Current clinical and research picture in paediatric anterior segment disorders

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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**

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 drug discovery consideration J Yanni, N Barney p239-244)

<table>
<thead>
<tr>
<th></th>
<th>VKC</th>
<th>AKC</th>
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<tbody>
<tr>
<td>Age</td>
<td>Younger</td>
<td>Older</td>
</tr>
<tr>
<td>Sex</td>
<td>M&gt;F</td>
<td>No diff</td>
</tr>
<tr>
<td>Duration</td>
<td>Limited (puberty)</td>
<td>Chronic</td>
</tr>
<tr>
<td>Time of year</td>
<td>Spring</td>
<td>Perennial</td>
</tr>
<tr>
<td>Conjunctival</td>
<td>Upper tarsus</td>
<td>Lower tarsus</td>
</tr>
<tr>
<td>involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cicatrization</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Cornea</td>
<td>Shield ulcer</td>
<td>Epithelial defects</td>
</tr>
<tr>
<td>Scarring</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Vascularisation</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Mechanism</td>
<td>Type IV</td>
<td>Type I and IV</td>
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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


- 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
- Steroid induced cataracts and glaucoma
- Behavioural/psychological

Cornea 2011 30(5) 491-6
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)

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

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

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

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


- 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 childhood phlyctenular keratoconjunctivits n=11 follow-up 6-12 months
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

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