Clinical Manifestations, Management, and Outcomes of Osteitis/Osteomyelitis Caused by *Mycobacterium bovis* Bacillus Calmette-Guérin in Children: Comparison by Site(s) of Affected Bones

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Objective To evaluate the clinical manifestations, management, and outcomes of *Mycobacterium bovis* Bacillus Calmette-Guérin (BCG) osteitis/osteomyelitis.

Study design We reviewed 71 cases of BCG osteitis/osteomyelitis registered in Taiwan's vaccine injury compensation program (VICP) in 1998-2014. Demographic, clinical, laboratory, treatment, and outcome data were compared according to site(s) of infection.

Results Involvement of a long bone of the lower extremity was present in 36.6% of the children, followed by foot bone (23.9%), rib or sternum (15.5%), upper extremity long bone (9.9%), hand bone (7%), multiple bones (4.2%), and vertebrae (2.8%). Children with lower extremity long bone involvement had a longer interval from receipt of BCG vaccine to presentation (median, 16.0 months; $P = .02$), and those with foot bone infection had higher rates of swelling (94.1%; $P = .02$) and local tenderness (76.5%; $P = .004$). Surgical intervention was performed in 70 children, with no significant difference in the number of procedures by site (median, 1.0 procedure per patient). Among the 70 children who received antimicrobial therapy, those with vertebral and multifocal infections had a longer duration of treatment ($P < .001$) and/or second-line antituberculosis medications ($P = .002$). Three children with vertebral and multifocal infections had major sequelae with kyphosis or leg length discrepancy. Outcomes were good for children with involvement of the ribs, sternum, and peripheral bones without multifocal involvement. The average time for functional recovery was 6.2 ± 3.9 months.

Conclusion Children with BCG osteitis/osteomyelitis in different bones had distinct presentations and outcomes. Pediatricians should consider BCG bone infection in young vaccinated children with insidious onset of signs and symptoms, and consider affected site(s) in the management plan. *(J Pediatr 2019;207:97-102).*

Bacillus Calmette-Guérin (BCG) is an important vaccine used to prevent tuberculosis (TB), especially meningeal TB and disseminated TB disease in children.[1] However, BCG vaccine can cause adverse effects, of which osteitis, or osteomyelitis, is a rare but serious complication.[2] In Taiwan, the Tokyo-172 vaccine strain is used for BCG vaccination of newborns and is included in the national vaccination program, with a coverage rate of nearly 100%. Active surveillance for BCG-related adverse events was initiated in 2008, and children diagnosed with BCG osteitis/osteomyelitis have been registered in the vaccine injury compensation program (VICP) in Taiwan.[3] The incidence of BCG osteitis/osteomyelitis in Taiwan was 30.1 cases per million vaccines in 2008-2012.[4]

BCG osteitis/osteomyelitis may proceed insidiously with a long incubation period. Because any bone can be affected, children can come to medical attention with a wide variety of symptoms and signs, making diagnosis challenging, and delays in diagnosis are frequent. Clinical manifestations suggesting BCG osteitis/osteomyelitis in children include fever; a mass or focal tenderness; warmth, redness, or swelling overlying the affected bone; and limited range of motion when a joint is involved. Children with affected bones of the lower extremities also can present with a limp or an inability to walk.[5-7] Surgical interventions and anti-TB medications are common treatment approaches.

The outcomes of BCG osteitis/osteomyelitis are variable in previous reports. A study in Taiwan reported poor prognosis for patients with vertebral osteomyelitis,[4] whereas in other studies, patients with involvement of the ribs, sternum, or humerus experienced good recovery.[5,6,8] In a recent study reported in Finland, 6.9% of patients with a lower limb infection developed a leg length discrepancy.[9] We hypothesized that clinical features and management of children with BCG osteitis/osteomyelitis differ according to the bone(s) involved. The aim of the present study was to describe and analyze the clinical

BCG	Bacillus Calmette-Guérin
MRI	Magnetic resonance imaging
TB	Tuberculosis
VICP	Vaccine injury compensation program

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presentations, therapy, and outcomes of children with BCG osteitis/osteomyelitis according to the site(s) of bone involvement.

