6

Tuberculosis in the Intensive Care Unit: The North American Perspective

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1 INTRODUCTION AND EPIDEMIOLOGY OF TUBERCULOSIS

There are many similarities between the recognition and management of patients with tuberculosis in the intensive care unit and in the outpatient clinic. However, there are also some key differences. This chapter will review special presentations of tuberculosis in critically ill patients, unique management issues in this population, and practical aspects of infection control.

Global estimates suggest that one third of the world's population has been infected by *Mycobacterium tuberculosis.* Ten percent of infected individuals will progress to active disease, at least half of them within the first two years following infection. All together, there are an estimated eight to sixteen million new cases a year with two to three million deaths. Less than 10% of these patients have coincident human immunodeficiency viral infection, however, when this occurs the case fatality rate is over 50% and progression from infection to active disease occurs at a rate of at least 8% per year. Whereas the greatest number cases remain concentrated in Southeast Asia, sub-Saharan Africa and eastern Europe, recent trends in global travel predict resurgence of disease outside of these regions (1).

After a thirty-year decline in the number of cases, there was an increase in the incidence within the United States between 1985 and 1992, followed by another decline through 2002 (2-4). Although all demographic groups were affected by this increase, over half of the cases in the United States

were immigrants, especially women from Asia or Central America. Enhanced transmission may have also contributed, reflected by a substantial rise in the incidence of cases in children four years of age or younger (2). Co-infection with HIV, as well as multi-drug resistance, also accounted for a large percentage of the increase with enhanced morbidity, particularly in Caucasian and African American men (4, 5). As patients with compromised immune systems are now living longer, it stands to reason that the incidence of tuberculosis in the ICU will also increase.

2 FORMS OF TUBERCULOSIS PERTINENT TO THE INTENSIVIST

Delayed recognition of tuberculous disease in hospital patients not only contributes to nosocomial spread, but also has been associated with an increased risk of mortality in hospitalized patients (6, 7). Nearly three quarters of hospitalized patients with active TB have overall management delays greater than 24 hours, and this is both with respect to suspicion of the disease, as well as its diagnosis and the initiation of treatment (8). Risk factors for a delayed diagnosis include age greater than 65 years, a lack of respiratory symptoms, the absence of hemoptysis or cavitary lung disease, and a misinterpretation of "unusual" chest radiographs (8, 9). Atypical pulmonary or extrapulmonary TB is associated with HIV co-infection, and recently with the use of infliximab or other immunomodulatory agents directed against tumor necrosis factor-α, possibly due to reductions in macrophage apoptosis necessary for mycobacterial killing within granulomas (10).

The identification of radiographic patterns of tuberculous disease can be a key to early recognition. Primary disease manifestations include unilateral hilar adenopathy with lower lobe infiltrates and/or pleural effusions (11). The classic distributions for reactivated tuberculosis include infiltration with or without cavitations of the apical and posterior segments of the upper lobes, followed by the superior segments of the lower lobes, and/or other segments in combination with upper lobe involvement (11). Other radiographic presentations tend to occur in patients with comorbidities such as cancer, diabetes mellitus and alcohol abuse (11, 12). These include exclusive infiltration of the middle or lower lobes, miliary TB, and tuberculomas (11). HIV co-infected persons, particularly those with advanced immune compromise, are particularly prone to such presentations and may even have "normal" chest radiographs despite active pulmonary disease. Unfortunately from a

diagnostic perspective, lower lobe presentations tend to be smear negative (11). The following sections will briefly provide information that, in combination with radiographic findings and microbiologic studies, may assist in making the diagnosis of tuberculosis in patients admitted to the ICU.

