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Consensus document

Executive summary: Clinical practice guidelines on the management of resistant tuberculosis of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) and the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC)☆,☆☆

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Abbreviations: B, bedaquiline; BSL, biosafety level; BPaL, bedaquiline, pretomanid, linezolid; BPaLC, bedaquiline, pretomanid, linezolid, clofazimine; BPaLM, bedaquiline, pretomanid, linezolid, moxifloxacin; CDC, Centre for Disease Control and Prevention; CLSI, Clinical and Laboratory Standards Institute; CNE, National Centre for Epidemiology; COVID-19, COronaVIrus Disease 2019; CPG, Clinical Practice Guideline; D, delamanid; DNA, deoxyribonucleic acid; DOT, directly observed therapy; DR, drug-resistant or resistant to antituberculosis drugs; DR-TB, TB caused by a strain of *M. tuberculosis* resistant to any of the antituberculosis drugs; DST, drug susceptibility test; E, ethambutol; ECDC, European Centre for Disease Prevention and Control; ESTC, European Union Standards for Tuberculosis Care; EU/EEA, European Union and European Economic Area; FQs, fluoroquinolones; GeSIDA, AIDS Study Group-SEIMC; GRADE, Group Reading Assessment and Diagnostic Evaluation; H, Isoniazid; HIV, human immunodeficiency virus; HR, Hazard ratio; L, linezolid; LTI, latent TB infection; M, moxifloxacin; MDR, multidrug-resistant; MGIT, Mycobacterial Growth Indicator Tube; MIC, minimum inhibitory concentration; MDR-TB, TB caused by a strain of *M. tuberculosis* resistant to at least isoniazid and rifampicin; MS, multi-susceptible; MTB, *Mycobacterium tuberculosis*; *MTBC*, *Mycobacterium tuberculosis* complex; NAAT, nucleic acid amplification techniques; P, pretomanid; PAS, para-aminosalicylic acid; PCR, polymerase chain reaction; PICO, Patient, Intervention, Comparison, and Outcome; PII-TB&MNT, Integrated Research Program on Tuberculosis and Non-Tuberculous Mycobacteria; PPV, Positive Predictive Value; preXDR-TB, TB caused by a strain of *M. tuberculosis* resistant to isoniazid, rifampicin, and a fluoroquinolone; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; R, rifampicin; RENAVE, National Epidemiological Surveillance Network; RR, resistance to rifampicin; RR-TB, TB caused by a strain of *M. tuberculosis* resistant to rifampicin; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; SEIMC, Spanish Society of Infectious Diseases and Clinical Microbiology; SEPAR, Spanish Society of Pneumology and Thoracic Surgery; TB, tuberculosis; VOT, Video Observed Treatment (telematically); WHO, World Health Organization; XDR, extensively drug-resistant; XDR-TB, TB caused by a strain of *M. tuberculosis* resistant to isoniazid, rifampicin, a fluoroquinolone, and bedaquiline or linezolid; Z, pyrazinamide.

☆ The complete consensus document is available as Appendix B in Supplementary Material.

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ABSTRACT

The Spanish Society of Pneumology and Thoracic Surgery (SEPAR) and the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) have developed together Clinical Practice Guidelines (GPC) on the management of people affected by tuberculosis (TB) resistant to drugs with activity against *Mycobacterium tuberculosis*. These clinical practice guidelines include the latest updates of the SEPAR regulations for the diagnosis and treatment of drug-resistant TB from 2017 to 2020 as the starting point. The methodology included asking relevant clinical questions based on PICO methodology, a literature search focusing on each question, and a systematic and comprehensive evaluation of the evidence, with a summary of this evidence for each question. Finally, recommendations were developed and the level of evidence and the strength of each recommendation for each question were established in concordance with the GRADE approach. Of the recommendations made, it is worth highlighting the high quality of the existing evidence for the use of nucleic acid amplification techniques (rapid genotypic tests) as initial tests for the detection of the *M. tuberculosis* genome and rifampicin resistance in people with presumptive signs or symptoms of pulmonary TB; and for the use of an oral combination of anti-TB drugs based on bedaquiline, delamanid (pretomanid), and linezolid, with conditional fluoroquinolone supplementation (conditioned by fluoroquinolone resistance) for six months for the treatment of people affected by pulmonary multidrug-resistant tuberculosis (MDR-TB). We also recommend directly observed therapy (DOT) or video-observed treatment for the treatment of people affected by DR-TB.

