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New therapeutic approach for multidrug resistant pulmonary tuberculosis

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Abstract

English:

Tuberculosis (TB) is an infectious and contagious disease caused by Mycobacterium tuberculosis, and it mainly affects the lungs. As Romania has consistently ranked first in the European Union (EU) in terms of the incidence and prevalence of TB in the past years, this paper aims to bring to the attention of physicians the new therapeutic regimens and ways to approach patients with multidrug resistant TB and extended resistance.

Keywords

drug resistant tuberculosis • new therapeutic regimen

Noi abordări terapeutice în tuberculoza pulmonară multidrogrezistentă

Rezumat

Romanian:

Tuberculoza este o boală infectocontagioasă dată de Mycobacterium tuberculosis, care afectează în general plamanii și se transmite pe cale aeriană de la o persoană la alta. Deoarece Romania se menține pe prima poziție ca număr de cazuri în Uniunea Europeană, lucrarea de față își propune să aducă în atenția medicilor noile scheme terapeutice și modalitați de abordare a pacienților cu Tuberculoză multidrog rezistentă și extins rezistentă.

Cuvinte-cheie

tuberculoza rezistentă • noi regimuri terapeutice

Introduction

Tuberculosis (TB) is an infectious and contagious disease caused by *Mycobacterium tuberculosis*, and it mainly affects the lungs, but may affect other organs and parts of the body. In 90% of cases the disease is transmitted by the airborne route from one human to another (1).

Despite the remarkable progress recorded in the diagnosis and treatment of TB, over the past century, 49,752 cases of TB were reported in the European Union and the Economic Area European Union (EU/EEA) in 2019.

The TB endemic in Romania has had a declining trend since 2002. However, the country has consistently ranked first in the European Union (EU) in terms of the incidence and prevalence of TB. In 2019, a total of 11,070 new cases and recurrences of drug-sensitive TB were reported, at an equivalent incidence rate of 57.1%. Regarding resistant TB, there were 310 cases of multidrug resistant tuberculosis (MDR-TB) and 38 cases of extensively drug-resistant tuberculosis (XDR-TB). In 2020, the values were significantly lower than in previous years, with a total of new cases and recurrences at 7193 and an incidence rate of 37.3% for drug-sensitive TB and 209 new cases of MDR, respectively, at 17 XRD. The epidemiological indices for 2020 may not be in

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line with the reality in the field, given the profound alteration in healthcare activity in the first year of the COVID-19 pandemic.
In order to correctly frame patients and establish treatment regimens, a classification of *M. tuberculosis* is used according to the pattern of antibiotic susceptibility and resistance, resulting in the following definitions of resistance:
MDR-TB is tuberculosis caused by a strain of *M. tuberculosis* with (at least) resistance to isoniazid (INH) and rifampicin (RMP). Pre-extensively drug-resistant tuberculosis (TB-preXDR) refers to the disease caused by a strain of *M. tuberculosis* with resistance to isoniazid (INH), RMP and also resistant to fluoroquinolones (Q) or to second-line injectable antibiotics [kanamycin (Km), capreomycin (Cm), amikacin (Ak)], but never to both classes of antibiotics.
Extensively drug-resistant tuberculosis (TB XDR) refers to the disease caused by a strain of *M. tuberculosis* with INH, RMP and concomitant resistance to fluoroquinolones as well as second line injectable antibiotics (2,3).
In Romania, MDR-TB cases are also classified by their therapeutic history:
New case – a patient who did not receive TB treatment in combination (INH+RMP+other) for more than 1 month before the current episode.
Case of MDR-TB previously treated only with first-line drugs: the patient who received TB treatment for more than 1 month prior to the current episode, but only with first-line tuberculosis drugs.

