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Managing severe tuberculosis and its sequelae: from intensive care to surgery and rehabilitation

Simon Tiberi[1,2,a], Marcela Muñoz Torrico[3,b], Ananna Rahman[1,c], Maria Krutikov[1,d], Dina Visca[4,e], Denise Rossato Silva[5,f], Heinke Kunst[2,g], Giovanni Battista Migliori[4,h]

1. Barts Health NHS Trust, Royal London Hospital, Division of Infection, London, United Kingdom.
2. Blizard Institute, Barts and the London School of Medicine and Dentistry, Centre for Primary Care and Public Health, London, United Kingdom.
3. Clínica de Tuberculosis, Instituto Nacional de Enfermedades Respiratorias, Ciudad de México, DF, México.
4. Istituti Clinici Scientifici Maugeri – IRCCS – Tradate, Italia.
5. Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, Porto Alegre (RS) Brasil.

a. http://orcid.org/0000-0001-9424-6551
b. http://orcid.org/0000-0002-8453-3634
c. http://orcid.org/0000-0002-1918-9726
d. http://orcid.org/0000-0002-3982-642X
e. http://orcid.org/0000-0003-2298-1623
f. http://orcid.org/0000-0003-0230-2734
g. http://orcid.org/0000-0002-0380-1116
h. http://orcid.org/0000-0002-2597-574X

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ABSTRACT

Multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) continue to challenge physicians and public health specialists. Global treatment outcomes continue to be unsatisfactory, positive outcomes being achieved in only 54% of patients. Overall outcomes are even worse in patients infected with highly resistant strains. Treating MDR-/XDR-TB is difficult because of frequent adverse events, the long duration of drug regimens, the high costs of second-line drugs, chronic post-infectious sequelae, and loss of organ function. Ongoing research efforts (studies and trials) have various aims: increasing the rates of treatment success; understanding the potentialities of new and repurposed drugs; shortening the treatment duration; and reducing the rates of adverse events. It is hoped that better access to rapid diagnostics, increased awareness, and treatments that are more effective will reduce the rate of complications and of lung function impairment. This article aims to discuss the management of severe tuberculosis (defined as that which is potentially life threatening, requiring higher levels of care) and its sequelae, from intensive care to the postoperative period, rehabilitation, and recovery. We also discuss the nonpharmacological interventions available to manage chronic sequelae and improve patient quality of life. Because the majority of MDR-/XDR-TB cases evolve to lung function impairment (typically obstructive but occasionally restrictive), impaired quality of life, and low performance status (as measured by walk tests or other metrics), other interventions (e.g., smoking cessation, pulmonary rehabilitation, vaccination/prevention of secondary bacterial infections/exacerbations, complemented by psychological and nutritional support) are required.

Keywords: Extensively drug-resistant tuberculosis; Tuberculosis, multidrug-resistant; Critical care; Smoking cessation.

INTRODUCTION

Tuberculosis, also known as the "white plague", continues to be a public health priority. In its most recent Global Tuberculosis Report,[1] the World Health Organization (WHO) estimated that 1.6 million tuberculosis-related deaths occurred in 2017. In addition, half a million cases of multidrug-resistant tuberculosis (MDR-TB, defined as infection with a strain of *Mycobacterium tuberculosis* that is resistant to at least isoniazid and rifampin) have been reported worldwide, and 8.5% of those were cases of extensively drug-resistant tuberculosis (XDR-TB, defined as infection with an MDR-TB strain that is also resistant to fluoroquinolones and at least one second-line injectable drug).

Although recent studies have demonstrated that higher tuberculosis treatment success rates are achievable,[2] the overall rate of treatment success among MDR-TB patients worldwide is currently below 55%, treatment success rates being lower than 20% in difficult-to-treat cases in which the resistance profile is XDR or beyond.[1,3] Drug abuse, smoking, and alcohol dependence can further aggravate outcomes.[4-9] Treating MDR-/XDR-TB is challenging because of frequent adverse events, the lengthy duration of costly second-line drug regimens, and the fact that patient management is often onerous,[4-9] not to mention the financial and social impact of the illness on the affected individuals and their families. There are ongoing research efforts (studies and trials) with a variety of aims[1,4,10-12]: increasing treatment success rates; understanding the potentialities of new and repurposed drugs; shortening the treatment duration; and reducing the rate of adverse events.

