Incipient and Subclinical Tuberculosis: Defining Early Disease States in the Context of Host Immune Response

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Latent Mycobacterium tuberculosis infection (LTBI) and active tuberculosis (TB) are 2 ends of a spectrum of states ranging from asymptomatic infection to overt disease. While progressing from LTBI to TB, patients often undergo asymptomatic states with detectable manifestations indicative of disease. Such asymptomatic disease states frequently remain undiagnosed, and their manifestations and duration are mostly dependent on host immune response. Various terms referring to such states are used in the literature, often interchangeably and without explicit definitions. Defining these intermediate states in concrete terms is important for pragmatic reasons, as they might impact upon the diagnostic performance of TB biomarkers and could also present targets for therapeutic interventions. We here propose definitions for 2 commonly used terms, “incipient” and “subclinical” TB, to describe asymptomatic disease states occurring at opposite ends of the host response spectrum. We propose using the term “incipient TB” when referring to early, contained disease in asymptomatic, relatively immunocompetent persons. In contrast, we propose using the term “subclinical TB” to refer to disease in asymptomatic, immunocompromised individuals in whom it is largely associated with loss of effective containment. The rationale for this article is to facilitate the discussion of such early disease states, especially in relation to their impact on TB biomarker discovery and assessment of new diagnostics, and with regard to treatment decisions and ultimately outcome.

While one-third of the world’s population is infected with Mycobacterium tuberculosis, only ~10% of those ever develop disease [1]. The risk for transition from latent M. tuberculosis infection (LTBI) to active tuberculosis (TB), as well as the speed of progression to clinically detectable disease depends largely on the immune competency of the host. Although LTBI and TB are commonly seen as binary states, they reflect 2 ends of a continuous spectrum. It can take months to years to develop symptomatic and bacteriologically detectable TB [2]. During this time, asymptomatic states with manifestations and duration dependent on the host immune response remain mostly unidentified.

The nuanced rather than binary spectrum of host immune response to M. tuberculosis determines similarly nuanced clinical, histologic, and immunologic features of TB disease. The increasing occurrence of TB in association with human immunodeficiency virus (HIV) infection or exogenous immunosuppression highlights the spectrum of diverse and atypical manifestations. This has implications for an elaboration of early disease states according to immune context. Terms such as “incipient” and “subclinical” TB have come increasingly into use for characterizing asymptomatic patients with radiographic and/or microbiologic evidence of TB or patients who in retrospect could be defined as having had early states of TB. We believe that the presence of detectable manifestations compatible with TB justifies categorizing these states as early forms of disease, even in the absence of symptoms. The detection of such asymptomatic disease states would be
extremely valuable, especially in HIV-infected persons, for whom early multiple-drug antituberculosis treatment appears to be associated with reduced mortality [3]. Further, the spectrum of immune response, inflammatory reaction, and mycobacterial burden in these various contexts can be expected to impact on the accuracy estimates for novel TB biomarkers and diagnostics. Thus, early disease states require distinction and definition in the context of the host immune response and its resulting host damage.

Many terms are used, often interchangeably and without explicit definitions, to describe less overt forms of TB. Commonly used examples are “inactive,” “preclinical,” “minimal,” “incipient,” and “subclinical” TB, in contrast to “active” or “clinical” TB. While early disease states are often described in high-risk patient groups, such as HIV-infected persons, these terms are seldom used in the context of the host immune response. A few articles have recently expanded upon the paradigm of LTBI [4–7]. However, a review and delineation of the commonly used terms for early disease states—“incipient” and “subclinical” TB—is lacking. Therefore, the objectives of this article are to describe the states that precede overt TB, discuss their presentation in the context of the host response, and propose definitions and distinctions. The rationale is to facilitate the discussion of early disease states in more concrete terms, especially in relation to their impact on TB biomarker discovery and assessment of new diagnostics, and with regard to treatment decisions and ultimately outcome.

**DISTINCTION BETWEEN LTBI AND TB IN THE CONTEXT OF THE DAMAGE-RESPONSE FRAMEWORK**

As elegantly outlined by Casadevall and Pirofski [8], the states that follow infection, such as persistence or latency of a microorganism versus disease, are outcomes of the host-microbe interaction that differ in the amount of damage incurred by the host over time. These states are generally continuous and differ only in the amount of damage incurred by the host. When damage exceeds a certain threshold amount, such that it impairs homeostasis, signs of disease become evident (Figure 1A). In that respect, disease is a state of infection. LTBI and TB differ by the amount of host damage, such that in the former the damage is not sufficient to produce clinical manifestations, whereas in the latter clinical manifestations are evident. Even though the terms infection, latency, and disease have been defined in the literature (Table 1) [8], the question in the case of TB remains: Where should the line be drawn between LTBI and early disease states, since radiographically and/or microbiologically detectable manifestations can be clinically asymptomatic?

