UKMi North West

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A summary of prescribing recommendations from NICE guidance

Tuberculosis

NICE NG33; 2016

This guideline offers advice on the care of people with, or at risk of contracting TB. It updates and replaces NICE CG117/PH37.

Definition of terms

TB	tuberculosis
IGRA	interferon-gamma release assay
NAAT	nucleic acid amplification tests
DOT	directly observed therapy
CKD	chronic kidney disease
CNS	central nervous system
BNF-C	British National Formulary for Children

Preventing TB – see NICE guideline

BCG vaccination –see NICE pathway

Latent TB - diagnosis

Identification of latent TB – general principles

- Offer TB testing to close contacts of a person with pulmonary or laryngeal TB, people who are immunocompromised and at high risk of TB, and new entrants from high incidence countries presenting for healthcare.
- The upper age limit for offering to test and treat latent infection is 65 years.
- In any patient, regardless of BCG history, consider a Mantoux test as positive if skin induration is ≥5mm.

Adults

- Offer Mantoux testing to adults aged 18 to 65 years who are close contacts of a person with pulmonary or laryngeal TB.
- If the Mantoux test is:
  - inconclusive, refer person to a TB specialist,
  - positive, consider an IGRA.*
- When large numbers of people may need to be screened, consider a single IGRA* for people aged 18 to 65 years.

Immunocompromised adults

- For adults who are immunocompromised, risk assess to establish whether testing should be offered, consider:
  - risk of progression to active TB based on how severely and for how long they have been immunocompromised,
  - risk factors for TB infection, such as country of birth or recent contact with an index case with suspected infectious or confirmed pulmonary or laryngeal TB.
- For adults who are severely immunocompromised (including those with HIV and CD4 counts <200cells/mm^3, or after solid organ or allogeneic stem cell transplant), offer an IGRA* and a concurrent Mantoux test.*
- For other adults who are immunocompromised and at risk of TB, consider an IGRA* alone or with a concurrent Mantoux test.*

New entrants from high-incidence countries

- Offer Mantoux testing* as initial diagnostic test or if unavailable, offer an IGRA.*

* If any test for latent infection is positive, assess for active TB; if this assessment is negative, offer treatment for latent TB infection. See Prescribing.

Children and young people

- Only consider using IGRA alone if Mantoux testing is not available or is impractical. This includes situations in which large numbers need to be tested.
- Refer children <2 years in close contact with a person with **smear-negative** pulmonary or laryngeal TB to a specialist to determine the appropriate testing strategy for latent TB.
- If latent TB is suspected in children/young people who are immunocompromised, refer to a TB specialist

Neonates

- If a neonate has been in close contact with a person with **smear-positive** pulmonary or laryngeal TB who has not had at least 2 weeks of anti-TB treatment:
  - assess for active TB,
  - start ***isoniazid (with pyridoxine)***,
  - carry out a Mantoux test after 6 weeks of treatment.
- If the Mantoux test is:
  - inconclusive, refer to a TB specialist,
  - positive, reassess for active TB. If reassessment is negative, continue drug treatment for a total of 6 months.
  - negative, reassess for active TB and consider an IGRA. If the IGRA is:
    - negative, stop treatment and give a BCG vaccination,
    - positive, reassess for active TB. If reassessment is negative, continue drug treatment for a total of 6 months.

Children aged 4 weeks to 2 years

- If a child has been in close contact with a person with **smear-positive** pulmonary or laryngeal TB who has not had at least 2 weeks of anti-TB treatment:
  - assess for active TB,
  - start treatment** for latent TB and carry out a Mantoux test,
- If Mantoux test is:
  - inconclusive, refer to a TB specialist,
  - positive, reassess for active TB. If reassessment is negative, complete treatment** for latent TB.
  - negative, continue treatment** for latent TB, reassess for active TB after 6 weeks and repeat the Mantoux test,
- If the repeat Mantoux test is negative, consider an IGRA,
  - if the IGRA is negative, consider stopping treatment** for latent TB and give a BCG vaccination if the child has not already had one,
  - if either test is positive, reassess for active TB. If reassessment is negative complete treatment** for latent TB.