This paper aims to provide an overview of the management of tuberculosis in the intensive care setting, the role of adjunctive surgery, and the rehabilitation of patients affected by tuberculosis. The manuscript can be read in its entirety—as a pathway from admission to intensive care, surgical intervention (when indicated), rehabilitation, and recovery—or in its separate units. An additional aim is to remind the reader that patients

Correspondence to:
Giovanni Battista Migliori. Istituti Clinici Scientifici Maugeri IRCCS, Via Roncaccio 16, 21049, Tradate, Italia.
Tel.: 39 0331 829404. E-mail: giovannibattista.migliori@icsmaugeri
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are seldom entirely back to their former selves when they have completed the prescribed drug therapy regimen, because a long rehabilitation/convalescence phase typically ensues. Therefore, the importance of nonpharmacological interventions (e.g., pulmonary rehabilitation with supervised exercises, chest/breathing exercises, expectoration techniques, vaccination, and smoking cessation) should be explored in surviving patients in order to improve the functional residual capacity, limit end organ damage, and minimize the chronic sequelae of tuberculosis.

METHODS

We searched for articles in English, Spanish, or Portuguese, published between November 1, 2014 and June 1, 2018, on Google, Google Scholar, PubMed, and ClinicalTrials.gov. The following search terms were used: "tuberculosis"; "MDR-TB"; "XDR-TB"; "severe tuberculosis"; "intensive care and tuberculosis"; and "tuberculosis and surgery". Targeted searches were also performed for articles dealing with pulmonary rehabilitation, smoking cessation, or quality of life. The WHO definitions are used throughout the manuscript.[13,14]

TUBERCULOSIS IN THE INTENSIVE CARE SETTING

Despite the success of curative therapy, a significant proportion of tuberculosis patients are hospitalized every year, 1-3% requiring admission to the ICU for close monitoring or organ support.[15] The indications for ICU admission include the following: complications of tuberculosis (including respiratory failure and conditions requiring surgical interventions, such as hemorrhage, pneumothorax, and pleural effusion); the severe forms of tuberculosis (e.g., tuberculous meningitis with impaired consciousness requiring intubation) or severe clinical manifestations of comorbidities (e.g., liver disease, renal disease, and uncontrolled diabetes); and life-threatening events resulting from adverse reactions to antituberculosis drugs (e.g. organ failure, severe seizures, and anaphylaxis).

The most common reasons for admission to the ICU are acute respiratory failure (in > 90%), septic shock (in 20-34%), and multiorgan failure (in 34-44%).[15-17] Other causes include renal failure (in 10%), neurological disorders (in 20%), and meningeal tuberculosis (in 20%).[15,17] In addition, patients with tuberculosis can be admitted to the ICU for extrapulmonary manifestations of the disease, including spinal, pericardial, bone marrow, hematological, and genitourinary disease,[17] as well as for bacterial coinfections, antituberculosis drug toxicity, thromboembolic complications, or pulmonary hemorrhage.[16-19] Patients with tuberculosis can also become critically ill because of factors indirectly related to their tuberculosis, such as diabetic ketoacidosis, alcohol withdrawal, and electrolyte imbalances.[17,18] ICU admission due to HIV coinfection occurs in 68.7% of tuberculosis patients in high-incidence countries and in 40% of those in low-incidence countries.[15]

Most tuberculosis patients who are admitted to the ICU have an established diagnosis of tuberculosis, although there are some who do not present with the typical clinical or radiological signs of tuberculosis. In such cases, a high index of suspicion is required in order to make the diagnosis. A diagnosis of tuberculosis should be suspected in patients who are contacts of tuberculosis patients and in those who have risk factors for the disease.[20] The possibility of reactivation of latent tuberculosis infection due to stress or immunosuppression should also be considered.[21]