Methods

Between January 1999 and December 2014, children with suspected BCG osteitis/osteomyelitis or in whom BCG osteitis/osteomyelitis could not be ruled out were identified via Taiwan's VICP. The diagnosis was made based on a record of BCG inoculation and the development of osteitis/osteomyelitis with a well-defined lesion, a positive culture, and/or a polymerase chain reaction test confirming *Mycobacterium bovis* and/or histopathology revealing granulation tissue with caseous necrosis without a history of exposure to TB. Parents/guardians submitted claims to the VICP and signed written consent forms on behalf of their children. The children's hospital information was stored in the Taiwan Centers for Disease Control database, where it is made available for research purposes. The medical records of hospitalization were reviewed retrospectively, and demographic data, clinical information, laboratory test results, therapy regimens, surgical procedures, and outcomes were collected. A telephone interview or direct visit was made if a patient's outcome could not be clearly determined from the medical record. The children were followed for 2-9.5 years after the diagnosis of BCG osteitis/osteomyelitis.

The sites of infected bones were categorized into 7 groups on the basis of region as follows: vertebra, rib or sternum, upper extremity long bone (humerus, radius, and ulna), hand bone (carpus, metacarpus, and phalange), lower extremity long bone (femur, tibia, and fibula), foot bone (tarsus, metatarsus, and phalange), and multiple bones (involvement of more than 1 bone). Data are presented as median and range or mean ± SD for continuous variables and as percentages for categorical variables. Differences between groups were analyzed using the Student *t* test or ANOVA with least squares means and post hoc tests for continuous variables, and the χ^2 or Fisher exact test with standardized residual post hoc tests for categorical variables. All *P* values were based on 2-sided tests and were considered statistically significant at <.05. All statistical analyses were conducted using SPSS version 21.0 (IBM, Armonk, New York).

Results

A total of 71 children with *M bovis* BCG-associated osteitis/osteomyelitis were identified in Taiwan's VICP from 1999 to 2014, of whom 37 (52.1%) were male. All 71 children were administered BCG vaccine intradermally into the lateral aspect of the left upper arm. Fifty-eight children (81.7%) had involvement of extremity bones, and 13 (18.3%) had involvement of axial bones; the distribution of bone sites is shown in the **Figure**. All children with multifocal infections had 2 bony lesions, in 2 bones. Two children (2.8%) were diagnosed with primary immunodeficiency with chronic granulomatous disease, and 4 children (5.6%) were born prematurely.

The median age at BCG inoculation was 13 days (range, 1-229 days) (**Table**). The median interval between vaccination and onset of symptoms was 13.9 months (range, 3-36 months), and the median age at disease onset was 14.4 months (range, 3.2-38.8 months). Most of the children (73.2%) developed initial symptoms by 7-18 months after BCG vaccination. Children with lower extremity long bone involvement generally had the longest incubation period (median, 16.0 months; *P* = .02) and older age at onset of symptoms (median, 16.0 months; *P* = .02). The median time from the first clinical visit to a correct diagnosis was 1.0 month (range, 0.2-13.0 months). The time to a correct diagnosis was longer in the children with infection of a foot bone (median, 2.0 months; *P* = .02); these children had a median of 3 median visits (range,