Children/young people aged 2 to 17 years

- Offer Mantoux testing to those who have been in close contact with a person with pulmonary or laryngeal TB.
- If the Mantoux test is:
  - inconclusive, refer to a TB specialist,
  - positive, assess for active TB; if this assessment is negative offer treatment** for latent TB infection.
  - negative, offer IGRA* after 6 weeks and repeat Mantoux test.*

Healthcare workers – see NICE pathway

Under-served groups – see NICE pathway

** See Prescribing

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Prescribing

Latent TB – standard recommended regimen

- For people, including those with HIV infection and those <65 years with evidence of latent TB who have been in close contact with a person who has suspected infectious or confirmed active pulmonary or laryngeal drug-sensitive TB, offer either:
  - ***3 months of isoniazid (with pyridoxine) + rifampicin*, OR**
  - ***6 months of isoniazid (with pyridoxine).***
- For adults aged 35 to 65 years, offer drug treatment only if hepatotoxicity is not a concern.
- Base choice of regimen on person's clinical circumstances. Offer:
  - ***3 months of isoniazid (with pyridoxine) + rifampicin*** in people <35 years, if hepatotoxicity is a concern after an assessment of both liver function (including transaminase levels) and risk factors.
  - ***6 months of isoniazid (with pyridoxine)*** if interactions with rifamycins are a concern e.g. in people with HIV or who have had a transplant.

Active TB - standard recommended regimen

Without CNS involvement

- Offer:
  - ***isoniazid (with pyridoxine), rifampicin, pyrazinamide + ethambutol for 2 months* THEN,**
  - ***isoniazid (with pyridoxine) + rifampicin for a further four months.***

With CNS involvement

- Offer:
  - ***isoniazid (with pyridoxine), rifampicin, pyrazinamide + ethambutol for 2 months, THEN***
  - ***isoniazid (with pyridoxine) + rifampicin for a further 10 months***
- Modify the treatment regimen according to susceptibility testing.
- Use fixed-dose combination tablets as part of any TB treatment regimen.
- **Do NOT** offer anti-TB treatment dosing regimens of fewer than 3 times per week.
- Offer a daily dosing schedule to those with active pulmonary TB.
- Consider a daily dosing schedule as first choice in patients with active extrapulmonary TB.
- Consider 3 times weekly dosing for people with active TB only if a risk assessment identifies a need for DOT and enhanced case management, but DOT is not possible.

Latent TB - treatment

- Be aware that certain groups of people with latent TB are at increased risk of going on to develop active TB, including;
  - people with HIV, diabetes, CKD, silicosis, or receiving haemodialysis,
  - children <5 years old,
  - people with excessive alcohol intake or who are injecting drug users,
  - people who have had solid organ transplantation,
  - people who have a haematological malignancy or are receiving chemotherapy,
  - people who have had a gastrectomy or jejunoileal bypass,
  - people having treatment with anti-tumour necrosis factor alpha or other biological agents.
- People in these groups who choose not to receive treatment should be advised of the risks and symptoms of active TB.
- Offer testing for HIV before starting treatment.
- Offer adults testing, and consider testing children/young people, for hepatitis B and C before starting treatment.
- For people, including those with HIV infection and those <65 years with evidence of latent TB who have been in close contact with a person who has suspected infectious or confirmed active pulmonary or laryngeal drug-sensitive TB, offer standard treatment.**
- Explain risks and potential benefits of each treatment regimen and select a suitable regimen in discussion with the person, if they wish to proceed with preventive treatment.
- If a person also has severe liver disease e.g. Child-Pugh level B or C, work with a specialist multidisciplinary team with experience of managing TB and liver disease.
- Manage treatment with caution, ensuring careful monitoring of liver function, in:
  - people with non-severe liver disease,
  - people with abnormal liver function (including abnormal transaminase levels) before starting treatment for latent TB infection,
  - people who misuse alcohol or drugs.
- Ensure people having treatment for latent TB who also have social risk factors, such as misusing alcohol or drugs or being homeless, are linked to support services. They should also have an assessment of social needs and stability, including potential barriers to adherence or treatment completion.

