



La congiuntivite VERNAL vista dall'allergologo pediatra

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La cheratocongiuntivite vernal

La **cheratocongiuntivite vernal** è una patologia **infiammatoria oculare cronica** stagionale, generalmente bilaterale, localizzata a livello della congiuntiva tarsale e/o bulbare, tipica dell'età pediatrica, spesso associata all'atopia inquadrata nel **capitolo delle congiuntiviti allergiche** in quanto caratterizzata da una infiammazione ad **EOSINOFILI** (ma non allergica *sensu strictiori*)



Malattie da Ipersensibilità

Ipersensibilità allergica
(meccanismo **immunologico**
definito o fortemente sospetto)

Ipersensibilità non allergica
(meccanismo immunologico
escluso) (es. intolleranza al lattosio)

IgE-mediato

Non IgE-mediato

Non atopico

Atopico

Insetti

Elminti

Farmaci

Altro

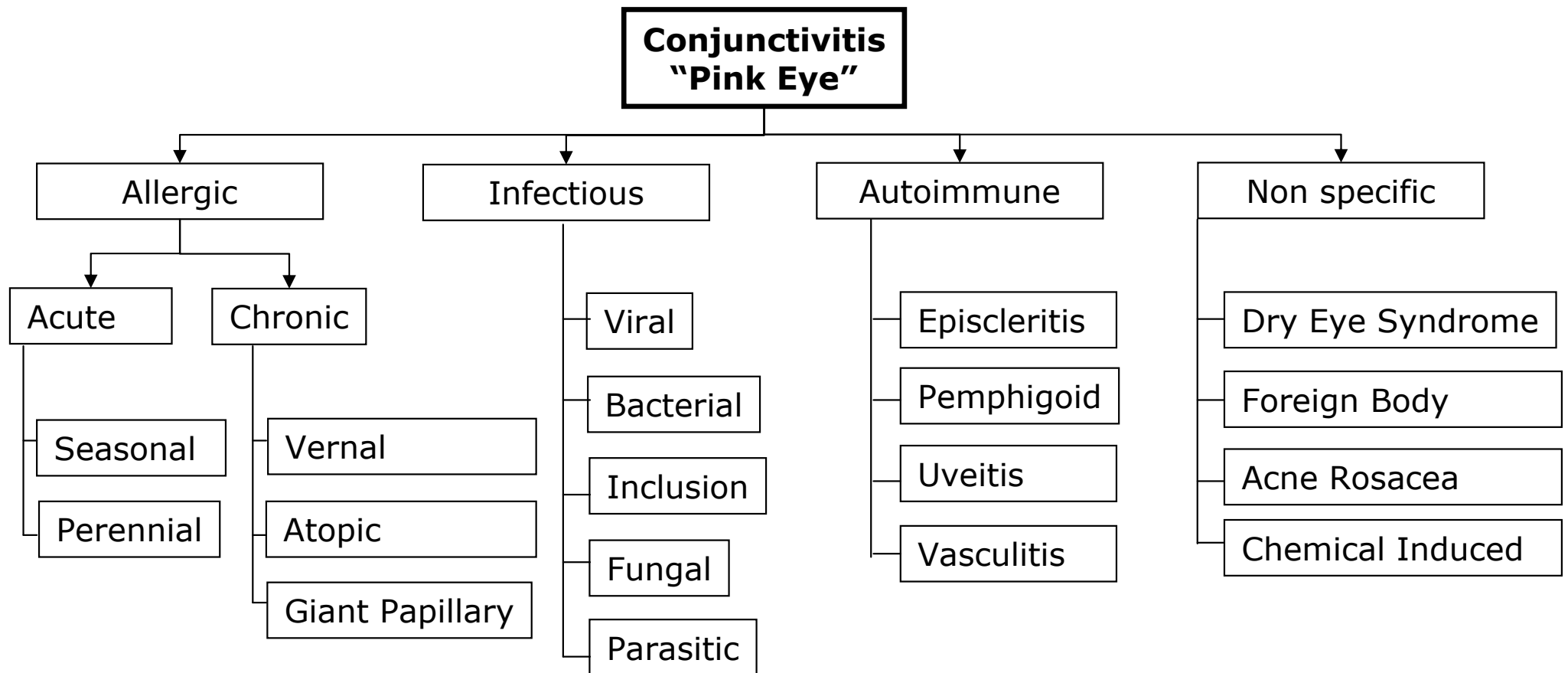
Linfociti T (es. DAC, celiachia)

Eosinofili (es. gastroenterite eosinofila, NARES)

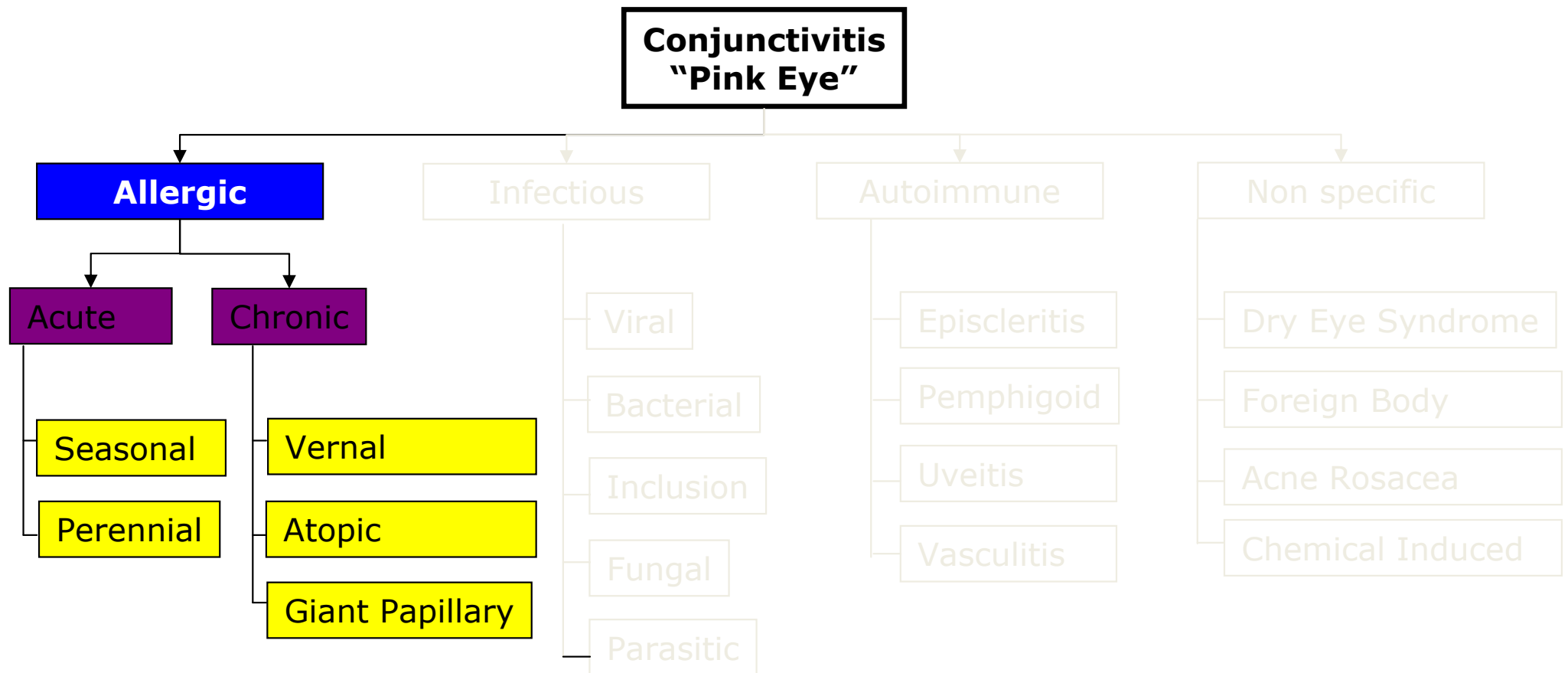
IgG mediato (es. alveolite allergica)

Altro

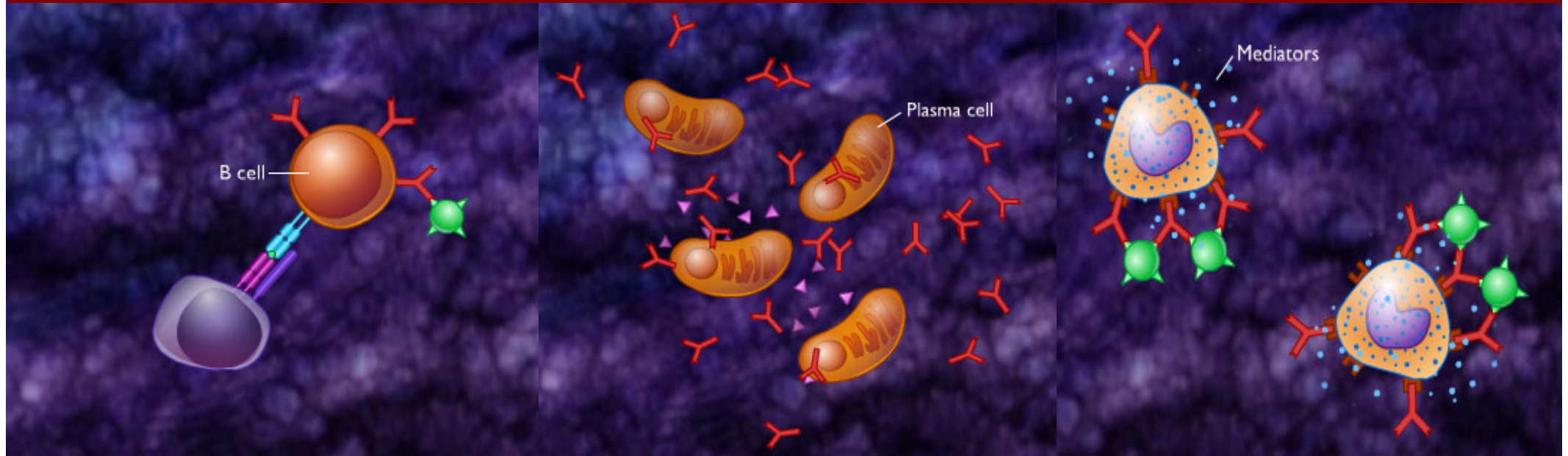
Diagnosi differenziale dell'**occhio** **arrossato**



