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Published 2015 by the American Thoracic Society

Revised Definitions of Multidrug-Resistant Tuberculosis Treatment Outcomes: Closer to the Reality?

To the Editor:

The case and outcome definitions of patients with multidrug-resistant tuberculosis (MDR-TB) (resistance to both isoniazid and rifampicin) have recently been revised by the World Health Organization (WHO) (1). One of the reasons was that some of the treatment outcome definitions were exceptionally complicated to apply, and as they were applied retrospectively, they had limited use in clinical decision making. The objective of our study was to compare the treatment results of a large cohort of patients with MDR-TB, using the 2008 definitions and the 2013 outcome definitions applied retrospectively.

Methods

Study design and study population. We have conducted a retrospective multicentric cohort study of data collected routinely in five Médecins Sans Frontières drug-resistant TB programs in Armenia, Georgia, Kenya, Swaziland, and Uzbekistan. Patients were enrolled between 2001 and 2009 and received an individualized treatment regimen based on drug susceptibility testing results according to the updated WHO recommendations (2–5). Patient monitoring included monthly sputum smear microscopy and cultures during the treatment duration. No post-treatment follow-up was systematically done. Extensive drug resistance was

Supported by Médecins Sans Frontières.

Author Contributions: Conception and design: M. Bonnet, P.d.C., E.S.-P., and F.V. Analysis: M. Bastard, M. Bonnet, E.S.-P., C.H., and F.V. Interpretation of results: M. Bonnet, P.d.C., A.K.K., A.H., K.K., S.K., T.D., A.T., E.S.-P., C.H., and F.V. Drafting the manuscript for important intellectual content: M. Bastard, M. Bonnet, P.d.C., A.T., E.S.-P., C.H., and F.V.

Table 1. Treatment Outcomes of Patients with Multidrug-Resistant Tuberculosis, Using the 2008 and 2013 World Health Organization Definitions (N = 1,455)

	2008 Definitions		2013 Definitions	
	N	%	N	%
Cure	505	34.7	511	35.1
Treatment completed	303	20.8	106	7.3
Success	*808*	*55.5*	*617*	*42.4*
Death	127	8.7	60	4.1
Failure	165	11.3	551	37.9
Lost to follow-up*	333	22.9	211	14.5
Not evaluated†	22	1.6	16	1.1

*Defaulter in the 2008 definitions.
†Transferred out or still receiving treatment in the 2008 definitions.

defined as resistance to ofloxacin and at least one second-line injectable drug.

2013 WHO outcomes definitions. Treatment outcomes were routinely applied using the 2008 WHO definitions (4). In 2013, WHO revised the outcome definition (1). The definitions of being lost to follow-up (defaulter) and death remained unchanged.

In the 2008 definitions, cure was defined as a patient who has completed treatment with at least five consecutive negative cultures from samples collected at least 30 days apart in the final 12 months of treatment. If only a single positive culture was reported during that time and there was no clinical evidence of deterioration, a patient may be considered cured, provided this positive culture was followed by a minimum of three consecutive negative cultures taken at least 30 days apart. In the 2013 definitions, cure is defined as a patient who has completed treatment with no evidence of failure and three or more consecutive negative cultures taken at least 30 days apart after the intensive phase.

In the 2008 and 2013 definitions, treatment success was defined as a patient who is either cured or completed treatment.

According to the 2008 treatment outcome definitions, failure was defined as when two or more of the five cultures recorded in the final 12 months of therapy were positive, if any one of the final three cultures was positive, or when a clinical decision was made to terminate the treatment because of serious adverse reactions. In the revised definition, failure is defined as when treatment is terminated or if there is a need for a permanent regimen change of at least two anti-TB drugs because of lack of conversion by the end of the intensive phase, bacteriological reversion in the continuation phase after conversion to negative, evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, or adverse drug reactions (1).

As the treatment was individualized and no maximum duration for the intensive phase was defined, we chose a 6-month cut-off for culture negativation.

Statistical analysis. Patients' characteristics at treatment initiation were summarized using frequencies and percentages for categorical variables and median and interquartile range for continuous variables. Using follow-up data on culture results and drug susceptibility testing entered into the database, we retrospectively assessed the outcome of patients using the 2013 WHO definition. Treatment outcomes are reported using both the 2008 and 2013 WHO definitions. The reason for being classified as failure using the 2013 WHO definition was also reported. Analyses were performed using Stata 12.1 software (Stata Corporation, College Station, TX).

