

# Acute Anterior Uveitis and HLA-B27: What's New?

2

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## Core Messages

- Acute anterior uveitis (AAU) accounts for 90% of all uveitis cases seen by the general ophthalmologist.
- About half of all AAU cases are HLA-B27-associated.
- HLA-B27+ AAU represents a distinct clinical entity with important ocular and extraocular consequences.
- The typical ocular phenotype of HLA-B27+ AAU is that of acute onset, unilateral inflammation of the iris and ciliary body, with a tendency towards recurrent attacks and more severe inflammation, including hypopyon formation. Males are affected more frequently than females.
- All patients with AAU must have a dilated fundus examination to confirm the diagnosis is anterior uveitis, and careful clinical assessment regarding possible associated systemic inflammatory disease.
- All patients with AAU should be investigated with HLA-B27 typing, syphilis serology, and a chest X-ray at a minimum.
- 50% of patients with HLA-B27+ AAU will develop an associated seronegative spondyloarthropathy (SpA), whilst approximately 25% of the patients initially diagnosed with HLA-B27-associated systemic disease will develop AAU.
- HLA-B27 is the strongest known genetic risk factor for AAU. There are multiple subtypes of HLA-B27, which may be differentially associated with disease.
- In addition to genetic factors, environmental factors play a critical role in the pathogenesis of AAU.
- Bacterial triggers have been strongly implicated in the development of AAU and recurrent episodes of ocular inflammation.
- Human uveal antigen-presenting cells express TLR4, the receptor for LPS, and may provide a critical molecular link between microbial triggers and the development of AAU.
- Topical corticosteroids and cycloplegic agents are the mainstay of treatment.

## 2.1 Introduction

Acute anterior uveitis (AAU) is by far the most common form of uveitis [6]. It is characterized by a breakdown in the blood–aqueous barrier and acute inflammation of the iris and ciliary body. Immunopathologically, there is up-regulation of cell adhesion molecules on the uveal vasculature and aqueous humor expression of pro-inflammatory cytokines such as tumor necrosis factor (TNF)- $\alpha$ , interferon (IFN)- $\gamma$  and chemokines that selectively recruit and activate inflammatory cells (neutrophils, monocytes and lymphocytes) into the uvea and anterior chamber (AC). These cells are visible clinically on slit lamp biomicroscopy. The breakdown in the blood–ocular barrier results in leakage of serum proteins from the uveal vasculature

into the AC, which is visible on biomicroscopy as aqueous flare and fibrin formation. Keratic precipitates (KPs) represent inflammatory cells that have precipitated on the corneal endothelium. Thus AAU is a prototypical inflammatory disease in which the clinician is uniquely able to visualize the inflammatory response in vivo and all of its sequelae using the slit lamp biomicroscope, and to correlate it with the immunopathological process.

About 50% of all cases of AAU are associated with the presence of HLA-B27, a class I major histocompatibility complex (MHC) [8]. HLA-B27-associated AAU represents a distinct clinical phenotype that may be associated with severe intraocular inflammation as well as systemic inflammatory diseases such as the seronegative spondyloarthropathies (SpA). There has been some recent

progress in our understanding of the clinical features and the immunopathogenesis of this group of diseases. The aim of the present chapter is to highlight these advances for the clinician managing patients suffering from AAU.

## 2.2 Epidemiology of Acute Anterior Uveitis and HLA-B27

The annual incidence of uveitis has been reported to be between 17 and 52 per 100,000 population, with a prevalence of between 38 and 714 per 100,000 population [6]. Anterior uveitis is the predominant form of uveitis in most populations studied, accounting for approximately 50–60% of all cases of uveitis seen in tertiary referral centers. In the general community, AAU accounts for up to 90% of all uveitis cases once referral study bias has been removed [22]. In one study, the mean annual incidence and prevalence rates of anterior uveitis were, respectively, 21 and 69 per 100,000 population, whilst the total incidence and prevalence rates of all cases of uveitis in that community were 23 and 75 per 100,000 population, respectively [29].

