidosis commonly manifests as localized cutaneous disease in immunocompetent hosts. The disease can be fatal, especially in individuals with risk factors for disease. Melioidosis with encephalomyelitis can result in severe residual disability. Prompt diagnosis requires a high index of clinical suspicion in endemic areas.

Keywords. melioidosis; pediatric; Burkholderia pseudomallei; neuromelioidosis; cutaneous melioidosis.

Melioidosis is a tropical infectious disease of humans and animals due to infection with the gram-negative bacterium Burkholderia pseudomallei. This organism resides in soil and water. Transmission occurs primarily via percutaneous inoculation and inhalation. Less commonly, vertical or nosocomial acquisition, transmission to laboratory staff, or ingestion can occur (such as via mastitis-infected breast milk) [1–3]. A recent matched case-control study from Thailand suggested that ingestion of B. pseudomallei from unchlorinated domestic water supplies and other water sources such as rivers may be more common than previously thought [4]. Infection in endemic regions is predominantly seasonal, with approximately 80% of cases occurring during the wet season (November–April in the Northern Territory, Australia) [2]. Northern Australia and Southeast Asia are recognized as endemic hotspots. Cases have also been reported in India; China and Taiwan;
Indian Ocean locations such as Mauritius; the Americas; and Africa [5, 6].

Exposure to B. pseudomallei most commonly results in subclinical disease with or without seroconversion [7]. In northeast Thailand, serological studies suggest 1 per 4600 antibody-producing exposures result in clinical infection in that region [8]. The clinical spectrum of disease ranges from localized cutaneous infection to overwhelming sepsis and death [7]. The incubation period ranges from 1 to 21 days (mean, 9 days) for acute presentations [2]. The vast majority of cases present with acute illness, although chronic disease (symptoms present >2 months) is recognized to occur in approximately 10% of cases. Rare cases have been documented of activation from latency, with melioidosis occurring up to 62 years after initial infection [2, 9].

Historically, pediatric melioidosis accounts for 5%–15% of the total number of cases in endemic regions [2, 10, 11]. Nevertheless, clusters of cases in children have been the sentinel events to unmask the presence of melioidosis in remote locations in Papua New Guinea [12] and Brazil [13]. The Royal Darwin Hospital is a 350-bed tertiary care facility located in the tropical “Top End” of the Northern Territory. It services an area of 516,945 km² and a population of 230,000 (60,000 aged ≤16 years). Approximately 55% of the population resides in Darwin, and 30% of the population is Indigenous [14].

All confirmed cases of melioidosis in the Top End since 1989 have been prospectively recorded. The first 15 pediatric cases have been previously described [15, 16], and results of the 20-year Darwin prospective study have been reported elsewhere [2]. We now present the cumulative results over 24 years for pediatric patients. Our objectives were to compare the epidemiology and clinical spectrum of disease in children with adults and to summarize our approach to the management of pediatric patients with suspected melioidosis.

METHODS

Culture-confirmed cases of melioidosis in the Top End were identified from the Darwin Prospective Melioidosis Study database from 1 October 1989 until 30 September 2013. Approval for the study was obtained from the Human Research Ethics Committee (HREC) of the Northern Territory Department of Health and Menzies School of Health Research (HREC No. 02/38).

Patients were managed in conjunction with the Royal Darwin Hospital infectious diseases department. Children were categorized as aged ≤16 years. Chronic melioidosis was defined as symptoms present for >2 months. Septic shock was defined by the presence of hypotension with end-organ dysfunction unresponsive to fluid replacement [17]. Potential recreational exposure was defined as skin contact with environmental soil or water. Patients were followed until death or therapy completion. Gross nutritional assessment was based on admission weights. World Health Organization definitions were used to define children aged ≤10 years who were moderately or severely underweight. In children aged >10 years, weight <3rd percentile was used to define those at least moderately underweight [18].

Statistical analysis was performed using Stata (version 12). The χ² test was used for categorical analysis and P values <.05 were considered significant.

RESULTS

There were a total of 820 culture-confirmed cases of melioidosis. Forty-five cases (5%) were in children aged 7 months to 16 years. Twenty-four children were male (53%) and 49% were Indigenous. Twelve (27%) resided in urban Darwin, 12 (27%) lived within the Darwin rural outskirts, 17 (38%) were from remote Indigenous communities, and 4 (9%) were from rural townships.

