

GIMBE[®]

Gruppo Italiano per la Medicina Basata sulle Evidenze

Evidence-Based Medicine Italian Group

Workshop

L'EBM nell'ambulatorio del pediatra di base

Sesto S. Giovanni (MI), 24 settembre 2005



arseducandi

Società Scientifica per l'Educazione Continua

Workshop Clinici Interattivi (3)

ASMA NEL BAMBINO

Dalle evidenze scientifiche

all'appropriatezza degli interventi sanitari

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Scenario Clinico (1)

- Carlo è un bambino nato da parto spontaneo, allattato al seno esclusivo fino al 6° mese con parametri auxologici normali.
- Anamnesi familiare positiva per atopia: il padre, sin da bambino, è affetto da rino-congiuntive stagionale.
- All'età di 8 mesi, episodio di dermatite eritemato-desquamativa a livello delle pieghe cutanee (cavo popliteo, polsi, gomiti) e del volto, con evidenti lesioni da grattamento, insorte con l'inizio del divezzamento e l'introduzione di cibi solidi.

Scenario Clinico (2)

- All'età di due anni e 6/12, durante il periodo invernale, la mamma di Carlo mi contatta telefonicamente perché il bambino presenta, da due giorni, un lieve rialzo febbrile, (max 38.0 °C), scolo sieroso dal naso e qualche accesso di tosse.
- Vista l'epidemia influenzale in corso, tranquillizzo la mamma, prescrivo paracetamolo al bisogno e fisso un appuntamento in ambulatorio per l'indomani.
- Obiettivamente, Carlo presenta modica dispnea espiratoria; all'ascoltazione rilevo sibili espiratori diffusi su tutto l'ambito polmonare.

Wheezing in infants

- Il respiro sibilante nell'infanzia è caratterizzato dalla presenza di fischi e rantoli di tonalità acuta, principalmente in fase espiratoria
- Spesso è associato ad infezione virale acuta, bronchiolite o asma (condizioni non facilmente distinguibili a livello clinico).
- Nella maggior parte dei casi gli episodi acuti sono scatenati da infezioni respiratorie virali.
- I risultati di uno studio di coorte (826 neonati seguiti fino a 6 anni di età) indicano che per il respiro sibilante nell'infanzia si possono distinguere 3 categorie prognostiche.

Wheezing in infants

- 1. Persistent.** With risk factors for atopic asthma (elevated IgE levels, familiar history of asthma), who initially suffered wheeze during viral infections and in whom the wheezing persisted into school age.
- 2. Transient.** With reduced lung function, as infants, but no early markers of atopy; also suffered wheeze during viral infections but stopped wheezing after the first 3 years of life
- 3. Late onset.** Who did not wheeze when aged under 3 years but had developed wheeze by school age

CLINICAL QUESTIONS



3. Asma nel bambino

A. Quale trattamento avresti prescritto a Carlo, al suo primo episodio di “wheezing”?

1. Ipratropio bromuro
2. β_2 -agonisti short acting (per via inalatoria)
3. Steroidi (per os)
4. Steroidi (per via inalatoria)
5. Nessun farmaco

Asthma and other wheezing disorders in children

Search date October 2004

Duncan Keeley and Michael McKean

Linee guida asma 2003-2005

- Prodigy. November 2004
- National Heart, Lung and Blood Institute (NHLBI), World Health Organization (WHO), October 2004 (score AGREE 56%)
- **SIGN-BTS. June 2004** (score AGREE 88%)

Asthma and other wheezing disorders in children

clinical
evidence

Search date October 2004

Duncan Keeley and Michael McKean

OPTION

INHALED IPRATROPIUM BROMIDE

One systematic review of RCTs provided insufficient evidence about the clinical effects of inhaled ipratropium bromide compared with placebo or added to β_2 agonists.

