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The Current Situation of Diagnosis and Treatment of Tuberculosis in Childhood in China

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Abstract

Tuberculosis (TB) remains a major public health problem worldwide and China is one of 22 high-burden countries. Tuberculosis is a chronic infectious disease caused by *Mycobacterium tuberculosis* infection, period of pediatric tuberculosis (TB) in the most common primary tuberculosis. Children after initial contact named tuberculosis bacili is main with the body's immunity, bacterial virulence and quantity. Recently, pediatric TB incidence certainly has a rising trend, the original hairstyle tuberculosis is named tuberculosis bacili of primary infection occurred after first invasion of the lung, is the main type of pediatric tuberculosis, the vast majority of the total number of children of various tuberculosis. Adult tuberculosis (TB), and the presence of resistant strains, bring children tuberculosis prevention and control of the difficulties, childhood tuberculosis prevention and control of can only strengthen and not weaken. From 1979 to 1979, our country has carried on the four national tuberculosis epidemiological sampling survey (flow), childhood tuberculosis accounts for about 10% of all TB, estimates that new TB patients more than 100 children each year, about 250000 death Childhood tuberculosis diagnosis is difficult, the lack of diagnostic gold standard, always views the tuberculin skin test (tuberculin skin test, TST), the typical imaging and clinical manifestations, in recent years, some new diagnostic method for diagnosis of childhood tuberculosis. The Molecular biology technology, molecular device MTB/RIF system linear probe technique; the basis of etiology examination for diagnosis of tuberculosis. Because of its low incidence, low light symptoms, sputum smear positive rate and diagnosis difficult, childhood tuberculosis are easy to be overlooked. According to the types and present status of tuberculosis and activity, and check the lungs outside have other parts of the body without the existence of active tuberculosis, to determine treatment. There are systemic therapy, anti-tuberculosis drug treatment (chemotherapy) chemicals, hormone therapy, surgical therapy. In this paper, the children and clinical manifestations of the disease is associated with TB diagnosis and treatment measures and the research progress of the status quo of the diagnosis and treatment in recent years.

Keywords: Tuberculosis; Childhood; Diagnosis; Treatment

Introduction

Tuberculosis (TB) is a multi-system disease caused by remarkably stable pathogen-*Mycobacterium tuberculosis*. The burden of TB on mankind continues to be enormous, with one-third of the world's population (1.7 billion people) infected with the bacillus, the vast majority of which resides in developing countries. In adults the predominant manifestation is the pulmonary form of the disease. In children, however, manifestations involving more than one system are common; extra-pulmonary forms of the disease are as common as the pulmonary ones, at least in hospital settings. The symptoms and signs in children are so vague that diagnosis is often difficult. Physicians err in both ways: missed diagnosis is as common as over-diagnosis. With the advent of HIV/AIDS and the resurgence of TB, global attention has been more sharply focused on the adult forms of pulmonary tuberculosis. There is a real danger that tuberculosis in children may take a back seat.

Tuberculosis can be controlled either by preventing the infection from occurring or by treating early infection after it has occured. An efficient tuberculosis control program with early detection of infectious adults and their cure is the best long-term approach to the reduction of TB disease in children. The DOTS strategy advocated by the WHO has the potential to have a significant impact on the epidemiology of tuberculosis by achieving high cure rates and thereby decreasing community transmission. BCG vaccination, through effective against disseminated forms of the disease in childhood, has very little impact on adult forms of the disease. Chemoprophylaxis or preventive therapy is effective, but difficult to implement on a mass scale and is only recommended for special high-risk groups in developing countries.

The status quo of tuberculosis in childhood in China

Of an estimated nine million ne Tuberculosis (TB) remains a major public health problem worldwide.w cases of tuberculosis (TB) occurring across the globe each year, children account for nearly half a million (490 000), with two-thirds residing in 22 high-burden countries (HBCs) [1] and China is one of 22 high-burden countries. In 2011 alone, 64 000 childhood deaths (among ≤ 15 years) were attributed to TB [2]. Current WHO-recommended case detection methods (sputum smear positivity) identify only an estimated 5% of TB cases among children [3]. The prevalence of childhood TB accounts for a large proportion of the epidemiology of TB, and it has been

increasing in recent years [4]. The problem is more serious in China, especially in the western region [5].

