Classifying new anti-tuberculosis drugs: rationale and future perspectives

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S U M M A R Y

The classification of anti-tuberculosis (TB) drugs is important as it helps the clinician to build an appropriate anti-TB regimen for multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB cases that do not fulfil the criteria for the shorter MDR-TB regimen. The World Health Organization (WHO) has recently approved a revision of the classification of new anti-TB drugs based on current evidence on each drug. In the previous WHO guidelines, the choice of drugs was based on efficacy and toxicity in a step-down manner, from group 1 first-line drugs and groups 2–5 second-line drugs, to group 5 drugs with potentially limited efficacy or limited clinical evidence. In the revised WHO classification, exclusively aimed at managing drug-resistant cases, medicines are again listed in hierarchical order from group A to group D. In parallel, a possible future classification is independently proposed. The aim of this viewpoint article is to describe the evolution in WHO TB classification (taking into account an independently proposed new classification) and recent changes in WHO guidance, while commenting on the differences between them. The latest evidence on the ex-group 5 drugs is also discussed.

1. Introduction

The World Health Organization (WHO) has recently updated the classification of new anti-tuberculosis (TB) drugs based on a meta-analysis and expert panel recommendations.[1] During the period between the publication of the first WHO anti-TB drug classification and the revised version, an independent proposal for a new classification was made available in the literature.[2] Evidence for further reclassification is lacking and will only be forthcoming with data from new randomized controlled trials (RCTs) aimed at developing better (more effective and tolerated) regimens. However, even though a new classification is not required, discussion on possible future steps has begun,[2] with particular focus on some of the existing second-line anti-TB drugs.

The classification of anti-TB drugs is important as it helps the clinician to build an appropriate anti-TB regimen for multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB cases that do not fulfil the criteria for the shorter MDR-TB regimen.[3,4]

The aim of this viewpoint article is to describe the evolution in WHO TB classification (taking into account an independently proposed new classification) and recent changes in WHO guidance, while commenting on the differences between them. The latest evidence on the ex-group 5 drugs is also discussed.

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2. Classifications

In the previous WHO guidelines (2011), the choice of drugs was based on efficacy and toxicity in a step-down manner, from group 1 to group 5 (Table 1). Group 1 included first-line drugs and groups 2–5 included second-line drugs. Group 5 included the drugs with (at the time) potentially limited efficacy or limited clinical evidence.[3,4]

According to the new WHO drug classification (2016), patients with rifampicin-resistant or MDR-TB require a regimen with at least five effective TB medicines during the intensive phase: pyrazinamide and four core second-line TB drugs (see Table 1), one each from group A and group B, and at least two from group C. If the minimum number of effective TB medicines cannot be composed, an agent from group D2 and other agents from D3 should be added to bring the total to five. If pyrazinamide is compromised or cannot be used, the regimen can be reinforced with a drug from group C or D (preferably D2, and if not, from D3). Agents from group D1 are added if they are considered to add benefit (e.g., high-dose isoniazid in patients without high-level isoniazid resistance).[1] The total number of TB medicines included in the regimen needs to balance the expected benefit with the risk of harm and non-adherence.

Based on recent evidence on given compounds, some drugs are likely to increase or decrease in importance in the future.[2]

2.1. Group 1

In accordance with drug susceptibility testing (DST), all active group 1 drugs (Table 1) should be included in the regimen, taking into consideration that isoniazid, rifampicin/rifabutin, and pyrazinamide are core drugs and ethambutol is a companion drug. Streptomycin is no longer used routinely.

High-dose isoniazid can be added to an MDR/XDR-TB regimen when the *katG* mutation is not detected by line probe assay, but should not be counted as one of the four active drugs[1,3,4] (although recent evidence suggests the mutation confers intermediate resistance only). Pyrazinamide should always be used, as DST is unreliable; however, it should not be counted as one of the four active drugs.[1,3,4] Rifabutin should be considered if sensitivity is proven and a favourable mutation profile exists.[5] More specifically, if rifampicin resistance is detected with rifabutin susceptibility, rifabutin should be added to the regimen, but not counted as one of the four active drugs.[5]

As the new WHO classification is aimed at managing drug-resistant cases and not all cases, as in the previous classification, group 1 drugs lose priority. In the new WHO classification they belong, in fact, to group D1.

2.2. Group A

According to the new WHO classification,[1] group A now includes fluoroquinolones and group B includes injectable second-line drugs. Fluoroquinolones (particularly the later generation fluoroquinolones such as high-dose levofloxacin, gatifloxacin, or moxifloxacin) are core drugs, demonstrating bactericidal and sterilizing activity and a good safety profile;[2,3,6,7] their use predicts a favourable outcome in the treatment of MDR-TB.[7–11] They are the best agents for the treatment of MDR-TB.

