2317: Treatment for defined patients with RR-TB, MDR-TB, pre-XDR TB and XDR-TB including bedaquiline and delamanid: Consensus Methods Report

Contents

Background

Clinical Commissioning Policy Statement

NHS England has an existing, routinely commissioned, clinical commissioning policy statement for the treatment of defined patients with MDR and XDR TB which permits the sequential use of bedaquiline and delamanid in these patients. This policy was supported by an independent evidence review. However, since the publication of the existing policy in 2021, the World Health Organisation (WHO) have updated their MDR-TB guidelines (2022) which recognise that there is a subset of defined patients in whom bedaquiline and delamanid may be used concurrently when limited other treatment options are available, and if sufficient monitoring is in place.

A PPP was presented to Clinical Panel Gateway 1 in June 2022, which stated that there is no robust clinical trial evidence for this group of patients, which was also acknowledged by the WHO in their updated guidelines. Therefore, the proposition was put forward for a

modification to the existing routinely clinical commissioned policy based on clinical consensus, without a further independent evidence review. Prior to Clinical Panel Gateway 1 this was presented to the National Clinical Directors for Respiratory Medicine at NHS England, who agreed with this course of action and validated the value of this proposition.

The outcome of Clinical Panel in June 2023 was that this existing clinical commissioning policy statement covering the use of bedaquiline and delamanid should be updated via formal consensus methods and resubmitted to Clinical Panel Gateway 2.

Consensus Methods

The clinical commissioning policy statement for the treatment of defined patients with MDR-TB and XDR-TB has been updated in line with the NHS England 'Formal Consensus Methods' document. This is based on the modified nominal group technique (Bernstein et al., 1992) which is the most commonly used method for the development of consensus in health care (Murphy et al., 1998). This technique uses structured small group discussion to achieve consensus among participants. A Facilitator develops a set of statements relevant to the policy proposition and populates a consensus questionnaire template with the relevant statements. Group members are asked to individually rank their agreement with each statement, based on the available evidence and their own clinical experience. Following this, the Facilitator produces an anonymised summary of the percentage agreement for each statement and considers comments received from Group members. The percentage agreement for each statement is discussed at the subsequent Group meeting. Statements that have reach the consensus threshold are agreed and can be used to inform the drafting of eligibility criteria. Statements that do not have a consensus agreement are discussed and redrafted. The Group comments can be used to draft additional statements as appropriate. New statements, or those without consensus, are subsequently presented on the standard questionnaire template for each Group member to reconsider after the meeting. This process continues until consensus is reached for all statements.

Objectives

1. To consider the updated WHO guidelines on 'Drug Resistant tuberculosis treatment' 2022 (WHO, 2022) and WHO information notes on the use of bedaquiline in children and adolescents with drug-resistant tuberculosis 2023 (WHO, 2023).
2. To produce an updated set of eligibility criteria for the existing NHS England clinical commissioning policy statement for the treatment of defined patients with RR-TB, MDR-TB, pre-XDR-TB and XDR-TB[1] in line with NHS England Formal Consensus Methods.

Group Membership

The NHS England Formal Consensus Methods do not specify a minimum number of participants required for quoracy. Quoracy specific to this Group was defined as representative responses from the following categories:

- Clinician
- Pharmacist

[1] Note that the change in population to this Clinical Commissioning Policy Statement reflects the WHO 2022 updated definitions for patients with drug resistant TB, and the population for which NHS England is the responsible commissioner for bedaquiline and delamanid. This policy is for a defined subset of patients in whom a WHO recommended regimen cannot be constructed and who require an individualised treatment regimen.

- Lead Commissioner
- Public Health
- Patient public voice representative (PPV)

In this case, the Facilitator role was performed by the National Clinical Policy Lead. The individuals asked to form the Group were all members of the PWG. Further information on the PWG members is available in the PWG Appendix (standalone document).