The management of tuberculosis in the ICU is daunting given the frequent complexity and poor outcomes associated with the disease. For cases of infection with drug-susceptible strains of *M. tuberculosis*, the WHO guidelines recommend standard quadruple therapy with rifampin, isoniazid, ethambutol, and pyrazinamide.[22] It is also necessary to seek advice from clinicians with expertise in managing the treatment of MDR-TB, XDR-TB, and tuberculosis involving coinfection with other pathogens.[23,24]

The mode of delivery of antituberculosis drugs in the ICU setting depends mainly on intestinal absorption, which can be delayed or altered due to gastroparesis, intestinal paralysis, enteral nutrition, edema due to hypoalbuminemia, and critical illness-associated changes in the gut microbiota.[25] In addition, the pharmacokinetics of antituberculosis drugs can be altered during critical illness.[26] In an observational case series of critically ill tuberculosis patients who received quadruple therapy administered via a nasogastric tube, therapeutic blood levels were achieved in only 30%.[27] Although rifampin is available in an intravenous formulation in some countries (not currently in Brazil), other antituberculosis drugs generally are not. In most cases, antituberculosis drugs are administered parenterally.[20,25] Furthermore, although some drugs can adhere to the nasogastric tube (e.g., rifampin), they can be administered intravenously to achieve and maintain therapeutic blood levels, which makes them more efficacious.[25] The fact that first-line drugs are rarely available in an intravenous formulation results in the widespread use of second-line drugs such as fluoroquinolones and aminoglycosides.

In the ICU, corticosteroids are frequently administered in conjunction with antituberculosis drugs. There is evidence that adjuvant treatment with corticosteroids reduces mortality in non-HIV-infected patients with tuberculous meningitis or pericarditis.[28] In a recent meta-analysis, corticosteroids were reported to reduce mortality in all forms of tuberculosis, with a more pronounced effect in patients with a severe form of the disease, such as miliary tuberculosis.[29,30]

Due to the variable pharmacokinetics and pharmacodynamics of antituberculosis drugs, it is essential to remain vigilant regarding drug toxicity and interactions, by carrying out active drug safety

monitoring. This is especially true for rifampin, which will interact with many drugs used in the ICU setting because of its effect of inducing cytochrome P450.[21,25]

Among tuberculosis patients requiring admission to the ICU, mortality is > 50%, ranging from 20% to 70%.[15,17,31,32] Mortality is even higher among patients on mechanical ventilation, one study reporting a mortality rate of 80% in tuberculosis patients with ARDS who required mechanical ventilation.[15] Risk factors for mortality include ARDS, multiorgan failure, sepsis, mechanical ventilation, renal replacement therapy, a high Acute Physiology and Chronic Health Evaluation II score, and a high Sequential Organ Failure Assessment score.[17,24,31,32] We find it interesting that diabetes and HIV have not been associated with increased mortality, possibly because they are overshadowed by the aforementioned risk factors.[17,24,25,31,32]

Tuberculosis patients admitted to the ICU are a heterogeneous population, and the complexities of tuberculosis exacerbate that heterogeneity. Mortality remains high, and the disease is associated with considerable morbidity. Most of the studies on the topic have been case reports and retrospective analyses. There is therefore a need for prospective studies in this area, especially regarding rapid diagnostic methods, novel treatments (including the use of immunomodulatory agents and host-directed therapies), and intensification of tuberculosis treatment.

ADJUNCTIVE SURGERY IN THE MANAGEMENT OF TUBERCULOSIS

Historically (before the development of antituberculosis drugs), surgery was the only treatment available for tuberculosis. Surgical procedures could be grouped into those that artificially collapse the lung and those in which the affected tissue is excised. Procedures in the first group include lung collapse by artificial induction of pneumothorax and thoracoplasty involving the removal of a rib or ribs (to collapse the lung cavity).[33] Procedures in the second group are more widely accepted by the medical community and include the following[33]: wedge resection, first described by Tuffler in 1891; pneumonectomy, first described by Lilienthal in 1933; and lobectomy, first described by Freedlander in 1935. The advent of combination therapy for tuberculosis, in 1952, allowed the infection to be eradicated through noninvasive means and subsequently reduced the number of operations performed in the affected patients.[33-35]