HLA-B27-associated AAU is the most important form of anterior uveitis (acute and chronic forms combined), accounting for 18–32% of all cases of anterior uveitis (see Table 2.1 for common causes of acute and chronic

anterior uveitis). As will be discussed later, HLA-B27 is the strongest known genetic risk factor for AAU. The lifetime cumulative incidence of AAU in the general population has been reported to be about 0.2%, but this increases to 1% in the HLA-B27-positive population [19].

HLA-B27+ AAU demonstrates a clear gender preponderance, with males being about 2.5 times more likely to be affected than females. The first attack of HLA-B27+ AAU occurs between 20 and 40 years of age in the great majority of cases, and these patients are about a decade younger than their HLA-B27 negative counterparts at the time of disease onset [8].

### 2.2.1 Global Patterns of HLA-B27+ Acute Anterior Uveitis

In the general Caucasian population, the prevalence of HLA-B27 is approximately 8%, whereas the HLA-B27 antigen is present in about half of the patients suffering from AAU [8]. There is a global variation in the prevalence of the HLA-B27 gene, and due to this, as well as potential variations in other genetic and environmental factors that are relevant to disease pathogenesis; there are distinct global patterns of AAU. For example, the relatively lower frequency of HLA-B27+ AAU in Asia reflects the lower prevalence of HLA-B27 in this area; it is as low as 0.5% in Japan [6, 8].

**Table 2.1.** Common causes of acute and chronic anterior uveitis

Acute anterior uveitis (AAU)	Chronic anterior uveitis
HLA-B27+ AAU	Juvenile idiopathic arthritis (JIA)
Ocular involvement only	
Ankylosing spondylitis	
Reactive arthritis	
Psoriatic arthropathy	
Inflammatory bowel disease	
Undifferentiated SpA	
Idiopathic AAU (HLA-B27 negative)	Fuch's heterochromic iridocyclitis
Sarcoid uveitis	Idiopathic
Behçet's disease	Sarcoid uveitis
Posner–Schlossman Syndrome	Syphilitic uveitis
Lens-associated uveitis	Herpetic (herpes zoster/simplex)
Syphilitic uveitis	

### Summary for the Clinician

- AAU is the most common form (90%) of uveitis
- Approximately half of all patients with AAU are positive for HLA-B27
- There are global variations in the prevalence of HLA-B27 AAU
- HLA-B27 AAU represents a distinct clinical entity with clinically important ocular and extraocular implications
- Males are affected about 2.5 times more frequently with HLA-B27 AAU than females
- First attack of HLA-B27 AAU usually occurs between 20 and 40 years of age

## 2.3 HLA-B27 and Disease

HLA-B27 is a human leukocyte antigen (HLA) class I molecule whose strong associations with disease set it apart from most HLA antigens, and so it has been the subject of much research over the past 35 years. HLA

molecules are encoded on the short arm of chromosome 6. HLA antigens are vital to normal immune surveillance and the generation of immune responses to foreign antigens. These molecules are critically important in various physiologic and pathologic immune processes, including antiviral responses, organ transplantation immunology and tumor immunology, and play a key role in the pathogenesis of an expanding list of immune-mediated inflammatory diseases. HLA antigens are divided into HLA class I and class II molecules, which have distinct structural and functional characteristics (Table 2.2). HLA molecules present antigenic peptides to T lymphocytes via distinct antigen processing and HLA-restricted presentation pathways, with the common goal of initiating the antigen-specific adaptive immune response.

**Table 2.2.** HLA class I and class II molecules

	HLA class I	HLA class II
Subclass	HLA-A, -B, -C (classical)  HLA-E, -F, -G (non-classical)	HLA-DR, -DQ, -DP
Cellular expression	Most human somatic cells  No/minimal expression on uveal or corneal endothelial cells	Antigen-presenting cells  Dendritic cells  Macrophages Monocytes
Antigen (Ag) presented	Endogenous or intracellular peptides (self or viral origin)	Exogenous or extracellular peptides
T cell presentation	Presents Ag to CD8+ (cytotoxic) T lymphocytes	Presents Ag to CD4+ (helper) T cells
Examples of well-known disease associations	HLA-B27 and AAU, AS.  HLA-29 and birdshot retinochoroidopathy  HLA-B51 and Behçet's disease	HLA-DR, -DQ subtypes and VKHD  HLA-DR15 and pars planitis  HLA-DR4 and sympathetic ophthalmia

