A Comparison of Outbreak- and Nonoutbreak-Related Multidrug-Resistant Tuberculosis Among Human Immunodeficiency Virus–Infected Patients in a South African Hospital

Leonard V. Sacks, Stella Pendle, Dragana Orlovic, Lucille Blumberg, and Constantinos Constantinou

From the Sizwe Tropical Diseases Hospital and the South African Institute for Medical Research, Johannesburg, South Africa

Nosocomial multidrug-resistant tuberculosis (MDR-TB) in human immunodeficiency virus (HIV)–infected people is recognized in Europe and America. We report the first such outbreak in South Africa. Six hospitalized women, identified by DNA fingerprinting, were infected with an outbreak strain of MDR-TB while receiving treatment for drug-susceptible tuberculosis. The putative source case was identified as an HIV-positive woman who underwent prolonged hospitalization for chronic cavitary tuberculosis. Compared with other HIV-positive patients in the hospital, outbreak patients were more immunocompromised, had fewer cavitary lung changes, and were less likely to have been treated before. They had high fevers, infiltrative patterns on chest radiographs, and a mean survival of 43 days. When individual isolation is not possible, separating highly immunocompromised patients with first-time tuberculosis from previously treated patients with cavitary lesions and from those with established drug resistance may reduce nosocomial transmission.

Outbreaks of tuberculosis, both drug-resistant and drug-susceptible, have been recognized in several institutions [1–4]. They are common in HIV-infected patients [5] and tend to be characterized by rapid clinical progression [6] and very high mortality rates [7]. In some instances, outbreaks have been identified among patients already receiving treatment for tuberculosis [4]. Bacteriologic characteristics [7, 8], host factors such as HIV-positivity [5] and human leukocyte antigen type [9, 10], NRAMP1 gene polymorphisms [11], and environmental factors (including the infectiousness of the source case, the period of exposure, local ventilation, and the nature of exposure) may play a role.

We believe that no such outbreaks of multidrug-resistant tuberculosis (MDR-TB) in HIV-infected patients in Africa have been recognized to date. Although the global magnitude of drug resistance is becoming clearer [12, 13], national and global epidemiological studies are not comprehensive, particularly since regions with poor control programs and laboratory facilities are underrepresented [13]. Failure to recognize the problem may be restricted to specific regions or institutions demonstrating inappropriate complacency with regard to infection control. On the basis of our experience with an MDR-TB outbreak in a Johannesburg hospital, we aimed to characterize the setting for this type of outbreak so that such situations could be recognized and so that cases and potential sources could be targeted with infection control procedures.

Patients and Methods

Sizwe Tropical Disease Hospital is a 500-bed government referral center for patients with tuberculosis and other infectious diseases in the greater Johannesburg area. Most of the patients come from lower-income groups, with high unemployment rates, poor housing, and overcrowding. Patients whose diagnosis at admission is tuberculosis are followed by means of a baseline acid-fast bacilli (AFB) smear, monthly AFB smears while cough remains productive, monthly weight determinations, and periodic chest radiography. Initial sputum culture and drug-susceptibility testing is ordered if there is any suspicion of drug resistance, for reasons such as previous treatment or exposure to patients with MDR-TB. Drug-susceptibility testing may be subsequently requested if patients’ responses to therapy are unsatisfactory.

Upon completion of therapy, patients are encouraged to return for 12- and 18-month follow-up visits. HIV testing is undergone by all consenting patients at the time of admission, and a CD4 cell count is obtained for those whose test results are positive. This information is saved on a central computerized database. Drug-susceptible tuberculosis is treated with a standard short-course regimen (isoniazid, rifampin, pyrazinamide, and ethambutol for 8 weeks, and then isoniazid and rifampin while cough remains productive, monthly weight determinations, and periodic chest radiography). Initial sputum culture and drug-susceptibility testing is ordered if there is any suspicion of drug resistance, for reasons such as previous treatment or exposure to patients with MDR-TB. Drug-susceptibility testing may be subsequently requested if patients’ responses to therapy are unsatisfactory.

Upon completion of therapy, patients are encouraged to return for 12- and 18-month follow-up visits. HIV testing is undergone by all consenting patients at the time of admission, and a CD4 cell count is obtained for those whose test results are positive. This information is saved on a central computerized database. Drug-susceptible tuberculosis is treated with a standard short-course regimen (isoniazid, rifampin, pyrazinamide, and ethambutol for 8 weeks, and then isoniazid and rifampin for the remaining 16 weeks). Directly observed therapy is practiced while patients are in the hospital but is not uniformly enforced for outpatients. Antiretroviral therapy is not provided for the HIV-positive patients. Individual isolation facilities are not available for the ~200 tuberculosis patients in the hospital at any one time.
In September 1997 a patient presented with relapsing symptoms while receiving therapy for drug-susceptible tuberculosis. A highly resistant isolate of *Mycobacterium tuberculosis* was cultured from the sputum. A prospective study was initiated to identify any further possible cases of nosocomially acquired MDR-TB in the hospital.

