

# Uveitis associated with Juvenile Idiopathic Arthritis

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PReS Latin American Pediatric Rheumatology Course, Sao Paolo, June 2015

- Epidemiology
- Presentation and Prognosis
- Assessment
- Treatment

## Uveitis in JIA

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## Epidemiology

JIA: major course of chronic intraocular inflammation in children

81% of patients with uveitis

95% of patients with anterior uveitis

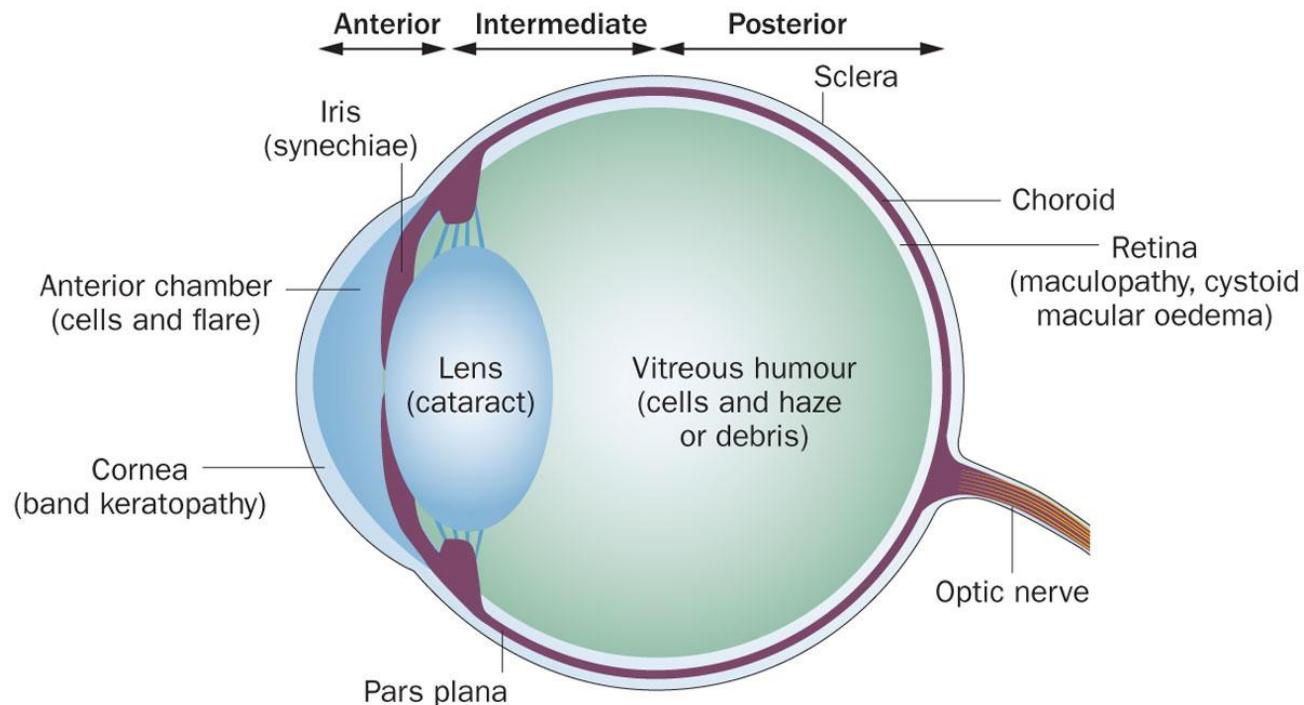
Uveitis: one of most severe extra-articular complications JIA