Defining Consensus

In line with the NHS England Formal Consensus Methods, the following thresholds have been used to define consensus:

- **Statements with ≥80% agreement** can be used to inform the drafting of criteria taking into account each statement and comments from group members.
- **Statements with 60-80% agreement** a judgement should be made based on the nature of comments from the Group:
    - If comments indicate that there was agreement with the general principle covered by the statement and that the comments could be addressed with some minor amendments incorporating the comments, the statements can be used to inform the drafting of criteria.
    - If not, statements should be re-drafted by the Facilitator based on the comments from Group members and used to populate a subsequent consensus questionnaire.
- **Statements with <60% agreement** should generally be regarded as not having consensus agreement and discarded, unless there are obvious and addressable issues identified from the comments. If so, these can be re-drafted by the Facilitator.

Summary of Voting Rounds

The initial statements circulated by the Facilitator were based on the existing eligibility criteria in the NHS England clinical commissioning policy statement for the treatment of defined patients with MDR and XDR TB. These had been modified to include the concurrent use of bedaquiline and delamanid based on the updated WHO guidelines on ‘Drug Resistant tuberculosis treatment’ 2022 and subsequent WHO information notes on the use of bedaquiline in children and adolescents with drug-resistant tuberculosis 2023 (WHO, 2023) and delamanid in children and adolescents with drug-resistant tuberculosis 2023 (WHO, 2023).

Round 1

In accordance with the Formal Consensus Methods, the initial set of statements (below) was drafted by the Facilitator. These statements were based on the eligibility criteria in the existing clinical commissioning policy statement but had been modified by the Facilitator to reflect the update WHO (2022) guidelines. These statements were distributed to group members via email. Individual responses were received and collated by the Facilitator ahead of a Teams meeting with the PWG. All statements were discussed, including the collated scores for each statement.

Fourteen statements were circulated in Round 1. Consensus (>80%) was reached for 7 of these statements. Eight statements were subsequently redrafted (including one statement

where consensus was reached, due to clarification required around the wording of this statement.)

It was noted during the course of the meeting that additional 'Stopping Criteria' and 'Monitoring Criteria' in the existing policy statement had not been copied across for inclusion. These were subsequently considered in Round 2 of the consensus methods.

The full details of Round 1 Consensus Statements are located in Annex A Table 1.

Round 2

Based on the consensus reached in Round 1, the below statements were circulated to the Group by the Facilitator.

Twenty one statements were circulated in Round 2. Consensus (>80%) was reached for 19 of these statements. Two remaining statements had a percentage agreement of 75%. However, following group discussion consensus was reached on these statements without the need for redrafting.

The full details of Round 2 Consensus Statements are located in Annex A Table 2.

Further amendments following consensus

Following the use of consensus methods to determine the eligibility criteria, the above statements were incorporated into the updated NHS England Clinical Commissioning Policy Statement, which was circulated to the PWG for comments on the background text and sign off. It was subsequently noted as part of discussions that national MDR-TB MDT should be renamed as 'UK MDR-TB Clinical Advice Service (CAS)' in line with current nomenclature. This amendment was made across all documents after the consensus rounds. All changes made to the Clinical Commissioning Policy Statement outside of the eligibility criteria are summarised in Change Form, which has been submitted to Clinical Panel.

Conclusion

In conclusion, the updated eligibility criteria for the NHS England Clinical Commissioning Policy Statement 'Treatment for defined patients with RR-TB, MDR-TB and XDR-TB including bedaquiline and delamanid' was reached via formal consensus methods, as outlined in the NHS England Formal Consensus Methods document. All additional changes to the text in this document outside of the eligibility criteria are summarised in the Change Form.

Prior to presentation at Clinical Panel, the updated clinical commissioning policy statement has been reviewed and approved by the Respiratory NCD and the Director of the National Clinical Policy Team.

