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Scientific Letter

[Translated article] Drug Resistant Tuberculosis: New WHO Definitions and Their Implication in the SEPAR Guideline☆

Tuberculosis con resistencia a fármacos: nuevas definiciones de la OMS y su implicación en la Normativa de SEPAR

To the Director:

Given the difficulties in diagnosing and treating patients with drug-resistant tuberculosis (DR-TB) in general, and rifampicin-resistant tuberculosis (RR-TB) in particular, the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) published guidelines in 2017 to facilitate the management of these entities[1]. These SEPAR guidelines were updated in 2020[2] to include the accumulated evidence on new drugs and their rational and sequential use[3–5], and to adapt the recommendations to those published by the WHO in 2019[6,7] and 2020[8,9]. The WHO has now published new definitions of RR-TB[10], prompting us to revisit the SEPAR guidelines.

RR-TB, which is also resistant to isoniazid (H), was given a specific name: multidrug-resistant TB (MDR-TB)[6,9,11]. Both RR-TB and MDR-TB were subsequently found to have a similar prognosis, due to resistance to R, the most important drug in the treatment of TB[12]. This is now called MDR/RR-TB, and prevalence in 2019 was 465,000 cases worldwide[11]. This definition of MDR/RR-TB remains unchanged in the new WHO publication[10].

Five to10 years ago, only 2 groups of drugs had demonstrated good efficacy in the treatment of patients with MDR/RR-TB – fluoroquinolones (FQ) and second-line injectable drugs (SLID), which included 3 drugs: amikacin, kanamycin, and capreomycin[13]. Since the prognosis of MDR/RR-TB patients depended fundamentally on the efficacy of these 2 drug groups, in 2006 the WHO coined a new term: extensively resistant TB (XDR-TB), which encompassed cases of MDR-TB that were also resistant to any FQ and at least 1 SLID[12,13]. However, clinicians often used another term that was never officially accepted: pre-XDR-TB, which were MDR/RR-TB cases that were also resistant to FQ or SLID, but not both. Thus, there was pre-XDR-TB that was resistant to FQ but sensitive to SLID; and pre-XDR-TB that was resistant to SLID but sensitive to FQ. Over time, the prognosis of pre-XDR-TB with FQ resistance was seen to be clearly worse than that of pre-XDR-TB with SLID resistance[12,14].

Fortunately, the prognosis of resistant TB has improved remarkably in the last 5 years, thanks in particular to the introduction of new drugs with good anti-*M. tuberculosis* activity (bedaquiline [Bdq], delamanid, pretomanid), and the discovery that other antibiotics used for other infections (FQ, linezolid [Lzd], clofazimine [Cfz]) are also very effective in TB[3,13]. This evidence prompted the WHO to perform a meta-analysis in 2018[3] to study the potential role of each drug with anti-*M. tuberculosis* activity in the treatment of MDR/RR-TB. The main conclusions of the study were: 1) the best drugs were FQ, Lzd, and Bdq, and these therefore were included in group A of the new classification of rational drug use in the 2019 WHO guidelines[6] and in group 2 of the 2020 SEPAR guidelines[2]; and 2) the efficacy of the SLIDs was clearly lower than previously thought[3], and their toxicity means that they must be reserved for special situations in which no other medicines are available and when adverse effects can be closely monitored[3,9,12].

Following the removal of SLIDs from the state-of-the-art arsenal and the arrival of new active drugs for the treatment of MDR/RR-TB, the WHO organized a meeting in late 2020 to redefine the concepts of drug-resistant TB[10]. They did not alter the definitions of TB-RR/MDR, but they did modify the definition of XDR-TB, and have now officially included the definition of pre-XDR-TB. It is accepted that pre-XDR-TB is MDR/RR-TB that is also resistant to FQ, and all mention of SLIDs has been eliminated. This changes the concept of XDR-TB in cases who present pre-XDR-TB plus resistance to at least 1 of the other drugs included in WHO group A (SEPAR group 2), i.e, currently, resistance to Lzd or Bdq, or both[10]. The definition refers to group A drugs, and will also apply to any other drugs included in this group in the future.

Although these new WHO definitions[10] (summarized in Table 1) are both correct and important, they have very little impact on the

Table 1
Differences in the definitions of drug-resistant tuberculosis in the 2020 SEPAR guidelines[2] compared to the new 2021 WHO definitions[10].

