Current clinical and research picture in paediatric anterior segment disorders

Jane Ashworth
Consultant Paediatric Ophthalmologist
Manchester Royal Eye Hospital

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Clinical topics in paediatric anterior segment disorders

- Atopic and vernal keratoconjunctivitis
- Prevention of corneal graft rejection
- Limbal stem cell transplantation
- Pain and inflammation post-paediatric cataract surgery

- Blepharokeratoconjunctivitis
- Pain management post-paediatric squint surgery

Atopic and vernal keratoconjunctivitis

- Immune mediated ocular surface inflammatory conditions

- **Atopic KC**-seasonal and perennial allergic conjunctivitis
- Adults and children, males and females
- Atopy, eczma

- **Vernal KC**-seasonal exacerbations
- Resolves by puberty
- Boys>girls 3:1

Atopic keratoconjunctivitis

- Effects 20-40% of those with atopic dermatitis
- Bilateral, symmetrical
- Itchy, watery, photophobia, stringy mucoid discharge
- Conjunctival papillae
- Epithelial defects, corneal scarring and vascularisation

Treatments for atopic keratoconjunctivitis in children

- **Antihistamines**-levocabastine, azelastine*, emedastine*
- **Mast cell stabilisers-** sodium chromoglycate*, nedocromil*, lodoxamide*
- **Combined action**–bepotastine, olopatadine* ketotifen*
- **Topical steroids**

- **Topical NSAIDS**
- **Immune modulators-**Cyclosporin, Tacrolimus
- **Sublingual immunotherapy**

Swamy, et al. Topical non-steroidal anti-inflammatory drugs in allergic conjunctivitis: meta-analysis of randomized trial data Ophthalmic Epidemiology Volume 14, Issue 5, 2007. Pages: 311

A randomised trial of topical cyclosporin 0.05% in topical steroid-resistant atopic keratoconjunctivitis Ophthalmology 2004, 476-482)

A randomised placebo-controlled clinical trial of tacrolimus ophthalmic suspension 0.1% in severe allergic conjunctivitis. Ohashi et al J Ocul Pharmacol Ther 2010 26(2):165-173

Sublingual immunotherapy for allergic conjunctivitis: Cochrane Eyes and Vision group July 2011, Calderon et al, Clin Exp Allergy 2011 41(9) 1263-72

Evidence for treatment of Atopic Keratoconjunctivitis in children

- Many clinical trials (362) but poor quality
  - Include both adult and children
  - Lack of objective inclusion criteria
  - Lack of quantifiable primary outcomes
  - Lacking evaluation of efficacy and safety
  - Disease relapses and recurrence rates omitted
  - Short term outcomes only

Clinical trial in allergic conjunctivitis: a systematic review. Mantelli et al Allergy 2011(7)919-24

Owen et al Topical treatments for seasonal allergic conjunctivitis:systemic review and meta-analysis of efficacy and effectiveness Brit J General Practice 2004 54 451-456

Comparison of VKC and AKC

(Ocular Therapeutics 2008, Ocular Allergy:Clinical, therapeutic and drugc discovery consideration J Yanni, N Barney p239-244)

	VKC	AKC
Age	Younger	Older
Sex	M>F	No diff
Duration	Limited (puberty)	Chronic
Time of year	Spring	Perennial
Conjunctival involvement	Upper tarsus	Lower tarsus
Cicatrization	Rare	Common
Cornea	Shield ulcer	Epithelial defects
Scarring	Common	Common
Vascularisation	Rare	Common
Mechanism	Type IV	Type I and IV

Vernal Keratoconjunctivitis

- Prevalence in Western Europe 3.2 per 10,000 inhabitants
- Prevalence of corneal complications 0.8/10,000
- Geographical variation-hot, dry areas

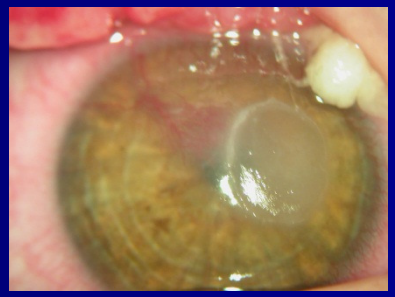
Prevalence of VKC: a rare disease? Bremond-Gignac et al, BJO 2008 (8) 1097-102)

- Presents between age 3-5, resolves by adulthood
- Seasonal exacerbations, boys>girls, family history of atopy
- Symptoms- watering, photophobia, mucous discharge

VKC revisited: a case series of 195 patients with long-term follow-up Ophthalmology 107(6) 2000 1157-1163

