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Purified Protein Derivative (PPD)-Tuberculin Anergy and HIV Infection: Guidelines For Anergy Testing And Management Of Anergic Persons At Risk Of Tuberculosis

INTRODUCTION

The occurrence of tuberculosis among persons with human immuno- deficiency virus (HIV) infection has prompted the development of guidelines for the management of those who may have both tuberculous and HIV infections (7). These guidelines include the recommendation that all persons who are known to be infected with HIV, or are at increased risk of HIV infection, receive a tuberculin skin test (Mantoux test with tuberculin units 5 {TU} of purified protein derivative {PPD}-tuberculin). Those persons who have at least a 5 mm reaction to PPD should be considered for 1 year of isoniazid preventive therapy, unless otherwise contraindicated.

The Division of Tuberculosis Elimination (DTBE) in CDC's Center for Prevention Services has considered requests for information regarding screening for anergy among persons infected with HIV who are at increased risk of tuberculous infection but do not react to a tuberculin skin test. Recent reports have suggested that anergy to tuberculin among asymptomatic persons infected with HIV may be more common than initially suspected. Thus, the guidelines presented below are intended for the evaluation and management of persons who may have tuberculous infection and HIV-induced anergy to delayed-type hypersen- sitivity (DTH) skin test antigens, including PPD-tuberculin. These guidelines were developed by DTBE and gratefully acknowledge: Col. John Brundage, M.D., Washington, DC; Sotiros Chaparas, Ph.D., Baltimore, MD; Gail Gutierrez, R.N., Los Angeles, CA; Norman Markowitz, M.D., Detroit, MI, Edward Nardell, M.D., Cambridge, MA; Kenrad Nelson, M.D., Baltimore, MD; and Lee Reichman, M.D., Newark, NJ.

ASSESSMENT OF DTH RESPONSIVENESS

Many diseases and infections, including cancer and certain viral infections (especially HIV infection), and some immunosuppressive drugs may result in a transient or continuing suppression of cellular hypersensitivity mediated by T-lymphocytes. The degree of suppression may be reflected in a patient's inability to mount a DTH response to one or several skin-test antigens.

Most healthy people have a DTH response to several bacterial, viral, and fungal antigens. However, only four are available as standardized antigens for use by a Mantoux-type procedure (0.1 ml of antigen administered intracutaneously): tuberculin, coccidioidin, histoplasmin, and mumps. No other antigens intended for assessing a person's ability to elicit a DTH response have been standardized for this use by the Mantoux procedure.

Only a small proportion of the population is sensitive to tuberculin; sensitivity to histoplasmin and coccidioidin is restricted to endemic regions of infections. Therefore, some investigators have used antigen preparations, such as trichophyton, intended for the diagnosis and/or treatment of immediate type hypersensitivity reactions. Other investigators have found tetanus toxoid to be useful in assessing DTH responsiveness. However, none of these products are licensed for use as DTH skin-test antigens, and none are certified for lot-to-lot reproducibility for this purpose.

The Food and Drug Administration has licensed for the evaluation of cellular hypersensitivity a multiple puncture device (MULTITEST CMI(R)) that delivers seven DTH antigens percutaneously. Even though the concentration of antigen loaded onto such devices may be consistent from lot to lot, the amount of antigen deposited in the skin is unknown and may vary because of the nature of the subject's skin and the method of administration. Although the sensitivity of these tests may be high, their use as quantitative tools for assessment of anergy is limited. In contrast, responses to antigens administered by a Mantoux-type procedure, in which a known quantity of a known concentration of a standardized antigen is deposited in the skin, may be more accurate indicators of a waning or increasing cellular hypersensitivity.

DTH RESPONSE IN HIV INFECTION

Investigators have evaluated groups of persons with HIV infection for their ability to mount a DTH response and have related the results to other measures of HIV infection -- most commonly, CD4 T-lymphocyte counts.