Active TB – diagnosis. See NICE pathway

All age groups

- If TB is a possibility, microbiology staff should consider carrying out TB culture on samples, even if not requested.
- If clinical features are consistent with a diagnosis of TB, start treatment without waiting for culture results.
- Consider completing the standard recommended regimen even if subsequent culture results are negative.

Pulmonary (including laryngeal) TB. See NICE pathway

All age groups

- Take a chest X-ray; do further diagnostic investigations if chest X-ray appearances suggest TB.
- Send multiple respiratory samples for TB microscopy and culture before starting treatment or, failing that, within 7 days of starting treatment in people with life-threatening disease.

Adults and young people aged 16 to 18 years

- Request rapid diagnostic NAATs for the *M tuberculosis* complex (*M.tuberculosis, M.bovis, M.africanum*) on primary specimens if there is a clinical suspicion of TB, and:
  - the person has HIV infection, **OR**
  - rapid information about mycobacterial species would alter the person's care, **OR**
  - the need for a large contact-tracing initiative is being explored.

Children and young people

- Offer rapid diagnositic NAATs in children/young people aged ≤15 years with suspected pulmonary TB, usually only one NAAT is needed per specimen type (e.g. spontaneous sputum, induced sputum, or gastric lavage).

Extrapulmonary TB – diagnosis. See NICE pathway

Contact tracing. See NICE pathway

- Once a person has been diagnosed with active TB, inform relevant colleagues so that the need for contact tracing can be assessed without delay. Do not delay until notification.
- Assess the need for infection control measures.

** See Prescribing

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Infection control. See NICE pathway

Active TB - treatment

- Once a diagnosis of active TB is made:
  - refer the person to a clinician with training in, and experience of, the specialised care of people with TB,
  - children should be managed by a TB specialist, and by paediatric trained nursing staff, where possible,
  - the TB service should include specialised nurses and health visitors,
  - if these arrangements are not possible, seek advice from more specialised colleagues throughout treatment period.
- Offer patients with active TB drug treatment**, based on whether the patient has CNS involvement.
- Test people with active spinal TB who have neurological signs or symptoms for CNS involvement. Manage direct spinal cord involvement (e.g. spinal cord tuberculoma) as TB of CNS.
- For people with active spinal TB without CNS involvement, do not extend treatment beyond 6 months for residual effects (e.g. persistent bending of the spine or vertebral loss).
- Test people with disseminated (including miliary) TB who have neurological signs or symptoms for CNS involvement. If there is evidence of CNS involvement, treat as for TB of CNS.
- Treat active peripheral lymph node TB in people who have had an affected gland surgically removed with the standard recommended regimen.
- For people with active TB of the lymph nodes, do not routinely extend treatment beyond 6 months for newly enlarged lymph nodes or sinus formation, or for residual enlargement of the lymph nodes or sinuses.

Treatment of people with comorbidities or coexisting conditions

- Work with a specialist multidisciplinary team with experience of managing TB and the comorbidity or coexisting condition if the person has:
  - HIV, **OR**
  - severe liver disease (e.g. Child-Pugh level B or C), **OR**
  - stage 4 or 5 CKD (e.g. glomerular filtration rate of <30mL/min/1.73m^2), **OR**
  - diabetes, **OR**
  - eye disease or impaired vision, **OR**
  - pregnancy or breastfeeding, **OR**
  - a history of alcohol or substance misuse.
- For people with HIV and active TB, **without** CNS involvement: **Do NOT** routinely extend treatment beyond 6 months.
- For people with HIV and active TB, **with** CNS involvement: **Do NOT** routinely extend treatment beyond 12 months.
- Take into account drug-to-drug interactions e.g. antiretroviral drugs.

