Multidrug-resistant Tuberculosis in Military Recruits

Grace Freier,* Allen Wright,* Gregory Nelson,*
Eric Brenner,† Sundari Mase,‡ Sybil Tasker,§
Karen L. Matthews,¶ and Bruce K. Bohnker¶

We conducted a tuberculosis contact investigation for a female military recruit with an unreported history of multidrug-resistant tuberculosis (MDRTB) and subsequent recurrence. Pertinent issues included identification of likely contacts from separate training phases, uncertainty on latent MDRTB infection treatment regimens and side effects, and subsequent dispersal of the contacts after exposure.

In 2004, a 19-year-old female recruit came to the Naval Hospital in Beaufort, South Carolina, with a history of congestion and rhinorrhea for 4 days. Radiographic examination showed right upper and lower lobe infiltrates. Her initial recruit screening tuberculin skin test (TST) result had been reactive. Consultation with her physician in California indicated similar radiographic findings 2 years earlier; her condition had been diagnosed as smear-negative tuberculosis (TB). She received oral treatment of 300 mg isoniazid daily, 600 mg rifampin daily, and 1,500 mg pyrazinamide daily for 2 months. After a negative sputum culture, isoniazid and rifampin were continued for 9 months (1,2). Based on unchanged radiographic findings and 9 months of treatment, her disease was considered to be nonactive and she returned to training. Subsequently, she failed to complete training and was separated from the military.

The Study

Approximately 3 months after her initial treatment, the index patient was hospitalized in California for TB resistant to isoniazid and rifampin, which met the definition of multidrug-resistant tuberculosis (MDRTB). Initial isolate susceptibility in California showed resistance to isoniazid, rifampin, ethambutol, and streptomycin. Additional isolate susceptibility tests in Denver showed sensitivity to ethionamide, cycloserine, p-amino salicylic acid, clofazimine, levofloxacin, and pyrazinamide, but resistance to isoniazid, rifampin, streptomycin, amikacin/kanamycin, amoxicillin/clavulanate, and rifabutin.

After notification of the recruit’s hospitalization in California, Navy personnel began a TB contact investigation (7). Recruit populations are highly transient, as persons are frequently added or removed for various medical, dental, legal, or physical performance reasons. Some persons had multiple exposures to the index patient while in the training platoon and subsequently in various processing units. Thus, the contact investigation identified numerous persons who may have had contact with the index patient; these were categorized as “close” or “casual” contacts. Close contacts included persons who shared living quarters with the index patient; casual contacts included persons who had less definable contact with the index patient.

The investigation identified 13 close contact and 8 casual contact new reactors, defined as ≥5 mm TST indurations in persons who had negative tests previously (2). These persons were considered likely to have been infected with the MDRTB strain, though none demonstrated active disease. Table 1 shows that the close contact group had a TST reactor proportion of 9.09%. Table 2 shows a 3.1% TST reactor rate for the casual contact group (risk ratio [RR] 2.86, 95% confidence interval [CI] 1.22–6.74, p = 0.011). The index patient was assigned to the recruit-training platoon for 3 weeks, a rehabilitation squad for 9 days, and the separation platoon for 4 days. The TST reactor proportion for persons with >3 weeks of exposure in the recruit-training platoon was substantially lower than shorter duration of exposure in the rehabilitation and separation units (RR 0.19, 95% CI 0.05–0.66, p = 0.0032). A possible explanation for this apparent paradox would be increasing infectiousness during this later period, which is supported by progressive clinical symptoms seen in the index patient.

The optimal treatment protocol for new TST reactors from likely MDRTB sources is undefined, which leads to extensive consultation with TB experts to determine treatment timing and medications (3–10). The imminent transfer of reactors to new duty stations and the upcoming holiday leave period complicated the recommendations. Timing options included the following: 1) start medication immediately, retain reactors on base 7–10 days to verify medication tolerance, and allow self-medication during the transfer to their next duty station; 2) start medication immediately, allow self-medication during holiday leave, and continue therapy at their next duty station; or 3) delay treatment until reactors complete 2–3 weeks of holiday leave and initiate treatment at their next duty station. Ultimately, the graduating recruits were allowed holiday leave and began therapy at their next duty station.

