

HLA-B27 acute anterior uveitis: decoding an immunological ophthalmic challenge



**I Gusti Made Ayu Juliari¹, Ida Ayu Ary Pramita¹,
I Wayan Eka Sutyanawan², Michael Chandra Sarsono³**

¹ Infection and Immunology Division, Ophthalmology Department, Prof. Ngoerah Hospital, Udayana University, Bali, Indonesia

Head: I Gusti Made Ayu Juliari, MD

² Pediatric and Strabismus Division, Ophthalmology Department, Prof. Ngoerah Hospital, Udayana University, Bali, Indonesia

Head: I Wayan Eka Sutyanawan, MD, PhD

³ Ophthalmology Resident, Prof. Ngoerah Hospital, Udayana University, Bali, Indonesia
Head: Putu Yuliawati, MD, PhD

HIGHLIGHTS

HLA-B27 anterior acute uveitis management demands multidisciplinary collaboration to control inflammation, prevent recurrence, and preserve vision.

ABSTRACT

HLA-B27-associated acute anterior uveitis is a common recurrent form of non-infectious ocular inflammation. The condition is characterized by sudden-onset, unilateral anterior chamber inflammation with cells, flare, and fibrin, often accompanied by severe pain and photophobia. It is strongly linked to the HLA-B27 allele and frequently presents as an initial manifestation or comorbidity of seronegative spondyloarthropathies, including ankylosing spondylitis, reactive arthritis, psoriatic arthritis, and inflammatory bowel disease. This review outlines a distinct clinical phenotype, rationale for diagnostic testing, and a strategic management approach prioritizing acute inflammation control and long-term recurrence prevention. While timely treatment generally yields a favorable prognosis, complications like cystoid macular edema and secondary glaucoma underscore the need for multidisciplinary care and vigilant monitoring. This narrative review aims to provide a coherent clinical and pathophysiological framework to optimize patient outcomes.

Key words: HLA-B27, acute anterior uveitis, spondyloarthropathy, diagnosis, management

INTRODUCTION

HLA-B27-associated acute anterior uveitis is a recurrent, non-infectious ocular inflammatory disease characterized by sudden-onset pain, photophobia, and anterior chamber inflammation [1, 2]. This condition poses a substantial clinical burden due to its high recurrence rate and potential for chronic, vision-compromising complications such as glaucoma, cataract, and cystoid macular edema [3, 4]. A notable concern is the diagnostic delay that can exacerbate disease progression and complicate management. Addressing this gap requires an integrated approach combining urgent ophthalmic care with long-term systemic evaluation. HLA-B27-associated acute anterior uveitis is frequently the presenting sign or a key comorbidity of systemic seronegative spondyloarthropathies (SpA), including ankylosing spondylitis (AS), reactive arthritis, psoriatic arthritis, and inflammatory bowel disease (IBD) [2, 5]. This review aims to provide current evidence on the detailed immunopathogenesis, clinical features, diagnostic approaches, and management strategies for controlling HLA-B27-associated acute anterior uveitis.

ANATOMY OF THE UVEAL TRACT

The uveal tract, an integral component of the vascular tunic, comprises three parts: the iris (anterior uvea), the ciliary body (pars plicata located anteriorly, and pars plana located posteriorly), and the choroid (posterior uvea). These structures have specific relevance to the pathogenesis and management of HLA-B27-associated acute anterior uveitis. The iris, formed from mesodermal and neuroectodermal tissues, is the most anterior part of the eye. Its stroma is key in acute anterior uveitis due to its permeability, which influences the flow of inflammatory cells and proteins, leading to flare in the anterior chamber. Differences in iris color, determined by melanocyte density, do not directly affect uveitis but highlight genetic components that may correlate with susceptibility. The ciliary body and choroid support aqueous humor dynamics, which are crucial for understanding intraocular pressure variations observed in acute anterior uveitis patients [6].

Histologically, the iris is organized from anterior to posterior: anterior border layer (consisting of fibroblasts and melanocytes), stroma (mainly collagen, fibroblasts, melanocytes, and the pupillary sphincter muscle), anterior myoepithelial layer (forming the dilator muscle), and posterior pigmented epithelium [7]. The iris stroma consists of melanocytes, non-pigmented cells, collagen fibers, and matrix containing hyaluronic acid. Aqueous humor flows freely through the loose stroma at the anterior border of the iris, which contains many crypts and crevices of varying size, shape, and depth. The structure of the iris stroma is constant despite differences in iris color; only the amount