Over the last few decades, the emergence of drug-resistant *M. tuberculosis* strains has reduced success rates for treatment with drug therapy alone and has increased the number of tuberculosis patients who require surgery. Scarring and fibrous tissue can protect bacteria from the host immune response, allowing them to continue to replicate, thus preventing the eradication of infection and driving the development of drug-resistant mutations. Surgical removal of the affected tissue allows the antimicrobial therapy to penetrate the remaining lung more effectively and eradicates the foci of bacillary growth.[36] The largest case series to date was published in 2018 by Giller at al.,[37] who documented 5,599 thoracic surgical procedures in tuberculosis patients treated in Russia during a 17-year period. The authors reported an overall mortality rate of 0.1%, also reporting treatment success rates of 93.0% and 92.1% in patients with MDR-TB and XDR-TB, respectively.

Most surgical procedures in tuberculosis patients have been performed on a case-by-case basis, and current evidence is therefore from observational studies with a paucity of reliable data on the indications, individual procedure outcomes, and cure rates related to surgery used in combination with an antituberculosis treatment regimen. Consequently, the WHO issued a consensus statement in 2014,[34] followed by an update of the MDR-TB treatment guidelines in 2016,[38] with a section focusing on the role of surgery in tuberculosis treatment. The WHO consensus statement referenced a 2013 systematic review conducted by Marrone et al.,[39] who found the overall success rates of pulmonary resection in combination with antituberculosis therapy to be 88-92%, with a reduction in overall all-cause mortality, when that treatment combination is performed in appropriate settings on carefully selected patients. Evidence from a study conducted in Peru suggested that the addition of surgery can reduce the overall cost of MDR-TB treatment because it allows the duration of the treatment regimen to be shortened.[40]

The indications for surgery in patients with tuberculosis, as listed by Dara et al.,[35] are divided into three main sections: emergency—profuse lung hemorrhage and spontaneous tension pneumothorax; urgent—irreversible progression of disease despite tuberculosis therapy and recurrent or recalcitrant hemoptysis; and elective—localized cavities with persistent smear/culture positivity for *M. tuberculosis* after 4-6 months of directly observed antituberculosis therapy, MDR-/XDR-TB in which antituberculosis treatment has failed, and complications of tuberculosis requiring surgical intervention, including pneumothorax (which can be spontaneous), pyopneumothorax, pleural emphysema (with or without bronchopleural fistula), and aspergilloma. The 2014 WHO consensus statement stipulated that patients should receive at least 4-6 months of an appropriate antituberculosis regimen before surgery and their suitability as surgical candidates should be assessed, ensuring adequate postoperative pulmonary functional residual capacity.[34] The procedure should be performed at a center with adequate facilities and by a highly-skilled surgeon with experience in tuberculosis. Because the mortality rate reported for lobectomy (2-3%) is lower than that reported for pneumonectomy (7-8%), the former is the preferred procedure. Postoperatively, patients should continue to receive antituberculosis

therapy for at least 4 months, depending on the characteristics of the underlying disease.

The most recent WHO MDR-TB guidelines, updated in 2016,[38] also recommend elective partial lung resection (lobectomy or wedge resection) in conjunction with an appropriate MDR-TB treatment regimen. That recommendation is based on three meta-analyses that collectively found treatment outcomes to be significantly better in patients treated with the combination of surgery and drug therapy than in those treated with drug therapy alone (81.9% vs. 59.7%; OR = 2.62, 95% CI: 1.94-3.54).[41-43] However, the guidelines also stressed the superiority of partial lung resection over pneumonectomy in achieving a cure, as well as in improving overall outcomes.

We believe that there is a role for surgery in the treatment of complicated tuberculosis infection, especially infection with drug-resistant strains, with the potential to shorten treatment duration and improve outcomes. Better retrospective data surveillance is needed in order to inform clinicians of the indications for surgery, the optimal surgical procedures, and their potential outcomes.

REHABILITATION

The sequelae of pulmonary tuberculosis (PTB) can cause significant pulmonary impairment and morbidity, particularly in young adults. Therefore, the completion of tuberculosis treatment might mark the beginning of a chronic respiratory disease. Unfortunately, there have been only a few studies addressing this issue, and most of them have assessed respiratory function only through the use of simple spirometry.