Introduction and rationale

Tuberculosis (TB) continues to be a global health problem in the world. One of the problems that make it difficult to control the disease is the emergence of *Mycobacterium tuberculosis* (MTB) strains resistant to drugs (DR) commonly used for its treatment. Isoniazid-resistant TB, rifampicin-resistant TB (RR-TB), and multidrug-resistant TB (MDR-TB), i.e., resistant to at least isoniazid and rifampicin, have been associated with poorer treatment outcomes and increased mortality. In recent years, new anti-MTB drugs have emerged that have facilitated the creation of shorter, safer, better-tolerated, and more effective treatment regimens for people affected by DR-TB.

The management of DR-TB poses many uncertainties, is complex, and requires the participation of specialists with experience in this field. The available evidence has increased considerably, and its reading and critical analysis are of vital importance to be able to make recommendations adapted to the characteristics of people affected by DR-TB. For this reason, The Spanish Society of Pneumology and Thoracic Surgery (SEPAR) and the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) have worked together to develop a Clinical Practice Guidelines (CPG) on the management of people affected by DR-TB. This CPG will update previous recommendations on DR-TB published in 2017 and 2020 by SEPAR. The current CPG is developed with a high-quality systematic methodology and critical analysis of the evidence, implementing Patient, Intervention, Comparison, and Outcome questions (PICO) and Group Reading Assessment and Diagnostic Evaluation (GRADE) approaches. The working group identified 14 key questions included in the document, ten of which are PICO questions and four refer to complementary questions that facilitate the understanding of the recommendations made in the guidelines, and serve to place its content in context. Paediatric TB has not been addressed in this document. To consult the recommendations on the treatment of TB in children, we suggest referring to the updated documents of the Spanish Paediatric Society (13).

Clinical aspects covered

The CPG addresses the management of people affected by DR-TB and covers epidemiological, microbiological, and clinical aspects. The DR-TB considered in this guideline is isoniazid-resistant TB, RR-TB, MDR-TB, pre-extensively resistant TB (preXDR-TB), and extensively resistant TB (XDR-TB).

Who is it for?

The CPG is aimed at health professionals who treat, and care for people affected by DR-TB.

Objectives of the document

This CPG aims to evaluate the available evidence on the management of people affected by DR-TB and to offer recommendations that can help to better manage these people.

Questions

Supplementary question 1: What is the epidemiological situation of resistant TB globally and in Spain?

Internationally, the World Health Organization (WHO) publishes TB resistance data, in the form of genotypic RR-TB identified via molecular tests. Xpert MTB/RIF is the most widely used test, following the recommendation regarding its implementation in 2010. It should be noted that most cases of RR-TB are also resistant to isoniazid, so it is used as a marker of MDR-TB. The WHO estimates that, in 2022, there were around 410,000 new cases of RR-TB, which

represents a decrease of 8.9% compared with 2021; however, the irruption of the SARS-CoV-2 pandemic in RR-TB reporting, continuity of care, and dynamic systems must be taken into account. The proportion of RR-TB cases in relation to new TB cases was 3.3% in 2022, and 17% for previously treated cases. In 2022, only 175,650 people diagnosed with RR-TB were able to access adequate treatment, representing only 43% of the estimated cases for that year; and only 73% of bacteriologically confirmed TB cases were tested for rifampicin resistance. There are no up-to-date data on the global prevalence of isoniazid monoresistance, although, in 2018, the WHO estimated that around 8% of TB cases were monoresistant to this drug (and rifampicin-susceptible). In 2022, the estimated number of cases of preXDR-TB was 27,075, and the proportion of XDR-TB cases was 11.2% of the preXDR-TB cases.

In Spain, information regarding the total number of people affected by DR-TB is not disaggregated, so it is difficult to know the number of people affected by isoniazid-resistant TB, RR/MDR-TB, preXDR-TB, and XDR-TB independently. The percentage of MDR-TB between 2015 and 2021 in Spain ranged from 1.1 to 4.9% of all TB cases. However, in recent years, it has ranged between 2 and 2.5%, with significant variations by geographical area, and with incidence rates highly dependent on aggregate cases or outbreaks given the low annual number of people diagnosed. These percentages increase by 1–1.5 percentage points if only TB with rifampicin monoresistance is considered. Information on people affected by isoniazid-resistant TB is not published in the RENAVE reports. However, data published from a national survey of sentinel hospitals, showed that 6.4% of people affected by TB have isoniazid resistance.

Supplementary question 2: What are the current definitions of MDR, preXDR, and XDR-TB?

For the development of these guidelines, we have used the most recent WHO definitions, which are those most internationally accepted, and those used in our national surveillance system:

- MDR-TB: TB caused by *M. tuberculosis* strains with resistance (phenotypic and/or genotypic) to at least isoniazid and rifampicin.
- preXDR-TB: TB caused by *M. tuberculosis* strains that meet the definition of MDR-TB, adding resistance to a fluoroquinolone (levofloxacin or moxifloxacin).
- XDR-TB: TB caused by *M. tuberculosis* strains that meet the definition of MDR-TB with resistance to a fluoroquinolone, and at least one other group A drug (currently, bedaquiline or linezolid).