Vernal keratoconjunctivitis

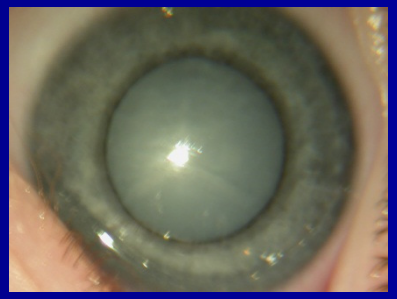
- **Palpebral** VKC-giant papillae of tarsus, ptosis, superior corneal punctate epitheliopathy
- Vernal plaque or 'shield' ulcers

- **Limbal** VKC-Horner-Trantas dots

Complications of Vernal Keratoconjunctivitis in children

- Loss of vision
- Corneal scarring
- Keratoconus
- Limbal stem cell deficiency Cornea 2011 30(5) 491-6
- Steroid induced cataracts and glaucoma
- Behavioural/psychological



Vernal keratoconjunctivitis- treatment

- Antihistamines- topical and/or oral
- Mast cell stabilisers
- Combined action topical
- Topical steroid

- Topical cyclosporin A

Tailored approach to the treatment of vernal keratoconjunctivitis
Sacchetti et al Ophthalmology 2010, 117(7) 1294-1299

Other treatments in Vernal Keratoconjunctivitis

- Oral steroids, NSAIDs, aspirin
- Injection of sub-tarsal short and long-acting steroids
- Cryoablation/surgery of tarsal cobblestones

- Debridement of ulcer/superficial keratectomy
- Amniotic membrane

Drugs used in clinical trials for treatment of VKC since 1992 (Modified from Ocular Therapeutics 2008)

Class	Drug
Immunomodulators	Topical Cyclosporine A Tacrolimus ointment (FK506)
Antihistamine	Levocabastine 0.05%
Non-steroidal anti-inflammatories	Flurbiprofen 0.03% Ketoralac 0.5% Indomethacin 1.0%
Mast cell stabilisers	Nedocromil sodium 2.0%* Sodium chromoglycate 2.0%* or 4.0% Lodoxamide 0.1%
Steroids (topical)	Fluoromethalone 0.1% Mepragoside gel 0.5%
Antibiotics	Mitomycin C 0.01%

Current evidence for topical treatment in VKC

- Systematic review and meta-analysis of randomised clinical trials on topical treatments for VKC

Mantelli and Bonini BJO 2007 91 (12)1656-1661

- 27 RCTs (n=2184 eyes), 10 in meta-analysis
  - Not possible to compare efficacy due to lack of standardised criteria of disease and outcomes
  - Need for randomised controlled trials assessing long-term effects

Clinical trials in VKC-topical cyclosporin compared with ketotifen

- Randomised, double-masked, controlled 2 year study of cyclosporin topical 0.05% compared with ketotifen
- 30 male, 4 female mean age 14+/- 7 years
- Ability to prevent flare-ups and reduce disease duration
- 0.1% CyA compared with 0.15% dexamethasone 0.15% to treat flare-ups

Lambiase et al J of Allergy and Clinical Immunology 128 (4) 2011, p896-897

Vernal keratoconjunctivitis study endpoints

- **Recurrence rate** (100% increase in hyperaemia, itching, Trantas dots, Oxford fluorescein and epitheliopathy scores)
- **Symptoms score**-itching, photophobia, redness, tearing, secretion and blurry vision (graded 0-3)
- **Signs score**-Conjunctival hyperaemia, mucous discharge, tarsal and/or limbal papillae (graded 0 to 3)
- **Safety**-adverse events, compliance, drug tolerability, drop-out rate

Lambiase et al
J of Allergy and Clinical Immunology 128 (4) 2011, p896-897

Vernal keratoconjunctivitis- additional study endpoints

- Visual acuity- (amblyopia, compliance, refractive error)
- Corneal scarring/vascularisation

- Quality of Life (symptoms and daily activities- QUICK score)

  Development and testing of the Quality of Life in children with vernal keratoconjunctivitis Questionnaire Sacchetti et al Am J Ophthalmol 2007 114(4) 557-563

Clinical trials in Paediatric Vernal Keratoconjunctivitis

- Large numbers of paediatric patients- multi-centre
- Defined criteria for diagnosis of VKC and inclusion- clinical grading system Bonini et al Curr Opin Allergy Clin Immunol 7 2007 436-441
- Long-term treatment effects
- Endpoints

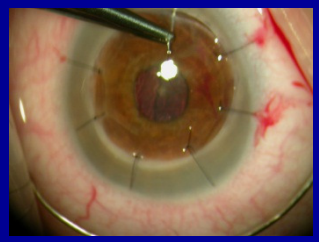
Prevention of corneal transplant rejection in children

