Original Article

Tuberculosis among Healthcare Workers at Chiang Mai University Hospital, Thailand: Clinical and Microbiological Characteristics and Treatment Outcomes

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SUMMARY: Tuberculosis (TB) among healthcare workers (HCWs) highly affects morbidity and TB transmission in hospitals. A retrospective cohort study of TB among HCWs (HCW-TB) was conducted using a registered database from 2003 to 2016 at Chiang Mai University Hospital to determine clinical and microbiological characteristics and treatment outcomes of HCW-TB. A total of 76 patients comprising 54 nurses (71.1%), 12 physicians (15.8%), and 10 paramedics (13.2%) were diagnosed with TB disease. The men to women ratio was 25:51, with a mean age of 37.0 ± 11.6 years, a median work duration of 12.0 years (5–20) and a body mass index of 19.4 ± 2.5 kg/m². Within the HCW-TB group, 28 (36.8%) worked in the Medical Department, 12 (15.8%) worked in the Outpatient Department/Emergency Room, and 9 (11.8%) worked in the Surgical Department. Pulmonary TB (PTB) was the most common manifestation of HCW-TB (92.1%). Sputum acid-fast stains were positive among 28 (40.0%) HCWs with PTB. Mycobacterium tuberculosis cultures were positive in 26 (34.2%) patients. Drug susceptibility testing showed sensitivity to all first-line drugs (75.0%), resistance to any one first-line drug (20.8%), and multidrug-resistant TB comprised 4.2%. The end-of-treatment success rate was 100%. Therefore, TB control guidelines should be strictly implemented to prevent TB transmission in healthcare settings.

INTRODUCTION

Tuberculosis (TB) remains a major global health problem and one of the top 10 causes of death worldwide. In 2016, the World Health Organization (WHO) reported 10.4 million new TB cases, and people living with human immunodeficiency virus (HIV) accounted for 1.2 million (11%) of all new TB cases. In 2015, the WHO ranked Thailand in 25th place among a high TB burden for 30 (11%) of all new TB cases. In 2015, the WHO ranked Thailand in 25th place among a high TB burden for 30 high TB burden countries and reported an incidence of TB at 172 per 100,000 population and multidrug-resistant TB (MDR-TB) at 6.6 per 100,000 (1). Due to the TB burden among healthcare workers (HCW-TB), the WHO developed guidelines to measure and monitor the incidence and prevalence of TB in HCWs through TB CARE I and TB CARE II to improve the quality of the monitoring TB program, particularly in high burden countries (2,3).

HCWs have a high risk of TB due to frequent exposure to diagnosed and undiagnosed active TB patients, especially in a healthcare setting with inappropriate TB control (4–8). The risk of transmission varies for each setting, occupational group, the TB burden, and patient population (8).

In Thailand, data on HCW-TB is scarce. Only one study has been conducted on risks of TB transmission among HCWs (9), and no report has been published on treatment outcomes of HCW-TB. Our setting entails a 1,400-bed tertiary care and referral university hospital located in northern Thailand, with a high TB prevalence among HIV-positive patients, together with a limited area for TB isolation. In 2015, the incidence of HCW-TB at our hospital was 240 per 100,000 population (TB registered database, 2015; unpublished data). TB registration for HCWs leads to early TB screening, resulting in earlier diagnosis, isolation and treatment, improved outcomes, and prevention of serious illness and mortality (2).

The objectives of this study were to determine clinical and microbiological characteristics and drug-susceptibility testing (DST), to evaluate treatment outcomes among HCWs, as well as to compare clinical signs and symptoms, radiological evidence, TB-confirmed diagnoses, and outcomes between smear-positive and smear-negative pulmonary TB (PTB).

MATERIALS AND METHODS

From 2003 to 2016, we conducted a retrospective cohort study of HCW-TB from a registered database at Chiang Mai University Hospital, Chiang Mai, Thailand, and end-of-treatment (EOT) outcomes were evaluated. The DST of microbiologically culture-confirmed TB cases was reported.

The study was approved by the Ethics Committee of the Faculty of Medicine, Chiang Mai University (Certificate of approval No. 221/2016).