Everard ML, Bara A, Kurian M, Elliott TM, Ducharme F

Anticholinergic drugs for wheeze in children under the age of two year

*The Cochrane Database of Systematic Reviews
2005, Issue 3*

Acute Wheeze in infants

Inhaled ipratropium bromide

1. Utile
2. Probabilmente utile
3. Da valutare caso per caso
- 4. Di utilità non determinata**
5. Di utilità discutibile
6. Inutile o dannoso

Asthma and other wheezing disorders in children

clinical
evidence

Search date **October 2004**

Duncan Keeley and Michael McKean

OPTION

SHORT ACTING β_2 AGONISTS

One RCT in infants aged 3 months to 2 years found that nebulised salbutamol improved respiratory rate and clinical symptom score compared with placebo but found no significant difference in hospital admission. Another RCT that included infants aged less than 18 months and children up to 36 months found no significant difference in change from baseline in clinical symptom scores with nebulised salbutamol compared with placebo. Nebulised β_2 agonists may cause tachycardia, tremor, and hypokalaemia. Two RCTs in children aged up to 5 years found no significant difference in hospital admission with delivery of salbutamol through a metered dose inhaler plus spacer compared with nebulised salbutamol. Another RCT in infants aged 1–24 months found no significant difference in improvement of symptoms with delivery of terbutaline through a metered dose inhaler plus spacer compared with nebulised terbutaline. Nebulised β_2 agonists may cause tachycardia, tremor, and hypokalaemia.

Acute Wheeze in infants

Short acting β -agonists (salbutamol by nebuliser)

1. Utile
- 2. Probabilmente utile**
3. Da valutare caso per caso
4. Di utilità non determinata
5. Di utilità discutibile
6. Inutile o dannoso

Chavasse R, Seddon P, Bara A, McKean M.

**Short acting beta agonists for
recurrent wheeze in children
under two years of age**

*The Cochrane Database of Systematic Reviews
2005, Issue 3*

Asthma and other wheezing disorders in children

clinical
evidence

Search date October 2004

Duncan Keeley and Michael McKean

OPTION

ORAL CORTICOSTEROIDS

One small RCT found no significant difference in daily symptom scores with oral prednisolone compared with placebo.

Clinical Evidence. September 2005

Acute Wheeze in infants

Oral Corticosteroids

1. Utile
2. Probabilmente utile
3. Da valutare caso per caso
- 4. Di utilità non determinata**
5. Di utilità discutibile
6. Inutile o dannoso

Asthma and other wheezing disorders in children

clinical
evidence

Search date October 2004

Duncan Keeley and Michael McKean

OPTION

HIGH DOSE INHALED CORTICOSTEROIDS

One systematic review found that high dose inhaled corticosteroids reduced the requirement for oral corticosteroids compared with placebo but the difference was not statistically significant. The review also found a clear preference for the inhaled corticosteroids by the children's parents over placebo. The clinical importance of these results is unclear.

Clinical Evidence. September 2005

Acute Wheeze in infants

High doses inhaled corticosteroids

1. Utile
2. Probabilmente utile
3. Da valutare caso per caso
- 4. Di utilità non determinata**
5. Di utilità discutibile
6. Inutile o dannoso

McKean M, Ducharme F

Inhaled steroids for episodic viral wheeze of childhood

*The Cochrane Database of Systematic Reviews
2005, Issue 3*

MAIN RESULTS

- Five RCTs in children with a history of mild episodic viral wheeze were identified. There were three studies of preschool children given episodic high dose inhaled corticosteroid (1.6 - 2.25 mg per day). The primary outcome was episodes requiring oral corticosteroids.
- Episodic high dose inhaled corticosteroids showed a reduced requirement for oral corticosteroids (RR 0.53, 95% CIs 0.27-1.04). This treatment was preferred by the children's parents over placebo
- Maintenance low dose inhaled corticosteroids did not show any clear reduction over placebo in the proportion of episodes requiring oral corticosteroids

McKean M al. Cochrane Library, 2005

CONCLUSIONS

- Episodic high dose inhaled corticosteroids provide a partially effective strategy for the treatment of mild episodic viral wheeze of childhood.
- There is no current evidence to favour maintenance low dose inhaled corticosteroids in the prevention and management of episodic mild viral induced wheeze.

Scenario Clinico (3)

- Prescrivo salbutamolo per aerosol (5 gocce su 3 ml di soluzione fisiologica 3 volte/die).

CLINICAL QUESTIONS



3. Asma nel bambino

B. In un bambino dell'età di Carlo (due anni e 6 mesi), l'erogazione di salbutamolo con inalatore predosato + distanziatore è più efficace della nebulizzazione tramite aerosol?