**Identification of outbreak cases.** Following identification of the index case, we investigated for MDR-TB any patient successfully treated in the hospital for tuberculosis during the previous year (with a satisfactory clinical response and confirmed negative sputum smears for AFB) who experienced a relapse of signs and symptoms suggestive of active tuberculosis, including a newly positive AFB smear (either while an inpatient or during follow-up). In such cases, any new isolate showing drug resistance was submitted for DNA fingerprinting. A characteristic fingerprint identified the patient as an outbreak case.

Sputum for susceptibility testing was collected and processed on the day that each patient presented with recurrent symptoms, and those same cultures were used for DNA fingerprinting. Collection dates differed for each of the patients.

**Retrospective search for a source case.** The complete electronic database of the hospital, containing the records of patients with tuberculosis admitted between January 1996 and March 1998, was reviewed. All patients with multidrug-resistant isolates were identified. Any isolate with resistance to five or more drugs was suspected to be the outbreak strain and was subjected to restriction fragment length polymorphism (RFLP) analysis.

To characterize the risk factors for contracting outbreak-related MDR-TB and to identify clinical features suggesting the development of an outbreak in a tuberculosis facility, we compared outbreak cases with all other HIV-positive MDR-TB cases in the hospital during the same period, using the computerized patient database.

Chest radiographs obtained on initial admission were evaluated as described previously [14]. A transparent grid of squares (3 cm × 3 cm) was placed over each chest film. The number of squares showing >50% lung tissue was taken to indicate the total visible lung. The sum of squares showing cavitation, fibrosis, or infiltration was expressed as a percentage of the total visible lung to indicate numerically the proportion of lung affected by each radiographic pattern. Each radiograph was independently scored by two physicians experienced in the management of tuberculosis, and the mean of their results represented the final score.

RFLPs of isolates were characterized at the South African Institute for Medical Research with use of the standardized protocol described by van Embden et al. [15] and van Soolingen et al. [16]. RFLP patterns were compared visually.

Drug-susceptibility testing was performed by means of a modified proportion method [17] with a critical drug concentration, with use of the radiometric BACTEC7 system [18] (Becton Dickinson, Sparks, MD) for isoniazid, rifampin, ethambutol, and streptomycin, and with Löwenstein-Jensen and Middlebrook 7H11 media for other antimicrobials. Isolates were confirmed as *M. tuberculosis* by PCR with IS6110 primers.

Positive sputum smears were reported as 1+ positive (10–99 organisms per 100 high-power fields [HPFs]), 2+ positive (1–10 organisms per HPF), or 3+ positive (>10 organisms per HPF).

**Statistical analysis.** Continuous variables were compared by Student’s *t* tests. Categorical variables were compared by χ² tests or the Fisher exact test when an expected cell value was <5. All *P* values were two-tailed and regarded as significant if *P* < .05. Calculations were performed with use of Epi Info version 6 [19].

**Results**

**Index case.** On 29 September 1997, a 27-year-old HIV-positive woman who had been in the hospital for 13 weeks for antituberculous therapy developed a fever (temperature, 40°C). The diagnosis of tuberculosis at admission was based on the presence of AFB in her sputum, and she had responded well to supervised short-course therapy with isoniazid, rifampin, pyrazinamide, and ethambutol. Her weight increased from 44 kg to 50 kg. Her sputum converted from smear-positive to smear-negative, and her cough resolved.

While investigating the new onset of fever, we noted that she had lost 4 kg in weight despite continuing her treatment with isoniazid and rifampin. A chest radiograph showed new infiltrates, and her sputum was again 3+ smear-positive for AFB. Culture yielded an isolate of *M. tuberculosis* resistant to isoniazid, rifampin, ethambutol, pyrazinamide, ethionamide, terizidone, thiacetazone, and ofloxacin. Her condition deteriorated rapidly, and she died 18 days later.

Among all the hospital inpatients and outpatients being followed for recently treated tuberculosis (within 12 months), a total of five additional patients who presented with relapsing active tuberculosis were identified over the next 10 months. All five were young, HIV-positive women, and each of their new isolates revealed a multidrug-resistant phenotype. RFLP analysis performed on these five isolates and on the isolate from the index case confirmed that all six shared the identical fingerprint (figure 1).