Participants: All TB case reports among HCWs registered in the database from 2003 to 2016 were retrospectively reviewed. PTB disease was defined as follows: positive symptoms such as cough, chest pain, fever, coughing up sputum, hemoptysis, weight loss, or dyspnea with abnormalities of chest radiographies. Sputum smear-negative
PTB and extra-pulmonary TB (EPTB) were also included (10). HCWs were defined as all people engaged in actions whose primary intent was to enhance health, including other personnel working in healthcare facilities that may have been in contact with either TB patients or infectious materials from TB patients, including physicians, nurses, and paramedics, in addition to administration/office staff, cleaners, and patient transport personnel (11).

Data collection: Demographic data recorded in TB case reports within the HCW registration database included sex, age, comorbidity, and body mass index (BMI). HCWs were categorized into 3 groups: i) physicians; ii) nurses; and iii) paramedics (comprising pharmacists, laboratory and radiological technicians, cleaners, and patient transport personnel). Data records on work place, duration of work, history of treatment (new/retreatment), type of TB registration (pulmonary/extra-pulmonary), type of TB notification (new case, relapse, failure), clinical signs and symptoms (cough > 2 weeks, sputum production, fever, hemoptysis, weight loss, chest pain, or dyspnea), radiographic findings, microbiological evidence with drug sensitivity, anti-TB regimens, duration of treatment, and adverse drug reactions, were assessed. The EOT outcomes were categorized as follows: success, including cure in the case of smear-positive PTB; completed treatment in the case of smear-negative PTB; and failure (relapsed, TB-related death). All the HCW-TB patients that had been followed up for long-term survival and treatment failure after EOT were evaluated.

Statistical analysis: Demographic data were expressed using descriptive statistics. Categorical variables were expressed as counts and percentages. Continuous variables were expressed as mean and standard deviation (SD), or as median and interquartile range (IQR). Clinical and radiological findings, and outcomes were compared between smear-positive and smear-negative PTB groups and analyzed using Fisher’s exact test for categorical data and the Student’s t-test or the Wilcoxon rank-sum test for continuous data. Survival analysis was used to compare survival outcomes between smear-positive and smear-negative PTB. A p-value < 0.05 was considered statistically significant. All statistical analyses were performed using STATA ver. 12 (StataCorp, College Station, TX, USA).

RESULTS

A total of 76 diagnosed of HCW-TB patients were included in this study, comprising 54 (71.1%) nurses, 12 (15.8%) physicians, and 10 (13.2%) paramedics. Baseline characteristics showed a men to women ratio of 25:51, a mean age of 37.0 ± 11.6 years (36.8% were in an age group ≤ 30 years), a median work duration of 12.0 years (IQR 5, 20) with 30.3% having a work duration period 6–10 years, 17.1% 11–20 years, and 22.4% ≥ 30 years. A mean BMI of 19.4 ± 2.5 kg/m² (min-max, 14.6–27.1) was recorded. Concerning a history of active TB exposure, 69 (90.8%) patient with active TB, co-workers, and family members who had TB, respectively (Table 1). PTB (92.1%) was the most common manifestation of HCW-TB, including smear-positive (40.0%) and smear-negative PTB (60.0%), and EPTB (7.9%). The diagnostic methods to confirm TB included positive sputum acid-fast stains (n = 33, 43.4%) and positive of Mycobacterium, as being previously exposed to TB patients, co-workers, and family members who had TB, respectively (Table 1).