Alternatively, the term RR-TB is defined as TB caused by *M. tuberculosis* strains that have demonstrated resistance to rifampicin, usually by molecular testing, and for which resistance to other first-line drugs is not normally available or there is susceptibility to these drugs. This term is often used when molecular tests are available that only detect rifampicin resistance, in the *rpoB* gene, and is often used as an indicator of MDR-TB as in most cases people affected by RR-TB have associated isoniazid resistance.

Supplementary question 3: What are the possible outcomes of MDR-TB treatment?

The WHO programmatic outcome definitions from 2021 have common definitions for susceptible TB and DR-TB, to facilitate monitoring and surveillance, as well as facilitate comparability across regions. The definitions are as follows:

- Cured: A person with pulmonary TB confirmed bacteriologically at the start of treatment, as recommended by the national programme, with evidence of bacteriological response and no evidence of failure. The bacteriological response is defined as microbiological conversion to negative of the culture without subsequent reversion to positive. These terms signify the following:
  - Bacteriological conversion: the presence of two consecutive negative cultures or smears, taken on two occasions at least seven days apart, are available.
  - Bacteriological reversion: the presence of two positive cultures at least seven days apart, after previous bacteriological conversion or in patients with no previous bacteriological confirmation of TB.
- Treatment completed: A person with TB who completed treatment as recommended by the national programme, yet does not meet the definition of cured or treatment failure.
- Treatment success: This is the sum of cured and treatment completed.
- Treatment failure: A person with TB whose treatment needs to be terminated prematurely or permanently modified to a new treatment regimen or strategy. Reasons for the change include:
  - Absence of clinical or bacteriological response.
  - Adverse events caused by anti-TB drugs.
  - Evidence of additional resistance to drugs from their treatment regimen.
- Lost to follow-up: A person with TB who does not start treatment or whose treatment is interrupted for more than two consecutive months without medical justification.
- Not evaluated: A person with TB for whom no treatment outcome is assigned. This includes patients who have been "transferred out" to another treatment unit and whose treatment outcome is unknown. It does not include a person with TB lost to follow-up.
- Died: Death from any cause before starting or during the course of treatment. A distinction is made between the cause of death related to TB and another cause not related to TB.
- Sustained treatment success: applies to a person with TB assessed at six and 12 months after successful treatment, who is still alive and TB-free. If there is a new episode, it would include recurrence, which in turn can be divided into relapse and reinfection; relapse being a new episode of TB with the same strain as the previous episode (endogenous reactivation), while reinfection constitutes a new episode of TB with a new strain (exogenous reinfection).

Supplementary question 4: Which are the anti-tuberculosis drugs used in DR-TB and how are they classified?

The current WHO classification separates the drugs used in DR-TB into three groups: A, B, & C (Table 1).

Table 1
WHO classification of the drugs for formulating treatment for people with tuberculosis caused by a strain of *M. tuberculosis* resistant to some drugs used to treat drug-susceptible tuberculosis.

Group	Drug
A	Levofloxacin or moxifloxacin Bedaquiline Linezolid
B	Clofazimine Cycloserine or terizidone
C	Ethambutol Delamanid Pyrazinamide Imipenem–cilastatin or meropenem Amikacin or streptomycin Ethionamide or prothionamide Para-aminosalicylic acid (PAS)

Table 2
Expert panel classification of drugs for formulating treatment for people affected with tuberculosis caused by a strain of *M. tuberculosis* resistant to some drugs used to treat drug-susceptible tuberculosis.

Group		Drugs
1	Oral drugs shown to be effective in combination and have a low proportion of adverse events that require treatment modification. Use preferably in the order proposed.	Levofloxacin/moxifloxacin Bedaquiline Delamanid/pretomanid Linezolid/tedizolid[a] Clofazimine
2	Drugs shown to be effective in combination and that either must be administered parenterally, or have an intermediate/high proportion of adverse events that require treatment modification. Use preferably in the order proposed.	Imipenem/meropenem (+clavulanic acid) Amikacin Cycloserine/terizidone
3	Oral drugs with limited efficacy and with a low/moderate proportion of adverse events requiring treatment modification.	Pyrazinamide Isoniazid at high doses Ethambutol
4	Oral drugs that could be effective, but with insufficient evidence and with a low proportion of adverse events that require treatment modification.	Faropenem
5	Intravenous drugs that could be effective but lack evidence, and with insufficient reporting of adverse events in extended treatments.	Ceftazidime avibactam

[a] In those who do not tolerate linezolid, or it cannot be administered due to interactions, tedizolid could be an alternative.

