MAJOR ARTICLE

# Treatment Outcomes for HIV-Uninfected Patients with Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis

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***Background.*** Multidrug-resistant (MDR) tuberculosis (TB) is more difficult to treat than is drug-susceptible TB. To elucidate the optimal therapy for MDR TB, we assessed the treatment outcomes and prognostic factors for patients with MDR TB.

***Methods.*** This study included patients who received an individualized treatment regimen for MDR TB at Samsung Medical Center, a tertiary referral hospital in Seoul, Korea, from January 1995 through December 2004. To identify the prognostic factors related to favorable treatment outcomes, univariate comparison and multiple logistic regression were performed.

***Results.*** Of 155 patients, 18 (12%) had newly diagnosed MDR TB, 81 (52%) had previously received treatment with first-line drugs, and 56 (36%) had received treatment with second-line drugs. The isolated strains were resistant to a median of 5 drugs. Twenty-seven patients (17%) had extensively drug-resistant (XDR) TB at the start of treatment. Outcome assessment revealed that 102 patients (66%) were cured or completed therapy. The treatment success rates did not differ significantly between patients with non-XDR MDR TB and those with XDR TB (66% vs. 67%). Surgical resection was performed more frequently for patients with XDR TB than for those with non-XDR MDR TB (48% vs. 17%). Combined surgical resection, body mass index $\geqslant$18.5 (calculated as the weight in kilograms divided by the square of the height in meters), use of $>$4 effective drugs, and a negative sputum smear result were independent predictors of a favorable outcome.

***Conclusions.*** Early aggressive treatment comprising at least 4 effective drugs and surgical resection, when indicated, may improve the outcome for patients with MDR TB or XDR TB.

Multidrug-resistant (MDR) tuberculosis (TB) is more difficult to treat than is drug-susceptible TB [1]. Key problems include the limited availability of effective drugs, the reduced efficacy of second-line drugs, an increased number of adverse reactions to the drugs, and the long duration of therapy. In addition, concerns about extensively drug-resistant (XDR) TB have been raised. XDR TB is defined as resistance to both rifampin and isoniazid (the definition of MDR TB) in addition to any fluoroquinolone and at least 1 of the following injectable anti-TB drugs: capreomycin, kanamycin, and amikacin [2]. XDR TB may have evolved greater resistance through inappropriate treatment of MDR TB with second-line drugs, including fluoroquinolones and injectable drugs [3, 4]. Patients with XDR TB are more likely to have an unfavorable outcome, compared with patients with non-XDR MDR TB [5–7].

Treatment guidelines for MDR TB were recently published [8, 9]; however, several controversial issues remain, including the number of anti-TB drugs required, the required duration of parenteral drug administration, the role of standardized versus individualized regimens, and the contribution of surgery [10]. In addition, an optimal treatment strategy for XDR TB has not been established, because the inability to use fluoroquinolones and injectable agents means the inability to use the most-potent options for second-line drugs.

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**Table 1. Baseline clinical characteristics of 155 patients with multidrug-resistant tuberculosis (TB).**

| Characteristic | Patients ($n$ = 155) |
|---|---|
| Male sex | 82 (53) |
| Age, median years (IQR) | 40 (27–54) |
| Median BMI (IQR) | 20.0 (18.0–22.2) |
| Comorbid condition | |
| Diabetes mellitus | 24 (15) |
| Chronic liver disease | 8 (5) |
| Malignancy | 5 (3) |
| Treatment history | |
| None | 18 (12) |
| First-line drugs only | 81 (52) |
| Second-line drugs | 56 (36) |
| Median no. of drugs to which the isolates were resistant (IQR) | 5 (3–6) |
| Extensively drug-resistant TB | 27 (17) |
| Positive sputum smear result | 131 (85) |
| Cavity (or cavities) on chest radiograph | 110 (71) |
| Bilateral disease | 107 (69) |

**NOTE.** Data are no. (%) of patients, unless otherwise indicated. BMI, body mass index (calculated as the weight in kilograms divided by the square of the height in meters); IQR, interquartile range.