A history of PTB is undoubtedly related to lung function impairment and lung function test abnormalities.[44,45] Lung damage can occur in the bronchial airway, the lung parenchyma, or both. A number of population-based studies using spirometry and bronchodilator tests have demonstrated that individuals with PTB have airflow obstruction that does not respond to bronchodilator administration[46,47] Therefore, PTB is a well-recognized risk factor for the development of COPD in young adults with no history of smoking.[48] PTB has also been described as a frequent cause of bronchiectasis and tracheobronchial stenosis. At the parenchymal level, the severity can be quite variable: single or multiple cavities can be seen, with or without areas of scarring; or there can be areas of complete lung destruction. The presence of lung destruction confers a poor prognosis, especially if the destruction is extensive.[49] Such damage can also involve the pleura and promote the development of diffuse pleural fibrosis, resulting in restrictive lung disease. In addition to the variety of pulmonary abnormalities caused by PTB sequelae, the remaining areas of damaged lung increase the risk of further complications such as the development of aspergilloma and infection with nontuberculous mycobacteria.

There is still a need to carry out more studies to understand the pathophysiology of PTB sequelae, thoroughly assessing its impact on pulmonary function and patient quality of life. However, it is clear that such sequelae cause pulmonary impairment and contribute significantly to the burden of chronic respiratory diseases worldwide.[44,50] Therefore, it is necessary to perform a complete pulmonary evaluation (with imaging examinations and pulmonary function tests) at the end of treatment in PTB patients, as is done in patients with other chronic respiratory diseases, in order to improve their quality of life.

As a result of the lung destruction due to PTB, affected patients frequently have persistent respiratory symptoms, which limit their activities of daily living and reduce their quality of life.[51,52] Therefore, pulmonary rehabilitation at the end treatment is an appropriate measure. Pulmonary rehabilitation has been proven to improve the perception of dyspnea, exercise tolerance, and health-related quality of life in patients with COPD or other chronic respiratory diseases.[53,54] Although there are few data regarding its use in patients with PTB sequelae, some studies have suggested that it is beneficial for such patients.[55-59] It might even be possible to adapt the rehabilitation program to specific circumstances, so that it is made accessible to individuals in low-resource settings.[56] In addition to its role in the management of PTB sequelae, pulmonary rehabilitation can be a useful tool in the multidisciplinary management of surgical candidates, as well as in patients with severe tuberculosis who require ICU admission and long hospital stays, in order to decrease the risk of further respiratory complications and to prevent or reverse muscle atrophy.[60,61] The indications for pulmonary rehabilitation can include evidence of lung damage (resulting in obstructive or restrictive lung disease), exercise-induced oxygen desaturation, and impaired quality of life.

A recent review of the available literature on chronic sequelae after the completion of antituberculosis treatment[44] focused specifically on sequelae and their functional evaluation, as well as on lung destruction and the pulmonary interventions available (e.g., long-term oxygen therapy, ventilation, and respiratory therapy). The authors recommended that future studies not only evaluate the outcomes of antituberculosis drug therapy but also include a complete description of the pathophysiological status of the patients, including radiological aspects (Figure 1); spirometry findings and bronchodilator response (Figure 2); assessment of lung volumes by plethysmography (Figure 3); DLCO (Figure 4); arterial blood gases; six-minute walk distance; and quality of life (evaluated with validated tools such as the Saint George's Respiratory Questionnaire). If rehabilitation programs are implemented, it is essential to collect information on pre- and post-rehabilitation outcomes, as well as on the costs of the intervention.

