



# Research Journal of **Microbiology**

ISSN 1816-4935



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## ***Mycobacterium tuberculosis* Infection: A Data Based Review on Tuberculosis in Khuzestan, Iran**

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### **ABSTRACT**

The knowledge about tuberculosis situation in a community by collecting required information, enable the health policy makers to employ the appropriate measures to control the disease. The aim of this article was to review the information about tuberculosis in Khuzestan. A systematic review of the literature on tuberculosis from 2000 to 2010 using computerized bibliographic databases which include Pub Med, Current Content, Scopus and Iranmedex was made to find better understanding about tuberculosis in Khuzestan. Annual risk of infection rate in Khuzestan was 0.5% and the estimated case of smear positive pulmonary tuberculosis was approximately 25 per 100000 population. The main risk factors of tuberculosis and its mortality in the province were smoking, imprisonment, injection drug usage and diabetes. Multi-drug resistant *M. tuberculosis* was documented by using PCR method in tuberculosis patients in the region. However, extensively drug resistant *M. tuberculosis* which is an important problem expected to be concerned was not yet emerged in the region of study. According to reviewed information, it was concluded that teaching hospitals have an important role in improving pre-treatment counseling and national tuberculosis program indices, such as increased sputum positivity, cured rate and probably, decreased treatment failure and defaulted rate.

**Key words:** *Mycobacterium tuberculosis*, tuberculosis, infection, Khuzestan, drug resistance

### **INTRODUCTION**

The past decades have been associated with the characterization of *M. tuberculosis* (MTB) as the major cause of morbidity and mortality. The effective screening tests for latent Tuberculosis (TB) detection specially in immunocompromised people to prevent clinical TB were introduced. The definition of the house contact infection as well as community and nosocomial infection was determined. The factors that influence on the transmission of TB infection and progressing to disease were recognized. Moreover, the knowledge about the natural history of MTB infection, host immunological responses, pathogenesis of pulmonary and extra pulmonary TB was developed. By progress in the development of diagnostic tools, detection of all clinical forms of disease, etiologic agent specially Multidrug resistant (MDR) TB and therapeutic interventions to prevent or cure infection became possible (Fitzgerald *et al.*, 2010). This transmissible disease represents a

substantial risk to health care workers as well as general population due to the prevalence of TB infection in the community, specially in high risk population such as intravenous drug users, prisoners and HIV positive persons (Mirhaghani and Nasehi, 2002). The aim of this paper was to review the information about the TB prevalence, family and occupational exposure, natural history, pathogenesis, risk factors, diagnosis and treatment of TB in Khuzestan. Information regarding all aspects of the disease, enable state health policy makers to employ the appropriate measures to control the TB in the region. A systematic review of the literature on TB from 2000 to 2010 using computerized bibliographic databases which include Pub Med, Current Content, Scopus, Embase and Iranmedex was made to find better understanding about TB in Khuzestan.

## **EPIDEMIOLOGY**

MTB infects one third of the world's population and causes millions of cases of TB worldwide each year (WHO, 2008). TB remains common throughout the world with an estimated 9 million new cases (incidence) and 3 million deaths per year worldwide (Raviglione and O'Brien, 2008). The great majority of these cases (95%) and deaths (98%) are in developing countries (WHO, 2000). In 1993, the World Health Organization (WHO) declared it a global public health emergency (WHO, 2007). TB continues to be a major public health problem in Iran despite the implementation of national tuberculosis program (NTP); this may be attributed to risk factors such as drug addiction, imprisonment and HIV infection (Mirhaghani and Nasehi, 2002). In 1999 the highest and lowest rates of TB in the provinces of Iran were reported to be 137 per 100000 and 10 per 100000 population, respectively with an average of 26 per 100000 population for the country. The overall incidence of TB in Iran is 13.9/100,000 (Salek *et al.*, 2008). This prevalence is partly due to the vast immigration from neighbouring countries with high TB incidence to Iran. In one study, the prevalence of TB in Afghan immigrants in Kerman province of Iran was reported as 12% (Moradi *et al.*, 2008).