Results

Patients' characteristics at treatment initiation. A total of 1,455 MDR-TB-confirmed patients (56.9% males) were included in the study. At treatment initiation, median age was 32 years

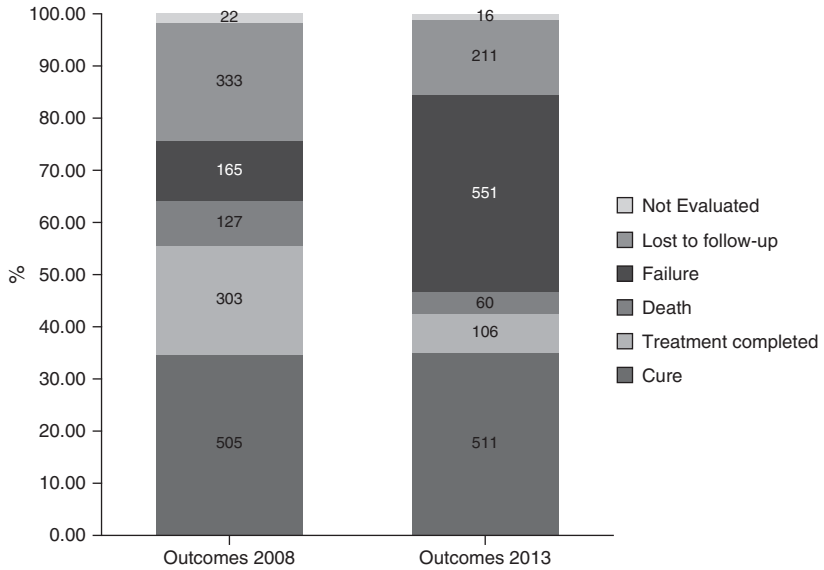

Figure 1. Distribution of treatment outcomes of patients with multidrug-resistant tuberculosis, using the 2008 and 2013 World Health Organization definitions (number and percentage; N = 1,455).

(interquartile range, 24–43 yr), and median body mass index was 18.6 kg/m^2 (interquartile range, 16.6–20.9 kg/m^2). Among the patients, 69.7% were previously treated for TB with first-line drugs, and 10.8% with second-line drugs. Among the 1,455 patients with MDR-TB, 56.5% of *Mycobacterium tuberculosis* strains were resistant to first-line drugs only, 27.1% were resistant to at least one second-line injectable drug, 5.0% were resistant to ofloxacin, and 2.5% were extensively drug-resistant. No information on second-line drug testing could be retrieved for 14% of the *M. tuberculosis* strains from the patients.

Treatment outcomes. In Table 1 and Figure 1, we present the treatment outcomes according to the 2008 and 2013 WHO definitions.

Among the 551 (37.9%) patients with MDR-TB retrospectively classified as failure, 503 were classified on the basis of bacteriological results: 300 (54.4%) had no culture conversion by Month 6, 82 (14.9%) amplified resistance to fluoroquinolones or second-line injectable drugs, and 126 (22.9%) experienced bacteriological reversion. The remaining 43 (7.8%) patients with MDR-TB were classified as failures because treatment was terminated as a result of adverse drug reactions. All patients defined as failures per the 2008 definitions also met the 2013 definition of failure.

After applying the revised 2013 definitions, 112/505 (22.2%), 79/303 (26.1%), 67/127 (52.8%), 122/333 (36.6%), and 6/22 (27.3%) of the patients with MDR-TB classified as cured, treatment completed, death, defaulter, and still receiving treatment or transfer out with the 2008 definitions were reclassified as treatment failure, respectively.

Among patients classified as treatment success per the 2008 definitions, 39.4% (318/808) had at least five follow-up cultures after the end of the intensive phase. Among patients classified as treatment success per 2013 definition, 83.7% (515/617; $P < 0.001$) had at least three follow-up cultures after the end of intensive phase.

The definition of cure was met by 62.5% (505/808) and 82.8% (511/617; $P < 0.001$) of the patients classified as treatment success per the 2008 and 2013 definitions, respectively.

Discussion

Although better than those reported globally (6), the treatment outcomes reported according to the 2008 definitions were disappointing, but similar to those reported in the literature (7), despite all efforts made to ensure adequate treatment and adherence.

