**Current Ophthalmology Practice Patterns for Syphilitic Uveitis**

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## Synopsis

The International Ocular Syphilis Study Group reports that syphilitic uveitis is most often posterior, associated with secondary syphilis, diagnosed serologically and treated with penicillin. Serologic testing of all patients with uveitis ensures timely identification.

**Abstract**

Background: Syphilitic uveitis is re-emerging alongside the systemic infection. In July 2017, an international group of uveitis-specialized ophthalmologists formed the International Ocular Syphilis Study Group to define current practice patterns.

Methods: 103 Study Group members based in 34 countries completed a 25-item questionnaire focused on caseload, clinical presentations, use and interpretation of investigations, treatment, and clinical indicators of poor prognosis.

Results: Members managed a mean of 6.1 patients with syphilitic uveitis in clinics that averaged 707 annual cases of uveitis (0.9%); %); 53.2% reported increasing numbers over the past decade. Patients presented to more members (40.2%) during secondary syphilis. Uveitis was usually posterior (60.8%) or pan (22.5%); complications included optic neuropathy, macular oedema, and posterior synechiae. All members diagnosed syphilitic uveitis using serologic tests (simultaneous or sequential testing algorithms), and 97.0% routinely checked for HIV co-infection. Cerebrospinal fluid analysis was ordered by 90.2% of members, and 92.7% took uveitis plus VDRL or FTA-ABS to indicate neurosyphilis. Patients were commonly co-managed with infectious disease physicians, and treated with penicillin for at least 10 to 14 days, plus corticosteroid. Features predicting poor outcome included optic neuropathy (86.3%) and initial misdiagnosis (63.7%). Reasons for delayed diagnosis were often practitioner-related. 82.5% of members tested every patient they managed with uveitis for syphilis.

Conclusion: This comprehensive report by an international group of uveitis-specialized ophthalmologists provides a current approach for the management of syphilitic uveitis.

## Introduction

The latest analysis by the World Health Organization (WHO) demonstrates that the prevalence and incidence of syphilis continue to be high worldwide. Based on data collected between 2005 and 2012, regional prevalence varies between 0.2% and 1.8% and regional incidence varies between 0.9 and 4.4 cases per 1,000 persons (women or men); corresponding pooled global figures are 0.5% and 1.5 cases per 1,000 persons (women or men) respectively.[1] Syphilis prevalence and incidence remain highest in the African region, but have been rising in high income countries since approximately 2000. One comprehensive review shows a significant increase in the syphilis notification rates in 23 of 27 high-income countries across North America, Europe and the Asia-Pacific Region, and highlights that this increase is due primarily to an increasing number of infections among men who have sex with men (MSM).[2]

An uncommon, but serious manifestation of syphilis is uveitis (or inflammation inside the eye).[3] Surveillance data have provided an estimated risk of "ocular syphilis" – almost always presenting as uveitis – as just 0.6% to 2.7% of total infections.[4-6] However, the vision is frequently impacted in this condition: in the largest series published to date, including 85 persons from The Netherlands, 58.8% presented with reduction in vision to a level that typically limits driving (Snellen visual acuity < 6/12) and 29.4% suffered blindness (Snellen visual acuity < 6/60).[7] Current studies from the United States,[6,8] Western Europe[9,10] and Brazil[11] suggest syphilitic uveitis is increasing in prevalence and incidence, in parallel with the systemic infection.

Consistent with increasing numbers of individuals suffering from syphilitic uveitis, multiple articles are presently being published about cohorts of patients with the condition. In the last 5 years alone, multiple independent studies from countries in the Americas, Western Europe and Australasia have reported on different clinical subjects relating to this form of uveitis, including regional epidemiology, ophthalmic features, ocular and systemic diagnostics, anti-microbial drug and corticosteroid treatments, and prognosis.[5,7,9,11-23] Recently a group of 103 clinicians, specializing in the management of uveitis and based in 34 nations, came together as the International Ocular Syphilis Study Group to provide a global perspective of current practice patterns for syphilitic uveitis. This article presents the collective experience of this group on clinical presentations and outcomes, as well as the preferred approach to investigation and treatment.