Case of MDR-TB previously treated with second-line drugs

Patient who has previously received TB treatment for more than 1 month with line IIa drugs, whether with or without line I drugs (4).
TB MDR and XDR can be identified by direct antimicrobial susceptibility testing (DST) using solid growth media, Lowenstein Jensen (LJ) or liquid growth media techniques, such as BACTEC MGIT 960. The resistance is assessed in two steps: first-line DST for resistance to RMP and INH and a second-line DST for resistance to the following anti-tuberculosis drugs: streptomycin, ethambutol, kanamycin, amikacin, capreomycin, ofloxacin and ethionamide.
Diagnosing of MDR and XDR TB using solid growth media takes approximately 7–10 weeks for first-line drugs resistance testing (INH, RMP with the method of absolute concentrations in LJ medium) and another 4–6 weeks for second-line drugs resistance testing (with the method of proportions in the medium LJ), in addition to the 3 weeks necessary for the primary culture. If methods based on liquid growth media are used, the time is reduced to 10–14 d for line I ABG (if the culture is obtained in liquid media, from specimens with positive microscopy), to which is added 7–14 d for second-line DST in the same MGIT system.
In Romania, when a patient is diagnosed with TB, the treatment is initiated by pulmonologists. The duration and patterns of treatment depend on the type, classification and diagnosis. Most patients in Romania have drug-sensitive TB that is treated with the standard regimens.
The treatment and management of patients with MDR-TB involves a much longer treatment period than in the case of drug-sensitive TB, of at least 2 years (18 months after conversion to culture), with second-line drugs. The MDR-TB treatment system is based on the National MDR TB Management Guide (GNMT), developed in 2005, which no longer reflects recent recommendations in the WHO guidelines. The guide is being updated to reflect new recommendations, including diagnostic algorithms, side effects management and patient registration, but has not yet been approved by the Ministry of Health (1).
A Van Deun et al., in a study published in 2018 on the principles of establishing an MDR-TB regimen, believe that anti-TB drugs should be grouped according to microbiological activity (Table 1) (5). Thus, in some of the drugs the bactericidal activity predominates, in others the bacteriostatic one, and some may have both bactericidal and bacteriostatic activity.
On 16–20 July 2018, the WHO convened a group to analyse the latest published data on the treatment of resistant TB using the international GRADE system (Grading of Recommendations, Assessment, Development and Evaluation). At the end of this meeting the treatment principles were developed for long regimen and short regimen for the treatment of patients with resistance.
The principles of treatment for the long regimen are as follows:

- Ahead of enrolment on MDR-TB treatment, all patients should receive appropriate counselling to enable informed and participatory decision-making.
- Patient information material needs to reflect the new changes so that patients are appropriately informed about their treatment options.
- Social support to enable adherence to treatment is very important to ensure a patient-centred approach to the delivery of care.
- Active TB drug safety monitoring and management (aDSM) is essential for all patients enrolled on MDR-TB treatment.

The treatment of MDR-TB patients can be standardised or individualised and has been designed to include all five drugs considered to be active. The drugs were grouped into three categories (last classification had five groups – Table 2) based on the latest evidence of efficacy and safety).

- Group A: priority drugs: moxifloxacin/levofloxacin, bedaquiline and linezolid.
- Group B: medicines to be added: clofazimine, cycloserine/terizidone.

Table 1. Activity of anti-tuberculosis drugs and their use (5).

	Characteristics*				MDR/XDR	TB treatment	Regimen
	Bactericidal activity	**Sterilising activity**	**Resistance prevention**	**Use in a Core drug†**	**Companion drug used for its high bactericidal effect‡**	**Companion drug used for its sterilising effect**	**Other companion drugs**
RMP§	High	High	High				
FQ (GFX/MFX high-dose)¶	High	High	High	X			
BDQ	High	High	High	X			
DLM	High	High?	High	?	X		
Second-line injectables#	High	Low	High		X		
LZD	High	Low	High		X		
Imipenem/meropenemþ amoxicillin-clavulanate	High	?	High		X		
CFZ**	Low	High	High			X	
PZA††	Low	High	Low			X	
ETH/PTH‡‡	Moderate/high	Low	Moderate				X
INH high-dose	Low/moderate§§	Low	High				X
EMB	Low	Low	Moderate				X
CS	Moderate	Low ?	Moderate				X
PAS	Low	Low	Moderate				?