12-30% of all JIA patients

65% bilateral

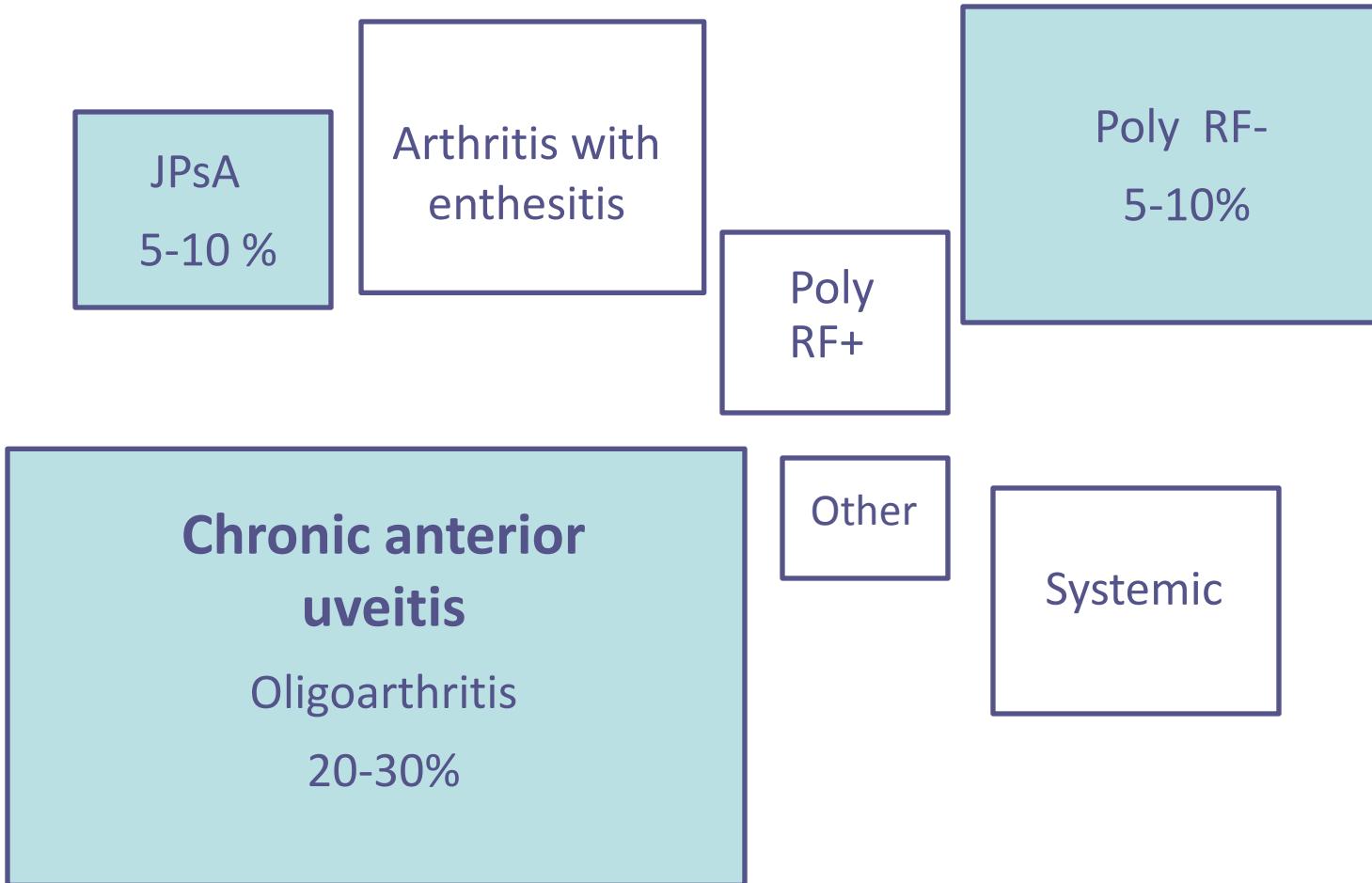
# Uveitis in JIA

# Epidemiology

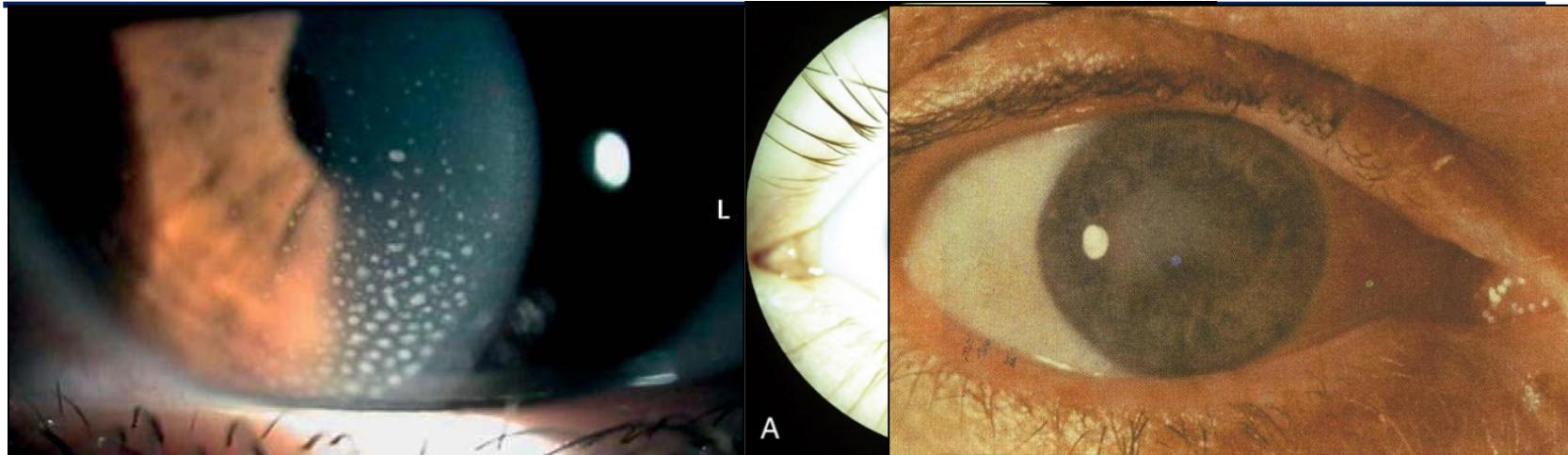


## Types of uveitis in JIA

Chronic anterior	68.3%
Acute anterior	16.2%
Recurrent anterior	12%
Panuveitis	3.5%