## Materials and Methods

In July 2017, a subset of the membership of the International Ocular Inflammation Society (IOIS) formed the International Ocular Syphilis Study Group. The IOIS is a global scientific society, which is dedicated to the study of inflammatory eye diseases. At the time of this project, the IOIS membership totalled 268 clinicians and scientists: 103 clinical members joined the Study Group, which aimed to establish current practice patterns in the management of syphilitic uveitis. These members were based in the following 34 countries: Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Denmark, Egypt, France, Germany, Greece, India, Indonesia, Italy, Japan, Malaysia, Mexico, Norway, Peru, Poland, Portugal, Singapore, South Africa, Spain, Switzerland, Taiwan, Thailand, the Netherlands, Tunisia, Turkey, the United Kingdom, the United Arab Emirates and the United States. All Study Group members completed a 25-question

survey that was formulated by GO, JMF, TEA, PJM and JRS, using online survey software (surveymonkey.com). Members reported on: case load and routes of referral; clinical presentations, including stage of syphilis, uveitis subtype and ophthalmic complications; use of investigations, including serological studies, examination of cerebrospinal fluid (CSF) and testing for human immunodeficiency virus (HIV); interpretation of uveitis as a manifestation of neurosyphilis; treatment, including choice and duration of antibiotic, and adjunctive corticosteroid therapy; clinical indicators of poor prognosis, and standard follow-up policy. The survey questions are provided in Supplementary Table 1.

**Results**

Members of the International Ocular Syphilis Study Group reported their recent clinical load of syphilitic uveitis. In 2016, 97 of 103 members (94.2%) managed a mean of 6.1 patients with syphilitic uveitis in clinical practices that averaged 707 total annual cases of uveitis. Considering only those 42 members with high volume clinical practices that involved consultations with at least 500 patients with uveitis per year, the mean number of patients with syphilitic uveitis managed in 2016 was 10.0, with total annual cases of uveitis averaging 1350. Amongst 79 members who were able to compare numbers of cases managed over the prior decade, 42 (53.2%) reported they had observed an increase in the number, 29 (36.7%) reported no change in number, and 8 (10.1%) reported a decrease in number.

For 73.8% of Study Group members (n = 76 of 103), the most frequent referral of a patient with syphilitic uveitis was from a fellow ophthalmologist who had identified uveitis, but not determined the cause. Some members reported other frequent routes for

their referrals, including: from another ophthalmologist with the diagnosis of syphilitic uveitis (n = 3, 2.9%); from a non-ophthalmologist health practitioner with the diagnosis of syphilis (n = 2, 1.9%); and HIV-positive individuals requesting ophthalmic screening (n = 7, 6.8%). Patients with uveitis most commonly presented to Study Group members (n = 102) during the secondary stage of syphilis (n = 41, 40.2%), followed by latent and tertiary stages (n = 23, 22.6% and n = 26, 25.5%, respectively), and the primary stage (n = 3, 2.9%). Following the Standardization of Uveitis Nomenclature anatomic classification,[24] 102 members reported the form of syphilitic uveitis they managed most frequently was posterior or pan- uveitis (n = 62, 60.8% or n = 23, 22.5%, respectively), while anterior and intermediate uveitis were less often identified as the most frequently treated form (n = 4, 3.9% and n = 2, 2.0%, respectively). Study Group members encountered multiple ocular complications in their practices of syphilitic uveitis, including most commonly, optic neuropathy (n = 69 of 100 members, 68.3%), cystoid macular oedema (n = 51, 50.5%) and posterior synechiae (n = 51, 50.5%). Routes of referral and clinical presentations of syphilitic uveitis are presented in Table 1.