AAU, Acute anterior uveitis; AS, ankylosing spondylitis; VKHD, Vogt-Koyanagi-Harada disease

The strong association between HLA-B27 and inflammatory diseases, such as ankylosing spondylitis (AS), reactive arthritis (including Reiter's syndrome) and AAU has been known for over 30 years [2, 3, 8]. Within this spectrum of HLA-B27-associated inflammatory diseases, AS demonstrates the strongest association, with around 90% of patients possessing the HLA-B27 antigen. Nearly a third of these patients develop HLA-B27+ AAU during the clinical course of their extraocular inflammatory disease. Despite extensive research for other genes, HLA-B27 is still the strongest known genetic risk factor for the development of AAU, but how it predisposes to disease remains an enigma. Possession of the HLA-B27 antigen increases the relative risk of AAU by 26 times [3]. Although 45–70% of patients with AAU are HLA-B27 positive compared to only 4–8% of the general Caucasian population, it should be appreciated that 99% of subjects that have the HLA-B27 gene are healthy and will not develop associated diseases during their lifetime. This implies that other genetic factors and environmental factors such as microbial triggers play an important role in the development of AAU (as discussed in Sect. 2.3.2).

X ray crystallography has demonstrated the three-dimensional structure of HLA-B27. It is a heterodimeric membrane-bound glycoprotein consisting of a polymorphic  $\alpha$  chain, which is noncovalently linked to non-polymorphic  $\beta$ -2-microglobulin. The  $\alpha$  chains contain two peptide-binding domains ( $\alpha$ 1 and  $\alpha$ 2) which form antigen-binding clefts that bind short peptides of 8–12 amino acids [20].

### 2.3.1 New Developments in the Immunogenetics of HLA-B27

Recent studies have shown that HLA-B27 is not a single allele but a family of at least 31 different alleles that encode for HLA-B27 subtypes (named HLA-B\*2701 to HLA-B\*2728) [17]. There is a varied distribution of these HLA-B27 subtypes in different populations, and this may account for the varying strengths of HLA-B27-disease association that are observed in different ethnic groups. The more common subtypes, HLA-B\*2705 (accounts for about 90% of HLA-B27+ individuals of northern European descent), B\*2702 and B\*2704, have been shown to be strongly associated with AS [17]. Both HLA-B\*2705 and B\*2702 were also strongly associated with AAU in a study of Dutch patients [11]. There has not been a study of other HLA-B27 subtypes and their association with AAU. However, at least two subtypes, HLA-B\*2706 (common in Southeast Asia) and B\*2709

(found in Sardinia) appear to lack a disease association with AS [17]. These HLA-B27 subtypes vary from each other by only one or several amino acids, mostly at the antigen-binding region of the molecule, and are thus expected to alter the range of antigenic peptides bound and presented to T cells by HLA-B27. The finding of differential HLA-B27 subtype disease association thus suggests that the antigen-presentation function of HLA-B27 may play an important role in the pathogenesis of disease. Such observations support the “arthritogenic” or “uveitogenic” peptide hypothesis for AS or HLA-B27+ AAU pathogenesis, which proposes that disease is a consequence of self-reactive cytotoxic T lymphocytes (via molecular mimicry) that are activated against a peptide found only in the joint or uvea [8, 17].

Recent studies using animal models of HLA-B27-associated inflammatory diseases have clearly demonstrated the direct pathogenic role of HLA-B27. HLA-B27 transgenic rats and mice that express human HLA-B27 antigens were found to spontaneously develop a multisystemic inflammatory disease resembling the spectrum of human HLA-B27-associated spondyloarthropathies (SpA) [8, 18, 31]. Of particular interest, these transgenic animals were healthy if kept in a germ-free environment, but once moved to a normal environment and exposed to commensal microbes, acute development of enterocolitis, ankylosing arthritis, enthesitis, psoriasiform skin lesions and inflammatory male genital lesions were triggered [32]. This provides further evidence to support not only the importance of genetic factors but that of environmental factors and in particular, microbial triggers, in the development of HLA-B27-associated diseases (see the next section). Interestingly, however, AAU was not a prominent feature of the HLA-B27 transgenic animal models.