of pigment in the anterior layer and inner stroma differs. Blood vessels originate from the major arterial circle and run radially towards the pupil center. At the collarette (the thickest part of the iris), there are anastomosing arterial-venous arcades forming the minor vascular circle. Iris capillaries have a relatively large diameter with non-fenestrated endothelium, surrounded by a basement membrane, pericytes, and collagen fibers. Nerves in the iris are bundles of myelinated and unmyelinated nerves, serving sensory, vasomotor, and muscular functions. The dilator muscle is composed of smooth muscle cells containing myofilaments and melanosomes, and is innervated by sympathetic and parasympathetic nerves. Sympathetic stimulation causes the dilator muscle to contract, whereas parasympathetic stimulation causes it to relax. The pupillary sphincter muscle consists of circular smooth muscle near the pupillary margin and receives primary innervation from parasympathetic nerves originating from the Edinger-Westphal nucleus and traveling with the oculomotor nerve (CN III) [6, 8]. The ciliary body is an annular structure with a triangular cross-section, continuous with the iris anteriorly and the choroid posteriorly. The ciliary body is divided into the anterior pars plicata (forming ciliary processes that produce aqueous humor) and the posterior pars plana. Histologically, the ciliary body has a bilayer epithelium (i.e., pigmented and non-pigmented layers) on its inner surface, stroma (containing fibroblasts, melanocytes, and leukocytes), and ciliary muscle [6, 7].

The choroid is a highly pigmented and vascular layer located between the sclera and the neurosensory retina. The choroid consists of five layers: Bruch's membrane, the choriocapillaris (a dense anastomotic capillary network), two vascular layers (Sattler's and Haller's), and the outermost stromal layer (suprachoroid) [7].

PHYSIOLOGICAL IMMUNE RESPONSE

The anterior chamber of the eye is a fluid-filled cavity containing aqueous humor, which is a specialized medium for intercellular communication between immune cells and cells of the iris, ciliary body, and corneal endothelium. Aqueous humor has a relatively lower protein concentration compared to serum and consists of a complex mixture of immunomodulatory cytokines, neuropeptides, and complement inhibitors. This mixture collectively contributes to the immunological response of the eye [9].

In a healthy state, the immune environment of the uvea is dominated by cells of myeloid lineage (leukocytes). In the iris and ciliary body, conventional (myeloid) dendritic cells and tissue macrophages are the main populations. These dendritic cells are often functionally immature and require further activation signals to trigger T-cell responses. Besides leukocytes, stromal cells of the uvea play an active role in

immunity. Melanocytes throughout the uvea can respond to pathogen molecular patterns via toll-like receptors (TLRs) and produce chemokines such as interleukin 8 (IL-8) and monocyte chemoattractant protein 1 (MCP-1). Additionally, iris pigment epithelial (IPE) cells have strong immunomodulatory functions, including the ability to directly inhibit T-cell activation and induce CD8⁺ regulatory T-cell (Treg) differentiation through mechanisms dependent on cell contact and factors like TGF β [7].

In the anterior chamber, there is a partial blood-ocular barrier at the ciliary body where fenestrated capillaries filter plasma macromolecules with a certain concentration gradient into the interstitial tissue. The presence of tight junctions between pigmented and non-pigmented ciliary epithelium strengthens this barrier, preventing interstitial macromolecules from directly entering the aqueous humor via the ciliary body. Nevertheless, a small number of plasma macromolecules can pass through the non-pigmented epithelial barrier and enter the anterior chamber via the iris surface through direct diffusion [9].

HUMAN LEUKOCYTE ANTIGEN B27

Human leukocyte antigen B27 (HLA-B27) is a type of human leukocyte antigen class I that plays an important role in the human adaptive immune system. HLA-B27 is a major histocompatibility complex (MHC) class I molecule consisting of a non-covalently bound heavy chain with β_2 -microglobulin and short peptides (usually 8–10 amino acids). This heavy chain has 3 extracellular domains: α_1 and α_2 form the peptide-binding cleft with 6 pockets (A-F), while α_3 interacts with cellular receptors; there is also a transmembrane and cytosolic domain. Three distinctive features differentiate HLA-B27 from other HLA class I molecules: substitution of glutamine with methionine at position 45, the presence of an unpaired cysteine (Cys67) enabling homodimer and oligomer formation, and a lysine residue at position 70 that increases the reactivity of this cysteine. This molecule also exhibits high polymorphism with over 200 subtypes, where subtypes such as HLA-B2705, HLA-B2704, and HLA-B2702 are more common in Caucasian, Chinese, and Mediterranean populations, respectively [10–13].

Under normal conditions, HLA-B27 functions as an APC molecule, presenting peptides from intracellular proteins, including peptides from viruses and microorganisms, to cytotoxic CD8⁺ T cells. This process allows the immune system to recognize and destroy infected cells, thus protecting the body from infection. Normally functioning HLA-B27 does not cause self-tissue damage. However, the role of HLA-B27 becomes complex when associated with autoimmune diseases, such as spondyloarthropathy and acute anterior uveitis. In these conditions, HLA-B27 is suspected to be involved in presenting peptides similar to self-antigens

or microbial peptides that resemble self-antigens. This can trigger the activation of autoreactive T cells, leading to inflammation [14, 15].