- Indications for corneal transplant
  - anterior segment developmental anomaly
  - corneal dystrophies
  - Keratoconus
  - Scarring secondary to infection, trauma

- Different tissue properties and behaviour in paediatric compared to adult-
  - early removal of sutures to help prevent graft rejection

Prevention of rejection in paediatric corneal transplants

- Current regimes
  - intensive topical steroids
  - long term, low frequency topical steroids



- Evidence from adults
  - **Topical cyclosporin A** increases risk of rejection in low-risk grafts compared to prednisolone acetate 1%, or in patients with previous rejection episodes (Price Ophthalmology 113 2006 1785-90, Javadi et al BJO 2010 94(11) 1464-7, Sinha et al, Graefes Arch Clin Exp Ophthalmol 2010 248(8)1167-72 Unal BJO 2008 92(10)1411-4
  - **Systemic cyclosporin A** of no benefit in high risk PK and high incidence of side-effects (Shimazaki et al Am J Ophthalmol 2011 152(1)33-39
  - Mycophenolate mofetil

Prevention of paediatric corneal graft rejection study design

- Patient numbers, age groups
- Follow-up time
- Endpoints
  - Rejection episodes, number and severity
  - Visual acuity (amblyopia treatment compliance, refractive error/astigmatism)
  - Graft clarity (iris visibility, imaging techniques)
  - Corneal vascularisation
  - Corneal thickness
  - Safety and tolerability

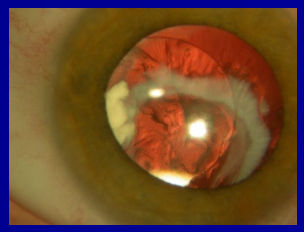
Limbal stem cell transplantation in children

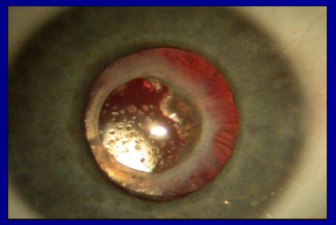
- Current knowledge from adults
- Indications
  - Anirida
  - Stevens-Johnson and toxic epidermal necrolysis
  - Severe chemical injury
- Problems
  - Issues around culture of stem cells
  - Very rarely likely to be indicated in children

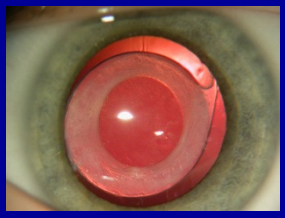
Reduction of pain and inflammation in paediatric cataract surgery

- Incidence of cataract 3.5 per 10,000 by age 15 (200-300 children born each year in UK) Rahi et al IOVS 2001 (42) 1444-8
- General anaesthesia-per and post-operative pain

- Post-op inflammation
- Consequences -
  - capsular fibrosis,
  - glaucoma,
  - pupil phimosis,
  - membrane formation

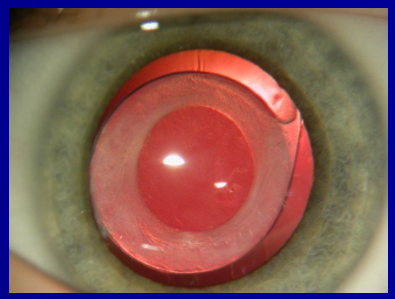






Current regimes to control pain and inflammation in paediatric cataract surgery

- **Pain-**
  - Intravenous fentanyl,
  - Intravenous paracetomol,
  - Topical anaesthetic,
  - Subtenons local anaesthetic



- **Inflammation-**
  - Intracameral heparin,
  - Subconjunctival steroids,
  - Orbital floor steroids,
  - Topical steroids,
  - Oral steroids

Evidence for inflammation prevention in paediatric cataract surgery

- **Intracameral recombinant tissue plasminogen activator** in congenital cataracts
  - double masked randomised clinical trial
  - 34 eyes of 26 patients
  - mean age 8 years (3-14 years)

- Lower intraocular fibrin in r-TPA group in first 14 days but not significant at days 30 and 90
- Lower IOL precipitates at 3 months
- All patients on peri-ocular, systemic and topical steroids

Siatiri et al BJO 2005 89(11) 1458-61

Evidence for pain management in paediatric cataract surgery

- **Comparison of topical lignocaine gel and fentanyl** for perioperative analgesia in children undergoing cataract surgery
  - Prospective randomised controlled trial
  - n=100
  - No difference in post-op need for supplementary fentanyl