The most striking effect of applying the WHO revised outcome definitions was the dramatic increase in the proportion of patients reported as failures. The proportions of success, defaulter, and death decreased. Many (36.6%) of the patients classified as defaulters per the 2008 definition were reclassified as failures by the revised definition. This may indicate that many patients interrupt their treatment when they see no improvement, as shown by a recent study (8). As only the first outcome assigned is recorded for outcome monitoring, not surprisingly, the majority of deaths were reclassified as failures. To a lesser extent, some of the patients reported as successes were reclassified as failures as first outcome. This reflects the fact that despite the lack of efficacy of the initial treatment, the final outcome could still be favorable when treatment adaptation was possible.

The new definition of cure makes it more possible to meet the criteria for cure, as the high number of negative cultures required by the 2008 definition was unrealistic, with most patients who are clinically cured being unable to produce sputum in the last months of treatment.

The 2013 definition of a failing treatment better corresponds to an ineffective treatment and better reflects the reality faced by patients and clinicians. It should act as a red flag for the clinician, indicating that the treatment must be changed.

Although these findings remain to be confirmed in prospective cohorts and in other settings, they indicate that failures were largely underestimated by the 2008 definitions. This highlights the poor efficacy of the current regimens and underlines the urgent need for a more effective regimen that now seems within reach with the advent of new TB drugs (9–11). ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Defining Patient and Family Engagement in the Intensive Care Unit

To the Editor:

Healthcare is in the midst of significant change, with substantial shifts in emphasis and priorities. Patient-centered care has become central to the core goals of better health, better quality, and lower costs while highlighting the necessity of incorporating patients' efforts, needs, and perspectives into healthcare at all levels (1). Patient and family engagement (PFE) is critical to patient-centered care (2), and important theoretical and empirical work has identified key elements and implications of PFE, especially for management of chronic illnesses and preference-sensitive clinical decision making (3). We believe that the ultimate goal of active, mutually respectful partnership among clinicians and patients/families is urgent and important. However, consistent terminology and definitions of PFE are still lacking (4). This deficit is particularly striking in intensive care units (ICUs), which pose special challenges to outpatient models of PFE: the emotional stakes are high, time is greatly compressed, surrogates play a central role, and the specter of death often dominates decision making.

In 2013, the Gordon and Betty Moore Foundation created the Libretto Consortium, a collaboration of Beth Israel-Deaconess Medical Center, Brigham and Women's Hospital, Johns Hopkins University, and the University of California, San Francisco, intended to reengineer critical care (5). The Libretto Consortium PFE Integration Group brings together specialists in critical care, social work, nursing, psychology, lay advisor management, health services research, patient experience, shared decision making, and patient-centered care. In direct collaboration with lay partners that employed a modified Delphi technique (6), including iterative identification of content and revisions of draft definitions by authors over email, with intermittent meetings of Patient-Family Advisory Councils (PFACs) (7) and solicitation of community input at authors' hospitals for further content identification, review, and refinement of draft definitions, the group developed a definition of PFE to identify and describe conceptual elements of ICU-relevant PFE.

Through this process, we developed a definition, including both a short-form and a long-form definition. The short-form definition appears here; the long-form definition is available as Table E1 in the online supplement.

This new definition and conceptual clarification is important to responding to the unique demands imposed by critical illness and the ICU environment. PFE applies differentially in three often overlapping phases of life-threatening illness (acute, convalescent, and dying). Acutely, life is threatened and aggressive treatment is required. The priorities are physiological stabilization, honoring values, providing emotional support, and considering palliative care where indicated. During convalescence, recovery from post–intensive care syndrome is actively pursued, and full engagement in rehabilitation is important. One-seventh of ICU patients will die from their critical illness (8); individuals may transition from the acute or convalescent phase to the dying phase. At least half of ICU survivors suffer from post–intensive care syndrome, which represents a new onset chronic disease associated with physical, cognitive, and psychiatric disability (9).

Critical illness, the ICU environment, and the long recovery from critical illness present unique challenges for patients and families. Engagement and decision making may be particularly burdensome for families because of high levels of acute stress and the risk for death. A call for patient responsibility, such as for a "nonadherent" diabetic to be engaged in his glucose control, will not apply straightforwardly in the ICU; in our definition, we

Supported by the Gordon and Betty Moore Foundation.

Author Contributions: S.M.B. and R.R. drafted the manuscript; all authors conducted research and drafted the definition, revised the manuscript for important intellectual content, and provided approval of the final version of manuscript.

This letter has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org