The majority of children (38 [84%]) had no identified risk factors known to predispose to melioidosis [2]. Three children died (7%); all had identifiable risk factors (rheumatic heart disease, congenital heart disease, and pineal germinoma requiring high-dose steroids). Other predisposing conditions included chronic lung disease (n = 2) and type 1 diabetes mellitus (n = 2). Four of 27 (15%) children with primary cutaneous disease had recognized risk factors for disease compared with 5 of 18 (28%) with noncutaneous disease. Notably, 1 child had nodal tuberculosis, another had been on long-term inhaled corticosteroids for asthma, and 1 had coexistent anicteric hepatitis A, although these are not recognized risk factors. Six children were underweight (moderate n = 5, severe n = 1), 5 of whom had no other identified risk factor. Nutritional status was not recorded for 7 children.

Thirty-six children (80%) presented during the wet season (1 November–30 April). Of the 9 cases diagnosed during the dry, 1 had been exposed and presumptively infected during the preceding wet season. Thirty-seven cases (82%) were considered acute and 7 were chronic (16%). The median time from symptom onset to diagnosis was 13 days (range, 1 day–4 months). One child was thought to have activation of latent disease after a skin lesion developed at a laceration site exposed to creek water 13 months prior. Thirty-eight children (84%) reported potential recreational exposure to B. pseudomallei and 19 (42%) reported a specific inoculating event; 14 of these (74%) had primary cutaneous disease.

Table 1 lists the principal diagnosis and secondary foci for the 45 pediatric patients. Seven children were bacteremic (16%); 4 fulfilled the criteria for septic shock (9% overall). The child with pineal germinoma also likely succumbed to disseminated infection, although blood cultures were not obtained and an autopsy was not performed. Burkholderia pseudomallei was cultured
from a chest wall abscess at the portacath insertion site. Five children (11%) required admission to the intensive care unit. All were intubated, 3 required inotropic support, and 1 received granulocyte colony-stimulating factor (G-CSF). All 5 survived, with intravenous meropenem. Echocardiography was normal. She had no known risk factors for melioidosis, and no immune deficiency was found on investigation. Of the 3 who died, 1 died at home, 1 died upon arrival to hospital, and the other died on the ward 43 hours following presentation.

There were 3 cases of primary neurological melioidosis (7%) in children without risk factors: (1) a 9-year-old with primary brainstem encephalitis, bulbar weakness, and flaccid quadriaparesis with negative cerebrospinal fluid (CSF) culture but positive throat/sputum culture and with persisting residual quadriaparesis; (2) a 3-year-old with brainstem encephalitis and left seventh nerve palsy who did not have CSF collected but yielded a positive culture from a scalp boil; and (3) a 14-year-old with rhombencephalitis and negative CSF but positive sputum culture. The latter 2 cases had near-complete resolution of symptoms at discharge.

Twenty-two children (49%) received standard induction therapy with intravenous ceftazidime or meropenem for a minimum of 14 days, followed by eradication treatment with oral trimethoprim-sulfamethoxazole (TMX-SMP) prescribed for 3 months. Ten children received initial intravenous ceftazidime or meropenem but for a duration of <14 days. Five children received alternative antibiotic regimens including ceftazidime/doxycycline (n = 4) or ceftriaxone (n = 1). Four children with localized cutaneous disease received 3 months of oral therapy alone, with subsequent cure and no relapse. Four children did not receive antibiotics with specific B. pseudomallei activity. This included 2 fatal cases, where diagnosis occurred posthumously. The other 2 untreated children had primary cutaneous disease with spontaneous healing of small B. pseudomallei culture-positive skin sores. At least 17 children (38%) had received prior antibiotics without specific melioidosis cover, such as penicillin, flucloxacillin, or oral cephalosporins. The median length of hospital stay was 14 days (range, 0–87 days).

Seventeen children (38%) reported 19 adverse treatment-related events. These included myelosuppression (TMX-SMP = 5, meropenem = 1, ceftazidime = 3), rash (TMX-SMP = 7, ceftazidime = 1), vomiting (TMX-SMP = 1), and drug fever in 1 child, attributed to ceftazidime.