Table 1. Referral patterns and clinical presentations to uveitis-specialised ophthalmologists in patients with syphilitic uveitis (n = 103 International Ocular Syphilis Study Group members responding, unless otherwise stated).

| Clinical Variable | Number (%) |
|---|---|
| Most common route for referral | |
| • Referred by ophthalmologist with diagnosis of uveitis | 76 (73.8) |
| • Referred by ophthalmologist with diagnosis of syphilitic uveitis | 3 (2.9) |
| • Referred by non-ophthalmologist with diagnosis of syphilis | 2 (1.9) |
| • HIV-positive patients referred for ophthalmic screening | 7 (6.8) |
| • No common route | 15 (14.6) |
| Most frequent stage of syphilis* (n=102 members responding) | |
| • Primary | 3 (2.9) |
| • Secondary | 41 (40.2) |
| • Latent | 23 (22.6) |
| • Tertiary | 26 (25.5) |
| • No difference in frequency | 9 (8.8) |
| Most frequent form of uveitis* (n=102 members responding) | |
| • Anterior uveitis | 4 (3.9) |
| • Intermediate uveitis | 2 (2.0) |
| • Posterior uveitis | 62 (60.8) |
| • Panuveitis | 23 (22.5) |
| • No difference in frequency | 11 (10.8) |
| Ocular complications of syphilitic uveitis* (n=101 members responding) | |
| • Optic neuropathy | 69 (68.3) |
| • Cystoid macular oedema | 51 (50.5) |
| • Posterior synechiae | 51 (50.5) |
| • Cataract | 42 (41.6) |
| • Retinal vascular occlusion | 36 (35.6) |
| • Epiretinal membrane | 25 (24.8) |
| • Ocular hypertension/glaucoma | 22 (21.8) |
| • Retinal detachment | 15 (14.9) |
| • Retinal neovascularization | 15 (14.9) |
| • Hypotony | 5 (5.0) |
| • Choroidal neovascularization | 4 (4.0) |

All 103 Study Group members relied on serologic testing to make a diagnosis of syphilitic uveitis. A majority of members (n = 62, 60.2%) requested non-treponemal and treponemal tests simultaneously. However, a substantial number (n = 41, 39.8%) preferred a sequential testing algorithm, with approximately one-half of these practitioners using the traditional algorithm and the remainder using the reverse algorithm. Eleven members (10.7%) had also employed polymerase chain reaction (PCR) to detect *Treponema pallidum* in ocular fluid. Lumbar puncture and analysis of CSF were ordered routinely or for specific indications by 42 (40.8%) and 51 (49.5%) Study Group members, respectively; common indications included optic nerve involvement and HIV positivity. Amongst the members who provided their criteria for diagnosis of neurosyphilis in a patient with syphilitic uveitis, 89 of 96 (92.7%) judged the presence of ocular inflammation plus positive CSF VDRL or FTA-ABS to establish this condition. Smaller numbers agreed that lesser evidence indicated neurosyphilis, including 46 of 88 (52.3%) accepting uveitis plus an abnormal CSF cell count or protein level, and 33 of 91 (36.3%) accepting uveitis alone as sufficient for the diagnosis. Serologic testing for HIV infection was recommended in all patients presenting with syphilitic uveitis by 98 of 101 (97.0%), and if a first test for HIV was negative, 33.7% of the group (n = 34 of 101) repeated the test 3 months later. Approach and interpretation of investigations in the patient with syphilitic uveitis are summarized in Table 2.

Table 2. Approach and interpretation of investigations in patients with syphilitic uveitis (n = 103 International Ocular Syphilis Study Group members responding, unless otherwise stated).

| Clinical Variable | Number (%) |
|---|---|
| Serologic testing for syphilis | |
| • Performed | 103 (100%) |
| • Traditional testing algorithm (initial non-treponemal test followed by treponemal test) | 21 (20.4) |
| • Reverse testing algorithm (initial treponemal test followed by non-treponemal test) | 20 (19.4) |
| • Simultaneous treponemal and non-treponemal tests | 62 (60.2) |
| *T. pallidum* PCR on ocular fluid | |
| • Performed | 11 (10.7) |
| CSF examination | |
| • Routinely performed | 42 (40.8) |
| • Sometimes performed | 51 (49.5) |
| • Patients with optic nerve involvement | 36 (70.6) |
| • HIV-positive patients | 25 (49.0) |
| • Other situations* | 22 (43.1) |
| • Not performed | 10 (9.7) |
| Criteria for diagnosis of neurosyphilis | |
| • Presence of intraocular inflammation + positive CSF VDRL or FTA-ABS (n=96 members responding) | 89 (92.7) |
| • Presence of intraocular inflammation + abnormal CSF cell count or protein level, but negative CSF VDRL or FTA-ABS (n=88 members responding) | 46 (52.3) |
| • Presence of intraocular inflammation alone (n=91 members responding) | 33 (36.3) |
| Serologic testing for HIV (n=101 members responding) | |
| • Routinely performed | 98 (97.0) |
| • Sometimes performed | 3 (3.0) |
| • Not performed | 0 (0.0) |
| Repeated (at 3 months) serologic testing for HIV if first test negative (n=101 members responding) | |
| • Performed | 34 (33.7) |