All these outbreak patients were initially hospitalized between April and July 1997 (figure 2). Patients 3, 5, and 7 presented with pulmonary tuberculosis, and drug-susceptible isolates of *M. tuberculosis* were obtained from all. For patients 2, 4, and 6, chest infiltrates, fever, and weight loss were noted at presentation. Although *M. tuberculosis* was not isolated from these patients at their initial presentation, the diagnosis was made by the finding of AFB in clinical specimens and was confirmed by a good clinical response to therapy for tuberculosis, including resolution of cough, conversion of sputum smears to negative, and weight gain.
All six were accommodated in two large adjacent wards, each with 24 beds and a shared ablution facility. Despite a policy to leave the ward windows open, this is often not possible on winter nights (May to July), when temperatures frequently approach freezing. Isolation facilities were not available and patients mingled freely, socializing on the veranda outside the ward.

Patients 2, 3, 5, and 7 were discharged to home after a mean of 11 weeks in the hospital. They were unaware of having any exposure to tuberculosis outside the hospital. All were readmitted because of recurrence of symptoms and were confirmed to have contracted the outbreak strain. Patients 4 and 6 developed new MDR-TB while still hospitalized for the original tuberculosis episode and remained in the hospital until their deaths.

The outbreak cases occurred within a narrow time interval, prompting us to review the setting in which the disease was contracted. The hospital houses ~200 patients with tuberculosis at any one time. Most are referred for complicated tuberculosis, drug resistance, or concurrent illnesses, and many are debilitated, making outpatient management impractical. Current statistics show that 64% of the patients with tuberculosis are HIV-infected and 14% carry MDR-TB strains. Thirty-seven percent of the patients have been treated previously for tuberculosis. Most patients present with cavitary lung disease. The median hospital stay is 2 months, and patients usually remain hospitalized until sputum smears are negative.

In an attempt to identify the putative source patient, we reviewed the records of all the patients with MDR-TB identified in the electronic database, which covered the period of January 1996 to March 1998. Drug-susceptibility results were available for 451 of the 618 patients with diagnosed tuberculosis. Sixty-five of these patients were infected with MDR-TB. Six of them carried strains that were resistant to five or more drugs and were suspected to be the outbreak strain. These six isolates were subjected to RFLP testing, and one shared an RFLP pattern with the outbreak strain (figure 1).

The putative source patient was identified as a 37-year-old woman who was hospitalized on 25 February 1997 in one of the two wards where the other outbreak cases originated. She had been treated for tuberculosis as an outpatient in 1992 with a full 6-month course. There was no subsequent history of exposure to tuberculosis. When she presented again she was first seen at her local health clinic, from which she was referred to our hospital once MDR-TB was identified.

She was found to be HIV-positive, with a CD4 cell count of 362/μL. An MDR-TB isolate recovered at the time of admission was resistant to isoniazid, rifampin, ethambutol, pyrazinamide, ethionamide, terizidone, and thiacetazone. At presentation, chest radiography showed obvious large cavities (9% of visible lung) at the right apex, with some interstitial infiltration. She was afebrile. She was treated with streptomycin, ofloxacin, roxithromycin, and clofazimine. The chronic, indolent course of her disease was similar to those of several patients in this hospital from whom multidrug-resistant strains had been recovered.

**Figure 1.** DNA fingerprints of isolates of multidrug-resistant *Mycobacterium tuberculosis* from patients infected with the outbreak strain (lanes 4, 7, 8, 9, 10, and 12) and fingerprints of other multidrug-resistant isolates from other patients in the hospital (lanes 1, 2, 3, 5, 6, and 11). Lane 11 was for a drug-susceptible isolate obtained from one outbreak victim at the time she was admitted to the hospital, before becoming infected with the outbreak strain. Her subsequent multidrug-resistant strain is shown in lane 12. (Lanes 11 and 12 were run separately from the rest and have been aligned for comparison).

**Figure 2.** Reconstruction of a nosocomial outbreak of multidrug-resistant tuberculosis (MDR-TB), by dates reflecting periods during which the seven patients were hospitalized with drug-susceptible (–sensitive) and drug-resistant tuberculosis (TB) (S = source case; I = index case).
Sputum smear findings ranged between 1+ positive (six specimens) and 3+ positive (one specimen) throughout the 6 months of her admission, and her weight dropped from 54 kg to 50 kg. She was never isolated and spent the entire period of hospitalization in one of the two wards where the outbreak cases occurred, with unlimited access to both of the wards and the veranda. Despite reluctance by the medical staff to discharge her to her two-room house, for fear of infecting the two young children living with her, social reasons forced her to leave the hospital in August 1998. She continued her treatment at home, where she died in November.