Alavi and Sefidgaran (2008) revealed that the Annual Risk of Infection (ARI) rate in Khuzestan was as 0.5% and the estimated case of smear positive pulmonary TB was approximately 25 per 100000 population (2008). The main risk factors of tuberculosis and its mortality in Khuzestan were smoking, imprisonment, injection drug usage and diabetes (Alavi and Salami, 2008). Another study in Khuzestan showed that the public knowledge about TB have an effective role on its incidence, control and management (Alavi and Sefidgaran, 2009). In recent decades, epidemiological studies has mainly been shifted towards molecular epidemiology and in case of TB, several genotyping methods are widely employed to study the molecular epidemiology of MTB which is investigated in details by Khosravi and Seghatoleslami (2009). The genotyping can be used for tracing transmission from person to person, distinguishing exogenous reinfection from endogenous reactivation in cases of recurrent tuberculosis and identifying laboratory cross-contamination (Mathema *et al.*, 2006).

Centers for Disease Control and Prevention (CDC) offers three main standardized typing methods of Restriction Fragment Length Polymorphism (RFLP) analysis, spacer oligonucleotide typing (spoligotyping) and Mycobacterial Interspersed Repetitive Unit (MIRU) analysis which the first one is the most common genotyping method. In a recent study from Iran, PCR-RFLP method was successfully used for evaluation of recent transmission of TB in two adjacent North western provinces of Iran (Asgharzadeh *et al.*, 2007a) and to investigate the genetic variation among MTB isolates (Asgharzadeh *et al.*, 2007b). Moreover, in two studies in Khuzestan, genetic characteristics of MTB isolates were investigated by PCR based Restriction Enzyme Analysis (REA) technique (Khosravi and Barazandeh, 2005; Khosravi and Hashemi, 2007).

Apart from TB epidemiology, there are reports from Khuzestan and other parts of Iran regarding the prevalence of nontuberculous mycobacteria in patients suspected to have tuberculosis and this shows that we need to draw our attention to these mycobacteria as well and include them in our laboratory-based screening (Khosravi *et al.*, 2009; Farivar *et al.*, 2006).

## **MICROBIOLOGY**

The MTB complex comprises seven species in the genus of *Mycobacterium* that are causes of human TB. The species MTB causes the vast majority of human TB. *M. bovis* causes disease in human through animal contact and consumption of unpasteurized milk and cases of human to human transmission. *M. africanum* and *M. canetti* are both rare causes of TB in Africa. *M. caprae*, *M. miaoti* and *M. pinnipedii*, have been reported to cause TB in human as well (Herrera-Leon *et al.*, 2009). The term acid-fast bacilli is synonymous with mycobacteria (*Nocardia* and some other organisms are also acid fast) in Ziehl-Neelsen staining. The mycobacteria are slightly bend rods and the limited number to make a positive sputum is about 10000 bacilli per one milliliter of sample (Fitzgerald *et al.*, 2010; Mirhaghani and Nasehi, 2002). Sensitivity increases by collection of a second and third sputum samples. Culture is the gold standard for detecting mycobacterium in clinical specimens (Apers *et al.*, 2003). However, due to time consuming of culture method, nowadays, certain molecular methods are widely used for rapid diagnosis of pulmonary and extrapulmonary MTB infections. Khosravi *et al.* (2010) in their works among TB patients in Khuzestan province used PCR for diagnosis of cutaneous tuberculosis (Khosravi and Omidian, 2006) and tuberculosis of urinary tract. The latter study showed the high sensitivity of PCR as 100% comparable to culture method while the sensitivity for direct smear staining was 41.6%. The obtained rate of TB urinary in their study was 5.0%. Since the detection rate of culture and PCR was identical, they suggested PCR as a rapid alternative technique to culture method, especially for confirmed cases of urinary TB (Khosravi *et al.*, 2010).