Abbreviations: PCR = polymerase chain reaction, CSF = cerebrospinal fluid, HIV = human immunodeficiency virus

*Other situations included: recommendation by co-managing internist; posterior eye involvement; neurological symptoms; and cost.

A majority of Study Group members (n = 64 of 103, 62.1%) referred patients with syphilitic uveitis to an infectious disease physician for antibiotic treatment, although some ophthalmologists (n = 25, 24.3%) prescribed these drugs themselves based on their own expertise or the advice of an infectious disease specialist. Most members treated their patients with different forms of penicillin, including intravenous aqueous crystalline penicillin G (n = 63, 61.8%), and intramuscular benzathine penicillin G (n = 25, 24.5%) and procaine penicillin G (n = 2, 2.0%). A small number preferred to treat with other antibiotics, including intravenous ceftriaxone (n = 7, 6.9%) and oral doxycycline (n = 1, 1.0%). Treatment was almost always continued for 10 to 14 days or longer (n = 63, 66.3% and 28, 29.5% of 95 members, respectively). Of 102 members, 32 (31.4%) routinely prescribed adjunctive corticosteroid therapy, and 68 (66.7%) prescribed this therapy for selected patients. Corticosteroids were given topically (n =70 of 100 members, 70.0%), by local injection (n = 16, 16.0%) and/or systemically (n = 82, 82.0%). When adjunctive systemic corticosteroid therapy was used, this was most often initiated during, but after the start of antibiotics (n = 45 of 82 members, 54.9%). However, 14 members (17.1%) started the corticosteroid at the same time as the antibiotic; 4 members (4.9%) started the corticosteroid after the course of antibiotic; and 19 members (23.1%) adjusted the timing of corticosteroid treatment depending on the clinical situation. The treatment of syphilitic uveitis is described in Table 3.

Table 3. Treatment of patients with syphilitic uveitis (n = 103 International Ocular Syphilis Study Group members responding, unless otherwise stated).

| Clinical Variable | Number (%) |
|---|---|
| Approach to antibiotic treatment of syphilis | |
| • Prescribe antibiotics based on own expertise | 12 (11.7) |
| • Prescribe antibiotics as advised by an infectious disease physician | 13 (12.6) |
| • Refer patient to infectious disease physician for treatment | 64 (62.1) |
| • Other approaches to antibiotic treatment | 14 (13.6) |
| Preferred antibiotic (n=102 members responding) | |
| • Aqueous penicillin G (intravenous) | 63 (61.8) |
| • Penicillin G benzathine (intramuscular) | 25 (24.5) |
| • Ceftriaxone (intravenous) | 7 (6.9) |
| • Procaine penicillin G (intramuscular) plus probenecid (oral) | 2 (2.0) |
| • Doxycycline (oral) | 1 (1.0) |
| • Tetracycline (oral) | 0 (0.0) |
| • Combinations of or different antibiotics | 4 (3.9) |
| Duration of antibiotic treatment (in days) (n=95 members responding) | |
| • Less than 10 | 4 (4.2) |
| • 10-14 | 63 (66.3) |
| • 14-21 | 19 (20.0) |
| More than 21 | 9 (9.5) |
| Adjunctive corticosteroid therapy (n=102 members responding) | |
| • Routinely prescribed | 32 (31.4) |
| • Sometimes prescribed | 68 (66.7) |
| • Not prescribed | 2 (1.9) |
| Administration of corticosteroid (n=100 members responding) | |
| • Topically applied (eye drops) | 70 (70.0) |
| • Locally injected | 16 (16.0) |
| • Systemic | 82 (82.0) |
| • Initiated with antibiotic treatment | 14 (17.1) |
| • Initiated during but after start of antibiotic treatment | 45 (54.9) |
| • Initiated after antibiotic treatment completed | 4 (4.9) |
| • No standard timing of administration | 19 (23.1) |