To gain greater insight into the optimal therapeutic strategy for these patients, we retrospectively assessed the outcomes in patients with MDR TB who received treatment with individualized regimens based on the results of drug-susceptibility tests (DSTs) during a recent 10-year period at a tertiary care referral hospital in Korea, in which there is an intermediate TB burden and a low prevalence of HIV infection [11]. We also analyzed the relationship between favorable outcome of treatment and variables that might influence the outcome, including the specific effect of a number of drugs and resectional surgery.

## PATIENTS AND METHODS

***Study population.*** MDR TB was defined by a culture positive for *Mycobacterium tuberculosis* with in vitro resistance to both isoniazid and rifampin. Isoniazid, rifampin, ethambutol, pyrazinamide, and streptomycin were considered to be the first-line drugs. We included 155 patients with MDR TB who were referred to and given treatment with second-line drugs for at least 3 months from January 1995 through December 2004 at the university-affiliated tertiary care hospital Samsung Medical Center in Seoul, Korea. We excluded 17 patients who had been transferred to a national TB hospital after they received treatment for <3 months at our hospital. Permission was obtained from the Institutional Review Board of Samsung Medical Center to review and publish information from the patients' records. Informed consent was waived because of the retrospective nature of the study.

The drug susceptibility of the *M. tuberculosis* isolates was determined with use of the absolute concentration method with Löwenstein-Jensen medium at the Korean Institute of Tuberculosis (Seoul, Korea), which is a World Health Organization–designated Supranational Reference Laboratory. The drugs and their critical concentrations for resistance were as follows: isoniazid, 0.2 $\mu$g/mL; rifampin, 40 $\mu$g/mL; ethambutol, 2 $\mu$g/mL; streptomycin, 10 $\mu$g/mL, kanamycin, 40 $\mu$g/mL; capreomycin, 40 $\mu$g/mL; ofloxacin, 2 $\mu$g/mL; prothionamide, 40 $\mu$g/mL; cycloserine, 30 $\mu$g/mL; and para-aminosalicylic acid, 1 $\mu$g/mL. Pyrazinamide susceptibility was determined with use of the pyrazinamidase test [12]. The drugs to which the isolates were susceptible were defined as effective drugs. DSTs were not performed for amikacin, levofloxacin, moxifloxacin, amoxicillin-clavulanate, or clarithromycin during the study period.

***Medical and surgical treatment.*** All individualized treatment regimens were based on a combination of the first- and second-line drugs to which the strains displayed susceptibility. Daily doses were administered in accordance with published guidelines [8, 13, 14]. When available, the regimens included at least 3 effective drugs on the basis of the DST results, in accordance with previous World Health Organization guidelines [13]. For cases in which 3 effective drugs could not be supplied or in cases involving extensive disease, drugs with unproven activity (amoxicillin-clavulanate, clarithromycin, and rifabutin) were included in the regimen.

As a rule, treatment was given for 18–24 months, including at least 12 months after culture conversion (defined as $\geq$2 consecutive negative results of cultures performed at least 4

**Table 2. Rates of drug resistance among 155 *Mycobacterium tuberculosis* isolates.**

| Drug | No. (%) of resistant isolates ($n$ = 155) |
|---|---|
| Isoniazid | 155 (100) |
| Rifampin | 155 (100) |
| Ethambutol | 107 (69) |
| Pyrazinamide | 92 (59) |
| Streptomycin | 44 (28) |
| Kanamycin | 39 (25) |
| Capreomycin (or viomycin) | 18 (12) |
| Cycloserine | 13 (8) |
| Prothionamide | 36 (23) |
| Para-aminosalicylic acid | 45 (29) |
| Ofloxacin | 65 (42) |

weeks apart). In general, treatment was provided on an outpatient basis. Forty-five patients were hospitalized for a short time at the start of second-line therapy. Treatment was directly observed during the hospitalization period, and the drugs were self-administered with the support of trained nurses during outpatient therapy. Sputum smear examinations and cultures were performed monthly for the first 6 months and then at 2–3-month intervals until the end of treatment.

Although the decision to perform surgical resection was made by the attending physicians, the general indication was MDR TB refractory to or deemed likely to be unresponsive to medical treatment on the basis of resistance patterns. All candidates for surgery were required to have sufficient pulmonary function to tolerate resection and a localized lesion with a high bacterial burden, such as a cavity (or cavities). For those patients with bilateral lesions, the area with the greatest bacterial burden was resected, and the remaining lesion (i.e., in the ipsilateral or contralateral lung) was managed with medical therapy.