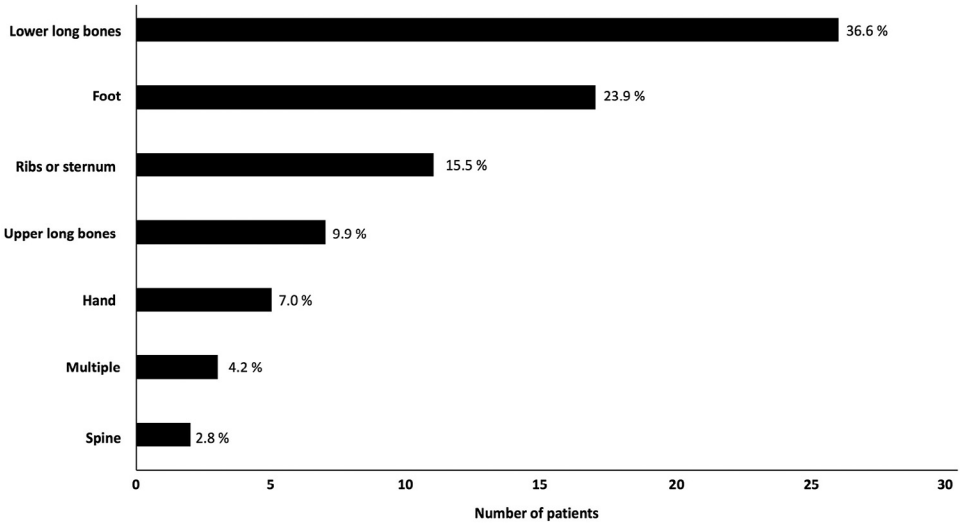

Figure. Distribution of site(s) of BCG osteitis/osteomyelitis in the enrolled children.

Table. Demographic data, clinical manifestations, and management of children with BCG osteitis/osteomyelitis by site of bone involvement

Characteristics*	Total (N = 71)	Vertebra (n = 2)	Rib or sternum (n = 11)	Upper extremity long bone (n = 7)	Hand (n = 5)	Lower extremity long bone (n = 26)	Foot (n = 17)	Multiple bones (n =3)	*P* value
Demographic data, median (range)									
Age at vaccination, d	13 (1-229)	3 (2-4)	14.0 (1-30)	7 (2-45)	40 (13-229)	20.5 (2-84)	7 (1-29)	8 (3-60)	.004
Interval from vaccination to symptom onset, mo	13.9 (3-36)	16.8 (16.0-17.5)	10.3 (3.0-27.0)	8.9 (5.9-15.6)	16.5 (3.9-25.1)	16.0 (10.4-36.0)	10.8 (4.1- 21.0)	13.0 (5.3-24.9)	.02
Age at onset of symptoms, mo	14.4 (3.2-38.8)	16.9 (16.1-17.6)	10.3 (3.2-27.6)	9.1 (6.4-16.0)	17.7 (5.5-25.7)	16.0 (11.2-38.8)	11.4 (4.2-21.0)	15.5 (5.5-24.9)	.02
Time to diagnosis, mo	1.0 (0.2-13.0)	0.7 (0.4-1.0)	0.5 (0.3-1.3)	1.0 (0.5-2.0)	1.0 (0.5-4.7)	1.0 (0.2-2.5)	2.0 (0.4-13.0)	2.0 (1.0-3.0)	.02
Medical visits before diagnosis	3.0 (1-20)	2.0 (2-2)	2.0 (2-6)	3.0 (1-3)	3.0 (1-7)	3.0 (1-7)	4.0 (2-20)	5.0 (4-7)	.14
Signs and symptoms, %									
Fever	21.1	50	18.2	14.3	0	23.1	17.6	66.7	.40
Erythema	33.8	0	18.2	28.6	80.0	30.8	41.2	33.3	.31
Swelling	77.5	0	90.9	57.1	100	69.2	94.1	66.7	.02
Warmth	22.5	0	0	14.3	40	26.9	23.5	66.7	.16
Tenderness	54.9	0	9.1	42.9	60.0	65.4	76.5	66.7	.004
Mass	51.4	0	54.5	85.7	20.0	48.0	58.8	33.3	.23
Limp*	64.6	100				69.2	52.9	66.7	.59
Management									
Surgical procedures, median (range)	1.0 (0-3)	2.0 (1-3)	1.0 (1-3)	1.0 (1-2)	1.0 (1-2)	1.0 (1-3)	1.0 (0-2)	1.5 (1-2)	.096
Hospital length of stay, d, median (range)	9.0 (0-241)	132.5 (24-241)	9.0 (2-33)	3 (2-18)	6.0 (4-25)	13.0 (2-70)	8.0 (0-33)	38.0 (4-87)	<.001
Duration of antimicrobial therapy, mo, median (range)	12.0 (0-38)	32.0 (26.0-38.0)	12.0 (3.0-25.0)	12.0 (9.0-12.0)	12.0 (9.0-12.0)	12.0 (6-21)	12.0 (6-24)	12.0 (12-12)	<.001
Regimens besides isoniazid, ethambutol, and rifampicin, %	24.3	100	9.1	16.7	20	30.8	6.3	100	.002

*Includes limp, abnormal/unsteady gait, or weakness. The rate was only calculated only in the children with vertebral, lower long bone, foot, and multiple bone involvement.