Several groups have recently addressed the paradigm of LTBI, emphasizing that the term presents an oversimplification [4–7]. We concur with the investigators who differentiate between quiescent and active infection, while acknowledging that the spectrum is continuous [5–7]. They define “quiescent infection” as a controlled state with some bacteria persisting in nonreplicating forms, while “active infection” is characterized by bacterial replication maintained at a “subclinical” level by the host immune response. However, as addressed before, the challenge remains to determine at which threshold within active infection early disease begins. Such determination should be based on different criteria in relatively immunocompetent than in immunosuppressed hosts.

**HOW IMMUNE COMPETENCY AFFECTS THE PRESENTATION OF TB**

A century plus of clinical experience made clinical diagnosis, in association with supportive microbiology, pathology, and radiology, the gold standard for TB diagnosis. However, not only the risk for disease, but also the speed of disease progression and the hitherto classic appearance of TB are remarkably altered by immunodeficiency. For example, classic tuberculous granulomas are increasingly disorganized with increasing immunodeficiency [9–11]. Employing a scoring system similar to that used for leprosy, Di Perri et al [9] scored transbronchial biopsy specimens from HIV-infected patients with pulmonary TB for bacillary burden and granulomatous component. The most organized granulomas characterized by epithelioid and multinucleated giant cells, lymphocytes, monocytes, and caseous necrosis had the highest and the nonorganized inflammatory infiltrates had the lowest granuloma scores. They showed that bacillary burden score increased and granuloma score decreased in tandem with declines in CD4 cell counts [9]. Another example are inhibitors of proinflammatory cytokines, such as tumor necrosis factor alpha (TNF-α) antagonists, which promote the transition from LTBI to TB disease [12, 13]. TB pathology occurring in the context of anti-TNF-α drugs is distinct from classic TB and may be characterized by fibrosis, lymphoid inflammation, and an absence of granuloma formation [10].

In HIV-associated TB, progressive impairment of granuloma formation with consequent ineffective containment of M. tuberculosis as CD4 cell counts decline presumably accounts for the range of atypical chest X-ray (CXR) findings, including lower rates of cavitation, atypical mid and lower lung zone infiltrates, hilar adenopathy, and even normal findings despite positive sputum cultures for M. tuberculosis [14–20]. Not surprisingly, the occurrence of normal CXR findings, extrapulmonary manifestations, and detectable mycobacteremia increases with decreasing CD4 cell counts [14, 21–26]. Similarly, a higher proportion of extrapulmonary manifestations occurs in patients receiving anti-TNF-α therapy compared with more immunocompetent patients [10, 27, 28]. Symptom development is also associated with the host immune
response. HIV patients with advanced immunodeficiency can have widespread TB with positive histopathology and/or M. tuberculosis cultures from multiple sites attesting to disease dissemination, despite a paucity of localizing inflammatory symptoms [22, 26, 29, 30]. In adults, advanced age, with its waning immune competence, is also characterized by atypical TB manifestations evidenced by significantly less fever, night sweats, and cavitary lesions with hemoptysis compared with younger age (reviewed in [31]). Similarly, TB manifestations in children can vary according to age and are influenced by the maturity of the immune system. While disseminated forms of disease are more common during early childhood years, symptoms are often absent (up to ~50%) or nonspecific at younger compared with older age [32–37].

While relative immunodeficiency is permissive of increased bacillary replication and subsequent disease development, the other side of the spectrum, associated with a strong immune response, also leads to disease manifestations (Figure 1). The occurrence of paradoxical reactions illustrates this well. Paradoxical worsening of signs and symptoms of TB occurs temporally related to withdrawal of immunosuppressants, or in HIV-infection with the introduction of antiretroviral treatment (ART) [38–41]. ART-associated TB due to an overtly inflammatory response is commonly referred to as having LTBI. On the other hand, individuals with characteristic TB symptoms, compatible radiographic abnormalities, and confirmatory mycobacterial cultures have definite TB. In the absence of positive cultures, symptomatic persons with characteristic radiology and/or histopathology are categorized as having culture-negative TB. This diagnosis is confirmed by resolution of abnormalities on antituberculous multidrug therapy. Interestingly, the proportion of culture-negative TB is high (~25% of all TB cases) in areas such as New York City, where clinicians have sensitive imaging and invasive sampling modalities available to establish the diagnosis [44]. While ~11% of all TB patients in New York City are currently found to be coinfected with HIV, the proportion of HIV-associated TB among culture-negative TB cases is unknown.