***Outcome definitions.*** We used the MDR TB treatment outcome definitions developed recently by an international expert consensus group [15]. A patient was classified as cured if he or she completed treatment and consistently had negative culture results (with at least 5 negative results) during the final 12 months of treatment. Patients who completed treatment but who did not meet the definition for cure or who experienced treatment failure were considered to have completed treatment. Patients who did not receive treatment for ⩾2 consecutive months were defined as having defaulted treatment. Treatment failure was defined as ⩾2 positive culture results recorded during the final 12 months or a positive result of any 1 of the final 3 cultures. Death was defined as death due to any cause during therapy. Patients were referred to as having transferred out if they were transferred to another institution and the treatment outcome was unknown. For analysis purposes, cure and completed treatment were classified as favorable outcomes, whereas death, treatment default, treatment failure, and transfer out were classified as unfavorable outcomes.

***Statistical analysis.*** All results are expressed as number (percentage) or median and interquartile range (IQR; because the majority of data did not follow a normal distribution). Categorical variables were analyzed with use of Pearson's $\chi^2$ test or Fisher's exact test; continuous variables were analyzed with use of the Mann-Whitney $U$ test or Kruskal-Wallis test. To evaluate the predictors for a favorable outcome, we compared selected clinical variables between the favorable outcome and the unfavorable outcome groups, using univariate comparison and subsequent multiple logistic regression. In regression, stepwise and backward selection procedures were used to select variables to be maintained in the final model, with use of a $P$ value <.05 as the criterion for statistical significance.

## RESULTS

***Baseline characteristics.*** A total of 155 patients (82 male patients and 73 female patients; median age, 40 years [IQR, 27–54 years]) with bacteriologically confirmed pulmonary MDR TB were included in the study (table 1). None of the 98 patients tested for HIV had a positive result. The baseline characteristics of the patients are summarized in table 1. The degree of drug resistance was high at the start of treatment. The infecting strains of *M. tuberculosis* were resistant to a median of 5 drugs (IQR, 3–6 drugs). Twenty-seven patients (17%) had XDR TB at the start of treatment. The resistance rates to ethambutol, pyrazinamide, and streptomycin were 69%, 59%, and 28%, respectively. Among the second-line drugs, resistance to ofloxacin was most common (resistance rate, 42%) (table 2).

***Medical and surgical treatment.*** Forty-five patients (29%) were hospitalized for a short time at the start of second-line therapy. The median duration of hospitalization was 7 days (IQR, 5–15 days).

The patients received a median of 6 drugs (IQR, 5–7 drugs) for ⩾3 months; the median number of effective drugs was 4 (IQR, 3–5 drugs). The treatment regimen included 1 injectable agent for 113 patients (73%); the injectable agents were administered for a median duration of 6 months (IQR, 5–11 months). The treatment regimen included 1 fluoroquinolone for 147 patients (95%; levofloxacin was given to 133 patients, moxifloxacin was given to 11 patients, and ofloxacin was given to 3 patients), although 58 (39%) of the 147 patients had bacilli resistant to ofloxacin in vitro. Treatment was given for a median duration of 24 months (IQR, 18–30 months).

Resectional surgery was performed for 35 patients (23%) after a median duration of medical treatment of 6 months (IQR, 1–14 months). Pneumonectomies were performed for 14 patients, lobectomies or bilobectomies were performed for 20 patients, and a segmentectomy was performed for 1 patient.

**Table 3. Comparison of characteristics and treatment outcomes between patients with extensively drug-resistant (XDR) tuberculosis (TB) and those with non-XDR multidrug-resistant (MDR) TB.**