Table 3
Recommended doses of drugs used in the treatment tuberculosis caused by a strain of *M. tuberculosis* resistant to some drugs used to treat drug-susceptible tuberculosis.

Drug	Route	Daily dose
Levofloxacin	Oral, IV	15–20 mg/kg/day, once daily (750–1500 mg/day)
Moxifloxacin	Oral, IV	7.5–10 mg/kg/day, once daily Usual dose: 400 mg Max dose: 600–800 mg/day, especially when combined with an enzyme inducer (e.g., rifampicin)
Bedaquiline	Oral	400 mg/day 14 days, then 200 mg 3 times a week Alternative, 200 mg/day 8 weeks, followed by 100 mg/day 18 weeks
Pretomanid	Oral	200 mg/day
Delamanid	Oral	>30–50 kg: 50 mg/12 h >50 kg: 100 mg/12 h
Linezolid	Oral, IV	600 (300–1200) mg/day[a]
Tedizolid	Oral, IV	200 mg/day
Clofazimine	Oral	100–200 mg/day
Imipenem–cilastatin	IV	1 g 3–4 times/day or 1–1.5 g/12 h
Meropenem	IV	1 g 3–4 times/day or 1.5–2 g/12 h
Clavulanic acid (+ carbapenem)	Oral, IV	125–250 mg 2–3 times/day (administer 30 min before carbapenem drugs)
Amikacin	IM, IV	15–20 mg/kg Max: 1000 mg
Cycloserine/terizidone	Oral	15 mg/kg/day, once daily (250–1000 mg/day)
Pyrazinamide	Oral	20–30 mg/kg If <50 kg: max. 1.5 g; 50–75 kg: max. 2 g; >75 kg: max. 2.5 g
Isoniazid (high doses)	Oral, IV, IM	15–20 mg/kg/day
Ethambutol	Oral, IV	15–25 mg/kg/day Max. 2 g/day
Faropenem	Oral, IV	200–300 mg/8 h
Ceftazidime–avibactam	IV	2/0.5 g/8 h

IV: intravenous; IM: intramuscular; kg: kilograms; g: grams; mg: milligrams; DR-TB: drug-resistant tuberculosis; h: hours.
[a] We recommend the use of a linezolid dose of 600 mg per day (better efficacy-safety ratio). Higher doses have a higher bactericidal potential but also a high rate of adverse events that require treatment discontinuation. Doses of 300 mg per day have been shown to be effective with a good safety profile but the available evidence is inferior.

The expert panel proposes a classification based on proven evidence of combinations, prioritising those oral drugs that have a better balance between efficacy and safety. Thus, the panel suggests the following classification of drugs with anti-MTB activity for the treatment of people affected by MDR-TB (see Table 2). Table 3 shows the recommended doses for the main drugs used in the treatment of MDR-TB.

PICO question 5: What are the main diagnostic tools for drug-resistant tuberculosis?

We recommend performing some of the nucleic acid amplification techniques (NAAT) recommended by the WHO for the detection of the MTB genome, and, at least, the simultaneous detection of genotypic rifampicin resistance in initial respiratory specimens from people with presumptive symptoms or signs of pulmonary TB (strong recommendation, moderate quality of evidence). Rapid molecular tests for resistance to other anti-TB drugs or sequencing technologies can provide rapid and reliable information on resistance to other anti-TB drugs (conditional recommendation, low quality of evidence). We recommend performing NAAT on samples of extrapulmonary origin rather than not performing them (conditional recommendation, low quality of evidence).

We recommend performing mycobacterial culture in respiratory samples from people with presumptive symptoms or signs of pulmonary TB rather than not doing so (strong recommendation, high quality of evidence). We recommend using cultures in liquid

(preferably) and solid media for all clinical samples from people with presumptive symptoms or signs of pulmonary TB rather than using only one media (conditional recommendation, low quality of evidence). We recommend performing a mycobacterial culture of extrapulmonary samples rather than not doing so (strong recommendation, low quality of evidence).

We recommend performing smear tests, versus not performing them, in all people affected by presumptive pulmonary (or extrapulmonary) TB, especially to facilitate the follow-up of people affected by TB and to design the contact study (strong recommendation, moderate quality of evidence). Negative results do not exclude pulmonary (or extrapulmonary) TB. The performance of at least three smear tests on three different samples is recommended to improve sensitivity. The use of concentrated respiratory specimens and fluorescence microscopy is recommended (strong recommendation, moderate quality of evidence).

PICO Question 6: What is the usefulness of molecular (genotypic) testing in the diagnosis of rifampicin-resistant tuberculosis and for the other drugs used in the treatment of drug-resistant tuberculosis?