Adjunctive corticosteroids

- At the start of an anti-TB treatment regimen:
  - offer adults, children/young people with active TB of CNS dexamethasone or prednisolone, initially at a high dose with gradual withdrawal over 4 to 8 weeks.
  - offer adults with active pericardial TB oral prednisolone at a starting dose of 60mg/day, gradually withdrawing it 2 to 3 weeks after starting treatment.
- Offer children/young people with active pericardial TB oral prednisolone in line with the BNF-C and gradually withdraw 2 to 3 weeks after starting treatment.

Criteria for surgery – see NICE pathway

Drug-resistant TB

- For people with TB **without** CNS involvement, that is resistant to just one drug consider treatments in **Table 1**.
- For people with drug-resistant TB **with** CNS involvement, involve a specialist with experience in managing drug-resistant TB in decisions about most appropriate regimen and duration of treatment.

Table 1: Treatment regimen for people with TB (without CNS involvement) resistant to one drug

Drug resistance	Initial phase (first 2 months)	Continuation phase
Isoniazid	Rifampicin, pyrazinamide and ethambutol	Rifampicin and ethambutol for 7 months (up to 10 months for extensive disease)
Pyrazinamide	Rifampicin, isoniazid (with pyridoxine) and ethambutol	Rifampicin and isoniazid (with pyridoxine) for 7 months
Ethambutol	Rifampicin, isoniazid (with pyridoxine) and pyrazinamide	Rifampicin and isoniazid (with pyridoxine) for 4 months
Rifampicin	As for multidrug-resistant TB	

Multidrug-resistant TB

- For people with clinically suspected TB, a TB specialist should request rapid diagnostic NAAT for rifampicin-resistance on primary specimens and start infection control measures if a risk assessment for multidrug resistance identifies any of the following:
  - history of previous TB drug treatment, particularly if there was known to be poor adherence to that treatment,
  - contact with a known case of multidrug-resistant TB,
  - birth or residence in a country in which the World Health Organisation reports that a high proportion (≥5%) of new TB cases are multidrug-resistant.
- If rapid diagnostic NAAT for rifampicin-resistance is positive:
  - continue infection control measures until pulmonary or laryngeal disease has been excluded,
  - manage treatment along with a multidisciplinary team with experience of managing multidrug-resistant TB,
  - offer a treatment regimen involving at least 6 drugs to which the mycobacterium is likely to be sensitive,
  - test for resistance to second-line drugs.
- If rapid diagnostic NAAT for *M.tuberculosis* complex is positive but rifampicin-resistance is not detected, treat as drug-susceptible TB with standard recommended regimen.**
- If the rapid diagnostic NAAT for *M.tuberculosis* complex is negative in a person at high risk of multidrug-resistant TB:
  - obtain further specimens for NAAT and culture, if possible,
  - use rapid rifampicin-resistance detection on cultures that become positive for *M.tuberculosis* complex,
  - consider waiting for results of further tests before starting treatment if the person is well,
  - if urgent treatment is needed, consider managing as multidrug-resistant TB until sensitivity results are available.
- When definitive phenotypic susceptibility results are available, modify treatment as needed.
- Consider more intensive clinical follow-up for people with multidrug-resistant TB. This includes people having DOT throughout treatment because of complexity of treatment and risk of adverse events.

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- Discuss options for organising care for people with multidrug-resistant TB with clinicians who specialise in this.
- Seek the person's views and take them into account, and consider shared care.
- Consider surgery as a therapeutic intervention in people with potentially resectable multidrug-resistant disease if:
  - optimal medical therapy under direct observation has not worked **OR**,
  - medical therapy is likely to fail because of extensively drug-resistant TB (i.e. resistance to at least isoniazid and rifampicin, one injectable agent [capreomycin, kanamycin or amikacin] and one fluoroquinolone).