Diagnosi differenziale dell'**occhio** **arrossato**



Congiuntiviti allergiche IgE mediate

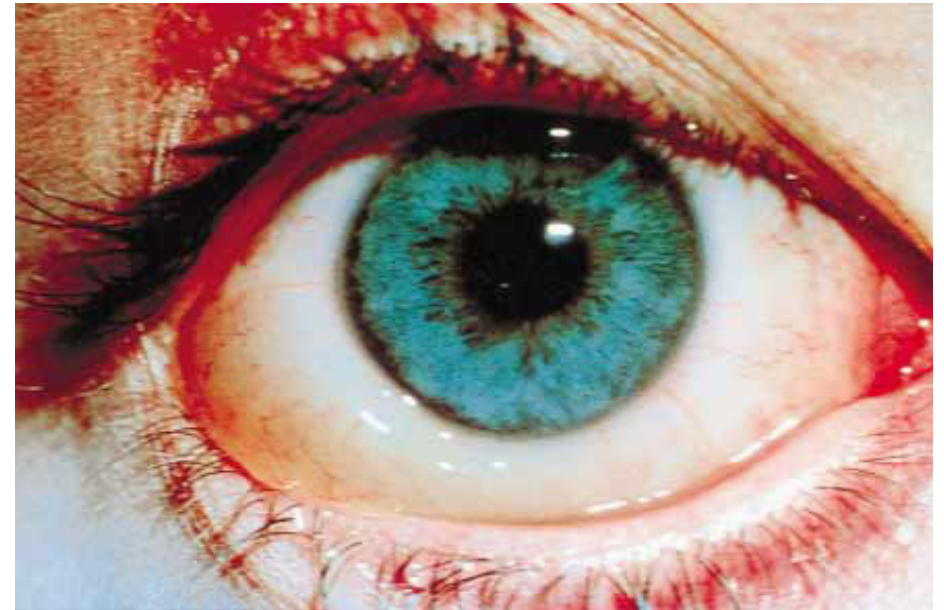
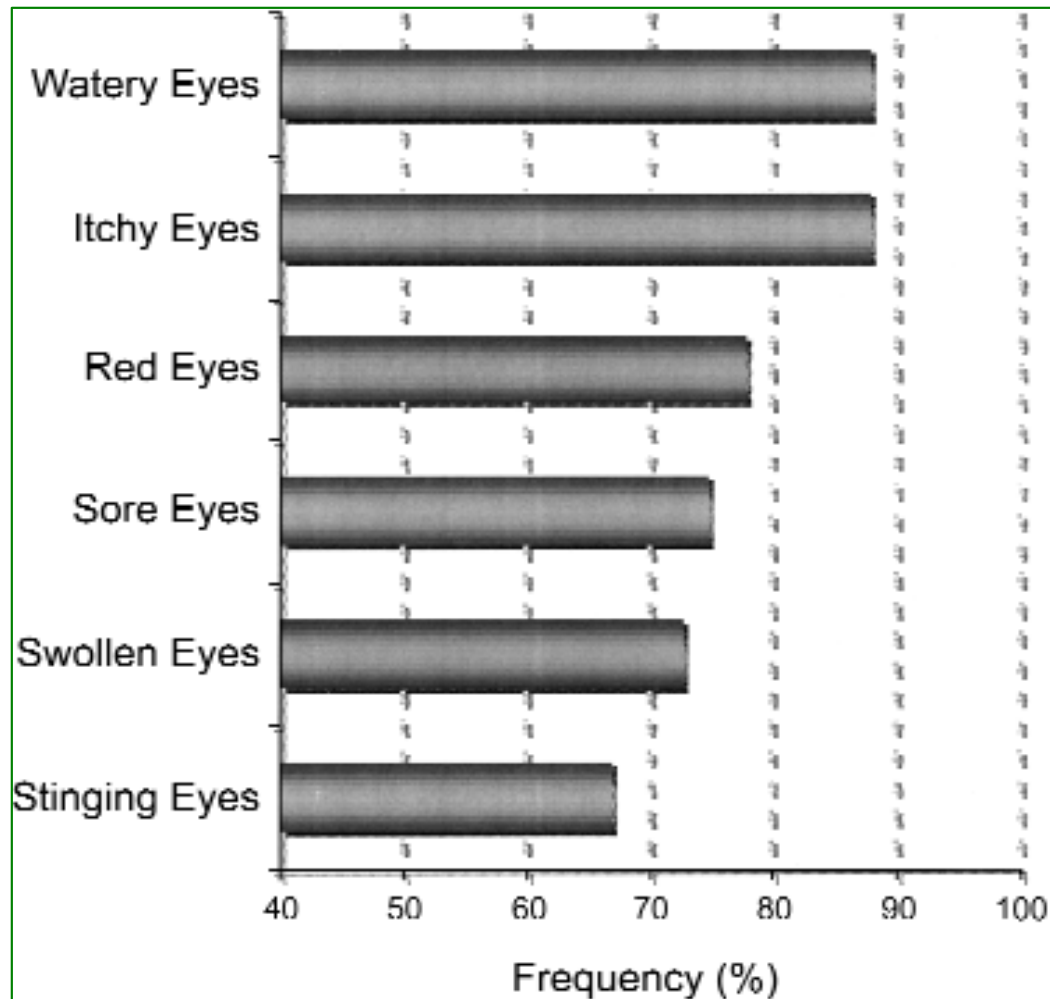


- Seasonal Allergic Conjunctivitis (SAC)
- Perennial Allergic Conjunctivitis (PAC)

Congiuntiviti allergiche IgE mediate

- SAC è la più comune: 50% di tutte le congiuntiviti allergiche (*pollini*)
- PAC è una variante di SAC: persiste per quasi tutto l'anno (*acari, animali*)
- Il 79% delle PAC presenta aggravamenti stagionali

Congiuntiviti allergiche IgE mediate



- Comunemente associata alla riniti allergica (stagionale o perenne) → **OCULO-RINITE ALLERGICA**

Congiuntiviti allergiche IgE mediate

- Raramente essudato trasparente o biancastro
- Possibile edema delle palpebre associato
- Sintomi generalmente bilaterali
- Soggetti che hanno una storia di atopia
- Raro il coinvolgimento della cornea e i danni permanenti del visus
- L'allontamento dell'allergene e l'ITS eradicano i sintomi
- La terapia antistaminica è generalmente efficace



Congiuntiviti allergiche non IgE- mediate

CHERATOCONGIUNTIVITE ATOPICA



CONGIUNTIVITE VERNAL



CONGIUNTIVITE PAPILLARE GIGANTE



Generalità sulla vernal



- Esordio **tra i 4 e i 7 anni**
- **Frequente risoluzione spontanea** nella II decade di vita (pubertà)
- Maggiore frequenza nel **Sesso maschile (M/F: 3/1)**
- Frequente esordio e riacutizzazioni in **primavera/estate** ("vernal" = primaverile)
- Regioni dal **clima caldo e temperato**: Medio Oriente, bacino del Mediterraneo, regioni settentrionali ed occidentali dell'Africa, India, Giappone, America centrale e meridionale
- Frequente associazione con **l'atopia (50% dei casi)**
- Ruolo dell'allergia poco chiaro (nessun allergene dimostrato avere un ruolo causale)