1. No

2. Sì

- We found no systematic review.
- We found three RCTs comparing delivery of short acting β_2 agonists through metered dose inhaler versus nebuliser.
 - 64 children aged 1–5 years with acute recurrent wheezing
 - 42 infants, mean age < 2 years with acute wheezing
 - 34 infants aged 1–24 months with acute wheezing
- None of RCTs found significant difference in hospital admissions with delivery of salbutamol through a metered dose inhaler plus spacer versus nebulised salbutamol
- Nebulised β_2 agonists may cause tachycardia, tremor, hypokalaemia.

Acute Wheeze in infants

Delivery through metered dose inhaler versus nebuliser

1. Utile
2. Probabilmente utile
3. Da valutare caso per caso
- 4. Di utilità non determinata**
5. Di utilità discutibile
6. Inutile o dannoso

McKean M, Ducharme F, Cates CJ

**Holding chambers versus nebulisers
for β_2 -agonist treatment
of acute asthma**

*The Cochrane Database of Systematic Reviews
2005, Issue 3*

Asthma and other wheezing disorders in children

clinical
evidence

Search date October 2004

Duncan Keeley and Michael McKean

OPTION

METERED DOSE INHALER PLUS SPACER DEVICES VERSUS NEBULISERS FOR DELIVERING β_2 AGONISTS

One systematic review, in children with acute but not life threatening asthma who were old enough to use a spacer, found no significant difference in hospital admission rates with a metered dose inhaler plus a spacer compared with nebulisation for delivery of β_2 agonists (fenoterol, salbutamol, or terbutaline) or β agonist (orciprenaline). Children using a metered dose inhaler with a spacer may have shorter stays in emergency departments, less hypoxia, and lower pulse rates compared with children receiving β_2 agonist by nebulisation

β_2 AGONIST DELIVERY

ACUTE ASTHMA

pMDI + spacer is at least as good as a nebuliser at treating mild and moderate exacerbations of asthma in children from the age of two and adults.²⁰³⁻²⁰⁵

> 12 years	2-12 years	< 2 years
1 ⁺⁺	1 ⁺⁺	

A

A

Children aged ≥ 2 and adults with mild and moderate exacerbations of asthma should be treated by pMDI + spacer with doses titrated according to clinical response.

There are no data to make recommendations in children under two or in severe (life-threatening) asthma.

Scenario Clinico (4)

- Rivedo Carlo in ambulatorio dopo una settimana per un controllo dopo la sospensione della terapia.
- L'episodio si è completamente risolto: permane una modesta tosse catarrale, ma l'ascoltazione toracica è nella norma.
- Rassicuro la mamma e le consiglio di:
 - ripetere lo stesso trattamento, se dovessero presentarsi simili episodi.
 - contattarmi in caso di attacchi più gravi e/o se la terapia non dovesse risultare efficace

STEP 1: MILD INTERMITTENT ASTHMA

Inhaled short-acting β_2 agonist as required

FREQUENCY OF DOSING OF INHALED SHORT-ACTING β_2 AGONISTS

There is no consistent evidence of any benefit or harm from regular (four times daily) use of short-acting β_2 agonists compared with as required use.^{159,160} Unless individual patients are shown to benefit from regular use of inhaled short-acting β_2 agonists then as required use is recommended.

Using two or more canisters of β_2 agonists per month or >10-12 puffs per day is a marker of poorly controlled asthma.¹⁶¹

> 12 years	5-12 years	< 5 years
1++	1++	1++
2++	4	4

B

D

D

Patients with high usage of inhaled short-acting β_2 agonists should have their asthma management reviewed.

Scenario Clinico (5)

- In occasione del bilancio di salute dei 3 anni la mamma riferisce che negli ultimi sei mesi si sono verificati tre episodi di bronco-ostruzione di lieve entità, analoghi al primo, caratterizzati da tosse (anche notturna) e dispnea espiratoria senza febbre o altri sintomi associati.
- Tutti gli episodi, gestiti dalla mamma in piena autonomia, si sono risolti con la somministrazione di salbutamolo per aerosol (alle dosi consigliate) per circa 7 gg.