Stable radiographic abnormalities compatible with TB in asymptomatic, relatively immunocompetent persons are often interpreted as resolved or “old” rather than active disease.

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**Table 1. Definitions of Infection, Latency, and Disease According to Casadevall and Pirofski [8]**

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Infection</td>
<td>The acquisition of a microorganism by the host</td>
</tr>
<tr>
<td>Latency</td>
<td>A state of host–microorganism interaction in which a microorganism persists in a host and can be associated with damage that can be evident at the cellular or tissue level, but is not associated with disease</td>
</tr>
<tr>
<td>Disease</td>
<td>A clinical outcome of host damage that occurs after a threshold amount of damage has occurred</td>
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**Figure 1.** A, Adaptation from Casadevall and Pirofski [8] reflecting the damage-response framework of microbial pathogenesis; B, Conceptual view of early TB disease states based on host response
However, some abnormalities, such as fibrotic lesions in the upper lung lobes or pulmonary nodules, could also indicate the transition to or reactivation of disease. A large-scale population-based study of TB in the 1960s and 1970s in Czechoslovakia showed that ~30% of persons diagnosed with culture-proven TB had fibrotic lesions on CXR 2–3 years prior to diagnosis [45]. In the International Union Against Tuberculosis Trial (IUAT) in the 1970s, 28,000 persons with stable pulmonary fibrotic lesions were randomized to placebo or varying durations of isoniazid preventive therapy (IPT) [46]. In the placebo group, the incidence of progression to TB within a 5-year observation period was 11.6/1000 in the group with lesions under 2 cm², and almost double, 21.3/1000, in the group with lesions over 2 cm². The benefit of prolonged IPT was greater in the group with larger lesions compared with the group with smaller lesions. From the observations of the high rate of progression to overt TB in the placebo group, especially in patients with lesions over 2 cm², one can infer that many of these patients, especially those with larger lesions, had incipient disease.

A Hong Kong study demonstrated a high rate of progression to TB over 30 months in 93 (53%) of 176 initially culture-negative individuals with TB compatible CXR abnormalities. These abnormalities consisted of localized pulmonary lesions; <5 cm² in 22%, 5–15 cm² in 41%, and >15 cm² in 38% without further characterization [47]. About a third of the culture-negative patients were asymptomatic, while most of the remainder had cough mainly without sputum production. Such high rate of progression of culture-negative radiographically demonstrable disease is the basis for the recommendation of multidrug antituberculous therapy. Even in the absence of symptoms, multidrug therapy is recommended in certain regions, albeit for a shortened duration of 4 instead of 6 months [48, 49].

Increased sophistication of and indications for thoracic imaging provide greater opportunity to identify radiographic abnormalities indicative of TB [50]. Positron emission tomography (PET) can also demonstrate metabolic activity in pulmonary nodules that histologically show granuloma with or without AFB [51]. Whether such PET positive granulomatous lesions, in the absence of both clinical symptoms and a positive culture for *M. tuberculosis*, should be characterized as disease is unclear from the literature due to the lack of longitudinal studies.

Based on results from large-scale prospective studies [45], we propose the term “incipient TB” to describe the constellation of upper lobe opacities over 2 cm² in size, not attributable to another disease and occurring in an asymptomatic, apparently immunocompetent host with prior TB exposure. We believe that radiographically demonstrable host damage coupled with a high risk of progression distinguishes incipient TB, a very early form of disease, from LTBI. Practically speaking, identifying incipient TB as a potential forerunner of overt TB is relevant so that treatment could be deployed to prevent progression.

**EARLY DISEASE STATES IN IMMUNOCOMPROMISED HOSTS: PROPOSAL FOR DEFINING THE TERM “SUBCLINICAL TB”**

HIV-infected persons have an up to 30 times higher risk of progression from LTBI to TB than immunocompetent persons [52], and once they progress, coinfection leads to the acceleration of both diseases [53]. Recognition of the worsening TB epidemic in countries with high HIV prevalence has led to enhanced screening for and detection of TB in HIV-infected individuals living in TB-endemic regions [54]. As a consequence, a novel diagnostic category referred to as “subclinical TB” has recently been described [3, 55, 56].