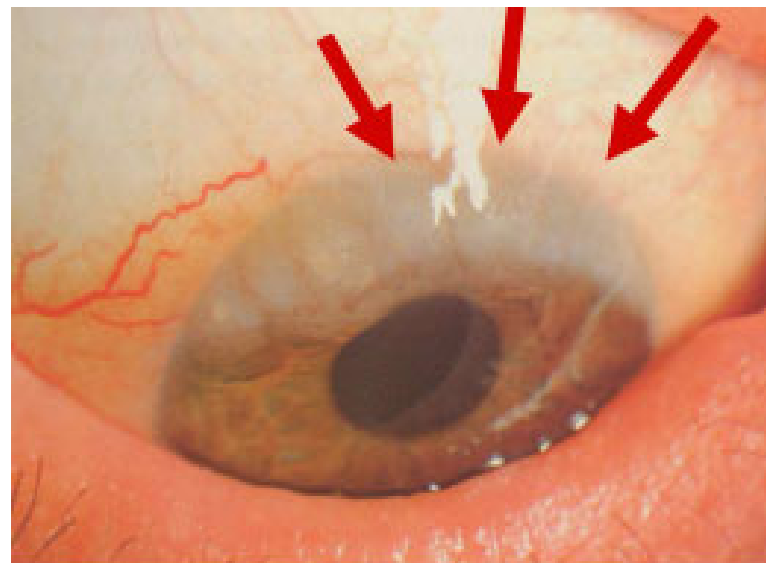
FORME CLINICHE DI VERNAL

3

Tarsale: papille larghe di forma e dimensioni differenti



Limbare: noduli di Trantas' e infiltrati del limbus



...e forme **MISTE**

Fisiopatologia della vernal



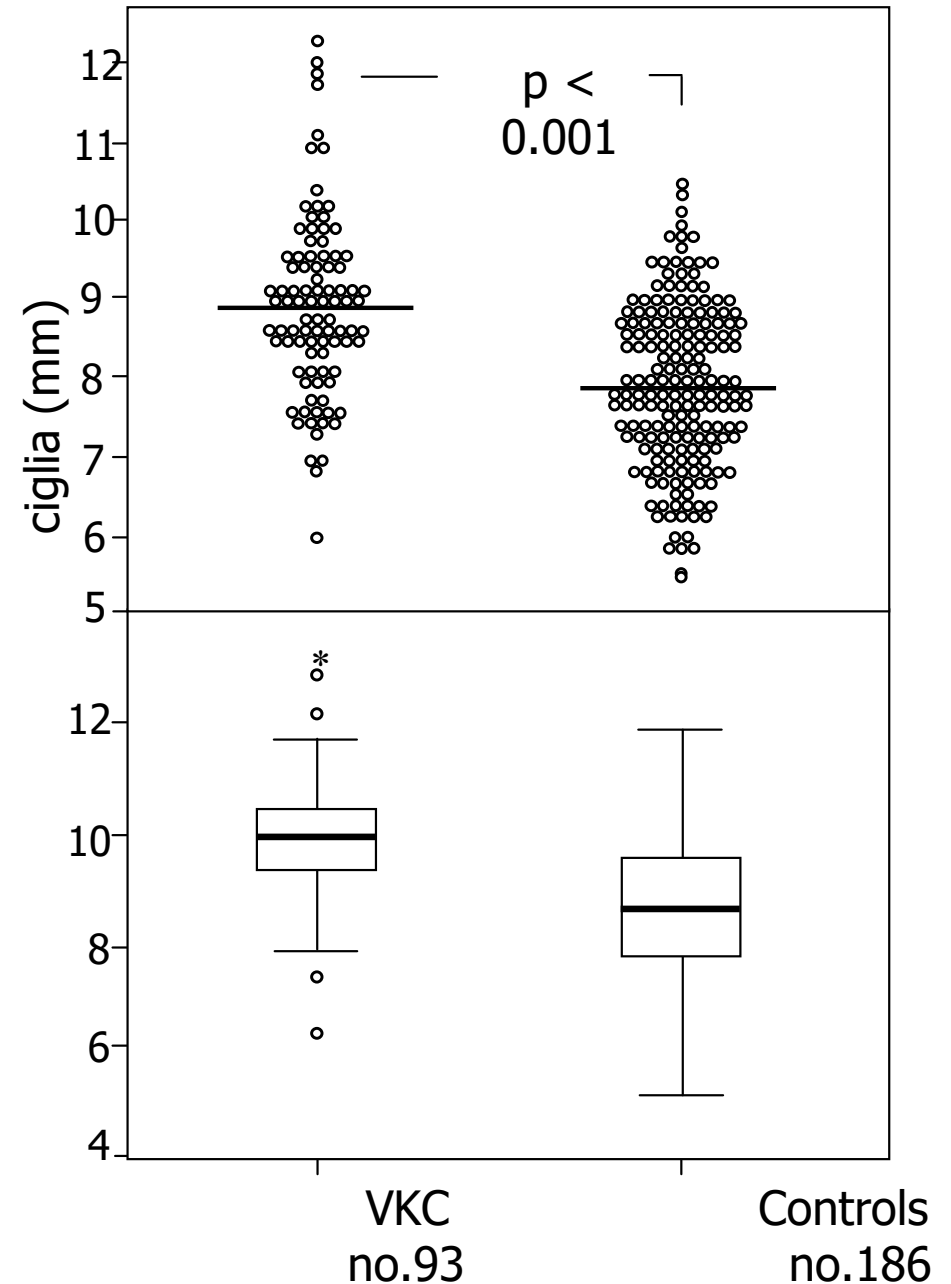
- ✓ Eziologia (= causa) sconosciuta
- ✓ Frequenza 1/10.000 (Europa)
- ✓ Malattia età-dipendente
- ✓ Infiammazione eosinofila
- ✓ Associazione con l'atopia ($\approx 50\%$ dei pazienti ha altre malattie allergiche e/o test allergologici positivi) [senza ruolo causale]
- ✓ Meccanismi IgE-mediati (spt "tarsali") e non IgE-mediati (spt "limbari")
- ✓ Allontanamento dell'allergene (e l'ITS) non modifica i sintomi
- ✓ Rapporto certo con esposizione solare
- ✓ Possibile ruolo di meccanismi autoimmuni (associaz. severità/ autoimmunità)