| Characteristic | Patients with non-XDR MDR TB ($n$ = 128) | Patients with XDR TB ($n$ = 27) | $P$ |
|---|---|---|---|
| Age <45 years | 76 (59) | 20 (74) | .153[a] |
| Female sex | 61 (48) | 12 (44) | .761[a] |
| BMI ⩾18.5 | 92 (72) | 19 (70) | .893[a] |
| Treatment history | | | |
| None | 15 (12) | 3 (11) | .158[b] |
| First-line drugs only | 71 (55) | 10 (37) | |
| Second-line drugs | 42 (33) | 14 (52) | |
| Negative sputum smear result | 20 (16) | 4 (15) | 1.000[b] |
| Absence of a cavity (or cavities) | 12 (9) | 5 (18) | .245[b] |
| Unilateral disease | 42 (33) | 6 (22) | .279[a] |
| Median no. of drugs to which the isolate was resistant (IQR) | 4 (3–6) | 8 (6–9) | <.001[c] |
| Median no. of drugs used (IQR) | 6 (5–7) | 6 (4–8) | .176[c] |
| Median no. of effective drugs (IQR) | 4 (3–5) | 2 (1–3) | <.001[c] |
| Surgical resection | 22 (17) | 13 (48) | <.001[a] |
| Favorable outcome | 84 (66) | 18 (67) | .917[a] |

**NOTE.** Data are no. (%) of patients, unless otherwise indicated. BMI, body mass index (calculated as the weight in kilograms divided by the square of the height in meters); IQR, interquartile range.

[a] Determined by Pearson's $\chi^2$ test.
[b] Determined by Fisher's exact test.
[c] Determined by Mann-Whitney $U$ test.

Of the 35 patients who underwent a resectional surgical procedure, 24 (69%) had positive smear results and 4 (11%) had negative smear results and positive culture results at the time of the procedure.

Postoperative complications occurred in 10 (29%) of the 35 patients (surgical wound problems in 3, empyema in 3, bleeding in 1, a prolonged air leak in 1, pneumonia in 1, and postpneumonectomy syndrome in 1). Postoperative mortality occurred in 1 patient as a result of postoperative empyema. After surgery, all of the patients received a multidrug regimen that was generally the same as their preoperative regimen. The median duration of postoperative chemotherapy was 18 months (IQR, 12–23 months), with exclusion of data for 1 patient who died of a postoperative complication.

***Treatment outcomes.*** The assessment of treatment outcomes revealed that 86 patients (55%) were cured, 16 (10%) completed therapy, 10 (6%) died, 15 (10%) defaulted treatment, 22 (14%) experienced treatment failure, and 6 (4%) were transferred to another medical center. In total, 102 patients (66%) had favorable outcomes, and 53 (34%) had unfavorable outcomes.

Among the 35 patients who underwent a resectional surgical procedure, treatment success was achieved in 31 (89%); 26 of these patients were cured, and 5 patients completed treatment. One patient died of postoperative empyema, and 3 patients experienced treatment failure.

Treatment success was achieved for 71 (59%) of the 120 patients who received medical treatment and did not undergo a surgical procedure; 60 patients were cured, 11 patients completed treatment. Forty-nine patients (41%) had poor outcomes; 9 died, 15 defaulted treatment, 19 experienced treatment failure, and 6 were transferred out. Among the 71 patients who achieved sputum culture conversion with medical therapy but without surgery, 13 had already achieved culture conversion during first-line drug therapy (before the identification of MDR TB) and had negative culture results when second-line treatment was started. For the remaining 58 patients who achieved sputum culture conversion during second-line drug therapy, the median duration from the start of therapy to the time of culture conversion was 2 months (IQR, 1–5 months).

The treatment success rates did not differ significantly between patients with non-XDR MDR TB and patients with XDR TB (66% vs. 67%; $P = .917$), although the numbers of drugs to which the isolates were resistant, the numbers of previously used drugs, and the numbers of effective drugs were significantly different between the 2 groups. Surgical resection was performed more frequently for patients with XDR TB than for those with non-XDR MDR TB (48% vs. 17%; $P < .001$) (table 3).

Treatment success rates increased during the study period; favorable outcomes were observed in 19 (49%) of 39 patients within the first 4 years, whereas favorable outcomes were ob-

**Table 4. Patient characteristics and treatment outcomes for 155 patients with multidrug-resistant tuberculosis (TB), by treatment period.**