## **ROUTE OF TRANSMISSION**

Almost all infections with MTB are due to inhalation of droplet nuclei-infectious particles from a person with pulmonary TB aerosolized by coughing, sneezing, or talking. Other modes of transmission are rare e.g., ingestion of contaminated milk (*M. bovis*), skin inoculation (contamination of an abrasion in pathologists and laboratory personnel) and during irrigation of cutaneous lesions to health care workers (Ijaz *et al.*, 2002). A considerably higher prevalence of active tuberculosis among household contacts compared to contacts outside the household (18.2 vs.1.6%) was reported by Alavi *et al.* (2010a) in Ahvaz, center for Khuzestan province (2010). The prevalence rate of TB among contacts is higher than upper limits of rates in the Iranian general population (1.6 vs.0.2%) (Alavi and Salami, 2008).

## **TUBERCULIN SKIN TEST**

The Tuberculin Skin Test (TST) is used to determine whether an individual is infected with MTB by using Purified protein derivative (PPD) to perform this test. A 5-Tuberculin Unit (TU) dose of PPD is usually used for this test (Anonymous, 2000). False-positive reactions represent nontuberculous mycobacterial infection. False-negative reactions occur in at least 20% of all persons with known active TB. Most false-negative test results in patients with TB are attributed to general illness and become positive 2 to 3 weeks after effective treatment is initiated. Malnutrition, sarcoidosis, intercurrent viral infections (including HIV-1 infection with  $<200$  CD4+T cells/mm<sup>3</sup>), vaccination with live-virus vaccines, reticuloendothelial disease and corticosteroid

therapy may cause false-negative tuberculin reactions (Fitzgerald *et al.*, 2010). TST results are negative during the first 3 to 9 weeks of initial infection. The TST has limitations, including false-positive results from environmental mycobacterial exposure or BCG vaccination and operator dependent variability in test placement and reading. Therefore, several new tests including QuantiFERON-TB Gold (QFT-G) test, antibody against MTB antigens (ATA) and enzyme-linked immunospot (ELISPOT) assay to detect latent infection have been developed (Mazurek *et al.*, 2005; Ewer *et al.*, 2003). Alavi and Albaji (2009) in their comparative study among HIV infected patients in Ahvaz the capital city of Khuzestan, showed that ATA failed to diagnose latent tuberculosis infection (LTBI) with 8.8% sensitivity and 11% specificity, so they concluded that TST in spite of its limitation is yet a useful tool for LTBI diagnosis in the region (2010). In another study in Ahvaz, it has been shown that ELISA using A60 antigen can not alone represent active tuberculosis at early stage but it may facilitate to assess the active disease when combined by clinical evaluation and other laboratory diagnostic tests (Khosravi *et al.*, 2005). Based on sensitivity and specificity of tuberculin testing, three cutoff levels have been recommended for positive reactions, 5, 10 and 15 mm. The 5 mm cutoff is used for immunocompromised persons and recent contact of patients with active tuberculosis. The 10 mm is used for other high-risk groups, and the 15 mm is used for low-risk groups. Ninety percent of persons with 10 mm of induration and virtually all with greater than 15 mm of induration to 5 TU are infected with MTB (Anonymous, 2000). Induration of less than 10 mm may be cross-reactions caused by infection with other mycobacterial species or prior BCG vaccination. In a tuberculin survey performed among school-aged children in Ahvaz tuberculin testing using 5TU-PPD was a valuable diagnostic test for latent TB and active TB in childhood. BCG vaccination had no remarkable effect on the interpretation of tuberculin reactivity (Alavi and Salami, 2008).

In a similar study on school-aged children from Iran, the induration diameter of administrated PPD was reported as less than 5 mm in 95.33% and 5-9 mm in 4.66% of studied children, so they concluded that repeated BCG vaccination may be necessary for children entering primary schools (Sakha and Behbahan, 2008).

## **SIGNS AND SYMPTOMS**

Infection with MTB is usually asymptomatic although, some persons may have nonspecific constitutional symptoms such as anorexia, fatigue, weight loss, chills, fever and night sweats (Mirhaghani and Nasehi, 2002; Diel *et al.*, 2004). A productive cough is usually present but is nonspecific. In patients with chronic bronchitis, endobronchial erosion may usually cause a minor hemoptysis. Chest pain is usually due to extension of inflammation to the parietal pleura. Pleurisy with effusion is often an early post primary event but may also complicate chronic pulmonary tuberculosis. Rarely, chest pain leads to discovery of tuberculosis empyema (Fitzgerald *et al.*, 2010). Symptoms often pertain to site of the disease. For instance, painful pharyngeal ulcers; indolent and nonhealing ulcers of the mouth or tongue; hoarseness and dysphagia that are due to laryngeal involvement. Tuberculous otitis media cause the symptom related to site of infection. Gastrointestinal symptoms, are due to enteric ulceration, perforation, or mass formation. Finally, anal pain that is due to tuberculous perirectal abscess and fistula formation. Physical findings are not specific, in general underestimating the extent of the illness and may be absent in spite of extensive disease.