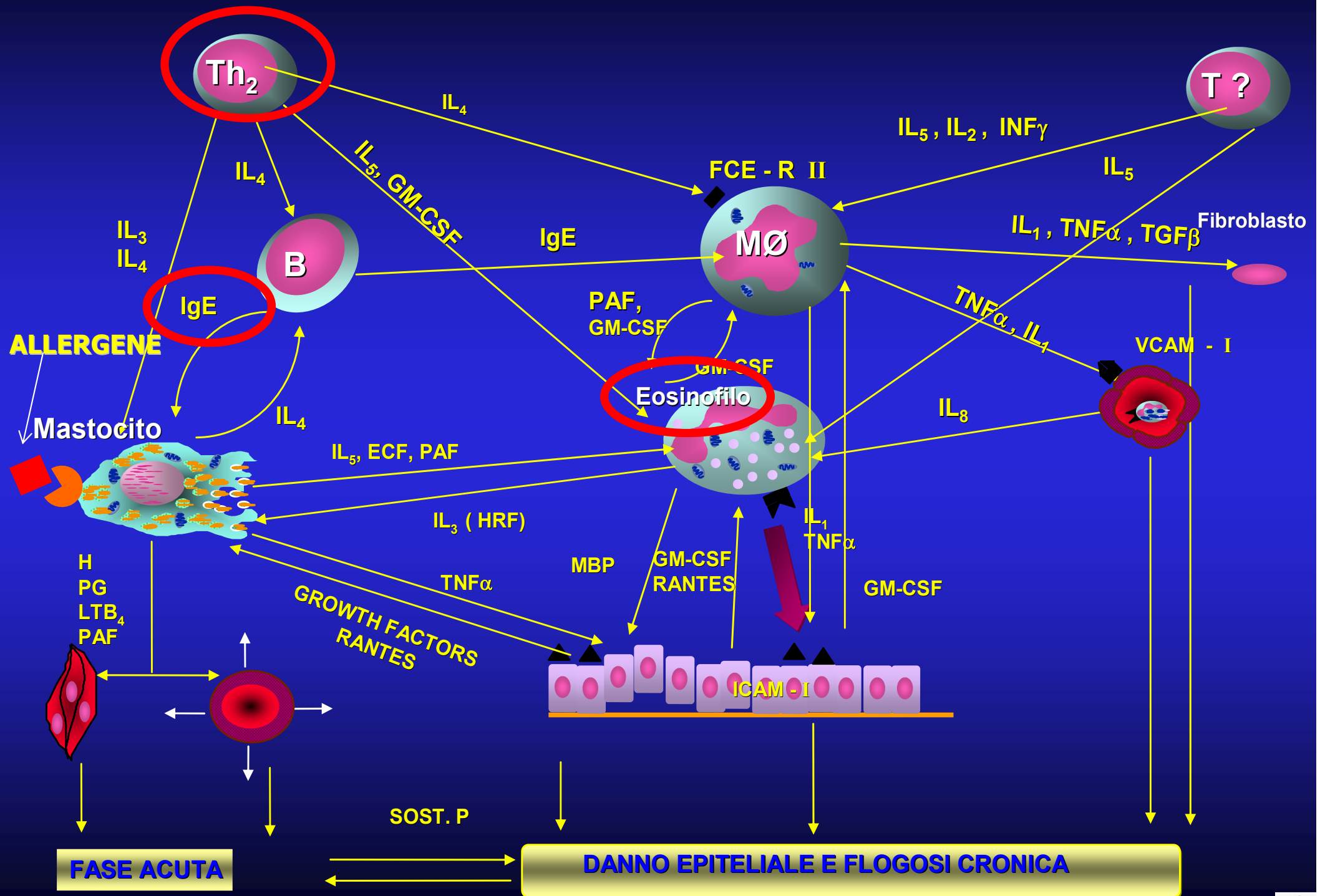


Lunghezza delle ciglia in bambini con VKC e controlli

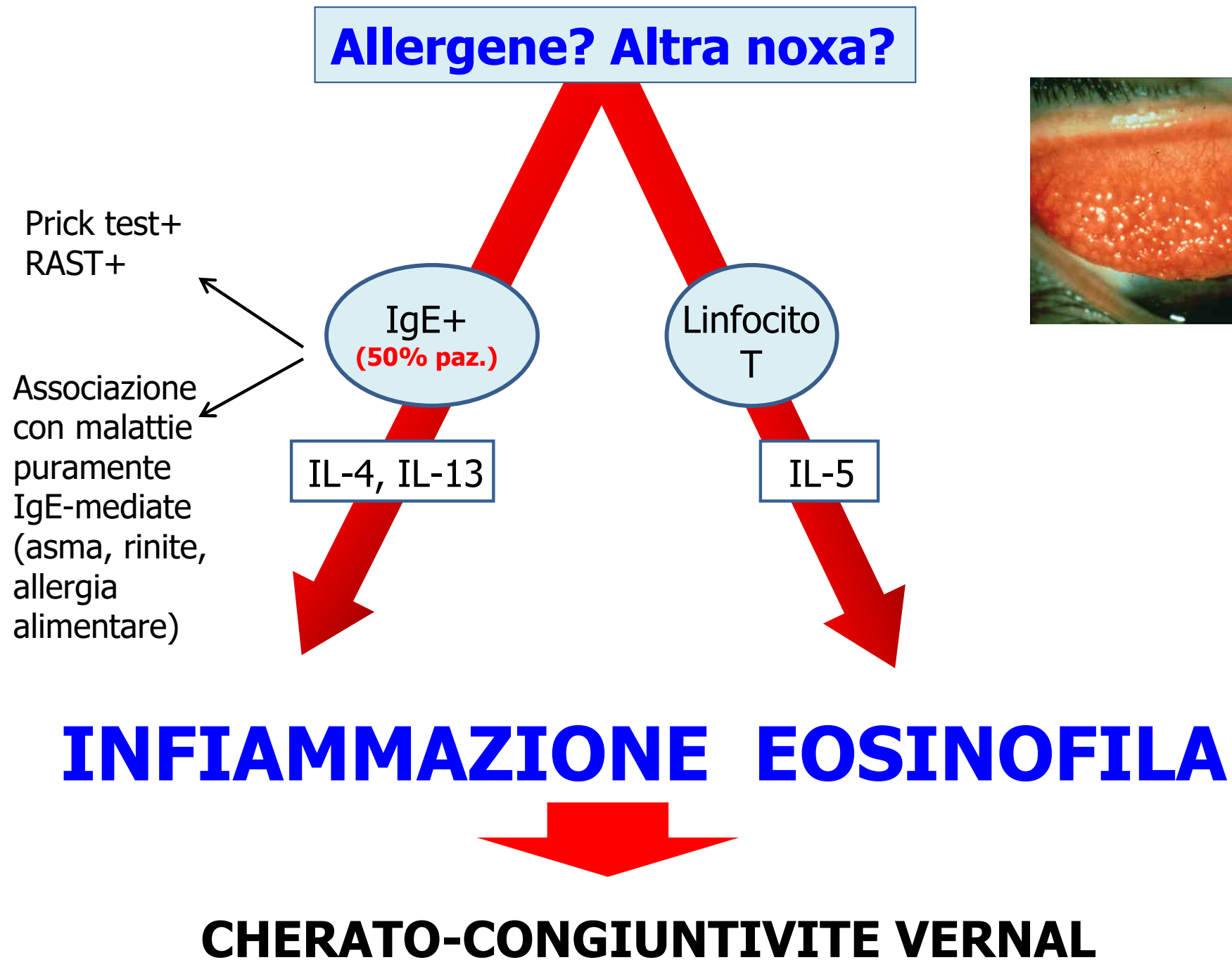


**Bambini con
keratocongiuntivite
Vernal hanno le ciglia
superiori
significativamente più
lunghe di controlli
appaiati per sesso ed
età**





Meccanismi della ipersensibilità nella Vernal



Cheratocongiuntivite vernal

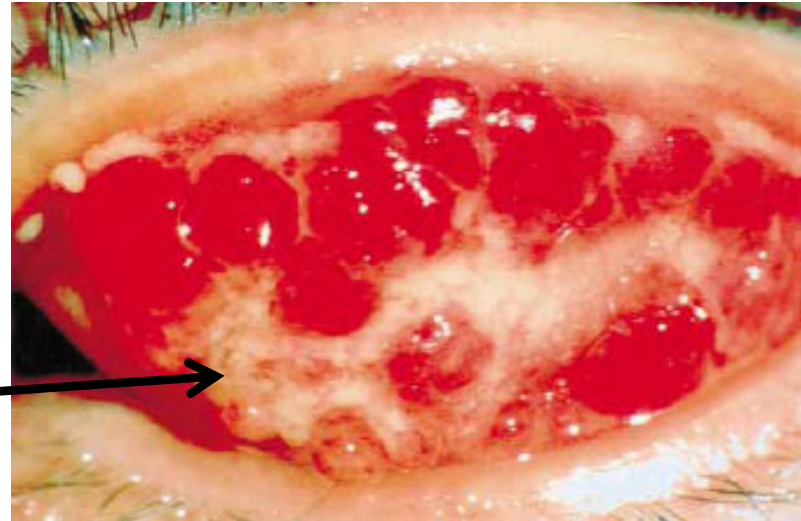
SINTOMI

- ✓ prurito intenso
- ✓ lacrimazione
- ✓ bruciore
- ✓ sensazione di corpo estraneo
- ✓ **Fotofobia**
- ✓ **Secrezione biancastra filamentosa**
 - aggravati da vento, polvere, luce intensa, clima caldo, sudore

Cheratocongiuntivite vernal

SEGNII OCULARI

- Papille al limbus (*noduli di Trantas*)
- Essudato filante muco-fibrinoso



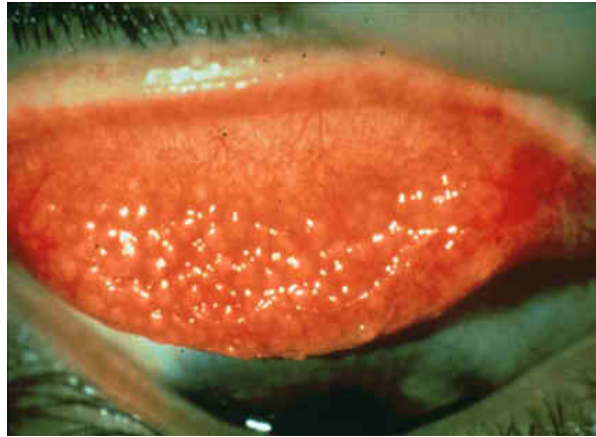
Caratteristiche cliniche

Prurito, bruciore, iperemia ed edema congiuntivale, lacrimazione, fotofobia, sensazione di corpo estraneo, **muco filamentoso** nel fornice congiuntivale.

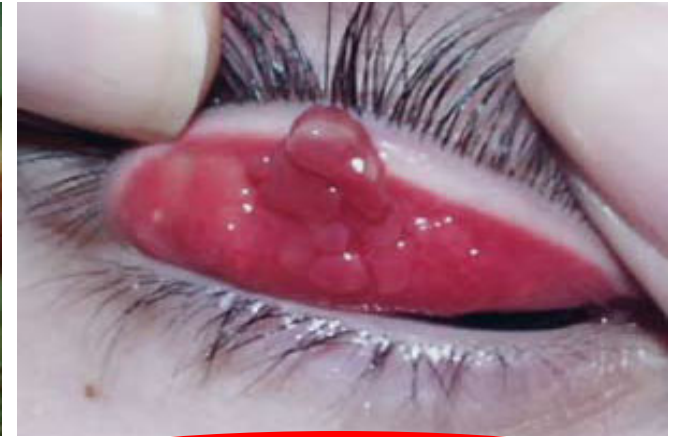
Complicanze

Ulcere a scudo, placche, cheratite puntata epiteliale, cheratocono, neovascolarizzazioni, pseudogerontoxon

SEGNI CONGIUNTIVALI

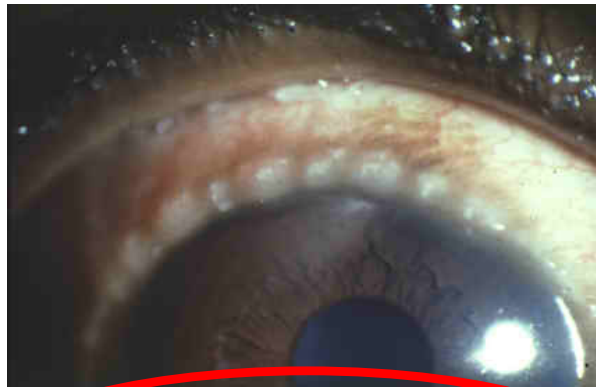


Ipertrofia papillare



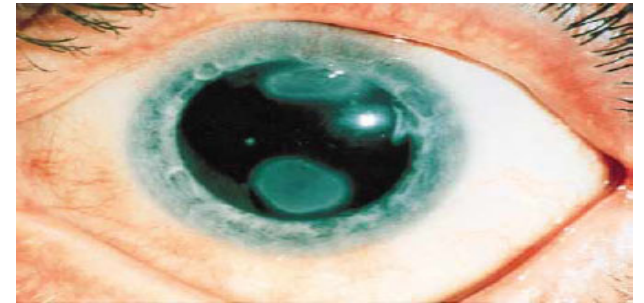
Papille giganti ad acciottolato

SEGNI LIMBARI

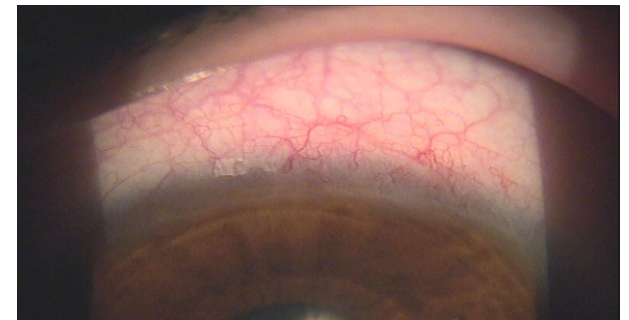


Noduli di Horner-Trantas:
eosinofili in degenerazione e
detriti di cellule epiteliali

SEGNI CORNEALI



Ulcere a scudo



Neovascolarizzazioni

POSSIBILI PATOLOGIE ASSOCIATE ALLA VERNAL

- Asma bronchiale
- Rinite allergica
- Allergia alimentare
- Dermatite atopica
- NARES
- Bronchite eosinofila?