Cigarette smoking is a definite risk factor for various pulmonary infections, including tuberculosis. A number

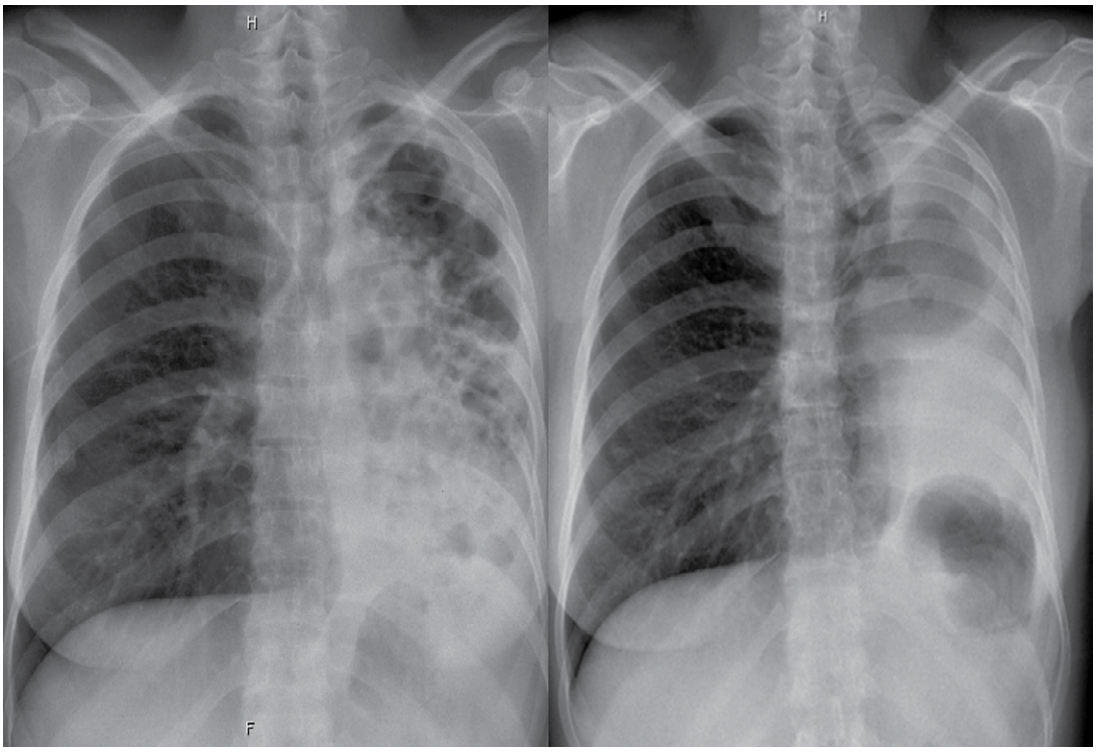

Figure 1. Pre- and post-treatment X-rays of a patient with multidrug-resistant tuberculosis, showing sequelae on the left side.

		Pred	A1	% (A1/P)	A2	% (A2/P)	D%(A2/A1)
Hora			02:21:51		03:13		
Fecha			15-06-11		15-06		
FVC	[L]	3.17	1.90	60	2.08	65	9
FEV_1	[L]	2.74	1.00	37	1.21	44	21
FEV_1 % FVC	[%]		52.76		58.42		11
MMEF 75/25	[L/s]	3.62	0.37	10	0.44	12	17
PEF	[L/s]	6.51	2.68	41	2.83	43	6
FET	[s]		7.37		8.51		15
V backextrapolation ex	[L]		0.02		0.04		159

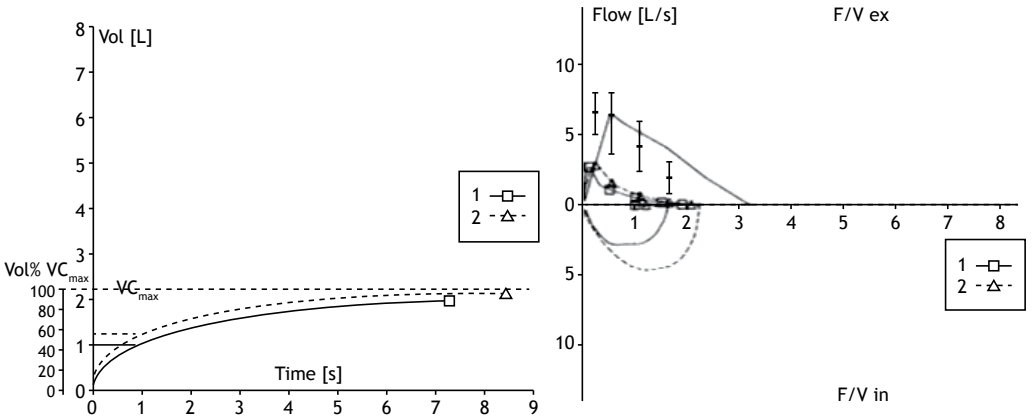

Figure 2. Spirometry findings in a patient with severe multidrug-resistant tuberculosis, at the end of antituberculosis treatment.