2.3. Group B

The second-line injectable drugs have only bactericidal and no sterilizing activity. As their safety profile is clearly worse than that of fluoroquinolones, they remain a step below them on the ranking.[2,4,6]

Table 1
Summary of the existing classifications of anti-tuberculosis drugs (1 and 2) and possible future changes based on recent evidence (3)

(1) WHO 2011 TB drugs classification		(2) WHO 2016 TB drugs classification		(3) Possible future evolutions	
Group 1 First-line oral anti-TB drugs	• Isoniazid • Rifampicin • Ethambutol • Pyrazinamide	*Group A* Fluoroquinolones	• Levofloxacin • Moxifloxacin • Gatifloxacin	*Group A* Fluoroquinolones	• Levofloxacin • Moxifloxacin • Gatifloxacin
Group 2 Injectable anti-TB drugs (injectable or parenteral agents)	• Streptomycin • Kanamycin • Amikacin • Capreomycin	*Group B* Second-line injectable agents	• Amikacin • Capreomycin • Kanamycin (Streptomycin)	*Group B* Other core second-line agents	• Bedaquiline • Delamanid • Ethionamide/ prothionamide • Cycloserine/ terizidone • Linezolid • Clofazimine
Group 3 Fluoroquinolones	• Levofloxacin • Moxifloxacin • Gatifloxacin • Ofloxacin	*Group C* Other core second-line agents	• Ethionamide/ prothionamide • Cycloserine/ terizidone • Linezolid • Clofazimine	*Group C* Second-line injectable agents	• Amikacin • Capreomycin • Kanamycin • Meropenem/ clavulanate
Group 4 Oral bacteriostatic second-line anti-TB drugs	• Ethionamide/ prothionamide • Cycloserine/terizidone • p-Aminosalicylic acid	*Group D* Add-on agents (not core MDR-TB regimen components)	D1 • Pyrazinamide • Ethambutol • High-dose isoniazid	*Group D* Add-on agents (not core MDR-TB regimen components)	• Pyrazinamide • Ethambutol • High-dose isoniazid • p-Aminosalicylic acid • Amoxicillin– clavulanate • Rifabutin
Group 5 Anti-TB drugs with limited data on efficacy and long-term safety in the treatment of drug-resistant TB	• Linezolid • Clofazimine • Amoxicillin/ clavulanate • Imipenem/cilastatin • Meropenem • High-dose isoniazid • Thioacetazone • Clarithromycin		D2 • Bedaquiline • Delamanid D3 • p-Aminosalicylic acid • Imipenem–cilastatin • Meropenem • Amoxicillin–clavulanate • (Thioacetazone)		

WHO, World Health Organization; MDR-TB, multidrug-resistant tuberculosis.

Furthermore, the second group in the drug hierarchy (group B) may in future include three core oral medicines, linezolid, bedaquiline, and delamanid (and eventually sutezolid, tedizolid, and pretomanid), if these drugs prove to be more effective and better tolerated than the injectables.[2] This has been proposed in a recent article as group 3 (similar to the current group B, because in this article group 1 is composed of first-line drugs).[2]

Moreover, having an oral group B could mean that it may soon be possible to have an injectable-free regimen to treat MDR-TB patients; this will mean potentially less toxicity, less monitoring, and fewer hospital stays and visits, and possibly better adherence.

2.4. Group C

Linezolid, clofazimine, ethionamide/prothionamide, and cycloserine/terizidone are included in group C. Linezolid is a core oral drug with bactericidal and sterilizing action;[2] there is ample evidence of its efficacy, including RCTs and meta-analyses.[12,13] The drug is generic and active, its documented toxicity being the primary barrier to continued use. However, this can be mitigated with lower doses and therapeutic drug monitoring.[13,14] Linezolid has the efficacy needed to be part of a future hypothetical all-oral group B. With effectiveness in mind, the second drug in this group could be ethionamide/prothionamide, which has moderate bactericidal activity but with an appreciable toxicity profile.[4] The third agent could be clofazimine, as this has possible sterilizing activity and good tolerance. The last one could be cycloserine, the worst of the four, with practically no bactericidal or sterilizing activity and with a poor toxicity profile.[2,4]

2.5. Group D

Group D1 includes pyrazinamide, ethambutol, and high-dose isoniazid. Group D2 includes bedaquiline and delamanid. These may have the efficacy needed to be part of a future hypothetical all-oral group B, given that evidence on their safety is growing, although it is still incomplete. Data regarding their safe combination and whole treatment duration over the recommended 6 months are gradually emerging.