### Summary for the Clinician

- Although other genes are almost certainly involved, HLA-B27 remains the strongest known genetic risk factor for AAU.
- HLA-B27 is not a single allele. Instead, there are multiple subtypes of HLA-B27, which appear to have differential associations with disease. The more common subtypes, HLA-B\*2705, B\*2702 and B\*2704, are strongly associated with AS and AAU.
- Transgenic animals expressing human HLA-B27 spontaneously develop a multisystemic inflammatory disease.

### 2.3.2 Role of Microbial Triggers in Immune-Mediated Inflammation

It is clear that specific environmental factors play a critical role in the development of HLA-B27 AAU, as the great majority of HLA-B27-positive individuals do not develop inflammatory diseases despite the strong relative genetic risk of developing AS or AAU. In particular, there is extensive evidence from both clinical and experimental studies that support the role of microbial triggers in the development of AAU. Reactive arthritis and uveitis are prototypical examples of the development of noninfectious immune-mediated inflammation following a triggering genitourinary or gastrointestinal tract infection. *Chlamydia trachomatis* and Gram-negative bacteria, such as certain species of *Salmonella*, *Shigella*, *Campylobacter*, *Klebsiella* and *Yersinia*, have been implicated in the pathogenesis of HLA-B27+ AAU [8]. The precise pathogenic mechanism remains unclear, but putative “uveitogenic” peptides from these bacteria have been shown to have the necessary sequences to be able to be bound and presented by HLA-B27 to T cells. It has been proposed that these microbe-derived antigens may trigger CD8+ T cell immune responses that cross-react with self-tissue antigens (molecular mimicry) that are uniquely found in the uvea or joint tissue, resulting in autoimmune tissue inflammation [8].

Microbial triggers have been implicated in the pathogenesis of recurrent attacks of HLA-B27+ AAU. Raised antibody levels against *Salmonella*, *Campylobacter jejuni*, *Klebsiella pneumonia* and *Yersinia* were found to be associated with recurrent attacks of AAU [15]. Furthermore, a close relation between the recurrences of AAU and chronic asymptomatic ileocolitis has been observed, implicating a pathogenic role for mucosal infection in the development of anterior uveitis [1].

It is also of interest that many animal models of anterior uveitis involve the induction of ocular inflammation with microbial cell wall components, such as endotoxin or lipopolysaccharide (LPS) of Gram-negative bacteria, and peptidoglycan (PGN) or lipoteichoic acid (LTA) of Gram-positive bacteria [8, 9]. The eye appears to be highly and selectively sensitive to the pro-inflammatory effects of LPS in endotoxin-induced uveitis (EIU), with no significant abnormalities observed in other organs in response to the uveitogenic dose of LPS. EIU is the most widely used animal model for AAU, and a low dose of LPS given at a site remote from the eye induces an acute breakdown in the blood–aqueous barrier and

the influx of acute inflammatory cells into the anterior uvea and AC [8, 26]. Some of the recent developments in our understanding of innate immunity and the Toll-like receptors (TLR) have led to new insights into the potential mechanisms behind these important observations linking microbial triggers and inflammatory disease, including AAU (see Sect. 2.5.2) [9].

### 2.3.3 HLA-B27-Associated Inflammatory Disease

HLA-B27 is associated with not just AAU but a spectrum of seronegative spondyloarthropathies (SpA). The strongest disease association of HLA-B27 is with ankylosing spondylitis (AS), but the other HLA-B27-associated inflammatory diseases include reactive arthritis, inflammatory bowel disease (IBD) and its associated arthropathy, psoriatic arthropathy, and undifferentiated SpA. From the available data, it is estimated that more than half of the patients with HLA-B27+ AAU will develop AS or one of the other SpA, whilst approximately 25% of the patients initially diagnosed with HLA-B27 associated systemic disease will develop AAU during their lifetime [8]. The ophthalmologist must be aware of these systemic disease associations of HLA-B27 AAU, as he is uniquely placed to recognize a unifying systemic HLA-B27-related diagnosis in patients with AAU and symptoms of joint, skin or GIT dysfunction. This requires careful clinical assessment, follow-up and referral to the relevant internist for further investigation.