2.1 Respiratory Failure/ARDS

Although uncommon, both bronchopulmonary and miliary tuberculosis can cause substantial hypoxemia (13-17), and the occurrence of respiratory failure has been associated with delay in microbiologic diagnosis (18). Almost all of the reported cases had a risk factor for developing active disease, including ethanol abuse, malnutrition, diabetes mellitus, or chronic use of corticosteroids (14-18). Fever, cough, and dyspnea were uniformly present for at least a week prior to presentation and often much longer, which is in contrast to the usual rapid course of prodromal illness for nontuberculous bacterial or viral causes of respiratory failure (14). With this type of subacute presentation, common signs or laboratory findings that may help with the differential diagnosis in favor of tuberculosis include hepatomegally, anemia, hypoalbuminemia, and consumptive coagulopathy (13-16, 18).

The incidence of respiratory failure leading to mechanical ventilation in patients with established miliary disease or tuberculous pneumonia is estimated at 18.9 and 0.8% respectively (17). This progression in both cases appears to be tightly linked to the onset of the adult respiratory distress syndrome (ARDS), suggesting that patients with bronchopulmonary disease are relatively spared from ARDS possibly due to the localized concentration of mycobacterial antigens (17). After adjusting for severity of illness, the hospital mortality for all patients with tuberculosis requiring mechanical ventilation was similar to patients with ARDS from any cause (69 vs. 56%) but higher than the mortality from nontuberculous bacterial pneumonia requiring mechanical ventilation but without ARDS (36%) (17). The reasons postulated for this increased mortality include a delay in appropriate anti-microbial therapy, difficulties associated with the administration and tolerance of anti-tuberculosis drugs, and the frequent lack of quick improvement even in the setting of appropriate therapy.

2.2 Septic Shock

Whereas hypotension commonly complicates respiratory failure due to Gram-negative pathogens, septic shock is felt to be uncommon ($\leq$7%) in patients with tuberculous ARDS (16). Indeed, it is seen almost

exclusively in immunocompromised patients with miliary disease (19-21), occasionally with a clear chest film on admission (19, 22). Tuberculous septic shock has also been described as a complication of prior therapy with prednisone for co-infection with *Pneumocystis carinii* in the setting of HIV (20). As mycobacterial blood cultures using the lysis-centrifugation method have recently been shown to be at least as sensitive as bone marrow biopsies for diagnosing disseminated tuberculosis (23), these should be considered for any immunocompromised patient presenting with septic shock.

2.3 Adrenal Insufficiency

Prior to the availability of antibiotics, tuberculosis was responsible for nearly 70% of all cases of Addison's disease (24). However, in a recent retrospective case series, granulomas were only found in 52 of 871 autopsies from patients with active tuberculosis, yielding an overall incidence of adrenal involvement of 6% of all patients with TB (25). An additional 3 cases were detected among surviving patients undergoing 270 adrenalectomies for indications without suspicion of TB. In this series, thirty percent of the patients had extrapulmonary disease, and the adrenal gland was the fifth most common site, behind liver, spleen, kidney and bone (25). Interestingly, only seven of the 55 patients with adrenal involvement presented with signs and symptoms of Addison's disease (25). This is consistent with biochemical studies revealing subnormal cortisol responses to administration of cosyntropin in only 8 of 88 patients with active disease prior to starting therapy and in only one of these 88 patients after four weeks antibiotic therapy (26). Nonetheless, given the prevalence of relative adrenal insufficiency in ICU patients (27), this entity must be considered in any patient with tuberculosis presenting with septic shock and replacement of stress-dose steroids may be beneficial (28). Conversely, tuberculosis must be considered as a potential explanation for patients presenting with adrenal insufficiency.