# Chronic anterior uveitis



Insidious onset, asymptomatic, (rarely headache, photophobia)

Within 5-7 (mean 1.8) yrs after onset arthritis

Preceding arthritis in 3-7%

Advanced changes at presentation: posterior synechiae,  
band keratopathy, cataract

Highest risk: early onset of arthritis, presence ANA  
(girls, oligoarthritis)

## Acute anterior uveitis

JPsA  
5-10 %

Arthritis with  
enthesis

Poly  
RF+

Poly RF-  
5-10%

## Chronic anterior uveitis

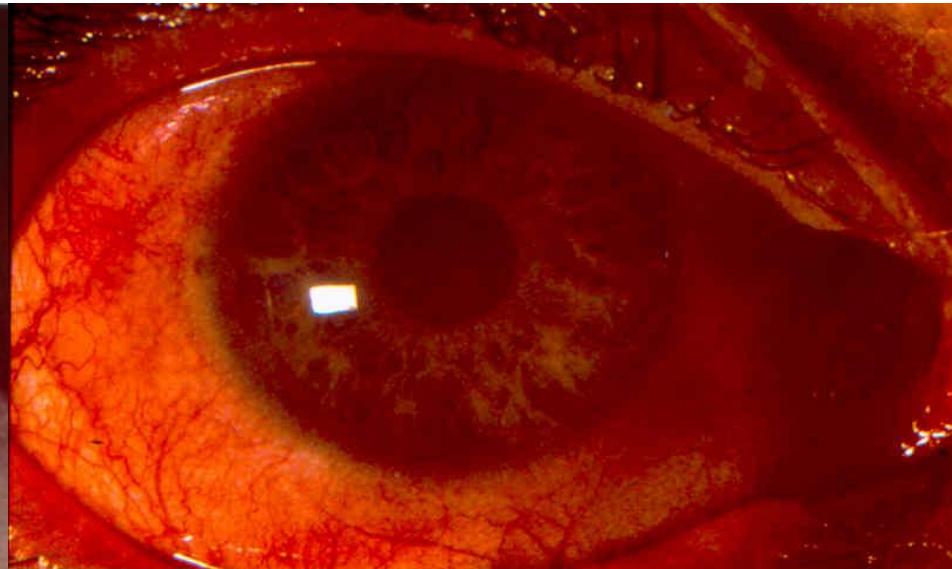
Oligoarthritis  
20-30%

Other

Systemic

# Acute anterior uveitis

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glaucoma,  
edema

Acute uveitis, often unilateral  
Painfull red eye  
Duration 2- 3 weeks,  
Rarely complications: cataract,  
macular

## Uveitis in JIA

## Prognosis

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Ant/post synechiae	8-75%
Cataracts	20.5 (15-26)%
Glaucoma	18.9 (14-24)%
Band keratopathy	15.7 (11-22)%

Rarely: cystoid macular edema, papillary edema,  
retinal detachment, phtysis

→ Adverse visual outcome      9.2 (4-16) %

# Complications of Uveitis in JIA

## Risk factors

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Young age at onset

Male gender

Short interval between arthritis and uveitis onset

Uveitis preceding arthritis

At first presentation: complications (synechiae, cataract)  
impaired vision (<20/60)

Long duration of active uveitis ( $\geq 1$  AC cells or  $\geq 0.5$  vitreous haze)

Bilateral uveitis

Posterior synechiae

Abnormal intraocular pressure ( $< 5$  mmHg or  $> 21$  mmHg)