#### Summary for the Clinician

- Environmental factors, in particular microbial triggers, are clearly important in the pathogenesis of AAU.
- *Chlamydia trachomatis* and Gram-negative bacteria have been implicated in the pathogenesis of HLA-B27+ AAU, including certain species of *Salmonella*, *Shigella*, *Campylobacter*, *Klebsiella* and *Yersinia*.
- Microbial products, such as LPS of Gram-negative bacteria, have been used to induce various animal models of AAU. The most widely adopted model of AAU is endotoxin-induced uveitis (EIU).
- Patients with HLA-B27 AAU are at increased risk of developing an associated systemic inflammatory disease, and vice versa.

### 2.4 Other Genetic Risk Factors for Acute Anterior Uveitis

Observations, including those from twin concordance studies and of familial aggregation of AAU, indicate that there are other non-HLA-B27 genes, both within and outside the MHC, that predispose to the development of AAU. HLA-B27-positive first-degree relatives of patients with HLA-B27 AAU have a higher risk (13%) of developing AAU than HLA-B27-positive individuals without affected relatives (1%) [12]. Recent genome-wide scans of families with multiple affected members with AAU have identified several chromosomal regions associated with AAU, including regions on chromosomes 3, 5, 9, 13 and 15. Strong linkage was observed at a locus at chromosome 9p21–9p24 that uniquely associated with AAU but not with AS [21].

Chemokines play a pathogenic role in AAU by recruiting inflammatory cells to the AC (see Sect. 2.5.1). A recent study has reported a significantly increased frequency of a functional polymorphism in the promoter region of the gene for the chemokine CCL2/monocyte chemoattractant protein (MCP)-1 in patients with HLA-B27+ AAU compared to HLA-B27+ healthy controls [35].

Similarly, there are also probably as-yet-unidentified genetic risk factors for idiopathic HLA-B27-negative AAU. For example, MHC class I chain-associated gene A (MICA) A4 allele was found to be at significantly higher frequency in patients with HLA-B27-negative AAU compared to that in ethnically matched HLA-B27-negative controls [14].

### 2.5 Current Understanding of AAU Pathogenesis

There have been recent advances in our understanding of the immunopathogenesis of AAU due to the existence of several good animal models of AAU, as well as the development of powerful new research tools, such as intravital microscopy for studying leukocyte interactions with the uveal vasculature in vivo during the various stages of experimental AAU, advances in molecular biology (such as DNA microarrays that can rapidly screen for tens of thousands of genes), and advances in proteomics. However, although we are now able to dissect the multitude of molecular steps in the evolution of acute intraocular inflammation and the individual effects of modulating these pathways, there is still much to be learned. For example, the critical initial processes involved in the breakdown of ocular immune privilege, the restriction of inflammation to one eye, the triggering of recurrent attacks of AAU, or the processes responsible for the progression of AAU



to chronic inflammation are unknown. The elucidation of these immune mechanisms may lead to the development of truly revolutionary therapies for halting AAU early and preventing the development of sight-threatening, recurrent or chronic anterior uveitis.

### 2.5.1 Cytokines

Cytokines are soluble mediators produced by various cells of the innate and adaptive immune system that orchestrate, coordinate and integrate these two arms of the immune response. Cytokines typically have pleiotropic effects, including pro-inflammatory, anti-inflammatory and chemoattractant functions. Leukocyte extravasation from the blood into the tissue is a regulated multistep process involving a series of coordinated interactions between leukocytes and endothelial cells involving selectin-mediated rolling, integrin-mediated firm adhesion, and chemokine-mediated migration. Chemokines are of pathogenic importance in the selective intraocular recruitment of neutrophils, monocytes and CD4+ T lymphocytes in uveitis.