HLA-B27 UVEITIS

HLA-B27-associated acute anterior uveitis is an acute form of non-infectious anterior uveitis associated with the presence of the HLA-B27 allele, typically presenting suddenly with symptoms such as eye pain, redness, and photophobia. This condition is generally unilateral or asymmetrically bilateral and has a tendency to recur either in the same eye or alternating between eyes. The age of onset most commonly occurs in young adults (20–40 years), and HLA-B27-associated acute anterior uveitis is often the initial ocular manifestation of spondyloarthropathies such as ankylosing spondylitis, psoriatic arthritis, reactive arthritis, or IBD [9, 16].

Epidemiology

The prevalence of HLA-B27 in the general population varies by ethnicity and geographical region, ranging from 4–13% in Caucasian populations, but is lower in Asian and African populations. Among all anterior uveitis cases, about 50% in young adults in Western countries are associated with HLA-B27. Onset typically occurs in the third to fourth decades of life, with a higher ratio of males to females [17, 18]. A retrospective analytical study in Indonesia by Kevin and Lutflamida showed that HLA-B27 is the most common etiology of acute anterior uveitis, accounting for 34% of all cases, and is significantly found in male patients (3:1). This finding indicates that HLA-B27-associated anterior uveitis has a high proportion in Indonesia, even exceeding figures reported in previous national epidemiological studies which were more dominated by infectious uveitis. HLA-B27 plays an important role in the pathogenesis of acute anterior uveitis in Indonesia. Therefore, awareness, a diagnostic approach, and comprehensive collaborative management are required for individuals suspected of having HLA-B27-associated acute anterior uveitis, with clinical signs of anterior uveal inflammation, especially in males [19].

The main risk factor for developing HLA-B27 uveitis is the expression of the HLA-B27 antigen itself, which increases susceptibility to recurrent intraocular inflammatory episodes. HLA-B27 is a MHC class I found positive in 40–50% of patients with acute anterior uveitis. Several autoimmune diseases, collectively classified as seronegative spondyloarthropathies, such as ankylosing spondylitis, reactive arthritis, inflammatory bowel disease, and psoriatic arthritis, are closely associated with non-granulomatous anterior uveitis and HLA-B27. About one in four HLA-B27-positive patients will develop spondyloarthropathy or ocular abnormalities [20]. A meta-analysis by D'Ambrosio et al. reported that about 50–60% of patients with HLA-B27-associated acute ante-

rior uveitis have associated systemic disease, especially AS. Furthermore, males have a higher tendency for recurrent episodes and complications, including posterior synechiae, cataract, and ocular hypertension. This study emphasizes that genetic factors (HLA-B27), male gender, and rheumatological comorbidities are important risk factors for both disease onset and prognosis [16].

Immunopathogenesis

HLA-B27-associated acute anterior uveitis is viewed as an “MHC-I-opathy,” a group of inflammatory diseases strongly linked to the MHC class I antigen presentation pathway and the endoplasmic reticulum aminopeptidase (*ERAP1/ERAP2*) genes. Initially, there were arthritogenic peptides presented by HLA-B27 and ERAP, altering the peptidome presented to CD8+ T cells, triggering cross-reaction against self/microbial antigens. Concurrently, there was misfolding of HLA-B27 in the endoplasmic reticulum, activating the unfolded protein response and promoting IL-23 production, enhancing the IL-23/IL-17 axis and formation of HLA-B27 heavy chain homodimers that can interact with NK/T cell receptors (e.g., KIR3DL2), supporting Th17 expansion. These processes lead to increased pro-inflammatory mediators (IL-17, TNE, chemokines) in the anterior segment, overcoming ocular immune privilege and resulting in a characteristic acute anterior uveitis (acute onset, pain, photophobia, cells/flare, fibrin) [2, 14, 15, 21] (fig. 1).

Clinical manifestation and systemic associations

The clinical manifestations of HLA-B27-associated acute anterior uveitis can be assessed through targeted history tak-