1-20 visits) before being diagnosed with BCG-associated osteitis/osteomyelitis.

Clinical manifestations varied by site of bone infection (**Table**). Signs and symptoms included fever (21.1%), redness (33.8%) or swelling (77.5%) overlying the affected bone, local warmth (22.5%) or tenderness (54.9%), a palpable mass (51.4%), and limping or the inability to walk (64.6%). Swelling (94.1%; $P = .02$) and local tenderness (76.5%; $P = .004$) were more common in children with foot bone involvement compared with those with involvement of other sites.

There were no significant differences in laboratory test results based on site of bone involvement. The mean white blood cell count was 13 000 ± 8800 cells/μL, mean C-reactive protein level was 1.78 ± 3.12 mg/dL, and mean erythrocyte sedimentation rate was 29.9 ± 25.0 mm/hour. The tuberculin skin test was performed in 39 children; 84.6% had positive results, with an average size of 15.2 ± 3.0 mm. The rates of positive acid-fast stain, culture, and polymerase chain reaction results from biopsy specimens/surgical sites of 68 children were 45.8%, 70%, and 93.7%, respectively. Sixty-eight children underwent biopsy and histology of bone specimen(s), all of which showed granulation tissue or typical caseous necrosis.

Surgical intervention was performed in 70 children (98.6%), with a median of 1.0 procedure (range, 0-3 procedures) per patient. There was no difference in the number of surgeries according to site of bone involvement. Overall, 13 children (18.3%) underwent multiple surgeries. Sixty-six children underwent excisional debridement, and 4 children underwent aspiration biopsy. Of the 66 children with excisional debridement, 7 underwent a second surgery and 3 underwent a third surgery due to lack of response to medical treatment. Seven children received extensive debridement, of whom 3 (42.9%; $P = .001$) had major sequelae. The patient who did not undergo surgery was a boy who developed osteomyelitis at age 10 months and in whom BCG lymphadenitis in the left axillary and supraclavicular area had been previously confirmed by excisional biopsy. He had underlying chronic granulomatous disease and received a 2-year course of chemotherapy.

In the whole cohort, the median hospital length of stay was 9 days (range, 0-241 days). Children with vertebral involvement had the longest hospital stay (median, 132.5 days; $P < .001$), followed by those with involvement of multiple bones (median, 38 days; $P < .001$).

Seventy children (98.6%) received antibiotic therapy for a median duration of 12 months (range, 3-38 months). The patient who did not receive chemotherapy had a small lesion of the talus and underwent an open arthrotomy with synovectomy, curettage, and an artificial bone graft. No major sequelae were noted during a 6-year follow-up in this patient. Children with vertebral involvement had the longest duration of therapy (median, 32 months).

Among the children with vertebral involvement, 1 patient presented with progressive lower limb weakness at age 16.1 months, and magnetic resonance imaging (MRI) of the spine revealed an epidural abscess over the T4 and T5 vertebrae. The patient underwent T2-T5 laminotomy and transpedicular corpectomy and was then started on isoniazid, rifampin, and pyrazinamide therapy. Pyrazinamide was discontinued after the diagnosis was revised from TB to BCG infection. Fourteen months later, MRI revealed progression of the abscess and a gibbus deformity with a kyphotic angle of 80 degrees. Second-line anti-TB medication therapy with levofloxacin and amikacin was administered for the next 7 months, after which a second surgery was performed; therapy was then continued for a total course of 38 months.