Each step of the cell recruitment process is important in the pathogenesis of experimental AAU, and selectively inhibiting any step will partially abrogate uveal inflammation. There is significant redundancy in the process, with another pro-inflammatory pathway being able to largely take over the role of one that has been selectively inhibited.

High aqueous humor levels of various pro-inflammatory cytokines, such as TNF- $\gamma$ , IFN- $\gamma$ , IL-2 and IL-12, and low intraocular expression of the anti-inflammatory cytokine IL-10 have been shown in human AAU [8]. Elevated aqueous humor expression of chemokines that selectively recruit the acute inflammatory cells in AAU have been demonstrated in patients with active AAU. IL-8/CXCL8 (recruits neutrophils), interferon-gamma-inducible protein (IP)-10/CXCL10, MCP-1/CCL2, RANTES (regulated upon activation, normal T cell expressed and secreted)/CCL5 and macrophage inflammatory protein (MIP)-1 $\beta$ /CCL4 (recruits monocytes and activated T cells) were significantly elevated during the active stages of AAU and correlated with the clinical severity of the disease [34].

### 2.5.2 Toll-Like Receptors (TLR)

Recent progress in our knowledge of a family of innate immune receptors called Toll-like receptors (TLRs) has shed new light on our understanding of the normal host

immune defense against microbes and the pathogenesis of a wide range of infectious and noninfectious autoimmune diseases. TLRs are a family of so-called pattern recognition receptors (PRR) that recognize "signature patterns" of microbes called "pathogen-associated molecular patterns" (PAMPs). Ten human TLRs have been identified to date, each of which recognize PAMPs from a unique class of microbes; for example, TLR4 responds to LPS of Gram-negative bacterial cell wall whilst TLR2 recognizes Gram-positive bacterial cell wall components [9, 23, 30]. Thus, the discovery of TLRs has conferred a degree of specificity to innate immunity that had not been previously recognized [23]. Activation of TLRs by their ligands results in the initiation of a pro-inflammatory cascade, the activation of the transcription factor NF $\kappa$ B, leading to the production of pro-inflammatory cytokines, chemokines and activation of immune cells. Thus, these PRRs allow the innate immune system to respond rapidly to microbes at host/environment interfaces that express high levels of TLRs [9, 30]. There has been immense research on this family of receptors in the past decade, and they have since been implicated in the pathogenesis of a variety of inflammatory diseases, including IBD, AS and psoriasis [5, 30, 36]. Notably, all of these diseases can be complicated by AAU and are recognized systemic associations with HLA-B27+ AAU. In IBD, it is thought that inappropriate and hyper-responsive inflammation triggered by various TLRs to commensal gut bacteria may play a critical role in the observed chronic intestinal inflammation.

Functional TLR4 expression by uveal antigen-presenting cells (APC) in the normal human iris and ciliary body has been recently demonstrated [4, 7, 9]. This provides a novel mechanism by which the various implicated microbial triggers could initiate the development of AAU, and explains the apparent high sensitivity of the uvea to LPS (now recognized as being the ligand for TLR4). LPS activation of perivascular TLR4-expressing uveal dendritic cells (DCs) could lead to the production of pro-inflammatory cytokines and the activation of vascular adhesion molecules, a breakdown in the blood-ocular barrier, and the recruitment of inflammatory cells to the AC [7, 9]. TLR4 is absolutely essential for inflammatory responses to LPS. In the animal model for AAU, the C3H/HeN strain of mice (which are highly sensitive to developing EIU) has normal functional TLR4, whilst the congenic C3H/HeJ strain with nonfunctional TLR4 does not develop EIU [9, 30].

Perturbations in the expression and function of TLR4 and TLR2 have been observed in patients with active AAU, further supporting the potential pathogenic role of these PRRs in the development of AAU [10]. These TLRs could provide the missing molecular link between the

observations of microbial triggers and the development of AAU and other immune-mediated inflammatory disorders, but further studies are still required.