Mtei et al [3] define subclinical TB as microbiologic evidence (sputum smear and/or culture positive) of TB in an asymptomatic HIV-infected individual without radiographic abnormalities on CXR. During a TB vaccine trial in Tanzania, they screened 498 patients with CD4 counts >200 cells/mm³ for active TB by interview, physical exam, CXR, and mycobacterial smears and cultures. Among these, they found 10 cases with overt TB and an additional 10 cases of smear and/or culture-positive TB with no other evidence of TB, an entity that they defined as “subclinical TB” after excluding laboratory cross-contamination. Interestingly, the mean CD4 count in subjects with subclinical TB was ~400 cells/mm³ and not statistically significantly different from subjects without TB or with overt TB. However, this observation might have been biased by the fact that only subjects with counts >200 cells/mm³ were enrolled in this study. Years later, Bakari et al [57] provide an extended account of all patients treated for presumptive TB (n = 136) in the same vaccine trial with, by then, 1,176 subjects enrolled. Of the 136 subjects treated for TB, 38 (28%) had microbiologic confirmation, including 13 (10%) with a normal CXR and no symptoms, while 58 (43%) were treated for presumed disease based on CXR findings alone. Similarly, screening of 250 HIV-infected persons enrolling in an IPT clinical trial in India identified 10 smear-negative but *M. tuberculosis* culture-positive persons with minimal or no symptoms and normal CXRs [58]. The CD4 cell count of those 10 persons ranged from 72 to 552 (median, 263) cells/mm³. Further studies from TB endemic regions indicate that the proportion of subclinical TB is likely higher in HIV-infected patients with CD4 cell counts <200 compared with those with counts >200 [59].

Agizew et al [60] recently described a screening program for IPT in which HIV-infected asymptomatic patients in Botswana underwent interview, physical exam, and CXR. Screening for TB prior to IPT was prompted by concerns that IPT would lead to INH resistance if subjects with TB were unwittingly treated with monotherapy. Of 2732 subjects screened, 302 had an abnormal CXR, of whom 43 (14%) were diagnosed with TB. Diagnosis was based on microbiological evidence or resolution of CXR abnormalities on treatment. All but 3 of these 43 patients...
eventually developed TB-associated symptoms, mostly within 3 months of the screening, thereby substantiating that the initial diagnosis did reflect detection of early TB and demonstrating the high risk of progression over a short time from asymptomatic “subclinical” to symptomatic disease.

The lack of CXR abnormalities in HIV-infected patients with microbiologic evidence of TB is not a new observation. Several groups have described normal CXR findings in HIV-associated TB, mostly in patients with CD4 cell counts <200 cells/mm³ [14, 18, 26, 61]. Among 146 mostly symptomatic, HIV-infected pulmonary TB patients, Palmieri et al. [61] found a significantly shorter duration of fever in smear-negative, culture-positive patients with normal CRXs compared with smear-negative or smear-positive, culture-positive patients with abnormal CXRs. Yet there was a statistically significantly increased risk of death in the group with normal CRXs compared with those with abnormal CXRs (HR = 3.0, P = .004; median survival, 6.4 vs 18.8 and 20.2 months, respectively). This risk was not associated with differences in CD4 cell counts (median, 54 cells/mm³ vs 92 and 72, respectively) but could have been due to delayed initiation of antituberculous therapy. It is also well known that CXRs have limited sensitivity for the detection of other early infectious disease states in immunocompromised patients, likely reflecting the reduced inflammatory response (reviewed in [62]). For example, up to 10% of AIDS patients with Pneumocystis jiroveci pneumonia have normal CXRs [63], and patients with neutropenia can have delayed or very subtle radiographic abnormalities [64]. Furthermore, regarding symptoms, it is not uncommon for patients with HIV-associated TB to be asymptomatic [65], even with abnormalities on CXR and/or a positive respiratory culture for *M. tuberculosis* [66]. These observations support that a paucity of inflammatory responses is not unusual in immunocompromised persons with TB and is largely responsible for the lack of typical CXR abnormalities and/or symptoms.

We propose to use the term “subclinical TB” in association with immunosuppressed states, referring to either microbiologic and/or radiographic evidence of pulmonary TB in an asymptomatic immunocompromised host. Although subclinical TB may be immunologically heterogeneous with respect to the presence of radiographic abnormalities or positive bacteriology, it represents active disease occurring in patients who are asymptomatic at the time of screening and would not be identified otherwise. Practically speaking, recognition of subclinical TB allows for the timely initiation of treatment that appears to reduce mortality [3].

**TB BIOMARKER AND DIAGNOSTICS PERFORMANCE IN THE CONTEXT OF THE HOST IMMUNE RESPONSE**

Current diagnostic tests classify patients as having LTBI or TB. Gold standard tests confirming disease require the detection of *M. tuberculosis* in respiratory or other body samples, either in form of isolation by culture or detection of *M. tuberculosis*–specific nucleic acids by molecular methods [67, 68]. If such methods are not available, diagnosis is typically based on microscopy to identify acid fast bacilli (AFB) in sputum smears, which is limited by a sensitivity of 50% or less and detects mostly advanced stages of pulmonary cavitary disease [69]. Despite progress in immune-based diagnostics for LTBI and TB [70], and extensive research to identify new TB biomarkers and diagnostics (reviewed in [71–73]), there are currently no reliable biomarkers for the detection of disease states that precede bacteriologically positive TB.