| Characteristic | Treatment period | | | P |
|---|---|---|---|---|
| | 1995–1998 (*n* = 39) | 1999–2001 (*n* = 42) | 2002–2004 (*n* = 74) | |
| Age <45 years | 26 (67) | 22 (52) | 48 (65) | .322[a] |
| Female sex | 19 (49) | 17 (40) | 37 (50) | .597[a] |
| BMI ⩾18.5 | 27 (69) | 27 (63) | 57 (77) | .284[a] |
| Treatment history | | | | |
| None | 4 (10) | 3 (7) | 11 (15) | .768[a] |
| First-line drugs only | 21 (54) | 22 (52) | 38 (51) | |
| Second-line drugs | 14 (36) | 17 (41) | 25 (34) | |
| Negative sputum smear result | 4 (10) | 6 (14) | 14 (19) | .466[a] |
| Absence of a cavity (or cavities) | 11 (28) | 11 (26) | 23 (31) | .849[a] |
| Unilateral disease | 14 (36) | 10 (24) | 24 (32) | .467[a] |
| Median no. of drugs to which the isolate was resistant (IQR) | 5 (4–6) | 4 (3–6) | 5 (3–6) | .523[b] |
| Aminoglycoside resistance | 23 (59) | 19 (45) | 31 (42) | .215[a] |
| Ofloxacin resistance | 20 (51) | 15 (36) | 30 (41) | .345[a] |
| Extensively drug-resistant TB | 10 (26) | 6 (14) | 11 (15) | .293[a] |
| Median no. of drugs used (IQR) | 5 (4–6) | 6 (5–6) | 7 (6–8) | <.001[b] |
| Median no. of effective drugs (IQR) | 3 (2–4) | 4 (3–5) | 4 (3–5) | .008[b] |
| Surgical resection | 11 (28) | 4 (10) | 20 (27) | .060[a] |
| Favorable outcome | 19 (49) | 24 (57) | 59 (80) | .002[a] |

**NOTE.** Data are no. (%) of patients, unless otherwise indicated. BMI, body mass index (calculated as the weight in kilograms divided by the square of the height in meters); IQR, interquartile range.

[a] Determined by Pearson's $\chi^2$ test.
[b] Determined by Kruskal-Wallis test.

served in 24 (57%) of 42 patients and 59 (80%) of 74 patients during the 2 subsequent 3-year intervals ($P = .002$) (table 4). Despite the increase in favorable outcome rates over time, the characteristics of the patients and the severity of disease were similar during the 3 successive intervals. However, the number of drugs used ($P < .001$) and the number of effective drugs used ($P = .009$) increased significantly over the same periods.

***Prognostic factors.*** On the basis of the clinical variables included in univariate comparison between the favorable outcome and the unfavorable outcome groups, the final multiple logistic regression model predicting favorable outcome revealed that combined surgical resection (OR, 11.35; 95% CI, 3.02–42.74; $P < .001$), body mass index ⩾18.5 (calculated as the weight in kilograms divided by the square of the height in meters; OR, 9.07; 95% CI, 3.67–22.42; $P < .001$), use of >4 effective drugs (OR, 4.76; 95% CI, 1.89–11.97; $P = .001$), and negative sputum smear results (OR, 4.42; 95% CI, 1.02–19.16; $P = .047$) were independent predictors of favorable outcome (table 5).

## DISCUSSION

There are many controversial issues regarding the best management strategy for MDR TB. One of the most controversial issues is the number of drugs required for treatment [10]. In 1994 and 1997, the American Thoracic Society [16] and World Health Organization [13], respectively, recommended the use of at least 3 drugs, whereas in 2003, the American Thoracic Society [8] recommended the use of at least 3 previously unused drugs, including 1 injectable agent to which there is in vitro susceptibility, and 4–6 medications for patients with MDR TB resistant to other first-line drugs. The most recent World Health Organization guidelines strongly recommend use of "at least 4 drugs with either certain, or almost certain, effectiveness" [9, p. 41]

Here, the use of at least 4 effective drugs, which were prescribed on the basis of DST results, was associated with a favorable outcome, supporting the aforementioned international guidelines. A drug that was included in a patient's previous failed treatment regimen was included in the treatment regimen if the DST results indicated susceptibility to the drug; however, the drug was not considered to have "certain effectiveness." The inclusion of these drugs is the reason for the increase in the total number of prescribed drugs in the latter part of the study. Interestingly, a recent study of outcomes of individualized MDR TB treatment regimens in Latvia reported that the use of >5 drugs was associated with a favorable outcome [17].