Cheratocongiuntivite vernal

DIAGNOSI

- ✓ Anamnesi (cronicità, stagionalità, secrezione, atopia)
- ✓ Esame obiettivo + biomicroscopio (segni oculari)
- ✓ Citologia oculare (ricerca eosinofili nello scraping)
- ✓ Test allergologici cutanei / RAST (precisazione diatesi atopica, caratterizzazione comorbidità)

(n.b. test negativi non escludono una vernal !!!)

EOSINOFILI CONGIUNTIVALI

Advanced

Help

[Display Settings:](#) Abstract

Exp Eye Res. 1997 Jun;64(6):905-12.

Characterisation of the normal conjunctival leukocyte population.

[Hingorani M¹](#), [Metz D](#), [Lightman SL](#).

Author information

¹Institute of Ophthalmology, London, UK.



Abstract

Lymphoid cells are present in normal mucosal tissue as scattered cells or organised into MALT. Knowledge of the non-pathological conjunctival lymphoid tissue is a vital basis for the further study of ocular surface inflammatory disorders. Therefore, we used immunohistochemistry to examine the leukocyte population of tarsal and bulbar conjunctiva from normal patients with no ocular or systemic inflammatory disease. CD3+ T cells were the most frequently occurring, and macrophages the second most frequently occurring, conjunctival cell type and were seen in the epithelium and substantia propria. There were greater numbers of leukocytes in the bulbar than in the tarsal area and this reached statistical significance for CD3+ T cells and CD57+ NK cells. In both bulbar and tarsal conjunctiva, B cells and neutrophils were seen in the epithelium and substantia propria, but plasma cells, NK cells and mast cells were present only in the substantia propria. No eosinophils were seen. CD8+ cells outnumbered CD4+ cells in the epithelium (CD4:CD8 0.3) but this was reversed in the substantia propria (CD4:CD8 1.3 tarsal, 2.8 bulbar). Most epithelial T cells and half the stromal T cells were CD45Ro+. IL-2R (CD25) staining was infrequent in the tarsal but not the bulbar area. The greater number and activation of T cells in the bulbar region may relate to greater antigen exposure. HLA-DR+ cells were mainly macrophages, but also included dendritic cells in the epithelium and a few epithelial cells. The conjunctival lymphocytes do have certain features of MALT cells, apart from mucosal recirculation, homing and promotion of sIgA production. Conjunctival IEL, like gut IEL, are predominantly CD8+, are found in the basal epithelium, are HML-1+, and have very high expression of CD45Ro. Substantia propria lymphocytes have more equal CD4 and CD8 numbers and frequently express CD45Ro. We found only one example of organised conjunctival lymphoid tissue in our study and suggest that the presence of CALT in humans is not universal.

PMID: 9301471 [PubMed - indexed for MEDLINE]

MeSH Terms, Substances

MeSH Terms

125%



Cheratocongiuntivite vernal

Note di terapia



- Modesta efficacia farmaci tradizionali (*antistaminici, cromoni, FANS*)
- Efficaci i **cortisonici**, usati per periodi prolungati
- Rischio di effetti collaterali:
 - ✓ Ipertensione oculare
 - ✓ Glaucoma
 - ✓ Cataratta



Terapia VKC

Leonardi et al. Ophthalmol Ther 2013; 2: 73-88

- ***Evitare triggers:***
vento, acqua salata,
sfregamento degli occhi,
contatto con allergeni.
- Uso di ***occhiali da sole***.
- ***Profilassi ambientale***.
- ***Terapia farmacologica:*** stabilizzatori mastcellule,
antistaminici anti-H1, FANS, corticosteroidi,
antimetaboliti, **immunosoppressori**.
- ***Terapia chirurgica*** (solo per gravi lesioni corneali).

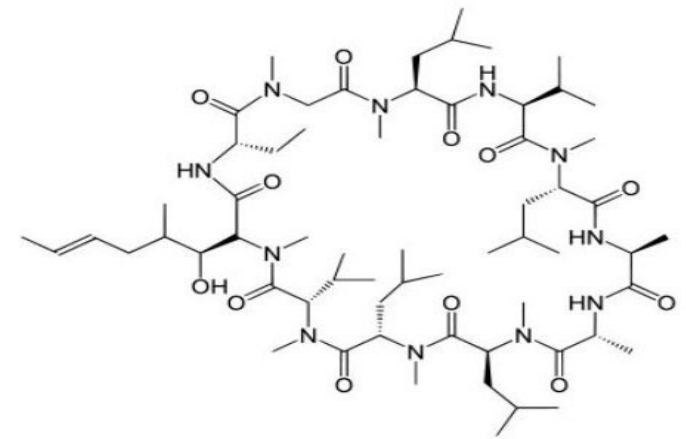


Cheratocongiuntivite vernal

Note di terapia

- Ciclosporina in soluzione oculare
- Tacrolimus per via oculare
- Farmaci non registrati e “off label” anche come formulazione

Ciclosporina



- Endecapeptide ciclico neutrale
- Blocca attivazione e proliferazione dei linfociti T
- Inibisce la trascrizione dell'IL-2 ed IL-5
- Blocca la funzione presentante l'antigene delle APC
- Riduce capacità dei neutrofili di rispondere ai fattori chemiotattici
- Inibisce l'attivazione e la degranulazione di mast-cellule ed eosinofili

Esperienza Cl. Pediatrica – Cl. Oculistica Università di Bari

- **Arruolati 235 bambini con VKC (178 M e 57 F ; M/F=3/1) età media 7 aa tra 2004 e il 2010 c/o Clinica Pediatrica “Maggiore” - Divisione di Immunoallergologia pediatrica - Università di Bari**



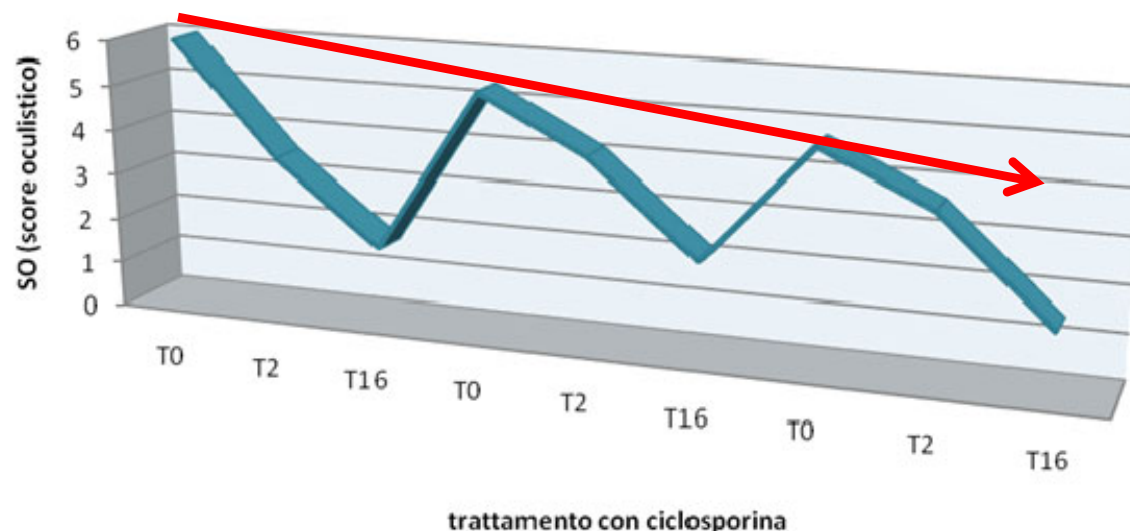
- **Accurata anamnesi personale e familiare**
- **Diario *score* sintomi soggettivi (SS) e segni obiettivi (SO) occhi**
- **Valutazione Oculistica dell'epitelio corneale al biomicroscopio**
- **Prick tests inalanti e alimenti**
- **PRIST e RAST**
- **Citologia nasale e congiuntivale (conta eosinofili con *light microscopy*)**
- **Dosaggio ECP sierica ed Eosinofili totali**
- **Dosaggio ciclosporinemia**
- **Dosaggio autoanticorpi (ANA, ab Anti TGB e TPO); screening celiachia/ fx tiroide**
- **Tipizzazione Antigeni HLA: classe I e II**

Materiali e metodi

- Trial clinico aperto:
Ciclosporina collirio 1% (*Sandimmun*®) in veicolo acquoso (*Lacrimart*):
1 goccia per occhio 4 volte al giorno per 4 mesi
3 cicli : follow-up di 3 anni
- Rivalutazione a **2 (T2)** e a **16 settimane (T16)** :
 - ✓ rideterminazione degli **scores**;
 - ✓ dosaggio **ciclosporinemia**;
 - ✓ conteggio cellule endoteliali attraverso l'uso di un **microscopio speculare** (Konan Noncon Specular Microscope SP/9000, Hyogo, Giappone).