### Summary for the Clinician

- Increased levels of pro-inflammatory cytokines and chemokines are found in the aqueous humor of patients with active AAU
- Toll-like receptors (TLR) are a family of pattern recognition receptors that recognize a variety of microbial products and lead to inflammation
- TLRs have been implicated in the pathogenesis of numerous inflammatory diseases, including HLA-B27-associated AS, IBD and AAU
- EIU, the animal model for AAU, is critically dependent on functional TLR4, the receptor for LPS of Gram-negative bacteria
- Uveal APCs in the human eye express TLR4, and perturbations in the TLRs have been observed in patients with AAU

**Table 2.3.** Standardized (SUN<sup>a</sup>) grading system for AC cell and flare severity [30]

Grade	AC cells	AC flare
0	None	None
0.5+	1–5 cells in the field <sup>b</sup>	-
1+	6–15 cells <sup>b</sup>	Faint
2+	16–25 cells <sup>b</sup>	Moderate (iris and lens details are clear)
3+	26–50 cells <sup>b</sup>	Marked (iris and lens details are hazy)
4+	>50 cells <sup>b</sup>	Intense (fibrin or plasmoid aqueous)

<sup>a</sup>Standardization of Uveitis Nomenclature (SUN)

<sup>b</sup>Field size used is a 1 mm by 1 mm slit beam. The presence or absence of a hypopyon should be noted separately in addition to the AC cellular activity grade

AAU [8]. There is a subset of idiopathic HLA-B27-negative AAU that is clinically difficult to distinguish from HLA-B27-positive AAU.

## 2.6 Clinical Features of Acute Anterior Uveitis

### 2.6.1 HLA-B27 and Clinical Phenotype

AAU presents with the clinical features of acute inflammation in the anterior segment of the eye (primarily the iris, ciliary body and AC). The typical phenotype of HLA-B27-positive AAU is that of abrupt onset of unilateral, often alternating, nongranulomatous AAU, characterized by the acute onset of a red, photophobic, painful eye and significant cellular and protein extravasation into the aqueous humor, clinically detectable as AC cells and flare on slit lamp examination. There is a standardized international grading system for grading AC cells and flare activity (Table 2.3, Standardization of Uveitis Nomenclature) [16]. HLA-B27-positive AAU has a high tendency to recur, and shows a significant association with other HLA-B27-related systemic diseases [8]. An episode lasts 6–8 weeks on average, and in cases of recurrent AAU, the intervals between the recurrent attacks are highly variable (from months to years).

In contrast, HLA-B27-negative anterior uveitis tends to be a more heterogeneous entity that is more likely to become bilateral or chronic uveitis, and which is infrequently associated with systemic diseases. Recurrent inflammation is not uncommon in HLA-B27-negative

### 2.6.2 Ocular Complications

Although AAU is generally associated with a good visual prognosis, it is not without its complications or visual morbidity, especially with recurrent attacks of ocular inflammation. In a study on the causes of visual impairment and blindness in intraocular inflammatory diseases, 10% of patients with HLA-B27-associated anterior uveitis suffered legal blindness or severe visual impairment [28]. Another case series found that 7% of their 175 patients with HLA-B27-associated uveitis demonstrated significantly decreased final visual acuity (>2 Snellen lines) [24]. The most important cause of reduced vision in patients with AAU is cystoid macular edema (CME), which has been reported to be as high as 17–25% [8, 24, 25], although these figures are almost certainly higher than those seen in the community, due to the influence of referral bias in these studies.

Posterior synechiae is by far the commonest complication of AAU. With the development of recurrent AAU or chronic inflammation, cataract and secondary glaucoma (as complications of the inflammation itself or induced by corticosteroid therapy) frequently cause visual impairment. Complications in patients with HLA-B27 related AAU are related to the number of recurrent attacks [27, 33].

### Summary for the Clinician

- HLA-B27-positive AAU exhibits a distinct clinical phenotype compared to its HLA-B27 negative counterpart. This includes a tendency for recurrent attacks of inflammation, increased tendency for more severe AC inflammation including fibrinous reaction and hypopyon formation, and significant associations with extraocular inflammatory disease.
- There is a new international grading system for AC inflammatory activity (the Standardized Uveitis Nomenclature).
- About 10% of patients with HLA-B27-associated anterior uveitis suffer significant visual impairment due to sight-threatening complications such as CME, cataracts and secondary glaucoma.