**Table 5. Predictors of favorable outcomes for 155 patients with multidrug-resistant tuberculosis (TB).**

| Characteristic | No. (%) of patients | | Univariate analysis: *P* | Multivariate logistic regression | |
|---|---|---|---|---|---|
| | Favorable outcome (*n* = 102) | Unfavorable outcome (*n* = 53) | | OR (95% CI) | *P* |
| Age <45 years | 63 (62) | 33 (62) | .952[a] | … | |
| Female sex | 50 (49) | 23 (43) | .506[a] | … | |
| BMI ⩾18.5 | 88 (86) | 23 (43) | <.001[a] | 9.07 (3.67–22.42) | <.001 |
| Treatment history | | | | | |
| None | 15 (15) | 3 (6) | .106[a] | … | |
| First-line drugs only | 55 (54) | 26 (49) | | … | |
| Second-line drugs | 32 (31) | 24 (45) | | … | |
| Negative sputum smear result | 21 (21) | 3 (6) | .015[b] | 4.42 (1.02–19.16) | .047 |
| Absence of a cavity (or cavities) | 32 (31) | 13 (24) | .373[a] | … | |
| Unilateral disease | 40 (39) | 8 (15) | .002[a] | … | |
| Non-XDR MDR TB | 84 (82) | 44 (83) | .917[a] | … | |
| ⩾4 Effective drugs used | 67 (66) | 23 (43) | .008[a] | 4.76 (1.89–11.97) | .001 |
| Surgical resection | 31 (30) | 4 (7) | .001[b] | 11.35 (3.02–42.74) | <.001 |

**NOTE.** BMI, body mass index (calculated as the weight in kilograms divided by the square of the height in meters); XDR, extensively drug resistant.

[a] Determined by Pearson's $\chi^2$ test.
[b] Determined by Fisher's exact test.

Recent studies have demonstrated that both surgical treatment and chemotherapy can provide more favorable results than can chemotherapy alone [18–23]. The major surgical indication for MDR TB is persistent cavitary disease. The reasons for surgical resection in our patients included the difficulty of antibiotic penetration and the large number of organisms contained in the lesions. Patients who had a cavity (or cavities) beyond the range of resection were not considered to be good candidates for resectional surgery [24]; however, the patients with active disease involving multiple nodules or segmental consolidations, even beyond the range of resection, were considered to be good candidates for surgery, if sufficient drugs remained available.

The proper timing of surgery for patients with MDR TB has not been established. It is recommended that patients receive chemotherapy for at least 2 or 3 months before surgery and that, if possible, they should have a negative culture result before lung resection [9, 25]. However, this may not always occur. It is paradoxical that, in some patients with MDR TB, negative sputum culture results cannot be achieved without surgical resection of the infected lung. Most patients with MDR TB that is successfully treated with chemotherapy achieve sputum culture conversion within 2–3 months after the start of treatment [26–28]. Treatment outcomes are worse for patients who do not achieve sputum culture conversion within 2–3 months after the start of treatment [28]. Thus, we considered resectional surgery in our patients at 4–5 months after the initiation of second-line drug therapy when the culture results from after 2–3 months of treatment were available. The extended administration of a failed individualized regimen does not contribute to the cure of patients with MDR TB. Such disease progression makes successful pulmonary resection even more challenging. Early surgical intervention (e.g., within 6 months after intensive chemotherapy) could be beneficial, even if the patient has a positive result of smear or culture.

Interestingly, the treatment outcomes for the patients with XDR TB were not different from those for the patients with non-XDR MDR TB, although the number of effective drugs used was significantly lower for patients with XDR TB. An increasing number of cases of XDR TB are being reported globally [29]. In Korea, 15%–20% of patients with MDR TB meet the criteria for XDR TB in both the public and private sector [7, 30, 31]. Recently published studies have demonstrated that the occurrence of XDR TB is an independent poor prognostic factor in HIV-uninfected patients with MDR TB [5–7]. In our cohort, surgical resection was more frequently performed for patients with XDR TB than for those with non-XDR MDR TB (48% vs. 17%). This suggests that even XDR TB can be successfully treated with aggressive management, including resectional surgery.

In conclusion, in our retrospective cohort, combined surgical resection, body mass index ⩾18.5, use of >4 effective drugs, and negative sputum smear results were independent predictors of a favorable outcome of MDR TB treatment. Early aggressive treatment comprising at least 5 effective drugs, in addition to

resectional surgery, when indicated, may improve the outcome for patients with MDR TB and XDR TB.

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