We recommend the use of the NAAT suggested by the WHO as an initial test for the detection of the MTB genome and, at least, the simultaneous detection of genotypic resistance to rifampicin in an initial respiratory sample from people affected by presumptive TB (strong recommendation, moderate quality of evidence). We recommend NAAT capable of detecting resistance to other anti-TB drugs, especially isoniazid, regardless of the outcome of rifampicin resistance in initial respiratory specimens (conditional recommendation, low quality of evidence). We recommend NAAT with the capacity to detect resistance to other anti-TB drugs, especially fluoroquinolones, in people affected by RR-TB or MDR-TB, to help design the treatment regimen (conditional recommendation, moderate quality of evidence). We recommend the use of sequencing technologies that can provide a complete individual profile of anti-TB drug resistance (conditional recommendation, low quality of evidence). We recommend performing NAAT on samples of extrapulmonary origin rather than not performing them (conditional recommendation, low quality of evidence).

PICO Question 7: Is there a standardised methodology for conducting phenotypic studies of resistance to anti-tuberculosis drugs?

In everyone with presumptive symptoms or signs of pulmonary and extrapulmonary TB, an effort proportionate to the clinical context should be made to obtain a sample suitable for microbiological study (strong recommendation, moderate quality of evidence). All MTB-positive isolates in our setting must have a phenotypic study of resistance to isoniazid and rifampicin (strong recommendation, high quality of evidence). Additionally, all MTB-positive isolates in our setting must have a phenotypic study for pyrazinamide and ethambutol (conditional recommendation, low quality of evidence). In those with RR/MDR-TB, the phenotypic resistance study should be extended to fluoroquinolones, linezolid, bedaquiline, pretomanid/delamanid, clofazimine, and amikacin (conditional recommendation, very low quality of evidence). Testing for phenotypic resistance to other drugs must be carried out by consensus between a physician expert in the treatment of people affected by TB and a microbiologist with experience in mycobacteria. The recommended methods are the modified proportions method in solid medium (Löwenstein–Jensen, 21 days) and the modified proportions method in liquid medium (Middlebrook, 7–14 days). The critical concentrations established by consensus for the different drugs with the Mycobacterial Growth Indicator Tube (MGIT) are isoniazid 0.1 μg/ml, rifampicin 0.5 μg/ml, amikacin 1–1.5 μg/ml, ethambutol 5 μg/ml, levofloxacin 1 μg/ml, moxifloxacin 0.25 μg/ml, clofazimine 1 μg/ml, bedaquiline 0.25 μg/ml, delamanid 0.06 μg/ml, and pretomanid < 2 μg/ml (conditional recommendation, low quality of evidence). Alternatively, the economical and standardised method of 96-well plate microdilution can be used.

PICO Question 8: Which drug combinations and treatment durations safely improve the outcomes of people affected by isoniazid-monoresistant tuberculosis and people affected by rifampicin-monoresistant tuberculosis?

1. *Recommendation on isoniazid monoresistance*

In people affected by rifampicin-susceptible pulmonary TB (and the anti-TB drugs recommended in this regimen) and confirmed isoniazid resistance, i.e., isoniazid monoresistance, treatment with rifampicin, ethambutol, pyrazinamide, and a fluoroquinolone for six months is recommended (conditional recommendation, low quality of evidence). The fluoroquinolones recommended by this study group are levofloxacin or moxifloxacin. The expert group considers that treatment based on rifampicin, pyrazinamide, and a fluoroquinolone, if susceptibility to rifampicin and fluoroquinolones is confirmed, could also obtain similar favourable results to treatment with ethambutol, thus limiting adverse events (conditional recommendation, low quality of evidence).

Several considerations should be taken into account when implementing this recommendation. If isoniazid-monoresistant TB is confirmed by genotypic or phenotypic testing prior to initiating treatment, starting with the regimen of rifampicin, ethambutol, pyrazinamide, and fluoroquinolone is advisable. We recommend having a phenotypic or genotypic susceptibility test for fluoroquinolones before initiating this regimen (strong recommendation, moderate quality of evidence). If isoniazid-monoresistant TB is confirmed after starting treatment with an isoniazid, rifampicin, pyrazinamide, and ethambutol-based regimen, and resistance to rifampicin and fluoroquinolones has been definitively ruled out, we recommend starting a regimen with rifampicin, ethambutol, pyrazinamide, and fluoroquinolone for six months or up to six months if the person has received at least four months of fluoroquinolones. If fluoroquinolones cannot be used, we recommend using a regimen based on rifampicin, pyrazinamide, and ethambutol for six to nine months (conditional recommendation, low quality of evidence).