In the clinical practices of most Study Group members (n = 74 of 103, 71.9%), all patients with syphilitic uveitis received long-term follow-up after resolution of the inflammation; some members (n = 26, 25.2%) selected patients for follow-up based on presence of ocular complications, HIV positive status and risk factors for re-infection with *T. pallidum*. Study Group members agreed that multiple factors predicted poor visual outcome in syphilitic uveitis, including optic neuropathy (n = 88 of 102 members, 86.3%), initial misdiagnosis (n = 65, 63.7%), HIV co-infection (n = 40, 39.2%), retinal involvement (n = 41, 40.2%) and bilateral disease (n = 21, 20.6%). Reasons cited by Study Members for a delay in the diagnosis of syphilis were often practitioner-related, including not ordering serologic tests (n = 27, 29.7%), lack of medical knowledge or suspicion of syphilis (n = 27, 29.7%), and initial misdiagnosis (n = 19, 20.9%). Eighty-five of 103 members (82.5%) performed syphilis testing in every patient who presented to them with uveitis. The approach to follow-up and prediction of the outcome of syphilitic uveitis are presented in Table 4.

Table 4. Approach to follow-up and prediction of outcome for patients with syphilitic uveitis by uveitis-specialised ophthalmologists (n = 103 International Ocular Syphilis Study Group members responding, unless otherwise stated).

| Clinical Variable | Number (%) |
|---|---|
| Patients followed after resolution of uveitis | |
| • All patients | 74 (71.9) |
| • Some patients | 26 (25.2) |
| • Patients with ocular complications | 26 (100) |
| • HIV-positive patients | 17 (65.4) |
| • Patients judged at high risk of re-infection with *T. pallidum* | 9 (34.6) |
| • No patients | 3 (2.9) |
| Features predictive of poor visual outcome (n=102 members responding) | |
| • Optic neuropathy | 88 (86.3) |
| • Initial misdiagnosis | 65 (63.7) |
| • HIV-positive patient | 40 (39.2) |
| • Retinal involvement | 41 (40.2) |
| • Bilateral disease | 21 (20.6) |
| Factors delaying the diagnosis of syphilis (n=91 members responding) | |
| • Serology not ordered | 27 (29.7) |
| • Lack of medical knowledge or suspicion for syphilis | 27 (29.7) |
| • Initial misdiagnosis | 19 (20.9) |
| • Variable clinical presentations | 16 (17.6) |
| • Limited access to appropriate medical care | 14 (15.4) |
| • Poor compliance | 13 (14.3) |
| • Delayed presentation | 9 (9.9) |
| • False negative serology | 7 (7.7) |
| • Inappropriate initial treatment | 7 (7.7) |

Abbreviation: HIV = human immunodeficiency virus

## Discussion

Syphilitic uveitis is re-emerging internationally, in parallel with the increasing incidence of the systemic infectious disease.[6,8,25] We present a description of current practice patterns by collating the experience of a group of 103 clinicians – members of the International Ocular Syphilis Study Group – who specialize in the management of uveitis, and evaluate an average of approximately 700 cases of uveitis annually. In keeping with recently published, detailed surveys of individual practices,[25-27] the number of cases of uveitis caused by ocular syphilis is less than 1% of the total case load, but just over one-half of Study Group members have observed an increase in the number of cases of syphilitic uveitis over the past decade. Members of the Study Group most commonly encounter uveitis in the setting of secondary syphilis, but also during latent and tertiary syphilis, and occasionally during primary syphilis. For approximately 85% of members, these patients present most frequently with posterior uveitis or panuveitis. Complications of syphilitic uveitis are protean, affecting both anterior and posterior eye, and visually significant. In particular, cystoid macular oedema and optic neuropathy, identified by one-half and two-thirds of members, respectively, are well-established causes of vision loss that may be irreversible in patients with uveitis.[28]