# Uveitis in JIA

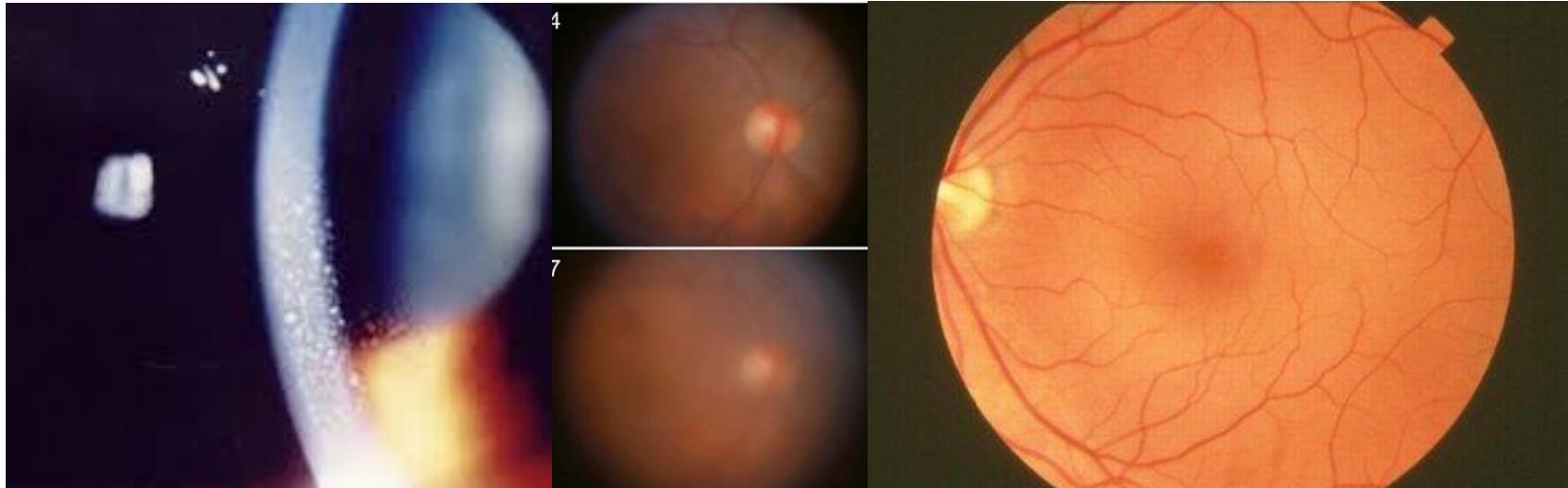
# Risk factors visual loss

	≤20/50* (Crude†)			≤20/50* (Adjusted‡)			≤20/200* (Crude†)			≤20/200* (Adjusted‡)		
	HR	95% CI	P Value	HR	95% CI	P Value	HR	95% CI	P Value	HR	95% CI	P Value
Age at diagnosis (per year)	0.99	0.99–1.00	<0.01				0.99	0.99–1.00	<0.01			
Female gender	1.03	0.80–1.34	0.82				1.04	0.75–1.44	0.81			
Nonwhite race	1.33	1.02–1.73	0.03				2.63	1.99–3.46	<0.01			
Bilateral disease	0.89	0.54–1.44	0.63				0.59	0.35–1.01	0.05			
Uveitis duration	0.98	0.97–0.99	<0.01				0.99	0.98–1.01	0.34			
Posterior synechiae	1.63	1.30–2.05	0.01	1.58	1.25–1.99	<0.01	1.44	1.07–1.93	0.02	1.54	1.14–2.09	<0.01
Band keratopathy	1.17	0.94–1.44	0.13	1.20	0.97–1.49	0.10	1.38	1.06–1.81	0.02	1.32	1.00–1.74	0.05
Abnormal IOP§	1.26	0.99–1.61	0.06	1.33	1.03–1.70	0.03	1.14	0.83–1.56	0.42	1.10	0.79–1.51	0.59
Prior ocular surgery	1.76	1.39–2.25	<0.01	1.73	1.36–2.21	<0.01	3.40	2.35–4.92	<0.01	2.93	2.01–4.26	<0.01
AC cells¶												
0 AC cell grade	1.00			1.00			1.00			1.00		
0.5+ AC cell	1.37	1.12–1.69	<0.01	1.13	0.86–1.49	0.37	1.15	0.89–1.49	0.29	1.10	0.92–1.54	0.19
1+ AC cell	1.43	1.14–1.80	<0.01	1.41	1.12–1.78	<0.01	1.53	1.15–2.03	<0.01	1.37	1.03–1.84	0.03
2+ AC cell	1.51	1.13–2.03	<0.01	1.49	1.11–2.00	<0.01	1.80	1.29–2.53	<0.01	1.82	1.30–2.55	<0.01
3+ AC cell	1.74	1.11–2.73	0.02	1.68	1.07–2.64	0.02	3.33	2.18–5.08	<0.01	2.43	1.46–4.06	<0.01
4+ AC cell	2.45	0.91–6.62	0.08	2.23	0.83–6.01	0.11	6.99	3.29–14.84	<0.01	6.42	2.98–13.84	<0.01
Any vitreous cell or haze¶	1.29	1.05–1.59	0.02	1.32	1.07–1.62	0.01	1.43	1.10–1.95	<0.01	1.50	1.14–1.97	<0.01
Use of oral corticosteroids¶	1.26	1.02–1.56	0.03	1.43	1.15–1.79	<0.01	1.29	0.99–1.69	0.06	1.31	1.00–1.73	0.05
Use of IMT¶	0.39	0.21–0.74	<0.01	0.40	0.21–0.75	<0.01	0.79	0.57–1.08	0.14	0.80	0.62–1.02	0.08
logMAR score¶	1.09	0.94–1.27	0.25	1.13	0.97–1.32	0.12	2.47	2.13–2.87	<0.01	2.43	2.08–2.86	<0.01

- Epidemiology
- Presentation and Prognosis
- **Assessment**
- Treatment

# Uveitis in JIA

# Assessment



- Slit lamp      Anterior chamber cells and flare  
                    Vitreous cells and haze/debris  
                    Fundus and macula
- Intraocular pressure
- Visual acuity