Because the index patient’s isolate was resistant to isoniazid and rifampin, several medication options were
considered. The literature was reviewed and options assessed for medications, adverse effects monitoring (clinical vs. biochemical), duration (4, 6, 9, 12, or 24 months), and self-administered versus directly observed therapy. Three options emerged: 1) no medication with close clinical and radiologic monitoring for 2–3 years; 2) monotherapy with a fluoroquinolone; or 3) two-drug regimen consisting of pyrazinamide and a fluoroquinolone. This third option, initially strongly considered from prior recommendations (4), was not chosen because published case series suggested poor tolerance and unacceptable hepatotoxicity (8,9). By consensus, US Navy and Centers for Disease Control and Prevention (CDC) infectious disease specialists recommended a fluoroquinolone for at least 12 months. In vitro studies suggest that gatifloxacin and moxifloxacin have greater activity against *Mycobacterium tuberculosis* than older fluoroquinolones, though treatment efficacy for latent TB infection has not been documented in the literature (11,12). Ultimately, gatifloxacin was selected based on availability on the Department of Defense formulary. Therefore, the recruit reactors at high risk for latent TB infection from the MDRTB isolate were counseled, and 400 mg gatifloxacin was administered orally daily. Although the Food and Drug Administration had not approved gatifloxacin to treat TB, this protocol represented the most appropriate therapy, based on the limited data available.

Upon arrival for training, recruits receive a single-step TST and have historically demonstrated a baseline TST reactor proportion of 0.35% (13). However, several of the reactors in the casual exposure category were not recruits and had vague and limited exposure histories. For example, 1 reactor drove a bus that the index patient may have ridden. Persons in these positions do not routinely undergo TST screening and would be in populations with unknown TST conversion rates. Using the “concentric ring approach,” further investigation on base was deferred since the conversion proportion of personnel with positive TST results could not be separated from the background level in the local population (2). Military personnel would continue to receive TST surveillance consistent with the most current Navy medicine policy (1).

Only 6 of the 13 reactors in the higher-risk groups remained on active duty, and their transfer required explicit coordination to ensure appropriate follow-up. In collaboration with CDC, military preventive medicine personnel communicated with 5 state departments of health to ensure appropriate follow-up for the other 7 TST reactors in the high-risk group. More than 30 state health departments were notified of other casual contacts that were dropped from training.

**Conclusions**

This contact investigation illustrates the complexities associated with the public health management of MDRTB exposures in military recruit training settings. It demonstrates the importance of close coordination of efforts among military medical personnel, expert tuberculosis consultants, CDC, and state health departments in such cases. It shows some of the uncertainties in the clinical management of reactors associated with exposure to MDRTB sources, exacerbated in this case by military related factors. It highlights the complexities associated with public health management of MDRTB exposure and demonstrates the necessity of response preparedness, close consultation, communication, and coordination of efforts.

---

**Table 1. Close contact tuberculin skin test (TST) reactor rates by exposure location**

| Exposure Category          | Total | Old Reactors | TST | New Reactor | Reactor rate (%) |
|----------------------------|-------|--------------|-----|-------------|------------------|
| Recruit training platoon only | 67    | 1            | 65  | 4           | 6.15             |
| Recruit processing units only | 53    | 1            | 48  | 5           | 10.04            |
| Multiple exposures         | 38    |              | 30  | 4           | 13.33            |
| All close contacts         | 158   | 2            | 143 | 13          | 9.09             |

---

**Table 2. Tuberculin skin test (TST) reactor rate by exposure duration**

| Contact duration | Total | Old Reactors | TSTs placed | New reactor | Reactor rate (%) |
|------------------|-------|--------------|-------------|-------------|------------------|
| **Casual contacts** |       |              |             |             |                  |
| Likely none      | 25    | 0            | 19          | 1           | 5.26             |
| Possible         | 256   | 13           | 233         | 7           | 3.00             |
| **Close contacts** |       |              |             |             |                  |
| Unknown          | 34    | 1            | 33          | 1           | 3.03             |
| >3 weeks†       | 70    | 1            | 70          | 3           | 4.29             |
| Sep 13-Oct 12   | 42    | 0            | 31          | 6           | 19.35            |
| 1-3 weeks       |       |              |             |             |                  |
| Oct 12-21       | 12    | 0            | 9           | 3           | 33.33            |
| <1 week         |       |              |             |             |                  |
| Oct 21-26       | 0     |              |             |             |                  |
| **Total**       | 439   | 15           | 395         | 21          | 5.32             |

*The close contacts were more likely to convert than the incidental contacts. Risk ratio (RR) 2.86, 95% confidence interval (CI) 1.22–6.74, p = 0.011.
†The close contacts with >3 weeks of exposure were less likely to convert than those with <3 weeks of exposure. RR 0.19, 95% CI 0.05–0.66, p = 0.0032.
This outbreak preceded recently published guidance on TB investigations and treatment, although it was generally handled consistent with that guidance (14,15).