## **TUBERCULOSIS IN AIDS**

HIV-infected patients are predisposed not only to reactivation of remote infection but also to rapid progression of recently acquired infection (De Jong *et al.*, 2004). It is unclear whether AIDS

increases susceptibility to acquisition of new infection. Management of tuberculosis in AIDS may be complicated by concomitant intravenous drug use and homelessness (Raviglione and O'Brien, 2008). Interestingly, long before the AIDS epidemic, illicit intravenous drug use was shown to favor an increased incidence of extra pulmonary disease. In a study it has been shown that nearly 50% of hospitalized HIV positive injecting drug users in Ahvaz were infected with MTB (Alavi, 2008). TB and infection with Hepatitis C Virus (HCV) were reported as the most important co-infections in AIDS patients in Iran (Sharifi-Mood and Metanat, 2006).

## **DIAGNOSIS**

A strong suspicion of pulmonary TB often is made based on chest X-ray. A positive sputum smear, usual in extensive disease, provides additional evidence in support of a diagnosis. The best diagnostic sputum specimen is an early morning sample (Yam, 2006). Although, two sputum specimens are sufficient in some settings; three specimens are recommended because of greater sensitivity (Raviglione and O'Brien, 2008). An alternative way to fiber optic bronchoscopy with the comparable yield, is sputum induction by hypertonic saline aerosols. This is an effective substitute in ambulatory patients. A negative tuberculin reaction does not exclude TB. Granuloma formation on histological examination, even with acid-fast bacilli is still only strong presumptive evidence, because similar findings may be produced by mycobacteria other than tuberculosis (Fitzgerald *et al.*, 2010). Granulomas in the absence of acid-fast bacilli can be seen with other infectious diseases and noninfectious causes (e.g., sarcoidosis, autoimmune disease). Definitive diagnosis requires culture and speciation. According to National Program against TB and Khuzestan CDC a case is considered pulmonary TB when criteria for TB are documented. Cases with at least two sputum smear positive for acid fast bacillus (SSP-AFB) or, a chest radiography (C-X ray) suggestive of tuberculosis plus one SSP-AFB or, sputum culture positive for MTB and one SSP-AFB were defined as pulmonary tuberculosis (PTB).

## **DRUG RESISTANCE**

The emergence of drug-resistant tuberculosis is an increasing problem in both developed and developing countries mostly due to inadequate and poor treatment adherence (Nikalje and Mudassar, 2011). The widespread use of two main components of anti-TB drugs, i.e., isoniazid (INH) and Rifampin (RIF) and incomplete treatment due to misused or mismanaged of prescribed drugs, have led to the emergence of RIF- and INH-resistant or multidrug resistant (MDR) strains (Sekiguchi *et al.*, 2007). The rate of MDR-TB is significantly high in many parts of the world, especially in heavily populated countries such as China and Iran. According to the reports from Iran, the prevalence of resistance to at least one drug is 5% among new cases of TB and the prevalence of MDR-TB among previously treated cases reaches to 48.2% (Espinal *et al.*, 2001). So, testing of MTB isolates for drug susceptibility is important to guide therapy (National TB Controllers Association/CDC, 2004). In recent years, molecular tests to detect chromosomal mutations associated with mycobacterial drug resistance have been developed. These are the most useful tests for INH and RIF resistance which predicts poor treatment outcomes and is a surrogate marker for MDR-TB (Nachamkin *et al.*, 1997). The patients with cavitory disease and advanced AIDS, homelessness and drug users, are most likely to acquisition or development of drug-resistant infections (De Jong *et al.*, 2004). In recent reports on drug resistance in Iran, after streptomycin, INH with 23% resistance in new cases of TB showed the next highest rate of resistance. Mirsaeidi *et al.* (2007) were previously reported a frequency of primary drug resistance to INH as 9.8-15%. So, there is a need for early detection and effective management of INH-resistant TB

in Iran due to significant increase of INH resistance in recent years. In 2006 survey in Khuzestan, the rate of MDR-TB was reported as 8.7% by conventional MIC method and 6.2 by PCR technique (Khosravi *et al.*, 2006).