From 1979 to 1979, our country has carried on the four national tuberculosis epidemiological sampling survey (flow), the knowledge of tuberculosis epidemic situation in our country and develop tuberculosis control program played a huge role. Four flow adjustable 0-14 years old children TB infection rates were 8.8%, 9.6%, 7.5% and 8.8% respectively. Seven years old age group 1979, 1984/85, 1990, the infection rate was 7.3%, 7.8%, 6.6%.1979, 1990, 2000 children active tuberculosis prevalence of 241.7/10, 172.1/10, 91.8/10, respectively; Children bacteria Yang TB prevalence in 1990, 2000 as of 12.7/10, 12.3/10; Incidence of childhood smear-positive pulmonary tuberculosis in 1979, 1990 and 1979, respectively, of 7.5/10, 7.5/10, 6.7/10. In recent years, with the global TB epidemic rise, childhood tuberculosis has increasing trend [6] the world health organization (WHO) published the 2015 global TB report. In 2014 a new global in as /960, our country is 94/m; Prevalence worldwide as of 174/10, 89/10 in China; The global incidence of 133/10, as of 68/10 in China. In 2014, the global new tuberculosis patients (9.6 million) is a slight increase in 2013.3.2 million 5.4 million new patients in men, women, children under the age of 15, 1 million. In 2014 new MDR-TB patients 480000 cases. Throughout the year, 1.5 million people die of tuberculosis. Children's immune system is not perfect, because children tuberculosis person progress fast, easy development of disseminated TB (tuberculosis of su li sex or tuberculous meningitis) [7]. And children tuberculosis may also have stronger infectivity [8].

Childhood tuberculosis accounts for about 10% of all tuberculosis [9], estimates that every year more than 100 new children tuberculosis person [10], about 250000 [11] death. Because of its low incidence, milder symptoms, sputum smear positive rate is low, the characteristics of diagnostic difficulties [12], childhood tuberculosis are easy to be overlooked. But children tuberculosis reflects the recent spread of tuberculosis, and can predict future TB epidemic [13], so it is of great significance in the tuberculosis epidemiology.

The pathogenesis of tuberculosis

The pathogenesis of pediatric tuberculosis (TB) includes the following two aspects:

1. The cell-mediated immune response. Macrophage phagocytosis and digestion of n/med tuberculosis bacili, and pass specific antigen to T helper lymphocytes ($CD4^+$cells), macrophages (mainly) dendritic cells secrete son-12, induction of $CD4^+$cells to THL polarization, secretion and release of IFN-gamma. IFN-gamma further promote monocyte accumulation, activation, proliferation and differentiation, and produce a large number of reactive product, release the oxidase and digestive enzymes and sterilization, to devour and destroy more *Mycobacterium tuberculosis*. IFN-gamma reinforced cytotoxic T lymphocyte (CTL), $CB8^+$cells and natural killer (NK) cell activity, dissolve had antigen of *Mycobacterium tuberculosis* and the role of macrophages. The cellular immune response, but eventually kill n/med tuberculosis bacili, but may also lead to a host cell and tissue destruction. When the cellular immune response is not enough to kill n/med tuberculosis bacili, n/med tuberculosis bacili fair by macrophages by lymphatic spread to the lymph nodes.

2. The late onset of allergy. Is the host of n/med tuberculosis bacterium and its products have a supernormal immune response, also is mediated by T cells, macrophages as effector cells. Under certain conditions, such as local accumulation amount of antigen is low, the reaction is advantageous to the prevention of exogenous reinfection in local and fight spread bacteria, but in most cases, due to the late hairstyle allergy direct and indirect effect, causing cell death and caseous change, even the hollow.

Pediatric tuberculosis is given priority to with primary tuberculosis, airframe immunity can be obtained after infected with TB bacilli. 90% can be a lifetime don't come on; 5% due to the low immunity right away, is for the primary tuberculosis. The other 5% only in reduced immunity when the disease in the future, called secondary pulmonary tuberculosis, is a major type of adult tuberculosis. Early dye *Mycobacterium tuberculosis* in addition to the secretive lymph nodes in the chest, can also with bacteremia early infection to other organs, and long-term latent, become a source of extrapulmonary tuberculosis incidence.