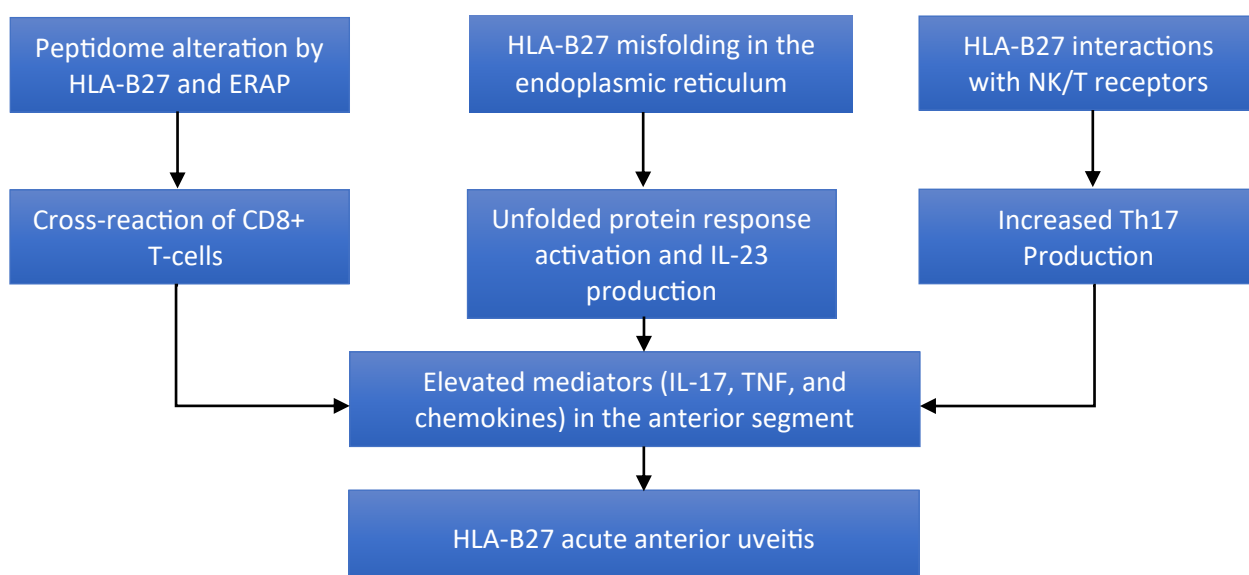
ing, a complete ophthalmological examination, and a general physical examination to detect systemic involvement. This comprehensive approach is crucial for establishing the diagnosis, assessing prognosis, and planning appropriate management. In history taking, besides the main typical ocular complaints of sudden eye pain, photophobia, blurred vision, tearing, eye redness (especially ciliary injection), and eyelid twitching, the onset of ocular complaints must be determined. In HLA-B27-associated acute anterior uveitis, symptoms appear with a sudden onset, whereas in non-HLA-B27 acute anterior uveitis, the onset is often slower with milder inflammatory symptoms [2, 4]. Furthermore, it is important to explore the history suggestive of HLA-B27 etiology and associated systemic diseases. Questions should cover family history, musculoskeletal symptoms, and other symptoms. When exploring family history, it should be asked whether immediate family members (parents or siblings) have a history of spondyloarthropathy, psoriasis, IBD, or recurrent uveitis. Stiffness and low back pain that improve with activity and worsen at rest, especially in the morning, is known as morning stiffness. Pain or swelling of peripheral joints (arthritis) asymmetrically, especially in large joints of the lower limbs. History of skin disorders (erythematous scaly plaques as in psoriasis), chronic gastrointestinal complaints such as recurrent diarrhea, abdominal pain, or blood in stool (suggestive of IBD), and history of previous urethritis or conjunctivitis (which may point to reactive arthritis) [16, 18, 20].

Physical and ophthalmology examinations

Slit-lamp examination is key to confirming the diagnosis. HLA-B27-associated uveitis generally manifests as acute

FIGURE 1

Conceptual framework of HLA-B27 as an MHC-I-opathy [21].



non-granulomatous anterior uveitis. Typical findings include flare (inflammatory cells and increased protein) in the anterior chamber with often severe grading. Keratic precipitates are found as fine, white, non-pigmented deposits, typically accumulating in the inferior part of the corneal endothelium. In severe cases, fibrin exudate forming webs in the anterior chamber, or even hypopyon accumulation, can be found. Additionally, intraocular pressure is often low in the acute phase due to hyposecretion of aqueous from ciliary body inflammation, although in some cases, secondary intraocular pressure elevation may occur due to trabeculitis or peripheral synechiae. Formation of posterior synechiae, especially if mydriasis is inadequate, is a frequent complication. Attacks often occur unilaterally but have a high tendency for recurrence and can alternate between the left and right eyes in subsequent episodes. In the long-term course of the disease, complications that may arise include posterior synechiae, cataract, secondary glaucoma, and cystoid macular edema, all contributing to decreased visual acuity [2, 3, 5].

A brief general physical examination in the consultation room may include skin examination, joint examination, and other examinations. Skin examination can begin by looking for psoriatic lesions (erythematous scaly plaques on the scalp, elbows, knees, or intertriginous areas) and mucosal lesions. Joint examination by inspection and palpation to look for signs of arthritis, such as swelling, redness, warmth in the joints, and even deformities. Particular attention to the distal interphalangeal joints of the fingers/toes and the pattern of dactylitis ("sausage finger"). Other examinations, albeit limited, may note tenderness of the sacroiliac joints through specific maneuvers (e.g., pressure on the iliac crest or Patrick/FABER test). Rheumatological consultation is highly recommended for further evaluation, confirmation of systemic disease diagnosis (such as ankylosing spondylitis, psoriatic arthritis, or IBD), and co-management of long-term therapy, especially if systemic or biological therapy is needed. This multidisciplinary team approach has been proven to optimize control of both local ocular and systemic inflammation, reduce the risk of recurrence, and prevent long-term complications [4, 5, 20].

HLA-B27-ASSOCIATED SERONEGATIVE SPONDYLOARTHROPATHIES

Ankylosing spondylitis

Ankylosing spondylitis (AS) can vary in severity, from asymptomatic to paralysis. Symptoms of AS include low back pain and morning stiffness that improve with movement. AS specifically affects young males aged 20–40 years. Imaging examination of the sacroiliac region can be used to screen for joint inflammation. Early diagnosis of AS is

crucial because non-pharmacological interventions such as exercise, physical therapy, and smoking cessation can slow progression [9].