References

1. World Health Organization, WHO consolidated guidelines on tuberculosis Module 4: Treatment - drug-resistant tuberculosis treatment, 2022 update. Available at: https://www.who.int/publications-detail-redirect/9789240063129 (Accessed: 7 November 2023)

2. Bernstein SJ, Laouri M, Hilborne LH, Leape LL, Kahan JP, Park R, et al. Coronary angiography: a literature review and ratings of appropriateness and necessity. Santa Monica, USA: RAND; 1992.

3. Murphy MK, Black NA, Lamping D, McKee C, Sanderson C, Askham J, et al. Consensus development methods, and their use in clinical guideline development. Health Technology Assessment. 1998;2

4. World Health Organization, WHO use of bedaquiline in children and adolescents with multidrug and rifampicin resistant tuberculosis—information note. 2023 updated. Available at: Use of bedaquiline in children and adolescents with multidrug- and rifampicin-resistant tuberculosis: information note (who.int) (Accessed: 9 November 2023)

5. World Health Organization, WHO use of delamanid in children and adolescents with multidrug and rifampicin resistant tuberculosis—information note. 2023 updated. Available at: https://www.who.int/publications-detail-redirect/9789240074309 (Accessed: 9 November 2023)

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Date: 09/11/23

Annex A: Consensus Tables

Annex A

Table 1: Round 1 Consensus Statements

Statement	Percentage Agreement	Outcome
Inclusion Criteria		
Bedaquiline should only be used in those aged 5 years and over and 15kg or more; delamanid, for those aged 3 years and/or 30kg or more.	67%	Redraft
Laboratory confirmed RR-TB/MDR/XDR-TB with resistance to fluoroquinolones or the injectable drugs (kanamycin, amikacin, capreomycin).	100%	Consensus reached but redrafted due to comments on wording
Where microbiological evidence is lacking but compelling circumstantial evidence indicates very likely RR-TB/MDR/XDR-TB aetiology (e.g. sputum smear negative active disease in a close contact of a patient with laboratory confirmed RR/MDR/XDR-TB). These will be discussed on a case-by-case basis and in conjunction with the appropriate specialist MDR-TB centre and approved by the ICB Public Health Lead.	60%	Redraft
Inability to construct a WHO recommended MDR-TB regimen EITHER through phenotypic or genomic defined resistance pattern OR because of intolerance/ drug interactions (functional RR-TB, functional MDR-TB or functional XDR-TB).	100%	Consensus reached
Exclusion Criteria		
There are currently no exclusion criteria in this policy. No exclusion criteria are required.	100%	Consensus reached
Starting Criteria		
The case must be discussed, and treatment agreed with the MDT of the MDR- TB treatment centre or the regional MDT in conjunction with an MDR-TB treatment centre; paediatric cases must also be discussed, and treatment agreed by the Paediatric Infectious Diseases Centre.	60%	Redraft
The patient must be managed under directly observed therapy (DOT) or video observed therapy (VOT).	80%	Consensus reached but redrafted based on comments
Bedaquiline and/or delamanid should be used as part of combination therapy in line with WHO-recommended MDR-TB treatment regimens taking into consideration: • in vitro resistance to a drug OR • known adverse drug reactions, poor tolerance OR	100%	Consensus reached

• contraindication to any component of the combination regimen		
The WHO-recommended MDR-TB treatment regimen is as described in the latest WHO treatment guidelines for drug-resistant tuberculosis (currently 2022) – see section on 'Dosing'	100%	Consensus reached
Stopping Criteria		
There are no stopping criteria within this policy. No stopping criteria are required.	40%	Redraft with additional stopping criteria
Monitoring Criteria		
There are no monitoring requirements within this policy currently. No monitoring is required.	0%	Redraft with additional monitoring requirements
Dosing Criteria		
The recommended dosing for adults (aged 18 years or older): • Bedaquiline: 400mg daily for 14 days, followed by 200mg three times per week • Delamanid: 100mg twice daily Source: www.tbdrugmonographs.co.uk	100%	Consensus reached
Recommended dosing for bedaquiline in children (aged 5 years and older) by weight. Taken from The Sentinel Project, 2022: • 1-15kg: Consult with a Specialist • 16-23.99kg: 200mg daily for 14 days, followed by 100mg three times per week • 24-29.99kg: 200mg daily for 14 days, followed by 100mg three times per week • >30kg: 400mg daily for 14 days, followed by 200mg three times per week	50%	Redraft
Recommended dosing for delamanid in children (aged 3 years and older and/or 30kg or more) by weight. Taken from The Sentinel Project, 2022: • 30-49.99kg: 50mg twice daily • 50kg or above: 100mg twice daily	75%	Redraft based on comments