| Table 1. Baseline characteristics of TB among HCWs (n = 76) |
|------------------------------------------------------------|
| Demographic data                                           |
| Sex, men:women                                             | 25:51 (32.9:67.1) |
| Age (yr) (mean ± SD)                                       | 37.0 ± 11.6       |
| ≤ 30                                                      | 28 (36.8)         |
| 31–40                                                     | 22 (28.9)         |
| ≥ 41–50                                                   | 9 (11.8)          |
| ≥ 51–60                                                   | 17 (22.4)         |
| Group of HCWs                                              |
| nurse                                                     | 54 (71.1)         |
| physician                                                 | 12 (15.8)         |
| paramedical                                               | 10 (13.2)         |
| BMI (kg/m²) (mean ± SD)                                    |
| ≤ 18.5                                                    | 31 (40.8)         |
| 18.5–24.9                                                 | 43 (56.6)         |
| ≥ 25.0–29.9                                               | 2 (2.6)           |
| ≥ 30.0                                                    | 0 (0.0)           |
| Work duration (yr)                                         |
| ≤ 5                                                       | 23 (30.3)         |
| 6–10                                                      | 13 (17.1)         |
| 11–20                                                     | 23 (30.3)         |
| 21–30                                                     | 8 (10.5)          |
| ≥ 31                                                      | 9 (11.8)          |
| Working department                                         |
| Medical                                                   | 28 (36.8)         |
| Outpatient/Emergency Room (OPD/ER)                        | 12 (15.8)         |
| Surgical                                                  | 9 (11.8)          |
| Pediatric                                                 | 5 (6.6)           |
| Radiology                                                 | 4 (5.3)           |
| Anesthesia                                                | 3 (3.9)           |
| Rehabilitation                                             | 3 (3.9)           |
| Laboratory                                                | 2 (2.6)           |
| Orthopedic                                                | 2 (2.6)           |
| Otorhinolaryngology                                        | 2 (2.6)           |
| Private ward                                               | 2 (2.6)           |
| Others                                                    | 4 (5.3)           |
| (Gynecology, 1; Laundry, 2; Hemodialysis unit, 1)         |
| Comorbidity                                               |
| Hypertension                                              | 19 (25.0)         |
| dyslipidemia                                              | 4 (5.3)           |
| allergic rhinitis                                         | 5 (6.6)           |
| asthma                                                    | 4 (5.3)           |
| HIV infection                                             | 2 (2.6)           |
| cancer                                                    | 2 (2.6)           |
| osteoporosis                                              | 1 (1.3)           |
| diabetes mellitus                                         | 1 (1.3)           |
| History of TB exposure                                     |
| family member                                             | 1 (1.3)           |
| co-worker                                                 | 34 (44.7)         |
| patient with active TB                                     | 69 (90.8)         |

HIV, human immunodeficiency virus; BMI, body mass index.
**tuberculosis** (MTB) cultures \((n = 26, 34.2\%)\). Chest radiographs were undertaken for 90.8% of patients, computerized tomography (CT) scans were performed for 9.2% of patients, and a molecular test was performed using Xpert MTB/RIF (Cepheid, Brea, CA, USA) in 2.6% of patients, and tissue biopsy was undertaken in 7.9% of patients, as shown in Table 2.

Table 3 demonstrates the comparison between smear-positive \((n = 28)\) and smear-negative \((n = 42)\) PTB patients, and 100% of smear-positive patients presented at least one TB symptom, while 38.1% of the smear-negative group had no TB symptoms \((p = 0.001)\). The most commonly presenting symptom, found to be significantly higher in the smear-positive than the smear-negative group, was a cough that had been present for more than 2 weeks \((92.9\% \text{ vs. } 26.2\%, p < 0.001)\), followed by weight loss \((32.1\% \text{ vs. } 11.9\%, p = 0.038)\), and sputum production \((25.0\% \text{ vs. } 4.8\%, p = 0.013)\). The length of time from the onset of symptoms to TB diagnosis was 21 days vs. 12 days \((p = 0.035)\), and cultures confirmed MTB in 67.9% vs. 11.9% \((p < 0.001)\), respectively.

Radiologic findings showing abnormalities compatible with TB \((n = 69, 98.6\%)\) included nodular opacity \((n = 62, 89.9\%)\), cavitation \((n = 18, 26.1\%)\), and effusion \((n = 4, 5.8\%)\). A single lobe of lung involvement was the most common TB lesion site \((82.9\%)\), especially in the right upper lobe \((54.4\%, \text{ data not shown})\) and 17.1% in ≥ 2 lobes (Table 3). In one patient, no infiltration was evident on chest radiographs, however, a CT scan was performed to confirm TB. DSTs were performed for *M. tuberculosis* isolated from 24 patients (Table 4). Eighteen isolates \((75.0\%)\) were susceptible to all first-line drugs, 5 isolates \((20.8\%)\) were drug-resistant, and 1 isolate \((4.2\%)\) was multi-drug resistant.