Reactive arthritis

Reactive arthritis, previously known as Reiter's syndrome, is a classic triad consisting of nonspecific urethritis, polyarthritis, and conjunctival inflammation. Although uncommon, reactive arthritis can be accompanied by non-granulomatous anterior uveitis. Reactive arthritis is found in less than 2% of spondyloarthritis cases and is more common in young adult males (90%). An episode of diarrhea or dysentery without urethritis (with pathogens such as *Ureaplasma urealyticum*, *Chlamydia*, *Shigella*, *Salmonella*, and *Yersinia* sp.) can trigger reactive arthritis. Joint pain symptoms can appear asymmetrically in the knees, ankles, wrists, and feet. About 70% of reactive arthritis patients have sacroiliitis. Ocular clinical manifestations can be found in 20% of reactive arthritis cases in the form of conjunctivitis, punctate and subepithelial keratitis, and acute non-granulomatous anterior uveitis [9].

Inflammatory bowel disease

Acute non-granulomatous anterior uveitis can be found in 12% of patients with ulcerative colitis and 2.4% in Crohn's disease. Although rare, the digestive disease may be asymptomatic and follow the onset of uveitis. About 20% of IBD patients have sacroiliitis, and 60% of them are HLA-B27 positive. Patients with IBD can also have sclerouveitis, but these cases are usually HLA-B27 negative and lack sacroiliitis. HLA-B27-negative patients with IBD are more likely to develop intermediate uveitis [9].

Psoriatic arthritis

Psoriatic arthritis is diagnosed by the presence of characteristic skin abnormalities (erythematous hyperkeratotic rash), inflammation of the distal interphalangeal joints, and nail tissue involvement ("sausage" appearance). About 20% of patients report sacroiliitis, and IBD appears more often than expected. Approximately 25% of patients develop anterior uveitis slowly and bilaterally. Uveitis tends to be more severe in HLA-B27-positive patients. Anterior uveitis in psoriasis patients without arthritis has very different clinical manifestations, with a mean age older than that of idiopathic uveitis or HLA-B27-associated uveitis [9].

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of HLA-B27-associated acute anterior uveitis includes inflammatory conditions such as conjunctivitis (differentiated by the absence of cells in the anterior chamber), keratitis (with typical corneal infiltrates), as well as infectious etiologies like *Herpes simplex*, *Varicella zoster*, toxoplasmosis, tuberculosis, and secondary syphilis,

requiring specific laboratory tests. HLA-B27-associated uveitis often resembles idiopathic non-granulomatous unilateral uveitis with hypopyon, fibrin exudate, and posterior synechiae, but is differentiated from granulomatous uveitis (e.g., tuberculosis) by its fine keratic precipitates pattern without nodules. Studies from the last 5 years emphasize differentiation based on acute onset, alternating bilaterality, and systemic associations such as ankylosing spondylitis, with HLA-B27 testing helping predict recurrence, although not a definitive diagnosis [2].

DIAGNOSTIC APPROACHES AND REASONING

Diagnosing HLA-B27-associated acute anterior uveitis requires a dynamic approach tailored to the clinical presentation. In patients with typical signs and symptoms of HLA-B27-associated acute anterior uveitis (e.g., young adult male with acute unilateral onset, severe pain, photophobia, severe flare and cells, fibrin, and a history of inflammatory back pain or arthritis), the recommended action is to refer the patient for early consultation with a rheumatologist and/or directly perform HLA-B27 testing. This proactive approach enables early identification of systemic disease and the prompt initiation of collaborative management [5].

In atypical cases with uncertain diagnosis, it is recommended to follow a stepwise approach based on the uveitis guideline, where supporting investigations are arranged in 3 stages to efficiently, systematically, and resource-appropriately establish the uveitis etiology according to the facilities and human resources available at each healthcare facility. Stage 1 investigations are initial routine examinations recommended for all patients suspected of uveitis, including complete blood count, erythrocyte sedimentation rate (ESR) and/or CRP (C-reactive protein), Mantoux test or interferon gamma release assay (IGRA), syphilis serology, chest X-ray, liver and kidney function tests, diabetes mellitus screening, and anti-HIV screening. Typically, stage 1 suffices in establishing a diagnosis because it covers the most common and readily diagnosable conditions, making it a cost-effective strategy. Additionally, in specific clinical conditions, tests such as a helper T lymphocyte (CD4) count if immunodeficiency is suspected, an aqueous tap if an infectious cause is strongly suspected, or a diagnostic vitrectomy if malignancy is indicated can be added. If the diagnosis is not established after stage 1 or based on specific clinical findings and disease history, stage 2 investigations tailored to the anatomical classification of uveitis and suspected etiology can be performed, for example, HLA-B27 testing for acute anterior uveitis, *Toxoplasma* serology for posterior uveitis, or chest CT scan and ACE level for granulomatous uveitis [22].