Table 2: Round 2 Consensus Statements

Statement	Percentage Agreement	Outcome
Inclusion Criteria		
Laboratory confirmed RR-TB/MDR/pre-XDR/XDR-TB	100%	Consensus reached
Where microbiological evidence is lacking but compelling circumstantial evidence indicates very likely RR-TB/MD-TB/pre-XDR/XDR-TB aetiology (e.g., sputum smear negative active disease in a close contact of a patient with laboratory confirmed RR-TB/MDR-TB/pre-XDR TB/XDR-TB). These will be discussed on a case-by-case basis at the national BTS MDR-TB forum and in conjunction with the appropriate specialist MDR-TB centre.	100%	Consensus reached
Inability to construct a WHO recommended MDR-TB regimen EITHER through phenotypic or genomic defined resistance pattern OR because of intolerance/ drug interactions (functional RR-TB, functional MDR-TB, functional pre-XDR TB or functional XDR-TB).	100%	Consensus reached
Starting Criteria		
The case must be discussed, and treatment agreed at the national BTS MDR-TB MDT and in conjunction with the appropriate specialist MDR-TB centre.	100%	Consensus reached
The patient must be managed effectively with close supervision and follow up, and where appropriate offered directly observed therapy (DOT) or video observed therapy (VOT).	100%	Consensus reached
Stopping Criteria		
A patient is cured (as defined in the treatment guidance, WHO 2022).	100%	Consensus reached
Maximum duration of treatment of up to 24 months is reached.	75%	Consensus subsequently reached following discussion that this was limit specified in the original policy statement based on clinical evidence
Unacceptable toxicity or side effects cause by bedaquiline or delamanid occur.	100%	Consensus reached
Significant QT interval prolongation ≥500ms or the development of a significant arrhythmia.	100%	Consensus reached
Patients are non-compliant with supervision of treatment.	75%	Consensus reached following discussion

		with minor amends to wording
Monitoring Criteria		
An obligatory framework must be in place for monitoring QT interval prolongation or development of arrhythmia with pre-treatment ECG to determine baseline QT interval and monitoring at two weeks then monthly throughout treatment; repeat if symptomatic or after the addition of any new medication known to prolong QT (TB Drug Monographs, 2023).	100%	Consensus reached
Caution is required if concurrent administration of drugs recognised to prolong cardiac QT interval (e.g. clofazimine, moxifloxacin, neuroleptics, and some anti-emetics); if this is unavoidable monitor ECG after the introduction of the drug and monthly thereafter for the duration of treatment.	100%	Consensus reached
The baseline and ongoing monitoring recommendations of the TB drug monograph, (http://www.tbdrugmonographs.co.uk) must be followed.	100%	Consensus reached
Concurrent administration of bedaquiline with CYP3A4 inducers (such as the rifamycins) is contraindicated in view of its metabolism via this route.	100%	Consensus reached with minor amends to wording
Bedaquiline should be used with caution when given together with drugs that inhibit liver enzyme function (e.g. ketoconazole or lopinavir/ritonavir effect on CYP3A4) as this could increase bedaquiline concentration and toxicity.	100%	Consensus reached
Do not administer delamanid if serum albumin is <2.8g/dL.	100%	Consensus reached
Increase ECG monitoring frequency for the full delamanid treatment period in patients who start delamanid with serum albumin 2.8g/dl to 3.4 g/dl or fall into this range.	100%	Consensus reached
Concurrent administration of strong CYP3A inducers (e.g. carbamazepine) is contraindicated in view of delamanid's metabolism via this route.	100%	Consensus reached with minor amends to wording
Caution is required in patients with known cardiac risk factors for QT interval prolongation (e.g. known congenital QTc-interval prolongation or any condition known to prolong QTc interval or QTc > 500 ms; history of symptomatic cardiac arrhythmias or clinically relevant bradycardia; any predisposing cardiac conditions for arrhythmia; electrolyte disturbances; medicinal products known to prolong QTc interval).	100%	Consensus reached