Doustdar *et al.* (2008a) investigated the prevalence and diagnostic potential of the most commonly reported mutations associated with INH and RIF resistance in Khuzestan and they analyzed parts of the *katG* gene and *fabG1-inhA* and *oxy* *Rahp* C regulatory regions in some INH-resistant isolates. According to their findings the rate of mutations in mentioned genes were detected in 58.3, 18.7 and 39.6% of isolates, respectively. Also, mutations in the RIF-resistance-determining region (RRDR) of the *rpoB* gene were identified in 96.6% of RIF-resistant isolates (Doustdar *et al.*, 2008b).

Since different genotypes of MTB show various affinities to acquire resistance-related mutations, these authors were determined the relative significance of various mutations in the *pncA* gene in Iranian pyrazinamide (PZA)-resistant MTB isolates. They analyzed the association of different genotypes with PZA resistance by investigation of *pncA* mutations using direct sequencing which these mutations were identified in 70.58% of the isolates.

Of immense concern is transmission of MTB resistant to first and second line anti TB drugs which is called extensively drug resistant (XDR) TB (LoBue, 2009). This recently emerging drug resistance have lately been reported in South Africa and Iran (Gandhi *et al.*, 2006; Masjedi *et al.*, 2006, 2010). All XDR-TB cases were in HIV co infected individuals and 98% were died. Although, precise global estimates of XDR-TB prevalence are not known because many surveys do not test for resistance to second-line drugs, approximately 7% of MDR-TB isolates worldwide may be XDR-TB (LoBue, 2009).

In a study undertaken by Velayati *et al.* (2009) XDR tuberculosis was reported at a rate of 5.4%. Besides they were introduces a super XDR tuberculosis or totally drug resistance TB (TDR) for the first time from Iran at the rate of 10.3% among Iranian and non-Iranian patients (Velayati *et al.*, 2009).

## **TREATMENT**

Before availability of anti TB drugs, 50% of pulmonary TB patients died within 2 years and 25% were cured (Mirhaghani and Nasehi, 2002). Fortunately now, TB patients are cured with successful treatment by effective anti TB regimen. Usually, failures occur because of drug resistance or an inappropriate regimen but most because of no adherence to therapy (Andrews *et al.*, 2007). For this reason, WHO has recommended Directly Observed Treatment Short course (DOTS). Standard regimen including INH (5 mg kg<sup>-1</sup> maximum 300 mg), RMP (10 mg kg<sup>-1</sup> maximum 600 mg), PZA (25 mg kg<sup>-1</sup>) and EMB (15 mg kg<sup>-1</sup>) all given once daily by mouth should be initiated in persons suspected of having TB. Therapy should be given daily throughout the entire course of treatment. These four drugs should be continued for 2 months. At the end of 2 months, PZA and EMB can be discontinued and INH and RMP continued to complete a 6-month course (Mirhaghani and Nasehi, 2002). In a study the improvement of cure rate of TB patients by DOTS strategy was reported. Based on the findings, the rates of cured cases, treatment failures, defaulted and death in the hospitalized TB patients (HTB) were 80.6, 8.9, 4.5 and 5.9%, respectively. This rate in the outpatients TB (OTB) were as 66.6, 17.3, 10.1 and 5.9%, respectively. As part of their study, a pre-treatment counseling had been done for majority of both HTB and OTB patients. They also concluded that teaching hospitals can have an important role in improving pre-treatment counseling and NTP indices, such as increased sputum positivity, cured rate and