## 2.7 Clinical Management of AAU

The investigation of AAU should be governed by the clinical history, the review of systems, and examination findings. In particular, careful attention should be paid to symptoms of possible associated systemic diseases, such as inflammatory back pain of AS, skin changes of psoriasis, or gastrointestinal symptoms of IBD. Dilated fundus examination is mandatory in the assessment of any patient with “anterior uveitis,” in order to ensure that the disease is confined to the anterior segment and that the symptomatic anterior uveitis is not part of an intermediate or panuveitis.

There is no consensus on the extent of investigations indicated for the first episode of AAU. We recommend HLA-B27 typing, a chest X ray and syphilis serology as the minimum investigations for patients with their first attack of AAU. The HLA-B27 status has significant implications regarding the potential risk of further recurrent episode(s) of AAU (often a primary concern for the patient suffering their first attack) and the risk of developing HLA-B27 associated SpA. Syphilis serology remains a cost-effective investigation for syphilis, an increasingly common, treatable infectious cause of all forms of uveitis, including AAU [13]. A chest X-ray is recognized as being a useful screening investigation for asymptomatic pulmonary sarcoidosis, which may present as acute uveitis.

The mainstay of AAU treatment consists of topical corticosteroids, the intensity of administration of which is tailored to the severity of the AC inflammation. The general principle is to hit the inflammation hard early on in its course with intensive topical steroids, such as with prednisolone acetate 1% drops hourly initially. More severe

inflammation associated with fibrin formation, hypopyon or severe pain may require subconjunctival steroid therapy or oral corticosteroids. Topical cycloplegic agents, such as atropine or homatropine, are essential for minimizing posterior synechiae formation and providing symptomatic relief from pain and photophobia. Topical steroids are slowly tapered over 6–8 weeks once the inflammatory activity is controlled. The total treatment course should cover at least 6–8 weeks to minimize premature cessation of topical steroids, which would be associated with a relapse in the partially treated inflammation (rather than a true recurrence) and would ultimately prolong the overall treatment course and increase the risk of developing chronic uveitis.

Systemic treatment with corticosteroids may be required to treat very severe uveitis that is resistant to maximum topical and local corticosteroid therapy. Other immunosuppressive agents are rarely needed to manage patients with recurrent AAU. Drugs such as salazopyrine and methotrexate are commonly used to treat IBD and SpA, and anecdotally there is evidence that this may decrease the frequency and severity of attacks of AAU. Chronic anterior uveitis associated with CME and reduced vision may, in selected patients, benefit from systemic immunosuppressive therapy. Exciting new biologic treatment modalities are being evaluated, including anti-TNF $\alpha$  therapy, anti-VEGF (vascular endothelial growth factor) therapy, and HLA-B27 peptide oral tolerance [8]. However, there is insufficient evidence to support the use of these newer agents at present, and more studies are required to establish their clinical indications, efficacy and safety.

## 2.8 Conclusions

AAU is a common condition that affects relatively young patients and can cause significant distress to the patient, with recurrent, unpredictable attacks of acute inflammation. Furthermore, AAU can be associated with sight-threatening complications such as CMO, and therefore it represents an important cause of visual impairment. The unique association between HLA-B27 AAU and its related systemic inflammatory diseases demands a comprehensive and holistic approach to managing patients with AAU, often requiring careful follow-up and liaison between multiple specialists. The great majority of uveitis cases seen by the general ophthalmologist will be AAU, and about half of these will be HLA-B27+ AAU, thus highlighting their clinical importance. Recent advances in our understanding of the genetics, immunology and pathogenesis of this condition will hopefully lead to improved care of our patients suffering from AAU.



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Uveitis and Immunological Disorders

Progress III

Pleyer, U.; Forrester, J.V. (Eds.)

2009, XIV, 120 p. 30 illus., 23 illus. in color., Hardcover

ISBN: 978-3-540-69458-8