One child with cystic fibrosis presented with 3 separate episodes of melioidosis. Genotyping showed the B. pseudomallei strains to be genetically distinct, consistent with reinfection [2]. There was 1 instance of relapsed melioidosis (2%) in a 16-year-old previously healthy Indigenous boy who re-presented 2 months after completion of 14 days of ceftazidime/3 months of doxycycline for nonbacteremic pneumonia. He re-presented with pneumonia and responded to treatment with 14 days of ceftazidime/3 months of TMX-SMP. Genotyping confirmed identical isolates. Doxycycline was used initially due to incorrectly attributed resistance of the primary isolate to TMX-SMP. The median duration of follow-up for children was 5.5 months (range, 3.5–144 months). Seven children were lost to follow-up (including 2 from interstate and 1 who returned overseas).

There were striking differences between pediatric (n = 45) and adult (n = 775) cohorts. Children were more likely to report an inoculating event resulting in disease (42% vs 20%; P < .001). Primary cutaneous melioidosis was more frequent in children (60% vs 13%; P < .001). Pneumonia was the commonest principal diagnosis in adults (54% vs 20% in children; P < .001). The presence of bacteremia was significantly lower in children (16% vs 59%; P < .001), and fewer children required admission to intensive care (11% vs 26%, P = .024). There was no statistical difference in mortality between children and adults (7% vs 14%.

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### Table 1. Foci of Infection in 45 Cases of Pediatric Melioidosis, 1989–2013

<table>
<thead>
<tr>
<th>Principal Diagnosis</th>
<th>No.</th>
<th>% of All Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteremic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5 (2 fatal)</td>
<td>11</td>
</tr>
<tr>
<td>Septic arthritis/osteomyelitis</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>7</td>
<td>16</td>
</tr>
<tr>
<td>Nonbacteremic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin abscess</td>
<td>22</td>
<td>49</td>
</tr>
<tr>
<td>Soft tissue abscess(es)</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Encephalomyelitis</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Otitis externa</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Pulmonary colonization</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>37</td>
<td>82</td>
</tr>
<tr>
<td>Secondary focus&lt;sup&gt;b&lt;/sup&gt;/internal organ abscesses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary pneumonia</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Skin abscesses</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Septic arthritis</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Secondary brain infection</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Percutaneous endoscopic gastrostomy site infection</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Soft tissue abscesses</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Total&lt;sup&gt;c&lt;/sup&gt;</td>
<td>14</td>
<td>29</td>
</tr>
</tbody>
</table>

<sup>a</sup> An additional fatal case did not have blood cultures (see text).

<sup>b</sup> Subsequent to principal diagnosis.

<sup>c</sup> One patient had 2 secondary foci of disease.
DISCUSSION

This 24-year prospective study of melioidosis in the Northern Territory of Australia has highlighted the differing clinical spectrum of disease between our adult and pediatric populations. Here, children are more likely to present with primary cutaneous disease without bacteremia. Most lack predisposing risk factors. Contrasting, in adults, risk factors including diabetes mellitus, chronic renal failure, hazardous alcohol use, chronic lung disease, and immunosuppression occur in 60%-90% of cases [2, 5–7]. Despite prior reports of lower mortality for children with melioidosis compared to adults [5, 10], mortality rates did not differ between the groups in our study, even with the significantly lower rates of bacteremia in children. This finding may reflect the small number of children included in our study or improved awareness and earlier detection of melioidosis over time. The faster institution of antimicrobials and life-saving tertiary care contributed to adult mortality decreasing from >30% to 14% over the study period [2].

Interestingly, there has not been a single case of pediatric melioidosis parotitis in the Darwin prospective study, in stark contrast to the high rates reported from Southeast Asia (30%-40% of pediatric cases) [10, 19–21]. This regionally specific occurrence may reflect ingestion or aspiration of B. pseudomallei-contaminated water from unchlorinated domestic water supplies and other water sources [4]. This may also explain the higher rates of liver abscesses seen in Thailand [6] compared to Australia [2].

The first report of melioidosis encephalomyelitis came from Australia in 1992 [22]. This clinical syndrome appears to be far less common in Southeast Asia, where brain involvement usually involves cerebral abscesses secondary to bacteremic spread [23, 24]. Melioidosis with encephalomyelitis manifests as brainstem encephalitis with cranial nerve palsies (especially cranial nerve VII), or as myelitis with peripheral motor weakness [25]. It has also been described in children from tropical north Queensland [11, 26]. Studies in mice have supported the hypothesis that B. pseudomallei may directly invade the brain via movement along olfactory and/or trigeminal nerve root pathways following colonization of the nasal mucosa [27, 28]. Recent analysis of B. pseudomallei isolates from patients from the Darwin prospective study has shown a correlation between presentation with encephalomyelitis and the presence of the Burkholderia mallei–like actin polymerization bimA gene. To date, this has rarely been found in B. pseudomallei isolates from outside Australia [29]. Further studies are required to elucidate the epidemiology and pathogenesis of melioidosis with encephalomyelitis to see if it is indeed limited both in geographical location and to genetically restricted strains of B. pseudomallei. This has implications for clinical surveillance and vaccine development as melioidosis encephalomyelitis, like cutaneous melioidosis, usually occurs in people without the classical risk factors.