Dr Freier served as a general medical officer at Naval Hospital Beaufort-Branch Medical Clinic, Parris Island, South Carolina, when she wrote this article. She is currently completing her residency in pediatrics at Naval Medical Center, Portsmouth, Virginia. Dr Freier’s research interests include military recruit medicine and pediatric infectious disease.

References
1. BUMEDINST 6224.8 of 14 Sept 1993. [cited 2005 Mar 03]. Available from http://navymedicine.med.navy.mil/Files/Media/directives/6224-8%20ch-1.pdf
2. Diagnostic standards and classification of tuberculosis in adults and children. Am J Respir Crit Care Med. 2000;161:1376–95.
3. Centers for Disease Control and Prevention. Targeted tuberculosis testing and treatment of latent tuberculosis infection. MMWR Morb Mortal Wkly Rep. 2000;49:1–54.
4. Centers for Disease Control and Prevention. Management of persons exposed to multidrug-resistant tuberculosis. MMWR Morb Mortal Wkly Rep. 1992;41:59–71.
5. Papastavros T, Dolovich TR, Holbrook A, Whitehead L, Loeb M. Adverse events associated with pyrazinamide and levofloxacin in the treatment of latent multidrug-resistant tuberculosis. CMAJ. 2002;167:131–6.
6. American Thoracic Society; CDC; Infectious Diseases Society of America. Treatment of tuberculosis. MMWR Recomm Rep. 2003; 52(RR-11):1–77.
7. Passannante MR, Gallagher CT, Reichman LB. Preventive therapy for contacts of multidrug-resistant tuberculosis. A Delphi survey. Chest. 1994;106:431–4.
8. Horn DL, Hewlett D, Alfalfa C, Peterson S, Opal SM. Limited tolerance of ofloxacin and pyrazinamide prophylaxis against tuberculosis. N Engl J Med. 1994;330:1241.
9. Ridzon R, Meador J, Maxwell R, Higgins K, Weismuller P, Onorato I. Asymptomatic hepatitis in persons who received alternative preventive therapy with pyrazinamide and ofloxacin. Clin Infect Dis. 1997;24:1264–5.
10. Bloomberg HM, Leonard MK, Jasmer RM. Update on the treatment of tuberculosis and latent tuberculosis. JAMA. 2005;293:2766–84. Erratum in: JAMA. 2005;294:18.
11. Alvirez-Freites EJ, Carter JL, Cynamon HL. In vitro and in vivo activities of gatifloxacin against Mycobacterium tuberculosis. Antimicrob Agents Chemother. 2002;46:1022–5.
12. Aubry A, Pan XS, Fisher LM, Jarlier V, Cambau E. Mycobacterium tuberculosis DNA gyrase: interaction with quinolones and correlation with anti-mycobacterial drug activity. Antimicrob Agents Chemother. 2004;48:1281–8.
13. Gamble-Lawson C, Bowman C, Suesw W, Riegodedios A, Bohnker BK. Tuberculosis in the US Navy and Marine Corps: a 4 year retrospective analysis (2000–2003). Navy Medical Surveillance Report. 2004. [cited 2005 Nov 7]. Available from http://www-nehc.med.navy.mil/downloads/prevm/Dec04.pdf
14. Centers for Disease Control and Prevention (CDC). Controlling tuberculosis in the United States. Recommendations from the American Thoracic Society; CDC, and the Infectious Diseases Society of America. MMWR Morb Mortal Wkly Rep. 2005;54:1–37.
15. Centers for Disease Control and Prevention (CDC). Guidelines for the investigation of contacts of persons with infectious tuberculosis. Recommendations from the National Tuberculosis Controllers Association and CDC. MMWR Morb Mortal Wkly Rep. 2005;54:1–37.

Address for correspondence: Bruce K. Bohnker, 808 Seaborn Way, Chesapeake, VA 23322, USA; email: bkb@juno.com

The opinions expressed by authors contributing to this journal do not necessarily reflect the opinions of the Centers for Disease Control and Prevention or the institutions with which the authors are affiliated.