BDQ, bedaquiline; CS, cycloserine; CFZ, clofazimine; DLM, delamanid; EMB, ethambutol; ETH, ethionamide; FQ, fluoroquinolone; GFX, gatifloxacin; INH, isoniazid; LVX, levofloxacin; LZD, linezolid; MFX, moxifloxacin; MDR-TB, multidrug-resistant tuberculosis; PAS, para-aminosalicylic acid; PTH, prothionamide; PZA, pyrazinamide; RMP, rifampicin; XDR-TB, extensively drug-resistant.

*Also depends on susceptibility. In patients with MDR-TB, INH and RMP resistance assumed to be present.

†Core drug: bactericidal and sterilising, administered throughout treatment.

‡High early bactericidal activity to rapidly kill existing core drug-resistant mutants and rapidly reduce the bacillary load, to prevent the selection of resistant mutants during bacillary replication. The bactericidal activity of the 'other companion drugs' is less significant.

§The drug with the highest sterilising action; used in RMP-susceptible TB.

¶Among FQs, LVX and ofloxacin are less effective than later generation drugs, which include high-dose GFX (800 mg if 50 kg body weight), high-dose MFX (800 mg if 750 kg) and very high-dose LVX (1500 mg for 55–64 kg, 1750 mg for 765 kg).¶¶

#Early bactericidal effect, but the effect is of short duration (4). Important as companion drug during the early phase of the treatment, especially to prevent FQ resistance and treatment failure. Moreover, as the cumulative dose is associated with severe adverse drug reactions such as hearing loss, it is prescribed only during the intensive phase.

¨A powerful sterilising drug. Used throughout treatment, it likely contributes substantially to the success of the shorter treatment regimen.

††Has important sterilising activity.

‡‡Included for their bactericidal effect, which is probably not very high, but higher than that of CS or PAS. Also, ETH and PTH are less toxic.

§§A high dose (15 mg/kg)¶¶ will still have a variable (low to moderate and some still high) effect on most INH-resistant bacilli, depending on the resistance level. For INH-susceptible TB, the bactericidal activity of normal dose INH is high and its sterilising activity moderate.

¶¶Dosages only for FQs and isoniazid. Dosages are not shown for drugs administered at normal dosage. The recommendations for the normal standard dosages are published in regularly updated WHO guidelines.

- Group C: medicines to supplement (when some of the first two groups cannot be used): ethambutol, delamanid, pyrazinamide, imipenem/cilastatin, meropenem, amikacin (streptomycin), ethionamide (protionamide) PAS.

Kanamycin and capreomycin are no longer recommended, as they may increase the risk of recurrence and abandonment. Levofloxacin or moxifloxacin should be included in the treatment of MDR/RR-TB patients on longer regimens. Bedaquiline should be included in longer MDR-TB regimens for patients aged 18 years or more. Bedaquiline may also be included in longer MDR-TB regimens for patients aged 6–17 years. Linezolid should be included in the treatment of MDR/RR-TB patients on longer regimens. Clofazimine and cycloserine or terizidone may be included in the treatment of MDR/RR-TB patients on longer regimens. Delamanid may be included in the treatment of MDR/RR-TB patients aged 3 years or more on longer regimens.

A treatment regimen should include all group A medicines (BdqLfx/MfxLzd), plus group B medicines (CfzCs/Trd). Where one or more drugs are not available they will be replaced with group C drugs.

Table 2. Grouping of medicines recommended for use in longer MDR-TB regimens (5).