2. *Recommendation on rifampicin monoresistance*

We recommend that people affected by rifampicin-monoresistant TB be managed like people affected by MDR-TB (see PICO question 9) (conditional recommendation, very low quality of evidence).

PICO Question 9: How many drugs, which drug combination and treatment duration safely (percentage of grade 3 or higher adverse effects) improve (treatment success rate) the final outcomes of people affected by MDR-TB?

We recommend that the management and follow-up of people affected by RR/MDR-TB be carried out by specialist TB units with experience in the management of people affected by DR-TB (conditional recommendation, very low quality of evidence).

In people over 14 years of age with pulmonary RR-TB, with no information on isoniazid resistance, or with pulmonary MDR-TB, with genotypic or phenotypic susceptibility to fluoroquinolones, we recommend treatment with bedaquiline, linezolid, pretomanid, and moxifloxacin (BPaLM) for six months (strong recommendation, high quality of evidence). We recommend replacing pretomanid with delamanid if the former is not available maintaining the same treatment duration (strong recommendation, moderate quality of evidence).

In people affected by extrapulmonary MDR-TB, the recommendation is to follow the same regimens as for pulmonary RR/MDR-TB (conditional recommendation, very low quality of evidence). In people affected by MDR-TB with bone or central nervous system (CNS) involvement, we recommend consulting with an experienced specialist TB Unit (conditional recommendation, very low quality of evidence). In general, people with disseminated, osteoarticular, or CNS TB may benefit from longer treatment (conditional recommendation, very low quality of evidence).

We recommend the use of the same shortened treatment regimens in pregnant women with RR/MDR-TB (conditional recommendation, very low quality of evidence). There is little information on the use of pretomanid in pregnant women and people younger than 14 years. However, delamanid has safety and efficacy data in these populations, so we recommend prioritising its use (conditional recommendation, very low quality of evidence).

If the proposed regimens cannot be used, treatment should be personalised according to allergies, interactions, safety profile, type of TB, and DST, using, if possible, an effective and safe oral drug combination for 9–12 months (conditional recommendation, very low quality of evidence). In the case of injectable drugs, we recommend that their use should be as short as possible, preferably less than eight weeks, with a total treatment duration of between 9 and 12 months, which can be reduced to six months if a combination containing bedaquiline is used together with the injectable drug (conditional recommendation, low quality of evidence).

In people affected by RR/MDR-TB living with HIV, we recommend applying the same regimens and durations as in people affected by RR/MDR-TB without HIV, as long as there are no additive interactions or adverse events, at least in people with CD4 $\geq$ 50 cells/μL (strong recommendation, moderate quality of evidence). Otherwise, the treatment regimen should be personalised (conditional recommendation, low quality of evidence). The recommendation is to start antiretroviral therapy within the first two weeks after initiating anti-TB therapy, especially in those with CD4 < 50 cells/μL (strong recommendation, high quality of evidence). In the case of tuberculous meningitis, delaying the initiation of antiretroviral therapy at least four weeks after the start of anti-TB treatment is recommended due to the risk of complications associated with immune reconstitution syndrome, choosing the optimal time depending on the patient's clinical situation (conditional recommendation, moderate quality of evidence).

PICO Question 10: How many drugs, which drug combination and treatment duration safely improve the final result for people affected by preXDR-TB or XDR-TB?

We recommend that the management and follow-up of people affected by preXDR/XDR-TB be carried out by specialist TB Units with experience in the management of people affected by DR-TB (conditional recommendation, very low quality of evidence).

In people over 14 years of age with pulmonary preXDR-TB, we recommend oral treatment with a three-drug regimen consisting of bedaquiline, linezolid, and pretomanid for six months (strong recommendation, high quality of evidence). If there are contraindications or non-availability of pretomanid, the recommendations are: (1) replace pretomanid with delamanid (fairly similar activity) and continue with a three-drug regimen (strong recommendation, moderate quality of evidence); (2) use a four-drug regimen (bedaquiline, linezolid, delamanid, and clofazimine) (strong recommendation, moderate quality of evidence). The duration of treatment is not modified if it is decided to supplement treatment with clofazimine and replace pretomanid with delamanid, or simply substitute pretomanid with delamanid (strong recommendation, moderate quality of evidence). We recommend extending treatment with the same regimen beyond six months if sputum culture at 16 weeks is still positive (conditional recommendation, low quality of evidence).