An additional consideration is that melioidosis encephalomyelitis is the one presentation of melioidosis where a confident diagnosis can be made without a positive culture but where a classical clinical presentation occurs in an endemic region, with supportive CSF analysis and neuroimaging results together with serological findings [2, 25]. Otherwise, serological testing without culture confirmation is considered inadequate to confirm a diagnosis. This is especially true in endemic locations where background seropositivity rates exceeding 50% have been reported [5, 6, 30]. In addition to the 3 culture-confirmed cases in the series reported here, a further 3 culture-negative pediatric cases of melioidosis encephalomyelitis were treated at Royal Darwin Hospital over the study period. None of these children had identified risk factors, but all had prior environmental exposure. The cases were (1) an 11-year-old with brainstem involvement but predominant myelitis and residual severe flaccid paraparesis, and indirect hemagglutination (IHA) titer to B. pseudomallei 1:1280; (2) a 4-year-old with an IHA titer of 1:320 also with residual severe flaccid paraparesis; and (3) an 8-year-old with predominant myelitis and an IHA titer of 1:640 with a residual foot drop. This patient had a prior slow-healing skin lesion on the thigh of the most affected side, which was not cultured. While speculative, this raises the possibility of spinal cord infection via nerve root translocation of bacteria secondary to skin inoculation with B. pseudomallei. Trigeminal or facial nerve translocation of B. pseudomallei into the brain may also have occurred in the child in this series who presented with brainstem encephalitis and who had a culture-positive scalp boil.

Neonates represent a patient subgroup that merits special consideration. A systematic review of neonatal melioidosis in 22 patients aged <28 days reported a crude mortality of 72.5% [1]. This mortality rate far exceeds that reported for adults in our cohort (14%), or indeed any patient subgroup reported globally to date (northeast Thailand describes overall mortality rates of 40%; 35% in children) [5]. Modes of transmission were reported in 10 of the 22 neonatal cases identified. Acquisition via ingestion of infected breast milk occurred in 1 case and vertical transmission associated with placental microabscesses occurred in another. Eight cases were attributed to community-acquired or healthcare-associated infection (such as contamination of chlorhexidine/cetrimide antiseptic solutions or multidose vials or reuse of medical equipment).

One 7-month-old infant in our study with bacteremic pneumonia with secondary neuromelioidosis has been reported previously [2]. Although acquisition in this case was attributed to

$p = .178$). There were also no differences between sex, ethnicity, or seasonal presentation.
ingestion of *B. pseudomallei*–containing breast milk, the mother also had pulmonary melioidosis. Genotyping showed *B. pseudomallei* from the mother’s sputum matching the child’s isolate, so respiratory transmission cannot be discounted.

Isolation of *B. pseudomallei* by culture is currently the diagnostic gold standard, but takes up to 7 days [5, 31]. Direct polymerase chain reaction assays of clinical samples have been used in trials but, while providing a more rapid diagnosis, they have to date been less sensitive than blood cultures for detecting bacteremic melioidosis [5, 32]. Direct immunofluorescence microscopy has been developed for rapid diagnosis in Thailand. This has good specificity but its sensitivity is less than that of culture [33]. Most recently, a rapid point-of-care antigen detection test using a dipstick lateral flow immunoassay has shown promise when tested on sputum and pus. This is unfortunately also less sensitive than culture for blood samples [34].

At Royal Darwin Hospital, current initial intensive therapy for children with disseminated melioidosis involves a minimum of 14 days of ceftazidime for ward patients or meropenem for those admitted to intensive care (Table 2). Prolonged intravenous therapy (4–8 weeks) is given to those with extensive pneumonia, neurological melioidosis, osteomyelitis, septic arthritis, or other deep-seated infections. Patients admitted to intensive care receive G-CSF, unless contraindications exist. Eradication therapy comprises oral TMX-SMP plus folic acid for a further 3 months [5]. In Thailand, amoxicillin-clavulanate is not infrequently used as an alternative to TMX-SMP for the eradication phase of therapy in children [5, 31].

