Developing a pathway for the diagnosis and management of ocular tuberculosis. The pan-LOndon Ocular tuberculosis Pathway – LOOP.

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Ocular Tuberculosis (OTB) is a complex and heterogeneous condition that is poorly characterised and understood. There are a variety of ophthalmic phenotypes that are recognised as 'typical' in the global literature;

1. Peripheral occlusive retinal vasculitis, or Eales Disease
2. Serpiginous-like (or ampiginous) chorioretinitis
3. Choroidal granuloma

In rare conditions with poorly characterised phenotypes, such as OTB, it is challenging to develop agreed diagnostic criteria and hence build knowledge of the disease in a robust way. In 2017, all referrals from a large tertiary centre (Moorfield's Eye Hospital) to tuberculosis (TB) services around London were audited. Ninety-four cases were referred for an opinion or for treatment. Of these, 75% did not fit into 'classical OTB phenotypes' and were made up of chronic anterior uveitis, intermediate uveitis, retinal vasculitis without ischaemia and scleritis.

Patients referred for an opinion were likely to be treated with anti-tuberculosis therapy (ATT) if there was additional evidence of TB disease remote to the eye. Where there was no evidence of TB disease remote to the eye, patients tended to be referred back to ophthalmic teams untreated. Frequently, ophthalmologists received feedback from TB services indicating that they required clearer directions to justify ATT in the management of this group of patients, including evidence that sarcoidosis, toxoplasmosis or syphilis had been considered and were unlikely.

The current method of referral falls short of best care, provoking patient anxiety when their ophthalmologist and TB team appear to disagree about the significance of TB in the aetiology of their ocular disease.

One of the challenges in managing patients with presumed OTB is the lack of clear guidance on diagnosis, investigation and management. Whilst there is increasing data to suggest that treating patients with ATT in addition to immunosuppressive therapy reduces relapses of uveitis and improves outcomes, the evidence is limited. The majority of published series are highly heterogeneous and retrospective in design and there are no randomised trials comparing treatment outcomes Previous international consensus work has demonstrated that there is significant variation in local and regional practice (1), particularly in regard to extent of investigation for extraocular disease activity and duration of treatment beyond six months. Recently, there have been robust collaborations between multiple institutions (2) as well as large-scale international retrospective studies (3, 4) that have used large cohorts to analyse the benefit of ATT, the limited sensitivity of polymerase chain reaction (PCR) in diagnosis and the prognosis of specific ocular phenotypes. Currently, there are no prospective data available to inform outcomes for different OTB phenotypes. Nor are there agreed guidelines for the management of possible OTB.

In order to improve the quality of the evidence base, and of the care provided for this group of patients, we engaged with stakeholders across London to achieve consensus on the diagnosis and management of OTB. Initially, we carried out a listening exercise with representatives from the uveitis department at Moorfields Eye Hospital, St Thomas' Hospital Medical Eye Unit and the Western Eye Hospital. We then approached each of the five

segments in London that manage TB (Figure 1). We met with doctors and allied health care professionals (AHPs) from infectious diseases, public health and respiratory medicine, to gather expertise and start consensus-building through multi-disciplinary discussion.

The process was iterative, and concessions made to create a pathway that would be acceptable to the majority of stakeholders. When new TB services were approached (e.g. North Central London), members from an already engaged service (e.g. North East London) were part of the discussion panel. This enabled evolution and refinement of previously agreed concepts. Using this approach, the current version of the pan-**LO**ndon tuberculosis **P**athway (LOOP) was developed after three years of discussion. Here, we present LOOP Version 1.9 (Figure 2), which outlines management for patients with OTBIn addition to diagnosing OTB, the referring ophthalmologist will carry out blood tests and a chest radiograph. There are several areas where consensus could not be reached:

1. Investigations carried out by each unit will be at the discretion of the treating doctor and will include some, or all, of: plain chest radiograph; thoracic computerised tomography (CT) scan; fluorodeoxyglucose positron emission tomography (FDG-PET) scan.

2. The use of ethambutol (E) and moxifloxacin (M) – particularly in light of recent Medicines & Healthcare products Regulatory Agency (MHRA) guidance (5).

3. The duration of treatment. There are no prospective randomised trials comparing outcomes from 6, 9 or 12 months of ATT. The eye is a sanctuary site and prolonged treatment makes clinical sense; in line with a central nervous system TB (CNS) protocol. However, the presence of intraocular inflammation breaks down the blood-retinal barrier and allows penetration of drugs into the eye. It is unclear whether proactive management of the inflammatory component of OTB would sufficiently reverse the breakdown of the blood-retinal barrier and mean that 6-12 months would be required. There was lack of consensus regarding the duration of treatment in LOOP and recognition that there is a need for a clinical trial to answer

this question. In the interim, the group agreed that 9 months of treatment would be a sensible 'half-way house' between those advocating for 6 months and those for 12 months.

LOOP was launched at the London Inflammatory Ocular Network (LION), an organisation designed to provide clinical governance structure to clinicians working in inflammatory eye disease across London. In order to avoid confusion, we recommend that all referrals from ophthalmology to TB services are template-based and request either:

1. Treatment for active OTB – 9 months of ATT (until future trials inform the dutation of ATT for OTB).

   or

2. Treatment for latent TB prior to commencing an immunosuppressant (especially anti-TNF agents).

Patients who are at high risk of *latent TB* are screened as part of public health England (PHE) guidance most commonly via primary care. Details of high-risk criteria and the investigation algorithm can be found at https://www.gov.uk/government/publications/latent-tb-infection-ltbi-testing-and-treatment (6). These patients are not included in LOOP as latent TB screening does not fall under the remit of harmonising the diagnosis and treatment of OTB. We acknowledge that there will be times when a positive IGRA is found in a high risk patient with uveitis caused by another disease-process. These patients can be referred to their local TB services to be managed in accordance to local guidelines.

The current version of LOOP is now active, and we will audit referrals and outcomes on a biannual basis. Outcomes will feedback into LOOP and we hope to improve and refine it over the years ahead. We are keen to emphasise that LOOP V1.9 does not represent the 'correct' or 'definitive' way to manage OTB. Its primary aim is to harmonise the diagnosis

and management of OTB and provide a way of collecting high quality homogeneous data to improve the care of patients with presumed OTB. There will inevitably be patients in whom the risk of treatment with ATT outweighs the benefit and we advise ophthalmologists to use their best judgement when referring to TB services. We are also working with stakeholders across the UK to produce a National Clinical Statement on the diagnosis and management of ocular TB for the British Thoracic Society.

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Titles and legends to figure

Figure 1 – The prevalence of tuberculosis in London in 2017. The yellow boxes superimposed represent the five TB services across London. The blue circles represent hospitals that have been involved in the development of the pathway. NE – North East, NC - North Central, W – West, SW – South West, SE – South East.

Figure 2 – LOOP Version 1.9. The top dark-grey and light grey boxes (dark and light blue in online colour version) take place within the referring ophthalmology department. The bottom dark-grey boxes (grey in online colour version) take place at the local TB service. * - A patient may not be treated if they decline ATT, the clinician considers treatment is not indicated, the risks of treatment outweigh the benefits or there is a contraindication to treatment. TB – Tuberculosis, IGRA – Interferon Gamma Release Assay, CT – Computerised Tomography, PET- FDG - fluorodeoxyglucose positron emission tomography, TST –

Tuberculin skin test, R – Rifampicin, H – Isoniazid, Z – Pyrazinamide, E- Ethambutol, M – Moxifloxacin.