2.4 Massive Hemoptysis

Tuberculosis is still felt to be a major etiologic consideration in patients with massive hemoptysis, defined as anywhere from 100 mL of blood in 24 hr to 1000 mL in several days, with an associated acute mortality of 7 to 32 percent (29, 30). Often, this is in the setting of active disease with a high burden of organisms. It can occur either with bronchiolar ulceration and necrosis of adjacent bronchial vessels during acute disease, or by rupture of a Rasmussen's aneurysm from the pulmonary arterial circulation eroding through a thick walled cavity (30). Additionally, massive hemoptysis can occur after resolution of active disease by the

broncholithic passage of a calcified lymph node (30). Early surgical intervention has been recommended for definitive treatment, with few studies to document overall efficacy in this high-risk population (29). Securing the airway, often by the use of a double-lumen endotracheal tube, is essential followed by bronchoscopic localization of the source of bleeding as the diagnostic procedure of choice (30) and by blood replacement. Temporizing measures including iced saline irrigation, topical epinephrine or fibrinogen, balloon tamponade, and /or vessel embolization appear to be associated with variable success (30). Unfortunately, and despite these measures, bleeding can be massive and exsanguination may occur.

2.5 Other Presentations

In the last few decades, the number of cases of extrapulmonary tuberculosis has been relatively fixed at roughly 4000 per year in the U.S., and some of these cases have been accompanied by pulmonary involvement (31, 32). However, the incidence of extrapulmonary disease appears to be increasing (17.5% of all tuberculous cases in 1986 vs. historical values of about 11 to 13%), reflective of a decline in pulmonary cases and a rise in the number of immunocompromised patients particularly with HIV co-infection (31, 32). The sites of infection for these cases are listed in decreasing order of prevalence; lymphatic (5.4% of the total), pleural (4.0%), genitourinary (2.1%), bone and joint (1.7%), other (1.6%), miliary (1.3%), meningeal (0.8%), and peritoneal (0.6%) (32). Unfortunately, these data have not been stratified according to the level of disease severity (i.e. ICU vs. hospital ward vs. community). Nonetheless, selected extrapulmonary presentations will be discussed here as they pertain to the potential contribution to nosocomial spread of tuberculosis within an ICU or to an increased acute mortality rate associated with delayed diagnosis.

Patients with either genitourinary, lymph node or dermatologic forms of tuberculosis tend to present to the intensive care unit for unrelated reasons and may or may not have pulmonary involvement. Both urinary TB and scrofula have a similar pathogenesis involving the erosion of preexisting granulomas through local tissue planes (33, 34). Although the potential exists for limited environmental shedding of viable organisms, this routinely is without aerosol formation such that nosocomial spread is very unlikely by this route, unless there is high velocity irrigation of diseased bone, joint or skin. Urinary TB is suggested by unexplained (i.e. “sterile”) pyuria, particularly in the presence of renal calyx dilatation, focal calcium deposits, cavity formation, or multiple segments of partial ureteral

obstruction (33). Lymph node tuberculosis is suggested by the presence of an indurated, cool subcutaneous nodule over the neck, clavicle, knees or ankles with a sinus tract draining caseous material, and is often a reflection underlying soft tissue or bone/joint involvement, necessitating radiographic investigation of these areas (34). Other dermatologic hallmarks of tuberculous reactivation with or without pulmonary involvement include lupus vulgaris (coalescent red-brown papules forming a plaque with raised edges and scarred centers on the head and neck), and less commonly tuberculosis cutis orificialis (nonhealing periorificial ulcers in immunocompromised patients). Fortunately in all of these cases, acid-fast stains of spun urine samples, drainage or biopsy material, are very sensitive and can facilitate diagnosis, and offer an explanation for pulmonary infiltrates when these are present.