Recent case series support the use of oral therapy alone for localized cutaneous melioidosis. In addition to our 4 patients, at least 22 cases of primary cutaneous disease reported in the literature were successfully treated with oral therapy without relapse [20, 21]. That 2 of the patients in our series had resolution of culture-confirmed cutaneous melioidosis without specific therapy is an important observation that reflects a poorly understood aspect of the natural history of infection with *B. pseudomallei*. One of the shortcomings of our study, however, was that 7 children were lost to follow-up.

At Royal Darwin Hospital, we consider oral therapy with high-dose TMX-SMP for patients with localized cutaneous disease, provided that there are no underlying risk factors and that dissemination or infection at other sites, including lymph node involvement, has been excluded. Our recommended doses for TMX-SMP have recently been lowered in view of the high rates of associated adverse effects. Table 2 lists our suggested approach to the management of children with melioidosis. All children are thoroughly investigated, regardless of presentation, to exclude other foci of disease [35]. Notably, more than half the patients with intra-abdominal foci do not experience abdominal pain [6]. A positive throat/sputum result is considered indicative of pulmonary involvement, even in the presence of a normal chest radiograph. Nasal swabs should be considered for those who present with neurological disease.

In conclusion, pediatric melioidosis is uncommon even in endemic locations. Recognition of this infection is challenging. Whereas most cases in Australia involve localized cutaneous disease in the immunocompetent host, severe sepsis and death can occur, especially in those with predisposing risk factors. Melioidosis encephalomyelitis is a syndrome of unclear pathogenesis that can result in severe residual neurological disability in previously healthy children. The possibility of coexisting malnutrition potentiating disease remains to be elucidated. Neonates represent a specific high-risk group. Prompt diagnosis and treatment require a high index of clinical suspicion in endemic areas, appropriate diagnostic cultures, and early specialist involvement in those with severe disease.

### Notes

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**Table 2. Investigations and Treatment for Pediatric Melioidosis at Royal Darwin Hospital**

<table>
<thead>
<tr>
<th>Investigations&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Treatment</th>
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</table>
| CXR | Disseminated disease: ceftazidime 50 mg/kg (up to 2 g) IV every 6 h or meropenem 25 mg/kg (up to 1 g) IV every 8 h for at least 14 d<sup>e</sup>  
Eradication therapy: trimethoprim + sulfamethoxazole 6 + 30 mg/kg (up to 240 + 1200 mg) orally every 12 h for at least 3 mo<sup>d</sup> plus folic acid 0.1 mg/kg (up to 5 mg) orally, daily for at least 3 mo  
Localized disease<sup>a</sup> | Initial intensive therapy: ceftazidime 50 mg/kg (up to 2 g) IV every 6 h for at least 14 d or meropenem 25 mg/kg (up to 1 g) IV every 8 h for at least 14 d<sup>e</sup>  
Eradication therapy: trimethoprim + sulfamethoxazole 6 + 30 mg/kg (up to 240 + 1200 mg) orally every 12 h for at least 3 mo<sup>d</sup> plus folic acid 0.1 mg/kg (up to 5 mg) orally, daily for at least 3 mo  
Trimethoprim + sulfamethoxazole dose for children and adults >60 kg is 320 + 1600 mg orally every 12 h.  
Providing the absence of risk factors for disease, and exclusion of disseminated foci, including lymph node involvement.  
Consider nasal swabs for those who present with neurological disease  
Throat and rectal swabs  
Wound swabs (where appropriate)<sup>b</sup>  
Sputum for culture (where possible)<sup>b</sup>  
Urine culture  
Abdominal and pelvic ultrasound  
CXR  
| Abbreviations: CXR, chest radiography; IV, intravenous.  
<sup>a</sup> For all children, regardless of presentation, to exclude disseminated foci.  
<sup>b</sup> Specimens collected in and/or directly plated on Ashdown’s selective broth/agar.  
<sup>d</sup> First line for neurological melioidosis, with dose doubled to 50 mg/kg (up to 2 g) IV every 4 hours for 8 weeks.  
<sup>e</sup> Trimethoprim + sulfamethoxazole dose for children and adults >60 kg is 320 + 1600 mg orally every 12 h.  
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Providing the absence of risk factors for disease, and exclusion of disseminated foci, including lymph node involvement.
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Potential conflicts of interest. All authors: No reported conflicts.

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References