Recent case reports show the safe and effective use of bedaquiline up to 18 months[15] and the concomitant use of both group D2 drugs.[16] Bedaquiline has all of the characteristics of a core drug, targeting both actively replicating and dormant bacilli.[17] RCTs provide some evidence on efficacy and safety,[18,19] while additional experience derived from observational studies and compassionate use programmes completes the current picture.[15,20–22] Concerns regarding the safety of bedaquiline arose from the unexplained higher number of deaths in the bedaquiline group in a licensing study.[18]

The most common adverse reaction associated with bedaquiline is a QTc interval increase on electrocardiogram.[18,19] An RCT with long-term follow-up to 120 weeks reported that bedaquiline was well tolerated and led to good outcomes.[20] The reporting of adverse events is crucial for recommendations on bedaquiline use;[23] therefore monitoring, active pharmacovigilance, and proper management of adverse reactions are foremost among the five criteria in place for the use of this agent. Finally, a possible issue is cross-resistance with clofazimine[24] (although recent evidence tends to suggest that this may not be clinically relevant) and the increased QT prolongation with clofazimine and bedaquiline combination (which appears to be a causative factor leading to increased QTc in previous bedaquiline studies).[25]

Delamanid can also be considered a core drug because of its bactericidal and sterilizing activity; it does not show cross-resistance with other anti-TB drugs.[26] Some RCTs and observational studies have addressed its efficacy,[26] and there are also some positive experiences from its compassionate use.[26] WHO recommendations on delamanid use[27] include the same five implementation criteria as in the case of bedaquiline.[23]

As mentioned above, a significant limitation of bedaquiline and delamanid use is that, so far, they can be utilized only for the first 6 months of treatment. When treating XDR-TB patients, these drugs are added to an optimized background regimen that often includes weak and poorly tolerated medications (from the limited options remaining), with severe side effects mandating interruption of either the whole treatment or of the offending compound. When this happens, the regimen becomes even weaker and, once bedaquiline or delamanid is completed after 6 months, the regimen is prone to fail.

The possibility of maintaining bedaquiline and/or delamanid for the entire duration of treatment will be an important step forward, as well as their use in patients with MDR-TB patterns of resistance beyond XDR-TB,[10] or the so-called pre-XDR-TB (e.g., TB sustained by strains resistant to either fluoroquinolones or second-line injectables).[2,15,16]

After the proposed reclassification of groups 2 and 3 to group B and group A, respectively, the injectable second-line drugs might have the characteristics of a future group C, as recently suggested (Table 1).[2]

Indeed, they remain core second-line drugs thanks to their bactericidal activity, but given their cumulative toxicity (4–8 months of treatment increases the likelihood of ototoxicity or nephrotoxicity) and the requirement for parenteral or intramuscular administration, they would rank lower than the previously described compounds.[2] Although experience is still limited, meropenem/clavulanate has demonstrated efficacy and is bactericidal. A recent phase 2 study[28] and observational studies[29] compel us to consider meropenem/clavulanate a core drug at the same level as the second-line aminoglycosides. Meropenem was found to be more active than imipenem in a recent study.[30]

Ertapenem has been used successfully as switch therapy for cases treated at the hospital with meropenem who needed to be discharged, as it can be administered once daily intramuscularly.[31]

If the efficacy and safety profile of certain drugs like linezolid, bedaquiline, and delamanid is confirmed, they might move up the anti-TB drug hierarchy, as recently suggested.[2] At present bedaquiline and delamanid are recommended in XDR-TB or MDR-TB cases only, when no other options are available or tolerated.[23,27]

Recognizing and promptly managing possible adverse events remains a priority, as recommended by the WHO,[23,27] for the new drugs as well as for the other second-line drugs (e.g., thionamides, cycloserine, and p-aminosalicylic acid, among others).

Among the factors contributing to the programmatic success of a given drug, the availability of the drug and of the laboratory tests to confirm susceptibility or resistance, as well as the cost-effectiveness profile, is highlighted.

Establishing a hierarchy of second-line anti-TB drugs is difficult, as we try to evaluate the effect of a single component within a multidrug regimen where there is a lot of background noise.

3. Conclusions

In conclusion, the WHO has recently provided an important and useful evidence-based new classification of anti-TB drugs, which is the present roadmap allowing clinicians to correctly design safer and more effective MDR- and XDR-TB treatment regimens. As more evidence becomes available, further changes are likely to occur, particularly with the new drugs and some of the previous group 5 drugs.

It is hoped that ongoing RCTs will soon provide the necessary information to further improve the clinical and programmatic approach to the management of MDR- and XDR-TB cases.

Acknowledgements

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