Since 1985, in eight U.S. Army medical centers, approximately 8,000 clinical evaluations have been conducted among more than 2,000 individuals diagnosed with HIV-1 infection (Brundage J, Walter-Reed Army Institute for Research, personal communication). Clinical evalu- ations were conducted to assess the Walter Reed Clinical Stage and included assays of CD4 counts and responses to a panel of DTH skin tests (including Candida albicans, mumps, trichophyton, and tetanus toxoid). Cutaneous anergy, defined as no reaction to any of the skin tests, was reported in <10% of evaluations conducted when CD4 counts were 500/mm superscript 3. In all CD4 defined strata, particularly those>200/mm superscript 3, the presence of anergy had prognostic significance with regard to the time of occurrence of the first opportunistic infection (2).

Among antigens routinely used in Army medical centers, mumps produced more positive reactions than Candida or tetanus toxoid. Trichophyton reactivity occurred in <15% of both HIV-infected and HIV- uninfected persons. However, studies of skin-test performance at a single Army medical center indicated that Candida and tetanus toxoid in 1:10 dilutions performed as well as mumps (Birx-Raybuck D, Walter- Reed Army Institute for Research, personal communication). Among persons with CD4 counts below 500/mm superscript 3, presence of anergy varied inversely with CD4 count. Anergy to both mumps and Candida was reported for approximately 80% of persons with CD4 counts <50/mm superscript 3.

In a multicenter National Institutes of Health (NIH) study of pulmonary complications of acquired immunodeficiency syndrome (AIDS), 1,240 patients infected with HIV are being followed (Markowitz N, Henry Ford Hospital, personal communication). DTH responsiveness is measured by mumps and Candida (trichophyton was removed from the anergy panel because it elicited many fewer DTH responses than the other two antigens). Results from this study showed a relation between anergy and CD4 counts, with increasing anergy at counts <400/mm superscript 3 and anergy among two-thirds of study subjects with counts <200/mm superscript 3. In general, DTH responsiveness was lower among intravenous drug users (IVDUs) than among patients in other HIV transmission categories. Candida and mumps antigens produced equivalent results and together elicited more responses than either antigen alone.

Several investigators have used the MULTITEST CMI(R) in studies of DTH responsiveness (3, Dassey D, Los Angeles County Health Department, personal communication). Based on varying criteria to define a positive

DTH response, anergy appears to be more common among HIV- seropositive IVDUs than among HIV-seropositive persons who are in other HIV transmission categories. Anergy is also more common among persons infected with HIV who are asymptomatic than among comparable persons without HIV infection. Among the antigens included in this test, Candida and tetanus toxoid produced the largest proportion of positive DTH responses (generally defined as a reaction of greater than or equal to 2 mm of induration).

There have been no comprehensive studies relating DTH respon- siveness and biologic markers of HIV infection other than CD4 counts. Although available information suggests that the CD4 count correlates highly with anergy, approximately 10% of asymptomatic persons with early HIV infection and CD4 counts above 500/mm superscript 3 will have no detectable DTH response to a panel of antigens, as will a comparable percentage of apparently healthy persons without HIV infection. Conversely, a small proportion of persons with symptomatic, advanced HIV disease and CD4 counts below 200/mm superscript 3 will be able to mount a DTH response.

STUDIES OF PPD TESTING IN HIV INFECTION

Studies conducted in various settings among persons with and without HIV infection have suggested that HIV infection can depress tuberculin reactions before signs and symptoms of HIV infection develop.

In a study of HIV infection among postpartum women in Uganda, 27 (82%) of 33 HIV-seronegative women had reactions greater than or equal to 3 mm to Old Tuberculin (OT) as did 29 (48%) of 61 HIV-seropositive women (4). The median reaction sizes for persons in the two groups were 10.6 mm and 7.5 mm respectively ($p<.01$). In other tuberculin skin-test studies among asymptomatic HIV-seropositive and HIV- seronegative IVDUs in Switzerland (5) and prisoners in Italy (6), significantly ($p<.001$) lower rates of PPD reactivity have occurred among those with HIV infection. In Italy, the mean CD4 count for those with HIV infection was 569/mm superscript 3, and the CD4/CD8 ratio was 0.6 both values were substantially lower than the normal value.

