Prevention und Detection of Tuberculosis-Infektions

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1 Tuberculosis

1.1 Bacille Calmette-Guérin (BCG)-Vaccination

The BCG-strain utilized for vaccination was won by serial passage through bacterial culture media using the resulting attenuation of virulence of *Mycobacterium bovis*. The first human BCG-trial was done in 1921. The BCG-vaccines used today differ due to changes in the bacterial strains and production methods. The vaccine consists of live, replicable bacteria which are subcutaneously or intradermally injected [4, p. 444].

In the United States BCG-vaccines are only assessed for their ability to induce a delayed hypersensitivity. The efficiency of the BCG-vaccines is still in open discussion [4, p. 450-1]. Protection rates between 0% and 80% are reported—with no reasonable explantation for the large range. According to some clinical data regarding TBC infections in humans the differences between BCG strains are not the determining factor for the efficiency of the protection against a TBC infection [2, 9].

A large placebo controlled study with 15 years of follow-up in Madras, India showed no significant difference in the number of cases of new infection between vaccinated and placebo group [16].

According the the ACIP the best control of TBC has to be seen in the combination of efficient diagnosis, chemotherapy and prevention. Even though BCG vaccination of hospital personal was recomended in endemic regions, the latest guidelines suggest that protection can best be achieved by periodic tuberculin skin testing and resulting chemotherapy in case of conversion [4, p. 450-1].

A BCG vaccination should be considered in cases of newborns and children if their skin test is negative and they are known to be in contact with persons in whom the TBC infection is not adequately controlled. Furthermore newborns and children should be vaccinated if their risk of infection is considered to be greater than 1% per annum and other forms of prevention are considered inadequate. Osteomyelitis and dissiminated BCG infections are known to have occured in HIV-positive or otherwise immunocompromised patients following a BCG immunization. These patients should not be vaccinated using BCG. Even though the WHO recomends BCG immunization in asymptomatic HIV-positive children if they are exposed to a higher than normal risk of TBC infection [4, p. 2301].

1.2 Tuberculin-Skin-Test

The tuberculin skin test is the screening method of choice. The Mantoux-Test (intra cutan application of 5 tuberculin units (TU) purified protein derivative (PPD) is superior to the tine test having an increased sensitivity as well as specifity. Even though the Tine-Test is still used for the screening of large populations with a low exposition risk [4, p. 151]. Cross-reactivity has been seen in cases of infection with other mycobacteria than *M. tuberculosis* as well as in cases of vaccination using BCG [3][4, p. 151, p. 159, p. 2301]. Generally speaking, the deeper the induration at the injection site the more likely the *M. tuberculosis* infection. An increase of the test dosis to 250TU PPD increases the number of unspecific reactions.

The significance of the reaction to 5TU PPD is most of all dependent on other mycobacteria in the environment. Thus in Alaska where there are no cross reacting mycobacteria in the environment an induration of $5mm$ in diameter is an undisputable sign of a tuberculosis infection. In Georgia where *M. avium* ubiquitary in the environment an induration of $15mm$ in diameter is a sign towards a *M. tuberculosis* infection. In most areas of the world an induration of more than $15mm$ after application of a 5TU PPD dosis is a sure sign of a TBC infection. In cases of a close contact to a person with a known TBC infection or patients with a positive chest x-ray as well as in patients with a modulated immune system a diameter of $5–15mm$ should be judged as a positive test result [4, p. 2301-2].

In immunocompetent persons the Mantoux test will positive 2 to 4 weeks after infection with *M. tuberculosis*. This reaction is a sign of the curing process of the cell mediated

immunity [4, p. 158-9]. With age the reactivity of the skin is reduced at a rate of 5%/year.

Repeated testing results in a booster effect which can be misinterpreted as a conversion reaction. This misinterpretation can be eliminated if all persons with a diameter of less than $10mm$ are retested within a week [15]. The booster effect is most often seen in the elderly and in areas were non-tuberculose mycobacteria are frequent. In the elderly a booster-effect can be seen in skin testing with 5TU PPD in the third or fourth sequential test.