One of the greatest challenges for TB biomarkers and diagnostics is to distinguish between LTBI and TB and to identify the transition from the former to the latter. This is not surprising because the evolution to disease is continuous and dependent on the immune status of the host. Consequently, the evaluation of biomarkers and diagnostics has to be in the context of both immune competency as well as host response. For example, pathogen biomarker would be expected to have a higher yield in cases with high mycobacterial burden. Since HIV-associated subclinical TB is often a disease due to impaired granuloma formation and consequent early dissemination of disease, pathogen biomarkers might have a higher diagnostic value in these states compared with early states of non-HIV TB.

Differential test performance according to immune status has been observed with the recently developed urinary antigen test for detection of lipoarabinomannan (LAM), a glycolipid antigen of the mycobacterial cell wall. While this test has a higher sensitivity (20%–67%) in HIV-associated TB, it has a very low sensitivity (6%–21%) in non-HIV TB [59, 74–78]. Furthermore, just as the occurrence of normal CXRs in HIV-associated TB is inversely associated with CD4 cell counts [14, 18], so too is the sensitivity of the urinary LAM test higher at lower CD4 cell counts [59]. Similar observations have been made regarding TB biomarkers based on humoral immune response. For example, antibody responses to certain mycobacterial proteins, such as the malate synthase (MS) and the MPT51, are significantly higher in early states of HIV-associated TB compared with non-HIV TB [79]. Furthermore, antibody responses to a number of mycobacterial proteins, such as ESAT-6, CFP10, MS, MPT51, and PPE55 have been detected months to years prior to the bacteriological confirmation of TB in HIV-infected persons [80–82], indicating a humoral immune response to a potentially high mycobacterial burden even in the time preceding detectable disease. In contrast, tests based on measurements of cell-mediated immune responses to TB, such as the interferon-gamma release assays (IGRAs), appear to be more informative in immunocompetent persons. Results are often indeterminate in children and adults with immunocompromising conditions, and the likelihood of an indeterminate IGRA result in nonimmunocompromised children is inversely correlated with age [83–85]. On the other hand, a very
strong ESAT-6 response by T cells from recently exposed HIV-uninfected household contacts might indicate incipient disease and predict subsequent development of TB ([86] and reviewed in [87]). These data demonstrate that immune states characterized by antigen excess or exuberant inflammation are often differentially characterized by pathogen-based and immune-based assays.

While the search for novel biomarkers to predict the progression to disease is ongoing, these examples highlight the critical need to distinguish and define early TB disease states in the context of the host immune response. However, assessing the true specificity of sensitive biomarkers poses a challenge in the absence of better diagnostic gold standards for early disease states. Thus, the reduced specificity of urinary LAM or serum antimycobacterial antibody detection in patients at high risk for TB might actually represent detection of an early disease state that eludes diagnosis by conventional means [59,74–79]. Therefore, we emphasize the existence of early TB states and propose to define them based on the immunologic, microbiologic, radiographic, and clinical criteria provided in this article.

**SUMMARY AND CONCLUSIONS**

While *M. tuberculosis* is a single organism, the spectrum of TB is manifold. The definitions of terms proposed here for early disease states in asymptomatic individuals are based on their occurrence at the opposite ends of the host immune response. Their recognition is increasingly relevant in the current era when infections like HIV or immunosuppressive drugs perturb LTBI toward transition to TB. Incipient TB occurs in asymptomatic, relatively immunocompetent individuals and is characterized by radiographic abnormalities. In contrast, subclinical TB occurs in asymptomatic, immunocompromised hosts and is characterized by either positive mycobacteriology with normal or abnormal chest radiology or abnormal radiology alone. While incipient TB is early TB with containment of disease, subclinical TB is largely associated with loss of effective containment. Therefore, incipient TB can remain stable for years. In contrast, despite limited prospective data, subclinical TB appears to be rapidly progressive if left untreated. Although incipient TB can be the forerunner of subclinical TB, we caution against using the terms “incipient” and “subclinical” interchangeably but rather in the context of the host immune response. Precise definitions of these early disease states are important so that appropriate interventions for patients at risk for progression can be instituted. Taking these states into account should also allow for more realistic accuracy estimates of novel TB biomarkers and diagnostics.

**Notes**

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