In an ongoing study of IVDUs in Baltimore, 31 (34%) of 90 seronegative persons were PPD positive (greater than or equal to 10 mm), compared with two (9%) of 22 seropositive persons (using greater than or equal to 5 mm to define a positive reaction) ($p<.05$) (Graham N, Nelson K, Johns Hopkins University, personal communication). In this study, persons were also tested for DTH using Candida and mumps antigens; eight (11%) of 76 HIV-negative persons were anergic, compared with eight (44%) of 18 HIV-seropositive persons (p="0.001)." In the NIH study described above, positive reactions to PPD were three times more common among HIV-seronegative controls than among HIV- seropositive persons (approximately 15% vs. 5%), and the highest skin- test positivity rate (28%) occurred among HIV-seronegative IVDUs.

Studies of tuberculosis disease associated with HIV infection indicate that a substantial proportion of tuberculosis patients will have PPD anergy if their tuberculosis is concurrent with other HIV- related opportunistic infections. In Florida, among patients who were reported to the tuberculosis and AIDS registers as having both diseases, the probability of tuberculin anergy varied inversely with the interval between the diagnosis of tuberculosis and the diagnosis of AIDS decreased (7). In Los Angeles, 26 (55%) of 47 tuberculosis patients who were HIV-seropositive had positive (greater than or equal to 5 mm) PPD responses; the mean CD4 count for the PPD-positive patients was 220/mm superscript 3, compared with 66/mm superscript 3 for PPD-negative patients (Gutierrez G, Los Angeles County Health Department, personal communication).

RECOMMENDATIONS FOR EVALUATION FOR ANERGY OF HIV-INFECTED PERSONS

Because of recent findings of apparent PPD anergy among asymptomatic persons with HIV infection who have a high probability of tuberculous infection, persons with HIV infection should be evaluated for DTH anergy in conjunction with PPD testing. Emphasis for anergy testing should be placed on persons who have an increased risk of tuberculous infection (e,g,, IVDUs or those born in a country endemic for tuberculosis). Although HIV-infected persons who also have evidence of immunosuppression (e,g., have had AIDS-defining diagnoses or total CD4 counts <500/mm superscript 3) have an increased probability of anergy, approximately 10% of asymptomatic persons with higher CD4 counts may also be anergic. Therefore, the degree of immunosuppression should not be a selective factor in considering a person for anergy testing. Anergy testing should also be

considered for persons who are among risk groups for tuberculous and HIV co- infection but who refuse HIV testing.

Companion testing with two DTH skin-test antigens (i.e., Candida, mumps, or tetanus toxoid), to which most healthy persons in the population would be sensitized, is recommended. At present, mumps antigen is the only product standardized for DTH to which most of the population would be expected to react. Although Candida antigen also performs satisfactorily, it is not yet licensed for DTH testing, and there may be lot-to-lot variation in potency and responsiveness. Given the apparently good performance of tetanus toxoid in DTH testing, that antigen may also be useful (a 5:1 dilution with phenol-buffered diluent is commonly used). Because of the expectation that second strength (250 TU), PPD tuberculin, would be less sensitive than the other antigens in eliciting a DTH response, second strength PPD is not recommended for anergy evaluation; (nor is it recommended for evalua- tion for tuberculous infection). Although anergy testing with a panel of antigens administered by the multiple puncture method may give useful results, it is costly and subject to the limitations discussed earlier,

Tests administered by the standard Mantoux method (0.1 ml) are recommended to be given concurrently with a PPD tuberculin (5 TU) skin test. Rather than testing all HIV-seropositive individuals with an anergy panel, anergy testing may be reserved for persons who are found to be tuberculin-negative. However, anergy testing at the time of initial tuberculin testing is preferable, because of logistical problems and nonadherence associated with repeat testing and reading. The skin test responses should be measured 48-72 hours after administration. Any amount of induration to the DTH antigens is considered evidence of DTH responsiveness; erythema alone is not considered to be evidence of DTH responsiveness. Persons unresponsive to DTH (including PPD) are considered to be anergic.

ln general, persons with a positive DTH response to one or more of the DTH antigens but not to PPD tuberculin are not considered to be infected with Mycobacterium tuberculosis. However, a negative PPD reaction should never be used to exclude the diagnosis of active tuberculosis, even among persons who react to other DTH antigens. Reactions of greater than or equal to 5 mm to PPD are considered to be evidence of tuberculous infection, regardless of the reactions to the companion antigens.