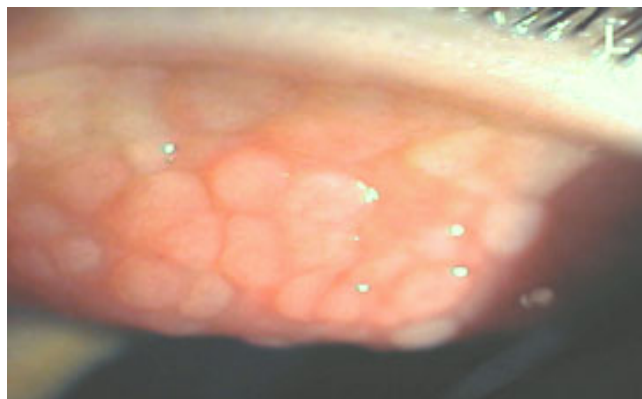
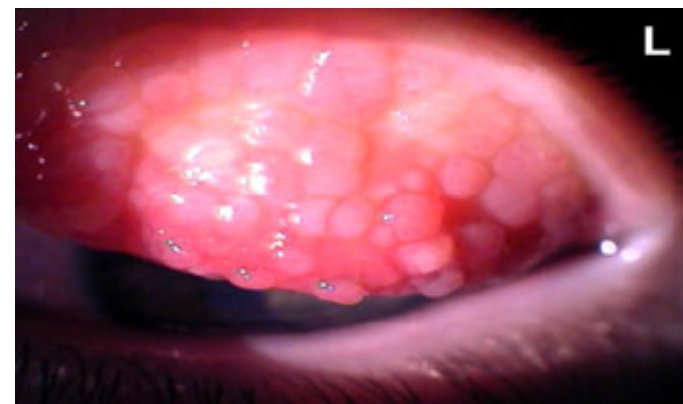
Risultati - 1

- Miglioramento SS e SO ai tempi T0, T2 e T16 dopo ogni ciclo.



- SO significativamente inferiore al tempo T0 del secondo e del terzo ciclo: **mantenimento del miglioramento clinico.**

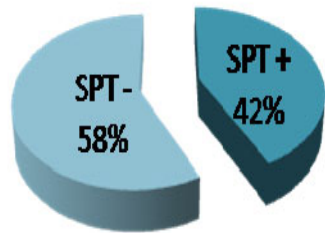
Prima...



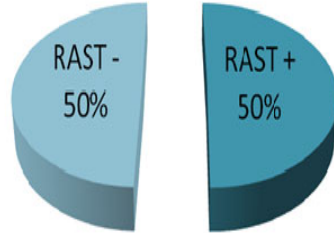
...dopo ciclosporina 1%

Risultati - 2

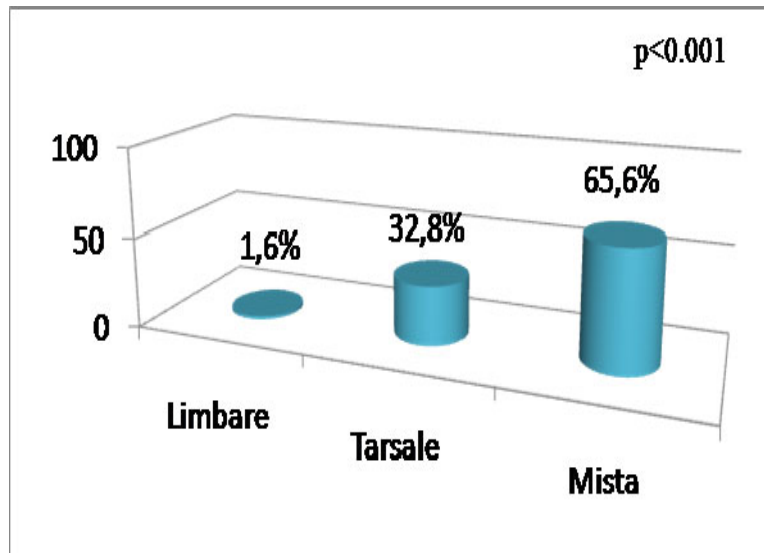
Risultati SPT



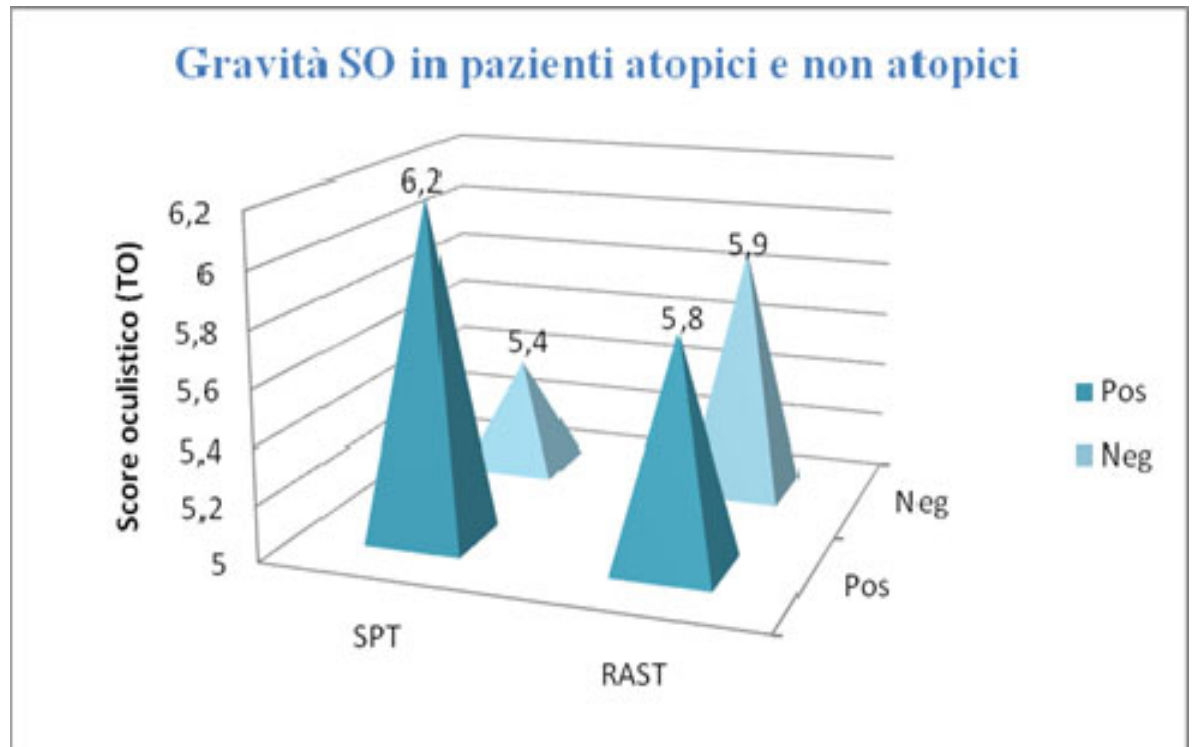
Risultati RAST



- Soggetti atopici 50% del campione: **atopia** fattore predisponente.
- Gravità clinica **non** correlata alla presenza di atopia.

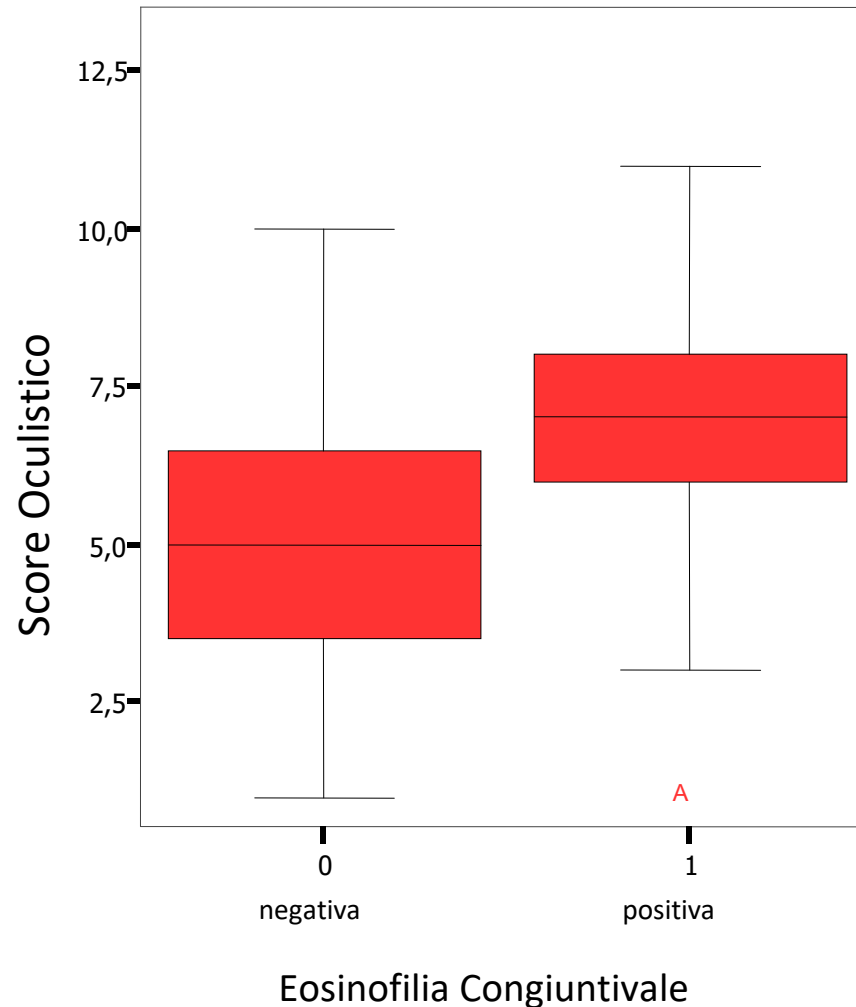


Forme **miste** più frequenti e con **Score Oculare** a T0 più grave.