<table>
<tr><th colspan="3">Dosing</th></tr>
<tr><td colspan="1">

- Recommended dosing for bedaquiline in children is by a joint weight and age-based approach. Taken from WHO Information Note: Use of bedaquiline in children and adolescents with MDR-TB and RR-TB, 2023:

<table>
<tr><th>Weight bands</th><th>Age (months)</th><th>Dose*</th></tr>
<tr><td><3kg</td><td>-</td><td>Consult with Specialist</td></tr>
<tr><td rowspan="2">3-<7kg</td><td>0-<3 months</td><td>30mg once daily for 14 days, followed by 10mg once daily three times per week (M/W/F)</td></tr>
<tr><td>≥3 months</td><td>60mg once daily for 14 days, followed by 10mg once daily three times per week (M/W/F)</td></tr>
<tr><td rowspan="3">7-<10kg</td><td>0-<3 months</td><td>30mg once daily for 14 days, followed by 10mg once daily three times per week (M/W/F)</td></tr>
<tr><td>3-<6 months</td><td>60mg once daily for 14 days, followed by 20mg once daily three times per week (M/W/F)</td></tr>
<tr><td>≥6 months</td><td>80mg once daily for 14 days, followed by</td></tr>
</table>

</td><td>100%</td><td>Consensus reached with minor amends</td></tr>
</table>

		40mg once daily three times per week (M/W/F)		
10-<16kg	3-<6 months	60mg once daily for 14 days, followed by 20mg once daily three times per week (M/W/F)		
	≥6 months	120mg once daily for 14 days, followed by 60mg once daily three times per week (M/W/F)		
16-<30kg	-	200mg once daily for 14 days, followed by 100mg once daily three times per week (M/W/F)		
30-<46kg	-	400mg once daily for 14 days, followed by 200mg once daily three times per week (M/W/F)		
≥46kg	-	400mg once daily for 14 days, followed by 200mg once daily three times		

		per week (M/W/F)		

*When available, bedaquiline 20mg dispersible tablets should be prioritised for young children over the adult 100mg formulation. Non-availability of the child-friendly formulation should not be a barrier to treating children with bedaquiline. Bedaquiline 100mg tablets crushed and suspended in water have been shown to be bioequivalent to tablets swallowed whole.

• Recommended dosing for delamanid in children is by a joint weight and age-based approach. Taken from [WHO Information Note: Use of delamanid in children and adolescents with MDR-TB and RR-TB, 2023]:			100%	Consensus reached

Weight bands	Age (months)	Dose*
<3kg	-	Consult with Specialist
3-<5kg	-	25mg once daily
5-<10kg	<3 months	25mg once daily
	≥3 months	25mg twice daily
10-<16kg	-	25mg twice daily
16-<30kg	-	50mg once daily in the morning, followed by 25mg once daily in the evening
30-<46kg	-	50mg twice daily

≥46kg	-	100mg twice daily		

*When available, delamanid 25mg dispersible tablets should be prioritised for young children over the 50mg tablet. Non-availability of the child-friendly formulation should not be a barrier to treating children with delamanid. Delamanid 50mg tablets dissolved in water have been shown to be bioequivalent to tablets swallowed whole.