All HCW-TB patients completed the treatment provided by the physicians, including a standard short-course chemotherapy (2HRZE/4HR; 96.1%), (2HRZES/1HRZE/5HRE; 2.6%), and treatment for MDR-TB, 1.3%. Concerning EOTs, the success rate was 100% \((44.7\% \text{ of patients were cured, and } 55.3\% \text{ of patients completed treatment})\). None of the patients relapsed. Ten \((13.2\%)\) patients developed adverse drug reactions which included anti-TB drug-induced liver injury (ATDILI; 5.3%), nausea and/or vomiting (3.9%), and skin reactions (3.9%). Regarding survival status for long-term follow-up, 1 patient \((1.3\%)\) with smear-positive PTB died 1 year after EOT from the primary disease (Table 5).

### Table 2. Type of TB registration and TB confirmed diagnosis \((n = 76)\)

| Type of TB          | No. (%) |
|---------------------|---------|
| Pulmonary TB (PTB)  | 70 (92.1) |
| smear-positive      | 28 (40.0) |
| smear-negative      | 42 (60.0) |
| Extra-pulmonary TB (EPTB) | 6 (7.9) |
| TB lymphadenitis     | 4 (66.7) |
| TB bone and joint   | 1 (16.7) |
| TB skin             | 1 (16.7) |
| Diagnostic methods  |         |
| acid-fast bacilli (AFB)-positive | 33 (43.4) |
| culture growth: *M. tuberculosis* | 26 (34.2) |
| chest radiogram     | 69 (90.8) |
| CT scan             | 7 (9.2)  |
| molecular test by Xpert MTB/RIF | 2 (2.6)  |
| others (tissue biopsy) | 6 (7.9)  |

**CT**, computed tomography.

### Table 3. Clinical sign and symptom and radiological finding of PTB \((n = 70)\)

| Clinical sign/symptom       | All PTB No. (% \((n = 70)\)) | PTB smear-negative \((n = 42)\) | PTB smear-positive \((n = 28)\) | \(p\)-value |
|-----------------------------|--------------------------------|--------------------------------|--------------------------------|-------------|
| cough > 2 wk                | 37 (52.9)                      | 11 (26.2)                      | 26 (92.9)                      | < 0.001     |
| cough ≤ 2 wk                | 17 (24.3)                      | 13 (31.0)                      | 4 (14.3)                       | 0.111       |
| fever                       | 8 (11.4)                       | 6 (14.3)                       | 2 (7.1)                        | 0.357       |
| hemoptysis                   | 7 (10.0)                       | 2 (4.8)                        | 5 (17.9)                       | 0.074       |
| weight loss                  | 14 (20.0)                      | 5 (11.9)                       | 9 (32.1)                       | 0.038       |
| sputum                      | 9 (12.9)                       | 2 (4.8)                        | 7 (25.0)                       | 0.013       |
| chest pain                   | 7 (10.0)                       | 4 (9.5)                        | 3 (10.7)                       | 0.871       |
| dyspnea                     | 5 (7.1)                        | 1 (2.4)                        | 4 (14.3)                       | 0.054       |
| At least 1 clinical sign/symptom | 54 (77.1)                      | 26 (61.9)                      | 28 (100.0)                     | 0.001       |
| No clinical sign/symptom    | 16 (22.9)                      | 16 (38.1)                      | 0 (0.0)                        |             |
| Duration of symptoms before TB diagnosis (day) median (IQR) | 20 (7.21) | 12 (7.21) | 21 (13.25) | 0.035 |
| History of TB exposure      | 66 (94.3)                      | 59 (92.9)                      | 7 (25.0)                       | 0.665       |
| Diagnostic methods          |                                 |                                |                                |             |
| TB culture: *M. tuberculosis* | 24 (34.3)                      | 5 (11.9)                       | 19 (67.9)                      | < 0.001     |
| Radiological finding        |                                 |                                |                                |             |
| nodular opacity             | 62 (88.6)                      | 38 (90.5)                      | 24 (85.7)                      | 0.540       |
| cavity                      | 18 (25.7)                      | 7 (16.7)                       | 11 (39.3)                      | 0.034       |
| effusion                    | 4 (5.7)                        | 3 (7.1)                        | 1 (3.6)                        | 0.093       |
| Lung involvement            |                                 |                                |                                |             |
| single lobe                 | 58 (82.9)                      | 36 (85.7)                      | 22 (78.6)                      | 0.550       |
| ≥ 2 lobes                   | 12 (17.1)                      | 6 (14.3)                       | 6 (21.4)                       |             |