Risultati - 3

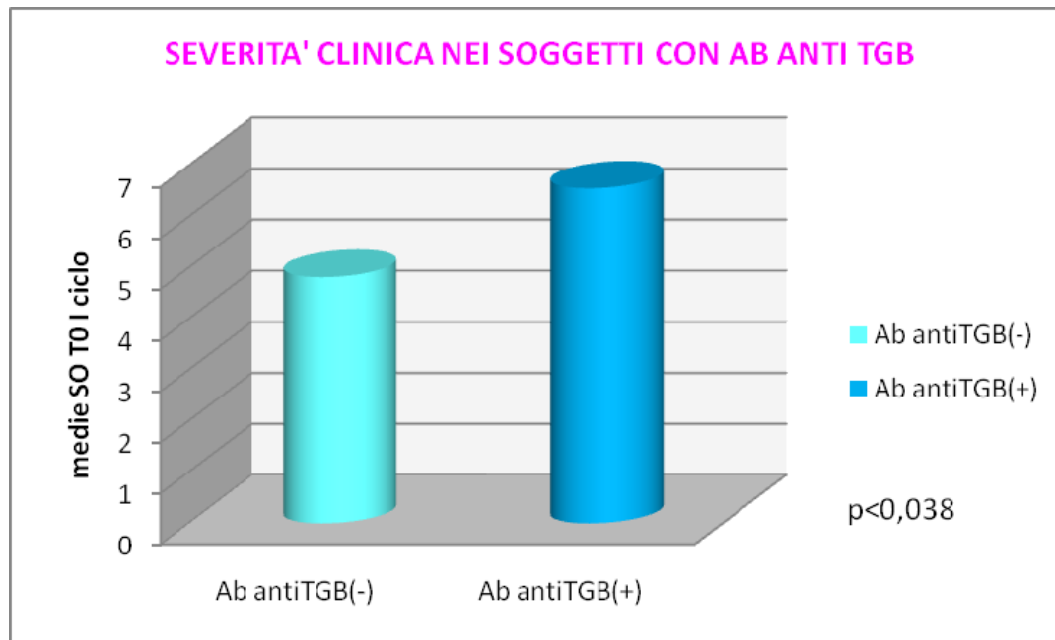
- Correlazione significativa tra **eosinofilia alla citologia congiuntivale** e **Score Oculare elevato**.
- Correlazione significativa tra **eosinofilia totale** e **Score Oculare elevato** (r Rho Spearman=0.25; $p=0.003$).
- Correlazione significativa tra **ECP** e **Score Oculare all'inizio del trattamento** (r Rho Spearman= 0,194; $p= 0.01$).



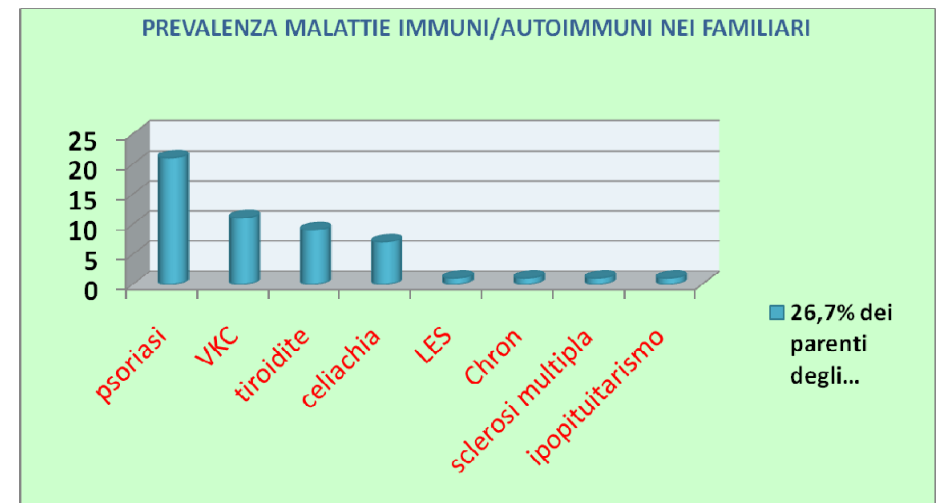
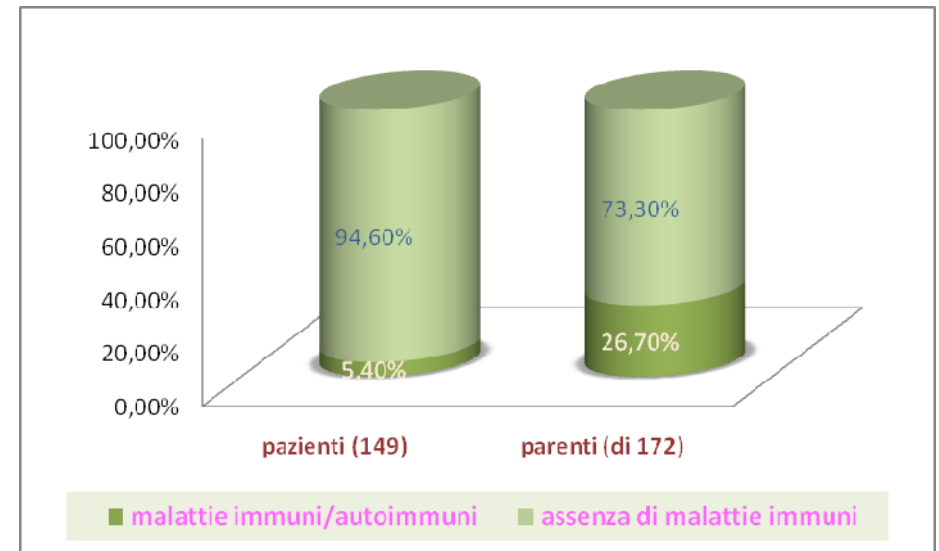
Gli eosinofili hanno un ruolo decisivo nella patogenesi della VKC.

Risultati - 4

Grafici di distribuzione malattie autoimmuni in base ad anamnesi personale o familiare :



La media degli **Score Oculari** era significativamente superiore nei pazienti che presentavano **anticorpi anti-TGB** rispetto ai soggetti negativi per lo stesso marker



Attività scientifica sulla vernal delle UUOO di Oculistica e Pediatria Università di Bari

SHORT REPORT
New insights into childhood Vernal keratoconjunctivitis-associated factors
Riccardina Tesse¹, Laura Spadavecchia², Pietro Fanelli³, Claudia Pagliarulo¹, Mariella Capozza¹, Brigita Favaro¹, Lucio Armento² & Luciano Cavallaro¹
Government of Basilicata, the Department of Pediatrics, University of Bari, Bari, Italy; ²Division of Pediatrics, University of Bari, Bari, Italy; ³Division of Pediatrics, University of Bari, Bari, Italy

Keywords

Vernal keratoconjunctivitis; Thymus; Autoantibodies; Autoantibodies (immune system); Autoantibodies (immune system)

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Introduction

Vernal keratoconjunctivitis (VKC) is a seasonal ocular inflammatory disease affecting children and/or adults, characterized by greater prevalence in boys living in warm climates. VKC is considered to be primarily, but not solely, an immunological (Etiology-related) disease (1,2). Conjunctival inflammation (Etiology-related) is characterized by the presence of eosinophilic infiltrates in the conjunctiva, along with giant cells, T cells, and neutrophils. The inflammatory effector cells play an active role in VKC inflammation, releasing by themselves surface adhesion molecules and epithelial cells that play a role in the recruitment of inflammatory cells. The response by eosinophils, neutrophils, mast cells, and eosinophilic receptors, human leukocyte antigen (HLA) polymorphisms, as well as acting as a mechanism of resistance to the therapy of various substances used to control signs and symptoms of VKC, have been investigated in several studies. Several multifactorial drugs with different mechanisms of action, such as anticholinergics, mast cell stabilizers, and immunosuppressive molecules, have been used in other studies. In our study, we have previously demonstrated the efficacy and safety of low-

dose cyclosporine in the treatment of children with severe VKC, supporting the hypothesis that this ocular disease may have an immune-based inflammatory component (3). The aim of this study was to investigate whether a family history for conditions other than atopy and serological analysis in Caucasian children. For the first time, the serological analysis of HLA markers expressed in VKC children was also carried out.

Methods

We studied 197 children (M:F ratio 5:1) consecutively enrolled during the first decade of life, with diagnosis of VKC made by an ophthalmologist by using each eye for objective signs and symptoms as previously described (3). Children were enrolled in the study if they had a family history of atopy and immunological disorders was recorded by the specialized pediatric allergologist at the time of the first visit of each patient. The

Treatment of severe vernal keratoconjunctivitis with 1% topical cyclosporine in an Italian cohort of 197 children

Tesse R, Spadavecchia L, Fanelli P, Rizzo G, Procoli U, Brunetti L, Cardinale F, Minicello VL, Bellizzi M, Armento L. Treatment of severe vernal keratoconjunctivitis with 1% topical cyclosporine in an Italian cohort of 197 children.
Pediatr Allergy Immunol 2010; 21: 330-335.
© 2009 John Wiley & Sons A/S

The purpose of our study was to verify the efficacy of prolonged cycles of 1% topical cyclosporine in improving severe form of vernal keratoconjunctivitis (VKC) in childhood and investigate for factors affecting the response to therapy. We conducted an open trial involving 197 children with severe VKC, who received topical cyclosporine 1% for 3 months. Ocular subjective symptoms (SS) and objective signs (OS) were scored in all children at entry, 2 weeks and 4 months. Skin prick and microscope endothelial cells evaluation were also performed; immunoglobulin E and cyclosporine levels were assessed. The core values for severity of SS and OS were significantly decreased after 2 weeks and 4 months, compared with those at entry. At the end of therapy, nor were endothelial cells nor immunoglobulin E levels were significantly decreased. Patients who started the therapy at the beginning of the year received long-term regimens of treatment with cyclosporine faster improvement of ocular signs and symptoms, in all other patients. Our findings suggest that 1% cyclosporine administered topically at the beginning of the year, long-term period might be the most effective treatment and local inflammation in severe forms of VKC in