of population-based studies have shown that smoking increases the risk of developing latent or active tuberculosis.[62] In addition, smoking has been linked to adverse outcomes (treatment failure or death), relapse, and an increased risk of developing drug-resistant tuberculosis,[63] as well as to worsening of the initial pattern of drug resistance. A coherent smoking cessation approach, including a wide range of interventions (e.g., psychosocial and pharmacological interventions), has been proven to increase the treatment success rates in tuberculosis patients while decreasing the risk of further pulmonary complications.[64-66] Therefore, the WHO recommends integrating early and effective smoking cessation measures, starting at the primary health care level, into tuberculosis control plans.[67] Because of the similar risk posed by alcohol abuse, comparable interventions have also been recommended for individuals with alcohol dependence.[68,69]

FINAL CONSIDERATIONS

In conclusion, the existence of effective therapy notwithstanding, tuberculosis is frequently encountered in the ICU, and the disease represents a distinct challenge with poor outcomes. The emergence of drug-resistant strains of *M. tuberculosis* has recently restored thoracic surgery to a prominent position among interventions designed to combat tuberculosis. When combined with effective drug therapy, surgery has been associated with favorable outcomes in cases of MDR-/XDR-TB. There is recent evidence that chronic post-infectious sequelae of tuberculosis are common even after effective therapy, more so after surgery.[44] That suggests that the majority of tuberculosis cases will evolve to lung function impairment (typically obstructive but occasionally restrictive), impaired quality of life, and reduced performance status (as measured by walk tests or other metrics). Therefore, other interventions—pulmonary rehabilitation (including supervised exercise, chest/breathing exercises, and expectoration), smoking cessation therapy, and prevention (of secondary bacterial infections and exacerbations), complemented by psychological and nutritional support—are required in order to protect or restore functional residual capacity, thereby improving quality of life and slowing the progression to frailty.

		Pred	Best	A1	Act2	Act3	Act4	Act5	Act6	Act7	Act8	Act9	Act10	Act11	%(B/P)
Fecha			15-06-11												
Hora			02:48:10												
ITGV	[L]	2.60	3.04		3.03	3.07	3.02	3.06							117
RV	[L]	1.49	2.03		2.11	2.25	2.08	2.04							136
VC	[L]	3.15	2.04		1.92	2.04	2.00	1.97							65
IC	[L]	2.11	1.02		1.00	1.22	1.06	0.96							48
ERV	[L]	1.11	1.01		0.92	0.82	0.94	1.01							91
TLC	[L]	4.72	4.07		4.03	4.29	4.08	4.02							86
RV % TLC	[%]	31.9	49.94		52.3	52.5	51.1	50.9							157
R tot	[KPa * s/L]	0.30	1.02	1.05	0.98	1.03	0.98	0.97	1.02	0.96	1.03	1.07	1.08		341
R IN	[KPa * s/L]		0.72	0.74	0.66	0.74	0.74	0.71	0.64	0.61	0.76	0.68	0.74		
R EX	[KPa * s/L]		1.33	1.36	1.27	1.33	1.25	1.21	1.35	1.24	1.33	1.44	1.45		
Delta volue	ITGV [L]				0.17	0.05	0.17	0.09	0.18						
BF Res	[l/min]		90.63		88.2	93.8	88.2	90.9	93.8	93.8	96.8	88.2	90.9		