In adults with pulmonary preXDR/XDR-TB who are not candidates for treatment with the above regimens (due to drug intolerance, drug interactions, safety profile of the regimen, susceptibility study, or amplification of resistance during treatment), we recommend personalising treatment with drugs with expected or documented activity in the susceptibility study. We recommend at least four to five drugs, prioritising oral treatment regimens over injectable drugs (conditional recommendation, low quality of evidence). If an all-oral treatment regimen can be constituted, these four-five selected drugs should include as many drugs as possible with potent sterilising activity, such as bedaquiline, delamanid/pretomanid, linezolid, or clofazimine, and should be maintained throughout the course of treatment. The recommended treatment duration in these cases is between 9 and 20 months. Durations nearing nine months generally have comparable success rates and lower rates of adverse events compared with durations nearing 20 months (conditional recommendation, low quality of evidence). If the treatment regimen includes an injectable drug and bedaquiline, the duration of the injectable drug may be limited to eight weeks. If the treatment regimen includes an injectable drug but bedaquiline cannot be used, the recommendation is to maintain the injectable treatment for as short a time as possible. The duration of the injectable drug may be guided by the negativisation of sputum cultures and the appearance of adverse events and normally does not exceed three months. Once the injectable drug has been withdrawn, we recommend maintaining at least three to four oral drugs until the end of treatment (conditional recommendation, low quality of evidence).

In people affected by extrapulmonary preXDR/XDR-TB, the same regimens as for pulmonary preXDR/XDR-TB are recommended (conditional recommendation, very low quality of evidence). In people affected by preXDR/XDR-TB with bone or CNS involvement, we recommend consulting with an experienced specialist TB Unit (conditional recommendation, very low quality of evidence). In general, people with disseminated, osteoarticular, or CNS TB may benefit from longer treatment duration (conditional recommendation, very low quality of evidence).

We recommend the use of the same shortened treatment regimens in pregnant women with pre-XDR/XDR-TB (conditional recommendation, very low quality of evidence). There is little information on the use of pretomanid in pregnant women and people younger than 14 years. However, there are safety and efficacy data for delamanid in this population, so we recommend prioritising its use (conditional recommendation, very low quality of evidence).

In people affected by preXDR/XDR-TB living with HIV, we recommend applying the same regimens as in people affected by preXDR/XDR-TB without HIV, provided that there are no additive interactions or adverse events, at least in those with CD4 $\geq$ 50 cells/μL (strong recommendation, moderate quality of evidence). Otherwise, the treatment regimen should be personalised (strong recommendation, low quality of evidence). For the recommendation regarding when to initiate antiretroviral therapy see question 9.

Table 4
Monitoring proposal for people affected by RR/MDR-TB under treatment.

Procedures[a]	Baseline study	Months of treatment						
		1	2	3	4	5	6[b]	
Complete clinical evaluation	X	X	X	X	X	X	X	
Weight management	X	X	X	X	X	X	X	
Visual acuity and colour vision assessment[c]	X	X	X	X	X	X	X	
Evaluation of possible symptoms/signs of peripheral neuropathy[d]	X	X	X	X	X	X	X	
Hemogram	X	X	X	X			X	
Fasting blood glucose	X	X	X	X	X	X	X	
Creatinine and ionogram	X	X	X	X	X	X	X	
Liver function tests	X	X	X	X	X	X	X	
Thyroid hormones[e]	X		X		X		X	
HIV and viral hepatitis testing	X							
Pregnancy test (women of childbearing age)	X							
Chest X-ray	X			X			X	
Nucleic acid amplification test (MTBC identification and genotypic resistance study)	X							
Sputum smear[f]	X	X	X	X	X	X	X	
Sputum culture	X	X	X	X	X	X	X	
Drug susceptibility testing[g]	X							
Electrocardiogram[h]	X	X	X	X	X	X	X	X

MTBC; *Mycobacterium tuberculosis* complex; HIV: human immunodeficiency virus.

[a] In people affected by extrapulmonary TB, microbiological follow-up should be determined according to clinical criteria. The frequency of all procedures can be customised according to medical criteria.

[b] For treatments longer than six months, we recommend monthly evaluations starting at the sixth month.

[c] Special attention should be paid to people treated with ethambutol or linezolid.

[d] Special care in people treated with linezolid.

[e] Only if treated with ethionamide or prothionamide.

[f] We recommend a smear test every 1–2 weeks until negativisation to guide isolation indications. Subsequently, we recommend monthly check-ups.

[g] In case of persistence of a positive smear test two months after the start of treatment, consider repeating the drug susceptibility test. In case of sustained positivity of the culture, after its negativisation, consider repeating the drug susceptibility test.

[h] An ECG should be performed 15 days after starting treatment in people with drugs that prolong QT (bedaquiline, fluoroquinolones, delamanid/pretomanid, clofazimine), then we recommend ECG one month after the start of treatment, and monthly thereafter.

PICO Question 11. In what situations would surgical treatment be indicated in patients with DR-TB?