The relation between CD4 count and prognosis for HIV-infection has been established. CD4 testing of all HIV-positive persons is recomm- ended for determining the degree of HIV immunosuppression and for deciding about the need for other treatment measures (e.g., zidovudine, Pneumocystis carinii pneumonia {PCP} prophylaxis). However, CD4 testing is not a substitute for anergy testing. At present, other surrogate markers of HIV infection (e.g., serum neopterin, beta-2-microglobulin, p24 antigen) are not helpful in this regard.

MANAGEMENT OF ANERGIC, HIV-INFECTED PERSONS

CDC and the American Thoracic Society recommend that tuberculin reactions greater than or equal to 5 mm be considered positive for persons who are HIV-seropositive (regardless of Bacillus of Calmette and Guerin {BCG} vaccination status) and that such persons be considered for isoniazid prophylaxis (1). On the basis of data cited earlier, persons infected with HIV who have negative tuberculin skin- test reactions (i.e., <5 mm) and anergy as defined earlier may also need to be considered for isoniazid preventive therapy based on an individual clinical and epidemiologic assessment of the likelihood of infection with M. tuberculosis.

Preventive therapy should be considered for anergic persons who are known contacts of infectious tuberculosis patients and for those from groups in which the prevalence of tuberculous infection is greater than or equal to 10%. This recommendation is based on suggested marked benefit from isoniazid preventive therapy among IVDUs who are HIV-infected and who have negative tuberculin skin test reactions (8). Presumably, those IVDUs who are also anergic would achieve an even greater benefit from preventive therapy.

In the United States, groups at increased risk of tuberculosis include IVDUs, prisoners, homeless persons, migrant laborers, and persons born in countries in Asia, Africa, and Latin America with high rates of tuberculosis (9). Infection rates among these groups are generally greater than or equal to 10%. All such persons should be carefully evaluated for active tuberculosis (with a chest radiograph and clinical assessment) before beginning

preventive therapy.

Anergic persons who are at increased risk for tuberculosis but elect not to take isoniazid preventive therapy should be carefully educated about the signs and symptoms of tuberculosis in HIV infection. They should be instructed to promptly seek medical assessment should any of these signs or symptoms develop.

RESEARCH PRIORITIES

Further studies to define the relation between anergy and co- infection with HIV and M. tuberculosis are needed. Studies that will more accurately define the risk of tuberculosis among persons infected with HIV who are anergic are especially important. Studies are also needed to determine the usefulness of repeating anergy tests (e.g., 2- step testing as is suggested for certain persons being PPD tested). For these studies, only a single lot of any DTH antigen preparation should be used, and the investigator should be aware that changes in lots or manufacturer may result in antigens of markedly different potencies. This may result in misinterpretation of cellular hyper- sensitivity status if a patient is being monitored periodically with such antigens, or may introduce bias when comparing groups of patients tested with different lots or products from different manufacturers. Finally there are needs for accurate surrogate tests for anergy and more sensitive tests to determine the presence of tuberculous infection among anergic persons.

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Summary of guidelines for anergy testing

10. All persons with HIV infection should receive a PPD-tuberculin skin test (5TU, PPD by Mantoux method).

11. Because of the occurrence of anergy to PPD among persons with HIV infection at risk of tuberculosis, persons with HIV infection should also be evaluated for DTH anergy at the time of PPD testing.

12. Companion testing with two DTH antigens (Candida, mumps, or tetanus toxoid) administered by the Mantoux method is recommended. However, a multipuncture device which administers a battery of DTH antigens may be used.

13. Any induration to a DTH antigen measured at 48 hours to 72 hours is considered evidence of DTH responsiveness; failure to elicit a response is considered evidence of anergy.

14. Those persons with a positive (greater than or equal to 5mm induration) PPD reaction are considered to be infected with M. tuberculosis and should be evaluated for isoniazid preventive therapy after active tuberculosis has been excluded.

15. Persons who manifest a DTH response but have a negative PPD reaction are, in general, considered not to be infected with M. tuberculosis.

16. Anergic, tuberculin-negative persons whose risk of tuberculous infection is estimated to be greater than or equal to 10% should also be considered for isoniazid preventive therapy after active tuberculosis is excluded.

17. Although CD4 counts should be performed as a part of the evalu- ation and management of persons with HIV infection, this measurement is not a substitute for anergy evaluation.

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