2009 19(4) 371-5 Sinha Paediatric Anaesthesia

- **Subtenon block (lidocaine and bupivacaine) compared to intravenous fentanyl**
  - Prospective randomised controlled double-blind trial
  - n=114
  - Primary outcome number of patients requiring rescue analgesia in 1st 24 hours
  - Subtenons block safe and superior alternative to iv fentanyl

Ghai et al Anaesthesia and Analgesia 2009 108(4)1132-8

Pain relief following strabismus surgery in children

- Over 6000 squint surgeries in children in UK per year (RCO Paed Subcommittee 2007/8)
- **Randomised controlled trials of sub-tenons local anaesthetic for post-operative pain control**
  - Lidocaine (n=260, age 4-10 years)

  Seo et al Eur J Anaesthesiol 2011 28(5)334-9
  - Ropivacaine 0.2% n=79 age 1-65 adults included

  Kacko et al Curr Eye Research 2010 35(6)529-35
  - Levobupivicaine n=27 age 1-16 years

  BJO 2009 93(3) 329-32
- **Endpoints**-
  - Frequency of emergence agitation,
  - Visual analogue scale pain scores,
  - Supplemental analgesia requirement
  - Patient satisfaction,
  - Wong-Baker pain scores
  - FLACC (face legs arms cry consolability)

Paediatric Blepharokeratoconjunctivitis

- Staphylococcal hypersensitivity, phlyctenular keratoconjunctivitis, paediatric ocular rosacea
- Common- 15% of referrals to eye clinic

BKC in children. Hammersmith et al Arch Ophthalmol 2005 123:1667-1670

Gupta et al JAAPOS 2010 14(6) 527-9

- More severe in Asian/Middle eastern
- Age of onset 6 months-16 years

Jones et al Ophthalmology 2007 114(12)2271-80.

Farpour JPOS 2001 38(4)207-12

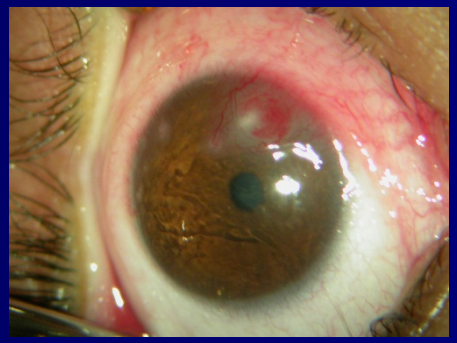
Symptoms and signs of blepharokeratoconjunctivitis

- **Symptoms**
  - watering,
  - irritation,
  - photophobia,
  - crusting

- **Signs**
  - blepharitis, meibomian cysts,
  - pannus and corneal vascularisation,
  - punctate epitheliopathy,
  - conjunctival or corneal phlyctenules,
  - subepithelial infiltrate,

Complications of blepharokeratoconjunctivitis

- Visual loss/amblyopia
- Corneal scarring and vascularisation



Blepharokeratoconjunctivitis-treatment regimes

- Lid hygiene
- Topical antibiotics-chloramphenicol or fucithalmic
- Oral antibiotics-erythromycin, dose and duration
- Topical lubricants-preservative free
- Topical steroids

BKC in children:diagnosis and treatment M Viswalingham BJO 2005:89:400-3

- Oral flax seed oil

Jones et al Ophthalmology 2007 114(12)2271-80

Blepharokeratoconjunctivitis treatment- current evidence

- No randomised controlled trials
- Retrospective non-comparative, interventional case series (n=4,9,27,23,615)

- Prospective interventional non-comparative case series
  - Systemic erythromycin, topical CPL and steroids in severe cases n=44

  Viswalingam BO 2005 89 400-3
  - Topical cyclosporin 2% qds in steroid-dependant childhoood phlyctenular keratoconjunctivits n=11 follow-up 6-12 months

  Doan et al Am J Ophthalmol2006 141 62-66

Trial design for blepharokeratoconjunctivitis

- Paediatric cases, adequate numbers, adequate duration
- Disease definition and classification
- Comparative-antibiotics, topical/systemic, dose and duration
- Defined endpoints and recurrence rate

Study endpoints in blepharokeratoconjunctivitis

- Symptoms and signs score
- Ability to get off topical steroids/oral antibiotics
- Extent of scarring/vascularisation
- Visual acuity
- Quality of life scores
- Safety/tolerability

Current clinical and research picture in paediatric anterior segment disorders

- Lack of good quality evidence in some common paediatric anterior segment conditions
  - Need disease definitions and classification
  - Paediatric trials, age subsets,
  - Adequate numbers and follow-up times,
  - Defined and appropriate endpoints

Financial interests

- Jane Ashworth has received an educational grant, travel expenses and speaker honorarium from Biomarin Europe Ltd