Although uncommon, tuberculous pericarditis and meningitis have a high mortality rate, and are more likely than other presentations to escape diagnosis until the time of autopsy (35-37). Whereas pericardial involvement almost always reflects the presence of clinically silent tuberculosis at other sites (35), the meningeal form often presents with a normal chest radiograph and occasionally represents the only site of involvement in a previously healthy patient without identifiable risk factors (36). Unfortunately, the clinical presentations for these two extrapulmonary manifestations do not distinguish them from non-tuberculous etiologies. Additionally, the sensitivity of acid-fast smears of pericardial and cerebral spinal fluid are low. However, tuberculosis must be in the differential diagnosis for patients presenting to the ICU with tamponade, particularly immunocompromised patients or those from select racial/ethnic groups or communities with a relatively high rate of TB who also have a bloody, lymphocytic and/or monocytic exudative effusion (35). Similarly, tuberculosis must be strongly considered for critically ill patients with mental status changes, signs and symptoms consistent with meningitis, who also have a lymphocytic pleocytosis with a glucose less than 40 in their cerebral spinal fluid with a negative Gram stain and cryptococcal antigen. Adenosine deaminase (ADA) analysis and/or the polymerase chain reaction (PCR) coupled with gene probing of this fluid may help speed diagnosis (see below). Determining the level of interferon-γ (IFN-γ) in these fluids may also be useful in diagnosis. Finally, due to the intensity of the inflammatory and fibrotic reactions at these two sites, adjunctive corticosteroids (in addition to standard therapy) are recommended in the management of patients with either tuberculous pericarditis or meningitis (38).

3 ADVANCES IN DIAGNOSIS

Submission of clinical specimens for acid fast staining and culture remains the gold standard for diagnosis, particularly with respect to drug susceptibility determination for the isolate (39). Unfortunately, the sensitivity of microscopic examination is highly variable depending on the source of the specimen. For example, although the culture sensitivity and specificity for sputum samples from patients with active pulmonary disease is 85 and 98% respectively, up to fifty percent of the samples can be smear negative, necessitating submission of multiple specimens and potentially contributing to diagnostic delay (39). Analysis of adenosine deaminase levels from a variety of fluids has high specificity, although sometimes lacks sensitivity (40). Additionally, the level of IFN-γ has recently received attention, particularly in making the diagnosis of tuberculous pleural effusion (41). Thus, there has been intense effort in the development of rapid diagnostic tests.

Two areas of advance include tests to better recognize latent infection (see the infection control section below for expanded discussion), as well as those directed at diagnosing active disease in the setting of negative acid fast smears. With respect to the former, there are a variety of assays to measure the production of gamma interferon, or the cells producing it, in response to stimulation with *M. tuberculosis*-specific antigens (42-44). These have been validated in patients at high risk for latent infection with reasonable sensitivities, however, they are not yet widely available and have not been approved for patients with active disease. By contrast, the U.S. Food and Drug Administration (FDA) has approved the Enhanced MTD test for the diagnosis of active disease using respiratory specimens. This oligonucleotide amplification test has recently been validated in 338 patients clinically stratified as to whether they had low, intermediate, or high pretest probabilities of active disease, according to evaluation of their symptoms, risk factors, tuberculin skin test results, and plain chest films (45). With excellent positive and negative predictive values (59%/100%; 100%/95%; 91%/51%) in the three pretest groups respectively, this test clearly outperformed microscopic examination (ppv 36%, 30%, 90%; npv 96%, 71%, 37%) (45). Other PCR based assays exist, some of which are also being tested with extrapulmonary samples (46-48). Thus, confirmation of positive smear results, or probing smear negative samples from high risk patients can now be rapidly and reliably performed, minimizing the delay to diagnosis and initiation of treatment.

Finally, there have also been advances in the methods used for drug susceptibility testing. The Mycobacteria Growth Inhibition Test (MGIT) BACTEC system is fully automated, and does not require radiometric methods standard to conventional testing protocols. The performance of this test has been good. However, there are at least two reports suggesting that it may be prone to contamination (49, 50) raising a cautionary note prior to wide spread implentation.