IQR, interquartile range.
Every HCW-TB and where there is no evidence of active we conduct active surveillance of the close contacts of sources of TB transmission among HCWs in our hospital, Our TB clinic is the hub of TB care among HCWs in our hospital, (12). However, in high burden countries such as Thailand, the possibility of TB exposure outside the hospital may increase the risk of TB, depending on duration of exposure to active TB patients and the immune status of contacts susceptible to TB, such as people with HIV/AIDS. In 2015, the incidence of TB among HCWs in our hospital (4). The risk of TB transmission can vary depending on setting, occupational group, TB burden, patient population, use of personal protective equipment, and the effectiveness of TB infection control measures (12). However, in high burden countries such as Thailand, the possibility of TB exposure outside the hospital may increase the risk of TB, depending on duration of exposure to active TB patients and the immune status of contacts susceptible to TB, such as people with HIV/AIDS. In 2015, the incidence of TB among HCWs in our hospital was 240 per 100,000 population, 3-fold higher than the general population (17,26). For example, the incidence of HCW-TB in South Africa has been reported to be from 25 to 5,361 per 100,000 annually, which is 5- to 10-fold higher than their general population (15,17).

Among HCWs, incidence of TB varies according to their occupations. Nurses with TB had the highest incidence (71.1%), then physicians (15.8%), and paramedics (13.2%), in our study. The close contact involved in caring for patients increased the risk of exposure to TB among the nurses, especially in centers with inadequate TB control (18). A comparable Kenyan study showed that 74% of 190 HCW-TB patients involved nurses, physicians, and paramedical staff (19). Similarly, a report of 41 HCW-TB patients in Taiwan revealed that 41.5% and 29.3% were nurses and physicians, respectively (20). One study in India confirmed a higher annual risk of TB transmission among nurses than in the general population (21).

Work location is 1 factor determining the risk of TB among HCWs. HCWs working at TB clinics, inpatient TB wards, laboratories, and general and emergency rooms have an increased risk of TB (17). We found a high number of TB patients had been working in the Medical Department (36.8%), followed by the OPD/ER (15.8%), and the Surgical Department (11.8%). The average number of TB admissions in our hospital was 300 patients annually, especially to the Medical Department. As the largest department in our institute with a higher number of patients admitted than in other departments, a greater opportunity exists to fail to diagnosis or delay diagnosis and isolation of active TB patients. The TB clinic and ward is also attended by the Medical Department personnel. According to a South African HCW-TB report, working in a TB ward is a risk factor for TB (22). We found the highest cases of TB among HCWs with a work duration within 5 years and that between 11 and 20 years (30.3%). The average lifetime risk after developing TB is from 5% to 10% with the highest risk being within the first 5 years of infection (23). Previously published reports indicate that between 5% and 15% of individuals with MTB will progress to active TB (24), whereas the remainder retain a persistent risk of developing active TB throughout their lifetime (25).

We found 1 case of primary MDR-TB among the HCWs and an incidence rate of 20 per 100,000 population, whereas the MDR-TB incidence of new TB cases in Thailand was 6.6 per 100,000 population, which indicated 3-fold higher incidence rate in our hospital than in the general population (1). Similar to South Africa, the incidence of MDR-TB among HCWs was more than 5-fold higher than in the general population (17,26).

Due to the high rate of exposure to active PTB cases (92.1%) for HCW-TB and no available genotypic study to confirm nosocomial transmission of TB in our institute, adherence to TB prevention and control policies is emphasized for both patients and staff occupational health and safety. Most HCW-TB patients presented with PTB symptoms (77.1%), while 22.9% had subclinical TB, or
no TB symptoms and an abnormal annual chest radiograph check-up, requiring early notification to be diagnosed by a chest physician. In a similar TB review, of 50% of all people with culture-positive TB, at least 25% presented no TB symptoms (27). In our subclinical TB group, we found smear-positive results (3.6%) to be an important risk factor for TB transmission to patients and other HCWs in the hospital. In contrast, only 1 case of symptomatic TB had an unremarkable chest radiograph; however, a CT scan demonstrated classic TB hilar and mediastinal lymphadenitis, with right main bronchial invasion by the right lower paratracheal nodes. Xpert MTB/RIF and TB culture of broncho-alveolar lavage were confirmed MTB in this patient.