To differentiate HLA-B27-associated acute anterior uveitis from other conditions mentioned in the differential diagnosis, a series of supporting investigations can be utilized, rang-

ing from ocular imaging to genetic and systemic laboratory tests. Most patients show no posterior segment involvement, but in a small proportion, mild vitritis, cystoid macular edema, epiretinal membrane, or retinal vasculitis may be found. Cystoid macular edema is one of the main causes of long-term vision loss, making its detection crucial for prognosis and management [4]. Optical coherence tomography (OCT) is particularly valuable as it can show cystoid macular edema, retinal thickening, or epiretinal changes, thus playing a key role in prognostication. By quantifying cystoid macular edema incidence detected by OCT, routine imaging recommendations can be better supported, allowing for a more comprehensive management strategy even when posterior involvement is not initially apparent. Incorporating a comparative analysis figure further justifies OCT inclusion, demonstrating its predictive capability regarding potential long-term vision issues. Fluorescein angiography can detect macular leakage, retinal vasculitis, or non-perfusion areas. Ultrasound biomicroscopy or B-scan is used when the ocular media are opaque to evaluate the vitreous and retina [2].

Confocal microscopy, specifically in vivo confocal microscopy (IVCM), plays a role in differentiating HLA-B27-associated anterior uveitis through analysis of keratic precipitates on the corneal endothelium. In HLA-B27-positive patients, IVCM shows a “stippled appearance” pattern of keratic precipitates consisting of single leukocytes or small clusters, differing from the globular, infiltrating, or dendritiform patterns in non-HLA-B27 uveitis, such as infection (e.g., toxoplasmosis or CMV) or granulomatous conditions (sarcoidosis, Vogt–Koyanagi–Harada syndrome). This finding is consistent across individual patients’ corneas and changes over time with treatment, making IVCM a potential non-invasive tool for early differential diagnosis before HLA-B27 testing is confirmed [23].

MANAGEMENT STRATEGY

The main management of HLA-B27-associated acute anterior uveitis is pharmacological therapy, with topical corticosteroids as first-line. Corticosteroid preparations, such as prednisolone acetate 1% or difluprednate, are administered intensively to suppress anterior inflammation. Administration of mydriatic-cycloplegic agents (e.g., homatropine or atropine) is important to reduce pain from ciliary muscle spasm and prevent the formation of posterior synechiae. In cases with elevated intraocular pressure, antiglaucoma medication (β -blockers, carbonic anhydrase inhibitors) may be added, except for prostaglandin analogs, which may worsen inflammation [5, 24].

If the response to topical corticosteroids is inadequate or inflammation is severe, systemic corticosteroids (oral or intravenous) are used to control the inflammation. A study at JEC found that oral methylprednisolone was the most fre-

quently administered systemic therapy, with an average duration of 3.07 weeks and significant improvement in visual acuity after therapy [24]. In patients with recurrent episodes or active systemic disease, immunomodulatory therapy such as methotrexate, azathioprine, or mycophenolate mofetil may be considered. Biological therapy, especially anti-TNF- α (adalimumab, infliximab), has proven effective for refractory cases and in patients with active spondyloarthritis, although cost constraints are often encountered in developing countries like Indonesia [2, 4, 25].

Non-pharmacological approaches are also important, including control of concomitant systemic diseases such as ankylosing spondylitis or IBD through multidisciplinary collaboration with rheumatologists or gastroenterologists. Patient education regarding the recurrent nature of the disease, early signs of recurrence, and the importance of treatment adherence is key to preventing complications. Monitoring intraocular pressure and routine fundus examination with OCT helps in early detection of complications such as secondary glaucoma or cystoid macular edema [5]. Surgical intervention is not the primary therapy but may be required if complications are unresponsive to medical therapy. Cataract due to long-term corticosteroid use or extensive posterior synechiae may require cataract extraction with special techniques (e.g., intraoperative synechiolysis). Data from a study at JEC show complex cataract as the most frequent complication (64.5%), most of which required phacoemulsification after inflammation was controlled [24]. Secondary glaucoma uncontrolled with medication may require trabeculectomy or glaucoma shunt implantation. Vitrectomy may be considered in cases with dense vitritis or persistent macular complications [2].

Overall, the management of HLA-B27-associated acute anterior uveitis requires a stepwise approach and individualized therapy. Pharmacological therapy is the first and most important line, accompanied by complication prevention through mydriatics and intraocular pressure control. If there are severe recurrences or active systemic disease, immunomodulators and biological agents become options. Surgical intervention is considered only for persistent ocular complications. With the right strategy, most patients can maintain good vision despite the risk of recurrent episodes throughout their lives [5, 24].

COMPLICATIONS

The formation of posterior synechiae is the most common complication in HLA-B27-associated uveitis, resulting from intraocular inflammation in the aqueous. However, the rate of posterior synechiae varies widely in the literature. In a study by Al-Ani, cataract formation occurred in 22.1% of subjects, with increased risk in older subjects, chronic inflammation, and intermediate uveitis [4]. The de-

velopment of cataract in uveitis can be a complication of inflammation or secondary to corticosteroid use. There is conflicting evidence regarding whether the risk of cataract formation is higher in HLA-B27-positive uveitis, but no significant difference was found in a meta-analysis [16].