probably, decreased treatment failure and defaulted rate (Alavi and Sefidgaran, 2009). Another study showed that three month therapeutic regimen (rifampicin, isoniazid and ofloxacin) is as effective as six month therapeutic regimen and may be considered effective treatment for adult patients with unprogressive smear negative pulmonary TB (Alavi, 2009). Besides, it has been shown that vitamin D as a supplemental drug, does not improve the overall treatment outcome among pulmonary TB patients but it may be able to increase the rate of sputum clearance of MTB (Alavi *et al.*, 2010b). Overall cure rate in case (with vit D) and control (without vit D) was 93.8 and 95.8%, respectively, with no significant difference. The rate of sputum negativity at the end of 1st, 2nd, 3rd and 4th months for patient group were 66.7, 78.5, 93.8 and 93.8%, respectively while this rate was 35.4, 66.7, 91.7 and 95.8%, respectively for control group. There was a significant difference between two groups at the end of first and second months of treatment commencement ( $p < 0.05$ ).

**Treatment of MDR-TB:** For treatment of TB which is resistant to both INH and RIF (MDR-TB), susceptibility testing for second-line drugs should be performed and treatment individualized according to the susceptibility test results. In some settings, standardized second-line regimens are used. If a suboptimal regimen is prescribed, resistance to additional drugs may emerge and the opportunity for success may be lost. In a study from Latvia, 66% of MDR-TB patients completed therapy or were cured (Leimane *et al.*, 2005). According to NPT, patients with MDR-TB are recommended to treat with Cat 2 protocol (Mirhaghani and Nasehi, 2002). For those MDR-TB cases that are susceptible to fluoroquinolones, a fluoroquinolone should always be administered along with other drugs including injectable agents [aminoglycosides; streptomycin, kanamycin, or amikacin] (Caminero *et al.*, 2010). The risk of treatment failure is increased if the MTB isolate is also resistant to fluoroquinolones. In a case control study in Ahvaz, it has been shown that an offered regimen (rifampin, isoniazid, ethambutol, pyrazinamid, amikacin and ofloxacin) for 3 months and then, if sputum was negative (rifampin, isoniazid and ethambutol) for 15 months and if sputum was yet positive (ethambutol, pyrazinamid, clofazimine and ofloxacin) for 15 months, resulted in 90% of conversion rate (in 4 months) of sputum in patients who were treated with the offered regimen. Whereas this rate was 60% (in 9 months) for those who were under treatment of Cat 2 in DOTS strategy (Alavi *et al.*, 2006).

**Treatment of XDR-TB:** Treatment of XDR-TB which is defined as resistance to INH, RIF, any fluoroquinolone and at least one of three injectable second-line drugs (amikacin, kanamycin, or capreomycin) is difficult and is usually associated with poor outcomes. The risk of treatment failure and death has been higher than in patients with MDR-TB in some series but not all. Treatment with at least five drugs to which the organism is susceptible is recommended. We found no data about XDR-TB and its treatment in Ahvaz in medical references so far but our most recent study is underway and the results will be presented in near future (Caminero *et al.*, 2010). In a recent study, herbal immunotherapy has been used in conjunction with chemotherapy for patients with XDR-TB and based on the findings, this treatment was significantly more effective compared to conventional non-intervention therapy in control group (Prihoda *et al.*, 2009).

## **TB CONTROL**

The national program to control TB in Iran is based on DOTS strategy. The main goals of this program are: (1) case finding new cases (at least 70%) and (2) treatment (at least 85%) them. Overall rates are ranged between 54 to 65% for case finding and 66 to 93% cure rate for



treatment that are lower than national goals (Nachamkin *et al.*, 1997). BCG is used in neonates and young children in Iran as well as throughout much of the world. Most evidence indicates that BCG vaccination of children results in a 60 to 80% decrease in the incidence of tuberculosis (Lalvani, 2007). More than 98% children in Khuzestan are vaccinated with BCG (Alavi and Salami, 2008).

## CONCLUSION

According to reviewed information, it was concluded that due to significance of prevalence of Tb in our region, we need to screen all aspects of the disease including the situation of drug resistance on the regular basis. Teaching hospitals have an important role in improving pre-treatment counseling and national tuberculosis program indices, such as increased sputum positivity, cured rate and, probably, decreased treatment failure and defaulted rate.

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