SEPAR 2020 definitions[2]	WHO 2021 definitions[10]
RR tuberculosis: TB resistant to at least rifampicin (R)	**MDR/RR-TB**: no change
MDR tuberculosis: TB resistant to at least isoniazid (H) and rifampicin (R)	Both types of resistance are often grouped as MDR/RR-TB in both epidemiological and therapeutic studies **Pre-XDR TB**: MDR/RR-TB plus resistance to any fluoroquinolone[a] This is a new definition
XDR tuberculosis: MDR-TB plus resistance to at least 1 fluoroquinolone and a second-line injectable drug: kanamycin, amikacin, capreomycin	**XDR tuberculosis:** MDR/RR-TB, plus resistance to any fluoroquinolone[a], and at least 1 of the other drugs included in WHO group A (SEPAR group 2), currently, in other words, resistance to Lzd or Bdq, or both[b].

[a] Refers to levofloxacin and moxifloxacin which are currently used in the treatment of TB.

[b] WHO group A currently includes fluoroquinolones, bedaquiline, and linezolid. The definition refers to drugs in group A, so the concept of XDR-TB would also apply to any new drugs included in this group in the future.

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Table 2
Changes required to bring the 2020 SEPAR drug-resistant tuberculosis guidelines[2] in line with the new 2021 WHO definitions of resistant tuberculosis[10].

Reference in 2020 SEPAR guidelines	2020 SEPAR guidelines	Changes after implementation of new 2021 WHO definitions
Definitions	RR-TB, MDR-TB, XDR-TB	Change to the new WHO definitions (MDR/RR-TB, pre-XDR-TB, XDR-TB) listed in Table 1
Table 3. Recommendation 2.b	For cases that only have **XDR-TB** and no resistance to Bdq or Lzd, the 6-month pretomanid regimen (6 Bdq-Lzd-pretomanid) that is not yet marketed in Spain must be assessed	For cases that only have **pre-XDR-TB** and no resistance to Bdq or Lzd, the 6-month pretomanid regimen (6 Bdq-Lzd-pretomanid) that is not yet marketed in Spain must be assessed
Table 4. Recommendation 4	**XDR-TB patients**: assess 6 Bdq-Lzd-pretomanid	**Pre-XDR-TB patients**: assess 6 Bdq-Lzd-pretomanid[a]
Treatment regimens	Treatment of patients with **XDR-TB** or even broader resistance patterns These forms of TB are so difficult to manage (in clinical practice and in protocols) that they should be treated by highly specialized clinicians and in units that can guarantee close supervision of the treatment and the proper management of adverse reactions	**Pre-XDR-TB and XDR-TB patients**[b]: The recommendation is unchanged

[a] According to the new WHO definition, the 6 Bdq-Lzd-pretomanid regimen cannot be used in XDR-TB because there is resistance to Bdq or Lzd or both.
[b] Patients with pre-XDR and XDR-TB, due to their complexity, should be treated according to the 2020 guidelines for XDR (the former concept).

clinical strategies recommended in the updated SEPAR guidelines published in 2020[2]. This is because the vast majority of the recommendations addressed the diagnosis and treatment of MDR/RR-TB, the most common form, and these remain unchanged. Even the small section which, at that time, was devoted to the *"Treatment of patients with XDR-TB or even broader resistance patterns"* remained unchanged, and the advice that *"XDR-TB must be treated by highly specialized clinicians and in units that can guarantee close supervision of the treatment and the proper management of adverse reactions"* remains in force.

These new WHO definitions[10], then, would only require the following changes in the 2020 SEPAR guidelines[2] (detailed in Table 2):

1 Inclusion of the new pre-XDR and XDR-TB definitions.
2 Inclusion of the pretomanid regimen (6 Bdq-Lzd-pretomanid) indication in the current pre-XDR-TB, but not in the new XDR-TB definition.

The WHO has also just released a rapid communication updating the use of molecular tests to detect TB and DR-TB[15], most of which were already recommended in the SEPAR 2020 guidelines[2]. The most important innovation is the inclusion of Xpert MTB/XDR (Cepheid), a low-complexity technique similar to Xpert MTB that in less than 2 hours detects mutations linked to resistance to H, FQ (perhaps the great advantage of this technique), amikacin, and etionamide, and is indicated in patients in whom RR-TB has been detected by any method. Another novelty is the Genoscholar PZA-TB II, which can be used to detect pyrazinamide resistance, although this technique is more complex. It would also be advisable to implement techniques to diagnose resistance to Bdq and Lzd, given the importance of these drugs in the therapeutic arsenal and new definitions of resistant TB.

In conclusion, the update of the 2020 SEPAR guidelines[2] changes little, although we must take into account the revised WHO definitions of DR-TB in respect of the new meaning of pre-XDR-TB and the change in the definition of XDR-TB. Furthermore, rapid detection of FQ resistance, and thus of pre-XDR-TB, is also an important development.

Finally, we would like to underline the importance of the new drugs, especially bedaquiline, and support institutional efforts to make them available across Spain. The Plan for TB Prevention and Control will no doubt be of assistance in this initiative and will help implement the new guidelines[16].

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Conflict of interests

The authors declare that they have no conflict of interests directly or indirectly related with the contents of this manuscript.