4 TREATMENT AND MANAGEMENT ADVICE

The treatment of patients with active tuberculosis with or without HIV coinfection has recently been reviewed (51, 52), and extensive guidelines have been updated by a joint commission of the American Thoracic Society, the Center for Disease Control and Prevention, and the Infectious Disease Society of America (38). Briefly, there are now ten antibiotics with FDA approval (and several with anti-tuberculous activity but not formal approval) for the use against *M. tuberculosis.* Despite this repertoire, the preferred initial regimen remains isoniazid, rifampin, ethambutol, and pyrazinamide. Whereas isoniazid has the most killing activity against rapidly dividing mycobacteria, rifampin or other rifamycins have become the cornerstone of tuberculous therapy because of their sterilizing ability in dormant populations. Pyrazinamide has preferential activity in acidic environments and is therefore useful cavitary disease. Ethambutol helps maintain susceptibility to rifamycins in the setting of pre-existing isoniazid resistance, and may add to a regimens early mycobactericidal activity. Other first-line drugs include rifapentine and rifabutin (not FDA approved). Second-line agents include cycloserine, ethionamide, streptomycin, amikacin/kanamycin, capreomycin, p-aminosalicylic acid, ciprofloxacin (or other fluoroquinolones) and clofazamine. The initial phase of treatment should include four drugs for at least two months, followed by a continuation phase with two drugs (preferably isoniazid and rifampin) determined by culture susceptibilities and the site and extent of disease burden (38).

Although well-accepted, reduced-frequency (i.e. intermittent) regimens exist for both the initial and continuation phases, critically ill patients should receive daily therapy due to the risk of altered pharmacokinetics in this population. Because ethambutol and pyrazinamide are only available for oral administration, every effort should be made to initiate early feeding and drug delivery via a Dobhoff or similar tube, even within twelve hours of major abdominal surgery and in advance of the return of

bowel sounds and flatus. If the oral route cannot be tolerated due to severe gastroparesis, vomiting, or diarrhea with malabsorption, parenteral therapy can be initiated with isoniazid, rifampin, streptomycin and a fluoroquinolone, followed by a transition to a standard regimen when bowel function is restored. Other factors influencing pharmacokinetics include the presence of renal dysfunction, necessitating dose adjustments for most agents. Moreover, patients with severe liver dysfunction at baseline should not be given a standard regimen due to the combination of multiple potentially hepatotoxic agents. In this case, a preferable regimen might be rifampin, ethambutol, and a fluoroquinolone or aminoglycoside (38). If there are major pharacokinetic concerns about an individual critically ill patient, it is possible and perhaps desirable to monitor drug levels (53), however, these targets are not well established making this area of therapy controversial (38). Finally, many of these antibiotics have significant drug interactions with agents commonly used in the ICU, including anticoagulants, anticonvulsants, cardiovascular agents, psychotropic drugs, and steroids or other drugs used in organ transplantation. Thus, clinical vigilance is needed, often supplemented by therapeutic drug monitoring of the non-tuberculous agents (38).

5 CONTROLLING TB TRANSMISSION IN THE INTENSIVE CARE UNIT

Effective tuberculous infection control requires a thorough understanding of the transmission of this organism. The acts of breathing, coughing, sneezing, speaking and singing normally cause the release of droplets of varying size, which also carry tubercle bacilli from an individual with active pulmonary disease. The largest of these droplets rapidly settle onto surfaces, which are contaminated but generally not considered infectious from a pulmonary standpoint. Evaporation of medium particles causes the formation of droplet nuclei roughly 1 to 5 μm in size. Animal experiments have shown that nuclei of this size are required to directly infect the alveolus, and that particle deposition in the larger airways does not render a productive infection. These nuclei remain airborne and infectious for several hours (54).

Preventing nosocomial spread of TB requires attention to all of the following; 1) clinical suspicion, 2) prospective isolation of high risk patients prior to establishing diagnosis, 3) engineering controls of ambient air to prevent dissemination of aerosols from an infected patient's room, 4) personnel protection in the form of masks, 5) rendering infectious

patients non-infectious by the initiation of effective therapy, and 6) administrative policies and programs to follow up with and initiate treatment of inadvertently exposed personnel (54, 55). Unfortunately, attempts to use clinical risk factors to reduce the numbers of patients with non-tuberculous disease requiring respiratory isolation during their workup have unacceptably high failure rates (20% or more) (56, 57). Thus, many institutions have adopted policies such that the decision to send sputum for AFB analysis on any hospitalized patient mandates respiratory isolation until three smears are negative.