The other patient with vertebral involvement presented with an unsteady gait at age 17.3 months, and MRI revealed a gibbus deformity of the thoracic spine, a paraspinal abscess at T6-T9, and an epidural abscess at T7-T8. Partial excision of T8 and extensive debridement of the paraspinal area were performed. First-line anti-TB medications were prescribed. The patient showed a poor clinical response to chemotherapy after a 12-month course of treatment, and second-line therapy with moxifloxacin was started. The total duration of chemotherapy was 26 months.

Compared with children with other sites of bone involvement, the children with vertebral and multiple bone involvement were more frequently treated with second-line anti-TB agents (ie, streptomycin, amikacin, macrolides, levofloxacin, or moxifloxacin) in addition to isoniazid, ethambutol, and rifampicin ($P = .002$). Among the 3 children with multiple bone involvement, 1 child with infection of the distal femur and proximal tibia had a complicated course (undergoing 2 debridement procedures and sequestrectomy due to the persistent leg weakness and pain, with the addition of clarithromycin due to poor wound healing), whereas 2 children who received fluoroquinolone in combination with the first-line anti-TB medications at the start of chemotherapy had good outcomes.

Among the whole cohort, 3 children (4.2%) had major sequelae, including 2 patients with thoracic vertebral involvement that caused severe kyphosis and 1 patient with involvement of multiple bones around the knee and a leg length discrepancy that necessitated surgical correction 8 years later. The remaining 68 children recovered completely, with an average time to recovery of function or disappearance of signs and symptoms of 6.2 ± 3.9 months. There was no difference in recovery time ($P = .14$) by site of involvement.

Discussion

In our present analysis of children with BCG osteitis/osteomyelitis according to site of bone involvement, the distribution of affected bones was similar to that reported in previous studies, with bones of the extremities, and especially the lower limbs (60.6%), the most common sites of involvement.[10,11] How BCG vaccine leads to osteitis is not clearly understood, but hematogenous seeding is the most likely mechanism, considering the distance between the inoculation site and locations of infection. Factors associated with BCG osteitis/osteomyelitis include the vaccine strain, host susceptibility, and genetic defects. A decline in the incidence of osteitis in Finland coincided with the replacement of the Copenhagen BCG strain with the Glaxo strain,[2,11] revealing a relationship between the

BCG vaccine strain and the occurrence of osteitis/osteomyelitis. No cases of BCG osteitis/osteomyelitis have been recorded in the United Kingdom, where Glaxo BCG vaccine is used, which may also indicate a difference in host susceptibility.[12] Mendelian susceptibility to mycobacterial diseases has been reported with genetic defects in the interferon-γ pathway, which lead to a specific risk for mycobacterial infections, including with *M bovis*.[13] Two children with chronic granulomatous disease in our cohort had BCG osteitis/osteomyelitis with multiple bones involved. Previous studies have reported that congenital immunodeficiency often coexists with multifocal BCG osteitis/osteomyelitis,[14] suggesting that immune function should be evaluated in such patients. The majority of the children with BCG osteitis/osteomyelitis in our cohort had only 1 bony lesion and did not appear to have immune dysfunction of Mendelian susceptibility to mycobacterial diseases, based on their otherwise normal medical history. Our findings are also supported by a study from Thailand, where the same BCG Toyko-172 strain is used, in which none of the children with BCG osteitis was an immunocompromised host.[15]

As in previous studies,[10,16,17] in our cohort there was a long incubation period between vaccination and the onset of initial symptoms. Our children with infection of a lower extremity long bone had a longer incubation period/older age at disease onset, possibly because of increased physical activity and microtrauma to the bone in toddlers. BCG-related bony infection should be considered in older children with insidious symptoms suggesting chronic inflammation in a lower extremity long bone. In addition, children with infection of bones in the foot had localized symptoms and signs and a delayed diagnosis. BCG-associated osteitis/osteomyelitis should be considered in a vaccinated child who has unexplained and prolonged local swelling or tenderness of the foot.