Riccardina Tesse¹, Laura Spadavecchia², Pietro Fanelli³, Giovanni Rizzo¹, Ugo Procoli¹, Luigia Brunetti¹, Fabio Cardinale¹, Vito L. Minicello¹, Mario Bellizzi¹ and Lucio Armento²
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Key words: vernal conjunctivitis; topical cyclosporine; childhood

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Vernal keratoconjunctivitis (VKC) is a seasonal allergic ocular disease, which usually affects boys during the first decade of life, and spontaneously disappears during the second decade. Typical clinical signs and symptoms of the disease include itching, photophobia, tearing, foreign body sensation, sticky mucous discharge, giant papillae on the upper tarsal conjunctiva or at the limbus (often leading to palpebral ptosis) or better nodules, and superficial keratitis or even into corneal shield ulcers. Permanent changes to the cornea, such as keraticopy, corneal

and/or steroid-induced glaucoma or cataract, may occur and be accompanied by permanent visual impairment (1,2). Vernal keratoconjunctivitis is widespread in warm regions, such as the Mediterranean area, the Arab, Persian, Pakistani, Indian and Equatorial Africa. Based on a different clinical presentation, it is possible to distinguish a tarsal form, a limbal form and a mixed form of VKC. The tarsal form is characterized by the presence of giant papillae on the upper tarsal conjunctiva, and the limbal form is characterized by the presence of nodules at the limbus. The mixed form is characterized by the presence of both tarsal and limbal forms. The tarsal form is characterized by the presence of giant papillae on the upper tarsal conjunctiva, and the limbal form is characterized by the presence of nodules at the limbus. The mixed form is characterized by the presence of both tarsal and limbal forms.

Efficacy of 1.25% and 1% topical cyclosporine in the treatment of severe vernal keratoconjunctivitis in childhood

Spadavecchia L, Fanelli P, Tesse R, Brunetti L, Cardinale F, Bellizzi M, Rizzo G, Procoli U, Bellizzi M, Armento L. Efficacy of 1.25% and 1% topical cyclosporine in the treatment of severe vernal keratoconjunctivitis in childhood.
Pediatr Allergy Immunol 2006; 17: 527-532.
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Cyclosporin eyedrops 2% have been used for treatment of corticosteroid-resistant vernal keratoconjunctivitis (VKC) cases. The purpose of our study was to verify the efficacy of 1.25% and 1% topical cyclosporine in improving severe form of VKC in childhood. Twenty children with severe VKC were enrolled in a double-blind, placebo-controlled study. They received cyclosporine 1.25% or 1% for 3 months. This an open trial was conducted during the first 3 months of the study and they received cyclosporine 1% for 4 months. Ocular subjective symptoms and objective signs were scored in all children at entry, 2 weeks and 4 months. Skin prick and microscope endothelial cells evaluation were also performed. The mean score for severity of SS and OS were significantly decreased after 2 weeks and 4 months, compared with those at entry. At the end of therapy, nor were endothelial cells nor immunoglobulin E levels were significantly decreased. Patients who started the therapy at the beginning of the year received long-term regimens of treatment with cyclosporine faster improvement of ocular signs and symptoms, in all other patients. Our findings suggest that 1% cyclosporine administered topically at the beginning of the year, long-term period might be the most effective treatment and local inflammation in severe forms of VKC in

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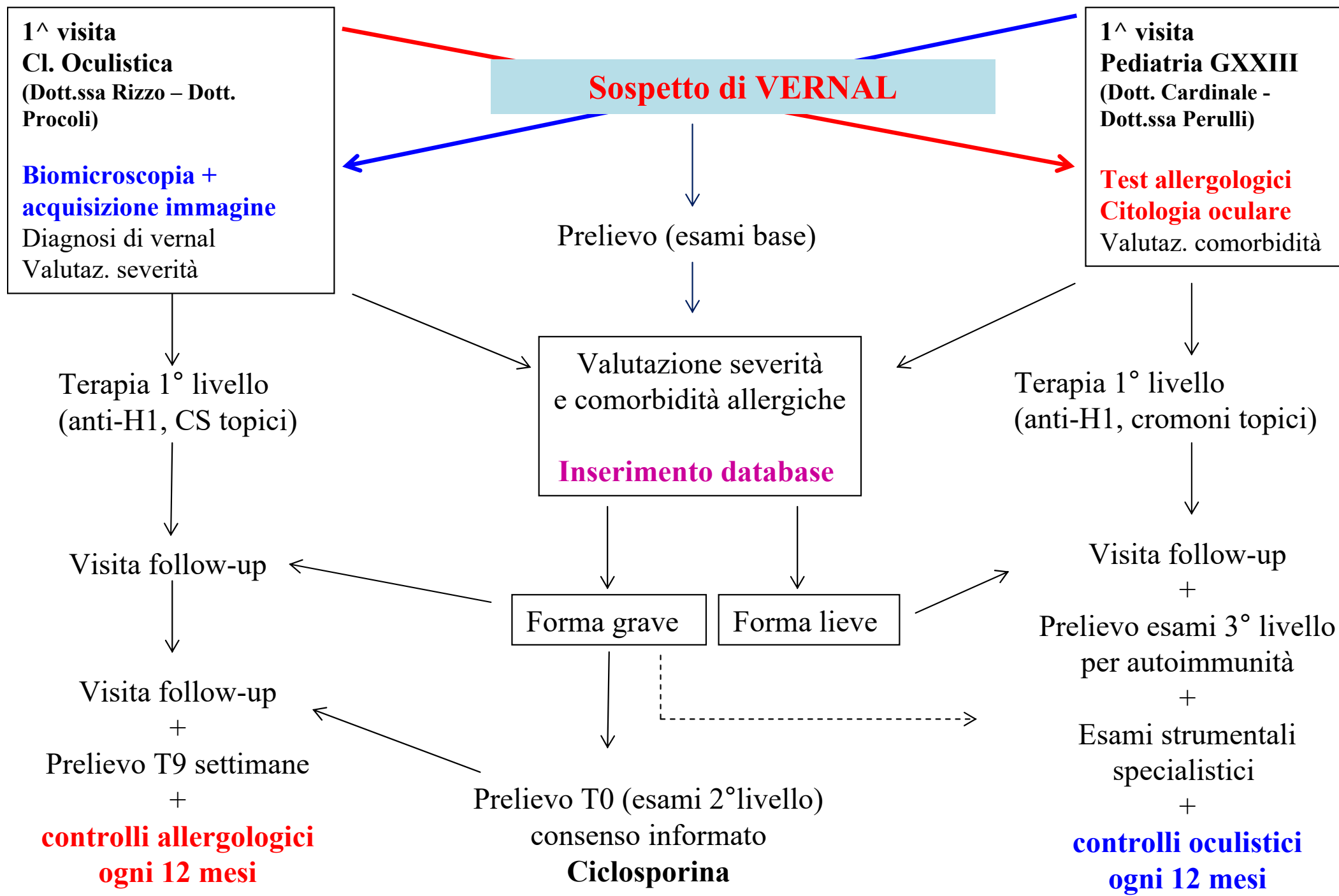
Vernal keratoconjunctivitis (VKC) is a seasonal allergic ocular disease, which usually affects boys during the first decade of life, and spontaneously disappears during the second decade. Typical clinical signs and symptoms of the disease include itching, photophobia, tearing, foreign body sensation, sticky mucous discharge, giant papillae on the upper tarsal conjunctiva or at the limbus (often leading to palpebral ptosis) or better nodules, and superficial keratitis or even into corneal shield ulcers. Permanent changes to the cornea, such as keraticopy, corneal

and/or steroid-induced glaucoma or cataract, may occur and be accompanied by permanent visual impairment (1,2). Vernal keratoconjunctivitis is widespread in warm regions, such as the Mediterranean area, the Arab, Persian, Pakistani, Indian and Equatorial Africa. Based on a different clinical presentation, it is possible to distinguish a tarsal form, a limbal form and a mixed form of VKC. The tarsal form is characterized by the presence of giant papillae on the upper tarsal conjunctiva, and the limbal form is characterized by the presence of nodules at the limbus. The mixed form is characterized by the presence of both tarsal and limbal forms. The tarsal form is characterized by the presence of giant papillae on the upper tarsal conjunctiva, and the limbal form is characterized by the presence of nodules at the limbus. The mixed form is characterized by the presence of both tarsal and limbal forms.



PROTOCOLLO OPERATIVO DI GESTIONE DELLA VERNAL

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ESAMI PER CHERATOCONGIUNTIVITE VERNAL

ESAMI DI BASE

- ☐ Prick test inalanti
- ☐ Emocromo con formula
- ☐ IgE totali
- ☐ IgE specifiche – Immuno-CAP (acari, cipresso, olivo, Phleum pratense, logliarello, parietaria, assenzio, artemisia, alternaria, cladosporum, epitelio di gatto, epitelio di cane, blatella, cavallo)
- ☐ ECP sierica
- ☐ Citologia congiuntivale

ESAMI STRUMENTALI SPECIALISTICI

- ☐ FeNO
- ☐ Citologia nasale
- ☐ Spirometria

ESAMI PRELIMINARI ALLA TERAPIA CON CICLOSPORINA (T0, T9 settimane)

- ☐ GOT GPT gamma-GT, azotemia, creatinina, glicemia
- ☐ es. urine
- ☐ ciclosporinemia (T9 settimane)

ESAMI AL FOLLOW-UP (una tantum o ogni 2-3 anni, a discrezione del medico)

- ☐ ANA
- ☐ EMA, anti-transglutaminasi
- ☐ FT3, FT4, TSH
- ☐ Anticorpi anti-TPO, anticorpi anti-Tireoglobulina