From a practical standpoint, the riskiest patients to the ICU personnel are any patients with respiratory symptoms admitted prior to the suspicion of tuberculosis. Initiation of mechanical ventilation dramatically reduces the risk of transmission of aerosols because it is a closed system and the exhalation port is filtered. However, this does not eliminate the need for isolation and personnel masking due to unexpected breeches that can occur. As discussed above, patients exclusively with extrapulmonary tuberculosis are much less contagious due to the lack of aerosol formation. Unless concomitant pulmonary involvement can be excluded by negative sputum AFB smears, these patients should also be isolated.

Unfortunately, inadvertent exposure of ICU personnel can occur prior to suspicion, isolation, and implementation of respiratory protection. Any exposed personnel should have a PPD test within the first week following exposure to document prior exposure history, followed by a second PPD test three months later. With documented exposure to a patient with active disease, the "cut point" for a positive result becomes 5 mm of induration, reduced from the 10 mm point normally used for health care personnel so as to increase the sensitivity of the test. According to recently revised guidelines, a positive PPD test is an indication to consider treatment to prevent the occurrence of latent disease, regardless of age. This recommendation reflects a lower incidence of isoniazid-related hepatitis than previously documented, in combination with the recent resurgence in TB incidence. If the isolate from the index patient is susceptible, isoniazid (5 mg/kg PO daily, max 300 mg/day) remains the standard for a course of therapy for nine months. Shorter regimens may be effective including the combined use of rifampin and pyrizinamide, however, the latter may be associated with increased risk of liver toxicity. Successful completion of a prophylactic regimen reduces the risk of development of active disease by 93% (58).

6 A LOOK TO THE FUTURE

The ultimate goal in TB research is the development of a safe, effective, and durable vaccine for the prevention of primary infection, and possibly therapeutic benefit in the setting of active disease. Several candidate vaccines and immunization strategies are under investigation (59), however, a major limitation is that the production of gamma interferon, the main correlate of protective immunity in animal models, does not predict mycobacterial immunity in humans (60). Thus, at least five candidate vaccines are being tested in large Phase 3 clinical trials without the benefit of preliminary surrogate data from Phase 2 studies (59).

Genomic technology and information will also have a large impact on the management of this disease. Genotype information from mycobacterial isolates is already being used for epidemiological research, as well as for the identification of new antigens to be used as targets for subunit vaccines (61). Additionally, efforts are underway to identify genetic factors that contribute to variability in the immune response to tuberculous infection in humans. Several candidate genes, including gamma interferon, interleukin-10, and the natural resistance-associated macrophage protein 1 (NRAMP-1), have polymorphisms that are associated with an increased risk of active disease in select populations (62, 63). A genome-wide linkage analysis also suggests that there may be X-linked gene polymorphisms associated with susceptibility in Africans (64).

Unfortunately, genetic association studies have a high false positive rate, such that the ability to apply human genomic data to clinical practice will require careful evaluation of its clinical validity and utility. Making the transition from the epidemiological identification of a genetic risk factor to a surrogate endpoint for clinical outcome can be greatly facilitated when there is a reproducible biochemical assay that correlates with both the genetic changes and the outcome surrogate. An example of this may be the nucleotide receptor, $P2X_7$. Polymorphisms of this gene have been associated with protection from smear-positive disease in a Gambian population (65). This gene encodes an ion channel and pore expressed by most classes of leukocytes, and is involved with phagolysosomal maturation and killing of intracellular mycobacteria (66). Individuals with other loss-of-function genetic defects in this $P2X_7$ pore have monocytes that are less able kill the BCG strain *in vitro* (67). This $P2X_7$ pore is defective in roughly 15% of healthy adults and can be screened rapidly (68), thus providing the foundation for future clinical trials evaluating the

risk of reactivation from latent disease. Collectively, genomic advances may allow for rapid diagnosis of tuberculosis in critically ill patients and could even direct the administration of immunomodulatory adjunctive therapy.

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