## Anterior chamber inflammation

Cell counts in aqueous humor

Anterior chamber flare

Grading by SUN criteria

Slit lamp

Laser flare photometry

### **Box 2 | Criteria for uveitis activity\***

#### **Grading schemes**

Anterior chamber cells<sup>‡</sup>

- Grade 0 (<1) Inactive disease
- Grade 0.5+ (1–5)
- Grade 1+ (6–15)
- Grade 2+ (16–25)
- Grade 3+ (26–50)
- Grade 4+ (>50)

Anterior chamber flare

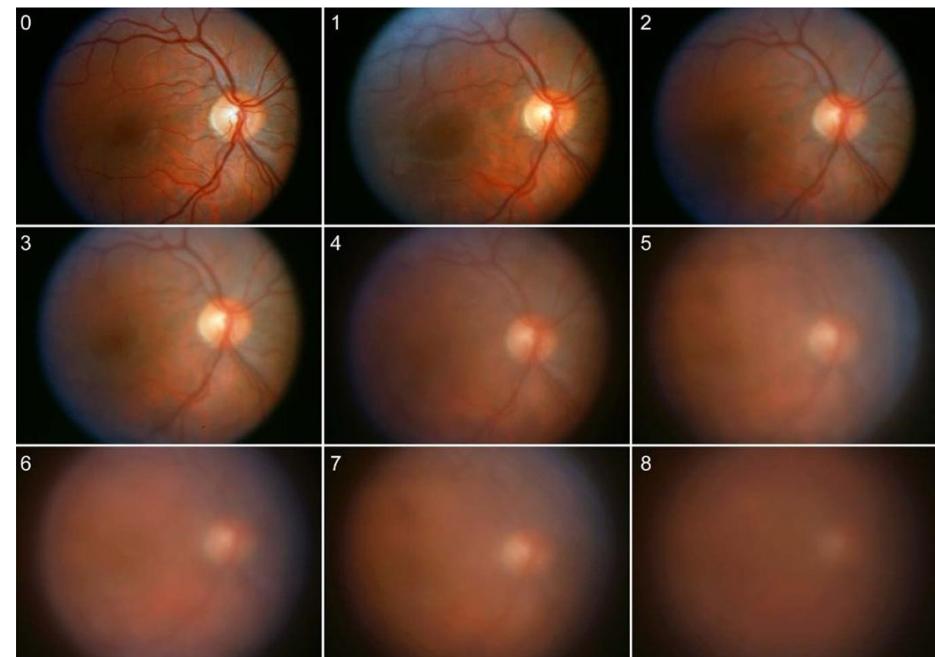
- Grade 0: None
- Grade 1+: Faint
- Grade 2+: Moderate (iris and lens details clear)
- Grade 3+: Marked (iris and lens details hazy)
- Grade 4+: Intense (fibrin or plastic aqueous)

\* Standardisation of Uveitis Nomenclature (SUN) international working group, Am J Ophthalmol 2005

## Intermediate and posterior uveitis

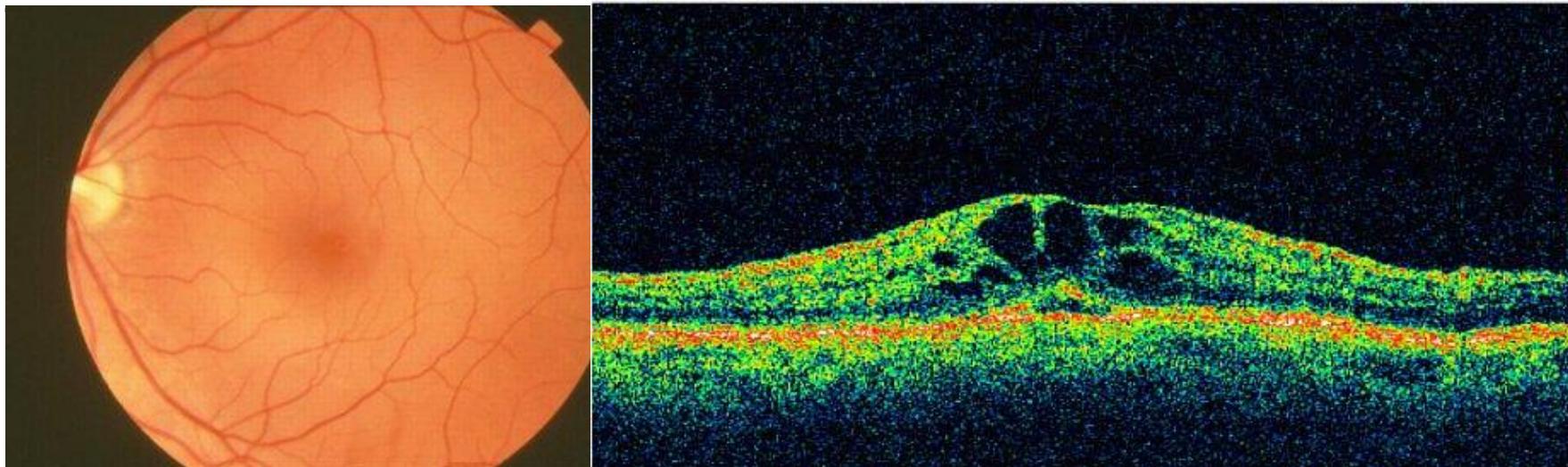
Vitreous haze  
cells and protein exudation  
obscuration fundus details

