CORRESPONDENCE

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Early detection of tuberculosis in patients with smear-negative pulmonary tuberculosis

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A recent study conducted by Kwak et al. [1] published in the *Korean Journal of Internal Medicine* reported a delayed diagnosis of over 50% of pulmonary tuberculosis with initial smear-negative. The initial diagnosis is often based on clinical symptoms, and the identification of evidence for *Mycobacterium bacilli* in the laboratory is necessary to establish a more accurate result.

Medical information, physical and laboratory examination are needed to diagnose tuberculosis, and Indonesia is the third country with the largest burden, after China and India. Furthermore, rapid detection is necessary to initiate anti-tuberculosis therapy to prevent widespread of this disease. Acid-fast bacilli (AFB) staining and culture are commonly used for the detection of *Mycobacterium tuberculosis*. Other diagnostic methods such as tuberculin, interferon-gamma release, and polymerase chain reaction (PCR) can also be used in a clinical setting [2].

AFB staining is the oldest method to diagnose tuberculosis, and it is easy, low cost, and widely available in most primary public health. It cannot detect a low load of tuberculosis bacteria in the sputum, such as, in cases of paucibacillary tuberculosis, which often yield false-negative. Furthermore, the accuracy depends on the quality of the specimen. When AFB staining is negative, and the clinical symptoms for tuberculosis are highly present, culture for *M. tuberculosis* or chest-ray should be performed. The culture is considered as the gold standard; however, there are two major limitations of this method. First, the growth of *M. tuberculosis* in Lowenstein Jensen is very slow, and it reduces the rapid diagnosis of tuberculosis. In developing countries like Indonesia, the facility is only available in specific laboratories or hospitals. A rapid and accurate diagnostic examination is needed to accelerate diagnosis.

The newest method to detect tuberculosis is molecular assay with a shorter turnaround time. The molecular technique is the GeneXpert MTB/RIF assay based on quantitative real-time-PCR to detect the presence of *M. tuberculosis* in less than 2 hours. GeneXpert MTB/RIF has many advantages, and it uses a closed amplification system that potentially reduces cross-reaction contamination. In addition, it provides information about rifampicin resistance encoded by the *rpoB* gene and it is responsible for 96% of cases. It can be easily used in resource-limited settings. Therefore, it can replace the microscopic tests because it can detect bacteria in smear-negative. According to World Health Organization, GeneXpert can be used as a preliminary in patients with suspected pulmonary tuberculosis.

The study by Kwak et al. [1] reported that among tuberculosis patients with a smear-negative and positive culture, more

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than 90% underwent MTB PCR or Xpert MTB/RIF testing, and 47.8% had positive results. The study was divided into two groups. Patients that received anti-tuberculosis treatment after the confirmation of positive culture were enrolled in the missed tuberculosis group. In contrast, those that received anti-tuberculosis treatment before obtaining the culture results were enrolled in the control group. Results of positive PCR were reason to administer anti-tuberculosis therapy in the control group. Therefore, positive PCR was associated with a faster tuberculosis diagnosis [1]. GeneXpert/RIF was only conducted in several referrals to primary public health or hospitals, especially in patients suspected of multidrug-resistant tuberculosis.

However, the study by Kwak et al. [1] reported that the sensitivity of PCR was only 47.8%. Another study by Notopuro et al. [3] reported that from 28 suspected tuberculosis patients, the diagnosis using the PCR technique resulted in sensitivity, specificity, positive predictive value, and negative predictive value of 100%, 82.4%, 89.7%, 100%, respectively. Therefore, the bacterial burden in patients from South Korea was lower than that from Indonesia [3].

The study by Kwak et al. [1] reported that older age, high body mass index, and negative PCR results were significantly associated with delay in diagnosis. Meanwhile, the median days from culture testing to begin the tuberculosis treatment were significantly higher in patients administered with anti-tuberculosis treatment after positive cultures compared to those before positive cultures (25 days vs. 3 days), respectively [1]. Delay in diagnosis will significantly reduce drug administration, increase transmission, and treatment failure. Based on the Indonesian Health Profile in 2016, the treatment success rate of tuberculosis did not meet the minimum criteria (83.6%) since the target was 90%. The success rate of the treatment is associated with high adherence and early detection of new cases. Delay in treatment or diagnosis occurs either as patient or provider (health care) delay.

Delay in diagnosis of pulmonary tuberculosis reported by Kwak et al. [1] was similar to the study conducted by Lestari et al. [4]. The results showed that out of 414 TB patients, 74.6% seek informal or private health care providers. They experienced a complicated service to obtain a diagnosis from both public and private health care providers. Furthermore, the median time from the onset of symptoms to the diagnosis of tuberculosis and to begin the treatment was 62 and 65 days, respectively. Patients with several pre-diagnosis visits or diagnosed by private clinicians had longer treatment delays.

GeneXpert/RIF is not widely available in healthcare facilities in Indonesia, and this was confirmed in a study by Saktiawati et al. [5], where clinical examination, sputum smear, chest X-ray, culture, follow-up for 1.5 or 2.5 years, the sensitivity and specificity of 90% and 99.5% were stated. In addition, the GeneXpert/RIF should be prioritized since sputum smear and chest X-ray are still used. The method is time-saving, more accurate, and can detect tuberculosis cases on negative sputum smears and the presence of drug-resistant bacteria compared to the conventional AFB staining.

In conclusion, GeneXpert/RIF accelerates tuberculosis detection, especially in smear-negative cases, and reduces treatment time. Patients with risk factors should be prioritized to obtain a tuberculosis diagnosis as soon as possible. Therefore, early detection is needed through rapid and accurate diagnostic tests to prevent delays in diagnosis

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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