References

1. Caminero JA, Cayla JA, García-García JM, García-Pérez FJ, Palacios Gutiérrez JJ, Ruiz Manzano J. Diagnóstico y tratamiento de la tuberculosis con resistencia a fármacos. Arch Bronconeumol. 2017;53:501–9, http://dx.doi.org/10.1016/j.arbres.2017.02.006.
2. Caminero JA, García-García JM, Cayla JA, García-Pérez FJ, Palacios Gutiérrez JJ, Ruiz Manzano J. Actualización de la normativa SEPAR. «Diagnóstico y tratamiento de la tuberculosis con resistencia a fármacos». Arch Bronconeumol. 2020;56:514–21, http://dx.doi.org/10.1016/j.arbres.2020.03.021.
3. Ahmad N, Ahuja SD, Akkerman OW, Alffenaar JC, Anderson LF, Baghaei P, et al. The Collaborative Group for the Meta-analysis of Individual Patient Data in MDR-TB Treatment 2017 Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual data and meta-analysis. Lancet. 2018;392:821–34, http://dx.doi.org/10.1016/S0140-6736(18)31644-1.
4. Rapid communication: key changes to treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB). Geneva: World Health Organization; 2018 (WHO/CDS/TB/2018.18) Licence: CC BY-NC-SA 3.0 IGO [accessed 21 Feb 2021]. Available from: https://apps.who.int/iris/bitstream/handle/10665/275383/WHO-CDS-TB-2018.18-eng.pdf
5. Caminero JA, Scardigli A. Classification of anti-TB drugs: A new potential proposal based on the most recent evidence. Eur Respir J. 2015;46:887–93, http://dx.doi.org/10.1183/13993003.00432-2015.
6. WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO [accessed 21 Ene 2020]. Available from: https://www.who.int/tb/publications/2019/consolidated-guidelines-drug-resistant-TB-treatment/en/
7. Rapid communication: Key changes to treatment of drug-resistant tuberculosis. Geneva: World Health Organization; 2019 (WHO/CDS/TB/2019.26). Licence: CC BY-NC-SA 3.0 IGO [accessed 21 Ene 2020]. Available from: https://www.who.int/tb/publications/2019/rapid_communications_MDR/en/
8. World Health Organization, Licence: CC BY-NC-SA 3.0 IGO [accessed 21 Ene 2020]. Available from: https://apps.who.int/iris/handle/10665/330395, 2020.
9. World Health Organization, Licence: CC BY-NC-SA 3.0 IGO [accessed 18 Feb 2021]. Available from: https://www.who.int/publications-detail-redirect/9789240006997, 2020.
10. Meeting report of the WHO expert consultation on the definition of extensively drug-resistant tuberculosis, 27-29 October 2020. Geneva: World Health Organization; 2021. CC BY-NC-SA 3.0 IGO [accessed 30 Ene 2021]. Available from: https://www.who.int/publications/i/item/meeting-report-of-the-who-expert-consultation-on-the-definition-of-extensively-drug-resistant-tuberculosis
11. World Health Organization, Licence: CC BY-NC-SA 3.0 IGO [accessed 27 Oct 2020]. Available from: https://www.who.int/publications/i/item/9789240013131, 2020.
12. Caminero JA, García-Basteiro AL, Rendon A, Piubello A, Pontali E, Migliori GB. The future of drug-resistant tuberculosis treatment: Learning from the past

and the 2019 World Health Organization consolidated guidelines. Eur Respir J. 2019;54:1901272, http://dx.doi.org/10.1183/13993003.01272-2019.
13. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis. Emergency update 2008. World Health Organization Document WHO/HTM/TB/2008.402: 1-247 [accessed 23 Feb 2021]. Available from: https://www.who.int/tb/publications/tb-drugresistance-guideline/en/.
14. Falzon D, Gandhi N, Migliori GB, Sotgiu G, Cox HS, Holtz TH, et al. Resistance to fluoroquinolones and second-line injectable drugs: impact on multidrug-resistant TB outcomes. Eur Respir J. 2013;42:156–68, http://dx.doi.org/10.1183/09031936.00134712.
15. Update on the use of nucleic acid amplification tests to detect TB and drug-resistant TB: rapid communication. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO [accessed 17 Feb 2020]. Disponible en: https://www.who.int/publications/i/item/update-on-the-use-of-nucleic-acid-amplification-tests-to-detect-tb-and-drug-resistant-tb-rapid-communication
16. Plan para la Prevención y Control de la TB en España. Madrid: Ministerio de Sanidad, Consumo y Bienestar Social; 2019 [accessed 1 Jun 2019]. Disponible en: https://www.mscbs.gob.es/en/profesionales/saludPublica/prevPromocion/PlanTuberculosis/docs/PlanTB2019.pdf

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