Patients in whom a repeated testing can be assumed (e.g. hospital personal) a second test should be performed after a negative inital first test in order to obtain a new base line for further tests [8]. False negative test results are coupled with a modulated cellular immune response. This can be due to simultaneous viral infections (HIV, measels, herpes), malign lymphoreticular neoplasias, malnutrition, sarcoidosis, immunosupressive medication, especially corticosteroids [4, p. 151], diabetes mellitus, chronic liver failure and severe general deseases [4, p. 462][12, p. 401-2].

About 50% of the patients with a milliar TBC as well as 25% of those with tuberculosis of the lungs have a negative skin test [13]. This has to be judged as a pointer towards a negative prognosis [4, p. 151].

Even when considering these restrictions the tuberculin skin test can give valueable information with regard to an acute TBC infection. One has to be careful not to draw the conclusion that a negative tuberculin test excludes a tuberculosis from the list of possible differential diagnoses [4, p. 2301].

1.3 Prophylaxis

Chemoprophylaxis is used for the control of a latent TBC infection. In metropolitan areas two thrids of all TBC cases are due to latent infections. In rural areas this number is significantly higher [5].

The usual regime of chemical prophylaxis consists of Isoniazid (INH) $300mg/d$ (Adults) and 10-15mg/kgKG$/d$ up to a maximum of $300mg/d$ for children over a period of 6 to 12 month respectively. In controlled studies the prevalence was reduced by 54% to 88% [1]. It has to be noted that the efficiency of the chemoprophylaxis is mostly determined by the compliance of the patients. In cases with a very high compliance the prevalence could be reduced by more than 90%, in patients with signs of pulmonary TBC residing in old people's homes the reduction was 98% [6, 10].

The possibility of a hepatotoxicity is the main problem of INH-prophylaxis. Even though 10% of all the INH patients have abnormal high Liver parameters a hepatitis is seen in only 1% of the patients. Usually the hepatitis commences 4 to 8 weeks after the start of the therapy. The hepatitis risk increases with the age of the patients: There are no cases of an INH induced hepatitis in subjects under the age of 20 where as in the age group ranging from 50 to 69 the probability is 2-3%.

Patients with a high risk of TBC infection and a positive tuberculin reaction should get chemoprophylaxis regardless of their age. Patients at risk are:

- Persons with close contact to patients with a newly diagnosed TBC infection.
- Persons who recently converted in the tuberculin test.
- Persons with a suspicious thorax X-ray resulting in a diagnosis of an inactive TBC.
- Foreigners who immigrated during the last two years from countries with endemic TBC.
- Persons with a known or suspected HIV infection.
- Persons with an elevated risk of TBC infection due to a different disease (silicosis, gastrectomy, jejunoileal bypass, weight below 90% of the ideal weight, chronic kidney disease, diabetes mellitus, immunosupressive corticoid therapy, malign hematopoetic neoplasia, other forms of immunosupression due to desease of therapy).

The treatment of patients with few risk factors—the so called low risk tuberculin reactors—is an issue of widespread discussion. The current recomendation states that patients younger than 35 years of age with a 5TU PPD induced induration of more than $15mm$ after $48h$ should be treated with chemoprophylaxis. Furthermore children under the age of 5 should be treated if they had a recent contact with a person with an open TBC, even if the 5TU PPD reaction of the children is negative, as a primary prophylaxis. A skin test should be done 3 months after the start of the chemotherapy. In case of a positive reaction the therapy should be continued. In cases of INH resistance the switching to a different prophylactic agent, e.g. Rifampicin, is recomended. It has to be taken into account that a change of chemotherapy easily results in a selection of resistant clones [11]. HIV-positive patients in TBC endemic regions seem to benefit from INH prophylaxis even if their skin test is negativ [14]. An INH prophylaxis should be done in all cases where a HIV-positive person had contact with a pations with TBC. HIV-positive patients exposed to a TBC infection should be subjected to another chemoprophylaxis even if they have had a previous INH prophylaxis.

HIV-tests should be performed in all cases of newly diagnosed TBC infection in order to gain the benefits of an early antiviral HIV therapy. Paradoxical reactions are seen in cases of a TBC/HIV coinfection: after an early reduction of the clinical symptoms a rebound is seen in 36% of the cases. During the rebound fever, infiltrates of the lungs and a peripheral as well as a mediastinal lymphadenophatia have been described regularly. The paradoxical reactions are self limiting and last for 10 to 40 days. Some of the reactions are so severe that a short term application of a glycosid is neccessary [5].

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