CLINICAL QUESTIONS



C. Considerata la frequenza/gravità degli attacchi asmatici, ritieni appropriata per Carlo una profilassi?

1. No
2. Sì, con β_2 -agonisti long-acting
3. Sì, con steroidi per via inalatoria
4. Sì, con sodio cromoglicato
5. Sì, con antagonisti dei leucotrieni
6. Sì, con anti-istaminici

STEP 2: INTRODUCTION OF REGULAR PREVENTER THERAPY

For steps 2, 3, and 4, treatments have been judged on their ability to improve symptoms, improve lung function, and prevent exacerbations, with an acceptable safety profile. Improvement of quality of life, while important, is the subject of too few studies to be used to make recommendations at present.

INHALED STEROIDS

Inhaled steroids are the most effective preventer drug for adults and children for achieving overall treatment goals.¹⁶²⁻¹⁶⁶

> 12 years	5-12 years	< 5 years
1 ⁺⁺	1 ⁺⁺	1 ⁺⁺

A A A

Inhaled steroids are the recommended preventer drug for adults and children for achieving overall treatment goals.

The exact threshold for introduction of inhaled steroids has never been firmly established. Two recent studies have shown benefit from regular use of inhaled steroids in patients with mild asthma.^{526,527} Benefit in these studies was seen even with an FEV₁ of 90% predicted.

> 12 years	5-12 years	< 5 years
1+	1+	

B

B



Inhaled steroids should be considered for patients with any of the following:

- exacerbations of asthma in the last two years
- using inhaled β_2 agonists three times a week or more
- symptomatic three times a week or more, or waking one night a week.



Lung function measurements cannot be reliably used to guide asthma management in children under 5 years of age.

OTHER PREVENTER THERAPIES

Inhaled steroids are the first choice preventer drug. **Long-acting inhaled β_2 agonists should not be used without inhaled corticosteroids.**⁵²⁹ Alternative, less effective preventer therapies in patients taking short-acting β_2 agonists alone are:

- Chromones
(Sodium cromoglicate has an inconvenient dosing frequency)⁵²⁰
 - Sodium cromoglicate is of some benefit in adults¹⁷⁰
 - The evidence of benefits of sodium cromoglicates in children is contentious.^{568,569,520} This is under active review
 - Nedocromil sodium is of some benefit^{170,519}
- Leukotriene receptor antagonists have some beneficial clinical effect (*and an effect on eosinophilic inflammation*)^{165 171 172}
- Theophyllines have some beneficial effect (*side-effects are more common and monitoring of plasma levels is required*).^{157 164}
- Antihistamines and ketotifen are ineffective.¹⁷⁵

	> 12 years	5-12 years	< 5 years
	1+		
		1+	
	1++	1+	
	1++	1++	1++
	1+	1+	1+
	1++	1++	1++



Long-acting inhaled β_2 agonists should not be used without inhaled corticosteroids.

Leone FT, Fish JE, Szefler SJ, et al.

Collaboration of American College of Chest Physicians, American Academy of Allergy, Asthma, and Immunology, and American College of Allergy, Asthma, and Immunology.

**Systematic review of the evidence
regarding potential complications of
inhaled corticosteroid use in asthma**

Chest 2003;124:2329-40

- ICS use is not associated with a reduction in **bone density** in children with asthma (grade A).
- Therapy with ICSs is associated with a decrease in **short-term growth rates** in children, but the overall effect is small and may not be sustained with long-term therapy (grade A).
- The **adult height** attained by asthmatic children treated with ICSs is not different from that of nonasthmatic adults (grade C).
- There is insufficient information on the difference of ICS formulations in their growth-related effects (grade C)

Scenario Clinico (6)

- Dopo 15 gg la mamma di Carlo, molto allarmata, mi riferisce telefonicamente che il figlio, da circa tre ore, presenta tosse e respira con molta difficoltà, nonostante il trattamento aerosolico con salbutamolo (5 gocce su 3 ml di soluzione fisiologica eseguito già due volte).
- Percepisco, dalla voce della signora, che non si tratta della solita e banale richiesta di visita domiciliare, per cui decido di andare subito a visitare il bambino.