Study Group members rely on serologic testing to diagnose syphilis as the cause of uveitis; analysis of intraocular samples by PCR is seldom utilized. A diagnostic approach that has been promoted by uveitis specialists for several decades involves simultaneous testing for non-treponemal and treponemal antigens, rather than the traditional algorithm of a non-treponemal test, followed by treponemal test if the former is positive.[29] This approach has been taken to avoid falsely negative non-treponemal tests,

particularly early or late in the course of the infection, when uveitis may first present. Following recent introduction of automated, low-cost treponemal immunoassays, many diagnostic laboratories are adopting a reverse testing algorithm, i.e., treponemal test followed by non-treponemal test, when the former is positive.[30] Thus, while approximately 60% of Study Group members continue to follow the simultaneous testing model, 20% have moved to the reverse testing algorithm. In addition to serologic testing, most members order CSF analysis in patients with uveitis secondary to syphilis. Over 90% of members follow the recommendation of the United States Centers for Disease Control and Prevention (CDC) when diagnosing neurosyphilis, requiring the presence of intraocular inflammation, plus positive CSF VDRL and/or FTA-ABS,[31] but one-third of members also consider uveitis alone to indicate neurosyphilis. There is a strong association between HIV infection and syphilis, which is believed to reflect multiple factors, including common sexual transmission, and modulatory effects of HIV and highly active anti-retroviral therapy on the immune system.[32] Accordingly, 97% of Study Group members order serologic testing for HIV in any patient who is diagnosed with syphilitic uveitis.

The CDC recommends ocular syphilis be managed according to their guidelines for neurosyphilis.[31] That recommendation is 10 to 14 days of treatment with intravenous aqueous penicillin G, intramuscular procaine penicillin G (with oral probenecid) or, in the case of penicillin allergy, intravenous ceftriaxone. A majority of Study Group members liaise with an infectious disease physician to treat their patients and follow this medical approach. Addition of corticosteroid has been suggested to avoid a Jarisch-Herxheimer reaction, which is the inflammatory response that often accompanies initiation of antimicrobial treatment in syphilis[33] and may exacerbate uveitis.[34] Almost

all Study Group members prescribe adjunctive corticosteroid, which typically is delivered systemically or in the form of eye drops. The preference for these delivery routes is consistent with the difficulty of removing locally injected corticosteroid in the event of a complication, and with the recent report of delayed resolution of syphilitic uveitis in patients who receive local corticosteroid injections.[19]

Syphilitic uveitis causes long-term visual disability in a significant number of persons: among one cohort of patients with ocular syphilis, who were treated and followed at Johns Hopkins School of Medicine, and described in detail, one in 5 eyes lost visual acuity to a level below 20/40, which prohibits driving in many countries.[14] Thus, a valuable output of our work was the collation of poor prognostic factors based on the expertise of Study Group members. Multiple factors were considered predictive of poor visual prognosis, including initial misdiagnosis, HIV co-infection, posterior eye involvement, bilateral disease and the complication of optic neuropathy. Delayed diagnosis and treatment have been associated with a relatively poor visual prognosis in several studies.[7,17,19] Patient-related factors were identified as one common reason for a delay in diagnosis. However, syphilitic uveitis is a great masquerader, and lack of recognition was identified as a major issue in delayed diagnosis. A related consideration was failure to order serologic testing for syphilis.

In summary, we have presented a description of practice patterns for syphilitic uveitis. One potential limitation of our work relates to participation bias, since Study Group members came from one professional society, albeit the largest international society with specific interest in inflammatory eye disease. Another potential limitation stems from the fact that the field is rapidly evolving as syphilis re-emerges and new

management approaches are applied. For example, within a relatively short period, more members may embrace PCR testing of ocular fluid, as is being applied routinely in more common intraocular infections.[35] Despite these limitations, our work presents a unique, current and comprehensive description of the management of syphilitic uveitis by a large and international group of ophthalmologists who specialize in the treatment of inflammatory eye disease. Arguably our most important observation is the role of syphilis serologic testing in the timely diagnosis of syphilitic uveitis. Over 80% of Study Group members test any patient who presents with uveitis for syphilis.

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There are no competing interests for any author.

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GFO, JMF, TEA, PJM & JRS designed survey; GFO administered survey; RMS, JMM & JRS collated survey responses; RMS, JMM &JRS drafted manuscript; GFO, JMF, TEA & PJM reviewed and edited draft. All authors approved submission.

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