The complication rate of cystoid macular edema ranges from 2.4% to 30% of reported HLA-B27-positive cases. In a comparison of HLA-B27-positive and negative patients with anterior uveitis, cystoid macular edema was found 5 times more frequently in HLA-B27-associated disease, corresponding to an 8-fold increase in the need for systemic corticosteroids in this group, although this was not consistent across the meta-analysis. Chronic inflammation and intermediate uveitis are risk factors for cystoid macular edema [4].

PROGNOSIS

The prognosis of HLA-B27-associated acute anterior uveitis is generally quite good if the diagnosis is established early and adequate therapy is given. Most patients can maintain good visual acuity between attack episodes, although the disease is recurrent and often flares unilaterally in an alternating manner. Response to topical corticosteroids is usually rapid, but the risk of complications such as posterior synechiae, secondary glaucoma, cataract, and cystoid macular edema remains a determinant of long-term prognosis. However, in patients with recurrent attacks, severe inflammation, or involvement of systemic diseases such as ankylosing spondylitis and IBD, the risk of permanent vision loss increases. Ocular complications, particularly cystoid macular edema and glaucoma, are the main causes of persistent significant vision loss. Therefore, visual prognosis depends heavily on long-term inflammation control, patient adherence to therapy, and early detection of complications through routine follow-up and a multidisciplinary approach [4].

UNRESOLVED ISSUES AND FUTURE DIRECTIONS

Bacterial triggers such as *Chlamydia*, *Salmonella*, *Shigella*, and *Klebsiella* have been implicated in HLA-B27-associated acute anterior uveitis, yet researchers still do not fully understand the precise pathogenic mechanisms by which these microorganisms initiate disease. Current research has not examined the aqueous humor microbiome in patients with acute and recurrent anterior uveitis, creating a significant knowledge gap. This gap has opened new avenues for therapeutic exploration. Researchers are now investigating strategies such as selective depletion of pathogenic bacteria, recolonization with beneficial bacteria through probiotics or fecal microbiota transplantation, and the use of prebiotics to promote the growth of protective bacterial species [26].

CONCLUSION

HLA-B27-associated acute anterior uveitis is a non-infectious inflammatory condition of the anterior segment of the eye characterized by sudden onset, recurrent nature, and often unilateral, with a tendency to alternate between eyes. This disease is closely linked to the expression of the HLA-B27 allele, predominantly via the IL-23/IL-17 axis. It presents a distinct, recurrent clinical phenotype that is often the sentinel sign of a systemic spondyloarthropathy. Effective management requires ophthalmologists to act as

diagnosticians and coordinators of care, integrating rapid control of ocular inflammation with strategic, long-term immunomodulation to prevent recurrence. Collaboration with rheumatology, gastroenterology, and dermatology partners is pivotal in this process to optimize visual outcomes and patient quality of life. By inviting these disciplines to co-author local protocols, we can reinforce the multidisciplinary spirit essential for successful patient management and spur collective ownership of the treatment approach.

CORRESPONDENCE

I Gusti Made Ayu Juliari MD, PhD

Infection and Immunology Division, Ophthalmology Department, Prof. Ngoerah Hospital, Udayana University Jl. P.B. Sudirman, Dangin Puri Klod, Kec. Denpasar Bar., Kota Denpasar, Bali 80232
e-mail: Juliari@unud.ac.id
phone: +6289635784814

ORCID

I Gusti Made Ayu Juliari – ID – <http://orcid.org/0009-0004-1610-360X>
Ida Ayu Ary Pramita – ID – <http://orcid.org/0000-0001-9579-3741>
I Wayan Eka Sutyanawan – ID – <http://orcid.org/0000-0002-0649-3438>
Michael Chandra Sarsono – ID – <http://orcid.org/0000-0002-8615-7388>

Cite as: Juliari IGMA, Pramita IAA, Sutyanawan IWE et al. HLA-B27 acute anterior uveitis: decoding an immunological ophthalmic challenge. *Ophthalmotherapy*. 2026; 13(2): A251926.