Figure 1 shows representative fingerprints of outbreak cases and the source case, all with 15 characteristic bands. For one of these patients, a previous drug-susceptible isolate from her initial admission (during which she was exposed to the outbreak strain) was available and clearly showed a different RFLP pattern. Five other patients in the hospital database, who were in the hospital between January 1996 and March 1998, carried strains resistant to five or more drugs. RFLP tests were performed on these isolates, and all showed unique patterns.

Figure 2 shows a reconstruction of the outbreak as it evolved during 1997. For each of the six outbreak patients, the interval between the date that the patient was first admitted and the date that symptoms of MDR-TB developed ranged between 13 and 29 weeks, with a mean of 19 weeks. All six outbreak patients presented with cough, high fevers, weight loss, and new radiological infiltrative patterns affecting between 11% and 41% of visible lung.

Table 1 compares the clinical features of the outbreak patients with those of 18 other HIV-coinfected patients among the 65 MDR-TB cases referred to the hospital. The outbreak patients were significantly younger than nonoutbreak patients (though this may reflect the pattern of social interaction of the patients). They had lower CD4 cell counts on admission. Of the seven patients infected with the outbreak strain, only the source patient reported a previous course of antituberculous treatment, 5 years prior to the current course. The remaining six outbreak patients were receiving their first course of therapy for tuberculosis at the time that they were infected with the outbreak strain. In contrast, 17 of the 18 nonoutbreak MDR cases reported one or more previous courses of therapy for tuberculosis in the years preceding the present illness.

The outbreak strain was resistant to a mean of six drugs. For one patient, resistance only to isoniazid and rifampin was known. For the rest, resistance was found to between six and eight drugs. Six isolates were resistant to isoniazid, rifampin, and ethambutol, 5 to pyrazinamide, 5 to thiacetazone, 4 to ethionamide, 4 to terizidone, and 4 to ofloxacin. MDR isolates from nonoutbreak patients were resistant to a mean of three drugs (range two to six drugs). All outbreak patients died, a mean of 43 days (range, 11–107 days) after the diagnosis of MDR-TB was made. Only four of the 18 nonoutbreak patients died, a mean of 136 days after admission for MDR-TB. Extrapulmonary disease was diagnosed for one patient in each group. A multidrug-resistant isolate was recovered from the CSF of the outbreak patient with extrapulmonary disease.

The mean of the maximum temperatures recorded during the week that outbreak patients presented with MDR-TB was high compared with that for nonoutbreak patients during the first week of presentation.

On admission, radiological cavitation and fibrosis were present in all nonoutbreak patients (table 1) but were negligible in the outbreak patients, of which only two had cavities (involving 2% of visible lung in one and 5% in the other). It is interesting that the source patient’s chest radiograph was more typical of those of nonoutbreak patients, with 9% upper-lobe cavitation. Her indolent clinical course, higher CD4 cell count, and history of previous therapy differed from the disease profile of the other outbreak patients she infected.

Discussion

Nosocomial outbreaks of MDR-TB and, recently, multidrug-resistant *Mycobacterium bovis* have been reported in North America, South America, and Europe [1, 2, 3, 4, 20]. In African countries, clustering of MDR-TB among HIV-infected patients in outbreak settings has not been identified as a concern [21, 22]. Our discovery of just such an outbreak in South Africa indicates that this may now be one. While differences may exist between our population and other African countries in terms of drugs and facilities used for the treatment of tuberculosis, highly infectious drug-resistant strains are evidently a threat in Africa, and surveillance of such infections is clearly a public health priority.

We identified several characteristics of patients contracting
superinfections due to a multidrug-resistant outbreak strain. Tuberculosis in outbreak patients (despite diagnosis of their drug-susceptible tuberculosis before the time of multidrug-resistant superinfection) presented like primary tuberculosis, with minimal cavitary or fibrosis and rapid progression. They were severely immunocompromised and had no record of previous courses of treatment for tuberculosis.

In contrast, HIV-infected patients with nonoutbreak MDR-TB had usually been treated for tuberculosis before, and they demonstrated better immunity, with indolent cavitary disease. Radiological differences between outbreak and nonoutbreak cases were described by Fishman et al. [23], who also reported that cavitation was not characteristic of outbreak cases. The extent of cavitation in HIV-positive patients has been directly correlated with CD4 cell counts, and the radiographic changes in our outbreak cases may reflect severe immunosuppression at the time of M. tuberculosis infection [24].