Fundus photographs  
Nussenblatt grading system



# Uveitis in JIA

# Assessment



## Fundus and macula

Fundoscopy with retinal exam

(Fluorescein angiography)

Optical coherence tomography

thickness of macula and fovea

maculopathy, cystoid macular edema

# Proposed Outcome Measures for Prospective Clinical Trials in Juvenile Idiopathic Arthritis–Associated Uveitis: A Consensus Effort From the Multinational Interdisciplinary Working Group for Uveitis in Childhood

*Heiligenhaus et al, Arthr Care and Research, 2012*

Grade of cells in anterior chamber

Grade of flare in anterior chamber\*

Number of visits with active uveitis

Visual acuity (appropriate test for age)

Development of structural complications

Slit-lamp examination

Slit-lamp examination for routine clinical practice and prospective trials

Laser flare photometry for prospective trials

Records of treating physician

Duration of activity over a minimum of 4 visits/year

Best-corrected visual acuity

Thresholds:  $\leq 20/50$ ,  $\leq 20/200$ , and no light perception

Estimate contribution of amblyopia, yes/no

Synechiae, yes/no

Initial and additional

Ocular hypotony, yes/no

Ocular hypertension, yes/no

Glaucoma, yes/no

Cataract, yes/no

Band keratopathy in the central cornea, yes/no

Macular edema, yes/no

Funduscopy for routine clinical practice

Funduscopy and optical coherence tomography for prospective trials

Epiretinal membrane formation, yes/no

Funduscopy for routine clinical practice

Funduscopy and optical coherence tomography for prospective trials

## Guidelines for Ophthalmologic monitoring in JIA

Type	ANA	Age @ onset (years)	Disease duration (years)	Risk category	Frequency eye exam. (months)
Pauci/poly	+	$\leq 6$	$\leq 4$	High	3
Pauci/poly	+	$\leq 6$	>4	Moderate	6
Pauci/poly	+	$\leq 6$	>7	Low	12
Pauci/poly	+	>6	$\leq 4$	Moderate	6
Pauci/poly	+	>6	>4	Low	12
Pauci/poly	-	$\leq 6$	$\leq 4$	Moderate	6
Pauci/poly	-	$\leq 6$	>4	Low	12
Pauci/poly	-	>6	N/A	Low	12
Systemic	N/A	N/A	N/A	Low	12

# Uveitis in JIA

## Screening guidelines

JIA subgroup	ANA	Age at JIA onset (yrs)	JIA duration (yrs)	Recommended screening intervals (months)
OA, RF-PA, PsA, AA	+	≤6	≤4	3
OA, RF-PA, PsA, AA	+	≤6	>4	6
OA, RF-PA, PsA, AA	+	≤6	≥7	12
OA, RF-PA, PsA, AA	+	>6	≤2	6
OA, RF-PA, PsA, AA	+	>6	>2	12
OA, RF-PA, PsA, AA	-	≤6	≤4	6
OA, RF-PA, PsA, AA	-	≤6	>4	12
OA, RF-PA, PsA, AA	-	>6	n.a.	12
ERA	n.a.	n.a.	n.a.	12
RF-PA, Sys A	n.a.	n.a.	n.a.	12
Patients with uveitis	n.a.	n.a.	n.a.	According to uveitis course

*Heiligenhaus et al, Rheumatology 2007*

# Treatment of JIA-associated uveitis

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- Corticosteroids
- Nonbiologic immunosuppressive drugs
- Biologic agents
- Surgery

# Steroids for JIA-associated uveitis

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- Topical corticosteroids

Prednisolone acetate 1% or dexamethasone phosphate 0,1%

Once daily to hourly (goal: AC cell grade 0)

Cave cataract if > 3 drops daily

- Local and Systemic corticosteroids

If no improvement/prognostic factors for impending loss of vision\*

Subconjunctival/orbital floor dexamethasone, triamcinolone acetonide

Oral prednisone 1-2 mg/kg, IV pulse MP 30 mg/kg 1-3 days

\* poor initial vision, cataract, dense vitreous opacities  
macular edema, ocular hypotony, glaucoma