Improving adherence

- Allocate a named TB case manager to everyone with active TB as soon as possible but within 5 days of diagnosis. The clinical team should inform patients who their named TB case manager is and provide contact details.
- TB case managers should work with the person diagnosed with TB to develop a health and social care plan, and support them to complete therapy successfully. They should:
  - offer a risk assessment to every person with TB, to identify their needs and whether they should have enhanced case management including DOT,
  - educate the person about TB and the treatment,
  - develop an individual care plan after discussion with the person. Gain the person's consent to the plan and agree a review date,
  - coordinate discharge planning, especially for people on DOT,
  - involve representatives from other allied professions and key workers from all organisations who work with the person, if appropriate,
  - explore appropriate ways that peers and voluntary organisations can provide support.
- Offer DOT as part of enhanced case management in people who:
  - do not adhere to treatment (or have not in the past),
  - have been treated previously for TB,
  - have a history of homelessness or drug or alcohol misuse,
  - are in prison or have been in the past five years,
  - have a major psychiatric, memory, or cognitive disorder,
  - are in denial of the TB diagnosis,
  - have multidrug-resistant TB,
  - request DOT after discussion with the clinical team,
  - are too ill to administer the treatment themselves.
- In children whose parents are members of any of the above groups, offer DOT as part of enhanced case management and include advice and support for parents to assist with treatment completion.
- Re-evaluate the need for DOT throughout the course of TB treatment whenever the person's (or in the case of children, parents') circumstances change.
- Encourage people to follow their treatment plan, involve people in treatment decisions from the start. Emphasise the importance of following the treatment plan when agreeing the regimen.
- Multidisciplinary TB teams should implement strategies for active and latent TB to encourage people to follow the treatment plan and prevent people stopping treatment early. See NICE pathway.

Recommendations – wording used such as 'offer' and 'consider' denote the strength of the recommendation.

Drug recommendations – the guideline assumes that prescribers will use a drug's Summary of Product Characteristics (SPC) to inform treatment decisions.

Re-establishing treatment after interruptions because of adverse events

- For people who have experienced a treatment interruption because of drug induced hepatotoxicity:
  - investigate other causes of acute liver reactions, **AND**
  - wait until aspartate or alanine transaminase levels fall below twice the upper limit of normal, bilirubin levels return to normal and hepatotoxic symptoms have resolved, **THEN**
  - sequentially reintroduce each of the anti-TB drugs at full dose over a period of ≤ ten days, starting with ethambutol and either isoniazid (with pyridoxine) or rifampicin.
- In people with severe or highly infections TB who need to interrupt standard therapy because of a reaction, consider:
  - for hepatotoxicity: continuing treatment with a combination of at least two anti-TB drugs of low hepatotoxicity (such as ethambutol and streptomycin, with or without a quinolone, such as levofloxacin or moxifloxacin) and monitor with a liver specialist for further reactions.
  - for a cutaneous reaction: continuing treatment with a combination of at least two anti-TB drugs with a low risk of cutaneous reactions (such as ethambutol and streptomycin) and monitor with a dermatologist for further reactions.
- If another reaction of a similar or greater severity occurs because of reintroducing a particular drug, do not give that drug in future regimens and consider extending the total regimen duration accordingly.

Follow up

- Follow-up clinic visits should not be conducted routinely after treatment completion.
- Tell patients to watch for symptoms of relapse and how to contact the TB service rapidly through primary care or a TB clinic. Key workers should ensure that patients at increased risk of relapse are particularly well informed about symptoms.
- Patients who have had drug-resistant TB should be considered for follow-up for 12 months after completing treatment. Patients who have had multidrug-resistant TB should be considered for prolonged follow-up.
- Multidisciplinary TB teams should aim to find people with active TB who are lost to follow-up, or who stop using services before completing diagnostic investigations. They should report all those lost to follow-up to local Public Health England teams, GPs, the referring organisation and specialist outreach teams.

Rapid access TB services – see NICE guideline

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