Group	Medicine	Abbreviation
Group A Include all three medicines (unless they cannot be used)	Levofloxacin or Moxifloxacin Bedaquiline Linezolid	Lfx/Mfx Bdq Lzd
Group B Add both medicines (unless they cannot be used)	Clofazimine Cycloserine or Terizidone	Cfz Cs/Trd
Group C Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol Delamanid3,4 Pyrazinamide5 Imipenem-cilastatin OR Meropenem Amikacin (OR Streptomycin) Ethionamide OR Prothionamide *p*-aminosalicylic acid	E Dlm Z Ipm-Cln Mpm Ak (S) Eto Pto PAS

Longer regimen for MDR/RR-TB: 18 Bdq(6 m)-Lfx/Mfx-Lzd-Cfz (18-month treatment regimen composed of bedaquiline for the first 6 months and levofloxacin or moxifloxacin, linezolid, clofazimine for 18 months). All MDR/RR-TB patients may be treated with longer regimens; however, the longer regimen is preferably given to those MDR/RR-TB patients who are not eligible for shorter all-oral regimens, including those with quinolone resistance.

As Cfz is not marketed in our country, the WHO recommendation is that it be replaced with Del. Evidence on the safety and effectiveness of Bdq beyond 6 months was insufficient for review; extended Bdq use in individual patients will need to follow 'off-label' use best practices. Optimal duration of use of Lzd is not established. Use for at least 6 months was shown to be highly effective, although toxicity may limit its use. The position of Dlm will be re-assessed. Evidence on the safety and effectiveness of Dlm beyond 6 months was insufficient for review; extended use of Dlm in individual patients will need to follow 'off-label' use best practices. Evidence on concurrent use of Bdq and Dlm was insufficient for review. Z is only counted as an effective agent when DST results confirm susceptibility. Amoxicillin-Clavulanic acid is administered with every dose of Imp-Cln or Mpm but is not counted as a separate agent and should not be used as a separate agent (6).

In 2020, the WHO issued the latest recommendations on treatment regimens for resistant TB. Except for the long regimen presented above and which remains unchanged from the 2018 short communication, we present the latest recommendations on INH resistance and the short regimen for MDR-TB:

- Regimen for isoniazid-resistant TB: 6 (INH)REZ-Lfx [6-month treatment regimen composed of RMP, ethambutol, pyrazinamide, levofloxacin. Isoniazid can be added if 4-drug FDC (HREZ) will be used]. The Hr-TB regimen is recommended once isoniazid resistance has been confirmed and RMP resistance excluded. RMP resistance needs to be excluded using rapid molecular tests (e.g. Xpert MTB/RIF). It is not advisable to give a regimen for Hr-TB unless isoniazid resistance is confirmed or highly suspected.
- Shorter regimen for MDR/RR-TB: 4–6 Bdq(6 m)-Lfx/Mfx-Cfz-Z-E-Hh-Eto/5 Lfx/Mfx-Cfz-Z-E (shorter all-oral bedaquiline-containing regimen). When deciding whether the shorter all-oral bedaquiline-containing MDR-TB regimen can be offered, several eligibility criteria need to be considered. The regimen may be offered to patients with confirmed the shorter all-oral bedaquiline-containing regimen for MDR/RR-TB 15 MDR/RR-TB (with at least confirmed resistance to RMP), for whom resistance to fluoroquinolones has been ruled out, in the following situations:
  - no resistance or suspected ineffectiveness of a medicine in the shorter regimen (except isoniazid resistance);
  - no exposure to previous treatment with second-line medicines in the regimen for more than 1 month (unless susceptibility to these medicines is confirmed);
  - no extensive TB disease and no severe extra pulmonary TB;
  - not pregnant;
  - children 6 years old and above (6). The decision on which regimen offers the best option for cure in a patient may also depend on other considerations (e.g. preferences of patients and clinicians).

If the shorter all-oral bedaquiline-containing MDR-TB regimen cannot be used, the patient needs to be reassessed for a longer all-oral MDR-TB regimen. The healthcare provider may opt for a longer all-oral treatment regimen even in patients who are eligible for the shorter all-oral bedaquiline containing MDR-TB regimen. This could be motivated by uncertainty about drug

susceptibility while the patient's condition requires an immediate start of treatment and cannot wait for DST results (7).

Authors' contributions

All authors had a contribution in elaborating this article.

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