Simple laboratory tests do not identify children with BCG osteitis/osteomyelitis. When the disease is suspected, a surgical specimen should be obtained for histologic examination, culture, and molecular testing. Culture is time-consuming and insensitive, with only 70% positive results. Positive histopathologic findings are expected but cannot discriminate between *M bovis* BCG and other species of the *M tuberculosis* complex infection. Molecular testing to confirm the *M bovis* BCG strain infection is optimal to allow for prompt initiation of effective therapy.

No randomized controlled trials of treatment for BCG osteitis/osteomyelitis exist to guide therapy. Koyama et al reported that a 6- to 12-month regimen of isoniazid and rifampicin was effective,[10] and Hesseling et al recommended regimens with at least 4 anti-TB drugs for a minimum of 9 months, along with a prolonged course of isoniazid.[11,18] Based on the good prognosis and recovery time of approximately 6 months in our cohort, it is our practice to treat children with a single lesion at any site other than vertebrae with a 6- to 9-month course of isoniazid and rifampicin. For children with vertebral or multiple sites of bony involvement in this study and others, first-line anti-TB medications have been associated with failure,[5] and regimens including second-line anti-TB medications have been associated with rapid response and good recovery.[19] Therefore, combination therapy with 2 or 3 first-line agents (eg, isoniazid + rifampicin ± ethambutol) and 1 second-line agent (eg, levofloxacin, macrolide) as an initial or rescue regimen is warranted.[20]

In most of our children, a single surgical procedure was performed to collect a specimen to confirm the diagnosis. Excessive debridement of bony lesions may be harmful.[4,16,21] Only 3 of our 71 children experienced major sequelae, all of whom underwent extensive debridement during the initial surgery. Two children had thoracic vertebral osteomyelitis that caused severe kyphosis at 5-year follow up. In previous reports, 6 children with BCG vertebral lesions with good outcomes had undergone only minor surgery or biopsy.[11,17,22-25] In our cohort, 1 patient had involvement of multiple bones around the knee that caused a leg length discrepancy necessitating surgical correction 8 years later. No major sequelae were noted in the remaining 25 children with lower limb involvement. The overall rate of long-term complications in our cohort was 2.1%. In a study reviewing orthopedic complications in 160 adults who had developed BCG osteitis from the Copenhagen or Glaxo BCG strain received in infancy, 6.9% of the questionnaire respondents reported a leg length discrepancy and 1.3% reported a minor gait abnormality at a follow-up of 19-47 years.[9] Our lower rate of late complications may be due to a less-virulent Tokyo-172 BCG strain used in Taiwan. However, in 2 other studies that retrospectively reviewed fewer cases of BCG osteitis in limbs attributed to the Tokyo-172 BCG strain, sequelae occurred in 12.5% of patients (1 of 8 with a median 4.1 years of follow-up had clinical growth disturbance)[26] and 20% of patients (1 of 5 with leg length discrepancy and abnormal gait at an 18-month follow-up).[15] It is noteworthy that the children in these 2 reports underwent surgical debridement; in comparison, the majority of our children with limb involvement underwent only diagnostic biopsy or minor surgical debridement. In our opinion, surgery should be performed as a diagnostic procedure rather than as treatment in children with BCG osteitis/osteomyelitis, in whom antimicrobial therapy should be the mainstay of treatment. Long-term follow up is needed to uncover the possible late sequelae of growth disturbance.

This study has several limitations. First, the relatively small sample size restricted our ability to reach some comparative conclusions between groups. We might have missed some cases, because only children registered in the VICP were included. In addition, although the VICP is a nationwide organization, children who were not correctly diagnosed with BCG osteitis/osteomyelitis would not have been included in this study. However, because children aged <5 years diagnosed with extrapulmonary TB are required to send specimens to the Taiwan Center for Disease Control for testing for BCG infection, the rate of loss should be low. We were unable to analyze the results of antimicrobial susceptibility testing of *M bovis* BCG because many children had a negative culture; therefore, we cannot provide specific recommendations for antimicrobial therapy.

Our present study and previous works suggest that antimicrobial therapy should be targeted by site of infection. Further

studies are needed to establish optimal individualized management for BCG osteitis/osteomyelitis according to the affected bone(s) and knowledge of antimicrobial susceptibility. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

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