We found HIV-TB co-infection in 2 HCWs (2.6%), 1 died at 1 year after completing treatment due to AIDS-related lymphoma. One HCW-TB report over a 5-year period in KwaZulu-Natal, South Africa, found that 11% to 16% of HCWs were positive for serologic HIV testing, and that HIV was the single greatest risk for TB among HCWs (22). The WHO estimated 1.2 million people are living with TB-HIV worldwide, and 400,000 people died from HIV-associated TB in 2015 (1). Given HIV is the strongest risk factor for both primary and reactivation TB, with high morbidity and mortality, testing all HCW-TB patients for HIV status is important (2).

MDR-TB is a significant risk factor for treatment failure and TB mortality, especially in HIV-positive patients (28). A study of outcomes of 360 Ukrainian patients with MDR-TB showed that only 18.1% of patients achieved treatment completion or cure, while 36.4% died, and treatment failure occurred in 10.3% of the patient in the study (29). A retrospective study of 188 patients with MDR-TB in Thailand reported unfavorable outcomes in over one-third of patients due to poor adherence to treatment (30). Our study had 1 case of primary MDR-TB. This HCW worked in the HIV/AIDS clinic, which represented one of the highest risks for MDR-TB transmission. She had no past history of TB and contact investigation found no active TB among her family members. Therefore, the exposure to MDR-TB patient was likely to have occurred in her workplace, which was the suspected source of MDR-TB transmission. The EOT outcome was a cure following an 18-months MDR-TB regimen, due to good treatment adherence and no comorbidity.

Adverse effects of anti-TB drugs affect treatment outcomes. Failure to complete the standard treatment regimen from adverse drug reactions has been associated with development of multi-drug resistance (20). A study of ATDILI in Shanghai demonstrated a 12.9% incidence during standard anti-TB therapy, which was associated with poor treatment outcomes (31). On the contrary, the rate of ATDILI was only 5.3% in our study. The lower adverse drug events in our study might be explained by the patients' relatively younger age group, and the low rate of comorbidities. High adherence to therapy resulted in a higher rate of completing the standard treatment regimen and improved TB treatment outcomes among the HCWs. All the successful treatment outcomes were also attributable to an intensive education program regarding TB self-management plans, close monitoring during treatment, and follow-up by a TB-coordinator as well as chest physicians responsible for monitoring/treating TB among HCWs.

To the best of our knowledge, the present study was the first long-term cohort study to evaluate treatment outcomes of HCW-TB in Thailand. All the HCWs with TB completed the treatment, including the patients with MDR-TB. The success rate in our study was 100%, while the success rate of TB treatment in the general Thai population is reported to be 80%. Our study success rate met the 'End TB Strategy at Global and National Levels' intervention target, with recommended target levels of more than 90% (1).

Our study had limitations. First, this study was conducted at a single university hospital. Therefore, our results may not correspond with national epidemiologic data and may not be applied to other healthcare settings and systems in Thailand. However, our study is valuable not only to present the TB burden among HCWs in a university hospital in Thailand, but also to increase awareness of TB transmission in any hospital system nationwide. Second, the purified protein derivative skin test was not conducted before HCWs started the work. Third, the interferon-gamma release assays and molecular typing such as restriction fragment length polymorphism or variable number of tandem repeats were unavailable in our hospital during the study period. Therefore, confirmation of the source of TB in HCWs could not be determined. Further molecular epidemiological studies are required to investigate TB outbreak transmission among HCWs.

Nevertheless, the occurrence of TB among HCWs in our study reflected TB difficulties and raises awareness on preventing transmission in hospitals. TB was also found within a particular group of HCWs, which supports the need for regular surveillance for early identification of new active TB patients in some HCW subgroups.

In conclusion, the incidence of TB among HCWs was higher than that among the general population. Nurses were the highest risk group for TB. Drug-resistant TB, especially primary MDR-TB, was identified among HCWs. TB may present as asymptomatic with an abnormal chest radiograph. Therefore, annual active TB screenings among HCWs may lead to early detection and treatment, and improve outcomes. TB control guidelines should be strictly implemented to prevent TB transmission in healthcare settings.

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Conflict of interest None to declare.

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