Diagnosis

Childhood tuberculosis diagnosis is difficult, the lack of diagnostic gold standard, always views the tuberculin skin test (tuberculin skin test, TST), the typical imaging and clinical manifestations, contact TB diagnosis of childhood tuberculosis is the most commonly used method [14], in recent years, some new diagnostic method for diagnosis of childhood tuberculosis. Immunological diagnostic methods of TST, gamma interferon release experiment (interferon gamma release assay, IGRAs) [15]. Molecular biology technology, molecular device MTB/RIF system linear probe technique; The basis of etiology examination for diagnosis of tuberculosis.

Childhood tuberculosis than adults are more difficult to diagnosis, the misdiagnosis and missed diagnosis is high, the clinician particularly pediatricians should fully learn the characteristics of childhood tuberculosis, comprehensive of the above methods, increase the rate of clinical diagnosis of childhood tuberculosis [16].

Risk Factors

The strongest risk factors for childhood tuberculosis infection are socio-economic, mainly the effects of poverty. Under nutrition, overcrowding and the resultant possibility of close contact with an infectious case are some of the better known risk factors. The effect of an infectious case on children in a community was studied by Nair et al. in a rural area in South India [17]. Within clusters of households around a sputum-positive case, a sputum negative case and households without tuberculosis, the proportion of child contacts infected were 26%, 15% and 10%, respectively. The risk was significant up to the fourth house away from the index case. In addition, several other risk factors have been identified, the most important of which is HIV infection with its associated immunosuppression.

Infection and disease

There is a thin line between infection and disease in children. Primary infection is usually asymptomatic and goes unrecognised in over 90%, manifested only by a positive tuberculin skin test later. Development of progressive primary disease or extra pulmonary TB is influenced by factors including age, nutritional and immune status of the child and genetic factors as well as virulence of the organism and size of the infecting dose. Age has a strong influence on the development of disease; infection in an infant or child <2 years is particularly likely to be followed by disease, especially in the form of tuberculosis meningitis or miliary tuberculosis. The incidence of

disease following infection falls progressively with age to a low point between 5 and 10 years increasing again in adolescence [18]. The most vulnerable period for a child to develop disease is immediately after infection. Narmada et al. found that the incidence of new tuberculosis disease among children living in a crowded area in Chennai, South India was 1.2/1000/year among the previously uninfected, 8.8/1000 among the previously infected and 20.0/1000/year among the newly infected [19]. The size of tuberculin induration also correlated with the development of tuberculosis disease at a later time, with morbidity rates rising from 7/1000 among children with 0-11 mm induration size to 63/1000 among those with 18 mm and 104/1000 in children with 24 mm or larger induration. Children with large reaction sizes should be considered especially vulnerable and followed closely. Detection of tuberculosis infection also depends on the sensitivity of the test being employed. CT scans have shown intra-thoracic lymphadenopathy not visualised on chest X-rays [20]. Most of these would have gone unnoticed and would have healed spontaneously. PCR with its extreme sensitivity also has the potential to diagnose children with tuberculosis infection but no disease, who would otherwise have been unrecognised. Previously the diagnosis depended on recognising the disease but today sensitive techniques have now made it possible to detect early infection.

Tuberculosis mortality in children

Tuberculosis is among the 10 major causes of mortality in children. Globally almost 500 children die every day from tuberculosis. Mortality in children has been shown to correlate with the socio-economic state of the population. The annual tuberculosis mortality rate among children in an urban slum in Chennai was 239/100 000 compared to 52 and 55/100 000 for the same age group in the rural areas of Tamilnadu and Bangalore [21]. Mortality from disseminated forms of tuberculosis disease such as tuberculosis meningitis causes the highest case-fatality in early childhood. Chakraborty has estimated that against an ARI of 1% (incidence of infection), the TBM mortality rate in the ages 0-4 years could be 1.5/100 000 [22]. The outcome of tuberculosis also depends on age: the case fatality ratio for all forms of tuberculosis in children in South Africa from 1970-1980 was 7% <1 year, 3% 1-4 years and 1% 5-9 years of age [23].