References

- Goodchild C, O'Rourke M, Haroon M et al. 5-year longitudinal study of clinical and patient-reported outcomes in acute anterior uveitis. *Eye (Lond)*. 2021; 35(2): 651-8.
- Wakefield D, Clarke D, McCluskey P. Recent Developments in HLA B27 Anterior Uveitis. *Front Immunol*. 2020; 11: 608134.
- Kim JJ, Park CY. A case of severe flare reaction observed in HLA B27 associated acute anterior uveitis. *BMC Ophthalmol*. 2020; 20(1): 201.
- Al-Ani HH, Sims JL, Niederer RL. Long term complications and vision loss in HLA-B27 uveitis. *Eye (Lond)*. 2023; 37(8): 1673-7.
- Werkl P, Rademacher J, Pleyer U. HLA-B27-positive anterior uveitis : Clinical aspects, diagnostics, interdisciplinary management, and treatment. *Ophthalmologie*. 2024; 121(Suppl 1): 12-22.
- American Academy of Ophthalmology. Basic and Clinical Science Course, Section 02: Fundamentals and Principle of Ophthalmology. 2025.
- Reekie IR, Sharma S, Foers A et al. The Cellular Composition of the Uveal Immune Environment. *Front Med (Lausanne)*. 2021; 8: 721953.
- Pradeep T, Mehra D, Le PH. Histology, Eye. In: StatPearls. StatPearls Publishing, Treasure Island (FL) 2025.
- American Academy of Ophthalmology. Basic and Clinical Science Course, Section 09: Uveitis and Ocular Inflammation. 2025.
- Alexander M. Ankylosing Spondylitis Pathogenesis and Pathophysiology. In: Ankylosing Spondylitis – Recent Concepts. Armas JB (ed.). IntechOpen, London 2023. <https://doi.org/10.5772/intechopen.109164>.
- Lenart I, Truong LH, Nguyen DD et al. Intrinsic Folding Properties of the HLA-B27 Heavy Chain Revealed by Single Chain Trimer Versions of Peptide-Loaded Class I Major Histocompatibility Complex Molecules. *Front Immunol*. 2022; 13: 902135.
- Loll B, Rückert C, Uchanska-Ziegler B et al. Conformational Plasticity of HLA-B27 Molecules Correlates Inversely With Efficiency of Negative T Cell Selection. *Front Immunol*. 2020; 11: 179.
- McDermott GC, Choufani M, Monshizadeh A et al. HLA-B27 Testing in Clinical Practice: A Retrospective Analysis of Testing Indications and Rheumatology Referral Patterns. *J Rheumatol*. 2025; 52(10): 1021-7.
- Navid F, Chen L, Bowness P et al. HLA-B27 and spondyloarthritis: at the crossroads of innate and adaptive immunity. *Nat Rev Rheumatol*. 2025; 21(2): 77-87.

15. Sibley CH. Autoinflammation and HLA-B27: More than an Antigen. *Ocul Immunol Inflamm.* 2016; 24(4): 460-9.
16. D'Ambrosio EM, La Cava M, Tortorella P et al. Clinical Features and Complications of the HLA-B27-associated Acute Anterior Uveitis: A Metanalysis. *Semin Ophthalmol.* 2017; 32(6): 689-701.
17. Standardization of Uveitis Nomenclature (SUN) Working Group. Classification Criteria for Spondyloarthritis/HLA-B27-Associated Anterior Uveitis. *Am J Ophthalmol.* 2021; 228: 117-25.
18. Pineda-Sierra JS, Cifuentes-González C, Rojas-Carabali W et al. Clinical characterization of patients with HLA-B27-associated uveitis and evaluation of the impact of systemic treatment on the recurrence rate: a cross-sectional study. *J Ophthalmic Inflamm Infect.* 2023; 13(1): 38.
19. Kevin K, Lutfiyanda R. Pattern of anterior uveitis in KMN eyecare. *Int J Retina.* 2023; 6(2): 110.
20. Toufik H, Ghassem MA, Majjad A et al. Spondyloarthritis Associated with Uveitis: A Review. *Middle East Afr J Ophthalmol.* 2023; 30(3): 177-81.
21. Kuiper JJ, Prinz JC, Stratikos E et al. EULAR study group on "MHC-I-opathy": identifying disease-overarching mechanisms across disciplines and borders. *Ann Rheum Dis.* 2023; 82(7): 887-96.
22. Kementrian Kesehatan RI. Pedoman Nasional Pelayanan Klinis (PNPK): Tata Laksana Uveitis. 2024.
23. Postole AS, Knoll AB, Auffarth GU et al. In vivo confocal microscopy of inflammatory cells in the corneal subbasal nerve plexus in patients with different subtypes of anterior uveitis. *Br J Ophthalmol.* 2016; 100(11): 1551-6.
24. Mahayani NMW, Susiyanti M, Sjamsoe S et al. Clinical profiles and evaluation of HLA-B27 related anterior uveitis in 2018 – 2023 at JEC Eye Hospitals and Clinics. *Intisari Sains Medis.* 2024; 15(3): 1032-9.
25. Hien DL, Pham BH, Nguyen QD. How Do We Manage HLA-B27-associated Ocular Inflammation Refractory or Intolerant to Conventional Immunomodulatory Therapy? *J Ophthalmic Vis Res.* 2020; 15(4): 442-5.
26. Rosenbaum JT, Asquith M. The Microbiome and HLA B27-associated acute anterior uveitis. *Nat Rev Rheumatol.* 2018; 14(12): 704-13.

Authors' contributions:

All authors have made substantial contribution of the following: the conception and design of the study, or acquisition of data, or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, and final approval of the version to be submitted.

Conflict of interest:

None.

Financial support:

None.

Ethics:

The content presented in the article complies with the principles of the Helsinki Declaration, EU directives and harmonized requirements for biomedical journals.