Scenario Clinico (7)

- Carlo si presenta molto sofferente, ansioso e pallido, ma nonostante la dispnea, risponde alle mie domande.
- Obiettivamente:
 - rientramento del giugulo e dei muscoli intercostali;
 - sibili espiratori accompagnati rantoli umidi a bolle medie;
 - frequenza respiratoria 40/min
 - frequenza cardiaca 120/min

CLINICAL QUESTIONS



3. Asma nel bambino

D. Avresti predisposto per Carlo un ricovero ospedaliero immediato?

1. No
2. Sì

Age 2-5 years

ASSESS ASTHMA SEVERITY

Moderate exacerbation

- SpO₂ ≥ 92%
- Able to talk
- Heart rate ≤ 130/min
- Respiratory rate ≤ 50/min

Severe exacerbation

- SpO₂ < 92%
- Too breathless to talk
- Heart rate > 130/min
- Respiratory rate > 50/min
- Use of accessory neck muscles

Life threatening asthma

- SpO₂ < 92%
- Silent chest
- Poor respiratory effort
- Agitation
- Altered consciousness
- Cyanosis

Treatment

**IF POOR RESPONSE
ARRANGE ADMISSION**

**IF POOR RESPONSE
REPEAT β_2 AGONIST AND
ARRANGE ADMISSION**

**REPEAT β_2 AGONIST VIA
OXYGEN-DRIVEN
NEBULISER WHILST
ARRANGING IMMEDIATE
HOSPITAL ADMISSION**

*BTS – SIGN
2004*

CLINICAL QUESTIONS



E. Quale trattamento ritieni appropriato per un attacco asmatico moderato in un bambino di 3 anni che non risponde al trattamento con salbutamolo?

1. Steroidi per via inalatoria
2. Steroidi per via sistemica
3. Ipratropio bromuro per via inalatoria
4. 1 + 3
5. 2 + 3

STEROID THERAPY

Steroid tablets

The early use of steroids for acute asthma can reduce the need for hospital admission and prevent a relapse in symptoms after initial presentation.^{258 259} Benefits can be apparent within three to four hours.

2+

1+

A Give prednisolone early in the treatment of acute asthma attacks.

A soluble preparation dissolved in a spoonful of water is preferable in those unable to swallow tablets. Use a dose of 20 mg for children 2-5 years old and 30-40 mg for children > 5 years.

Oral and intravenous steroids are of similar efficacy.^{260 296 297}

Inhaled steroids

There is insufficient evidence to support the use of inhaled steroids as alternative or additional treatment to steroid tablets for acute asthma.^{263 299-301}



Do not initiate inhaled steroids in preference to steroid tablets to treat acute childhood asthma.

IPRATROPIUM BROMIDE

There is good evidence for the safety and efficacy of frequent doses of ipratropium bromide used in addition to β_2 agonists for the first two hours of a severe asthma attack. Benefits are more apparent in the most severe patients.³⁰²

1+

A If symptoms are refractory to initial β_2 agonist treatment, add ipratropium bromide (250 mcg/dose mixed with the nebulised β_2 agonist solution).

Frequent doses up to every 20-30 minutes (250 mcg/dose mixed with the β_2 agonist solution in the same nebuliser) should be used early. The dose frequency should be reduced as clinical improvement occurs.

✓ Repeated doses of ipratropium bromide should be given early to treat children poorly responsive to β_2 agonists.

Scenario Clinico (8)

- Per la gravità dell'attacco e per la scarsa risposta terapeutica al salbutamolo prescrivo:
 - ipratropio bromuro per aerosol (120 mcg 2 v/die)
 - betametasone per os (0,1-0,2 mg/kg/die)
- Avverto la mamma, nel caso in cui il bambino non dovesse migliorare entro 2-3 ore, di richiamarmi e/o portarlo al PS.
- In serata, Carlo respira meglio, la tosse è diventata produttiva e la mamma non nota più rientramenti al giugulo ed agli spazi intercostali.

Scenario Clinico (9)

- In seguito a tale episodio i genitori di Carlo mi chiedono, con insistenza, di approfondire la diagnosi
- Prescrivo test allergometrici che mostrano:
 - PRIST > 10 IU/ml;
 - RAST per inalanti negativi;
 - Prick Test positivo (> a 5 mm) per graminacee, Dermatophagoides Pteronissinus e Dermatophagoides Farinae

Scenario Clinico (10)

- I genitori, preoccupati per la frequenza e la gravità dell'ultimo episodio, decidono autonomamente dopo qualche giorno di consultare un allergologo che pone diagnosi di “asma episodico frequente” e prescrive:
 - terapia iposensibilizzante specifica per os:
SLIT sublingual immunotherapy
 - montelukast (1 cpr da 4 mg la sera per 3 mesi)

CLINICAL QUESTIONS



3. Asma nel bambino

F. Ritieni efficace l'immunoterapia per la prevenzione secondaria dell'asma?

1. No
2. Sì

Abramson MJ, Puy RM, Weiner JM

Allergen immunotherapy for asthma

*The Cochrane Database of Systematic Reviews
2005, Issue 3*

CONCLUSIONS

- Immunotherapy reduces asthma symptoms and use of asthma medications and improves bronchial hyper-reactivity.
- One trial found that the size of the benefit is possibly comparable to inhaled steroids.
- The possibility of adverse effects (such as anaphylaxis) must be considered.