# Nonbiologic immunosuppressive drugs for JIA-uveitis

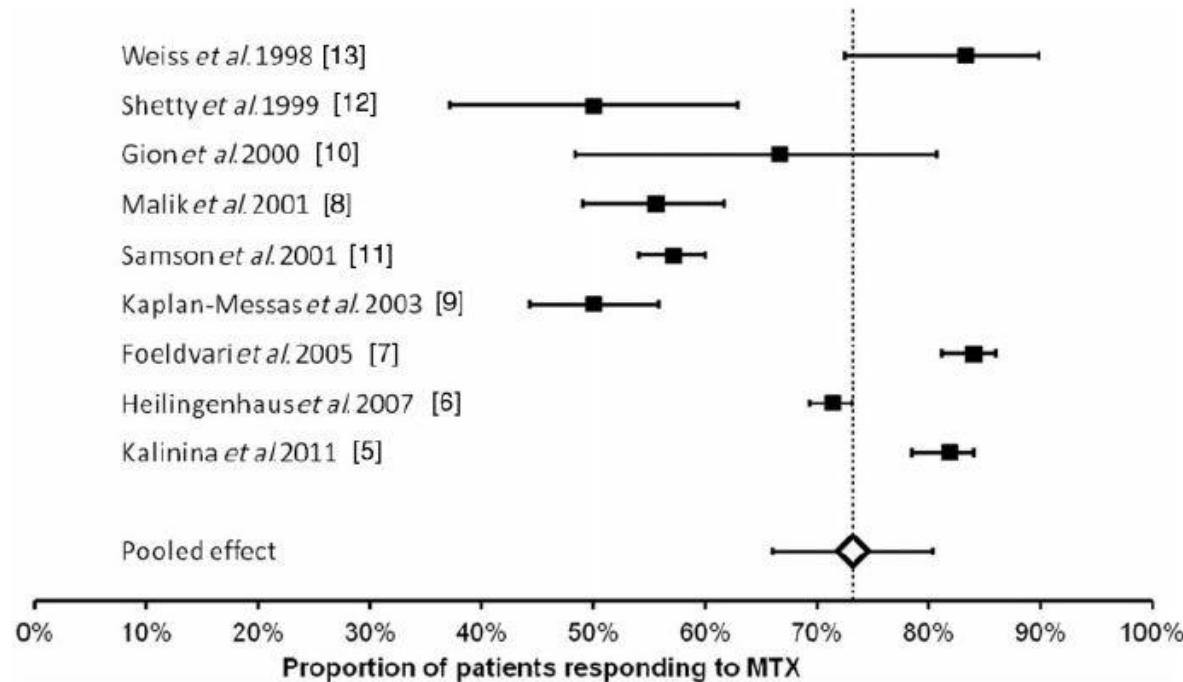
Drug name	Mechanism	Dosage and route	Common adverse effects	Evidence
Methotrexate	Cellular adenosine release <sup>100</sup>	10–15 mg/m <sup>2</sup> once weekly, oral or subcutaneous	Gastrointestinal discomfort, nausea, elevated liver enzyme levels	Systematic review and meta-analysis of retrospective case series ( <i>n</i> =135): improvement in 73% <sup>70</sup>
Azathioprine	Purine nucleoside analogue, inhibits DNA replication	1 mg/kg once daily, increasing up to a maximum of 3 mg/kg once daily	Gastrointestinal discomfort, bone marrow suppression, liver function impairment	Retrospective case series ( <i>n</i> =41): uveitis inactivity in 61.5% as initial monotherapy; 66.7% as combination therapy <sup>101</sup>
Mycophenolate mofetil	Inhibitor of inosine-5-monophosphate dehydrogenase	300 mg/m <sup>2</sup> twice daily, increasing to 600 mg/m <sup>2</sup> twice daily	Gastrointestinal discomfort, leukopenia, hair loss	Retrospective case series ( <i>n</i> =17, <i>n</i> =52, <i>n</i> =85, not all with JIA; various outcome measures): response in 55–88% <sup>102–104</sup>
Ciclosporin	Calcineurin inhibitor; blocks T-cell proliferation	2.5–5.0 mg/kg daily in 2 doses	Gastrointestinal disturbance, hypertension, renal and liver dysfunction, lipid abnormalities	Retrospective case series ( <i>n</i> =82, <i>n</i> =14): uveitis inactivity in 24% as monotherapy, 48.6% as combination therapy <sup>105,106</sup>
Tacrolimus	Calcineurin inhibitor; blocks T-cell proliferation	50–150 µg/kg twice daily	Gastrointestinal disturbance, hypertension, renal and liver dysfunction, lipid abnormalities, blood disorders	Retrospective case series ( <i>n</i> =62, mostly adults with idiopathic uveitis): enabled glucocorticoid tapering and improved visual acuity <sup>107</sup>

- Persistent/recurrent uveitis activity, new uveitis complications despite cs
- Immunosuppressives before biologics
- No randomized trials, only observational reports, case series

# Methotrexate for JIA-uveitis

Methotrexate efficacy in childhood chronic uveitis using a systematic review and meta-analysis: Improvement intraocular inflammation in 73% of JIA patients

**Fig. 1** Proportion of children with refractory ACU responding to MTX in each study and the overall effect size showed by the pooled analysis, 95% CI are shown.