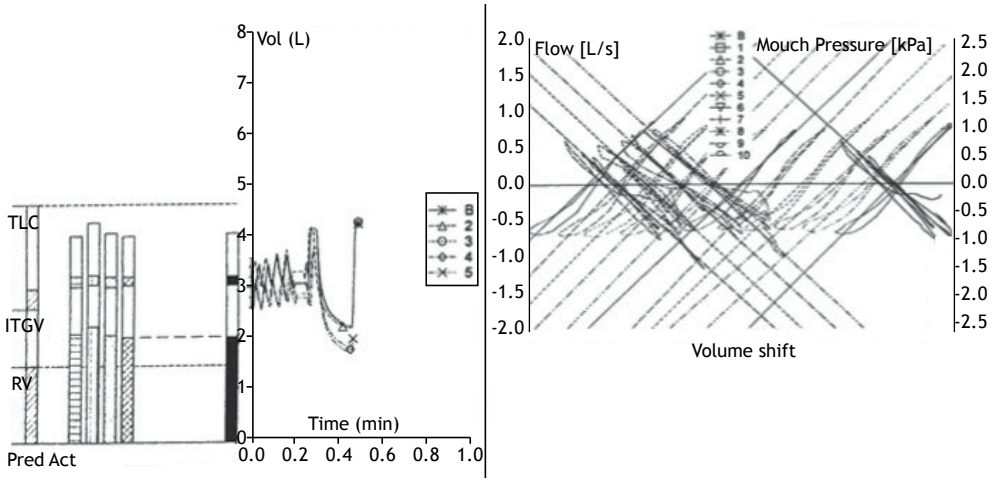

Figure 3. Plethysmography showing air trapping in a patient with multidrug-resistant tuberculosis, after the completion of antituberculosis treatment.

		Pred	Act1	Act2	Act3	A4	B	%(B/P)
Fecha			15-06-11					
Hora			03:13:56p.					
TLCOc SB	[ml/min/mmHg]	25.14	10.98»	11.86»			11.39»	45»
TLCOc/BSA	[mmol/min/kPa/m]		2.36	2.55			2.45	
TLCO/VA	[ml/min/mmHg/L]	5.33	3.95»	4.30»			4.12»	77»
RV-He	[L]	1.49	0.84	0.92			0.88	59
TLX-He	[L]	4.72	2.94	2.91			2.92	62
RV%TLC-He	[%]	31.88	28.67	31.56			30.12	94
VA	[L]	4.567	2.787	2.761			2.774	61
TA	[s]		10.80	11.10			10.95	
VIN	[L]	3.151	2.095	1.992			2.043	65
VC max (Spir)	[L]		2.21	2.21			2.21	
FI He	[%]		9.950	9.950			9.950	
FA He	[%]		5.898	5.702			5.800	
FI CO	[%]		0.300	0.300			0.300	
FA CO	[%]		0.096	0.087			0.092	
Hb	[g/100 ml]		13.50	13.50			13.50	
Discard vol	[L]		0.75	0.75			0.75	
Sample vol	[L]		0.60	0.60			0.60	
Insp. time	[s]		0.60	1.20			0.90	
Exp. time	[s]		0.20	0.20			0.20	
ATS Error codes			0	140			0	

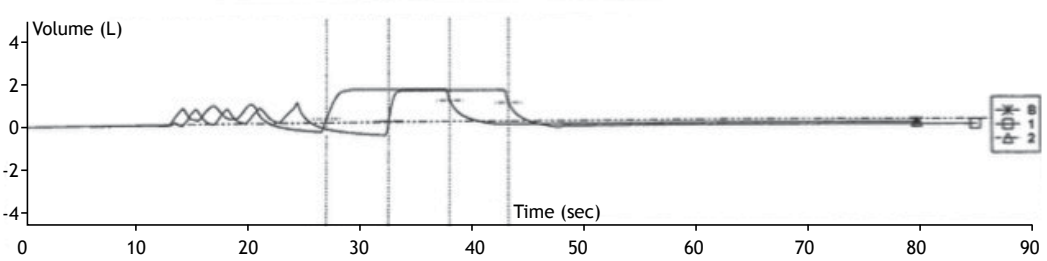

Figure 4. Severe (39%) reduction in DLCO in a patient with multidrug-resistant tuberculosis.

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