MAIN RESULTS

- Seventy-five trials were included
 - 36 trials of immunotherapy for house mite allergy
 - 20 pollen allergy trials;
 - 10 animal dander allergy trials
 - 2 Cladosporium mould allergy
 - 1 latex
 - **6** trials looking at **multiple allergens**

- Three reviews have demonstrated consistent beneficial effects of the treatment compared with placebos. Allergens used in the studies included mites, pollen, animal danders, and moulds.
- However, there are as yet no properly controlled studies making direct comparisons between conventional asthma pharmacotherapy and allergen immunotherapy.

- The preparation of materials for immunotherapy, dose frequency and duration of therapy has not been optimised and the risk benefits compared with pharmacotherapy require careful consideration.
- Immunotherapy may reduce asthma symptoms and use of asthma medications, but the size of benefit compared to other therapies is not known.
- Further comparative studies are needed

3. Asma nel bambino

G. Ritieni appropriata la prescrizione del montelukast?

1. No
2. Sì

Asthma and other wheezing disorders in children

Search date **October 2004**

Duncan Keeley and Michael McKean

OPTION

ORAL LEUKOTRIENE RECEPTOR ANTAGONISTS

One RCT in children aged 6–14 years found that, compared with placebo, oral montelukast (a leukotriene receptor antagonist) increased from baseline the mean morning forced expiratory volume in 1 second and reduced the total daily β_2 agonist use, but found no significant difference in daytime asthma symptom score or in nocturnal awakenings with asthma. Another RCT in children aged 2–5 years found that, compared with placebo, oral montelukast improved average daytime symptom scores and reduced the need for rescue oral steroid courses, but found no significant difference in average overnight asthma symptom scores. We found no RCTs directly comparing oral montelukast with inhaled corticosteroids.

Asthma prophylaxis

Oral leukotriene receptor antagonists (montelukast)

1. Utile
- 2. Probabilmente utile**
3. Da valutare caso per caso
4. Di utilità non determinata
5. Di utilità discutibile
6. Inutile o dannoso

Ducharme FM, Di Salvio F

**Anti-leukotriene agents compared
to inhaled corticosteroids in the
management of recurrent and/or
chronic asthma in adults and children**

*The Cochrane Database of Systematic Reviews
2005, Issue 3*

MAIN RESULTS

- 27 trials met the inclusion criteria, but only 3 trials focused on children and adolescents.

CONCLUSIONS

- Inhaled steroids at a dose of 400 mcg/day of beclomethasone or equivalent are more effective than anti-leukotriene agents given in the usual licensed doses.
- Inhaled glucocorticoids should remain the first line monotherapy for persistent asthma.

STEP 2: REGULAR PREVENTER THERAPY

Add inhaled steroid 200-400 mcg/day* †
or leukotriene receptor antagonist
if inhaled steroid cannot be used

Start at dose of inhaled steroid appropriate to severity of disease.

* BDP or equivalent

† Higher nominal doses may be required if drug delivery is difficult

Scenario Clinico (11)

- Durante il successivo periodo estivo, Carlo mantiene un periodo di benessere, senza presentare alcun episodio bronco-ostruttivo.
- All'inizio dell'autunno, si presentano altri due episodi di asma lieve, trattati con salbutamolo per aerosol (5 gocce su 3 ml di sol. fisiologica 2 volte/die) con buona risposta terapeutica.

Scenario Clinico (12)

- Oggi Carlo ha compiuto 6 anni di età, frequenta la prima elementare e da circa 12 mesi non ha più attacchi asmatici.
- Durante la scorsa primavera si è presentato alla mia attenzione per la presenza di starnuti, prurito nasale e congiuntivale e modesta iperemia congiuntivale.