# Methotrexate for JIA-uveitis

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- Early Methotrexate Therapy May Prevent the Onset of Uveitis in JIA  
*Papadopoulou J Ped 2013*
- Methotrexate is associated with reduced need for cataract surgery  
*Sijssens, Am J Ophthalmol 2007*
- Prolonged (> 3 yrs) MTX therapy and longer (>2yrs) uveitis inactivity before MTX withdrawal: reduced relapse after withdrawal  
*Ayuso, Am J Ophthalmol 2011*



Girl, 13 yrs, acquired heterochromia:  
Anterior/posterior uveitis



Bilateral uveitis progression:  
R/systemic steroids and MTX



Persistent inflammation,  
increased IOP, Cushing

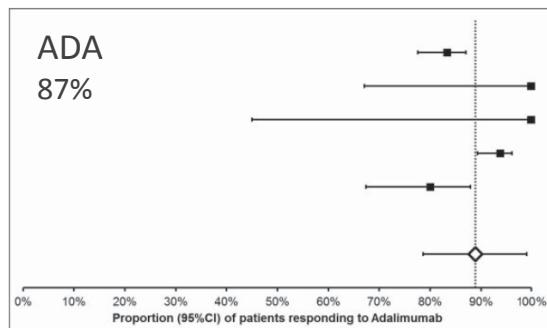
R/ Adalimumab SC:  
Control uveitis, stop steroids

# Biologic agents for JIA-associated uveitis

Drug name	Target	Drug class	Dosage and route	Evidence
Etanercept	TNF	Dimeric fusion protein	Not recommended for treatment of JIA-associated uveitis	RCT: no more effective than placebo Case reports of new uveitis on etanercept <sup>76,81</sup>
Infliximab	TNF	Chimeric (mouse–human) mAb	6 mg/kg intravenous initially, then 3–10 mg/kg Second dose at 2 weeks, then every 4–8 weeks depending on response	Several case series showing efficacy <sup>81</sup>
Adalimumab	TNF	Fully human mAb	24 mg/m <sup>2</sup> subcutaneously every 2 weeks In practice often 20 mg subcutaneously every 2 weeks (body weight <30 kg) or 40 mg subcutaneously every 2 weeks (body weight ≥30 kg)	Several case series showing efficacy RCTs in progress <sup>81,84</sup>
Golimumab	TNF	Fully human mAb	50 mg subcutaneously every 4 weeks	Case series ( <i>n</i> =3) showing efficacy <sup>108</sup>
Tocilizumab	IL-6	Humanized mAb	10 mg/kg (body weight <30 kg), 8 mg/kg (body weight >30 kg) intravenously every 4 weeks	Case series ( <i>n</i> =3) and case report showing efficacy <sup>86,109,110</sup>
Abatacept	CD80/CD86 (CTLA4)	Fully human fusion protein	10 mg/kg intravenously at weeks 0, 2 and 4, then every 4 weeks	Case series ( <i>n</i> =7, <i>n</i> =2) showing efficacy <sup>87,111,112</sup>
Rituximab	CD20	Chimeric (mouse–human) mAb	375 mg/m <sup>2</sup> or 750 mg/m <sup>2</sup> intravenously, in two doses 2 weeks apart	Case series ( <i>n</i> =10, <i>n</i> =8) showing efficacy in most patients <sup>113,114</sup>

- Etanercept not superior to placebo, new-onset and flares of uveitis in JIA with ETN, greater incidence of uveitis in national registries
- Adalimumab and Infliximab similar efficacy in meta-analysis
- Regained control of uveitis after switch to Adalimumab

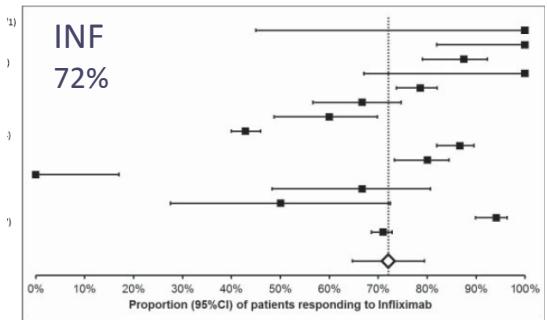
# Anti-TNF agents in childhood chronic uveitis



A

## Systematic Review and Meta-Analysis Effectiveness of individual anti-TNF agents

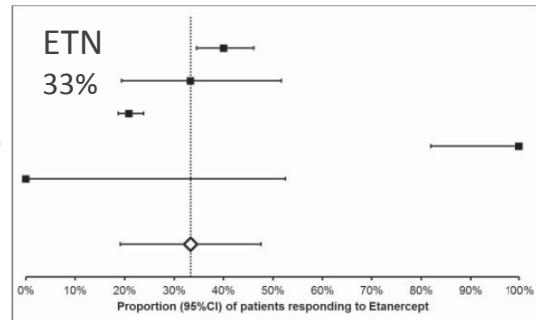
229 children with chronic uveitis refractory to steroids and at least 1 DMARD



B

INF and ADA similar benefits in treatment of childhood autoimmune uveitis, superior to ETN

Persistent remission more common with ADA



Simonini, Arthr Care Res 2014