Adjuvant surgical therapy to improve prognosis is not recommended in people affected by pulmonary MDR/preXDR/XDR-TB (strong recommendation, low level of evidence). Surgery could be associated with the recommended pharmacological treatment to improve the cure and prognosis of people affected by DR-TB in situations where localised lesions are present and a persistent clinical, microbiological, and/or radiological lack of response is demonstrated, despite optimised treatment by a TB Unit with experience in the management of people affected by DR-TB (conditional recommendation, very low level of evidence).

PICO Question 12. How often and which complementary tests should be performed during clinical follow-up in people affected by DR-TB depending on the combination of treatment drugs?

Monitoring of the microbiological response to treatment with monthly smear tests and sputum culture is recommended in people affected by MDR-TB with lung involvement (conditional recommendation, very low quality of evidence). Sputum culture has a higher sensitivity than smear tests in detecting failure or relapse (strong recommendation, moderate quality of evidence). Serial periodical chest X-ray studies are recommended, or earlier if there is evidence of clinical worsening (conditional recommendation, very low quality of evidence).

Clinical monitoring and monthly follow-up with blood counts and renal and hepatic biochemistry are recommended (conditional recommendation, low quality of evidence). An electrocardiogram with corrected QT measurement at baseline is recommended 15 days after the start of treatment and monthly thereafter in those receiving drugs with the potential to prolong QT, i.e., bedaquiline, fluoroquinolones, delamanid/pretomanid, and clofazimine (conditional recommendation, low quality of evidence). Frequent ophthalmologic monitoring is recommended for people receiving treatment with ethambutol and/or linezolid (conditional recommendation, low quality of evidence). A psychiatric assessment prior to cycloserine administration is recommended, as well as monitoring for the appearance of psychiatric symptoms during follow-up (conditional recommendation, low quality of evidence). Thyroid profile monitoring is recommended in people being treated with ethionamide/prothionamide and/or PAS (conditional recommendation, low quality of evidence). Routine testing of therapeutic levels of the drugs for DR-TB treatment is not recommended; however, they may be useful in specific cases to monitor therapeutic ranges and limit the appearance of toxicity, particularly with amikacin and linezolid (conditional recommendation, low quality of evidence). The recommendation is to educate people on DR-TB treatment so that they can identify adverse events early and contact their medical team quickly (conditional recommendation, low quality of evidence).

Monitoring of people affected by DR-TB is recommended according to Table 4 (conditional recommendation, low quality of evidence).

PICO Question 13. Does face-to-face follow-up, compared to telematics, improve final outcomes and reduce adverse events in people affected by DR-TB?

Individualising the type of follow-up according to the possibilities of the healthcare centre, as well as the preferences and risk factors of the person affected by TB is recommended (conditional recommendation, very low quality of evidence). We recommend

directly observed therapy (DOT) in people affected by DR-TB (conditional recommendation, very low quality of evidence). The panel considers that telematic follow-up, using video-observed treatment (VOT), results in adherence and cure outcomes similar to DOT in people affected by TB (conditional recommendation, moderate quality of evidence).

PICO Question 14. Should contacts of people affected by RR/MDR/preXDR/XDR-TB be offered treatment for latent tuberculosis infection? Which drug or combinations of drugs safely reduce the development of active TB in high-risk contacts of people affected by RR/MDR/preXDR/XDR-TB?

In people who have had contact with a person with RR/MDR-TB and are at risk of progression to active TB, we recommend the administration of an effective and safe strategy to reduce the risk of progression to RR/MDR-TB, such as a fluoroquinolone (levofloxacin or moxifloxacin) for six months if the index case is affected by TB that is susceptible to fluoroquinolones (conditional recommendation, low quality of evidence). If the index case is affected by TB that is resistant to fluoroquinolones, treatment with delamanid during six months could be preferentially considered, alternatively, treatment with linezolid could be implemented (conditional recommendation, very low quality of evidence). Another alternative would be to design a personalised treatment based on the DST of the index case (conditional recommendation, very low quality of evidence).

If treatment is not administered to people at risk of progression, we recommend regular close monitoring for at least two years to detect early TB (conditional recommendation, very low quality of evidence).

Conclusions

The CPG on DR-TB management is the joint effort of professionals with extensive experience in TB management. These guidelines present the recommendations agreed upon by SEIMC and SEPAR. The content of this guideline was drawn up by and correspond to both scientific societies. This guideline updates the 2017 and 2020 SEPAR guidelines. The purpose of these recommendations is to share knowledge with all professionals and facilitate the correct management of this disease. Due to the constant evolution of DR-TB treatment, the current guidelines will be reviewed periodically, particularly when relevant and clinically interesting developments arise.

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Conflict of interest

None.

Artificial intelligence involvement

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Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.eimc.2024.08.001.