Treatment

Pediatric tuberculosis (TB) is a chronic infectious disease, need for a quite long period of treatment, can effectively control the growth of pathogenic bacteria, to kill and eliminate the remaining bacteria in lesions, can make the diseased tissue repair, to achieve lasting cure. Therefore, before the treatment principles and methods, first should be clear of TB type, the current progress of lesion, the presence of active. Next, should pay attention to the patient's general condition, especially in liver and kidney function, in the process of treatment, must have the plan of follow-up, observe whether the medicine is timely and symptoms do you have any change, non-toxic side effects, etc., should avoid to contact, scarlet fever, measles and whooping cough of acute infectious diseases, prevent infected TB illness worse. Diagnosis of tuberculosis (TB), will determine the corresponding treatment principle. According to the types and present status of tuberculosis and activity, and check the lungs outside have other parts of the body without the existence of active tuberculosis, to determine treatment. There are systemic therapy, anti-tuberculosis drug treatment (chemotherapy) chemicals, hormone therapy, surgical therapy.

Systemic therapy

Systemic therapy, is the basis of comprehensive treatment. Through systemic therapy, and fully mobilize the body's resistance to disease, they can better give play to the role of antimicrobial chemotherapy, obtain better treatment effect. Systemic treatment generally include:

The reasonable nutrition is mainly supply is rich in protein and vitamins, especially vitamin A, D, C food.

Bedroom air circulation, fresh, daylighting is better.

Suitable for indoor and outdoor activities, in addition to the acute poisoning symptoms, cough, high failure who should stay in bed, generally in accordance with the condition proper indoor-outdoor activity can be performed.

Anti-tuberculosis chemical drugs

1. Anti-TB drug treatment goal is to:

- Kill lesions of n/med tuberculosis bacterium;
- To prevent blood line spread.

2. Therapeutic principles as follows:

- Early treatment;
- The appropriate dose;
- Combination;
- Regular medication;
- Stick to the whole;
- Block therapy.

Common anti-TB drugs at present, can be divided into two categories:

- Sterilization drug
- The whole sterilization drugs: such as isoniazid (isoniazid, INH) and rifampicin (rifampin RFP).
- Half an antiseptic: such as streptomycin (streptomycin, SM) and pyrazinamide (pyrazinamide, PZA).

Bacteriostatic drugs: commonly used with ethambutol (ethambutol EMB) and ethyl sulphur smoke amine (ethionamide, ETH).

Against drug-resistant strains of several new anti-tb drugs.

Composite of older drugs dosage forms, such as Rismate (300 mg contained INH l50ra9 and RFP); Rifater (contained INH, RFP and PZA), etc.

Derivatives of older drugs, such as spray at the butyl (Rifapentine) is a kind of long-term rifamycin derivatives, outside of rifamycin drug-resistant *Mycobacterium tuberculosis* has strong sterilization effect.

New chemicals, such as power line of lung disease (Dipasic), is a kind of independent synthetic new anti-TB drugs, tolerance is a good INH class products, can delay 1 nh resistance.

Hormone therapy

Adrenal cortical hormone can relieve symptoms, reduce allergic reaction, reduce inflammation and suppress connective tissue proliferation. Properly used hormone therapy as early as possible, therefore, can make the heating temperature drop, increase appetite, effusion absorption. But with no special effects for tuberculous and individual cases after once use hormone withdrawal, not easily if stop

using repetition can make the symptoms, and side effect, therefore should not be abused.

Surgical Therapy

For surgical therapy is mainly used for pulmonary lobectomy or side of pneumonectomy, sometimes for intrathoracic lymph node excision and stripped the pleura. What circumstance available surgical therapy? Indications are as follows:

- Type hollow tuberculosis after chemotherapy, the hole is not closed.
- The cheese venereal focal or tuberculoma medical treatment is invalid.
- The lung lymph node enlargement, a wide range of caseous changes or liquefied by chemotherapy treatment is invalid, or associated with persistence and pulmonary bronchial stenosis not Zhang Zhe, feasible intrathoracic lymph node excision.
- Fiber cirrhosis or lung tissue calcifications with recurrent hemoptysis.
- Intumescent lymph node protracted war cause lung, for the development of bronchiectasis.

The treatment of childhood tuberculosis should follow three basic principles: (1) as soon as possible to reduce the body burden;(2) ensure that MTB effectively eradicate the body;(3) to reduce side effects to the lowest [24].

The status of treatment in China

China global fund TB project covers modern tuberculosis control strategy, fixed-point hospital, the floating population, double infection, multi-drug resistant TB/HIV and TB prevention and control of the judicial administrative system and health systems strengthening, and other areas to work .Projects across the country 31 provinces (autonomous regions and municipalities directly under the central government) and the Xinxiang production and construction corps. Coverage of each area according to the characteristics of the project work, is not the same.