Our outbreak patients shared several characteristics with those identified in other reports [5]. They were all HIV-positive and significantly immunocompromised, with mean CD4 cell counts of 119/µL. In the setting of nosocomial exposure, we found it important to recognize acute febrile illnesses in such patients as a possible harbinger of multidrug-resistant superinfection. Clearly, we may have underestimated the extent of the outbreak, since we did not investigate patients with continuously positive sputum smears who failed to respond to therapy following their initial presentation. Nor were we able to investigate outpatients who were lost to follow-up or those who presented longer than 10 months after the index case was identified. Ongoing surveillance will help decide whether the highly immunocompromised patients in this outbreak were identified because of greater susceptibility to MDR-TB or because of shorter incubation periods than in other patients.

The source patient in our hospital showed features transitional between outbreak and nonoutbreak patients. On the one hand, she was HIV-positive, she was infected with a highly resistant isolate, and the outcome was fatal. On the other hand, cavitary disease was present, the course of her disease was relatively indolent, she had a higher CD4 cell count, and she had a history of treated tuberculosis.

Biological characteristics of the outbreak strain may play a role in the spread of the disease. Virulence of M. tuberculosis is variable [25] and appears to be one of the factors determining the spread of the outbreak strain rather than other multidrug-resistant strains in the hospital at the time. The unusually rapid course of the infection in our outbreak victims is reminiscent of other reports [1, 2], confirming the virulence of such strains.

The variability in the drug-susceptibility patterns of the outbreak isolates was unexpected, but this has been well documented in other outbreaks [4, 7]. Changes in the characteristics of the organism with aging and technical variation, particularly when MICs are near the breakpoint, may affect the result.

Infection control measures developed in affluent settings recommend isolation of all tuberculosis patients in negative-pressure rooms, possible adjunctive use of ultraviolet light, and the use of respirators by staff members [26, 27]. In this country with a tuberculosis incidence in 1994 of 311/100,000 [28] and an HIV prevalence of up to 14% in surveys at antenatal clinics (personal communication, Department of Health, South Africa), this approach cannot be applied in the face of very limited resources. Hospitals such as ours, housing up to 200 tuberculosis patients with many permutations of drug resistance and HIV status, emphasize the problem.

Our results suggest that where isolation facilities are limited, several strategies should be considered to prevent the nosocomial spread of MDR-TB. The outbreak patients we identified were all significantly immunocompromised, did not have the features of chronic cavitary tuberculosis, and were unlikely to have a history of tuberculosis treatment prior to hospitalization, unlike patients with nonoutbreak MDR-TB. While new cases may still develop that involve patients with a different clinical profile, we felt that such patients in our hospital were most at risk and should be housed separately from patients with a history of tuberculosis or chronic cavitary disease for whom drug-susceptibility results were not yet available.

In particular, attempts should be made to discharge susceptible patients as soon as possible. Nonoutbreak patients entering the hospital with MDR-TB typically had a history of tuberculosis, mostly with evidence of long-standing cavitary disease. Until drug-susceptibility results were available, such patients in our hospital were suspected of having MDR-TB, and we felt they should also be separately cohorted. Because of the long period of exposure to the source case, we felt it imperative to separate patients with known drug resistance from the rest and to obtain susceptibility results as soon as possible for new admissions.

Early discharge of patients with MDR-TB remains contentious. While treatment of such individuals may be possible on an outpatient basis, the impact on contacts must be studied. Previous experience in New York City suggests that wide dissemination of resistant strains may then occur in the community [7].

A system for early recognition of nosocomial transmission is important, and surveillance as well as awareness of the possibility is crucial. In our institution this was facilitated by an electronic database on admitted patients.

Engineering issues are more challenging in institutions with limited resources and large numbers of patients with tuberculosis, MDR-TB, and HIV infection. We noted that transmission in this outbreak occurred during the months of the South African winter, a time when windows in the wards were closed at night because of the cold. Where possible, improvements in heating may allow good ventilation throughout the year.

Containing such outbreaks may be difficult in developing countries where HIV disease and MDR-TB are prevalent, and
outbreaks may be recognized only after scores of patients have been infected [4]. Ultimately, the control of drug resistance relies heavily on the control of tuberculosis in the community. All efforts should be made to ensure early diagnosis and the establishment of prompt, effective treatment programs outside the hospital to reduce the prevalence of drug resistance.

Acknowledgment

The authors thank Andre Trollip for performing the drug-susceptibility assays on isolates.

References