1. Modern tuberculosis control strategy in the world

Modern tuberculosis control strategy in the nationwide 31 provinces (autonomous regions and municipalities directly under the central government), and all parts of the Xinxiang production and construction corps. Global fund is only in addition to the Shandong, Zhejiang, Jiangsu, Beijing, Tianjin, Shanghai, Guangdong, in the outside of the western 24 provinces (autonomous regions and municipalities directly under the central government) and the Xinxiang production and construction corps in 268 (city) of all the 2230 counties (districts) to provide funds to support.

1. The fixed-point hospital TB control field

Fixed-point hospital TB control areas covered in Fujian, Gansu, Guangxi, Huizhou, Heilongjiang, Hunan, Jiangxi, Inner Mongolia, Ningxia, Shandong, Shanxi, Shaanxi, Sichuan, Yunnan, Zhejiang, Chongqing and other 16 provinces (autonomous regions and municipalities directly under the central government);Project covers 55 to 80 counties (city) (area).

1. The TB prevention and control of the floating population

TB prevention and control of the floating population area covers the 28 except in Qinghai, Ningxia and Jilin provinces (autonomous regions and municipalities directly under the central government) and the Xinxiang production and construction corps of 75 to 198 counties (cities) (area).

1. Dual infection prevention and control of TB/HIV

Dual infection prevention and control of TB/HIV areas covered in Anhui, Guangdong, Guangxi, Huizhou, Hainan, Hubei, Henan, Hubei, Hunan, Jiangxi, Shandong, Shanxi, Shaanxi, Sichuan, Xinxiang, Yunnan and other 16 provinces (autonomous regions) in 68 to 134 counties (city) (area).

Of multi-drug resistant tuberculosis prevention and control field

Multidrug-resistant tuberculosis prevention and control of field on July 1, 2010, Fujian, Guangdong, Hubei, Henan, Heilongjiang, Hubei, Hunan, Jiangsu, Inner Mongolia, Shandong, Sichuan and Zhejiang 12 provinces (autonomous regions) of the 41 (city); January 1, 2012 new launch the 12 provinces (autonomous regions) in Jiangsu, Hubei, Sichuan, Fujian, Hunan 8 to 5 provinces (municipalities), and Anhui, Ningxia, Gansu, Guangxi, Qinghai, Shaanxi, Shanxi, Jiangxi, Jilin, Liaoning, Xinxiang, Yunnan 18 of 12 provinces (city), the cumulative cover 24 provinces (autonomous regions) in (city) in 67.

The prevention of tuberculosis

Tuberculosis can be prevented either by preventing the infection from occurring or by treating infection as early as possible. In areas where there is a high prevalence of tuberculosis, almost everyone is exposed to it. Hence any preventive measure has to be applied on a mass scale. The most widely used preventive measure is vaccination with BCG. WHO recommends the use of neonatal BCG as the preventive measure against tuberculous meningitis and miliary tuberculosis. BCG does not prevent infection but it prevents the progression of haematogenous spread to extra pulmonary sites. The evidence for its effect against pulmonary tuberculosis is less clear. Efficacy reported from several trials varies between zero to over 96% and protective efficacy wanes with time [25]. The only way to effectively prevent tuberculosis is to prevent the infection. The key to achieving this is to find and treat all sputum-positive tuberculosis adults. Case finding and treatment is the only method expected to have an important short-term impact on transmission. The DOTS strategy is the breakthrough of the present century for the control of tuberculosis. If practised meticulously,it has the potential to eradicate tuberculosis.

However, there is the danger that a badly implemented DOTS strategy could increase the occurrence of drugresistant tuberculosis. It should therefore be taken seriously by all involved. In this way, the transmission of tuberculosis can be effectively interrupted. Preventive therapy is difficult to implement on a mass scale. However, it has been found to be very effective in low prevalence countries. In children who are at high risk, such as close contacts of patients with smear-positive tuberculosis, children with HIV, or children on immunosuppressive therapy, chemoprophylaxis should be considered. Both chemoprophylaxis and vaccination protect the individual but do not have any significant short-term impact on transmission. Ultimately, improvement of socio-economic conditions and better access to health care, which were responsible for the decline of tuberculosis in the developed world, will provide the long-term solution.

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